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Abstracts

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OFP-01 | Joint Session: Uropathology / Nephropathology

OFP-01-001
The influence of the presence of intraductal carcinoma of the prostate on the grade group system's prognostic performance
T. Tsuzuki[1], M. Kato[2]
[1] Department of Surgical Pathology, Aichi Medical University Hospital, Japan, [2] Department of Urology, Nagoya University Graduate School of Medicine, Japan

Background & Objectives: Although the presence of intraductal carcinoma of the prostate (IDC-P) influences biochemical failure in radical prostatectomy patients, no data are available regarding the impact of its integration into the classification Grade Group system. Thus, the aim of this study was to enhance the utility of the Grade Group (GG) system by integrating the presence of IDC-P.
Methods: This study was a retrospective evaluation of 1019 patients with prostate cancer who underwent radical prostatectomy between 2005 and 2013 without neoadjuvant or adjuvant therapy. Data on age, prostate-specific antigen (PSA) level at diagnosis, pathological T stage (pT), the presence of Gleason pattern 5 (GP5), the presence of IDC-P, and surgical margin status were analysed to predict PSA recurrence after prostatectomy.
Results: IDC-P was detected in 157 patients (15.4%). GGs were as follows: GG1 without IDC-P, n=163; GG2 without IDC-P, n=470; GG3 without IDC-P, n=160; GG4 without IDC-P, n=27; GG5 without IDC-P, n=42; any GG with IDC-P, [n=157; GG 2 (n=29); GG3 (n=60); GG4 (n=13); GG5 (n=55)]. Any GG with IDC-P showed a significantly worse prognosis than any other GG without IDC-P ($p< 0.0001$). In a multivariate analysis, integration of the IDC-P into the GGs was significant prognostic predictors ($P < 0.0001$).
Conclusion: Integrating the presence of IDC-P into the GG system will result in more accurate predictions of patient outcome.

OFP-01-002
Distinct genetic alterations and luminal molecular subtype in nested variant of urothelial carcinoma
V. Weyerer[1], R. Weisser[1], E.A. Moskalev[1], F. Haller[1], R. Stoehr[1], M. Eckstein[1], U. Zinnall[2], N.T. Gaisa[3], E. Compèrat[4], A. Perren[5], B. Keck[6], Y. Allory[7], G. Kristiansen[8], B. Wullich[6], A. Agaimy[1], A. Hartmann[1], S. Bertz[1]
[1] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander University Erlangen, Germany, [2] Institute of Medical Systems Biology, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany, [3] Institute of Pathology, RWTH Aachen University, Germany, [4] Hôpital Tenon, HUEP, Sorbonne University, Paris, France, [5] Institute of Pathology, University of Bern, Switzerland, [6] Department of Urology and Paediatric Urology, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nuernberg, Germany, [7] Department of Pathology, Hôpital Foch, Universitè Versailles-Saint-Quentin-en-Yvelines, Universitè Paris-Saclay, Suresnes, Francle; Institut Curie, CNRS, UMR144, Paris, France, [8] Institute of Pathology, University Hospital Bonn, Germany

Background & Objectives: Nested variant of urothelial carcinoma (NVUC) is rare and only few small series exist. Molecular characteristics and the classifying marker profile as well as therapeutic targets of this specific variant are mostly unknown. Aim of this study was to characterise NVUC on the molecular level in one of the largest cohorts to date. In addition, we applied an immunohistochemical marker panel in order to define the molecular subtype of this variant.
Methods: 60 NVUC cases were collected from different departments. *TERT* promoter mutation analysis was carried out in all samples using SNaPshot analysis. Target sequencing of 48 cancer related genes by Next Generation Sequencing (NGS) analysis was performed in a subset of 26 cases. Immunohistochemical markers CD44, CK5, CK14, EGFR, p63, FOXA1, GATA3, CD24 und CK20 were used to elucidate the molecular subtype.
Results: A total of 62.5% of NVUC cases harbored a mutation of the *TERT* promoter. Additionally, *TP53* and *JAK3* were among the most frequently mutated genes identified by NGS analysis. Subtyping revealed that all NVUC express luminal markers such as CD24, FOXA1, GATA3 and CK20.
Conclusion: Summarized, NVUC belong to the luminal molecular subtype. Moreover, a subset of NVUC seems to be characterised by mutations of the Wnt- and inflammatory pathway, including *JAK3* mutations, indicating a different biological background compared to conventional urothelial bladder cancer.

OFP-01-003
A new auto-annotation method and machine learning strategy for detection and annotation of cancer areas in prostate biopsies
L. Björk[1,2], J. Gustafsson[3], F. Hikmet Noraddin[3], K. Eurèn[2], C. Lindskog[3]
[1] Karolinska Institutet, Sweden, [2] Contextvision, Sweden, [3] Uppsala Universitet, Sweden

Background & Objectives: Prostate cancer is one of the most diagnosed cancer forms and a leading cause of cancer-related death in males. The examination and Gleason scoring of prostate biopsies is however a major bottleneck in the pathology workflow, and studies have shown that the inter-observer variability in scoring is high. For increasing accuracy and speeding up the decision process, there is a high demand for implementation of an image analysis tool to support pathologists. The aim of the present investigation was to develop a strategy for un-biased, specific

detection of cancer areas in clinical prostate biopsy images, and use the outlined areas as training material for machine learning algorithms.
Methods: Prostate sections were stained towards Cytokeratin 5/6, p63, Cytokeratin 8/18 and AMACR, and digitalized using immunofluorescence slide scanning. The same slides we stained with hematoxylin and eosin (HE) and scanned in brightfield. The immunofluorescence stainings generated high-resolution multiplex images marking specific structures in the prostate biopsies, accurately outlining the cancer containing areas. The multiplex images where then overlaid with corresponding HE images, and the antibody stained structures thus served as masks to accurately mark cancer areas in the HE images. The HE images along with marked cancer areas were used for training models to distinguish benign prostate glands from cancerous glands using machine learning algorithms.
Results: The multiplex images with added annotation specifically outlining the parenchyma using the epithelial biomarker generated a high-resolution annotation mask suitable for machine learning. Preliminary data on the first 63 biopsies show that the model can accurately outline cancerous glands with high precision. The results were confirmed in an independent set of HE images manually annotated by three different pathologists.
Conclusion: In summary, we have developed a robust and powerful method for specific and objective visualisation of cancer areas in prostate biopsy images, and used these images for machine-learning in order to develop a highly accurate decision support tool for pathologists.

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OFP-01-004

Detection of PD-L1 RNA expression in immunohistochemically negative patients. Are the negatives a heterogenous group?

U. Sommer[1], M. Großer[1], D. Aust[1,2,3], K. Jöhrens[1], P. Hönscheid[1,3], G. Baretton[1,2,3]
[1] Institut für Pathologie, University Hospital Carl Gustav Carus, Medical Faculty, Technische Universität Dresden, Germany, [2] Tumour and Normal Tissue Bank of the University Cancer Center (UCC), University Hospital Carl Gustav Carus, Medical Faculty, Technische Universität Dresden, Germany, [3] Core Unit for Molecular Tumour Diagnostics (CMTD), National Center for Tumour Diseases (NCT) Dresden, Germany

Background & Objectives: Immune-checkpoint inhibition is an already well established therapy for advanced urothelial carcinoma (UC). Identification of patients who are likely to respond to PD-1 or PD-L1 blockade is of paramount importance for clinical decision making. In different clinical trials a correlation between immunohistochemical PD-L1 expression and response to checkpoint inhibition has been shown. Interestingly, there are patients who respond to immunecheckpoint therapy despite lack of PD-L1 expression. These observations and experiences suggest that there might be differences in biology of the tumours, which are only partially revealed by the various available diagnostic antibodies/kits. We investigated PD-L1 RNA expression in metastasized UC in order to be able to detect potential differences in the tumours one step ahead of the protein level.
Methods: 21 formalin-fixed, paraffin-embedded (FFPE) resection specimens from patients with metastasized UC were immunostained for PD-L1 (E1L3N-antibody, Cell Signaling). Consecutively RNA ISH was performed to detect PD-L1 RNA (ViewRNA ISH Tissue 2-Plex Assay, Thermo Fisher) and the PD-L1 target specific probe set (VA1-14391-01).
Results: While protein and RNA expression on tumour and immune cells show comparable results in the IHC positive patient group, we found PD-L1 RNA expression on tumour cells in the IHC negative group. IHC negative patients did not show PD-L1 RNA expression on their immune cells.
Conclusion: It appears that the immunohistochemically negative tumours are a heterogeneous group and a part of them respond to an immununchekpoint blockade. The detection of PD-L1 RNA may be an extended diagnostic step that improves the prediction of therapy Response.

OFP-01-005

Genomic landscape of young-onset bladder cancer and it's prognostic implication on adult bladder cancer

Y.M. Cho[1], S. Im[2], C.O. Sung[1], K.S. Kim[1], N.H. Cho[3], Y.M. Kim[4], G.Y. Kwon[5], K.C. Moon[2], S. Choi[6], J.S. Lim[6], Y.J. Choi[7], S.J. Jung[8], S.D. Lim[9], S.H. Paick[9], O. Lee[10], H.W. Kang[10], S.H. Rha[11], H.S. Hwang[1], J. Park[12], S.Y. Yoon[12], J. Kim[2]
[1] Asan Medical Center, Republic of Korea, [2] Seoul National University, Republic of Korea, [3] Yonsei University College of Medicine, Republic of Korea, [4] Ulsan University Hospital, Republic of Korea, [5] Samsung Medical Center, Republic of Korea, [6] Chungnam National University College of Medicine, Republic of Korea, [7] The Catholic University of Korea, Republic of Korea, [8] Inje University Busan Paik Hospital, Republic of Korea, [9] Konkuk University, Republic of Korea, [10] Chungbuk National University Hospital, Republic of Korea, [11] Dong-A University, Republic of Korea, [12] Asan Institute of Life Science, Republic of Korea

Background & Objectives: Bladder cancer is common in elderly men, and it is a highly mutated tumour with frequent *TP53* and *FGFR3* mutation. Young-onset bladder cancer (YBC) is extremely rare; therefore, its genomic characteristics are unknown and appropriate management strategy is yet to be defined. This study is aimed to delineate the genomic landscape of YBC and to compare it to those of adult bladder cancer (ABC).
Methods: Twenty nine cases of biopsy-proven YBCs diagnosed at 20 years or younger were collected through a nation-wide search of the archived files from the Korean Genitourinary Study Group of the Korean Society of Pathologists. Whole exome sequencing and RNA sequencing were performed on 21 and 11 cases, respectively, and the results were compared with those of adult bladder cancer (ABC) retrieved from public database.
Results: Driver mutations were found in all cases. Common mutations included *HRAS* mutations (10 cases) and *FGFR3* gene fusions (7 cases). Others were *KRAS* mutations (2 cases), arm-level deletion of chromosomes 4p and 10q (1 case), and *ERCC2* mutation (1 case). *TP53* and *FGFR3* point mutations were not found. The gene expression profiles of YBC corresponded to those of the good prognostic group of ABC. None of YBC cases and ABCs with YBC-like mutations had progressed to muscle-invasive tumour.
Conclusion: YBC had distinct driver genetic alterations such as *HRAS* mutation and *FGFR3* gene fusion and showed good prognosis. YBCs and ABCs with YBC-like mutations may be managed with less aggressive surveillance.

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OFP-01-006

Intra and interpatient genetic features of intraductal carcinoma of the prostate

M. Downes[1], A. Hodgson[1], S. Chen[2], H. He[2], S. Liu[3], D. Vesprini[3]
[1] Sunnybrook Health Sciences Centre, Canada, [2] Princess Margaret Cancer Centre, Canada, [3] Radiation oncology, Sunnybrook Health Sciences Centre, Canada

Background & Objectives: Intraductal carcinoma of prostate (IDC) is a morphologic pattern that is associated with adverse patient outcome. The

molecular underpinnings of IDC are not yet fully elucidated, particularly in comparison with background prostate.
Methods: A pilot analysis was conducted using 10 randomly selected patients who underwent radical prostatectomy and who had IDC. IDC was confirmed using immunohistochemistry. Benign prostatic tissue, conventional acinar adenocarcinoma and IDC were sampled from each case using needle punches. DNA extraction was performed with the RecoverAll total nucleic acid isolation kit and samples (n=30) were run on a Thermo Fisher Ion Torrent S5XL platform using the Oncomine Comprehensive Assay v3. Copy number variants (CNVs) and single nucleotide variants (SNVs) within and between patient samples were evaluated. Bioinformatic analyses was performed using the computing environment R.
Results: 2/10 patients had *BRCA2* mutations in benign, acinar carcinoma and IDC, suggestive of an underlying germline defect. No significant differences for SNVs were detected within or between patients using this panel. CNV analysis demonstrated a trend towards gain of the proto-oncogene *MYC* in IDC and also *EZH2* compared with matching benign and acinar adenocarcinoma with reduced gain of *p53* and loss of *PTEN*.
Conclusion: BRCA2 mutations (perhaps germline) exist in our cohort of IDC cases. This finding could have implications for genetic testing and therapeutic options (ex. PARP inhibitors). In addition, gains in *MYC* and *EZH2* with reduced gain in *p53* and loss of *PTEN* were noted in the IDC component, providing some insight into the molecular evolution of this entity.

OFP-01-007
Papillary renal cell carcinoma with prominent spindle cell stroma - tumour mimicking MESTK , clinicopathologic analysis of 5 cases
J. Rogala[1], K. Pivovarcikova[2], M. Ulamec[3,4], R. Alaghehbandan[5], F. Kojima[6]
[1] Department of Pathology, Regional Specialist Hospital, Wrocław, Poland, [2] Department of Pathology, Charles University, Medical Faculty and Charles University Hospital Plzen, Czech Republic, [3] Clinical Department of Pathology and Cytology "Ljudevit Jurak", University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia, [4] Department of Pathology, School of Medicine, University of Zagreb, Zagreb, Croatia, [5] Department of Pathology, Faculty of Medicine, University of British Columbia, Royal Columbian Hospital, Vancouver, Canada, [6] Shin-ichi Murata, Department of Human Pathology, Wakayama Medical University, Wakayama, Japan

Background & Objectives: Papillary Renal Cell Carcinomas (PRCCs) are traditionally divided on type 1 and type 2. Recent studies confirm relative uniformity within type 1 PRCCs in contrast to type 2, showing broad spectrum of morphologic, immunohistochemical and molecular featutes. We selected a series of unusual PRCCs with spindle cell stroma resembling mixed epithelial and stromal tumour (MESTK) of kidney to assess clinicopathological features.
Methods: Five cases of PRCCs with prominent spindle cell stroma (PRCCSCS) were analysed using morphologic , immunohistochemical and array CGH methods.
Results: Tumours revealed papillary to tubulopapillary architecture. Epithelial cells were mainly eosinophilic, nuclear grade 2 and 3 (WHO/ISUP). Spindle cell stroma showed no malignant or heterogenous elements. Mitotic index was low in both compartments.
Epithelial cells were positive for CK7, AMACR, vimentin and FH. Stroma was positive for vimentin, actin and focally for CD34. Estrogen and progesterone were negative in both elements.
Copy numer variation pattern was variable (multiple gains and losses).
Conclusion: PRCCSCS is distinct variant of PRCC, which cannot be futher subclassified according to WHO 2016. MESTK, sacromatoid RCC and RCC with leiomyomatous stroma are main differential diagnoses.

OFP-01-008
TFEB-amplified renal cell carcinoma: a comprehensive study of 7 novel cases
S. Kammerer-Jacquet[1], C. Gandon[1], F. Dugay[2], M. Beaumont[2], K. Bensalah[3], M. Belaud-Rotureau[2], N. Rioux-Leclercq[1]
[1] Department of Pathology, University Hospital, Rennes, France, [2] Department of Cytogenetics, University Hospital, Rennes, France, [3] Department of Urology, University Hospital, Rennes, France

Background & Objectives: First described in 2014, renal cell carcinoma (RCC) with *TFEB* amplification (6p21) is a rare entity whose diagnosis is challenging. The prognosis and therapeutic implications remain unclear.
Methods: We report herein the clinical, histological, immunohistochemical and genetic features of 7 novel cases. The pathological and immunohistochemical features were centrally reviewed by expert uropathologists. Fluorescence in situ hybridization (FISH) confirmed the diagnosis and comparative genomic hybridization (CGH) was performed to determine quantitative and structural genetic alterations.
Results: *TFEB*-amplified RCC were locally advanced with initial lymph node involvement in one case and liver metastasis in another case. They were high grade eosinophilic tumours with papillary or pseudopapillary architecture and frequent melanocytic marker expression. The FISH analysis demonstrated high-level *TFEB* amplification with two *TFEB* concurrent translocations. The CGH analysis identified complex alterations with frequent losses of 1p, 2q, 3p, 18q and gain of 8q. *VEGFA* was co-amplified in all cases. In the follow-up, one patient had a lymph node recurrence and another one developed bone metastases.
Conclusion: *TFEB*-amplified RCC is a rare entity with variable morphology whose diagnosis is confirmed by FISH analysis. The complex alterations identified by CGH analysis is concordant with an aggressive clinical behaviour. The co-amplification of *VEGFA* could suggest a potential benefit from anti-angiogenic therapy.

OFP-01-009
Improvement of vascular invasion scoring in stage I testicular non-seminomas to predict relapse during surveillance after orchiectomy
J. Lobo[1], H. Stoop[2], A. JM Gillis[3], K. van Kerckhoven[4], L. Budel[5], M. den Bakker[5], L. HJ Looijenga[6], J.W. Oosterhuis[2]
[1] IPO Porto, Portugal, [2] Erasmus MC Rotterdam, The Netherlands, [3] PMC Utrecht, The Netherlands, [4] Cabinet Tolbiac, France, [5] Maasstad Ziekenhuis, Rotterdam, The Netherlands, [6] PMC Utrecht & Erasmus MC Rotterdam, The Netherlands

Background & Objectives: Vascular invasion (VI) has been identified as an informative risk factor for relapse in stage I testicular non-seminomas (NS), used to tailor treatment options. We investigated inter-observer agreement in VI reporting and studied the potential additional value of immunohistochemistry for vascular markers for predicting relapse.
Methods: Patients (n=52) with stage I testicular NS undergoing surveillance (1993-2006) were included (median follow-up of 66 months). Two FFPE blocks with >1cm^2 tissue and tumour/normal parenchyma interface were stained with H&E and CD31, FVIII and D2-40. Slides were assessed by five independent observers (two general and three germ cell tumour (GCT)-dedicated pathologists) and agreement was assessed using Cohen's Kappa statistic. Sensitivity, specificity and accuracy of VI scoring in predicting relapse were calculated.
Results: Agreement between general pathologists was inferior when compared to concordance among GCT-dedicated pathologists (k=0.25 vs. k=0.49-0.54, respectively), as was performance in predicting disease relapse (particularly specificity of 43% vs. 86%, respectively). Most disagreements corresponded to over-scoring VI by general pathologists. Immunohistochemistry increased overall sensitivity (71%) but decreased specificity (71%). All patients (n=8) with both blood and lymphatic VI

developed relapse. In multivariable analysis only VI had an independent impact in predicting relapse.
Conclusion: Assessment of VI should be performed by a GCT-dedicated pathologist. Immunohistochemistry for vascular markers improves sensitivity of detecting VI and allows detection of high-risk patients with both blood and lymphatic VI, potentially of interest for tailored chemotherapy.

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OFP-01-010

Correlation of mismatch repair deficiency with expression of PD-L1 and CD8 in high grade urothelial carcinoma of bladder

M. Downes[1], A. Hodgson[1], B. Xu[2]
[1] Sunnybrook Health Sciences Centre, Canada, [2] Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: Mismatch repair (MMR) deficiency has been associated with therapeutic susceptibility to inhibitors of the PD-1/PD-L1 axis. In this study, we sought to correlate loss of MMR protein expression with CD8 and PD-L1 expression in a cohort of high grade urothelial carcinoma (HGUC).
Methods: Triplicate tissue microarrays (TMAs) were constructed with tumour tissue from 207 HGUCs. TMA sections were stained with CD8, MLH1, PMS2, MSH2, MSH6 and PD-L1 (SP263). CD8 was scored in a hotspot fashion (1 representative 40x field/core scored; averaged across 3 cores). MMR expression was assessed in tumour nuclei and membranous PD-L1 expression was evaluated in immune cells and tumour cells. Cases with loss of MMR expression on TMA sections were evaluated with MMR and PD-L1 stains using whole tissue sections.
Results: 207 cases were evaluable. Loss of MMR expression was confirmed in 4 cases (2%) on whole tumour sections; 3 cases showed MLH1/PMS2 loss while one case showed MSH2/MSH6 loss. CD8 expression was higher in MMR-deficient cases compared to other cases in the cohort (mean 108.2 vs. 34.7, p=0.007). PD-L1 expression was positive in 3 MMR-deficient cases but the MSH2/MSH6 loss case was PD-L1 negative. PD-L1 expression was seen in 20% (41/203) of cases with retained MMR proteins.
Conclusion: MMR deficiency is rare in HGUC however, these tumours show a higher rate of PD-L1 positivity and increased CD8+ infiltrate compared to MMR intact HGUCs. The very low rate of MMR deficiency does not warrant routine use of these stains in HGUC.

OFP-01-011

MiT family translocation renal cell carcinoma: an immunohistochemical panel for the differential diagnosis

A. Caliò[1], M. Brunelli[1], D. Segala[2], G. Martignoni[1]
[1] University of Verona, Italy, [2] Ospedale Pederzoli, Peschiera del Garda, Italy

Background & Objectives: Due to the wide morphological spectrum of MiT family translocation renal cell carcinoma(RCC) the differential diagnosis is challenging and includes clear cell RCC, papillary RCC, clear cell papillary RCC and epithelioid PEComa.
Methods: We collected 34 MiT family translocation RCCs (26 Xp11 and 8 t(6;11)RCCs) and performed an immunohistochemical panel including PAX8, cathepsinK, HMB45, Melan-A, CD10, CD13, CK7, CK8-18, carbonic anhydraseIX(CAIX), α-methylacyl-CoA racemase(AMACR), S100A1, parvalbumin, GATA3, CD68(PG-M1), SDHB and fumarate hydratase(FH). FISH analysis for *TFE3* and *TFEB* rearrangement was carried out.
Results: *TFE3* and *TFEB* translocation was observed in 26 and 8 tumours respectively. PAX8 was positive in almost all cases(90%). CathepsinK was observed in all t(6;11)RCCs and 14 of 26 Xp11 RCCs(54%). All but one t(6;11)RCC expressed melanogenesis markers. Among Xp11 RCCs, nine(36%)showed a patchy staining for HMB45; whereas Melan-A was observed in 3 multicystic tumours. Proximal tubular markers, CD10 and CD13, were positive in 27 of 30(90%) and 14 of 28(50%)tumours. Distal tubular markers, parvalbumin and GATA3, stained 11 of 26(42%) and 0 of 34 cases. Patchy staining for CAIX was found in 9 of 29(31%); AMACR and S100A1 were diffusely positive in the majority of tumours. Focal immunolabelling for CK7 and CK8-18 was observed in 4 of 30(13%) and in 20 of 31(64%)tumours. None of them expressed CD68(PG-M1). SDHB and FH were retained in all cases.
Conclusion: An immunohistochemical panel including cathepsinK, melanogenesis markers, CAIX, CD68(PG-M1), CK7 and GATA3 is useful in the differential diagnosis. The findings also suggests the differentiation toward to proximal tubules in MiT family translocation RCC.

OFP-01-012

Immune cell infiltration in paediatric renal allografts: mononuclear phagocytes correlate with rejection, re-transplantation and fibrosis in a retrospective study

J. Schmitz[1], S. Senger[1], A. Khalifa[1], A. Tramm[2], N. Richter[3], T. Ahlenstiel-Grunow[2], L. Pape[1], J.H. Bräsen[1]
[1] Institute of Pathology, Hannover Medical School, Germany, [2] Paediatric Nephrology, Hannover Medical School, Germany, [3] Clinic for General, Abdominal and Transplant Surgery, Hannover Medical School, Germany

Background & Objectives: Standardised markers of immune cell infiltration in renal transplantation may improve diagnostics. To date, no larger study investigating the role of immune cells in renal paediatric allografts exists and their impact on long-term outcome is poorly understood.
Methods: All graft samples (n=202) from 59 paediatric patients (63 % male, mean age 10 years) transplanted 2000-2017 at our center were re-evaluated according to recent Banff criteria and stained for macrophages, dendritic cells, B cells and T cells (CD68, CD206, CD163L1, CD209, CD20, CD3). Quantification of immune cells was performed in whole slide images (WSI) using image analysis software (QuPath). Results were obtained separately for cortex, medulla and extrarenal tissue and displayed as percentages (%) of positively stained area.
Results: In TCMR (T cell mediated) and ABMR (antibody mediated rejection) cortical macrophages were more frequent than in samples without rejection ($p<0.05$; Kruskal-Wallis test); B cells were most abundant in TCMR ($p<0.001$). In re-transplanted (2nd to 4th) organs a higher density of macrophages than in first allografts was observed ($p<0.05$). Protocol biopsies had lower macrophage numbers than indication biopsies ($p<0.01$; Mann-Whitney U test). Infiltration of dendritic cells revealed higher densities in i-IFTA1, i-IFTA2 and i-IFTA3 compared to i-IFTA0 ($p<0.05$) within renal cortex. Macrophage numbers correlated with fibrosis (% IFTA; Spearman's $r>0.4$, $p<0.001$).
Conclusion: Infiltrating immune cells, particularly mononuclear phagocytes, are highly abundant in paediatric renal transplants in rejection, re-transplantation and fibrosis and might influence long-term graft function. Actually, our morphologic findings are correlated with clinical data and outcome.

OFP-01-013

Genotype-phenotype correlation for novel COL4A4 splice site mutation causing autosomal Alport spectrum disorders

P. Senjug[1], T. Nikuseva Martic[2], M. Senjug Perica[3], M. Oroz[4], M. Horacek[5], M. Cuk[6], S. Abdovic[6], J. Vlasic - Matas[7], K. Galesic[8], D. Galesic Ljubanovic[1,5]
[1] Unit of Nephropathology and Electron Microscopy, Department of Pathology and Cytology, Dubrava University Hospital, Zagreb, Croatia,

[2] Department of Biology and Medical Genetics, School of Medicine, University of Zagreb, Croatia, [3] Division of Rheumatology, Srebrnjak Children's Hospital, Zagreb, Croatia, [4] University of Zagreb, School of Medicine, Croatia, [5] Institute of Pathology, School of Medicine, University of Zagreb, Croatia, [6] Department of Paediatrics, Children's Hospital Zagreb, Croatia, [7] Polyclinic Dr. Vlasic, Split, Croatia, [8] Department of Nephrology and Dialysis, Dubrava University Hospital, Zagreb, Croatia

Background & Objectives: Alport spectrum disorders are genetically heterogenic disorders caused by COL4A3, COL4A4 or COL4A5 mutations. Aim of this study was to correlate mutational status with pathohistological and clinical characteristics of patients with novel COL4A4 splice site mutation.
Methods: Four patients, three male and one female, from four unrelated families (age range 2-61 years) with pathohistological diagnosis of Alport syndrome (AS) or thin glomerular basement membrane nephropathy (TBMN) were tested by NGS sequencing (Illumina MiSeq platform) for COL4A3, COL4A4 and COL4A5 genes mutations. Testing was performed as a part of project "Genotype-Phenotype correlation in Alport's syndrome and Thin Glomerular Basement Membrane Nephropathy" founded by the Croatian Science Foundation. Novel splice acceptor pathogenic variant c.193-2A>C was found in COL4A4. The youngest patient was homozygous and others were heterozygous for the mutation.
Results: All the patients presented with proteinuria and haematuria at the time of kidney biopsy. The homozygous patient in light microscopy had only increased number of immature glomeruli, while electron microscopy showed typical findings for AS. From the group of heterozygous patients, two showed focal segmental glomeruloscerosis in light microscopy. Electron microscopy revealed TBMN with focal lamellation in one patient, typical AS in second and TBMN in third patient.
Conclusion: Diagnostic process of AS spectrum disorders can be challenging. Although genetic testing gives insight into potential disease severity and provides basis for genetic counselling there is variability in phenotype of disorders with the same mutation. Renal biopsy remains method that provides information about degree of renal parenchyma damage.

Supported by Project "Genotype-Phenotype correlation in Alport's syndrome and Thin Glomerular Basement Membrane Nephropathy" founded by the Croatian Science Foundation.

OFP-01-014
Glomerular CD68-positive cells - a new prognostic marker in renal transplant pathology

H. Hopfer[1], R. Silva[2], T. Menter[1], M. Lindström[3], N. Deigendesch[1], C. Wehmeier[4], S. Schaub[4]
[1] Institut für Medizinische Genetik und Pathologie, Universitätsspital Basel, Switzerland, [2] Serviço de Anatomia Patológica, Centro Hospitalar de S. João, Porto, Portugal, [3] Clinical Pathology, Skane University Hospital, Malmö, Sweden, [4] Transplantationsimmunologie und Nephrologie, Universitätsspital Basel, Switzerland

Background & Objectives: Transplant glomerulitis is a key feature of antibody-mediated rejection. Leukocytes occluding the glomerular capillaries define its morphological pattern. It is difficult to recognize and its scoring only has a fair interobserver agreement. We aimed to determine and validate a well reproducible immunohistochemical marker for glomerulitis, and looked at its prognostic value.
Methods: Receiver operator curves (ROC) using CD3, CD45, or CD68 positive cell counts in the glomeruli of kidney transplant biopsies with glomerulitis or without relevant pathology were used to determine cut-offs. Findings were independently validated, tested for interobserver agreement, and compared to other rejection patterns. The prognostic value was investigated in a cohort of patients (n=95) transplanted in the presence of donor-specific antibodies (DSA).
Results: A cut-off >5.5 CD68 positive cells in the most affected glomerulus ($CD68_{max}$) resulted in an area under the curve (AUC) of 0.966. $CD68_{max}$ correlated with the percentage of glomeruli with CD68 counts above the cut-off ($\rho = 0.875$). Three risk groups (baseline, low, high) with prognostic impact on graft survival were established using ROC comparing cases with glomerular Banff scores 0 vs. 1 (AUC = 0.891, cut-off > 3.9 % of glomeruli) and 1 vs. 2-3 (AUC = 0.867, cut-off >64.4 %). Interobserver agreement was good and independent of the level of expertise. In the DSA positive cohort, the risk groups proved to be an early and independent prognostic marker of poor graft function.
Conclusion: Addition of a CD68 stain to the routine analysis of kidney transplant biopsies provides additional diagnostic and prognostic information.

OFP-01-015
Is it possible to predict parameters of the Oxford classification in primary IgA nephropathy/Berger's disease from clinical laboratory data?

C. Silva[1], M.L. Monteiro[1], M. Vieira[1], L. Araújo[1], L.H. Pereira[1], L. Araújo[2], L. Rocha[1], J. Machado[1], M. Reis[1]
[1] Institute of Biological and Natural Sciences, Discipline of General Pathology, Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil, [2] Faculty of Mathematics of Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil

Background & Objectives: IgA nephropathy (IgAN), the most common primary glomerulonephritis, has a broad range of histological and clinical manifestations. This study assessed sensitivity, specificity and accuracy of clinical data at the time of biopsy in predicting Oxford classification parameters and investigated if subtypes of segmental glomerulosclerosis (FSGS) influence clinical presentation
Methods: Renal biopsies from 103 patients with IgAN were analysed using ROC curves, univariate and multivariate logistic regression.
Results: Patients were predominantly M0, E0, S1, T3 and C0. Hypertension increases the chance of M1 in 2.54x. For each unit of increased creatinine, 2.6x more chances of E1. S1 is predicted by proteinuria with 75% sensitivity and 90.9% specificity. For each unit of GFR increase, a reduction of 6% in the chance of T2 comparing to T0. If hypertension, 5x more chances of T2 than T0. For each unit of creatinine increase, 2.8x more chances of crescents. Creatinine showed 75.8% sensitivity and 75% specificity for C prediction. For each unit of GFR, the chance of C is reduced by 4%. Hypertension and proteinuria were also related with C. Proteinuria was the only parameter with significative difference between S0 and S1 groups. FSGS subtypes related to proteinuria were cellular and peri-hilar. Subtypes related to podocytopathies showed no correlation with clinical data.
Conclusion: With the future availability of noninvasive methods for diagnosis of IgAN, predict Oxford classification parameters using clinical data will be essential, an approach we showed to be possible. FSGS lesions not related to podocytopathies may also influence clinical parameters.

Sunday, 8 September 2019, 08:30 - 12:00, Galliéni 4
OFP-02 | Digestive Diseases Pathology – GI

OFP-02-001
Becoming a dysplastic Barrett's oesophagus expert: quantification of expertise and continuous structural education in the set-up of a national digital review panel

M. van der Wel[1], L. Brosens[2], K. Biermann[3], M. Doukas[3], C. Huysentruyt[4], A. Karrenbeld[5], F. ten Kate[6], G. Kats-Ugurlu[5], J. van der Laan[7], I. van Lijnschoten[4], F. Moll[8], J. Offerhaus[2], A. Ooms[9], K. Seldenrijk[10], M. Visser[11], J. Tijssen[12], J. Bergman[12], S. Meijer[1]
[1] Department of Pathology, Amsterdam UMC, University of Amsterdam, The Netherlands, [2] University Medical Center Utrecht, The Netherlands,

[3] Erasmus MC, The Netherlands, [4] PAMM, The Netherlands, [5] Department of Pathology University of Groningen, The Netherlands, [6] UMCU, The Netherlands, [7] Haga Hospital, The Netherlands, [8] Isala, The Netherlands, [9] Pathan, The Netherlands, [10] Pathology-DNA, The Netherlands, [11] Symbiant, The Netherlands, [12] Amsterdam University Medical Centers, The Netherlands

Background & Objectives: Assessment of dysplastic Barrett's oesophagus (BE) biopsies is subject to observer variability. Subsequently, most guidelines require review of dysplastic cases by BE-expert pathologists and in the Netherlands, we therefore set up a national digital BE-expert review panel. Goal is to stratify BE patients according to progression risk, leading to lower health care costs. So far, no definition of 'BE-expert' pathologist exists. We aimed to set up a review panel, objectively quantify expertise and homogenize assessment within a group of BE-pathologists.
Methods: Fifteen pathologists individually assessed 5x60 digitized BE biopsy sets, including the complete spectrum of BE-pathology with both study- and real time panel review cases. At study entrance, participating pathologists were heterogeneous in experience, work setting (community or academic hospital) and weekly BE workload. Outcomes measured were observer agreement; concordance; % of cases diagnosed 'indefinite for dysplasia' or significantly misdiagnosed cases. All outcomes were compared to benchmark values, constructed using a gold standard diagnosis.
Results: In 5 years, 15 pathologists assessed 31500 slides, yielding 6000 individual case diagnoses. After completing each set, pathologists discussed discrepant cases in face to face group discussions, receiving individual performance feedback before proceeding to the next study step. Over a timeline of 5 study sets, the pathologist group evolved from heterogenous reviewers to a homogenous BE-expert pathologist group that adhered to the values for all benchmark quality criteria.
Conclusion: All pathologists met the benchmark values for all outcomes. We show that expertise is reproducible and can be quantified, using a structured approach to form a national digital BE-review panel. A heterogeneous pathologist group evolved into a homogeneous expert panel with reproducible case assessments, greatly improving patient care. This training program can be applied to other challenging diagnostic pathology areas.

OFP-02-002

Are tumour budding and tumour grade the same in colorectal cancer?

I. Zlobec[1], H. Dawson[1], A. Blank[1], J. Bokhorst[2], I. Nagtegaal[3], A. Lugli[1]
[1] University of Bern, Switzerland, [2] Radboud University Medical Center, The Netherlands, [3] Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands

Background & Objectives: Both tumour budding (BD) and tumour grade are considered additional prognostic factors in colorectal cancer. The International Tumour Budding Consensus Conference (ITBCC) guidelines state that these two features are not the same. Whereas tumour budding is defined by single cells/small cell clusters up to four cells, tumour grade is determined by the degree of glandular formation. The aim was to determine the correlation of both features and the association of each with clinicopathological data.
Methods: A retrospective cohort of 511 patients with full histopathological and outcome data were reviewed for tumour grade (G1, G2, G3) and tumour budding (ITBCC: BD1, BD2, BD3). Statistical associations were analysed in univariate and multivariate analysis.
Results: Tumour grade and BD were correlated ($p<0.0001$). 34% of G3 cases were BD1. Only one G1 case was BD3. Both grade and BD were associated with more advanced TNM stage, lymphatic and vascular invasion ($p<0.0001$, all). High tumour grade was additionally linked to mucinous histological subtype, right-sidedness and mismatch-repair deficiency whereas higher BD score correlated with perineural invasion, lower Klintrup-Mäkinen score and worse overall survival ($p=0.043$). Of the two features, BD was independent of grade in multivariate survival analysis.
Conclusion: Both features are reflective of a more aggressive tumour. However, the associations of G3 with histological subtype, sidedness and mismatch-repair deficiency suggest a process that differs from BD, which is hypothesized to reflect epithelial-mesenchymal transition (EMT). Tumour grade and BD should be considered different parameters in colorectal cancers.

OFP-02-003

Expression of the inhibitory receptor CD94/NKG2A on CD8+ tumour-infiltrating lymphocytes in colorectal cancer: a new promising druggable immune checkpoint in a context of HLA-E/b2microglobuline overexpression by tumour cells

C. Bossard[1], J. Eugene[2], N. Jouand[2,3], K. Ducoin[2], R. Oger[2,3], J. Podevin[4], J. Bennouna[4,5], S. Bezieau[6,7], C. Volteau[7], W. El Alami Thomas[8], O. Kerdraon[9], P. Fourquier[10], E. Thibaudeau[9], A. Jarry[2,3], J. Mosnier[11,5], N. Gervois[2,3]
[1] Pathology Department, University Hospital, Nantes, France, [2] CRCINA, INSERM, Universitè d'Angers, Universitè de Nantes, Nantes, France, [3] LabEx IGO «Immunotherapy, Graft, Oncology», Nantes, France, [4] Institut des Maladies de l'Appareil Digestif, Oncologie Digestive, Centre Hospitalier Universitaire Hôtel Dieu, France, [5] Universitè de Nantes, Facultè de Mèdecine, France, [6] Service de Gènètique Mèdicale, Centre Hospitalier Universitaire Hôtel Dieu, Nantes, France, [7] Plateforme de Biomètrie, CHU de Nantes, France, [8] Institut d'Histopathologie, Nantes, France, [9] Dèpartement de Biologie des Cancers, Institut de Cancèrologie de l'Ouest, Nantes, France, [10] Service de Chirurgie Viscèrale et Digestive, Hôpital privè du Confluent, Nantes, France, [11] Service d'Anatomie et Cytologie Pathologiques, Centre Hospitalier Universitaire Hôtel Dieu, Nantes, France

Background & Objectives: We previously demonstrated that HLA-E/β2m overexpression by tumour cells in colorectal cancer (CRC) is associated with an unfavorable prognosis (*Bossard et al, 2012*). However, the expression of its specific receptor CD94/NKG2 by intraepithelial tumour-infiltrating lymphocytes (IEL-TIL), the exact phenotype and function of CD94/NKG2+ TILs as well as the relation with the microsatellite status (MS) of CRC remain unknown.
Methods: Two independent cohorts of CRC (retrospective n=234; prospective n=28) were analysed in the current study. On the retrosepctive cohort, we assessed IEL-TILs density (CD8, NKp46, CD94) and expression profile of HLA-E and β2m by immunohistochemistry on Tissue microarray in relation with the clinicopathological and molecular characteristics. The prospective cohort allowed us to isolate TILs from primar tumour, analyse *ex vivo* their precise phenotype by flow cytometry, and confirm the inhibitory function of CD94/NKG2A receptor expressed by CD8+ TILs using a redirected lysis assay.
Results: HLA-E/β2m was preferentially overexpressed in microsatellite instable CRC compared with microsatellite stable CRC (45 % vs 18 % respectively, $p=0.0001$). HLA-E/β2m+ CRC, irrespective of the Microsatellite status, were significantly enriched in $CD94^+$ IEL-TIL whose density was independently associated with a worse overall survival ($p=0.03$). *Ex vivo* analyses demonstrated that $CD94^+$ TILs mostly corresponded to $CD8^+$ αβ T cells, and mainly co-expressed a functional NKG2A inhibitory chain.
Conclusion: Our results strongly suggest that tumour cells of CRC, especially MSI CRC, via aberrant overexpression of HLA-E/β2m, contribute to paralyze the antitumour immune attack in engaging the inhibitory CD94/NKG2A receptor on $CD8^+$ IEL-TILs.Therefore, HLA-E/β2m - CD94/NKG2A represents a promising new inhibitory immune checkpoint involved in CRC that could be targeted with the recently generated humanized anti-NKG2A monoclonal antibody.

DHOS (PROG/09/03), Ligue contre le cancer, DHU Oncogreffe, Nantes (RC14-0416-1), Cancéropôle Grand Ouest (Amgen RC16-0212-1). Plan Cancer 2009-2013 AAC

OFP-02-004

E-learning for instruction of scoring the tumour-stroma ratio (TSR) in colon carcinoma amongst international pathologists, as part of the UNITED study.

M. Smit[1], G. van Pelt[1], R. Al Dieri[2], R. Tollenaar[1], H. van Krieken[3], W. Mesker[1] on behalf of the UNITED group[1]

[1] Leiden University Medical Centre, The Netherlands, [2] European Society of Pathology, Belgium, [3] Radboud University Medical Centre Nijmegen, The Netherlands

Background & Objectives: The tumour-stroma ratio (TSR) was validated by many international research groups and showed to be an independent prognostic parameter for survival. The UNITED study (Uniform Noting for International application of the Tumour-stroma ratio as Easy Diagnostic tool) is developed to validate the TSR prospectively as additional high-risk parameter next to the TNM classification.
As part of the UNITED study, a training and reproducibility study for scoring the TSR is set up using an E-learning module.
Methods: The E-learning started with an auto-instruction based on instruction video and written protocol. Thereafter, three sets of 40 colon carcinoma cases were scored for TSR. Between the second and third set a wash-out period of 2 months was set. Inter- and intra-observer agreements were calculated to evaluate reproducibility.
After completion of the E-learning, pathologists will continue scoring the TSR in the prospective study to validate the TSR prospectively in a cohort comprising 1500 patients colon cancer stage II and III.
Results: Twenty-two hospitals from 17 countries are participating in the UNITED study. Forty-one colorectal cancer pathologists started the E-learning, of whom 70% (n=28) finished the whole cycle so far. The median kappa score was κ=0.72 for the training set, κ=0.77 for the test set and κ=0.78 for the repetition test set. The median intra-observer agreement is κ=0.78.
Conclusion: E-Learning is an effective method to instruct pathologists for scoring the TSR. The results improved from the first to the second set and did not fall back in period of time for the last set. After validation of the TSR in the prospective study, the TSR will be ready to use in daily practice.

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OFP-02-005

For better or worse: clinical correlation of SOX9 expression in irradiated rectal cancer

X. Duan[1], B. Trac[1], X. Ding[1]

[1] Loyola University Medical Center, USA

Background & Objectives: Sex-determining Region Y box 9 (SOX9) has been shown to play a fundamental role in epithelial-mesenchymal transition (EMT) and is dysregulated in colorectal cancer. Its role in carcinogenesis remains controversial since SOX9 has been associated with both positive and negative prognostic factors in multiple cancers. Sox9 expression and clinical correlation are also not clear in irradiated rectal cancer. The objective of this study is examining the clinical correlation of SOX9 expression in irradiated rectal cancer.
Methods: Sections from both normal and cancerous tissue were taken before and after radiation in 25 patients with locally advanced rectal cancer who received neoadjuvant chemoradiation therapy followed by surgery. SOX9 expression was evaluated by immunohistochemistry using a 4-tier grading system for intensity of expression (0=none, 1=low, 2=moderate, 3=high) and percentage of SOX9-positive cells. Demographics, tumour characteristics and outcomes were extracted from medical records and SPSS (Chicago, IL) was used for statistical analysis.
Results: In this study, the mean age of patients was 60.4 (32-72). 80% of them were male and the majority were Caucasians (76%). 92% of patients had at least T3 tumours and 68% had stage III disease. Mean diameter of tumour pre-treatment was 4.95 cm (3-8) and post-radiation was 2.79 (0.4-5.3). Down-staging occurred in 15 (60%) patients, but only 2 (8%) had complete pathologic response. Six (24%) patients had positive nodes identified after surgery. In cancer specimens, 96% were graded as moderate or high expression before radiation, which changed to 88% after radiation. Percentage of SOX9 positive cells is also different with 91.7% of cells positive before radiation and 66.7% after radiation. The high percentage of SOX9 positive cells and moderate or high expression were both associated with complete pathologic response (p=0.008). Reduced tumour size after radiation occurred in all patients including cases with decreased intensity of SOX9 expression (p=0.005), however decreased SOX9 expression tends to occur in patients with larger tumour size. Although not statistically significant, decrease in percent positivity and intensity after radiation both trended toward significance for distant recurrence (p=0.07). SOX9 expression was not associated with other tumour characteristics or oncologic outcomes.
Conclusion: Our findings indicate that percentage of SOX9 positivity and moderate or high intensity of expression in rectal cancer specimens decrease after radiation. Oncologic outcomes appear to be improved when intensity of expression and percent positivity remain elevated, for example, in complete pathologic response. When expression decreases after radiation, distant recurrence and larger post-radiation tumour size are more common. Although its role remains controversial, our findings suggest that SOX9 may be an important marker and potential target for tumour response and oncologic outcomes for rectal cancer after radiation.

OFP-02-006

Poor clinical significance of tissue calprotectin levels in bowel mucosa for the prediction of complicated course of the disease in children with ulcerative colitis. A pilot study

O. Fabian[1], O. Hradsky[1], T. Lerchova[1], F. Mikus[1], J. Zamecnik[1], J. Bronsky[1]

[1] Motol University Hospital, Czech Republic

Background & Objectives: To evaluate the usefulness of immunohistochemical (IHC) detection of tissue calprotectin (T-CPT) in bowel mucosa in children with ulcerative colitis (UC). We focused at correlation of T-CPT with levels of faecal CPT (F-CPT) and endoscopic and microscopic disease activity at the time of diagnosis and tested whether T-CPT could serve as predictor of complicated course of the disease.
Methods: Forty-nine children with newly diagnosed UC between 6/2010-1/2018 entered the study. Endoscopic activity was objectivised using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), clinical activity by Paediatric Ulcerative Colitis Activity Index (PUCAI) and microscopic activity by Geboes and Nancy score. The IHC staining for CPT antigen was performed on bioptic samples from 6 bowel segments and the number of CPT+ cells was counted per 1HPF. During the minimal follow-up of 12 months we searched for presence of particular complications.
Results: As outcome for Cox regression model we used tree endpoints: A) Acute Severe Colitis, colectomy, anti-TNF treatment; B) A+ systemic corticotherapy; C) B+ systemic 5-aminosalicylic acid therapy. Neither levels of T-CPT nor values of UCEIS, Geboes or Nancy score predicted the given complications. We found F-CPT levels (HR 2.42 and 2.52) and PUCAI>40 points (HR 2.98) as predictors of time to endpoints B and C. We found a good correlation between T-CPT levels and Geboes (k=0.65) and Nancy score (k=0.62).

Conclusion: T-CPT correlated well with microscopic scores. F-CPT and PUCAI appears to be better predictor of unfavourable outcome in patients with UC.

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OFP-02-007

Risk factors for intraductal tumour spread of submucosal gland in early squamous cell neoplasia: analysis of endoscopically resected specimens

I. Chang[1,2,3,4], W. Wang[5]

[1] Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University, Taiwan, [2] Department of Pathology, Taipei Medical University Hospital, Taiwan, [3] Department of Pathology, Wan Fang Hospital, Taipei Medical University, Taiwan, [4] Department of Pathology, Shuang Ho Hospital, Taipei Medical University, Taiwan, [5] Department of Internal Medicine, E-Da Hospital/I-Shou University, Kaohsiung, Taiwan

Background & Objectives: The oesophageal gland duct may serve as a pathway for the spread of early oesophageal squamous cell neoplasia (ESCN) to a deeper layer. However, the risk factors and significance of ductal involvement (DI) in patients receiving complete endoscopic submucosal dissection (ESD) has yet to be investigated.

Methods: We consecutively enrolled patients with early ESCN who were treated with ESD. The resected specimens were retrospectively reviewed for the number, morphology, resected margin, distribution and extension level of DI, which were then correlated to clinical factors and survival. A total of 160 lesions were analysed. Totally, 317 DIs in 61 lesions (38.1%) were identified. Of these, 14 had DIs extended to lamina propria, 17 to muscularis mucosae, and 30 to the submucosal layer.

Results: Multivariate logistic regression analysis showed that tumours located in the upper oesophagus (OR=2.93, 95%CI,1.02-8.42), large tumour circumferential extension (OR=5.39, 95%CI,1.06-27.47), advanced tumour invasion depth (OR=4.12, 95%CI,1.81-9.33) and numerous Lugol-voiding lesions in background mucosa (OR=2.65, 95%CI,1.10-6.37) were risk factors for DI. The maximally extended level and total number of ducts involved were significantly correlated with the depth of cancer invasion ($P<0.05$). The patients with DI had worse overall survival and recurrence-free survival (both $P \leq 0.015$) than those without DI after successful ESD.

Conclusion: DI is not uncommon in early ESCN. Due to the maximal ablation depth of radiofrequency ablation (RFA) limited to muscularis mucosae, these deeply extended ducts will not be eradicated, which may potentially cause tumour recurrence or even buried cancer. Our findings may guide clinical decision making with regards to endoscopic treatment and surveillance.

OFP-02-008

Site of residual oesophageal cancer after neo-adjuvant chemoradiotherapy with regard to the anatomical layers and radiation target volumes at histopathologic examination

Z. Faiz[1,2], V. Mul[3], A. Karrenbeld[2], G. Kats-Ugurlu[2], J. Plukker[1], K. Muijs[3]

[1] Department of Surgical Oncology University of Groningen, The Netherlands, [2] Department of Pathology University of Groningen, The Netherlands, [3] Department of Radiotherapy University of Groningen, The Netherlands

Background & Objectives: Neoadjuvant chemoradiotherapy (nCRT) followed by surgery leads to a significant rate of pathologic complete response (pCR) in patients with curatively treatable oesophageal cancer (EC). EC patients with a clinical complete response are probably candidates for a watchful wait strategy in the near future.

Methods: Between October 2009 and March 2018, we included totally embedded oesophagus-cardia resection specimens from 151 consecutive patients marked preoperatively for radiation field target volumes after nCRT with carboplatin/paclitaxel and 41.4Gy radiotherapy (CROSS regimen).

Results: According to the Mandard tumour regression grade system, pCR (ypT0N0) was detected in 18.8% (n=27), whereas 21 patients had nearly no response (TRG 4-5). Of the remaining non-complete responding patients with TRG 2-3 (n=95), residual tumour only in lymph nodes (ypT0N+) was observed in 7.4% (n=7). Among the remaining patients with ypT1-2, residual tumour was more common in the submucosa (18.9%) and muscularis propria (18.9%), while among those with ypT3-4 it was more often in the adventitia than outside the oesophageal wall (73.9% vs 7.4%; $p < 0.05$). In 8.4% residual tumour was found outside the gross tumour volume (GTV), whereas microscopic residual cells were seen outside the clinical target volume (CTV) in 18.9%. In one patient with ypT0N+ residual nodal disease was observed outside the CTV.

Conclusion: After nCRT, 18.8 % of the EC patients had a pCR, while 7.5 % of the non-complete responders with ypT0 still had residual tumour in the lymph nodes. In one of these ypT0N+ patients the residual tumour was found outside the CTV.

OFP-02-009

Mechanotransduction in mice colon tumourigenesis: a pathologically reactivated physiological embryonic mechanosensitive pathway

E. Farge[1], M. Fernandez-Sanchez[1], D. Meseure[2]

[1] Institut Curie - Inserm, France, [2] Platform of Experimental Pathology, Department of Diagnostic and Theranostic Medicine Institut Curie, Paris, France

Background & Objectives: The tumour microenvironment may contribute to tumourigenesis due to mechanical forces such as fibrotic stiffness or mechanical pressure caused by the expansion of hyper-proliferative cells. Here, we explore the contribution of the mechanical pressure exerted by the tumour growth onto non-tumourous adjacent epithelium.

Methods: We thus developed a method that allows to deliver defined mechanical pressure *in vivo*, by subcutaneously inserting a dorsal magnet close to the mouse colon. The implanted magnet generated a magnetic force on ultra-magnetic liposomes (UML), stabilized in the mesenchymal cells connective tissue surrounding colonic crypts after intravenous injection. The pressure induced magnetically quantitatively mimicked the endogenous early tumour growth stress in the order of 1kPa.

Results: In the early stage of mouse colon tumour development in the Notch+ APC1638N/+ mouse model, we observed mechanistic pressure stress in the non-tumourous epithelial cells caused by hyper-proliferative adjacent crypts overexpressing active Notch, associated with increased Ret and β-catenin signalling.

Exertion of magnetic pressure mimicking that of tumour growth led to rapid Ret activation and downstream phosphorylation of β-catenin on Tyrosine 654, which impairs its interaction with the E-cadherin in adherens junctions, and which was followed by β-catenin nuclear translocation after 15 days. As a consequence, elevated expression of β-catenin target genes was observed at one month, together with crypt enlargement accompanying the formation of early tumourous aberrant crypt foci (ACF).

Conclusion: Mechanical activation of the tumourigenic β-catenin pathway suggests unexplored modes of tumour propagation based on mechanical signalling pathways in healthy epithelial cells surrounding the tumour, which may contribute to tumour heterogeneity[1-3].

We found the mechanotransductive phosphorylation of the Y654 site of b-catenin by the first morphogenetic movements of embryogenesis,

leading to its release into the cytoplasm and nucleus, as due to its mechanical opening to Src family kinase phosphorylation[4], and involved and conserved in earliest mesoderm and endoderm differentiation in the vertebrate zebrafish and un-vertebrate Drosophila[5].
We thus propose the pathological re-activation of the mechanosensitive β-catenin signalling in tumourigenesis physiologically involved in early embryonic patterns differentiation.
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OFP-02-010

The prognostic impact of the colorectal cancer microenvironment components and their spatial relationships

I.P. Nearchou[1], C.G. Gavriel[2], D.J. Harrison[2], P.D. Caie[2]
[1] University of St Andrews, United Kingdom, [2] School of Medicine, University of St Andrews, United Kingdom

Background & Objectives: The tumour immune infiltrate contributes majorly in tumour progression and patient survival outcome. However, the aggressive potential of colorectal cancer cannot be manifested without capturing the interplay between cancer cells and the host's immune response. In this study, we examined the prognostic value of tumour buds (TBs) reflecting tumour progression, the tumour immune infiltrate and their spatial relationships in stage II colorectal cancer.
Methods: Two multiplex immunofluorescence antibody panels comprising CD3+, CD8+, CD68+, CD163+, pancytokeratin and Hoechst were applied in two sequential whole slide images (n=232). Cell quantification and the evaluation of their spatial interactions was performed through automated image analysis. Exported features were processed through machine learning algorithms for the development of a new prognostic risk model.
Results: TB (p=0.001) and lymphocytic density (p<0.001) were found to be prognostically significant independently. Though, their integration with their spatial relationship (p<0.001) reported a more significant cohort stratification than the clinical gold standard of pT stage (p=0.003) in a training cohort (n=114) and two independent validation cohorts (n=56 and n=62). Inclusion of the macrophage cell data in a new prognostic model allowed the low-risk patients to be identified with 100% sensitivity. No clinico-pathological features were selected for any of the models by the machine-learning workflow.
Conclusion: Here we demonstrate how the integration of automated image analysis and machine learning in studying the tumour heterotypic microenvironment can lead to the more accurate stratification of patients with stage II colorectal cancer.

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OFP-02-011

Cell line-derived xenografts: a possible in vivo model to investigate tumour budding in colorectal cancer

I. Zlobec[1], L.M. Georges[2], O. de Wever[3], J.A. Galván[4], H. Dawson[1], A. Lugli[1], P. Demetter[5]
[1] University of Bern, Switzerland, [2] Department of Pathology, Erasme Hospital, Universitè Libre de Bruxelles, Belgium, [3] Laboratory of Experimental Cancer Research, University of Ghent, Belgium, [4] University of Bern, Institute of Pathology, Switzerland, [5] Department of Pathology, Institut Jules Bordet, Universitè Libre de Bruxelles, Belgium

Background & Objectives: Tumour budding is recognized as a major adverse prognostic factor in colorectal cancer. Standard H&E, immunohistochemistry, laser capture microdissection and RNA or DNA sequencing have been performed to help elucidate the mechanisms of tumour budding, but only capture a snapshot of the process. The aim of this study is to determine whether cell line-derived mouse xenografts (CDX) could represent a suitable *in vivo* model of tumour budding.
Methods: Tumours from mouse xenografts generated by orthotopic implantation of different cell lines (HCT-8, HT-29, COLO320, RKO) were evaluated for tumour budding. HT-29 and HCT-8 were representative of high-grade and low-grade budders and selected for next-generation Tissue Microarray (ngTMA) construction by sampling intratumoural (ITB) and peritumoural (PTB) budding. Immunohistochemistry for E-cadherin, β-catenin, Ki-67, ZEB1, SNAIL1, Caspase-3, TWIST1 and double-staining for Vimentin/Ku80 were performed. A control group of 52 patients with low- and high-grade budding was included.
Results: Comparing HT-29 CDX and human high-grade budding cases, PTB counts were 45 and 30 buds/TMA core (p=0.07) and ITB counts were 22.6 and 12 buds/TMA core (p=0.0099). In HT-29 CDX and high-grade budding cancers, ITB and PTB were significantly correlated (r=0.45; r=0.62). Ku80 staining in the CDX model confirmed the human origin of cells identified as buds. Immunohistochemistry profiles were similar in CDX and human cancers.
Conclusion: Tumour budding occurs to various degrees in CDX mouse models and is morphologically and phenotypically similar to budding in human colorectal cancer. Such an *in vivo* model will help to investigate the more functional aspects related to the tumour budding process.

OFP-02-012

Comprehensive molecular analysis of recurrence in gastrooesophageal adenocarcinoma

F. Renaud[1], G. Piessen[1,2], M. Figeac[3], C. Dejeante[4], M. Messier[4], L. Delattre[5], A. Adenis[6], D. Chatelain[7], C. Boulagnon-Rombi[8], C. Eveno[1,2], I. Van Seuningen[2,3], C. Mariette[1,2], E. Leteurtre[1,2], M. Buisine[1,2]
[1] CHU, Univ.Lille, France, [2] Inserm UMRS 1172, France, [3] Univ.Lille, France, [4] CHU, Inserm UMRS 1172, Lille, France, [5] CHU, Lille, France, [6] Montpellier Cancer Institute, Inserm U1194, France, [7] Amiens University Hospital, Amiens University, France, [8] Reims University Hospital, Reims University, France

Background & Objectives: Gastrooesophageal adenocarcinomas (GEAs) are characterised by recurrences in more than 50% of patients. There is a critical need to understand the molecular features of the recurrence to interfer more effectively in the late stages of cancer progression. The main objective of the study was to assess the molecular profile of GEAs recurrence and to compare this profile with the one of the primary tumour.
Methods: A total of 84 untreated, surgically resected GEAs with 91 paired samples of metachronous distant and/or locoregional metastases were included. Recurrence was defined as local, locoregional or distant metastasis occurring at least 6 months after the first histological diagnosis. Expression of HER2, EGFR, c-MET, ALK, ROS, EBV, MLH1, PMS2, MSH2, MSH6, p53, E-cadherine, ARID1A was analysed by

immunohistochemistry/in situ hybridization. Chromosomal, genomic and methylation alterations were analysed using CGH array, NGS and bisulfite pyrosequencing, respectively.
Results: Frequent expression of tyrosine kinases receptors HER2, c-MET and EGFR was detected in the recurrence (42% versus 29% in the primary). Most tumours displayed chromosomal instability (65%), mesenchymal profile including genome stable tumours (24%), microsatellite instability (7%) and EBV (4%). Chromosomal alterations were more frequent in the recurrence. Frequently mutated genes were *TP53* 67%, *CDH1* 21%, *ARID1A* 14%, *SMAD4* 13%, and *PIK3CA* 10%. Interestingly *PI3KCA* mutation was associated with the recurrence in GEAs. Methylation profiles were similar between primary and recurrence.
Conclusion: Molecular profiles are different between primary and recurrence in GEAs. This should be considered to improve treatment of patients with advanced disease.

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OFP-02-013
Confocal microscopy as an alternative microscopic diagnosis that saves time and money for pathology departments: pilot study on colorectal polyps
J. Guerrero[1], G. Fernandez-Esparrach[2], J. Perez-Anker[3], H. Cordova[2], I. Archilla[1], A. Garcia-Herrera[1], M. Pellise[2], A. Gines[2], S. Puig[3], J. Malvehy[3], M. Cuatrecasas[4]
[1] Pathology Department, Hospital Clinic. University of Barcelona, Spain, [2] Gastroenterology Department, Hospital Clinic. University of Barcelona, Spain, [3] Dermatology Department, Hospital Clinic. University of Barcelona, Spain, [4] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic of Barcelona, Spain

Background & Objectives: Colorectal cancer (CRC) screening programmes have accomplished a significant reduction in mortality caused by this disease. Colonoscopy, as an early cancer detection procedure, allows the identification and removal of polyps for the gold-standard histological analysis. The increasing number of colonoscopies has created bottlenecks in pathology departments due to the huge number of samples to be analysed. We aim to use alternative ways of diagnosis to overcome such bottlenecks.
Methods: In this pilot study, we analysed by conventional histology and confocal microscopy 20 polyps from 12 patients. Real time scanning of the tissue was made with the confocal laser microscope VivaScope® 2500M-G4TM. Afterwards, conventional histopathologic process was performed. Confocal images were reviewed by three pathologists blind to the haematoxylin and eosin (H&E) results. Diagnosis with both methods were compared.
Results: Eighteen (90%) polyps were tubular adenomas and 2 were sessile serrated adenomas. Confocal diagnosis was reliable and concordant with H&E in 100% cases, but in 3 cases (15%) some histological details were missed due to image resolution issues.
Conclusion: Confocal microscopy allows whole scanning of the tissue in real time and does not interfere with a subsequent pathological analysis. It is a promising tool with a high reliability and reproducibility compared to gold standard diagnostics. Its main advantages are the time saving (2-5 minutes) compared to conventional histopathology analysis, and limited required personnel. This alternative morphology-based diagnostic method may contribute to reduce the rising workload in pathology departments derived from CRC screening programmes and bring significant economic savings.

OFP-02-014
Histopathological and molecular features of adenomatuous and serrated colon adenomas, characteristics and overlapping features, challenges in the nomenclature
B. Bambul Sıgırcı[1], I. Yılmaz[1], S. Erdamar Çetin[2], E. Yarıkkaya[1], M. Cin[3], E. Pasaoglu[1], B. Yeni[1], N. Dursun[3]
[1] University of Health Sciences, Department of Pathology, Turkey, [2] Acıbadem University, Department of Pathology, Turkey, [3] University of Health Sciences, Istanbul Health Practice and Research Hospital, Department of Pathology, Turkey

Background & Objectives: It is well established that colorectal cancer develops from a series of precursor epithelial polyps, including tubular adenomas (TA), villous/tubulovillous adenomas (VA/TVA), sessile serrated adenomas (SSA) and traditional serrated adenomas (TSA). The criteria for diagnosing adenomas are determined. However, there can be overlapping feautures within these lesions. The aim of this study is to settle the characteristics and overlapping features of colonic adenomas.
Methods: A total of 140 adenomas (70 conventional adenomas, 35 SSA/P and 35 TSA) H&E stained slides were retrieved from our archive. All these cases were reclassified according to the criteria. Demographics were obtained from charts. Macroscopically, whether the adenoma possesses sessile or polypoid structure; microscopically filliform and villous architecture of the lesion and occurrence of serration, ectopic crypt, eosinophilic cytoplasm, silender nucleous, dilatation of crypt base, presence of mucinous hypersecretion on the base and surface, adenomatous dysplasia, serrated dysplasia and the degree of dysplasia of the lesions were examined. Current criteria for each lesion first investigated in the binary system (available / unavailable) and in quartet system (0: <10% 1: 10-25% 2: 25-75% 3: 75% and above). Thirteen cases with multiple parameters belonging to each lesion were named as hybrids. KRAS, NRAS, BRAF mutation, MSI analysis and MLH1 promoter methylation analysis were performed in 50 of the cases that have additional non-neoplastic control tissue.
Results: The diameter of the lesion was found to be smaller in SSAs. Macroscopically sessile configuration was seen in SSAs and hybrid group, only small percentage of the other lesions show sesile structure (p< 0, 001). The presence of dilatation of crypt base, serration and mucinous hypersecretion was the most descriptive findings in SSAs (p< 0, 001). Serration, ectopic crypt, and eosinophilic cytoplasm are distinctive features for TSAs (p< 0, 001). Adenomatous dysplasia was definitive feature of TA/VA/TVAs. Serration was seen in 50% of TA/VA/TVAs and they had ectopic crypts in 23 cases. But in most of the cases with such features less than 25% of the adenoma displayed those characteristics. At least focal adenomatous dysplasia was also seen in 20 of SSAs and 22 of TSAs. Serrated dysplasia was seen in 10% of the TA/VA/TVAs. BRAF mutation was found in 6 SSA/P , 4 TSAs and 1 hybrid case. The KRAS mutation was detected in 11 TA/VA/TVAs, 2 SSA/P, 6 TSAs and 8 hybrid cases. NRAS mutation and MSI were detected in none of the cases. MLH1 promoter methylation was seen in 4 TA/VA/TVAs, 4 SSAs and 2 TSAs.
Conclusion: All histopathological findings can be seen in all types of adenomas. This showed that none of these parameters are particular to a lesion. In most of the cases, the unexpected feature was present in less than 25% of the lesion. Thus, the value 25% can be used as a cut off. But there are a small number of cases which show unexpected features covering more than 25%. In addition, in molecular analysis of the cases, unexpected mutations were detected. This can be an evidence of mixed/ hybrid lesions.

University of Health Sciences Scientific Research Project

OFP-02-015
How many biopsies are needed to assess the Peritoneal Regression Grading Score (PRGS) in peritoneal metastasis?
W. Solass[1], D. Nann[1], J. Steinke[1], G. Nadiradze[2], P. Horvath[2], R. Archid[2], H. Bösmüller[1]
[1] Institute of Pathology and Neuropathology, University Hospital Tuebingen, Eberhard-Karls-University Tuebingen, Germany, [2]

Department of General and Transplant Surgery, University Hospital Tuebingen, Eberhard-Karls-University Tuebingen, Germany

Background & Objectives: Peritoneal metastasis (PM) are associated with a poor prognosis and a median survival of 3- 6 months. Multimodal therapy approaches especially intraperitoneal chemotherapy is increasingly used. Therefore repetitive peritoneal biopsies are obtained to assess tumour response. 2016 a group of European pathologists proposed a regression grading Score for PM- the Peritoneal Regression Grading Score (PRGS). This 4-tied score evaluates therapy response of peritoneal metastases (PM) of various origin and has been validated as a reproducible and useful tool in a multicentric comparative study. But the number of biopsies needed for reliable assessment of tumour response is still unclear.
Methods: We performed a retrospective analysis of 210 laparoscopies in 89 patients with PM of various origins. In these patients routinely 4 biopsies from all 4 abdominal quadrants were taken. The analysis of the 4-tied PRGS was performed by an independent pathologist. Statistical evaluation concerning the needed number of biopsies and the loss or gain of information in the clinical framework has been evaluated.
Results: Out of 246 histological examinations, 120 (95,2%) showed agreement in ≥ 2 biopsies, 37 (29,3%) in ≥ 3 biopsies and only 18 (14.2%) in all 4 biopsies. The diagnostic reference (gold standard) was definded as the PRGS calculated from 4 biopsies. The mean loss of information was 0.29 ± 0.11 PRGS points with 3 biopsies and 0.50 ± 0.17 with 2 biopsies. 49 patients with repeated laparoscopies were eligible for tumour response assessment: 35 patients (71%) had a histological response (stable or improved PRGS), 14 (29%) a disease progression (worse PRGS). Mean difference in PRGS between 1st and 2nd laparoscopy was 0.23 ± 0.87. PPV and NPV of 3 biopsies for determining tumour response was 100%, resp. 60.9% (95% CI 45.0% to 73.2%) with an accuracy of 81.6%. PPV and NPV of 2 biopsies for determining tumour response was 96.2% (95% CI 78.9% to 99.4%), resp. 56.2% (95% CI 43.0% to 69.1%) with an accuracy of 77.6% (95%CI 63.4 to 88.2%).
Conclusion: One or two biopsies are not enough to determine PRGS. Three biopsies allow proper clinical decision making in 4 out of 5 patients. Whenever possible, biopsies should be taken in all abdominal quadrants to assess therapy response in PM. Further investigations on a larger cohort needs to be done.

Sunday, 8 September 2019, 17:15 - 19:15, Thalie
OFP-03 | Cytopathology

OFP-03-001
Negative ThyroSeq® genomic testing for indeterminate thyroid nodules: the Memorial Sloan Kettering Cancer Center experience
D. Buonocore[1], O. Lin[1], J. Cohen[1]
[1] Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: The current American Thyroid Association guidelines suggest the use of molecular studies in the management of patients with an indeterminate cytology diagnosis. ThyroSeq®, one of the most used thyroid molecular tests in the U.S. has a reported high negative predictive value(NPV). We propose to evaluate the NPV of ThyroSeq® at a major cancer center in the U.S. in which the prevalence of malignancy is high.
Methods: Cytology material from 252 thyroid nodules diagnosed as indeterminate were submitted for ThyroSeq® analysis. The results were negative in 151 of 252 cases and among these cases, 23 nodules were surgically resected. The ThyroSeq® results were correlated with the surgical diagnosis.
Results: Surgical resection with intent to remove the tested nodule was performed in 20 of the 23 nodules. They were commonly removed due large size, growth or patient's preference. Three nodules were resected due to the presence of a concurrent suspicious nodule. A benign diagnosis was confirmed in 15 of 23 cases. Three cases were diagnosed as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), while 5 cases represented classic papillary carcinoma (n=2) and follicular carcinomas (n=3). The NPV in our series was only 78.2% if NIFTP was considered a benign lesion and 65.2% when NIFTP is included as a malignant lesion.
Conclusion: The NPV of ThyroSeq® is lower than reported previously and a negative ThyroSeq® result should be correlated with other clinico-radiological findings, particularly, in institutions with a high cancer prevalence.

OFP-03-002
Ultrasound guided fine needle aspiration of thyroid: inadequacy rate with rapid on-site evaluation
C. Sebastiano[1], O. Lin[1], J. Girshman[1], D. Buonocore[1], J. Cohen[1]
[1] Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: Recent meta analysis data in the literature has shown an average inadequacy rate for thyroid ultrasound guided fine needle aspiration (UFNA) of 13%. We investigated the inadequacy rate for UFNA recently performed at our institution with rapid on site evaluation (ROSE).
Methods: We searched the electronic medical record for cases of thyroid UFNA performed at our institution over one year. Procedures were performed by interventional radiologists or interventional cytopathologists and all underwent ROSE by a cytotechnologist and cytopathologists using telecytology, or by the cytopathologist performing the procedure. In most cases a single pass was obtained. Specimens were considered adequate if at least 6 clusters of 10 follicular cells were present.
Results: A total of 618 cases were identified; 461 performed by a radiologist and 157 by a cytopathologist. 607 cases were reported at ROSE and confirmed at sign-out as adequate, 3 as inadequate at ROSE but adequate at sign out, 6 at ROSE and sign-out as inadequate, and 2 as adequate at ROSE but inadequate at sign out. The overall inadequacy rate was thus 8/618 (1.29%); 6/461 (1.30%) for cases performed by a radiologist and 2/157 (1.27%) for those performed by a cytopathologist.
Conclusion: Thyroid UFNA performed with ROSE substantially reduces the inadequacy rate at our institution as compared to the average reported in the literature. Comparable inadequacy rates are found in procedures performed by radiologists and cytopathologists. By lowering the inadequacy rate ROSE reduces the need for re-biopsy, cutting costs and avoiding additional patient discomfort and anxiety.

OFP-03-003
The diagnostic utility of zinc finger E-box binding homeobox (ZEB1) for identification of pulmonary sarcomatoid carcinoma in limited specimens
K. Viswanathan[1], A. Borczuk[1]
[1] New York Presbyterian-Weill Cornell Medicine, USA

Background & Objectives: Although uncommon, pulmonary sarcomatoid carcinoma carries a worse prognosis due to poor response to chemotherapy. A histologic spindle and/or giant cell component is required for diagnosis, and recent studies implicate Zinc Finger E-box binding Homeobox 1 (ZEB1), a key transcriptional regulator of the epithelial-mesenchymal transition program, in sarcomatoid progression. However, whether ZEB1 has diagnostic use in limited specimens, including cell block (CB) preparations, remains unclear.
Methods: Sarcomatoid (SARC, n=14), small cell (SCLC, n=8) and large cell neuroendocrine carcinoma (LCNEC, n=8), typical (TC, n=9) and atypical carcinoid (AC, n=10), squamous cell carcinoma (SQ, n=7), and adenocarcinoma (ADC, n=7) CBs with 71 SARCs, 9 SCLCs, 10 LCNECs, 20 TCs, 21 ACs, 71 SQs, 402 ADCs, 16 large cell carcinoma (LCC) and 17 other non-small cell lung carcinoma (NSCLC) surgicals

between 2007-2018 were retrieved. ZEB1 IHC (Sigma) was graded 0 to 3+, with ≥1+ and >5% staining considered positive.
Results: Nuclear ZEB1 was seen in 79% SARCs (11/14), 12.5% SCLCs and 12.5% LCNECs (both 1/8), but not in TC, AC, SQ or ADC CBs. In surgicals, 76.1% SARCs (54/71), 12.5% LCCs (2/16), 11.8% NSCLCs (2/17), 30% LCNECs (3/10), 11.1% SCLCs (1/9), 0% TCs (0/20), 0% ACs (0/21), 0% SQs (0/71) and 0.2% ADCs (1/402) demonstrated ZEB1 expression. ZEB1 sensitivity and specificity were 78.6% and 95.9% in cytologic specimens, and 76.1% and 98.4% in surgical specimens, respectively.
Conclusion: ZEB1 is sensitive and highly specific in identifying sarcomatoid carcinoma in limited cytologic and surgical specimens. Diagnostic pitfalls include high grade neuroendocrine tumours and large cell carcinoma, which can be resolved by morphologic considerations.

OFP-03-004
The value of fine needle aspiration cytology in the examination of parathyroid lesions; role of immunocytochemistry and washout fluid analysis
E. Bakuła-Zalewska[1], J. Długosińska[2], O. Stanowska[3], P. Goralski[2], J. Gałczyński[2]
[1] Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [2] Department of Oncological Endocrinology and Nuclear Medicine Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [3] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland

Background & Objectives: To discerning parathyroid from thyroid in fine needle aspiration (FNA) smears is difficult. The majority FNA of parathyroid lesions is unintended, as intrathyroidal parathyroid adenomas and cysts are often mistaken for thyroid lesions. However, the US-guided FNA for examination of parathyroid has been recently increasingly used to distinguish abnormal parathyroid glands from lymph nodes, to localize atypical or intrathyroidal parathyroid glands and parathyroid lesions in recurrent disease.
Methods: Seventy-three patients underwent parathyroid FNA either unintended during the sampling of suspicious thyroid nodules (35 patients) or performed specifically to localize parathyroid lesions (38 patients). In addition to the examination of smears, measurement of parathyroid hormone in the needle washouts (FNA-PTH testing) was performed in all patients and immunocytochemical examination (IC) on 15 FNA specimens.
Results: All of the examined FNA samples were correctly diagnosed as parathyroid lesions in the examination of FNA smears completed by FNA-PTH testing and/or IC. Overall organoid and cribriform or trabecular architecture of three-dimensional and frequently crowded clusters with overlap of cells and occasional loose clusters with acinar-follicular and/or papillary formations were seen in all FNA smears. Cells with small, dark nuclei with stippled chromatin, and clean or bloody, colloid-free background was another signs suggestive of parathyroid origin.
Conclusion: The architectural pattern in the FNA smears helps to distinguish between parathyroid and thyroid aspirates. FNA-PTH testing is a very useful adjunct to determine whether the specimen obtain by FNA represents parathyroid or thyroid lesions. IC on FNA specimen is yet another technique which increases the diagnostic accuracy.

OFP-03-005
The value of an abnormal cytology result in a cervical screening cotest study with E6/E7 mRNA. Increased risk for CIN2+ after a 3-year follow-up
R. Granados[1], M. Gil[1], A. Gutierrez-Pecharromán[1], J. Duarte[1], A. Villar[1], I. Solis[1], J.A. Aramburu[1], J.M. Rodríguez-Barbero[1], P. Bajo[1], T. Corrales[1], E. Camarmo[1]
[1] Hospital Universitario de Getafe, Spain

Background & Objectives: To determine the increase of CIN2+ risk in HPV-positive women with an abnormal cytology (HPV+/Cyt+) in contrast to those with a negative Pap (HPV+/Cyt-) after a 3 year follow-up (FU).
Methods: After cotesting 5,053 women with LBC cytology and APTIMA® HPV, 3,9% (n=155) were HPV+/Cyt+ (ASCUS+) and 5,9% HPV+/Cyt-. The baseline risks for CIN2+ in those groups was 55,2% (48/87) and 14,9% respectively. Women without a high-grade lesion were followed for 3 years by cotest and/or biopsy. Statistical risk assessment was calculated.
Results: 58 women from the HPV+/Cyt+ group had adequate 3-year FU. A high-grade (CIN2+) lesion was found in 14 cases (24,1%), all of them with persistent HPV infection. Abnormal cytology (ASCUS+) was seen in 13 (92,9%) of them. 54% of HPV+/Cyt+ and 70,9% of HPV+/Cyt- women ($p<0,05$) underwent HPV clearance within 3 years and none of them had either cytological HSIL or a CIN2+ lesion. Cumulative risk for CIN2+ was 79,3% in the HPV+/Cyt+ group and 43,5% in HPV+/Cyt- women ($p<0,05$).
Conclusion: The cumulative risk for developing a CIN2+ lesion 3 years after a positive HPV test with mRNA is much higher in women with abnormal cytology at baseline (79,3% vs 43,5%). The rate of HPV clearance is lower than the one observed in HPV-positive/Cytology-negative women. Although cytology does not increase the sensitivity of mRNA HPV for CIN2+, its impact in the positive predictive value of a positive cotest and in patient management is noteworthy.

OFP-03-006
BRAF mutation prediction from metastatic melanoma cytological smear using deep learning: an ongoing project
L. Nicolè[1], S. Suweis[2], R. Cappellesso[1], A. Fassina[3]
[1] University of Padua, Italy, [2] Physics and Astronomy Department, University of Padua, Italy, [3] Department of Medicine, Surgical Pathology & Cytopathology Unit, University of Padua, Italy

Background & Objectives: Visual inspection of cytological smears is one of the main methods used to assess suspicious nodes or mass during follow up of patients with malignant melanoma (MM). If metastatic MM (mMM) is detected, analysis for BRAF mutational status is mandatory in order to identify those cases that are suitable for targeted-therapy. Image analysis based on convolutional neural networks (CNN) showed encouraging results in tissue classification and mutation predictions suggesting that deep-learning models can be effective ancillary tools to improve the diagnosis.
Methods: In this study, we started to explore different architectures and components of deep CNNs (https://arxiv.org/pdf/1512.07108.pdf) and test their accuracy in recognizing BRAF mutational status from digital scanned May-Grunwald-Giemsa stained smears.
We have collected 50 stained smears of 30 cases of BRAF-mutated and 20 cases of BRAF-wild type mMM (magnification 200x of 1000*1000 pixel each). From these smears we have extracted patches of around 30*30 pixels from each single image, thus creating an overall database of 55000 cases. We have used 2/3 of these cases to train the different types of CNNs and the reaming 1/3 as test set.
Results: To date, trained algorithm has not achieved satisfactory accuracy (overall accuracy about 60%) in BRAF status prediction.
Conclusion: Preliminary results highlighted a great dependence of classifier algorithm from input data to achieve a satisfactory level of learning after training. To fill this gap we are enlarging the case series selecting additional cases to training the classifier algorithm.

OFP-03-007
Metabonomics profiling of malignant peritoneal effusion with 1H-NMR spectroscopy
L. Nicolè[1], L. Zennaro[2,3], P. Vanzani[2,3], A. Fassina[1]
[1] University of Padua, Italy, [2] Department of Molecular Medicine, University of Padua, Italy, [3] Consortium INBB, Section of Padua, Rome, Italy

Background & Objectives: Metabonomic profiling of human malignancies remain a field poorly investigated. Effusion is an optimal biospecimens suitable for metabonomic investigation. With this study we addressed a preliminary metabonomic profiling of malignant Ascitic Effusion (mAE) from patients with Ovarian cancer (OC), Hepatocellular carcinoma (HCC), and benign Ascitic Effusions (bAE) from patients with non neoplastic diseases.
Methods: We have collected 49 samples comprising 20 mAE from OC, 9 mAE from HCC and 20 bAE. Storage of the samples has been done according to a protocol described in our previous study (Zennaro et al. 2018), and profiling was carried out with 1H-NMR spectroscopy. After spectra acquisition principal component analysis was applied to classify the effusions
Results: Our preliminary data suggest how metabonomic profiling could be effective to classify effusions. In particular, 1H-NMR spectroscopy could be useful in effusions with low cellularity or in cases where morphology or other classical ancillary tests failed to achieve a diagnosis. From the multivariate statistical analysis (PCA and PLS-DA) performed on the 1H-NMR spectra recorded, the differentiation of the metabolic profiles between mAE and bAE in OC results to be clear, and mainly due to triglycerides, beta-hydroxybutyrate (BHB), acetate, acetoacetate, lactate, pyruvate and glucose. In particular, all the mentioned metabolites increase in mAE, while glucose decreases. Conversely, in mAE from HCC the metabolites responsible for the difference in the metabolic profiles seem to be different from the ones found as important in OC.
Conclusion: Globally our preliminary data suggest the feasibility of 1H-NMR spectroscopy as diagnostic tool in particular in such cases with poor cellularity. However, due to the few mAE samples collected till now from HCC, such preliminary results must be confirmed with additional cases.

OFP-03-008

Ultrasound data may be used to stratify the risk of malignancy of thyroid nodules classified as follicular neoplasm on fine needle aspiration cytology: a retrospective study of 109 cases

D. Pinto[1], C. Martins[2], D. Felizardo Montezuma[3], S. Canberk[4,5], F. Schmitt[4,5]
[1] Centro Hospitalar de Lisboa Ocidental, EPE, Portugal, [2] Escola de Medicina da Universidade do Minho, Portugal, [3] Instituto Português de Oncologia de Coimbra, Portugal, [4] IPATIMUP, Portugal, [5] Faculdade de Medicina da Universidade do Porto, Portugal

Background & Objectives: The reported risk of malignancy for thyroid nodules classified as Follicular Neoplasm/Suspicious for Follicular Neoplasm (FN/SFN) on fine needle aspiration (FNA) cytology is between 15 and 30%. Diagnostic lobectomy usually follows. Therefore, many unnecessarily surgeries are performed. We wondered if ultrasound (US) characteristics could be used to further stratify the risk of these nodules.
Methods: FNAs of the thyroid performed at our institution between 2015 and 2017, with a diagnosis of FN/SFN, were selected. Histology, cytology and US images were reviewed. Histological diagnoses were divided into three categories: non-neoplastic, adenoma/NIFTP and malignant. US images were evaluated regarding delimitation, encapsulation and echogenicity. A compound score of these variables was developed.
Results: 109 cases were included. Histologically, 37 (33.9%) were classified as non-neoplastic, 25 (22.9%) as adenoma/NIFTP and 47 (43.1%) as malignant. On US, 81 (74.3%) were well-circumscribed, 61 (56.0%) encapsulated and 74 (67.9%) isoechoic. Poor circumscription and absence of a capsule were associated with a lower prevalence of adenoma/NIFTP and a higher prevalence of carcinoma (p=0.0266 and p=0.0147, respectively). Non-isoechoic nodules were associated with a lower prevalence of adenoma/NIFTP (p=0.0266). The compound score was able to stratify nodules between high and low-risk groups, practically excluding adenomas/NIFTPs from the high-risk group, which also showed a higher prevalence of carcinoma (p=0.0202).
Conclusion: In conclusion, delimitation, encapsulation and echogenicity of a thyroid nodule as evaluated by US appear to be correlated with the final histological diagnosis. These results hint that US data may be used to complement the cytological diagnosis, enhancing clinical follow-up.

OFP-03-009

Correlation between the ultrasound-guided thyroid fine-needle aspiration cytology with molecular testing and surgical histopathology results

H. Seneldir[1], G. Kir[1], T. Soylemez[1], R.B. Girgin[1], N. Ozbay[1], F. Ozen[2], H. Ankaralı[3], G. Bas[4], O. Alimoglu[4]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University Molecular Biology and Genetics Department, Turkey, [3] İstanbul Medeniyet University Biostatistics and Medical Informatics Department, Turkey, [4] Istanbul Medeniyet University, Department of General Surgery, Turkey

Background & Objectives: Molecular testing has been proposed to refine the assessment of cancer risk in thyroid nodules with indeterminate cytology. The aim of this study is to compare the genotypic alterations for BRAF, NRAS, and KRAS mutations of FNA samples in indeterminate and malignant category with subsequent histology of surgical specimens in our routine practices.
Methods: We reviewed 150 cases diagnosed as atypical by ultrasound-guided thyroid FNA cytology on the basis of the Bethesda system who had undergone molecular testing. FNA samples were tested for BRAF, NRAS, and KRAS point mutations by real-time polymerase chain reaction (RT-PCR). Out of these 150 cases, 71 had undergone surgical procedure and histopathology results, were compared with both cytology and molecular status. According to the final pathological results, we divided the cases, as benign and malign groups.
Results: According to the Bethesda System the 71 cases were distributed as 13 AUS/FLUS, 24 FN/SFN, 13 SM, and 21 malign categories. Of the 71 cases of atypical cytology, 48 cases (67.6 %) were diagnosed as malignant, and 23 cases (32.4 %) were diagnosed as benign at surgical specimens. In 71 nodules, 37 samples (52.1%) had point mutations. Overall positive predictive value of cytology evaluation was 67.6 % and overall positive predictive value of cytology and molecular testing was 89.2 % (p=0.004).
Conclusion: The addition of molecular testing to FNA cytology may increase the positive predictive value of cytology.

OFP-03-010

The accuracy of p16/Ki67 dual staining and HPV DNA test in the detection of CIN2+ in women with HSIL cytology: preliminary findings from a Canadian study

R. Alaghehbandan[1], S. Ratnam[2], L. Gilbert[2], D. Jang[3], M. Schell[3], R. Needle[2], A. Wadhawan[3], D. Costescu[3], G. Zahariadis[2], M. Chernesky[3]
[1] Department of Pathology, Faculty of Medicine, University of British Columbia, Royal Columbian Hospital, Vancouver, Canada, [2] Public Health and Microbiology Laboratory, Eastern Health, Canada, [3] McMaster University, Canada

Background & Objectives: An ongoing Canadian study is assessing the clinical efficacy of the CINtec PLUS assay (Roche) for triaging women with low-grade squamous intraepithelial lesion (LSIL). As part of this study, we compared the accuracies of CINtec PLUS assay and HPV DNA test (cobas 4800, Roche) to identify high-grade cervical intraepithelial neoplasia or worse (CIN2+) in women with LSIL cytology.
Methods: LSIL cases seen at the colposcopy clinic, Juravinski Hospital, Hamilton were prospectively enrolled with informed consent. Cervical specimens were collected at enrolment in ThinPrep for routine Pap. The remnant from the ThinPrep vials was used for CINtec PLUS immunostaining to detect biomarkers p16/ki-67 and HPV testing. Biopsy confirmed CIN2+ served as the clinical endpoint.

Results: There were 196 (54.3%) patients testing positive for p16/ki-67, and 197 (54.6%)testing positive for HPV with 47 testing positive for HPV genotypes 16/18, and 150 for 12 other HR-HPV. The sensitivity and specificity of p16/Ki-67 in detecting CIN2+ were 94.6% and 50%, respectively. Superior performance was observed for p16/Ki-67 dual staining for detecting CIN2+ with an area under the ROC curve of 0.723 ($p<0.001$) compared to 0.277 for HPV testing.
Conclusion: Both p16/Ki-67 dual staining and HPV testing showed similar performance in detecting CIN2+ lesions among women with LSIL. However a significantly better performance was observed with p16/Ki-67 dual staining.

OFP-03-011
Contribution of TERT promoter mutation status to preoperative diagnosis of thyroid carcinoma
M. Bella-Cueto[1], R. Carrera[1], M.d.C. Ramos[1], M. Rodriguez[1], J.A. Vazquez[1], R. Onieva[2], I. Capel[1], C.M. Blazquez[1], F.J. Andreu[1], M. Escoda[1], M. Prenafeta[1], S. Barcons[1], V. Perez[1], A. Cano-Palomares[1], F.X. Guirao[1], L. Nebot[1], E. Gallardo[1], M. Rigla[1], N. Combalia[1]
[1] Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí. Universitat Autònoma de Barcelona, Spain, [2] Universitat Autònoma de Barcelona, Spain

Background & Objectives: Thyroid nodules are common among population, but barely 4% corresponds to malignant neoplasms. Ultrasound-guided fine needle aspiration biopsy (FNAB) is a worldwide used tool to guide the patients' management, but in some entities the main diagnostic criteria of malignancy must be evaluated in the surgical specimen. C228T mutation of telomerase reverse transcriptase promoter (*TERTp*) has been identified as specific of malignancy, but its detection by pyrosequencing has been slightly reported. The aim of our study is to determine the incidence of C228T *TERTp* mutation by pyrosequencing in thyroid nodules classified by FNAB as consistent with follicular neoplasm, and to establish the profitability of its detection in the corresponding FNAB material.
Methods: Inclusion criteria: Patients with thyroid nodules classified by FNAB as consistent with follicular neoplasm and followed by thyroidectomy between 1993 and 2015. Methods: cases were retrieved from the Pathology Department archives. Demographics, clinical data, and cytological and histological diagnoses were recorded. Selected material from paraffin blocks was processed by pyrosequencing to detect C228T *TERTp* mutation. In mutated cases, FNAB material was also studied.
Results: 62 cases fulfilled the inclusion criteria. C228T *TERTp* mutation was detected in 9 tumours (14,5%), and in the corresponding FNAB material of 7 of them - the ones with enough material to perform the study-. In 4/9 cases a delayed completion thyroidectomy was needed.
Conclusion: Study of C228T *TERTp* mutation status by pyrosequencing can be of help to detect malignant thyroid nodules, eventually indicating total thyroidectomy as the first and definitive surgery, avoiding a second intervention.

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OFP-03-012
Thyroid nodules with AUS/FLUS cytology: what happens next?
J. dos Santos[1], R. Machado-Neves[1], T. Amaro[1], M. Honavar[2]
[1] Pathology Department - Hospital Pedro Hispano, Portugal, Portugal, [2] Unidade Local de Saúde de Matosinhos - Portugal, Portugal

Background & Objectives: Fine-needle aspiration (FNA) has a significant role in assessing the malignancy risk of thyroid nodules. Our aim is to study thyroid nodules with cytological diagnosis of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS).
Methods: Retrospective study of 3186 thyroid FNAs between January 2014/December 2018. 334 (10,5%) classified as AUS/FLUS; 112 underwent surgery. Results of repeated FNA and histology were evaluated.
Results: Study of 112 patients with AUS/FLUS who underwent surgery: 92 women, 20 men; aged 17-83 years; nodule of median size 23,5 mm (10-62 mm). After the first AUS/FLUS FNA, 40 patients underwent surgery immediately: 33 (82,5%) were benign nodules (colloid goiter, follicular adenomas, Hurthle cell adenomas, thyroiditis), 7 (17,5%) were malignant/with malignant potential (papillary carcinomas, noninvasive follicular neoplasm with papillary-like nuclear features [NIFTP], well differentiated tumour of uncertain malignant potential). FNA was repeated in 72 cases: 4 (5,6%) unsatisfactory/non-diagnostic, 4 (5,6%) benign, 4 (5,6%) follicular neoplasm, 2 (2,8%) suspicious for malignancy, 4 (5,6%) malignant, 54 (75%) AUS/FLUS. Of these repeated AUS/FLUS FNAs, the surgical pathology diagnosis was benign in 47 (87%) (colloid goiters, follicular adenomas, Hurthle cell adenomas) and malignant/with malignant potential in 7 (13%) (papillary carcinomas, papillary microcarcinoma, NIFTP). Overall, 91 (81,3%) of the nodules were benign and 21 (18,75%) were malignant or had malignant potential.
Conclusion: Our results are in concordance with the risk of malignancy predicted by the Bethesda classification for AUS/FLUS. AUS/FLUS FNAs should be repeated since this may change the initial diagnosis and the therapeutic approach.

Monday, 9 September 2019 08:30 - 12:00, Galliéni 4
OFP-04 | Breast Pathology

OFP-04-001
Hormone- and HER2-receptor assessment in 33,046 breast cancer patients: a nationwide comparison of positivity rates between pathology laboratories in the Netherlands
C. van Dooijeweert[1], I. Deckers[2], I. Baas[3], E. van der Wall[3], P. van Diest[4]
[1] Department of Pathology, University Medical Center Utrecht, The Netherlands, [2] PALGA Foundation (the nationwide network and registry of histo- and cytopathology in The Netherlands), Houten, The Netherlands, [3] Department of Medical Oncology, University Medical Center Utrecht, The Netherlands, [4] University Medical Center Utrecht, The Netherlands

Background & Objectives: Patient management of invasive breast cancer (IBC) is to a large extent based on hormone- and HER2-receptor assessment. High-quality, reliable receptor assessment is of key-importance as false results may lead to under- or overtreatment of patients. Surveillance of case-mix adjusted positivity rates has been suggested as a tool to identify laboratories with insufficient testing assays, as this covers the whole process of receptor assessment and enables laboratories to benchmark their positivity rates against other laboratories.
Methods: We studied laboratory-specific variation in hormone- and HER2-positivity rates of 33,046 breast cancer patients using real-life nationwide data. All synoptic pathology reports of IBC resection-specimens, obtained between 2013-2016, were retrieved from the nationwide Dutch Pathology Registry (PALGA). Absolute and case-mix adjusted positivity rates were compared to the mean national proportion and presented in funnel plots in separate analyses for estrogen (ER), progesterone (PR) and HER2. Case-mix adjustment was performed by multivariable logistic regression.
Results: 33,794 IBC lesions from 33,046 patients of 39 pathology laboratories were included. After case-mix adjustment, mean positivity rates were 87.2% for ER (range: 80.4-94.3), 71.3% for PR (62.5-77.5%), and 9.9% for HER2 (5.5-12.7%). Overall, 14 (35.9%), 17 (43.6%) and 11 (28.2%) laboratories showed positivity rates outside the 95% confidence interval for ER, PR and HER2 respectively.
Conclusion: This nationwide study shows that absolute variation in hormone- and HER2-receptor positivity rates between Dutch pathology

laboratories is limited. Yet, the considerable number of outlying laboratories shows that there is still need for improvement. Continuous monitoring and benchmarking of positivity rates may help to realize this.

Funding by: The Quality Foundation of the Dutch Association of Medical Specialists (SKMS)

OFP-04-002

Significant inter- and intra-laboratory variation in grading of invasive breast cancer: a nationwide study of 33,043 patients in the Netherlands

C. van Dooijeweert[1], P. van Diest[2], S. Willems[1], C. Kuijpers[1], E. van der Wall[3], L. Overbeek[4], I. Deckers[4]

[1] Department of Pathology, University Medical Center Utrecht, The Netherlands, [2] University Medical Center Utrecht, The Netherlands, [3] Department of Medical Oncology, University Medical Center Utrecht, The Netherlands, [4] PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands, Houten, The Netherlands

Background & Objectives: Accurate, consistent, and reproducible grading by pathologists is of key-importance for identification of individual patients with invasive breast cancer (IBC) that will or will not benefit from adjuvant systemic treatment. We studied the laboratory-specific grading variation using nationwide real-life data to create insight and awareness in grading variation.

Methods: Synoptic pathology reports of all IBC resection-specimens, obtained between 2013-2016, were retrieved from the nationwide Dutch Pathology Registry (PALGA). Absolute differences in laboratory-proportions of grade I-III were compared to the national reference. Multivariable logistic regression provided laboratory-specific odds ratios (ORs) for high- versus low-grade IBC.

Results: 33,792 IBC pathology reports of 33,043 patients from 39 laboratories were included, of which 28.1% were reported as grade I (range between laboratories 16.3-43.3%), 47.6% as grade II (38.4-57.8%), and 24.3% as grade III (15.5-34.3%). Based on national guidelines, the indication for adjuvant chemotherapy was dependent on histologic grade in 29.9% of patients. After case-mix correction, 20 laboratories (51.3%) showed a significantly deviant OR. Significant grading differences were also observed among pathologists within laboratories.

Conclusion: In this cohort of 33,043 breast cancer patients we observed substantial inter- and intra-laboratory variation in histologic grading. It can be anticipated that this has influenced outcome including exposure to unnecessary toxicity, since choice of adjuvant chemotherapy was dependent on grade in nearly a third of patients. Better standardization and training seems warranted.

Funding by: The Quality Foundation of the Dutch Association of Medical Specialists (SKMS)

OFP-04-003

The prognostic value of the tumour-stroma ratio validates in subgroups of breast cancer, especially in grade III tumours

W. Mesker[1], K. Vangangelt[2], A. Green[3], I. Heemskerk[2], D. Cohen[2], H. Putter[2], E. Rakha[3], R. Tollenaar[2]

[1] Leiden University Medical Centre, The Netherlands, [3] University of Nottingham, United Kingdom

Background & Objectives: The tumour-stroma ratio (TSR) is a promising prognostic parameter based on tumour-associated stroma within the primary tumour. The heterogeneous cancer types of breast cancer with various histological subtypes complicate clinical decision making. This large validation study aims at the prognostic implication of TSR in the various subgroups of breast cancer in a digital pathology environment.

Methods: A total of 2385 haematoxylin and eosin stained tissue slides of primary breast cancer patients from 1809 patients were assessed for TSR via a digital application for the evaluation of microscopic images. A percentage of less than or equal to 50% stroma was categorized as stroma-low and more than 50% stroma was categorized as stroma-high.

Results: TSR showed to be an independent prognostic parameter for both RFP (HR 1.34, 95% CI 1.09-1.65, p = 0.005) and BCSS (HR 1.52, 95% CI 1.17-1.96, p = 0.001). The prognostic effect of the TSR was highest in grade III tumours. Stroma-low/grade III tumours had a statistically significant better prognosis compared to stroma-high/grade III tumours (BCSS: HR 1.87, 95% CI 1.35-2.59, p < 0.001 and RFP: HR 1.82, 95% CI 1.33-2.50, p < 0.001).

Conclusion: The prognostic effect of the TSR validates in most subgroups. In this study, the prognostic effect of the TSR is highest in grade III tumours. TSR could contribute to clinical decision making for breast cancer therapy.

OFP-04-004

High Pregnane-X-Receptor (PXR) expression is correlated with poor prognosis in invasive breast carcinoma

D. Pouloudi[1], C. Giaginis[2], S. Gourzi[1], P. Alexandrou[1], G. Tsourouflis[3], A. Michail[4], N. Tsoukalas[1], S. Albesher[1], P. Politis[4], L. Nakopoulou[1], S. Theocharis[1]

[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [2] Department of Food Science and Nutrition, University of the Aegean, Myrina, Lemnos, Greece, [3] 2nd Department of Propedeutic Surgery, School of Medicine, National and Kapodistrian University of Athens, Greece, [4] Section of Molecular Biology, Biomedical Research Foundation, Academy of Athens, Greece

Background & Objectives: Pregnane X Receptor (PXR) is involved in human malignancy, either by directly affecting carcinogenesis or by inducing drug-drug interactions and chemotherapy resistance. The clinical significance of PXR expression in invasive breast carcinoma was evaluated in our study.

Methods: PXR protein expression was assessed immunohistochemically on formalin fixed paraffin-embedded breast invasive carcinoma tissue sections obtained from 148 patients and was correlated with clinicopathological parameters, molecular phenotypes, tumour cells' proliferative capacity and overall and disease-free patients' survival. Additionally, the expression of PXR was examined on human breast carcinoma cell lines of different histological grade, hormonal status and metastatic potential (MDA-MB231, MDA-MB468, MDA-MB453, MCF-7, T47D).

Results: PXR positivity was noted in 79 (53.4%) and high PXR expression in 48 (32.4%), out of 148 breast carcinoma cases. High PXR expression was positively associated with nuclear grade (p=0.0112) and histological grade of differentiation (p=0.0305), as well as with tumour cells' proliferative rate (p=0.0051), and negatively with luminal-A subtype (p=0.0295). Associations between high PXR expression and estrogen and progesterone receptor negative status were also recorded (p=0.0314 and p=0.0208, respectively). High PXR expression was associated with shorter overall patients' survival times (p=0.0009). In multivariate analysis, high PXR expression was identified as an independent prognostic factor of overall patients' survival (p=0.0082). PXR expression alterations were also noted in breast cancer cell lines of different hormonal status.

Conclusion: The present data supported evidence that PXR was highly expressed in invasive breast carcinoma and related with a more aggressive phenotype, being also a strong and independent poor prognosticator.

OFP-04-005

The immune microenvironment in young patients with triple negative breast cancer

H. McKenzie[1,2], G. Martland[3], D. Eccles[1], E. Copson[1,2], G. Thomas[1,2]

[1] University of Southampton, United Kingdom, [2] University Hospital Southampton NHS Foundation Trust, United Kingdom, [3] Poole Hospital NHS Foundation Trust, United Kingdom

Background & Objectives: Triple negative breast cancers (TNBC) comprise 15-20% of breast cancers and are associated with adverse outcomes; the prognosis for younger women is worse. Tumour-infiltrating lymphocytes (TILs) significantly correlate with improved survival in many cancers. Conversely, tumoural expression of programmed death ligand 1 (PD-L1) is associated with T-cell exhaustion and is commonly a negative prognostic marker. Mechanisms suppressing the immune response in TNBC remain unclear.
Methods: We evaluated immunological markers in a prospective cohort of young patients (<41 yrs) with TNBC (POSH; n=350). We evaluated stromal TILs, cancer-associated fibroblasts (smooth muscle actin; SMA), CD8 (effector T-cells) and PD-L1 (on tumour cells). Survival analyses were summarised with Kaplan-Meier curves (log-rank test). Multivariable Cox regression analysis and variable correlation analyses were also performed.
Results: TILs were significantly associated with good prognosis; relative to low TILs (<20%), the hazard ratio for overall survival for those with high TILs (>60%) was 0.106 (0.015-0.762; p=0.026). Relative to low PD-L1 expression, the hazard ratio for those with high expression was 0.374 (0.207-0.675; p=0.001). TILs negatively correlated with expression of SMA, r=-0.211 (p=0.001) and positively correlated with expression of PD-L1 (r=0.598, $p=1.792^{-32}$).
Conclusion: TILs are significantly prognostic in young women with TNBC. High PD-L1 expression is also associated with improved survival. Notably, the presence of CAFs in the tumour stroma inversely correlated with TILs suggesting that these cells may be immunosuppressive. These data suggest that inhibiting CAFs may be a strategy to improve clinical response to immunotherapy and we are currently evaluating the efficacy of CAF targeting in murine immunotherapy models.

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OFP-04-006

Utility of a gene expression panel as a screening tool for human mammary tumour virus infection in breast cancer

C. Scatena[1], P. Civita[2], F. Lessi[2], P. Aretini[2], M. Menicagli[2], C. Marchiò[3], C.M. Mazzanti[2], G. Bevilacqua[1], A.G. Naccarato[1]
[1] University of Pisa, Italy, [2] Fondazione Pisana per la Scienza, Italy, [3] University of Turin, Italy

Background & Objectives: Etiology of human breast cancer (BC) is unknown, with the exception of hereditary tumours. On the other hand, the Mouse Mammary Tumour Virus (MMTV) is recognized as the etiological agent of mouse mammary carcinoma. Several data suggest the existence of a human equivalent of MMTV (HMTV) such as the presence of viral sequences in human BC or, intriguingly, saliva, offering a possible route of infection. However, the identification of HMTV in BC tissue may be inaccurate due to the difficulty in DNA amplification or the loss of the virus during progression, as earlier hypothesized. The aim of the present study was to obtain a gene panel able to determine if a BC is due to the HMTV viral infection regardless of presence of viral sequences.
Methods: The panel was built through a systematic search from bibliographic datasets. 31 formalin-fixed, paraffin-embedded specimens were selected to test the panel: 7 HMTV positive BC (pBC), 7 HMTV negative BC (nBC), 7 hereditary BC (HBC) and 9 specimens of normal breast tissue (NBT) as controls. The experiment was conducted according to TruSeq Gene Expression Panel (NextSeq500-Illumina). Data were performed by Principal Component Analysis (PCA).
Results: The pBC group was clearly discriminated from the nBC group. Interestingly, the nBC group co-localized with the HBC group, whereas, the NBT group localized far from all the other groups.
Conclusion: These data point out the HMTV specificity of the gene panel selected and its possible use as a screening tool or classifier in BC.

OFP-04-007

Correlation of the results of Ki67 in intrinsic subtypes of invasive breast carcinomas with the effect of systemic neoadjuvant treatment

W.P. Olszewski[1], M. Chraszczewska[2], J. Plisiecka[1]
[1] Department of Pathology, Center of Oncology, Warsaw, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland

Background & Objectives: The study used 78 breast cancer cases qualified for neoadjuvant treatment. In the evaluated group, there were 28 cases of triple-negative (ductal) carcinomas, 25 cases of HER2 positive (non-luminal) carcinomas, 8 cases of Luminal B (HER2 positive) carcinomas and 17 cases of luminal B (HER2 negative) carcinomas. Clinically all tumours were in Stage III.
Methods: In order to more accurate measurements than the routine Ki67 evaluation, Ki67 was reassessed in the CB material. Ki67 was evaluated in 500 cells. Three pathologists carried out an independent assessment of Ki67. Residual Cancer Burden value, percentage of pCR and the decrease in cellularity were measured in all post treatment histologic material.
Results: It was shown that higher Ki67 index correlates with the degree of response assessed as the calculated Residual Cancer Burden value, percentage of pCR and the decrease in cellularity in the subgroups of triple-negative and HER2 positive (ductal) cancers. In the groups of luminal B cancers, such correlation was not found.
Conclusion: The Ki67 index predicts the response to neoadjuvant treatment assessed as the calculated Residual Cancer Burden value, percentage of pCR and the decrease in cellularity in HER2 positive cancer and triple-negative (ductal) subtype.

OFP-04-008

Independent HER2-targeted therapy resistance predictors: intratumoural heterogeneity in breast carcinoma HER2 gene copy number and protein expression

H. Nitta[1], R. Horii[2], R. Maruyama[2], M. Nojima[3], M. Matsuura[2], D. Munroe[1], P. Banks[4], F. Akiyama[2]
[1] Roche Tissue Diagnostics, USA, [2] Japanese Foundation for Cancer Research, Japan, [3] The University of Tokyo, Japan, [4] University of North Carolina at Chapel Hill, USA

Background & Objectives: We employed two methods for the detection of HER2 genetic heterogeneity (GH; a mixture of classic HER2 positive and negative tumour cells) and non-GH (NGH; a mixture of classic HER2 positive tumour cells and HER2 gene amplified tumour cells without HER2 protein): 1) visual microscopic HER2-intratumoural heterogeneity (ITH) and 2) quantitative HER2-diversity (based on enumeration of large numbers of individual cells in respect to HER2 gene copy number and protein expression levels) in relation to neoadjuvant trastuzumab-based chemotherapy.
Methods: Archived tissue samples from 102 neoadjuvant trastuzumab-treated HER2-positive breast cancer patients were studied with the HER2 gene-protein assay (a combination of immunohistochemistry and bright-field *in situ* hybridization). HER2-ITH was microscopically assessed for HER2 gene (amplified, non-amplified) and protein (positive, negative). Quantitative analysis was for gene copy number (≥6, 5-4, ≤3) and protein expression (3+, 2+, 1+, 0) among individual tumour cells. Logistic regression analyses of the results were compared in relation to pathological complete response (pCR, 49%) and non-pCR (51%).
Results: Visual HER2 GH and NGH was detected in 8.8% and 30.4% of the cohort, respectively. Fewer NGH patients achieved pCR compared to homogenous patients (p=0.0189, OR=2.925). Quantitative analysis showed that patients with higher HER2 gene copies and less protein

expression variation achieved pCR more frequently (AUC=0.723). Furthermore, HER2-ITH indicators were strengthened with the diagnostics ability of conventional pathological markers (AUC=0.780 to 0.855, sensitivity 76.0%, specificity 84.3% in ROC analysis).
Conclusion: Visual microscopy and quantitative HER2-diversity enumeration identified ITH as independent resistance factors to neoadjuvant trastuzumab-based chemotherapy.

OFP-04-009
Investigation of microRNA expression profiles related to morphological heterogeneity in triple-negative breast cancer
M. Koleckova[1], Z. Kolar[2], J. Ehrmann[1], M. Svoboda[3], O. Slaby[3], J. Bouchal[1], K. Bouchalova[4], M. Janikova[5], J. Srovnal[6], L. Radova[3]
[1] Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Olomouc, Czech Republic, [2] Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic, [3] Central European Institute of Technology, Masaryk University, Brno, Czech Republic, [4] Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Olomouc, Czech Republic, [5] University Hospital Olomouc, Czech Republic, [6] Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Olomouc, Czech Republic

Background & Objectives: Triple-negative breast cancers (TNBCs) are morphologically a heterogeneous group of breast carcinomas with no or minimal hormone receptor and HER2 protein expression or gene amplification. Due to its aggressive nature, novel therapeutic targets are urgently required to improve pathological complete response and clinical outcomes. In tumours, microRNAs (miRs) exhibit both oncogenic and tumour-supressor function. The aim of this study was to indentify a possible association between miRs expression profile and intratumoural morphology within different samples of TNBC.
Methods: We analysed the tumour miRs expression in relation to morphological heterogeneity of 25 TNBC samples of a diameter less than 2 cm obtained from patients without previous neoadjuvant chemotherapy with respect to tumour morphology preservation. We used microdissection techniques for the isolation of tumour cells from areas with specific morphology from paraffin sections, isolation of total RNA, miRs microarray analysis to compare tumour morphology with their profile.
Results: The analysed tumours were invasive carcinomas NST with medullary features, with central fibrosis/necrosis, tendency to spindle cell and/or apocrine metaplastic differentiation and extensive lympho/plasmocytic infiltration. In morphologically distinct parts of tumours we revealed seven candidate miRs represented by miR-93-5p, miR-106b-5p, miR-145-5p, miR-182-5p, miR-200c-3p, miR-205-5p and miR-361-5p which corresponded with areas of the predominantly medullar, spindle cell, clear cell, lymphocyte rich, precancerous and normal morphology .
Conclusion: We confirmed a possible association of specific miRs expression with specific morphological pattern in TNBC. Our results indicate miRs relevance for formation different neoplastic and non-neoplastic morphological conditions including lympho/plasmocytic infiltration. Additional examinations are needed for distinguishing of primary and/or subsequent role of miRs in these processes.

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OFP-04-010
Ultra-fast and automated immunohistofluorescent multistaining using a microfluidic tissue processor
G. Cappi[1], D.G. Dupouy[1], M.A. Comino[1], A.T. Ciftlik[1]
[1] Lunaphore Technologies SA, Switzerland

Background & Objectives: Simultaneous detection of multiple markers, on a single tissue section, allows investigating the complex tumour-environmental interactions. The existing multiplexing procedures, based on iterative cycles, are resource-expensive and impractically long, impeding their implementation in daily routine. Here we aimed to develop a fully automated ultra-fast work-flow for multiplexed immunofluorescence-staining employing the tyramide signal amplification (TSA) method by using a microfluidic tissue processor (MTP).
Methods: Formalin-fixed-paraffin-embedded (FFPE) sections of tissue micro-arrays, containing ten human breast carcinoma and one liver cancer cases, underwent manual deparaffinization and antigen retrieval. The multiple staining and elution steps were automatically executed on the microfluidic device without intervention needed. The elution step on the MTP was optimised to reach comparable efficiency to the standard elution method performed in a microwave oven. Four markers, namely CK (cytokeratin), ER/PR (estrogen/progesterone receptor) and Her2 (human epidermal growth factor receptor 2), were detected by a fluorescent TSA reaction mediated by the horseradish peroxide (HRP) enzyme conjugated to a secondary antibody.
Results: The developed protocol for a single plex lasts in average 15 minutes for the immunostaining and 5 minutes for the antibodies removal. Using the MTP technology, we established a 4-plex automated multistaining of clinically relevant biomarkers for breast cancer diagnosis within 84 minutes. The performance of the automated steps showed perfect agreement with the state-of-the-art.
Conclusion: With a turn-around time shorter than existing monoplex immunohistochemistry methods, our automated multiplexing technology has the potential to enable multistaining in routine without disturbing the current laboratory workflow, opening perspectives for implementation of -omics approaches in tissue diagnostics.

OFP-04-011
PD-L1 testing in triple negative breast cancer
F. Dobritoiu[1,2], A. Chefani[2], K. Billingham[3], M. Chenard[4], R. Vaziri[5], M. Lacroix-Triki[6], A. Waydelich[7], G. Erb[7], P. Toro[8], S. Wedden[2,9], C. D'Arrigo[2]
[1] Emergency University Hospital, Bucharest, Romania, [2] Poundbury Cancer Institute, Dorchester, United Kingdom, [3] Great Western Hospital Swindon, United Kingdom, [4] CHU de Strasbourg, Dèpartement de Pathologie, France, [5] Worcestershire Acute Hospitals, Department of Pathology, United Kingdom, [6] Gustave Roussy Cancer Campus, Dèpartement de Pathologie, Villejuif, France, [7] Roche TD, EMEA LATAM, Roche Diagnostics, France, [8] Roche TD, EMEA LATAM, Roche Diagnostics, Spain, [9] CADQASCIC, Dorchester, United Kingdom

Background & Objectives: Overall survival for triple negative breast cancer (TNBC) is low despite good response to chemotherapy; however, recently, FDA approved atezolizumab for advanced TNBC with SP142 inmmunohistochemistry assay as a Companion Diagnostic (CDx) and EMA and NICE are considering approval. Percentage of PD-L1(+) immune cells (IC) is used for patient selection, with threshold set at 1%. Today, there is no data on TNBC PD-L1 heterogeneity and the choice of tissue tested may influence patient selection. This study compares PD-L1 expression in core biopsy (CB) and surgical excision tissue samples in order to determine which specimen is optimal.
Methods: We investigated 73 cases of invasive TNBC with matched CB and excision samples (up to 5 tissue blocks/case). PD-L1 status was evaluated by IHC with SP142 CDx on Ventana Benchmark using the approved scoring algorithm. All PDL1(+) tumour-associated IC were quantified as % of tumour area. Tumours were classified as PD-L1(+) (≥1%) or PD-L1(-) (<1%). Each slide was scored independently. For each case, a final PD-L1 status was obtained by averaging all excision slides.
Results: 38/73 cases (52%) were PD-L1(+) as final diagnosis. 16/73 cases (22%) had PD-L1(-) on core and PD-L1(+) on final diagnosis. 16% had discordant PD-L1 status between excision blocks.

Conclusion: We showed that there are 42% fewer PD-L1 (+) cases when assessed on CB alone. No PD-L1(+) cases on CB became negative on final diagnosis. A PD-L1(-) CB should trigger retesting on excision and, because of the discrepancy amongst blocks from the same excision, if the initial block is PD-L1(-), retesting on additional excision blocks should be considered. This will ensure that patients are not denied this therapeutic option.

OFP-04-012

Automatic quantification of HER2 amplification in invasive breast cancer using chromogenic in situ hybridization (CISH) and computational pathology

M.S. Hossain[1,2], T. Nakamura[1], M. Hanna[2], N. Uraoka[2], D. S. Ross[2], M. R. Hameed[2], M. Yamaguchi[1], Y. Yagi[2]
[1] Tokyo Institute of Technology, Japan, [2] Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: HER2 gene amplification has prognostic and therapeutic indications in breast cancer. Fluorescent in situ hybridization (FISH) and CISH are the standard assays to determine the amplification status. CISH is evaluated by counting at least 20 cancer nuclei manually, according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines. However, this process is time prohibitive. We propose a system to quantify the HER2 amplification status automatically from CISH whole slide images (WSI) using computational pathology
Methods: Breast pathologists annotated tumour regions from CISH WSI at 40x (0.13 um/pixel). We detected singular nuclei using machine learning from annotations, then HER2 and CEP17 signals based on RGB intensity. Our model mirrors the ASCO/CAP guidelines. We assessed nuclei where CEP17≥2 and HER2>CEP17, then quantified 20 nuclei with highest (HER2-CEP17) differentiation values. Finally, the HER2 status was determined as amplified if HER2/CEP17 ratio≥2.0 or non-amplified if <2.0. Additionally, another 20 nuclei were quantified if the ratio was ≥1.8 and ≤2.2
Results: We randomly selected 13 patient specimens that were diagnosed with invasive breast carcinoma with prior immunohistochemistry and FISH. Then quantified the 13 cases using the proposed method which included 9 positive and 4 negative cases. Results of the proposed automatic quantification were compared with pathologists manual CISH counting. The correlation coefficient between the manual and automatic CISH ratio was 0.97 which indicates the efficacy for the proposed method
Conclusion: The proposed method has a high concordance with manual quantification. In the future, invasive cancer regions will be detected using deep learning and the final system will enable automatic annotation of cancer regions followed by the automatic quantification

OFP-04-013

CEP17 copy number gain: correlation of 15 cases with clinicopathological parameters and HER-2 gene amlification. Experience from a single institute

S. Gamrani[1], A. Douida[1], A. Mazti[1], F. El Agy[1,2], B. Efared[1], H. El Fatemi[1,3]
[1] Department of Pathology, Hassan II University Hospital, Fez, Morocco, [2] Faculty of Medicine and Pharma, Molecular Biology, Fez, Morocco, [3] Faculty of Medicine and Pharmacy of Fez, Morocco

Background & Objectives: As Anti-Her-2 containing therapy has become an important treatment for Her-2 positive breast cancer. The ratio of human epidermal growth factor receptor 2 (HER2) to CEP17 by fluorescent in situ hybridization (FISH) with the centromeric probe CEP17 is evaluated to determine HER2 gene status as a standardised method. But during the interpretation of FISH, the result may be critical in tumours with chromosome 17 polysomy defined as increased copy number of chromosome enumeration prob (CEP>2,5). The purpose of our study was to highlight the clinocopathologics significant of chromosome 17 polysomy.
Methods: This is a retrospective analysis of a large series of 203 cases of primary invasive breast carcinomas with equivocal HER2 IHC staining (IHC HER2 2+) whom her-2 fluorescence in situ results and clinicopathological data were available from 2012 to 2018 at the Department of Pathology of Hassan II University Hospital of Fes, in which we identify 15 cases of chromosome 17 polysomy.
Results: As results, among 203 cases of invasive breast carcinoma analysed by FISH, 20% of the cases showed HER-2 gene amplification. A total of 15 (7,5%) cases showed the presence of polysomy 17. Absence of polysomy 17 was seen in the remaining 188 cases. The two groups polysomy and non polysomy 17 were classified according to the HER2 gene amplification status. Among 15 cases, 11 (73,3%) were HER-2 non-amplified, 4 (25,7%) were HER-2 amplified. Among 188 non polysomy cases, 152 (80%) were HER-2 non amplified, 36 (20%) were HER-2 amplified. Polysomy 17 showed a significant association with poor pathological parameters including low age (under 50ans p=0,06), low mitotic score (p=0,05), high nuclear ploemorphism score (p=0,03) high histological grade (p=0,03), presence of node metastasis (p=0,04), not otherwise specified histological type (p=0,009). Showed more often in positive hormone receptors status and high KI-67 proliferation index. Similarly, in HER-2 non amplified gene, polysomy 17 showed an association with almost the same aggressive histological variable.
Conclusion: In our study, we identified 7,35% cases of polysomy 17. We revealed that the polysomy 17 can serve as a poor prognostic marker in invasive breast cancer. We also highlight the prognostic value of polysomy 17 in luminalB/HER-2 negative.

OFP-04-014

The impact of standardised structured reporting of pathology reports for breast cancer in the Netherlands

A. Snoek[1], N. Hugen[1], L. Overbeek[2], I. Nagtegaal[1]
[1] Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands, [2] PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands, Houten, The Netherlands

Background & Objectives: With the increasing complexity of modern oncological patient management and the growing amount of information needed from the pathologist, traditional narrative reports (NRs) do not suffice. Both completeness and readability are shown to increase with standardised synoptic reporting (SSR). In the Netherlands SSR for breast cancer was introduced in 2009. We explored the impact of this introduction on completeness of reporting, individual patient treatment and outcome.
Methods: Using the Netherlands Cancer Registry and national pathology archive , a retrospective, population based cohort study was conducted. Data of breast cancer resections from 2007-2014 were collected to compare NR and SSR for all outcome measures.
Results: 76,796 cases were included of which 26,671 (34.7%) reports were SSR. Overall completeness was higher for SR than for NR (93.6% versus 90.1%). SR were significantly more complete for most individual parameters, except for histological type, pT and lymph node count, where SR and NR were equal. Of the HER2-positive patients with SR, 69.2% received anti-HER2 targeted therapy compared to 58.7% HER2-postive patients with NR. Patients with an incomplete pathology report had a higher crude probability of death, which remained significant for patients with a NR after adjustment for patient and tumour characteristics (HR: 1.24 (95%CI 1.03-1.51)).
Conclusion: In this large nationwide cohort of breast cancer resections, we demonstrate that SR are more complete than NR. More complete pathology reports are expected to improve communication between specialists regarding parameters important for adjuvant breast cancer

treatment decisions, subsequently improving breast cancer care and patient outcomes.

OFP-04-015

Correlation between primary tumour and axillary lymph node response to neoadjuvant chemotherapy in breast cancer patients

G. Kir[1], Z.C. Olgun[1], I.N. Okten[2], H. Ankarali[3], R.B. Girgin[1], M.K. Melemez[4], O. Alimoglu[5]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, Department of Oncology, Turkey, [3] Istanbul Medeniyet University, Department of Statistics, Turkey, [4] Istanbul Medeniyet University, Turkey, [5] Istanbul Medeniyet University, Department of General Surgery, Turkey

Background & Objectives: There can be inconsistencies between primary tumour and axillary lymph node response to neoadjuvant chemotherapy (NAC) in breast cancer patients. The aim of this study is to evaluate this correlation.
Methods: A retrospective study was carried out in 114 node-positive breast cancer patients, who had axillary dissection, from 2 centers between 2009-2019 who treated with NAC before surgery. Tumour response was evaluated pathologically as complete response(CR)/partial response(PR)/without response(WR) by using Sataloff et. all, 1995 for primary tumour and axilla seperately.
Results: Seventy-eight patients (69%) had statistically significant consistency between NAC responses of primary tumour and axilla(p:0,0001, kappa coefficent: 0.509). We had one patient with major inconsistency between NAC responses (CR at primary tumour and WR at axilla). After 19 months follow up she was devoid of disease. Multivariate cox regression analysis revealed that CR and PR were independent predictors of disease free survival(DFS). (Primary tumour CR - CI:0.007-0.402, p:0.005; Primary tumour PR – CI:0.059-0.352, p: 0.000; Axilla CR - CI:0.012-0.654 p:0.018; Axilla PR - CI:0.073-0.529 p:0.001). There were no significant differences between CR and PR for both primary tumour and axilla regarding DFS (CI:0.342-21.893, p:0.343; CI:0.263-19.315, p:0.458 respectively). Due to small number of mortality we couldn't reach statistical significance for overall survival.
Conclusion: We observed significant correlation between NAC responses of primary tumour and axilla. Both CR and PR of primary tumour and axilla were independent predictors of DFS.

Monday, 9 September 2019, 17:15 - 19:15, Apollon
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OFP-05-001

Tumour-intrinsic mechanisms drive the immune contexture in pancreatic cancer

H. Sadozai[1], M. Wartenberg[1], T. Gruber[1,2], M. Schenk[1], I. Zlobec[3], J. Brugger[1], B. Gloor[4], E. Vassella[1], A. Perren[1], E. Karamitopoulou[1]
[1] Institute of Pathology, University of Bern, Switzerland, [2] Graduate School for Cellular and Biomedical Sciences, University of Bern, Switzerland, [3] University of Bern, Switzerland, [4] Department of Visceral Surgery and Medicine, Inselspital University Hospital Bern and University of Bern, Switzerland

Background & Objectives: The biological mechanisms underlying the immune profiles of pancreatic ductal adenocarcinoma (PDAC) are poorly understood and warrant further investigation as they can unveil novel treatment strategies. We compared the immune, genetic and morphologic characteristics of three survival-stratified PDAC-cohorts to identify survival-associated profiles.
Methods: PDAC-tissue from long-term- (LTS, n=30, overall survival (OS) >60 months); mid-term- (MTS, n=30, OS:12-60 months) and short-term survivors (STS, n=40, OS:3-12 months) was analysed by immunohistochemistry on tissue microarrays for immune cell populations and signaling molecules. Intratumoural cytokine-profiles were assessed by mRNA *in situ* hybridization. Further, we performed next generation sequencing for "hotspot" mutations in oncogenes and tumour suppressor genes. Clinicopathologic features, including tumour budding were integrated.
Results: LTSs exhibit low mutational frequency in the main genetic drivers *CDKN2A*and *SMAD4*, a T lymphocyte enriched microenvironment including an expanded number of $CD4^{+}$T cells, a Th1 tilted cytokine-profile, high MHC class I along with low pSTAT3 levels and low-grade tumour budding. Conversely, STSs display a high mutational frequency in all known PDAC key genetic drivers (*KRAS*, *TP53*, *CDKN2A*and *SMAD4*) and an immunosuppressive microenvironment rich inTregs and M2-polarized macrophages with fewer effector T cells. They also display a Th2 skewed cytokine-profile, low MHC class I along with high pSTAT3 levels and high-grade tumour budding. Finally, MTSs exhibit high mutational frequency in non-key driver genes and immune–rich tumours but a largely Th2 skewed cytokine-signature.
Conclusion: Within each PDAC-subgroup different mechanisms shift the balance between tumour-intrinsic signaling and anti-tumour immune activity with impact on morphology and clinical features of these tumours.

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OFP-05-002

A gene expression signature of microvascular invasion in hepatocellular carcinoma in formalin fixed-paraffin embedded biopisies

A. Beaufrère[1,2], S. Caruso[3], G. Couchy[3], J. Zucman-Rossi[4], N. Potè[5,6], V. Paradis[1,2]
[1] Pathology Department, Beaujon University Hospital, AP-HP, Clichy, France, [2] INSERM U1149, Beaujon University Hospital, Clichy, France, [3] INSERM UMR 1162, Gènomique Fonctionnelle des Tumeurs Solides, Paris, France, [4] INSERM, UMR 1162, Gènomique Fonctionnelle des Tumeurs Solides, Institut Universitaire d'Hèmatologie, Paris, France, [5] Department of Pathology, Hôpital Bichat AP-HP, France, [6] INSERM UMR 1149, Centre de recherche sur l'inflammation, Paris, France

Background & Objectives: The presence of microvascular invasion (mVI) is a major risk factor of tumour recurrence after surgery and mortality in hepatocellular carcinoma (HCC). mVI is only detectable by microscopic examination of the surgical specimen. The goal of our study was to define a gene expression signature associated with mVI in HCC, applicable on formalin fixed-paraffin embedded (FFPE) biopsies using a Nanostring approach.
Methods: A total of 108 FFPE archived HCC samples were included, of which 69 preoperative biopsies were available with a paired surgical specimen. Total mRNAs were extracted from samples. Gene expression was assessed using Nanostring technology. In a training set of 69 HCC samples (39 surgical samples and 30 biopsies), we defined a gene expression signature associated with mVI based on expression of 200 genes. This mVI signature was validated in an independent set of 39 biopsies.
Results: Training and validation sets were similar for all clinicopathological criteria particularly on mVI (52% vs 67%, p=0.14). A 10 gene-signature, strongly associated with mVI, was obtained in the training set. In the validation set, this signature predicted mVI with an accuracy of 82%. The sensitivity and the specificity were respectively of 0.92 and 0.62. Of note, there was an excellent correlation of gene expression between biopsies and corresponding surgical samples (14 paired specimens, mean correlation index = 0.92 [0.87-0.95]).

Conclusion: This study provides a relevant surrogate signature of mVI in HCC, that may be applied in clinical practice on routine tumour biopsy, and then integrated into the therapeutic strategy of patients.

OFP-05-003

Imaging mass spectrometry to differentiate between pancreatic adenocarcinoma and cholangiocarcinoma

C. Bollwein[1], A. Jacob[1], J. Pereira Lopes Goncalves[1], S. Deininger[2], K. Schwamborn[1], W. Weichert[1]
[1] Technical University of Munich, School of Medicine, Institute of Pathology, Germany, [2] Bruker Daltonik GmbH, Bremen, Germany

Background & Objectives: Both pancreatic adenocarcinoma and cholangiocarcinoma originate from epithelial cells of the pancreatico-biliary system. The histomorphological similarities between both carcinomas represent a challenge in pathological diagnostic. Imaging mass spectrometry (IMS) allows the visualization of protein/peptide expression profiles in a spatially resolved manner and enables direct correlation with histological features, thus offering an unbiased approach for tissue classification.
Methods: Tissue microarrays comprising samples from pancreatic adenocarcinoma (n=107) and cholangiocarcinoma (n=122) were subjected to on-tissue tryptic digestion and incubated in a humid environment followed by matrix application (alpha-cyano-4-hydroxycinnamic acid) using an automated sprayer. Samples were analysed utilizing a Bruker RapifleX MALDI-TOF mass spectrometer. Subsequently, matrix was removed, sections were stained by hematoxylin and eosin and scanned using the Aperio slide scanner for histopathological annotation. Data analysis was performed by using the SCiLs Lab and FlexImaging 5.0 software.
Results: For statistical analysis the sample set was divided into a training (60% of samples), a validation (20% of samples), and a test set (20% of samples). In the test set, 21 out of 22 pancreatic adenocarcinoma samples and 23 out of 27 cholangiocarcinoma samples could be classified correctly.
Conclusion: IMS could reliably differentiate between pancreatic adenocarcinoma and cholangiocarcinoma. Thus, this technology might offer an alternative way to aid in everyday pathology practice.

OFP-05-004

Transarterial chemoembolisation enhances programmed death-1 and programmed death ligand-1 expression in hepatocellular carcinoma

A. Montasser[1,2], A. Beaufrère[1,3], F. Cauchy[4], O. Soubrane[4], N. Colnot[1], S. Tessiore[1], M. Albuquerque[1,3], V. Paradis[1,3]
[1] Pathology Department, Beaujon University Hospital, AP-HP, Clichy, France, [2] Pathology Department, Theodor Bilharz Research Institute, Giza, Egypt, [3] INSERM U1149, Beaujon University Hospital, Clichy, France, [4] Department of HPB and Pancreatic Surgery, Beaujon University Hospital, AP-HP, Clichy, France

Background & Objectives: Over 70% of Hepatocellular Carcinomas (HCCs) are diagnosed at advanced stage and are candidates to locoregional treatment and/or Sorafenib therapy with low response rate, short overall survival and high cost. With the introduction of immune checkpoint inhibitors as modalities of cancer treatment, we aim to evaluate the potential of transarterial chemoembolization (TACE) to induce immune profile changes in HCC.
Methods: A total of 73 surgically-resected HCCs with (23) and without (50) preoperative TACE were included in the study. The immunohistochemical expression of PD-1 and PDL-1 was assessed in both groups in relation to clinical features, status of non-tumoural liver, morphologic characteristics of the tumour, mismatch repair status, and digitally computed tumour/stroma ratio. Biopsies realized before TACE were similarly analysed. Data of follow-up of patients for recurrence and cancer-related events were retrieved from patients' archives.
Results: HCCs pre-operatively treated with TACE showed significantly higher PDL-1 expression by tumour cells than those with no prior TACE (2% vs 0.36%, P <0.001). Expression of PD-1 and PDL-1 by inflammatory cells was significantly higher in resected tumours than in corresponding biopsies obtained before TACE (9.1% vs 1.4% and 9.5% vs 1.8% respectively, P < 0.001).
Conclusion: Treatment by TACE seems to induce an increase in PD-1 and PDL-1 expression in HCC. This may induce better response to immune checkpoint inhibitors which could be considered as a line of treatment in these patients.

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OFP-05-005

Vessels encapsulating tumour clusters (VETC) is a powerful predictor of aggressive hepatocellular carcinoma (HCC)

S. Renne[1], H.Y. Woo[2], N. Rudini[3], S. Allegra[3], H. Yano[4], M. Donadon[5], L. Viganò[5], J. Akiba[6], H. Sun Lee[7], H. Rhee[8], Y.N. Park[2], M. Roncalli[3,9], L. Di Tomaso[3,9]
[1] Humanitas Clinical and Research Center - IRCCS, Italy, [2] Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea, [3] Department of Pathology, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy, [4] Department of Pathology, Kurume University School of Medicine, Japan, [5] Department of Hepatobiliary Surgery, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy, [6] Department of Diagnostic Pathology, Kurume University Hospital, Japan, [7] Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Republic of Korea, [8] Department of Radiology, Yonsei University College of Medicine, Seoul, Republic of Korea, [9] Department of Biomedical Sciences, Humanitas University, Rozzano, Italy

Background & Objectives: A vascularization pattern named VETC was recently described to be related to rapid tumour dissemination and high recurrence rates. Our aim was to evaluate VETC against consolidated and novel prognostic markers on a large series of surgically resected HCC with various etiologies from different geographic areas.
Methods: VETC was assessed in a large multi-institutional cohort of 544 resected HCC cases from Italy, Korea and Japan, and matched against a full spectrum of clinical and pathological variables. VETC, documented using CD34 immunostaining, was easily reproducible and reliably detectable in whole sections and small sized tissues of TMA.
Results: VETC-HCC were detected in 18.9% of the cases. VETC was significantly associated to several clinical and pathological features such as: AFP level, tumour size >5 cm, Edmonson grade, macrotrabecular pattern, compact pattern, inflammatory infiltrates, and microvascular invasion. VETC was associated with early recurrence [HR: 1.52 (1.06-2.19), p= 0.023], worse OS [HR: 2.26 (1.37-3.72), p= 0.001] and DFS [HR: 1.66 (1.21-2.27), p= 0.002] at multivariable analysis. VETC impacted on survival in patients stratified for etiology (HCV/HBV), vascular invasion and specific molecular phenotypes (β-catenin/GS+). This peculiar vascular pattern was enriched in the recently reported macro-trabecular massive HCC subtype, which was seen in 7.9% (43/544) and associated with high AFP levels, poor tumour differentiations.
Conclusion: VETC pattern was easily detectable in a consistent fraction of HCC and was a powerful pathological finding impacting on survival. The study of this pattern promises to be a new tool to further accommodate HCC therapy to the intrinsic tumour biology.

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OFP-05-006

Intraductal papillary neoplasm of the bile duct: clinicopathological characteristics and insulin-like growth factor II mRNA binding protein 3 (IMP3) expression in 24 cases

E. Buyuktalanci[1], A. Damirli[2], F. Tekin[3], A. Uğuz[4], îV. Unalp[4], M. Zeytunlu[4], D. Nart[1], G. Ersoz[3], O. Ozutemiz[3], F. Yılmaz[1]

[1] Ege University Faculty of Medicine Department of Pathology, Turkey, [2] Azerbaijan Republic Ministry of Health Unification Forensic Medical Expertise and Pathological Anatomy, Azerbaijan, [3] Ege University Faculty of Medicine Department of Gastroenterology, Turkey, [4] Ege University Faculty of Medicine Department of General Surgery, Turkey

Background & Objectives: Intraductal papillary neoplasm of the bile duct (IPNB) is rare but is one of the precursors of cholangiocarcinoma (CC). The oncofetal protein IMP3, is proposed as a marker for high-grade dysplasia in the biliary tract. In this study the clinicopathologic characteristics and IMP3 expression of IPNB are analysed.
Methods: Clinicopathologic data of 24 IPNB cases operated between 2000 and 2018 were retrospectively analysed. Immunohistochemical staining for IMP3 antibody was performed. Statistical analyses were made using SPSS.
Results: There were 15 female and 9 male patients with a mean age of 58 (44-76, range). Tumour locations were: intrahepatic (41.7%), hilar (20.8%) and extrahepatic (37.5%). The mean tumour size was 4.42 cm (1.5-12, range). Epithelial subtypes were pancreatobiliary (83.4%), intestinal (8.3%) and mixt (8.3%). The degree of dysplasia was low (12.5%), intermediate (8.3%) and high (75%). Of the 24 cases, 5 were non-invasive, 4 were focally invasive (FI) and 15 were invasive (20.8%, 16.6% and 62.5%, respectively). Perineural invasion (PI) was detected in 20.8%, vascular invasion in 37.5% and lymph node metastasis (LNM) in 16.7% of the cases. IMP3 was expressed in 20%, 50% and 100% of non-invasive, FI and invasive tumours, respectively. Invasive tumours had significantly higher IMP3 expression than non-invasive or FI tumours (p: 0.017). Presence of PI and LNM were significantly correlated with overall survival (p:0.01 and p:0.000, respectively) regardless of the location of the tumour and IMP3 status.
Conclusion: Our data confirms the importance of IMP3 as a marker for invasion but not as a prognostic determinant.

OFP-05-007

SMAD4 deficient pancreatic adenocarcinoma are poor prognosis tumours associated with histopathological aggressive features

T. Fenouil[1], C. Caligaris[2], A. Bertrand[2], S. Santis[2], L. Bartholin[2], V. Hervieu[1]

[1] Hospices Civils de Lyon, France, [2] Centre de Recherche en Cancerologie de Lyon, France

Background & Objectives: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer characterised by incidence/death ratio close to 1. Besides it is expected to become the second cause of death by cancer in 2030. The major steps of PDAC carcinogenesis are the activation of KRAS oncogene followed by inactivation of tumour suppressor genes. Loss of SMAD4 occurs in approximately 60% of tumours as a late event in carcinogenesis. A certain number of studies try to assess the prognostic role of SMAD4 loss using immunohistochemistry in order to better stratify patients, without reproducible results. This study aim to confirm the reduction of overall survival (OS) in SMAD4 deficient tumours and better characterise their histopathological features.
Methods: This bicentric, retrospective study is based on a cohort of 424 PDAC diagnosed between 2004 and 2017, in Hospice Civils de Lyon. All the slides were reviewed by two pathologist, including one expert, blindfold to independently retrieved survival data. SMAD4 status was assess based on immunohistochemistry (Ventana UltraBench, clone SP306).
Results: Patients with SMAD4 deficient tumour have a worse prognosis with decreased OS compared to those with SMAD4 expressing tumours (respectively 1208 days vs 1559 days, $p < 0.05$). Moreover we found that SMAD4 deficient tumours present more often perineural invasion ($p< 0.01$), necrosis ($p < 0.05$), higher N status ($p < 0.05$) and higher invaded nodes ratio ($p < 0.01$).
Conclusion: Here we report histopathological characterization of SMAD4 deficient tumours. We also confirm the worse prognosis of these tumours and their association with necrosis, lymph node and perineural invasion.

OFP-05-008

Quantitative analysis of tumour budding and subcellular localisation of E-cadherin on a cohort of periampullary carcinomas - a machine learning approach

E. Kocsmar[1], G. Lotz[1], A. Kiss[2], M. Hoerner[3], E. Petrova[4], S. Timme[3], A. Csanadi[3], M. Werner[5,6,7], U. Wellner[4], P. Bronsert[5,6,7]

[1] 2nd Department of Pathology, Faculty of Medicine, Semmelweis University, Hungary, [2] 2nd Department of Pathology, Semmelweis University, Hungary, [3] Institute of Surgical Pathology, University Medical Center Freiburg, Germany, [4] Department of Surgery, UKSH Campus Lübeck, Germany, [5] Department of Surgical Pathology, University of Freiburg, Faculty of Medicine, Germany, [6] German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Germany, [7] Tumourbank Comprehensive Cancer Center, University of Freiburg, Faculty of Medicine, Germany

Background & Objectives: Tumour budding and the closely related epithelial mesenchymal transition (EMT) have prognostic impact on overall survival. However, precisely quantified evaluations of correlation between tumour cell cluster (TCC) size, EMT and prognosis are still missing. Our aim was to classify the periampullary carcinomas (PC) into groups according to their budding behavior and EMT signature and use machine learning approaches to predict patients' outcome.
Methods: PC samples of 172 patients were stained with E-cadherin immunohistochemistry. Cell number and EMT features of invasion front TCCs were evaluated by assessing fractions of cells with different subcellular localization of E-cadherin (membranous, cytoplasmic, mixed). Elastic net penalized feature selection was performed on 5 cell intervals of TCC sizes and relating cell fractions with membranous, cytoplasmic or mixed E-cadherin expression. Prognostic significance of the defined budding categories were entered into subsequent Cox regression model with standard clinicopathological parameters.
Results: Overall median of TCCs/tumour was 42 (range: 3-283) and TCC size was 16 cells (range: 2-36 cells). Number of TCCs in a given interval inversely correlated with their size ($p<0.001$). Feature selection identified 6-10 cell and 31-35 cell TCCs as having prognostic value, moreover, the cytoplasmic E-cadherin expression in TCCs of 10-15 and 26-30 cells. In multivariate model, budding category was an independent prognostic factor ($p<0.001$).
Conclusion: Machine learning-based detailed quantitative analysis of invasion front TCCs demonstrated that not only tumourbuds (<5 cells) but also bigger TCCs have strong prognostic impact in the periampullary carcinomas, contributing to establishing a more advanced grading system.

OFP-05-009

Expression of GRP78 protein is increased in pancreatic ductal adenocarcinoma, pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm

X. Ding[1], B. Trac[1], X. Duan[1]
[1] Loyola University Medical Center, USA

Background & Objectives: The poor prognosis of pancreatic ductal adenocarcinoma (PDAC) is associated with late detection, aggressive tumour biology and chemotherapeutic resistance. According to the Response Evaluation Criteria in Solid Tumours (RECIST), for pancreatic cancer patients treated palliatively with gemcitabine and nab-paclitaxel, no complete responses were observed, and partial response was only observed in 37% of patients, and progressive disease in 22% of patients. GRP78 is a major endoplasmic reticulum (ER) chaperone protein critical for protein quality control of ER, It is found that GRP78 is preferably required for cancer cell survival, promotes tumour progression and enhances drug resistance. The study aims to explore whether the expression of GRP78 protein in PDAC, pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) is increased compared to the normal pancreatic ducts using immunohistochemical (IHC) staining method.
Methods: The expression of GRP78 were assessed using IHC in 45 cases of formalin-fixed paraffin-embedded tissues, in which normal ducts (38), high grade PanIN (PanIN-HG, 16), low grade PanIN (PanIN-LG, 14), low grade IPMN (IPMN-LG, 26), high grade IPMN (IPMN-HG, 9), and PDAC (20) were examined. Immunostaining intensity of GRP78 protein was categorized as no or weak staining (0-1+) and strong staining (2-3+). Fisher's exact test with two tails was performed using the GraphPad statistical software.
Results: GRP78 expression was identified in cytoplasm of normal pancreatic ducts, IPMN and PDCA with a fine granular pattern. All PDAC, PanIN-HG and IPMN-HG show strong expression of GRP78 while the normal ductal cells show only minimal expression of GRP78. 73% of IPMN-LG and 30% PanIN-LG expresses GRP78 strongly. Statistical analysis revealed significant difference in GRP78 expression level between normal ductal cells and all five pathological conditions including PDCA, PanIN-HG, PanIN-LG, IPMN-HG and IPMN-LG (all p<0.0001).

	Normal ducts	IPMN-LG	IPMN-HG	PanIN-LG	PanIN-HG	PDAC
Total	38	26	9	14	16	20
No or weak staining (0-1+)	37	7	0	10	0	0
Strong staining (2-3+)	1	19	9	4	16	20
% of strong staining	**3%**	**73%**	**100%**	**30%**	**100%**	**100%**

Conclusion: This study shows that the expression level of GRP78 is significantly increased in PDAC, PanIN and IPMN compared to the normal ductal cells. It appears that there is a progressive increase in GRP78 expression from IPMN-LG and PanIN-LG to IPMN-HG and PanIN-HG, and to PDAC. Increased GRP78 expression may contribute poor responsiveness of PDCA to conventional chemotherapy.

OFP-05-010

Prognostic value of desmoplastic stroma in intra-hepatic cholangiocarcinoma

N. Guedj[1], L. Blaise[1], F. Cauchy[2], A. Beaufrère[1], M. Albuquerque[3,4], O. Soubrane[2], M. Ronot[1], V. Paradis[3,4]
[1] Hopital Beaujon, France, [2] Department of HPB and Pancreatic Surgery, Beaujon University Hospital, AP-HP, Clichy, France, [3] Pathology Department, Beaujon University Hospital, AP-HP, Clichy, France, [4] INSERM U1149, Beaujon University Hospital, Clichy, France

Background & Objectives: Intrahepatic cholangiocarcinomas (ICC) are primary tumours of the liver characterised by the presence of a desmoplastic stroma. Its prognostic role is still an open question. In malignancies, tumour stroma may be benefit, acting as a barrier against cancer diffusion or pejorative, by supporting the tumoural cells. The aim of the present study was to evaluate the prognostic value of stromal compartment in ICC through a multiparametric morphological analysis.
Methods: Forty-nine patients (61 years) with ICC surgically resected were included. For all cases, tumour paraffin blocks of ICC were selected. Stromal area and Cancer-Associated Fibroblats (CAF) number, were automatically quantified on Sirius red staining and alpha smooth muscle actin expression, respectively. Activated stroma index (ASI) was calculated as the ratio of CAF number and stromal area. Collagen fiber reticulation properties were analysed using second harmonic generation imaging.
Results: High stromal area was inversely correlated with vascular invasion (62.5% vs 95.7%, p=0.006) and positively correlated with well differentiated tumours (60% vs 12.5%, p=0.001). Patients with high stromal area had a better disease free survival (DFS) than patients with low stromal area (60 % vs 10 %, p=0.077). Low ASI was correlated with a better DFS (60% vs 10%, p=0.05). High collagen reticulation index was correlated with a worsened overall survival (42% vs NR, p=0.026).
Conclusion: Desmoplastic stroma seems to exert protective effect in patients with ICC. Stromal collagen reticulation may provide additional clinically relevant information in malignancies.

OFP-05-011

MSI in intestinal immunophenotype in ampullary and pancreatic cancer

G. Setdikova[1], E. Eremeeva[1], O. Paklina[1], D. Rotin[1,2]
[1] Botkin Clinical Hospital, Russia [2] Hospital Haim Sheba, Tel-ha-Shomer, Ramat Gan, Israel

Background & Objectives: Dual IHC pattern (intestinal and pancreatic) is usual in ampullary carcinoma (AC) and pancreatic ductal adenocarcinoma (PDA). They report that Microsatellite instability (MSI) occurs more frequently in AC than in PDA.
The aim is to estimate the frequency of MSI microsatellite instability and to compare obtained data in intestinal IHC pattern of AC and PDA.
Methods: 60 cases with intestinal IHC pattern (CK20 +, Muc 2 +) - 30 of AC and 30 of PDA) were evaluated. The determination of mismatch repair deficiency was identified by means of 4 IHC antibodies panel including the markers MLH-1, PMS2, MSH2, MSH6.
Results: MSI in AC group was found in 57% (17/30) of cases. The majority of cases (12/17) (71%) demonstrated the deficiency of the PMS2 of mismatch repair protein. The combinations of MLH1/PMS2 and MSH2/MSH6 occurred in 2/17 and 3/17, respectively. In PDA group MSI was determined only in 2/30 (7 %) cases (MLH1/PMS2). In all 60 cases, there was no history of familial disease neither signs of synchronous/metachronous tumours of other locations. No statistically significant association between the presence of MMR in AC and pathological pattern of the tumour.
Conclusion: The study showed that MSI is common in AC with intestinal phenotype. The prognostic, predictive and diagnostic role of that phenomena needs further investigations.

OFP-05-012

PTEN protein expression in pancreatic ductal adenocarcinoma: relevance for tumour biology and relationships to AKT and TGF-beta pathways proteins

A. Handra-Luca[1]
[1] APHP University Paris Nord, France

Background & Objectives: PTEN is considered a tumour suppressor of the AKT/mTOR pathway. Animal model studies have shown that loss of

PTEN function is involved in the progression of pancreatic cancer. K-RAS signaling, by interfering with TGF-beta and PTEN (Chow et al, 2007) may result in a switch mechanism from growth suppression to growth promotion in pancreatic cancers.
We aimed to study the relevance of PTEN expression in pancreatic adenocarcinomas (PDAC).
Methods: We examined immunohistochemical expression of PTEN protein in a series of 99 PDAC treated by surgery (without neoadjuvant treatment). Protein expression patterns were analysed with regard to tumour features and to AKT and TGFbeta pathway protein expression (mTOR and SMAD4, respectively).
Results: PTEN was expressed in 54 PDACs in a nuclear pattern and in 12 tumours in a cytoplasmic pattern. Nuclear PTEN was higher in T2 PDACs as compared to T1 PDACs (as well as mTOR) and was decreased in T3 PDACs as compared to T2 PDACs (as well as mTOR and SMAD4) ($p<0.05$ for all comparisons). Nuclear PTEN correlated to cytoplasmic mTOR and to nuclear SMAD4 ($p<0.01$).
Conclusion: The results of our study indicate a complex role for PTEN in pancreatic carcinogenesis, possibly at the step of extrapancreatic tumour invasion. The relationship between PTEN and SMAD4 only with regard to extrapancreatic T3 stage tumours (and not with T1 stage tumours) may explain a stage-specific interaction and role.

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Monday, 9 September 2019, 17:15 - 19:15, Hermès
OFP-06 | Joint Session: Endocrine Pathology / Head and Neck Pathology

OFP-06-001
IgG4 thyroiditis: similarity to and differences from IgG4-related disease
K. Kakudo[1], K. Inomata[2], Y. Li[3]
[1] Department of Pathology, Kindai University Nara Hospital, Japan, [2] Department of Clinical and Laboratory Medicine, Yamashita Thyroid Hospital, Japan, [3] Department of Pathology, Shandong Provincial Hospital, China

Background & Objectives: IgG4-related disease (RD) is clinically characterised by tumour-like enlargement of affected organs, increased serum IgG4 levels and the alleviation of symptoms after steroid therapy. Pathologically, it is characterised by lymphoplasmacytic infiltration, sclerosis and an increased number of IgG4-positive plasma cells. In 2009, our group first reported the infiltration of IgG4-positive plasma cells in a subset of Hashimoto's thyroiditis (HT). HT can be divided into IgG4 thyroiditis (aggresive subtype) and non-IgG4 thyroiditis (good prognosis group).
Methods: A total of 120 cases of HT from 5 Asian hospitals were retrospectively collected. Quantitative assessment of IgG4 staining was performed on 120 surgically treated thyroid glands with HT. The clinical data, including demographic information, clinical, laboratory and sonographic findings, medical history, treatments, and disease outcomes, were obtained from the referral forms submitted at the time of the operation and patients' medical records.
Results: The 120 cases were divided into 33 (27.5%) IgG4 thyroiditis cases and 87 (72.5%) non-IgG4 thyroiditis cases using cutoff points (20 IgG4-positive plasma cells per high-power microscopic field and IgG4/IgG ratio of 30%) proposed by our group. The following parameters were significantly different between IgG4 thyroiditis and non-IgG4 thyroiditis; age at surgery (52.3 vs 58.1 years old), male to female ratio (25.9 vs 5.4%), serum IgG4 level (263.7 vs 80.9 mg/dL) and subclinical hypothyroid status (45.5 vs 12.0%).
Conclusion: IgG4 thyroiditis is a destructive fibro-inflammatory lesion and has a higher risk for hypothyroid status. Systemic involvement was not found in our IgG4 thyroiditis cases. Recently, Inomata et al. reported that the target antigens of IgG4 thyroiditis are thyroglobulin and its isoforms. As thyroglobulin is an organ-specific protein, this observation is consistent with the solitary nature of IgG4 thyroiditis.

OFP-06-002
Is preoperative RAS or BRAF K601E mutations cytologic detection useful for clinical management of indeterminate thyroid nodules, according to the new WHO classification?
L. Ravella[1], J. Lopez[2,3], F. Descotes[4], J. Giai[5,6], V. Lapras[7], M. Denier[7], F. Borson-Chazot[8], J. Lifante[9], M. Decaussin-Petrucci[10]
[1] Pathology Department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bènite, France, [2] Biochemistry and Molecular Biology Department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bènite, France, [3] Cancer Research Center of Lyon, Team EMT and cancer cell plasticity, Lyon 1 University, France, [4] Department of Biochemistry, Molecular Biology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Benite, France, [5] CNRS, UMR 5558, Laboratoire de Biomètrie et Biologie Evolutive, Equipe Biostatistique-Santè, Villeurbanne, France ; Universitè Lyon 1, Villeurbanne, France, [6] Hospices Civils de Lyon, Service de Biostatistique et Bioinformatique, France, [7] Radiology Department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bènite, France, [8] Endocrinology Department, Groupement hospitalier Est, Hospices Civils de Lyon, Bron, France, [9] Endocrine Surgery Department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bènite, France, [10] Department of Pathology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Universite Lyon 1, Pierre Benite, France

Background & Objectives: The diagnostic value of *RAS* and K601E *BRAF* mutations in fine-needle aspiration of thyroid indeterminate cytologic nodules is not well established. Our aim was to evaluate the histologic characteristics, the risk of malignancy associated with such mutations and their potential interest for preoperative clinical management of nodules.
Methods: We evaluated 69 indeterminate thyroid nodules with *RAS* or K601E *BRAF* mutations. All cytologic specimens were indeterminate according to the thyroid Bethesda System. Diagnosis of malignant, benign or indolent neoplasms was classified according to the 2017 WHO classification. Carcinoma, NIFTP (Non-Invasive Follicular Thyroid neoplasm with Papillary like features) and WDTUMP (well-differentiated tumour of uncertain malignant potential) were considered "surgical", as they require surgical excision. Adenoma was considered "non-surgical". The risk of malignancy and the risk of "surgical pathology" were evaluated.
Results: Pathologic evaluation of the 69 mutated nodules demonstrated benign, indolent and malignant histology in 17 cases (25%), 21 cases (30%) and 31 cases (45%) respectively. The risk of malignancy was 45%, and the risk of surgical pathology was 75%. The majority of carcinomas were follicular variant of PTC (Papillary Thyroid Carcinoma).
Conclusion: Preoperative *RAS* or *BRAF* K601E mutations detection in cytologic indeterminate thyroid nodules carries a high risk of surgical pathology, and may benefit from a surgical management. Most surgical lesions harboring those mutations are low risk follicular variant of PTC or NIFTP, which may be in favor of an initial lobectomy.

OFP-06-003
Risk stratification for pheocromocytoma and paraganglioma: a comparison of pathological scores for prediction of metastatic potential
F. Ambrosi[1], A. De Leo[2], M. Grillini[3], S. Selva[3], G. Zavatta[3], G. Di dalmazi[3], D. Santini[1], C. Ceccarelli[2]
[1] Pathology Unit, Sant'Orsola-Malpighi Hospital, University of Bologna, Italy, [2] Pathology Unit, Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Italy, [3] Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Italy

Background & Objectives: The Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) has been proposed for predicting the metastatic potential in pheochromocytoma and paraganglioma (PPGL) to overcome the limitations of the Pheochromocytoma of the Adrenal Scaled Score (PASS). The objective of the study was to compare PASS and GAPP scoring systems for risk assessment in a single-institution case series.
Methods: GAPP and PASS scores were assessed and compared in 50 consecutive PPGLs. Immunohistochemistry for SDHA/SDHB was performed for each case.
Results: Lymph-node metastasis occurred in 8% (4/50) of patients, with a mean follow-up of 40.7 months. According to GAPP score, 26% (13/50) of cases were well-differentiated, 62% (31/50) moderately-differentiated and 12% (6/50) poorly-differentiated. Based on GAPP score, all well-differentiated PPGLs were non-metastatic, while 2/31 (6.5%) moderately-differentiated and 2/6 (33.3%) poorly-differentiated PPGLs were metastatic. In contrast, PASS score ≥4 resulted in 66% of cases. Metastasis occurred in 1/17 (5.9%) PPGL with a PASS <4 and 3/33 (9.1%) PPGLs with a PASS ≥4. Therefore, GAPP scoring system significantly predicted metastasis (p=0.05), in contrast to PASS (p=0.82). The metastatic disease didn't correlate with ki-67 index and mitotic activity. Loss of SDHB resulted in 10.6% (5/47) PPGLs: four cases moderately-differentiated and one poorly-differentiated with metastatic disease.
Conclusion: The GAPP scoring system is a valid tool to discriminate PPGLs with benign behavior and to predict the metastatic disease. However, other prognostic criteria are required in order to assess the metastatic potential in moderately-differentiated PPGL group, and GAPP should be integrated into a multidisciplinary approach for better management of patients.

OFP-06-004

Does the site of the origin of the microcarcinoma within the thyroid matter? A multicenter pathologic and clinical study for risk stratification

A. De Leo[1], A. Repaci[2], M.L. Bacchi Reggiani[3], D. De Biase[4], D. Di Nanni[5], C. Di Gioia[6], G. Grani[7], E. Solaroli[8], C. Durante[7], S. Filetti[7], G. Tallini[9]
[1] Pathology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Italy, [2] Endocrinology Unit, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi Hospital, Italy, [3] Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Italy, [4] Department of Pharmacy and Biotechnology (Dipartimento di Farmacia e Biotecnologie) - Molecular Diagnostic Unit, Azienda USL di Bologna, University of Bologna, Italy, [5] Pathology Unit, S. Orsola-Malpighi Hospital, University of Bologna, Italy, [6] Department of Radiological, Oncological and Pathological Sciences, "Sapienza" University of Rome, Italy, [7] Department of Internal Medicine and Medical Specialties, "Sapienza" University of Rome, Italy, [8] Endocrinology Unit, Ospedale Maggiore, Bologna, Italy, [9] Department of Medicine (Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale) - Molecular Diagnostic Unit, Azienda USL di Bologna, University of Bologna School of Medicine, Italy

Background & Objectives: Risk stratification of papillary microcarcinoma (mPTC) is problematic. This study analyses the impact of the mPTC origin within the thyroid on clinicopathologic features.
Methods: A multicenter cohort of 298 mPTCs from six Italian medical institutions was analysed. The distance of the tumour centre from the thyroid capsule was measured micrometrically and correlated with clinicopathologic features and *BRAF*V600E.
Results: Four mPTC groups based on size and distance from the thyroid capsule were identified: Group A, subcapsular tumour <5 mm; Group B, capsular tumour (i.e. a tumour reaching the thyroid capsule) <5 mm; Group C, subcapsular tumour ≥5 mm; Group D, capsular tumour ≥5 mm. Univariate analysis demonstrated significant differences between the four groups, with Group D showing the most aggressive features and Group A the most indolent ones. Multivariate analysis correlated Group D tumours with (i) microscopic features: presence of psammoma bodies within the tumour, tall cell features, tumour fibrosis, with an inverse correlation to follicular growth pattern; (ii) characteristics of tumour growth: infiltrative border, unicentric tumour with intraglandular tumour spread, vascular invasion, psammoma bodies in the parenchyma surrounding the tumour; (iii) clinicopathologic features: tall cell or classic papillary carcinoma diagnoses, *BRAF*V600E mutation, lymph node metastases, ATA risk group, with an inverse correlation to nodular hyperplasia, to the presence other thyroid neoplasms, to a diagnosis of Papillary microtumour or to that of NIFTP.
Conclusion: Group D mPTCs have unfavourable features and likely endowed with the potential to progress to clinically relevant tumours. Group A mPTCs show bland features and likely have limited malignant potential.

OFP-06-005

Immunohistochemical evaluation of CXCR4 chemokine receptor expression in metastatic and nonmetastatic well-differentiated pancreatic neuroendocrine tumours

V. Delektorskaya[1], O. Solovieva[1], Y. Patyutko[1]
[1] N.N. Blokhin National Medical Research Center of Oncology, Russia

Background & Objectives: Pancreatic neuroendocrine tumours (PanNETs) are a heterogeneous group of neoplasms with unpredictable clinical course and biological behaviour. CXCR4 chemokine receptor overexpression is associated with tumour progression, invasion, angiogenesis, and metastasis in various types of tumour. Data on CXCR4 expression in pancreatic neuroendocrine neoplasms are limited. We aimed to assess the prevalence and prognostic significance of CXCR4 expression in both primary and metastatic PanNETs.
Methods: CXCR4 expression was evaluated by immunohistochemistry using the monoclonal rabbit anti-human CXCR4 antibody UMB-2 on a panel of 52 primary metastatic and nonmetastatic PanNETs and 20 liver metastases. The expression was correlated with clinicopathological data and prognosis.
Results: Membrane positivity for CXCR4 was detected in 17/52 primary PanNETs (32.7%, 12 metastatic and 5 nonmetastatic) and in 7/20 liver metastases (35.0%). CXCR4 was expressed with a high IRS in metastatic G3 tumours. CXCR4 expression was associated with higher WHO grade, Ki-67 index, and distant metastasis ($p < 0.001$). Furthermore, CXCR4 was positively related to loss of ATRX/DAXX nuclear expression and negatively PR and SSTR 2A staining patterns. However, no statistical differences were found between CXCR4 expression and PanNET prognosis.
Conclusion: The expression of CXCR4 is associated with tumour progression and frequently observed in more advanced and metastatic PanNETs. CXCR4 may represent a potential tissue-based biomarker of an aggressive phenotype among PanNETs.

OFP-06-006

Papillary thyroid carcinoma: phenotypical and molecular differentiation by microRNA profiling

F. Galuppini[1,2], M. Fassan[2], S. Barollo[3], N. Valeri[4], L. Cascione[5], M. Rugge[2], I. Merante Boschin[6], C. Mian[4], G. Pennelli[2]
[1] Women's & Children's Health Department (SDB), University of Padua, Italy, [2] Pathology Unit, Department of Medicine (DIMED), University of Padua, Italy, [3] Endocrinology Unit, Department of Medicine (DIMED), University of Padua, Italy, [4] Division of Molecular Pathology, The Institute of Cancer Research, London, United Kingdom, [5] Institute of Oncology Research, Università della Svizzera Italiana, Bellinzona,

Switzerland, [6] Departments of Surgical Oncologic and Gastroenterologic Sciences (DiSCOG), University of Padua, Italy

Background & Objectives: Papillary thyroid carcinoma (PTC) is a heterogeneous neoplasia, comprising several histological variants which are associated with specific mutational profiles and distinct clinical and prognostic features. To better characterise these particular subtypes of PTC, identify the microRNAs (miRNAs) expression profile represents an important step towards the comprehension of the molecular mechanism underlying their biological behaviour. The present study aims to widely investigate the miRNAs expression profile of PTCs cohorts with different morphology, molecular profile and biological behaviour, including Hobnail variant, BRAF p.K601E mutated PTCs and Classic variant samples.
Methods: Among 3,242 consecutive patients with histological diagnosis of PTC at University Hospital of Padua between 2008 and 2016, we selected a series of 35 formalin-fixed paraffin-embedded cases according to PTC variants and *BRAF* status (17 Hobnail-PTC, 9 p.K601E *BRAF*-mutated PTC and 9 Classic-PTC). Comprehensive miRNA expression profile of the series was assessed by microarray analysis with NanoString nCounter platform and selected miRNAs were validated by quantitative RT-PCR and *in situ* hybridization (ISH).
Results: MicroRNA profiling consistently disclosed histotype and mutation-specific signatures. In particular, three miRNAs (miR-21-5p, miR-146b-5p and miR-205-5p) were significantly overexpressed in the Hobnail variant in comparison to p.K601E *BRAF*-mutated and classic-type PTCs. The validation analysis (RT-PCR and ISH) confirmed these results.
Conclusion: The present study demonstrated that in PTCs specific histological variants and *BRAF* mutations are associated with different miRNA expression profiles. Further studies may investigate the downstream pathogenetic role of these miRNAs in thyroid neoplasms.

OFP-06-007

Genetic heterogeneity in adjacent normal mucosa of oral squamous cell carcinoma is a marker of poor prognosis

L. Morandi[1], A. Gabusi[2], D.B. Gissi[2], L. Montebugnoli[2], S. Asioli[1], A. Tarsitano[3], C. Marchetti[3], T. Balbi[4], M.P. Foschini[1]
[1] Department of Biomedical and Neuromotor Sciences, "M. Malpighi" Section of Anatomic Pathology at Bellaria Hospital, University of Bologna, Italy, [2] Department of Biomedical and Neuromotor Sciences, Section of Oral Sciences, University of Bologna, Italy, [3] Department of Biomedical and Neuromotor Sciences, Section of Maxillo-facial Surgery at Policlinico S. Orsola-Malpighi, University of Bologna, Italy, [4] Unit of Anatomic Pathology, S. Orsola Hospital, Bologna, Italy

Background & Objectives: Intra-tumoural heterogeneity (ITH) displayed by tumour cells represents a diagnostic challenge when assessing tumour mutational profile aimed to the delivery of effective targeted therapies. In Oral Squamous cell carcinoma (OSCC), ITH has been reported both in tumour cells and in related adjacent mucosa. The presence of genetic heterogeneity in the adjacent mucosa can be interpreted as evidence of the field cancerization phenomenon (field heterogeneity, FH). Aim of this study was to investigate the clinical impact of ITH and FH on loco regional control.
Methods: Ten OSCC patients who received radical surgery and staged T2-T4 (5 recurrent and 5 non-recurrent) were enrolled in this study. Multiple areas were sampled from the bulk of the tumour and the adjacent non-neoplastic mucosa. NGS mutational analysis of 10 OSCC driver genes were investigated and used to calculate ITH and FH among different area of the tumour.
Results: Mutational analysis highlighted that a single sample is often scarcely accurate in assessing genetic profiles of tumours. High values of ITH were found in both groups with a tendency to be higher in recurrent OSCC (p=0,095). Interestingly, the FH was found significantly lower in the non-recurrent OSCC group (p=0,032).
Conclusion: In agreement with the theory of field cancerization, FH correlates with higher risk of developing loco-regional recurrences and second primaries. In our series, local outcome of OSCC seems to be influenced by the biology of adjacent mucosa more than by the clonal architecture of the bulk of the tumour.

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OFP-06-008

Prognostic impact of DNA methylation analysis in adjacent area of surgically resected oral squamous cell carcinoma during follow up

L. Morandi[1], D.B. Gissi[2], R. Rossi[2], A. Tarsitano[3], A. Gabusi[2], L. Montebugnoli[2], C. Marchetti[3], M.P. Foschini[1]
[1] Department of Biomedical and Neuromotor Sciences, "M. Malpighi" Section of Anatomic Pathology at Bellaria Hospital, University of Bologna, Italy, [2] Department of Biomedical and Neuromotor Sciences, Section of Oral Sciences, University of Bologna, Italy, [3] Department of Biomedical and Neuromotor Sciences, Section of Maxillo-facial Surgery at Policlinico S. Orsola-Malpighi, University of Bologna, Italy

Background & Objectives: Oral Squamous Cell Carcinoma (OSCC) showed a significant risk to develop local recurrences or second primary tumours during follow-up. Recently, we developed a non-invasive assay based on oral brushing and DNA methylation analysis to early detect OSCC. In the present study using this assay, we investigated the adjacent area of surgical resection in a series of OSCC during follow-up for prognostic purposes.
Methods: 42 consecutive OSCC patients were sampled during routine follow-up after 6 months from surgical treatment, brushing the regenerative mucosa covering the region that underwent the surgical OSCC excision. DNA methylation level of *ZAP70, GP1BB, KIF1A, ITGA4, LINC00599, MIR193, MIR296, TERT, LRRTM1, NTM, EPHX3, FLI1* and *PARP15* was evaluated by quantitative Bisulfite-NGS. After calculating a score by Linear-Discriminant-Analysis, the samples were dichotomized using a predefined threshold previously developed for early diagnosis. One-Way-ANOVA and Kaplan-Meier curves served to evaluate any significant difference between patients who experienced a second neoplastic manifestation and the group who did not.
Results: 6/42 (14,3%) patients developed a second neoplastic manifestation during follow-up period (mean follow-up: 14.3 months), of which 5 showed a positive methylation score. Additional 11 patients exceeded the threshold but up to date they have not experienced any second manifestation. Among the remaining 26 negatives, only one developed a recurrence. A positive score correlated with a worse locoregional control of disease ($p<0.05$).
Conclusion: The DNA methylation analysis of 13 genes can be a useful non-invasive method to identify surgically treated OSCC patients at risk of developing a second neoplasia.

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OFP-06-009

Integrated genomics of olfactory neuroblastoma: pathologic and therapeutic implications

M. Classe[1], H. Yao[2], X. Su[2], C. Creighton[3], A. Burgess[4], R. Mouawad[5], M. Wassef[6], X. Leroy[7], B. Verillaud[4], G. Mortuaire[7], F. Bielle[4], D. Khayat[8], G. Malouf[9]
[1] Institut Gustave Roussy, France, [2] MD Anderson, USA, [3] Baylor College of Medicine, USA, [4] Assistance Publique Hôpitaux de Paris, France, [5] Leo Pharma, France, [6] Bichat Hospital, APHP, France, [7] Centre Hospitalier Règional et Universitaire de Lille, France, [8] Clinique Bizet, France, [9] Hôpitaux Universitaire de Strasbourg, France

Background & Objectives: Olfactory neuroblastomas (ONBs) are rare tumours arising in the skull base. Classification tools are poor, notably, no molecular classification of ONB has been reported. Literature data about their cell of origin, the existence of molecular therapeutic targets or their immune environment being scarce, the biology of these tumours is still poorly understood.
Methods: Using a well described series of 59 ONBs coming from 4 different centers, we performed a multiomics analysis based on exome, transcriptome and methylome analysis, but also on histopathological and immune characteristics.
Results: We highlighted 2 sub-types of ONB. The neural type is a well differentiated, poorly aggressive tumour showing neurons characteristics and sharing phenotypic similarities with olfactory neuron progenitors. The basal type is a less differentiated tumour, displaying an aggressive phenotype, with embryonic phenotypical characteristics, sharing similarities with basal renewing cells of the olfactory epithelium. We showed that the mutational load was higher in basal tumours, with notably recurrent IDH2 R172 mutations associated with a CpG Island Methylator Phenotype (CIMP).
Conclusion: This work is the first attempt to generate a comprehensive molecular classification of ONBs using a multiomics analysis. It paves the way towards a new molecular classification which will allow a better stratification of patients and will open the field of new therapeutic strategies for this rare tumour.

OFP-06-010

Clinicopathological characterisation and outcomes analysis of a single-institutional cohort of early-stage oral tongue squamous cell carcinoma treated by surgery alone

J. Filipe[1], M. Labareda[2], S. Esteves[3], E. Netto[2] and I. Fonseca[1,4]
[1] Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [2] Serviço de Radioterapia, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [3] Unidade de Investigação Clínica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [4] Instituto de Anatomia Patológica, Faculdade de Medicina, Universidade de Lisbon, Portugal

Background & Objectives: Early-stage oral tongue squamous cell carcinoma (OTSCC) prognosis and treatment remain controversial. The aim of this study was to assess the impact of clinicopathological features in outcomes of a cohort of patients with early-stage OTSCC treated by surgery only.
Methods: A retrospective analysis of 71 cases of early-stage OTSCC treated by surgery only at our Institution between 2006 and 2010, staged as pT≤2N0 at time of treatment (AJCC, 7thed) was performed. Tumour thickness, depth of invasion (DOI), histologic grade, margins, lymphovascular invasion (LI), perineural invasion (PI), worst pattern of invasion (WPOI) and lymph node dissections, when performed, were re-evaluated. Kaplan-Meier method was used for recurrence-free survival (RFS) and disease-specific survival (DSS) analysis; log-rank test was performed for subgroup comparison.
Results: Median age was 62years and median follow-up of 6.3years. 66% of the tumours were pT1. Lymph node dissection was performed in 44% of the patients. 3 cases had tumour DOI>10mm, and were re-staged to pT3 (AJCC, 8thed). Surgical margins were positive or ≤1mm in 14%. PI was present in 6% and LI in 3%. All cases had WPOI<5. The 5-year DSS and RFS rates were 86% and 64%, respectively. DOI ≥5mm was associated with poorer DSS (p=0.006). PI correlated with recurrence and with lower DSS (p=0.006 and p<0.001, respectively).
Conclusion: In our cohort of patients, 4% of T2 OTSCC were upstaged after pathological characterization using the 8th AJCC staging system. Tumour DOI≥5 mm and the presence of PI correlated with poorer prognosis.

OFP-06-011

Evaluation of programmed death ligand-1 expression and efficacy outcomes in patients with squamous cell carcinoma of the head and neck from KEYNOTE-040 using two scoring techniques

K. Emancipator[1], L. Huang[1], J. Juco[1], D. Aurora-Garg[1], T. Bal[1], E.E.W. Cohen[2], K. Harrington[3], D. Soulières[4], C. Le Tourneau[5], L. Licitra[6], B. Burtness[7], R. Swaby[1]
[1] Merck & Co., Inc., USA, [2] Moores Cancer Center, UC San Diego Health, USA, [3] The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, United Kingdom, [4] Centre Hospitalier de l'Universitè de Montrèal, Canada, [5] Institut Curie, Paris and Saint-Cloud, INSERM U900 Research Unit, France, [6] Fondazione IRCCS Istituto Nazionale dei Tumouri and University of Milan, Italy, [7] Yale University School of Medicine and Yale Cancer Center, USA

Background & Objectives: Tumour proportion score (TPS) is used to measure programmed death ligand 1 (PD-L1) expression in tumour cells, whereas combined positive score (CPS) measures PD-L1 in tumour and immune cells. A post hoc analysis from the open-label, phase 3 KEYNOTE-040 (NCT02252042) trial was performed to determine whether CPS is a suitable alternative for TPS in patients with head and neck squamous cell carcinoma (HNSCC) under evaluation for second-line therapy.
Methods: Patients with platinum-refractory HNSCC received pembrolizumab (200 mg Q3W) or chemotherapy/biotherapy. Pathologists scored tumour samples for TPS and CPS using the PD-L1 IHC 22C3 PharmDx assay. Scoring methods were compared based on objective response rate (ORR; RECIST v1.1), overall survival (OS), and progression-free survival (PFS). Cutoffs were evaluated by receiver operating characteristic (ROC) analysis using ORR.
Results: PD-L1 expression was evaluated in 475/495 enrolled patients. ORR for pembrolizumab versus chemotherapy was 26.2% versus 8.5% (TPS ≥50%), 28.1% versus 7.7% (CPS ≥50), 10.6% versus 11.6% (TPS <50%), and 10.0% versus 12.0% (CPS <50). OS and PFS curves showed congruence between corresponding groups by TPS and CPS, better survival in the pembrolizumab versus chemotherapy arm in the PD-L1^{high} group, and similar survival in the PD-L1^{low} group. ROC analyses confirmed that appropriate cutoffs occurred at TPS 50% and CPS 50.
Conclusion: CPS 50 can be used interchangeably with TPS 50% to determine PD-L1 status in patients with HNSCC undergoing evaluation for second-line treatment. Data from the ROC analyses further suggest that CPS may be more sensitive than TPS at lower cutpoints (CPS ≥1).

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OFP-06-012

Surgical follow-up of ThyroSeq® positive thyroid nodules: the Memorial Sloan Kettering Cancer Center experience

D. Buonocore[1], O. Lin[1], J. Cohen[1]
[1] Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: The current American Thyroid Association guidelines suggest the use of molecular studies in the management of patients with an indeterminate cytology diagnosis. ThyroSeq®, one of the most used thyroid molecular tests in the U.S., has been reported to have high positive predictive value(PPV). We propose to evaluate the PPV of ThyroSeq® at a major cancer center in the U.S. in which the prevalence of malignancy is high.
Methods: Cytology material from 252 thyroid nodules diagnosed as indeterminate were submitted for ThyroSeq® analysis. The results were reported as positive in 94 cases. Sixty-one of these 94 cases were surgically resected. The ThyroSeq® results were correlated with the surgical diagnosis.

Results: Fourteen of the 62 nodules were benign on resection including; 5 nodular hyperplasia, 5 Hashimoto's thyroiditis, 2 follicular adenomas, and 4 oncocytomas. Additionally, there were 9 noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), a tumour with unclear malignant potential. NRAS was the most commonly detected mutation in the benign nodules, it was present in 6 of the 16 nodules and 4 of 9 NIFTPs. NRAS was also the most common mutation detected in malignant lesions, being present in 15 of 36 cases while BRAFV600E was detected in only 4 cases.
Conclusion: In our experience the ThyroSeq® PPV was 73.8% and falls to 59.0% when NIFTP is excluded. The most common mutation in benign and malignant lesions was NRAS (25/61).

Monday, 9 September 2019, 17:15 - 19:15, Thalie
OFP-07 | Dermatopathology

OFP-07-001
Assessment of circulating tumour cells and circulating cell-free DNA in patients with metastatic melanoma
M. Badrignans[1], B. Tournier[2], G. Jeudy[3], S. Dalac[3], C. Chapusot[2], L. Martin[1,2,4], M. Aubriot-Lorton[1,2]
[1] Service de Pathologie, CHU Dijon, France, [2] Plateforme de Gènètique des Cancers solides et des Hèmopathies malignes, CHU Dijon, France, [3] Service de Dermatologie, CHU Dijon, France, [4] Unitè d'innovation en Gènètique et Epigènètique des cancers, CHU Dijon, France

Background & Objectives: Circulating tumour cells (CTCs) and cell-free DNA (ctDNA) released by tumours in the blood, could be useful as non-invasive biomarkers of patients with metastatic melanoma. Our prospective study evaluates the feasibility of an isolation device of CTCs (ScreenCell®), and determines if the variation of CTCs and ctDNA are correlated with therapeutic efficacy.
Methods: Five patients were included before they received the first line of treatment. Every three months, they had clinical and radiological evaluations, and peripheral blood tests (CTCs and ctDNA). CTCs were isolated according to the manufacturer instructions and counted by two observers (MB, MHA). ctDNA were isolated with QIASymphony Circulating DNAkit. BRAF mutations were detected by ddPCR.
Results: Among the 5 melanoma, only one had a BRAF mutation. The inter-observer's (R^2=0.98) and intra-observer's (R^2=0.99) correlation for CTCs were excellent. Cytological criteria of malignancy were easily recognizable, with only 0.76±0.6 "uncertain malignant cell" (UMC) per filtration. The negative sample contains 0.67±0.58 UMC / filtration. During patient follow up, the evolution of CTCs and radiological tumour burden were similar. ctDNA and CTC's variations were similar in the case with BRAF mutation. Otherwise, ctDNA had only slight variations but without relapse.
Conclusion: ScreenCell® is a reliable, reproductive and non-invasive test for CTCs isolation in routine. CTCs are more informative than ctDNA, for the follow up of melanoma especially when BRAF is not mutated. CTCs variations seem to appear earlier than tumour's growth, but clinical studies are needed to prove that CTCs can detect relapse before imagery.

OFP-07-002
Intravascular nevus cell protrusion and aggregates in otherwise common melanocytic nevi
G. Tudor[1], O. Stefan[1], V. Nica[1], R. Tanasa[1], V. Chitu[1,2], C. Caruntu[2], C. Popp[1], M. Cioplea[1], S.A. Zurac[1,2]
[1] Colentina Clinical Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: Melanocytic nevi are common, benign, pigmented skin tumours formed by proliferation of melanocytes which may present a number of unusual features, such as the vascular affinity of nevus cells and its consequences. This study aims to highlight the associated intravascular pseudoemboli and nevus cell protrusion in benign intradermal nevi.
Methods: We have reviewed a total of 1154 compound and intradermal melanocytic nevi diagnosed between 2017-2018 in our department and have selected 78 (6.75%) cases with intravascular nevus cell protrusion (IVNP) and 2 (0.17%) cases with intravascular nevus cell aggregates (IVNcA); immunohistochemistry for S100, CD34 and D2-40 (podoplanin) was performed.
Results: The IVNcA and IVNP lesions were mostly located on the torso (58.75%), followed by the head and neck region (30%) and the limbs (1.25%); 8 cases had no clinical records regarding the location (10%). Female-to-male ratio was 2.5:1, with a median age of 32 years (between 16-80 years). The maximum diameter ranged from 0.2 cm to 2.3 cm (median 0.7 cm); median tumour thickness: 0.31 cm. IVNPs were tipically situated in the upper/mid dermis and IVNcAs were identified in the upper dermis. In all cases intravascular protruding tumour cells were covered by CD34/D2-40 positive cells (endothelial cells).
Conclusion: This is the largest study that evaluates morphologically and immunohistochemically the presence of IVNPs and IVNcAs within benign melanocytic nevi. Our results describe the demographic characteristics of patients with IVNPs and IVNcAs within common melanocytic nevi, creating the premises for further studies.

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OFP-07-003
Effective treatment of Merkel cell carcinoma cell lines by the combined inhibition of BCL-2 and PI3Ka
E. Chteinberg[1], W. Gerritsen[1], E. Speel[1], V. Winnepenninckx[1], A.K. Kurz[2], M. Zenke[2], A. zur Hausen[1]
[1] Maastricht University Medical Centre+, The Netherlandsk, [2] University Hospital RWTH Aachen, Germany

Background & Objectives: Merkel cell carcinoma (MCC) is a highly malignant skin cancer of unknown cellular origin. MCC is characterised by a typical trilinear differentiation: epithelial, neuroendocrine, early B-lymphoid. In addition, MCCs highly express BCL-2 and PI3Kα on the protein level.
Specific inhibition of BCL-2 and PI3Kα has been introduced in the treatment of some non-Hodgkin lymphomas and leukemias. We tested the combined inhibition of BCL-2 and PI3Kα in MCC cell carcinoma lines (MCCcls).
Methods: Four MCCcls (MKL-1, MKL-2, WaGa and MCC13) and one B-acute lymphoblastic cell line REH, all previously shown to express PI3Kα and -except MCC13- BCL-2, were treated with different concentrations of the BCL-2 inhibitor Navitoclax for 72h. Cell viability was assessed by the XTT assay (ThermoFisher), IC_{50} were determined, and cleaved PARP detection by Western-blotting was used as read-out for the induction of apoptosis. The combined effects of Navitoclax and the PI3Kα inhibitor (Byl719) were analysed. The p-values were calculated by a One-Way ANOVA.
Results: Navitoclax treatment alone effectively decreased the viability of all cell lines except MCC13. Increased cleaved PARP levels following increasing concentrations of Navitoclax treatment revealed that its effects indeed was mediated by apoptosis. IC_{50} values of MCCcls were 2 to 10 times higher compared to REH. The combination of Navitoclax and Byl719 revealed a significant ($p < 0.05$) synergistic effect in all cell lines except MCC13.

Conclusion: Our results point to a novel and important therapeutic option using a combination treatment of Navitoclax and Byl719 in stage III/IV MCC patients primarily or secondarily not responding to immunotherapy.

OFP-07-004

E-cadherin and N-cadherin expression pattern in common melanocytic nevi

O. Stefan[1], G. Tudor[1], C. Constantinescu[1], C. Luca[1], D. Boda[2], C. Caruntu[2], M. Cioplea[1], L. Nichita[1,2], S.A. Zurac[1,2]
[1] Colentina Clinical Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: Cadherins constitute a family of transmembrane glycoproteins that mediate cell-to-cell adhesion and play an important role in the maintenace of normal tissue architecture. Our study aims to evaluate the role of E-cadherin and N-cadherin in the pathogenesis of intravascular nevus cell protrusion (IVNP) and intravascular nevus cell aggregates (IVNcA) within common melanocytic nevi (CMN).
Methods: We have selected a study group including 30 CMN with IVNP and IVNcA and a control group that comprised 30 CMN without IVNP and IVNcA, matched individually by age, sex and anatomical location of the lesion. We assesed immunohistochemically the expression of E-cadherin and N-cadherin within both groups, followed by calculating the *odds-ratio* (*OR*) and assessing the *p*-value using the *Fisher's exact test*.
Results: The glycoproteins had 7 patterns of expression in both study and control groups: superficial, deep, superficial&deep, superficial>deep, deep>superficial, patchy and no expression.
For E-cadherin we identified a tendency towards deep pattern of expression in IVNP and IVNcA nevi comparing with superficial and superficial&deep patterns in CMNs (OR=3.5; p=0.037).
For N-cadherin no statistical significant differences in expression patterns were present (OR=0.3; p=0.084).
Conclusion: Melanocytic lesions with IVNP and IVNcAs depict certain E-cadherin expression patterns more frequently than CMN without IVNP and IVNcAs, but its role in the pathogenesis of the vascular affinity of melanocytes is still to be debated.

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OFP-07-005

A PD-L1 IHC 28-8 PharmDX ring trial on metastatic melanoma: practical aspects

V. Siozopoulou[1], K. De Winne[1], E. Smits[2,3], J. Jacobs[1,2], K. Zwaenepoel[1,2], P. Pauwels[4]
[1] Department of Pathology, Antwerp University Hospital, Belgium, [2] Center for Oncological Research, University of Antwerp, Belgium, [3] Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, Belgium, [4] Laboratory of Pathological Anatomy, Antwerp University Hospital, Edegem, Belgium

Background & Objectives: A Belgian ring trial for PD-L1 IHC staining in melanoma was organized by the pathology department of Antwerp University Hospital.
Methods: The trial went on from December 2017 until July 2018 and a total of 14 different laboratories participated. One site participated with two different protocols.The first and last slides of 6 selected melanoma cases were stained with PD-L1, using PD-L1 28-8 pharmDX kit of Agilent on an Autostainer Link 48 platform. Each participating laboratory received 2 unstained slides and was asked to return 1 PD-L1 stained slide per case and to report the used protocol and their given PD-L1 score. The stained slides were evaluated by a team of 2 experienced pathologists. Comparison of the evaluation by the pathologists of the different laboratories and the evaluation by the team of referent pathologists was communicated to the laboratories.
Results: The majority (80%) of the laboratories used the 22C3 clone in an in house assay. Approximately 60% have a Ventana Benchmark apparatus at their disposal. The most challenging cases were those around the 5% cut-off (based on the CheckMate 067 study at that time). High amount of melanin resulted in a systematic overestimation of the PD-L1 expression. The overall interlaboratory concordance was 65%. The use of different clones, platforms, protocols and detection kits didn´t have played an important role in the scoring.
Conclusion: Independent of different platforms and clones, PD-L1 stainings resulted in similar conclusions in about 65% of cases. Abountant melanin deposition causes overestimation.

OFP-07-006

Imbalance between types I and VI collagen promotes skin fragility in human and experimental diabetes

J.T. De Miranda[1], V.P. Toledo[1,2], Z.A. Queiroz[1], L.K. Ramos da Silveira[1,2], A. dos Santos Filho[3,2], A.P. Pereira Velosa[3], S. Catanozi[1,4], V.l. Capelozzi[1,5], W. Rosolia Teodoro[1,2]
[1] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [2] Rheumatology Division, Brazil, [3] Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [4] Department of Endocrinology, Brazil, [5] Department of Pathology, Brazil

Background & Objectives: One third of people with diabetes develop skin complications from the long-term effects of the hyperglycemia on the microcirculation and on skin collagen. Previous works have demonstrated significant imbalance between collagen fibers in diabetic skin. This study aimed to compare the expression of the fibrillary Type I collagen (Col I) and the anchorage Type VI collagen (Col VI) on skin from human and experimental diabetes.
Methods: Diabetes was induced in Wistar male rats by streptozotocin inoculation. The animals were euthanized at 7 (n=10, DG7d) and 30 days (n=10, DG30d). Matched control group was inoculated with saline (n=10; CG7d; n=10, CG30d). Skin biopsies were obtained from patients with diabetes (n=5) with high serum glucose levels and from heath individuals (n=4). We used immunofluorescence and histomorphometry to evaluate Col I and Col VI fibers in skin biopsies
Results: Skin from DG7d and DG30d diabetic rats showed a dermal fibrosis thus resulting in abnormal and significant increased deposition of the Col VI fibers and decreased deposition of Col I when compared to controls ($p<0.0001$). Human diabetic skin biopsies also showed a dermal fibrosis histologic pattern and so demonstrated comparable abnormal and increased deposition of Col VI (17.99±0.98 vs 5.01±0.21; $p<0.0001$) and decreased Col I (2.55±1.0 vs 18.78±2.46, $p<0.0001$) when compared to control.
Conclusion: We concluded that an in situ imbalance between Col VI and Col I modulates skin fibrosis in human and experimental diabetes emerging as a promising therapeutic option for recovering skin fragility.

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OFP-07-007

Melanomas with spindle cell differentiation: a review of clinical, pathological and molecular characteristics

M. Gonzalez Farre[1], S. Tormo Mainar[2], E. Andrades López[3], J. Lloreta Trull[1], B. Espinet Solà[1], B. Bellosillo Paricio[1], A. Torner Calvo[1], R.M. Pujol Vallverdu[2], B. Lloveras Rubio[1,4,5], S. Segura Tigell[2], C. Barranco Sanz[1]
[1] Pathology Department, Hospital del Mar, Barcelona, Spain, [2] Dermatology Department, Hospital del Mar, Spain, [3] Institut Hospital del Mar d'Inverstigacions Mèdiques (IMIM), Spain, [4] Universidad Autónoma de Barcelona, Spain, [5] Institut Hospital del Mar d'Investigacions Mèdiques, Spain

Background & Objectives: Melanomas with spindle cell differentiation can be difficult to diagnose both clinically and histologically. A retrospective review of the clinical and pathological characteristics, the immunohistochemical (IHC) and molecular profiles of a series of melanomas with spindle cell differentiation was performed.
Methods: Ten skin biopsies with a predominantly fusocellular pattern were selected from the melanoma's record of our hospital. Immunohistochemical techniques (MelanA, HMB45, S100 and SOX10), ultrastructural studies (6 cases), FISH techniques (RREB1, MYB, CEP6, CCND1 probes) and *BRAF* (V600E) mutation through Sanger sequencing (6 cases) and Idylla system (4 cases) were done.
Results: Ten patients (8 men and 2 women) with an average age of 78 years were included in the study. Four patients presented multiple locoregional relapse, 2 distant metastases and 5 died. The lesions showed a spindle cell proliferation of predominantly dermal location. The medium Breslow Index (BI) was 6.55mm and the mitotic index 4.55/mm^2. All cases expressed S100 and SOX10 but only five were immunoreactive for MelanA and HMB45. Ultrastructural study identified aberrant melanosomes in 5 of 6 cases. Molecular studies demonstrated a *BRAF* mutation in 2 of 10 evaluable cases.
Conclusion: Fusocellular melanomas are a distinctive clinicopathologic subtype that may pose important diagnostic challenges to both clinicians and pathologists. They show high proliferative activity, locoregional aggressiveness and elevated mortality rates. Immunohistochemically, common melanocytic markers (MelanA and HMB45) are frequently negative, whereas SOX10 is very helpful in this setting. *BRAF* mutation is often negative.

OFP-07-008
YAP1 expression in Merkel Cell Carcinoma
A. Sykaras[1], G. Kyriakopoulos[1], G. Kazamias[1], C. Stamou[1], S. Pantelakos[1], P. Dolkiras[1], C. Kouvidou[1]
[1] Department of Pathology, Evangelismos General Hospital, Athens, Greece

Background & Objectives: The transcriptional co-activator Yes-associated protein (YAP1) is a critical downstream effector of the Hippo signaling pathway that controls organogenesis and tumourigenesis. YAP1 is implicated in many cancers and acts as oncogene or tumour suppressor gene, depending on cancer type. In particular, expression of YAP1 is upregulated in Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) of the skin whereas YAP1 expression is lost in high-grade neuroendocrine tumours of the lung, especially small cell lung carcinoma (SCLC). Our aim is to evaluate YAP1 expression in Merkel Cell Carcinoma (MCC), a high-grade neuroendocrine carcinoma of the skin.
Methods: We performed immunohistochemistry using a monoclonal anti-human YAP1 antibody on formalin-fixed paraffin embedded (FFPE) sections of five MCC tumour specimens. The specimens included two primary MCC (one Merkel Cell Polyoma Virus-MCPyV positive and one MCPyV negative) and three metastatic MCC to lymph nodes (two MCPyV positive and one MCPyV negative). We used sections of two BCC and two SCC specimens as external positive controls.
Results: YAP1 expression was completely abolished in all MCC specimens. In agreement with the literature, there was aberrant expression of YAP1 (strong nuclear and faint diffuse cytoplasmic stain) in BCC and SCC specimens.
Conclusion: Our preliminary results suggest that YAP1 expression is lost in MCC. This finding is in line with the concept that YAP1 is lost in high-grade neuroendocrine tumours and may suggest that YAP1 has a tumour suppressor function in the context of MCC development. We are currently expanding our analysis to a large cohort of MCC specimens, trying to validate our preliminary data and correlate the YAP1 expression pattern with the presence of MCPyV and the expression of other neuroendocrine markers.

OFP-07-009
A 5-year retrospective analysis of all cutaneous metastases from a single dermatopathology unit
A.C. Lisievici[1], T.A. Georgescu[2], M. Leventer[3], G. Dodan[3], T. Tebeica[4]
[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Bucharest Emergency University Hospital, Romania, [3] Department of Dermatovenerology, Dr. Leventer Centre, Bucharest, Romania, [4] Department of Pathology, Dr. Leventer Centre, Bucharest, Romania

Background & Objectives: Cutaneous metastases are uncommon lesions associated with poor prognosis, which sometimes embody the first presentation of malignancy. Some autopsy studies revealed that approximately 2% of those with visceral cancer had cutaneous metastases, while other series observed that the skin represents the 18th most frequent metastatic site involved by all tumours. Moreover, the diagnosis may not always be at hand for the practicing pathologist, considering that the clinical aspects are often misleading.
Methods: This is a retrospective study including 44 cases of cutaneous metastasis that were diagnosed in our Dermatopathology unit, during a period of five years (2015-2019). We thoroughly re-examined the Hematoxylin-Eosin and immunohistochemically stained slides, aiming to establish clinico-pathological correlations. A median of 7 immunohistochemical markers were used in order to come to the final diagnosis. More than half all cases had clinical aspects suggestive for metastasis and 53% had no history of neoplastic disease.
Results: 82% presented as nodules, 16% mimicked an inflammatory lesion and 2% presented as neoplastic alopecia. Median age was 61 years (24-86 years) and 69.7% were females. Breast carcinoma was the most frequent primary tumour (n=16), followed by melanoma (n=13), gastrointestinal tract adenocarcinoma (n=6), squamous carcinomas (n=4), and pulmonary carcinoma (n=2). Tumour emboli were noticed in 27%, ulceration of the epidermis only in 18% and epidermotropism in 20%. Of all melanoma metastases, 58% were distant, while the rest represented in-transit metastases.
Conclusion: Cases clinically presenting as inflammatory lesions (plaque, eczema) correlated best with breast origin. Vascular invasion was also most frequently encountered in this type of carcinoma. Metastases located on the abdomen correlated with the gastrointestinal origin of the tumour, with the exception of one case of metastatic high-grade serous carcinoma of the ovary, which presented as sister Mary Joseph nodules.

OFP-07-010
Hypopigmented parasoriasis en plaque; an ignored variant
R. Abdel Hay[1]
[1] Cairo University, Faculty of Medicine, Egypt

Background & Objectives: Parapsoriasis en plaque (PSEP) is a chronic dermatosis whose biological distinction from early mycosis fungoides (MF) is still not clearly defined. Our aim was to verify whether an uncommon hypopigmented disorder sharing many mutual features with should be considered as a hypopigmented variant.
Methods: 50 patients presenting with this unusual hypopigmented disorder were included. Patients were subjected to proper history taking, general and dermatological examination, laboratory investigations, histopathological examination and IHC staining to exclude differential diagnoses of hypopigmented lesions.
Results: All other disorders had been excluded. Clinically, the lesions were comparable to those of classic small-plaque parapsoriasis with digitiform extensions of most the lesions. Histopathologically, there was mild epidermal hyperplasia, reduced basal pigmentation, and decreased number of melanocytes at the base of the epidermis. Focal parakeratosis, foci of mild spongiosis, and focal exocytosis were encountered in the 94% of cases. The dermis showed scanty superficial perivascular infiltrate of lymphocytes and histiocytes with frequent extension into the papillary dermis. No interface changes or atypical lymphoid cells. IHC staining

showed CD3 immunopositivity. CD8+ T cells predominance over CD4+ T cells was reported in 88% of cases.
Conclusion: Based on our findings we deliberate this hypopigmented disorder as a variant of the PSEP family with all features of PSEP and thus could be mentioned as hypopigmented PSEP.

OFP-07-011
The role of CD123 positive plasmacytoid dendritic cells in cutaneous lupus erythematosus
N. Roy[1], G. Gupta[1], R. Ramakrishnan[2]
[1] Imperial College Healthcare NHS Trust, United Kingdom, [2] North West London Pathology, United Kingdom

Background & Objectives: Cutaneous lupus erythematosus(CLE) demonstrates clustering of CD123 positive plasmacytoid dendritic cells (PDC) that has diagnostic utility. Our study aims to identify diagnostic & prognostic value of CD123 positive PDC in CLE.
Methods: CLE diagnosed between 2013 & 2017 were reviewed with respect to histology & immunofluorescence (IMF). Immunohistochemistry (IHC) to CD123 was performed & semi-quantitative criteria were developed for assessing staining intensity & patterns of distribution.
Results: 72/81(88%) cases stained for CD123, 45(55%) strong & 27(33%) weak. Predominant distribution was perivascular 56/72 (90%) with perifollicular in 39/72 (54%). Proportion of cells stained was 3+ in 26/45(57%) & 2+ in 18/45 (40%) with strong staining while mostly 1+ cells with weak 25/27(92%). With IMF, 12/31 (38%) demonstrated IgG, & 11/31 (35%) also showed C3. 11/12 IMF positive cases also showed CD123 (91%) staining; 6/11 (55%) strong & 5/11 (45%) weak, thus demonstrating positive correlation with the histological diagnosis. 35/38 (92%) cases with no IMF data showed CD123 staining, again, demonstrating a positive correlation with the histological diagnosis.
Conclusion: Our study re-iterates the routine diagnostic utility of the CD123 demonstrating positivity in 88% of cases of CLE. It is therefore a useful adjunct & of diagnostic value in distinguishing lupus from other lymphoid infiltrates, particularly CTCLs. CD123 therefore should be used routinely in diagnosis of cutaneous lymphoid infiltrates.

OFP-07-012
Profiling the tumour immune microenvironment in pleomorphic dermal sarcomas suggests its potential effectiveness for immunotherapy
K. Noh[1], S. Klein[2], C. Mauch[3], S. Wagener-Ryzek[1], M. Schoemmel[4], R. Buettner[5], A. Quaas[2], D. Helbig[3]
[1] Institute of Pathology, University Hospital Cologne, Germany, [2] Institute for Pathology, Cologne, Germany, [3] Department of Dermatology, University Hospital Cologne, Germany, [4] Department of Internal Medicine, University Hospital Cologne, Germany, [5] University Hospital Cologne, Germany

Background & Objectives: Immunotherapies, with their high objective response rates and long-lasting clinical benefits, have revolutionized cancer treatment. Pleomorphic dermal sarcoma (PDS) is a very rare cutaneous tumour with local recurrences and distant metastases occurring in up to 28% and 20% cases, respectively. With only limited treatment options in advanced stages, there is a strong rationale to explore immunotherapies in PDS. However, in order to achieve this, the immune microenvironment in PDS first needs to be explored.
Methods: We collected 14 PDS cases that underwent primary surgical resection at University Hospital Cologne. With FFPE materials, we performed a comprehensive immune-phenotype analysis using immunohistochemistry and multiplex gene expression analysis, as well as quantitative assessment of immune cells and immune response markers through quantitative image-analysis.
Results: Eight out of fourteen PDS cases (57%) showed abundance of CD8-positive T-lymphocyte infiltration. Three cases that had above median level of infiltration (hereinafter referred to as CD8-high) displayed high expression levels of immune-related cytokines, immunotherapy response markers, MHC-I expression, and infiltration by PD-L1-, PD-1- and LAG-3-expressing immune cells. The multivariate analysis revealed that CD8-high group highly expressed CD74, LYZ and HLA-B while the CD8-low cases overexpressed CXCL14. In addition, M2 tumour-associated macrophages (TAMs) were localized at the tumour invasion front.
Conclusion: We provide the first comprehensive immune-phenotype profiling of PDS. These results will aid in further assessment of PDS cases and formulate the qualification criteria for immunotherapy in individuals presenting with advanced stages of this rare skin malignancy.

Monday, 9 September 2019, 17:15 - 19:15, Galliéni 5
OFP-08 | Joint Session: Neuropathology / Ophthalmic Pathology

OFP-08-001
Deregulated expression of imprinted DLK1-DIO3 region in glioblastoma stem-like cells: tumour suppressor role of lncRNA MEG3
M. Martini[1], L. Ricci-Vitiani[2], G. Marziali[2], M. Bucciarelli[2], V. Lulli[2], Q.G. D'Alessandris[3], R. Pallini[4]
[1] Institute of Pathology, Rome, Italy, [2] Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Italy, [3] Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italia, [4] Institute of Neurosurgery, Catholic University School of Medicine, Italy

Background & Objectives: Glioblastoma (GBM) stem-like cells (GSCs) are thought to be responsible for the maintenance and aggressiveness of GBM, the most common primary brain tumour in adults. LncRNAs have emerged as important players in cancer. This study aims at elucidating the involvement of deregulations within the imprinted *DLK-DIO3* region on chromosome 14q32 in GBM pathogenesis.
Methods: RT-PCR analyses were performed on GSCs and GBM tissues. Al results were correlated with the clinical features. Methylation analyses, gene expression and Reverse-Phase protein Array profiles were used to investigate the tumour suppressor function of *MEG3*. Statistical analysis was performed appropriately.
Results: Loss of expression of genes and non-coding RNA within the DLK1-DIO3 locus, mediated by epigenetic silencing, was observed in GSCs and GBM tissues. Kaplan-Meier analysis showed lower expression of *MEG3* and *MEG8* lncRNAs significantly correlated with short survival in GBM patients. *MEG3* restoration impairs tumourigenic abilities of GSCs *in vitro* inhibiting cell growth, migration and colony formation and decreases *in vivo* tumour growth reducing infiltrative growth. These effects were associated with modulation of genes involved in cell adhesion and EMT.
Conclusion: Our data show that *MEG3* is involved in a complex network that regulates cell adhesion, DNA damage, cell proliferation and stemness by targeting a multitude of genes. The analysis of *MEG3* signatures, coupled with functional *in vitro* and *in vivo* assays, identifies known as well as unexplored pathways that can be targeted with innovative therapies.

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OFP-08-002
Ki-67 and MCM6 labelling index are correlated with overall survival in anaplastic oligodendroglioma, IDH1-mutant and 1p/19q codeleted: a multicenter study from the French POLA Network
C. Pouget[1], S. Hergalant[2], E. Lardenois[1], S. Battaglia-Hsu[2], H. Rèmi[2], C. Carpentier[3], C. Dehais[4], F. Rech[5], L. Taillandier[6], C. Colin[7], D. Figarella-Branger[8], G. Gauchotte[1]

[1] Department of Pathology, CHRU, Nancy, France, [2] INSERM U1256, NGERE, Faculté de Mèdecine de Nancy, Universitè de Lorraine, France, [3] CRICM - UMRS975, Paris, France, [4] AP-HP, Groupe Hospitalier Pitiè-Salpêtrière, Service de neurologie 2-Mazarin, Paris, France, [5] Department of Neurosurgery, CHRU, Nancy, France, [6] Department of Neurology, CHRU, Nancy, France, [7] AP-HM, Hôpital de la Timone, Service d'Anatomie Pathologique et de Neuropathologie, Marseille, France ; Aix-Marseille Univ, CNRS, INP, Institut Neurophysiopathologie, Marseille, France, [8] AP-HM, Hôpital de la Timone, Service d'Anatomie Pathologique et de Neuropathologie, Marseille, France ; Aix-Marseille Univ, CNRS, INP, Institut Neurophysiopathologie, Marseille, France

Background & Objectives: Anaplastic oligodendroglioma (AO), IDH-mutant and 1p/19q codeleted (IDHmut+/1p19qcodel) are high grade gliomas. Only few prognostic markers were studied in this specific histomolecular subgroup. The primary aim of this study was to evaluate and compare the prognostic value of two proliferation markers, MCM6 and Ki-67, in a French multicenter series of IDHmut+/1p19qcodel AO (POLA network), using immunohistochemistry. Further transcriptomic approaches were implemented to uncover the molecular pathways associated with the overexpression of these markers.
Methods: Two hundred and thirty-one IDHmut+/1p19qcodel AO cases were included from the French national POLA network. MCM6 and Ki-67 labelling index (LI) were evaluated using computer color image analyser. Transcriptomic data were analysed in a subset of 68 microarray samples from the French POLA Network.
Results: High MCM6 (≥ 50%) and Ki-67 (≥ 15%) LI correlated with shorter overall survival (P=0.013 and P=0.004, respectively). A high proliferation index, defined by MCM6 ≥ 50% and/or Ki-67 ≥ 15%, was independently correlated to a shorter survival (P=0.027; multivariate Cox model including age, mitotic index, MCM6 and Ki-67). Transcriptomic analyses revealed that while the high mRNA level of both MCM6 and Ki-67 were positively associated with clusters enriched in gene functions like cell cycle progression, DNA replication, mitosis, pro-neural phenotype as well as neurogenesis, they were negatively associated with clusters of other functions like microglial cell activation, immune response, positive regulation of myelination, oligodendrocyte development, beta-amyloid binding, and postsynaptic specialization.
Conclusion: In conclusion, both MCM6 and Ki-67 LI were correlated to overall survival. Because multivariate analyses showed that overexpression of MCM6 and/or Ki-67 was independently correlated to shorter survival, these two easy-to-use and costless markers could be used in association in daily practice in order to predict clinical outcome. Transcriptomics showed that IDHmut+/1p19qcodel AO are highly proliferative tumours with upregulated pro-neural phenotype associated genes, and downregulated immune response, glial differentiation, and myelin-related function.

OFP-08-003
Ultra-mutated IDH wild-type glioblastomas in patients younger than 50 years have peculiar histopathology and better prognosis

V. Barresi[1], M. Simbolo[2], A. Mafficini[2], M.L. Piredda[2], M. Caffo[3], S.M. Cardali[3], A. Germanò[3], S. Cingarlini[2], C. Ghimenton[4], A. Scarpa[5]
[1] Department of Diagnostics and Public Health, Section of Anatomical Pathology, University and Hospital Trust of Verona, Italy, [2] University of Verona, Italy, [3] University of Messina, Italy, [4] Hospital Trust of Verona, Italy, [5] Department of Diagnostics and Public Health, Section of Anatomical Pathology and ARC-Net Research Center, University and Hospital Trust of Verona, Italy

Background & Objectives: Glioblastomas (GBM) are classified into *IDH*-mutant and *IDH-wild type* (*IDH-wt*). The latter are rare in adults <50 years. This study aimed at identifying the mutational asset of *IDH-wt* GBMs in patients aged 18-50 years for which limited data is available.
Methods: Sixteen (14.8%) *IDH*-wt GBMs were found among 108 GBMs from patients aged 18-50 years diagnosed at Messina Polyclinic, Italy, and were explored for mutations and copy number variations in 409 genes, tumour mutational burden (TMB) and mutational spectrum.
Results: All 16 *IDH-wt* GBMs had TMB >14 mutations/Mb, and 4/16 cases were ultra-mutated (TMB >100 mutations/Mb). All ultra-mutated GBMs had mutational spectrum consistent with DNA mismatch repair (MMR) impairment and one had also increase in C>A transversions of the type associated with *POLE* inactivation. Accordingly, three cases had somatic mutations in MMR genes, and one had also *POLE* mutation. All 4 ultra-mutated GBMs featured at least 25% giant cells and they had significantly better prognosis than non-ultramutated GBMs (P= 0.036).
Conclusion: We identified an ultra-mutated distinct subgroup among *IDH*-wt GBMs in adults <50 years that had improved prognosis and could be recognized histologically by the presence of at least 25% homogenously dispersed giant cells. Since high TMB is associated with response to immune checkpoint inhibition, the identification of distinctive molecular and pathological subtype of *IDH*-wt GBM may have implications for immunotherapy.

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OFP-08-004
Clinical variability in Gerstmann-Sträussler-Scheinker syndrome with the P102L mutation

R. Matej[1], A. Tesar[2], M. Smetakova[1], E. Parobkova[1], R. Rusina[2]
[1] Department of Pathology and Molecular Medicine, Third Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic, [2] Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University, and General University Hospital, Prague, Czech Republic

Background & Objectives: P102L Gerstmann-Sträussler-Scheinker syndrome is a rare genetic prion disease caused by a mutation at codon 102 in the prion protein gene. The usual clinical presentation includes early ataxia with gait disturbance, sensory symptoms in the lower extremities, and late cognitive decline. We compared data from seven Czech patients with neuropathologically confirmed Gerstmann-Sträussler-Scheinker syndrome and retrospective data from 87 published P102L cases.
Methods: We focused on gender, age of onset, duration of disease, onset of dementia, presence of ataxia, duration of cognitive impairment, MRI/CT abnormalities, polymorphism in codons 129 and 219, changes in deep tendon reflexes, and sensory symptoms. We used descriptive statistics (the Wilcoxon-Mann-Whitney parametric hypothesis test, principal component analysis, and Density Based Sequential Cluster Analysis) to define typical phenotypes. Moreover, we provided detailed neuropathological and biochemical investigations of seven Gerstmann-Sträussler-Scheinker syndrome cases diagnosed in the Czech Republic.
Results: Analysis of data from our patients and from previously published cases suggest the existence of four clinical phenotypes ("typical Gerstmann-Sträussler-Scheinker syndrome," "Gerstmann-Sträussler-Scheinker syndrome with areflexia and paresthesia," "pure dementia Gerstmann-Sträussler-Scheinker syndrome," and "Creutzfeldt-Jakob disease-like Gerstmann-Sträussler-Scheinker syndrome") each with distinct disease duration and clinical manifestation, irrespective of similar neuropathological changes and biochemical properties of the pathological prion protein. Our analysis also suggests that Gerstmann-Sträussler-Scheinker syndrome is probably far more common than previously estimated.
Conclusion: Gerstmann-Sträussler-Scheinker syndrome is a rare genetic prion disease with higher prevalence than previously estimated, and despite its clinical variability and similarities in neuropathological and

biochemical investigations, four different phenotypical subgroups can be identified.

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OFP-08-005

Frequency of mismatch repair protein deficiency and PD-L1 in high grade glioma in adolescent and young adults

M. Al-Hussaini[1], S. Ghnimat[1], G. Almuhaisen[2]
[1] King Hussein Cancer Center, Jordan, [2] Mu'tah University, Jordan

Background & Objectives: CNS tumours in adolescents and young adults (AYA) are rarely reported in literature, and the association with cancer predisposition syndrome is not established. PD-L1 is used to predict the potential response of patients to immunotherapy. A link between mismatch-repair protein deficiency (MMRP-D) and response to immunotherapy is established. We aim to investigate the frequency of MMRP-D in AYA with high grade glioma, and any potential association with PD-L1.
Methods: Cases diagnosed with high grade gliomas in the age group 15-39 years were retrieved. Cases were stained for MLH-1, PMS2, MSH-2, and MSH6, PD-L1 and P53. A total of 96 cases including 54 males (56.0%) were retrieved. The median age at diagnosis was 31. 93 (97.0%) were in the cerebrum, including 49 (51.0%) glioblastoma. Subtotal resection/ biopsy (n=86) was mostly performed. Radiotherapy (n=82 cases) and chemotherapy (n=39 cases) were received. At time of collection of data, 49 patients were dead.
Results: Six cases were MMRP-D (MLH-1/ PMS-2 loss n=1, PMS-2 loss n=1, MSH-2/ MSH-6 loss n=1, MSH-6 loss n=3 cases). only one case showed loss of MSH-2/ MSH-6 in both tumour and normal cells indicating a germ line mutation (Biallelic mismatch repaid deficiency). PD-L1 was positive 23 (23.9%) cases (range, 5.0-90%). Only a single case showed MMRP=D in association with positive PD-L1. 35 cases were positive for P53 stain (range from 10-90%). 18 cases were positive for PD-L1 and P53.
Conclusion: Unlike our previously reported high frequency of MMRP-deficiency in high grade gliomas in paediatrics, especially the biallalic germline mutation, MMRP-deficiency does not appear to be prevalent in high grade gliomas in AYA. Expression of PD-L1 in a quarter of cases might suggest a role of immunotherapy in high grade glioma.

OFP-08-006

The quantification of the methylation status of methyl-guanil-methyl-transferase gene (MGMT) by prosequencing from macrodissected paraffin embedded tumours is a relevant prognostic parameter in glioblastoma

M.A. Idoate[1], P. Gómez Roca[1], E. Benitez[1], C. De Andrea[1], J. Echeveste[1], A. Arcadi[1]
[1] Pathology Department. University Hospital and School of Medicine, University of Navarra, Spain

Background & Objectives: The enzyme methyl-guanyl_methyl-transferase (MGMT) is a relevant protein that repairs the DNA that counteracts the effect of temozolamide on glioblastomas (GBM). The hypermethylation of the promoter of the MGMT gene inactivates the tumour enzyme, which is related to a greater survival of the patients. It is postulated that the quantification of the methylation status of MGMT could be a significant parameter. However, there are a few studies about quantification by pyrosequencing of tumour obtained by using macrodissection of formalin-fixed paraffin-embedded (FFPE) samples in GBM.
Methods: A retrospective review of the clinical and pathological characteristics of a wide series of 60 GBM, well characterised clinically and molecularly, was carried out in the period between 2009 and 2016. A quantitative determination of the MGMT methylation status was made by pyrosequencing from macrodissected FFPE samples. In all cases the percentage of tumour cells in the macrodissected sample was >40%. Four highly discriminating methylated/non-methylated CpG islands were tested. The final result was obtained by averaging the methylation percentage of the 4 CpG islands in each case. Two approaches to data management were evaluated, the first one considering that values of 25% and higher methylation was the prognostic risk factor, and the second considering the methylation factor in quartiles of their sample distribution (<5% , 5%-9.4%, 9.4-20% and >20% methylation). The results have been correlated with relevant clinical and oncological parameters. A complete statistical study has been applied.
Results: Kaplan Meier analysis showed that the MGMT status methylation was an independent prognostic factor in respect with the age, KPS and tumour resection. For a cut-off value >25% of MGMT methylation the correlation with survival was especially strong (Wilcoxon, p=0.01). The median survival of patients with GBM with MGMT> 25% was 24.62 months and a 2 years overall survival of 100%, while that of the group with a MGMT <25% was 14 months and a 2 years survival of 18%. In addition, in the quartiles cases the MGMT was highly significant prognostic parameter with a Log-Rank test of p=0.002 and a Wilcoxon test of p=0.001. The median of overall survival of patients in the first quartile with a MGMT <5% was 13.6 months (IC95% 8.4-15.5) and for the fourth quartile (MGMT >20%) was 24.8 months (IC95% 21.1-30.4).
Conclusion: It is concluded that the quantification by pyrosequencing from DNA obtained by using macrodissection of FFPE samples is a good procedure to evaluate the methylation status of the MGMT in GBM. The MGMT methylation status constitutes a relevant independent prognostic parameter to be applied in the routine diagnosis of GBM.

OFP-08-007

The place and prognostic value of TERT promoter mutation in molecular classification in grade II-III glial tumours and primary glioblastomas

N. Kaya Terzi[1], I. Yilmaz[2], A.B. Oz[3]
[1] University of Health Sciences, Sultan Abdulhamid Han Training Hospital, Istanbul, Turkey, [2] Ministry of Health Istanbul Provincial Health Directorate Istanbul Sultan Abdulhamid Han Sample Training and Research Hospital, Department of Pathology, Turkey, [3] University of Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey

Background & Objectives: Diffuse gliomas, the most common primary malignant brain tumours, were classified by the World Health Organization as class II-IV gliomas. After 2016, in addition to the IDH, 1p / 19q and ATRX status, two mutations in the promoter region of TERT gene are frequently identified.
Methods: In our study, we identified 84 patients with grade II-IV glioma with IDH, ATRX and 1p / 19q status. All tumour samples were subjected to molecular genetic screening (Sanger sequencing for IDH and TERT mutations, fluorescence in situ hybridization for 1p/19q codeletion) after histological diagnosis (immunohistochemistry for IDH1 R132H, ATRX and p53) for a more precise / molecular diagnosis. The confidence intervals were calculated at the 95% confidence level and differences at $p < 0.05$ were considered statistically significant.
Results: Primary glioblastomas had the highest frequency of *TERT* promoter mutations (p=0.006) followed by oligodendrogliomas (p<0.001); astrocytomas showed the lowest frequency (p=0.107). *TERT* promoter mutations were found associated with high grade (grade III + IV) tumours when compared to lower grade (grade II) lesions ($P < 0.033$). *TERT* promoter mutations were more frequent in patients older than 55 years of age at diagnosis ($P=0.023$). Best overall survival was associated with the presence of both *TERT* promoter and *IDH* mutations (median survival 38.07 months), which resembles oligodendroglial progression. In

survival analysis in patients with primary glioblastomas we did not observe any effect of the *TERT* promoter mutations. Survival in gliomas with a wild TERT mutation and 1p19q codeleted (median survival 58.2 months) was higher than without TERT mutation and 1p19q codeletion (median survival 42 months). In this study we could not reach statistical significance (P = 0.957) for survival analysis, because of the lack of the number of TERTp mutant cases.
Conclusion: Molecular classifications proposed in the literature include the combination of the IDH, the 1 p / 19q codeletion and the telomere maintenance mechanism as defined by alterations in TERT. To determine if the TERT status provides additional prognostic information, we analysed the relationship between overall survival in glioma patients classified according to the WHO 2016 criteria in our study. We saw that the discovery of TERTp mutations in numerous gliomas has opened the door for a better glioma molecular classification. In the future new studies will help in elucidating the value of *TERT* promoter mutations as biomarkers in clinical practice and eventual therapeutic targets.

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OFP-08-008
Clinicopathological characterisation of gliomas with H3-K27M mutation: a case series
P. Amoroso Canão[1], R. Pestana Silva[1]
[1] Centro Hospitalar Universitário de São João, Portugal

Background & Objectives: Diffuse midline glioma with histone 3 lysine-27-methionine (H3-K27M) mutation is a new entity in the 2016 WHO Classification of Tumours of the Central Nervous System. This tumour typically occurs in a midline location and predominates in children. Regardless of the presence of high-grade histological features, the tumour is always assigned a WHO grade IV. In the present case series, we aimed to study the pathological features of gliomas with H3 K27M mutation diagnosed at a Portuguese tertiary centre, since 2016.
Methods: We selected all gliomas with H3 K27M mutation (2016-2018) and reviewed their clinicopathological features.
Results: We identified five cases of gliomas with H3 K27M mutation (3 males, 2 females). Mean age of diagnosis was 33,2 years (range: 12-45 years). Four were located in the thalamus and one in the cerebellum. All tumours had astrocytic phenotype and one had, focally, oligodendroglioma-like features. One tumour had only low grade histological features. All cases were identified using H3-K27M mutant protein antibody by immunohistochemistry. Despite treatment, all tumours showed radiological progression and two patients died of disease.
Conclusion: Glioma with H3-K27M mutation is a heterogeneous entity, with a wide spectrum of histological features. Immunohistochemistry using H3-K27M mutant protein antibody is an important diagnosis tool that should be considered in tumours of the Central Nervous System arising in the midline location.

OFP-08-009
Two fatal cases of amoebic encephalitis in Japanese farmers
H. Yoon[1], K. Kuroda[1]
[1] Nagasaki University Hospital, Japan
Background & Objectives: *Balamuthia mandrillaris* is the main pathogenic protozoa causing granulomatous amoebic encephalitis (GAE), which is a rare and progressively fatal disease. Patients with GAE present with fever, headache, nausea and vomiting, which is similar to those of patients with bacterial meningitis. If patients are not diagnosed and treated promptly with appropriate agents, they rapidly progress to death. Here we present two cases of Japanese farmers with GAE due to *Balamuthia mandrillaris*. Immunohistochemistry and PCR are valuable for early diagnosis.
Methods: Immunohistochemistry was carried out using antibodies: 1) 1:500 diluted sera of a previously known patient with GAE due to *Balamuthia mandrillaris*, 2) polyclonal rabbit one against *Balamuthia mandrillaris* and 3) polyclonal rabbit one against *acanthoamoeba*.
PCR using genomic DNA from FFPE sections was done for detection of *Balamuthia mandrillaris* and *acathoamoeba*.
Results: Both cases showed extensive necrotizing granulomatous inflammation in the brain haemisphere. Histologically there were numerous amoeba trophozoites admixed with occasional cysts in brain tissue, in particular, around blood vessels. One case developed multiple skin macules on the chest that showed panniculitis containing many amoeba trophozoite. Both immunohistochemistry and PCR confirmed the amoeba were of *Balamuthia mandrillaris*.
Conclusion: An accurate diagnosis of GAE caused by *Balamuthia mandrillaris* is very difficult, partly because the trophozoites of *Balamuthia mandrillaris* can morphologically mimic macrophages. The indirect immunoperoxidase staining using the patient's own diluted serum or specific antibody was quite valuable in identifying the organisms within the lesion. PCR should serve an excellent tool for early diagnosis.

OFP-08-010
Clinical significance of Ephrin receptor (Eph)-A1, -A5 and -A7 expression in uveal melanoma
M. Gajdzis[1], P. Gajdzis[2], S. Theocharis[3], R. Kaczmarek[1], P. Donizy[2], P. Sarantis[3], J. Klijanienko[4]
[1] Department of Ophthalmology, Wroclaw Medical University, Poland, [2] Department of Pathomorphology and Oncological Cytology, Wroclaw Medical University, Poland, [3] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [4] Department of Pathology, Institut Curie, Paris, France

Background & Objectives: Uveal melanoma (UM) is the most common primary intraocular malignant tumour in adults with high metastatic potential and unfavourable prognosis. Ephrin receptors (Eph) are a subpopulation of tyrosine kinase receptors that play important role in various aspects of cancer formation and progression. Moreover, Eph inhibitors are currently being explored as anti-cancer agents in clinical trials. The aim of the present study was to evaluate the clinical significance of Eph-A1, -A5 and -A7 expression in UM.
Methods: Eph-A1, -A5 and -A7 protein expression was assessed immunohistochemically on paraffin-embedded tissues from 94 patients with UM and was statistically analysed with clinicopathological features as also with overall and disease-free survival.
Results: High expression of Eph-A1 was positively correlated with a smaller tumour size ($p = 0.048$), absence of extrascleral extension ($p = 0.030$), lower mitotic activity ($p = 0.042$) and presence of vitreous hemorrhage ($p = 0.014$). High expression of Eph-A5 was associated with intact chromosome 3 ($p < 0.001$), absence of distant metastases ($p = 0.010$) and presence of vitreous hemorrhage ($p = 0.013$). No relevant associations were found for Eph-A7 expression. Survival analysis showed that only Eph-A5 expression was associated with statistically significant longer overall patients' survival rate ($p = 0.031$).
Conclusion: High Eph-A1 and -A5 expression should be considered as beneficial prognostic factors in UM patients. The expression of Eph-A1, -A5 and -A7 in UM cells indicates their possible use as candidates for targeted therapy.

OFP-08-011
Histone Deacetylase-2 expression predicts survival in uveal melanoma patients
S. Theocharis[1], P. Gajdzis[2], G. Levidou[3], D. Pouloudi[1], M. Gajdzis[4], P. Donizy[2], V. Milionis[1], S. Albesher[1], P. Korkolopoulou[5], J. Klijanienko[6]
[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [2] Department of

Pathomorphology and Oncological Cytology, Wroclaw Medical University, Poland, [3] Humanpathologie Dr. Weiß GmbH, Germany, [4] Department of Ophthalmology, Wroclaw Medical University, Poland, [5] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [6] Department of Pathology, Institut Curie, Paris, France

Background & Objectives: Uveal melanoma (UM) represents the most common primary intraocular malignancy in adults, exerting high metastatic potential and poor prognosis. Histone Deacetylases (HDACs), through post-translational histone modifications and subsequent gene expression alterations, play a key role in carcinogenesis. Aim of this study was to evaluate the clinical significance of HDAC-2 expression in UM.
Methods: HDAC-2 expression [percentage and intensity of staining as categorical variables, and their product immunoreactivity scoring system (IRS)], classified into 4 levels: negative, mild, moderate and strong) was assessed immunohistochemically in 74 UM tissue specimens and was correlated-with tumours' clinicopathological characteristics and with patients' overall (OS) and disease free survival (DFS).
Results: UM patients with negative/mild nuclear HDAC-2 IRS were older than those with moderate/strong IRS (p=0.05), whereas tumour size significantly differed among the four levels of IRS (p=0.0132). HDAC-2 nuclear and cytoplasmic IRS varied significantly among cases with different histological types, being higher in the epithelioid type (p=0.034 and p=0.042 respectively). Moderate/strong HDAC-2 nuclear IRS was more frequent in grades 2/3 and in cases with 8q chromosome gain (p=0.035 and p=0.047, respectively). Increased nuclear and cytoplasmic HDAC-2 IRS were correlated with favourable patients' OS, the latter in marginal terms (p=0.0415 and p=0.0846 respectively). In multivariate analysis HDAC-2 nuclear IRS remained significant (HR=0.309, p=0.003). HDAC-2 IRS was not correlated with patients' DFS.
Conclusion: HDAC-2 expression is correlated with important clinicopathological parameters and emerges as an independent, favorable prognostic factor in UM patients.

Tuesday, 10 September 2019, 08:30 - 12:00, Erato
OFP-09 | Joint Session: Autopsy Pathology / Cardiovascular Pathology / History of Pathology / IT in Pathology / Pathology in Favour of Developing Countries / Other Topics

OFP-09-001
Adult clinical necropsies: the gold standard of clinical practice are decreasing worldwide. And in Coimbra? A retrospective study from 2007 to 2018 comparing clinical and autopsy diagnoses
A. Lai[1], M.B. Pimentão[1], F. Ramalhosa[1], C. Faria[1], V. Almeida[1], H. Moreira[1], R. Almeida[1], J. Fraga[1], O. Caetano[1], M.A. Cipriano[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal

Background & Objectives: Clinical autopsies still are the gold standard of medical practice to find an accurate final diagnosis, despite the of great improvement of medical diagnostic procedures.
In order to demonstrate the importance of clinical autopsy, a retrospectively study of 134 adults autopsies, reported during 11 years (between 2007 and 2018), was performed.
Methods: The autopsies were classified in 3 categories: (1) clinical diagnoses confirmed through the autopsy, (2) clinical and autopsy diagnosis are different (3) absence of a clinical which was provided by autopsy findings, in order to compare the clinical information with the autopsy diagnosis.
Results: The majority of autopsies reported were male (79 patients or 59%) and the median age was 61 years old (range 19-89 years). The three departments with more autopsies requests were internal medicine (33 cases-25%), intensive care (32 cases-24%) and general surgery (11 cases-8%). The autopsy diagnosis more frequent were pulmonary thromboembolism (24 cases-18%) and pneumonia/bronchopneumonia (16 cases-12%). In fourteen cases, two diagnoses were considered, being pneumonia and bronchopneumonia diagnosis the most common. In 73 cases (54%) the clinical diagnosis was in agreement with the autopsy and, curiously, in 38% of cases the antemortem was different from postmortem diagnosis. In 10 cases (8%) the autopsy clarified the final diagnosis.
Conclusion: Our results reinforce the crucial role of clinical autopsies in medical quality management, so it is of the utmost importance "do not let the clinical autopsy die".

OFP-09-002
Morphological and virological diagnostics of myocarditis in patients with hypertrophic cardiomyopathy
E. Kogan[1], O. Blagova[1], A. Nedostup[1], V. Kadochnikova[2], A. Donnikov[2], Y. Frolova[3], S. Dzemeshkevich[3]
[1] First Moscow State Medical University (Sechenov University), Russia, [2] DNA Technology., Moscow, Russia, [3] Russian National Surgery Centre named after B.V.Petrovsky, Russia

Background & Objectives: To study the morphological changes and the frequency of viral genome detection in the myocardium in patients with true hypertrophic cardiomyopathy (HCM).
Methods: Study was performed on the material of biopsies (endomyocardial and operative) of the heart of 15 patients (11 women and 4 men, average age 42.9 ± 13.3 years, from 18 to 60 years) and 1 autopsy. Serial paraffin sections were stained with hematoxylin and eosin, picrofuchsin , CD45 was detected by immunohistochemistry (DakoCytomation). The levels of anticardial antibodies in the blood and the viral genome by PCR in myocardial tissue were determined (herpes viruses 1,2,6 types, zoster, Epstein-Barr, cytomegalovirus, parvovirus B19, entero / adenoviruses).
Results: Signs of myocarditis were found in 46.7%patients along with the changes typical for HCM (hypertrophy, degeneration, chaotic arrangement of cardiomyocytes),. The viral genome in the myocardium was detected in 73.3% of patients with true HCM (parvovirus B19, herpes viruses type 6, Epstein-Barr and their combinations), in the blood - in 33.3%, including in the blood and myocardium - in 20 %. Clinical suspicion of myocarditis was present in 3 patients (20%) with a combination of HCM and noncompact myocardium and was confirmed morphologically in all cases. Among 12 patients without clinical suspicion of myocarditis, its morphological signs were detected in 33.3% of cases.
Conclusion: Myocarditis with a high frequency is detected during myocardial biopsy in patients with HCM, including in the absence of clinical suspicion of it (intact systolic function), which must be considered when prescribing treatment to patients.

OFP-09-003
Canonical recognition and on-site palaeopathologic study of the Blessed Vincenzo dell'Aquila (1430-1504)
L. Ventura[1], M. Ioannucci[2], G. Tudico[1], A. Raffaele[3], C. Masciocchi[3,4]
[1] Division of Pathology, San Salvatore Hospital, L'Aquila, Italy, [2] Sacred Lipsanotheca, Metropolitan Archbishopry, L'Aquila, Italy, [3] Division of Radiology, San Salvatore Hospital, L'Aquila, Italy, [4] Department of Radiology, University of L'Aquila, Italy

Background & Objectives: Born to a humble family in the oldest part of L'Aquila (central Italy), Vincenzo worked as a shoemaker in his young age. In 1448, he entered the Regular Observance, a reform movement of the Franciscan Order. He received the gift of prophecy and was kept in great honour by the Aragonese Kings of Naples. After death he was greatly honoured by local people and authorities. His body was buried into the common grave of the friars and found intact when exhumed fourteen years later.

Methods: Previous recognitions of the body were performed in 1787, 1904, and 1987, but no special procedure aimed at paleopathologic investigation at that time. The fourth Canonical Recognition of the Blessed took place in February-march 2018. His mummy underwent external examination and on-site digital radiography.
Results: The extremely well-preserved, complete mummy belonged to an old male in good nutritional status. Marked dental wear and parodontal disease, in the absence of caries, were identified, along with artificial remodelling of face and feet. A huge swelling in the left groin, as well as parallel clean cuts of mummified skin were observed on shoulders and groins. No evidence of internal filling, sutures or fresh cuts was noted. Circular calcium deposits in the left costophrenic angle were displayed by radiography.
Conclusion: The absence of evisceration signs rules out artificial embalming, indicating a natural mummy. Clean cuts on shoulders and groin may be related to limb mobilization tests performed in ancient times. Calcification might be referred to pleural infection/effusion or splenic pathology.

OFP-09-004
Paleopathology of two mummified bodies from the Takarkori rock shelter (SW Libya, 6100-5600 years BP)
L. Ventura[1], C. Mercurio[1], G. Fornaciari[2]
[1] Division of Pathology, San Salvatore Hospital, L'Aquila, Italy, [2] Division of Paleopathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy

Background & Objectives: Two naturally mummified individuals from the Takarkori rock shelter (Tadrart Acacus Mountains, central Sahara, SW Libya), dating back to the Middle Pastoral period (ca. 6100-5000 years BP), were unearthed together with the skeletal remains of thirteen further individuals. Takarkori is considered a key site to understand Holocene human occupation in the central Sahara, giving insights on the funerary practices of pastoral groups in the region.
Methods: The partially mummified bodies of two females (TK-H1, TK-H9), respectively dating back to 6090±60 and 5600±70 years BP, underwent radiologic, CT scanning, and macroscopic examination. Selected samples of bones, tendons, intervertebral disks, skeletal muscles, vessels, skin and bowels were submitted to stereomicroscopy and histology examination.
Results: TK-H1 was a 30-35 years old woman, showing cranial vault porotic hyperostosis, a repaired left ulnar fracture, a sclerotic lesion of the femur consistent with enostosis (bone island), and multiple Harris' lines of proximal left tibia. TK-H9 was a skeletally mature individual, largely incomplete, without significant radiologic findings. Histology highlighted fibrous tissue with taphonomic changes, striated skeletal muscle, regular compact and lamellar bone, and visceral walls with endoluminal vegetal fibres and ectoparasites. Diffuse fungal colonization was also noted.
Conclusion: Along with the exceptional findings at Uan Muhuggiag and Fozzigiaren, the Takarkori bodies represent extraordinary mummified examples from that area. Although incomplete, they showed evidence of trauma and carential alterations. These individuals represent the oldest examples of mummies successfully submitted to histologic examination. Fungal spores, not to be confused with erytrocytes, are a constant finding in paleohistology, with no pathologic significance.

OFP-09-005
Histopathology and DNA evaluation of wet specimens from the Pathology Collection of Turin
L. Ferrari[1], J. Metovic[2], D. Rullo[3], D. Pulcinelli[4], A. Lombardi[4], F. Papola[4], L. Ventura[5]
[1] Division of Pathology Cardinal Massaia Hospital Asti, Italy, [2] Departments of Oncology Pathology Unit University of Turin Torino, Italy, [3] Division of Pathology San Salvatore Hospital L'Aquila, Italy, [4] Regional Centre of Immunohematology and Tissue typing San Salvatore Hospital L'Aquila, Italy, [5] Division of Pathology, San Salvatore Hospital, L'Aquila, Italy

Background & Objectives: The Pathology Collection of Turin houses around 300 wet specimens dating back to XIX-XX century. Most of them are in their original jars with labels describing year, necropsy number and diagnosis. Four cases originally diagnosed as uterine myosarcoma, lung cancer and pleural sarcomas underwent modern diagnostic revision and DNA evaluation by conservative sampling.
Methods: As the chemical composition of the storage fluids is unknown, pH value was measured in each specimen. Samples from the specimens were submitted to routine histology, histochemistry and immunohistochemistry. Additional tiny samples underwent DNA extraction and analysis by spectrophotometry and electrophoretic run in agarose gel. In order to verify DNA integrity, short tandem repeat (STR) analysis employed for personal identification was performed.
Results: The revised diagnoses were necrotic lung carcinoma, uterine leiomyosarcoma, lung metastases from squamous carcinoma of unknown primary and from uterine leiomyosarcoma. pH values were 2.56, 3.15, 4.45 and 4.65. The first two samples gave negative results on both spectrophotometric and electrophoretic analysis. The other two showed low DNA quantities of moderate quality. STR analysis displayed DNA fragmentation. The amplification of amelogenin STRs of chromosome X allowed the precise identification in one case.
Conclusion: Pathology Collections harbour diseases that no longer exist or with natural course unmodified. They are an actual biological archive and may represent a valid source for research on molecular features of ancient diseases. Despite unreliable immunohistochemical results, morphology and histochemistry addressed to final diagnosis. Although better preserved in alkaline medium, acceptable quantity/quality DNA may be obtained also from specimens in moderately acid pH.

OFP-09-006
The historical roots of theranostic revealed by the genealogical and phylogenetic portrayal of tumours by pathologists
C. Laboisse[1]
[1] Anatomie Pathologique Faculté de Médecine Université de Nantes, France

Background & Objectives: The representation of tumours first based in the 1800s on gross pathology and later on histopathology captures the ontological status (benign vs malignant) of tumours, considered for a long time as the sole contribution of pathology to therapy. In the1900s the genealogical relation between normal and neoplastic tissues unveiled by histopathology was used for therapeutic strategies.
Methods: The hormonal sensitivity of breast carcinomas was exploited by Beatson in 1896.The recapitulation by seminomas of the exquisite sensitivity of normal gonadal cells to X rays was exploited by Béclère who successfully proposed radiation therapy for this specific tumour type, thus creating the first theranostic in 1906. In 1943, the serendipitous observation of lymphopenias following exposure to nitrogen mustard led Goodman and Gilman to use this agent to treat lymphomas. In the 1980s the CD20 targeting immunotherapty of B-cell lymphomas was an extension of the genealogical imprint therapeutic strategy.
Results: During the 1980s advances in cancer genomics have spurred pathologists to add a new dimension to the portrayal of tumours by capturing their phylogeny i.e. the driver molecular events of neoplasia. Their work paved the way for the development of immunohistochemical and/or in situ hybridization companion tests intended as guides for adapting a drug to a specific patient. Interestingly the actionability of driver events was constrained by the tissue genealogy of tumours.
Conclusion: Finally, the ontophylogenetical portray of tumours is now exploited to determine the eligibility of patients for immune checkpoint blockade therapy

OFP-09-007

Scorenado: a customisable, user-friendly and open-source visual assessment tool for histological slides

M.D. Eichmann[1], S. Reinhard[1], I. Zlobec[1]
[1] University of Bern, Switzerland

Background & Objectives: Despite significant advances in the field of digital image analysis, visual assessment of histological slides by human experts is far from being rendered obsolete. This is due to the absence of reliable, broadly available, and ready-to-use image analysis algorithms and the increasing demand of expert image annotations for the development of state of the art image analysis algorithms. Here, we present Scorenado, a software solution for user-friendly visual assessment of whole-tissue slide and tissue microarrays (TMA) images, including image annotation quality evaluation.
Methods: For broad compatibility, Scorenado was developed as an open-source, cross-browser web tool in jQuery for individual users and groups in close collaboration with pathologists. It has been extensively tested in numerous histopathological research projects, generating a substantial amount of feedback on its usability and functionality, which has informed further development of the software. It runs on an Apache web server with PHP and on a Maria database. Additionally, Groovy scripts were written for the open-source software QuPath to automate the creation of TMA spot or tissue tile image collections for the use in Scorenado.
Results: Scorenado provides researchers with ready-to use annotation templates but also permits to define custom parameters of interest. It automatically optimises its graphical user interface accordingly. In combination with the randomisation of presented images, this facilitates visual assessment in a blinded, and time-efficient manner. Additionally, Scorenado includes inter- and intra-rater reliability assessment features for recorded image annotations. So far, Scorenado has been successfully used for visual assessment of tumour buds, immune cells, protein expression, and colorectal polyp tissue classes, totalling 97,332 TMA slide spots and 4,266 whole-tissue slide tiles.
Conclusion: Incorporating Scorenado into the research routine not only allows researchers to efficiently evaluate TMA and whole-tissue slides but also assists the evaluation of the quality of recorded image annotations. Finally, Scorenado greatly facilitates the creation of expert annotated datasets which may have the potential to significantly advance digital clinical histopathology.

OFP-09-008

Complete digital pathology for routine histopathology diagnosis: 2 year's experience at Granada University Hospitals, Spain

J.A. Retamero[1], J. Aneiros[1], R. G del Moral[1]
[1] Granada University Hospitals, Spain

Background & Objectives: Complete digital pathology for routine histopathology diagnosis has been implemented in few laboratories worldwide. Granada University Hospitals (GUH) which comprises two teaching and two peripheral district general hospitals integrated in the Spanish National Health System, implemented digital pathology for primary diagnosis in 2016. We describe the methodology adopted and resulting experience.
Methods: All the glass slides generated for routine histopathology diagnosis were digitized at x40 using the Philips IntelliSite Pathology Solution, that comprises an Ultra-Fast Scanner (UFS) and an Image Management System (IMS). All hematoxylin and eosin (H&E) stained preparations, as well as immunohistochemistry (IHC) and histochemistry slides were scanned. The existing sample tracking software and IMS were integrated to allow data interchange by means of Health Level 7 (HL7) protocol.
Results: More than 180,000 specimens have been reported using digital pathology as primary means of diagnosis. This comprises circa one million digitized glass slides. The scanning error rate during the implementation phase was below 1.5%, and subsequent slide production optimization reduced this rate to 1 per 1000. Since implementation, GUH pathologists signed out 21% more cases per year on average. .
Conclusion: Digital pathology is appropriate for primary histopathology diagnosis. Successful complete digitization relies on sample tracking and integration of the information technology infrastructure. Rapid and reliable scanning at 40x equivalent enabled the transition to a fully digital workflow. Digital pathology associated to efficiency gains in the pre- and analytical phases, and creates the foundation for the adoption of computational pathology.

OFP-09-009

Digital immunohistochemical evaluation of PDL1 in lung carcinomas highly correlates with manual method

B. Aszódi[1], T. Micsik[2]
[1] Semmelweis University, Budapest, Hungary, [2] 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

Background & Objectives: PDL1- blockers are immune checkpoint inhibitors, which offer a successful way of treatment in various solid cancers. The initiation of the threapy requires the definition of PDL1 immunpositiviy by Tumour/Combined Positivity Score (T/CPS) with different antibodies. It may sometimes be difficult. Our aim was to set up a Digital Image Analysis (DIA) algorythm for PDL1 immunohistochemistry and compare its results to manual microscopic evaluation.
Methods: 156 PDL1 (Dako 22C3 antibody) stained slides were scanned with Pannoramic Flash 250 Scanner (3DHistech, Hungary). DIA was trained on 50 randomly selected slides using 3DHistech's softwares. Subsequently, automatic whole slide image analysis was processed on 130 PDL1-slides.
Results: With various comparison of results, 0.75-0.89, strong correlation was found between the digital and microscopic evaluation of PDL1-slides. Clinical follow up is in progress to compare digital results with patients' response.
Conclusion: PDL1 immunohistochemical evaluation is usually required in order to begin immune checkpoint inhibitor therapy. There is inter - and intarobserver variability in results which can influence patients' therapy. Our Digital PDL1 Image Analysis algorythm successfully differentiated immune cells (lymhocytes and macrophages) from tumour cells and succeeded to define immunopositivity score in a standardised way - highly correating with traditional methods. Theoretically the standardised digital PDL1 evaluation could reduce intra- and interobserver variability, thus help better treatment targeting.

OFP-09-010

Convolutional neural networks can accurately distinguish histologic subtypes of pulmonary high-grade neuroendocrine tumours on digital whole-slide images

M. Ilie[1], F. Henderson[2], J. Benzaquen[3], S. Heeke[4], E. Long-Mira[1], S. Lassalle[1], J. Fayada[5], M. Hamila[5], M. Poudenx[3], C. Marquette[3], V. Hofman[1,5], P. Hofman[1,5]
[1] Universitè Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, Laboratory of Clinical and Experimental Pathology, Nice, France, [2] Indica Labs, Applications Department EMEA, London, United Kingdom, [3] Universitè Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, Department of Pulmonary Medicine and Oncology, Nice, France, [4] Team 4 IRCAN, Inserm U1081/CNRS 7284, IRCAN, Nice, France, [5] Universitè Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, Hospital-Integrated Biobank (BB-0033-00025), Nice, France

Background & Objectives: The histological distinction between small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) can be challenging in some cases, while bearing prognostic and therapy significance. Moreover, there are borderline high-grade neuroendocrine carcinomas that morphologically fall between LCNEC and SCLC. To assist pathologists with the differentiation of histologic

subtyping, we applied a deep learning classifier equipped with convolutional neural network (CNN; HALO-AI, Indica Labs, UK) to recognize pure and combined SCLC and LCNEC.
Methods: Slides of primary lung SCLC and LCNEC were obtained from the Laboratory of Clinical and Experimental Pathology (University Hospital Nice, France). The HALO-AI module trained with 10,324 image tiles extracted from 40 slides (SCLC and LCNEC) was evaluated on 20 slides (SCLC, LCNEC and combined SCLC and LCNEC) by F1-score and accuracy using manual tumour annotations by three senior pathologists.
Results: The tumour maps were false coloured and displayed side-by-side to original H&E slides with superimposed pathologist annotations. Subsequently, confusion matrices representing the classification performance was calculated for each digital slide. The trained HALO-AI yielded F1-scores of 0.86 (LCNEC), 0.83 (SCLC), and 0.81 (combined SCLC/LCNEC), respectively. The overall accuracy of distinguishing the two histotypes was 87%.
Conclusion: Our CNN model trained on a limited number of slides could work side-by-side with the pathologist to accurately differentiate between SCLC and LCNEC in challenging cases.

OFP-09-011

Pathology teaching: the use of art and active methodologies

J. Melo[1], V. Holanda Ferreira[2], F. Klezevski Pimentel[2], A. Santiago Nogueira[2], P. Rocha Aguiar Neto[2], L. Carvalho Figueira[2], D. Nunes Oliveira[1], M. Luiz Balancin[3], S.A. de Souza Júnior[2]
[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil, [3] Pathology Division, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil

Background & Objectives: Undergraduate pathology teaching is a life-long challenge to medical educators and pathologists alike. In the context of a Problem Based Learning (PBL) curriculum, we have employed artistic and creativity tools to enhance pathology learning and compliance in the undergraduate medical curriculum.
Methods: Discuss about pathology teaching.
Results: In the General Pathology module of the second year (MS2) healing and repair are studied and a painting workshop is held, in which sketches are made from the direct microscopic visualization of slides by the students, while discussing the phases and biological properties of the process. During second and third years, reporting and requesting a report is practiced to understand the clinical concepts of pathology practice. Theatre practice is employed to discuss pathogenesis between small student groups. Autopsy practices in a local coroner division is held during third year. In these practices, students perform an autopsy exam while supervised by instructors, generating awareness of the technical and ethical backgrounds of Medical practice. Digital resources are also employed, as a website to teach autopsy practice, digital flash cards and online tools as Socrative and Kahoot. In these applications, teachers or monitors can create virtual classrooms for interactive and simultaneous access of participants, allowing the monitoring of the pace of learning of students through a control panel that represents, immediately, the performance of students in real time.
Conclusion: The so-called active methodologies are being used, questioning and motivating students and teachers alike, engaging and enhancing the general perception and awareness of pathology as a clinical medical specialty.

OFP-09-012

Morphological features of liver biopsies from The Gambia, West Africa: first pathology report from the "Gambia Hepatitis Intervention Study" by the International Agency for Research on Cancer

B. Abedi-Ardekani[1], D. Nasrollahzadeh[1], R. Njie[2,3], S.O. Bittaye[3], C. Carreira[1], M. Salieu Jallow[4], M. Almonte[1], C.P. Wild[1]
[1] International Agency for Research on Cancer/WHO, France, [2] International Agency for Research on Cancer/WHO, Gambia, [3] GHIS Disease Control and Elimination, MRC Unit, Gambia, [4] Pathology Department, Edward Francis Small Teaching Hospital (EFSTH), Banjul, Gambia

Background & Objectives: Hepatocellular carcinoma (HCC) is the most common malignancy in The Gambia where the prevalence of Hepatitis B virus is high. The International Agency for Research on Cancer (IARC) initiated and follows the Gambia Hepatitis Intervention Study (GHIS) since 1986, as a randomized trial of infant Hepatitis B vaccination aiming to prevent HCC in adult life. The cohort of over 120,000 children is now in early 30's. Since 2015, liver biopsies taken from Gambian patients are evaluated at IARC. We report the morphological features of liver disease based on the pathology platform developed under this collaboration.
Methods: With the support from IARC and the local feasibilities, we set up the pathology workflow for liver biopsies. Biopsies from Gambian patients who fulfil the eligibility criteria for liver biopsy are processed in the local hospital (EFSTH) and the paraffin blocks are shipped to IARC for microscopic evaluation. We use modified hepatitis activity index (mHAI) and METAVIR to score the necroinflammatory activity (grade) and the degree of fibrosis (stage) of liver parenchyma. Diagnosis of HCC is confirmed by immunohistochemistry when any or both of HepPAr1 and Arginase 1 are positive. We grade the differentiation by applying two methods: four-tired Edmondson-Steiner as well as three-tired score of well, moderately, and poorly differentiated.
Results: From May 2015 to December 2018, we received 334 biopsies among them 211 were qualified as "satisfactory for evaluation". Insufficient tissue and/or low quality of tissue processing led to labelling them as "insufficient for diagnosis". 29 showed no significant pathological changes and 21 were diagnosed as "secondary" liver masses. Table below summarizes the morphological findings of 161 patients.

	Chronic hepatitis	HCC
Number*	84	77
Mean age (SD)	41.0 (14.0)	47.0 (15.0)
Male (%)	86%	85%
HBs-Ag positive	80%	48%
Grade by ISHAK; Mean (SD)	9.0 (4.0)	
Stage by ISHAK; Mean (SD)	4.0 (2.0)	
Activity by METAVIR; Mean (SD)	2.0 (1.0)	
Stage by METAVIRM; Mean (SD)	3.0 (1.0)	
Grade of HCC (Edmondson-Steiner)		
Well differentiated (I, II)		15%
Moderately differentiated (III)		69%
Poorly differentiated (IV)		16%
Elastography (MSTIF); Mean (SD)	22.7 (21.0)	62.0 (42.0)

*There are missing data for all estimates up to 29% of data.

Conclusion: Set up of efficient clinical and diagnostic approaches in a low-income country is challenging but possible. The supportive role of organisations such as IARC to provide necessary infrastructure and facilitate training programs is not negligible for this performance. In this context, we succeed to set up an adapted pathology workflow that enabled us to create and describe here the first documented pathology data on liver diseases, the most important public health problem, in The Gambia.

OFP-09-013

Sectioning-free virtual H&E imaging of tissue samples with two-photon microscopy

J.P. Kolb[1], M. Strauch[1], D. Weng[1], M. Wacker[1], W. Draxinger[1], S. Karpf[1], R. Huber[1]
[1] University of Lübeck, Germany

Background & Objectives: Paraffin sectioning is a time- and labor-intensive step in the routine pathology workflow. Frozen sectioning is much faster but results in a lower quality of the sections. We use two-photon microscopy (TPM) of bulk tissue samples to create images resembling standard H&E-stained slides without any sectioning. In addition to simplifying the pathology workflow, this rapid technology can provide 3-dimensional histological images that could lead to higher diagnostic value of the data.
Methods: In order to achieve an H&E compatible staining, bulk tissue samples are quick-stained (2-10 min) with acridine orange (nuclei stain) and sulforhodamine 101 (counterstain) without any sectioning. The tissue samples are imaged using our home-built two-photon microscope achieving high three-dimensional resolution volumetric data records. This is achieved through the inherent confocality of the nonlinear TPM process. Two separate spectral channels (nuclei- and counterstain) are recorded and merged to create an H&E-equivalent image ready for histological assessment and post-process digital sectioning.
Results: We successfully recorded sectioning-free H&E-like images with our two-photon microscope with considerably less work compared to conventional paraffin-sectioning. Comparison of TPM and conventional H&E sectioning by other groups has shown similar image quality, but the equivalence still needs to be proven conclusively. Further, additional speed improvements are required. This will be feasible using improved system hardware and also implementing parallel processing of the volumetric dataset.
Conclusion: Virtual H&E imaging with TPM will simplify the pathology workflow in the future if the challenges of higher imaging speed and data processing are met. The simple creation of 3D images and the potential combination with other imaging modalities (e.g. TPM fluorescence-life-time-imaging), might increase the diagnostic accuracy. Future research will investigate the comparability to standard H&E staining and fluorescent immunostains.

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OFP-09-014

A nationwide pulmonary carcinoid tumour cohort collected from the Finnish clinical pathology integrated biobanks

T. Vesterinen[1], K. Salmenkivi[1], H. Mustonen[2], T. Kuopio[3], E. Lappi-Blanco[4], T. Paavonen[5], P. Vainio[6], A. Knuuttila[7], C. Haglund[2], J. Arola[1]
[1] HUSLAB, Department of Pathology, University of Helsinki and Helsinki University Hospital, Finland, [2] Department of Surgery, University of Helsinki and Helsinki University Hospital, Finland, [3] Department of Biological and Environmental Science, University of Jyväskylä and Department of Pathology, Central Finland Health Care District, Finland, [4] Department of Pathology, Center for Cancer Research and Translational Medicine, Oulu University Hospital and University of Oulu, Finland, [5] Department of Pathology, Fimlab Laboratories and Department of Medicine and Life Sciences, University of Tampere, Finland, [6] Department of Pathology, University of Turku and Turku University Hospital, Finland, [7] Department of Pulmonary Medicine, Heart and Lung Center, and Cancer Center, University of Helsinki and Helsinki University Hospital, Finland

Background & Objectives: Finnish biobanks administer millions of tissue samples collected within the clinical diagnostics between 1990 and 2013. According to the Finnish Biobank Act, these samples can be coupled with patients' clinical data from the patient registries as well as with the data retrieved from the national health registries. As pulmonary carcinoid (PC) tumours are rare tumours, we decided to utilize biobanks to collect a nationwide PC tumour cohort.
Methods: We applied for clinical data and tissue material from primary PC tumour patients operated on between 2002 and 2011 from all appropriate Finnish biobanks (n=6). Data on PC incidence was retrieved from the Finnish Cancer Registry.
Results: According to the Finnish Cancer Registry, 227 PCs (216 typical carcinoid (TC) and 9 atypical carcinoid (AC) tumours) were diagnosed nationally from the primary tumour tissue sample (biopsy or resection) between 2002 and 2011. Processing time in the biobanks from application to material delivery varied between 6 and 24 months. Altogether, we received 125 resected PC tumours coupled with clinical data. After re-evaluation, 98 (78%) were classified as TC and 27 (22%) as AC. Here we describe the major reasons for relatively low number of tumours found in the biobanks as well as discuss the annotation bias observed in the primary diagnostic database. In addition, the bottlenecks and advantages of pathology integrated biobanking are discussed.
Conclusion: Finnish biobanks are a valuable resource for studying rare tumours. However, expert pathologists are needed to find the suitable samples. Moreover, re-classification of the samples collected during decades is a necessity.

Tuesday, 10 September 2019, 08:30 - 12:00, Galliéni 5
OFP-10 | Joint Session: Pulmonary Pathology / Thymic and Mediastinal Pathology

OFP-10-001

Vascular endothelial growth factor (VEGF) and its receptors expression in lung carcinoids: clinicopathological correlation

F. Fortarezza[1], F. Pezzuto[1], F. Lunardi[1], G. Comacchio[1], F. Rea[1], F. Calabrese[1]
[1] University of Padua, Italy

Background & Objectives: Lung carcinoids are neuroendocrine tumours classified in two histological subtypes, typical and atypical, based on the mitotic index and the presence of necrosis. They are considered low-grade tumours, although metastases, recurrences may occur, particularly in atypical forms. Several morphological features (proliferative index, tumour size and vascular invasion) have been studied for a better prognostic stratification, but the results are inconclusive. These tumours are usually highly vascularized thus the evaluation of angiogenetic factors has emerged as a diagnostic and therapeutic tool.
Methods: The aim of the study was the evaluation of the VEGF pathway, mainly involved in angiogenetic mechanisms. A retrospective and observational study was carried out on 79 lung carcinoids (62 typical, 17 atypical), consecutively resected from 2005 to 2011 at the Thoracic Surgery Division of Padua University. The expressions of VEGF and VEGFR1, VEGFR2, and VEGFR3 receptors were evaluated by immunohistochemical assay and then correlated with morphological (histotype, staging, proliferative index) and clinical (age, sex, tabagism, follow-up) features.
Results: Atypical carcinoids showed bigger tumour size ($p = 0.03$), higher proliferative index ($p < 0.0001$) and higher expression of VEGF ($p = 0.02$), VEGFR1 ($p = 0.01$), VEGFR2 ($p < 0.001$) and VEGFR3 ($p < 0.001$) than typical ones. Interestingly, VEGFR3 expression directly correlated with proliferative index ($p = 0.05$). VEGFR3 expressions were related to the presence of lymphnode metastatization independently from histotype ($p < 0.005$). Age, sex and tabagism did not influence tissue expression of any receptor.
Conclusion: High expression of the VEGF pathway, particularly VEGFR3, in atypical and typical metastatic carcinoids could be a substrate for mechanistic studies to validate its prognostic and predictive value.

OFP-10-002

Biomarkers in lung cancer: descriptive analysis of a centralised platform in Spain (Lungpath)

J. Martin Lopez[1], A. Brito Garcia[2], E. Gallego Dominguez[3], J. Bautista Laforga[4], J.L. Lopez Hidalgo[5], M.I. Esteban Rodriguez[6], M.d.C. Saez Rodriguez[7], I. Sansano Valero[8], M. Medina Perez[9], A. Benito Berlinches[10], F. Perez Ochoa[11], F. Dominguez[12], A. Sanchez Espinosa[13], H.H. Torres Rivas[14], N. Mancheño Franch[15], P. Machin Andreu[16], A. Lerin Martos[17], T. Hernandez Iglesias[18], A. Martinez Pozo[18], C. Salas Anton[1]

[1] Department of Pathology. Hospital Universitario Puerta de Hierro, Spain, [2] Hospital Universitario de Canarias. Santa Cruz de Tenerife, Spain, [3] Hospital Universitario Virgen de la Victoria. Malaga, Spain, [4] Hospital Universitario Doctor Peset. Valencia, Spain, [5] Hospital Universitario Campus de la Salud. Granada, Spain, [6] Hospital Universitario La Paz. Madrid, Spain, [7] Hospital Universitario Clinico San Carlos. Madrid, Spain, [8] Hospital Universitario Vall d´Hebron. Barcelona, Spain, [9] Hospital Universitario Reina Sofia. Cordoba, Spain, [10] Hospital Universitario Ramón y Cajal. Madrid, Spain, [11] Hospital Universitario Mutua de Terrassa. Barcelona, Spain, [12] Hospital de Cabueñes. Gijon, Spain, [13] Hospital Universitario de Cartagena, Spain, [14] Hospital Universitario Central de Asturias. Oviedo, Spain, [15] Hospital Universitario y Politècnico La Fè. Valencia, Saint Vincent and the Grenadines, [16] Consorci Sanitari Integral. Barcelona, Spain, [17] Hospital Sant Pau i Santa Tecla. Tarragona, Spain, [18] SEAP, Spain

Background & Objectives: Biomarker testing on pathology specimens is an essential requirement to properly treat lung cancer (LC) patients. Is undeniable the increasing number of LC predictive biomarkers, as the increasing development of targeted therapies. *LungPath* is an on-line tool developed by the Spanish Society of Pathology (*SEAP*) with free and voluntary participation of differents Departments of Pathology to registry, monitor and trace biomarker results in clinical practice. After initial data reclutation step, first objective is to realize a descriptive analysis of *LungPath*.

Methods: Descriptive analysis of *Lungpath*. Biomarkers determinations of LC patients were collected from March 2018 to January 2019, from 38 Spanish Departments of Pathology.

Results: Based on this real clinical practice database, 19.332 biomarkers were tested over a total of 4.773 samples from LC patients. Small lung biopsies (60%), surgical resection specimen (16,3%) and cell block cytology (10,7%), fine needle aspiration cytology (5,1%), blood (2,5%) and other non lung biopsies (5,4%).

The subtypes were adenocarcinoma (66%), squamous cell carcinoma (SCC) (19%), large cell neuroendocrine carcinoma (3,7%), large cell carcinoma (0,3%) and non-small cell lung cancer (NOS) (6,1%). The most frequently biomarker tested was EGFR mutation (91,4%) followed by ALK traslocation (80,1%), PD-L1 expression (58,1%) and ROS1 traslocation (56,2%) in non-squamous histology and PD-L1 expression (73,6%) in SCC. Plus forward information obtained.

Conclusion: No similar data regarding LC predictive biomarker has been published before in Spain.

Lungpath provide an opportunity to registry clinical practice data and in the future could be an useful tool to monitor, correlate results between different centers and improve the available knowledge regarding biomarkers in LC.

OFP-10-003

Evaluation of molecular testing in a Dutch cohort of metastatic non-small cell lung cancer patients from 2017

C. Kuijpers[1], M. van den Heuvel[2], A. van Lindert[3], R. Damhuis[4], S. Willems[1]

[1] Department of Pathology, University Medical Centre Utrecht, Utrecht, The Netherlands, [2] Department of Lung Disease, Radboudumc, Nijmegen, The Netherlands, [3] Department of Respiratory Medicine, University Medical Centre Utrecht, The Netherlands, [4] Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands

Background & Objectives: Adequate and timely testing for genetic alterations in non-small cell lung cancer (NSCLC) is necessary to consider targeted therapy when a certain genetic alteration is present. Previously, we demonstrated that in the Netherlands molecular testing was suboptimal in 2015, as 25% (EGFR/KRAS and ALK) to 50% (ROS1) of patients were not tested according to guidelines, and notable laboratory variation was present. Currently, by analyzing a cohort of metastatic NSCLC from 2017 we aim to assess whether the performance of molecular testing improved.

Methods: All fully registered stage IV non-squamous NSCLC with incidence year 2017 from the Netherlands Cancer Registry were matched to the Dutch pathology registry (PALGA). Using information extracted from pathology excerpts, proportions of tumours tested for EGFR/KRAS, BRAF, and HER2 mutation, ALK, ROS1, and RET rearrangement <3 months after diagnosis were determined.

Results: Of 2596 identified patients, we have currently analysed 511 (20%). Twenty-three patients were non-eligible after matching, leaving 488 patients. EGFR/KRAS testing was performed in 412 patients (84.4%). Of the EGFR/KRAS wildtype tumours (n=184), 167 (90.8%) were tested for BRAF, 158 (85.9%) for HER2, 157 (85.3%) for ALK, 110 (59.8%) for ROS1, and 73 (39.7%) for RET. Insufficient tumour tissue and inappropriate specimen were the most stated reasons for not testing.

Conclusion: These preliminary data show significantly higher EGFR/KRAS and ALK testing proportions compared to 2015. Further improvement remains possible to identify candidates for targeted therapy. At the ECP meeting, we expect to present the variation between laboratories for the entire cohort.

This work was funded by Roche, Pfizer, AstraZeneca.

OFP-10-004

Interlaboratory variation in PD-L1 positivity in non-small cell lung cancer patients: a comparison between histological and cytological material

B. Koomen[1], R. Voorham[2], C. Kuijpers[1], I. Deckers[2], S. Willems[1]

[1] Department of Pathology, University Medical Centre Utrecht, The Netherlands, [2] PALGA Foundation (the nationwide network and registry of histo- and cytopathology in The Netherlands), Houten, The Netherlands

Background & Objectives: Immunohistochemical expression of programmed death ligand 1 (PD-L1) is used to select patients with non-small cell lung cancer (NSCLC) for immunotherapy. PD-L1 immunohistochemistry (IHC) has been validated in histological material but is often performed on cytological material. This study aims to determine if interlaboratory variation in PD-L1 positivity differs between histological and cytological material.

Methods: Using the Dutch Pathology Registry (PALGA), pathology reports of NSCLC patients between 01-07-2017 and 30-06-2018 from all Dutch pathology laboratories were identified. For each laboratory, the proportion of reported PD-L1 positive cases was determined for histological and cytological material separately, using two cutoffs (1% and 50%). Proportions were compared between laboratories by creating funnel plots with 95%-confidence intervals (CI). For analysis of histological material, 4005 patients from 27 laboratories were included. For analysis of cytological material, 1098 patients from 21 laboratories were included.

Results: Analyzing histological material, 55.7% of cases were PD-L1 positive using the 1%-cutoff. Eight (29.6%) laboratories fell outside the 95%-CI, differing significantly from the mean. Using the 50%-cutoff, 30.5% of cases were PD-L1 positive. Three (11.1%) laboratories differed significantly from this average. Analyzing cytological material, 51.1% of

cases were PD-L1 positive using the 1%-cutoff. Eight (38.1%) laboratories differed significantly from the mean. Using the 50%-cutoff, 28.5% of cases were PD-L1 positive. Four (19.0%) laboratories differed significantly from the mean.
Conclusion: Interlaboratory variation in PD-L1 positivity was greater for IHC performed on cytological material than for IHC performed on histological material. Furthermore, variation was greater for the 1%-cutoff than for the 50%-cutoff in both material types.

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OFP-10-005
Reduced isolated red signal pattern of ALK FISH in lung cancer patients

I. Kocsmar[1], G. Smuk[2], G. Pajor[2], î Kocsmár[1], K. Szuhai[3], T. Tornóczky[2], G. Lotz[1]
[1] 2nd Department of Pathology, Faculty of Medicine, Semmelweis University, Hungary, [2] Department of Pathology, Medical School, University of Pècs, Hungary, [3] Department of Molecular Cell Biology, Leiden University Medical Center, The Netherlands

Background & Objectives: Autoimmune encephalitis can be triggered by infections, paraneoplastic disorders or it may be idiopathic, and present by variety of clinical manifestations, which can be acute or subacute. We report the case of a 53-year-old patient, with no history of epilepsy or other neurological disorder, presenting with acute onset aphasia and disorientation that rapidly evolved to altered mental status, generalized tonic-clonic seizures, respiratory difficulty and evolving to refractory status epilepticus, prompting admission to the intensive care unit.
Methods: The patient had a personal history of essential thrombocythemia and insulin-treated diabetes mellitus. Following extensive investigation, vascular, paraneoplastic, infectious and metabolic aetiologies were excluded. Cerebral CT and MRI, and cerebrospinal fluid analysis were normal. Serum and CSF evaluation of neuronal cell-surface antibodies (NMDA, AMPA, GABA, VGKC) was negative. Thyroglobulin antibodies and thyroid peroxidase antibodies were elevated in serum and negative in the cerebrospinal fluid.
Results: Despite aggressive immunomodulatory treatment there was no clinical improvement and after 46 days the patient died of a medical condition (septic shock). The main findings of the post-mortem neuropathologic examination were inflammatory lesions, namely microglial nodules, distributed in the limbic region (hippocampus, entorhinal cortex and periamygdaloid cortex) and brainstem, particularly in the pons. No inclusions suggestive of viral infection were identified.
Conclusion: Although the patient had high serum thyroid autoantibodies, the lack of response to high-dose corticosteroid therapy along with the neuropathological examination favour the diagnosis of seronegative limbic and brainstem encephalitis and do not support the hypothesis of Hashimoto's encephalopathy. We highlight the importance of neuropathological examination in refractory status epilepticus and further CSF studies are still being performed.

OFP-10-006
The new gold standard for detection of theranostic gene rearrangements in thoracic oncology is born: one-year prospective routine LD-RTPCR in 328 newly-diagnosed lung adenocarcinomas

N. Piton[1], P. Ruminy[2], M. Lanic[2], A. Lamy[1], F. Marguet[1], F. Guisier[1], M. Salaün[1], L. Thiberville[1], F. Jardin[2], J. Sabourin[1]
[1] Rouen University Hospital, France, [2] Centre Henri Becquerel, France

Background & Objectives: *ALK*, *ROS*, *RET* translocations and *MET* exon 14 skipping may be difficult to detect by routine techniques, especially when specimens are exiguous. We recently demonstrated in a retrospective small series of translocated lung adenocarcinomas of known status that LD-RTPCR assay could efficiently identify *ALK*, *ROS* and *RET* rearrangements with a sensitivity of 64% and with perfect specificity. Here, we report an upgraded version of this assay used in a routine prospective cohort of newly diagnosed lung adenocarcinomas.
Methods: Prospective cases of newly diagnosed lung carcinomas referred to the molecular platform of Rouen University Hospital between 2018 and 2019 for ALK and ROS IHC, high throughput molecular testing and sometimes FISH were tested in parallel with the LD-RTPCR assay. This technique was designed to detect at one go ALK, ROS and RET translocations (with identification of the partner gene) and MET exon 14 skipping at minimal cost (less than 5 euros) and with results in two days.
Results: 328 lung carcinomas were included in our study. The LD-RTPCR assay detected 9 of the 10 *ALK* and 3 of the 3 *ROS* translocated tumours positive for IHC and FISH, but also 5 of the 5 *MET* exon 14 skipping mutations observed by high throughput sequencing. In addition, it retrieved 5 molecular alterations that had been missed by the classical process: 3 *MET* exon 14 skipping mutations and 2 *RET* translocated tumours, then confirmed by other means.
Conclusion: We successfully implemented LD-RTPCR for gene translocation and *MET* exon 14 skipping detection in routine analysis. This technique is cheap, very fast, sensitive and specific, and easily upgradable (e.g. *NTRK* translocations). Owing to the overwhelming advantages of this assay, we recommend considering it as the new reference for systematic testing of lung adenocarcinoma in parallel with IHC and genotyping.
Normandie Valorisation, Rouen University Hospital, Boehringer

OFP-10-007
Birt-Hogg-Dubé (BHD) syndrome-associated lung cysts: histopathological analysis and differential diagnosis from miscellaneous cystic lung diseases

M. Furuya[1], Y. Nakatani[2]
[1] Yokohama City University, Japan, [2] Yokosuka Kyosai Hospital, Japan

Background & Objectives: Birt-Hogg-Dubé (BHD) Syndrome is a rare hereditary disorder caused by *FLCN* germline mutation. Almost all individuals with BHD syndrome have multiple lung cysts; however, the lung specimens are often misdiagnosed as blebs/bullae or emphysema. The aim of the study is to clarify histopathological clues to differentiate BHD syndrome-associated cysts from miscellaneous cystic lung diseases.
Methods: We investigated *FLCN* mutations and clinicopathological findings of 520 symptomatic individuals from 200 Japanese families with BHD syndrome. Lung specimens from 120 patients who underwent video-assisted thoracoscopic surgery (VATS) and an autopsied BHD syndrome-associated lung were reviewed.
Results: The cysts were preferentially distributed in the mediastinal and lower regions. A number of cysts in the pulmonary central/hilar regions abutted large bronchi and vessels. Microscopic analysis of specimens showed that a typical parenchymal cyst localized astride interlobular septa, with a lining of benign-looking alveolar epithelium on the inner surface, and that most cysts had rugby oval rather than round shapes as they intruded into and grew along the interstitial tissue surrounding bronchial trees and blood vessels.
Conclusion: Fibrous thickening and inflammation are frequently observed in the vicinity of subpleural cysts; however, near complete epithelial lining is demonstrated in most of BHD syndrome-associated cysts. Other cystic lung diseases that must be distinguished include lymphangioleiomyomatosis and cystic lesions of autoimmune diseases such as Sjögren's syndrome. Recognition of the aforementioned pathological features allow pathologists to reach the correct diagnosis.

OFP-10-008

Combined assessment of tumour mutational load, CD8+ T cell infiltration, and expression of PD-L1 and HLA class I in small biopsy specimens to predict immunotherapy response in non-small cell lung cancer

D. Hurkmans[1], M. Kuipers[2], J. Smit[2], R. Mathijssen[1], P. Postmus[2], P. Hiemstra[2], J. Aerts[3], R. van Marion[4], S. van der Burg[2], J. von der Thüsen[3]
[1] Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [2] Leiden University Medical Center, The Netherlands, [3] Erasmus Medical Center, Rotterdam, The Netherlands, [4] Erasmus University Rotterdam, The Netherlands

Background & Objectives: A combination of biomarkers is likely to provide more accurate prediction for response to immunotherapy in non-small cell lung cancer (NSCLC) patients than PD-L1 expression alone. In routine practice these need to be determined in small biopsy specimens, limiting the amount of material available for testing. The feasibility of assessment in small biopsy specimens of a series of mechanism-of-action based parameters was studied for response prediction of immunotherapy.
Methods: Retrospective cases of metastatic NSCLC patients (n=30) with sufficient remaining archival tissue, obtained prior to the first nivolumab administration, were selected. Tumour mutational load (TML) was determined using a next-genome sequencing panel (409 cancer-related genes). Immunohistochemistry was performed to score PD-L1, total $CD8^+$ T cell infiltration and HLA class I.
Results: In all 30 patients with adenocarcinoma (67%) or squamous cell carcinoma (33%) complete assessment of biomarkers was achieved, despite the availability of limited amounts of tissue. TML alone as well as combinations of high TML, PD-L1 expression, high $CD8^+$ T cell infiltrate, or no loss of HLA class I were significantly associated with better survival.
Conclusion: This study underscores the feasibility of multimodality, combinatorial determination of PD-L1 expression, TML, $CD8^+$ T cell infiltration and HLA class I expression as predictive biomarkers for the response to anti-PD-1 immunotherapy in a real-life setting in NSCLC.

OFP-10-009

Decreased PD-L1 immunostaining in cytological specimens after fixation in an ethanol based fixative

B. Koomen[1], W. Vreuls[2], M. de Boer[1], J. Hölters[3], A. Vink[1], S. Willems[1]
[1] Department of Pathology, University Medical Centre Utrecht, The Netherlands, [2] Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands, [3] Department of Pulmonology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

Background & Objectives: Expression of programmed death-ligand 1 (PD-L1) protein is used to select patients with non-small cell lung cancer (NSCLC) for immunotherapy. PD-L1 immunostaining is often performed on cytological material, but pre-analytical variables may affect PD-L1 expression. We studied if pre-fixation in an ethanol based fixative leads to a decrease in PD-L1 immunostaining, using a standardised assay (SP263) and a laboratory-developed test (LDT) (22C3).
Methods: Transbronchial needle aspirates from 42 NSCLC patients were fixed in both formalin and fixcyt (50% ethanol). Next, clots from both fixatives were processed into formalin-fixed paraffin-embedded blocks. From each block, serial sections were stained for PD-L1 with SP263 (Ventana Benchmark Ultra platform) and 22C3-LDT (Dako Omnis platform). Tumour proportion scores (TPS) were determined, using three categories (<1%, 1-49%, ≥50%). TPS was compared between paired samples from each patient.
Results: Using SP263, 19% of cases showed discordant results between formalin-fixed and fixcyt-fixed material, with 75% of discordant cases showing lower TPS in fixcyt-fixed material. Dichotomizing data using the 1%-cutoff showed a lower concordance level (kappa 0.71) than when the 50%-cutoff was used (kappa 0.88). Using 22C3-LDT, 24% of cases were discordant. Again, most of these (90%) showed lower TPS in fixcyt-fixed material compared to formalin. Concordance levels were equal for both cutoffs (kappa 0.72).
Conclusion: Cytological specimens pre-fixed in an ethanol based fixative showed decreased PD-L1 immunostaining with both SP263 and 22C3-LDT. Although concordance levels were still within the moderate or substantial range, pre-fixation in ethanol based fixatives may increase the risk of assigning patients to a lower PD-L1 TPS category.

OFP-10-010

Interstitial lung disease in systemic sclerosis is associated with autoimmunity to α1(V) chain of type V collagen

A.P. Pereira Velosa[1], L. Brito[2,3], Z.A. Queiroz[2], S. Carrasco[2,3], J. Tomaz de Miranda[2,3], C. Goldenstain-Schainberg[2,3], E. Roger Parra[2,4], V.L. Capelozzi[2,5], W. Rosolia Teodoro[2,3]
[1] Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [2] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [3] Rheumatology Division, Brazil, [4] Department of Pathology, Brazil, [5] Department of Rheumatology, Brazil

Background & Objectives: Interstitial lung diseases (ILD) are among the most serious complications associated with systemic sclerosis (SSc). Recently, type V collagen (ColV) has been associated to autoimmunity in pulmonary fibrosis. Our group have shown the pathogenic role of ColV in clinical and pre-clinical models of SSc. In this study, we evaluated the autoimmunity to α1(V) and α2(V) chains of the Col V in SSc-ILD.
Methods: Sera from 19 patients with SSc were tested for anticollagen V antibodies presence by flow cytometry. IgG fraction of the resulting pool of positive samples was isolated by affinity chromatography to further biotinylation (ColV-IgG+). Adsorption of the biotinylated IgG with α1(V) [ColV-IgG+/ads-α1(V)] and α2(V) [ColV-IgG+/ads-α2(V)] chains was employed to evaluate the spectrum of reactivity in lung biopsies obtained from SSc-ILD patients (n=4) by immunofluorescence. Eight ColV-immunogenic peptides were tested to evaluate the reactivity in ColV-positive sera samples of SSc patients.
Results: We found that 7 (36,84%) sera samples were reactive to ColV. The SSc-ILD lung tissue immunostained with ColV-IgG+ showed intense green fluorescence along of vascular basement membrane, bronchiolar smooth muscle and adventitial layer, contrasting with the tenue ColV expression in control lung (32,86±8,018 vs. 0,4688±0,4688, $p<0.05$). ColV-IgG+/ads-α1(V) showed decreased birefringence in SSc-ILD lung tissue compared to ColV-IgG+ (10,05±4,585 vs. 32,86±8,018, $p<0.05$) and ColV-IgG+/ads-α2(V) (10,05±4,585 vs. 30,21±4,286, $p<0.05$). ColV-positive sera samples of SSc patients presented immunoreactivity for Col5A1(599) and Col5A1(1.049) peptides.
Conclusion: We found that the autoimmunity to Col V is directed to α1(V) chain, emerging as promisor biomarker of prognosis and target therapy in SSc-ILD patients.

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OFP-10-011

Multivariate survival analysis reveals RAD51 protein as a superior prognostic factor compared to tumour infiltrating lymphocytes and PD-L1 expression in patients with resected non-small-cell lung carcinoma

M. Gachechiladze[1], J. Skarda[2], V. Kolek[3], P. Smickova[3], Z. Kolar[2], R. Stahel[4], W. Weder[5], U. Rulle[6], A. Soltermann[7], M. Joerger[8]
[1] Department of Clinical and Molecular Pathology, Palacky University Olomouc, Czech Republic, [2] Department of Clinical and Molecular Pathology, Palacky University and University Hospital Olomouc, Czech Republic, [3] Department of Tuberculosis and Respiratory Diseases, Palacky University and University Hospital Olomouc, Czech Republic,

[4] Oncology Clinic, University Hospital Zurich, Switzerland, [5] Clinic of Thoracic Surgery, University Hospital Zurich, Switzerland, [6] Institute of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland, [7] Institute of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland, [8] Department of Oncology and Haematology, Cantonal Hospital St.Gallen, Switzerland

Background & Objectives: DNA repair proteins have emerged as potential predictors for immunotherapy response alongside PD-L1 expression, tumour-infiltrating lymphocytes (TILs) and tumour mutational burden. The aim of the study was to analyse immunotherapy relevant alterations in PD-L1 expression in tumour cells and in TILs; TIL count; expression of the major homologous recombination (HR) protein RAD51; and their potential prognostic value in patients with resected non-small-cell lung carcinoma (NSCLC).
Methods: Tissue microarrays from 96 NSCLC patients from the University Hospital Olomouc, Czech Republic (training set) and from 1109 NSCLC patients from University Hospital Zurich, Switzerland (validation set), were stained by standard immunohistochemistry, using antibodies against: RAD51; T cell markers - CD3 and CD8; macrophage marker - CD68; and PD-L1. H-score for nuclear RAD51 and quantitative scores for total (tumour + stromal) CD3, CD8 and CD68 were calculated. PD-L1 expression was scored according to the guidelines of European Thoracic Oncology Platform.
Results: Low number of CD3, CD8, CD68 and PD-L1 positive TILs, and loss of nuclear RAD51 (H-score ≤ .10) were associated with poor overall (OS) and progression free (PFS) survivals. Low tumoural PD-L1 was associated with poor PFS in patients treated with neoadjuvant chemo-/radiotherapy (n=99). Multivariate analysis revealed that loss of RAD51 protein is an independent negative prognostic factor for PFS in training set (HR=1.8) and for PFS (HR=0.7) and OS (HR=0.7) in the validation set. All p values are <0.05
Conclusion: RAD51 immunohistochemical expression in tumour tissue is a strong and independent prognostic factor in patients with resected NSCLC and may complement PD-L1 and TIL for patients receiving immune checkpoint inhibitors. Further studies on RAD51 immunoexpression in patients with NSCLC is justified, particularly patients receiving immunotherapy.

OFP-10-012
Copy number variation by NGS predict HER2 amplification status by ISH in NSCLC

H. Kivrak[1], H. Özakıncı[1], T. Baglan[1], Y. Sahin[1], S. Dizbay Sak[1]
[1] Ankara University, Turkey

Background & Objectives: HER2 amplification is found in 1-19% in pulmonary adenocarcinomas and it is one of the mechanisms of acquired resistance to first-generation tyrosine kinase inhibitors. We aimed to investigate the correlation of copy number variation (CNV) of HER2 gene by NGS, with immunohistochemical expression and amplification as determined by in-situ hybridization (ISH).
Methods: We investigated 13 cases showing CNV of HER2 gene by NGS (GeneRead QIAact Lung DNA UMI Panel), HER2 protein overexpression and amplification were evaluated by immunohistochemistry (IHC) (clone 4B5) and silver ISH (INFORM HER2 Dual ISH DNA Probe) using HER2 testing guidelines for breast carcinoma.
Results: HER2 CNV was detected in 7.8 % of our non-small cell lung carcinoma (NSCLC) cases. Two of our cases showed additional pathogenic KRAS and EGFR mutations. Of the 8 cases that were evaluated by IHC; 2,2,3 and 1 cases were scored as 0,+1,+2 and +3 respectively. Unusual staining patterns (nuclear and/or cytoplasmic) were observed in 2 cases that were scored as 0. For the 7 cases that were evaluated by SISH, HER2/CHR17 ratios ranged from 1.27 to 7; 4 cases being ≥2. In an additional adenocarcinoma showing HER2 mutation (c.929C> T, p.S310F), focal membranous and diffuse cytoplasmic/nuclear positivity was detected by IHC.
Conclusion: HER2 CNV is not a rare event in NSCLC, and it shows a correlation with amplification, as determined with ISH. HER2 CNV/amplification is not a mutually exclusive driver event in lung carcinogenesis, as it is observed in cases with other driver mutations.

OFP-10-013
Isolation and next-generation sequencing of RNA from microdissected fibroblastic foci areas of patients with idiopathic pulmonary fibrosis

S.E. Vuljan[1], F. Lunardi[1], G. Esposito[2], F. Pezzuto[1], F. Fortarezza[1], M. Schiavon[1], F. Rea[1], F. Calabrese[1]
[1] University of Padua, Italy, [2] Veneto Institute of Oncology, Italy

Background & Objectives: Formalin-fixed paraffin embedded (FFPE) tissue is the most commonly used method to preserve and store tissue. However, its use is limited to molecular analysis due to RNA degradation and RNA-protein crosslinking during fixation which impacts on RNA quality. Laser capture microdissection (LCM) is a powerful method to isolate specific populations of cells from heterogeneous tissue. We performed a modified RNA extraction method from LCM FFPE tissue to recover sufficient RNA useful for subsequent RNA-sequencing (RNA-Seq) analysis.
Methods: We isolated fibroblastic foci (FF) areas from tissue of 10 idiopathic pulmonary fibrosis (IPF) patients using LCM. Total microdissected FF number/patient were 87 ± 33 with a mean total area of 396637,2 ± 951131,6 μm^2. RNA was extracted using an overnight lysis step followed by incubation at 80°C for 15 minutes. RNA was preserved by adding RNase inhibitors at the end of the extraction procedure. Quality was evaluated with a 2100 Bioanalyzer Agilent 6000 pico kit. Libraries were obtained with the SMARTer Stranded Total RNA-Seq kit pico input mammalian of Takara Bio. Quality was expressed as DV200.
Results: We successfully adapted a protocol to isolate RNA from small amounts of clinical LCM tissue samples. Using this approach, the mean quantity was 3181 ± 2502 pg/μl (mean±SD), ranging from 840 pg/μl to 7530 pg/μl. Quality evaluation showed a mean value of 50.5% of DV200 (low-medium quality) ranging from 41% to 70%. Final libraries were obtained with a 3.4-22.6 ng/μl quantity and a mean cDNA fragment length of 289 nucleotides.
Conclusion: These data show that this protocol, optimised in our laboratory, lead to the extraction of adequate RNA samples from difficult and limited FFPE tissues, in order to perform RNA-Seq analysis. The possibility to study gene expression in specific cells/areas of FFPE tissue represents an important issue for a better understanding of disease pathogenesis and for the identification of crucial biomarkers.

OFP-10-014
Visceral pleural invasion by tumour size, cancer type and pathologist in 1,560 resections

M. Bonert[1], J. Cutz[1], C. Finley[1], I. El-Shinnawy[1], S. Salama[1], G. Gohla[1], S. Alowami[1], D. Lukic[1], F. Tayyari[2], R. Juergens[3], A. Naqvi[1]
[1] McMaster University and St. Joseph's Healthcare Hamilton, Canada, [2] St. Joseph's Healthcare Hamilton, Canada, [3] McMaster University and Hamilton Health Sciences, Canada

Background & Objectives: Visceral pleural invasion (VPI) is a poor prognosticator in lung cancer and often upstages small tumours. We sought to assess the VPI rate.
Methods: All resections at a thoracic centre for lung primaries (accessioned between July 2012-Dec 2017) reported with a synoptic report were retrieved and analysed. VPI rates were calculated by diagnosis and tumour size. Pathologist VPI rate variation was assessed with funnel

plots centred on the group median rate (GMR) and an in silico kappa (ISK).
Results: The study period had 1,560 lung resections. 922 resections had tumours <=3 cm and 279 (30%) of these had VPI. Overall, VPI was seen in 11%, 27% and 40% of <=1, >1 & <=2 and >2 & <=3 cm lesions respectively; 12%, 32% and 49% of adenocarcinomas (ADN) and 9%, 22% and 30% of squamous cell carcinomas (SCC). Eleven pathologists interpreted >40 resections (range: 41-298) and together saw 1,406. There were zero $p < 0.001$ pathologist outliers for tumours <=3 cm in relation to the GMR; however, 3 of 11 pathologists were ($p < 0.001$) outliers for the VPI rate in <=3 cm tumours. The ISK for VPI in all tumours/VPI in <=3 cm tumours was 0.63/0.60; this is better than for lymphovascular invasion present (0.56) but worse than the diagnosis of ADN (0.91) and SCC (0.86).
Conclusion: VPI showed the expected variation by size and diagnosis. Funnel plots and the ISK suggest that pathologist interpretation is a significant factor and may be optimizable with statistical process control and judicious use of ancillary testing.

OFP-10-015
Interobserver variation in the classification of thymic lesions including biopsies and resection specimens in an international digital microscopy panel
J. Wolf[1,2], H. Blaauwgeers[3], A. Marx[4], F. van Nederveen[5], A.G. Nicholson[6,7], A. Roden[8], P. Ströbel[9], W. Timens[10], A. Weissferdt[11], J. von der Thüsen[2], M. den Bakker[12]
[1] Leiden University Medical Center, The Netherlands, [2] Erasmus Medical Center, Rotterdam, The Netherlands, [3] Onze Lieve Vrouwen Gasthuis, Amsterdam, The Netherlands, [4] Universitätsklinikum Mannheim, Germany, [5] PAL Laboratory, Dordrecht, The Netherlands, [6] National Heart and Lung Institute, Imperial College London, London, United Kingdom, [7] Department of Histopathology, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom, [8] Mayo Clinic, Rochester, USA, [9] Institute of Pathology, University Medical Center Göttingen, Germany, [10] University Medical Center Gronigen, The Netherlands, [11] MD Anderson Cancer Center, Houston, USA, [12] Maasstadziekenhuis, Rotterdam, The Netherlands

Background & Objectives: Thymic tumours are a rare entity in routine pathology practice. Although the WHO classification describes a number of well-defined categories, diagnosis remains challenging
Methods: 332 tumours consisting of 98 biopsies and 234 resection specimens were reviewed in a panel-based virtual microscopy approach by a group of 13 pathologists with expertise in thymic tumours over a period of six years. The specimens were classified according to the WHO classification. The data was subjected to statistical analysis and interobserver concordance (Fleiss Kappa) was calculated.
Results: The overall level of agreement was almost perfect (K=0.877) and differed slightly between the resection specimens (K=0.919) and the biopsies (K=0.777). By subclassifying thymomas according to the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up into groups including [B2, B3] vs [A, AB, B1] and [B3] vs [A, AB, B1, B2], the level of agreement decreased slightly (K=0.792 and K=0.846 respectively). The best agreements reached were in thymoma types A and AB. Difficulties arose in distinguishing thymoma (especially A and B3) from thymic carcinoma. Within the thymoma subgroup difficulties in distinction were seen within the B-group.
Conclusion: Overall agreement of distinguishing mediastinal lesions was good when assessed by pathologists with experience in dealing with this rare tumour. Digital pathology facilitates access to what is essentially a multinational resource. This platform provides a template for dealing with rare tumours where expertise is sparse.

Tuesday, 10 September 2019, 17:15 - 19:15, Athéna
OFP-11 | Joint Session: Soft Tissue and Bone Pathology / Infectious Diseases Pathology

OFP-11-001
Immunohistochemical and molecular analysis of NTRK-rearranged mesenchymal tumours
M. Le Quang[1], J. Massiere[2], A. Rullier[1], V. Velasco[3], J. Coindre[3,4], F. Le Loarer[5,6]
[1] CHU Bordeaux, France, [2] INSERM U1812, Institut Bergoniè, Bordeaux, France, [3] Institut Bergoniè, France, [4] Universitè de Bordeaux, France, [5] Department of Biopathology, Institut Bergonie, Bordeaux, France, [6] University of Bordeaux, Talence, France

Background & Objectives: Tropomyosin receptor kinases (Trk) can be activated through activating translocations which may be targeted with specific monoclonal antibodies. The family includes 3 transmembrane receptors (TRKA/C), involved in neural signalisation. Translocations involving these genes can be found in many tumours but are mostly recurrent in mesenchymal tumours. No definitive evidence is available regarding their morphological spectrum and performance of immunohistochemistry. Therefore we systematically assessed a series of these lesions.
Methods: *NTRK*-rearranged tumours were retrieved from our archives including 11 infantile fibrosarcomas, 41 biphenotypic sinonasal sarcomas, 5 lipofibromatosis-like neural tumours, 9 conventionnal lipofibromatosis, 1 high grade spindled sarcoma with neural phenotype, 20 myofibromas/myofibromatosis. TRK expression was assessed with 2 pan-TRK (clones A7H6R and EPR17341); and 1 NTRK-C (clone C44H5)antibodies. Tumours were tested by FISH with NTRK1 break-apart probes or whole RNA-sequencing (Truseq RNA exome, Illumina).
Results: All but one tumour displayed low grade features. The high grade case was a spindled proliferation expressing S100 and CD34 in a 66yo adult. Pan TRK expression was diffuse in all but one NTRK1-rearranged tumours (the high grade being negative). NTRK3-fused tumours were mostly negative for both pan-TRK and TRK-C staining with 2 different nuclear or cytoplasmic patterns of staining. Diffuse expression for TRK-C was seen in all biphenoptypic sinonasal sarcomas despite absence of underlying fusion. RNA-sequencing evidenced *NTRK1* fusions with *TPR* (n=1), *TPM3* (n=1) and *IRF2BP2* (n=1) in 5' and *LMNA* in 3' (n=2).
Conclusion: Pan-TRK immunostaining is highly sensitive to detect *NTRK1* but not *NTRK3* rearrangements. Positivity may be seen in *NTRK*-wild type tumours, warranting molecular testing.

OFP-11-002
Contribution of Raman Spectroscopy to diagnosis and grading of chondrogenic tumours
R. Gaeta[1], A. Franchi[2], M. D'Acunto[3], R. Capanna[1]
[1] University of Pisa, Italy, [2] Department of Translational Research and of New Technologies in Medicine and Surgery, University of Pisa, Italy, [3] Institute of Biophysics, National Research Council, Pisa, Italy

Background & Objectives: Raman Spectroscopy (RS) is a technique based on inelastic scattering of monochromatic light, usually a laser with wavelengths falling in the Ultraviolet-Visible-Near Infrared range. RS has demonstrated to be a label-free and non-destructive optical spectroscopy able to improve diagnostic accuracy in cancer diagnosis. We applied Raman spectroscopy imaging in order to discriminate and grade cartilaginous tumours.
Methods: The study group included three patients affected by enchondroma (EC) and seven affected by chondrosarcoma (CS) (three grade 1, two grade 2 and two grade 3). We performed spectroscopy

analyses with a Raman Imaging Microscope on formalin-fixed paraffin embedded unstained tumour tissue sections.
Results: Several differences in the amino acid composition were highlighted between the tumour types. In particular, the amount of β–Carotene progressively reduced from EC to high-grade CS, while the degradation of collagen increased with the CS grade. Interestingly, Linear Discrimination Analysis algorithm revealed major differences in chemical composition between the group of EC-grade 1 CS and the group of grade 2-grade 3 CS.
Conclusion: RS may be a useful tool in the histopathological analysis of cartilaginous tumours since it provides biochemical information related to tumourigenesis and progression of disease. Notably, the acquisition of a metastatic potential that characterises grade 2 and grade 3 CS was associated with a significantly different biochemical profile in comparison with Grade 1 CS and EC, that are considered benign or locally aggressive tumours. Our results may contribute to improve diagnostic accuracy and reduce inter-observer variability in the assessment of chondrogenic tumours.

OFP-11-003
Dedifferentiated liposarcoma with myxoid liposarcoma-like features and amplification of DNA damage-inducible transcript 3 (DDIT3) - an important diagnostic pitfall

A. Szumera-Cieckiewicz[1], O. Kuczkiewicz-Siemion[2], P. Wisniewski[2], A. Wojnowska[2], M. Grabowska-Kieryl[2], K. Olszewska[2], P. Rutkowski[3], H. Kosela-Paterczyk[3], M. Prochorec-Sobieszek[1]
[1] Institute of Haematology and Transfusion Medicine, Diagnostic Haematology Department, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland, [3] Maria Sklodowska-Curie Institute - Oncology Center, Department of Soft Tissue/Bone Sarcoma and Melanoma, Poland

Background & Objectives: Dedifferentiated liposarcoma (DDLSP) is characterised by fusiform-cell-rich dedifferentiated fields coexisting with adipocyte-rich well-differentiated areas. A key feature of DDLSP is an amplification of 12q13-15 region, which includes the *MDM2* and *DDIT3* gene. While MDM2 amplification is considered a pathognomic feature of DDLSP, *DDIT3* is typically rearranged in myxoid liposarcoma. Recent studied showed that *DDIT3* amplification is associated with myxoid-like morphology in DDLSP. The aim of our study was to present a case series of DDLSP with myxoid-like features harbouring both, *MDM2* and *DDIT3* amplification.
Methods: Six cases of DDLSP with myxoid-like morphology were investigated pathologically, immunohistochemically and geneticallly. Extended histopathological examination evaluated the presence of homologous lipoblastic differentiation and round-cell component. Immunohistochemistry panel including MDM2 staining was performed. Molecular analysis by fluorescence in situ hybridization was established to determine the status of *MDM2* and *DDIT3* genes.
Results: The patients mean age was 63.5 (range from 44 to 85 years) with a 2:1 male to female ratio. Tumours were localized retroperitoneally (3) and extra-retroperitoneally (3). Morphologic features resembling pleomorphic liposarcoma were identified in 2/6 (33%) cases. No round-cell component was found. All the cases demonstrated amplification of 12q15 and 12q13 regions containing *MDM2* and *DDIT3* genes, respectively. No rearrangement of DDIT3 was observed.
Conclusion: Our study demonstrates a correlation between *DDIT3* amplification and specific morphologic features, which is the second original report in the literature. *DIDT3*-amplified DDLSP with areas resembling myxoid and pleomorphic liposarcoma may be misclassified as myxoid or pleomorphic liposarcoma. It is important to be aware of this potential diagnostic pitfall.

OFP-11-004
Immunohistochemical analysis of 33 cases of chondroblastomas: a single institutional experience from India

B. Rekhi[1], S. Ghate[2], A. Shah[2], M. Ramadwar[3]
[1] Department of Pathology, Tata Memorial Hospital, Mumbai, India, [2] Department of Surgical Pathology, Tata Memorial Hospital, Mumbai, India, [3] Tata Memorial Hospital, Mumbai, India

Background & Objectives: Chondroblastoma is a relatively uncommon, primary benign bone tumour of young individuals; at times, fraught with a diagnostic challenge, especially in differentiating it from a giant cell tumour; osteosarcoma and chondrosarcoma. Lately, few studies have shown the diagnostic utility of DOG1 in chondroblastomas. The present study was undertaken to evaluate immunohistochemical (IHC) expression of S100protein, DOG1 and p63 in 33 chondroblastomas.
Methods: From January 2013 to December 2018 (6-year duration), 104 chondroblastomas were diagnosed with IHC staining, performed in 33 cases. Conventional Hematoxylin and Eosin stained microsections and IHC stained sections, in 33 cases were reviewed. The extent of IHC staining of p63, S100 protein and DOG1 was classified as focal (staining present in <50% of tumour cells) and diffuse (>50% of tumour cells).
Results: Seventy-four tumours occurred in males and 30 in females, with age-range of 7-55 years(median=18.4), frequently in tibia (35/104:33.65%), followed by femur, pelvis, calcaneum, talus, ribs, mandible and skull base. IHC staining for S100P was positive in 30/33cases (diffuse in 18; focal in 12); DOG1 in 13/16cases (diffuse in 6; focally in 7) and p63 in 8/13cases (diffuse in 1; focal in 7). Sensitivity and specificity for S100P, DOG1and p63 in chondroblastomas was (90.9%, 59.3%); (81.25%, 100%) and (64.3%, 46.6%), respectively.
Conclusion: S100 protein and DOG1 can be utilized for an objective diagnosis of a chondroblastoma, especially in diagnostic dilemmas, in view of certain associated therapeutic implications.

OFP-11-005
Superficial CD34+ fibroblastic tumour: clinicopathological, molecular and cytogenetic study of 4 cases

R. Perret[1], R. Carr[2], J. Massière[3], J.M. Coindre[1,4], F. Le Loarer[1,4]
[1] Department of Biopathology, Institut Bergonie, Bordeaux, France, [2] Department of Histopathology, South Warwickshire NHS Foundation Trust, Warwick Hospital, United Kingdom, [3] INSERM U1812, Institut Bergoniè, Bordeaux, France, [4] University of Bordeaux, Talence, France

Background & Objectives: Superficial CD34+ Fibroblastic Tumour (SCFT) is a recently described soft tissue neoplasm of borderline malignancy. To date fewer than 50 cases have been reported mainly concerning the clinical and histological features. Molecular studies have been rare, although a single case had a t(2;5) chromosomal translocation. We describe the clinicopathological, genomic and transcriptomic features of four new cases.
Methods: Three cases were retrieved from the consultation files of the Institut Bergonié (France) diagnosed in 2018-2019 and a further case came from Warwick Hospital (UK). Clinical data were obtained from the referring centers. Thorough histological examination was performed including immunohistochemistry. Array-Comparative genomic hybridization (aCGH, Agilent platform, 8x60k array) and whole RNA sequencing (RNAseq, Illumina, Truseq-exome) was undertaken in 2 and 3 cases, respectively.
Results: Patients were all males (age range 21 to 54 years). Tumours were located on the lower extremity (n=3) and shoulder (n=1). One case was a local recurrence. Histologically, all lesions were well circumscribed, composed of spindle and pleomorphic cells with low mitotic activity. Tumours expressed CD34 (4/4), Pan-CK (3/4), Desmin (2/4) and Androgen Receptor (2/3). aCGH genomic profiles were flat. Preliminary RNAseq results showed no translocations. One case had mutations of *FGFR1*/*TET2* and similar transcription profiles to myxoinflammatory fibroblastic sarcoma.

Conclusion: In this study SCFT had consistent clinicopathological features with simple aCGH profiles. Although translocations were not seen and studies are still ongoing, RNAseq data showed novel *FGFR1*/*TET2* mutations and transcriptomic resemblance with myxoinflammatory fibroblastic sarcoma in one case. These results support the concept of SCFT as a distinct entity and expand the genomic characterization of this uncommon tumour.

OFP-11-006

Denosumab-treated giant cell tumours of bone: what happens in a short-middle term follow up?

C. Fumagalli[1], E. Chenu[1], A. Sebio[1], A. Peiró[1], E. Moreno[1], J. Llauger[1], I. Gracia[1], S. Baguè[1], R. Orellana[1]
[1] Hospital de la Santa Creu i Sant Pau, Spain

Background & Objectives: Giant cell tumour of bone (GCTB) is a locally aggressive tumour that most often affects epiphysis and epiphysometaphyseal areas of long bones in young to middle-aged adults. Denosumab, a RANKL inhibitor, has been used as neoadjuvant therapy, mostly in non-surgical cases.
Aims of this study are to evaluate the efficacy of preoperative Denosumab therapy and the GCTBs' changes and to document local recurrences after surgery.
Methods: The cohort includes 23 patients (15females, 8males), median age: 37y-o. All patients underwent surgery after a median time of 11 months of Denosumab treatment (two cases developed adverse effects - mandibular osteonecrosis- and stopped the treatment earlier).
Results: Anatomical locations of GCTB: lower extremity 13, upper extremity 4, spine 1 and pelvis 3. Median size: 5,7 cm. All post-treatment surgical specimens showed histological changes related to Denosumab, consisting of absence/reduction of giant cells, fibrosis, neoossification and lympho-histiocytic infiltration.One case showed pseudosarcomatous change, and slight nuclear atypia was present in two biopsies.Two patients with R1 surgery had residual tumour.Three patients had local recurrences. 78% of cases are free of disease after a median follow up of 18 months (1-104).
Conclusion: The use of Denosumab has shown variable histological and radiological responses, with worrisome histological changes in some cases THAT could lead to a misdiagnosis of malignancy. Despite the adverse effects, the use of Denosumab allows more conservative surgery and a low rate of recurrences.

OFP-11-007

INSM1 immunohistochemical expression in a large cohort of Ewing sarcoma family of tumours

A. Llombart-Bosch[1], I. Machado[2], J.A. López-Guerrero[2], S. Navarro[1], F. Giner[3], P. Picci[4]
[1] Pathology Department, University Valencia, Spain, [2] Instituto Valenciano de Oncología, Valencia, Spain, [3] Pathology Department, Universitary Hospital "La Fe", Valencia, Spain, [4] Pathology Department, The Rizzoli Orthopaedics Institute, Bologna, Italy

Background & Objectives: Insulinoma-associated protein 1(INSM1) is an emerging nuclear neuroendocrine marker. Its expression has been tested in limited series of Ewing sarcoma family of tumours (ESFT). Given the potential neuroendocrine differentiation in ESFT, we aimed to determine INSM1 expression in a large series of genetically-confirmed ESFT and in a control cohort of tumours with well-known neuroendocrine differentiation or neoplasms with previously-reported neuroendocrine expression.
Methods: INSM1 immunohistochemistry on 433 ESFT, 54 Merkel cell Carcinomas(MCC), 97 synovial sarcomas (SS), 28 Solitary fibrous tumour (SFT), 200 GIST and 13 extraskeletal myxoid chondrosarcomas (EMC). Nuclear staining of moderate/strong intensity in at least 5% of tumour cells was considered positive.
Results: All MCC and 61% of ESFT were positive for INSM1. EMC, SFT, SS, GIST displayed INSM1 immunoreactivity in 70%, 21%, 2% and 0.5% of the cases, respectively. Staining was diffuse in all MCC and many ESFT and EMC but focal in SS, GIST and SFT. In ESFT, INSM1 staining was not correlated with histological subtypes.
Conclusion: INSM1 expression in ESFT is higher than previously described, nevertheless this finding does not distinguish these tumours from other "small round cell tumours" (SRCT) such as MCC, EMC or SS that may show focal or diffuse neuroendocrine differentiation. INSM1 immunoreactivity should be interpreted within a specific clinicopathological context, for instance strong and diffuse INSM1 expression in cutaneous SRCT, strongly supports the possibility of MCC but in soft tissue/bone tumours this immunoreactivity might prompt excluding the possibility of metastatic neuroendocrine tumour, EMC or ESFT.

OFP-11-008

PD-L1 expression and immune related gene profile in giant cell tumour of bone: an immunohistochemical and NanoString technology-based study

J. Metovic[1], L. Annaratone[2], A. Linari[3], S. Osella-Abate[2], C. Musuraca[3], F. Veneziano[3], C. Vignale[3], L. Bertero[2], P. Cassoni[2], M. Papotti[3]
[1] Departments of Oncology Pathology Unit University of Turin, Italy, [2] Department of Medical Sciences, University of Turin, Italy, [3] Department of Oncology, University of Turin, Italy

Background & Objectives: Giant cell tumour of bone (GCTB) is a relatively uncommon entity that, although in the vast majority of patients is presented as a benign disease, can develop local recurrences or progression.
Methods: A retrospective series of 70 cases including 46 GCTB and a control group of 24 aneurysmal bone cysts (ABC) has been selected in order to determine their immune-profile (PD-L1, CD4 expression, together with Ki67 index) and immune-related gene expression profile as detected by NanoString technology using nCounter PanCancer Immune Profiling panel. The results were correlated with clinicopathological features.
Results: PD-L1 expression was detected in 13/46 (28.3%) GCTB and in only 1/24 (4.2%) ABC cases (p=0.017). The majority of GCTB (38/46; 82.6%) had an intense CD4 expression, in comparison to only 10/24 (41.7%) ABC cases (p< 0.001). The mean Ki67 proliferation index of GCTB was 8.76 % (± 9.97), a significantly higher value than that of ABC (3.54% ±5.38) (p=0.020). In the GCTB group, by univariate analysis, PD-L1 expression was associated with a poorer disease free interval (DFI) (HR=4.15, C.I 1.52-11.31; p=0.005). Also, Kaplan-Meier survival analysis supported these data: DFI was significantly longer in PD-L1 negative compared to positive cases (log-rank test p=0.0026). Furthermore, in PD-L1 positive lesions, three genes (*CD27*, *CD6*, *IL10)* were significantly upregulated (p<0.01), while two others were down-regulated (LCK and TLR8, showing borderline significance).
Conclusion: PD-L1 immunoexpression may help to select GCTB patients with higher risk of recurrence, who might potentially benefit from immune checkpoint blockade.

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OFP-11-009

Histopathological findings in meningococcal infections as a cause of sudden-unexpected death

A. Fernandez-Rodriguez[1], B. Alves[1,2], B. Morentin[3], J. Arrieta[3], M.R. Mosquera[1], B. Alcalá[1], R. Abad[1], M.P. Suárez-Mier[1], I. Merino[1,4]
[1] Instituto Nacional de Toxicología y Ciencias Forenses, Madrid, Spain, [2] University of Aveiro, Portugal, [3] Instituto Vasco de Medicina Legal, Vizcaya, Spain, [4] Hospital Clínico Universitario de Valladolid, Spain

Background & Objectives: Meningococcal infection (MI) is a well-known cause of sudden-unexpected death (SUD) and post-mortem forensic analyses are often needed. Histopathological (HP) signs of a MI can be diverse. The aim of this study was to determine the most frequent pathological diagnosis in fatal cases of MI.
Methods: Twenty-eight cases of SUD due to MI in which microbiology had been requested to our institution were revised. In all of them post-mortem microbiology had confirmed the significant presence of *N. meningitidis* in sterile fluids and/or tissues. Microbiological and HP findings of the different tissues analysed were revised to assess the organs most commonly affected by MI.
Results: The most frequent organs studied were the heart and the lung (93%), followed by the liver (89%), while brain was not so common (75%). The most frequent diagnosis (61%) were signs of sepsis/septic shock (SS), followed by bilateral adrenal haemorrhage (BAH), myocarditis, and DIC (57%, 46%, and 43% respectively). BAH presented with SS in 39% cases, and with DIC in 32%, while myocarditis was present with SS in 36%. In 3 cases all 4 diagnosis (SS, BAH, DIX and myocarditis) were present. Meningitis was found only in 6 cases (21%).
Conclusion: The main form of fatal MI was sepsis/septic shock, often associated with BAH. Neurological affectation wasn't common, but the heart was often affected. It is necessary to include brain/meningeal, heart, liver, and adrenal tissue in the HP study of SUD, in order to search for MI as a possible cause of death.

OFP-11-010
Peculiarities of morphological verification of bacillary angiomatosis

A. Mustafina[1]
[1] Medical University of Karaganda, Kazakhstan

Background & Objectives: The damaging effect of Bartonella henselae can lead to different variants of the infection process, in particular in patients with a compromised immune system, to a multifocal angioproliferative reaction (bacillary angiomatosis). Pathomorphological changes in bacillary angiomatosis are well described. At the same time, the lack of anamnestic, clinical data and alertness at the pathologist, as well as the similarity with a number of other pathological processes often lead to difficulties in histological verification of this disease. The purpose of the study- a retrospective analysis of biopsy material to improve the quality of diagnosis of Bartonella infection.
Methods: The analysis of 28 cases of a skin biopsy from the archival material of the pathological-anatomical centre in Central Kazakhstan for 2016-2018, in which the histological conclusion included a description of lymphadenitis without mentioning the etiological factor (lymph nodes) or the pathological conclusion was descriptive (lymph nodes and skin). Retrospective diagnosis of bartonellosis was performed by indirect immuno-fluorescence reaction in order to detect the B. henselae particulate antigen or antibodies to it.
Results: In the analysis of 28 cases of skin biopsy in 3 patients were Bartonella in the form of clusters in close proximity to endothelial cells. Thus, 3 cases of bacillary angiomatosis were selected in which the etiology of the pathological process was confirmed by an indirect immunofluorescence reaction. In the analysed cases of vascular changes during skin biopsy, the histological pattern is characterised by angioproliferative lesions with the presence of proliferating endothelial cells, mixed macrophage-monocytic and polymorphonuclear neutrophilic infiltration. In each of the selected cases, a focal proliferation of microcapillaries delimited by enlarged convex, cubic or polygonal widely cytoplasmic endothelial cells, with or without signs of cytological atypia, is detected. Inflammatory infiltration is mixed (lymphocytic neurophilic) with leukocytoclysis and focal necrosis.
Conclusion: 1. Bacillary angiomatosis is characterised by angioproliferative changes with the presence of proliferating endothelial cells, mixed macrophage-monocytic and polymorphonuclear-neutrophilic infiltration.
2. To identify the etiological factor in the presence of the described changes, a comparison of clinical, anamnestic, serological and morphological data is necessary.

OFP-11-011
Validation of PCR for the diagnosis of leprosy in patients from Kiribas

J. Gardner[1], E. Towbridge[1], S. Chambers[1], T. Anderson[1]
[1] Canterbury district health board, New Zealand

Background & Objectives: A New Zealand team of infectious disease physicians have been assessing and treating patients with leprosy on a remote island nation in the Pacific Ocean called Kiribas. This project commenced in 2016 and to date 45 patients have been studied.
The main objective of this study was to validate the use of PCR for diagnosis and compare it against traditional histology and labour-intensive ZN staining.
Methods: Patients identified as having probable leprosy had matching punch biopsies of lesional skin tissue submitted for histology and modified ZN staining with a separate biopsy submitted in ethanol for PCR
PCR was set up specifically for this project and histology was used to validate it.
Results: In all cases of both lepromatous and tuberculoid leprosy the PCR confirmed the diagnosis with read numbers ranging from 15 to 38.
Additional cases of borderline histology with no acid-fast bacilli seen on histology but a clinical diagnosis of leprosy were able to be diagnosed by PCR alone!
The validation was successful.
Conclusion: In third world countries without easy access to histology PCR alone can be a stand-alone diagnostic test for this Important disease.

OFP-11-012
In-situ protein expression analysis of cancer testis antigen SSX2

A. Jungbluth[1], D. Frosina[1], C. Lezcano[1], J. Geronimo[1], E. Hernandez[1], K. Busam[1]
[1] Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: CT antigens (CTAs) such as NY-ESO-1 and MAGE are expressed in various malignancies and in normal tissues almost exclusively in testis. CTAs are highly immunogenic and due to their tumour-associated expression pattern, are employed as vaccine targets for cancer immunotherapy. SSX2 is another CTA which was identified by its involvement in t(X;18) translocation in synovial sarcoma. On an mRNA level, SSX2 is expressed in various malignant neoplasms. However, little is known about the in-situ protein expression of SSX2.
Methods: A novel anti-SSX2 monoclonal antibody (mAb) CL3202 (Sigma; AMAb91141) was identified and tested for specificity using FFPE tissues and cell line pellets with known SSX2 mRNA expression pattern. CL3202 worked best at 0.5ug/ml using heat induced antigen retrieval employing pH8 buffer for 30'. All assays were performed on an automated stainer platform (Leica Bond-3). Various malignancies were tested by IHC such as melanomas, as well as panels of carcinomas and sarcomas.
Results: More than 250 tumours were analysed. SSX2 was highly (100%) expressed in synovial sarcoma displaying a homogeneous expression in all tumours. Melanoma showed the second highest incidence of SSX2-positivity in 23% followed by squamous cell carcinoma of the lung (5%) being only heterogeneously expressed in parts of the tumour. All other carcinomas (liver, ovary, lung (adeno), kidney, colorectum) were SSX2 negative. A wide variety of sarcomas (osteo-, leimyo-, chondro-, lipo-sarcoma) as well as mesothelioma and seminoma were all SSX2 negative!

Conclusion: This is the first comprehensive analysis of SSX2 protein expression. SSX2 is homogeneously expressed in 100% synovial sarcoma. Expression in other tumours is considerably less and most prevalent in melanoma. SSX2 expression vastly differs from CTAs such as MAGE, NY-ESO1 and CT7. Due to its expression pattern, SSX2 may be a valuable vaccine target and/or diagnostic tool in synovial sarcoma.

Tuesday, 10 September 2019, 17:15 - 19:15, Thalie
OFP-12 | Paediatric and Perinatal Pathology

OFP-12-001

Renal cell carcinoma in children and adolescent, a retrospective analysis of a cooperative European cohort

T. Denize[1], S. Massa[2], C. Vokuhl[3], A. Valent[4], A. Testi[2], L. Dainese[1], L. Militti[5], E. Thebaud[6], R. Furtwaengler[7], K. Pritchard-Jones[8], N. Graf[7], F. Spreafico[9], A. Verschuur[10], G. Vujanic[11], P. Collini[2], A. Coulomb[1]
[1] Sorbonne University, APHP6, Pathology department, Armand Trousseau Hospital, Paris, France, [2] Diagnostic Pathology and Laboratory Medicine Department, Fondazione IRCCS Istituto Nazionale dei Tumouri, Milan, Italy, [3] Kiel Paediatric Tumour Registry, Department of Paediatric Pathology, University Schleswig-Holstein, Germany, [4] Institute Gustave Roussy, biology and medical pathology department, Villejuif, France, [5] Dip. Medicina di Laboratorio e Biotecnologie Diagnostiche U.O.C. Anatomia Patologica ASST Ovest Milanese - Ospedale di Legnano, Italy, [6] Paediatric oncology derpartment, CHU Nantes, France, [7] Saarland University, Paediatric Oncology & Haematology, Homburg, Germany, [8] University College London UCL, Developmental Biology and Cancer, London, United Kingdom, [9] Paediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumouri, Milan, Italy, [10] Paediatric oncology and haematology department, La Timone Hospital, Marseille, France, [11] Weill Cornel Medicine, Department of Pathology, Sidra Medicine, Doha, Qatar

Background & Objectives: Renal cell carcinomas (RCC) are rare in children and adolescent, accounting for less than 4% of kidney tumours. In order to get insight into their pathological characteristics, we analysed a large cooperative European cohort focusing on epidemiology, histological subtype, immunophenotype, and TFE3/TFEB status by FISH.
Methods: Cases collected from the French, Italian, German and British pathological databases were reviewed. TFE3-FISH analysis was performed on all cases and TFEB-FISH when morphology was suggestive. A wide immunohistochemical panel was performed.
Results: We collected 159 cases. Median age at diagnosis was 11 years (9m-18y) with a slight male predominance (1,1:1). Median tumour size was 6 cm. The most frequent histotype was MiT-family translocation RCC (MiTRCC) in 42%. Non-MiTRCC included papillary RCC type 1 (12%) and 2 (14%), chromophobe RCC (4%), adult clear cell RCC (3%), SDHB-associated RCC (1%), medullary/CDC RCC (3%), RCC associated with neuroblastoma (1%) and unclassified RCC (22%). In the MiTRCC, median age was 9y with a female predominance (sex ratio 1:1.7) whereas in the non-MiTRCC group, children were younger (mean 8y).
Conclusion: MiTRCC is the most common RCC histological subtype in children and adolescents, affecting more frequently girls, with frequent LN metastasis. TFE3-FISH analysis is the gold standard for MiTRCC diagnosis and should be systemically performed. NGS analysis is ongoing on non-MiTRCC in order to better classify this heterogeneous group.

OFP-12-002

BRAF V600E mutation: a significant biomarker for prediction of disease in paediatric Langerhans cell histiocytosis

E. Özer[1], A. Sevinc[2], D. Ince[3], R. Yuzuguldu[4], N. Olgun[3]
[1] Dokuz Eylul University Faculty of Medicine, Department of Pathology, Turkey, [2] Altinbas University School of Medicine, Turkey, [3] Dokuz Eylul University Faculty of Medicine, Department of Paediatric Oncology, Turkey, [4] Dokuz Eylul University School of Medicine, Turkey

Background & Objectives: Langerhans cell histiocytosis (LCH) is a rare disease presenting with usually a localized disease but sometimes a widespread aggressive disorder especially in children. Among the somatic mutations in RAF-MEK-ERK pathway, especially *BRAF* mutation has been detected so far in LCH. We aimed in this study to investigate the prognostic significance of the mutations of target genes playing a role in the RAF-MEK-ERK pathway in paediatric LCH.
Methods: Mutation analyses were performed on tumour DNA extracted from formalin fixed paraffin embedded biopsy specimens of 38 paediatric LCH cases using a direct sequencing technique for *BRAF*, *ARAF*, *MAP2K1* and *MAP3K1* genes. The mutational status was correlated statistically with survival, clinical progression (disease relapse), and the established clinical prognostic parameters of LCH such as age, gender, localization, multisystem disease, central nervous system risk lesions, and risk organ or special site involvement.
Results: *BRAF* V600E mutation was detected in 14 cases (36.8%) whereas *ARAF* mutation was found in only one case. No mutations were identified for *MAP2K1* and *MAP3K1* genes. The association of *BRAF* V600E mutation was significant in children with multisystemic disease, younger age (< 2 years), skin and special organ involvement. *BRAF* V600E mutation was an independent predictive parameter for disease relapse.
Conclusion: We therefore conclude that *BRAF* V600E mutation may be a significant marker for predicting disease progression in LCH and a candidate for targeted therapy for children with disease relapse and multisystemic disease.

Dokuz Eylul University's Research Trust and Turkish Paediatric Oncology Group

OFP-12-003

Histopathology of Steel syndrome due to new pathogenic variants of COL27A1 gene

A. Nadal[1], G. Frigola[2], O. Gómez[3], V. Borobio[3], A. Vallmajó[4], R. Oliva[5], M. Pauta[3], A. Borrell[3]
[1] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic de Barcelona, IDIBAPS, Spain, [2] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic of Barcelona, Spain, [3] BCNatal, Hospital Clínic, IDIBAPS, Barcelona, Spain, [4] Quantitative Genomic Medicine Laboratories, S.L., qGenomics, Esplugues de Llobregat, Spain, [5] Biochemistry and Molecular genetics,Hospital Clínic, IDIBAPS, Barcelona, Spain

Background & Objectives: Steel syndrome (STLS) was described in 1993. 37 cases are reported in the literature. Patients show characteristic facies, dwarfness, irreducible bilateral hip and radial head dislocation, and carpal bone coalition. *COL27A1* gene (9q32) mutations were recently described in the pathogenesis of the syndrome.
Methods: Two consecutive pregnancies in a nonconsanguineous couple were interrupted at 22 and 17 weeks of gestational age because of severe US scan anomalies. Complete autopsies with microscopic exam were done on both fetuses. Next-generation-based clinical exome sequencing was applied to the first fetus. Exome sequencing results, parental segregation, and affection of the second fetus were confirmed by Sanger sequencing.
Results: Both fetuses had short long bones, dysmorphic oval shaped facies with hypertelorism, absent humeral capitulum with flattened radial heads, and carpal bone coalition. The first fetus had deformities of both the femoral head and the acetabulum, the second one and an overt hip dislocation. Histologically, proliferative metaphyseal cartilage showed retardation and disorganization. Resting cartilage was hypercellular, organized in irregular nests limited by acellular matrix. Two previously

unreported variants in *COL27A1* gene (c.2548G>A -p.Gly850Arg- and c.3249 +1G>T -affecting the canonical splicing site of exon 29-) were found in both fetuses in compound heterozygosis with parental mendelian segregation. Each parent carried one of the mutations in heterozygosis. Mutation pathogenicity was confirmed *in silico*.
Conclusion: This is the first report to include histology of STLS. The *COL27A1* gene variants here described increase the number of mutations associated with STLS. Parental segregation indicates autosomal recessive inheritance.

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OFP-12-004
Features of PLAP expression in placental structures during allogeneic pregnancy (surrogate maternity, oocyte donation) on the background of preeclampsia, as an indicator of exosomal trophoblast activity
E. Rudenko[1], E. Kogan[1], T. Demura[1], N. Zharkov[1], N. Trifonova[1]
[1] I.M. Sechenov First Moscow State Medical University (Sechenov University), Russia

Background & Objectives: PLAP - placental alkaline phosphatase specific for the isolation of exosomes (vesicles up to 100 nm in size, containing miRNA and siRNA), of placental origin. PLAP-positive exosomes can be detected in the mother's blood already in the first trimester of pregnancy, their number increases during the process of maturation of the fetus and reaches its maximum at the time of delivery. The change in the profile of exosomes during various complications of pregnancy, including the development of preeclampsia, is shown.
Methods: The placental material and placental biopsy from 48 women who were pregnant as a result of in vitro fertilization, divided into 2 groups, were studied. The first group included 32 women after allogeneic pregnancy. Subgroups were formed on the basis of the presence or absence of pre-eclampsia. An immunohistochemical study using primary antibodies used mouse anti-PLAP (Dako,1: 200). Detection of exosomes in the cytoplasm of trophoblast cells and brush border of the syncytiotrophoblast was carried out using electron microscopy.
Results: PLAP expression was established in the apical part of the villi, the parietal trophoblast, as well as for singl cells of the EVTs of the placental bed. Giant multinucleated trophoblast cells were negative. The optical density staining for the syncytiotrophoblast chorionic villus was calculated. A significant decrease in the expression of the optical density of PLAP in STB was shown against the background of preeclampsia. An electron microscopy study confirmed the coincidence of PLAP localization in exosomal structures.
Conclusion: The relationship between the decrease in expression of PLAP and the number of placental exosomes in the pathogenesis of pre-eclampsia during allogeneic pregnancy has been established.

OFP-12-005
The study of polymorphism of HLA genes as a predictor of the development of hypertensive complications of pregnancy
E. Rudenko[1], E. Kogan[1], T. Demura[1], N. Trifonova[1]
[1] I.M. Sechenov First Moscow State Medical University (Sechenov University), Russia

Background & Objectives: After the first successful use of donor oocytes in 1984, the number of assisted reproductive technology cycles using donor eggs in the US and Europe continues to grow. Alogenic pregnancy is associated with a high risk of developing complications, especially hypertensive ones. Allogeneic pregnancy is characterised by a high degree of discrepancy in the HLA system. It is promising to study the polymorphism of HLA system genes as a molecular predictor of the development of hypertensive complications.
Methods: The study group consisted of 45 women and their children, born as a result of the programs of donation of oocytes and "Surrogate motherhood". HLA typing was performed in maternal and cord blood samples after delivery. HLA-DNA-TEH reagent kits were used for typing genes of the main human histocompatibility complex (HLA) class II (DQA1, DQB1 and DRB1) by the polymerase chain reaction (DNA technology, Russia). The obtained results were processed using the SPSS Statistics for Windows statistical software package (USA).
Results: In this work, a number of alleles with a protective effect (DQA1 * 0102, DQB1 * 0302, DRB1 * 13, etc.) were identified, with which in the genotype the probability of developing hypertensive pregnancy complications (gestational arterial hypertension, PONRP, pre-eclampsia) was significantly lower ($p < 0.01$). In both mothers and children, protective alleles were detected, in the presence of which we observed a decrease in the number of complications. We identified 8 protective alleles in mothers, and 7 in children.
Conclusion: In our work, we did not get convincing results indicating the role of the inconsistency in the HLA system in the development of obstetric complications during pregnancy with an allogeneic fetus. In the blood of the mother and fetus, a number of protective alleles were identified, in the presence of which the probability of developing hypertensive complications was deliberately lower.

OFP-12-006
New data about telocytes of placental villi
N. Nizyaeva[1], T.V. Sukhacheva[2], M.N. Nagovitsyna[1], R.A. Serov[2], N.E. Kan[1], A.I. Shcheogolev[1]
[1] V.I.Kulakov National Research Center for Obstetrics, Gynaecology and Perinatology of Ministry of Healthcare of the Russian Federation, Moscow, Russia, [2] A.N.Bakoulev Scientific Center for Cardiovascular Surgery, Moscow, Russia

Background & Objectives: is analysis of morphological features of telocytes in placenta villi in preeclampsia (PE).
Methods: Groups of study included 37 patients of reproductive age, 25-39 weeks of gestation: 22 patients with PE and 10 with uncomplicated full-term pregnancy (UP). We performed histological (hem&eosin) and immunohistochemistry studies on the paraffin-embedded slices of placenta, taking after cesarean section, using primary antibodies to CD117, CD34, vimentin, including the new marker for telocytes TMEM16a (DOG-1). Besides, 15 placental samples were examined using electron microscope «Philips CM100».
Results: TC in placenta in UP group were characterised by vimentin+, week CD117+, CD34+. We revealed TMEM16a+ in stem and intermediate villi in UP group, but in PE we observed TMEM16a expression weakening. Electron microscopy examination of placental samples in UP has been found TC in different villi types. Ultrastructural characteristics of TC indicated their heterogeneity and presence of at least three cell types. In PE telocyte in the stroma of intermediate villi acquired characteristics of fibroblasts and fibrocytes, while collagen deposition in the villous stroma led to abnormal angiogenesis.
Conclusion: Thus, the heterogenetic telocytes population with different immunophenotypes and ultrastructural characteristics was revealed in various sites of placenta, they are possibly associated to different functions.

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OFP-12-007
Perinatal acute respiratory failure: autopsy remains the best quality control tool
E. Castro[1], N.M. Patil[1], E. Popek[1]
[1] Pavilion for Women, Texas Children's Hospital, Baylor College of Medicine, USA

Background & Objectives: Clinically, acute respiratory failure is one of the most common problems seen in premature and term babies. The etiology varies from surfactant deficiency in premature babies, to meconium-aspiration syndrome (MAS), sepsis, pulmonary hypoplasia and hypertension in term babies. Autopsy examination of the fetus is an important quality control, and often establishes the etiology of perinatal respiratory depression. The aim of this study was to correlate autopsy findings with clinical impression in cases of failure to resuscitate in early neonatal period.
Methods: We reviewed 200 autopsy reports from 2000-2019 at our institution. Inclusion criteria were age (0-10 days) and clinical history of respiratory failure. Correlation of agreement between clinical and final autopsy diagnoses was calculated. Cases with imaging autopsy only were excluded.
Results: Infection was the leading etiology for perinatal respiratory failure (25% of cases), followed by lethal complex malformations (15%), placental causes (14%) and complex congenital heart disease (12%). Other etiologies included congenital diaphragmatic hernia and lung hypoplasia, cord accident, hemorrhage due to visceral rupture, non-immune hydrops, MAS, metabolic diseases, neoplasia and complications of prematurity. There was concordance between clinical and autopsy diagnoses in 45% of cases. The most frequent unexpected diagnosis was infection (23%).
Conclusion: The number of autopsy examination requests in the hospital setting have been declining worldwide. Our findings underscore the importance of autopsy examination as a quality control tool for early neonatal deaths.

OFP-12-008
Body stalk anomaly: a rare lethal fetal anomaly, rarely reported in a dichorionic diamniotic twin pregnancy
R. Castiglione[1], K. Baltz-Ghahremanpour[1], A. Bosse[1]
[1] Klinikum Stuttgart - Institute of Pathology, Germany

Background & Objectives: Body stalk anomaly (BSA) is the rarest, invariably lethal abdominal wall defect and may be associated to various abnormalities of neural tube and internal organs. It is characterised by a lack of development of abdominal wall: the abdominal organs lie externally in a sac of amnioperitoneum. The fetus is attached directly to the placenta by lack of or very short umbilical cord. BSA is rarely reported during twin pregnancy. It is generally not associated to genetic abnormalities.
Methods: Here we present the case of an BSA-affected male patient died 100 minutes after full-term birth in a context of dichorionic-diamniotic twin pregnancy. His twin brother showed no anomality of any sort. The mother was a healthy primipara without significant family history. Prior to autopsy, a radiological examination was performed.
Results: Macroscopic evaluation revealed a total lack of development of the abdominal wall and an incomplete, asymmetric development of the thorax wall. Liver, bowel, pancreas and spleen was located in extrafetal coelom. Only one kidney was available. Anal atresia was reported. Skeletal examination revealed a severe scoliosis and a rudimental, dorsal deviated left leg. No pathological finding were detected during the examination of the skull and upper extremities. A 1,5 cm short umbilical cord was documented at placenta examination. The histological examinations revealed no further alterations in the maturation of the organs.
Conclusion: BSA is a very rare, fatal disease. Here we documented a case of BSA in the extremely rare context of twin pregnancy, which represents a big challenge in the clinical management.

OFP-12-009
Cardiac defects in fetal postmortem examinations with aneuploidy
M. Farinha[1], L. Monteiro[2]
[1] IPO-Porto, Portugal, [2] CLHO, Portugal

Background & Objectives: To evaluate the spectrum of cardiac anomalies found in fetal autopsies in correlation with chromosomal aneuploidies.
Methods: Retrospective review of 296 fetal autopsies performed at CHLO during 2018. 54 cases with chromosomal abnormalities confirmed by karyotyping (20 males, 31 females and 1 undefined sex) were retrieved and analysed for presence and classification of cardiac anomalies. Cases were assigned to main categories of cardiac defects, and the most common associations were determined.
Results: Median maternal age was 37 years-old(range:22-48) and gestational age 18 weeks (range:13-34). Most common aneuploidy was trisomy21 (57%), followed by trisomy18(24%), X monosomy (13%), trisomy13 (4%) and triploidy (2%). Abnormal cardiac findings were identified in 32 fetuses (59%). Termination of pregnancy was performed in 45 cases (83%) with the other 9 (17%) resulting from spontaneous fetal demise. Most common malformations in trisomy21 were septal defects (26%), in trisomy18 Tetralogy of Fallot (38%) and in X monosomy left ventricular outflow tract obstructions (LVOTO;43%). Both cases of trisomy13 presented with LVOTO. A complex anomaly was found in the triploidy case.
Conclusion: Spontaneous fetal demise and termination of pregnancy due to unbalanced chromosomal abnormalities are frequent and associated with multiple congenital anomalies. Cardiac malformations are the most common alterations found. Our cohort presents lower frequency of cardiac defects comparing to the literature, and brings to attention the complexity and variability of phenotypic expression of aneuploidies.

OFP-12-010
Stillbirth and perinatal death: a retrospective study with application of ICD-PM to the autopsies performed between 2007 and 2018 in Coimbra
A. Lai[1], F. Ramalhosa[1], M.B. Pimentão[1], C. Faria[1], V. Almeida[1], H. Moreira[1], R. Almeida[1], J. Fraga[1], O. Caetano[1], C. Cerdeira[1], R. Pina[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal

Background & Objectives: Accordingly, with the estimates of WHO in 2016, each year occurs 2.6 million of stillbirths, with more than 95% taking place in low and middle-income countries. With the aim of reduce this mortality rate, the WHO released an action plan and recommends the use of ICD-PM (International Classification of Diseases – Perinatal Mortality) for international reporting of stillbirths and perinatal deaths. Portugal has one of the best perinatal mortality rate with 3,90 in 2016, but it is still possible to improve with the identification of the main changeable causes: maternal or health care.
Methods: In order to identify the main causes of stillbirth (>22weeks) and perinatal deaths, we retrospectively reviewed the stillbirths and perinatal autopsies performed in Centro Hospitalar e Universitário de Coimbra, in 2007 and 2018 years (not including medical termination of pregnancy).
Results: From a total of 183 stillbirths and perinatal autopsies, 107(58%) were male, 74(40%) female and 3(1,6%) undetermined. The median gestational age was 29weeks (range 22-41weeks), the median neonatal period was 1,5days and the median maternal age was 31years (range 16-45).
From the 82cases (45%) of antepartum death, 37 cases(45%) were due to "A3 – Acute antepartum event". In the category of intrapartum death, we had 77 cases (42%) were the major cause was "I3 – Acute intrapartum event" (35 cases-46%). In the neonatal death, we had 24 cases(13%), in which the "N7 – Respiratory and cardiovascular disorders" were the commonest cause (9 cases-37,5%). In addition, the mother conditions more frequent was "M1 – Complications of placenta, cord and membranes (126 cases-69%).
Conclusion: Despite our good perinatal mortality rate there is still some aspects that we can improve in medical care, public health and population education to achieve better assistance to pregnant women, their babies and their families.

OFP-12-011

Metabolic reprogramming and altered isotope fractionation of cancerous cells of neural origin in the light of advanced atomic level mass spectrometry

K. Taran[1], P. Paneth[2]
[1] Medical University of Lodz, Poland, [2] Lodz University of Technology, Poland

Background & Objectives: Isotope Ratio Mass Spectrometry advanced approach has been recently proved to be applicable to cancer biomarkers research. The method for the first time alights structural mechanisms of fundamental cancer cell biology. Most of isotope effects associated with biosythesis and metabolism exhibit different values depending of particular mechanisms of reactions that take place. The anaplerotic pathway glutamin metabolism is known to be unregulated in many cancer cells. In neuroblastoma biology glutamin is known to be necessary for the survival regardless of ATP acquisition.
Methods: There was performed a search for light isotope profiles of tumour cells and tissues from tumour surrounding in complete spectrum of neuroblastoma group with the use of a Sercon Continuous 20-22 Flow Isotope Ratio Mass Spectrometer coupled with an Elemental Analyser for simultaneous light isotopes estimation.
Results: Obtained changes in isotopic signatures of light isotopes in transformed cells in relation to the established knowledge of cancer cell isotopic profiles and metabolism confirm the metabolic reprogramming of tranformed cells and indicates that glutamin can become the major source of lipogenic acetylo-CoA through reductive carboxylation.
Conclusion: The IRMS method looks beyond traditional meanings of cancer investigation and confirm metabolic reprogramming by promoting lipolysis in the transformed neural cells from neuroblastoma group.

OFP-12-012

Vascular anastomoses in monochorionic twin placentas: a pathomorphological study using CT

A. Shchegolev[1], N. Tetruashvili[1], U. Tumanova[1], V. Lyapin[1], A. Kozlova[1], V. Bychenko[1], V. Sakalo[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: The use of CT in the placental studies can effectively identify and evaluate all vascular anastomoses.
Objective: to study of anastomoses in monochorionic diamniotic placentas at fetal growth retardation (FGR).
14 monochorionic diamniotic twin placentas were studied. Group-I - 7 placentas with FGR. Group-II - 7 placentas without FGR.
Methods: Conducted a phased macroscopic and CT examinations of the placental vessels using contrast-coloring mixtures of 4 colors. The mixture consisted of a dye and radiopaque substance in exactly calculated concentration. After catheterization of the vessels of both umbilical cords, the mixture was introduced stepwise. CT and visual assessment were performed at each stage. 3D reconstructions and color mapping of CT-tomograms was performed. The presence of anastomoses, their type, diameter and branching order were determined.
Results: In Group-I vascular anastomoses in the placenta were detected in 85.71%, and in Group-II in 57.14%. In Group-II 1 anastomosis was identified per 1 placenta in all cases, and in Group-I - 2 mainly. The anastomosing vessels average diameter in the FGR-group (4.4 mm) exceeded that in Group-II by 2.6 times (1.7 mm). The average value of the order of the anastomosing vessels branching in Group-II was 4, and in the FGR-group - 2.6.
Conclusion: In FGR-group, the highest percentage was for arteriovenous anastomoses - 57% of all cases, and veno-venous and arteriovenous anastomoses - on 43% of each. Only arterio-arterial anastomoses were detected in placentas without FGR.
In FGR, the percentage of anastomoses detection is higher, the anastomosing vessels diameter is greater, and their branching order is less than in placentas without FGR.

Tuesday, 10 September 2019, 17:15 - 19:15, Erato
OFP-13 | Joint Session: Molecular Pathology / Haematopathology

OFP-13-001

Expression of SOX11 in mantle cell lymphoma is associated with increased angiogenesis and immunosuppressive microenvironment

L. Veloza[1], P. Balsas[2], I. Ribera-Cortada[3], A. Martinez[1], V. Amador[2], E. Campo[1]
[1] Hospital Clinic, Spain, [2] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Spain, [3] Hospital Nostra Senyora de Meritxell, Andorra

Background & Objectives: The role of immune cells and angiogenesis in the clinical behaviour of mantle cell lymphoma (MCL) is not fully understood. Therefore, the objective of this study was to characterise the tumour microenvironment, correlate with SOX11 expression and overall survival (OS).
Methods: This study included 53 MCL (23 spleens:15 SOX11− and 8 SOX11+ and 30 lymph nodes: 6 SOX11− and 24 SOX11+). Angiogenesis was evaluated by analysing the intratumoural microvascular area (MVA) and microvascular density (MVD) by anti-CD34 immunohistochemistry. The T-cell infiltrate was studied by immunohistochemistry by counting CD3, CD4, CD8 and FOXP3+ cells and calculating the mean value of five representative intratumoural areas (40x magnification).
Results: SOX11+ MCL showed an increased angiogenesis than SOX11− (median MVA: 14.6 $x10^{-3}$ vs 5.0 $x10^{-3}$ $p<0.001$, median MVD: 18.8/μm^2 vs 14.2/μm^2, $p=0.016$). Cases with a high MVD and MVA presented a shorter OS ($p=0.004$ and $p=0.064$ respectively). In nodal MCL, SOX11+ cases presented fewer CD3+ T-cells (48 ±SD 27 vs 88 ±SD 31, $p=0.002$) and CD4+ T-cells (18 ± SD 10 vs 65 ±SD 33, $p<0.001$), and a lower CD4/CD8 ratio (0.9 ±SD 0.3 vs 2.7 ±SD 1.1, $p<0.001$). SOX11+ cases showed more Tregs (FOXP3+) (12 ±SD 9 vs 6 ±SD 4, $p=0.07$) and a higher FOXP3/CD3 ratio (0.2 ±SD 0.1 vs 0.06 ±SD 0.02, $p<0.001$), which was associated with a shorter OS in nodal MCL ($p=0.03$).
Conclusion: Our study suggests that SOX11 is associated with immunosuppression and angiogenesis, contributing to the aggressiveness in MCL. Hence, the MCL microenvironment could represent a potential therapeutic target.

OFP-13-002

Prognostic role of the microenvironment in follicular lymphoma treated with Rituximab and Rituximab+lenalidomide - results of a translational study of the SAKK35/10 trial

T. Menter[1], A. Tzankov[2], E. Zucca[3], E. Kimby[4], S. Hayoz[5], S. Dirnhofer[2]
[1] Institut für Medizinische Genetik und Pathologie, Universitätsspital Basel, Switzerland, [2] University Hospital Basel, Switzerland, [3] Oncology Institute of Southern Switzerland, Switzerland, [4] Department of Medicine at Huddinge, Karolinska Institutet, Sweden, [5] SAKK Coordinating Center, Switzerland

Background & Objectives: Follicular lymphoma (FL) constitutes a significant disease proportion of lymphomas and is prone to relapsing after therapy. Lately, new therapeutic approaches beyond conventional chemotherapy have emerged focusing on the interplay between lymphoma cells and the surrounding reactive cells of the microenvironment.
Methods: Here we report the immunophenotypic investigation of the microenvironment of a clinically well characterised cohort (study SAKK35/10) including 135 evaluable treatment naïve FL patients in need of treatment, who have been treated with either rituximab (R) only or a combination of rituximab and the immunomodulatory drug lenalidomide (R/R). After initial large-scale phenotypic analysis of 34 tissue-

microarrayed biopsies focusing on prognostic impact, several promising markers for T-cell subgroups were selected for further evaluation of the whole cohort of 135 patients.
Results: High ratio of CD4- to CD8-positive T cells (p=0.009) and an increased amount of PD1-positive T-cells (p=0.007) were associated with inferior progression free survival (PFS) in the whole cohort. Interestingly, the prognostic impact of PD1-positive T-cells and the CD4/CD8 ratio was lost in the R/R subgroup. In this group, high amounts of GATA3-positive TH2-equivalents were associated with better PFS (p<0.001) and overall survival (p=0.030).
Conclusion: We identified tumour microenvironmental characteristics which may allow prognostic stratification with respect to immuno- and combined immuno- and immunomodulatory therapy. Our analysis implicates that lenalidomide might help to overcome the adverse prognostic implication of higher amounts of regulatory T cells and that it may have particularly favorable effects in cases with higher amounts of TH2-equivalents as demonstrated by GATA3-positive T-cells.

OFP-13-003
PDL1 in lymphomas with Hodgkin Reed Sternberg (HRS) morphology: a troubleshooter
E. Leoni[1], L.F. Vivian[2], F. Magnoli[1,3], F. Sessa[2], M.G. Tibiletti[3], S. Uccella[2]
[1] University of Insubria, Varese, Italy, [2] Unit of Pathology, Department of Medicine and Surgery, University of Insubria, Varese, Italy, [3] Department of Pathology, ASST Sette Laghi, Varese, Italy

Background & Objectives: The immune checkpoint PD-1/PDL1 has emerged as a mechanism used by certain malignancies such Hodgkin lymphoma to evade immune control. Genetic abnormalities at 9p24.1 have been reported with high incidence in classical Hodgkin lymphomas (cHL) producing PDL1 overespression.
The aim of this study was to evaluate the PDL1 expression in cHL and in aggressive non-Hodgkin lymphomas morphologically characterised by the presence of HRS-like cells (NHL), in order to assess PDL1 diagnostic value.
Methods: Immunoreactivity for PDL1 and PD-1 was evaluated in a cohort of 13 HL and 16 NHL diagnosed between 2014 and 2018. Fluorescence in situ hybridization (FISH) on paraffin embedded specimens was performed to detect CD274 (a.k.a PDL1),PDCD1LG2 (a.k.a PDL2) gene cluster amplifications, usig Zyto Light SPEC CD274,PDCD1LG2/CEN 9 Dual Color Probe provided by ZytoVision (Bremerhave, Germany).
Results: All HL showed 2+ to 3+ PDL1 immunohistochemical expression. Among NHL, PDL1 expression was detected in only 4 (25%) cases: 3/3 anaplastic large cell lymphoma (ALCL) and 1/11 diffuse large B cell lymphoma. PD-1 expression was identified in a low percentage of T lymphocytes in all NHL and in most cHL, whereas the 2 nodular lymphocyte predominant HL showed PD-1 expression in >50% of T cells.
FISH analysis showed 9p polisomy in more than half cases without correlation with PDL1 immunohistochemistry whereas amplification of the target region was not observed.
Conclusion: Our study suggests that PDL1 espression is characteristic of cHL and ALCL, and represent a valid tool in differentiating HL from some NHL with HRS-like cells, especially T cell histiocyte rich large B cell lymphoma.

OFP-13-004
Enhancer Zeste Homolog 2 (EZH2) expression is associated with a shorter time to the first systemic therapy in follicular lymphoma
A. Szumera-Cieckiewicz[1], K. Sokol[1,2], G. Rymkiewicz[2], E. Paszkiewicz-Kozik[3], J. Poleszczuk[4], A. Borysiuk[2], M. Kotarska[3], J. Walewski[3], M. Prochorec-Sobieszek[5]
[1] Institute of Haematology and Transfusion Medicine, Diagnostic Haematology Department, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland, [3] Maria Sklodowska-Curie Institute - Oncology Center, Department of Lymphoid Malignancies, Poland, [4] Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Poland, [5] Department of Pathology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Background & Objectives: Enhancer of Zeste Homolog 2 (EZH2) is a catalytic subunit of polycomb repressive complex 2 and, EZH2 inhibitors are histone-modifying enzymes tested for the personalised treatment of hematological malignancies. EZH2 overexpression correlates with more aggressive clinical behavior and poor overall outcome i.e. in breast, prostate and endometrial cancer and, diffuse large B-cell lymphomas. *EZH2* mutational status in follicular lymphoma (FL) has been analysed recently but the significance of EZH2 protein overexpression is still not fully investigated.
Methods: 68 FL cases were revised according to an update of WHO 2017 diagnostic recommendations. From formalin fixed paraffin embedded FL 5 tissue microarrays were constructed (3 cores from different representative areas, 1 mm diameter). Immunohistochemical staining of EZH2 (Ventana, SP129, RTU) was performed. Scoring methods included semiquantitative assessment and digital image analysis with cut-off point ≥70% of strong nuclear reaction for expression. Selection of 35 patients that did not receive systemic induction treatment after the initial diagnosis was done; then the cohort was stratified by the time to the systemic treatment start: 1) patients for which systemic treatment started within the first 24 months; 2) those for which systemic treatment started after 24 months from diagnosis. Statistical differences for both pathological and clinical continuous and categorical variables were tested using Kruskal-Wallis ranks sum test and Pearson's chi-squared test with continuity correction, respectively.
Results: EZH2 was expressed in 22.85% of cases. It was observed in 14.3% *vs.* 62.5% (p<0.05) cases among groups of patients with systemic treatment after *vs.* within 24 months respectively. There were no differences in the clinical or other pathological characteristics is in the year of diagnosis between two groups.
Conclusion: EZH2 protein expression was more frequently observed in the group that required the introduction of systemic therapy within the first 24 months. EZH2 should be evaluated more comprehensively both with *EZH2* mutational status to determine a sensitive biomarker for a first line selection of patients for targeted EZH2 inhibitor therapies.

OFP-13-005
Gene cluster amplifications of PDL1/2 in aggressive primary extranodal DLBCL
S. Weissinger[1], M. Disch[2], M. Zahn[1], R. Marienfeld[1], P. Moeller[1], A. Viardot[3], J. Bloehdorn[3]
[1] University Hospital Ulm, Institute of Pathology, Germany, [2] University Ulm, Institute of Pathology, Germany, [3] University Hospital Ulm, Department of Internal Medicine III, Germany

Background & Objectives: Cancer cells are capable to evade the immune system through altered checkpoints. A considerable heterogeneity regarding responses to checkpoint blockade have been observed in lymphomas. The scope of this study was therefore to investigate gene cluster amplifications of the *PDL1/2* locus in a large cohort of primary extranodal DLBCL.
Methods: Amplifications of the *PDL1/2* locus on chromosome *9p24.1* were investigated by FISH in n=89 DLBCL (GCB n=22, nonGCB n=42), with primary involvement of ear nose throat (ENT), central nervous system, mediastinum (PMBCL), gastrointestinal, skin (comprising classic leg-type (LT) and other cutaneous DLBCL) and other sites. Each case was screened on single cell level for frequency of gains (relative copy gain + amplification), losses and polysomy.

Results: The average of the different aberrations (in % of counted tumour cells) did not show significant differences either in terms of subtype (nonGCB/GCB) nor with regard to location. Most aberrations were found in ENT (copy gain: 21%, copy loss: 17%) and in gastrointestinal DLBCL (polysomy: 21%). Concerning cutaneous and LT DLBCL, the most frequently aberration was polysomy in 18% of the tumour cells in cutaneous DLBCL, whereas in LT only 9% of those cells were found.
Conclusion: Collected data suggests that there is no significant difference in gene cluster amplification of *PDL1/2* or polysomy in investigated extranodal DLBCL, both with regard to the nonGCB/GCB subtype and location of primary involvement. Most aberrations were found in ENT (copy gain) and gastrointestinal DLBCL (polysomy).

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OFP-13-006

Characterisation of atypical dMMR (deficient MisMatch Repair) tumours: a study from a large cohort of 4948 cases

J. Selves[1], M. Jaffrelot[1], A.P. Laurenty[2], N. Fares[3], S. Icher[1], A.C. Brunac[1], M. Danjoux[1], J. Meilleroux[1], C. Toulas[4], E. Chipoulet[5], A. Staub[6], R. Guimbaud[3]
[1] CHU-IUCT-ONCOPOLE, France, [2] Clinique Croix du Sud Toulouse, France, [3] CHU-Toulouse, France, [4] Institut Claudius Regaud IUCT-ONCOPOLE, France, [5] Institut Claudius Regaud -IUCT-ONCOPOLE, France, [6] CH Montauban, France

Background & Objectives: MMR testing is now currently performed in several tumours, using two methods: MMR proteins immunohistochemistry (IHC) and molecular biology (MB) for assessing microsatellite instability (MSI). Classically, dMMR tumour corresponds to loss of expression of MLH1 and PMS2 or MSH2 and MSH6, associated with MSI. The aims of our study was to describe the frequency and the characteristics of atypical dMMR profiles.
Methods: All MMR testing performed in our MB platform between 2007 and 2017 (n=4948) were checked to select cases with both available IHC and MB (n=3800). The 585 dMMR cases were reviewed and atypical cases were defined by: microsatellite stability (MSS) with loss of expression of a pair of proteins; MSI-H with loss of expression of non-paired proteins or with expression of the four proteins; MSI-low. Biological data of atypical cases were controlled if necessary and clinical data were collected for each case.
Results: We identified 97 atypical cases and after controls, 19 cases (21 %) were re-classified allowing to finally identify 89 atypical cases.
Conclusion: We showed that 15% of dMMR tumours have an atypical profile. They mainly involve non-colorectal cancer with a strong prediction for genetic syndromes. Their therapeutic impact must now be evaluated.

IHC MB	PMS2 or MSH6 isolated loss 53	MLH1/PMS2/MSH6/ MSH2 normal expression 5	MSH2/MSH6 or MLH1/PMS2 loss 16	Aberrant loss of proteins 15
MSI-high	43	3		13
MSI-low	1	2	8	0
MSS	9		8	2
Clinical characteristics	*Genetic syndromes (73%)*	*Genetic syndromes*	*Non-Colorectal cancer (63%)*	*Complex inactivation of MMR proteins*

OFP-13-007

Clinical routine assessment of tumour mutational burden in non-small cell lung cancer and melanoma using three different targeted sequencing panels - a single center experience from the Laboratory of Clinical and Experimental Pathology (Nice, France)

S. Heeke[1], J. Benzaquen[2], E. Long-Mira[3], B. Audelan[4,5], V. Lespinet[6], O. Bordone[6], S. Lalvèe[6], K. Zahaf[6], M. Poudenx[2], P. Dugourd[7], M. Chassang[7], T. Passeron[7,8,5], H. Delingette[4,5], C. Marquette[2], V. Hofman[3,9], M. Iliè[3], P. Hofman[3,9]
[1] Team 4 IRCAN, Inserm U1081/CNRS 7284, IRCAN, Nice, France, [2] Universitè Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, Department of Pulmonary Medicine and Oncology, France, [3] Universitè Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, Laboratory of Clinical and Experimental Pathology, France, [4] Epione Team, Inria, Sophia-Antipolis, France, [5] University Côte d'Azur, Nice, France, [6] Laboratory of Clinical and Experimental Pathology, Biobank BB-0033-00025, CHU of Nice, France, [7] Department of Dermatology, CHU of Nice, France, [8] INSERM U1065, C3M, Nice, France, [9] Universitè Côte d'Azur, CHU de Nice, University Hospital Federation OncoAge, Hospital-Integrated Biobank (BB-0033-00025), France

Background & Objectives: Tumour mutational burden (TMB) has been proposed as a promising biomarker for the stratification of patients for anti-cancer immunotherapy. However, TMB is yet to be standardised. Various pre-analytical factors must be carefully controlled before a daily use of TMB is possible. The aim of this study was to analyse how the Oncomine TML and the Qiagen QIAseq TMB panels can be implemented in a clinical molecular pathology lab and if the clinical prediction could be compared to the FoundationOne assay.
Methods: Sixty non-small cell lung cancer and thirty-six melanoma patients with first- or second-line treatment with immune checkpoint inhibitors were included in this study. Formalin-fixed paraffin-embedded (FFPE) tissue sections were either analysed in-house using the Oncomine TML (Thermo Fisher, Waltham, USA) and the Qiagen QIAseq TMB panels (Qiagen, Hilden, Germany) or sent out to external testing with FoundationOne assay (Foundation Medicine, Cambridge, USA). Durable clinical benefit (DCB), defined by at least 6 months without disease progression was evaluated.
Results: TMB is well correlated between the panels ($R^2 > 0.7$) but correlation decreases in samples with lower tumour-cell content. Deamination of FFPE samples had a strong impact on the sequencing accuracy using the Oncomine TML and the QIAseq TMB panels and required enzymatic repair using Uracil-DNA glycosylase (UDG) highlighting specific sample requirements for precise TMB assessment. All panels were equally well correlated with DCB value in NSCLC but not in melanoma. Updated data will be present during the congress.
Conclusion: High TMB has been associated with DCB in NSCLC but not in melanoma patients. The Oncomine and QIAseq panels allow the "in-house" assessment of TMB with good correlation to the FoundationOne assay. However, further standardization for the TMB assessment in different centers and external quality controls are urgently needed for using the commercially available TMB panels in daily practice.

OFP-13-008

Novel role of NMI (N-myc interactor) in chemotherapy response through a mitochondrial dysfunction mediated mechanism and as a potential target for breast cancer therapy

K. Lee[1], E.H. Hwang[1], S.E. Kang[1], H.S. Ryu[2]
[1] Biomedical Research Institute, Seoul National University Hospital, Republic of Korea, [2] Department of Pathology, Seoul National University Hospital, Republic of Korea

Background & Objectives: Mitochondria have a central role in the cancer cell phenotypes of altered redox homeostasis, metabolic rewiring. Disruption of redox homeostasis is a crucial factor in the development of chemoresistance, which is a major obstacle to successful treatment with cancer patients. Recently, the involvement of NMI in drug resistance was sporadically reported but the mechanisms of NMI are still far from elucidation. In this study, we investigated NMI as a potential target of cancer therapy and investigated its contribution in breast cancer metabolism.
Methods: Clinical impact was assessed by IHC staining of NMI in FFPE tissue from 153 breast cancer patients who received adjuvant chemotherapy. The biological function of NMI was studied in vitro and in vivo, Using NMI inhibition (si/shRNA) or overexpressing cell lines, 3D cultures were performed on various ECM (matrigel, matrigel:collagen mix), cell titer-glo assays were performed for anticancer drug susceptibility. In vivo tumour formation capacity was assessed in NSG mice. Mitochondrial membrane potential and ROS were analysed by FACS using mitotracker (Red, Green), mitoSOX and DCFDA. Seahore analyser was utilized to assess the OXPHOS and glycolysis in breast cancer cells.
Results: We observed NMI1 expression were higher in non-complete response (nCR, n=78) compared to complete response (CR, n=78) by analysis of total 156 patients with locally advanced breast cancer who received neoadjuvant chemotherapy (IHC score 1.275 *vs.* 0.855, respectively; p=0.012). Biologically, si/shRNA-mediated knockdown of NMI expression in various breast cancer cells significantly suppressed cell proliferation in 3D culture systems, increased apoptosis and sensitivity to chemotherapeutic agents. Furthermore, silencing NMI expression inhibited xenograft tumour growth and lung and liver metastasis in NSG mice. Mechanically, silencing NMI expression increased high levels of hydrogen peroxide (H_2O_2) production, but not superoxide (O2-), subsequently reduced mitochondrial respiratory capacities in MDA-MB-231 and BT-20 breast cancer cells. Ablation of NMI also inhibited mitochondrial biogenesis in both cells as assessed by the number of mitochondria measured by transmission electron microscopy (TEM). Consistent with this result, mitochondrial membrane potentials (mtMPs) were also downregulated. Conversely, induction of NMI downregulated hydrogen peroxide and increased basal and maximal mitochondrial respiratory capacities.
Conclusion: Collectively, these results imply that NMI potentiates oxidative phosphorylation (OXPHOS) and protected cells to chemotherapeutic reagent from hydrogen peroxide-induced oxidative deaths through its role in mitochondrial biogenesis. Therefore, targeting NMI can be potential treatment for drug resistance in breast cancer cells.

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OFP-13-009

Whole exome sequencing of pancreatic and biliary intraductal tubulo-papillary neoplasms reveals a distinct genetic landscape

C. Groß[1], T. Engleitner[2], J. Weber[2], M. Jesinghaus[3], B. Konukiewitz[1], A. Muckenhuber[1], K. Steiger[1], W. Weichert[4], V. Adsay[5], G. Kloeppel[1], I. Esposito[6], R. Rad[2], A.M. Schlitter[1]
[1] Institute of Pathology, TUM School of Medicine, Technical University of Munich, Germany, [2] Institute of Molecular Oncology and Functional Genomics, TUM School of Medicine, Technical University of Munich, Germany, [3] Institute of Pathology, Technical University of Munich, Germany, [4] Technical University of Munich, School of Medicine, Institute of Pathology, Germany, [5] Koc University, School of Medicine, Department of Pathology, Turkey, [6] Institute of Pathology, Heinrich Heine University and University Hospital, Düsseldorf, Germany

Background & Objectives: Pancreato-biliary adenocarcinomas (PBAC) are highly aggressive neoplasms with poor prognosis. In contrast, intraductal tubulo-papillary neoplasms (ITPN), recently described rare PBAC precursor lesions, show a favorable prognosis despite the frequent occurrence of associated invasive PBAC at the time of diagnosis. ITPN molecular carcinogenesis as well as its relation to the cancer genes driving PBAC carcinogenesis are poorly understood. The aim of the present study was to analyse the mutational profile of ITPN using whole exome sequencing (WES) in order to identify driver genes and potential therapeutical targets.
Methods: In this study the genetic landscape of 17 ITPN of the pancreato-biliary system (11 biliary and 6 pancreatic cases) was examined. Tumour tissue and matching normal tissue were whole-exome sequenced to determine single nucleotide variants (SNV), Indels and copy-number variants (CNV).
Results: The identified somatic mutations predominantly involved few core signalling pathways despite high genetic heterogeneity with diverse mutational spectra: chromatin remodelling (e.g. *ARID1A/1B/2*), Wnt-pathway (e.g. recurrent *BCL9* mutations), MAPK signalling and TGF-ß signalling (e.g. *FGFR2*). No somatic SNV were found in classical cancer genes *KRAS*, *CDKN2A* and *GNAS*, *TP53* and *SMAD4* were affected in a minority of cases (6 %, respectively).
Identified chromosomal variations primarily affected four major pathways: chromatin remodelling, cell cycle, Wnt-signalling and mTOR-signalling. Recurrent chromosomal deletions were predominantly identified on chromosome 1p36, 3p14-22 (restricted to biliary ITPN), 6q21-22 and 14q21-22, whereas chromosomal gains were found on chromosome 1q, 8q and 20q.
Conclusion: Our study reveals for the first time the genetic landscape of biliary ITPN and highlight that the genetic profile of ITPN of the pancreato-biliary system profoundly differs from PBAC molecular carcinogenesis. ITPN largely lack alterations of the PBAC driver genes. Instead the genetic changes of ITPN focus on key signalling pathways (in particular chromatin remodelling and Wnt-pathway), recurrent chromosomal aberrations as well as recurrent alterations of druggable targets (e.g. *BCL9*).

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OFP-13-010

Methylation patterns in dysplasia in inflammatory bowel disease patients

S. Mata[1], I. Rosa[2], P. Silva[3], F. Magro[4], F. Carneiro[5], A. Peixoto[4], M. Silva[4], H.T. Sousa[6], J. Roseira[6], J. Parra[7], R. Barosa[8], A. Vieira[8], M.J. Brito[9], P. Lago[10], A. Coelho[11], J. Moleiro[2], J. Pereira da Silva[2], R. Fonseca[12], C. Albuquerque[3], A. Dias Pereira[13]
[1] Pathology Department, Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE, Portugal, [2] Gastroenterology Department, Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE, Portugal, [3] Molecular Pathobiology Investigation Unit, Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE, Portugal, [4] Gastroenterology Department, Centro Hospitalar de São João, EPE, Portugal, [5] I3S/Ipatimup; Centro Hospitalar de São João; FMUP, Portugal, [6] Gastroenterology Department, Centro Hospitalar do Algarve, EPE, Portugal, [7] Pathology Department, Centro Hospitalar do Algarve, EPE, Portugal, [8] Gastroenterology Department, Hospital Garcia de Orta, EPE, Portugal, [9] Pathology Department, Hospital Garcia de Orta, EPE, Portugal, [10] Gastroenterology Department, Centro Hospitalar do Porto, EPE, Portugal, [11] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Porto, Portugal, [12] Pathology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisbon, Portugal, [13] Gastroenterology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisbon, Portugal

Background & Objectives: Inflammatory Bowel Disease (IBD) with colonic involvement increases colorectal cancer risk. Guidelines recommend surveillance strategies based on the early detection of dysplasia.

The distinction between IBD-related and sporadic dysplasia in IBD patients is difficult. IBD-related carcinogenesis has distinctive features and some data favors the importance of abnormal DNA methylation in this carcinogenesis.
This study aims to define methylation patterns in patients with a colonic cancer or dysplasia diagnosis following an IBD diagnosis.
Methods: In this national multicentric cross-sectional study, 91 samples of colonic mucosa, with and without dysplasia, from 35 patients with IBD (ulcerative colitis in 29) were studied (9 patients with IBD-related dysplasia/cancer and 26 patients with sporadic dysplasia/cancer). The Cpg islands methylation patterns of 67 genes' promoter regions were analysed by Methylation-specific Multiplex Ligation-dependent Probe Amplification, using commercial kits (ME001, ME002, ME004, ME011, ME042) and Coffalyser.NET (MRC-Holland®) software.
Results: Of the 35 patients, 25 had at least 1 endoscopically described as adenoma-like lesion, 4 had at least 1 non-adenoma-like lesion, 3 had cancer and 3 had dysplasia in flat mucosa. No patient had both adenoma-like and non-adenoma-like lesions. Methylation of *IGF2, RARB, ESR1, CHFR, CDH13, WT1, GATA5, WIF1* genes' promoters was significantly associated to dysplasia/cancer; methylation of *MSH6, TIMP3* was significantly associated to IBD related dysplasia/cancer. *MSH6, MSH3, RUNX3, CRABP1, TP73, RARB, CDH13, PAX5, WT1, THBS1, TP53, SFRP1, WIF1, APAF1, BCL2* promoters' methylation were significantly associated to active IBD. *MSH6*'s methylation remained significantly associated to IBD related dysplasia/cancer in multivariate analysis (p=0,029).
Conclusion: Methylation analysis, namely of MSH6, may contribute to the classification of dysplastic lesions in IBD patients – to be further tested in a prospective study.

OFP-13-011
XIST promoter methylation status as putative molecular biomarker for testicular germ cell tumours
J. Lobo[1], S.P. Nunes[1], D. Barros-Silva[1], V. Miranda-Gonçalves[1], A. van den Berg[2], A. JM Gillis[2], L. HJ Looijenga[3], C. Jerónimo[1], R. Henrique[1]
[1] IPO Porto, Portugal, [2] PMC Utrecht, The Netherlands, [3] PMC Utrecht & Erasmus MC Rotterdam, The Netherlands

Background & Objectives: Testicular germ cell tumours (TGCTs) are developmental cancers, and this model has been the main driver in uncovering novel clinically relevant biomarkers. The process of X-chromosome inactivation by XIST expression due to promoter demethylation is observed in these tumours, based on their supernumerical X-chromosome constitution. Here we analyse the promoter methylation status of XIST in a series of TGCT tissues and derived cell lines.
Methods: A total of 250 FFPE TGCT samples, 4 (T)GCT cell lines and 54 testicular parenchyma samples were investigated for the methylation status of the XIST promoter region IV using bisulfite treatment and quantitative methylation-specific PCR (qMSP) analyses. Diagnostic performance was assessed with ROC curve analysis.
Results: Seminomas showed significantly lower content of methylated XIST fragments compared to Non-Seminomas or normal testis($p<0.0001$) (Seminoma vs. normal testis and vs. Non-Seminoma: AUC 0.81 and 0.83, respectively). Seminomas contained significantly higher content of demethylated XIST compared to Non-Seminomas($p<0.001$), similarly in the "Seminoma-like" cell line TCam2 compared to the Non-Seminoma cell lines NCCIT, 2102Ep and NTera2($p<0.0001$). A strong positive correlation between Johnsen score (JS) and XIST demethylation was identified ($r=0.75$, $p<0.0001$). Only 1/54 testis with JS<4(premeiotic cells only) showed presence of XIST demethylation.
Conclusion: Differential methylation status of XIST promoter occurs among TGCT subtypes and in testicular parenchyma with different Johnsen score. Further analysis in liquid biopsies is warranted.

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OFP-13-012
Detection of EGFR mutations in ctDNA in plasma samples of NSCLC patients by two simultaneously applied methods
A. Farkasova[1], K. Scheerova[1], L. Plank[2,1]
[1] MBC Ltd., Slovakia, [2] Department of Pathology, Comenius University Jessenius Medical Faculty and University Hospital, Slovakia

Background & Objectives: The circulating tumour DNA (ctDNA) analysis might contribute to the identification of specific genes mutational status of cancer patients. It can be used both at the baseline cancer primodiagnostics as well as for monitoring the treatment response. For patients with non-small cell lung cancer (NSCLC), it seems to be possible to use this analysis in particular to identify *EGFR* mutations that significantly affect the selection of an appropriate targeted therapy at baseline or during the treatment´s follow-up.
Methods: In the period Sept. 2018 – March 2019 we analysed ctDNA isolated from the separated plasma of NSCLC patients either when a/ the biopsy or cytology material was not suitable for *EGFR* gene mutation analysis or b/ when a relapse occurred during TKI anti-EGFR treatment following the primary analysis of tissue specimens. All the samples were examined by two simultaneously applied methods. The first analysis used ctDNA isolated with the cobas® cfDNA Sample Preparation Kit and was performed on cobas® Z480 platform (Roche Molecular Diagnostics) with the cobas® EGFR Mutation Test v2 CE-IVD kit. The second one used ctDNA isolated with QIAamp circulating nucleic acid kit (Qiagen) and the tests were performed on Cube 6i flow cytometer (Sysmex Inostics) using OncoBEAM^{TM} EGFR Kit v2 (RUO).
Results: a/ in the primodiagnostic samples (n = 25) both the methods allowed to identify the same numbers and types of mutations: exon 19 del mutation was detected in 4 (16 %) and L858R mutation in 3 patients (12 %), while a simultaneous exon 19 del and T790M mutation was identified in one patient (4 %); b/ in a setting of patients with relapse of disease during the anti-EGFR TKI treatment (n = 13), both the methods showed identical results in 11/13 (85 %) cases (5 without any mutation, 2 with exon 19 del, 2 with simultaneous exon 19 del and T790M mutation and 1 with exon 21 /L858R/ mutation). In remaining 2 cases (15 % of all) the Cobas method allowed to identify exon 19 del mutation only, while the examination with BEAMing method discovered a combination of exon 19 del together with T790M mutation.
Conclusion: This pilot study allows to conclude that ctDNA analyses could be used to assess the *EGFR* gene mutation status in situations, when the patient´s biopsy and/or cytology material is not quantitative sufficient and/or qualitatively suitable for the DNA tests. These methods might be applied also for the monitoring of the therapeutic response and early detection of relapse due to the emergence of resistant mutations. However, the necessity of an implementation of more sensitive methods into the routine practice should be verified in large series of cases.

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Tuesday, 10 September 2019, 17:15 - 19:15, Galliéni 4
OFP-14 | Gynaecological Pathology

OFP-14-001
Microsatellite instability and its relation to myoinvasive pattern in low stage/low grade endometrioid endometrial carcinoma

I. Ruz-Caracuel[1], A. Berjón[2], J.L. Ramón-Patiño[3], L. Yèbenes[2], î López-Janeiro[2], A. Hernández[4], M. Mendiola[2], A. Redondo[3], A. Peláez-García[2], D. Hardisson[2]
[1] Hospital Universitario La Paz, Spain, [2] Pathology, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, [3] Oncology, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, [4] Gynaecology, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain

Background & Objectives: Endometrial carcinoma is the most prevalent gynaecologic malignant neoplasm worldwide. Most of these cancers are low grade (grade 1-2), low FIGO stage (I or II) endometrioid carcinomas. In this group, microsatellite instability (MSI) has been considered as a marker of poor prognosis. Our objective is to study if there is a relation between microsatellite instability and any of the myoinvasive patterns described.
Methods: Endometrial cancers submitted for surgery in a single tertiary hospital between 2003 and 2015 (n=512) were selected for this study. Inclusion criteria were: (i) endometrioid endometrial carcinomas, (ii) grade 1 or 2 with (iii) FIGO stage I or II. Slides were reviewed to annotate the myoinvasive pattern present in each case according to the classification described by Cole & Quick, 2013; as well as the presence of mucinous and/or squamous differentiation. MSI was studied by immunoexpression of mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6). Those cases with follow-up and evaluable immunohistochemistry were considered for analysis (n=201). A chi-squared or Fisher´s exact test was used to evaluate correlations.
Results: Our series has the following distribution according to the main myoinvasive pattern: infiltrative glands (49.8%), broad front (10%), adenomyosis-like (9.5%), microcystic, elongated and fragmented glands (MELF) (9%), adenoma malignum (0.5%), and non-infiltrative (21.4%). MSI was positively correlated with relapse (p=0.007), infiltrative glands myoinvasive pattern (p=0.032), histological grade 2 (p=0.005), lymphovascular invasion (p=0.003), and mucinous differentiation (p=0.02).
Conclusion: In our series, MSI is an adverse factor correlated with relapse. The myoinvasive pattern associated with MSI is the presence of infiltrative glands.

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OFP-14-002

Detailed description of high-risk HPV in situ hybridisation patterns in endocervical adenocarcinoma and correlation with p16 immunohistochemistry

M. Shahi[1], L. Hoang[2], T. Kiyokawa[3], S. Stolnicu[4], R. Soslow[5], K. Park[6]
[1] University of Chicago, USA, [2] University of British Columbia, Canada, [3] Department of Pathology, the Jikei University School of Medicine, Japan, [4] Department of Pathology, University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Romania, [5] Memorial Sloan Kettering Cancer Center, USA, [6] Department of Pathology, Memorial Sloane Kettering Cancer Center, New York, USA

Background & Objectives: Cervical adenocarcinoma are Human Papilloma Virus (HPV) and non-HPV associated. p16 immunohistochemical (IHC) staining is used as a surrogate marker for HPV infection. High-risk HPV ribonucleic acid in situ hybridization (HR HPV RNA-ISH) is more sensitive and specific than p16 to detect HPV. There have been no descriptions of staining pattern of HPV RNA ISH in HPV associated adenocarcinomas. Herein, we describe various staining patterns in glandular epithelium infected by HPV and correlate with p16 and Ki-67 IHC expression.
Methods: IHC for p16 and Ki-67, and HR HPV RNA-ISH were performed on two tissue microarray (TMA) slides composed of 200 cases of invasive endocervical adenocarcinoma. p16 was scored as positive (diffuse strong/diffuse weak/patchy strong), or negative if absent. Ki-67 was scored semi-quantitatively. HPV ISH was scored for viral load, nuclear signal size, percentage of nuclei with coarse signal, pattern of nuclear signal, cytoplasmic signal amount and presence of "reservoir-like cells". Signals were either fine (small, stippled) or coarse (dense, prominent).
Results: 174 cores had interpretable p16 and HPV-ISH results. 138 cases (79.3%) showed concordant p16/HPV status, including 32 cases of p16-/HPV- (G1, 23.2%) and 106 cases of p16+/HPV+ (G2, 76.8%). 36 cases (20.7%) showed discordant p16 and HPV results including 8 cases of p16+/HPV- (G3, 22.2%) and 28 cases of p16-/HPV+ (G4,77.8%). Ki-67 average in the p16+/HPV+ G2 (56%) was significantly higher than in the p16- groups G1/HPV- (41%) or G4/HPV+ (44%), (p-value 0.002 and 0.01, respectively).
Conclusion: Proliferation rate was statistically higher in p16+/HPV+ cases than p16- cases regardless of HPV status. Ki-67 and viral load, were higher in HPV+ cases with diffuse strong p16 compared to variable/weak p16. The cases with reservoir-like cells showed a higher proliferation rate than cases without. There was no discernible correlation between HPV staining pattern and p16 positivity.

OFP-14-003

Programmed death-ligand 1 (PD-L1) in cervical invasive squamous cell carcinoma and squamous intra-epithelial lesions in HIV infected women: comparison with non-infected patients

M. Brito[1], P. Sequeira[1], A. Quintas[1], I. Silva[1], C. Martins[2], A. Fèlix[3]
[1] Hospital Garcia de Orta, Almada, Portugal, [2] Nova Medical School, Universidade Nova, Lisbon, Portugal, [3] Instituto Portugues de Oncologia de Lisboa, Nova Medical School - UNL, Portugal

Background & Objectives: Programmed death-ligand 1 (PD-L1) protein is overexpressed in HPV infected carcinoma cells and inhibits T lymphocyte cytotoxic activity. The status of PD-L1 is not well established in malignant neoplastic cells of HIV infected patients. The fact that PD-L1 membrane expression in tumour cells has been correlated with responses to anti-PD-L1 immunotherapy, makes this knowledge mandatory.
Our aim was to study PD-L1 expression in cervical neoplastic epithelial cells of HIV infected women in comparison with non-HIV infected patients.
Methods: We analysed 110 cervical samples: 53 HIV+ patients (12 squamous cell carcinomas (SCC), 7 High-Grade Intra-epithelial Squamous Lesions (HSIL) adjacent(adj) to SCC, 21 HSIL, 20 Low-Grade Intra-epithelial Squamous Lesions (LSIL)); 57 from HIV- patients (17 SCC, 17 adjHSIL, 20 HSIL, 20 LSIL). PD-L1 immunohistochemical-evaluation used SP263Ab (Roche). The neoplastic cells percentage of membrane staining was scored as: 0 (<1%); 1(≥1% to 5%); 2 (≥5-10%); 3 (≥10-20%); 4 (≥20-50%); 5 (≥50%). Data were analysed by Fisher's exact test.
Results: In HIV infected women, 8/9 invasive SCC (89.9%) were positive (22.2% score 5) and 8/10 invasive SCC (80%) in HIV non-infected women (10% score5). HSIL adjacent to carcinoma were positive in all 7 cases from HIV+ patients and negative in all non-HIV patients (n=17) (p<0,0001). As for HSIL, non-adjacent to invasive carcinoma, 4/21 cases (19%) were positive in the HIV+ group and none in the HIV- group. No positive cases were found in LSIL and normal epithelium in both groups.
Conclusion: 1. PD-L1 is highly expressed in SCC both in HIV- and HIV+ women.
2. HSIL, in HIV infected women, are more often positive for PD-L1, than in HIVnon-infected women, and this difference is statistically significant (p<0,0001) in HSIL adjacent to SCC. This expression may contribute to a higher progression of these lesions to carcinoma, in HIV infected women.

OFP-14-004

Supporting the hypothesis of a dualistic model for high-grade serous carcinoma: a genetic and pathological study

A. De Leo[1], G. Santandrea[2], C. Ceccarelli[3], G. Barbero[4], S. Ferrari[4], D. Turchetti[4], D. Rubino[5], A.M. Perrone[6], P. De Iaco[6], D. Santini[7]

[1] Pathology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Italy, [2] Pathology Unit, S.Orsola-Malpighi Hospital, University of Bologna, Italy, [3] Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Italy, [4] Medical Genetics Unit, S.Orsola-Malpighi Hospital, University of Bologna, Italy, [5] Oncology Unit, S.Orsola-Malpighi Hospital, University of Bologna, Italy, [6] Gynaecologic Oncology Unit, S.Orsola-Malpighi Hospital, University of Bologna, Italy, [7] Pathology Unit, S. Orsola-Malpighi Hospital, University of Bologna, Italy

Background & Objectives: High-grade serous carcinomas (HGSC) with BRCA deficiency have recently been described to exhibit characteristic pathological features such as solid, pseudoendometrioid, transitional cell-like morphology (SET variant), and a particular pattern of invasion in metastatic sites. The aim of the study was to investigate the correlation between BRCA mutational status, age, tumour morphology, serous tubal intraepithelial carcinoma (STIC), tumour-infiltrating lymphocytes (TILs) and peritoneal invasion patterns.
Methods: 75 cases of HGSC were analysed. Pathological features were evaluated and classified as previously described. BRCA1/2 analysis was performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour tissue through Next Generation Sequencing technology.
Results: BRCA1/2 mutations were found in 40.7% of cases (79.2% germline mutations and 20.8% somatic mutations). Morphologically, 52.5% of cases were classified as classic HGSC and 47.5% as SET variant. BRCA-associated HGSCs were statistically correlated with SET morphology (p=0.0005) and pushing pattern metastases, but not with age, STIC and TILs. Compared with classic HGSC, SET tumours were strongly associated with pushing pattern of invasion (p=0.0001) and high density of TILs (p=0.0001) with number of CD8+ lymphocytes >100/10HPFs (p=0.001). STIC was found in 62.7% of cases and was more frequent in classic HGSC.
Conclusion: SET-HGSC showed a statistically significant association with BRCA mutation, TILs with high number of CD8+ lymphocytes, and a pushing pattern of peritoneal invasion. These pathologic differences among the classic HGSC and the SET variant, together with their different relations to BRCA mutations, allow to identify two possible separable entities, thus supporting the hypothesis of a dualistic model of HGSC.

OFP-14-005

Trefoil factor 2 (TFF2) as a surrogate marker for endocervical gastric-type carcinoma

T. Kiyokawa[1], L. Hoang[2], C. Terinte[3], A. Pesci[4], S. Aviel-Ronen[5], I. Alvarado-Cabrero[6], E. Oliva[7], K.J. Park[8], R.A. Soslow[8], S. Stolnicu[9]
[1] Department of Pathology, the Jikei University School of Medicine, Japan, [2] Department of Pathology, Vancouver General Hospital, Canada, [3] Department of Pathology, Oncologic Institute Iasi, Romania, [4] Pathology-IRCCS Ospedale Sacro Cuore-Don Calabria, Italy, [5] Department of Pathology, Sheba Medical Center, Tel-Hashomer, Israel, [6] Department of Pathology, Hospital de Oncología Mexico City, Mexico, [7] Department of Pathology, Massachusetts General Hospital, USA, [8] Department of Pathology, Memorial Sloan Kettering Cancer Center, USA, [9] Department of Pathology, University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Romania

Background & Objectives: Gastric-type carcinoma (GAS) is a distinct subtype of endocervical adenocarcinoma (ECA), being the most common HPV-unrelated type with an aggressive behavior. HIK1083 is a specific marker for GAS, but not highly sensitive and only available in Japan. TFF2 is a mucin associated peptide expressed in normal gastric but not endocervical glands. This study was carried out to investigate whether TFF2 could be a surrogate marker which in conjunction to HIK1083 could separate GAS from other types of ECA.
Methods: ECA cases from 7 international institutions were reviewed by a panel of pathologists for consensus histotype based on recently developed International Endocervical Criteria and Classification (IECC). Tissue microarrays were constructed for 179 cases to analyse TFF2 and HIK1083 expression using immunohistochemistry. Both markers were similarly scored and any staining in >5% of tumour cells was considered as positive.
Results: Of 179 ECA cases, 126 were of usual-type, 24 GAS, 7 clear cell and 22 other types. Of 24 GAS cases, 7 (29%) were positive for TFF2 and 10 (42%) for HIK1083, including 5 showing positivity for both markers. Of 155 non-GAS cases, only 4 (2.6%) showed positivity for TFF2, and 2 (1.3%) for HIK1083, none of clear cell type.
Conclusion: Our results suggest that TFF2 is a promising surrogate marker to separate GAS from other types of ECA in association with HIK1083. However, since only 1/3 of GAS were positive for TFF2 in this series, caution must be paid that negative TFF2 does not exclude a diagnosis of GAS.

OFP-14-006

Progenitor cells in ovario-fimbrial zone of female uterine adnexa: a potential clue for epithelial tumours pathogenesis

A. Asaturova[1]
[1] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation, Russia

Background & Objectives: Ovarian cancer remains the most deadly gynaecological malignant disease in developed countries. Basically, poor prognosis of this disease can be explained by the ineffectiveness of screening programs due to the lack knowledge of the ovarian cancer pathogenesis. Since pluripotent cells play a key role in the development of neoplastic epithelial changes, verification of the of their localization in transition zones (TZs) will help to determine the possibility of simultaneous existence of several potential sources for ovarian carcinoma development.
Methods: We investigated 165 tissue samples of the ovary and fallopian tube from patients with benign extraovarian pathology (uterine fibroids and adenomiosis) and 25 samples with high-grade serous ovarian carcinoma (HGSC) [(55 fimbriae, 25 parafimbrial zones (PFZ), 25 paraovarian zones (POZ), 35 samples of ovarian surface epithelium (OSE)]. Transition zones were taken separately for morphological assessment. Immunohistohemiscal investigation involved LGR5, NANOG, LNX9, CD117, CD44 and Oct4 assessment. Statistics was done with Student's test with Boferroni correction.
Results: LGR expressed in 38 fimbriae, 22 PFZ, 21 POZ, 32 OSEs; NANOG expressed in 25 fimbriae, 20 PFZ, 24 POZ, 35 OSEs; LHN9 expressed in 27 fimbriae, 19 PFZ, 19 POZ, 25 OSEs; CD 117 expressed in 30 fimbriae, 10 PFZ, 15 POZ, 11 OSEs. Statistically significant difference in progenitor markers expression were shown between TZs, OSE and fimbriae, as well as between normal epithelium and HGSC and between TZs and epithelial cells elsewhere (p<0,05).
Conclusion: We investigated transitional zones of the uterine adnexa with progenitor cell markers and revealed that there is a significantly higher concentration of these cells in the transition zones where two types of the epithelia met. Thus, these zones can be a potential source (hot spot) for neoplasia development due to mutations in progenitor cells and further clonal expansion.

OFP-14-007

Diagnostic panel with p16, stathmin1 and laminin-gamma1 for serous tubal intraepithelial carcinoma

A. Asaturova[1], N. Kondrikov[2]
[1] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation,

Russia, [2] Moscow Regional Research Institute of Obstetrics and Gynaecology, Russia

Background & Objectives: Serous tubal intraepithelial carcinoma (STIC) is known to be a putative precursor for the most common and aggressive ovarian carcinomas, namely ovarian high-grade serous carcinoma. Precise and early diagnose this disease is therefore one of the priorities for tissue diagnosis in gynaecologic oncology. At the same time routinely applied algorithm for STIC diagnosis could not cover some grey zones in its diagnostics.
Methods: The study included 70 patients (125 fallopian tubes), all of the specimens were investigated morphologically and immunohistochemically (p53, Ki-67, p16, stathmin1 and laminin-gamma1). Statistics involved exact Fisher's test, χ2-test, Cohen's kappa.
Results: Expression of p16, stathmin1 and laminin-gamma1 was revealed in 85%, 77,5% and 90% of STIC consequently. In 4 tubes with STIC, only one of these tree markers was positive but we has no cases with all three negative expression. In STIC cases, expression of p16, stathmin1 and laminin-gamma1 was high both in the presence and in the absence of p53 expression in atypical cells. In most cases, positive expression of at least two of the three studied markers was shown. p16, stathmin1 and laminin-gamma1expressin does not differ between p53-positive and p53-negative STICs. Cohen's kappa for STICs with ambiguous p53 expression was moderate (0.55) when we used only p53 and ki-67 expression. P16/laminin-gamma1/stathmin1 diagnostic panel let us increased Cohen's kappa to good reproducibility (0.72), ($p<0.05$).
Conclusion: Lack of grey zones in STIC diagnostics and good reproducibility of diagnoses allows us to recommend p16, stathmin1 and laminin-gamma1 diagnostic panel for STIC diagnostics, especially in case of ambiguous p53 expression and/or borderline KI-67 expression.

OFP-14-008

Relationship between microcystic, elongated and fragmented pattern of myometrial invasion and histopathological prognostic factors in endometrioid endometrial carcinoma

S.D. Altindag[1], S. Yigit[1], S. Sen[2]
[1] Izmir Katip Celebi University Ataturk Training and Research Hospital, Department of Pathology, Turkey, [2] Izmir Katip Celebi University Ataturk Training and Research Hospital, Department of Gynaecology and Obstetrics, Turkey

Background & Objectives: Endometrioid endometrial carcinoma (EEC) is generally has a favourable prognosis. Recently, many studies have claimed that microcystic, elongated, and fragmented (MELF) pattern of myometrial invasion (MI) was associated with a poor prognosis. The purpose of this study is to examine relationship between MELF pattern with histopathologic parameters in EEC.
Methods: Hematoxylin and eosin slides of 234 cases of EEC with MI (from 2009 to 2014) were evaluated retrospectively from pathology archives. The association of MELF pattern with age, tumour grade, depth of MI, presence of lymphovascular space invasion (LVSI), cervical stromal invasion, lymph node metastasis, and International Federation of Gynaecology and Obstetrics (FIGO) stage was analysed.
Results: The mean age was 60.7 (33-83). Grade 1, 2, 3 were observed in 142 cases (60.7%), 76 (32.5%) and 16 (6.8%) respectively. MELF pattern was observed in 51 cases (21.8%). Presence of MELF pattern was significantly associated with deep (≥50%) MI ($p<0.001$), presence of LVSI ($p<0.05$), lymph node metastasis ($p<0.05$), and advanced (III-IV) FIGO stage ($p<0.05$).
Conclusion: In conclusion, MELF pattern invasion was found to be related statistically with deep MI, presence of LVSI, lymph node metastasis, and advanced FIGO stage. Therefore, MELF pattern can be associated with poor outcome.

OFP-14-009

Immunohistochemistry with CK17 and SOX2, in addition to p53, can be of diagnostic value for differentiated vulvar intraepithelial neoplasia (dVIN)

S. Dasgupta[1], S. Koljenović[1], H.C. van Doorn[1], V. Noordhoek Hegt[1], F.J. van Kemenade[1], P.C. Ewing-Graham[1]
[1] Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Background & Objectives: Differentiated VIN (dVIN) is a difficult histological diagnosis, as it often resembles non-neoplastic epithelial disorders (NNED), particularly lichen sclerosus (LS). We reviewed dVIN cases from a retrospective cohort and explored additional diagnostic immunohistochemical markers [i.e. Cytokeratin 17 (CK17) and SOX2]. CK17 is a differentiation marker upregulated in squamous dysplasia, and SOX2 is an onco-protein activated in squamous cell carcinoma.
Methods: In total, 160 dVIN cases (2014 – 2017) from Erasmus MC were reviewed by two pathologists. Immunohistochemistry with CK17 and SOX2, and conventional markers (p53, p16, MIB-1) was performed on a subset of cases comprising dVIN (n = 20), NNED (n = 9), normal vulvar tissue (n = 9). Receiver operating characteristic curves were plotted.
Results: The mean expression of CK17 ($p = 0.03$) and SOX2 ($p = 0.01$) were significantly higher in dVIN compared to NNED and normal vulvar tissue. Overexpression of p53 was seen in 60% of dVIN cases, 15% showed null pattern, and 25% showed wild type expression. All dVIN cases were p16 negative and showed increased MIB-1 expression in basal and suprabasal layers. The area under the curve of p53 was 0.78 for the diagnosis of dVIN, and that of p53, CK17, and SOX2 combined was 0.82.
Conclusion: Our preliminary results show that immunohistochemistry with CK17 and SOX2 can be of diagnostic value for dVIN when used in a panel along with p53.

OFP-14-010

Precursor lesions of vulvar squamous cell carcinoma - a systematic review

S. Dasgupta[1], P.C. Ewing-Graham[1], S.M. Swagemakers[1], H.C. van Doorn[1], V. Noordhoek Hegt[1], S. Koljenovic[1], F.J. van Kemenade[1]
[1] Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Background & Objectives: Vulvar intraepithelial neoplasia (VIN) is the precursor lesion of vulvar squamous cell carcinoma (VSCC). In this systematic review we provide a detailed overview of the updated nomenclature, histological diagnostic criteria, and available ancillary tools (immunohistochemical and molecular) for the various VSCC precursors. With a view to identify additional diagnostic biomarkers for VIN, datasets from gene expression omnibus (GEO) were analysed.
Methods: Biomedical bibliographic databases were searched with electronic search strategies; citation and hand searching were also performed. PRISMA guidelines were followed; the study was registered in PROSPERO [CRD42019107290]. Whole genome sequencing datasets of VSCC from GEO were imported into OmniViz for analysis. Differential expression of genes was identified using statistical analysis of microarrays (SAM). For functional annotation of microarray results, Ingenuity Pathway Analysis was used.
Results: The final selection comprised 105 references; a narrative synthesis was prepared. HPV-associated usual VIN (uVIN) is characterised by overt nuclear atypia and p16 positivity, while HPV-independent differentiated VIN (dVIN) is characterised by p53 overexpression. A new potential VSCC precursor, differentiated exophytic vulvar intraepithelial lesion (DEVIL), is characterised by PIK3CA mutation, and wild type p53 expression. From the GEO analysis, the molecules SPRR2G, S100A7A, and KRT17P, were found to be most significantly upregulated in dVIN; these are involved in epidermal maturation and promotion of chemotaxis. The molecules OLFM4, MAL, and APOD were most significantly downregulated in dVIN; these mediate cellular adhesions.

Conclusion: Updated knowledge of VSCC precursors will facilitate reproducible diagnosis amongst pathologists. GEO dataset analysis provides newer insights into potential biomarkers for VSCC precursor lesions.

OFP-14-011

Neuroendocrine tumours involving the cervix: the role of p16 and HPV-genotyping

A. Varelas[1], A.R. Lopes[2], A. Tavares[3], J. Ferreira[1], R. Vieira[1], R. Moreira Silva[1], R. Dias[1], R. Medeiros[3], H. Sousa[3], C. Bartosch[4]
[1] Portuguese Oncology Institute of Porto (IPO-P), Pathology Department, Portugal, [2] Portuguese Oncology Institute of Porto (IPOP-P), Oncology Department, Portugal, [3] Portuguese Oncology Institute of Porto (IPO-P), Virology Department, Portugal, [4] Department of Pathology IPOP, Portugal

Background & Objectives: Primary neuroendocrine carcinoma of the cervix, albeit rare, is an important diagnostic to ascertain, as it may have particular therapeutic and prognostic consequences. This tumour has a well-established association with HPV. We hypothesized that p16 immunoexpression and HPV-genotyping in a cervix neoplasia with neuroendocrine differentiation may be useful to distinguish primary from secondary origin.
Methods: We reviewed clinicopathological features of 25 patients with neuroendocrine tumours involving the cervix diagnosed at Portuguese Oncology Institute of Porto (1989-2019). Immunohistochemical profile (including neuroendocrine markers and p16) was evaluated and tumours' HPV-genotyping was performed.
Results: Patients had a median age of 59(range 25-78) years. Tumours had a median size of 7 (range 3.5-10) cm. Regarding stage at diagnosis, 14(56%) were confined to the cervix, 9(36%) had disseminated disease and 2(8%) were unknown. Diagnostic samples were mostly limited to biopsies(n=20) and 5 patients had hysterectomy specimens. Most were small cell neuroendocrine carcinomas(n=23) and 2 had features of large cell neuroendocrine carcinoma. All tumours showed at least chromogranin (20/23) or synaptophysin (17/20) expression; p16 was diffusely positive in 18/24 and correlated with HPV status in most cases (14/20). HPV was detected in 16 tumours (including HPV-18 and/or 16), 4 were HPV negative and 5 inconclusive. Within negative HPV tumours, one largely extended to the endometrium, one had a synchronous ovarian mass, and two had disseminated disease with liver, lymph node and bone involvement.
Conclusion: When evaluating a tumour with neuroendocrine differentiation, HPV-negativity, with or without p16 immunoexpression, may favour a secondary involvement of cervix, prompting for further diagnostic studies.

OFP-14-012

Invasive stratified mucin producing carcinoma of the uterine cervix - an unusual tumour with aggressive behaviour

L. Horn[1], R. Handzel[2], U. Siebolts[3], C.E. Brambs[4]
[1] Institute of Pathology, Germany, [2] Division of Gynaecologic Oncologic Surgery, Department of Obstetrics and Gynaecology (Institute of Trier), University Hospital Leipzig, Germany, [3] Division of Molecular Pathology, Institute of Pathology, University Hospital Halle/Saale, Germany, [4] Department of Obstetrics and Gynaecology, Technical University Munich, Germany

Background & Objectives: Invasive stratified mucin-producing carcinoma (i-SMILE) represents a recently recognized subtype of cervical adenocarcinoma (AC) developing in a background of a stratified mucin-producing intra-epithelial lesion (SMILE). Clinical and prognostic data on i-SMILE are limited. Here we report a case series and review the literature regarding prognostic outcome.
Methods: We report a series of five cases with histopathological, immunohistochemical (p16) and PCR analyses. The cases as well as the patients previously published in the literature were reviewed for follow-up information.
Results: Thirteen cases were identified. The mean age of 47.1 years (range 34 – 66) was not different from the usual type of cervical AC. 10/13 cases presented with tumours >2cm and a polypoid-exophytic appearance. Regardless of tumour size and stage of the disease, seven out of 11 patients developed recurrent disease after a mean of 7.8 months (range 6 weeks to 36 months). Five patients developed distant metastases (three of them in the lungs). Five out of the 11 informative cases died of the disease. All reported cases were positive for high-risk HPV (mainly HPV type 18) and associated with p16-overexpression.
Conclusion: i-SMILE represent a distinct subtype of invasive endocervical AC, associated high-risk HPV-infection and strong p16-overexpression. Clinically, i-SMILE may represent an aggressive tumour with early recurrent disease and substantial risk of distant metastatic disease, especially to the lungs.

Oral Free Paper Sessions One-Day CPS and Two-Day MDS

Sunday, 8 September 2019, 17:15 - 19:15, Clio
CP-03 | 1-Day Computational Pathology Symposium – Selected Abstracts

CP-03-001

Deep learning enables fully automated mitotic density assessment in breast cancer histopathology

M. Balkenhol[1], P. Bult[1], D. Tellez[1], W. Vreuls[2], P. Clahsen[3], F. Ciompi[1], J. van der Laak[1]
[1] Radboud University Medical Center, The Netherlands, [2] Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands, [3] Haaglanden Medical Center, The Netherlands

Background & Objectives: Mitosis counting is an important part of breast cancer grading, yet known to suffer from observer variability. Advances in machine learning enable fully automated analysis of digitized glass slides. The present study evaluated automatic mitosis counting and demonstrated applicability on triple negative breast cancers (TNBC).
Methods: A deep learning algorithm fully automatically detected mitoses in scanned H&E slides of 90 invasive breast tumours and determined the mitotic hotspot. Two independent observers assessed mitotic density on glass slides according to routine practice, and in the computer-defined hotspot. Automated mitotic counting was also performed in a TNBC cohort (n=597). Cox regression models were expanded with dichotomized mitotic counts, using the c-statistic to evaluate the additional prognostic value of every possible cut off value.
Results: Automatic counting showed excellent concordance with visual assessment in computer detected hotspots with intraclass correlation coefficients (ICC) of 0.895 (95% CI 0.845–0.930) and 0.888 (95% CI 0.783–0.936) for two observers, respectively. ICC of fully automated counting versus conventional glass slide assessment were 0.828 (95% CI 0.750–0.883 and 0.757 (95% CI 0.638–0.839), respectively. In the TNBC cohort, none of the cut off values improved the models' baseline c-statistic.
Conclusion: Automatic mitosis counting is a promising complementary aid for mitoses assessment. Our method was capable of fully automatically locating the mitotic hotspot in tumours, and was

capable of processing a large series of TNBC, showing that mitotic count was not prognostic for TNBC even when attempting alternative cut off points.

This study was funded by a Junior Researcher grant from the Radboud University Medical Center Institute for Health Sciences (RIHS).

CP-03-002

Automated grading of urothelial cell carcinoma of the bladder

I. Jansen[1], M. Lucas[1], J. Bosschieter[2], S. Meijer[3], O. de Boer[3], T. van Leeuwen[4], H.A. Marquering[4], J.A. Nieuwenhuijzen[2], D.M. de Bruin[4], C.D. Savci-Heijink[4]

[1] Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, The Netherlands, [2] Amsterdam UMC, location VUmc, The Netherlands, [3] Department of Pathology, Amsterdam UMC, University of Amsterdam, The Netherlands, [4] Amsterdam UMC, location AMC, The Netherlands

Background & Objectives: Although histological grade is an important predictor for recurrence and progression in non-muscle invasive bladder cancer (NMIBC), the reproducibility is low.

The aim of this study is to investigate the potential value of a deep learning architecture for the grading of urothelial cell carcinoma (UCC) of the bladder using histology slides of transurethral resection of bladder tumour (TURBT) specimen and assess its accuracy by the comparison with the consensus grading of three pathologists.

Methods: Histological glass slides of patients with NMIBC who underwent a TURBT between 2000-2016 in three hospitals in the Netherlands were included. The slides were independently reviewed by three pathologists, assigning the WHO'73 and WHO'04 grade, resulting in a four-tiered grading scheme. The slides were digitized, manually annotated by an expert observer and subsequently checked by a uropathologist. Firstly, a U-Net was trained to segment urothelium. Based on these segmentations, an ImageNet pre-trained DenseNet was trained for automated grading of the urothelial lesions based on the consensus score of the three pathologists.

Results: In total, 328 tissue samples of 232 patients were included. In 93% of the slides, the urothelium was accurately detected. In another 21% false positive regions were detected. Incorrect classification was mainly in slides with extensive color loss or in regions with inflammation. Detailed data on the UCC grading will be presented at the conference.

Conclusion: This feasibility study demonstrates the potential value of deep learning methods in classification of urothelial lesions.

I Jansen and M Lucas are paid by ITEA3. Grant number: ITEA151003.

CP-03-003

Unsupervised anomaly detection: application to colorectal liver metastasis

A. Serag[1], P. Maxwell[2], J. Diamond[1], A. Ion-Margineanu[1], A. Kennedy[1], R. McMillan[1], H. Qureshi[1], M. Saint Martin[1], M. Salto-Tellez[2], P. Hamilton[1], P. O'Reilly[1]

[1] Philips Digital & Computational Pathology, United Kingdom, [2] Queen's University Belfast, United Kingdom

Background & Objectives: The building of deep learning models needs large amounts of data with annotated examples. Obtaining expert labels for such models is difficult since detailed annotation is time-consuming. Here, we present an unsupervised learning approach capable of identifying anomalous patterns that can serve as imaging biomarker candidates. We show the application of the proposed approach for detecting colorectal metastases in liver biopsies.

Methods: We propose to use unsupervised learning to create a rich generative model of normal (i.e. non-tumour) local anatomical appearance. We use generative adversarial networks to solve the problem of creating an adequately representative model of appearance, while at the same time learning a generative and discriminative component. We use information from both image space and latent space to differentiate between observations that conform to the training data and such data that does not fit.

Results: The trained model is able to generate images that are visually similar to the non-tumour images. In the case of anomalous images (contain metastases), the pairs of input images and generated images show significant differences. The distributions of the anomaly score over non-tumour images from the training set and test set or over images extracted from metastatic cases show that the anomaly score is suitable for the classification of normal and anomalous samples *($P<0.001$)*.

Conclusion: We presented an unsupervised approach for colorectal metastasis detection in liver biopsies. Training patches were extracted from non-tumour images; avoiding the necessity of having detailed pathologist annotation. The approach may be applied across the whole range of computational pathology problems.

CP-03-004

Automated Ki67 hot-spot detection and analysis leads to higher Ki67 proliferation indices

M. Zwager[1], T. Koopman[1], H. Buikema[1], D. Omanovic[2], A. Schønau[2], H. Klingberg[2], B. van der Vegt[1]

[1] University of Groningen, University Medical Center Groningen, The Netherlands, [2] Visiopharm A/S, Hørsholm, Denmark

Background & Objectives: It is suggested that Ki67 proliferation hot-spot scoring is a prognostic and predictive marker in breast cancer. However, visual identification of Ki67 hot-spots is difficult and manual scoring is labour-intensive and prone to inter- and intra-observer variability. Automated detection and scoring of Ki67 hot-spots by digital image analysis (DIA) could aid in a standardised and reproducible assessment of the Ki67 proliferation index. The aim of this study was to compare manual Ki67 hot-spot detection and scoring with DIA Ki67 hot-spot detection and scoring.

Methods: Whole tissue sections of 117 consecutive invasive breast carcinomas were immunohistochemically stained for Ki67. Firstly, Ki67 hot-spots were detected by two independent observers and scored using a validated manual counting protocol. Secondly, manual Ki67 scores were compared with DIA on these manually annotated hot-spots. Thirdly, automated Ki67 hot-spot detection and Ki67 calculation was performed using DIA. Inter-observer agreement between manual scores and DIA in manually annotated hot-spots, and between manual observers was assessed using the coefficient of determination (R^2). Means of manual scoring and DIA results were compared.

Results: 102 cases were available for assessment. Correlation between both manual observers was suboptimal (R^2=0.78). Manual and DIA Ki67 scores in manually annotated hot-spots showed a strong correlation (R^2=0.90). Hot-spot detection by DIA (mean: 39.0%) led to higher hot-spot scores compared to manual scoring (means: 33.4% and 29.4%).

Conclusion: Automated Ki67 hot-spot detection and analysis is a reliable method that leads to higher hot-spot Ki67 proliferation indices.

CP-03-005

U-Net ensembles for accurate classification of oesophageal adenocarcinoma

B. Cardenas Guevara[1], V. van Oijen[1], D. Worrall[1], K. de Laat[2], M. van der Wel[2], M. Lucas[3], I. Jansen[3], H. Marquering[3], D. de Bruin[3], D. Savci-Heijink[2], O. de Boer[2], S. Meijer[2]

[1] Amsterdam Machine Learning Lab, University of Amsterdam, The Netherlands, [2] Department of Pathology, Amsterdam UMC,

University of Amsterdam, The Netherlands, [3] Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, The Netherlands

Background & Objectives: Oesophageal adenocarcinoma has a dismal prognosis and Barrett's oesophagus (BE) is the only known precursor lesion. BE progresses through a metaplasia-dysplasia-carcinoma sequence. Progression rates from non-dysplastic BE (NDBE) are low (0,5%), but a histopathological diagnosis of low grade dysplasia (LGD) is a strong independent risk factor for progression. As a result of significant interobserver variation, reported progression rates vary from 1- 40% and therefore International guidelines mandate a second opinion by an expert-pathologist.
We aim to develop a convolutional neural network for objective and reproducible diagnosis of dysplasia in BE at expert-pathologist level.
Methods: TIFF images from 400 digitized biopsies of 170 BE patients were annotated in high detail by an expert pathologist, generating binary classification masks for NDBE and dysplastic glands. Patches of the H&E staining and corresponding binary mask were extracted, resulting in 148.033 and 34.557 patches for training and testing, respectively. An ensemble of U-Nets was used, using a combination of the U-Net architecture with DenseNet and ResNet models, pre-trained on ImageNet. The ensemble consisted of four U-Nets with a down-sampling path using the DenseNet architecture and four other U-nets using the ResNet architecture. As metrics F1 coefficient and the pixel-wise accuracy was used.
Results: F1 scores (range 80.6 and 84.9%) and pixel-wise accuracy (range 86.5 to 90.6%) of individual models and combinations; the best performing combination was the ensemble consisting of a committee of eight DenseNet and ResNet models.

Model	F1-score	Pixel-wise accuracy
U-Net	80,6%	86,5%
U-Net + ResNet-34	81.9 %	87.6 %
U-Net + ResNet-152	83.1 %	88.9 %
U-Net + DenseNet-161	82.8 %	88.1 %
Ensemble DenseNet and ResNet	84.9 %	90.6 %

Conclusion: U-Net ensembles that classify precursor lesions of oesophageal adenocarcinoma can be used for accurate risk stratification of patients with BE.

CP-03-006
Artificial intelligence driving automated pathology: iCAIRD and beyond
P. Caie[1], N. Dimitriou[1], I.P. Nearchou[1], O. Arandjelović[1], D. Harrison[1]
[1] University of St Andrews, United Kingdom

Background & objectives: Artificial Intelligence (AI) can be trained to recognise complex patterns and morphology within digitised histopathology specimens and use them to aid clinical reporting. These patterns may be already known, where the pathologist trains the AI model. However, cancer is a complex disease and the tissue may harbour undiscovered but clinically significant morphological patterns. AI can also be used to identify and report such novel features without human bias and error. This talk will demonstrate how the two above methodologies were successfully used in colorectal (CRC) and bladder cancer examples and how they will be used for the automatic reporting of gynaecological specimens in the iCAIRD initiative.
Methods: Machine learning workflows were designed to analyse unbiasedly extracted data from the automated analysis of immunofluorescence labelled urine cytology (n=624) and whole slide CRC specimens (n=173). H&E labelled whole slides of CRC were analysed using AI after both pathology trained feature recognition (n=650) and without any human direction (n=75).
Results: Bladder cancer diagnosis was reported from urine cytology samples with 95% sensitivity and 70% specificity. CRC survival was predicted with an AUROC of 0.94 in the immunofluorescence labelled cohort using 123 automatically extracted features and with >95% accuracy in the H&E stained digitised slides when applying no human input.
Conclusion: The use of AI allows clinically significant features to be reported with or without human training and error. This work demonstrates AI's ability to automatically report clinical specimens and how the technology can track toward clinical translation such as with the iCAIRD initiative.

CP-03-007
Implementation of the ContextVision INIFY(TM) tool for the automatic detection of prostatic cancer in a fully digital routine workflow
F. Fraggetta[1], S. Lionti[1], G. Giuffrida[1], C. Emmanuele[1], P. Pepe[2]
[1] Pathology Unit Cannizzaro Hospital, Italy, [2] Urology Unit Cannizzaro Hospital, Italy

Background & Objectives: Validation of an Artificial Intelligence (AI) prototype tool INIFY™ (ContextVision Company, Sweden) for the detection of prostatic cancer in bioptic samples were evaluated ia fully digital pathology laboratory at Cannizzaro Hospital in Catania, Italy
Methods: The procedure included the following steps: integration with the local laboratory information system (LIS) (Pathox ver.13) and possibility to open the INIFY™ web viewer. All cases submitted were confirmed by expert pathologists.
Results: The integration with the local LIS was obtained using a specific HL7 connection. between LIS and INIFY™ AI tool without problems. According to a default protocol only Whole Slide Images (WSI) belonging to prostatic bioptic samples were automatically submitted for analysis at the end of the scanning session, without need of manual intervention. After analysis the results were available within the virtual tray of the case: flipped image if cancer. A total of 4746 WSI of prostatic cancers were submitted to INIFY™ tool, with a success rate of 100%. The prototype tool showed high specificity at recognizing cancer but low sensitivity. However by using the INIFY™ viewer all the suspicious area were indicated.
Conclusion: The installation of ContextVision INIFY™ in the Catania Digital Pathology department showed a successful integration of this AI tool in a fully digital workflow, facility to use, working as computer-aided diagnosis. This tools could be a helpful instrument in a digital routine.

Monday, 9 September 2019, 08:30 - 09:30, Clio
MD-01 | 2-Day Molecular Diagnostics Symposium – Selected Abstracts

MD-01-001
Plasma cfDNA testing of patients with EGFR mutant non-small cell lung cancer: droplet-digital PCR versus next-generation sequencing compared to tissue-based results
C.M. Steendam[1,2], P.N. Atmodimedjo[1], E. de Jonge[1], M.S. Paats[1], C. van der Leest[2], E. Oomen - de Hoop[1], J.H. von der Thüsen[1], W.N. Dinjens[1], R.H. van Schaik[1], J.G. Aerts[1], H.J. Dubbink[1]
[1] Erasmus MC, Rotterdam, The Netherlands, [2] Amphia Hospital, Breda, The Netherlands

Background & Objectives: To compare the results of plasma cell-free DNA (cfDNA) droplet-digital PCR (ddPCR) and next generation sequencing (NGS) on detection of Epithelial Growth Factor Receptor (EGFR) primary activating mutations and p.T790M with results of tissue analysis in patients with EGFR mutated non-small cell lung cancer (NSCLC).

Methods: All patients with EGFR mutated NSCLC for which a pathology and a plasma specimen were available upon progression between November 2016 and July 2018 were selected. Concordance, Cohen's kappa and intraclass correlation coefficients were calculated.
Results: Plasma cfDNA and pathology specimens of 36 patients were analysed. Agreement between ddPCR and NGS was 86% (κ=0.63) for the primary activating mutation and 94% (κ=0.89) for p.T790M detection. Allele ratios were comparable with an intraclass correlation coefficient of 0,992 and 0,997 respectively. Discrepancies of some degree were found in 15 patients (41.7%). In 6 patients (16.7%), no mutations at all were detected in cfDNA. In 3 patients (8.3%), p.T790M was detected in plasma but not in pathology specimen, while in 3 other patients (8.3%), p.T790M was demonstrated in the pathology specimen but not in plasma. Concordance of cfDNA and pathology for the primary activating mutation was 69% for ddPCR and 83% for NGS. For the detection of p.T790M this was 75% (κ=0.49) for ddPCR as well as for NGS.
Conclusion: Mutual agreement is high between NGS and ddPCR in cfDNA on the level of a specific mutation, with comparable ratio results. Plasma testing of EGFR primary activating mutations and p.T790M shows high concordance with pathology results, for NGS as well as ddPCR, depending on the extent of the panel used. In NGS, more genetic aberrations can be investigated at once.

This work was supported by AstraZeneca.

MD-01-002
Circulating cell-free DNA in archived low-quality volume serum samples: rate of concordance with mutation in tumour
D. Nasrollahzadeh[1], B. Abedi-Ardekani[1], T. Delhomme[1], P.H. Avogbe[1], M. Foll[1], J. McKay[1], P. Brennan[1], R. Malekzadeh[2]
[1] International Agency for Research on Cancer/WHO, France, [2] Digestive Disease Research Institute Tehran, Iran

Background & Objectives: Cell-free DNA (cfDNA) is considered as non-invasive method for cancer detection with high specificity and variable sensitivity. Mainstream cfDNA studies are based on qualified samples which is plasma kept at -80, with no cycle of re-thawing, and minimum volume of 1 ml. In some archival studies, such standards were not met. We aim to investigate feasibility of cfDNA detection in archival serum samples kept at -20 with several cycles of re-thawing and volume less than or equal to 0.7 ml.
Methods: Leftover sera from a population-based study of oesophageal squamous cell carcinoma (ESCC) in Northern Iran- conducted 14 years ago- were used. Sera were applied for several serology assays and underwent between 4 and 6 cycles of re-thawing. *TP53* mutation data from formalin-fixed paraffin-embedded ESCC tissues was available for one-third of the cases. We extracted cfDNA from 44 ESCC and 39 controls (matched for storage condition). 27 *TP53* amplicons were deep sequenced on ion-torrent platform. Needlestack, a pipeline for calling variants with extremely low allelic fraction (AF) was applied. RVSB >0.85, Q-value<30, and minimum distance form highest AF <10 nt. were filtered.
Results: We were able to detect 20% of tumour tissue mutations concordantly in CfDNA of archival sera. After applying filtrations, 59 unique mutations were detected in all cfDNAs, out of them 24 were exclusively detected in ESCC cases and 29 found just in controls. None of the tumour mutations was detected among controls. One likely non-germline cfDNA mutation was detected in both case and control which had significantly higher AF in case than control.
Conclusion: Applying our method, detection rate of concordant *TP53* mutations in archived low- volume sera and cancerous tissue is comparable to results of the same gene in well-kept plasma. These results suggest the crucial role of bioinformatics pipeline in detectability of variants in cfDNA comparing to quality of sample. *TP53* variants in healthy resident of ESCC endemic area warrants further investigation.

MD-01-003
Global delivery of external quality assessment for lung cancer liquid biopsy testing
J. Fairley[1], M. Cheetham[2], M. Denis[3], E. Dequeker[4], C. Keppens[4], F. Fenizia[5], N. Normanno[5], S. Patton[6], E. Rouleau[7], E. Schuuring[8], K. Van Casteren[9], Z. Deans[1]
[1] GenQA/UKNEQAS, United Kingdom, [2] EMQN, United Kingdom, [3] Gen&Tiss, France, [4] ESP, Belgium, [5] Istituto Nazionale Tumouri "Fondazione Giovanni Pascale", IRCCS, Naples, Italy, [6] European Molecular Genetics Quality Network (EMQN), Manchester Centre for Genomic Medicine, St Mary's Hospital, United Kingdom, [7] Department of Pathology and Medical Biology, Institut Gustave Roussy, Villejuif, France, [8] ESP, The Netherlands, [9] Biomedical Quality Assurance Research Unit, KU Leuven, Belgium

Background & Objectives: Wide-spread implementation of cell free DNA (cfDNA) testing of plasma for cancer mutations requires quality assessment of these services to ensure patient safety. The international external quality assessment (EQA) provider consortium, IQNPath has delivered a second successful EQA run to determine the standard of cfDNA testing for lung cancer.
Methods: Five European EQA providers, under the umbrella of IQNPath, collaborated to deliver the assessment during 2018-19 to a total of 320 laboratories from 44 countries. A panel of bespoke manufactured plasma samples with varying mutations at a range of allelic frequencies were validated by a range of methodologies prior to distribution to ensure stability and reproducibility. The EQA samples were supplied for testing and reporting according to laboratory routine protocols. Peer reviewed criteria was applied to assess the standard of genotyping and reporting.
Results: The genotyping accuracy, variability of reporting content and formats will be discussed. Low allelic frequency samples were the most challenging and some methods did not detect these mutations. Reporting of such cases often did not address the risk that tumour DNA may have not been tested and limitations of the testing performed was not addressed when reporting the result.
Conclusion: The variability in the standard of genotyping and reporting highlights the need for EQA in this field and educational guidance to ensure the delivery of high-quality clinical service where testing of cfDNA is the only option for clinical management.

MD-01-004
Reflex tumour BRCA1/2 testing in ovarian carcinomas to stratify PARP inhibitor treatment and germline diagnostics
M. Ligtenberg[1], J.R. Vos[2], I.E. Fakkert[2], J.A. de Hullu[3], A.M. van Altena[3], A.S. Sie[2], H. Ouchene[2], R.W. Willems[1], I.D. Nagtegaal[1], M.C. Jongmans[2], A.R. Mensenkamp[2], G.H. Woldringh[2], J. Bulten[1], E.M. Leter[4], C.M. Kets[2], M. Simons[1], N. Hoogerbrugge[2]
[1] Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands, [2] Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands, [3] Department of Obstetrics and Gynaecology, Radboud University Medical Center, Nijmegen, The Netherlands, [4] Department of Clinical Genetics, Maastricht University Medical Center, The Netherlands

Background & Objectives: Women with ovarian carcinoma have a higher chance to benefit from PARP inhibitor therapy if their tumour has a somatic or germline *BRCA1/2* pathogenic variant. Germline *BRCA1/2* testing allows therapeutic and preventive choices in patients

and family members. This study evaluates the feasibility, effectiveness, and appreciation of reflex tumour *BRCA1/2* testing in newly diagnosed ovarian carcinoma patients to stratify patients for PARP inhibitor therapy and predisposition testing.
Methods: Reflex tumour *BRCA1/2* testing of newly diagnosed ovarian carcinomas was evaluated in seven hospitals between October 2015 and June 2017. Diagnostic yield, uptake, referral rates for genetic testing, and experiences of patients and gynecologists were evaluated.
Results: Reflex tumour *BRCA1/2* testing was performed for 315 (78%) of 406 eligible samples and was successful in 305 (97%). In 51 ovarian carcinomas a pathogenic *BRCA1/2* variant was detected (17%). Genetic counseling and germline testing was performed in 44 patients, revealing that 57% of the mutations were hereditary. Most participating gynecologists and patients were positive about the workflow.
Conclusion: Reflex tumour *BRCA1/2* testing in all newly diagnosed ovarian carcinoma patients to find somatic and germline *BRCA1/2* variants is feasible, effective and appreciated by patients and gynecologists. It serves as an effective pre-screen for genetic counselling and germline diagnostics. It extends personalised treatment choices based on tumour *BRCA1/2* status to patients with somatic pathogenic variants and patients that do not opt for hereditary testing.

This work was financially supported by AstraZeneca and is presented on behalf of the OPA working group.

MD-01-005
Exploitation of cfDNA extracted from bile as liquid biopsy source in pancreatobiliary cancers
C. Driescher[1], K. Ebner[2], W. Goering[1], L. Haeberle[1], V. Keitel[2], D. Haeussinger[2], I. Esposito[1]
[1] Institute of Pathology, Heinrich Heine University and University Hospital, Düsseldorf, Germany, [2] Department of Gastroenterology, Hepatology and Infectious Diseases, Heinrich Heine University and University Hospital, Düsseldorf, Germany

Background & Objectives: To date, accepted biomarkers in pancreatobiliary cancers lack sensitivity and specificity and diagnosis often requires invasive procedures. Therefore, there is an urgent need for reliable biomarkers allowing easy and repeatable sampling to ensure dynamic real-time evaluation of tumour biology. Compared to classic histopathological analysis, liquid biopsy is a less-invasive method, which detects cell-free DNA (cfDNA) released into body fluids from primary or metastatic tumours. cfDNA contains tumour-specific aberrations with possible prognostic and predictive value.
Methods: We extracted cfDNA from bile obtained from patients with pancreatobiliary cancers (n=12) during routine diagnostic procedures. Tumour-specific aberrations were detected by next generation sequencing using a panel of 50 oncogenes and tumour suppressor genes on a S5 Sequencing platform. Matched tumour tissue (n=7) served as control.
Results: Sequencing of cfDNA obtained from bile showed concordance with somatic mutations found in tumour tissues in 92% of cases. Eleven out of twelve mutations found in the tumour tissue were concordantly present in cfDNA sequencing results. In one case, an additional *KRAS* mutation was found in cfDNA, showing the ability of liquid biopsies to better display tumour heterogeneity. In cases were sequencing from tissue failed, e.g. due to insufficient DNA quality, cfDNA analysis could provide information about the mutational status of the tumour.
Conclusion: Overall, cfDNA sequencing provided additional information about tumour heterogeneity and sufficiently replaced tissue sequencing when aforementioned was not feasible. Therefore, cfDNA sequencing of bile represents a reliable method for detecting tumour mutations avoiding possible complications and limitations of tissue sampling in pancreatobiliary cancers. Although primary diagnosis still needs histologic confirmation, liquid biopsies obtained from bile enable disease monitoring (e.g. in primary non-resectable cancers) using less invasive procedures.

Tuesday, 10 September 2019, 08:30 - 09:30, Clio
MD-05 | 2-Day Molecular Diagnostics Symposium – Selected Abstracts

MD-05-001
Differentially expressed immune related genes in metastatic vs. non-metastatic LUMA, LUMB1 and TNBC primary breast carcinoma cases
A.M. Tokes[1], O. Rusz[1], C. Pollner-Szundi[1], L. Madaras[1], A. Kovács[1], B.î Molnár[2], I.î Vári-Kakas[3], J. Kulka[1]
[1] Semmelweis University Budapest, 2nd Department of Pathology, Hungary, [2] Semmelweis University Budapest, 1st Department of Surgery, Hungary, [3] University of Oradea, Department of Computers and Information Technology, Romania

Background & Objectives: It is increasingly clear that tumour progression largely depends of the cancer cell–stromal immune cell environment interaction. The aim of the study is to define the immune gene signature associated with metastatic potential of LUMA, LUMB1 and TNBC cases by using Nanostring technology.
Methods: We compared mRNA levels of 730 immune-related genes by using Nanostring technology in 35 primary breast carcinoma (BC) cases (12 LUMA (6 non-metastatic (NM) and 6 metastatic (M) BC), 11 LUMB1 (5NM and 6M) and 12 TNBC (6NM and 6M)) presenting ≥1% stromal TIL and with a minimum 6 year available follow up data. TIL was assessed on HE stained slides.
Results: The highest TIL ratio was observed in NM TNBC cases (mean-9, 66%) and the lowest in M LUMA cases (mean 1,16%). In M LUMA BCs compared to NM LUMA BCs we observed differences in genes mostly related to chemokines, cytokines and cell functions. Whereas CXCL14, CCL3L1, CCL28 considered to be associated with metastases presented higher expression in M LUMA BCs, BTLA, LTA, and GZMB were detected in lower amount. The significantly different gene set in metastatic vs. non metastatic LUMB1 BCs and TNBCs was more heterogeneous compared to LUMA BCs. Significantly upregulated genes in metastatic LUMB1 BCs and TNBCs compared to non-metastatic ones were VEGFA, CLEC5A, CCL28, CFB in LUMB1 and DUSP4, PPARG, GATA3, ALCAM in TNBC cases.
Conclusion: Genes involved in cancer immunity most probably related to tumour progression vary considerably among breast carcinoma subtypes. The involvement of chemokines and their receptors in breast cancer metastasis is only partly clear and needs further investigation.

NVKP_16-1-2016-0004

MD-05-002
Tumour mutational burden analysis: implementation in routine diagnostics
L. Kroeze[1], E. Kamping[2], D. von Rhein[2], E. Jansen[2], R. de Voer[2], M. Barberis[3], J. Botling[4], E. Garrido-Martin[5], F. Haller[6], L. Lacroix[7], B. Maes[8], S. Merkelbach-Bruse[9], V. Pestinger[10], N. Pfarr[11], A. Stenzinger[12], K. Grünberg[1], M. Ligtenberg[1]
[1] Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands, [2] Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands, [3] Division of Pathology and Laboratory Medicine, European Institute of Oncology, Milan, Italy, [4] Department of Immunology, Genetics and

Pathology, Uppsala University, Sweden, [5] Instituto de Investigación, University Hospital 12 de Octubre, Spanish National Center for Cancer Research (CNIO) and CIBERONC, Madrid, Spain, [6] Institute of Pathology, University Hospital Erlangen, Germany, [7] Department of Medical Biology and Pathology, Institute Gustave Roussy, Villejuif, France, [8] Laboratory for Molecular Diagnostics, Department of Clinical Biology, Jessa Hospital, Hasselt, Belgium, [9] Institute of Pathology University Hospital of Cologne, Germany, [10] Institute of Cancer & Genomic Science, University of Birmingham, United Kingdom, [11] Institute of Pathology, Technical University Munich, Germany, [12] University Hospital Heidelberg, Germany

Background & Objectives: Although the introduction of immunotherapy has benefitted many patients, more than half of the patients show no clear evidence of response, underlining the urge for new predictive biomarkers. Recent studies show that, in addition to PDL1 expression and microsatellite instability (MSI), tumour mutational burden (TMB; number of mutations/Mb) is an important novel biomarker that improves the selection of patients who could benefit from immunotherapy.
Methods: The TruSight Oncology 500 assay (TSO500, 523 cancer-related genes, 1.94Mb, Illumina) was tested for the determination of TMB, MSI, mutations and copy number variations (CNVs) on formalin-fixed paraffin-embedded material (n=55)
Results: Our validation indicates that the assay can clearly discriminate between samples with low (normal tissue) and high TMB. Use of 40 ng DNA is recommended, but results using 15 ng are comparable. All known CNVs (n=9) and pathogenic mutations (n=59) were detected, although 2 out of 6 complex indels (45 and 48 nucleotides) were not annotated by the TSO500 bio-informatic pipeline. Furthermore, our validation shows that the tumour cell percentage can influence the TMB value; a biological problem unrelated to the assay, but caused by heterogeneity of the variant allele frequencies due to an underlying deficiency in DNA repair. The TMB analysis is highly reproducible within and among laboratories (n=11), for which DNA from a third party was used.
Conclusion: The TSO500 assay can be used to perform comprehensive genetic analysis (mutations, CNVs, MSI and TMB) in a single assay using only 15 ng of DNA and can replace current more targeted NGS analyses.

This work was supported by Illumina, Bristol-Myers Squibb.

MD-05-003

Role of HR23b in response to HDAC inhibitors and their effect on immunotherapy targets

S. Wagener-Ryczek[1], C. Alidousty[1], C. Heydt[2], J. Fassunke[1], S. Merkelbach-Bruse[2], R. Buettner[1], M.A. Ihle[1]
[1] University Hospital Cologne, Germany, [2] Institute of Pathology University Hospital of Cologne, Germany

Background & Objectives: Deregulation of histone deacetylases (HDACs) plays an important role in tumourigenesis. Restoring a regular acetylation profile by HDAC inhibitors (HDACi) is a promising therapeutic approach. Human Rad Homolog B (HR23b), has been identified as a predictive biomarker and we showed previously that HDACi also exhibit antiproliferative and pro-apoptotic effects in sarcomas depending on HR23b expression. We therefore aim to elucidate the regulatory relationship between HR23b expression and sensitivity towards HDACi as well as its effect on immunotherapy marker.
Methods: A stable knockout of HR23b was generated in a malignant peripheral nerve sheath tumour (MPNST) cell line using CRISPR /Cas9-technology. Proliferation and apoptosis was measured with the ApoTox™Glo assay. Vorinostat was administered at IC_{50} concentration to wildtype and $HR23b^{KO}$ cells. Afterwards expression analysis of important signalling pathways was performed with the nCounter PanCancer Pathways panel. Furthermore, the effect of HDACi on key immunotherapy targets was investigated using a customised NanoString expression panel.
Results: We could show that HR23b dependent sensitivity towards HDACi is mediated by apoptosis induction via death receptor pathways. In contrast, HR23b loss reduces apoptosis induction and shifts response to autophagy. Furthermore, we observed a significant upregulation of anticancer immunotherapy targets (e.g. cancer testis antigens) enhancing the response to immunotherapy agents.
Conclusion: Understanding key pathways of HDACi induced apoptosis and the importance of HR23b as a predictive biomarker should help to select patients who may benefit from HDACi therapy. Especially the ability to enhance the endogenous antitumour activity as well as the upregulation of possible immunotherapy targets might enable promising combinatorial treatments.

MD-05-004

MET exon 14 skipping mutations in non-small cell lung cancer: efficient routine diagnostics, histopathology and clinical response upon targeted treatment

W. Geurts-Giele[1], M. Pruis[2], J. von der Thusen[3], I. Meijssen[1], W. Dinjens[4], J. Aerts[3], M. Lolkema[2], M. Paats[5], H.J. Dubbink[6]
[1] Pathology, Erasmus MC Cancer Institute, The Netherlands, [2] Medical Oncology, Erasmus MC Cancer Institute, The Netherlands, [3] Erasmus Medical Center, Rotterdam, The Netherlands, [4] Erasmus University Rotterdam, Netherlands, [5] Pulmonary Diseases, Erasmus MC Cancer Institute, The Netherlands, [6] Erasmus MC, Rotterdam, The Netherlands

Background & Objectives: Non-small-cell lung cancer (NSCLC) is one of the solid malignancies with the most evolved personalised treatments based on molecular characteristics of the tumour. Mutations in *EGFR*, *HER2* and *BRAF*, translocations of *ALK*, *ROS1*, *RET* and amplification of *MET* all lead to specific treatment options. Recently, in 2-4% of lung adenocarcinoma *MET* gene mutations leading to skipping of exon 14 were found, making patients eligible for treatment with *MET* tyrosine kinase inhibitors. We will present our experience with routine detection of *MET* exon 14 skipping mutations, histological features of *MET* mutated tumours and clinical follow-up of these patients.
Methods: Since 2015 our custom-made DNA-based pan-cancer NGS panel for routine molecular diagnostics was supplemented with four amplicons for detection of *MET* exon 14 skipping mutations. Putative *MET* exon 14 skipping mutations were evaluated for their effect on splicing by RT-PCR if sufficient tissue was available. Histopathological characteristics and clinical follow-up were investigated for all *MET* mutated NSCLC. Mutation frequency was calculated including all routine diagnostic requests on NSCLC for therapeutic purposes from January 2016 to May 2018.
Results: Of 1497 cases of NSCLC tested for therapeutic purposes in a 29-month period, 31 patients (2%) were identified with a MET exon 14 skipping mutation. *In silico* comparison with published data shows that our amplicon based NGS assay can detect up to 96% of *MET* exon 14 skipping mutations. In total, 46 cases of NSCLC with *MET* exon 14 skipping were detected (including 4 non-therapeutic requests and 11 requests outside the 29-month period). This concerned 34 unique mutations, of which 26 were confirmed by RNA analysis. The histologically evaluable tumours in this cohort (n=30) had a varied morphology, with pleomorphic / sarcomatoid (n=12) as well solid-type adenocarcinoma (n=9) comprising the majority, but also including non-mucinous lepidic-type adenocarcinoma / adenocarcinoma in-situ (n=7) and acinar (n=2) patterns. Eleven patients with *MET* exon 14 skipping mutations received targeted therapy; they either participated in clinical trials or received Crizotinib in compassionate use. We will present clinical responses for the 5 patients treated with Crizotinib.
Conclusion: *MET* exon 14 skipping mutations can be reliably detected in routine pathology tissue samples using DNA-based NGS analysis.

Routine identification of *MET* exon 14 skipping mutations adds substantially to personalised targeted treatment strategies for NSCLC patients.

MD-05-005

The diagnostic landscape and yield of predictive somatic molecular analyses for stratification of cancer therapy in the Netherlands

E. Steeghs[1], E.K. de Jong[1], R.W. Willems[1], Q.J. Voorham[2], P.A. Seegers[2], K. Grünberg[1], M.J. Ligtenberg[1,3]

[1] Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands, [2] PALGA: The Nationwide Network and Registry of Histology and Cytopathology, Houten, The Netherlands, [3] Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands

Background & Objectives: Unequal uptake of predictive analyses for cancer therapy, the rapid increase of molecular markers and targeted therapies, and detection of variants of unknown significance indicate the need for standardization and evaluation of predictive diagnostics. We studied molecular analyses (i.e. techniques, diagnostic yield) for gastrointestinal stromal tumours (GIST), melanoma, colorectal carcinoma (CRC), and non-small cell lung cancer (NSCLC) in the Netherlands.
Methods: Pathology reports containing predictive analyses are collected from all 46 pathology departments via the Dutch Pathology Registry (PALGA) between October 2017 and June 2019.
Results: In the first year, predictive molecular analyses for GIST (n=255), melanoma (n=1205), CRC (n=2325), and NSCLC (n=3355; evaluation of 6 months) were performed in 14, 22, 22, and 21 pathology departments, respectively. Targeted NGS was predominantly used (>80% for GIST, CRC, NSCLC, and >60% for melanoma), but also MassARRAY and single gene analyses were performed. In total 31% of the analysed patients may benefit from targeted therapies, defined by alterations in *KIT* or *PDGFRA* for GIST (88%), *BRAF* for melanoma (45%), *EGFR*, *BRAF*, *MET*, *ERBB2*, *ALK*, or *ROS1* (18%) for NSCLC, or absence of *KRAS*, *NRAS*, and *BRAF* mutations (36%) in CRC. Moreover, variants associated with resistance, that give access to clinical trials, and variants of unknown significance were reported.
Conclusion: We present an overview of the diagnostic landscape of predictive molecular analyses in the Netherlands. Next, these results will be enriched with clinical characteristics to obtain insight into the uptake of the molecular tests and their use in treatment decisions.

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Poster Sessions

Sunday, 8 September 2019, 09:30 - 10:30, Agora 3
PS-01 | Breast Pathology

PS-01-001

Breast implant-associated squamous cell carcinoma

L. Alfaro[1], M.J. Roca[1], A. Jimènez[1], C. Vázquez[2]

[1] Pathology Hospital 9 de Octubre, Valencia, Spain, [2] Surgery. Hospital 9 de Octubre, Valencia, Spain

Background & Objectives: Neoplasms associated with breast implants are very uncommon. Some cases of anaplasic lymphomas have been described and, less frequently, there have been reported isolated cases of squamous cell carcinoma in the international literature with a total amount of ten cases.
The common nexus of the described cases is a long time between the implant of the prosthesis and the development of squamous cell carcinoma.
Methods: We present the case of a 51-year-old woman who in 1998 developed a ductal carcinoma in the left breast with metastasis in 4 lymph nodes. She was treated with surgery and tamoxifen for 10 years. In 2001, right prophylactic mastectomy was performed with retropectoral implant of physiological saline serum. Seventeen years later, presented in the right breast, a prominent swelling with clinical inflammatory aspect, without fever.
Results: Surgical intervention was performed with an intraoperative frozen study that revealed infiltrating squamous cell carcinoma associated with the mammary periprosthetic capsule. The neoplasm appeared completely compoused by squamous cell cords moderately differentiated with some keratin pearls and dyskeratosis. No glandular neoplastic component was identified. The periprosthetic capsule had transition from areas of synovial metaplasia to squamous metaplasia, dysplasia and invasive carcinoma.
Conclusion: The few cases described do not allow us to recognize a specific mechanism of oncogenesis, but the possibility of a prolonged irritative process of a capsule that eventually developed metaplasia and squamous dysplasia seems a probable mechanism. It does not seem that factors of genetic susceptibility participate despite the previous association in our case of a contralateral ductal carcinoma

PS-01-002

Reliability of HER2 immunohistochemistry in invasive breast carcinomas with micropapillary features

N.E. Alkanat[1], L. Atakishieva[2], Z. Kadylbek[3], A. Uner[1], K. Kosemehmetoglu[1]

[1] Hacettepe University Faculty of Medicine, Department of Pathology, Turkey, [2] Kazan State Medical University, Russia, [3] Semey Medical University, Kazakhstan

Background & Objectives: Preceding studies on breast carcinomas with micropapillary features have pointed a discordance between HER2 immunohistochemistry (IHC) and florescent in situ hybridization (FISH) results. Accordingly, American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines highlighted the importance of tumour morphology in HER2 testing; 1+ HER2 IHC - "incomplete and intense staining" - may be HER-2 amplified by FISH in certain breast carcinoma subtypes. In this study, we aimed to identify HER2 status by IHC and FISH in invasive breast carcinomas with micropapillary features in our center.
Methods: Eighty-six carcinomas with micropapillary features diagnosed between 2014-2018 were included in the study and HER2 IHC results were recorded. 3-mm diameter tissue microarrays were constructed. 52/86 cases were tested using FISH (HER2 FastProbe) according to the 2018 ASCO/CAP recommendations.
Results: HER2 gene was amplified in 10/52 (19%) of the cases: Regarding to HER2 IHC, all of 3+ (n=7), 3 of 2+ (n=11) and none of 1+ (n=8) cases revealed HER2 amplification. It was remarkable that immunohistochemically 0 and 1+ scored cases showed no HER2 amplification.
Conclusion: HER2 IHC and FISH results were found to be concordant and HER2 IHC is a highly reliable tool in assessment of HER2 status in invasive breast carcinomas with micropapillary features.

PS-01-003

ASCO/CAP testing guidelines in breast cancer: impact of the updated recommendations

X. Ara-Mancebo[1], C. Alborch[1], E. Fuentes-Camps[1], S. Ramón y Cajal[1], V. Peg-Camara[1]

[1] Vall d'Hebron University Hospital, Spain

Background & Objectives: HER2 has become a pivotal marker in breast cancer, as patients with a tumour overexpressing this protein can benefit from a targeted therapy. In 2018, the new ASCO/CAP guidelines for HER2 testing were issued, featuring two major updates: the IHC 2+ (equivocal) definition, and the management of less frequent ISH groups. We aim to retrospectively evaluate how these changes affect the HER2 prevalence comparing them with the former recommendations.
Methods: We established two cohorts from our Institutional database: cases from January to May 2018, diagnosed based on 2013 ASCO/CAP guidelines (group A); and cases from June to September 2018, diagnosed based on the modified criteria (group B). We conducted a retrospective review comparing the results of each group.
Results: 584 patients were included, 317 in group A and 267 in group B. IHC results were as follows: IHC 0, 96 patients (30.3%) in group A vs. 95 (35.6%) in group B; IHC 1+, 121 (38.2%) vs. 113 (42.3%); IHC 2+, 61 (19.2%) vs. 33 (12.4%); IHC 3+, 39 (12.3%) vs. 26 (10.2%). ISH studies were performed in the IHC 2+ cases, with 6 (9.8%) amplified cases in group A vs. 3 (9.1%) in group B.
Conclusion: IHC 2+ cases decreased applying the new guidelines, with a consequent reduction in ISH tests. Besides, overall HER2 positive tumours also decreased, but not significantly (p=0.287).

PS-01-004
TMA or whole slides to assess TILs in early-stage triple-negative breast cancer

A. Artemyeva[1], D. Chuglova[1], V. Kushnarev[1], P. Krivorotko[1], A. Kudaybergenova[1]
[1] N.N. Petrov National Medical Research Center of Oncology, Russia

Background & Objectives: Triple-negative breast cancer is the group with the most unfavourable prognosis. TMA is a useful tool for any research but using TMA should be validated to study different population of lymphocytes.
Methods: From 1235 cases of early breast cancer (T1-2, N0) triple-negative was 132 cases. We studied TILs on H&E scanned slides in marked for TMA zones, using Salgado recommendations.Cases were assessed by experienced histopathologist.
Results: Distributions of TILs in specific cores was following: the first group (TILs in tumour stroma less than 10%) was the biggest and comprised 52 cases (44,1%), the second group (TILs in tumour stroma 20-40%) with 38 cases (32,2%), and in the third group we found the smallest number of cases (TILs more than 50%) with 28 cases (23,7%).
Conclusion: TMA spots should be created in order to specific aims. Otherwise they may not contain for example stroma at all or other specific detail. However, using of two or more cores with tool diameter of 2 mm can be helpful for displaying heterogenity of tumour.

PS-01-005
Stathmin expression is associated with immune cell responses and vascular proliferation in breast cancer

C. Askeland[1,2], E. Wik[1,2], I. Stefansson[1,2], K. Krüger[1], K. Collett[1,2], G. Knutsvik[1,2], J. Arnes[2], T. Aas[3], L.A. Akslen[1,2]
[1] Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, Section for Pathology, University of Bergen, Norway, [2] Department of Pathology, Haukeland University Hospital, Bergen, Norway, Norway, [3] Department of Surgery, Haukeland University Hospital, Bergen, Norway

Background & Objectives: Stathmin, a microtubule destabilizing protein, is linked to cell proliferation and tumour aggressiveness. By using transcriptional and protein data, we examined associations between Stathmin and stromal responses such as immune cell presence and vascular proliferation.
Methods: We studied human breast cancers from two cohorts (cohort I, n=176; cohort II, n=192), and mRNA data from TCGA and two METABRIC cohorts (n=2287). Stathmin protein expression was evaluated on TMA slides by a semi-quantitative staining index (SI; high expression: SI≥6). Proliferating microvessel density (pMVD) and vascular proliferation index (VPI=pMVD/MVD) were used as novel angiogenesis markers (cut-off upper quartile).
Results: Genes differentially expressed between Stathmin high versus low tumours were significantly involved in cell proliferation (top-ranked upregulated genes), and genes reflecting ESR1 and ER–related signalling were down-regulated in Stathmin-high tumours. Gene sets related to immune cell activation and VEGF signalling were enriched among Stathmin-high cases. Stathmin was associated with signature scores reflecting T-cell activation, as well as with higher expression of PD-1, PD-L1, CTLA4 and FOXP3 (P≤0.002). Further, Stathmin expression correlated significantly with a 32-gene vascular proliferation score (Spearman's rho 0.20-0.30; P<0.001). High Stathmin protein expression was associated with increased pMVD (cohort I-II; P=0.005-0.047) and high VPI (cohort II; P=0.007) in breast cancer tissues. Notably, Stathmin overexpression was significantly associated with high pMVD within the triple negative subgroup (cohort I; p=0.010).
Conclusion: Our findings indicate that high Stathmin expression identifies a subset of aggressive breast cancers characterised by ER negativity, high proliferation, immune cell activation and vascular proliferation.

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PS-01-006
Prognostic value of stromal CD10 expression in invasive breast carcinoma

R. Ayadi[1], D. Bacha[2], O. Belkacem[2], R. Yaiche[2], A. Ben Amor[3], S. Gharbi[2], S. Ben Slama[2], A. Lahmar[2], S. Bouraoui[2]
[1] Pathology Department, Military Hospital, Tunis, Tunisia. University of Tunis El Manar, Faculty of Medicine of Tunis, Tunisia, [2] Pathology department, Mongi Slim Hospital, University Tunis El Manar, Medicine Faculty of Tunis, Tunisia, [3] Department of Gynaecology-Obstetrics, Mongi Slim Hospital, University Tunis El Manar, Medicine Faculty of Tunis, Tunisia

Background & Objectives: Several studies have shown that CD10 expression in tumour stroma is associated with
biological aggressiveness in many tumours, by promoting their growth and metastases. As regards breast carcinomas, the prognostic value of stromal CD10 expression is still controversial with discordant results.
The aim of this study was to assess the prognostic value of stromal CD10 expression in invasive breast carcinomas.
Methods: We retrospectively analysed the immunohistochemistry stromal CD10 expression in 57 patients with non-specific type invasive (NST) carcinomas. Results were separated into three categories, based on positive cell proportions with 10 and 30% thresholds. The relationship between CD10 expression and clinical, histopathological and evolutive features were analysed by Chi2 and Fisher tests. Kaplan-Meier analysis was used to investigate CD10 prognostic value.
Results: The average age in our series was 56.4 years. Positive stromal CD10 expression was noted in 28 patients (49%). CD10 staining significantly reduced recurrence-free survival (p = 0.001), but had not influence on overall survival.
The expression showcased correlation with tumour size> 2 cm, grade III, negative estrogen receptors, amplified HER2, phenotypic profiles "HER2", “triple negative" and " luminal A ", Ki67 index ≥15%, presence of lymph node metastases, systemic metastases at diagnosis, and occurrence of local and systemic recurrences.
Conclusion: Stromal CD10 expression in invasive NST breast carcinomas may be considered as prognostic factor, predictive of low recurrence-free survival and associated with high invasive and metastatic potential.

PS-01-008

Agreement between immunohistochemically defined intrinsic subtype estimation and Prosigna breast cancer prognostic gene signature assay in a clinical cohort at the Medical University of Vienna

Z. Bago-Horvath[1], K. Tendl[1], L. Monschein[1], R. Exner[2], F. Fitzal[2], E. Bergen[3], M. Seifert[4], C. Singer[4], M. Rudas[1], L. Müllauer[1]

[1] Department of Pathology, Medical University of Vienna, Austria, [2] Department of Surgery, Medical University of Vienna, Austria, [3] Department of Medicine I, Medical University of Vienna, Austria, [4] Department of Obstetrics and Gynaecology, Medical University of Vienna, Austria

Background & Objectives: The present study evaluated the correlation of Prosigna breast cancer assay intrinsic subtype (IST) with immunohistochemical (IHC) IST estimation in a clinical cohort.

Methods: 150 tumours from 146 women with immunohistochemical luminal tumours were analysed by Prosigna assay. ER, PR, HER2 and Ki67 expression were accessed by IHC. Ki67 cutoff values of ≥20%, ≥30% and ≥40% were investigated for discriminating Luminal (Lum) A from LumB tumours. In addition, the role of the cutoff value of Ki67 ≥20% and ≥30% in combination with PR receptor expression and histopathological grading were evaluated, regarding clinical and genomic correlation for defining subtypes. Statistical analyses were conducted using Cohen's kappa coefficient.

Results: Of 146 patients (median age 55.5 years), 60% were lymph node positive. 119 (79.3%) tumours were of LumB subtype by Prosigna and 78 (52%) by IHC, respectively, using a Ki67 cutoff ≥20% for LumB disease. A fair agreement between Prosigna and IHC IST (κ=0,326) was demonstrated. Using a Ki67 cutoff ≥30 % slightly improved agreement (κ=0,411). Combining Ki67 with grade and low PR status did not improve agreement substantially.

Conclusion: Agreement between Prosigna luminal IST and IHC estimation proves to be fair at best, independently of Ki67 cutoff values between 20%-40%. Multigenomic tests, such Prosigna, can provide independent information for adjuvant therapy decision in cases where Ki67 IST estimation alone is not sufficient. These associations should be subjected to further investigation to improve cost-effectivity regarding the utilisation of the assay.

PS-01-009

Retrospective analysis of 2200 HER2 cases evaluated according to the 2013 ASCO/CAP guidelines and its correlation with the updated 2018 guideline and its impact in HER2 status

R.I. Bermudez Cameo[1], H.P. Almanzar Comas[1], B. Eizaguirre Zarza[1], S. Bakali Badesa[1], J.I. Franco[1], M.J. Viso Soriano[1], A. Sobrino Prados[1], A. Arellano Alvarez[1], N. Estrada Mallarino[1], C. Del Agua[1], E. Gimeno Esteras[1], V. Sanz Salvador[1], V. Malo Nieves[1]

[1] Hospital Universitario Miguel Servet Zaragoza, Spain

Background & Objectives: Human epidermal growth factor receptor 2 (HER2, ERBB2) is a valuable prognostic and predictive biomarker in breast cancer with an essential significance in selecting patients with invasive breast cancer, for treatment with HER2-targeted therapy. Its assessment is made by IHC and Fluorescence in situ hibridation (FISH). Since the 2018 ASCO/CAP guideline release, we have notice much clearer instructions and recommendations for HER2 status designation, and is our purpose to study the correlation between the 2013 and 2018 ASCO/ CAP guidelines and its impact in HER2 status.

Methods: We retrospectively reviewed the results of the HER2- IHC tests of 2200 cases of invasive breast cancer from our histopathology database, between January 2014 and December 2018, that were evaluated with the 2013 ASCO / CAP guideline and then re-evaluated with the updated version of 2018 and confirmed by FISH.

Results: The analysis of the correlation between both guides, revealed a change of status of HER2 IHC scores in a total of249cases. Among these cases according to the 2013 guideline were re-defined as 1+ or 2+ (n=248) and 3+ (n=1) by the 2018 scheme. 245 cases (11%), were converted from 2+ to 1+. 3 cases (0.14%) doubtful classified as 3+/2+ before, changed to 2+ (FISH not amplified) and only 1 case was converted from a doubtful 2+/3+ to 3+ (0.04%), confirmed later by FISH. The cases classified as 3+ (32%) and 0 (57%) by both guidelines, did not show significant changes.

Conclusion: 11.31% of all the cases were re-defined using the updated 2018 ASCO/CAP guideline. Most of them had changed from 2+ to 1+ (11%). Most of the doubtful cases classified as 3+ / 2+ with HER2 IHC scores, were redefined as 2+, as well as many 2 + / 1+, that changed to 1+, according the 2018 guideline. The new guideline is a helpful and better comprehensive tool to assess the HER2 status designation.

PS-01-010

Heterogeneity of cancer-associated fibroblasts in invasive carcinoma of no special type (IC NST)

T. Bezuglova[1], T. Bezuglova[1], L.V. Kaktursky[1], M. Mnikhovich[1], A. Asaturova[2], V. Kometova[3], I. Vasin[4], S. Snegur[4], D. Kusch[5], N. Malyugin[5]

[1] Research Institute of Human Morphology, Russia, [2] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I. Kulakov' Ministry of Healthcare Russian Federation, Russia, [3] Federal State Budget Institution National Medical Research Center of Obstetrics, Gynaecology and Perinatology Ministry of Healthcare of the Russian Federation (Moscow), Russia, [4] Ryazan Reginal Clinical Hospital, Russia, [5] Pirogov Russian National Research Medical University (Moscow), Russia

Background & Objectives: Cancer-associated fibroblasts (CAF) are a key component of tumoural stroma and play an important role in tumour progression. Tumour cells interact with their microenvironment, which includes CAF, immune cells, endothelial cells, pericytes, and components of extracellular matrix. All of them promote growth of tumour cells, have immunosuppressive and angiogenic functions, induce epithelial–mesenchymal transition (EMT). Six types of CAF were described: associated with a-smooth muscle actin (a-SMA), podoplanin, hyaluronate, fibroblast activation protein (FAP), protein S100A4, and platelet-derived growth factor (PDGF) expression.

Aim: To study heterogeneity of cancer-associated fibroblasts in IC NST.

Methods: We studied 82 cases of IC NST, using light microscopy, immunohistochemical study with antibodies to cytokeratin AE1/AE3, CK18, E-kadherin, vimentin, podoplanin, a-SMA, CD44 and study with alcian blue (pH 2,5-2,7) and PAS-reaction.

Results: In IC NST we identified 3 types of CAF: associated with CD44, a-SMA, podoplanin, and hyaluronate expression. Expression of all 4 markers was maximal in areas of invasive growth (areas of EMT) and was practically absent in central part of tumour parenchyma. Expression of CD44 and hyaluronate in CAF attest to their belonging to mesenchymal stem cells. CAF were identified immunohistochemically in all cases of EMT therefore we can assume that they stimulate EMT.

Conclusion: Three types of CAF were identified in stroma of IC NST. Connection between CAF and expression of CD44 by mesenchymal stem cells was defined. Maximal density of CAF was registered in areas of invasive growth (areas of EMT). CAF play a role in stimulation of growth and invasion of tumour cells and maintenance of EMT.

PS-01-011

Metastastic renal cell carcinoma of sarcomatoid type simulating generalised breast cancer; a case report and our experiences between 2000 and 2018

I. Björnheden[1]

[1] University and Regional Laboratories Region Skåne, Department of Pathology, Malmö, Sweden

Background & Objectives: We present a case of an 83-year-old woman with multiple subcutaneous lesions, bilateral nodules in breasts, intrathoracic and intrabdominal, and clinical suspicion of generalized breast cancer. A core needle biopsy was performed of a 3 cm deltoid subcutaneous mass, to confirm the diagnosis and guide choice therapy. Microscopy showed a pleomorphic spindle cell proliferation with large nuclei, coarse chromatin and multiple nucleoli, growing in loosely arranged netlike pattern, intermixed with necrosis and inflammation – not typical for usual breast cancers.
Methods: Extensive immunohistochemistry showed positivity only for pancytokeratins, vimentin, focal for carbonic anhydrase IX and PAX8, leading to the diagnosis of metastasis of sarcomatoid renal clear cell carinoma. Radiology showed a 4 cm mass in the left kidney, resembling an atypical cyst. Between 2000 - 2018, 151 cases of metastasis of clear cell renal carinoma were diagnosed in the University hospitals in Malmö/Lund - only 15 with metastasis as a first manifestation, and not a single one of these with sarcomatoid features.
Results: This case report serves as an excellent example of what a tremendous impact the pathological examination can have on the diagnosis and treatment of a patient, when there is a different clinical diagnosis suspected. Furthermore, our statistic results underline the unique presentation of this rare subtype of cancer, which makes it important for us to share with our colleagues all over the world.
Conclusion: This case of metastatic renal clear cell carcinoma of sarcomatoid type simulating generalized breast cancer is a rare entity, but it can not be forgotten, and a thorough pathological examination is needed to arrive at the correct diagnosis.

PS-01-012

Breast metastases from non-mammary neoplasms. A study of 20 cases

J. Bosch Schips[1], C. Fabregat[2], A. Stradella[2], L. Pèrez-Tapia[3,4], A. Petit[1], M.R. Taco[1], E. Guerra[1], I. Català[1], R. Campos de Pablo[1], G. Ippoliti[1], X. Matias-Guiu[1], M.T. Soler-Monsó[1,4]
[1] Department of Pathology, Bellvitge University Hospital/IDIBELL. L'Hospitalet de Llobregat, Spain, [2] Department of Clinical Oncology, Catalan Institute of Oncology. L'Hospitalet de Llobregat, Spain, [3] Department of Radiology, Bellvitge University Hospital/IDIBELL. L'Hospitalet de Llobregat, Spain, [4] Breast Unit, Catalan Institute of Oncology. L'Hospitalet de Llobregat, Spain

Background & Objectives: Metastases from non-mammary tumours in the breast (MNMTB) are rare. Their accurate diagnosis is of utmost relevance in the staging and treatment of neoplastic disease. We aimed to study the prevalence and the neoplastic lineages that may define this form of presentation.
Methods: We reviewed cases of MNMTB diagnosed in our center between 2009 and 2019. Hematological malignancies were ruled out. Clinico-pathological data were assessed.
Results: Twenty cases were selected, of which 17 were women (85%) and 3 men (15%), with a median age of 55 years (range 21-89). Diagnoses were performed by core needle biopsy only (CNB) in 13 cases (65%), fine needle aspiration only (FNA) in 5 cases (25%) and by CNB + FNA in 2 cases (10%). Fifteen cases (75%) were metastatic carcinoma, 4 (20%) melanoma, and 1 (5%) sarcoma. The most prevalent origin of MNMTBs for carcinoma was lung (5 cases - 25%), followed by ovary (4 cases – 20%) and kidney (2 cases - 10%). There was also 1 case (5%) of: Merkel cell carcinoma of the skin, atypical mediastinal carcinoid, cervical adenocarcinoma and oropharyngeal basaloid carcinoma. The MNMTB of sarcoma was from an embryonal gluteal rhabdomyosarcoma.
Five patients (25%) debuted synchronously (primary disease and MNMTB), while 15 patients (75%) already had a known primary tumour. The median interval between disease diagnosis and MNMTB was 38 months. With a mean follow-up of 11 months (range 1-65), 14 patients (70%) have died and 6 patients (30%) are still alive with disease.
Conclusion: In our series, the most prevalent metastases were those of lung cancer, followed by ovarian cancer and melanoma. To perform diagnosis, review of clinical history is essential: 75% of patients had a history of known primary tumour.
These findings emphasize the need to accurately establish these tumours as metastases, especially in high-grade triple negative tumours or cases with positive hormone receptors. This may require complementary immunohistochemical and molecular study to characterise the disease and avoid unnecessary therapeutic procedures.

PS-01-014

The relationship between tumour-infiltrating lymphocytes, vascular invasion and stromal elastosis in breast cancer

Y. Chen[1], T.A. Klingen[2], H. Aas[2], E. Wik[3,4], L.A. Akslen[3,4]
[1] Oslo University Hospital, Norway, [2] Vestfold Hospital, Norway, [3] Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, Section for Pathology, University of Bergen, Norway, [4] Department of Pathology, Haukeland University Hospital, Bergen, Norway

Background & Objectives: The tumour stroma plays a critical role in breast cancer progression. Here, we investigated associations between subtypes of tumour-infiltrating lymphocytes (TILs), vascular invasion, macrophage content, tumour stromal elastosis and detection mode in breast cancer.
Methods: We performed a population-based retrospective study from The Norwegian Breast Cancer Screening Program in Vestfold County (2004-2009) including 200 screen-detected and 82 interval cancers. The amount of TILs (CD3, CD4, CD8, CD45, FOXP3) and macrophages (CD163) was examined by immunohistochemistry on TMA-slides. Vascular invasion (CD31, D2-40) and presence of elastosis (high/low) were determined on regular slides.
Results: High amount of all TIL subtypes were significantly associated with lymphatic vessel invasion, and high counts of several subtypes (CD3, CD8, CD45, FOXP3) were associated with blood vessel invasion. Levels of TIL subtypes also associated with high tumour cell proliferation (by Ki67; except CD4). Further, TIL subtypes associated with low stromal elastosis (CD3, CD45, FOXP3), and interval detected tumours (CD3, CD8, FOXP3). All TIL subtypes associated with high macrophage content. Finally, high levels of CD3, CD4 and FOXP3 were associated with reduced recurrence free survival in Luminal-A tumours ($P<0.05$).
Conclusion: Different TIL subtypes relate to stromal features like vascular invasion, macrophage content, presence of elastosis, as well as tumour cell proliferation, and interval detected tumours. Our findings support a link between immune cells and vascular invasion in more aggressive breast cancer. Also, some TILs were prognostic within the Luminal A category.

PS-01-015

TILs in early-stage triple-negative breast cancer

A. Artemyeva[1], D. Chuglova[1], V. Kushnarev[1], R. Paltuev[1], N. Demina[2], A. Kudaybergenova[1]
[1] N.N. Petrov National Medical Research Center of Oncology, Russia, [2] Saint Petersburg State Paediatric Medical University, Russia

Background & Objectives: The group of triple-negative breast cancer has worse prognosis therefore it conciders as perspective field for study.
Methods: We studied TILs by direct microscopy HE slides using Salgado recommendations. From 1235 cases of early breast cancer (T1-2, N0) triple-negative breast cancer (TNBC) was only 132 cases (9,35%).
Results: Distributions of TILs was following: the first group (TILs less than 10%) was the largest and comprised 53 cases (44,9%); the second group (TILs 20-40%) – 35 cases (29,7%); the third group – 30 cases (25,4%).
Conclusion: Breast cancer for a long time considered as tumour with low immunogenicity. In our study we found that only one quarter of cases TNBC has marked infiltration TILs. It compises 2,43% from cohort of early-stage breast cancer.

PS-01-016

Changes in mammary myoepithelial biomarker expression associate with luminal epithelial proliferation and progression to invasive disease

V. Deckwirth[1], K. Rajakylä[1], S. Cattavarayane[1], P. Björkenheim[2], O. Vapaavuori[2], A. Sukura[1], S. Tojkander[1]
[1] Section of Veterinary Pathology / Faculty of Veterinary Medicine / University of Helsinki, Finland, [2] Small Animal Hospital / Faculty of Veterinary Medicine / University of Helsinki, Finland

Background & Objectives: Mammary myoepithelial cells (MEC) are important for organostructural homeostasis. Their absence determines stromal invasion. Several biomarkers characterise MECs in normal mammary. Their gradual loss is suggested to concur with malignant transformation of luminal epithelial cells, with subsequent break-down of the MEC barrier. However, molecular mechanisms behind this barrier function are poorly understood. We investigated the association of basal/MEC cytoskeletal biomarkers, including alpha-smooth-muscle-actin (α-SMA), cytokeratin-5 (CK5) and cytokeratin-14 (CK14) to various non-invasive luminal epithelial proliferations, and the role of these proteins in the homeostasis of normal MEC layer.
Methods: Myoepithelial cellular optical density was determined of normal, usual and atypical hyperplasia as well as ductal carcinoma in-situ structures from scanned immunohistochemical whole slide images of comparative canine mammary model patients. Human mammary cell lines, depleted by siRNA or Lentiviral-based RNA interference for CK5, CK14 and α-SMA, were utilized for screening biomarkers α-SMA, calponin, vimentin, dsg3, E-cadherin, P-cadherin, SLUG and cytokeratins in immunofluorescence stainings and Western blot experiments.
Results: We found that biomarker expression associated with ductal segment, cellular proliferation and malignancy. Furthermore, CK5, CK14 and α-SMA were essential for maintaining normal mammospheroid structures. Additionally, CK5, but not CK14, determined maturation of contractile MEC layer as indicated by loss of α-SMA, calponin, vimentin, SLUG, dsg3 and P-cadherin expression in CK5-deficient cells.
Conclusion: MEC cytoskeletal markers are lost along neoplastic progression. Of these, CK5 is crucial for full maturation of the mammary myoepithelial layer and its loss causes differentiation bias towards luminal cell type and loss of myoepithelial barrier function.

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PS-01-018

Cytomorphologic features and immunocytological findings that support the diagnosis of lobular breast cancer

S. Divani[1], A. Vardouli[1], G. Kalodimos[1], P. Skoufogiannis[1], A. Fericean[1], A. Staikou[2], A. Dinou[2]
[1] Volos General Hospital Greece, [2] Technician, Greece

Background & Objectives: Lobular breast presents a wide spectrum of differences from tumours of ductal phenotype.
The aim of this study was to identify and analyse the cytologic features and immunocytological findings that support the diagnosis of lobular breast cancer.
Methods: We retrospectively reviewed 352 malignant breast cases and we retrieved and analysed a series of 46 (13,06%) fine needle aspirates with the diagnosis of invasive lobular carcinoma confirmed histologically. The majority of patients 84,7% were postmenopausal. Immunocytochemistry for Estrogen, Progesteron receptors, E-Cadherin and the oncoprotein C-erbB2 was performed in all cases. The various findings were classified.
Results: Malignant cells showed: discohesive architecture (95,6%), little or no nuclear atypia (91,3%), low mitotic rate (97,8%), homogeneously distributed c fine chromatin (91,3%), linear or cord like arrangement (60,8%), intranuclear inclusions (26%), smooth regular nuclear membrane (93,47%) and signet ring shape (19,5%).
Loss of E-Cadherin was found in all cases.
ER was expressed in 95,6% and PR in 91,3% of all tumours. The majority of cases (95,6%) showed negative expression of C-erbB2 oncoprotein.
Conclusion: It is important to identify the lobular type of breast carcinomas since it has different clinical, radiological and cytomorphological features as well as different course and therapeutic management. Better knowledge of the key cytologic features of lobular carcinoma and variant types can reduce diagnostic failure.

PS-01-019

A 5-year study concerning multiple breast cancer heterogeneity

A. Dumitru[1], T. Georgescu[1], O. Voinea[1], A. Evsei[2], A. Birceanu-Corobea[3], M. Sajin[4,5]
[1] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [2] CESITO Center, Saint Mary Clinical Hospital, Bucharest, Romania, [3] „Sfanta Maria" Clinical Hospital, Bucharest, Romania, [4] SUUB, Romania, [5] UMF Carol Davila, Romania

Background & Objectives: At first, intra and intertumoural heterogeneity may be daunting. Multiple breast tumours are the ideal prototype for the study of tumour heterogeneity. The analysis of these lesions was performed in order to determine the impact that histopathological and immunohistochemical heterogeneity might have in terms of classification or the possible reassessment in order to change the therapeutic management. Even more, multifocality is not included among the prognostic factors in international guidelines on breast cancer, hence the usefulness of this study.
Methods: We selected 37 cases of multiple mammary cancers diagnosed over a 5-year period that did not benefit from neoadjuvant treatment, knowing that it may alter the expression of some immunomarkers and even the tumour histology. Immunohistochemical characterization has demonstrated the presence of expression heterogeneity with some tumours being reclassified. This has, at least virtually, a therapeutic impact. Moreover, immunohistochemical evaluation of metastases has shown that there are immunohistochemical mismatches at this level between primary tumours, secondary ones and their metastases.
Results: We proposed an algorithm for tumoural "dominance" in terms of aggressiveness based on morphological combined criteria (size, histotype), but also included immunohistochemical criteria using 4 markers. In 6 cases of multiple breast tumours, the dominant tumour was not the index tumour (the largest tumour focus on which staging and acillary test are usually performed). Immunohistochemical heterogeneity was also documented in 11 cases. Theoretically, this method appears to be a timely one, but difficult to apply in the current practice.
Conclusion: According to the results, the current staging system of multiple breast tumours is far from being a gold standard and does not really mirror the complex behaviour of these tumours. In this case, the pTNM system should incorporate a scoring system based on immunohistochemical criteria with predictive and prognostic value to select the most aggressive tumour foci.

PS-01-020

Influence of cold ischemia time to morphological and immunohistochemical features in breast carcinoma

H. Faistova[1], P. Kašparová[1], A. Ryska[1]
[1] The Fingerland Department of Pathology, University Hospital, Faculty of Medicine Hradec Kralove Charles University Prague, Czech Republic

Background & Objectives: The influence of preanalytical procedures is essential for evaluation of morphology, grade and receptor expression in breast cancer. The cold ischemia time (CIT) between operation and immersion in formaldehyde is one of the critical steps of preanalytic phase,

but it is frequently not monitored. In our study, we focused on role of CIT in breast resection specimens and on the possibility of its improvement.
Methods: A cohort of 23 paired specimens from core-cut biopsy (CCB) and resection of tumour (RES) was collected, CIT was recorded for each RES. Expression of estrogen and progesterone receptors and Ki67 were revised both for CCB and RES. The difference between value of each variable in CCB and RES was calculated. For evaluation of morphology in RES, nuclear features, cellular outlines, retraction artifacts and mitoses were evaluated independently by two observers on scale 0-3 and combined score (0-24) was calculated.
Results: The differences in morphology, ER, PR, Ki67 between CCB and RES were correlated with CIT. The differences between RES and CCB ranged for ER from -70% to +10% (mean=7%, median=0), for PR -60% to +20% (mean=8.4%, median=-5%) and for Ki67 -25% to +12% (mean=1.7%, median=0%), respectively. The morphology-score in RES ranged from 13 to 20 (mean=18.3, median=20). CIT varied in 27-4258 min (mean=630,65, median=135). There was no correlation of differences in individual variables and CIT values.
Conclusion: Even in cases with CIT longer than 3 days all markers were well evaluable. The extended CIT has not such strong influence on morphological and immunohistochemical features in our group of highly ER positive carcinomas as we expected. The possible explanation is relatively low sensitivity of nuclear markers ER, PR and Ki67 to CIT.

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PS-01-023
Adenoid cystic carcinoma of the breast: a retrospective analysis of a rare entity
G. Gupta[1], R. Ramakrishnan[2]
[1] Imperial College Healthcare NHS Trust, United Kingdom, [2] North West London Pathology, United Kingdom

Background & Objectives: Adenoid cystic carcinoma (ACC) is an uncommon breast malignancy, with 0.1% to 1% incidence. Our study aims to a) determine radio-logical & pathological characteristics of this tumour & b) evaluate prognosis/outcomes of surgical intervention in a tertiary care hospital.
Methods: A retrospective analysis of all ACC of breast at Charing Cross hospital over the past 15 years was carried out.
Results: Of 6865 breast cancers, 11 ACCs were identified accounting for 0.16%. Median age was 59 years. Radiology ranged from complex cysts to asymmetrical dense radiopaque foci with micro-calcifications. 3 patients underwent mastectomy, one patient received adjuvant radiotherapy. 8 patients had breast conservation surgery (BCS). 1 referred case had no follow up data.
Median tumour size was 23mm with predominant cribriform (8/10) & occasional solid patterns (2/10). No perineural invasion was noted. All tumours were triple negative.
7/10 cases underwent sentinel node biopsy (SNB) & none showed metastasis.
Median disease free survival was 40.5 months. There was 1 recurrence & 2 distant metastases to brain, adrenals, lung & liver. Two out of these 3 showed high grade features.
Conclusion: Breast-ACC is a rare triple negative tumour, best managed by BCS alone. Large tumours may occasionally need mastectomy with/without radiotherapy. Although indolent, recurrence & metastasis are not uncommon with high grade tumours & tend to portend poor prognosis. These findings reinforce the importance of tailored treatments & adequate follow-up.

PS-01-024
VENTANA HER2 dual ISH DNA cocktail assay; a HER2/Chr17 dual ISH automated assay with improved signals and higher first pass rate
G. Harlow[1], S. Mansor[2], S. Lax[3], P.R. Zollars[4], J. Bentz[5], A. Hanlon Newell[1], E. Walker[1], J. Su[1], R. Gniewek[1], D. Eng[1], R. Alam[1], A. Babic[1]
[1] Roche/Ventana Medical Systems Inc., USA, [2] KK Women's and Children's Hospital, Singapore, [3] GrazWest Institute for Pathology, Graz, Austria, [4] Clin-Path Associates PLC, USA, [5] Aurora Diagnostics, USA

Background & Objectives: Human epidermal growth factor receptor 2 (HER2) plays a central role as a prognostic and predictive marker in breast cancer specimens. A reliable HER2 diagnostic test is central to determining the eligibility of patients with breast cancer to targeted anti-HER2 therapies. Assessment of HER2 gene amplification status by in situ hybridization (ISH) is a widely accepted diagnostic test method. Multiple improvements have been made to the INFORM HER2 Dual ISH DNA Probe Cocktail Assay which has resulted in an increase in the first pass rate and a decrease in the assay run time.
Methods: We developed an improved oligonucleotide HER2/CHR17 dual ISH assay (VENTANA HER2 Dual ISH DNA Cocktail Assay) utilizing novel HER2 oligo probes labelled during synthesis with dinitrophenyl (DNP) and novel oligonucleotide probes labelled post-synthetically with digoxigenin which are specific to the chromosome 17 centromere. Improvements to the INFORM staining procedure and the detection chemistry were also made. To evaluate the first-pass-rate of the two Dual ISH assays five study sites each identified, retrieved, and stained 135 retrospective FFPE invasive breast carcinoma cases using both the INFORM assay and the VENTANA assay. First pass rates were determined for each assay by running them in parallel in a “real-world” clinical setting. Twenty nuclei (each containing red (Red ISH) and black (SISH) signals) were enumerated. If the HER2/Chr17 ratio fell between 1.8 to 2.2 (inclusive), an additional 20 nuclei were enumerated. A new ratio was formed on the basis of all 40 nuclei.
Results: VENTANA Dual ISH run times vs INFORM run times were reduced by 40%, 28%, and 31% on the VENTANA BenchMark ULTRA, XT, and GX respectively. The average assay first pass rate for the Ventana Dual ISH assay was 96%, the average INFORM assay first pass rate was 70%.
Conclusion: The VENTANA HER2/CHR17 Oligo Probe ISH assay is a technological advance in cancer diagnostics that holds promise for improved laboratory efficiency and better staining quality.

PS-01-027
Clinicopathologic charateristics of HER2-positive mucinous carcinoma of the breast
Y. Jang[1], E.Y. Cho[1], S.Y. Cho[1]
[1] Department of Pathology and Translational Genomics, Samsung Medical Center, Republic of Korea

Background & Objectives: Mucinous carcinoma (MC) is a rare type of breast cancer, estimated to be 2% of invasive breast cancer. MC is typically positive for estrogen receptor (ER), progesterone receptor (PR), and negative for HER2. However, HER2-positive MC rarely does occur. Clinicopathologic characteristics of HER2-positive MC have not been investigated well.
Methods: We experienced 24 HER2-positive pure MC among 591 pure MC (4.1%) from 1999 to June 2018. Medical records and pathology reports of all patients were obtained from electronic medical records. Microscopic findings, including nuclear and histologic grade, type A/B, presence of extensive intraductal component (EIC), arrangement of tumour cells, were reviewed.

Results: The mean age was 46. Five patients received neoadjuvant chemotherapy. The average tumour size was 2.7 (range 0.1 ~ 13) and T stage was as follows; pT1mi: 1, pT1: 10, pT2: 4, pT3: 1, pT4: 1. Lymph node metastasis was present in 7 cases. When compared to HER2-negative MC, HER2-positive MC presented with more advanced T stage ($p<0.01$), more frequent lymph node metastasis ($p<0.01$), and higher nuclear and histologic grade ($p<0.05$). Microscopically, there were 12 type A, 6 type B, 4 mixed type A and B among HER2-positive pure MC. EIC was present in 9 cases. Micropapillary component and signet ring cells were present in 6 and 14 cases, respectively. During follow up, distant metastasis developed in 3 patients.
Conclusion: Our results suggest that HER2-positive MC is a more aggressive subgroup of MC. Biologic heterogeneity of MC should be considered for adequate management.

PS-01-028
Residual pure lymphovascular invasion after neoadjuvant chemotherapy - a single Institution experience
Y. Jang[1], E.Y. Cho[1], S.Y. Cho[1]
[1] Department of Pathology and Translational Genomics, Samsung Medical Center, Republic of Korea

Background & Objectives: Pathologic complete response (pCR) is defined as absence of invasive carcinoma in the breast after neoadjuvant chemotherapy (NAC). Rarely, only lymphovascular invasion (LVI) remains after NAC. There are few studies describing dismal prognosis of these occasions. It is yet uncertain how to classify these LVI only cases.
Methods: We have searched pathology files that contained 'no residual tumour' and 'LVI' from 2006 to 2013. Cases with residual ductal carcinoma in situ (DCIS) were included. We reviewed electronic medical records, and microscopic slides.
Results:13 cases with LVI only cases after NAC were retrieved. All patients presented with lymph node metastasis clinically. Immunohistochemical phenotypes of initial biopsy were as follows; ER+/HER2+: 3, ER+/HER2-: 1, HER2+: 4, ER-/HER2-: 5. After NAC, DCIS remained in 8 cases. 9 cases showed residual tumour in the lymph node (ypN0(i+): 2, ypN1mi: 2, N1: 3, N2: 1, N3: 1). 1 of 4 ypN0 patients developed local recurrence and contralateral axillary metastasis, and two of 9 patients with residual nodal disease (1 ypN1, 1 ypN2) developed distant metastasis (one of these two patients died). When we classified cases according to the extent of LVI (1+, 2+, 3+), recurrence occurred only in the LVI 3+ group.
Conclusion: Our results showed much better prognosis of LVI only cases than previous studies. However, classifying LVI only cases as pCR would be inappropriate. Recurrence was not associated with residual nodal disease. Extent of LVI may have some relation to the patient outcome.

PS-01-030
Invasive carcinoma with neuroendocrine differentiation of the breast showing triple negative, large and basal cell-like features
T. Kawasaki[1,2], N. Teramoto[3], Y. Hoshida[4], Y. Murata[5], K. Sugiyama[2], M. Oiwa[6], C. Muramatsu[7], J. Ichikawa[8], I. Sugitani[1], S. Ueda[1], T. Hasebe[1], A. Osaki[1], K. Kaira[1]
[1] Saitama Medical University International Medical Center, Japan, [2] National Hospital Organization Nagoya Medical Center, Japan, [3] National Hospital Organization Shikoku Cancer Center, Japan, [4] National Hospital Organization Osaka Minami Medical Center, Japan, [5] National Hospital Organization Tokyo Medical Center, Japan, [6] Nagoya Medical Center, Japan, [7] Shiga University, Japan, [8] University of Yamanashi, Japan

Background & Objectives: The WHO classifies mammary carcinomas with neuroendocrine (NE) features as a special tumour entity representing <1% of invasive breast carcinomas. Almost all of these neoplasms, including only one previously-described case with basal marker expressions in a small cell carcinoma, are reactive for the estrogen receptor (ER) and/or the progesterone receptor (PgR). Herein, we present the first case, to our knowledge, of an invasive mammary carcinoma showing NE differentiation (ref. large cell neuroendocrine carcinoma, LCNEC) with triple-negative, basal-like profiles.
Methods: A 53-year-old postmenopausal Japanese woman had a mass in the outer portion of her right breast detected by ultrasound examination. Her familial history included one uncle with a pharyngeal carcinoma and another diagnosed with gastric carcinoma. Ultrasonography revealed an irregularly-shaped, focally ill-defined, hypo-echoic tumour as well as enlarged regional nodes. No other suspected lesions were revealed by either systemic CT or bone scintigraphy.
An irregularly-shaped, grey-whitish tumour, which measured 10x8 mm, was noted in the specimen obtained at breast removal.
Results: Histologically, the invasive tumour consisted of medullary growth of large carcinoma cells with well-developed vascular stroma and marked lymphocytic infiltration. Carcinoma cells had ovoid or irregularly-shaped nuclei with granular chromatins and distinct nucleoli. Mitotic figures were numerous (108/10 hpf). Macrometastases were identified in 5 of 8 regional lymphoglandula. Immunohistochemically, the carcinoma cells were reactive for synaptophysin, CD56, cytokeratin 5/6, cytokeratin 14 and c-kit, and negative for chromogranin, ER, PgR (Allred's scores: 0/0), HER1 and HER2. The MIB-1 index was 75.2%.
Conclusion: Although, in the breast oncology field, the outcomes of NEC, mostly expressing ER and/or PgR, remain controversial, our current case with a primitive NE neoplasm with LC and basal cell-like features, despite relatively small invasive lesions (pT1b) with tumour-infiltrating lymphocytes, had multiple lymphogenous metastases (pN2), with extra-nodal invasion. (*Pathology International*, in press)

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PS-01-031
High-molecular-weight insulin-like growth factor 2 secreting phyllodes tumour of the breast presenting as a hypoglycemic attack
T. Kawasaki[1,2], S. Ueda[1], Y. Ichinose[1], E. Hirokawa[1], H. Shimada[1], I. Sugitani[1], H. Sano[1], T. Hasebe[1], T. Takahashi[1], A. Osaki[1], T. Saeki[1], Y. Oikawa[3], I. Inoue[3], M. Noda[3], A. Shimada[3], Y. Nagashima[4], K. Kamada[1], S. Kanno[1], M. Urano[5], M. Kuroda[5], T. Utsumi[5], T. Hayashi[5]
[1] Saitama Medical University International Medical Center, Japan, [2] National Hospital Organization Nagoya Medical Center, Japan, [3] Saitama Medical University, Japan, [4] Tokyo Women's Medical University, Japan, [5] Fujita Health University, Japan

Background & Objectives: Non-islet cell tumour hypoglycemia (NICTH), among the significant causes of fasting hypoglycemia, has mainly been reported in solitary fibrous tumour, hepatocellular carcinoma and mesothelioma patients.
Methods: A 42-year-old premenopausal Japanese woman, who had had a palpable mass of the left breast for several months, was found unconscious at home by a family member early in the morning. She was emergently transported to our hospital. Clinical examination revealed a mass of approximately 15 cm in the entire left breast, with a circulatory skin disorder. The blood sugar level was 33 mg/dL, resulting in hypoglycemia, and a 50% glucose liquid injection immediately improved her awareness level. Thoracoabdominal computed tomography demonstrated a huge, lobulated left breast tumour

showing heterogeneous internal echoes without enlargement of the lymph nodes (axillary, supraclavicular, cervical, and mediastinum) or distant metastasis. We performed a vacuum-assisted core biopsy of the breast lesion, and the histologic diagnosis was a phyllodes tumour.

Results: The cut surface of the mastectomy specimen contained a relatively well-defined solid tumour, measuring 170x148x118 mm, partly with a typical phyllodes pattern. Histologically, this lesion was composed of proliferation of both epithelial and stromal components (i.e. fibroepithelial tumour). A focally permeative tumour border, moderate stromal cellularity with mild to moderate stromal atypia, and very focal stromal overgrowth were observed. Mitotic figures of the stromal cells were seen in six of 10 high-power fields. There were no malignant heterologous elements. Immunohistochemical examinations revealed the neoplastic cells to be diffusely positive for insulin-like growth factor (IGF)-2, while being negative for insulin and STAT6. The Ki67 (MIB-1) labelling index of the mesenchymal cells was 13.7%. Furthermore, Western blot analysis demonstrated large amounts of high-molecular-weight IGF-2 in the resected tumour tissue. Based on these pathological as well as biochemical findings, NICTH due to a borderline phyllodes tumour of the breast was identified. Postoperatively, her hypoglycemia immediately disappeared, and her blood glucose level stabilized near 120 mg/dL.

Conclusion: The possibility of NICTH should be kept in mind when examining a patient experiencing a hypoglycemic episode. Furthermore, although exceptionally rare, this unusual condition can occur with a mammary mass.

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PS-01-032

Expression of NF-kB, PI3K, WNT, Hedgehog and Notch in HER-2 positive breast cancer with low and high content of cancer stem cells

A. Brilliant[1], Y. Brilliant[1,2], N. Kazantseva[3], S. Sazonov[2]
[1] Institute of Medical Cell Technologies, Russia, [2] Ural State Medical University, Russia, [3] Sverdlovsk Regional Oncological Center, Russia

Background & Objectives: We investigated the expression of the NF-kB, PI3K signalling pathways, as well as WNT, Hedgehog, NOTCH in cells of ALDH1A-positive and -negative cases of HER-2 positive breast cancer

Methods: The material of 110 cases was explored. To determine the presence of stem cells in tumour population, the expression of ALDH1A1 in cancer cells was investigated. Expression of ER, PR, HER-2 and Ki-67 was studied by immunohistochemical method to identify cases of HER-2 positive breast cancer. The expression of signalling molecules PI3K, NF-kB, WNT, Notch, Hedgehog was explored by innunohistochemical method.

Results: All cases were investigated for ALDH1A1 expression and were divided into two groups - with low (expression of ALDH1A1 was estimated as 0, 1+) and high (expression of ALDH1A1 was estimated as 2+, 3+) content of cancer stem cells.

We found that 20% of cases of HER-2 positive breast cancer were positive for ALDH1A1.

Expression of explored signalling molecules in studied cases is shown in the table.

	NF-kB	PI3K	PTEN	NOTCH	WNT	HH
high ALDH1A1	100%	100%	9%	36%	36%	0%
low ALDH1A1	100%	100%	11%	30%	27%	7%

Conclusion: We found that cases with high content of cancer stem cells are more regulated by signalling pathways NOTCH and WNT. Expression of NF-Kb and PI3K signalling molecules (which are responsible for activation of eponymous signalling pathways) appeared in all cases, while expression of PTEN phosphatase, which inhibits PI3K signalling pathway, was more common for cases with low content of cancer stem cells. Signalling pathway Hedgehog was activated only in AlDH1A1-negative breast cancer.

PS-01-033

Pathological predictors of axillary node involvement in breast cancer patients

Y. Dergunova[1], V. Kometova[2], V. Bojenko[2], M. Dardyk[2], M. Rodionova[2], V. Rodionov[2]
[1] Ulyanovs Regional Clinical Oncological Center, Russia, [2] National Medical Research Center of Obstetrics, Gynaecology and Perinatology named after acamician V.I.Kulakov, Russia

Background & Objectives: The purpose of the study was to determine the predictors of regional lymph node involvement in breast cancer patients on the basis of biological characteristics of the primary tumour.

Methods: The retrospective study included 200 patients with verified unicentric invasive breast cancer $T_{1-4}N_{0-3}M_0$ treated from 2012 to 2015. The patients were divided into 2 groups:100 patients with lymph nodes metastases (N+) and 100 patients without metastases (N-).

Results: Tumour size (p=0,027), histological type (p‹0,001), grade (p=0,027), Integrated Pathological Index (IPI) (p‹0,001), lymphovascular invasion (p‹0,001) and HER2-status (p=0,0002) were the most powerful predictors of axillary lymph node involvement. There was no statistically significant correlation between ER-status (p=0,092), PgR-status (p=0,081), Ki-67 (p=0,132), molecular subtypes (p=0,213) and axillary lymph node metastases. Multivariate logistic regression for significant variables was used to create a nomogram.

Conclusion: Size of the primary tumour, histological type, grade, IPI, lymphovascular invasion and HER2-status are independent prognostic factors of axillary lymph node involvement and can be used by clinicians to plan axillary surgery volume in breast cancer patients.

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PS-01-034

Changes of oestrogen receptor, progesterone receptor and Her2/neu statuses of local metastases compared with primary tumour in breast cancer

K. Konyshev[1], S. Sazonov[1]
[1] Institute of Medical Cell Technologies, Ural State Medical University, Russia

Background & Objectives: Discordance of estrogen receptor (ER), progesterone receptor (PR) and Her2/neu status of primary and metastatic breast cancer is the possible reason of therapy failure. Objective: to evaluate discordance of ER, PR and Her2/neu statuses of breast cancer primary tumour and local metastases.

Methods: Samples of primary tumour and local metastasis obtained from 104 patients were stained immunohistochemically with antibodies to ER, PR (1D5, Pgr-636, Dako) and Her2/neu (4B5, Ventana). Silver-enhanced in situ hybridization (Ventana) was used when needed. Allred score and ASCO/CAP 2013 guideline were applied to define positive or negative tumour status. Frequencies of each biomarker positive to negative and negative to positive status change were compared using Fisher's exact probability test.

Results: We observed the following biomarker status changes in metastases compared with primary tumour. ER: totally – 10 cases out of 104 (9,6%, 95% CI 5,0-17,4%), positive to negative – 5 cases out of 73 (6,8%,

95% CI 2,5-15,9%), negative to positive – 5 cases out of 31 (16,1%, 95% CI 6,1-34,5%) (p=0,16). PR respectively: 17 out of 104 (16,3%, 95% CI 10,1-25,2%), 7 out of 58 (12,1%, 95% CI 5,4-23,9%), 10 out of 46 (21,7%, 95% CI 11,4-36,8%) (p=0,28). Her2/neu respectively: 9 out of 104 (8,6%, 95% CI 4,3-16,2%), 5 out of 16 (31,2%, 95% CI 12,1-58,5%), 4 out of 88 (4,6%, 95% CI 1,5-11,9%) (p=0,004).
Conclusion: ER, PR and Her2/neu statuses switched in 9,6%, 16,3% and 8,6% of cases in metastatic lesion compared with primary breast cancer tumour. Her2/neu-status more frequently changes from positive to negative then from negative to positive.

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PS-01-035

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) - case report and review of the literature

A. Kovács[1], U. Hansson[1], S. Bram Ednersson[1], B. Márton[2], K. Helou[3], T. Parris[3], S. Janeva[4]
[1] Dept of Clinical Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, [2] NU Hospital, Dept of Pathology, Trollhättan, Sweden, [3] Dept of Oncology, Institute of Clinical Sciences, Sahlgrenska Cancer Center, Sahlgrenska Academy at University of Gothenburg, Sweden, [4] Dept of Surgery, Sahlgrenska University Hospital, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sweden

Background & Objectives: Approximately 8000 women undergo breast implantation in Sweden annually, with 80% as aesthetic surgery and 20% as reconstruction after breast carcinoma treatment. Around 650 BIA-ALCL cases have been reported in the literature to date with nine patient deaths. BIA-ALCL incidence rates are on the rise as elective breast implantation increases. This condition is multifactorial, primarily due to genetic factors (*JAK/STAT3* activation and *MYC/TP53* dysregulation), Gram-negative biofilm around the implant, time and geographic differences.
Methods: Two patients aged 38 and 61 were diagnosed with ALK-negative BIA-ALCL, which developed after reconstructive breast implantation. Both patients had delayed, non-infective fluid collection around the breast implant. BIA-ALCL was diagnosed cytologically with late chronic seroma fluid and histopathologically in the fibrous scar tissue adjacent to the implant.
Results: The immunocyto-/immunohistochemical analysis showed positivity for CD45, CD30, CD8, CD15, granzyme, TIA-1 and perforin and negativity for ALK-1, CD3 and CD20 in the large anaplastic cells obtained from seroma fluid and identified in the fibrous capsule. Both implants had been removed and the patients had 1- and 2-year disease-free survival.
Conclusion: BIA-ALCL is a rare, but highly treatable type of T-cell lymphoma that can develop around breast implants, mainly with textured surfaces. Pain, swelling and induration around an implant of more than 12 months of age may warrant the diagnosis of BIA-ALCL. If the disease is limited to the fibrous scar tissue, removal of the implant and complete capsulectomy is curative. Clinicians should inform patients about the risks of the breast implant before surgery.

PS-01-036

Comparison of immunohistochemically assessed ER, PGR, HER2, and Ki-67 breast cancer biomarker status with the automated STRAT4 RT-qPCR-based diagnostic platform - a retrospective study on 100 breast carcinomas (core biopsies & matching surgical specimens)

A. Kovács[1], T. Parris[2], S. De Lara[1], S. Nasic[3], S. Janeva[4]
[1] Dept of Clinical Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, [2] Dept of Oncology, Institute of Clinical Sciences, Sahlgrenska Cancer Center, Sahlgrenska Academy at University of Gothenburg, Sweden, [3] Research and Development Centre, Skaraborg Hospital, Skövde, Sweden, [4] Dept of Surgery, Sahlgrenska University Hospital, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sweden

Background & Objectives: There is an increasing demand to provide reliable biomarker status for breast cancer patients, but with shorter turn-around times than traditional immunohistochemistry (IHC). Xpert® Breast Cancer STRAT4 is a standardised RT-qPCR-based platform that quantitates *ESR1*, *PGR*, *ERBB2*, *MKi67* mRNA expression in formalin-fixed, paraffin-embedded (FFPE) tissues in less than two hours. The aim of this retrospective study was to evaluate the concordance between IHC and the automated STRAT4 diagnostic platform.
Methods: The concordance between standard of care IHC/SISH and STRAT4 was performed using FFPE sections from 100 invasive breast carcinomas (core biopsy and matching surgical specimens) that were retrospectively evaluated for *ESR1*, *PGR*, *ERBB2* and *Mki67*. Macrodissection of the FFPE section was performed for the surgical specimen, but not the core biopsies.
Results: The overall percent agreement (OPA) between IHC/SISH and STRAT4 was 97% and 96% for ER status, 89% and 92% for PGR status, 76% and 77% for Ki-67 proliferation marker, and 88% and 90% for HER2 status in the core biopsies and matched surgical specimens, respectively. We observed changes in molecular subtype for 26 patients due to discordances in ER status (4 cases), Ki-67 status (10 cases), and HER2 status (12 cases).
Conclusion: Reliable ER, PGR, Ki-67 and HER2 biomarker status is necessary when selecting optimal postoperative therapy choices for breast cancer patients. Our data suggest that not only macrodissection, but even microdissection, can be useful to improve the OPA between IHC and STRAT4. The presence of ER/PGR positive normal tissue and ER positive and/or HER2 positive DCIS component may skew the biomarker outcome.

PS-01-038

PD-L1 status in triple negative and luminal B HER2-negative breast carcinomas after neoadjuvant therapy

G. Frank[1], O. Kuznetsova[1], L. Zavalishina[1], Y. Andreeva[1], M. Shomova[2], M. Vinogradov[2]
[1] FSBEI FPE RMACPE MOH Russian Federation, Russia, [2] State Budgetary Institution of Ryazan Region Regional Clinical Oncological Dispensary, Russia

Background & Objectives: To study the expression of PD-L1 in primary tumours (PT) and metastases (MTS) of triple negative (TNBC) and luminal B HER2-negative breast carcinomas (BC).
Methods: Tumour tissue samples from 42 patients with BC were used. 18 patients received neoadjuvant therapy. PD-L1 expression was detected with Ventana PD-L1 (SP142) (Roche) antibodies on the Ventana BenchMark Ultra (Roche) device. 3 independent experts evaluated results. The criterion for the positive status of the tumour was full or partial membrane staining of ≥ 1% of tumour (TC) or immune intratumourall cells (IC) located ≤1 mm from the tumour. PT and MTS were studied, statistics with X^2 criterion was used.
Results: Positive expression of PD-L1 in TC was detected in 12/42 cases (28.6%): 2/16 luminal B HER2 negative tumours (12,5%), 10/26 TNBC (38,5%). The positive IC was observed in 6/16 (37.5%) and 17/26 (65.5%) of cases, respectively.
PD-L1 expression in TC was in 3/8 tumours (37,5%) with RCB III (p<0,05). Positive staining of IC was in 4/10 (40.0%) RCB-II and 6/8 (75.0%) of RCB-III cases. PT and MTS showed differences in protein expression, but the status matched in 100% cases
Conclusion: Positive PD-L1 status was detected in 28.6% cases of triple negative and luminal B HER2 negative BC, with higher number of PD-L1-positive tumours (38.5%) in triple negative subtype.
Tumours with worse response to neoadjuvant therapy (according to RCB score) show higher PD-L1 expression in tumour cells (p<0,05)

PS-01-039

Association between clinicopathological markers and survival in hormone receptor-positive breast carcinoma treated with neoadjuvant chemotherapy

H. Lee[1], W. Han[2], S. Im[3], T. Kim[4], K. Lee[4], I.A. Park[5]
[1] Chungbuk National University College of Medicine Department of Pathology, Republic of Korea, [2] Department of Surgery, Seoul National University College of Medicine, Republic of Korea, [3] Department of Internal Medicine, Seoul National University College of Medicine, Republic of Korea, [4] Seoul National University College of Medicine Department of Internal Medicine, Republic of Korea, [5] Department of Pathology, Seoul National University College of Medicine, Republic of Korea

Background & Objectives: Residual cancer burden (RCB) is an important marker for patients with breast carcinoma treated with neoadjuvant chemotherapy (NACT). However, the association is not absolute for residual disease of hormone receptor-positive luminal type breast carcinoma. We analysed which clinicopathological variables including RCB grade and immunohistochemical (IHC) markers were associated with survival.
Methods: Expression of annexin-8, galectin-3, bcl-2, calreticulin, clusterin, ki-67, mucin-1, and p27 were assessed in tissue microarray slides of 55 post-NACT resection specimens from luminal type breast carcinoma patients treated by docetaxel and doxorubicin. Patients' age (≥45 vs. <45), RCB grade (RCB-II vs. RCB-III), lymphovascular invasion, and IHC markers were analysed according to disease-free survival (DFS) using Kaplan-Meier method and multivariate Cox proportional hazard model.
Results: Ten-year DFS of all patients was 65.7%. Only ki-67 index of ≥5% was associated with shorter DFS by Kaplan-Meier method (p=0.021). High expression of galectin-3 showed a tendency for shorter DFS (p=0.1). Patients' age, (p=0.29), RCB grade (p=0.52), lymphovascular invasion (p=0.44) and the other IHC markers were not associated with DFS. Multivariate Cox proportional hazard model showed that high ki-67 index was the only independent marker for shorter DFS (hazard ratio, 3.34; 95% confidence interval, 1.26-8.9; p=0.0151).
Conclusion: Ki-67 index in post-NACT resection specimen can be a surrogate marker for recurrence of luminal type breast carcinoma.

PS-01-040

Prevalence of incidental atypical proliferation lesions in reduction mammoplasty specimens: a 6-year retrospective analysis at a tertiary breast unit

J. Lee[1], F. Rashid[1], R. Ramakrishnan[1], K. Lessey[1], S. Shousha[1]
[1] North West London Pathology, United Kingdom

Background & Objectives: The reported incidence of unsuspected atypical proliferative lesions (APLs) ranges from 0.06 to 4.6% in reduction mammoplasty specimens. We aimed to calculate the prevalence of these lesions at our tertiary breast unit.
Methods: Data pertaining to age, gender, weight, suture orientation, laterality, clinical indication, number of blocks and outcomes was collected by retrieving and analysing archived histopathology reports from 2013 to 2018.
Results: 490 cases belonging to 488 patients were identified in the 6-year period (483 females, 5 males). The ages ranged from 16 to 80 years (median 48 years). A lack of 100% suture coverage was attributed to the piecemeal nature of some surgical specimens. Of interest, the suture orientation showed a steep improvement between 2016 and 2017.
There were two main cohorts: BENIGN comprising macromastia, gynaecomastia and miscellaneous; and POTENTIAL MALIGNANT including symmetrisation for contralateral cancer and risk-reducing mastectomy. 15 cases (3.1%) were eventually removed from the final analysis due to insufficient clinical information.
The most common APL was ALH/ISLN followed by FEA, DCIS, ADH and invasive carcinoma. The POTENTIAL MALIGNANT cohort showed a slightly higher incidence of APLs (n=18/475, 3.8%) compared to the BENIGN cohort (n=13/475, 2.7%).
Conclusion: There has been a steep improvement of suture orientation signifying an increased surgical recognition of the possibility of margin re-excision in incidental APLs. Clinical stratification based on a number of factors such as age, family history, pre-operative imaging and known genetic risk may guide appropriate management of such specimens whilst adopting a pragmatic approach to block-taking.

PS-01-041

Prognostic value of CEACAM1 in breast cancer in situ

M. Lyndin[1], R. Moskalenko[2], A. Romaniuk[2], B.B. Singer[3]
[1] Sumy State University, Medical Institute, Department of Pathology, Ukraine, [2] Sumy State University, Ukraine, [3] University of Duisburg-Essen, Institute of Anatomy, Germany

Background & Objectives: Ductal breast cancer can be divided into invasive and non-invasive types (cancer in situ – DCIS). Although there is information about molecular features of these tumours, DCIS remains none fully described pathology. Thus we need to find novel reliable diagnostic markers. One could be the carcinoembryonic antigen related cell adhesion molecules 1 (CEACAM1). This molecule was described in diverse invasive types of cancers. The aim our study presented here was to characterise the exact expression pattern of CEACAM1 in various types of DCIS.
Methods: The investigation was conducted on 20 samples with different types (papillary, cribriform, solid and comedocarcinoma) and grades (low and high) of DCIS. The presence of CEACAM1 was detected by the immunohistochemistry utilizing the mAb C5-1X/8 (0.1μg/ml).
Results: Low grade DCIS (papillary and cribriform) was characterised by apical expression of CEACAM1 on tumour cells which limited the lumens in tumour structures. The disappearance of spaces between cells (solid DCIS) was accompanied by a vanishing of CEACAM1. Comedocarcinoma (high-grade DCIS) were characterised by cytoplasmic and uniform membranous distribution of CEACAM1 with areas of its absence. Some DCIS cases (cribriform, solid and comedocarcinoma) were heterogeneous: I. with and without CEACAM1; II. with different patterns of CEACAM1 expression.
Conclusion: Ductal cancers *in situ* have different variants of CEACAM1 expression: papillary and cribriform – apical, solid – without CEACAM1, comedocarcinoma – cytoplasmic and uniform membranous. The growth of tumour malignancy leads to CEACAM1 distribution translocation and their disappearance. The presence or lack of CEACAM1 cannot be indicator of malignant intraductal tumours.

PS-01-042

HER2 status in breast cancer: immunohistochemistry and gene amplification in the Republic of Kazakhstan

S. Lyubko[1], E. Satbaeva[1]
[1] KazIOR, Kazakhstan

Background & Objectives: Human epidermal growth factor receptor 2 (HER2) overexpression is present in 15-20% of invasive breast cancers, and is an important predictive and prognostic marker.
Purpose. Determination of HER2 status in patients with invasive breast cancer (IBC).
Methods: Immunohistochemistry (IHC) was used to study material of 745 patients using Pathway anti-HER2/neu antibody (4B5). Equivocal HER2 (2+) status was specified by SISH hybridization and was performed by the INFORM HER2 DUAL ISH DNA Probe Cocktail (USA) implementing a silver tag (HER2 gene, SISH) and a red chromogen (Chr17, Red ISH).
HER2 status by SISH was determined according with ASCO CAP Guideline 2018 as positive, if HER2/CEP17 ratio ≥2 with HER2≥6, HER2/CEP17 ratio<2 with HER2≥6. As a positive control for counting signals were lymphocytes, fibroblasts, endothelial cells.

Results: The negative HER2 (0; 1+) was determined by IHC in 566 patients. Positive HER2 status (3+) was defined in 101cases. Equivocal HER2 (2+) was determined in 78 patients and refined using the SISH study. In 27 (33%) cases, amplification of the HER2 gene by SISH was detected. In 45 (58%) cases, there was a negative result (HER2/CEN17<2, HER2<4). In 6 (7%) cases it was not possible to assess.
Conclusion: The positive HER2 status of breast cancer was detected by IHC and SISH in 128 (17%) of cases, which correlates with data from different authors. In 6 cases evaluation of HER2 status was not possible due to errors in the pre-analytical stage.

PS-01-043
Metaplastic carcinoma of the breast, about a series of 15 cases

Z. Merad[1]
[1] CHU Sidi Bel Abbes, Algeria

Background & Objectives: They are tumours defined by the association with the adenocarcinomatous component, of a squamous, sarcomatoid, chondroid or osteoid contingent Described by Huvos et al. in 1973 [2]. Report the rarity of this type of cancer and study its histopathological characteristics.
Methods: We report a retrospective study of 15 cases of metaplasic carcinoma of the breast collected at the Department of Anatomy and Pathology Cytology of the CHU of Sidi Bel Abbes-ALGERIA between 2008 and 2014.
The average age of our series is 50 years with extremes ranging from 30 years to 75 years
The histopathological diagnosis was confirmed on operative parts mastectomy in 52% of the cases and directed on 48% of the cases.
Results: Macroscopic examination found a hard, whitish, irregular tumour with an average size of 3.3 cm (2cm-7cm), located at the level of the super-external quadrant.
Microscopic examination: the most frequent histological type was metaplasic carcinoma with epidermoid differentiation in 60% of cases, chondroitin in 20% of cases, osteoid in 13% of cases and fusiform cells in 07% of cases. A high histological grade was found in 80% of SBR III cases and 20% of cases were SBR grade II.
Conclusion: Metaplasic carcinomas of the breast are rare, aggressive tumours with poor prognosis.

PS-01-044
Biopathological significance of deregulated PIWIL1-4 proteins belonging to the PIWI-piRNA pathway in invasive breast carcinomas

D. Meseure[1], M. Lae[2], K. Drak Alsibai[3], A. Nicolas[1], S. Vacher[4], W. Chemlali[4], Y. Allory[5], A. Vincent-Salomon[6], I. Bieche[7]
[1] Platform of Experimental Pathology, Department of Diagnostic and Theranostic Medicine Institute Curie, Paris, France, [2] Department of Pathology, Centre Henri Becquerel, INSERM U1245, UniRouen Normandie Université, Rouen, France, [3] Department of Pathology, CHA Andrèe Rosemon, Cayenne, France, [4] Unit of Pharmacogenomics, Department of Genetics, Institute Curie, Paris, France, [5] Department of Pathology, Hôpital Foch, Université Versailles-Saint-Quentin-en-Yvelines, Universitè Paris-Saclay, Suresnes, France; Institute Curie, CNRS, UMR144, Paris, France, [6] Department of Diagnostic and Theranostic Medicine Institute Curie, Paris, France, [7] Unit of Pharmacogenomics, Department of Genetics, Institute Curie, Paris, France and Faculty of Pharmaceutical and Biological Sciences, Paris Descartes University, Paris, France

Background & Objectives: Invasive breast carcinomas (IBC) are highly heterogeneous malignant tumours, and triple-negative subtype (TNC) remains a major cause of death in women. Epigenetic abnormalities are early events in carcinogenesis that associate heterogeneity of DNA methylation, post-transcriptional modifications of histones and deregulation of noncoding RNAs (ncRNAs). Global DNA hypomethylation results in chromosomal instability, overexpression of oncogenes and reactivation of transposable elements (TE). Recently discovered Piwi-interacting RNAs (piRNAs) represent small noncoding regulatory RNAs that interact with the human four PIWIL1-4 RNA-binding proteins belonging to the Argonaute (AGO) family. *PIWIL1-3* are germinal genes while *PIWIL2-4* are both germinal and somatic genes. PIWIL proteins are pivotal in piRNAs biogenesis and PIWI-piRNA complexes constitute genetic, epigenetic and post-transcriptional regulators implicated in genomic integrity through suppression of transposable elements, maintenance of germinal and somatic differentiated and stem cells, and homeostasis *via* piRNA-mRNA induced activation or inhibition of genes expression. In a small number of recent studies, deregulated expression of PIWIL proteins and piRNAs was observed in various types of tumours. Due to contradictory results in the literature concerning expression levels of PIWIL proteins in IBCs, we investigated PIWIL1-4 expression at RNA and protein levels.
Methods: We analysed *PIWIL1-4* expression at RNA level by quantitative RT-PCR in a large series of 526 patients who had undergone partial or complete mastectomy for unilateral invasive primary breast cancer. At protein level, study of PIWIL1-4 expression was performed by immunohistochemistry (IHC) in a series of 200 patients belonging to the large series.
Results: PIWIL1-4 proteins were deregulated in IBCs with *PIWIL2* and *PIWIL4* downregulation (*PIWIL2*: Total 48,3%, NNN 52,5%, HER2+ 52,1%, RH+HER2- 50,3%, RH+HER2+ 25,9%; *PIWIL4*: Total 43,3%, NNN 28,7%, HER2+ 39,7%, RH+HER2- 47,3%, RH+HER2+ 53,4%) and *PIWIL1* and *PIWIL3* abnormal emergent expression (*PIWIL1*: Total 30%, NNN 25%, HER2+ 30%, RH+HER2- 31%, RH+HER2+ 21%; *PIWIL3*: Total 6%, NNN 4,2%, HER2+ 15%, RH+HER2- 4%, RH+HER2+ 25%) at RNA level. IHC analysis revealed underexpression of PIWIL2 (45% of IBCs) and PIWIL4 (49% of IBCs) and abnormal expression of PIWIL1 (35% of IBCs) and PIWIL3 (8% of IBCs). Significant correlations were observed at RNA and protein levels for PIWIL2 ($p = 0.0007$) and PIWIL4 ($p < 0.0001$). PIWIL1-4 mRNA expression levels were correlated with breast cancer molecular subtypes and classical clinicopathological prognosis factors. Compared to IBCs with PIWIL2 and PIWIL4 normal expression, IBCs with PIWIL2 and PIWIL4 downregulation were characterised by DNA and histone methyltransferases DNMT1, Suv39H1 and HP1 lower expression, decreased H3K9me3 and H3K27me3 repressing epigenetic marks and chromatin decondensation with abnormal expression of Alu sequences. PIWIL proteins were significantly correlated with molecules involved in cancer cell proliferation and epithelio-mesenchymal transition.
Conclusion: PIWIL2 and PIWIL4 proteins downregulation in IBCs could contribute to breast carcinogenesis through abnormal diffuse hypomethylation resulting in increased transcription of TEs and reactivation of numerous oncogenes, including pure germinal genes such as PIWIL1 and PIWIL3.

PS-01-045
Loss of GATA3 associates with aggressive breast cancer, a basal like phenotype, and immune cell activation

A.K. Myrmel Sæle[1,2], A.A. Svanøe[1], C. Askeland[1,2], G. Knutsvik[1,2], B. Davidsen[3], T. Aas[3], K. Collett[1,2], I.M. Stefansson[1,2], L.A. Akslen[1,2], E. Wik[1,2]
[1] Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, Section for Pathology, University of Bergen, Norway, [2] Department of Pathology, Haukeland University Hospital, Bergen, Norway, [3] Department of Surgery, Haukeland University Hospital, Bergen, Norway

Background & Objectives: GATA3 is linked to estrogen receptor biology, and low GATA3 associates with aggressive features in several tumours. Also, GATA3 is suggested to play a role in activation of immune cells. We examined how GATA3 relates to breast cancer phenotypes and markers of immune cell activation.

Methods: Two breast cancer (BC) cohorts were analysed. Cohort-I: Hordaland County; <70 years; n=565. Immunohistochemical staining of GATA3 on tissue microarrays of formalin-fixed paraffin-embedded BC tissue, scored by staining index (SI; 0-9). Cohort-II: mRNA data from METABRIC and TCGA (n=2283), including BRCA 1/2 germline mutations.
Results: Low GATA3 protein and mRNA expression associated with aggressive tumour features, such as high histologic grade, larger tumour diameter, ER and PR negativity, and HER2 positivity (all P≤0.001). Further, low GATA3 associated with high proliferation (by Ki67), triple negative and basal-like phenotypes, and reduced survival (P≤0.005). Low GATA3 also predicted *BRCA1* germline mutations (OR=7.3; 95% CI2.2-24.2). GATA3 expression correlated negatively with a luminal progenitor cell score, and positively with a mature luminal cell score (R2=0.66 and 0.70, P<0.001). Further, low GATA3 expression associated with activation of immune cell scores, and higher PD-1, PD-L1, CTLA4, and FOXP3 expression (P≤0.006).
Conclusion: Low GATA3 is a marker for aggressive BC, a basal-like profile and reduced survival, and points to *BRCA1* germline mutations. Loss of GATA3 associated with immune cell activation, and the potential of GATA3 as predictive marker for immunotherapy should be further elucidated.

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PS-01-046

Fascin-1 expression in breast cancer identifies patients with high risk for disease recurrence

A. Nonni[1], E.C. Tampaki[2], A. Tampakis[2], P. Efstratios[1], K. Kontzoglou[2], G. Kouraklis[2]
[1] 1st Dept of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [2] 2nd Department of Propedeutic Surgery, Medical School, National and Kapodistrian University of Athens, Greece

Background & Objectives: Breast cancer stem cells are considered to be a major cause of disease recurrence in breast cancer, as they appear to be chemo-resistant. Fascin-1 is a stem cell marker, its excessive expression in tumours is associated with aggressive tumour phenotype. The aim of the present study was to investigate the expression patterns of fascin-1 in breast cancer and to assess its possible clinical significance.
Methods: Expression of fascin-1 was assessed via immunohistochemistry in surgical specimens of a cohort comprised of 127 patients with resectable breast cancer. Results were correlated with clinicopathological characteristics and survival data. Progression free survival was defined as the primary outcome of the present study.
Results: Fascin-1 expression was strongly associated with the presence of triple negative cancers (p<0.0001). Tumours displaying high expression of fascin-1 presented correlations with high tumour grade (p=0.002) and high expression of Ki-67 (p=0.004). No statistically significant correlations were observed between fascin-1 expression and the stage of tumour (p=0.196) or the presence of lymph node metastasis (p=0.415). Patients with a high expression of fascin-1 demonstrated significantly higher rates of disease recurrence or death. More specifically, 5-year PFS was 51.8%, [95%CI] =33-52 for patients displaying high expression of fascin-1 in cancer cells versus 70.1%, [95%CI] =46-75 for patients with low expression of fascin-1 (p=0.032).
Conclusion: Expression of fascin-1 in breast cancer cells is associated with a significantly worse 5-year progression free survival recognizing therefore a group of patients with high risk for early disease recurrence.

PS-01-047

Differences in densities of sentinel lymph node CD1a and DC-SIGN-positive dendritic cells with respect to type of breast cancer metastasis

J. Szpor[1], A. Glajcar[1], D. Hodorowicz-Zaniewska[2], K. Okoń[1]
[1] Jagiellonian University, Collegium Medicum, Chair of Pathomorphology, Poland, [2] Jagiellonian University, Collegium Medicum, Chair of General, Oncological and Gastrointestinal Surgery, Poland

Background & Objectives: Sentinel lymph nodes (SLNs) are the first lymphoid organs on the lymphatic drainage from primary breast tumours and constitute the front line of immune defense against cancer. Dendritic cells (DCs) are the most potent antigen-presenting cells that in SLNs present tumour-derived antigens to lymphocytes. Depending on their maturation state DCs may either evoke anti-cancer response or induce immune tolerance.
Methods: In our study CD1a and DC-SIGN-positive DCs were identified by immunohistochemistry and their densities were investigated in cortical areas of 119 SLNs excised from invasive breast cancer patients with regard to metastatic burden in lymph nodes.
Results: We observed that DC-SIGN+ DCs are more numerous in macrometastatic than in micrometastatic SLNs (p<0.003) and their percentage in SLN tissue positively correlated with size of metastasis (R=0.4, p=0.040). In contrast, CD1a+ DCs tended to decrease from negative SLNs, SLNs with micrometastasis to SLNs with macrometastasis (p=0.055).
Conclusion: Therefore, we conclude that the densities of mature DC-SIGN+ DCs increase with higher metastatic burden, while immature CD1a+ DCs are associated with less advanced nodal stage.

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PS-01-048

The predictive role of stromal CD10 expression in invasive breast cancer treated with neoadjuvant chemotherapy

O. Olah-Nemeth[1], E. Majlat[1], G. Kelemen[2], R. Koszo[2], A. Voros[1]
[1] University of Szeged - Department of Pathology, Hungary, [2] University of Szeged - Department of Oncotherapy, Hungary

Background & Objectives: The therapeutic strategy of invasive breast cancer is based on routine histopathological tissue markers (estrogen-, progesterone receptor, HER2/Neu, Ki67) that are evaluated in tumour cells. However, the assessment of cancer stroma could be indispensable in therapeutic strategy designation. Studies have shown that stromal expression of CD10, a zinc-dependent metalloproteinase, is associated with biological aggressiveness of the tumour. In the present retrospective study we aimed to evaluate CD10 expression and association between CD10 expression and response to neoadjuvant chemotherapy in invasive breast cancer.
Methods: A total of 60 invasive breast adenocarcinomas were included. CD10 immunohistochemistry was performed on core biopsies taken before the neoadjuvant therapy. Stromal CD10 expression was determined and compared with well-known predictive and prognostic tissue markers as well as with groups defined according to the degree of tumour regression into no regression, partial regression and complete regression group.
Results: The number of CD10 positivity tumours was significantly higher in "no regression" group (p=0,019), thus stromal CD10 expression was found to be significantly associated with decrease in response to neoadjuvant chemotherapy, and increase in primary tumour size. No correlation was found between CD10 expression and routine prognostic markers or tumour grade.
Conclusion: Based on our data, CD10 expression can serve as an independent predictive marker for the effect of neoadjuvant chemotherapy in breast cancer patients. Therefore we propose to add CD10 immunohistochemistry to the routine dataset of prognostic and predictive markers for more precise assessment of patient-based and tumour-specific therapeutic strategy.

PS-01-051

HER2 gene amplification association with protein expression in equivocal (HER2 IHC 2+) breast carcinomas: consequences of cell-by-cell analysis on HER2 gen protein assay (GPA) slides

G. Pekar[1]
[1] Department of Oncology and Clinical Pathology, Lund University, Sweden

Background & Objectives: Identifying eligible cases for targeted therapy in the human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 2+ breast carcinoma group is challenging for the pathologists due to intratumoural heterogeneity when multiple subclones of tumour cells co-exist. In this study, our main aim was to find an eventual correlation between HER2 and CEP17 related parameters in different histological- and molecular phenotypic groups and revealing the association between the HER2 gene amplification and the translated protein expression intensity at a cellular level.
Methods: Clinicopathological data were retrospectively identified from women diagnosed with primary HER2 2+ IHC breast cancer at the Department of Oncology and Pathology Lund, between a period 2015-2017. The cohort comprised 122 cases assessing 1000 cells in each tumour by recording the HER2, chromosome enumeration probe 17 (CEP17) copies and the intensity of protein expression individually in all the tumour cells on reflex HER2 GPA slides. The HER2 testing was performed according to international guidelines.
Results: The average HER2 and CEP17 values showed a tendency to increase with histological grade in breast cancer with no special type (NST) histology though in NST grade 2 tumours with higher average CEP 17 value than in NST grade 3 carcinomas (2.23 and 2.16, respectively). Still, the tendency seems apparent there was no significant difference between histological tumour types and grades (p=0.146 to p=0.992). The HER2 copy numbers positively associated with protein expression intensity in the majority of tumour types and grades ($p_{NSTgrade2}$= 0.040). Luminal A- and B-like tumours showed the same positive correlation ($p_{LuminalA}$<0.0001, $p_{LuminalB}$=0.250), however in hormone receptor negative (HR-) carcinomas the inverse phenomenon was detected, namely the highest mean HER2 values were observed in a non-protein expressing cells.
Conclusion: As a result of our findings we propose that: following international guidelines search and count HER2 and CEP17 copies in tumour cells with the most intensive protein expression, regardless of tumour types, paying more attention to tumours with higher histological grade. In HR- breast carcinomas consider HER2 overexpressing and non-expressing cells for proper evaluation.

PS-01-052
The accuracy of HER2 status establishment between core needle and open excision biopsy in breast cancer: multi-Institutional study from southern Sweden
N. Mylona[1], C. Dekany[1], G. Pekar[1]
[1] Department of Oncology and Clinical Pathology, Lund University, Sweden

Background & Objectives: Human epidermal growth factor receptor 2 (HER2) status testing is a crucial part of breast cancer diagnostics and treatment. Tumour size, extent of in situ carcinoma component, histological grade, spatial distribution, as well as hormone receptor (HR) status could affect HER2 result in core needle biopsy (CNB) compared to open excision biopsy (OEB). The aim of this study was to investigate the concordance rate between biomarkers in pre-operative CNB and corresponding OEB with emphasis on HER2 status discrepancy in relation to histopathological parameters.
Methods: Clinicopathological data were recruited from women diagnosed with primary invasive breast cancer at the Department of Clinical Oncology and Pathology, Lund and Malmö University, Sweden during 2014-2018. The cohort comprised 419 cases matching histological grade, immunohistochemistry (IHC) based biomarkers including HER2 gen protein assay (GPA) and/or fluorescence in situ hybridization (FISH) on preoperative CNB and postoperative OEB from the same tumour according to guidelines.
Results: HER2 IHC scores with reflex GPA/FISH analysis revealed 378 negative cases and 25 positive cases in both CNB and OEB equaling a concordance rate of 96.2% with a substantial agreement (Cohen`s κ= 0.738). Notably, 16 tumours (3.8%) showed discordant HER2 status with CNB negative-OEB positive mismatch in 11 cases (2.6%) and CNB positive-OEB negative mismatch in 3 cases (0.7%). Additionally, 2 equivocal carcinomas on CNB turned into negative on OEB. The CNB negative-OEB positive discrepancy was observed in carcinomas with large extent (> 40 mm), higher histological grade (grade 2-3) and the majority with unifocal distribution, while CNB positive-OEB negative mismatch occurred mainly in extensive multifocal tumours with lower histological grade (grade 2). Interestingly, one IHC 3+ case was not amplified in CNB, and two IHC 3+ cases were equivocal with GPA in OEB series.
Conclusion: Insufficient HER2 status agreement was detected between preoperative biopsies and corresponding resected breast tumours with significant discordance for important prognostic and predictive biomarkers, particularly HER2. We still recommend the postoperative HER2 status reassessment in the future, but on the other hand the histopathological parameters such as extent, distribution and grade must be taken into consideration for proper neoadjuvant treatment planning.

PS-01-053
Three types of truncating CHEK2 germline mutations may differ by the frequency of somatic loss of the wild-type allele
G. Raskin[1], A. Iyevleva[2], S. Aleksakhina[2], A. Sokolenko[2], A. Ivantsov[2], E. Imyanitov[2]
[1] Academic A.M. Granov Scientific Center for Radiology and Surgical Technology, Russia, [2] N.N. Petrov Institute of Oncology, Russia

Background & Objectives: Germline mutations in CHEK2 gene represent the second most frequent cause of hereditary breast cancer (BC) after BRCA1 lesions. However, clinical and biological properties of CHEK2-associated BC remain poorly studied.
Methods: Clinical, immunohistochemical and molecular characteristics were compared in BCs obtained from carriers of distinct CHEK2 mutations (1100delC: n = 29; 5395del: n = 39; IVS2+1G>A: n = 23).
Results: BC associated with three types of truncating mutations had similar clinical and immunohistochemical features. Somatic loss of the wild-type allele was more frequent in CHEK2 5395del-associated tumours (10/18, 56%) than in BC from 1100delC (2/15, 13%) or IVS2+1G>A (2/13, 15%) mutation carriers (5395del vs. 1100delC+IVS2, p = 0.007). Mutant and wild-type CHEK2 alleles demonstrated similar levels of mRNA expression in BC without CHEK2 loss of heterozygosity (LOH). Exome sequencing revealed that CHEK2 LOH was associated with evident genomic instability.
Conclusion: Hereditary breast tumours associated with three types of CHEK2 truncating mutations may develop by different molecular mechanisms. It is important to determine, whether the substantial frequency of CHEK2 LOH in 5395del-driven tumours results in a specific pattern of chemosensitivity of this category of BC.

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PS-01-054
Significance of intratumoural HER-2 heterogeneity in invasive breast carcinomas
P. Ravazoula[1], D. Koumoundourou[1], E. Nikolatou[2], G. Michael[3]
[1] University Hospital of Patras, Greece, [2] Faculty of Health & Caring Professions, Technological Educational Institute of Athens, Greece, [3] Department of Obstetrics & Gynaecology, Patras University Medical School, Achaia, Greece

Background & Objectives: Breast cancer is an heterogenous disease. Several hypotheses have been proposed to explain the origin of intratumoural heterogeneity, but besides the differences between tumours cancer cells within one tumour of a patient at any given time frequently display intratumoural heterogeneity. The heterogeneity in biomarker expression among neoplastic cells might be attributed to several plausible events and procedures during tumour progress (angiogenesis, tissue infiltration, metastasis). Several studies focusing on the differential

parenchymal expression of cellular biomarkers with prognostic or predictive value have been recently published; efforts addressing HER-2 protein immunoexpression aim in targeted therapeutic interventions.
Methods: The expression of the HER-2 molecule has been studied in tissue specimens originating from eighty breast cancer patients. Immunohistochemical detection of HER-2 protein has been carried out in pairs of two separate blocks material originating from the same core biopsy. The intensity of immunoexpression has been graded with a practical scoring system (0-1+: negative staining, 2+: equivoval and 3+:positive staining).
Results: In 47 out of eighty studied paired samples, matching results have been obtained. In the remainder 21 (26.2%) a slight difference in immunoexpression has been documented (score 0/1+ and 2+, respectively) among the paired samples, while in 12/80 (15%) a significant difference has been observed (score 1+/2+ and 3+, respectively). In most cases the findings have been confirmed with in situ hybridization.
Conclusion: Our results corroborate the presence of heterogenous intratumoural expression of HER-2 protein, as suggested by previous studies. These findings underscore the necessity of assessing HER-2 immunoexpression in several tissue blocks due to the challenge for treatment selection when aiming to individualize patient's optimal therapeutic approach.

PS-01-055
Tyrosine aminoacyl-tRNA synthetase sensitises breast cancer to chemotherapy through Smac mimetics derived necroptosis mechanism: high-throughput proteomics and machine learning algorithm based feature selection analyses
H.S. Ryu[1], D. Han[2], K. Lee[3], K. Kim[4]
[1] Department of Pathology, Seoul National University Hospital, Republic of Korea, [2] Proteomics Core Facility, Seoul National University Hospital, Republic of Korea, [3] Biomedical Research Institute, Seoul National University Hospital, Republic of Korea, [4] Division of Clinical Bioinformatics, Biomedical Research Institute, Seoul National University Hospital, Republic of Korea

Background & Objectives: Although more than 70% of entire patients are currently receiving the chemotherapy regimen, pathologic complete response (CR) rate is still low, ranging from 23% to 32.7%. Therefore, the need for a marker predictive of response to a particular cytotoxic regimen, especially before neoadjuvant chemotherapy, is becoming all the more necessary to optimise therapeutic efficacy and to avoid unnecessary complications caused by systemic therapy.
Methods: We performed quantitative proteomics mass spectrometry in twenty paired FFPE biopsy breast cancer samples consist of non-responsive and responsive groups to chemotherapy. To define the best classifier to evaluate the predictive power of signatures, we employed four different machine learning algorithms and performed repeated cross-validation on the training set to classify samples between pathologic complete response (CR) and non-complete response (nCR) groups. The candidate proteins selected from the machine-learning algorithms were subsequently validated by immunohistochemistry of 123 cases of independent needle biopsy FFPE samples which obtained before chemotherapy. The further experimental model of breast cancer was performed to identify the molecular mechanism of how the biomarker potentiates sensitivity of multiple breast cancer cells to chemotherapy response and synergistic effect with a combination of necroptotic mimetics.
Results: The mass spectrometry-based proteomic analysis of FFPE set yielded 6,069 protein groups. The filtered dataset was subjected to statistical analysis using Student's t-test (p-value < 0.05), which resulted in 539 proteins with differential abundances. To identify the most meaningful changes in two conditions, the volcano plot was used. 13 proteins including YARS, TBC1D10C, SMCHD1, WARS, IGKV3-15, HTATIP2, KIAA1522, MAOB, MAPT, BSPRY, CAP2, ABAT, and NAT1 were prioritized. We searched for biological process in the Gene Ontology (GO) enrichment analysis in each proteomic cluster. Several immune responses process, apoptotic process, DNA replication process, and aminoacylation for protein translation process primarily were represented in the group with complete remission. On the other hand, cell adhesion process, cytoskeleton organization process, vesicle organization process and Golgi organization process overrepresented in breast cancer which showed poor responses to the therapy. The machine learning approaches using Random Forest algorithm demonstrated the highest AUC value, 0.978 (sensitivity 1.0 and specificity 0.714) with a combination of 11 proteins including STUB1, PDCD6, YARS, MAOB, PDCD4, NA, FLYWCH2, ABAT, FAM162A and WARS (Figure00, Table 00). For the accuracy prediction, four different algorithms demonstrated evenly high accuracy rates from 0.85 to 0.95 with a combination of STUB1, PDCD6, YARS, MAOB, WARS, RHBDF1 or KIAA1522. the selected seven candidates (KIAA1522, RHBDF1, WARS, YARS, MAOB, STUB1 and PDCD6) evaluated in the subsequent steps of verification using immunohistochemistry (IHC) in 123 patient cohorts. The predictive relevance of individual proteins, YARS and RHBDF1 to distinguish CR from nCR was AUC of 0.605 and 0.630 for all cases and approximately 10.2% higher AUC in luminal breast cancer (AUC=0.749 and 0.717). The overexpression of YARS induced chemotherapeutic sensitivity in hormone receptor-positive breast cancer cell lines such as T47D, which was confirmed with multiple molecular biology-driven assays. The further experimental model of breast cancer demonstrated that YARS induced tumour necroptosis which enhanced chemotherapy response and was synergized with a combination of SMAC mimetics that is a potent necroptosis inducer.
Conclusion: Our current study is the first report that confirmed the presence of YARS enhances a profound chemotherapeutic effect which is mediated by necroptosis in breast cancer in addition to the reliable predictive biomarker for chemotherapy response. In addition, a combination of YARS plus a Smac mimetic LCL161 led to a significant improvement in breast cancer response to chemotherapy. Smac mimetics are recently developed necroptosis inducer and considered as promising therapeutic targets that antagonize IAP proteins which have been known to be linked to treatment failure and unfavourable prognosis in various malignant tumours. Currently, Smac mimetics are undergoing in multiple clinical trials to overcome treatment resistance or as cancer therapeutics In the previous study, Smac mimetics triggers necroptosis when caspase 8 is inactivated in acute myeloid leukemia cell line, which is consistent with our data where caspase 8 was inactivated by YARS overexpression. Our present study also confirmed that YARS combined with Smac mimetics triggered MLKL and RIP phosphorylation which are downstream effectors of necroptosis and induces plasma membrane permeability and cell death. In summary, our discovery data provide a global molecular landscape for determining chemotherapy response in breast cancer at the proteome level. Furthermore, we provided a novel protein candidate to predict chemotherapy response and identify a novel protein YARS in combination with Smac mimetics synergistically induced necroptosis which produces more cell death in response to combined chemotherapy in breast cancer.

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PS-01-056
Prognostic role of immunological markers in triple negative breast carcinoma
H. Sahin Ozkan[1], M.U. Ugurlu[2], H. Kaya[1]
[1] Marmara University Faculty of Medicine, Department of Pathology, Turkey, [2] Marmara University Faculty of Medicine, Department of General Surgery, Turkey

Background & Objectives: Composition and interactions of tumour-immune-microenviroment (TIME) has become ever more important for the management of triple negative breast carcinoma (TNBC). Our aim is to evaluate the relationship between CD8, FOXP3, PD-L1, CD163 and histopathological parameters to understand their prognostic role.
Methods: 51 lumpectomy/mastectomy specimens, which had been diagosed as TNBC and not received neo-adjuvant therapy, were

immunostained with CD8 (C8/144B-Dako), FOXP3 (EP340-Epitomics), PD-L1 (SP263-Ventana), and CD163 (EP324-Epitomics). CD8, FOXP3, and CD163 expressions were separately evaluated in intratumoural(IT) and stromal(S) areas. PD-L1 expression was also individually considered in neoplastic cells (NC) and tumour-infiltrating-lymphocytes (TIL).
Results: All patients were female. Mean age was 52.7 (32-84) and mean survival was 48.3 months (3.4-83.7). There was a significant positive correlation between the expressions of each of the four antibodies ($p<0.01$). Among the histological subtypes, higher expressions of CD8 (IT), FOXP3 (IT&S), PD-L1 (NC), and CD163 (IT&S) were found in lymphocyte-predominant breast carcinomas ($p<0.05$). Expressions of CD8, FOXP3, and CD163 (IT&S), and PD-L1 (TIL) were negatively related to angio and lymphatic invasion ($p<0.01$). Perineural invasion was more frequent in the cases with lower CD8 (S) and FOXP3 (IT&S) and higher PD-L1 (TIL) expressions ($p<0.01$). pT stage was reversely related to CD8 (S) and PD-L1 (TIL), however, it had a positive association with PD-L1 (NC) and CD163 (IT) ($p<0.01$). Lower expressions of FOXP3 (IT&S), PD-L1 (TIL), and CD163 (IT) were observed to be related with exitus ($p<0.01$). Local recurrence was negatively associated with CD8 (S), FOXP3 (IT), PD-L1 (TIL), CD163 (S) ($p<0.01$). Expressions of CD8 (S), FOXP3 (IT&S), PD-L1 (NC&TIL), and CD163 (IT&S) were lower in the cases with distant metastasis ($p<0.01$).
Conclusion: TIME is an important prognostic parameter and a potential therapeutic marker. CD8, FOXP3, PD-L1, and CD163 antibodies are useful to consider TIME and to predict prognosis in TNBC.

PS-01-057

Relationship of Her2/neu and oestrogen receptor changes in local metastases compared with primary tumour in breast cancer patients with equivocal (2+) Her2/neu expression level in primary tumour

S. Sazonov[1], K. Konyshev[2]
[1] Institute of Medical Cell Technologies, Russia, [2] Institute of Medical Cell Technologies, Ural State Medical University, Russia

Background & Objectives: Differences in the expression of biomarkers in primary tumour tissue and metastases and the relationships of such differences in breast cancer patients are not clear until now. Objective: to reveal the relationship of estrogen receptor (ER) and Her2/neu changes in locoregional metastases compared with primary tumour in the group of breast cancer patients with equivocal Her2/neu expression level (2+).
Methods: 19 samples of primary tumour (Her2/neu expression 2+) and corresponding metastases were stained immunohistochemically with anti-ER (1D5, Dako) and anti-Her2/neu (4B5, Ventana) antibodies. Primary tumour samples were additionally analysed using SISH technology (Ventana). Staining results were evaluated using Allred score and ASCO/CAP 2013 guideline. Frequencies of Her2/neu and ER expression changes were compared using Fisher's exact probability test.
Results: Her2/neu expression level was lower in metastases then in the primary tumour in 16 cases (84,2%, 95% CI 59,5-95,8%) and higher – in 1 case out of 19 (5,3%, 95% CI 0,3-28,1%) ($p<0,001$). Her2/neu-statuses of primary tumour and metastases were the same in 84,2% (95% CI 59,5-95,8%) of cases. Among 16 cases with decreased Her2/neu expression level in metastases we registered 9 cases with increase and 2 cases with decrease of ER expression level ($p=0,023$).
Conclusion: We found simultaneous decrease of Her2/neu expression level, maintenance of Her2/neu-status and increase of ER expression level in local metastases compared with primary tumour of breast cancer in the cases with equivocal (2+) Her2/neu expression level in the primary tumour.

PS-01-058

Androgen receptor expression as a possible prognostic marker in male breast cancer

C. Scatena[1], R. Scarpitta[1], R. Biancotti[1], L. Diodati[2], M. Ghilli[2], A.G. Naccarato[1]
[1] University of Pisa, Italy, [2] University Hospital of Pisa, Italy

Background & Objectives: Male breast cancer (MBC) is a rare condition representing the 0.5-1% of all breast cancer cases. In contrast to female breast cancer (FBC), relatively little is known about MBC. Most MBCs are luminal A or B types, whereas basal-like and HER2 enriched types are rare. This distribution is clearly different compared to FBC, pointing to possible important differences in carcinogenesis. Increasing data deal with the role of the androgen receptor (AR) as a marker of prognosis in FBC, with contrasting results. Since the androgen – AR signalling exerts actions on key events during prostate carcinogenesis, the aim of the present study was to evaluate the role of AR in MBC.
Methods: 23 males with a diagnosis of invasive breast cancer were selected. Clinico-pathological data were collected. AR expression was measured by immunohistochemistry (SP107, Ventana Medical Systems; Ventana BenchMark AutoStainer). Pathological variables were compared by Spearman's rank correlation coefficient. Moreover, the Kaplan–Meier method and log-rank test were used to explore the impact of AR expression on disease free survival (DFS).
Results: 16 out of 23 patients (70%) displayed and increase of AR expression with the increase of Progesterone Receptor (PgR) expression (rho = 0,484; p = 0,019). Instead, 7 out of 23 patients (30%) with low levels of PgR displayed high levels of AR with a potential advantage in terms of DFS (p=0,081).
Conclusion: These preliminary data suggest a possible prognostic role of AR in MBC. Forthcoming molecular analysis will shed light to unknown underlying mechanisms.

PS-01-059

Expressed cartilaginous and osseous metaplasia in breast cancer: histological and immunohistochemical aspects

V. Sikora[1], M. Lyndin[2], N. Hyriavenko[1], R. Moskalenko[3], A. Piddubnyi[3], L. Karpenko[1], A. Romaniuk[3]
[1] Sumy State University, Medical Institute, Pathology Department, Ukraine, [2] Sumy State University, Medical Institute, Department of Pathology, Ukraine, [3] Sumy State University, Ukraine

Background & Objectives: The course of the breast cancer (BC) depends on the differentiation of the tumour, immunophenotype of the neoplastic cells and the qualitative and quantitative characteristics of the tumour microenvironment. Moreover, the expressed secondary changes significantly influence on the progression of the malignant process in the mammory gland. We present the case of the invasive breast cancer (non-specific type) of the right breast in a 64-year-old woman with the features of the expressed rare type of metaplasia.
Methods: Morphogenesis and immunophenotype of the tumour were studied by using the histological (H&E) and immunohistochemical (CKpan, Er, Pr, PRL, Her2neu, Ki-67, EGFR, MPO, GPA, CD3, CD79, CD68, OPN and OSN) methods.
Results: The high-grade invasive cancer of non-specific type with the expressed cartilaginous and osseous metaplasia was diagnosed. Immunohistochemical study revealed the strong expression for CKpan, OPN, OSN, PRL, moderate-EGFR, weak-Er, negative-Pr and Her2neu in the cancer tissue; Ki-67 expression was found in 7% of tumour cells. In the areas of osseous and cartilaginous tissue, the accumulation of single CD3, CD79α vs CD68 positive cells with MPO and GPA positive cells was revealed which confirms the formation of red bone marrow in the centre of metaplasia.
Conclusion: This clinical observation presents the case of the breast cancer, where the immunophenotype of cancer cells is the indicator of the possible osteo/chondrogenesis with the formation of bone marrow. Timely determination of the expression peculiarities of immunohistochemical markers in cartilaginous and osseous

metaplasia makes it possible to predict the course of the oncological disease and its metastasis.

PS-01-060

Clinicopathological and immunohistochemical characterisation of adenoid cystic carcinoma of the breast diagnosed in a single Institution

M. Souto Moura[1], G. Satta[2], M. Jácome[1], P. Lopes[1], F. Silva[1], M.J. Bento[1], C. Leal[1]
[1] Department of Pathology, IPO-Porto, Portugal, [2] Department of Medical, Surgical and Experimental Sciences, Unit of Pathology, University of Sassari, Italy

Background & Objectives: Adenoid cystic carcinoma (ACC) is a rare but distinct breast neoplasm resembling its counterpart in other organs. It is architecturally heterogeneous and composed of a dual cell population, expressing epithelial and myoepithelial markers. Nevertheless, there is some controversy in the literature regarding its immunohistochemical profile. The aim of this study was to characterise the clinical, histological and immunohistochemical features of ACC cases diagnosed in our Institution.
Methods: A retrospective analysis of patients with ACC of the breast in our Institution was carried out. Twelve cases were included (1987-2018). Histological pattern and Nottingham Histological Grade (NG) were evaluated. Immunohistochemistry with hormonal receptors (estrogen-ER and progesterone-PR), human epidermal growth factor receptor type 2 (HER2), p63, calponin, vimentin, S100, smooth muscle actin (SMA), CK7, CAM5.2, CK5/6, CD117 and CK14 was performed for each case.
Results: Mean tumour size was 2,2cm. NG was 1(n=7), 2(n=3) and 3(n=1). Six cases were predominantly tubular/cribriform and six had solid/basaloid areas. 75% were triple-negative. All cases stained for CK7 and vimentin and eleven for CD117 and p63, each. Remaining markers stained variably. In predominantly tubular/cribriform tumours CK7, CD117, p63 and vimentin clearly identified two different cell populations. In solid tumours there was more epithelial-myoepithelial staining overlap with these markers. NG3 case was the only with nodal and distant metastasis.
Conclusion: ACC has good prognosis and characteristic histological and immunohistochemical features. Nevertheless, in tumours with predominantly solid/less differentiated areas there is more histological and immunohistochemical heterogeneity, which makes the differential diagnosis with other basaloid salivary gland-like carcinomas of the breast more challenging.

PS-01-061

Analysis of clinical-pathological data with impact on overall survival (OS) in male breast carcinoma (MBC): an international multi-Institutional study of 217 cases

S. Stolnicu[1], E. Restekova[2], A. Dema[3], M. Comanescu[4], I. Alvarado-Cabrero[5], R. Buiga[6], M. Boros[7]
[1] Department of Pathology, UMFST, Targu Mures, Romania, [2] Department of Pathology, MD Anderson Cancer Center, Houston, USA, [3] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania, [4] Department of Pathology, "Victor Babes" Institute, Bucharest, Romania, [5] Department of Pathology, Hospital de Oncología Mexico City, Mexico, [6] Department of Pathology, Oncologic Institute "I. Chiricuta" Cluj, Romania, [7] Department of Pathology, University of Medicine and Pharmacy, Oradea, Romania

Background & Objectives: Male breast carcinoma is still inadequately characterised and data regarding the impact of different prognostic parameters are limited due to the small number of cases compared to female counterpart. The objective of this study is to evaluate clinical-pathological parameters in correlation with OS in male breast carcinoma.
Methods: All men diagnosed with invasive breast carcinoma in 6 international Institutions (1999- 2015) were identified by searching laboratory databases. Parameters analysed were the followings: age, tumour size, histological tumour type and grade, molecular biomarkers (ER, PR, ki-67, HER2), AR status, treatment and length of OS (months).
Results: 217 cases, with a mean age of 62y (range: 18- 85), right breast localization (52.53%), NST histological type (86.18%), G2 histological grade (55.4%), T2 (54.41%), N+ (65.89%) and Luminal A molecular subtype (85.29%) were identified. 5-year OS was 67.2% and 10-year OS was 48.5%. OS was 92.7% at 5 years and 73.8% at 10 years (in axillary lymph node negative cases) while OS was 59.7% at 5 year and 41.3% at 10 years in axillary positive male cancers (p=0.003).

PS-01-062

Higher tumour cell proliferation in breast cancer of the young

A. Svanoe[1], G. Knutsvik[1,2], B. Davidsen[3], C. Askeland[4,2], K. Krüger[1], T. Aas[3], I.M. Stefansson[4,2], L.A. Akslen[4,2], E. Wik[4,2]
[1] Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, University of Bergen, Norway, Norway, [2] Department of Pathology, Haukeland University Hospital, Bergen, Norway, [3] Department of Surgery, Haukeland University Hospital, Bergen, Norway, [4] Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, Section for Pathology, University of Bergen, Norway

Background & Objectives: Breast cancer (BC) in adolescents and young adults (AYAs; 15-49 years) is associated with aggressive tumour features. We aimed to investigate tumour cell proliferation in AYAs.
Methods: The proliferation marker Ki67 was analysed by immunohistochemistry on FFPE TMA-slides from two population based cohorts: One AYA series (n=355) and one series of patients aged 50-69 (n=546). mRNA data from METABRIC and TCGA (n=2283) was used to investigate gene expression signatures reflecting tumour proliferation.
Results: The AYAs demonstrated higher Ki67 levels compared to BC patients ≥ 50 years (median Ki67 10.4% and 7.0%, respectively; P<0.0005). Higher Ki67 levels were found among AYAs <40 years compared to those 40-49 years (median Ki67: 16.0% and 9.0%, respectively; P=0.009). High levels of Ki67 among AYAs were associated with high histologic grade, ER and PR negativity, larger tumour diameter, and shorter survival (all P<0.0005). When adjusting for tumour size, histologic grade and lymph node status, Ki67 maintained independent prognostic impact, also among ER positive AYA tumours. Higher mRNA proliferation scores in the young, and associations between high scores and shorter survival, validated our results (all P<0.0005).
Conclusion: BC of the young demonstrate higher tumour cell proliferation compared to older patients, and higher proliferation associate with aggressive tumour features and reduced survival among AYA patients. This might contribute to the more aggressive breast cancers observed in the young.

PS-01-063

Is breast cancer different in women younger than 40 years old?

I. Uglai[1], F. Voaides-Cojan[2], A. Budica[2], B.R. Nataras[1], C. Ciora[3], G.E. Olteanu[4,5], C. Suciu[2,6], D. Anderco[1], D. Grujic[2,6], C. Lazureanu[7,8], A. Dema[9]
[1] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania, [2] "Pius Brânzeu" Emergency County Hospital, Timisoara, Romania, [3] Department of Pathology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, [4] Department of Pathology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, [5] Centre for Gene and Cellular Therapies in Cancer - Oncogen, Romania, [6] "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [7] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania,

[8] Department of Pathology, Emergency County Hospital Timişoara, Romania, [9] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania

Background & Objectives: Breast cancer is commonly diagnosed over 50 years old, with only 5% of cases being under 40 years old. For the latter cases we focused our study on the occurrence rate, topography, histological and immunohistochemical features.
Methods: We have conceived a 5 years retrospective study (2014-2018), using the pathology department's database of "Pius Brânzeu" Emergency County Hospital Timisoara. During this time, 276 patients were diagnosed with primary breast carcinoma. Of these data we selected 25 patients which were younger than 40 years old at the time of diagnosis. The inclusion criteria in study were: age, breast invasive carcinoma and IHC performed.
Results: In our study, the average age of the patients diagnosed with breast carcinoma was 35.44 y.o. (9.09% of all cases). The annual rate of occurrence was 4-5 cases. The histological type for all 25 cases was invasive carcinomas NST, G2 grade-16 cases (64%), G3-9 cases (36%) with the immuneprofile: basal-like-12 cases (48%), luminal A-10 cases (40%) and luminal B-2 cases (8%). Regarding the topography, the left breast was involved in 12 cases (48%), the right-10 cases (40%) and 3 bilaterally.
Conclusion: The incidence of breast cancer in young women is steadily in time. About topography, the most affected side is the left breast. Breast cancer in young women seems to be an aggressive malignancy with a triple negative immune profile in most of the cases.

PS-01-064

Frequency of breast-conserving surgery in breast cancer, in real-life practice

M. Urezkova[1], A. Kudaybergenova[1], E. Turkevich[1], P. Krivorotko[1]
[1] N.N. Petrov National Research Medical Center of Oncology, Russia

Background & Objectives: Surgery for breast cancer is one of the main therapies. Since 1991 ACSCC has recommended breast-conserving surgery (BCS) for early-stage breast cancer. With BCS the criterion for optimally performed surgery is the clearance of the resection margins. The aim of this study determine the proportion of BCS and positive margins in our hospital to compare with international findings.
Methods: The study included 3635 cases of breast cancer operated in our center in 2013-2018 years.
Results: Total BCS was 1291 cases (39.1%). To compare with large studies Hwang investigated rate of BCS in 1990-2004 pointed 55% who received lumpectomy compare 45% for mastectomy; Norway study indicate 70% BCS in 1998-2009, Stefanie Corradini describing single-Institution life-practice in 1998-2014 detected 84.8% of patients treated with BCS and 15.2% with mastectomy. The positive resection margin (R1 resection) rate was determined in 5.8% of cases in our center. According to M. Morrow (2014) the frequency of the positive margin reaches 12-22%.
Conclusion: The proportion of BCS and the frequency of R1 resection in our study is significantly less than that described in international studies. The reason of these differences may be different surgical activity of the operating surgeons, and should be important in determining the subsequent treatment.

PS-01-065

Radiation-associated breast angiosarcoma - case series

B. Ilcheva[1], S. Bachurska[2], D. Tashkova[2], A. Fakirova[1], R. Hristoskova[1]
[1] Department of General and Clinical Pathology, Military Medical Academy Sofia, Bulgaria, [2] Department of General and Clinical Pathology, Medical University Plovdiv, Bulgaria

Background & Objectives: Radiation-associated breast angiosarcoma(RBA) is rare, aggressive soft-tissue neoplasma, which occurs after a breast-conserving surgery with adjuvant radiation therapy for breast carcinoma. Most tumours present as multifocal erythematouse plaques, nodes, areas of ecchymosis or skin thickening. Morphologically the majority of the RBAs are high grade with poor prognosis and high risk of local and systemic recurrences.
Methods: We present four cases of the RBA with emphasis on the clinical and morphological characteristics.
Results: Patients were aged 61 to 83 years old with invasive breast carcinoma, treated with breast-conserving surgery, radio-, chemo- and hormonal therapy. An interval between primary disease and development of the RBA was five years in three of the cases and eleven years the fourth case. In all patients the RBA presented as a skin lesion with involvement of the underlying mammary tissue. IHC panel of CK AE1/AE3, CD31 and CD34 were used for the final diagnosis.
Conclusion: RBA is a serious long-term complication after breast-conserving surgery and adjuvant therapy with high rates of local relapse. Its appearance may mimic reactive and benign conditions, which may lead to delay diagnosis. Complete clinical history and multidisciplinary approach are of the great value for the final diagnosis.

PS-01-066

The prognostic value of topoisomerase II-α for chemotherapy response and survival in breast cancer

L. Zakhartseva[1], M. Yanovytska[1], Y. Zakhartsev[2], M. Plodienko[1]
[1] National Medical Bohomolets University, Ukraine, [2] Kiev City Oncology Center, Ukraine

Background & Objectives: Topoisomerase II-α (topoIIα) protein is one of the intracellular targets for anthracycline-based therapy and is considered to have predictive value for antracycline-based chemotherapy regimens. Some studies indicate the value of this marker for survival prediction. Available data about topoIIα prognostic value remains controversial.
Methods: 128 paraffin-embedded tumour samples from core biopsy specimens with histologically confirmed breast cancer were evaluated by immunohistochemical analysis for topoIIα, estrogen and progesterone receptors, Her2/neu and Ki-67. The average observation time period was 21 months. Those samples where preoperative biopsy was done were evaluated (n=43) for chemotherapy response. Correlation regression analysis (Pearson's correlation coefficient) was used to analyse the data.
Results: Expression of topoIIα (evaluated as positive when higher than 20%) was detected in all molecular breast cancer subtypes. 76% was positive for topoIIα in luminal B subtype (n=50), 64% in Her2-enriched tumours (n=14), 50% was positive in triple-negative subtype (n=16) and 23% in luminal A subtype (n=48). Relationship between proliferative index and topoIIα expression was high and statistically significant (p=0,000). No statistically significant correlation between chemotherapy response, overall survival and expression of topoIIα was found.
Conclusion: Our data confirms that topoIIα expression is higher in aggressive subtypes of breast cancer (associated with high Ki-67) and can be interpreted as a kind of proliferative marker. It is associated with luminal B, Her2new-enriched and triple negative subtypes. Probably increased sensitivity to anthracycline-based chemotherapy among triple negative and HER2-positive breast carcinomas is independent of expression of topoisomerase IIα.

PS-01-067

The Immunogradient of CD8+ cell density in the tumour-stroma interface zone predicts overall survival of patients with hormone receptor-positive invasive ductal breast carcinoma

D. Zilenaite[1,2], A. Rasmusson[1,2], A. Nestarenkaite[1,2], R. Augulis[1,2,3], A. Laurinaviciene[1,2], V. Ostapenko[4], T. Poskus[5], A. Laurinavicius[1,2]
[1] National Center of Pathology, affiliate of Vilnius University Hospital Santaros Clinics, Vilnius, Lithuania, [2] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences of the

Faculty of Medicine of Vilnius University, Lithuania [3] Institute of Biosciences, Life Sciences Centre, Vilnius University, Lithuania, [4] National Cancer Institute, Vilnius, Lithuania, [5] Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Lithuania

Background & Objectives: Tumour infiltrating lymphocytes (TIL) are associated with better prognosis in triple-negative and HER2-positive breast cancer, and TIL assessment by digital image analysis (DIA) has been successfully implemented in colorectal and other cancers. However, results in hormone receptor-positive breast cancer (HRBC) based on manual scoring remain contradictory. Here we used an automated DIA method to extract prognostic value of novel *Immunogradient* indicators in CD8+ cell density profiles in HRBC.
Methods: Surgically excised HRBC samples from 102 patients were immunohistochemically stained for CD8, digitized and analysed by the HALO™ platform. The DIA data was subsampled by a hexagonal grid and explicit rules were then used to extract the tumour-stroma interface zone (IZ) and compute novel *Immunogradient* indicators from TIL density profiles across the IZ. The prognostic value was evaluated by survival analysis.
Results: The IZ *Immunogradient* indicators (mean CD8+ density in the tumour aspect of the IZ, Immunodrop, Centre of Mass) allowed prognostic stratification of patients in univariate analyses (hazard ratios: 0.21 (p=0.0002), 2.79 (p=0.0140), and 0.28 (p=0.0044), respectively). The best and independent indicator of better OS by multiple Cox regression model (hazard ratio: 0.23 (p=0.0007)) was an aggregated *Immunogradient* factor (AF), obtained by the sum of two factor scores (CD8+ density and "gradient towards the tumour"). Remarkably, the AF revealed a striking drop of patients' survival probability 5 years after surgery.
Conclusion: The *Immunogradient* indicator for CD8+ cell density is an independent predictor of better OS in HRBC patients with the particular diversion of OS 5 years after the surgery.

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PS-02 | Gynaecological Pathology

PS-02-003
Glycans expression in endometrium of infertile patients
A. Asaturova[1], N. Abdurakhmanova[1], G. Kulikova[1], M. Ziganshina[1], N. Faizullina[1], A. Shchegolev[1], G. Sukhikh[1]
[1] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation, Russia

Background & Objectives: Significant changes in the endometrial glycome, associated with an increase of expression of highly glycosylated proteins that having terminal sialic acid and fucose residues, occur during the window of implantation. Since sialoglycans and sulfated fucosylated glycoconjugates are key molecules mediating cell-cell contacts, disruption of their expression may be the reason for the lack of IVF. The aim was to evaluate the expression of sialo-, and sulfated fucosylated glycans in the endometrium of patients with different reproductive outcomes in IVF programs.
Methods: A histochemical and immunohistochemical analysis of paraffin-embedded endometrial samples was performed using an UEA-I, MAL-II lectins (Vector Labs) and anti-LeY (Abcam), anti-PNAd (MECA-79) (BD Pharmingen) monoclonal antibodies. We included 34 patients with tubal factors of infertility, which were divided into two groups: women with pregnancy after IVF (group 1) and patients who failed an IVF cycle (group 2). Quantitative analysis of optical density immuno- and hystochemical reactions was performed by Nikon Eclipse E 80 computer program.
Results: The increased expression of MECA-79 in the glycocalyx and cytoplasm of the glandular and luminal epithelium was established in group 1 compared with group 2. Similarly, the increase of cytoplasmic expression the LeY was found in the epithelium and fucosylated structures with core type 2 (UEA-I staining positive) in the cytoplasm of the glandular and luminal epithelium. On the contrary, a decrease expression of α2-*3*-linked *sialosides (*MAL-II) in the glycocalyx of the luminal epithelium was noted in group 1.
Conclusion: The presence of higher level MECA-79, specific for the sulfated oligosachharides epitope of L-selectin ligands, and fucosylated structures with core type 2 (containing Galβ1-4GlcNAc motif, including LeY) in mildsecretory phase was associated with a better pregnancy outcomes. This glycans may be considered as predictive markers of human uterine receptivity.

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PS-02-004
Unravelling genetic alterations in endometrioid endometrial cancer and correlation with molecular subgroups and immunologic tumour microenvironment
B. Willvonseder[1], K. Steiger[2], H. Bronger[3], G. Keller[1], W. Weichert[4], A. Noske[1], N. Pfarr[5], M. Boxberg[5]
[1] Institute of Pathology of the Technical University of Munich, Germany, [2] Institute of Pathology, TUM School of Medicine, Technical University of Munich, Germany, [3] Department of Obstetrics and Gynaecology, Technical University of Munich, Germany, [4] Technical University of Munich, School of Medicine, Institute of Pathology, Germany, [5] Institute of Pathology, Technical University Munich, Germany

Background & Objectives: Advanced endometrioid endometrial cancer (EC) carries a poor prognosis with immune-checkpoint blockage (ICB) emerging as therapeutic option. Antigen-presentation (AP), interferon-signalling (INF) and immune-checkpoint receptors (IC) have been associated with tumour immunology and ICB-response. Developing a next-generation-sequencing (NGS) panel, we determined molecular alterations in the above named immunologically relevant pathways and analysed correlations with EC molecular subgroups and immunologic microenvironment.
Methods: We investigated baseline molecular parameters (mismatch repair, TP53, ARID1A, PTEN, estrogen receptor) by immunohistochemistry/NGS in n=50 therapy-naïve EC. We quantified tumour-infiltrating lymphocytes (Pan-T-cells; T-killer-cells; regulatory T-cells; PD-1+ cells) and PD-L1 in tumour und immune cells. Our NGS panel contained n=54 genes of AP (e.g. HLA-A), AP machinery (e.g. B2M), INF (e.g. JAK2) and IC (e.g. PD-L1).
Results: Mutations in investigated genes were frequent (n=11 INF, n=10 AP machinery, etc). TP53-mutation and immunologic mutations were mutually exclusive, mutations in immunologic pathways were exclusively detected in PTEN-mutant EC ($p<0.03$). Presence and high number of mutations were more frequent in poorly differentiated EC ($p<0.05$). High PD-L1-expression in tumour and immune cells was correlated with presence and high number of immunologic mutations as well as high density Pan-T-cell and T-Killer-cell infiltrate ($p<0.05$) irrespective of affected pathway.
Conclusion: Molecular alterations in immunologic pathways were frequent and exclusively detected in PTEN-mutant EC. TP53-mutation and immunologic mutations were mutually exclusive. Mutations in immunologic pathways were closely correlated with a highly immunogenic subgroup of EC characterised by high PD-L1 expression and high density T-cell-infiltrate. This subgroup may potentially be predictive for ICB-response and might be further investigated in biomarker studies.

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PS-02-005

Ovarian immature teratoma: characteristics, treatment and outcomes of 20 women (1994-2012)

D. Chiba[1], N. Abdessayed[2], S. Chaieb[2], A. Baccouche[2], T. Zahmoul[3], S. Yacoub[2], B. Sriha[2], M. Mokni[2]
[1] Department of Pathology Farhat Hached Hospital, Tunisia, [2] Farhat Hached Hospital, Tunisia, [3] Cancer Registry of the Tunisian Center, Tunisia

Background & Objectives: Immature Teratomas (IT) of the ovary are a type of germ cell cancer that accounts for less than 3% of malignant ovarian cancer. These tumours are usually diagnosed in children and young women ranging from 10 to 30 years and have a good prognosis.
The aim of this study is to evaluate clinical and pathologic characteristics and treatment outcome in women diagnosed with ovarian immature teratoma.
Methods: Sousse registry cancer center database was used to identify women diagnosed with an immature teratoma from 1994–2012. Patient's clinical presentation, operative and chemotherapy details were included in a database. Follow up details regarding recurrence and management and future outcomes were also noted. Overall survival was calculated from the date of registration to last follow up. We identified a total of 20 women with Immature Teratoma. The median age at diagnosis was 28 years (range: 14–63 years).
Results: Pain was the predominant symptom and abdominal mass was the commonest clinical presentation. Sixtee (80%) presented with stage I disease, 2(10%) with stage II, and 2 with indeterminate stage. 11 (55%) of the tumours were found to be grade 1,6 (30%) grade2, and 3(10%) grade3. Initial management was surgical for all patients: 14 (70%) unilateral oophorectomy, 2 (10%) cystectomy only and 5(25%) bilateral oophorectomy with hysterectomy. Eleven (55%) patients received adjuvant-chemotherapy. Only one clinical stage II/Grade3 patient who received adjuvant-chemotherapy developed a recurrence and underwent a second surgery.
Conclusion: The median follow up was 5 years. All (100%) patients were alive after 5 years.
Most patients present with early-stage disease, are managed with fertility sparing surgery associated or no to chemotherapy and have an excellent prognosis. However, grade 2 or 3 tumours are associated with a greater chance of recurrence that can be fatal.

PS-02-006

Gynaecological tumours in the paediatric age: a clinico-pathological study

J. Costa[1], S. Alves[2], F. Silva[1], F. Leite[3], C. Bartosch[1]
[1] Department of Pathology IPOP, Portugal, [2] Department of Oncology IPOP, Portugal, [3] Department of Paediatrics, IPO-Porto, Portugal

Background & Objectives: Gynaecological tumours and tumour-like lesions in children and adolescents are rare, however the potential physical, psychiatric and social sequelae of these diagnoses may be devastating.
Methods: Observational retrospective cohort study describing the gynaecological tumours and tumour-like lesions diagnosed in patients aged 0-19 years at Portuguese Oncology Institute of Porto between 2000 and 2018. In total, 101 patients were included, comprising 98 (79.7%) tumours and 25 (20.3%) tumour-like lesions.
Results: Benign tumours: 45 (45.9%); borderline: 22 (22.5%); malignant: 31(31.6%). Most common sites: ovary (86.2%) and cervix (5.7%). Most common histologic types: germ cell tumours (50.0%) and epithelial tumours (38.8%). Tumour-like lesions: follicular cysts (n=9|39.1%), adnexal torsions (n=7|30.4%) and endometriosis (n=4|17.4). Frequency of lesions increased with age. Age of diagnosis for epithelial tumours was higher compared to germ cell tumours: 17 (6) vs.14 (18) years (median(range)), p=0.001. The majority of patients(n=91|90.9%) underwent conservative surgery, including cystectomy (n=24|24.8%) and unilateral salpingo-oophorectomy (n=54|53.5%). Twenty-two (21.8%) had chemotherapy and one had radiotherapy. Six (5.9%) patients relapsed and four (3.9%) died of disease.
Conclusion: Paediatric gynaecological lesions comprise a wide variety of rare histological tumour subtypes, warranting evaluation by an experienced pathologist. Conservative management of gynaecological tumours in the paediatric setting, with fertility sparing surgery and limited use of adjuvant therapies, allows high recurrence-free and overall survival with decreased later morbidities.

PS-02-007

Placental attachment pathology (PAP) in women with uterus scar and undifferentiated connective tissue dysplasia (UCTD)

T. Demura[1], E. Kogan[1]
[1] First Moscow State Medical University (Sechenov University), Russia

Background & Objectives: The morphological substrate of UCTD is impaired tissue repair with scar formation with further development of its disorganization (Demura et.al. 2012).
The aim: to study morphological substrate and molecular aspects of the PAP in women with a scar on the uterus and UCTD.
Methods: 10 removed uteri and placenta from women with different variants of the PAP, the postpartum period of which was complicated by bleeding or endometritis: 7 patients with UCTD and 3 - without. Morphological and immunohistochemical study were performed.
Results: In patients with UCTD, ingrowth of the chorionic villi was found in the area of the old uterine scar (n=7), in which mucoid swelling and fibrinoid necrosis were detected. There were 8 cases of Placenta accreta (5 cases with UCTD, 3 cases without), 2 cases of Placenta increta with UCTD. The area of the placental site in UCTD contains collagens I and III, with a slight predominance of the latter. A significant increase in the MMP-1, 2 was found in UCTD compared with the control ($p < 0.05$), while expression of TIMP-1 was reduced ($p < 0.05$). PAP in women with UCTD develops in the area of the scar formed after operation
Conclusion: In women with UCTD uterine scar tissue has abnormal ratio of collagens, MMPs and TIMP, that facilitates the invasion of the chorionic villi into the scar, resulting in the latter becoming and the source of bleeding and endometritis.

PS-02-008

A clinicopathologic study of mesonephric-like adenocarcinoma of the female genital tract

M. Fukunaga[1]
[1] Department of Pathology, Shin-yurigaoka General Hospital, Japan

Background & Objectives: Mesonephric adenocarcinomas (MAs) are rare neoplasms of the female genital tract that primarily arise in the cervix, and are defined as adenocarcinomas arising from mesonephric remnants based on the WHO classification. Adenocarcinomas of the uterine corpus and ovary characterised by morphological and immunophenotypical similarities with MA have been reported, and these tumours have been termed mesonephric-like adenocarcinoma (MLA).
Object is to clarify histologic diversity, histogenesis and biologic behaviour of MLAs of the ovary and endometrium.
Methods: Nine cases of MLA were clinicopathologically and immunohistochemically studied.
Results: There were five adenocarcinomas (ACs) and four carcinosarcomatous ACs (CSACs). ACs were found in the endometrium (2) and ovary (3). CSACs involved the ovary (2) and the endometrium (2). ACs exhibited glandular, retiform, and solid proliferations. Two ACs and one CSACS had mixed serous and endometrioid adenocarcinomas. One ovarian AC was associated with endometriosis. All tumours were

positive for CD10 and calretinin. Three patients with CSAC died of disease. No patients with AC died of disease

Conclusion: Diverse histological patterns were observed and no mesonephric remnants were found any case. Some MLAs may be considered as Mullerian adenocarcinomas with mesonephric differentiation. The possibility of MLA should be considered when encountering an unusual-appearing carcinoma, malignant mixed tumour, or even endometrioid adenocarcinoma. CSACs may be more aggressive than ACs.

PS-02-009

Malignant struma ovarii: a case of columnar variant of papillary thyroid carcinoma

A. González Antelo[1], K. Romero Figueroa[1], C. Sánchez Cendra[2], V. Peiro Valgañón[3], J. Calzas Rodríguez[2], R. Cardozo Rocabado[1], î Castaño Pascual[1], N. Cozar García[1]

[1] Department of Pathology, University Hospital of Fuenlabrada, Madrid, Spain, [2] Department of Medical Oncology, University Hospital of Fuenlabrada, Madrid, Spain, [3] Department of Nuclear Medicine, University Hospital of Fuenlabrada, Madrid, Spain

Background & Objectives: Malignant struma ovarii is an infrequent and challenging diagnosis. We submit a case of a columnar cell variant of papillary thyroid carcinoma in struma ovarii, previously diagnosed as endometrial adenocarcinoma.

Methods: A 57-year old patient presented with a history of hypermenorrhea. Echography images revealed a 4-cm benign cyst in her right ovary. She was lost to follow-up and, 10 years later, the lesion showed hyperrefringence, left ovary was affected and there were multiple adherences to the uterus and rectum. A hysterectomy and bilateral adnexectomy were decided.

Results: We received a left ovary with a ruptured capsule, occupied by a white, cystic lesion with necrotic and solid areas, and a fragmented right mass. An infiltrative hypercellular neoplasm with pseudoglandular pattern and some groups of fine papillae were found. It exhibited a pseudostratified epithelium formed by cells of little cytoplasm, elongated and hyperchromatic nuclei and focal subnuclear vacuolization. These findings were interpreted as an endometrial adenocarcinoma, endometrioid type. Despite adjuvant chemotherapy, the patient returned with peritoneal carcinomatosis and cytoreductive surgery was performed. The biopsy revealed a focus of classic papillary carcinoma. As both previous and current lesions tested positive for TTF-1, PAX-8 and thyroglobulin, our final diagnosis was a columnar cell variant of papillary thyroid carcinoma in struma ovarii. No synchronic tumours were found and the carcinoma was resistant to radioactive iodine therapy.

Conclusion: To the best of our knowledge, this is the first reported case of a columnar variant of papillary thyroid carcinoma in struma ovarii, a neoplasia whose early diagnosis is extremely difficult.

PS-02-013

TROP2 expression in endometrioid type endometrial carcinoma and correlation with the prognostic factors

O. Ilhan Celik[1], S.Y. Celik[1]

[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Endometrioid type (EEC) endometrial carcinoma is the most common malignancy of the female genital tract in developed countries. The incidence and the death rates have been increasing in the recent decades. It is known that the prognosis of EEC greatly depends on the grade and the stage and has good prognosis when diagnosed in early stages. However in some patients the disease recur in a short time after the treatment. In these recurrent diseases the prognosis worsen and the survivals shorten. So it is important to predict the patients at the time of initial diagnosis who will have worse prognosis in order to choose the appropriate treatment; so many studies have been maintaining to detect new prognostic markers like ours.

Methods: 102 females who underwent histerectomy with bilateral salpingo-oophorectomy and diagnosed as EEC histopathologically were evaluated retrospectively. TROP2, a transmembrane receptor glycoprotein coded by the tumour-associated calcium signal transducer 2 (TACSTD2) gene was applied to the tumoural sections immunohistochemically and the staining rates were compared with the current prognostic factors.

Results: TROP2 overexpression was statistically correlated with high nuclear and architectural grades, deep myometrial invasion, more lymph node metastasis and the presence of vascular invasion($p<0.05$).

Conclusion: This study exposed that TROP2 overexpression is correlated with worse prognosis as the parameters studied are classic prognostic parameters. TROP2 overexpression has been considered in various types of cancers including thyroidal, biliary, oral, pancreatic, laryngeal, nasopharyngeal, ovarian, gastric cancers, breast, lung, bladder, prostate, gallbladder cancer.

PS-02-014

Tumour budding in cervical carcinoma: associations with some clinical and pathological factors

T. Ivković-Kapicl[1], N. Stanulović[1], A. Mandić[1], Z. Nikin[1]

[1] Oncology Institute of Vojvodina, Serbia

Background & Objectives: Tumour budding is recognized as an important independent prognostic factor in colorectal carcinoma. The aim of this was to evaluate the grade of tumour budding in patients with cervical carcinomas and any associations with other clinical and pathological features

Methods: We observed pathohistological data of 91 patients (mean age: 53,8 years), who underwent radical hysterectomy and pelvic lymphatic dissection in the Oncology Institute of Vojvodina, between January 2010 and December 2018.

Results: 84 (85,07%) patients were diagnosed with squamous, 5 (13,43%) with adeno- and 2 (1,49) % with adenosquamous histological type of cervical carcinoma. According to tumour histological grade, patients were divided in 3 categories: G1 (15,3%), G2 (62,6%) and G3 (21,9%). Average diameter of the tumour was 25mm (81,6%< 4cm and 18,4% > 4cm). Metastasis in lymph nodes were present in 30 (32,9%) cases. Tumour budding was evaluated in a invasive front of the tumour. Based on the number of bud counts/10 HPF, 3 groups were formed: 1- no budding (35,1%), 2- less than 15 buds (32,9%), and 3- more than 15 buds (37,3%). We determined positive correlation between tumour budding grade and histological grade of the tumour ($p=0,04$), and also the diameter of the tumour ($p=0,05$). Futhermore, we obsereved presence of lymphovascular and perineural invasion and determined significant correlation between tumour bud count and those parameters ($p=0,02$).

Conclusion: As a quantitative measure of cancer cell dissociation, tumour budding is associated with established poor prognostic factors in cervical carcinoma and therefore sholud be considered as one of them.

PS-02-015

Power of cytology in women with HPV 16 or 18 positivity: is direct referral to colposcopy sufficient?

K.E. Kaçar[1], I.E. Seven[1], F. Eren[1]

[1] Marmara University, Turkey

Background & Objectives: The positivity of HPV 16 or 18 in women is associated with increased risk of cervical intraepithelial lesion and malignancy compared to other HPV types. In primary hrHPV screening guidelines, referral to direct colposcopy is recommeded for women with HPV 16 or 18 positive test results.

The aim of this study is to determine the correlation between the results of cervical cytology and colposcopic biopsy applied to HPV 16 or 18 positive women.
Methods: Women who were screened by both hrHPV and cervical cytology between January 2014 -December 2018 were evaluated. Among them, HPV 16 and 18 positive 101 patients who underwent colposcopy were included in the study.
Results: The cytology results of 48 of 101 women were NILM (negative for intraepithelial lesions or malignancies), 3 of them were inadequate. Although colposcopic biopsy results of 38 (79%) of them were in correlation with cytology, in 10 (21%) of them a cervical pathology was diagnosed [CIN1 (n:5), CIN2 or CIN3 (n: 4) and CIN can not be graded due to inadequate biopsy (n:1)]. Cytology slides of these 10 cases were re-evaluated. Interpretation error was detected in 4 of them and they were upgraded to ASC-US, ASC-H or SIL category. As a result, 6 (5.9%) patients would be misdiagnosed if they would have evaluated with smear only. 50 of 101 women had positive cytology results (ASC-US, LSIL, ASC-H or HSIL). Colposcopic biopsy diagnosis of 11 (22%) women were discordant with cytology and reported as non-neoplastic. The cytology results of these cases were ASC-US in (n:4), LSIL (n:3), ASC-H (n:2) and HSIL (n:2). Both the cytology and biopsy slides were re-evaluated and the results were confirmed. As a result, 11 (10.9 %) patients would be misdiagnosed if they would have evaluated with colposcopic biopsy only.
Conclusion: Cervical cancer screening methods are one of the few screening methods that are thought to reduce the incidence and mortality of invasive cancer and have proven effective in this respect. Therefore, it is important to perform this screening with the most appropriate method. According to the results of our study, colposcopic biopsy alone have a higher rate of missing a cervical pathology when compared to cytology alone. Therefore in women with HPV 16 or 18 positivity, cytology screening should not be ommitted before referral to colposcopy.

PS-02-016

Protein expression of KISS1 and KISS1R in human ovary in different stages of ontogenesis

A. Drobintseva[1,2], J. Krylova[1,3], V. Polyakova[4], I. Kvetnoy[4]
[1] D.O. Ott. Research Institute of Obstetrics, Gynaecology and Reproductology, Russia, [2] St. Petersburg State Paediatric Medical University, Russia, [3] Pavlov First Saint Petersburg State Medical University, Russia, [4] Ott`s Institute of Obstetrics, Gynaecology and Reproductology, Russia

Background & Objectives: Kisspeptins regulate the hypothalamic-pituitary-gonadal axis, the most important function of them is to trigger the onset of puberty. Studies of kisspetins expression in ovarian tissue are most often devoted to the reproductive period, but there is no data on what time of prenatal development the KISS1/KISS1R system begins and finish functioning. Aim. To investigation of the protein expression of kisspeptin and its receptor in human ovarian tissue at different stages of ontogenesis.
Methods: The material for the study was archival autopsy samples of ovaries from 10 foetuses (22-42 weeks), 2- children 1–10 years old (n=5), 3- children 11–15 years old (n=5), 4 - reproductive age 19-40 years old (n=23), 5 - premenopausal women 46-55 years old (n=11), 6- postmenopausal women 56-82 years old (n= 9). For IHC staining were used antibodies to Kiss1 (1:150, Abcam), Kiss1R (1:350, Abcam).
Results: The KISS1/KISS1R system begins to function during foetal development, and as early as the 22nd week of gestation, a positive reaction was recorded in the ovarian tissue. At reproductive age, the expression of kisspeptins remains at a consistently high level, during menopause, the expression of kisspeptins in the ovaries reaches its peak, which may be due to a compensatory mechanism for reducing the synthesis of ovarian estrogen. In postmenopausal period minimum values were fixed.
Conclusion: Study ascertain the expression of kisspeptin, its receptor in ontogenesis of human ovary.

PS-02-017

Expression of TMC6 protein in ovarian carcinomas predicts patient's response to chemotherapy

M. Manai[1], R. Doghri[2], G. Sahraoui[3], P. Finetti[4], M. Manai[5], F. Bertucci[4], K. Mrad[2], M. Driss[6], L. Charfi[2]
[1] Institute Salah Azaiez, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia, [3] Institute Salah Azaiez, Tunisia, [4] Institute Paoli Calmettes, France, [5] Facultè des Sciences de Tunis, Tunisia, [6] Department of Pathology, Salah Azaïez Institute, Tunisia

Background & Objectives: Ovarian Carcinoma (OC) is the most lethal gynaecological cancer. Identification of new therapeutic targets is crucial. Transmembrane channel like 6 (TMC6) expression found to be implicated in cancer aggressiveness.
Methods: We measured TMC6 protein expression in normal ovarian and OC samples and searched for correlations with clinicopathological features. TMC6 status was evaluated by immunohistochemistry in 50 tumour samples and 20 normal ovarian samples. We compared TMC6 expression in normal versus cancer samples and with clinicopathological features.
Results: In tumour samples, the staining was observed mainly in epithelial cells and to a lesser degree in stroma cells (p=1.27E-02, Fisher's exact test). TMC6 was overexpressed in 66% of OC samples *versus* 26% in normal samples (p=1.40E-07, Fisher's exact test). TMC6 expression was correlated to the menopausal status (p=4.20E-02, Fisher's exact test) and to sensibility to chemotherapy (p=3.31E-03, Fisher's exact test).
Conclusion: Epithelial TMC6 overexpression in tumours might contribute to a good response to chemotherapy. TMC6 can represent a potential therapeutic target for OC to improve the response to chemotherapy.

PS-02-019

Carboxypeptidase-M as a novel marker of endometrial cancer

B. Nagy[1]
[1] University of Szeged, Department of Pathology, Hungary

Background & Objectives: The substantial morphological overlapping between endocervical and endometrial cancers is a well-known daily diagnostic issue. With routine tissue sampling the H&E based morphological findings rarely enough to make a proper diagnosis. Therapeutic approaches necessitate attempts to distinguish these two very similar tumours of the uterus. Immunohistochemistry profiling is based on Vimentin, CEA, p16 and hormone receptor positivity. Using panel of reactions tumours usually identifiable, but there are cases that remain equivocal. An emerging need of a sensitive and/or specific marker is undisputable.
Methods: 50 consecutive tissue samples of curettage and hysterectomy specimens were examined. Epithelial cancer's immunohistochemical pattern of Vimentin, CEA, progesterone receptor, p16 and Carboxypeptidase M (CPM) was investigated. High throughput method of tissue microarray was used. Observation of the expression pattern and strength were registered.
Results: Endometrial and endocervical cancers express wide range of progesterone receptor and p16. Vimentin is a sensitive but not specific marker of endometrial cancer, while CEA suggests endocervical origin. Frank membranous expression of CPM was detected only in endometrial cancers, and all endometrial cancer expressed CPM, respectively.
Conclusion: Strong membranous Carboxypeptidase-M expression is a valuable immunohistochemical marker of epithelial endometrial cancer independently from the grade or morphological type. It is also a reliable marker to differentiate endometrial and endocervical cancers.

PS-02-020

Histoprognostic factors predicting lymph node metastasis in endometrial cancer

R. Narjess[1], N. Boujelbene[2], M. Driss[3], L. Charfi[2], H. Arbi[3], K. Mrad[2], R. Doghri[4]

[1] Institute of carcinology Salah Azaiz Tunis, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia, [3] Department of Pathology, Salah Azaïez Institute, Tunisia, [4] Department of Pathology, Salah Azaïez Institute, Tunis, Tunisia

Background & Objectives: Endometrial cancer (EC) is the most common malignancy of the female reproductive tract. Lymph node metastasis (LNM) is one of the most important prognostic factors for EC. We aimed to evaluate the value of pathological characteristics in predicting the risk of LNM in women with EC.

Methods: A single centre retrospective analysis was conducted in patients with EC who underwent systematic lymphadenectomy. Clinicopathologic data including age, type of surgical procedure, tumour histotype, tumour size, grade, count of lymph nodes removed, depth of myometrial invasion, cervical involvement and LN involvement were extracted from patient Institutional database. Chi-square and Fisher's exact tests were used for univariate analyses when appropriate. Variables with a p value <0.05 in the univariate analysis were included into a multivariate logistic regression analysis.

Results: A total of 68 patients were included. The median age was 62 years (range from 38 to 81 years). In univariate analysis, tumour size ≥ 50mm, non-endometrioid histologic type, presence of cervical involvement and lymphovascular invasion were found associated with LNM. However, lymphovascular invasion and histologic type were the only independent variable that predict LNM in multivariate analysis (p=0.01 and <0.0001 respectively). Deep (≥ 50%) myometrial invasion, grade 2-3 and total lymph nodes removed were not associated with LNM.

Conclusion: The current study demonstrates that lymphovascular invasion and non-endometrioid histologic type in EC increases the probability of LNM.

PS-02-021

TLR8 expression in placental samples in cases of preeclampsia and in intrauterine foetus growth restriction

N. Nizyaeva[1], E.Y. Amiraslsnov[1], N.A. Lomova[1], N.A. Savelyeva[1], M.N. Nagovitsyna[1], A.I. Shchegolev[1]

[1] V.I.Kulakov National Research Center for Obstetrics, Gynaecology and Perinatology of Ministry of Healthcare of the Russian Federation, Moscow, Russia

Background & Objectives: was to study TLR8 in placenta samples in cases of preeclampsia (PE) and intrauterine growth restriction (IUGR).

Methods: We performed histological (hem&eosin) and immunohistochemistry studies on the paraffin-embedded slices of placenta, taking after cesarean section, 26-39 gestation weeks, using TLR8 primary polyclonal antibodies (1:250; GenTex,USA). Groups with PE included 15 women with severe PE and 8–with moderate PE, 6 samples–with PE complicated IUGR. Control groups included 10 women with full-term uncomplicated pregnancy (UP). The intensity of immunohistochemical reaction was estimated by means of microscope imaging software NIS-Elements.

Results: TlR8 demonstrated more intensive expression in syncytiotrophoblast in cases of severe PE complicated by IUGR (70.97+10.7 and 76.32+21.5, respectively;p<0,01). In samples of full-term pregnancy, membrane and cytoplasmic staining was minimal (18.39+8.3 and 15.09+5.9, respectively; p<0,01). However, in severe preeclampsia without IUGR in syncytiotrophoblast there was decreased membrane staining. At the same time, with moderate PE, membrane staining was higher compared to cytoplasmic (43.4+15.8 and 32.03+ 16.2), than in UP (18,39+8,3 и 15,09+5,9, respectively; p<0.01). Increased TLR8 expression in placental samples in severe preeclampsia with or without IUGR were peculiar to cytoplasmic staining, while moderate preeclampsia and full-term pregnancy was characterised by membrane staining predominantly. It can be assumed severity of preeclampsia correlated to loss of TLR8 membrane expression of syncytiotrophoblast.

Conclusion: Disturbances of TLR8 in placental tissue may be an important role in the genesis of preeclampsia.

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PS-02-022

The placental and umbilical cord lesions in the genesis of foetal hypoxia

N. Nizyaeva[1], A.M. Prikhodko[1], A.V. Evgrafova[1], O.V. Tysyachny[1], D.A. Shuklina[1], O.R. Baev[1]

[1] V.I.Kulakov National Research Center for Obstetrics, Gynaecology and Perinatology of Ministry of Healthcare of the Russian Federation, Moscow, Russia

Background & Objectives: Was to evaluate the placental villous tree and umbilical cord lesions in the genesis of foetal hypoxia.

Methods: Two groups women with foetal hypoxia consisted of 26 (PH>7.05 - 7.15 (group I) and 32 patients (PH<7.0 (group II). Control group included 10 (PH > 7.15) women with uncomplicated full-term pregnancy (UP) and labor. Histological examination (hem&eosin) were performed on the paraffin-embedded placenta slices, received after cesarean section at 38-40 gestation weeks.

Results: Changes in the umbilical cord included: thinning umbilical cord, absolute shortness length, marginal or membrane attachment, decreased or increased spiral turns (coiling/length index less than 0,1, more than 0,45, respectively); sludges and microthrombi in umbilical blood vessels, hemorrhages & hematomas of Wharton's jelly. In the groups of foetal hypoxia these changes were present significantly more often than in UP(p<0.05). These features were the result of the acute hypoxia predominantly. In placental samples of group II, villous tree lesions reflected specific morphological sings for chronic hypoxia: old infarctions of the villous tree, increased number of syncytial knots, vascular branching angiogenesis, fibrosis of the villous stroma(p<0.05). In group I villous tree features were similar to UP.

Conclusion: According to FSL data revealed in the group of foetal hypoxia (PH<7.0) umbilical cord changes were associated with blood supply disturbances leading to acute hypoxia. The significant umbilical cord and villus tree lesions were observed in severe hypoxia group I (PH>7.05 - 7.15), interpreted as the combination of acute and chronic hypoxia manifestations.

PS-02-023

Intraoperative Pathologic Ultrastaging of Sentinel Lymph Node (InSLNpU) in endometrial carcinoma. Study on 67 patients

A. Pesci[1], G. Bogina[1], M. Ceccaroni[2], E. Munari[1], L. Bortesi[1], G. Querzoli[1], G. Zamboni[3]

[1] Pathology-IRCCS Ospedale Sacro Cuore-Don Calabria, Italy, [2] Gynaecology-IRCCS Ospedale Sacro Cuore- Don Calabria, Italy, [3] Pathology-IRCCS Ospedale Sacro Cuore-Don Calabria, Università di Verona, Italy

Background & Objectives: Sentinel lymph node (SLN) has been introduced to obtain information about the LN status in endometrial carcinoma (EC) since systemic lymphadenectomy (SLAD) is still controversial due to morbidity and insignificant survival effect.

Our aim was to evaluate the accuracy and feasibility of intraoperative pathologic ultrastaging of sentinel LN (InSLNpU) in a cohort of pts with EC.

Methods: 72 of the 109 EC diagnosed in the period 2016-2018 underwent SLN procedure (67 Endometrioid: 6G3, 7G2, 54G1, 2Clear Cell, 2Serous, 1Mixed). 67/72 cases had one or more LNS (range 1-8); in 5 cases no SLN was recognized. SLNs were bidissected, 1H&E and 1

unstained slide per level, 5 levels at 150 μm apart. Positive-SLNs were classified as: micromets (μ:0.2-2 mm) and macromets (m: > 2 mm). Positive-SLNs, on frozen, had 1 H&E for permanent. Negative-SLNs had 1 H&E, Keratin ICH and 1 unstained slide per 3 levels at 200 μm apart for permanent.
Results: Only one case had positive-InSLNpU (m); 66/67 was negative. The permanent sections confirmed the diagnosis in 62/66 cases (93.9%): 1 m, and 3 low-volume LN metastasis (1μ, and 2 ITC). 23/67 pts examined with InSLNpU had SLAD; 2 pts presented with mets, one with positive-InSLNpU and 1 negative-InSLNpU. Among the 21 cases SLAD negative, 2 were positive on permanent SLNpU (1 ITC, 1 μ).
Conclusion: InSLNpU is reliable and correlate with final pathologic assessment. Only 1/66 negative-InSLNpU showed metastasis (m). 3/66 showed low-volume LN metastasis, whose clinical significance is still controversial. InSLNpU could be applied on routine when necessary.

PS-02-024
CD8 T lymphocytes and FOXP3 T regulatory lymphocytes in patients with high-grade squamous intraepithelial lesions
M. Pukis[1,2], A. Mitildzans[3,4], D. Rezeberga[4,5], S. Isajevs[2,1]
[1] Centre of Pathology, Riga East University Hospital, Latvia, [2] Department of Pathology, University of Latvia, Faculty of Medicine, Riga, Latvia, [3] Department of Oncology, Riga East University Hospital, Latvia, [4] Department of Gynaecology and Obstetrics, Riga Stradins University, Latvia, [5] Department of Gynaecology, Riga East University Hospital, Latvia

Background & Objectives: Regulatory (FOXP3+) T cells (Tregs) comprise a subpopulation of CD4+ T cells that suppress autoreactive immune cells, thereby protecting organs and tissues from autoimmunity. Novel therapeutic strategies for cervical cancer and squamous intraepithelial lesions (SIL) focus on immune-modulatory and cancer vaccination approaches.
The aim of this study was to analyse the role of T regulatory cells (Tregs), CD4 and CD8 T lymphocytes in low and high grade squamous intraepithelial lesions (LSIL and HSIL).
Methods: 62 patients were enrolled in the study in Riga East University Hospital. Each patient had undergone a biopsy or electroexcision of the cervix. Immunostaining for CD4, CD8 and FOXP3 was performed on tissue samples of normal (n=10) and LSIL (n=32) and HSIL (20) lesions.
Results: Obtained results showed that patients the numbers of CD4 T-lymphocytes did not differed between the patients with LSIL and HSIL. However, patients with HSIL had significant CD8 T-lymphocytes upregulation compared to patients with LSIL (16± 4 vs. 8 ± 2 cells/mm^2, p = 0.001). In addition patients with HSIL with concomitant epithelial koilocytosis demonstrated increased numbers of FOXP3 positive T-lymphocytes compared to patients with LSIL (12± 6 vs. 6 ± 2 cells/mm^2, p = 0.02).
Conclusion: Upregulation of T regulatory lymphocytes in patients with HSIL suggested the pivotal role of Tregs for counteracting the host immune response for the progression from LSIL to HSIL. Prime targets for new immune-based non-invasive therapies for the HSIL treatment could be beneficial.

PS-02-025
Prognostic value of histopathological response in BRCA1-associated and sporadic high-grade serous ovarian carcinomas
G. Raskin[1], A. Ivantsov[2], T. Gorodnova[2], E. Imyanitov[2], A. Sokolenko[2]
[1] Academic A.M. Granov Scientific Center for Radiology and Surgical Technology, Russia, [2] N.N. Petrov Institute of Oncology, Russia

Background & Objectives: BRCA1-associated high-grade serous ovarian carcinomas (HGSOC) are characterised by a pronounced response to platinum-based treatment. We compared the prognostic value of histopathological response in the ovary and omental metastases in advanced stage HGSOC patients with and without BRCA1 mutations treated by platinum-containing neoadjuvant chemotherapy (NACT).
Methods: 85 women (31 BRCA1 carriers and 54 sporadic cases) with HGSOC, who underwent optimal interval debulking and had follow-up data, were included in the study. Histopathological chemotherapy response score (CRS) was assessed according to [Böhm et al., 2015]. Omental lesions were evaluated in 67 cases (22 BRCA1-associated and 45 sporadic tumours) where the initial presence of omental metastases was confirmed. Disease-free interval (DFI) was defined as the time between the end of adjuvant therapy and first relapse.
Results: BRCA1-associated HGSOC were characterised by a higher frequency of CRS2-3 as compared to sporadic cases [25/31 (81%) vs. 31/54 (57%), p = 0.03]. CRS in ovary did not associate with the DFI either in BRCA1-induced or in sporadic cases. CRS3 in omentum predicted longer DFI in BRCA1-associated but not in BRCA1-wild-type HGSOC [p = 0.03 and p = 0.08 for BRCA1 carriers and sporadic cases, respectively; Kruskal-Wallis test].
Conclusion: Prognostic value of CRS may differ between hereditary and sporadic HGSOC.

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PS-02-026
Clinicopathologic features of mismatch repair (MMR) protein-deficient endometrial carcinomas, tested by immunohistochemistry: a single Institutional experience
B. Rekhi[1], S. Menon[1], K. Deodhar[1]
[1] Department of Pathology, Tata Memorial Hospital, Mumbai, India

Background & Objectives: Few studies have described certain clinicopathologic features in mismatch repair protein (MMR)-deficient endometrial carcinomas, including none from our country.
Methods: Based on requisitions and certain clinicopathologic features, 44 cases of endometrial carcinomas were tested for MMR proteins, by immunohistochemistry, out of which 23 cases were found to be MMR-deficient.
Results: Age-range was 14-65 years(median=55); average tumour size was 5.3cm and lower uterine segment (LUS) involvement in 9/15 cases (60%). Histopathologically, all cases were endometrioid adenocarcinomas, with FIGO grade 2 (n=6) and 3 (n=17), displaying de-differentiated, undifferentiated and lymphoepithelioma (LE)-like patterns, in certain cases. Tumour infiltration ≥ half of myometrium was seen in 14/19 cases (73.6%); lymphovascular emboli in 9/18 cases (50%); and nodal metastasis in 4/9 cases. Immunohistochemically, tumour cells showed loss of MLH1 and PMS2 (n=19) and MSH2 and MSH6 (n=4); ER positivity (7/23) (30.4%) and wild-type p53 staining (10/12) (83.3%).
Conclusion: Certain clinicopathologic features are suggestive for MMR-deficient endometrial carcinomas, including large-sized tumours, involving LUS in ≤ 55-year-old patients, harboring high-grade, infiltrative EMACs, including de-differentiated, undifferentiated and LE-like patterns; showing less relatively frequent ER expression and wild-type p53 immunostaining. This constitutes the first report on these tumours from our country.

PS-02-027
Shotgun lipidomics for differential diagnosis of HPV-associated cervix transformation
V. Sergeeva[1], N. Starodubtseva[2], V. Chagovets[2], M. Nekrasova[2], A. Tokareva[3,4], A. Kononikhin[3,1], N. Nazarova[2], V. Frankevich[2]
[1] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia, [2] V.I. Kulakov National Medical Research Center of Obstetrics, Gynaecology and Perinatology, Russia, [3] V.L. Talrose Institute for Energy Problems of Chemical Physics, Russian Academy of Sciences, Russia, [4] Moscow Institute of Physics and Technology, Russia

Background & Objectives: Cervical cancer keeps one of the leading positions in female mortality causes. It is preceded by cervical intraepithelial neoplasia (low grade squamous intraepithelial lesion, LSIL and high-grade squamous intraepithelial lesion, HSIL). Lipids are potential indicators of pathological processes in a tissue, which is confirmed for such hyperproliferative disorders as breast cancer, glyoma, lung cancer, endometriosis, etc. The objective of this study was to differentiate stages of HPV-associated cervix epithelium transformation using shotgun lipidomics analysis of tissue Folch extracts.
Methods: Tissue samples from 74 HPV-positive women with cervicitis (n = 20), LSIL (n = 20), HSIL (n = 20) and cervical cancer (n = 15) were obtained along with a biopsy for histology. Cervical epithelial tissue lipidome was studied by shotgun label-free semi-quantitative approach based on ESI-MS/MS method with subsequent orthogonal projections to latent structures discriminant analysis (OPLS-DA) to build a classification model. Shotgun lipidomics allows obtaining molecular profile of a sample within few minutes.
Results: OPLS-DA of lipidomic data resulted in a statistical model differentiating benign, precancerous and malignant processes in the cervix. A potential diagnostic features for the early differentiation of HSIL and cervical cancer, represented by phosphatidylcholines (PC 32:0, PC 34:1, PC 36:2), phosphatidylethanolamines (PE 38:4, PE 40:5) and plasmalogens (PC O-16:3, PC O-38:5), were determined. Previously, these lipids were associated with suppression of apoptosis, stimulation of proliferation and impaired cell metabolism.
Conclusion: A diagnostic and potentially prognostic method for rapid classification of HPV-associated cervix transformation stage was proposed. This method can be used for early, rapid differential diagnostics of the neoplastic process severity as a supplement to the histological examination (analysis time is about 25 minutes).

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PS-02-028

Assessment of the relation between mismatch repair protein status and histopathologic parameters in resection specimens of endometrial cancers

T. Soylemez[1], G. Kir[1], R.B. Girgin[1], S.R. Dur[2], I. Tosun[3], H. Ankarali[4], A. Karateke[5]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, School of Medicine, Turkey, [3] Umraniye Training and Research Hospital, Department of Pathology, Turkey, [4] Istanbul Medeniyet University, Department of Statistics, Turkey, [5] Istanbul Medeniyet University, Department of Obstetrics & Gynaecology, Turkey

Background & Objectives: The aim of the study was to analyse the correlation between DNA mismatch repair proteins (MMR) status and clinicopathological characteristics of endometrial cancers (EC).
Methods: A retrospective study was carried out in 131patients, who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy with/without regional lymphadenectomy from 2016 to 2018. For each case we evaluated:tumour histology, tumour grade, tumour-infiltrating lymphocytes, lymphatic invasion, vascular invasion, perineural invasion, cervical involvement, MELF pattern of invasion, myometrium invasion, tumour size, lymph node metastases and tumour necrosis. Immunohistochemical evaluation of the MMR proteins (MLH1, PMS2, MSH2, MSH6) were performed.
Results: 44 out of 131 (33%) cases showed immunohistochemical alteration of MMR proteins: 38 (29%) cases lost MLH1&PMS2, 1 (0,7%) case lost MLH1, 3 (2%) cases lost MSH2&MSH6, 1(0,7%) case lost MSH6, 1 (0,7%) case lost PMS2. On univariate analysis, we observed significant association between MMR protein deficiency status and higher tumour grade (p=0.039). Also, there was a marginal significance between MMR status and presence of lymphatic invasion (p=0.060). Binary logistic regression analysis revealed that higher tumour grade and presence of lymphatic invasion were independently correlated with MMR protein deficiency.
Conclusion: In our study, overall 33% of cases exhibited loss of MMR proteins and most were MLH1&PMS2 (86%) losses. Matthew et al. (USA) showed that loss of MSH6 protein expression was the commonest MMR defect in EC, whereas in our study we showed that the incidence of loss of MSH6 protein expression was 9%.

PS-02-029

Clinicopathologic association and prognostic value of MELF pattern in invasive endocervical adenocarcinoma (ECAs)

S. Stolnicu[1], L. Hoang[2], S. Segura[3], M. Boros[4], A. Pesci[5], S. Aviel-Ronen[6], T. Kiyokawa[7], I. Alvarado-Cabrero[8], K. Park[9], E. Oliva[10], R.A. Soslow[11]
[1] Department of Pathology, UMFST, Targu Mures, Romania, [2] Department of Pathology, Vancouver General Hospital, Canada, [3] Memorial Sloan Kettering Cancer Center, New York, USA, [4] Department of Pathology, University of Medicine and Pharmacy, Oradea, Romania, [5] Pathology-IRCCS Ospedale Sacro Cuore-Don Calabria, Italy, [6] Department of Pathology, Sheba Medical Center, Tel-Hashomer, Israel, [7] Department of Pathology, the Jikei University School of Medicine, Japan, [8] Department of Pathology, Hospital de Oncología Mexico City, Mexico, [9] Department of Pathology, Memorial Sloane Kettering Cancer Center, New York City, USA, [10] Department of Pathology, Massachusetts General Hospital, USA, [11] Department of Pathology, Memorial Sloan Kettering Cancer Center, USA

Background & Objectives: As Anti-Her-2 containing therapy has become an important treatment for Her-2 positive breast cancer. The ratio of human epidermal growth factor receptor 2 (HER2) to CEP17 by fluorescent in situ hybridization (FISH) with the centromeric probe CEP17 is evaluated to determine HER2 gene status as a standardised method. But during the interpretation of FISH, the result may be critical in tumours with chromosome 17 polysomy defined as increased copy number of chromosome enumeration prob (CEP>2,5). The purpose of our study was to highlight the clinocopathologics significant of chromosome 17 polysomy.
Methods: This is a retrospective analysis of a large series of 203 cases of primary invasive breast carcinomas with equivocal HER2 IHC staining (IHC HER2 2+) whom her-2 fluorescence in situ results and clinicopathological data were available from 2012 to 2018 at the Department of Pathology of Hassan II University Hospital of Fes, in which we identify 15 cases of chromosome 17 polysomy.
Results: As results, among 203 cases of invasive breast carcinoma analysed by FISH, 20% of the cases showed HER-2 gene amplification. A total of 15 (7,5%) cases showed the presence of polysomy 17. Absence of polysomy 17 was seen in the remaining 188 cases. The two groups polysomy and non-polysomy 17 were classified according to the HER2 gene amplification status. Among 15 cases, 11 (73,3%) were HER-2 non-amplified, 4 (25,7%) were HER-2 amplified. Among 188 non polysomy cases, 152 (80%) were HER-2 non amplified, 36 (20%) were HER-2 amplified. Polysomy 17 showed a significant association with poor pathological parameters including low age (under 50ans p=0,06), low mitotic score (p=0,05), high nuclear ploemorphism score (p=0,03) high histological grade (p=0,03), presence of node metastasis (p=0,04), not otherwise specified histological type (p=0,009). Showed more often in positive hormone receptors status and high KI-67 proliferation index. Similarly, in HER-2 non amplified gene, polysomy 17 showed an association with almost the same aggressive histological variable.
Conclusion: In our study, we identified 7,35% cases of polysomy 17. We revealed that the polysomy 17 can serve as a poor prognostic marker in invasive breast cancer. We also highlight the prognostic value of polysomy 17 in luminalB/HER-2 negative.

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PS-02-030

Microsatellite instabillity, a prognostic factor for early stage endometrial cancers

G.E. Tasar Kapakli[1], S. Lacin[2], A. Usubutun[3], Z. Arik[4], Y. Karakas[2], D. Yuce[5], M.C. Salman[6], A. Kars[2]

[1] Department of Medical Pathology, Hacettepe University Faculty of Medicine, Turkey, [2] Department of Medical Oncology, Hacettepe University Cancer Institute, Turkey, [3] Department of Medical Pathology, Hacettepe University Faculty of Medicine, Turkey, [4] Hacettepe University Institute of Oncology, Department of Medical Oncology, Turkey, [5] Hacettepe University Cancer Institute, Department of Preventive Oncology, Turkey, [6] Department of Obstetrics and Gynaecology, Hacettepe University Faculty of Medicine, Turkey

Background & Objectives: Endometrial cancer (EC) is a heterogeneous disease with diverse histological features and biological behaviour. Microsatellite instability (MSI) which occurs in cancerous tissue secondary to mismatch repair (MMR) defect of hereditary or somatic origin is a well-known feature further diversifying genetic tumour landscape. In this study, we aim to investigate the relationship between MSI and prognosis in patients with early stage EC.

Methods: The patients diagnosed with EC between 2004 and 2017 in Hacettepe University were retrospectively analysed in the study. The demographic characteristics, disease stage, menopausal status, and clinical and laboratory values were noted. Immunohistochemically MLH1, MSH2, MSH6 and PMS2 antibodies were used to detect microsatellite status within the tumour tissue samples. Peritumoural lymphocytes and tumour infiltrating lymphocytes are detected.

Results: The mean age of the 93 patients and menopause was 60.6 ± 9.8 and 49.68 ± 4.5 years, respectively. The median follow-up period was 28 (1-110) months. At the time of diagnosis, number of the patients with stage IA, IB, II, III, and IV were 5, 64, 8, 14, and 2, respectively. Forty-three patients were grade 1, 23 patients grade 2, and 27 patients were grade 3. In terms of microsatellite status, 59 patients (63.4%) were microsatellite stable (MSS) and 34 patients (36.6%) were microsatellite instable (MSI). There was no significant association between MSI and tumour stage or grade ($X^2 = 1.97$ p = 0.74 and $X^2 = 3.2$, p = 0.19, respectively). There was a significant relationship between peritumoural lymphocyte infiltration rate (pTIL) and MSI. PTIL ratio was higher in tumoural tissues with MSI, whereas pTIL was low in MSS tumour tissues ($X^2 = 28.6$, $p < 0.0001$). Patients with MSI tended to have poorer survival than patients with MSS irrespective of disease stage; mOS rates were 76 and 91 months, respectively (p = 0.086). However, patients with early stage disease and MSI had significantly poorer survial in comparison to patients with similar disease stage and MSS: Overall survival rates for patients with MSI and MSS were 75.8 and 94.7 months, respectively (Log-rank p = 0.048).

Conclusion: There is a limited number of studies assessing the association between MSI and clinical outcomes in EC. Our study hints at the presence of potential relationship between MSI and pognosis in patients with MSI. Similar to previous studies performed with various types of tumours we found that EC with MSI attract more immune cells to tumour microenvironments. Interestingly, patients with MSI tended to have poorer prognosis despite augmented immune-cell inftration.

PS-02-031

The effect of adjuvant chemotherapy on survival in patients with FIGO stage I high-grade serous ovarian cancer

J. van Baal[1], K. Van de Vijver[2], M. Algera[1], M. van der AA[3], G. Sonke[1], W. van Driel[1], G. Kenter[1], F. Amant[1], C. Lok[1]

[1] The Netherlands Cancer Institute, The Netherlands, [2] Ghent University Hospital, Belgium, [3] Netherlands Comprehensive Cancer Organisation (IKNL), The Netherlands

Background & Objectives: The benefit of adjuvant chemotherapy for FIGO stage I, high-grade serous ovarian cancer (HGSOC) after optimal staging procedures is a matter of debate. We investigated the effect of adjuvant chemotherapy on recurrence-free survival (RFS) and overall survival (OS) in a population-based cohort study.

Methods: Patients diagnosed in the Netherlands between 2002-2014 with FIGO stage I HGSOC who underwent surgical staging were included. Data on clinical characteristics, histopathology and survival were collected from the Netherlands Cancer Registry and Dutch Pathology Registry.

We identified 393 patients of whom 223 patients underwent optimal staging procedures. Of 223 optimally staged patients, 101 (45%) patients received adjuvant chemotherapy. Following staging and chemotherapy, 21% (21/101) of patients had recurrent disease, compared with 38% (46/122) of patients after staging without chemotherapy.

Results: Five-year RFS was 81% after staging plus chemotherapy and 59% after staging only. Median time to recurrence was 32.2 and 26.8 months, respectively. In the group of patients who underwent staging and chemotherapy, 21% had died, compared with 31% in the group of patients after staging alone. Five-year and ten-year OS were 84% and 78% after staging and adjuvant chemotherapy, whereas five-year and ten-year OS were 83% and 62% after optimal staging only (p=0.07).

Conclusion: After correction for age and FIGO stage, multivariable analyses demonstrated a significant OS benefit from adjuvant chemotherapy surgery (p=0.02). Adjuvant chemotherapy improves RFS and long-term OS in patients with FIGO stage I HGSOC after optimal staging.

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PS-02-032

The importance of BRCA mutational analysis starting from Formalin Fixed Paraffin Embedded (FFPE) tissue: the Catania experience

S. Vatrano[1], A. Pettinato[1], G. Scandurra[2], S. Lionti[1], J.M. Curduman[1], M.G. Tranchina[1], G. Scibilia[3], P. Scollo[3], F. Fraggetta[1]

[1] Pathology Unit Cannizzaro Hospital, Italy, [2] Oncology Unit Cannizzaro Hospital, Italy, [3] Gynaecology Unit Cannizzaro Hospital, Italy

Background & Objectives: To underline the importance of switch BRCA tumour testing in Ovarian cancer patients to identify simultaneously both germline and somatic pathogenic mutations with a single test, using targeted next generation sequencing (T-NGS) from Formalin Fixed Paraffin Embedded (FFPE) tissue for predictive purposes.

Methods: A total of 43 tumour samples with ovarian cancer were collected at the Cannizzaro Hospital (Catania, Italy). Upon clinical request, the BRCA1/2 genetic analysis was performed by means of T-NGS using The GeneReaderTM NGS System (GeneRead®QIAact BRCA 1/2 Panel, Qiagen). For all cases we performed on parallel the analysis starting from peripheral blood samples.

Results: All FFPE samples were sequenced successfully obtaining confident data. In many cases we performed Laser Microdissection to exclude areas which could invalidate mutational test. The genetic results obtained from tumour tissue were confirmed with that derived from correspondent blood (concordance 100%). Sixteen samples (30%) harboured deleterious mutations in the investigated genes, 12 (23%) were germline and four (7%) somatic. All but one were genetic variants previously identified and reported in the main mutational databases. Of note we obtained a composed heterozygous genotype in four cases, who harboured pathogenic mutations with therapeutic implications. The turn-around time (10 days) was in according with clinicians' request.

Conclusion: Our data underlines the importance of switching BRCA mutation analysis to somatic test in order to identify both somatic and germline deleterious mutations with clinical and therapeutical implications. The present job is one of the few which speculates about BRCA somatic study.

PS-02-033

Adult granulosa cell tumour with high-grade transformation: report of a series with FOXL2 mutation analysis

Y. Fashedemi[1], M. Coutts[2], O. Wise[3], B. Bonhomme[4], I. Soubeyran[4], S. Croce[4], W.G. McCluggage[5]

[1] Department of Cellular Pathology, Basildon University Hospital, United Kingdom, [2] Department of Pathology, Maidstone General Hospital, United Kingdom, [3] Department of Pathology, St Thomas Hospital, London, United Kingdom, [4] Department of Biopathology, Institute Bergoniè, Comprehensive Cancer Center, Bordeaux, France, [5] Department of Pathology, Belfast Health and Social Care Trust, Northern Ireland, United Kingdom

Background & Objectives: Adult granulosa cell tumour (AGCT) is a low-grade malignant neoplasm with a significant propensity for late recurrence and metastasis. Almost all AGCTs are composed of cells with bland nuclear features and even when these tumours recur or metastasise, the nuclear features are almost always low-grade. We report 5 cases of AGCT in patients aged 37 to 88 years composed of areas of typical AGCT with low-grade morphology admixed with areas of high-grade morphology, marked nuclear atypia and high mitotic activity.

Methods: The cases derived from the pathology archives of the Institutions to which the authors are affiliated together with the consultation practice of one of the authors (WGM). All available slides (haematoxylin and eosin and immunohistochemical stained) were reviewed.

Immunohistochemistry for p53, MIB1, inhibin and p16 was carried out on both the low-grade and high-grade components of the tumour in all 5 cases.

FOXL2 mutation analysis was undertaken in 4 cases.

Results: *FOXL2* mutation analysis of both the low-grade and high-grade components confirmed the presence of missense point mutation, confirming that the high-grade component represents transformation of typical AGCT rather than the coexistence of another sex cord-stromal tumour. In cases where immunohistochemistry was undertaken, there was wild-type staining of p53 in the low-grade and mutation-type expression in high-grade components; p16 was more diffusely expressed in high-grade component. Follow-up in 3 of the 4 stage IA neoplasms (6-9 months) revealed no tumour recurrence.

Conclusion: High-grade transformation is uncommon in AGCTs and given the limited follow-up in our cases, the clinical significance is uncertain. However, given that 1 of our cases was advanced stage at diagnosis and that there have been occasional case reports of aggressive behaviour in AGCTs with high-grade transformation, this may herald an aggressive clinical course.

Sunday, 8 September 2019, 09:30 - 10:30, Agora 3
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PS-03-001

Necrotising lymphadenitis might be induced by over expression of Toll-like receptor7(TLR7) caused by reduction of TLR9 transport in plasmacytoid dendritic cells (PDCs).

S. Asano[1], H. Sato[2], H. Naito[2], K. Yamazaki[1], K. Mori[1], H. Wakasa[3], H. Suzuki[4]

[1] Pathology Center/Iwaki Medical Center, Japan, [2] Oral Surgery/Iwaki Medical Center, Japan, [3] Pathology/Surgical Pathology Japan, Japan, [4] Paediatrics/Iwaki Medical Center, Japan

Background & objectives

The pathogenesis of necrotizing lymphadenitis (NEL), characterised by blastic transformation of $CD8^+$ cells and apoptosis of $CD4^+$ cells, remains obscure. With NEL, innumerable plasmacytoid dendritic cells (PDCs), produce large quantities of interferon-α (IFN-α), are observed in lymph nodes. Although functions of PDCs are already recognized as innate-immunity mediated by Toll-like receptor7 (TLR7) and TLR9, no report of the relevant literature describes a study. As described herein, we explain the role of TLR7 and TLR9 in the PDCs of NEL.

Methods: During 1989-2016, data cases of NEL were collected. Lymph node samples were fixed in 10%-formalin, in 2.5%-glutaraldehyde for electron microscopy (EM) and fixed in 95%-ethyl alcohol for imprint cytology. For immu nohistochemical analysis (IHC), formalin-fixed paraffin-embedded tissue sections, were using an automated stainer. Statistical analyses of changes of cells ($CD4^+$, $CD8^+$, $CD123^+$, $Mx1^+$, $TLR7^+$, $TLR9^+$ and $UNC93B1^+$ cells) were facilitated by image analysis software (Image J 1.48 v; NIH, USA).

Results: We examined 70 patients (M/F=24/46). The peak of onset was in the 20s. Most patients complained of painful cervical lymph nodes. Peripheral white blood cell counts, 46.6% of patients showed lower than 4,000/mm^3. Histological features included immunoblasts, PDCs, histiocytes, and macrophages, the latter with phagocytized nuclear debris derived mainly from apoptotic lymphocytes. The number of $CD8^+$, $Mx1^+$, $CD123^+$, $TLR7^+$ and $UNC93B1^+$ cells in affected lesions increased over time, but the number s of $TLR9^+$ cells did not change.

Conclusion: NEL is a systemic non-autoimmune disorder with characteristic clinical features. The pathogenesis of the disease remain obscure, but it might be associated with the imbalance between TLR7 and TLR9 of PDCs. Presumably, overexpression of TLR7 induced adaptive immunity. Results show that PDCs play an important role of in the immune response of a person when affected by the disease.

PS-03-002

Cancer stem-cell markers assessment in oropharyngeal squamous cell carcinoma: practical or not?

M. Biskup-Fruzynska[1], A. Stanek-Widera[1], T. Rutkowski[2], M. Snietura[2], A. Kopec[2], B. Nikiel[2], D. Lange[1]

[1] Tumour Pathology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center Gliwice Branch, Poland

Background & Objectives: Cancer stem cells (CSC) have been investigated in various human neoplasms and in some proved as predictive factors. The aim of the study was to analyse the expression of CSC markers in oropharyngeal squamous cell carcinomas (OPSCC) and its correlation with histopathological and clinical data.

Methods: Tissue samples from 92 OPSCC cases diagnosed and treated in our Institution from 2002 to 2018 with HPV status tested by PCR were subjected to immunohistochemical assays for CD44, ALDH1A1, CD98, Ki67 and PHH3. Markers' expression was assessed by light microscopy and correlated with patients' and tumours' characteristics and clinical outcomes.

Results: The study group comprised 64 male and 28 female patients (mean age 58,8), 53 HR-HPV(+) and 39 HR-HPV(-), 53,3% in at least AJCC stage III. Significantly higher expression of CD44 was found in HR-HPV(-) tumours ($p<0,0001$). CD44 was also the only parameter that demonstrated significant differences in overall survival between „low" and „high expressors" ($p=0,0473$). Significantly higher PHH and Ki67 counts were noted in the HR-HPV(+) group ($p=0,0118$ and $0,0049$, respectively). Lower PHH3 and Ki67 counts were identified in CD44(+) and CD98(+) tumours, respectively, which is consistent with CSC being mostly quiescent, slow-dividing cells. ALDH1A1 and CD98 expression was not found statistically significant in correlation with the evaluated features.

Conclusion: The results suggest that CSC marker CD44 might be useful in the management of OPSCC patients. The obtained data need revision after digital image analysis as human eye might be an imperfect tool for membranous and cytoplasmic staining evaluation.

PS-03-003

Metastatic angiosarcoma in the jawbone: case report and review of metastatic tumours in oral cavity in "Hospital Universitario La Paz" in the last 15 years

O. Cerezo-Aranda[1], O.B. Popescu[1], E. Ruiz-Bravo[1]
[1] Hospital Universitario La Paz, Spain

Background & Objectives: We report a case of metastatic angiosarcoma in the jawbone as first manifestation. Angiosarcoma is a high grade, malignant neoplasm of cells that demonstrate endothelial differentiation. It accounts for less than 1% of sarcomas and very few primary cases are reported in oral cavity.
Methods: We present a 53 years old male with a rapidly growing mass in vestibular gum. CT shows an insuflating mass in left jawbone extending to maxillary sinus. Biopsy of the maxillar mass is performed. On CT-PT there is an intense captation focus corresponding to a 5cm mediastinal mass that invades pericardium and aorta. There were also other masses in cervical spine, sternal manubrium and clavicula.
Results: We receive several fleshy fragments which microscopically correspond to a cellular proliferation with irregular, different sized vascular channels, lined by highly pleomorphic cells with a high amount of mitotic figures. Inmunohistochemically, cells express vimentin, CD31 and focal keratin AE1/AE3 and are negative for HHV8, SMA, desmin, CD99 and BCL2. Final diagnose is metastatic angiosarcoma, with a probable cardiac origin.
Conclusion: Metastatic angiosarcoma is a very rare tumour. Besides, the fact of metastatizing in oral cavity makes this case extremely uncommon. We made a review in our hospital for metastatic tumours in oral cavity in the last 15 years with a result of 10. All of them, except the present case were carcinomas from different origins (mainly pulmonary and digestive). Nevertheless, when an angiosarcoma is found in oral cavity, we have to take into account that it could be a metastatic one.

PS-03-004

Immunoexpression of mTOR downstream targets in seven cases of secretory carcinoma of salivary gland origin

M. Custódio[1], B. Tavares Sedassari[2], S. COM de Sousa[1], M.F. Setúbal Destro Rodrigues[2], A. Altemani[3], F. Daumas Nunes[1]
[1] University of São Paulo, Brazil, [2] Universidade Nove de Julho, Brazil, [3] University of Campinas, Brazil

Background & Objectives: The secretory carcinoma of salivary gland origin is a very rare neoplasm recently described as the counterpart of the secretory breast carcinoma. Both neoplasms frequently have the ETV6-NTRK3 fusion gene as a result of a balanced chromosomal translocation. This fusion gene can constitutively activate important signalling pathways in cancers, such as Akt/mTOR and MAPK. Therefore, we aimed to assess the expression of the mTOR downstream targets S6 ribosomal protein, eIF4E and 4E-BP1 in the secretory carcinoma from salivary glands.
Methods: After searching in our pathology files, we retrieved seven cases of secretory carcinoma diagnosed by a combination of immunohistochemistry and/or molecular testing. Immunohistochemical assessment was made against phospho-S6 ribosomal protein, phospho-4E-BP1 and eIF4E. Twenty-seven other salivary carcinomas were included for comparison.
Results: eIF4e was diffusely positive in the cytoplasm of most cases, both for secretory carcinoma (5/7) and for other salivary carcinomas (25/27). 4E-BP1 was less frequently expressed in both groups, being its expression especially seen in the cytoplasm and nucleus of 3/7 cases of secretory carcinoma and in only 8/27 of other salivary carcinomas. Regarding S6 ribosomal protein, (2/7) 28.6% and (15/27) 55.5% of secretory carcinoma and other salivary cancers, respectively, were positive in a focal cytoplasmic pattern.
Conclusion: mTOR downstream targets are present in secretory carcinoma in different expression patterns, although only eIF4E was highly expressed in the majority of cases.

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PS-03-005

Immunoexpression of prolactin receptor is not restricted to the secretory carcinoma in salivary glands

M. Custódio[1], B. Tavares Sedassari[2], F. Daumas Nunes[1], A. Altemani[3], S. COM de Sousa[1]
[1] University of São Paulo, Brazil, [2] Universidade Nove de Julho, Brazil, [3] University of Campinas, Brazil

Background & Objectives: Prolactin receptor is crucial for the development of lactating-competent mammary glands. Recently, it has been proposed that secretory carcinoma of salivary gland origin could have a lactating-like differentiation based on its morphology and some immunohistochemical features. This salivary carcinoma is a very rare neoplasm similar in many aspects to its breast counterpart. Therefore, we aimed to assess the expression of the prolactin receptor in secretory carcinoma of salivary gland origin. We hypothesized that the expression of this receptor would be restricted to this type of salivary tumour.
Methods: Prolactin receptor (D4A9) immunostaining was performed in seven cases of secretory carcinoma and twenty-seven other salivary carcinomas (AdCC, adenoid cystic carcinoma=9; MEC, mucoepidermoid carcinoma=10, SDC, salivary duct carcinoma=4; ACC, acinic cell carcinoma=4).
Results: A weak and focal staining was seen in the cytoplasm of 3/7 cases of secretory carcinoma. Tumour secretion was weakly stained in one case. Among the other salivary carcinomas, 11/27 were positive (AdCC=2; MEC=6; SDC=1; ACC= 2). Almost all of them had a focal and weak staining in the cytoplasm. Interestingly, the expression of prolactin receptor was also observed in normal salivary glands. Strong staining was seen in a subset of acinar cells and weak staining in some intra e interlobular ducts. Mucous cells rarely stained.
Conclusion: Among salivary carcinomas, the expression of prolactin receptor is not restricted to the secretory carcinoma. The staining was observed both in normal salivary glands and their derived tumours, which suggests a different function for this receptor in salivary glands.

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PS-03-006

Comparison of three PD-L1 immunohistochemical assays in head and neck squamous cell carcinoma

E. de Ruiter[1], F. Mulder[2], E. Speel[3], M. van den Hout[2], R. de Roest[4], E. Bloemena[5], L. Devriese[6], S. Willems[7]
[1] Department of Pathology, University Medical Center Utrecht, The Netherlands, [2] Department of Pathology, Maastricht University Medical Center, The Netherlands, [3] Maastricht University Medical Centre+, The Netherlands, [4] Department of Otolaryngology/Head and Neck Surgery, Amsterdam University Medical Center, The Netherlands, [5] Department of Pathology, Amsterdam University Medical Center, The Netherlands, [6] Department of Medical Oncology, University Medical Center Utrecht, The Netherlands, [7] Department of Pathology, University Medical Centre Utrecht, the Netherlands

Background & Objectives: Soon, expression of programmed death ligand 1 (PD-L1) will be implemented as predictive biomarker for immunotherapy in head and neck squamous cell carcinoma (HNSCC). Several antibodies are available for PD-L1 testing and multiple staining and scoring methods are used. This study aimed to compare the performance of two PD-L1 standardised assays (SP263 and 22C3) and one laboratory-developed test (LDT) (22C3) in HNSCC using the tumour proportion score (TPS) and the combined positive score (CPS).
Methods: Pre-treatment biopsies from 147 HNSCC patients were collected in a tissue-microarray (TMA). Serial sections of the TMA were immunohistochemically stained for PD-L1 expression using SP263 on

the Ventana Benchmark Ultra platform, 22C3 on the Dako Link 48 platform, and 22C3 as an LDT on the Ventana Benchmark Ultra. Stained slides were assessed for TPS and CPS. Cutoffs of ≥1% and ≥50% for TPS, and ≥1% and ≥20% for CPS were used.
Results: Concordance between the different staining assays was moderate for TPS (intraclass correlation coefficient (ICC) 0.70) as well as for CPS (ICC 0.53). When stratifying patients by clinically relevant cutoffs, considerable differences between the assays were observed: for TPS, concordance was moderate (kappa 0.56), while for CPS, concordance was poor (kappa 0.44). Generally, SP263 stained a higher percentage of cells than the other assays, especially when using the CPS.
Conclusion: Moderate concordance was observed between three different PD-L1 immunohistochemical assays and considerable differences in PD-L1 positivity were observed when using clinically relevant cutoffs. This should be taken into account when using PD-L1 expression to guide clinical practice.

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PS-03-007
Comparison of multiple methods detection of high-risk human papillomavirus infection in 148 Polish patients with oropharyngeal carcinoma
M. Durzynska[1], A. Szumera-Cieckiewicz[2], M. Prochorec-Sobieszek[3]
[1] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland, [2] Institute of Haematology and Transfusion Medicine, Diagnostic Haematology Department, Poland, [3] Department of Pathology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Background & Objectives: Human papillomavirus (HPV) is now recognized as an etiologic factor in oropharyngeal carcinoma. Evaluation of HPV has a prognostic significance, but there is no agreement about the most appropriate method of virus detection so far.
The aim of this study was to determine the optimal assessment of HPV infection in oropharyngeal carcinoma using different methods. We also investigated the correlation between clinical and histological patients profile and HPV status.
Methods: Paraffin blocks were collected from 148 patients with primary oropharyngeal cancer diagnosed between 2007 and 2017 in Oncology Cancer Centre-Institute in Warsaw. The immunohistochemical (IHC) expression of p16 was detected with CINtec p16 Histology. DNA HPV was tested by in situ hybridization (ISH) using Inform HPV III Family 16 probe and by polymerase chain reaction (PCR) using automatic system Cobas 4800.
Results: There were different results of HPV positive cases according to using method IHC, ISH and PCR: 56%, 48% and 58% of cases. The combination of IHC and ISH classified 46% of the samples as HPV-positive, whereas the combination of IHC and PCR and the combination of IHC, ISH, and PCR classified 53% cases as HPV-positive. There were correlations between HPV status and patients sex, history of smoking, tumour site, tumour staging, nodal involvement and morphology subtype of squamous cell carcinoma.
Conclusion: The current study suggests that using a combination of IHC, ISH, and PCR in a three-tiered, staged algorithm leads to the appropriate assessment of HPV. The prevalence of HPV infection in 148 Polish patients is approximate to results from western countries.

PS-03-008
Salivary gland duct polycaryocytes: features of 6 cases
A. Handra-Luca[1]
[1] APHP University Paris Nord, France

Background & Objectives: Salivary gland duct polycaryocytes may be observed on labial minor salivary gland biopsies, similarly to breast specimens. The precise etiology, whether treatment-related or not, is not well established.
The aims of this study were to report the clinico-pathological features of 6 cases.
Results: The gender ratio was 4:2 (female:male), the age ranged 33-73 years. The clinical diagnoses were amylosis (1) and dry syndrome (5). The medical history suggested hypophysis adenoma in 2 cases. The histology diagnosis was that of chronic sialadenitis: grades 1, 2 and 4 (1,2 and 3 cases respectively). Granulomas were detected in 1 case, oncocytic metaplasia in 4. A history of corticoid treatment was known for 1 case. Polykariocytes (1-6/biopsy) were detected in the basal lining of the duct epithelium (interlobar and excretory ducts, 4 and 2, respectively), on 1 or 2 tissue sections (2 and 4 biospsies, respectively). When observed on 2 sections, they belonged to the same level of section. Therefore P63 staining may be of limited help for the differential diagnosis with fibroblasts. There was no inflammation at contact to the polycaryocytes or inflammatory exocytosis. Oncocytic metaplasia was detected in all samples, for one of them in the same duct as the polycaryocytes.
Conclusion: In conclusion, minor salivary gland duct polykaryocytes may be detected in the context of chronic sialadenitis (associated or not to granuloma), in excretory or interlobular ducts, however not as part of the inflammatory lesions (inflammatory exocytosis). Further studies are required for precising their etiology.

PS-03-010
Histological features and outcomes of polymorphous adenocarcinoma of minor salivary glands: a retrospective study of 38 cases
S. Lerias[1,2], I. Fonseca[1,2]
[1] Instituteo Portugues de Oncologia de Lisboa, Francisco Gentil, Portugal, [2] Instituteo de Anatomia Patologica, Faculdade de Medicina da Universidade de Lisboa, Portugal

Background & Objectives: Although most polymorphous adenocarcinomas (PAC) have an indolent course, some cases show varying recurrence rates. In this study, we aimed at identifying the pathological features that can determine recurrence rates in 38 PAC.
Methods: We reviewed 38 cases of PAC with clinical, histological and prognostic data diagnosed over a period of 16 years (2002-2018). Statistical analysis was performed using T-test and Chi-squared test.
Results: 26 (68%) of the patients were females, with a mean age at diagnosis of 61.3yrs. The median follow-up period was 6.7yrs. The most common site was the palate. Average tumour size was 2.5cm. Recurrence occurred in 7 cases, including 3 local recurrences, 1 nodal recurrence, and 3 distant metastasis, up to 9yrs after the initial resection. 37% of the patients were pT1, 34% pT2 and 26% pT4. 9 patients were initially treated with surgery, 29 with surgery and radiotherapy. The 5-years overall survival rate was 100%, and 5 patients died of disease (range 8 to 16.7yrs). Histologic evaluation showed that solid architecture was predominant (41%), followed by cribriform (30%). Recurrent cases were more likely to have bone invasion (p=0.04), lymphovascular invasion (p=0.03), lymph node metastasis (p=0.02), atypical mitosis (p=0.02), optically clear nuclei (p=0.04) and ≥30% papillary architecture (p=0.01).
Conclusion: Bone invasion, lymphovascular invasion and lymph node metastasis are significant parameters that can predict adverse clinical behaviour in PAC. Atypical mitosis, optically clear nuclei and the percentage of papillary pattern are associated with high rates of recurrence and should be documented as relevant prognostically parameters.

PS-03-011
Diagnostic and prognostic significance of HuR protein expression in salivary gland tumours
G. Levidou[1], P. Sarantis[2], G. Tsourouflis[3], N. Tsoukalas[2], E. Dana[2], M. Karamouzis[4], J. Klijanienko[5], S. Theocharis[2,6]

[1] Humanpathologie Dr. Weiß GmbH, Germany, [2] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [3] 2nd Department of Propedeutic Surgery, School of Medicine, National and Kapodistrian University of Athens, Greece, [4] Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Greece, [5] Department of Pathology, Institute Curie, Paris, France, [6] Department of Pathology, Institute Curie, Paris, France

Background & Objectives: HuR protein is a post-transcriptional regulator of several genes expression, being correlated with carcinogenesis or/and cancer patients' prognosis. Research data on the role of HuR protein in salivary gland tumours (SGTs) remain limited, whereas there is a paucity of information regarding its prognostic significance. In this study we aim to investigate the potential diagnostic and prognostic significance of HuR protein expression in SGTs.
Methods: HuR expression (positivity, intensity of staining and their combination as H-score) was assessed immunohistochemically in 50 SGT tissue specimens (29 benign and 21 malignant) and was statistically correlated with the clinicopathological characteristics for all cases and patients' survival rate in malignant SGTs.
Results: Nuclear HuR immunostaining was observed in all (100%) and cytoplasmic in 42.5% of SGTs cases. Increased cytoplasmic and nuclear HuR immunostaining was more frequently found in malignant compared to benign SGTs (p=0.031 and p=0.006, respectively). Significant difference was also found in cytoplasmic and nuclear HuR H-score between low grade and high gradeSGTs (p=0.003 and p=0.008 respectively). Finally, in survival analysis cytoplasmic HuR H-score was correlated with unfavourable patients' prognosis (p=0.022).
Conclusion: HuR protein seems to have a diagnostic role discriminating malignant and benign SGTs and additionally, is correlated with a more aggressive phenotype, emerging as a significant adverse prognosticator for patients with malignant SGT.

PS-03-012

Sinonasal small round blue cell tumours with expression of neuroendocrine markers - a clinicopathological characterisation of 14 cases and literature review

S. Lopes Petronilho[1], J. Costa[1], R. Henrique[1], M. Jácome[1]
[1] Pathology Department, IPO-Porto, Portugal

Background & Objectives: Reaching the final diagnosis of small round blue cell tumours (SRBCT) is universally challenging, but the inherent complexity of the sinonasal (SN) region entails additional difficulties. Differential diagnoses include epithelial, neuroectodermal, mesenchymal and hematolymphoid neoplasms, which morphologically and immunohistochemically overlap. In particular, neuroendocrine (NE)-marker expression has been described in several "non-neuroendocrine" tumours, perpetuating the debate on how to properly define a NE-neoplasm.
Aim: To review clinicopathological features of SN-SRBCT with NE-differentiation.
Methods: We retrospectively identified 14patients diagnosed with non-hematolymphoid SN-SRBCT with expression of NE-markers (synaptophysin/chromogranin/CD56), in IPO-Porto (2013-2018). These included 6 Olfactory Neuroblastomas (ON) and 8 Epithelial Neoplasms (EN), namely 6 small-cell Neuroendocrine Carcinomas (NEC); 1 Undifferentiated Carcinoma (SNUC) and 1 Adenocarcinoma (ADC). Clinical(age/sex/treatment/follow-up), radiological (site/size) and pathological (diagnosis/morphology/immunohistochemistry) data were collected from the patients' files.
Results: EN occurred exclusively in males. ON occurred equally in both sexes, and in older patients (median:57vs51). Overall, median size was 4,9cm (range:3,2-7,6). Most tumours (93%) primarily involved the nasal cavity and infiltrated adjacent structures. Cytokeratins were diffusely positive in all EN, but focal (40%)/negative (60%) in ON. There was less Synaptophysin (80%vs100%) and more Chromogranin (80%vs60%) expression in NEC (vs ON). CD56 was expressed in all but 1 (ADC) case, being the only positive NE-marker in SNUC. EN treatment always included Chemotherapy+/-Radiotherapy, while 40%ON were exclusively surgically managed.
Conclusion: NE-markers are variably expressed in SN-SRBCT of different origins, highlighting that this feature is not pathognomonic of NEC. Our series is thus consistent with previously published data. Differentiating NECs from ON is of particular importance, and integration of clinical, radiological and histological features is essential for the accurate diagnosis and further optimal management of these patients.

PS-03-013

Salivary gland biopsy for Sjögren syndrome: is it worth it?

R. Machado-Neves[1], A. Lopes[2], J. dos Santos[2], R. Pereira[2], M. Honavar[1]
[1] Pathology Department - Hospital Pedro Hispano, Portugal, [2] Internal Medicine Department - Hospital Pedro Hispano, Portugal

Background & Objectives: Labial accessory salivary gland biopsy is a minimally invasive procedure, frequently used for the diagnosis of Sjögren's syndrome (SS). Focal lymphocytic sialadenitis is one of the six criteria of the American-European Consensus Group Classification for the diagnosis of SS. The Chisholm-Mason scale is used to evaluate focal lymphocytic infiltration in the salivary gland. Infiltrates of ≥1 focus of lymphocytes per 4 mm^2 are considered positive, corresponding to Chisholm-Mason scores 3 and 4. We correlated the biopsy findings with the clinical manifestations.
Methods: A retrospective analysis of the clinical files and histological slides of salivary gland biopsies performed from April 2014 to December 2017 at Hospital Pedro Hispano, Matosinhos, Portugal.
Results: 179 biopsies were performed, 129 (72%) with a clinical suspicion of SS and the rest for diverse clinical diagnosis (mainly amyloidosis and sarcoidosis). Of the 129 patients with clinical suspicion for SS, the mean age was 57 years (23-89) and 111 (86%) were female. 52 (40%) had score ≥3 on the Chisholm-Mason scale. Before the salivary gland biopsy, only 9 (7%) patients met diagnostic criteria of SS. This number rose to 25 (19%) based on the result of the biopsy.
Conclusion: Labial salivary gland biopsy is a simple procedure which is critical for some clinical purposes. In our group of patients, a positive result on salivary gland biopsies more than duplicated the number of patients diagnosed as SS.

PS-03-014

Tumour budding seems to be independent to epithelial-mesenchymal transition in intestinal-type sinonasal adenocarcinoma

V. Maffeis[1], R. Cappellesso[2], F. Galuppini[3,4], M. Boscolo[5], L. Ventura[5], A. Fassina[2]
[1] Surgical Pathology & Cytopathology Unit, Department of Medicine-DIMED, University of Padua, Italy, [2] University of Padua, Italy, [3] Women's & Children's Health Department (SDB), University of Padua, Italy, [4] Pathology Unit, Department of Medicine (DIMED), University of Padua, Italy, [5] Department of Statistics, University of Padua, Italy

Background & Objectives: Intestinal-type sinonasal adenocarcinoma (ITAC) is a rare malignant tumour morphologically, immunophenotypically, and molecularly resembling colorectal adenocarcinoma (CRC). Tumour budding is a well-established adverse prognostic marker in CRC and other tumours, such as oral squamous cell carcinoma, with features of epithelial-mesenchymal transition (EMT). The aim of this study was to assess tumour budding in ITAC and to evaluate its possible association with EMT markers in this setting.
Methods: 32 FFPE surgically resected specimens of CK20 and CDX2 positive ITAC have been evaluated for tumour budding according to the

international recommendations developed for CRC. The expression of the EMT markers E-cadherin, ZEB2, SLUG, and SNAIL was evaluated by immunohistochemistry (IHC). Results were stratified using clinical and follow-up data (2/32 patients had metastatic disease and 4/32 died of disease).
Results: Tumour budding was observed in 13/32 (40.6%) ITAC cases including all the 9 patients with relapse (p = 0.07). Absence of tumour budding was observed only in patients without relapse and it was associated with low ZEB2 expression (p = 0.03). No others association with E-cadherin, SLUG, and SNAIL emerged. Occupational exposure to wood and leather dust was not related to the presence of tumour budding.
Conclusion: Tumour budding is associated with a worse prognosis in ITAC. However, current findings do not seem to support an involvement of EMT in this specific setting. Further larger studies are needed to address this point.

PS-03-015
Odontogenic cysts of inflammatory origin: reclassification according to the 2017 World Health Organisation Classification
I. Msakni[1], F. Gargouri[1], R. Hedhli[2], N. Mansouri[1], A. Saidi[1], A. Bouziani[1], B. Laabidi[3,4]
[1] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia, [2] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia, [3] Tunis El Manar University, Medicine School of Tunis, Tunisia, [4] Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: The 2017 World Health Organisation (WHO) head and neck classification brought several changes. One was the reinstatment of a specific classification of the odontogenic cysts. There were two types odontogenic cysts of inflammatory origin. Radicular cyst associated with non-vital teeth and Inflammatory collateral cyst arising on the roots of partially or recently erupted teeth as a result of inflammation of the pericoronal tissues.
Our aim was to reclassify odontogenic cysts of inflammatory origin according to the 2017 WHO classification.
Methods: It was a retrospective study of odontogenic cysts of inflammatory origin collected at our department over a period of 5 years (2012-2017). The slides were reviewed based on clinical and radiological information.
Results: We collected 83 inflammatory odontogenic cysts. Radicular cyst was observed in 48 cases. The median age was 39 years (sex ratio=4,33). Inflammatory collateral cyst was observed in 18 cases. The median age was 36 years (sex ratio=5). Seventeen were unclassifiable inflammatory cysts.
After revision of the slides, 49% of inflammatory collateral cysts (n = 21) were reclassified to radicular cysts, 14% of radicular cysts (n = 6) to unclassifiable inflammatory cyst and one case of unclassifiable inflammatory cyst to dentigerous cyst.
Conclusion: In our study, histological diagnosis after revisions of the slides based on clinical and radiological information did not agree with the initial diagnosis in 34% of cases. This is due to the lack of clinical and radiological data for the pathologist, but also to the absence of a specific classification to odontogenic cysts up to the year 2017.

PS-03-016
Primary intraosseous carcinoma of jaw: a clinicopathological study of 4 cases
M.I. Oviedo Ramírez[1], A. Caballero Illanes[1], A. Salazar Nicolás[1], L. Barona García[1], M.I. Ortuño Moreno[1], V. Caballero Illanes[2], V. Villanueva San Vicente[2], E. Martínez Barba[1]
[1] Servicio de Anatomía Patológica. Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [2] Hospital Clínico Universitario Virgen de la Arrixaca, Spain

Background & Objectives: Adequate and timely testing for genetic alterations in non-small cell lung cancer (NSCLC) is necessary to consider targeted therapy when a certain genetic alteration is present. Previously, we demonstrated that in the Netherlands molecular testing was suboptimal in 2015, as 25% (EGFR/KRAS and ALK) to 50% (ROS1) of patients were not tested according to guidelines, and notable laboratory variation was present. Currently, by analyzing a cohort of metastatic NSCLC from 2017 we aim to assess whether the performance of molecular testing improved.
Methods: All fully registered stage IV non-squamous NSCLC with incidence year 2017 from the Netherlands Cancer Registry were matched to the Dutch pathology registry (PALGA). Using information extracted from pathology excerpts, proportions of tumours tested for EGFR/KRAS, BRAF, and HER2 mutation, ALK, ROS1, and RET rearrangement <3 months after diagnosis were determined.
Results: Of 2596 identified patients, we have currently analysed 511 (20%). Twenty-three patients were non-eligible after matching, leaving 488 patients. EGFR/KRAS testing was performed in 412 patients (84.4%). Of the EGFR/KRAS wildtype tumours (n=184), 167 (90.8%) were tested for BRAF, 158 (85.9%) for HER2, 157 (85.3%) for ALK, 110 (59.8%) for ROS1, and 73 (39.7%) for RET. Insufficient tumour tissue and inappropriate specimen were the most stated reasons for not testing.
Conclusion: These preliminary data show significantly higher EGFR/KRAS and ALK testing proportions compared to 2015. Further improvement remains possible to identify candidates for targeted therapy. At the ECP meeting, we expect to present the variation between laboratories for the entire cohort.

PS-03-017
Comparative analysis of claudin expression in odontogenic tumours
E. Phattarataratip[1], K. Sappayatosok[2]
[1] Chulalongkorn University, Thailand, [2] Rangsit University, Thailand

Background & Objectives: Claudins are integral to the structure and function of tight junctions. Altered claudin expression has been shown to affect disease behaviour and patient prognosis in various neoplasms. The objectives of this study were to analyse the claudin-1, -4 and -7 expression in odontogenic tumours and characterise their expression pattern in distinct tumour cell types in relation to the recurrence potential.
Methods: Sixty-nine cases of odontogenic tumours, including 43 ameloblastomas (AM), 17 adenomatoid odontogenic tumours (AOT), 6 ameloblastic fibromas (AF) and 3 ameloblastic carcinomas (AC) were investigated for claudin-1, -4 and -7 expression immunohistochemically. The staining was analysed semi-quantitively and categorized into 4 levels, based on the percentage of positively stained neoplastic epithelial cells.
Results: Claudin-1 was expressed in all AOT and AF, whereas most AC (66.7%) showed no expression. Claudin-1 staining was moderate-to-intense in odontogenic epithelium of AF, but weak in those of AM. Claudin-7 was noted in all tumours studied, while claudin-4 expression was limited and mainly localized in squamous cells of AM and AC. AM showed higher claudin-4, but lower claudin-7 expression than AOT. AC showed reduced claudin-1 immunoreactivity, compared to AOT. Low claudin-1 in AM was significantly associated with increased recurrence.
Conclusion: Odontogenic tumours are differentially expressed claudin proteins. The loss of claudin-1 may underlie the locally invasive nature of AM.

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PS-03-018
Clinical significance of Histone Deacetylase (HDAC)-1, -2, -4 and -6 expression in salivary gland tumours
D. Pouloudi[1], M. Manou[1], P. Sarantis[2], N. Tsoukalas[2], G. Tsourouflis[3], E. Dana[1], M. Karamouzis[4], J. Klijanienko[5], S. Theocharis[1]
[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [2] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece,

[3] 2nd Department of Propedeutic Surgery, School of Medicine, National and Kapodistrian University of Athens, Greece, [4] Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Greece, [5] Department of Pathology, Institute Curie, Paris, France

Background & Objectives: Histone Deacetylases (HDACs), through post-translational histone modifications and subsequent gene expression alterations, are thought to play a key role in carcinogenesis. Aim of this study was to evaluate the clinical significance of different HDAC members' expression in salivary gland tumours (SGTs) and their potential use as diagnostic or prognostic biomarkers.
Methods: HDAC-1, -2, -4 and -6 expression (positivity, intensity of staining and their combination as H-score) was assessed immunohistochemically in 58 SGT tissue specimens (36 benign and 22 malignant) and was statistically correlated with the clinicopathological characteristics for all cases and patients' survival rate in malignant SGTs.
Results: HDAC-1, -2, -4 and -6 were abundantly expressed in SGTs, although their expression was not different between benign, low grade (LG) malignant and high grade (HG) malignant SGTs. Increased HDAC-2 and HDAC-6 intensity of staining was noted in HG malignant compared to LG malignant and benign SGTs ($p = 0.017$ and $p = 0.028$, respectively). HDAC-2 positivity was significantly associated with longer overall survival (OS) of patients with malignant SGT ($p = 0.028$). HDAC-2 positivity and absence of HDAC-6 expression were associated with prolonged OS of patients with high-grade malignant SGT ($p = 0.003$ and $p = 0.043$, respectively). Additionally, high HDAC-2 H-score was significantly associated with longer OS for HG malignant SGT patients ($p = 0.027$).
Conclusion: For patients with malignant SGTs, HDAC-2 expression emerges as an important positive prognostic factor whereas HDAC-6 expression as negative one.

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PS-03-019
Immunohistochemistry analysis of PD-L1 expression in head and neck cancer

M. Ramos[1], A. Baldion[1], D. Suarez[1], S. Perdomo[1], M. Palau[1], A. Avello[1], A. Hakim[1], A. Escallon[1], V. Ospina[1], P. Beltran[1], G. Ucros[1], A. Muñoz[1], O. Torres[1], P. Rodriguez[1]
[1] Hospital Universitario Fundacion Santa Fe de Bogota, Colombia

Background & Objectives: Anti-PD-L1 agents have shown potential in improving survival in head and neck cancer (HNC) patients. However, no standardised measurement for expression of PD-L1 has been defined. Our objective is to measure PD-L1 expression by immunohistochemistry in HNC with different antibodies and scores.
Methods: 38 samples of HNC from the Hospital Universitario Fundacion Santa Fe de Bogotá, a cohort from the InterCHANGE study were used. Immunohistochemistry analysis was made with tissue microarrays. Ventana SP263 and Dako 22C3 antibody assays were used. Positivity of PD-L1 was calculated using the Tumour Proportion Score (TPS) and Combine Proportion Score (CPS), scores of ≥1 were considered positive. Staining intensity was measured, ranging from 1 to 3 crosses.
Conclusion: PD-L1 expression varied according to the antibody and the score used. Ventana's antibody showed a more intense staining, facilitating the overall assessment of PD-L1 expression. A larger study sample comparing antibodies and cutoff points is granted to define a standardised measure of PD-L1 expression.

PS-03-020
Tumour microenvironment characteristics and their correlations in laryngeal squamous cell carcinoma

L. Ruiter[1], A. de Lange[1], M. Wekking[2], M. Philippens[3], S. Willems[1]
[1] Department of Pathology, University Medical Center Utrecht, The Netherlands, [2] Department of Pathology, Radboud University Medical Center Nijmegen, The Netherlands, [3] Department of Radiotherapy University Medical Center Utrecht, The Netherlands

Background & Objectives: The tumour microenvironment (TME) is crucial for tumour growth and plays an important role in treatment failures and recurrences of cancer. Individual specialized cell types construct the TME biology and the course of the tumourigenesis. The aim of this study is to find correlations between TME characteristics, such as vascularization, immune cell influx and tumour features like hypoxia, keratinization and tumour cell proliferation in laryngeal squamous cell carcinoma (LSCC).
Methods: 10 patients with LSCCs were stained for proliferation (Ki67), hypoxia (Hif-1a), vascularization (CD31), immune cells (CD45) and scored for keratinization. For Ki67 and Hif-1a, the average coverage of the tumour islands were scored. For CD31 and CD45, the average coverage of the tumour stroma were scored. Correlations were calculated using the Spearman Rank test.
Results: Vascularization and the amount of immune cells showed a strong positive correlation (r=0,63 p=0,05) in LSCC. Tumour cell proliferation was strongly positively associated with hypoxia (r=0,58 p=0,08), strongly negatively correlated with vascularization (r=-0,53 p=0,11) and moderately negatively correlated with the amount of immune cells (r=-0,42 p=0,23). Keratinization and vascularization were strongly positively associated (r=0,62 p=0,05). Hypoxia and vascularization showed moderate correlation (r=-0,35 p=0,33).
Conclusion: Vascularization showed a positive correlation with immune cells. Tumour cell proliferation showed a positive correlation with hypoxia and a negative association with the amount of immune cells and vascularisation.

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PS-03-021
MUC4 as a potential marker for differentiating MASC and PLGA in minor salivary glands

C. Taverna[1], A. Franchi[2], M. Santucci[1], M. Baněčková[3], A. Skalova[3], A. Agaimy[4]
[1] Division of Pathological Anatomy, Department of Health Sciences University of Florence School of Human Health Sciences, Italy, [2] Department of Translational Research and of New Technologies in Medicine and Surgery, University of Pisa, Italy, [3] Department of Pathology, Charles University, Faculty of Medicine in Plzeň, Czech Republic, [4] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuernberg, Germany

Background & Objectives: Mammary analogue secretory carcinoma (MASC) is a low grade salivary gland tumour which occurs both in major and in minor salivary glands. MASC is known for its wide morphological, architectural and immunohistochemical spectrum, thus it can mimic other salivary gland neoplasms.
In minor salivary glands, polymorphous (previously called low grade) adenocarcinoma (PLGA) shares with MASC some morphological features and S100 positivity.
We investigated MUC4 expression in PLGA and MASC to establish it as potential marker in differentiating these two entities.
Methods: Tumours from 33 patients were analysed, including 11 PLGA and 22 MASC. Clinical and pathological data were collected (15 male, 18 female; 28-86 years old). Immunohistochemical data for MUC4 and S100 were evaluated considering both the staining intensity and the percentage of positive cells. All MASC underwent ETV6-FISH analysis for confirmation.
Results: All MASC cases showed moderate (3 cases, 13,6%) to strong (17 cases, 77,2%) positivity for MUC4, as opposed to none of the PLGA

cases. Interestingly, all 5 minor salivary gland MASC expressed MUC4 with high intensity.
Conclusion: The results of our study show that MUC4 could be a useful marker in the differential diagnosis between MASC and PLGA, particularly on limited biopsy material from minor salivary glands and in cases with strongly overlapping morphological features.

PS-03-022
Clinical significance of Ephrin Receptor (EPH)-A1, -A2, -A4 and -A5 expression in salivary gland tumours
S. Theocharis[1], D. Pouloudi[1], P. Sarantis[1], G. Levidou[1,2], N. Tsoukalas[1], G. Tsouroufli[3], E. Dana[1], M. Karamouzis[4], J. Klijanienko[5]
[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece [2] Department of Pathology, Humanpathologie, Erlangen, Germany, [3] 2nd Department of Propedeutic Surgery, School of Medicine, National and Kapodistrian University of Athens, Greece, [4] Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Greece, [5] Department of Pathology, Institute Curie, Paris, France

Background & Objectives: Aberrant expression of different members of the Eph/ephrin system family, which comprises the Eph receptors (EPHs) and their ligands (ephrins), has been reported in various malignancies. Aim of our study was to evaluate the clinical significance of EPH-A1, -A2, -A4 and -A5 expression in salivary gland tumours (SGTs).
Methods: EPH-A1, -A2, -A4 and -A5 protein expression (positivity, intensity of staining and H-score) was assessed immunohistochemically in 58 SGT tissue specimens (36 benign and 22 malignant), of different histological types, and was statistically correlated with the clinicopathological characteristics for all cases and patients' survival for malignant SGTs.
Results: EPH-A1, -A2, -A4 and -A5 were highly expressed in both benign and malignant SGTs. Differences in EPH-A2 H-score were noted between benign, low grade (LG) and high grade (HG) malignant SGTs (p=0,001). Additionally, higher EPH-A2 H-score was noted in HG compared with LG malignant SGTs (p=0,015). Marginal difference in cytoplasmic EPH-A4 H-score was noted between with HG and LG malignant SGTs (p=0,053). Increased EPH-A1, -A4 and -A5 H-score was statistically significantly correlated with decreased overall survival (OS) rate in patients with malignant SGTs (p = 0.0227, p=0,0226 and p=0,0016, respectively), while the respective correlation of EPH-A2 H-score was of marginal significance (p = 0.0587).
Conclusion: EPH-A2 expression was able to discriminate between benign, LG and HG malignant SGTs. Additionally, high EPH-A1, -A4 and -A5 expression proved as adverse prognosis indicators for malignant SGT patients.

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PS-03-023
High concordance of the PD-L1 22C3 antibody LDT protocol on BenchMark XT compared to the PD-L1 IHC 22C3 pharmDx kit for urothelial carcinoma (UC) and head and neck squamous cell carcinoma (HNSCC)
G. Vainer[1], T. Neuman[1], Y. Fellig[2], K. Meir[2], N. Hirshoren[2], O. Gofrit[2], L. Huang[3], J. Juco[3], T. Bal[3]
[1] The Hebrew University - Hadassah medical center, Jerusalem, Israel, Israel, [2] Hadassah-Hebrew University Medical Center, Israel, [3] Merck & Co., Inc., USA

Background & Objectives: Pembrolizumab is an anti-PD-1 drug which is approved for several indications including UC and HNSCC. Using our previously described 22C3 antibody LDT for the BenchMark XT, we demonstrated high concordance between PD-L1 assessments via the TPS NSCLC compared to PD-L1 IHC 22C3 pharmDx FDA approved assay. For other cancers, like UC and HNSCC, PD-L1 is evaluated by CPS therefore additional studies are needed to establish comparability.
Methods: As a pilot, we compared the concordance of 45 cases (34 UC and 11 HNSCC) scored by a single pathologist (GV). Nevertheless, the final study will include ~120 UC and ~120 HNSCC cases, and scores of several pathologists. We used the clinical cutoffs of CPS≥10 or ≥1, for UC and HNSCC, respectively. After obtaining the PD-L1 status using this LDT and the 22C3 pharmDx assay, we analysed the agreement of both assays.
Results: Using the 22C3 pharmDx assay, 18 and 27 cases were positive and negative, respectively. Using the 22C3 based LDT, 20 and 25 cases were positive and negative, respectively. Thus, these assays demonstrated >95% concordance rates (2/45 discordant scores) and interclass correlation coefficient of 0.91 (ICC of UC and HNSCC was 0.94 and 0.83, respectively). Moreover, morphological evaluation showed high similarity for PD-L1 staining pattern, and dynamic range.
Conclusion: This preliminary data demonstrated that the 22C3 antibody based LDT on BenchMark XT demonstrated high concordance with FDA-approved assay. The suggests that this LDT is also applicable to UC and HNSCC**.** A much larger study is currently in progress.

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PS-03-024
Pattern of MMP8 expression in gingival biopsy for the diagnosis of different types of periodontitis
V. Zakharava[1], L. Kazeko[2], A. Anfinahenava[2], T. Liatkouskaya[1,3]
[1] Belarusian State Medical University, Belarus, [2] BSMU, Belarus, [3] Goethe-Institut Minsk, Belarus

Background & Objectives: Periodontal diseases represent a numerous and diverse group of diseases in both clinical and morphological manifestations. The lack of clear clinical and radiological signs of diagnosis of periodontitis establish the relevance of studying biomolecular markers in determining the prognosis of periodontitis in the early stages of the disease.
Objective: To study the features of MMP-8 expression in patients dependent upon the type of periodontitis.
Methods: A biopsy of gingival material was analysed from 63 patients with either rapidly progressive (RPP, n=26), chronic simple (CSP, n=5), or chronic complex (CCP, n=29) periodontitis, and a control group (gingivitis only, n=3). Morphometric analysis of the MMP-8 expression was performed using Aperio Image Scope v9.0 software. U-test was applied, p<0.05.
Results: Expression of MMP-8 have occurred in all samples in the form of cytoplasmic staining of the inflammatory infiltrate cells in both the group of patients with signs of gingivitis and all forms of periodontitis. The positive expression of MMP-8 was greatest in the group of patients with signs of gingivitis (2.72%), decreased in various forms of periodontitis RPP group (0.55%), CSP group (1.93%) and was the lowest in the CCP group (0.09%). In the group of patients with RPP the positivity of MMP-8 expression did not have statistically significant differences with that in the group of CSP (p = 0.87) but was significantly larger than in the CCP group (p = 0.002). The intensity of MMP-8 expression was highest in the groups of patients with signs of gingivitis and CSP and the lowest in the groups of patients with RPP and CCP who had no significant differences in this indicator.
Conclusion: The results suggest the most a useful indicator for the differential diagnosis of RPP with CSP can be considered the positivity of the MMP-8 expression (which is significantly lower in the CSP group) with comparable expression intensity between groups, and for CSP group the intensity of expression (which has significantly higher in the patients with chronic simple periodontitis) with comparable of the area of the expression of this marker between groups. The identified features of MMP-8 expression can be used to diagnose and predict the course of periodontitis at the stage of disease manifestation.

Sunday, 8 September 2019, 09:30 - 10:30, Agora 3
PS-04 | Molecular Pathology

PS-04-001
Down-regulation of TGFB1 gene expression in patients with colorectal cancer in association with primary tumour location and metastatic disease
E. Aleksandrova[1], M. Gulubova[2]
[1] Trakia University, Medical Faculty, Stara Zagora, Bulgaria, [2] Trakia University, Medical Faculty, Department of General and Clinical Pathology, Bulgaria

Background & Objectives: The complex role of the pleiotropic cytokine transforming growth factor-beta 1 (TGF-β1) in colorectal cancer (CRC) development and progression has been widely studied. Recently, altered gene expression profiles of the *TGFB1* gene in CRC patients has been associated with poor prognosis and increased metastatic potential. In line with recent findings our aim was to investigate mRNA levels of *TGFB1* in patients with CRC in association with clinical features of the studied subjects.
Methods: A group of 63 CRC patients from the region of Stara Zagora, Bulgaria were included in the present study. Total RNA, consequently reverse transcribed to cDNA, was extracted form fresh frozen biopsy specimens from the tumour and adjacent non-tumoural tissue. Relative mRNA levels were determined with TaqMan-based quantitative real-time polymerase chain reaction and the results were presented as n-fold mean difference (RQ-relative quantity) of the target gene relative to calibrator.
Results: *TGFB1* mRNA levels were significantly lower in tumour tissue compared to non-tumoural mucosa of the studied subjects (p=0.006, *t*-test). We also observed significant down-regulation of *TGFB1* gene in tumours located in the colon (dCt mean= 9.00) compared to localization in the rectum (dCt mean=13.34) or the sigma (dCt mean=12.43), (p=0.001, ANOVA). Additionally, our results indicated lower gene expression in cases without distant metastases compared to metastatic cases (p=0.074, *t*-test) with mean dCt values 12.63 and 10.04, respectively.
Conclusion: Our results suggest that down-regulation of *TGFB1* in CRC patients might be a possible mechanism of colorectal carcinogenesis involved in the localization and progression of the disease.

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PS-04-002
Molecular profiling of breast cancer intra-tumour heterogeneity
S. Baldacchino[1], E. Borg[2], J. Scerri[3], J. DeGaetano[4], C. Saliba[5], C. Scerri[6], P. Schembri Wismayer[2], G. Grech[1]
[1] Department of Pathology, University of Malta, [2] Department of Anatomy, University of Malta, [3] University of Malta, Department of Physiology and Biochemistry, University of Malta, [4] Department of Pathology, Mater Dei Hospital, Malta, [5] Centre for Molecular Medicine and Biobanking, University of Malta, [6] Department of Physiology and Biochemistry, University of Malta

Background & Objectives: Despite the efficacy of targeted therapy, some HER2 positive breast cancer patients do not respond to trastuzumab with an 88% 4-year overall survival (n=43). A death rate of 12% persists at 15 years from diagnosis of patients on tamoxifen for 10 years. Tumour heterogeneity is a known mechanism for resistance. Understanding heterogeneity allows for combinatorial targeted therapies to target the distinct tumour clones and achieve remission.
Methods: Heterogeneous cases were identified by 3 methods in separate studies: 1) by histopathological report, 2) by morphology from Haematoxylin & Eosin staining (H&E) and 3) by variation in HER2 staining. Tumour sampling was performed using laser microdissection or using 0.5mm cores. FFPE samples were lysed and profiled using two multiplex (14-plex and 40-plex) magnetic bead-based RNA expression assay as previously described (Baldacchino et al., 2018, JOVE).
Results: At diagnosis, 3.5% of breast cancer cases were reported as heterogeneous. Nonetheless, on second viewing, 17.5% of cases (n=97) were observed heterogeneous by H&E on morphology. Similarly, 17% of HER2 positive cases (n=294) showed heterogeneous HER2 staining. Expression profiles were analysed from multiple areas of each primary tumour. Distinct molecular subtypes of breast cancer were identified in 9/23 (39%) cases while 11/23 (48%) showed a distinct proliferation rate, using Ki67 and AURKA. Differential expression of Epithelial-Mesenchymal transition (EMT) markers (8/12, 67%), PP2A complex markers (7/12, 58%) and vascularisation markers (5/12 42%) were observed within heterogeneous breast cancer.
Conclusion: Tumour heterogeneity can manifest into distinct morphologies characterised by differential expression of genomic, transcriptomic and protein biomarkers. With the ever-increasing biomarkers for targeted therapeutics, identifying heterogeneity effectively will enable combinatory treatments enabling better response.

PS-04-003
Detection of novel HNF1B mRNA splicing variants in selected tissues
M. Bartu[1], J. Rosmusová[2], J. Kopejsková[2], L. Hadravsky[2], J. Hojný[1], K. Němejcová[1], I. Tichá[1], P. Dundr[1]
[1] Institute of Pathology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic, [2] Institute of Pathology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

Background & Objectives: Hepatocyte nuclear factor-1-beta (HNF1B) is a transcription factor crucial for kidney, urogenital tract, pancreas, gastrointestinal tract and liver development. It's involvement in cell cycle regulation and tumourigenesis has yet to be explained. Our aim was to characterise the spectrum of HNF1B mRNA splicing variants across different tissues for further expression analysis.
Methods: RNA (RQN>8.8) isolated from RNAlater stored tissues (uterine corpus, ovary, large intestine, kidney, pancreas and prostate carcinomas, all with paired normal tissues) was subjected to cDNA synthesis by SSIII transcriptase and random hexamers. Four random samples of each tissue type were pooled and analysed using in-house multiplex PCR (mPCR) of all present exon-exon junctions and NGS (Illumina).
Results: In total, 37/39 of the detected splicing variants were novel. Four predominant HNF1B transcripts, including two known (3q, Δ7_8) and two novel (Δ7, Δ8) splice variants were detected in all tissue types. In high grade serous carcinoma only four predominant transcripts were detected. In other tissue types multiple (14-28) variants were detected. The data suggests the expression of several tissue-specific transcript variants (e.g. Δ2_6 or Δ5_7), while the remaining variants were detected across the majority of the analysed tissue types.
Conclusion: The applied mPCR and NGS approach revealed a series of novel isoforms with unknown functions. The expression profiles of predominant or tissue specific variants will be analysed to complete the splicing pattern across different tissues.

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PS-04-004
Dual EGFR mutations: five years experience in one center
E. Bozkurtlar[1], H. Kaya[1]
[1] Marmara University School of Medicine, Department of Pathology, Turkey

Background & Objectives: The detection of EGFR mutations of lung cancer predicts the response to EGFR inhibitor therapies. This study was conducted to demonstrate our cohort's frequencies of dual EGFR mutations.
Methods: The cases of this study were tested at our center from 2014 to 2019.The cases were examined in Rotor-Gene Q®, a real time-PCRcycler, with EASY® EGFRKit.
Results: The EGFR mutation rate was found to be 11,9% among 2138 cases. The mean age of whole EGFR mutated cohort was 62. The most common mutations were 58% (N=148) on Exon 19del and 27% (N=69) on Exon 21. Fifteen cases (0,7% of 2138 EGFR screened cases) had dual mutations of EGFR and, 8 of 15 cases (0,37% of 2138 EGFR screened cases) had no previous anti-EGFR therapy history. The distribution of dual EGFR mutations was 2 cases with exon 21 and exon 20 T790M, 2 cases with exon 19 and exon 21, 2 cases with exon 18 and exon 19, 1 case with exon 19 and exon 20 T790M and,1 case with exon 18 and exon 21.
Conclusion: The frequency of EGFR of our cohort was 11,9%, similar to the Caucasian populations of the previous reports, and, also associated with gender (Female/male ratio: 3,8). The most common EGFR mutations were exon19 del and exon 21, respectively. The frequency of dual EGFR mutations of our untreated cases was 0,37%. We could not reveal any "most common mutation" in our dual EGFR mutation group.

PS-04-006
CTNNB1 and APC genes mutations analysis in a series of desmoid tumours
P. Cervera[1], S. Melloul[2], Y. Ditchi[3], Y. Parc[1], T. Andre[1], E. Guillerm[1], C. Colas[4], F. Coulet[1], J. Flèjou[1]
[1] APHP Sorbonne Université, France, [2] APHP, France, [3] Hôpital St Joseph, France, [4] Institute Curie, France

Background & Objectives: Desmoid tumours are slowly proliferating, non-metastasizing tumours with a highly invasive capacity, which can be life-threatening in the case of intra-abdominal localization in familial adenomatous polyposis syndrome (FAP), with a significant risk of recurrence. Because of the severe implications arising from the diagnosis of FAP desmoid tumour, it is critically important to distinguish desmoid tumours in FAP from sporadic desmoid, especially in young patients. According to Knudson's 'two-hit' theory, the occurrence of somatic inactivation of the APC gene in addition to germline inactivation, is a fundamental step in the onset of desmoids. In this study, we explore the two-hit theory in a series of FAP desmoids and the occurence of an APC second hit in sporadic CTNNB1 mutated desmoids.
Methods: Sanger sequencing and targeted next generation sequencing were performed in a series of paraffin embedded desmoid tumours in 86 patients.
Results: 50 (including 20 male) of 86 patients (49 male and 37 female) were diagnosed with a FAP desmoid. It was located in the abdominal wall or into the peritoneum of the abdominal cavity, and occasionally subcutaneously. 36 were diagnosed with a sporadic desmoid of more ubiquitous location. In all the FAP desmoids, a second hit APC gene mutation have occurred, with no CTNNB1 mutation. On the contrary, no APC mutation, have occurred in the sporadic desmoids.
Conclusion: In this desmoid tumours series, CTNNB1 and APC genes mutations are mutually exclusive inferring that highlighting a CTNNB1 mutation, exclude the diagnosis of FAP desmoid tumour.

PS-04-007
Soluble epoxide hydrolase as an important player in differentiation of intestinal cell: a lesson from cell culture and colorectal carcinoma tissue samples
K. Cizkova[1], Z. Tauber[1], K. Koubova[1], J. Firic[1], J. Ehrmann[2]
[1] Department of Histology and Embryology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic, [2] Department of Clinical and Molecular Pathology & Laboratory of Molecular Pathology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic

Background & Objectives: Soluble epoxide hydrolase (sEH) metabolize active CYP epoxygenase-generated metabolites of arachidonic acid to less active diols and may play a role in cell differentiation. In intestines, the increase in sEH expression was detected in apical part of villi or on the surface epithelium of colon and also in *in vitro* differentiated HT-29 and Caco2 colorectal carcinoma cell lines. The differentiation of absorptive intestinal cells is associated with increase in villin expression which assures the stability of microvilli of brush border.
Methods: Undifferentiated, sodium butyrate-differentiated HT-29 and spontaneously differentiated Caco2 cell lines were treated by TPPU (inhibitor of sEH). The expression of villin was measured by InCellELISA. The colorectal carcinoma and normal tissue samples were obtained from 45 patients in total (both samples from each patient). Detection of sEH and villin was performed by two-step immunohistochemical method.
Results: Administration of sEH inhibitor to differentiated HT-29 and Caco2 cell lines led to significant decrease of villin expression in comparison to control cells. The expression of both, sEH and villin was significantly decrease in carcinoma samples in comparison to normal tissue obtained from the same patient. Moreover, the decrease in sEH and in villin expression in patient samples revealed moderate positive association.
Conclusion: Our *in vitro* data suggest that sEH play an important role in differentiation of intestinal cells. This is supported by decrease of sEH and villin in tissue samples of patients with colorectal carcinoma.

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PS-04-008
Multi-center evaluation of tissue classification by mass spectrometry imaging
S. Deininger[1], C. Bollwein[2], R. Casadonte[3], P. Wandernoth[3], K. Kriegsmann[4], M. Kriegsmann[5], T. Boskamp[1], J. Kriegsmann[3], W. Weichert[2], P. Schirmacher[5], A. Ly[1], K. Schwamborn[2]
[1] Bruker Daltonik GmbH, Bremen, Germany, [2] Technical University of Munich, School of Medicine, Institute of Pathology, Germany, [3] Proteopath GmbH, Germany, [4] University Hospital Heidelberg; Department of Haematology, Oncology and Rheumatology, Germany, [5] University Hospital Heidelberg, Institute of Pathology, Germany

Background & Objectives: It is possible to perform tissue phenotyping based on mass spectrometric imaging data. However, comprehensive studies assessing the variation across different sites and their impact on tissue classification are largely lacking. Here, we have evaluated how well tissue classification based on Matrix-Assisted-Laser-Desorption/Ionization (MALDI) mass spectrometric imaging (MSI) can generalize across sites.
Methods: A tissue microarray (TMA) comprised of human FFPE samples representing 6 different tumour entities (leiomyoma, seminoma, mantle cell lymphoma, melanoma, invasive ductal carcinoma of the breast and squamous cell carcinoma of the lung) was used. These samples were prepared for MALDI-MSI and measured at three different sites using a standard protocol. The baseline performance of the classification task was evaluated by using cross-validation on the individual TMAs. We then evaluated how well a classification model based on data from two sites performed on the data of the remaining site.
Results: Selecting the relevant mass features for training the classifier was necessary for performance of classification. Treating the entire cores

as representative for the respective tumour entity, the baseline performance for the classification was an accuracy of 82.6% correct classifications. Accuracy over sites was 74.1%. With detailed histological annotations the classification accuracy was 92% on the individual TMAs and to 84% accuracy when applied over sites.
Conclusion: Initial results indicate that MALDI-MSI can be performed at a level that allows relevant multi-center research studies. MALDI imaging based tissue classifiers are able to generalize across sites. A detailed histological annotation of the tissue improves the performance of the classifiers.

PS-04-009

A novel method for isolation of tumour and healthy cells from FFPE carcinoma samples improves genetic analysis by next-generation sequencing

M. Delso-Vallejo[1], C. Poggel[1], R. Hilgers[1], J. Gaiser[1], J. Soyka[1], A. Bosio[1], S. Küffer[2], P. Ströbel[2], O. Hardt[1]
[1] Miltenyi Biotec, Germany, [2] Miltenyi Biotec, Germany, [3] Institute of Pathology, University Medical Center Göttingen, Germany

Background & Objectives: Vast archives of formalin-fixed paraffin-embedded (FFPE) samples represent an easily accessible resource in retrospective large-cohort studies for biomarker or neoantigen identification in cancer research. Despite the convenient handling and storage of FFPE samples, there are also some drawbacks to be considered. Solid tumours are heterogenous samples composed of both tumour and a non-tumour cells, and proportions of these two cell compartments can vary depending on the tumour type, disease stage, treatment, and other factors. The presence of non-tumour cells introduces a considerable bias in the molecular analysis of bulk FFPE samples. Therefore, enrichment of tumour cells prior molecular analysis is critical to obtain reliable results.
Methods: We present a fully automated protocol for the dissociation of FFPE samples that enables subsequent isolation of tumour and non-tumour cells from carcinomas, based on the expression of cytokeratin and vimentin. Dissociation is performed using the new FFPE Tissue Dissociation Kit in combination with the gentleMACS™ Octo Dissociator with Heaters. After dissociation, we tested different carcinoma samples for ploidy analysis using flow cytometry, and mutation analysis by next generation sequencing.
Results: Reliable analysis of the ploidy content of cytokeratin-positive carcinoma cells was achieved using vimentin-positive non-tumour cells as internal control. Furthermore, automated FFPE dissociation did not compromise DNA stability, and isolation of carcinoma cells (>95% purity) significantly enriched tumour-specific single nucleotide variants, e.g.: KRAS and TP53 genes.
Conclusion: This new automated protocol for FFPE dissociation allows the specific isolation of tumour and non-tumour cells to enhance the sensitivity of genetic analysis of carcinomas.

PS-04-012

Comparison between Fluorescence In Situ Hybridization (FISH) and Dual In Situ Hybridization (DISH) in the determination of HER2 status in breast cancer among Filipinos

G.A. Espiritu[1], E. dela Fuente[2], M. Diwa[1]
[1] Makati Medical Center, Philippines, [2] San Juan de Dios Educational Foundation Inc. - Hospital, Philippines

Background & Objectives: HER2 monoclonal antibody has been effective in the treatment of breast cancer with HER2 overexpression. Fluorescent in situ hybridization (FISH) has been used for determination of *HER2* amplification in cases of breast cancer with equivocal HER2 expression by immunohistochemistry (IHC). We determined the concordance between FISH and a relatively new method, dual in situ hybridization (DISH), in evaluating *HER2* status of breast cancers among Filipinos.
Methods: DISH results of 140 breast cancer patients with equivocal (2+) HER2 immunohistochemical staining at Makati Medical Center from October 2012 to September 2016 were reviewed. FISH testing was performed using dual-color PathVysion *HER2* DNA Probe Kit (Abbott Molecular, Illinois). FISH and DISH results were categorized according to the 2013 ASCO/CAP scoring criteria for in situ hybridization. Overall concordance and kappa coefficient were determined.
Results: Thirty-eight of 140 DISH results reviewed had available paraffin blocks with adequate tumour cells and were therefore subjected to FISH testing. Demographics included 38 females with median age of 56 years old (range: 19 to 77 years old). Twenty-seven (27) cases (71.05%) had higher histologic/ nuclear grades. The median tumour size was 1.9 cm (range: 0.7 to 6.0 cm). Overall concordance was 63.16% with kappa coefficient of 0.2267. Both testing methods were predominated by nonamplified cases.
Conclusion: The overall concordance did not fulfil the ASCO/CAP recommendation of 95% concordance. The findings are consistent with three other studies done in the last 5 years. Given the technical advantage of DISH over FISH, further investigation of its correlation with treatment response in a larger, multicenter cohort is warranted to determine more suitable cut-off values.

PS-04-013

Tumour mutation burden: from recommendations for testing to external quality assessment schemes

F. Fenizia[1], B. Besse[2,3], Z.C. Deans[4], E.M. Dequeker[5,6,7], M. Horan[8], S. Patton[9], E. Rouleau[10], E. Torlakovic[11], N. Wolstenholme[9], N. Normanno[1]
[1] Istituto Nazionale Tumouri "Fondazione Giovanni Pascale", IRCCS, Naples, Italy, [2] Department of Cancer Medicine, Gustave Roussy, Villejuif, France, [3] Paris-Sud University, Orsay, France, [4] UK NEQAS for Molecular Genetics, Department of Laboratory Medicine, Royal Infirmary of Edinburgh, Little France Crescent, United Kingdom, [5] Biomedical Quality Assurance Research Unit, Department of Public Health and Primary Care, KU Leuven, Belgium, [6] University Hospital UZ Leuven, Departement of Medical Diagnostics, Belgium, [7] European Society of Pathology (ESP), Anderlecht, Belgium, [8] RCPAQAP Molecular Genetics, St. Leonard's, Sydney, Australia, [9] European Molecular Genetics Quality Network (EMQN), Manchester Centre for Genomic Medicine, St Mary's Hospital, United Kingdom, [10] Department of Pathology and Medical Biology, Institute Gustave Roussy, Villejuif, France, [11] Department of Pathology and Laboratory Medicine, College of Medicine, University of Saskatchewan, and Saskatchewan Health Authority, Saskatoon, Canada

Background & Objectives: Immune checkpoint inhibitors (ICI) are changing the paradigm of treatment of several tumour types. Tumour mutation burden (TMB) has been associated with benefit to ICIs in multiple cancer types, representing a possible predictive biomarker. TMB measures the total number of mutations per coding area of a tumour genome. Different NGS panels for TMB calculation in clinical practice are under development. Appropriate external quality assessment (EQA) schemes are required to ensure that patients receive a TMB test of adequate quality.
Methods: The International Quality Network for Pathology (IQN Path), with the endorsement of ESMO, is conducting a project to organize EQA schemes for the evaluation of TMB in clinical practice. The first part of the study is the identification of adequate control material. Therefore, ten formalin-fixed paraffin-embedded tumour cell lines provided from SeraCare will be assessed for TMB using different approaches. Five tumour cell lines will be then chosen to be used as a standard reference material. This reference will be further validated in a pilot EQA scheme for TMB. Thirty laboratories will be selected to participate in the EQA through a survey that will assess which centres offer TMB testing, their expertise and the technology used for testing.

Results: We will present the results of the survey and the validation of the control material performed within the pilot EQA scheme for TMB.
Conclusion: The use of TMB as predictive biomarker poses different challenges for molecular pathology laboratories. The ESMO-IQNPath project will help harmonize TMB testing in clinical practice.

PS-04-014

Concordance of Ventana SP218 PTEN IHC and CST138G6 PTEN IHC assays with known PTEN genetic status in prostate cancer

R. Fish[1], P. Scorer[1], P. Lao-Sirieix[2], M. Kockx[3], E. de Bruin[4], M. Roudier[4], A. Sharp[5], B. Ehrhardt[5], C. Barker[1]
[1] Precision Medicine Laboratories, Precision Medicine and Genomics, IMED Biotech Unit, AstraZeneca, Cambridge, United Kingdom, [2] Oncology Companion Diagnostics Unit, Precision Medicine and Genomics, IMED Biotech Unit, AstraZeneca, Cambridge, United Kingdom, [3] HistoGeneX Laboratories, Belgium, [4] Translational Science, IMED Biotech Unit, AstraZeneca, Cambridge, United Kingdom, [5] Quantitative Biology, Discovery Sciences, IMED Biotech Unit, AstraZeneca, Cambridge, United Kingdom

Background & Objectives: *PTEN* tumour suppressor is a major inhibitor of the PI3K pathway, involved in cell growth regulation, and one of the most commonly altered genes in prostate cancer. *PTEN* deleterious mutations occur in 10-70% of surgically resected prostate and over 50% of metastatic prostate cancers. This study was undertaken to show inter-reader and inter-assay agreement between two PTEN immunohistochemistry (IHC) assays in samples from patients with a known *PTEN* genetic status.
Methods: 97 prostate biopsy samples, previously sequenced by FMI (Foundation Medicine Inc) using the FoundationOne CDx Clinical Trial Assay, were stained with two different PTEN antibodies, Ventana SP218 mAb and CST138G6, validated on the Ventana Benchmark XT and Labvision platforms respectively. Concordance at matched cut-offs were analysed between assays and readers, reported and compared with sequencing data.
Results: Using two cut offs, H score (<10) and percent tumour staining (<50%), inter-assay concordance was 92-96%. There was a consistent and moderate variability between the two PTEN IHC pathologist scoring evaluations with overall percent agreement on PTEN status for each assay of 89-94%. Both IHC assays were capable of aligning PTEN protein loss with *PTEN* genetic loss; only 2 of 29 samples with genetic loss consistently scored as PTEN protein proficient by both IHC assays and both pathologists.
Conclusion: This study showed that Ventana SP218 and CST138G6 IHC assays demonstrated inter-reader and inter-assay agreement. Both assays were capable of aligning PTEN protein loss with genetic status. Therefore, IHC could potentially provide a cheap and fast assay to identify prostate cancer patients whose tumours are PTEN deficient.

PS-04-015

Somatic mutations in KRAS, NRAS and BRAF genes in patients with colorectal cancer from Lower Silesia Region - a preliminary report

L. Fulawka[1], L. Hajac[1], M. Glosna[2], D. Michalowska[1]
[1] Lower Silesian Oncology Centre, Poland, [2] Wroclaw Medical University, Poland

Background & Objectives: Mutational status of KRAS/NRAS/BRAF in colorectal cancer tumours is associated with the clinical response and resistance to anti-EGFR mAbs (epidermal growth factor monoclonal antibodies) such as cetuximab and panitumumab.
Here, we report preliminary results from an ongoing study aimed at molecular profiling of KRAS, NRAS, BRAF genes. Obtained data were correlated with clinico-pathological features in colorectal cancer.
Methods: In 2017-2019 period, KRAS/NRAS/BRAF somatic mutation analysis was carried in 396 patients with colorectal cancer treated in Lower Silesian Oncology Centre in Wroclaw.
Molecular tests were conducted with Idylla System (Biocartis), real-time PCR based molecular diagnostics system. The following tests were used: KRAS 3.0 and NRAS/BRAF 1.0. Quantitative analysis was performed automatically by algorithm included in the software provided by the manufacturer.
Detailed clinical and pathological data were collected for 172 patients by the date the poster was created.
Results: Mutations in KRAS gene were detected in 48% (190) patients. NRAS and BRAF genes revealed mutations in 4,8% (19) and 6,6% (26) cases, respectively. Non-diagnostic results were obtained in 4% (16) cases. The frequency of mutations (as a relative percentage of all mutated cases) is presented in the table below:

Gene	Mutation	%
KRAS	KRAS G12D	23,8%
	KRAS G12V	20,0%
	KRAS G13D	11,5%
	KRAS G12A	6,0%
	KRAS G12C	5,1%
	KRAS A146P/T/V	4,3%
	KRAS G12S	3,4%
	KRAS Q61H	1,7%
	KRAS G12R	1,3%
	KRAS A59T/E/G	1,3%
	KRAS Q61L/R	1,3%
	KRAS K117N	0,9%
	KRAS Q61K	0,4%
NRAS	NRAS Q61K	2,1%
	NRAS Q61R	1,7%
	NRAS G12D	0,9%
	NRAS G12C	0,9%
	NRAS G13R/V	0,9%
	NRAS Q61L	0,9%
	NRAS Q61H	0,4%
	NRAS A146T/V	0,4%
BRAF	BRAF V600E/D	11,1%

Relationship between frequency of KRAS/NRAS/BRAF mutations and detailed clinical and pathological data (including TNM, histological grade, tumour size, localization of primary tumour and metastases) for limited numer of patients was presented in the poster.
Conclusion: The frequency of KRAS/NRAS/BRAF mutations in colorectal cancer from Lower Silesia Region are similar to frequencies reported by other investigators.

PS-04-016

NSD2 promotes triple-negative breast cancer cell proliferation, migration and invasion by inhibiting TIMP3 expression

B. Gao[1], Y. Li[2], Y. Pan[3]
[1] Department of Pathology, Affiliated Hospital of Dali University, Yunnan, China, [2] Department of Pathology, College of Basic Medical Science, Dali University, Yunnan, China, [3] The First Affiliated Hospital of Dali University, China

Background & Objectives: The triple-negative breast cancer (TNBC) is the most malignant type of breast cancer. Its pathogenesis and prognosis remain poor largely due to lack of effective targeted therapy. NSD2 (WHSC1/

MMSET) is a histone methyltransferase, which specifically catalyzes H3K36 dimethylation (H3K36me2). NSD2 is frequently overexpressed in multiple types of cancer and usually associated with malignant progression of tumours. However, the function of NSD2 remains unknown in TNBC. This study aimed to explore the role of NSD2 in TNBC.
Methods: To investigate the role of NSD2 in TNBC cell proliferation, migration and invasion in vitro, CCK8 assay, wound healing and transwell assay were performed in MDA-MB-231 cell line, using a recombinant lentivirus expressing NSD2-shRNA. Gene microarray was also performed in cells with stably knockdown of NSD2 to screen its potential downstream genes.
Results: Both NSD2 and H3K36me2 expression were significantly decreased in MDA-MB-231 cell line with stably knockdown of NSD2. NSD2 knockdown significantly attenuated the proliferation, migration and invasion of MDA-MB-231 cells. Among the differentially expressed genes resulted from knockdown of NSD2, TIMP3 was one of the upregulated genes, which functions as a tumour suppressor. NSD2 knockdown mediated upregulation of TIMP3 was also demonstrated by qPCR and western blot analysis.
Conclusion: NSD2 may work as a novel repression of TIMP3 and inhibiting NSD2 expression suppressed the proliferation, migration and invasion of TNBC cells by increasing TIMP3 expression, suggesting that NSD2 may be a potential therapeutic target of TNBC.

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PS-04-017

EZH2-miR-26a-5p-NSD2 axis contributes to cell proliferation and DNA repair and inhibit cell apoptosis in diffuse large B-cell lymphoma

Y. Pan[1], B. Gao[2], Y. Li[3]
[1] The First Affiliated Hospital of Dali University, China, [2] Department of Pathology, Affiliated Hospital of Dali University, Yunnan, China, [3] Department of Pathology, College of Basic Medical Science, Dali University, Yunnan, China

Background & Objectives: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma in adults with diverse biological and clinicopathological features. EZH2 and NSD2 (WHSC1/MMSET) are histone methyltransferases (HMTases) involving in the regulation of gene expression and oncogenesis. It has been reported that EZH2-NSD2 HMTase axis is coordinated by a microRNA network. However, the relationship between them in DLBCL has not been fully elucidated. The current study aimed to assess the expression of EZH2 and NSD2 and further explore the potential regulatory mechanism in DLBCL.
Methods: In this study, we performed immunohistochemical analysis to explore the expression pattern of EZH2 and NSD2 in 105 cases of DLBCL. U2940 cells were treated with different concentrations of GSK126, a selective inhibitor of EZH2, and then cell proliferation was assessed by CCK8 assay and soft agar colony formation assay. Cell cycle and cell apoptosis were analysed by flow cytometry. EZH2, NSD2, histone methylation levels and DNA repair proteins were detected by western blot analysis. MiRNA array in DLBCL, bioinformatic analysis and qPCR were performed to identify miRNAs by which EZH2-NSD2 axis is coordinated. EZH2-miRNA-NSD2 axis was verified in 293T cells transfected with EZH2-shRNA. Dual luciferase reporter assay was performed to confirm whether NSD2 is the target gene of identified miRNA.
Results: Both EZH2 and NSD2 were highly expressed and positively correlated with each other in DLBCL. Aberrant expression of EZH2 and NSD2 were also correlated with high level of Ki-67 proliferation index. Suppressing EZH2 activity using GSK126 resulted in inhibition of cell viability and colony formation of U2940 cells in a dose- and time- dependent manner. GSK126 also inhibited DNA synthesis, blocked cell cycle in G0/G1 phase, and induced cell apoptosis. EZH2, which mediates histone H3K27 trimethylation and is associated with gene silencing, was shown to be coordinately expressed and function upstream of NSD2, which mediates H3K36 and H4K20 dimethylationand is associated with active transcription of DNA damage repair genes, such as XPA and 53BP1. GSK126 could downregulated the expression of NSD2, H3K36me2, H4K20me2, XPA and 53BP1, meanwhile upregulated the expression of γH2AX, a marker of DNA damage. In addition, five miRNAs including miR-26a-5p, miR-30c-2-3p, miR-196a-5p, miR-200c-3p and miR-622, were downregulated in miRNA profiling of DLBCL and predicted as regulators of NSD2. GSK126 significantly increased the expression of miR-26a-5p in U2940 cells. Furthermore, the similar expression changes of these proteins and miR-26a-5p were observed in 293T cells transefected with EZH2-shRNA. MiR-26a-5p was demonstrated to bind to 3'-UTR of NSD2 gene and negatively regulate NSD2 expression.
Conclusion: Taken together, high expression of EZH2 indirectly upregulated NSD2 via suppression of miR-26a-5p. These results suggest that EZH2-miR-26a-5p-NSD2 axis plays a critical role in the proliferation, apoptosis and DNA repair of DLBCL and may represent an attractive therapeutic target in cancer.

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PS-04-018

KRAS/NRAS and BRAF molecular characterisation through Next-Generation Sequencing (NGS) techniques in colorectal cancer

M. Gonzalez Farre[1], M.C. Fernández Rodríguez[1], L. Masfarre[2], G.M. Parini[1], N. Navarro[2], E. Moragón[1], G. Piquer[1], R. Rueda[1], J. Gimeno[1], D. Naranjo-Hans[1], B. Bellosillo[1], B. Lloveras[3], M. Iglesias[1]
[1] Pathology Department, Hospital del Mar, Spain, [2] Oncology Department, Hospital del Mar, Spain, [3] Hospital del Mar, Spain

Background & Objectives: Evidence supports testing *BRAF* (V600) and *KRAS*, *NRAS* (exons 2, 3 and 4) mutations in colorectal cancers (CRC), since they provide prognostic and clinically actionable information for targeted therapy with anti-EGFR monoclonal antibodies. Several reference molecular tests and Next-generation sequencing (NGS) techniques are used.
Methods: From January 2018 to March 2019, the analysis of *KRAS/NRAS/BRAF* was performed through KRAS RGQ PCR, Therascreen RAS Pyro Extension and Therascreen BRAF Pyro (QIAgen®) in 22 CRC cases and through KRAS mutation kit and NRAS-BRAF mutation kit (Idylla, Biocartis®) in 51. All the cases were studied through the NGS Oncomine Solid Tumour DNA panel (Ion Torrent, Thermo Fisher®), covering hotspot regions in 22 genes.
Results: Among the 73 cases, *KRAS*, *NRAS* (exons 2, 3 and 4) and *BRAF* (V600) mutations were detected in 54 (73.97%) patients and 18 were wild-type for these positions. All the mutations observed by the reference tests were also detected by NGS (VAF 1.3-71.1%). Nevertheless, 4 more cases (6.15%) with infrequent mutations of *KRAS* (exon 2) were detected only by NGS because these specific mutations are not included with the reference tests. Additionally, mutations in other genes were detected in 58 cases (79,45%), predominantly in *TP53*, *PIK3CA* and *SMAD4*.
Conclusion: NGS allowed the detection of all the variants detected by the reference methods (based in qPCR/pyrosequencing). Nevertheless, 4 infrequent mutations in the *KRAS* gen were found in positions not covered by the reference tests, as well as additional mutations in other genes with potential implication for the clinical therapeutic management of these patients.

PS-04-019

Inflammation slightly increases PCA3 which does not affect its contribution to the refinement of prostate biopsy decision making in combination with percentage of free PSA, AMACR, EPCAM and PSGR

Z. Huskova[1], J. Knillova[1], M. Kral[2], Z. Kolar[3], J. Bouchal[4]
[1] Palacky University, Czech Republic, [2] Department of Urology, Faculty Hospital in Olomouc, Czech Republic, [3] Department of Clinical and

Molecular Pathology, Palacky University and University Hospital Olomouc, Czech Republic, [4] Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Olomouc, Czech Republic

Background & Objectives: Urinary biomarkers may help urologists to make decisions for the diagnosis of prostate cancer (PCa). In this study, we aimed to validate a panel of urine markers, %free PSA and inflammation in the cohort of PSA dilemma patients.
Methods: In the main cohort of 299 men, we tested the quadruplex transcripts (AMACR, PCA3, TRPM8, MSMB). In a smaller cohort of 146 men, we also analysed additional transcripts (CD45, EpCAM, EZH2, Ki67, PA2G4, PSGR, RHOA, TBP). After the prostate massage, the urine was collected, RNA isolated, qRT-PCR performed. The results were statistically processed with respect to the clinico-pathological parameters.
Results: Expressions of AMACR, PCA3, TRPM8 and EZH2, as well as %free PSA, were statistically different between BPH and CaP (p values 0.045, 0.004, 0.005, 0.019 and 0.003, respectively). The best combined model (%free PSA plus PCA3 and AMACR) achieved AUC 0.728 in the main cohort. In the subset of patients, the best AUC 0.753 was achieved for combination of PCA3, %free PSA, EPCAM and PSGR. Ct values of KLK3 strongly correlated with Ct values of other genes which play a role in prostate cancer (i.e. PCA3, AMACR, TRPM8, MSMB and PSGR). PCA3 (p=0.041) and serum PSA (p=0.005) were increased in patients with inflammation.
Conclusion: The percentage free PSA and urinary markers distinguish prostate cancer from benign hyperplasia and contribute to a more accurate indication for prostate biopsy.

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PS-04-020

Discovering triggers of IgA nephropathy progression by Matrix-assisted laser desorption/ionisation mass spectrometry imaging

M. Ivanova[1], O. Dyadyk[2], A. Smith[1], F. Magni[1]
[1] Università Milano-Bicoccà, Milan, Italy, [2] P.L. Shupyk National Medical Academy of Postgraduate Education (NMAPE), Kiev, Ukraine

Background & Objectives: IgA nephropathy (IgAN) is one of the most diffuse mesangioproliferative glomerulonephritis (MPGN) worldwide. The disease is well known for its multifaceted clinical nature and has many issues on predicting the outcome. The ongoing research of prognose predicting biomarkers is being reported. Matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) is a proteomics technique used for biomarker discovery directly on-tissue. Therefore, MALDI-MSI was used to investigate the molecular profile of IgAN to reveal proteins related to disease progression.
Methods: Kidney biopsies of 14 patients were enrolled with previously histopathologically confirmed diagnosis of IgAN and MPGN. Patients in both groups were divided into three categories (mild, moderate and advanced) based on stage of chronic kidney disease (CKD). MALDI-MSI analysis were performed on all bioptic tissues with following histological staining of the same sample for signal co-localisation. The average molecular profiles of IgAN and MPGN biopsies were obtained, compared to each other altogether and separately in each group.
Results: 14 discriminative peaks that distinguish IgAN average molecular profile from MPGN were putatively identified.
All MPGN patients had similar proteomic profile independently from the CKD stage while differences were observed between mild versus moderate/advanced IgAN.
No differences were noticed between mild IgAN versus mild/moderate MPGN.
Conclusion: IgAN, characterised by more aggressive course, shows different proteomic signature for moderate/advanced versus mild stage and minimal difference for advanced versus moderate stage IgAN patients. Therefore, the moderate stage of IgAN could be considered the point of most important irreversible changes having a remarkable altered proteins signature. These proteins with an altered expression could be proposed as possible progression biomarkers.

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PS-04-021

Fast immunofluorescence multiplexing using a microfluidic precision autostainer and tyramide signal amplification

A. Kehren[1], S. Adnane[1], B. Pelz[1], S. Brajkovic[1], C. Hoyt[2], D. Dupouy[1]
[1] Lunaphore Technologies SA, Switzerland, [2] Akoya Biosciences, USA

Background & Objectives: Immuno-oncology and targeted molecular therapies have acquired a central role in the treatment of multiple cancers. Consequently, high-throughput biomarker analysis and tumour immune profiling have seen an increased demand. Multiplexed immuno-assays are a powerful tool to address these needs, but still time- and resource-consuming. Our goal is to develop a fast and automated high-plex fluorescent immunostaining procedure, using a microfluidic-based device, that can be easily implemented as routine assay.
Methods: Tissue samples are formalin-fixed paraffin embedded (FFPE) sections of human tonsil. Slides are manually deparaffinized before being entirely processed (antigen-retrieval, staining, elution and counterstaining) by Lunaphore's autostainer, LabSat™. The OPAL™ tyramide signal amplification (TSA) system is used as detection method. Signal analysis is done on Mantra™ workstation. The 6-plex panel entails FoxP3, PD-L1, PD-1, CD68, CD8 and pan-CK, plus DAPI counterstaining.
Results: Our platform allowed to reduce drastically the incubation times due to active transport of reagents across the tissue. Thereby, the automated 6-plex assay could be performed in less than 4h30min. Protocol optimization resulted in high signal-to-background ratio for each marker, and removal of previous step antibodies over 99%. LabSat™ also guaranteed remarkable signal uniformity, even over large tissue sections.
Conclusion: LabSat autostainer enables 6-plex multistaining runs in a timely manner, opening the perspective of including tumour microenvironment screening in routine diagnostics. Moreover, the control over staining parameters provided by the microfluidic technology delivers high-quality results and very good reproducibility. We believe that our platform, combined with the OPAL TSA detection system, could pave the way for fast quantitative multiplexed biomarker analysis.

PS-04-022

A comparative study of "PD-L1-CAD-test" (BIOCAD) and "PD-L1 IHC 22C3 pharmDx Kit" (Dako)

G. Frank[1], O. Kuznetsova[1], L. Zavalishina[1], Y. Andreeva[1], L. Moskvina[1]
[1] Fsbei Fpe Rmacpe Moh Russia

Background & Objectives: A comparative study of the concordance of detection PD-L1 expression by «PD-L1-CAD-test» (BIOCAD) FCC (Federal Service for Surveillance in Healthcare) Approved in Russia) and PD-L1 IHC 22C3 pharmDx Kit (Dako) FDA Approved/FSS Approved in Russia) in Non Small Cell Lung Carcinoma.
Methods: 30 tissue samples of NSCLC were retrospectively collected. Cell lines and positive control (tonsil) were used for control staining. PD-L1 expression was studied at the same sections using BIOCAD test and Dako test with Avtosteiner Link 48. Each section was stained twice in 10 days for indentifying intralaboratory concordance. Staining of tumour and immune cells was assessed. PD-L1 status was considered positive in the case of full or partial staining 1% or more tumour cells with any expression intensity.
Results: Results were concordant in 100% of cases either for control and for diagnostic staining NSCLC (κ, 0.70; 95% confidence interval, 0.48-0.96). In 3 samples the number of positive immune cells was less with «PD-L1-CAD-test», but not more than 10%. In 4 cases the low intensity

of reaction with "PD-L1-CAD-test" was detected. The concordance of the tumour status after 10 days for both control materials and NSCLC samples was 100% (κ, 0.70; 95% confidence interval, 0.48-0.96).
Conclusion: The concordance of PD-L1 status with «PD-L1-CAD-test» (BIOCAD) and «PD-L1 IHC 22C3 pharmDx Kit» (Dako) was 100%. So, the «PD-L1-CAD-test» (BIOCAD) can be used in routine practice to determine PD-L1 status in NSCLC according to statistical criteria

PS-04-024
Elevated TCRB repertoire convergence and clonal expansion in the NSCLC tumour microenvironment of responders to anti-PD-1 monotherapy
K. Leonards[1], I. Alborelli[1], T. Looney[2], L. Quagliata[2], P.M. Jermann[1]
[1] University of Basel, Switzerland, [2] Thermo Fisher Scientific, USA

Background & Objectives: There is an outstanding need to identify predictive biomarkers for response to anti-PD-1 monotherapy for NSCLC. Here we investigated TCRB clonal expansion and TCR convergence within the pretreatment tumour microenvironment as predictors of response. For context, we compared the predictive value of these features with TMB values from the same tumours.
Methods: Total RNA from FFPE-preserved pretreatment NSCLC biopsies (11 responders, 14 non-responders) was extracted for TCRB repertoire sequencing via the Oncomine TCRB-SR assay (15-265ng RNA input; average 164ng) and the Ion Torrent Gene Studio S5. TMB values were obtained from FFPE-preserved gDNA from the same biopsies using the Oncomine Tumour Mutation Burden Assay. TCR convergence and clonal expansion were evaluated independently or in a combined model as predictors of response.
Results: TCRB sequencing revealed increased TCR convergence ($p = .02$, Wilcoxon) and clonal expansion ($p = .06$, Wilcoxon) in those who benefited from anti-PD-1 therapy. A logistic regression classifier combining both features was able to discriminate responders from non-responders with a sensitivity of .91 and specificity of .71 at the optimal cutoff, per the Youden's J method. The TCR-based classifier was able to identify responders who otherwise had low to intermediate (<10muts per Mb) TMB.
Conclusion: TCRB clonal expansion and convergence warrant further evaluation as potential predictive biomarkers of response. Importantly, TCRB sequencing may allow for identification of responders who are otherwise missed by TMB-based stratification.

PS-04-025
Immunocytochemical detection of selected proteins in myeloma cells after their treatment with epigenetic modulators
P. Luzna[1], K. Cizkova[1], Z. Kolar[1], K. Smesny Trtkova[1]
[1] Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

Background & Objectives: Tumour suppressor or cell cycle regulating genes, which may play important role in multiple myeloma pathogenesis, are often aberrantly methylated. Methylation of these genes can be followed by loss of their function. The aim of our study was to analyse the methylation status of CDKN2B (protein p15) and PDLIM4 (PDZ and LIM domain protein 4) tumour suppressor genes in 2 myeloma cell lines treated with 3 selected epigenetic modulators and to detect possible changes of these genes at their protein level by immunocytochemistry (ICC).
Methods: Two multiple myeloma cell lines (RPMI 8226, U266) were treated with 3 epigenetic modulators: Decitabine, Suberohydroxamic Acid and Disulfiram (all in various concentrations). After 48 hours, RNA and DNA were isolated and quantitative real-time PCR and methylation analysis (methylation-specific PCR and pyrosequencing) were done. Further, portion of the treated cells was spread on glass slides and two-step immunocytochemical detection of 2 desired proteins was performed.
Results: Immunocytochemical detection of PDZ and LIM domain protein 4 showed changes in its expression in both cell lines when treated and untreated samples were compared. This finding corresponds to the result of PDLIM4 gene methylation status and correlates with both expression and methylation analysis. Talking about CDKN2B, no methylation of this gene was detected in both cell lines. This fact was confirmed by the ICC analysis as well.
Conclusion: Protein expression in myeloma cell lines is usually detected by the time consuming ELISA method, however our study shows a high functionality of much more faster ICC staining. Here, ICC could serve as an effective tool for assessment of the methylation status of selected genes. Of course, further experiments are necessary to obtain useful information about demethylation effect of epigenetic modulators which might be used for multiple myeloma treatment in the future.

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PS-04-026
Silencing of E-cadherin in colorectal cancer cells changes their sensitivity to chemotherapy
M. Manethova[1,2], J. Soukup[1,2], V. Skarkova[3]
[1] The Fingerland Department of Pathology, University Hospital Hradec Kralove, Czech Republic, [2] Charles University Faculty of Medicine in Hradec Kralove, Czech Republic, [3] Faculty of Medicine in Hradec Kralove, Charles University, Czech Republic

Background & objectives: Colorectal carcinoma (CRC) is a malignant tumour with high incidence in developed countries. The treatment consists usually of multimodal approach including chemotherapy. Several factors including epithelial-mesenchymal transition may play the role in the development of chemoresistance during the treatment. We tried to elucidate the role of E-cadherin in the development of chemotherapy resistance in colon cancer cells, especially with drug sensitivity to irinotecan (IT) and oxaliplatin (OPT).
Methods: The effect of IT and OPT on the cell proliferation using WST-1 analysis were compared and IC50 values were determined in colon cancer cell line SW480 and its E-cadherin silencing variant (SW480/siCDH1) and in two primary cell lines 47B and 48B obtained from two patients who underwent surgery for CRC. The mRNA and protein level were studied using RT-PCR and western blot analysis. Simultaneously, metabolism of IT and OPT was evaluated using LC-MS analysis.
Results: The viability was significantly reduced after IT/OPT treatment in all tested cell lines. Higher expression of mesenchymal markers was detected in SW480/siCDH1 cells together with increased intracellular accumulation of IT/OPT compared to SW480 cells. SW480/siCDH1 cells were more sensitive to IT/OPT, compared to SW480 cells. Conversely, mesenchymal markers were highly expressed in primary CRC cells 47B, compared to 48B cells, but higher accumulation of IT/OPT and higher sensitivity to IT/OPT were detected in 48B cells compared to 47B cells.
Conclusion: In SW480/siCDH1 cells accumulated higher amount of IT and OPT and were more sensitive to both treatments, even if the mesenchymal markers were expressed significantly, compared to SW480 cells. On the other hand, cells expressing mesenchymal markers were more resistant to IT and OPT treatment and accumulated lower amount of IT and OPT, compared to cells with retained epithelial phenotype.

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PS-04-027
Acquired resistance mechanisms to EGFR tyrosine kinase inhibitors in lung cancer: coexistence of T790M with phenotypic small cell transformation

J. Martin Lopez[1], P. Martin Acosta[1], E. Tejerina Gonzalez[1], D. Garcia Fresnadillo[1], Y. Vicente Lago[1], L. Martín[1], M. Exposito Alcaide[1], C. Salas Anton[1]
[1] Department of Pathology. Hospital Universitario Puerta de Hierro, Spain

Background & Objectives: Patients with non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) activating mutation can obtain significant tumour regression with EGFR tyrosine kinase inhibitors (TKIs).
Several mechanisms of acquired resistance to EGFR TKIs have been reported: secondary mutations in EGFR, a by-pass tracks activation of EGFR, phenotypic tumour transformation and additional genetic alterations together with EGFR mutation.
Methods: We present a case of EGFR-mutated lung adenocarcinoma (ADC) with two acquired mechanisms of resistance to EGFR TKIs.
Results: A 50-year old female with stage IV lung adenocarcinoma (T2bN3M1b) activating EGFR mutation (exon 19 deletion) treated with TKIs. After initial response to treatment for almost 2 years, radiologic studies demonstrated progression with new histological samples demonstrating an adenocarcinoma with T790M mutation. MET amplification was not found. After 9 months with second generation TKIs in cytological and histological samples, we observed transformation to small-cell lung carcinoma (SCLC) validated with morphology and confirmed by immunohistochemistry (TTF1+, CD56+, synaptophysin+, Ki67 index: 90%). Small cell histology was not found in pre-resistance samples, which show conventional adenocarcinoma morphology. On a second reevaluation, 6 months later, we obtained new samples with combination of adenocarcinoma and SCLC and the same molecular alterations.
Conclusion: Histologic transformation into SCLC has been described as one of the resistance mechanisms to EGFR TKIs. Recognition of small cell carcinoma transformation in acquired resistance samples is critical because this probably requires a switch into other chemotherapy regimens. In some cases, this phenotypic transformation occurred in addition to another mechanisms of resistance such in the current case where two alterations were involved.

PS-04-028

Colocalization of Skp2 and Slug proteins and their possible interaction in aggressive prostate cancer

A. Mičková[1], G. Kharaishvili[2], M. Kral[3], M. Gachechiladze[1], M. Mistrik[4], J. Bouchal[5]
[1] Department of Clinical and Molecular Pathology, Palacky University and University Hospital, Olomouc, Czech Republic, [2] Department of Clinical and Molecular Pathology, Faculty Hospital in Olomouc, Czech Republic, [3] Department of Urology, Faculty Hospital in Olomouc, Czech Republic, [4] Laboratory of Genome Integrity, Institute of Molecular and Translational Medicine, Palacky University, Olomouc, Czech Republic, [5] Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Czech Republic

Background & Objectives: Skp2 is a substrate recruiting component of E3 ubiquitin-ligase complex, while Slug is a transcriptional repressor involved in epithelial-mesenchymal transition. Skp2 plays an important role in prostate cancer progression, e.g. via recently reported stabilization of EZH2 or Twist1, however, relationship with Slug needs further elucidation.
Methods: Prostate cancer patients cohort (N=101) was analysed by immunohistochemistry for the following proteins (Skp2, Slug, AR, Ki-67 and E-cadherin). Colocalization analysis was performed using Perkin Elmer Opal Multiplex kit, Vectra 3.0 imaging system and confocal microscope Carl Zeiss LSM 780. Prostate cancer PC3 cells were treated with a SCF^{Skp2} E3 ligase inhibitor MLN4924 and analysed by western blot.
Results: High Gleason score was significantly associated with higher Skp2 and lower E-cadherin expression ($p<0.001$ and 0.011, respectively). Skp2 slightly correlated with Slug and AR in the whole cohort (Rs 0.32 and 0.37, respectively), which was enhanced in patients with high Gleason score (Rs 0.56 and 0.53, respectively) or with metastasis to lymph nodes (Rs 0.56 and 0.37, respectively). Confocal microscopy revealed colocalization of Skp2 and Slug in prostate cancer cells. Chemical inhibition of Skp2 by MLN4924 upregulated p27 and decreased Slug expression which supports a possible link between Skp2 and Slug proteins.
Conclusion: Immunohistochemistry, colocalization studies and in-vitro experiments support association between Skp2 and Slug in aggressive prostate cancer.

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PS-04-029

Validation of a highly sensitive real-time PCR assay for detecting EGFR T790M mutation in liquid biopsy samples

M. Novy[1], I. Ticha[2], M. Vocka[3], K. Gesson[1], L. Petruzelka[3], C. Oberkanins[1]
[1] ViennaLab Diagnostics, Vienna, Austria, [2] Institute of Pathology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [3] Department of Oncology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

Background & Objectives: Epidermal growth factor receptor (EGFR) mutations are found in 10-30% of non-small-cell lung cancer (NSCLC) patients. Patients with activating EGFR mutations usually benefit from tyrosine kinase inhibitor (TKI) therapy, but 50% of patients acquire resistance due to the T790M mutation. Osimertinib has recently been approved to treat T790M-positive NSCLC patients.
Methods: We have developed a Taqman-based real-time PCR ("RealFast") assay for the detection of EGFR c.2369C>T (p.T790M) along with an endogenous control and including EGFR wild-type suppressor to facilitate mutant-enriched PCR. Eighty-six samples, including cfDNA from NSCLC patients and healthy donors, from EQA trials, commercial cfDNA reference standards, as well as NCI-H1975 cell line DNA and cloned T790M DNA spiked into wild-type DNA, have been analysed in two laboratories to validate assay perfomance.
Results: Out of 31 samples known to be positive for c.2369C>T, the RealFast assay detected 30 correctly. Mutation detection failed in one cfDNA reference sample due to low amount (0.1% in 5 ng) of template. Out of 54 negative samples, one positive result was obtained with the RealFast assay. For one NSCLC sample no confirmed EGFR status was available. A sensitivity of 96.8% and a specificity of 98.2% were calculated. The RealFast assay is capable of detecting 8 copies of c.2369C>T DNA in a minimum of 2.5 ng cfDNA.
Conclusion: The highly sensitive detection of mutated EGFR in low amounts of cfDNA make the EGFR T790M RealFast assay a useful tool for monitoring the T790M mutation status in liquid biopsy samples of NSCLC patients.

PS-04-030

Prostate cancer miRNA profiling in samples from laser capture microdissection - comparison of two library preparation methods

K. Okoń[1], G. Wątor[2], M. Seweryn[2], K. Miłek[3], A. Piechota-Polańczyk[4], P. Kapusta[2], P. Chłosta[5], P. Wołkow[2]
[1] Jagiellonian University, Collegium Medicum, Chair of Pathomorphology, Poland, [2] Jagiellonian University, Medical College, Centre for Medical Genomics - Omicron, Poland, [3] Jagiellonian University, Medical College, Chair of Pathomorphology, Poland, [4] Jagiellonian University, Department of Medical Biotechnology, Poland, [5] Jagiellonian University, Medical College, Chair of Urology, Poland

Background & Objectives: Prostate cancer is one of the most frequent cancers in males. This is both overtreated and potentially fatal disease,

thus new prognostic factors are needed. miRNAs are known to participate in carcinogenesis and are of possible prognostic significance; we currently study miRNA expression in prostate cancer in relationship to presence of TMPRSS2-ERG translocation. The objective of this preliminary analysis was to find the best approach to study miRNA expression in laser microdissected prostate cancer samples. This study was supported by a grant from National Science Centre, Poland (no. 2015/19/B/NZ5/00044).
Methods: Samples from 3 patients after radical prostatectomies were subjected to laser microdissection to pick up pure tumour cells and its stroma. The samples underwent miRNA isolation and NGS library preparations using 2 commercially available kits. In the first MiSeq run we pooled 8 libraries (2 kits per 4 samples from each of 2 patients). In the second run we pooled 6 samples (single sample of tumour in triplicates). Generated reads were aligned to mirBase 22.1 and counted as well as normalized using miRDeep2 software. Differential expression (DE) was performed using Bioconductor edgeR, dimension reduction was done using the UMAP algorithm.
Results: We identified several hundreds of miRNA transcripts for each sample. However, we observed a difference between two kits in the number of identified transcripts (median 387[266-547] vs 596[488-659], p=0,0023) as well as their diversity (median entropy 2,921[2,63-3,14] vs 3,53 [3,36-3,66]; p=0,00058). DE analysis revealed 271 differentially expressed miRNAs between two library preps. Dimension reduction analysis revealed two separate clusters of samples based on the method of preparing the library. The correlation coefficient (between library preps) for samples run in triplicate was only ~0,4.
Conclusion: One of the library preps resulted in a larger number of identified miRNA as well as more diverse expression profile. This difference completely dominated the batch effect of two independent MiSeq runs. Overall, our data indicate that it is unacceptable to compare miRNA gene expression profiles, prepared with different library prep kits.

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PS-04-031

Lung FFPE validation study using the Agena Bioscience MassARRAY System with iPLEX chemistry

D. Patel[1], S. Khan[1], M. Gandy[2], D. Allen[3], M. Rodriguez-Justo[4]
[1] University College London, United Kingdom, [2] The Doctors Laboratory, United Kingdom, [3] Health Services Laboratories, United Kingdom, [4] University College London Hospital, United Kingdom

Background & Objectives: The purpose of the study was to validate the MassARRAY MALDI-TOF Mass spectrometry system for future use with liquid biopsies enabling cell free DNA detection of somatic mutations for both diagnosis and disease monitoring. The system core technology was validated by comparing results from 62 pre-extracted formalin-fixed paraffin embedded (FFPE) samples that had previously undergone DNA sequencing using the IonTorrent next generation sequencer (NGS) to results obtained using iPLEX MassArray chemistry from Agena Bioscience.
Methods: DNA concentration was normalised to 10ng/μL after which PCR steps were performed using the Agena iPLEX HS Lung Panel which includes target specific primers for EGFR, BRAF, KRAS, ERBB2 and PIK3CA genes. Following the addition of mass-modifying nucleotides, samples were arrayed using the MALDI-TOF mass spectrometry system and transferred to an assigned chip where the samples were ionised, transitioned through a vacuum to the system detector. The time of flight was measured producing a mass versus charge graphical readout illustrating different targets detected within the panel profile.
Results: Increased sensitivity using the iPLEX HS chemistry was observed with 55 samples showing matched clinically actionable mutations across both MassArray and NGS, with six samples harbouring clinically actionable (EGFR, ERBB2, BRAF and KRAS) mutations detected only by MassARRAY.
Conclusion: The next stages of the project are to move to liquid biopsies for both diagnosis and therapeutic monitoring as part of lung and colorectal cancer screening programs at University College London Hospital.

D. Patel and S. Khan are first authors in equal proportions. The analytical reagents were supported by Agena Bioscience.

PS-04-032

Detection of the mutation burden status and microsatellite instability by targeted next generation sequencing applying a large gene panel

N. Pfarr[1], M. Boxberg[1], K. Riedmann[2], M. Jesinghaus[1], B. Konukiewitz[1], H. Glimm[3], P.J. Jost[2], S. Fröhling[4], W. Weichert[5]
[1] Institute of Pathology, Technical University Munich, Germany, [2] University Hospital rechts der Isar, Germany, [3] National Center for Tumour Diseases Dresden, Germany, [4] National Center for Tumour Diseases Heidelberg, Germany, [5] Technical University of Munich, School of Medicine, Institute of Pathology, Germany

Background & Objectives: Assessing tumour mutation burden in diagnostic samples might become an important test in routine diagnostics. Currently, exome sequencing is mainly used for TMB but has restrictions by the time for diagnosis and the limitation of tissue material. Therefore, the applicability of applying large gene panels becomes more and more important. We applied the Illumina TSO500 panel covering an exonic region of about 1.24 Mb to test the feasibility of targeted next generation sequencing using formalin-fixed paraffin-embedded tissue for assessing TMB.
Methods: Assay validation was performed 1) using DNA derived from known TMBhigh vs. TMBlow samples. 2) Comparison of data from whole exome sequencing (high vs. low) versus TSO500 from 21 FFPE tumour samples. 3) Testing of samples with high PD-L1 expression, high MSI status or POLE mutation. Sequencing was performed on a NextSeq® system with the NextSeq® 500 hi-Output Kit v2 (300 cycles) and 40ng DNA as input. Data analysis was performed using a bioinformatics pipeline ("TSO500 v1.3.0.39") provided by Illumina with a limit of detection of 5% allele frequency.
Results: We confirmed TMB status of all validation samples achieving a concordance of 100%. Furthermore, we were able to confirm the mutation burden status "high" or "low" derived from exome sequencing achieving a concordance of 94% between the different approaches. Testing of the samples from the third phase confirmed a high TMB for the MSI high and the POLE mutated cases whereas the PD-L1 cases showed only borderline values.
Conclusion: In conclusion, data generated by targeted NGS data approaches can be used to determine TMB and additionally MSI in tumour samples of different entities in high concordance with exome sequencing.

PS-04-033

Testing the feasibility of tumour mutation burden using the Oncomine Tumour Mutation Load Assay - Data from eight sites of the Immuno Oncology Consortia

N. Pfarr[1], J. Costa[2], B. Bellosillo[3], F. Fenizia[4], W. Dinjens[5], I. Alborelli[6], C. Heydt[7], M.P. Jansen[5], J.C. Machado[2], C. Vollbrecht[8], S. Merkelbach-Bruse[7], R. van Marion[5], M. Hummel[8], R. Chaudhary[9], C. Allen[10], N. Normanno[4]
[1] Institute of Pathology, Technical University Munich, Germany, [2] Institute of Molecular Pathology and Immunology of the University of Porto (Ipatimup), Portugal, [3] Hospital del Mar, Barcelona, Spain, [4] Istituto Nazionale Tumouri "Fondazione Giovanni Pascale", IRCCS, Naples, Italy, [5] Erasmus University Rotterdam, The Netherlands, [6] University of Basel, Switzerland, [7] Institute of Pathology University Hospital of Cologne, Germany, [8] Institute of Pathology, Charite Berlin, Germany, [9] Thermo Fisher Scientific, USA, [10] Thermo Fisher Scientific, United Kingdom

Background & Objectives: Testing the tumour mutation burden (TMB) status from formalin fixed paraffin embedded tissue applying exome sequencing is challenging. Oncomine Tumour Mutation Load

(TML) Assay is a PCR-based NGS assay analyzing 409 cancer genes (1.2 Mb exonic region) to assess TMB from low amount of tumour DNA. Immuno-Oncology Consortia (IOC) gathered eight clinical researchers for validating Oncomine TML assay through a three-phase study. Here we present the data from the phase two were FFPE samples with known FMI-TMB were resequenced applying the Oncomine TML assay.

Methods: Six FFPE samples with known FMI-TMB values and clinically important variants were provided from one of the eight partner sites. All sites resequenced these samples applying the Oncomine TML assay. Data analysis was performed using the Ion Reporter Software. Statistical analysis was performed to analyse the 1) correlation with FMI TMB, 2) reproducibility on FFPE samples and 3) Detection of variants found by FMI assay

Results: Strong correlation above 0.95, except for two sites, was observed between TML-TMB and FMI-TMB. A high reproducibility on FFPE samples across all sites with less than 10% CV on > 1 FMI-TMB samples and less than 40% CV on ≤ 10 FMI-TMB samples was observed. Furthermore clinically significant variants from FMI results could be confirmed in TML results with consistent allele frequency across sites for all called variants.

Conclusion: In phase two it could be shown that data generated with the Oncomine TML shows high correlation with TMB data from FMI. Furthermore data could be reproduced across the different consortia partner sites.

PS-04-034

Copy number alterations and somatic mutations in primary and recurrent BRCA1-associated high-grade serous ovarian carcinomas

G. Raskin[1], I. Bizin[2], T. Gorodnova[2], A. Ivantsov[2], E. Imyanitov[2], A. Sokolenko[2]

[1] Academic A.M. Granov Scientific Center for Radiology and Surgical Technology, Russia, [2] N.N. Petrov Institute of Oncology, Russia

Background & Objectives: BRCA1-associated ovarian cancers (OC) represent a specific biological type of tumours characterised by several molecular features, e.g. near mandatory presence of TP53 mutations and high level of genomic instability. Here we present the results of whole-exome analysis of paired (primary and recurrent) OC samples obtained from carriers of BRCA1 mutations.

Methods: 12 samples from six patients were subjected to whole-exome sequencing. Pattern of somatic mutations and copy number changes were analysed using GATK software. Global LOH status was rated as LOH-high (>25% loci exhibit LOH) in all samples and remained concordant in both primary and recurrent lesions. LOH at BRCA1 locus was seen in all primary and five recurrent tumours. TP53 mutations were detected in all cases and were identical in primary and recurrent lesions from the same patient.

Results: Frequent gains present in primary and relapsed tumours were 8q24 (MYC) and 3q26 (PIK3CA), whereas gain at 20q13 (SNAI1) was present in four recurrences but only in one primary lesion. Losses of genetic material were frequently observed, being concordant at 1p36 (ARID1A) and 11p15 (RASSF10) and discordant at 10q23 (PTEN) and 16q22 (CDH1). While analyzing the entire spectrum of somatic mutations, we revealed that only 37% of all mutations observed in recurrent tumours were detected in the corresponding primary carcinomas.

Conclusion: Transmission of mutations from primary to recurrent tumour was rather low and reflect some peculiarities of BRCA1-driven tumour's evolution. Paired primary and recurrent ovarian carcinomas demonstrate both concordant and discordant somatic events. Concordant mutations are likely to reflect core events emerged at earlier stages of OC progression, while discordant alterations may reflect adaptation of tumour clones to continuing treatment pressure.

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PS-04-035

Predictive biomarker analysis of non-small cell lung cancer patients

S. Sakellariou[1], E.A. Karatrasoglou[1], I. Chatziandreou[1], I. Giannopoulou[1], M. Michelli[1], A. Zougros[1], E. Rouppou[1], K. Stamopoulos[2], A.C. Lazaris[1], P. Korkolopoulou[1], A. Saetta[1]

[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [2] Agii Anargiri General Oncological Hospital of Kifissia, Athens, Greece

Background & Objectives: Lung cancer (LC) is the leading cause of cancer death worldwide. Many patients have metastatic disease at diagnosis and prognosis is dismal with 15% 5-year overall survival for all stages. Recently, promising therapies have emerged based on PD-1/PD-L1 immune checkpoint inhibitors (ICIs) which have been approved as frontline treatment for patients with non-small cell LC (NSCLC).

Methods: We examined the association between PD-L1 expression and driver gene mutations (EGFR, KRAS, ROS1) in 326 Greek NSCLC patients. PD-L1 immunoexpression using 22C3 PharmDx DAKO monoclonal antibody (mAb) was defined as high when tumour proportion score (TPS) was ≥50%, low if TPS was 1-49% and absent when TPS was <1%. EGFR and KRAS mutations were detected by COBAS and Pyrosequencing, respectively. ROS1 mutations were estimated by immunohistochemistry (D4D6 Rabbit mAb) whith positive cases (Hscore≥200) being confirmed by CISH. Data analysis was performed using SPSS v25.0.

Results: Our cohort included 261 adenocarcinomas, 40 SCC, 25 NSCLC-NOS (males=228, females=98). Median patient age was 67 years (range 31-96). PD-L1 expression was high in 23%, low in 41.7% and negative in 35.3% of cases. EGFR was mutated in 15%, KRAS in 27.6% and ROS1 in 5% of the cases PD-L1 expression was positively correlated with KRAS mutations (p =0.018).

Conclusion: PD-L1 expression in NSCLC in Greece is comparable to that reported worldwide. KRAS mutations may affect tumour microenvironment and patient's response to immunotherapy. ICIs could represent a therapeutic option for KRAS mutant patients. Further investigation into this notion is warranted.

PS-04-036

Multianalyte testing of FGFR with Modaplex technology

O. Schurat[1], M. Luimes[2], M. Böhme[1], K. Tabiti[1]

[1] Biotype Diagnostic GmbH, Germany, [2] Biotype Diagnostic GmbH, The Netherlands

Background & Objectives: A hallmark of cancer are genetic variations known to be widely involved in the process of carcinogenesis. Dysregulation of fibroblast growth factor receptor (FGFR) signalling has been observed in many cancer entities, and reported to have different meanings depending on tumour type. Here, we describe a novel method, the Modaplex technology, which enables simultaneous analysis of multiple modalities within a single experimental run.

Methods: The Modaplex technology combines and integrates PCR and Capillary Electrophoresis (CE). During PCR, a femtoliter amount of the ongoing reaction is separated by size via CE and the fluorescence of the individual DNA bands is measured. By collecting several data points during the thermocycling process for each individual band, an amplification curve for each target is recorded, followed by automatic determination of its quantifying cycle (Cq). The simple assay-development workflow allows for the design of various different modality assays, which can be run simultaneously.

Results: We developed a FGFR panel for simultaneous detection of different genetic aberrations. FGFR CNV and FGFR Mutation are assays targeting DNA, while FGFR Gene Expression and FGFR Gene Fusion target RNA. Each assay has a midsize complexity and comprises a minimum of six targets. Assays have been verified using artificial and reference material within a single experimental run.

Conclusion: We demonstrated that this technology allows for identification and quantification of multiple targets per well, the multi-

modal potential for the detection of different genetic aberrations in a single run and the capacity to process both DNA and RNA based assays simultaneously.

PS-04-037

SERPINA1 up-regulated expression in placental villi in pregnancy-related complications

V. Sergeeva[1], N. Nizyaeva[2], N. Starodubtseva[2], D. Ivanov[3], S. Pekov[4], A. Bugrova[1], O. Baev[2], M. Gapaeva[2], V. Sinitsyna[2], A. Kononihin[4], I. Popov[3], V. Frankevich[2]

[1] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia, [2] V.I. Kulakov National Medical Research Center of Obstetrics, Gynaecology and Perinatology, Russia, [3] Moscow Institute of Physics and Technology, Moscow, Russia, [4] V.L. Talrose Institute for Energy Problems of Chemical Physics, Russian Academy of Sciences, Russia

Background & Objectives: Preeclampsia (PE), a multisystem pathological condition of pregnancy, characterised by arterial hypertension with proteinuria, affects 5-8% of pregnancies. The main cause of preeclampsia lies in the incomplete transformation of the spiral arteries of the uterus. Previously, fragments of SERPINA1 in urine were proposed as diagnostic and prognostic markers, correlating with PE severity. SERPINA1, the protease inhibitor, may be synthesized by placenta structures. The aim of the study was to evaluate SERPINA1 expression in placental villi in cases of preeclampsia. Additionaly pathological changes in the placenta during pregnancy were visualed by MALDI-imaging mass spectrometry (MALD-MSI).
Methods: Histological (H&E) and immunohistochemical analysis (Ventana Medical Systems, Roche) of 45 placental tissues (15 women with uncomplicated pregnancy, 30 – PE cases) paraffin-embedded slices was performed using SERPINA1 primary polyclonal antibodies (1:500; Invitrogen). Additionally, cryo-slides (12 mkm) were covered with 2,5-dihydroxybenzoic acid by sublimation. MALDI-images were obtained using Bruker ultrafleXtreme mass spectrometer in positive ion mode. Then, MALDI matrix was washed out and slides were stained with H&E.
Results: SERPINA1 expression in cyto-syncytiotrophoblast, syncytial knots, decidual cells, amnion, macrophages, stromal cells, endothelium of blood vessels of placental villi, extravillous trophoblast, and in fibrinoid deposits was evaluated. Moreover, expression was significantly higher ($p<0,05$) in placental samples in cases of PE, then in control group. Syncytial knots and extravillous trophoblast were surrounded by fibrinoid deposits predominantly in PE group. A good match between the mass spectrometric image, built on individual lipid ions, and histological image was demonstrated. The main ions clearly distinguishing areas corresponding to different structures of the placenta were identified using Mann-Whitney U-test ($p<0.05$). For example, phosphatidylcholines PC 36: 4 and PC 32: 0 were characteristic for the stem and terminal villi of the chorion.
Conclusion: SERPINA1 upregulation in PE placentas was confirmed. High SERPINA1 concentration in fibrinoid deposits probably contributes to the restriction of trophoblast invasion, reducing the transformation of the spiral arteries of the uterus. A distinct lipid profile of various placental structures allows both visualizing these structures at the molecular level and identifying physiological and pathological changes in the placenta during pregnancy. In particular, abnormal trophoblast invasion leads to ischemia reperfusion injury and accumulation of lipid peroxidation products.

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PS-04-038

Protein misfolding in placenta and urine during preeclampsia

V. Sergeeva[1], N. Starodubtseva[2], K. Muminova[2], A. Bugrova[1], M. Indeykina[1], N. Nizyaeva[2], N. Zakharova[1], V. Sinitsyna[2], V. Frankevich[2], Z. Khodzhaeva[2], A. Kononihin[3]

[1] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia, [2] V.I. Kulakov National Medical Research Center of Obstetrics, Gynaecology and Perinatology, Russia, [3] V.L. Talrose Institute for Energy Problems of Chemical Physics, Russian Academy of Sciences, Russia

Background & Objectives: Protein misfolding, leading to the accumulation of aggregates, was detected for many pathologies (including cardiovascular, neurodegenerative and associated with pregnancy). Preeclampsia (PE), a severe pathology of pregnancy characterised by arterial hypertension, proteinuria and multiorgan dysfunction, remains the main cause of maternal and perinatal morbidity and mortality. Urine congophilia (a test for the presence of amyloid-like fibrils) is proposed for express diagnostics of pre-eclampsia (Buhimschi IA, et. al. Sci Transl Med. 2014). The aim of the study was to develop an approach for the differential diagnosis of hypertensive complications of pregnancy by urinary peptidome profiling by high-resolution mass spectrometry. Additionally we evaluate protein misfolding both in placenta and urine during preeclampsia.
Methods: Histological(H&E) and immunohistochemical (Ventana Medical Systems, Roche) analysis of 50 placental tissues (20 - PE, 15 women with uncomplicated pregnancy, 15 - control) was performed on the paraffin-embedded slices using Oligomer A11 primary polyclonal antibodies (1:2000;Invitrogen) and SERPINA1 primary polyclonal antibodies (1:500; Invitrogen). The study included 109 women divided into groups: preeclampsia (PE), PE superimposed on CAH (chronic hypertension), CAH, GAH and control group. Urine samples from each woman were analysed using nano-HPLC-MS/MS and a qualitative analysis by MALDI-MS was performed as previously described (Kononikhin A, et. al. J Proteomics. 2016). Identification and analysis of semi-quantitative data was carried out using complementary bioinformatics platforms (MaxQuant, PEAKS). Protein aggregation in urine was estimated using Congo Red test: 2 μl of Congo Red (5 mg/ml) was added to 100 μl of urine, 5 μl of the resulting mixture was applied to a nitrocellulose membrane (Amersham Protran 0.45NC), dried, scanned, then washed from unbound dye, dried and re-scanned.
Results: An approach for a comprehensive analysis of the urine peptidome was developed, which includes sample preparation using exclusive chromatography, identification of isolated peptides using nano-HPLC in combination with high resolution mass spectrometry, as well as semi-quantitative and statistical data analysis (Kononikhin A.S., et. al. Methods Mol Biol. 2018). Urine peptides were found to be highly specific to the presence/absence of hypertension during pregnancy. A characteristic panel of peptides, which are fragments of alpha-1-antitrypsin (SERPINA1), was revealed for a group of patients with preeclampsia (PE, PE superimposed on CAH). Urinary level of protein aggregation in PE was significantly higher ($p<0.01$) than in control group and correlated with oligomers and SERPINA1 expression in placenta. Oligomer A11 and SERPINA1 was significantly higher in placental samples in PE cases (cyto- and syncytiotrophoblast, syncytial knots, decidual cells (cytoplasm staining), endothelium blood vessels, extravillous trophoblast and fibrinoid deposits) then in other groups.
Conclusion: An approach for a comprehensive analysis of the urine peptide was developed, which includes sample preparation using exclusive chromatography, identification of isolated peptides using nano-HPLC coupled with high resolution mass spectrometry. A panel of peptides was formed, allowing to reliably differentiate hypertensive disorders in pregnant women. Fragments of alpha-1-antitrypsin confirmed their significance as markers of preeclampsia. In preeclampsia notable changes in protein processing with aggregates accumulation in various placental structures was found. The level of protein oligomers in placenta and urine positively correlated.

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Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-05 | Dermatopathology

PS-05-001
Ecrine porocarcinoma: 11 cases in 10 years
R.I. Bermudez Cameo[1], N. Torrecilla Idoipe[1], M.J. Viso Soriano[1], J.I. Franco[1], H.P. Almanzar Comas[1], S. Bakali Badesa[1], A. Sobrino Prados[1], N. Estrada Mallarino[1], A. Arellano Alvarez[1], C. Pardillos Marin[2], V. Sanz Salvador[1], A.B. Roche Latasa[1]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain, [2] Hospital Ernest LLuch Martin, Calatayud, Zaragoza, Spain

Background & Objectives: Eccrine porocarcinoma (EP) is a very rare anexial cutaneous tumours. According with some authors, they have an estimated prevalence between 0,005-0,01% of the total cutaneous tumours. It predominately occurs in elderly people, usually in extremities, particularly feet and legs. EP may develop de novo or complicate an ecrine poroma, chronic lymphatic leukemia, nevus sebaceous and actinic lesions. It has been reported a ratio of malignant transformation from benign poroma to malignant one to be around 18%. According with some papers, risk factors include exposure of the affected area to trauma, burning or radiotherapy, immunosuppressive drugs, prolonged exposure to ultraviolet light and AIDS. Wide local resection is recommended to prevent from potential recurrences, because it can reach 20%.
Methods: Retrospective analysis of diagnosed EP at University Hospital 'Miguel Servet' of Zaragoza, between years 2008 to 2018. It has been reported 11 cases of the 42.587 skin biopsies (involving the 0,02%). Every case was diagnosed by different surgery procedures (punch, shaved and resection).
Results: From the total, only 3 cases had morphological features of transition of ecrine poroma to EP (4%), identifying both histological features together. EP has a wide range of age, between 52 to 95 (average of 77), with a similar prevalence among women and men, 6 men and 5 women. EP were more frequently located at head and neck (8), follow by thorax-abdomen (3). None of them had appear at the extremities. None of them had presented any recurrences after a wide local resection.
Conclusion: EP is a very rare tumour, our report had shown some particularities comparing with other references: It represents 0,02% of the total skin biopsies. It is slightly more prevalent on than women, usually located at head and neck. It has not been observed any recurrences or distant metastasis. It has showed poroma areas in 3 EP. Morphological analysis of the skin tumours, cytological and architectural features of malignant neoplasia are indispensable to a correct diagnose.

PS-05-002
Secondary tumours of the skin: clinical-pathological aspects focusing on differential diagnosis
C. Cacchi[1], A. Rübben[2], R.U. Wahl[2]
[1] Institute for Pathology Uniklinik RWTH-Aachen, Germany, [2] Dermatology Unit Uniklinik RWTH-Aachen, Germany

Background & Objectives: Skin-Metastasis is an uncommon but clinically relevant event; aim of this study is to investigate the incidence and the characteristics of cutaneous metastasis.
Methods: We evaluate the type of malignancy, the localization, the number of the metastasis in the skin that were diagnosed in the last 5 years in our Institution :49 patients (17 and 32 women). We also stress the clinical and histological aspects regarding the differential diagnosis.
Results: We found following metastases :17 melanomas, 12 breast carcinomas, 8 squamous carcinomas, 2 carcinomas of the ovary, colon (3 cases) and lung (1 small cell, 3 adenocarcinomas). The others cases were: 1 merkel-cell carcinoma, an adenocarcinoma of the oesophagus and one adenocarcinoma –NOS. 82% of the cases were single cutaneous manifestation. The localization was: head and neck region (18%), thorax in (26%), back region (10%), abdominal region (22%) and upper (4%) and lower extremities (16%).
Conclusion: Secondary tumours of the skin are a rare but clinically relevant situation in the histological routine practice. A morphological and immunohistochemical correct approach beside a clinical-pathological correlation (for example to distinguish epidermotropic metastatic melanoma from primary melanoma) is mandatory.

PS-05-003
Primary cutaneous angioplasmocellular hyperplasia- an IgG4 related solitary skin lesion? A clinicopathologic study of 5 cases
A.I. Cioroianu[1], P.I. Stinga[2], C. Popp[1], S.A. Zurac[1,3]
[1] Colentina Clinical Hospital, Romania, [2] Colentina University Hospital, Romania, [3] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: Primary cutaneous angioplasmocellular hyperplasia(pCAPH) is a rarely reported entity (20cases presented in the literature), being unrecognized by many or considered a non-specific, reactive phenomena with a yet unrevealed etiopathogenesis by others.
Methods: Five cases of pCAPH met the selection criteria for inclusion in the study-4 males and 1 female,aged20 to 77 years, all presenting with a solitary skin nodule(size range between 1 and 1,4cm), involving the skin of the fingers(n=3),trunk(n=1),inguinal region(n=1). No specific predisposing factors were present. EVGstain and immunohistochemical markers were performed(CD34,CD31,SMA,CD3,CD20,CD38,Kappa and Lambda light chains,IgG,IgG4,CD117, HHV8) in order to obtain a complete picture of the entity.
Results: Microscopic examination of the selected cases showed a dermal-based proliferation of small vessels(mostly venules, scattered capillaries) surrounded by an abundant mixed inflammatory infiltrate predominantly composed of non-atypical polyclonal plasma cells, displaying a IgG4/IgG ratio between 30 and60%; a high number of IgG4 plasma cells/HPF was found in each case(range between 110 and 390/HPF);B lymphocytes generally outnumbered T lymphocytes; in one case was observed a slightly increased number of eosinophils; mast cells were frequent(range between 25 and 73/HPF).All cases were HHV8-negative. Ulceration of the suprajacent epidermis was detected in 4 cases. Other findings like obliterative phlebitis or storiform fibrosis weren't identified.
Conclusion: Our results were intriguing and raised the possibility of including pCAPH on the long list of the conditions that can be associated with IgG4 tissue plasma cells. An improved understanding of this peculiar entity and of the significance of IgG4 plasma cells rich inflammatory infiltrate will require more documented cases.

*Cioroianu and Stinga are first authors in equal proportion.
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PS-05-004
Frontal fibrosing alopecia: a clinicopathologic evaluation of eyebrow hair loss
V. Damaskou[1], A.C. Katoulis[2], K. Diamanti[2], A. Pouliakis[1], D. Mortaki[2], A. Zacharatou[1], E. Bozi[2], N. Koufopoulos[1], D. Sgouros[2], I.G. Panayiotides[1]
[1] 2nd Department of Pathology, National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece, [2] 2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece

Background & Objectives: Frontal fibrosing alopecia (FFA) is a form of scarring alopecia leading to frontotemporal hairline recession. Partial or complete loss of eyebrows is seen in most cases. Our goal was to study the features of eyebrow involvement.
Methods: We examined specimens from 21 patients with FFA and concomitant eyebrow involvement for more than two years; 16 (76%) had partial, and 5 (24%) complete eyebrow loss. All were females with a mean age of 65.6±7.3 years. Dermoscopy-guided punch biopsies, from the eyebrow (3 mm, on red or grey dots), were vertically sectioned and stained with Hematoxylin-Eosin, Masson's trichrome and Elastica-Van Gieson stains. Statistical analysis was performed by SAS 9.4 software using a 5% significance level.
Results: Features indicative of permanent hair loss were present in 13 eyebrow specimens (62%), whereas preservation of sebaceous glands was seen in 8 (38%); this finding was associated with neither the onset nor the clinical degree (partial or complete) of hair loss. We observed a strong correlation (100%, $p<0.0001$) between the presence of prominent solar elastosis and absence of sebaceous glands in the eyebrows.
Conclusion: Preservation of the sebaceous glands seems to confirm the clinical and dermoscopic observation that eyebrow loss in FFA may be reversible. Association of prominent solar elastosis with features of sebaceous gland destruction in the eyebrow suggests that actinic damage and permanent hair loss may be pathogenetically related. More extensive studies are necessary to confirm our results.

PS-05-005
Analysis of mTOR CXCR4 and PD-1 checkpoint pathways in Merkel cell neuroendocrine carcinomas: correlations with prognosis and viral status
L. Deschamps[1], J. Benhamou[2], P.E. Sugier[3], B. Vergier[4], A. Pham-Ledard[4], A. Carlotti[5], M. Avril[5], N. Ortonne[6], O. Zehour[6], A. Durlach[7], F. Grange[7], B. Balme[8], S. Dalle[8], U. Zimmermann[9], A. Blom[9], M.H. Lorton[10], S. Dalac[11], A. Couvelard[12], E. Maubec[2]
[1] Departement of Pathology, France, [2] Bichat APHP Hospital, France, [3] INSERM 1018, France, [4] Haut Levêque Hospital, France, [5] Cochin APHP Hospital, France, [6] Henri Mondor APHP hospital, France, [7] CHU Reims, France, [8] Hospices civils Lyon Sud Hospital, France, [9] Ambroise Parè APHP Hospital, France, [10] CHU Dijon, France, [11] Service de Dermatologie, CHU Dijon, France, [12] APHP- Bichat University Hospital, France

Background & Objectives: Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine carcinoma. Our objectives were to analyse clinicopathological prognostic factors and expression of molecules of 3 main signalling pathways (mTOR, CXCR4 and PD1/PDL1) in a large multicenter French retrospective study.
Methods: We collected 153 paraffin-embedded tumours from 144 patients. We analysed histological and immunochemical markers on whole slides (Ki-67, CD8, PD-1, PD-L1) or on Tissue Microarrays (CM2B4, CK20, CHROMOGRANINE A, CD56, SYNAPTOPHYSINE, CXCR4, SDF-1, pmTOR, 4EBP1, PS6, Rb, p53)
Results: Metastatic MCC (n= 52) significantly expressed more CXCR4 (p= 0.048) and PD-L1 (p=0.036) as compared to primary tumours. 77% (n=105) of MCC expressing CM2B4 were considered *Polyomavirus* positive. In those MCC-virus positive, we observed less elastosis (p=0.003), ulcerations (p=0.008), cytological atypias (p=0.0068), %Ki-67 (p=0.00009), alterations of p53 (p=0.008) and Rb (p=0.00009), and more CD8 lymphocytes (p=0.0016) expression and higher PD-L1 (p=0.04). The presence of *Polyomavirus* was correlated with significantly better overall survival (p=0.002).
Conclusion: Our large multicentric study, suggests the potential dual role of CXCR4 and PD-L1 in metastatic progression of MCC regardless of viral status, and confirms the importance of the immune reaction in MCC-virus positive with better overall survival. We highlight that the MCC-virus negative display an aggressive phenotype and molecular alterations (such as p53/Rb pathway) close to other neuroendocrine carcinoma in digestive system and other locations.

PS-05-007
Chanarin-Dorfman syndrome with systemic involvement in three siblings
C. Karaoglan[1], B. Cayhan[2], F. Topaloglu Demir[2], Z. Turkoglu[2], B. Duz[3], N. Buyukbabani[1]
[1] Istanbul Faculty of Medicine, Department of Pathology, Turkey, [2] University of Health Sciences, Haseki Training and Research Hospital, Division of Dermatology, Turkey, [3] University of Health Sciences, Haseki Training and Research Hospital, Division of Medical Genetics, Turkey

Background & Objectives: Chanarin-Dorfman Syndrome (CDS, OMIM: 275630) is a rare autosomal recessive disorder of neutral lipid metabolism. It is characterised by intracellular accumulation of neutral lipids in cytoplasmic lipid droplets. It involves multiple organs and systems, including skin, liver, skeletal muscle, eyes, ears and central nervous system. This condition typically presents with ichtyosiform non-bullous erythroderma. Mutations of ABHD5 gene have been determined as the cause of CDS. Herein, we present three siblings with CDS who have congenital ichthyosis and multi-system involvement.
Methods: Hematoxylin and Eosin, Scharlach and Oil Red-O stains were performed on skin biopsy frozen-sections.
Results: A 25-year-old woman, her 22-year-old sister and 16-year-old brother were referred to our Institution with dry skin and hyperpigmented fine scales present since birth. The patients were put on emollients medications, but skin scaling was persistent. Dermatological examination revealed widespread ichthyosis on the facial region, trunk, extensor and flexural regions and scalp in all patients. Physical examination and laboratory findings showed different degrees of involvement in liver, skeletal muscle, eyes and ears in the patients. ADHB5 mutation was detected in all patients. All skin biopsies showed compact hyperkeratosis, mild acanthosis and discrete vacuolization of basal keratinocytes, sweat glands and sweat ducts cells. Scharlach and Oil Red-O stains clearly and elegantly demonstrated the lipid content of these discrete vacuoles.
Conclusion: CDS is a rare lipid storage disease. It should be considered in patients who have congenital ichthyosis with extracutaneous symptoms. Frozen sections of simple skin biopsy examined by lipid stains can rapidly and effectively confirm the cytoplasmic lipid storage.

PS-05-008
Proliferative changes of atrophy simulated rat skin after using a vitamine containing ointment
M. Kostyaeva[1], I. Kastyro[1], P. Shmaevskiy[1], N. Ermakova[1], Y. Gushchina[1], V. Torshin[1], S. Ata[1]
[1] Peoples' Friendship University of Russia (RUDN University), Russia

Background & Objectives: The use of anti-inflammatory ointments containing glucocorticosteroids, leads to atrophic skin changes. In this study, we decided to study the reparative properties of the ointment containing vitamins A, E & D2 (OV), to restore the rat skin after its atrophy caused by the application of hydrocortisone ointment (HO).
Methods: The study was conducted on 24 Wistar rats. Each group included 8 animals: group1 - control, group2 - once a day for 5 days applied 1% HO to the skin area in the interscapular area, group3 – a dermatotropic drug within 5 days afret HO using. OV was applied dermally, daily after the skin atrophy model was formed with HO. H&E stained histological sections of the skin were studied in group 2 on day 5, and in group3 on day10.
Results: HO application in group1 led to thinning of the epidermis to one layer, in control:3–6 cell layers(CL). The stratum corneum was absent, the cells were flat, mitoses were absent.Hair follicles and sebaceous glands markedly atrophied. In group3 CL number was not only restored, but exceeded the

control values(6–9CL). Mitosis was noted in the malpighian&granular CL;spinous layers contained many keratohyaline granules. Horny layer was quite pronounced. The cells of the hair follicle regained their shape, but proliferation did not occur in the sebaceous glands.
Conclusion: Thus, a dermatotropic preparation containing vitamins A, E, and D2, significantly stimulates the reparative activity of the epidermis after drug atrophy. It is possible that this stimulation does not extend to the sebaceous gland stem cell line.

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PS-05-010
Histological and inmmunohistolochemical parameters of the skin under the influence of damaging and stimulating cosmetic procedures
Y. Kudrevich[1], E. Kuznetsova[2], O. Ziganshin[3], T. Zayats[3], G. Sichugov[3]
[1] Ural State Medical University, Russia, [2] Orenburg State Medical University, Russia, [3] South Ural State Medical University, Russia

Background & Objectives: The article presents the results of the research of the content of collagen types I and III in the skin, the growth factors of FGF2, EGF, VEGF before and after exposure to the skin of an erbium laser as monotherapy and under complex laser and biorevitalization. A comparative characteristic of these changes was made, conclusions were drawn about the effectiveness of the therapy
Methods: All patients were divided into two groups of 12 people. The first group underwent laser treatment of the face. The second group underwent a biorevitalization procedure. Fragments of skin was taken from all patients in 2 months after procedure. In skin samples using immunohistochemical methods with the help of monoclonal mouse antibodies, the following parameters were determined: bulk density of type I and III collagen, growth factors FGF2, EGF, VEGF.
Results: Collagen type III increased in all groups. Collagen type I increased more in the “laser" group compared with “laser + revitalization” group. FGF and VEGF increased more in the “laser + revitalization” group compared with the “laser” group. EGF increased more in the "laser" group compared with the "laser + biorevitalization" group.
Conclusion: Based on the data we can be conclud that cosmetic procedures stimulate neocollagenogenesis, contribute to the improvement of skin quality, its density, vascularization of the dermis will also be intensified, which will lead to increased skin trophism, enhanced metabolic processes, optimization and enhancement of regenerative processes.

PS-05-011
Comparative characteristics of the skin when using hyaluronic acid and placenta extract
Y. Kudrevich[1], E. Kuznetsova[2], O. Ziganshin[3], G. Sichugov[3], T. Sayats[3]
[1] Ural State Medical University, Russia, [2] Orenburg State Medical University, Russia, [3] South Ural State Medical University, Russian Federation

Background & Objectives: The study involved 40 women, all patients were divided into two groups. The first group received a biorevitalization procedure of the skin, the second group received injections of an extract of the placenta 5 times with an interval of a week. All patients’ piece of skin was taken before the procedure and 2 months after the procedure. The changes in skin indices was compared before and after the procedure
Methods: It was used immunohistochemical methods. It was determined the amount of IL8, IL10, IL20, Filaggrin, Laminin, EGF, VEGF, PDGF, Hyaronidasa with using mono- and polyclonal mouse and rabbit antibodies in the skin. These indicators were compared using different drugs to improve the quality of the skin before and after in the same group and between groups.
Results: After all procedures, IL10, EGF, VEGF significantly increased in the skin. The amount of IL20, Filaggrin, Laminin increased after biorevitalization, but these figures remained the same with the introduction of an extract of the placenta. PDGF decreased in all groups.
Conclusion: Hyaluronic acid and placental extract preparation had a positive effect on the skin. The vascularization of the dermis and trophic skin increased, the basement membrane tightened, the appearance of new cells was stimulated. These drugs have an effect through different mechanisms. Hyaluronic acid has a moisturizing and structuring effect, the extract of the placenta enhances skin tropism, stimulates local immunity.

PS-05-012
Extremely unusual clinical presentation of angiolymphoid hyperplasia with eosinophilia: true neoplasm or reactive process?
A.C. Lisievici[1], T.A. Georgescu[2], T. Panazan[3], T. Tebeica[4]
[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Bucharest Emergency University Hospital, Romania, [3] Clinical Emergency Hospital of Plastic Surgery, Reconstruction and Burns of Bucharest, Romania, [4] Department of Pathology, Dr. Leventer Centre, Bucharest, Romania

Background & Objectives: Angiolymphoid hyperplasia with eosinophilia (ALHE) also known as epithelioid hemangioma is a rare and benign vascular lesion usually located in the head and neck area and extremely rare on the trunk and extremities. It usually develops in the dermis, but rarely it can also involve the subcutis.
Methods: We report the case of a 32–year-old male presenting with a tender red nodule near the nail fold on the third finger of the left hand. First punch biopsy of the lesion was suggestive of a pyogenic granuloma, but the lesion recurred in a very short time and rapidly increased in size. The decision to surgically remove the lesion through an excisional biopsy was made, and the specimen was sent to our laboratory for histopatological examination.
Results: The excised specimen revealed an ulcerated proliferation of blood vessels lined by large and bland endothelial cells, with abundant cytoplasm and intracytoplasmic vacuoles, in the background of a dense fibrous stroma intermingled with an abundant lymphocytic infiltrate and featuring numerous eosinophils. Subjacent bone destruction was noted and the surgically resection margins were positive. The patient presented another recurrence within a few months.
Conclusion: To our knowledge, this is the first case report of bone invasive ALHE. Besides its unusual location, this case highlights an extremely unusual presentation of ALHE, an entity with a long history of disputed pathogenesis. Between a benign neoplastic process and a reactive vascular lesion, we favour the former hypothesis, based on the aggressive clinical course of our case.

PS-05-013
P16, P21 and ALK expression in blue nevi family
C. Luca[1], O. Stefan[1], G. Tudor[1], C. Constantinescu[1], V. Nica[1], L. Sticlaru[1], C. Caruntu[2], B. Mastalier[1,2], R. Andrei[1], S.A. Zurac[1,2]
[1] Colentina Clinical Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: Blue nevi and related tumours are a heterogeneous group of dermal dendritic melanocytes proliferations. They encompass a spectrum of lesions ranging from benign lesions (common blue nevus (BN) and cellular blue nevus (CBN)) to malignant blue melanoma/blue nevus like melanoma (MBM) and including also atypical CBN (tumour difficult to integrate as benign or malignant, thus remaining a challenging diagnosis even for experienced dermatopathologists). We investigated the utility of p16 and P21 immunohistochemical staining in

distinguishing BN/CBN from MBM; we look also for presence of ALK rearrangements in BN family.
Methods: We retrieved 8 BN, 8 CBN and 1 atypical CBN of a total of 1154 compound and intradermal melanocytic nevi diagnosed between 2017-2018 in our department; in the same period, we identified 3 MBM. We performed immunohistochemical tests for p16, p21 and ALK (as ALK rearrangements surrogate).
Results: 4 of 20 lesions were focally positive for ALK (2 CBN, 1 BN, 1 atypical CBN). P16 staining was positive in all tumours (**diffuse positivity**: 5 BN, 8 CBN, 1 atypical CBN, 1 MBM; **patchy/focal**: 3 BN and 2 MBM). P21 had mainly **patchy/focal expression** (3 CBN, 2 BN and 2 MBM), diffuse **expression** being present in 1 CBN and 1 MBM.
Conclusion: ALK rearrangement was recently described in Spitz tumours. We identified ALK staining patterns that have not been previously described in blue nevus tumours. However, its use to distinguish between benign BN and MBM, as well as the use of p16 and p21 for the same purpose, appears limited.

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PS-05-014
The expression of Notch signalling pathway in Merkel cell carcinoma
M. Matsushita[1,2], L. Oka Wardhani[1,3], T. Iwasaki[4], S. Kuwamoto[1], D. Nonaka[5,6], K. Nagata[1], M. Kato[1], Y. Kitamura[2], K. Hayashi[1]
[1] Division of Molecular Pathology, Department of Pathology, Tottori University Faculty of Medicine, Yonago, Japan, [2] Department of Pathobiological Science and Technology, School of Health Science, Tottori University Faculty of Medicine, Yonago, Japan, [3] Clinical Pathology Department, Medical Faculty of Sebelas Maret University, Japan, [4] Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan, [5] Department of Cellular Pathology, The Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [6] The Christie Hospital and University of Manchester, United Kingdom

Background & Objectives: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer and approximately 80% cases are associated with Merkel cell polyomavirus (MCPyV). Notch signalling pathway regulates cell fate in various tissues including skin during development and homeostasis. Aberrant activity of Notch signalling relates to various malignancies and it plays a role as either oncogene or tumour suppressor. We investigated the association of expression of Notch signalling pathway with MCPyV status and prognosis in MCC.
Methods: 19 MCPyV-positive and 19 MCPyV-negative MCCs were immunohistochemically stained with antibodies for NOTCH1, NOTCH2, NOTCH3, JAG1 and some other downstream factors of Notch signalling pathway and analysed.
Results: There was no statistically significant association of NOTCH1 and NOTCH2 expression with MCPyV-status and prognosis. NOTCH3 expression was significantly higher in MCPyV-positive MCC and Kaplan–Meier and multivariate analyses revealed that higher NOTCH3 expression was significantly correlated to better overall survival ($p=0.001$ and $p=0.033$, respectively). Higher JAG1 expression was found in MCPyV-negative MCC, but there was no significant association between its expression and prognosis. Expression data of the other downstream in Notch signalling pathway in MCC will be also shown.
Conclusion: In this study, we suggested that NOTCH3 and JAG1 expression may be related to tumourigenesis in MCC and NOTCH3 expression, as a tumour suppressor, is an independent predictor of MCC outcome.

PS-05-015
Correlating macrophage infiltration with BRAF status and prognostic features in melanoma using immunohistochemistry
M. Mc Cabe[1], L.F. Tremble[2], R. Werner[1], R. Tynan[1], P. Forde[2], C. Heffron[1]
[1] Cork University Hospital, Ireland, [2] University College Cork, Ireland

Background & Objectives: The likelihood of metastasis or recurrence in melanoma can be predicted by a number of clinicopathological factors. Macrophages have a wide variety of known tumourigenic properties. This study seeks to determine the profile of the macrophage infiltrate, whether it is associated with poor prognostic clinicopathological factors, and whether there is a correlation between macrophage infiltration and BRAF status.
Methods: 43 melanoma cases were retrieved and stained using CD-68, CD-163, and Arginase. The positive-staining cells were then counted by one pathologist and one trainee pathologist and the average of the two counts was calculated. The pathological reports were then reviewed and the reported parameters were compared with the degree of macrophage infiltration in each case.
Results: CD-163 stained positive in all cases with a range of 41-662. CD-68 was positive in 22 cases with a range between 0-257. BRAF was positive in 15 cases. More BRAF+ cases had a positive CD 68 (73.33%) and CD-163 (46.66%) compared with BRAF- cases (39% and 42.85% respectively). Higher Breslow tumours appeared to be more likely to have a macrophage infiltrate with 33.33% of tumours with Breslow stage 1-3 positive for CD-163 compared with 56% of tumours with Breslow stage 4.
Conclusion: Melanoma has a strong CD-163(M2) macrophage infiltrate. A greater number of tumours which stained positively for a macrophage infiltrate had poor prognostic features which is in keeping with what is known about tumour associated macrophages. Increased BRAF mutations and immunogenicity could both be a result of the same underlying process.

PS-05-016
Diagnostic algorithm for spitzoid tumours in children
N. Orlinskay[1], I. Shlivko[1], O. Garanina[1], D. Davydeko[1]
[1] FSBEI HE PRMU MOH, Russia

Background & Objectives: Spitz nevus (Spitz tumour, juvenile melanoma, spindle-shaped and epithelioid cell nevus) has a benign nature and a good life-prognosis, but may be histologically incorrectly diagnosed as melanoma. Therefore, the purpose of this study was the molecular study of tumour in children with the clinical diagnosis of Nevus Spitz.
Methods: During the 10-year period, according to clinical indications and dermatoscopic characteristics, 15 children aged 9 to 12 years old were operated on with the clinical diagnosis of Nevus Spitz. Immunohistochemical (IHC) staining was performed using antibodies to HMB-45, MELA, S100, MITF. FISH studies were conducted using probes targeting 5 loci, including CCND1 at 11q13, MYC at 8q24, RREB1 at 6p25, MYB at 6q23, CDKN2A at 9p21, and a CEP 6.
Results: Histological examination in 8 cases revealed no histological features typical for this tumour: lack of symmetry, uneven arrangement of the “nests” of cells, absence of Camino bodies. All tumours had high mitotic index of Ki67 - 10% and had atypical mitoses in their structure. Tumours expressed HMB-45, MELA, S100, MITF, which allowed to consider these neoplasms as malignant, therefore a FISH study was performed.
The absence of amplifications of CCND1, MYC, RREB1 and CDKN2A and deletion of MYB, which is characteristic of melanomas, has been established. Four-year observation of children showed no signs of malignant growth.
Conclusion: Thus, the histological and IHC characteristics of Spitz-like tumours in children are not indicative of malignant melanocytic lesions.

PS-05-017

T-cells, Merkel cell polyomavirus and survival in Merkel cell carcinoma: quantity and quality matter. A new simple eye-based "immunoscore" for pathologists!

C. Ricci[1], F. Ambrosi[2], A. Righi[3], L.R. Stefano[4], S. Uccella[5], M.G. Papotti[6], S. Asioli[7]

[1] Department of Biomedical and Neuromotor Sciences, Bellaria Hospital, Bologna, Italy, [2] Pathology Unit, Sant'Orsola-Malpighi Hospital, University of Bologna, Italy, [3] 2Department of Pathology, Rizzoli Institute, Bologna, Italy, [4] Service of Clinical Pathology, Lausanne University, Switzerland, [5] Unit of Pathology, Department of Medicine and Surgery, University of Insubria, Varese, Italy, [6] Department of Oncology, University of Turin, Italy, [7] Department of Biomedical and Neuromotor Sciences, "M. Malpighi" Section of Anatomic Pathology at Bellaria Hospital, University of Bologna, Italy

Background & Objectives: In Merkel cell carcinoma (MCC) prognosis is influenced by the density, the composition and the topography of different lymphocyte subclasses. Herein, we investigated the association between MCPyV, TILs subtyping (CD3+, CD8+, FoxP3+ and PD-L1), overall survival (OS) and disease-specific survival (DSS) in a cohort of 95 MCC patients.

Methods: This study enrolled 95 subjects from three different Italian centers. CD3, CD8 and FoxP3 have been scored as previously reported by*Sihto et al.*; the evaluation of PD-L1 on TILs suggested by *Lipson et al.* has been applied. We classified all cases in four "immunoscore" subgroups, on the basis of TILs and the number of positive immunological markers (TILs 0, TILs 1, TILs 2, TILs 3-4).

Results: MCPyV showed statistically significant differences among immunoscore subgroups. "Dead of disease" and "dead of disease + dead of other causes" patients were significantly lower in TILs 3-4 subgroup compared to the others. OS survival estimated by Kaplan-Meier function was longer in the TILs 3-4 subgroup starting from 36 months after surgery compared to the others TILs subgroups. For patients with available immunoscore, the only clinical-pathological features significantly associated with longer OS at univariate cox regression were MCPyV and TILs 3-4.

Conclusion: MCPyV prompts an immune response involving various lymphocytes subclasses (CD3, CD8, FoxP3 and PD-L1+) in MCC. CD8+ lymphocytes are the only singly-evaluated lymphocyte subclass that strongly influenced overall survival and disease-specific survival; whereas an "immunoscore" model obtained by TILs subtyping (CD3, CD8, FoxP3 and PD-L1) could provide useful prognostic information in MCC.

PS-05-018

Comparison of the pT1 primary cutaneous melanomas between the AJCC TNM 7th and 8th edition; a retrospective study in a single institute

S. Sirimsi[1,2], J. Lambert[3,2], S. Declercq[4], V. Siozopoulou[5]

[1] Antwerp University Hospital-Department of Pathology, Belgium, [2] University of Antwerp-Faculty of Medicine and Health Sciences, Belgium, [3] Antwerp University Hospital-Department of Dermatology, Belgium, [4] Middelheim Hospital of Antwerp, Belgium, [5] Department of Pathology, Antwerp University Hospital, Belgium

Background & Objectives: The AJCC TNM edition for primary cutaneous melanoma (PCM) was released in 2018 and includes evidence based changes, especially in pT1 category. The purpose of this study was to evaluate the migration in the pT1 category according to the AJCC TNM classification and to compare the performance of sentinel node procedure and the prognostic value.

Methods: Clinical and histopathological data on 141 patients with PCM in a single Institute, between 2009-2016 were analysed retrospectively. We compared pT1 melanoma classified according to the 7th and 8th edition of the AJCC TNM staging systems. The impact of the migration on the prognosis and the sentinel node procedure was examined.

Results: Among 141 patients with PCM 64,5%(n=91) patients were staged as pT1 category. Stage migration in pT1 category was observed in 26,4%(n=24) of the patients. 14,3%(n=13) of the patients showed an upgrade from pT1a to pT1b. This was due to an new stratification level at 0,8-mm Breslow thickness between pT1a and pT1b category. Another 12,1%(n=11) of patients underwent a downgrade from pT1b to pT1a. This was a result of the drop out of the mitotic-index in the new classification. Within this last group we showed a downgrading of 36,4%(n=4) nodular melanomas.

The demonstrated migration shows significant impact regarding the performance of sentinel procedure, but there was no difference in the prognosis in both categories.

Conclusion: We show a significant migration of PCM within the pT1 category, using TNM 7th versus 8th edition, that had an impact on the sentinel node procedure. There was no significant value concerning the prognosis in our study.

PS-05-019

Comprehensive evaluation of the mutational spectra detected in primary cutaneous melanomas: identification of novel loss-of-function mutants of TP53

I. Ticha[1], R. Jaksa[1], J. Hojny[1], M. Bartu[1], K. Nemejcova[1], N. Hajkova[1], R. Michalkova[1], E. Krkavcova[1], O. Kodet[2], L. Macurek[3], P. Dundr[1]

[1] Institute of Pathology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic, [2] Department of Dermatology and Venereology, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic, [3] Cancer Cell Biology, Institute of Molecular Genetics, ASCR, Prague, Czech Republic

Background & Objectives: Melanoma is a tumour with worldwide increasing incidence. Although the spectrum and frequency of mutations in melanoma have largely been catalogued, we performed NGS analysis of selected genes and an extensive evaluation of detected variants in a cohort of 115 primary cutaneous melanomas from Czech patients.

Methods: Genomic DNA from 115 FFPE primary cutaneous melanomas (including 46 nodular, 68 superficial spreading, and 1 acral lentiginous melanoma; TNM classification pT1=5,pT2=24,pT3=48,and pT4=38) underwent sequence capture NGS (Illumina) with a custom panel (219 kbp; Roche NimbleGen SeqCapEZprotocol). The data was processed by NextGENe (Softgenetics). The non-synonymous variants with a minimal average coverage >100x and a frequency ≥10% were comprehensively evaluated by in-house biostatistical pipeline. Impact of the *TP53* mutations was studied by functional assays.

Results: A total of 43/54 evaluated genes carried pathogenic or likely pathogenic mutations, most frequently involved in the MAPK signalling pathway (*BRAF*, *NRAS*, *MAP2K1*, *KDR*), DNA damage response (*ATM*, *BRCA1, BRCA2, KDR, PTEN*, *TP53*) or chromatin remodelling (*ARID1A*, *ARID2*). The most frequent *BRAF* (63/115;55%), and *NRAS* (36/115;31%) mutations were mutually exclusive, except for one case carrying mutation in both genes outside the hotspot codons. Several novel, probably pathogenic mutations were identified using *in silico* prediction approach (including *TP53*, *HNF1B*, *MET*, *PPM1D*, *CYP19A1*), functional assays confirmed pathogenicity of detected *TP53* mutations.

Conclusion: A spectrum of pathogenic mutations, including novel possibly pathogenic mutations across the analysed genes, was described. Biostatistical in-house pipeline was validated by functional assays, identifying new loss-of-function mutations of *TP53*.

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PS-05-020

Immunohistochemical expression of E- and N-cadherin in benign melanocytic nevi with halo phenomenon

A. Toma[1], M. Cioplea[2,3], L. Sticlaru[2,3], G. Turcu[2,4], R.I. Nedelcu[2,5], A. Brinzea[2,6], L. Peter[3], A. Vilaia[7], A.I. Savin[3]

[1] Pathology Department, Colentina University Clinical Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Colentina University Hospital, Pathology Department, Bucharest, Romania, [4] Colentina University Hospital, Dermatology 1 Department, Bucharest, Romania, [5] National Institute for Infectious Diseases Prof. Dr. Matei Balş, Bucharest, Romania, [6] Stefan Nicolau Institute of Virology,Bucharest, Romania, [7] Colentina Clinical Hospital, Bucharest, Romania

Background & Objectives: The halo phenomenon refers to the homogenous cell infiltrate surrounding the progressively degenerating nevus cells with spontaneous regression of the melanocytic lesion. Given the scarcity of data available in the literature regarding the morphological features of melanocytic nevus cells with halo phenomenon, we sought to characterise the nevus cells expression of two adhesion molecules, N-cadherin and E-cadherin.

Methods: An immunohistochemical study has been undertaken of cadherin expression in 23 benign melanocytic nevi. All lesions presented with a dense lymphocytic infiltrate coupled with different grades of melanocytic involution. Melanocytic immunostaining expression was analysed semi-quantitatively, assigning one of three grades, grade 3 representing intense staining equivalent to that seen in normal structures (epidermis for E-cadherin and nerve tissue or endothelium for N-cadherin).

Results: E-cadherin had moderate to intense level of staining in type A melanocytes, with gradually loss of intensity deeper into the dermis. N-cadherin immunostaining was generally weaker than E-cadherin, with reverse gradient staining in the dermal component of the nevi. E-cadherin expression in normal keratinocytes and melanocytes was weaker in areas with dense lymphocytic infiltrate than in non-inflamed area.

Conclusion: E-cadherin/N-cadherin expression in halo phenomenon nevi follows the pattern of expression of common nevi (E-cadherin expression in superficial nests and N-cadherin expression in profound areas) with a tendency towards intense E-cadherin expression in epithelioid melanocytes. However, presence of inflammatory infiltrate associates with decreasing of E-cadherin expression in both keratinocytes and neoplastic melanocytes.

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PS-05-021

Association of mismatch repair proteins with Merkel cell polyomavirus status and prognosis in Merkel cell carcinoma

L.O. Wardhani[1,2], M. Matsushita[2,3], T. Iwasaki[4], S. Kuwamoto[2], D. Nonaka[5,6], K. Nagata[2], M. Kato[2], Y. Kitamura[3], K. Hayashi[2]

[1] Clinical Pathology Department, Medical Faculty, Sebelas Maret University, Indonesia, [2] Division of Molecular Pathology, Department of Pathology, Tottori University Faculty of Medicine, Yonago, Japan, [3] Department of Pathobiological Science and Technology, School of Health Science, Tottori University Faculty of Medicine, Yonago, Japan, [4] Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [5] Department of Cellular Pathology, The Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [6] The Christie Hospital and University of Manchester, Manchester, United Kingdom

Background & Objectives: Merkel cell carcinoma (MCC) is a rare, aggressive, neuroendocrine skin cancer and most MCCs are related to Merkel cell polyomavirus (MCPyV) infection. Faulty DNA repair induces to mutation or aberration in oncogenes or tumour suppressor genes, causing cancer development. Loss expression of mismatch repair (MMR) proteins have been found in some cancers such as colorectal, gastric, and ovarian cancers. Therefore, we investigated the association of MMR signalling protein expression with MCPyV status and prognosis in MCCs.

Methods: 20 MCPyV-positive and 20 MCPyV-negative MCC samples from patients were immunohistochemically stained with antibodies to MLH1, MSH2, MSH6, and PMS2. Each protein expression was evaluated with modified H-score, and the association of expression data with clinicopathological factors were statistically analysed.

Results: MSH2, MSH6, and PMS2 were expressed higher significantly in MCPyV-positive than in MCPyV-negative cases (p=0.026, p=0.005, p<0.001, respectively), but there was no difference in MLH1 expression. In survival analyses, patients with higher MSH6 expression had better overall survival and disease-specific survival than otherwise by Kaplan-Meier (p=0.046 and p=0.008, respectively) and univariate (p=0.054, and p=0.02, respectively) analyses.

Conclusion: The lower expressions of MSH2, MSH6, and PMS2 in MCPyV-negative MCCs than in MCPyV-positive MCCs suggest that impairments of these MMR proteins may play more important roles in tumourigenesis mechanism in MCPyV-negative MCCs, and lower expression of MSH6 is associated with shorter survival in MCC.

PS-05-022

Would it be possible for the cases of pathologically diagnosed superficial perivascular dermatosis to provide more supportive and informative pathologic report? Dermatologic and pathologic study

C. Yoo[1]

[1] St Vincent Hospital, The Catholic University of Korea, Republic of Korea

Background & Objectives: Some of skin biopsy specimens are interpreted pathologically as superficial perivascular dermatosis (SPD). Generally, this description was applied for the cases which showed just mild to moderate perivascular lymphocytic infiltrations even though clinical settings were suggestive of a certain types of dermatologic conditions. And these pathologic findings were usually understood as nonspecific. This study was aimed to show whether it would be possible to make more supportive and informative pathologic reports for these SPD cases.

Methods: The pathologic slide re-examination was carried out for the SPD cases which were diagnosed in St. Vincent Hospital, the Catholic University of Korea from 2015 to 2018 years, and finally 247 cases were confirmed. We excluded the cases which showed remarkable epidermal change, infiltration of eosinophils, neutrophils or plasma cells, pigmentary incontinence, granuloma, remarkable perifollicular inflammatory cell infiltration, dermal fibrosis and inflammation in the subcutis. We reviewed the medical records of the study cases and dermatologic-pathologic correlations were done.

Results: Ages covered wide ranges and sex ratio was approximately 1:1. Dermatologically, macules, papules, purpura-like lesions or nodules were formed in variable sites. Lots of skin diseases were expected dermatologically before skin biopsy. Among them, most commonly encountered conditions were psoriasis, drug eruption, atopic dermatitis, vasculitis, erythema multiforme and urticaria, and they accounted for about half of them. Afterwards, erythema annulare centrifugum, several spongiotic and psoriasiform dermatitis, lupus erythematosus and a few tumourous lesions such as Bowen disease were followed.

Conclusion: Common skin diseases may have histology of SPD in their clinical course. Therefore, if clinical settings were reasonable, the SPD pattern may not be in conflict with these dermatologic impressions. Tumourous lesions, pigmentary lesions and some acute dermatopathies could be excluded from SPD. Some rare skin diseases could be thought to have SPD pattern unless particular histology was well known.

Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-06 | Electron Microscopy

PS-06-001
Primitive or metastatic pleural neoplasia? Transmission electron microscopy still gives a hand!
F. Fortarezza[1], F. Pezzuto[1], M. Della Barbera[1], G. Pasello[2], F. Rea[1], F. Calabrese[1]
[1] University of Padua, Italy, [2] Veneto Oncology Institute - IOV, Italy
Background & Objectives: The amyloidoses are an uncommon group of diseases characterised by abnormal extracellular deposition of misfolded protein fibrils leading to organ dysfunction. The histopathologic changes in a renal biopsy from a patient with systemic amyloidosis comprise a spectrum of vascular, glomerular and tubulointestitial amyloid deposition.
Methods: We identified 43 cases of renal amyloidosis after a retrospective review of all native renal biopsies evaluated in our department from 2010 through 2019. Demographic information, clinical and laboratory data were obtained from electronic records.
Results: Among the patients, a male predominance was noted (31 males, 12 females). The mean age of the patients at presentation for the entire group was 55 years (range, 26-85). Amyloid was of the AA type in 39 patients and AL type in 3 patients. The type of amyloid was undetermined in one case. Familial Mediterranean Fever (FMF) was the most common primary disease of amyloidosis.
Conclusion: The kidney is one of the most commonly involved organs in patients with systemic amyloidosis. It is also an important reason of renal failure. The AA/AL amyloidosis ratio differs between the countries. In our study, this ratio was found to be 13/1.

PS-06-003
Ultrastructural and immunohistochemical phenotype of myocardial telocytes in children
N. Nizyaeva[1], T.V. Sukhacheva[2], M.V. Samsonova[3], A.L. Cherniaev[3], A.I. Shchegolev[1], R.A. Serov[4]
[1] V.I.Kulakov National Research Center for Obstetrics, Gynaecology and Perinatology of Ministry of Healthcare of the Russian Federation, Moscow, Russia, [2] A.N.Bakoulev Scientific Center for Cardiovascular Surgery, Moscow, Russia, [3] Pulmonology Scientific Research Institute under Federal Medical and Biological Agency of Russian Federation, Russia, [4] A.N. Bakulev National Medical Research Center of Cardiovascular Surgery, Moscow, Russia

Background & Objectives: Telocytes is a new type of stromal cells of mesenchymal origin. Their special morphological features are small size, the presence of 2-5 long thin processes that surround cardiomyocytes, intramural vessels, nerve fibers.
Methods: The specimens of the right ventricular myocardium of 40 children with congenital heart disease (tetralogy of Fallot) aged 3–33 months were analysed. We performed electron microscopy and immunohistochemical study with C-kit/CD34/CD44/vimentin/desmin antibody.
Results: In the interstitium of the myocardium the spindle-shaped (1.8±0.6 μm) and polygonal-shaped telocytes (3.0±1.0 μm) with long processes of similar diameter (about 0.1 μm) were identified. Telocytes contained cisterns of the granular endoplasmic reticulum, the structures of the Golgi apparatus, mitochondria, intermediate filaments, centrioles. Lipid drops and myelin-like figures were rare. The processes of the telocytes were in contact with each other and with stem cells and macrophages. The identification of telocytes was based on a comprehensive analysis of their shape, size, localization and the immunohistochemical phenotype. Telocytes expressed C-kit+,CD34+,CD44+,vimentin+ markers separately and in addition they were detected with triple CD34+/vimentin+/desmin- immunofluorescent staining.
Conclusion: Ultrastructural features indicated a variety of functional status of myocardial telocytes in children: cells with proliferative activity contained centrioles, others were with synthetical activity contained abundant cisterns of the granular endoplasmic reticulum; in some telocytes intermediate filaments were found. Telocytes possessed multiple immunohistochemical phenotypes but none were specific only to them.

PS-06-004
Pathomorphological aspects of degenerative alterations of bone tissue in patients with osteoporosis
T. Pavlova[1], I. Bashuk[1]
[1] Belgorod State University, Russia

Background & Objectives: More than 250 mln people suffer from osteoporosis all over the world. Osteoporosis is considered third in frequency of death after diseases of cardiovascular system and malignant diseases in people of elder age. Fractures of bones on the background of systemic osteoporosis lead often to persistent disability and increase significantly the level of mortality.
Methods: The bone material was taken in 75 patients, who undergone arthroplasty of hip joint. After that the Scanning Electron Microscopy on microscope "FE1 Quanta 200 3D" with console for elemental analysis (Na, Mg, Al, S, Fe, C, N, O, P, Ca) was conducted.
Results: The decreasing of total square of bone tissue was observed. Bone plates of cancellous bone became thinner and perforated, making large cavities after its partial destruction. The lattice system of trabeculae became thinner and partially interrupted. Small number of osteons was located under periosteum. Microfractures of bone balks accompanied with hemorrhages and presence of blood clots. The osteogenic fiber-cellular tissue was detected. Osteocyte were altered, their sprouts were short and small.
Conclusion: SEM is reliable and resultative method of study of biological objects in pathology of bone tissue.

PS-06-005
Changes of nasal mucosa epithelium after CPAP on patients with obstructive sleep apnea syndrome
S. Rjabceva[1], V. Karnialiuk[2], L. Makaryna-Kibak[2], Y. Yaromenka[2], I. Siamionik[1], M. Derevyanko[1]
[1] Institute of Physiology of National Academy of Sciences of Belarus, Belarus, [2] Republican Scientific and Practical Centre of Otorhinolaryngology, Belarus

Background & Objectives: Obstructive sleep apnea syndrome (OSAS) is a common condition characterised by repeated episodes of upper airway obstruction during sleep. Continuous positive airway pressure (CPAP) is the "gold" standard of treatment for patients with moderate and severe sleep apnea. The aim of this study was to investigate effect to nasal epithelium in patients with severe OSAS without any nasal pathology after CPAP.
Methods: We evaluated the nasal epithelium before and after CPAP (6 months) in patients (n=10) with severe OSAS by electron microscope (EM).
Results: Before CPAP EM showed destructive-degenerative changes in the ciliated cells: cilia were small (the length of cilia was reduced), destruction of mitochondria and secretory granules, dilatation of endoplasmic network with general vacuolization of cytoplasm and reduce the ribosomes number. In few cases (n=3) we found subtotal destruction of organelles with formed amorphous matter in cytoplasm. The abnormal mucociliary clearance was detected by saccharin test (the average time was 24.91±1.1min). EM of the nasal mucosa after CPAP showed signs of normalization of ciliated cells: cytoplasmic organelles, secretory granules and cilia was correct structure. Clearly visible cilia were surrounded by amorphous masses. The average time of saccharin test was 17.6±0.8min ($p<0.05$).
Conclusion: CPAP could be used to normalize structure of nasal epithelium and mucociliary clearance.

Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-07 | Haematopathology

PS-07-001

Polymorphism in pro-inflammatory and immune-related genes in diffuse large B cell lymphoma susceptibility and overall survival in Arab descent population: a case -control study

S. Al-Khatib[1], L. Al-Etan[1], N. Abdo[1], A. Al-Mistarehi[1]
[1] Jordan University of Science and Technology (JUST), Jordan

Background & Objectives: The trends of incidence for NHL are variable and show significant age, gender, racial and geographic differences. Generally speaking, the overall incidence of NHL is higher in males than females, however, females show more extra-nodal involvement. Regarding geographic variation, the developing countries show lower incidence but higher grade of B-cell lymphomas in comparison with developed countries. The surrounding environment, infectious microorganisms, and life style all play an important role in NHL pathogenesis. Diffuse large B cell lymphoma (DLBCL) is the most common NHL. DLBCL is a diverse disease and several studies reveal that different genetic loci are linked with risk or outcome in DLBCL, among them, the most notably genes are the immunity genes as IL6, IL10, LEPR, CTLA-4, IL4RA, TNF-α and LT-a loci. There is a strong proof that changed immunological function imposes an increased risk for lymphoma. Inflammatory and immune response genes are the inventive messengers of adaptive immunity, which regulates the immune system function and growth of lymphoid tissue. The aim of this study is to analyse the relationship between 8 single nucleotide polymorphisms (SNPs) in five inflammation and immune-related genes (TNF rs1800629G>A, rs161525G>A, rs1799964T>C, LTA rs1800683G>A, rs909253C>T, TNFAIP8 rs1042541C>T, LEPR rs1327118C>G, LEP rs2167270G>C) and the overall risk and prognosis of DLBCL cases in Jordanian Arab population.

Methods: Study Population (subjects)

The study population composed of 125 patients whom diagnosed with DLBCL at KAUH from the period of 2013 to 2018 and 235 healthy cancer-free control subjects with similar geographic and ethnic background to patients. All cases of DLBCL has been diagnosed independently by a hematopathologist according to the 2008 WHO classification of tumours of haematopoietic and lymphoid tissues.

DNA extraction

Genomic DNA was extracted for the DLBCL patients from formalin-fixed and paraffin-embedded (FFPE) tissue using commercially available kit, DNeasy Blood & Tissue Kit (Qiagen Ltd., West Sussex, UK), using the manufacturer's protocols. Genomic DNA from control-subjects blood samples was extracted using the QIAamp® or Promega DNA Mini Kit according to the manufacture's instruction. The quality of extracted DNA was examined by agarose gel electrophoresis and ethidium bromide staining. The concentration and purity of extracted DNA was assessed by using NanoDrop 1000® spectrophotometer. The selected polymorphisms were analysed within candidate genes using Sequencing technique (Sequenom® iPLEX assay).

RNA extraction and real-time quantitative PCR

Total RNA was isolated with TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. The reverse transcription was performed using Transcriptor First Strand cDNA Synthesis Kit (Roche, Indianapolis, IN). Real-time PCR was performed with SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA) on a Bio-Rad CFX96 real-time PCR system. The RT-PCR conditions were as follows: sufficient denaturing at 95°C for 50 seconds, denaturing at 94°C for 50 seconds, annealing at 55°C for 50 seconds, elongation at 72°C for 50 seconds (30 cycles) and a final cycle at 72°C for 10 minutes. β-actin served as the internal positive control. The RT-PCR products were examined by gel electrophoresis.

Statistical analysis

All Overall survival (OS) was calculated from the date of diagnosis to the date of death or last visit for those who were alive at the time of final data collection and analysis. All statistical analyses were performed using IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). The clinical characteristics and response rate of the patients were compared using Chi square tests. Hardy–Weinberg equilibrium Test was estimated by a goodness-of-fit $\chi 2$ test. The Kaplan–Meier method was used to construct survival curves, and results were compared using a log-rank test. The association between polymorphism and the risk for DLBCL was calculated by unconditional logistic regression. The survival curves were displayed using GraphPad Prism 6 software. All significant variables (

Results: In this study, 125 DLBCL patients and 238 ethnically and geographically matched healthy controls were enrolled. Of the patients, 52.8% were males and 47.2% were females with mean age of 53.7 years (17 – 89). The mean age for the controls was 43.2 years (6-89) and 38.7% were males. Eight single nucleotide polymorphisms (SNPs) in four inflammation and immune-related genes (TNF rs1800629G>A, rs161525G>A, rs1799964T>C, LTA rs1800683G>A, rs909253C>T, TNFAIP8 rs1042541C>T, LEPR rs1327118C>G, LEP rs2167270G>C) were genotyped in all subjects (patients and controls). Our study revealed an increased risk of DLBCL associated with TNF rs1800629G>A in the co-dominant, dominant, and recessive models [odds ratio 2.18, 2.19, and 2.16, respectively; 95% confidence interval (CI) 1.11-4.31, 1.14-4.22, and 1.10-4.25, respectively; p value=0.047, 0.014; and 0.016, respectively]. As well the risk of DLBCL was increased with LEP rs2167270G>C in the recessive model [odds ratio 0.47; 95% confidence interval (CI) 0.24-0.93; p value= 0.32). Kaplan-Meier analyses of overall survival revealed that patients with dominant genotype (TT genotype in comparison with combined TC/CC genotypes) of TNF rs1799964 had higher overall survival rate (Log-rank p=0.028).

Conclusion: Our study is the first to address the relationship between TNF-α-308G>A polymorphism and risk of DLBCL in a Jordanian Arab population. Our results are consistent with polymorphism trends seen in Caucasians rather than Asians in that TNF-α-308A allele was significantly associated with higher risk of DLBCL in Caucasians (OR = 1.21, 95% CI: 1.11–1.32, $p < 0.001$), but it was associated with decreased risk of DLBCL in Asians (OR = 0.70, 95% CI: 0.57–0.86, $p = 0.001$) (based on a meta-analysis by Kan Zhai, Jie Ding and Yan Zhou). Additionally, our study is the first to show that patients with genotype TT of TNF SNP rs 1799964 than those with other genotypes after R-CHOP treatment.

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PS-07-002

Lymphomatoid papulosis type E with subcutaneous tissue infiltration and prominent rimming

J. Bosch Schips[1], O. Servitje[2], R. Penín[1], M. Panè[1], I. Salaverria[3], M. Varela[4], C. Muniesa[2], F. Climent[1]
[1] Department of Pathology, Bellvitge University Hospital/IDIBELL. L'Hospitalet de Llobregat, Spain, [2] Department of Dermatology, Bellvitge University Hospital/IDIBELL, Spain, [3] Department of Pathology, Hospital Clínic/IDIBAPS, Spain, [4] Department of Pathology, Catalan Institute of Oncology/IDIBELL, Spain

Background & Objectives: Lymphomatoid papulosis (LyP) type E is a rare variant of LyP. The infiltrates of atypical cells are angiocentric and angiodestructive and may simulate aggressive lymphomas such as extranodal T/NK-cell lymphoma, cutaneous gamma/delta T-cell lymphoma and anaplastic large cell lymphoma. We detail the clinicopathological and molecular features of 5 cases with the goal of identifying a pattern of infiltration previously unreported in the literature.

Methods: The main clinical data was retrieved from the patient's records. Hematoxylin and eosin stained slides and corresponding immunohistochemistry were analysed and molecular biologic assays were performed.

Results: Our series is comprised of 3 females and 2 males, with a median age of 58 years (range: 37-70).

All 5 cases had clinical manifestations, presenting as nodules that rapidly evolved into large ulcerations (diameter 1 to 7cm). One patient showed involvement of tongue as debut manifestation, while the other 4 initially developed lesions on the skin. The prognosis was excellent. The patient with oral disease debut subsequently presented skin involvement. One case developed Mycosis fungoides during patient follow-up.
In all cases, morphology showed dermal angiocentric infiltrates of pleomorphic cells with hemorrhage, necrosis and ulceration. An epidermotropic infiltrate was seen in 2 out of 3 cases with available epidermis. The subcutaneous tissue was affected in the 5 cases and in 3 of them the histological features included rimming of adipocytes by neoplastic lymphocytes. The neoplastic cells were positive for CD30 (100%), CD8 (60%), CD4 (40%) and TIA1 (60%). EBERs, EMA and ALK1 were negative. Monoclonal TCR gene rearrangements were found in 4 cases. Rearrangements of the IRF4/DUSP22 locus on 6p25.3 were absent in all 5 cases analysed by FISH.
Conclusion: We are describing a new pattern of subcutaneous tissue infiltration previously unreported in LyP type E, with neoplastic cells rimming hypodermic adipocytes. The identification of rimming should prompt differential diagnosis with subcutaneous panniculitic-like T-cell lymphoma.

PS-07-003

PAX5 is constitutively expressed in Merkel cell carcinoma and Merkel cell carcinoma cell lines and reveals a broad range of B-cell characteristic PAX5 splice variants

E. Chteinberg[1], W. Gerritsen[1], E. Speel[1], V. Winnepenninckx[1], J. van den Oord[2], A.K. Kurz[3], M. Zenke[3], A. zur Hausen[1]
[1] Maastricht University Medical Centre+, The Netherlands, [2] University of Leuven, Belgium, [3] University Hospital RWTH Aachen, Germany

Background & Objectives: Merkel cell carcinoma (MCC) is a highly malignant skin cancer of unknown cellular origin. MCC is characterised by a typical trilinear differentiation: epithelial, neuroendocrine, early B-lymphoid (co-expression of PAX5 and TdT). B-cells and B-cell leukemias express characteristic patterns of PAX5 splice variants. We tested the expression of PAX5 on protein and RNA level in MCC and MCC cell lines (MCCcls) including PAX5 splice variants.
Methods: MCCs (n=16) and MCCcls (MKL-1, MKL-2 and WaGa) were tested for PAX5 expression by immunohistochemistry (IHC) using different anti-PAX5 antibody clones (DAK-PAX5 (Dako) and SP34 (Roche)). The anti-PAX5 antibody D19F8 (cell signalling) was used for Western-blotting on MCCcls. RT-PCR was performed on RNA isolated from fresh frozen MCCs and MCCcls to test for splice variant expression.
Results: Specific nuclear PAX5 expression was detected in all MCCs and MCCcls by IHC using DAK-PAX5. In contrast, no expression was found using the SP34 clone except in one MCC. Western-blotting of the MCCcls confirmed PAX5 expression by using the anti-PAX5 antibody clone D19F8. In addition, next to full length PAX5 expression, many B-cell characteristic PAX5 splice variants (i.e. Δ2, Δ2/3, Δ2/4, Δ9, Δ8, Δ7/8, Δ8/9, Δ6/7/8) were identified in MCC tissues and MCCcls on the RNA level.
Conclusion: PAX5 IHC using DAK-PAX5 clone is superior to the SP34 clone in MCC and MCCcls, as confirmed by Western-blotting. PAX5 protein is constitutively expressed in all MCCs and MCCcls. The pattern of PAX5 splice variants in MCCs and MCCcls leans strong support to the hypothesis that MCC might originate from early B-cells.

PS-07-004

Bone marrow fibrosis in primary myelofibrosis: the role of MMPs and TIMPs

M. Dincă[1], R.-.Z. Bulf[1], P. Hărşan[1], L. Sticlaru[2]
[1] Clinical Hospital Colentina, Romania, [2] Colentina Clinical Hospital, Romania

Background & Objectives: The progressive bone marrow fibrosis in primary myelofibrosis (PMF) occurs most likely as a result of an imbalance between synthesis and degradation of collagen fibers, caused by the down-regulation of matrix metalloproteinases (MMPs) and up-regulation of tissue inhibitors of metalloproteinase (TIMP). Nevertheless, the pathogenesis of bone marrow fibrosis in PMF is incompletely elucidated. Our goal was to assess the megakaryocyte expression of MMP-1 and MMP-3, on one hand, and TIMP-1 and TIMP-2, on the other hand, in PMF bone marrow biopsies.
Methods: Twenty cases diagnosed with PMF were immunohistochemically studied for MMP-1, MMP-3, TIMP-1 and TIMP-2. MMPs and TIMPs expression levels were then correlated with the degree of myelofibrosis, which was graded according to the WHO criteria.
Results: We identified a significantly increased expression of MMP-3 in megakaryocyte cytoplasm in advanced (grade 2 and 3) myelofibrosis compared to prefibrotic/incipient fibrotic cases ($p = 0.0138$). Moreover, in cases with overt fibrosis, MMP-3 expression was also observed, with moderate or intense positivity, in myeloid precursors and bone marrow fibroblast. On the contrary, prefibrotic/incipient PMF and advanced PMF did not differ significantly from each other with regard to megakaryocyte expression of TIMP-1 and TIMP-2, although their levels were higher in plasma within the vascular bone marrow sinuses in cases with overt myelofibrosis. MMP-1 was almost undetectable in both prefibrotic and advanced stage of PMF.
Conclusion: We conclude that MMP-3 megakaryocyte expression is predominantly related to the stage of disease in PMF patients, which in turn seems not to influence expression of TIMP-1 and TIMP-2.

PS-07-005

Detection of gene fusion transcripts in Peripheral T-cell Lymphoma using a multiplexed targeted sequencing assay

F. Drieux[1], P. Ruminy[2], A. Abdel-Sater[3], P. Viailly[3], V. Marchand[3], M. Viennot[3], M. Lanic[2], V. Fataccioli[4], A. Dupuy[5], D. Vallois[6], L. Veresezan[7], J. Picquenot[7], C. Bossard[8], M. Parrens[9], F. Lemonnier[5], L. de Leval[10], F. Jardin[2], P. Gaulard[11]
[1] U1245 and Pathology Department, Centre Henri Becquerel, Rouen, France, [2] Centre Henri Becquerel, France, [3] U1245 Centre Henri Becquerel, Rouen, France, [4] U955 and Pathology Department, Hôpital Henri Mondor, Creteil, France, [5] U955, Hôpital Henri Mondor, Crèteil, France, [6] Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, [7] Pathology Department, Centre Henri Becquerel, Rouen, France, [8] Pathology Department, University Hospital, Nantes, France, [9] Pathology Department, Hôpital Haut-Lèvêque, CHU de Bordeaux, France, [10] Pathology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, [11] U955 and Pathology Department, Hôpital Henri Mondor, Crèteil, France

Background & Objectives: Peripheral T-cell lymphoma (PTCL) is a heterogenous group of mature T-cell neoplasm, comprising up to 30 entities according to the revised WHO classification. Over the past years, high-throughput technologies identified recurrent fusion transcripts of potential therapeutic relevance in PTCL. However, these techniques are difficult to integrate in the clinical routine practice. Here, we report a rapid and parsimonious ligation-dependent RT-PCR based assay for the detection of these gene fusions.
Methods: 58 probes targeting 32 fusion transcripts were designed and applied to RNAs from 256 PTCL biopsies, including 99 angioimmunoblastic T-cell lymphomas (AITL), 15 nodal PTCL with a TFH phenotype (TFH-PTCL), 43 ALK-negative anaplastic large cell lymphomas (ALCL), 14 ALK-positive ALCLs, 7 adult T-cell leukemia/lymphomas (ATLL), 5 primary intestinal T-cell lymphomas (TCL), 3 hepatosplenic TCLs, 1 cutaneous γδ-TCL, 13 NK/TCL, 1 panniculitis-like TCL and 52 PTCL not specified (NOS). To identify partner genes, sequencing was performed using a MiSeq system (Illumina).
Results: We detected fusion transcripts in 13/14 ALK-positive ALCLs (7 NPM1-ALK, 3 ATIC-ALK, 2 RNF213-ALK, 1 TPM3-ALK and 1 not found) and 12.4% (30/242) other cases. ICOS-CD28 was detected in 14 TFH-derived PTCLs and 2 ATLLs. The other rearrangements were

CTLA4-CD28 (1 TFH-PTCL), ITK-SYK (2 AITLs), ITK-FER (2 AITLs), IKZF2-ERBB4 (1 TFH-PTCL, 1 ATLL), TP63-TBL1XR1 (1 ALK-negative ALCL) and 5 VAV1 fusions (2 VAV1-THAP4 and 1 VAV1-STAP2 in 3 PTCL-NOS, VAV1-CD28 and VAV1-MYO1F in 2 AITLs).
Conclusion: We describe a multiplex assay for the detection of recurrent fusion transcripts in PTCL. Its simplicity and applicability in the routine practice make it an attractive tool to assist pathologists for the characterization of these heterogeneous diseases.

PS-07-006
Histiocytic necrotising lymphadenitis
Y. Krivolapov[1], I. Spiridonov[1], Z. Asaulenko[1]
[1] North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russia

Background & Objectives: Kikuchi-Fujimoto disease (KFD) is a rare, benign potentially-hyperimmune disease with a usually good prognosis, characterised by fever, lymphadenopathy and potential systemic involvement. KFD pathogenesis is not yet clear, though it is proposed to be a result of immune response against an unknown infectious agent, which leads to T-cell and histiocyte activation and apoptosis. In this paper, we used Sequential Immunoperoxidase Labeling and Erasing Method (SIMPLE) to elucidate the immunophenotype of the CD123+ cells always present in KFD, that is the purpose of our study.
Methods: A total of 5 biopsies of KFD patients were examined. Histological sections of lymph nodes, labelled BCL2, TCL1A, CD3, CD20, CD123, CD163, CD68, CD14, MPO, MNDA, PD-L1 through SIMPLE, were digitized via a Pannoramic 250 Flash III scanner. Scanned slides were synchronised via the Pannoramic Viewer program. Following that, CD123+ cell immunophenotype was analysed. Cell immunophenotypes were input and analysed in the MS Office Excel program.
Results: 5 subpopulations CD123+ cells were revealed based on the evaluation of the colocalizations of different antibodies:
1. MNDA+CD68+TCL1A+;
2. MNDA+CD68+TCL1A-;
3. MNDA+CD68-TCL1A+;
4. MNDA+CD68-TCL1A-;
5. MNDA-CD68-TCL1A-.
Conclusion: We suppose CD123+ cells in lymph nodes with KFD consist of 5 phenotypically different subpopulations, some of them are plasmacytoid dendritic cells. Further investigations need to determine role of the subpopulations in pathogenesis of KFD and other diseases.

PS-07-007
Histotopographic characteristics of megakaryocytes in Ph-negative JAK2 mutated chronic myeloproliferative neoplasms
Y. Krivolapov[1], Z. Asaulenko[1], I. Spiridonov[1], A. Selent'eva[1], L. Polushkina[2], A. Lepsky[3]
[1] North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russia, [2] Russian Research Institute of Haematology and Transfusiology, Saint-Petersburg, Russia, [3] St Petersburg University, Saint-Petersburg, Russia

Background & Objectives: The aim of study was to evaluate mean value (MV) of clusters in 1 mm^2 area and MV of megakaryocytes in one cluster in bone marrow biopsies of patients with Ph-negative chronic myeloproliferative neoplasms (CMPNs).
Methods: We examined 95 bone marrow biopsies of patients with JAK2-positive CMPNs: 30 patients with essential thrombocythemia (ET), 20 patients with polycythaemia vera (PV), 25 patients with primary myelofibrosis in prefibrotic stage (prefibr-PMF) and 20 patients with primary myelofibrosis in fibrotic stage (PMF). 10 patients with Hodgkin's lymphoma were analysed as the control group. The slides were digitized by a Pannoramic 250 Flash III scanner. The coordinates of all megakaryocytes in bone marrow samples were determined and processed with Python programming language (DBSCAN algorithm). We used one-way MANOVA to determine if the differences between groups were statistically significant.
Results: The MV of clusters in 1 mm^2 in ET=2.3±1.0, in PV=1.4±1.4, in prefibr-PMF=2.3±1.1, in PMF=1.8±1.1, in HL=0.3±0.2. The MV of megakaryocytes in one cluster in ET=5.9±2.4, in PV=6.5±6.4, in prefibr-PMF=8.0±4.4, in PMF=8.4±5.6, in HL=3.4±0.4. The largest cluster density was found in ET and prefibr-PMF. Bone marrow biopsies of patients with prefibr-PMF and PMF demonstrated clusters with largest number of megakaryocytes. There was a statistically significant difference in histotopographic characteristics of megakaryocytes in Ph-negative JAK2-mutated CMPNs, $F=7.87$, $p<0.0005$; Wilk's $\Lambda=0.443$, partial $\eta^2=0.238$.
Conclusion: The histotopographic characteristics of megakaryocytes are associated with type and stage of CMPN. Obtained results can be used for developing machine learning for scientific and practical needs.

PS-07-008
Clinicopathologic implication of PD-L1 gene alteration in primary adrenal diffuse large B cell lymphoma
K. Lee[1], J.M. Yang[2], J. Koh[3], Y.K. Jeon[3], J.H. Paik[2]
[1] Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea, [2] Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea, [3] Department of Pathology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

Background & Objectives: Primary adrenal diffuse large B cell lymphoma (DLBCL) is a rare subset of DLBCL with uncertain clinicopathologic features. We investigated these features relating with PD-L1 genetic altertaion in adrenal DLBCL.
Methods: Nineteen cases of adrenal DLBCL were analysed with PD-L1 gene alteration including translocation and amplification (PD-L1:chromosome 9 ratio>4) in comparison with non-adrenal cohort(n=90).
Results: Compared with non-adrenal DLBCL cohort, adrenal DLBCL was associated high international prognostic index (IPI; score 3-5; adrenal: 68%; non-adrenal: 38%; p=0.021) and poor Eastern Cooperative Oncology Group performance status (ECOG PS; ≥2; adrenal: 44%; non-adrenal: 11%; p=0.004). In addition, there was a tendency for high frequency of presence of B symptom, elevated serum LDH and activated B-cell-like (ABC) subtype in adrenal DLBCL without statistical significance. Adrenal DLBCL harbored more frequent PD-L1 gene alteration (37%, 7/19; translocation: 21%, 4/19; amplification: 16%, 3/19) than non-adrenal DLBCL (6%, 5/86; translocation: 3%, 3/87; amplification: 2%, 2/87; p=0.001). In adrenal cohort(n=19), PD-L1 gene alteration was associated with lack of bulky disease (8cm; p=0.047) but showed tendency for presence of B symptoms, high IPI, elevated LDH and poor ECOG PS.
Conclusion: Adrenal DLBCL frequently showed PD-L1 gene alteration. Adrenal DLBCL may represent a distinct subset of extranodal DLBCL and PD-L1 gene alteration may contribute to its pathogenesis.

PS-07-009
BCL2 in follicular lymphoma: the overrated guy?
F. Magnoli[1], C. Amaglio[1], D. Marchiori[1], L.F. Vivian[2], V. Martin[3], F. Sessa[2], M.G. Tibiletti[4], S. Uccella[2]
[1] University of Insubria, Varese, Italy, [2] Unit of Pathology, Department of Medicine and Surgery, University of Insubria, Varese, Italy, [3] Cantonal Institute of Pathology, Locarno, Switzerland, [4] Department of Pathology, ASST Sette Laghi, Varese, Italy

Background & Objectives: The translocation (14;18)(q32;q21) is considered the genetic hallmark of follicular lymphoma (FL). However, some authors have observed a proportion of FL lacking IGH/BCL2 translocation as high as 50% in their series, suggesting the existence of geographical differences and alternative mechanisms of genetic deregulation in BCL2- cases.
The aim of this study was to test the incidence of BCL2- FL in a series of Italian patients, evaluate its association with clinic-pathological features and investigate alternative genetic aberrations in this subset.
Methods: We collected 76 consecutive FLs between 2013 and 2016. All lymphomas underwent histopathological revision and were immunohistochemically characterised. Interphasic fluorescent in situ hybridization (FISH) was performed with break apart probes targeting BCL2, IGH, BCL6 and MYC on paraffin embedded and fresh frozen (FF) specimens. Conventional cytogenetic was applied to a subset of cases.
Results: BCL2 rearrangements and expression were detected in 54% and 87% of cases, respectively (p=0.04), with statistical significance dramatically increasing when considering intensity of staining (p<0.0001). BCL2 expression was related to a lower proliferative index (p=0.02). Among BCL2- cases, 6 showed IGH rearrangement, and were further tested: 1 had a variant BCL2 translocation, 1 had IGH/BCL6 rearrangement, the other 4 were negative for both BCL6 and MYC. FISH performed on FF specimens allowed to detect small positive clones in cases otherwise categorized as BCL2-. Finally, karyotype reconstruction documented 3q, 1p and BCL6 abnormalities in 3 cases, respectively.
Conclusion: Our study suggests that t(14;18) is not a constant finding in FL, its incidence being probably affected by geographical factors.

PS-07-010
Epstein-Barr virus related bone marrow failure with significant plasmacytosis mimicking multiple myeloma
L. Marinos[1], G. Kanellis[1], E. Pouliou[1], E. Economaki[1], A. Papanikolaou[1]
[1] Haematopathology Department/Evangelismos General Hospital, Athens, Greece

Background & Objectives: Epstein-Barr virus (EBV) is commonly related to a wide spectrum of neoplastic, inflammatory or reactive processes with variable clinical presentation and histology. One of its relatively rare and unusual manifestations is the induction of bone marrow failure due to extensive replacement of the hemopoietic lineages by a large number of plasmacytes. The early diagnosis of this condition is of primal importance since the severe bone marrow failure can have a potential fatal outcome for the patient.
The objective of this study is to alert pathologists on this situation through the presentation of the bone marrow histological findings of two patients.
Methods: A man and a woman aged 61 and 71 years-old respectively were admitted for sudden onset of fever and pancytopenia. A bone marrow biopsy was performed the findings of which are described .
The diagnostic approach included morphologic study of hematoxylin and eosin (H&E) stained slides, immunohistochemistry and in situ hybridization (ISH) for the detection of small RNA transcripts of EBV.
Results: Histology of the bone marrow disclosed an extensive plasmacytic infiltration (80% and 90% of the total cells respectively) with very few remaining cells of the hemopoietic lineages. Immunohistochemistry revealed polyclonality of the plasmacytes, while ISH detected the presence of EBV.
Conclusion: Bone marrow failure through EBV-induced plasmacytosis is a rare and potentially lethal manifestation of EBV infection.Its early diagnosis with bone marrow biopsy is of paramount importance and requires implementation of immunohistochemistry as well as ISH for the detection of the virus

PS-07-011
Expression of MYC, FOXP1, LMO2 and BCL2 in diffuse large B-cell lymphoma classified into GCB and non-GCB subtypes by immunohistochemistry. Correlation with clinical parameters
M. Melachroinou[1], V. Tzelepi[1], P. Patiou[1], E. Kourea[1], V. Zolota[1], A. Sarantopoulos[2], M. Tiniakou[2], E. Tzouvara[2], A. Kourakli[2], E. Solomou[1], A. Symeonidis[1]
[1] University of Patras, School of Medicine, Greece, [2] University Hospital of Patras, Greece

Background & Objectives: Based on microarray analysis diffuse large B-cell lymphoma (DLBCL) can be classified into three subtypes: germinal center B-cell-like (GCB), activated B cell-like (ABC), and unclassified. GCB subtype tend to have better prognosis than ABC and unclassified. Several studies have demonstrated that immunohistochemical (IHC) algorithms can reproduce the molecular classification. The aim of this study was to investigate the ability of IHC classification to prognostically stratify DLBCL patients treated with immunochemotherapy. Also, to evaluate the prognostic significance of MYC, FOXP1, LMO2 and BCL2 immunoexpression.
Methods: A total of 72 cases of DLBCL [40 nodal, 32 extranodal] were classified into GCB and non-GCB subtypes by Hans IHC algorithm [markers: CD10, BCL6, MUM1] and were examined for MYC, FOXP1, LMO2 and BCL2 immunoexpression. Clinical data were available for 50 patients.
Results: Between GCB [24/72 (33.3%)] and non-CGB group [48/72 (66.6%)] was not detected a significant difference in overall survival (OS) and disease-free survival (DFS). In non-GCB group, the overexpression of MYC and FOXP1 was associated with shorter DFS (p=0.037), and with better OS (p=0.048) and longer DFS (p=0.028), respectively. In addition, high levels of FOXP1 and low levels of LMO2 (p=0.032) were correlated with complete response to immunochemotherapy (p=0.032). In GCB group, MYC overexpression and MYC-BCL6 co-overexpression were associated with shorter DFS (p<0.001).
Conclusion: Our results did not confirm the prognostic stratification of DLBCL based on IHC algorithm. However, they suggest the potential use of MYC and FOXP1 as predictive and prognostic markers.

PS-07-012
Bone marrow histopathology in accelerated phase of BCR-ABL1 positive chronic myeloid leukemia
M. Murari[1], S. Sharma[1]
[1] SGPGIMS, Lucknow, India

Background & Objectives: Chronic Myeloid Leukemia is a triphasic myeloproliferative neoplasm. Currently, the accelerated phase is defined by clinical and laboratory criteria including leucocyte and platelet counts, basophilia and blasts. Marrow trephine biopsy in not routinely carried out in CML and the histopathological features of accelerated phase are not well characterised.
Methods: This study presents bone marrow trephine biopsy findings in 40 patients of BCR-ABL positive CML in accelerated phase. Marrow trephine biopsy cores were fixed in B5, decalcified, paraffin-embedded and stained with H&E, Reticulin and VG / Masson Trichrome stains, study of histomorphology and topographic distribution of hematopoietic and stromal elements was done.
Results: Marrow biopsy showed hypercellularity, predominantly myeloid hyperplasia (90%) and megakaryocytic hyperplasia (85%) with prominent clustering and dysplasia (65%). Blasts ranged 5-18%, interstitially dispersed in most, with random / paratrabecular clusters in 10% of cases. Fibroblastic proliferation with sinusoidal hematopoiesis was seen in 25% cases. Increased reticulin (grade I-II) was seen in most of the cases, 36.4 % had grade III fibrosis. Erythropoiesis was uniformly reduced. Five cases showed prominent myelofibrotic changes and reduction in hematopoietic elements.
Conclusion: Marrow histopathology in accelerated phase of CML is quite variable. Megakaryocytic dysplasia, blasts and marrow fibrosis were better evaluated in biopsy compared to marrow aspirates, however, basophilia was not well appreciated in the biopsy. The prognostic relevance of marrow histopathology and its correlation with peripheral blood findings would necessitate sequential observations on trephine biopsy.

PS-07-015

Peculiarities of megakaryocytes and platelets variation in the microelementosis condition

Y. Lyndina[1], V. Sikora[2], N. Gyryavenko[3], M. Lyndin[4], L. Karpenko[2], A. Romaniuk[1]

[1] Sumy State University, Ukraine, [2] Sumy State University, Medical Institute, Pathology Department, Ukraine, [3] Sumy State University, Department of Pathology, Ukraine, [4] Sumy State University, Medical Institute, Department of Pathology, Ukraine

Background & Objectives: The aim of our study was to characterise megakaryocytes and platelets variation under the influence of heavy metal salts and determine the peculiarities of these changes in recovery period.
Methods: The laboratory rats (n=48) were used for the conduction of experimental investigation. They were divided into two groups: control – animals which drank clean water and experimental – rats which drank water with heavy metal salts (Zn, Cu, Fe, Mn, Cr and Pb). The bone marrow structure and blood parameters were studied on 30, 90, 120 and 180 day.
Results: During 90 days of intoxication the amount of megakaryocytes increased on 40%(p=0.017). There were changes of shape, size (small and giant), nuclear-cytoplasmic ratio, polysegmentation of nuclei and loss of megakaryocyte-sinusoid contacts. It was found the platelets increase by 11% in the blood. Suspending the addition of pollutants to the animal's diet was accompanied by progressive restoration of bone marrow-blood parameters. Simultaneously with disappearance of megakaryocytes morphological variations the area of thrombocytopoiesis was decreased by 28%, the thrombocytes – by 5.3%.
Conclusion: The intake of heavy metal salts in elevated concentrations provokes significant disorders in thrombocytopoiesis which leads for platelets increase in the blood. Although there was a significant improvement bone marrow-blood characteristics during recovery period, their values do not reach the indicators of the intact group animals.

PS-07-016

Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement: a report of 7 cases

C. Rossi[1], D. Fanni[1], G. Martino[2], G. Faa[1,3], S. Ascani[4]

[1] Division of Pathology, Department of Medical Science, University Hospital San Giovanni di Dio, AOU Cagliari, University of Cagliari, Italy, [2] Institute of Haematology and Centre of Haemato-Oncology Reserch (CREO), University and Hospital of Perugia, Italy, [3] Temple University, Philadelphia, Pennsylvania, USA, [4] Pathologic Anatomy, Santa Maria Hospital, University of Perugia, Terni, Italy

Background & Objectives: Myeloid/lymphoid neoplasms (MLNs) with eosinophilia and gene rearrangement are rare diseases characterised by myeloid and/or lymphoid proliferation, eosinophilia, and a fusion gene with constitutive tyrosine kinase (TK) activity. These disorders are responsive to TK inhibitors (TKIs) excluding FGFR1-rearranged MLNs, for which there is currently no standardised therapy.
The aim of this study is to report 7 cases of MLNs collected from 2003 to 2018.
Methods: All patients underwent bone marrow (BM) core biopsy that showed hypercellular BM, hyperplasia of eosinophilic granulopoiesis and features of myeloproliferative neoplasms (MPNs). In 4 out of 7 patients with lymphadenopathy, excisional lymph node biopsy was performed revealing a T-lymphoblastic lymphoma (T-LBL). Gene rearrangement was assessed with cytogenetic and/or molecular analysis.
Results: In 6 out of 7 cases, the fusion gene has been identified: FIP1L1-PDGFRA (2/7), ETV6-PDGFRB (2/7) and ZMYM2-FGFR1 (2/7). In one case, no currently known TK fusion genes were recognized.
Two PDGFRA-rearranged patients (one with MPN+T-LBL), two PDGFRB-rearranged patients, one FGFR1-rearranged patient (MPN+T-LBL) and the one with unidentified rearrangement (MPN+T-LBL) were treated with imatinib: all achieved complete hematologic remission except the FGFR1-rearranged patient.
The other FGFR1-rearranged patient (MPN+T-LBL) was treated with polychemotherapy and allogeneic transplantation followed by relapse.
Conclusion: Our cases confirm responsiveness of PDGFRA/B-rearranged MLNs to imatinib and possible existence of not yet known fusion TKs, which may benefit from TKIs. Identification of LBL in MLNs avoids overtreatment/nonresponse to intensive chemotherapy recommended in LBL.
FGFR1-rearranged MLNs exhibit poor prognosis without an effective targeted treatment. Recently, pemigatinib, a selective, potent inhibitor of FGFR1, has shown promising results.

PS-07-017

Next-generation sequencing-based clonality assessment of immunoglobulin gene rearrangements distinguishes relapse from second primary classical Hodgkin lymphoma

D. van Bladel[1], M. van den Brand[1], J. Rijntjes[1], A. Brinkman[1], T. Reigl[2], N. Darzentas[3], C. Hess[1], K. Hebeda[1], P. Groenen[1], H. van Krieken[1], B. Scheijen[1]

[1] Radboudumc, The Netherlands, [2] CEITEC-Masaryk University, Czech Republic, [3] University Hospital Schleswig-Holstein, Germany

Background & Objectives: Classical Hodgkin lymphoma (cHL) is highly curable, however relapse still occurs in up to 30% of (advanced) cHL cases. Case reports and small series have shown that some of these relapses appear to be a new primary cHL. Conventional clonality assays for cHL has thus far been hampered by low frequencies of Hodgkin and Reed-Sternberg cells and limited DNA quality obtained from formalin-fixed paraffin-embedded tissues. Within the EuroClonality-NGS Working Group, we developed a novel approach to detect immunoglobulin heavy chain (IGH*)* and k light chain (IGK) gene rearrangements. The objective of our study is to determine the clonal relationship between diagnosis and recurrent cHL to assess the incidence of second primary malignancies.
Methods: We collected 70 paired diagnosis-recurrence cHL cases including early and late recurrences. Gene-specific IGH-VJ-FR3, IGHDJ, IGK-VJ and Intron-Kde primer sets were used to perform next-generation sequencing (NGS)-based clonality analysis with Ion Torrent PGM. Bioinformatics analysis is performed with the interactive web-based immunoprofiler ARResT/Interrogate.
Results: Preliminary results of 7 paired diagnosis-relapse samples demonstrates the presence of identical clonotypes in 2 cases, while distinct clonotypes were observed in 3 other cases suggesting a second primary lymphoma. No specific clonotype were identified in either diagnosis and/or relapse of the remaining 2 samples. Additional cases of recurrent cHL have to be analysed to reveal the true incidence of clonally unrelated lymphomas in recurrent cHL.
Conclusion: This study is an important step towards establishment of NGS-based clonality assessment in clinical practice for cHL, and eventually the improvement of therapeutic management of recurrent cHL.

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PS-07-018

Follicular lymphoma and in situ mantle cell neoplasm: a rare combination with peculiar genetic and clinical features

L.F. Vivian[1], F. Magnoli[1,2], F. Sessa[1], M.G. Tibiletti[2], S. Uccella[1]

[1] Unit of Pathology, Department of Medicine and Surgery, University of Insubria, Varese, Italy, [2] Department of Pathology, ASST Sette Laghi, Varese, Italy

Background & Objectives: Composite lymphomas are rare entities in which two or more different lymphomas coexist in the same site. Little is known about their clinical and prognostic implications. We present a

unique case of combination between a low-grade follicular lymphoma (FL) and an *in situ* mantle cell neoplasm (ISMCN), focusing on its morphological, immunophenotypical, genetic and clinical features.
Methods: We evaluated a 75-year-old female patient who first presented in 2012 with a cervical lymphadenopathy. Every newfound lesion was biopsied in the 6-year follow-up, until exitus. Tissue samples were routinely processed for morphological, immunohistochemical and cytogenetic evaluations. FISH analysis was performed using three different approaches: break-apart probes (BCL2, BCL6, CCND1); dual-color dual-fusion probe (IGH/BCL2); spectral karyotyping (SKY) FISH.
Results: In the first lymph node biopsy, a coexistence of FL grade 1-2 and ISMCN was diagnosed. Bone marrow trephine showed infiltration by FL and no signs of MCL. Two and four years later, respectively, a new cervical lymph node and a cutaneous lesion were sampled, showing FL localization without ISMCN or MCL. In 2018, the patient died of disease. In the first lymph node sample, SKY FISH revealed three clones including one diploid (46XX) and two abnormal ones (46,XX,t(11;14)(q13;q34),del(11)(q11q22)[13]/49,XXX,t(2,18)(p11;q21),+4, del(5)(q?),der(17)t(1;17)(q22-25; q25),+der(18)t(2;18)(p11;q21)[23]). FISH analysis confirmed the involvement of BCL2, BCL6 and CCND1 rearrangements respectively in 71%, 86% and 11.5% of nuclei.
Conclusion: The progression of the FL influenced the adverse outcome of the patient, whereas the ISMCN never progressed to an overt MCL. Accordingly, the ISMCN component had a simpler karyotype than the FL component. A careful cytogenetic analysis of composite lymphomas may provide significant prognostic information.

Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-08 | Infectious Diseases Pathology

PS-08-001
Hydatid disease: report of four cases localized to bone
Z.B. Erdem[1], O. Yalcin[1], S. Yildirim[2]
[1] Okmeydani Training and Research Hospital, Istanbul, Turkey, [2] Maltepe University Medical School, Istanbul, Turkey

Background & Objectives: Hydatid disease is an infectious disease caused by *Echinococcus* species. Echinococcus granulosus is the most common cause of hydatid disease. Hydatid cysts are mostly seen in liver and lung. Rarely spleen, kidney, central nervous system, cardiac muscle, bones and subcutis can be involved
Methods: We performed a retrospective analysis of pathology reports between the years 2009 and 2019. Four patients had cyst hydatid lesion located in bone.
Results: Patients ages ranged from 27 to 64 years; 3 of them were females and 1 of them was a male. Lesions were located in acetabulum, proximal of tibia, lumbar 2 vertebrae and mandible. Radiologically only one of them had a differential diagnosis of hydatid cyst. Others had osteosarcoma, giant cell tumour of bone and enchondroma as differential diagnosis radiologically. Grossly all specimens consisted of fragmented bones intermixed with white membranous pieces. Microscopic evaluation revealed that the white membranous pieces consisted of laminated and germinal membranes of the cyst hydatid wall. Some pieces showed thick fibrous capsule surrounding the cyst wall.
Conclusion: Hydatid cysts are slow growing lesions which are usually asymptomatic during this period. Nonruptured cysts cause symptoms by compressing to the adjacent structures. When ruptured, cysts can cause severe inflammatory and allergic reactions. Differential diagnosis of liver and lung lesions of hydatid disease is easier when compared to bone lesions. Bone involvement by hydatid disease doesn't have a characteristic appearence radiologically which makes it hard to distinguish from malignancies and other benign cystic lesions. Bone hydatid disease is a rare entity (%3 of all cases) and must be kept in mind when evaluating a cystic lesion of bone.

PS-08-002
Pulmonary amoebic abscess - resolved with application of metagenomics (universal pathogen detection)
K. Kashofer[1], A. Thueringer[2], L. Brcic[1], G. Gorkiewicz[1]
[1] Institute of Pathology, Medical University of Graz, Austria, [2] Medical University of Graz, Austria

Background & Objectives: Pulmonary amebic abscesses are often hard to diagnose since microorganisms cannot be readily captured in the background of a severely inflamed tissue.
Methods: Shotgun metagenomics was applied to extracted DNA from a lung abscess and resolved with next-generation sequencing. Human sequences were bioinformatically removed and the remaining non-human sequences identified by database queries. The bioinformatics pipeline used in our approach encompasses the PathSeq toolkit for metagenomics based pathogen detection (Kostic AD, Nature Biotech 2011).
Results: We report on a 58 year old female who presented with an abscess involving the lung and extending into the liver. Histology of the resected lung tissue showed a liquefactive necrosis but without identifiable microorganisms including amebal structures. However, serology was highly positive for Entamoeba histolytica (IHA, IgG ELISA) in this patient. Curiously, PCR for E. dispar and E. histolytica performed on DNA extracted from lung tissue was negative. Shotgun metagenomics performed on the tissue was able to detect Entamoeba histolytica DNA in low concentration (2 reads out of 3.47 Mio. reads) verifying the amebic origin of the pulmonary abscess.
Conclusion: This case highlights the power of metagenomics to resolve uncommon (infectious) diseases. This method represents a "universal pathogen detection" approach principally able to detect each possible microorganism in human tissue. Interestingly, targeted PCR failed in our case which indicates that in certain instances shotgun metagenomics seems to be more sensitive and represents therefore a superior detection method.

PS-08-003
Study of paediatric empyema thoracis treated by surgical decortication
M. Khawale[1], S. Singaravel[1]
[1] Department of Pathology, Bai Jerbai Wadia Children's Hospital, India

Background & Objectives: Paediatric empyema thoracis (PET) is a complication of bacterial pneumonia resulting in increased morbidity, primarily attributable to poverty, overcrowding and poor compliance to conservative therapy. Surgical decortication is a last resort, performed in neglected cases.
Methods: We conducted a study of PET treated by surgical decortication of two years duration at our urban tertiary care paediatric hospital in western India. We studied demographic features, clinical presentation, radiological details, laboratory data, microbiological findings and histopathology of pleural peels in these patients.
Results: Eighty six cases of PET were identified. The age range was 2 months to 11 years and 58% of patients belonged to the 1-5 years age group. The Male:Female ratio was 1.2:1. Almost all the patients presented with fever, cough and dyspnea. Radiology was available in 55 cases and the most common finding was loculated pleural effusion. Pleural fluid was examined in 25 cases and showed a total count ranging from 600-20,000 cells/cu mm with predominance of neutrophils. CRP was elevated in all cases. Microbiological findings were available in 55 cases and 18 cases were culture positive. The most commonly cultured organisms were *Klebsiella pneumoniae* and *Methicillin-resistant Staphylococcus aureus*. Histopathology showed suppurative inflammation (13 cases), granulation tissue (5 cases), fibrosis (11 cases), mixed pattern (50 cases), round cell tumour (1 case), necrotizing granulomatous inflammation (6 cases - 3 were positive for *Mycobacterium tuberculosis* on Gene Expert).

Conclusion: Early diagnosis and effective management of pneumonia would lower the morbidity in such cases.

PS-08-004

Co-infection of the human placenta and problem of the mother-to-child transmission of HIV

A. Kolobov[1]
[1] Saint Petersburg University, Russia

Background & Objectives: The immune parameters of the placenta of the HIV-infected woman during pregnancy have been linked to the mother-to-child transmission (MTCT) of HIV. The purpose of this study was to investigate the characteristics of the placentas and the expression of the CD14+ receptors in macrophages of the placentas of Russian HIV-infected women and to compare it with the expression of the immune receptors in placentas of women with co-infections and healthy women as controls.
Methods: The placentas were collected from three groups of patients: Group A – cases with children infected with HIV (11 placentas), Group B – cases with non-infected children born to HIV-infected mother (11 placentas) and Group C – placentas from women without any infection (16 placentas). In morphological analysis routine staining (hematoxylin and eosin) and microscope investigation were used. HIV-infection and the DNA-viruses of family *Herpesviridae* was confirmed immunohistochemically. CD14+ receptors expression was studied immunohistochemically.
Results: Placental infection was detected in 91% of placentas Group A, 64% of Group B. In Group A the placental inflammation (73%) represented combined bacterial and viral changes, and 18% had isolated viral inflammatory changes – HIV and DNA-virus. In Group B the majority of placentas had HIV changes (55%). Expression of CD14+ in cytoplasm of chorion villi cells and endotheliocytes was the highest in Group A (14.14 ±1.11%), followed by Group B (10.04±1.37%), when compared with control Group C (3.21±0.43%, $p<0.05$).
Conclusion: In our study there was a significant prevalence of bacterial and combined bacterial and viral inflammatory changes in the placentas with MTCT of HIV compared to the placentas of the women without MTCT. The presence of viral infections (HSV and CMV) and HIV was accompanied by the significant increase of CD14+ macrophages in the placentas at time of delivery.

PS-08-005

Severe infectious myocarditis with three distinctive microorganisms

O. Neagu[1], L. Luca[2], A. Tita[2], M. Bosa[2], D.I. Enea[1], M.C. Ceausu[1,3]
[1] University Emergency Hospital Bucharest, Romania, [2] "Mina Minovici" National Institute of Legal Medicine, Bucharest, Romania, [3] "Victor Babes" National Institute of Pathology, Romania

Background & Objectives: Myocarditis is an uncommon and puzzling diagnosis to establish in vivo. Depending on its stage and activity, the presentation includes acute heart failure, tachyarrhythmia or sudden death. Generally, the severe cases are confirmed during histopathological examination of the autopsy specimen.
Methods: We report three cases of myocarditis confirmed post-mortem, caused by peculiar infectious agents.
Results: A 66-year-old woman died in the hospital with signs of meningo-encephalitis two days after admission. The tissue samples demonstrated a mild encephalitis, interstitial pneumonia and myocarditis with lymphocytes, plasma cells and macrophages. An infection with Influenza virus was detected in her airways fluid.
Another bizarre case is a 19-year-old girl who was found dead, lacking any pathological history or trauma injuries. The heart fragment showed acute purulent myocarditis. A PAS stain identified hyphae and spores in the myocardial abscesses.
The third case is a 40-year-old man, with unknown identity, discovered lifeless on a street. He had innumerable whitish, confluent nodules, with caseous necrosis located in the lungs, liver, kidney and heart. Cirrhosis was also noted. Biochemistry tests confirmed tuberculosis.
Conclusion: Myocarditis is usually caused by a viral infection, but bacteria, fungi and parasites have also been documented. In our cases, we illustrated a complicated and lethal infection with a common Influenza virus, a highly disseminated tuberculosis with myocardial involvement, and an atypical fungal myocarditis in a young female.
The cardiac muscle requires rigorously examination during autopsy because it can clarify the final report regarding the cause of death. Ancillary tests are mandatory to sustain the infectious etiology.

PS-08-006

The role of intraoperative frozen section in the joint arthroplasty: retrospective review with CD66b staining

Y. Yoo[1], S. Park[1], S.H. Sung[1], H.P. Shin[2]
[1] Department of Pathology, Ewha Womans University College of Medicine, Seoul, Korea, Republic of Korea, [2] Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Republic of Korea

Background & Objectives: The preoperative diagnosis of infection in joint arthroplasty is important for clinical management. For decision making for joint infection, surgeons depend on intraoperative frozen section diagnosis. However, the evaluation of polymorphonuclear leukocytes (PMNs) in frozen section is sometimes difficult. We compared the intraoperative performances of the frozen section diagnosis to evaluate the utility of intraoperative frozen section and performed the immunohistochemical stain for PMNs (CD66b) for confirmation.
Methods: This study includes 74 patients with indicated surgery after arthroplasty of knee, hip, shoulder, and ankle. The presence of PMNs was determined on frozen sections intraoperatively and permanent sections, respectively. A histologic section, frozen or permanent, was considered positive for infection if there were more than 10 PMNs per HPF, excluding surface fibrin and inflammatory exudate, in at least five separate microscopic fields. In equivocal cases, the immunohistochemical stain (CD66b) was performed to identify PMNs.
Results: The ratio of male and female patients was 29:45. The mean age was 68.4 years. Postoperatively, 31 patients were diagnosed with infection (31/74, 42%). Of 31 patients with infection, sensitivity and specificity of frozen section were 97% (30/31) and 95% (40/42), respectively. Of 42 patients without infection, two cases showed false positive results in intraoperative frozen section diagnoses (2/42, 5%).
Conclusion: The frozen section revealed a significantly higher performance and concordance with the permanent histology. Therefore, the frozen section diagnosis is reasonably applicable to diagnostic work-up.

PS-08-007

Clinical and morphological features of five cases of caseous BCGitis

A. Sapargaliyeva[1], A. Pak[1], B. Alibekov[1]
[1] Pathology Bureau of the City of Almaty, Kazakhstan

Background & Objectives: BCGitis are among the most frequent complications of BCG vaccination. In accordance with the existing classification, there are simple and purulent BCGitis, and the latter ones are included in the group of severe complications requiring surgical treatment. We would like to discuss the morphological features of cases of caseous BCGitis without suppuration in five children.
Objectives: We conducted a morphological analysis of caseous BCGitis.
Methods: We conducted a morphological study of axillary lymph nodes of five children after axillary node dissection on the left. The age of patients varied from five months to twenty-two months during the initial examination (there were three boys and two girls). The material for analysis was provided by the National Center of Tuberculosis, where children were treated in the surgery department.

Results: Results: in all cases, caseous lymphadenitis was diagnosed. Massive focuses of caseous necrosis were surrounded by granulation tissue of varying degrees of maturity, which included round-cell cells and giant cells. In the lymph nodes of children (age group from 18 months to 22 months) in the foci of caseous necrosis, we identified massive deposits of calcium. In addition, two types of giant cells (foreign-body giant cells and Langhans giant cells) revealed signs of cell injury with intracellular fatty change and calcium accumulation. Lymph nodes had the appearance of conglomerates consisting of multiple small and large tuberculous foci. There were numerous epithelioid cell granulomas outside of the lymph nodes.
Conclusion: Caseous BCGitis is characterised by foci of caseous necrotic lesions within affected axillary lymph nodes, total destruction of lymph nodes' architecture and a high risk of dissemination of BCG infection.

PS-08-008
Clinical and morphological study of ten cases of pulmonary echinococcosis
A. Sapargaliyeva[1], A. Duysenova[2], A. Pak[1]
[1] Pathology Bureau of the City of Almaty, Kazakhstan, [2] Department of Infectious Diseases, Kazakh National Medical University, Kazakhstan

Background & Objectives: Cystic echinococcosis is common in Kazakhstan and its diagnosis is a clinical problem. Cystic echinococcosis often involves lungs in the pathological process. As a rule, echinococcal cysts in the lungs are detected by chance as well-defined nodules, which often lead to the erroneous diagnosis of "tuberculoma" and prescription of anti-tuberculosis drugs.
Objective: A retrospective analysis of ten cases of pulmonary echinococcosis. In all cases, patients were treated from tuberculosis.
Methods: All patients, including seven females and three males, were admitted by the Republican Center of Tuberculosis of the Republic of Kazakhstan with a diagnosis of pulmonary tuberculoma over the period of three years (from 2013 to 3015). All patients received anti-tuberculosis drugs and due to the lack of effect of the therapy, they went through surgical treatment, including segmentectomy (nine cases) and lobectomy (one case). The age of patients varied among males from 7 years to 16 years, among females from 23 years to 34 years. Five patients had close contact with a relative with active TB. All patients lived in rural areas.
Results: Morphological examination detected cystic echinococcosis in all cases. Hydatid cysts in lungs had typical structure and cysts' diameters were less than 3 cm. The definitive diagnosis of echinococcal cyst in the lung was based on the histological examination of resected lung tissue after the surgery.
Conclusion: Morphological diagnosis of pulmonary echinococcosis does not represent a problem. For general practitioners, diagnostic difficulties are associated with echinococcal cysts smaller than 3 cm in diameter, which, in the absence of sensitive laboratory (immunoblot) and visual (CT and MRI) diagnostic methods, lead to the diagnosis of tuberculosis.

PS-08-009
Inflammatory pseudotumour of the chest - a medical conundrum solved with 16S rRNA gene sequencing
M. Zacharias[1], L. Brcic[1], K. Kashofer[1], G. Gorkiewicz[1]
[1] Institute of Pathology, Medical University of Graz, Austria

Background & Objectives: Inflammatory pseudotumour (IP) is an exceedingly rare benign condition that often presents as a locally invasive mass, most often occurring in the lungs and the orbit. IP is named for its ability to mimic invasive malignancies on clinical presentation, imaging, and histology. Idiopathic soft-tissue inflammation is thought to be the cause of IP.
Methods: Culture-independent, panbacterial (16S rRNA gene) sequencing resolved with next generation sequencing was performed on resected tissue of IP.
Results: We present a case of an IP in an 8 year old boy, which developed in the chest wall several weeks after a minor trauma. Clinically sarcoma was suspected but histology specified the lesion as IP with a granulation tissue like appearance and abundant histiocytes in the tissue. 16S rRNA gene sequencing identified three bacteria in high concentration in the resected tissue, namely Fusobacterium nucleatum, Aggregatibacterium actinomycetemcomitans and Campylobacter rectus, the latter not captured with microbiological culture.
Conclusion: Our case sheds new light on the pathogenesis of IP. All three (opportunistic) pathogens belong to the oral microbiota and are frequently found in the interdental plaque. Retrospectively it turned out that the patient had a bad dental status. Supposedly, the preceding minor trauma led to tissue alterations (e.g. hematoma) which might have enabled endogenous (oral) opportunists to colonize this site which in turn lead to chronic inflammation and ultimately IP. Indeed, infection, trauma, and foreign bodies are among the numerous reported etiologies that may be involved in the pathogenesis of IP. Noteworthy, molecular pathogen detection performed in our case additionally detected the microaerophilic C. rectus in the lesion, which was missed in clinical microbiology with possible therapeutic implications.

PS-08-010
Pulmonary nocardiosis diagnosed by culture-independent, panbacterial (16S rRNA gene) sequencing - a series of 3 cases
M. Zacharias[1], L. Brcic[1], K. Kashofer[1], G. Gorkiewicz[1]
[1] Institute of Pathology, Medical University of Graz, Austria

Background & Objectives: Pulmonary nocardiosis (PN) is an infrequent but severe infection due to Nocardia spp. often associated with underlying diseases like COPD, HIV infection or cancer. The lung normally represents the primary site of infection with Nocardia. Besides chronic courses PN can disseminate (brain, skin) and eventually lead to death of patients. Nevertheless, diagnosis of PN is difficult since radiological findings are not specific and classical microbiological methods often fall short.
Methods: Culture-independent, panbacterial (16S rRNA gene) sequencing resolved with next generation sequencing was performed on resected tissue because of suspicious lung nodules.
Results: Three cases of PN were diagnosed by molecular means which were suspicious of pulmonary neoplasia. Captured sequences of Nocardia were most homologous to N. asiatica/abscessus, N. cyriacigeorgica, as well as N. pneumoniae, all species described in PN. Histological representation of lung lesions was not specific and showed diverse histology including chronic and acute inflammation.
Conclusion: Diagnosis of nocardiosis is difficult since clinical appearance is not specific and microbiological examination often fails in detection. Most frequent radiologic lung lesions are nodules, cavitations as well as consolidations often suspected to represent neoplasia. Thus histopathology coupled with molecular pathogen detection as used in our cases represents an important diagnostic measure to verify this potentially life-threatening disease.

PS-08-011
Histobacterioscopy studies in tuberculosis
V. Zinserling[1,2], M. Agapov[2], N. Semenova[1]
[1] VA Almazov Research Center, Russia, [2] Saint-Petersburg University, Russia

Background & Objectives: Histobacterioscopic studies of Mycobacteria tuberculosis (M) play an important role not only in practical ±diagnostics but also in understanding of pathogenesis of tuberculosis. There is practically no information about tissue forms of M in different clinical situations. Our aim was to reveal M in paraffin slices with the

help of different staining in deceased from different forms of tuberculosis (T)

Methods: We investigated 24 autopsy cases of fibrous-cavernous T (FCT) with long time treatment and 8 cases of T complicating HIV infection in AIDS stage which received no antituberculous medicaments. Paraffin slices were stained by H-E, Ziehl-Neelsen, auramin-rodamin (luminescent microscopy) and IHC with Mycobacterium tuberculosis Polyclonal Antibody (Termo, PA1-7231; PPD) serum against protein antigen B. We considered number, form and localization of M.

Results: In cases with FCT were typical structural changes with expressed granulomatous reaction. In cases of T complicating HIV alterative and exudative lesions were dominating. Results of histobacterioscopic studies are presented in the table.

Percentage of different forms of M in 10-50 view fields

	Ziehl-Neelsen			Auramin-rodamin			IHC		
	rods	cocci	irreg	rods	cocci	irreg	rods	cocci	irreg
FCT	88,13±2,14	9,33±**1,17**	2,5±**1,28**	64,38±**4,24**	27,29±**3,84**	8,33±**1,48**	57,29±**2,78**	28,71±**2,31**	14±**1,55**
HIV	93,13±**2,16**	5,38±**2,0**	1,5±**0,89**	86,75±**2,40**	8,13±**2,34**	5,13±**1,04**	79±**2,64**	12,75±**2,13**	8,25±**0,87**

In both groups M were located either extracellularly or on the cell surface.

Conclusion: We demonstrated that M are characterised by morphological polymorphism more distinct in the patients, which received long time treatment. Cocci and irregular forms are better revealed by auramin-rodamin and ICH than by Z-N stain. Exclusive extracellular localization of M requests reconsideration of certain aspects of pathogenesis of T.

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PS-09-001

#FNAFriday: how cytopathologists learn, teach and share knowledge on Twitter

E. Alcaraz-Mateos[1], J. Temprana-Salvador[2], T. Labiano[3], I.J. Expósito-Afonso[4], L. Pijuan[5], Z. Baloch[6], M.Y. Fuller[7], V. Fritzburg[8], E. Madrigal[9], V. Walavalkar[10], X.". Jiang[11]

[1] University Hospital Morales Meseguer, Murcia, Spain, [2] Vall Hebron University Hospital, Barcelona, Spain, [3] Hospitalary Complex of Navarra, Pamplona, Spain, [4] University Hospital of Canarias, Tenerife, Spain, [5] Hospital del Mar, Barcelona, Spain, [6] Hospital of the University of Pennsylvania, Philadelphia, USA, [7] Children's Hospital of Pittsburgh of UPMC, USA, [8] Rutgers, the State University of New Jersey, USA, [9] Massachusetts General Hospital, Boston, USA, [10] University of California San Francisco, USA, [11] Duke University Hospital, Durham, USA

Background & Objectives: Twitter is a social media network used by medical professionals. Hashtags are used to organize posts by topic. #FNAFriday is a hashtag created by one of the authors to share educational fine needle aspiration (FNA) cytopathology cases. This study aims to review the tweets tagged with #FNAFriday to assess impact/usefulness on the cytopathology community.

Methods: The Twitter search engine was used to review all tweets tagged with #FNAFriday (April 2015- February 2019). The following data were collected: author, date, pictures, stains, ancillary techniques, subspeciality, comments, retweets, and likes, among others.

Results: A total of 349 original tweets (11256Likes/7099Retweets/1208Comments) were collected from 47 accounts. The most represented subspecialties were endocrine, gastrointestinal, and head/neck. The average number of pictures was 3.22/Tweet and the most frequent stain was Papanicolaou, followed by Romanowsky-type stains, and hematoxylin&eosin (50%/43%/19%, respectively). Cell block (14%), histologic correlation (10%), immunohistochemistry (8.6%), molecular tests (2%), gross pictures (4.6%) and radiology (3.4%) were also part of the content. Most cases (63.7%) included the diagnosis and some of them (13.5%) were quiz.

Conclusion: - #FNAFriday hashtag has been adopted by the cytopathology community with robust engagement and continued growth in usage.
- Images are central to these posts, and correlation with gross findings, radiology, and ancillary studies is included.
- It results an effective way for cytologists to share knowledge and helps bring awareness of the FNA as an effective method for diagnosis.

PS-09-002

Electromyographic analysis of muscle activation while using different input devices in digital pathology

E. Alcaraz-Mateos[1], S. Mèndez-Ríos[2], I. Martínez González-Moro[2], E. Poblet[3]

[1] University Hospital Morales Meseguer, Murcia, Spain, [2] Department of Physiotherapy, University of Murcia, Spain, [3] Department of Pathology, Reina Sofía University Hospital, Murcia. Faculty of Medicine, University of Murcia, Spain

Background & Objectives: Dealing with digital pathology implies an adaptation to the digital environment and the digital image. The input device traditionally used for whole slide image (WSI) controlling is the conventional mouse, but some other devices are also available. The aim of this study is to assess the pattern and the amount of muscle activity of the arm while using different input devices and to improve the knowledge, from an ergonomic point of view, of the human-computer interaction.

Methods: A comparative study of 10 different input devices (conventional and vertical mouse, three trackballs, Ergopointer TM, Rollermouse TM, optical pen mouse, touchpad, Leap Motion TM) was carried out. Six medical students, familiarized with WSIs, performed a standardised circuit using a Fitts' Law based tissue array digitized at 20x. Electric activity of seven upper limb muscles (adductor pollicis, extensor pollicis longus, extensor digitorum, flexor digitorum, middle deltoid, upper trapezius, middle trapezius) was registered using a surface electromyography.

Results: Muscle activity (relativized with respect to repose) was found to be different when using each of the input devices: blue trackball (176%), Rollermouse (180%), Ergopointer (204%), conventional mouse (228%), and vertical mouse (244%) were the ones which demanded less activity, while optical pen mouse (323%), Leap Motion (359%), black trackball (369%), red trackball (539%), and the touchpad (593%) were the ones which required greater muscle mobilization. Adductor pollicis was the most activated muscle during the exercise.

Conclusion: Variability between the use of compared devices and muscle activity was found. Long-term use could produce different degrees of muscular fatigue.

Even though the election of an input device is a matter of personal preference, it is important to analyse its impact on ergonomics.
Muscle activity should be integrated together with other human-factor aspects since to achieve a holistic approach.

PS-09-003

RCPath validation protocol for digital pathology stage 1: our experience in a large tertiary academic centre

M. Elshiekh[1], M. Munonyara[1], C. Wright[1]
[1] North West London Pathology - Imperial College Healthcare NHS Trust, United Kingdom

Background & Objectives: We present our experience conducting validation training set phase 1 according to the Guidelines for Digital Pathology protocol published by the Royal College of Pathologists.
Methods: Thirty histopathology consultants covering ten histopathology subspecialties were invited to partake. Of these, fifteen pathologists reporting eight subspecialties (gastrointestinal, gynaecological, pulmonary, urological, renal, neuropathology, head & neck and breast) participated. Pathologists viewed digital slides first and recorded their diagnoses and confidence level. Glass slides for the same cases were then immediately examined and any change in diagnoses was recorded as well as confidence levels in glass slide diagnoses. The preferred diagnosis method for each case was also noted.
Results: A total of 183 slides were reviewed generating 552 responses. The mean diagnostic concordance was 96%. Discordances were minor and none were clinically significant. The mean diagnostic confidence was 6.6 for digital and 6.9 for glass diagnoses. In 19% of responses, pathologists preferred glass slides while the digital method was favoured in 2%. There was no preference in the majority of responses recorded (79%).
Conclusion: We learnt the following from phase 1 validation:
• Tissue sampling (size and thickness) and quality of slide preparation impact digital scanning procedures.
• Additional time required by scientific and medical staff to undertake phase 1 validation must be considered.
• Integration of digital pathology systems with the department's LIMS system is crucial to maximize efficiency.
• Digitizing pathology services offers safety, efficiency and workflow benefits.
• Insights learnt can help with preparing a better business case for digitization.
We are grateful to Philips who supplied scanners and digital support. This work wouldn't have been possible without support of NWLP scientific and consultant staff.

PS-09-005

A colorectal carcinoma in 3D: merging knife-edge scanning microscopy and deep learning

T. Haddad[1], N. Farahani[2], J. Bokhorst[1], F. Doubrava-Simmer[1], M. Goodman[2], F. Ciompi[1], I. Nagtegaal[3], J. van der Laak[1]
[1] Radboud University Medical Center, The Netherlands, [2] 3Scan, USA, [3] Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands

Background & Objectives: A three-dimensional visualization of a human carcinoma could provide invaluable diagnostic information and redefine how we perceive and analyse cancer invasion. As deep learning begins automating the diagnostic workflow and cutting-edge microscopy provides unprecedented ways of visualizing tissue, combining these methodologies could provide novel insight into malignant tumours and other pathologic entities. By combining Knife-Edge Scanning Microscopy with convolutional neural networks, we set out to visualize an entire three-dimensional colorectal carcinoma segmented into specific tissue classifications.
Methods: A Knife-Edge Scanning Microscope (KESM), developed by 3Scan (San Francisco, CA, USA), was used to digitize a whole-mount, H&E stained, formalin-fixed paraffin-embedded human tissue specimen obtained from the Radboudumc (Nijmegen, The Netherlands). Sparse manual annotations of 5 tissue types (tumour, stroma, muscle, healthy glands, background) were provided using KESM data to train a convolutional neural network developed by the Computational Pathology Group (Radboudumc) for semantic segmentation of the colorectal carcinoma tissue. A three-dimensional visualization was generated using 3Scan's proprietary visualization pipeline.
Results: The convolutional neural network was used to process roughly 1200 slices of KESM data. The stitched and rendered segmentation maps demonstrate the formalin-fixed paraffin-embedded carcinoma of approximately 5 millimeters in depth. As shown in the figure, the tumour invasive margin can be seen advancing into the surrounding tumour stroma.
Conclusion: Based on our findings, we were capable of training a segmentation model on the 3D KESM data to create an accurate representation of an entire formalin-fixed paraffin-embedded colorectal carcinoma tissue block segmented into five tissue classifications. Going forward, this can have much broader implications on the research and understanding of invasive tumours.

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PS-09-009

Artificial intelligence a supporting tool for automation and standardisation of the Gleason grading system

F. Marginean[1]
[1] Lund University, Department of Urology, Sweden

Background & Objectives: Prostate cancer (PCa) is the most widely diagnosed cancer worldwide. Correct identification of the stage, quantification on histological preparations, using Gleason grading, is essential for diagnosis with strong implications in the treatment options, outcome and predict factors. A great interest is in the automation and standardisation of the Gleason grading system based on lack of pathologists, time-consuming and low reproducibility. Using artificial intelligence (AI) we have developed an algorithm, based on convolutional neural networks.
Methods: The prototype algorithm was trained with 317 haematoxylin & eosin-stained PCa biopsies from Malmö University Hospital digitally scanned and annotated by two experienced uropathologists. The prototype algorithm was trained to detect the benign and cancerous areas and distinguish between Gleason grades 3, 4 and 5. The prototype algorithm was tested and validated on the 36 biopsies. The algorithm was adjusted, re-trained on the 100 haematoxylin & eosin-stained PCa biopsies and improved until satisfactory result was obtained.
Results: The algorithm was able to discriminate between cancerous and non-cancerous areas with a Pearson correlation between pathologist and algorithm of r2= 0.94. The algorithm could also satisfactorily detect different Gleason patterns: (r^2= 0.75), Gleason grade 4 (r^2= 0.43) and Gleason 5 (r^2= 0.83). Overall diagnosis estimated by the algorithm was correct on 80% of the tested slides.
Conclusion: Artificial Intelligence propose a supporting tool for automation and standardisation of the Gleason grading system in the digital pathology era. It promise to improve reproducibility, reduce interobserver variability and time-consuming.

PS-09-010

Should I try to learn pathology from YouTube? A medical student's critical journey into learning general pathology on YouTube

J. Melo[1], G. Guerra Moita[2], G. Bitu dos Santos Ponte[2], L. Matias Marques[2], V.M. Maia Amorim De Morais[2], C. Alves Carneiro[2], H. Castelo Branco Roque[2], V. Feitosa Muniz[2], D. Nunes Oliveira[1], M. Luiz Balancin[3]

[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil, [3] Pathology Division, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil

Background & Objectives: Pathology teaching in Brazilian Medical Schools is a challenging scenario. The discrepancy between scarce time resources available and its cardinal role in Medicine demands innovative teaching tools. Students, as active learners also rely on non-orthodox online methods, from scientific material to YouTube videos. To evaluate the nature and quality of information freely available on YouTube about basic pathology, directed to students. To engage medical students into a critical review of pathology concepts by encouraging them to screen these videos for mistakes.
Methods: Second to Fourth year medical students evaluated YouTube videos from major Brazilian Portuguese speaking channels and gone through a basic pathology concepts check-list for errors. Videos and student annotations were reviewed by practicing pathologists.
Results: 65 videos were viewed by the students and reviewed, ranging from 2-82 minutes of duration (median 15 min); views ranged from 145 to 1026235; subscribers from 20 to 1611416. Authors were medical students (23), physicians (16, six pathologists), veterinary physicians (2), others with a biomedical background (19) and undisclosed (5). Four channels were linked to academic Institutions. Major errors were evidenced in 7 videos (44%), minor in (56%); academia-related channels evidenced less misconceptions than general channels (p=0.04). There was no statistical correlation between errors and the amount of views or subscribers (p=0.99), although one of the most influent channel (over 315k subs) had major and minor errors
Conclusion: YouTube is not a reliable source of information for technical knowledge, although this kind of activity was engaging as a "teaching from bad examples" by medical student's perception.

PS-09-011
Application of convolutional neural networks for glands instance segmentation in the images of colon epithelial neoplasms
I. Mikhailov[1], A. Khvostikov[1], A. Krylov[1], N. Oleynikova[1], P. Malkov[1], O. Kharlova[1], N. Danilova[1]
[1] Lomonosov Moscow State University, Russia

Background & Objectives: There are difficult tasks in the diagnosis of colon epithelial neoplasms: lack of quantitative criteria of basal dilation of the crypts and spread of the serration, determination of potential malignancy. Automatic mucous glands segmentation using a convolutional neural network (CNN) is the first step to real diagnostic algorithm development.
Methods: We propose a two step algorithm for glands segmentation. The first step produces semantic segmentation using a UNet-based CNN, while the second performs gland instance segmentation using a novel CNN architecture that predicts parameters for active contour model. This allows to segment each individual gland. We have designated closed-contour glands and "open glands" (glands with open contour).
Results: The network was first trained on Warwick-QU dataset (165 images), fine network tuning was performed on the collected PATH-DT-MSU dataset (19 images, colon biopsy material). 12 images were hyperplastic polyps; 6 images were SSA/P and one was normal colon tissue.
Our segmentation algorithm is characterised by Dice coefficient 0.87 on Warwick-QU and 0.78 on PATH-DT-MSU dataset. Dice coefficient decreased because of presence of «open glands» and the glands with adhered contours.
Conclusion: It is necessary to create alternative collections of annotated histological images of colon epithelial neoplasms and to use full-size images obtained in the pathology examination of the real colon biopsies because images are cut off and only contain closed-circuit glands (mag.x200, x400) in the Warwick-QU. In contrast there are full-size real images with the presence of "open glands" (mag.x100) in PATH-DT-MSU dataset.

PS-09-012
Using deep neural network to count Ki-67 positive cells in neuroendocrine tumours of the gastrointestinal tract
N. Mola[1], S. Leh[1]
[1] Haukeland University Hospital, Norway

Background & Objectives: Calculation of the Ki-67 index in neuroendocrine tumours (NET) of the gastrointestinal tract is time consuming. Automatic quantification of biomarker expression is a typical application of digital pathology. In the present study a cloud based machine-learning platform, Aiforia™, was used to train a deep convolutional neural network (CNN) in order to detect Ki-67 positive tumour cells in gastrointestinal NETs.
Methods: 29 digital slides of NETs (resolution 0.23 μm/pixel) were used as training data set. The images were uploaded to the Aiforia™ platform. The algorithm was trained by supervised learning. The algorithm consisted of two layers. The first layer detected tumour regions and the second layer segmented positive and negative tumour cell nuclei within the first layer. The performance of the algorithm was initially tested in non-annotated areas of the training data set.
Results: The interface for developing a CNN algorithm on the Aiforia™ platform was intuitive and user friendly. Erroneous detection of mucosa epithelium as tumour was overcome by additional annotations in order to represent all the possible variations of tumour cells as target and mucosa epithelium as background. In the second layer, cell nuclei segmentation was overall adequate, however especially overlapping nuclei continue to be an intricate task.
Conclusion: We present an easy to use machine-learning platform which has the potential to assist the pathologist in the calculation of the Ki-67 index in NETs. For a final evaluation an independent test set will be used and the model's results will be compared to the ground truth, manual counting by a pathologist.

PS-09-013
The new generation of AI tools: allowing pathologists to design their own algorithms
J. Gildenblat[1], C. Sagiv[1], N. Sagiv[1], I. Ben Shaul[1]
[1] DeePathology.ai, Israel

Background & Objectives: Digital pathology is the enabler for computer vision and deep learning algorithms. In the last few years many companies offer dedicate algorithms for various tasks in pathology that pathologists and researchers can use. In many cases, especially in pharma research, pathologists would like to design their own algorithms according to their data and needs. The aim of the DeePathology AI Platform is to provide pathologists with the ability to design customized algorithms on their own data. This approach can bridge the gap between the expert pathology knowledge and state of the art computer vision and machine learning capabilities.
Specifically, we plan to discuss the Cell Detection problem. The DeePathology.ai Cell Detection Studio is a do it yourself tool for pathologists to train deep learning cell detection algorithms on their own data. Using this tool, deep learning cell detection solutions can be easily created by the pathologist very quickly.
Methods: Common problems in the process of developing AI solutions for the medical field are highly unbalanced datasets on one hand and limited annotation resources on the other hand.
The use of Active Learning can dramatically help with both issues.
The task of Cell Detection is very important in digital pathology. For example, analyzing the quantity and density of immune cells can provide important indications on the progress of cancer.
This is a tedious task when manually done by pathologists and thus, automating this process is desirable.

Automating cell detection requires annotating large amounts of data, which is usually very unbalanced.
In the talk we will use the example of the DeePathology.ai Cell Detection Studio to demonstrate how Active Learning can be used for medical imaging annotation.
We will also present our approach for using active learning with unbalanced datasets.
Results: The Cell Detection studio was applied to various use cases of Cell Detection tasks.
We show how the pathologist can create annotated data set of thousands of examples within hours and how a customized cell detection algorithm is created along with a report on number of cells, their features and more.
Conclusion: Digital pathology is a game changer. It is also an enabler for the design of algorithms.
The challenge is to bring AI capabilities to the hands of pathologists and provide genuine Pathologist Assistant System.
The DeePathology AI platform allows pathologists and researchers to design and use state of the art Deep Learning algorithms without being AI experts.

Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-10 | Nephropathology

PS-10-001
Eradication of Helicobacter Pylori alleviates proteinuria in Primary Focal Segmental Glomerulosclerosis - a case series
M. Bosnjak[1], N. Kojc[1], A. Aleš Rigler[2]
[1] Institue of Pathology, Faculty of Medicine, University of Ljubljana, Slovenia, [2] Department of Nephrology, University Medical Center Ljubljana, Slovenia

Background & Objectives: Along with chronic gastritis, there is evidence that *Helicobacter Pylori (HP)* is associated to several extra-digestive pathologies A few studies therefore reported both the presence of HP antigens in the glomeruli and a beneficial effect of HP eradication therapy on daily proteinuria in cases of membranous nephropathy (MN).
The focus was to demonstrate the yet unaccounted-for ameliorating effect of HP eradication on clinical course in three patients with Focal Segmental Glomerulosclerosis (FSGS), an important cause of nephrotic syndrome in adults.
Methods: The patients were selected based on kidney biopsy findings (proven FSGS), presence of HP gastritis on gastric biopsy as well as exclusion of significant comorbidities. A triple eradication therapy was subsequently warranted. The follow-up was clinical.
Results: Two of the patients had concomitant HP gastritis at presentation and the third was in partial remission on combined immunosuppression when HP gastritis was diagnosed. Immunosuppression with prednisone (0.8mg/kg) was administered along with HP eradication therapy, which resulted in rapid and long lasting complete remission. None of the patients relapsed to date and none requires maintenance immunosuppression.
Conclusion: Contrary to MN, the positive influence of HP eradication on daily proteinuria values has not been observed previously in FSGS. Given that spontaneous remission rate is <5% in nephrotic FSGS patients and that relapses are relatively common (25-36%), HP might play a yet unaccounted-for role in disease pathogenesis. We therefore recommend HP-oriented diagnostic methods when FSGS patients complain of dyspepsia.

PS-10-002
Glomerular disease associated with myeloproliferative and myelodysplastic/myeloproliferative neoplams
M. Buettner-Herold[1], C. Sticht[2], T. Wiech[3], S. Porubsky[4]
[1] Department of Nephropathology, Institute of Pathology, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Germany, [2] Center of Medical Research, University Medical Centre Mannheim, University of Heidelberg, Germany, [3] Institute of Pathology and Nephropathology Section, University Hospital Hamburg Eppendorf, Germany, [4] Institute of Pathology, University Medical Centre Mannheim, University of Heidelberg, Germany

Background & Objectives: Myeloproliferative neoplasms (MPN) and myelodysplastic/ myeloproliferative neoplasms (MDS/MPN) represent clonal hematopoietic diseases characterised by proliferation of myeloid cells. The spectrum of glomerular alterations associated with MPN has been addressed by only few reports. For MDS/MPN no data is available. Our aim was to systematically evaluate kidney biopsies performed in patients with known MPN or MDS/MPN.
Methods: Retrospective analysis of kidney biopsies in patients with the diagnosis of MPN or MDS/MPN was performed. The cohort (n=27) encompassed patients with chronic myeloid leukemia (CML, n=5), polycythemia vera (PV, n=8), primary myelofibrosis (PMF, n=4), essential thrombocythemia (ET=2) and chronic myelomonocytic leukemia (CMML, n=3) as well as MPN or MDS/MPN without further specification (MPN=4, MDS/MPN=1). In order to control for age-related phenomena, the findings were compared to age- and sex-matched zero-time graft biopsies.
Results: Patients manifested with proteinuria (89%), partially in nephrotic range (37%), hematuria (64%) and kidney failure (100%). In comparison to controls, MPN and MDS/MPN patients showed a significantly higher ratio of sclerosed glomeruli and mesangial expansion. Moreover, ultrastructural signs of endothelial damage and subendothelial edema represented frequent findings (89%). Mesangiolysis (19%) and other features compatible with thrombotic microangiopathy (33%) constituted other less frequent findings. Extramedullary hematopoiesis was present in 3 cases (11%).
Conclusion: Patients with MPN and MDS/MPN show glomerular scarring that exceeds age-related phenomena. Some of the biopsies indicate that a low-level chronic endothelial damage or thrombotic microangiopathy might represent the mechanisms resulting in mesangial and glomerular sclerosis. In addition to the anti-neoplastic therapy, optimization of risk factors for kidney failure and early recognition of renal complication should be recommended.

PS-10-003
Proposal for a semi-quantitative algorithm functional in the assessment of lupus nephritis lesions
I.D. Caruntu[1], T. Azoicai[1], E.R. Avadanei[1], L. Lozneanu[1], S. Giusca[1]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Background & Objectives: The study points out the histological changes in lupus nephritis (LN), aiming to refine the assessment of specific lesions defined by ISN/RPS Classification.
Methods: We analysed 53 renal biopsies diagnosed as LN by light and immunofluorescence microscopy. A semi-quantitative algorithm for corpuscular, tubular, interstitial and vascular lesions was conceived and applied. Score values between 0 and 3/4 was done for the severity of each type of lesion – with a final score for renal corpuscles (RC_S, maximum value of 33) and tubulo-interstitial components (TI_S - maximum value of 18). NIH activity and chronicity indices were also settled.
Results: The algorithm revealed a large variability of lesions' extension and gravity within each class of LN, supporting the active and/or chronic status that complete diagnosis. Hence, for 2 cases in class II, RC_S values were 3 and 5, and IT_S was 2. 4 cases in class III had RC_S values of 8-9 and IT_S of 3. 19 cases in class IV presented RC_S values between 8-19 and IT_S between 4-11. 24 cases in class V showed RC_S between 5-25, and IT_S of 0-13. For 6 cases in class VI, RC-S values were 20-22, and IT_S were 9-14. Our results indicated significant correlations between the RS-S and IT-S values and the NIH activity and chronicity indices.

Conclusion: Our algorithm offers a reproducible tool for a more objective evaluation of renal biopsies and the differentiation between classes and subclasses of LN. Larger studies are compulsory for proving the clinical significance of the proposed scores.

PS-10-004

Kidney biopsy codes for pathologists, status update

A. Dendooven[1], M. Helbert[2,3,1], H. Peetermans[2], T. Nguyen[4], S. Leh[5]
[1] University of Antwerp, Belgium, [2] Ziekenhuis Netwerk Antwerpen (ZNA), Belgium, [3] University Hospital Antwerp (UZA), Belgium, [4] UMC Utrecht, The Netherlands, [5] Department of Pathology, Haukeland University Hospital, Norway

Background & Objectives: Kidney biopsy registries all over the world benefit research, teaching and health policy strategy. Because registries are mainly using locally developed coding systems for pathology diagnoses; comparison, exchange or accumulation of data are hampered. Consequently, there is great need for a standardised, interoperable coding system.
The "Kidney Biopsy Codes (KBC)" project aims to provide a complete and structured set of terms and codes applicable to every non-neoplastic kidney biopsy.
Methods: Work package 1 (WP1) investigated coding praxis of kidney biopsy registries and analysed strengths and weaknesses of established international coding systems. WP2 developed principles for the KBC system during a consensus workshop. WP3 addresses the technical design and generates the KBC as such. WP4 will conduct a review process. WP5 will build structures for maintenance and further development. The KBC system is built and tested via an international team of pathologists, nephrologists, coding specialists and IT professionals.
Results: WP1 identified multiple problems with existing coding systems. Key principles for the new KBC system (WP2) were to code for more than one morphological pattern and to code along multiple axes. Based on these principles a hierarchical coding system was drafted (WP3) where both morphological pattern(s), biopsy diagnosis and a certainty factor are elements building up the code.
Conclusion: The KBC project aims to provide a comprehensive, generally applicable, interoperable and easy-to-update coding system for kidney biopsy diagnoses. A code list is drafted that contains several axes and thus ensures for tagging of both ordinary and unconventional cases, even when the diagnosis is unclear.

PS-10-005

Anticoagulant-related nephropathy: report of 6 cases

M. Frelih[1]
[1] Institute of Pathology, Medical Faculty Ljubljana, University of Ljubljana, Slovenia

Background & Objectives: Anticoagulants are prescribed for number of thromboembolic disorders. With their use comes the risk for hemorrhage. They can cause glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts with subsequent deterioration of kidney function. Another mechanism of injury by RBC casts is heme toxicity. In literature, most common and first described anticoagulant causing this type of kidney injury is warfarin, but lately also novel oral anticoagulants are found to be the cause.
Methods: Here, we report pathological findings in 6 cases of anticoagulant-related nephropathy (ARN) that were found in our database during years 2014-2018.
Results: All cases presented with acute kidney injury, 5 of them also had preexisting chronic kidney disease. Of 6 cases, 5 were related to warfarin use and 1 to dabigatran use. Only three had the data about anticoagulant therapy written on requisition form at the time of biopsy.
All kidney biopsies showed acute tubular injury associated with occlusive RBC casts. 5 of them had underlying undiagnosed mild IgA nephropathy. There was disproportion between the number of RBC tubular casts, the degree of acute tubular injury and the degree of glomerular injury by IgA nephropathy.
Conclusion: Pathologists should be aware of this entity and ARN should be suspected when there is disproportion between the number of RBC tubular casts and the severity of underlying kidney disease, and seek clinical data regarding anticoagulant therapy. Clinicians should closely monitor kidney function in patients on anticoagulant therapy.

PS-10-006

IgG4 related kidney disease: report of 21 cases

H. Gakiopoulou[1], K. Stylianou[2], H. Theodoropoulou[3], S. Havaki[4], D. Pouloudi[5], A. Stofas[6], D. Petras[7], A. Gerakis[8], D. Vlahakos[9], D. Goumenos[10], E. Daphnis[2], H.M. Moutsopoulos[11]
[1] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [2] Department of Nephrology, Heraklion University Hospital, Crete, Greece, [3] Renal Unit, General Hospital "Alexandra", Athens, Greece, [4] Department of Histology and Embryology, School of Medicine, National and Kapodistrian University of Athens, Greece, [5] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [6] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [7] Nephrology Department, Hippokrateio Hospital, Athens, Greece, [8] Department of Nephrology, Hygeia Hospital, Athens, Greece, [9] Division of Nephrology, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Greece, [10] Department of Nephrology, University Hospital of Patras, Greece, [11] Department of Pathophysiology, School of Medicine, National & Kapodistrian University of Athens, Greece

Background & Objectives: The spectrum of renal involvement in the context of IgG4 Related Disease (IgG4RD) is not fully elucidated. The aim of this study was to record and analyse our experience on the basis of renal biopsies diagnosed as renal involvement in the context of IgG4RD.
Methods: Light microscope including histochemistry, immunohistochemistry for IgG/IgG4, PLA2R and THSD7A, immunofluorescence and electron microscope.
Results: During a 5 year period, 22 renal biopsies from 21 patients all over Greece, were diagnosed as having renal involvement in the context of IgG4RD. There were 14 male and 7 female patients with a mean age of 67 years (range: 45-84 years). Most patients presented with an acute or progressive deterioration of their renal function, often on a background of an unexplained chronic renal failure. Only three patients had a clinical suspicion of IgG4RD based either to a measurement of serum IgG4 and/or to a previous biopsy in another organ showing IgG4RD.The renal biopsy findings can be divided into 3 groups: a) IgG4 related tubulointerstitial nephritis (TIN) without glomerulopathy (11 patients), b) IgG4 related TIN concomitant with glomerulopathy (7 patients) and c) glomerulopathy without TIN (3 patients). The most common glomerulopathy concomitant with TIN was membranous glomerulopathy (MG). All patients in the third group had a MG IgG4 (+)/PLA2R (-)/THSD7A(-) and compatible clinical & laboratory findings.
Conclusion: Diagnosis of IgG4RD is often first established by the renal biopsy. TIN with or without glomerulopathy or glomerulopathy alone consist possible ways of renal involvement in the context of IgG4RD.

PS-10-007

The REDD1/autophagy pathway mediates the release of TF- and IL-17A-bearing Neutrophil Extracellular Traps (NETs) in human Systemic Lupus Erythematosus (SLE), promoting thromboinflammation and fibrosis

E. Frangou[1], H. Gakiopoulou[2], A. Chrysanthopoulou[3], K. Kambas[3], A. Mitsios[3], I. Angelidou[3], T. Arambatzioglou[3], G. Bertsias[4], P. Verginis[5], K. Ritis[3], D.T. Boumpas[6]

[1] Department of Nephrology, Limassol General Hospital, Cyprus & Medical School, University of Cyprus, Nicosia, Cyprus & Biomedical Research Foundation of the Academy of Athens, Greece, [2] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [3] Medical School, Democritus University of Thrace, Alexandroupolis, Greece, [4] Rheumatology, Clinical Immunology and Allergy University of Crete School of Medicine, Heraklion, Greece, [5] Biomedical Research Foundation of the Academy of Athens, Greece, [6] Biomedical Research Foundation of the Academy of Athens, Greece & 4th Department of Medicine, "Attikon" University Hospital, Greece & Joint Rheumatology Program, National and Kapodistrian University of Athens Medical School, Greece

Background & Objectives: NET release represents a novel neutrophil effector function in SLE pathogenesis. We investigated the molecular mechanism underlying NET release and how NETs mediate end-organ injury in SLE.

Methods: Serum and neutrophils from healthy individuals and SLE patients (in active disease and in remission) were isolated. Cultures of *ex vivo* neutrophils and *in vitro* stimulation or inhibition studies were performed. Autophagy levels, NET release and proteins on NETs were studied by immunofluorescence, immunoblotting, qPCR and ELISA. The effector function of NETs was investigated in a primary fibroblast culture. Kidney and skin biopsies from patients with proliferative lupus nephritis (LN) and active discoid lupus, respectively, were studied with immunofluorescence.

Results: Autophagy is increased in neutrophils from active SLE patients, leading to increased NET release that is abolished by hydroxychloroquine. Serum from active SLE patients upregulates the hypoxia- and stress-response protein DDIT4/REDD1 in healthy neutrophils, leading to increased autophagy and NET formation. Endothelin-1 (ET-1) and hypoxia-inducible factor-1α (HIF-1α) were key mediators of this effect. Tissue factor (TF) and interleukin-17A (IL-17A) on SLE NETs were bioactive, as evidenced by thrombin generation and activation/differentiation of skin fibroblasts to collagen-producing myofibroblasts. These findings were abolished by HIF-1α inhibition by L-ascorbic acid or ET-1 inhibition by bosentan of *in vitro*-stimulated neutrophils, as well as by TF or IL-17A blockade on NETs. TF- and IL-17A-bearing NETs were observed in kidney and skin biopsies from patients with proliferative LN and active discoid lupus, respectively.

Conclusion: The REDD1/autophagy/NET axis is involved in end-organ injury and fibrosis in SLE and represents a candidate for drug repositioning in SLE therapy. Autophagy-mediated release of TF- and IL-17-bearing NETs in active SLE provides a link between thromboinflammation and fibrosis, and may account for the salutary effects of hydroxychloroquine in SLE.

PS-10-008

Secondary oxalate nephropathy: a case series of 18 patients

H. Gakiopoulou[1], N. Givalos[2], M. Papasotiriou[3], K. Stylianou[4], H. Theodoropoulou[5], E. Psimenou[6], I. Giatras[7], A. Stofas[8], D. Petras[9], A. Gerakis[7], E. Dafnis[4], D. Vlahakos[10], D. Goumenos[3]

[1] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [2] 2nd Department of General Surgery, General Hospital of Attica "KAT", Greece, [3] Department of Nephrology, University Hospital of Patras, Greece, [4] Department of Nephrology, Heraklion University Hospital, Crete, Greece, [5] Renal Unit, General Hospital "Alexandra", Athens, Greece, [6] Renal Unit, General Hospital "Alexandra" Athens, Greece, [7] Department of Nephrology, Hygeia Hospital, Athens, Greece, [8] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [9] Nephrology Department, Hippokrateio Hospital, Athens, Greece, [10] Division of Nephrology, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Greece

Background & Objectives: To present a case series of 18 patients with a diagnosis of secondary oxalate nephropathy attributed either to enteric malabsorption (gastric bypass, chronic pancreatitis, bariatric surgery, pancreatic adenocarcinoma, hemicolectomy) or to increased intake of oxalate precursors (vitamin C, oxalate-containing foods).

Methods: In a 5 year period, we identified 18 renal biopsies (investigated with light microscope, immunofluorescence and electron microscope-when needed), with a diagnosis of secondary oxalate nephropathy. There were 11 male and 7 female patients aged 40-88years (mean: 68,4years).

Results: All patients presented with unexplained acute renal failure (mean Cr: 7,7mg/dl, range: 3.1-23mg/dl, median:6mg/dl), without significant proteinuria, without active urine sediment. Half of the patients had arterial hypertension and/or diabetes mellitus and/or abnormal BMI. Four of these patients showed changes of adaptive focal segmental glomerulosclerosis and/or diabetic nephropathy and/or hypertensive nephrosclerosis. All biopsies showed acute tubular injury with abundant transparent crystals into the tubular lumens and into the cytoplasm of epithelial tubular cells, with birefringency under polarized light, suggestive of calcium oxalate deposits. In most biopsies rupture of tubular basement membranes was seen. Various interstitial inflammation (from scarce to diffuse) with some eosinophils in most cases and various interstitial fibrosis/tubular atrophy (IFTA) were noticed. The outcome of most patients was poor and probably worse in patients with diabetes mellitus and arterial hypertension.

Conclusion: Oxalate nephropathy is not a rare condition among patients undergoing renal biopsy for an unexplained acute renal failure with an inactive urine sediment. Clinical suspicion should be raised in the presence of risk factors. Histologic recognition is essential to avoid inappropriate treatments and to guide reversal of the causative factors.

PS-10-009

Clinicopathological characteristics of 3 patients with atypical anti-glomerular basement membrane disease

I. Işık Gönül[1], B. Ozbas[2], O. Helvaci[2], U. Derici[2], T. Arinsoy[2]

[1] Gazi University Medical School Department of Pathology, Turkey, [2] Gazi University Medical School, Department of Nephrology, Turkey

Background & Objectives: Anti-glomerular basement membrane disease (anti-GBM) is a rare autoimmune disorder characterised by severe pulmonary and renal involvement in the form of necrotizing crescentic glomerulonephritis.

Methods: Three cases of anti-GBM disease with atypical clinicopathological findings were diagnosed in the last 2 years. Clinical and renal biopsy findings of these cases were evaluated.

Results: Kidney biopsy findings of these 3 patients were heterogeneous; first patient's biopsy revealed proliferative glomerulonephritis with crescents. The second patient's biopsy showed nodular glomerulosclerosis with crescents. The third patient's biopsy was characterised by classical necrotizing diffuse crescentic glomerulonephritis. For all patients' biopsies, the immunofluorescence revealed a linear staining with IgG along the glomerular basement membranes. Electron microscopy was not utilized for any of the cases. Anti-GBM antibodies were negative in the serum for the first and third patients. The first patient was a 25-year-old male with hemoptysis, darkening in urine color, and pretibial edema. Despite an aggressive treatment, the patient died with severe ARDS and heart failure. The second patient was a 28-year-old male with weakness, hemoptysis, swelling in the eyes and hands. Anti-GBM antibody was positive in the serum. The patient has been followed

on a thrice weekly hemodialysis program with pulmonary relapse. The third patient was a 60-year-old male with sore throat, cough and hemoptysis. The patient was discharged with twice weekly hemodialysis program.
Conclusion: Atypical anti-GBM disease may present itself with non-characteristic clinical and unexpected histological features. The first step to correct diagnosis is to be aware of the disease.

PS-10-011
Tubuloreticular inclusions in renal microvasculature of renal allografts
H.J. Jeong[1], B.J. Lim[1], Y.S. Kim[1], K.H. Huh[1], S.I. Kim[1], M.S. Kim[1]
[1] Yonsei University, Republic of Korea

Background & Objectives: Tubuloreticular inclusions (TRIs) may be present in microvasculature of renal allografts, but their significance has not been well explored.
Methods: Twenty-six renal allograft cases having TRIs in peritubular capillaries (PTCs) or glomerular endothelial cells (GECs) were reviewed and correlated with clinical features. TRIs were present in PTCs in 17 cases, in GECs in 7 cases and in both in two cases.
Results: The diagnoses were acute or chronic T cell-mediated rejection (TCMR) (n=2), suspicious for acute TCMR (n=3), acute or chronic antibody-mediated rejection (AMR) (n=6), combined acute AMR and TCMR (n=2), acute tubular injury (n=2), polyomavirus nephropathy (n=2), IgA nephropathy (IgAN) (n=1), and tubular atrophy and interstitial fibrosis (n=8). TRIs in PTCs were mostly associated with rejection (n=5), viral infections (n=6), or both (n=4), and with peritubular capillaritis. However, TRIs in GECs were found in diverse conditions and not associated with glomerulitis.
Conclusion: TRIs in PTCs, but not in GECs may be a sensitive indicator for microvascular injury in the context of AMR and viral infection.

PS-10-014
Renal involvement in familial Mediterranean fever
A.A. Ozagari[1], K.G. Eken[1], M. Sevinc[2], G. Ozcelik[3], F. Kabukcuoglu[1]
[1] University of Health Sciences Sisli Hamidiye Etfal Hospital, Department of Pathology, Turkey, [2] University of Health Sciences Sisli Hamidiye Etfal Hospital, Department of Nephrology, Turkey, [3] University of Health Sciences Sisli Hamidiye Etfal Hospital, Department of Paediatric Nephrology, Turkey

Background & Objectives: Familial Mediterranean fever (FMF) is a hereditary disease with recurrent attacks. One of the complications of the disease is amyloidosis which primarily affects the kidneys. Several types of glomerular disease can also be seen in FMF, and FMF-related glomerulonephritis may be more common than it is thought.
Methods: This study is a retrospective analysis of data from patients with FMF undergoing kidney biopsy, over 14 years (2005–2019). Demographic data, clinical and pathology findings of these patients were evaluated.
Results: Of the 37 patients, 22 (60%) were female and 15 (40%) were male with an age range of 5 to 59 years (mean 26 years). The duration of FMF at the time of biopsy was 2 months to 20 years (mean 6 years). All patients had proteinuria above 0.5 g/24h (mean 3.3g /24h). On microscopic examination of the renal biopsies 11 (30%) patients were found to have amyloidosis, 9 (24%) IgA nephropathy, 7 (19%) mesangial proliferation without immun complex deposition, 5 (13%) minimal change disease, 2 (5%) focal segmental glomerulosclerosis (FSGS), 1 (3%) membranous nephropathy, and 1 (3 %) membranoproliferative glomerulonephritis (MPGN). One patient had concomitant amyloidosis and IgA nephropathy.
Conclusion: Spectrum of renal involvement in FMF patients is highly variable, only 30% of the cases diagnosed as amyloidosis in our series. In patients with FMF and renal involvement, non-amyloid renal lesions are not uncommon and should be considered in the differential diagnosis in addition to amyloidosis.

PS-10-016
Comparative characterics of IgA nephropathy and IgA vasculitis with glomerular extracapillary proliferation in adults
Y. Rogov[1], M. Dmitrieva[2], T. Letkovskaya[3], V. Savosh[3], K. Komissarov[4]
[1] Belarusian Medical Academy of Postgraduate Education, Belarus, [2] City Clinical Pathology Bureau, Belarus, [3] Belarusian State Medical University, Belarus, [4] State Institution "Minsk Scientific and Practical Center of Surgery, Transplantology and Haematology", Belarus

Background & Objectives: Nowadays IgA nephropathy (IgAN) and IgA vasculitis (IgAV) are considered as local and systemic manifestations of the same entity, associated with IgA deposits in mesangial matrix and vascular walls. Glomerular extracapillary proliferation (GEP) can be observed in both of conditions. The aim of this study was to compare clinical evidence and morphological features in IgAN and IgAV adult patients with GEP.
Methods: All kidney biopsies stained by hematoxylin-eosin, PAS, Masson trichrome, Congo red, Jones silver have been evaluated on light microscopy. Immunofluorescence (IF) staining for IgG, IgA, IgM, C3c, C1q, fibrinogen, k and λ light chains was performed on paraffin sections. All cases were confirmed by dominant/codominant mesangial IgA deposition in glomeruli on IF. IgAV patients had extrarenal manifestation (skin rush, gastrointestinal vasculitis, arthralgia). Median follow up period was 14 (6-33) month (range, 25% -75%).
Results: Among 694 native kidney biopsies examined from 2011 to 2015 years 29.7% cases (n=206) were diagnosed with IgAN and 2.7% (n=19) - with IgAV. Mean age was 34.2±11.7 years. Male prevalence observed 1.9 times often (42/22) in IgAN and 1.8 times (7/4) - in IgAV ($p>0.05$). The first group demonstrated GEP in 31.1% (n=64), the second group - in 57.9% (n=11) biopsies ($\chi^2=5.63$; $p=0.0176$). IgAV patients revealed higher percent of cellular and fibrocellular crescents ($U=185.0$; $p=0.038$). Crescent development risk was 2.75 times higher (95% CI; 1.15-6.55) in IgAV, in contrast with IgAN. There was no statistically significant difference in proteinuria, serum urea and creatinin levels ($p=0.569$, $p=0.590$, $p=0.540$ respectively), as well as in global and segmental glomerulosclerosis and interstitial fibrosis percentage ($p=0.309$, $p=0.747$, $p=0.964$ respectively).
Conclusion: IgAN and IgAV with GEP are similar by clinical course and morphological features. The greater severity of GEP in IgAV was associated with more frequent patient mortality, but did not affect the need for kidney replacement therapy.

PS-10-017
M-ToR inhbitors nephrotoxicity: 3 cases series
A. Sanz Zorrilla[1], F. Leiva-Cepas[1], A. Martínez López[1], R. Sánchez Sánchez[1], R. Ortega Salas[1]
[1] University Hospital Reina Sofía, Spain

Background & Objectives: Calcineurin inhibitors have been the immunosuppressants of choice in recent decades in kidney transplantation, however, in recent years, m-ToR inhibitors have replaced them progressively due to their lower incidence of side effects. Specifically at the kidney level, there is a controversy over whether the latter cause an increase in proteinuria with long-term glomerular damage.
Methods: Three cases are presented, the first case is a 40-year-old man transplanted by CKD secondary to idiopathic haemolytic uraemic syndrome and treated with everolimus, which debuts with nephrotic proteinuria two months post-transplant. The second case is a 60-year-old woman kidney transplant 27 years ago for CKD secondary to insulin-dependent diabetes, which, due to circumstances arising from the pathological process, begins to be treated with sirolimus, at which time it starts with proteinuria of 8 g / dl. The last case is a 66-year-old woman transplanted by IgA nephropathy and treated with m-ToR inhibitors, she also developed proteinuria over time.
Results: Both biopsies show glomeruli with segmental sclerosis, hyalinosis more evident in the first case, and podocytic hyperplasia more striking in the second, with no evidence of acute or chronic rejection in either of the two:

changes suggestive of nephrotoxicity by m-ToR inhibitors (diagnoses within the clinical context exposed and supported by immunohistochemical techniques), and in the first case, with ultrastructural study.
Conclusion: Calcineurin inhibitors produce hypertension and nephrotoxicity, and although m-ToR inhibitors have been shown to be superior, it has been proven by their use that they are not free of iatrogenic effects (proteinuria is the most frequent clinical finding and glomerular sclerosis) the most constant histological finding in proportion proportional to podocyte damage) as evidenced in our case. Podocyticc desdifferenciation has been proved by specific inmunohistochemical techniques which are not present in the normal adult podocyte. Our three cases as Letavernier. E y cols. cases, show how m-ToRs can produce this kind of podocytopathies. The presence of inmaturity podocytes may cause glomerulosclerosis and be the consequence of decreased expression of inmunohistochemical markers such a synaptopodin.

PS-10-018

Characterisation of acute tubular injury in cholemic nephropathy (bile cast nephropathy) by immunohistochemistry and mass spectrometry

J. Schmitz[1], J. Merl-Pham[2], W. Dai[1], A. Khalifa[1], K. Diahovets[1], Y. Mederacke[3], I. Mederacke[3], T. Feldkamp[4], U. Kunzendorf[4], A. Wagner[5], N. Richter[5], L. Pape[6], S. Hauck[2], W. Gwinner[7], J.H. Bräsen[1]
[1] Institute of Pathology, Hannover Medical School, Germany, [2] Research Unit Protein Science, Helmholtz Centre Munich, German Research Center for Environmental Health, Germany, [3] Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Germany, [4] Department of Nephrology and Hypertension, University Hospital Schleswig-Holstein, Kiel, Germany, [5] Clinic for General, Abdominal and Transplant Surgery, Hannover Medical School, Germany, [6] Paediatric Nephrology, Hannover Medical School, Germany, [7] Department of Nephrology and Hypertension, Hannover Medical School, Germany

Background & Objectives: Morphologically, cholemic nephropathy (CN) is characterised by extensive acute tubular injury (ATI) and bile-stained tubular casts consisting of sloughed epithelial cells and acellular material. CN occurs in patients with cholestatic liver disease and is diagnosed by positive Hall's stain. Recently, we described loss of aquaporin 2 expression in collecting ducts in a small cohort of patients with elevated bilirubin and CN.
Methods: Now, we characterised ATI in CN by staining for several ATI (NGAL, KIM1, FACL4, cCasp3, THP) and recovery markers (Ki67) in 39 patients with CN (n=16), oxalate nephropathy (OX-N, n=6), CNI (calcineurin inhibitor) toxicity (n=6) and light chain cast nephropathy (CAST, n=11). Biopsies before transplantation (zero-biopsies, n=5) served as controls. Additionally, mass spectrometry (LC-MS/MS) of the paraffin samples was performed to identify new markers for diagnosis and potential targets for therapy.
Results: In CN, expression of THP and NGAL was higher than in OX-N and expression of NGAL and FACL4 was higher than in CAST. More Ki67 positive tubular nuclei were detected in CN than in CNI toxicity and OX-N. Mass spectrometry showed higher amounts of aldo-keto reductases in CN samples (up to 200-fold) than in OX-N, CNI toxicity and controls. Currently, immunohistochemistry for verification and localisation of these enzymes in the renal tissue is performed.
Conclusion: Positive stains of injury markers confirmed the tubulopathy caused by bile acids. High FACL4 (ferroptosis marker) and Ki67 (proliferation marker) expression in CN samples might reflect high turnover and recovery potential. The high prevalence of aldo-keto reductases points to an anti-toxic defense mechanism.

PS-10-019

Clinical significance of zero-time renal transplant biopsies

M. Horacek[1], P. Senjug[2], M. Knotek[3], D. Galesic Ljubanovic[2,1]
[1] Institute of Pathology, School of Medicine, University of Zagreb, Croatia, [2] Unit of Nephropathology and Electron Microscopy, Department of Pathology and Cytology, Dubrava University Hospital, Zagreb, Croatia, [3] Department of Nephrology, University Hospital Merkur, Zagreb, Croatia

Background & Objectives: Zero-time renal biopsy is biopsy performed before or immediately after the transplantation with the purpose of pathohistological assessment of morphologic characteristics of donated kidney tissue. Aim of this study was to investigate morphological findings of zero-time biopsies analysed at Unit of Nephropathology and Electron Microscopy at Dubrava University Hospital, Zagreb.
Methods: Retrospective research of pathology reports was performed for period from 2006 to 2018. Total of 316 zero-time renal biopsies were performed in Clinical hospital Merkur (84%) and Clinical hospital Osijek (16%) and analysed in our department.
Results: Recipient age ranged from 16 to 84 years (median 51). Acute tubular injury was present in 90% of biopsies, mainly in its moderate form (51%). In 17% of biopsies some form of glomerular pathology was present. Most common entity was thin glomerular basement membrane (13%) and followed by diabetic nephropathy (2%), IgA nephropathy (1%), thrombotic microangiopathy (0.3%) and immune-complex mediated glomerulonepritis (0.3%). Chronic changes of tubulointerstitium and blood vessels were evaluated according to Banff criteria. Lowest grades of interstitial fibrosis and tubular atrophy (ci0 and ct0) were the most common. In 13% of specimens, arteries showed moderate or severe fibrointimal thickening (cv2 and cv3) while arterioles were even more affected with 36% of specimens showing moderate or severe arteriolosclerosis (ah2 and ah3).
Conclusion: Zero-time renal biopsy shows morphological condition of transplanted kidney and is of importance for comparison with further protocol or indication biopsies, treatment and diagnostic evaluation and clinical trials.

PS-10-021

Analysis of tubulointerstitial fibrosis in patients with diabetes mellitus

V. Sipovski[1], A. Smirnov[1]
[1] Nephrology Research Institute, Russia

Background & Objectives: The progression of diabetic nephropathy (DN) often is combined with non-diabetic glomerulopathies (NDGP), which can affect the prognosis and treatment of patients. However, the information about such influences is not enough.
The objective of such study is to investigate the effect of NDGP on fibrotic processes in kidney parenchyma.
Methods: Patients with DN-gr.№1 were divided on gr.№2-"pure" DN and gr.№3- DN with NDGP. Histopathological analysis (focal sclerosis (FS), glomerulosclerosis (GS), hyalinosis of arterioles (GA), severity of leukocyte infiltration in tubulointerstitium (ITIN), peritubular capillaritis (PTC), tubular atrophy (TA) were performed semiquantitatively, Immunohistochemistry were performed for α-SMA by EnVision detection system for marking of myofibroblasts.
Results: The 51 patients were in gr. №1, 30 patients in gr. № 2, 21 patients in gr. №3. The patients with IgA- nephropathy (20 %) were the most common glomerulonephritis (GN) followed by focal segmental glomerulosclerosis (FSGS)-35%. HCV –associated GN was the most common among secondary GN. No significant between-group differences were observed with the majority of laboratory and morphological markers. The activity of myofibroblasts correlated with tubular atrophy (*"r"= **0,53)***, focal sclerosis(*"r"= **0,43)***, the stage of diabetes(*"r"= **0,49)*** in gr. №2 in comparison with gr. № 3. The PTC correlated with tubular atrophy (*"r"= **0,47)***, focal sclerosis(*"r"= **0,50)*** and ITIN (*"r"= **0,59)*** in gr. №2 in comparison with gr. № 3.
Conclusion: The fibrosis in tubulointerstitium of patients with DN correlated with quantity of myofibroblasts and PTC. There were not

established significant differences in fibrotic processes of the renal parenchyma in patients with and without NDGP.

PS-10-022

Renal involvement in Fabry disease: a clinical, histopathological and ultrastructural study

G. Terinte-Balcan[1], E. Rusu[2], I. Gener[2], M. Gherghiceanu[3]
[1] Emergency University Hospital, Bucharest, Romania, [2] Fundeni Clinical Institute, Romania, [3] Victor Babes National Institute of Pathology, Romania

Background & Objectives: Fabry disease represents a genetic disorder in which the deficiency of the lysosomal enzyme alpha-galactosidase leads to accumulation of glycosphingolipids. The aim of this study is to present the clinical and histological aspects of Fabry nephropathy.
Methods: We conducted a retrospective study of the patients diagnosed with Fabry disease at the Victor Babes National Institute of Pathology, Ultrastructural Department between 2016 and 2019. We selected 7 cases. 2 patients were male. The average age was 47.3 years (range 30 - 61 years). Glomerular filtration rates were between 49 and 123 ml/min (average 90 ml/min). All cases presented with proteinuria (range 0.1 – 0.8 mg/dl), except for one female patient. One male patient had microhematuria.
All patients underwent a kidney biopsy. The accumulation of lysosomes was quantified on semi-thin sections using the score developed by the International Study Group of Fabry Nephropathy.
Results: The average number of glomeruli was 6.14 (range 3 – 8). 2 of the cases presented with segmental sclerosis and other 2 with global sclerosis. The average value of lysosome accumulation in the podocytes was 1.5 (range 0.4 – 2.6). All cases presented with inclusions in the parietal cells of the Bowman capsule. All patients had inclusions in the distal convoluted tube and in the tunica media, except for one case.
Conclusion: In order to asses the prognosis of patients with Fabry disease, it is important to accurately quantify the renal involvement. In our series, the extent of inclusions in the epithelial cells correlated with reduced glomerular filtration rates.

PS-10-023

Autoantibodies against Phospholipase A2 Receptor in Brazilian patients: an overview through idiopathic membranous nephropathy and class V lupus nephritis

D.C. dos Santos[1], C.J. Figueira[1], P.F. dos Reis[2], V.d.S. Silva[2], R. Bruder[3], R.M. Viero[1]
[1] Department of Pathology, Botucatu Medical School, São Paulo State University (UNESP),Botucatu, Brazil, [2] Department of Internal Medicine, Botucatu Medical School, São Paulo State University (UNESP),Botucatu, Brazil, [3] Clinical Laboratory, Botucatu Medical School, São Paulo State University (UNESP),Botucatu, Brazil

Background & Objectives: Detection of M-Type Phospholipase A2 antigen (PLA2R) in the kidney biopsies is a sensitive test for the diagnosis of primary membranous nephropathy (MN). The studies have been shown that secondary forms of MN are PLA2R negative. We evaluated the prevalence and clinical significance of PLA2R in MN and class V lupus nephritis (SLE).
Methods: We reviewed the records of 71 patients of MN and 29 patients with SLE over a 12-year period. PLA2R antigen in all kidney biopsies were analysed by immunohistochemistry using rabbit polyclonal PLA2R1 antibody (Novus Biologicals), and circulating PLA2R antibody in 21 serum samples of aleatory patients by ELISA (Euroimmun).
Results: In 65 of 71 (91,5%) patients with MN, PLA2R was detected in a granular pattern in the glomerular capillary walls. Three of 65 patients have secondary MN associated to Psoriasis (1), HIV and lues (1) and lues(1). Four patients with primary MN were negative for PLA2R in the biopsies. Circulating anti-PLA2R antibodies were detected in 2 of 21 (9,5%) patients, both sera were sampled during active disease. Four patients with nephrotic proteinuria were negative for circulating anti-PLA2R antibodies. All patients with negative circulating anti-PLA2R antibodies showed PLA2R antigen positive in the kidney biopsies.
In 7 of 29 patients with SLE PLA2R was positive in the kidney biopsies (24,1%).
Conclusion: PLA2R antigen in kidney biopsies is a useful test for the diagnosis of primary MN in the retrospective material, although our study do not confirm previous findings of the absence of PLA2R antibodies in SLE.

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PS-10-024

ANCA-associated glomerulonephritis in the elderly. A biopsy-proven retrospective study

M. Wagrowska-Danilewicz[1], O. Stasikowska-Kanicka[2], M. Bonczysta[3], M. Danilewicz[3]
[1] Nephropathology Department, Medical University of Lodz, Poland, [2] Department of Nephropathology, Medical University of Lodz, Poland, [3] Pathology Department, Medical University of Lodz, Poland

Background & Objectives: Aging has been highlighted as a global public health problem. The number of patients with kidney diseases in the population increases as well. Antineutrophil cytoplasmic antibody – associated glomerulonephritis (ANCA -GN) is primarily a disease of the elderly. The aim of the study was to compare the clinical, laboratory data and microscopic lesions in the renal biopsy in ANCA-associated glomerulonephritis in the adult patients ≤ 64 years (Group I) and in patients ≥65 years (Group II).
Methods: From January 2009 till January 2019 ANCA-associated glomerulonephritis were diagnosed in 32 patients ≤ 64 years, and in 53 patients ≥65 years. Baseline data including sex, age, ANCA serotype, eGFR, serum creatinine, proteinuria, and hematuria were obtained. Diagnosis was based on examination of biopsy tissue with histological confirmation of pauci -immune necrotizing glomerulonephritis together with a possitive ANCA titer. Microscopic lesions were scored according to the histopathological classification for ANCA-associated glomerulonephritis.
Results: Most patients were MPO-ANCA positive. PR-3 ANCA patients were younger than MPO ANCA patients. All patients had severe kidney disease (median creatinine 6 mg/dL, 35% needed temporary dialysis). The sclerotic histological class was observed in the 12% of the patients with MPO-ANCA, as compared to 3% with PR3-ANCA. In crescentic class of ANCA-GN the value of e-GFR and serum creatinine levels significantly differed as compared with other histological classes of ANCA-associated GN.
Conclusion: In conclusion, our study revealed no significant differences in baseline characteristics between both studied groups except of the higher frequency of MPO-ANCA serotype and the sclerotic histological class of ANCA-GN in patients ≥65 years.

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Monday, 9 September 2019, 09:30 - 10:30, Agora 3
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PS-11-001

Gliosarcoma: a single etiopathogenic mechanism behind this rare tumour?

C. Alborch[1], D.A. Vargas-Galván[1], X. Ara-Mancebo[1], E.M. Fuentes-Camps[1], S. Ramón y Cajal Agüeras[1], E. Martínez Sáez[1]
[1] Vall d'Hebron University Hospital, Spain

Background & Objectives: Gliosarcoma (GS) is a rare type of IDH-wildtype glioblastoma (GB) (2%). It mainly affects adult males (40-60 yo), and is usually supratentorial and peripherally located. Histologically, the GS is characterised by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation. The most accepted etiopathogenic mechanism is a monoclonal origin of both components with phenotypic dedifferentiation because of common molecular alterations.
Methods: Glioblastoma patients diagnosed at the HUVH Pathology department from 1999 to 2017 were identified (603 cases), selecting those with GS histology. Clinicopathological data were collected. Immunohistochemical study for psMAD2, H3G34R, SOX2, IDH1, p53, ATRX, GFAP and CD34 was performed.
Results: In our series, GS represent 1,9% of GB (12/603), with a striking male predominance (10/12 cases) and a middle age of 61 yo at diagnosis. Histologically the tumour showed a biphasic pattern: glial and mesenchymal, with epithelioid phenotype in the glial component in 3/12 cases. The mesenchymal component had a muscular differentiation in 6/12 cases, chondroid in 1/12 and solitary fibrous tumour-like phenotype in 1/12. All cases were IDH, ATRX and H3G34R wildtype. p53 overexpression was seen in 46% of cases. pSmad2 and SOX2 showed intense and diffuse positivity in 25% of cases and their expression was patchy and heterogeneous in 75%.
Conclusion: Our GS series has demographic and morphological features similar to the reported ones for GS. We found different patterns of expression of epithelial-mesenchymal transition (pSmad2) and neural stem cell (SOX2) markers. These data would support tumour's pathogenesis heterogeneity that could lead to different behaviours and therapies.

PS-11-003

The role of skeletal muscle biopsy in the diagnostic algorithm of mitochondrial myopathies in children and adults - a retrospective study of the histopathological aspects

D. Costache[1], A. Vrâncianu[1], M. Niculae[1], E. Manole[2,3], A. Bastian[1,4]
[1] Pathology Department, Colentina University Clinical Hospital, Bucharest, Romania, [2] Research Center Colentina University Clinical Hospital, Bucharest, Romania, [3] Molecular Biology Laboratory, "Victor Babeş" National Institute of Pathology, Bucharest, Romania, [4] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: Mitochondrial myopathies (MM) comprise a clinically and genetically heterogeneous group of neuromuscular disorders, frequently multisystemic, in which the precise diagnosis is a real challenge. MM are due to defective oxidative phosphorylation caused by different pathogenic mtDNA and nuclear DNA mutations. Patients may present their first signs and symptoms at any age, but clinical and/or morphological evidence of myopathy is not always present. The purpose of this study is to highlight the usefulness of muscle biopsies in the work-up of MM.
Methods: We conducted a retrospective study on 41 clinically suspected cases of MM from a total number of 586 muscle biopsies performed between 2014-2018, using the Colentina University Clinical Hospital Pathology Department database. The skeletal muscle tissue was obtained by open biopsy technique; muscle cryosections were processed using histological, histochemical, enzyme histochemical techniques, of which the most relevant for MM diagnosis were modified trichrome Gomori, succinate dehydrogenase, cytochrome c oxidase IV reaction and complementary techniques of electron microscopy on resin-embedded tissue.
Results: We confirmed 14 MM cases, youngest aged 9 months, by identification of diagnostic "ragged red"/"ragged blue" fibers, lacking cytochrome c oxidase activity. Ultrastructurally we noticed an increase in number and size of the mitochondria, subsarcolemmal/perinuclear accumulation of abnormal mitochondria, with concentric and circular cristae. In 6 cases other diagnoses were established: Becker muscular dystrophy, Pompe disease, core disease and a desminopathy with secondary mitochondrial dysfunction.
Conclusion: The morphological aspects enabled us to establish the diagnosis with major impact on clinical management and directed further confirmatory genetic testing.

PS-11-004

The benefits of apparent diffusion coefficient maps for high-grade glioma delineation

M. Hendrych[1], H. Valeková[2], R. Jancalek[2], B. Musilová[3], M. Hermanová[1]
[1] 1st Department of Pathology, St. Anne's Hospital and Faculty of Medicine, Masaryk University Brno, Czech Republic, [2] Department of Neurosurgery, St. Anne's Hospital and Faculty of Medicine, Masaryk University Brno, Czech Republic, [3] Department of Neurosurgery, Faculty of Medicine, Masaryk University Brno, Czech Republic

Background & Objectives: Apparent diffusion coefficient (ADC) maps provide voxel-based measures of the mean water diffusivity. As increased cellularity leads to restriction of water molecule diffusion, ADC maps can have better ability to describe and delineate gliomas rather than a structural MRI. The aim of our project was to determine whether the histological features and boundary of high-grade gliomas (HGG) might be predicted on the basis of ADC values.
Methods: Our cohort comprised 24 patients with HGG in which targeted biopsy based on conventional MRI were performed. Tumour tissue samples were collected separately from following regions: T1WI+, T2WI+, and regions of surgical approach T1WI-T2WI-. The samples underwent histopathological analysis for nestin, proliferation index Ki-67, and vascular density by expression of endothelial antigen CD31. The results of histopathological analysis were related to the corresponding findings on MRI, and the respective ADC was subtracted for each sample. The samples were stratified by expression of nestin into a tumour core, peritumoural brain zone (PBZ = HGG infiltrating zone) and tumour-free brain zone.
Results: We demonstrated a statistically significant ($p < 0.05$) relationship between the ADC value and the histological features of HGG. Increasing ADC in the vicinity of HGG was linked with decreasing cellularity, proliferation index Ki67 and vascular density. We have also shown statistically significant difference ($p < 0.05$) of the ADC values for the PBZ and the brain tissue with no histological sign of tumour infiltration. On the contrary, the characteristics based on the MRI regions were overlapping ($p > 0.05$).
Conclusion: Reported findings suggest that the ADC value might be superior in specifying the boundary of histological infiltration of HGG to structural MRI. ADC imaging could be used for more accurate planning of surgical resection and radiation therapy in patients with diagnosis of HGG.

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PS-11-005

Effect of stress in nasal septum surgery on the formation of dark neurons in the hippocampus in rat

I. Kastyro[1], M. Kostyaeva[1], V. Torshin[1], N. Ermakova[1], G. Khamidulin[1], Y. Guschina[1], A. Kavalenko[1], P. Pryanikov[2]

[1] Peoples' Friendship University of Russia (RUDN University), Russia, [2] Pirogov Russian National Research Medical University (RNRMU), Russia

Background & Objectives: *Background*. Surgical interventions in the craniofascial area are a strong stress factor due to its particular sensitivity, especially in the nasal septum. In this regard, the issue remains high-quality anesthesia.
Objective. To study effect of stress after modelling septoplasty on the formation of dark neurons (DN) in the hippocampus in rats.
Methods: The study was conducted on adult males-rats. In 1&2groups, premedication with Phenazepamum was carried out. Group1: 30rats, local anesthesia(LA) with 2%lidocaine solution; Group2: 30 rats, LA with 2%ultracain solution, postoperative analgesia with diclofenac for 6 days. Group3,4 were controls, (10 animals). In groups1–3, pretrepantation brain fixation was performed; in Group4, similar fixation was not performed and artifact DN were counted. We studied the number of DN in the hippocampus on toluidine blue Nissl stained brain sections on days 2,6&14 after surgery.
Results: In group 2, in the CA1, CA2, CA3 & DG zones, there were fewer DN compared with group 1 on day 6 ($p<0.001$), and on day 14 in group 2, the number of dark neurons was comparable with group 3 in areas CA1 and CA2 ($p<0.05$). In group 4, compared with group 3, the number of DN was significantly higher in all hippocampal zones($p<0.01$).
Conclusion: DN quantitative changes in CA1, CA2, CA3 and DG zones of the hippocampus may indicate the severity of surgical stress when using different anesthetic managment when simulating acute inflammation on the nasal septum that occurs during septoplasty.

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PS-11-007

Description and target mutation profile of rare glioneuronal tumours

L.L. Sousa Veras[1], M. Bisarro dos Reis[1], M. de Medeiros Matsushita[1], W. dos Santos[1], R. Manuel Reis[1]
[1] Barretos Cancer Hospital, Brazil

Background & Objectives: Rosette-forming glioneural tumours (RFGNT) and papillary glioneuronal tumour (PGNT) are rare low grade glioneuronal neoplasms that account for < 1% of intracranial tumours. The objective of this study was to describe and performed the mutation status of these tumours in two cases (one rosette-forming and other papillary).
Methods: One RFGNT and one PGNT were diagnosed at Barretos Cancer Hospital, Brazil. In the case of PGNT was performed immunohistochemistry for GFAP, EMA, ki67 and synaptophysin and in RFGNT case was performed ATRX, OLIG2, GFAP, NEU-N, MAP2, NF, synaptophysin, EMA, P53 and Ki67. DNA was isolated from formalin-fixed paraffin-embedded (FFPE) tissue of tumour and normal adjacent areas. The somatic mutations was analysed via massively parallel sequencing of 50 cancer driver genes (Ion AmpliSeq Cancer Hotspot Panel V2 - *SMARCB1, RB1, TP53, ERBB4, FBXW7, BRAF, KIT, GNAS, HRAS, EGFR, PDGFRA, PIK3CA, CDKN2A, ERBB2, ABL1, JAK2, KRAS, NRAS, NOTCH1, ATM, FGFR1, STK11, PTPN11, APC, SMAD4, PTEN, SMO, CTNNB1, RET, IDH2, SRC, EZH2, VHL, MPL, NPM1, FLT3, FGFR3, CDH1, KDR, HNF1A, MLH1, ALK, IDH1, GNAQ, AKT1, JAK3, FGFR2, GNA11, MET, CSF1R*). Torrent Suite Software and Variant Caller Plugin were used to call the variants and Ion Reporter™Software was used to annotate variants.
Results: The patient diagnosed with PGNT is female and 12 years old, the case showed immuno-positivity for GFAP, synaptophysin and 1% of ki67. The other patient with RFGNT is male and 36 years old, the case showed immuno-positivity for ATRX, OLIG2, MAP2, 7% of Ki67 and focal positivity for synaptophysin, NF and NEU-N. The sequencing resulted in amplicon coverage of at least 300× across the 207 amplicons of all samples analysed and mean deep for variant analyses were 2003 for PGNT and 1871 for RFGNT. Somatic variants were detected in cancer tissue of PGNT (n=15) and RFGNT (n=15), however the variants were also seen in normal adjacent tissue in both cases (n=14 and 16, respectively). In addition, the variants were classified as polymorphisms, not protein-affecting or likely neutral for oncogenesis according to Cancer Genome Interpreter.
Conclusion: These data suggest that the tumourigenesis of these rare rosette-forming glioneural tumours and papillary glioneuronal tumour is not driven by mutation in these 50 classic cancer related genes.

PS-11-008

Identification of specific diagnostic pathological features on 131 combined nerve and muscle biopsies in peripheral neuropathies (PN): a retrospective study

R. Tanasa[1], A. Bastian[2,3], E. Manole[1,4], C. Constantinescu[1], V. Nica[1], G. Tudor[1], O. Stefan[1], C. Luca[1], G. Grigore[1]
[1] Colentina Clinical Hospital, Romania, [2] Pathology Department, Colentina University Clinical Hospital, Bucharest, Romania, [3] Carol Davila University of Medicine and Pharmacy, Romania, [4] Victor Babes National Institute of Pathology, Romania

Background & Objectives: PN are prevalent but insufficiently understood neurological disorders with very diverse etiologies. Sural nerve biopsy, combined with muscular biopsy, integrated into the clinical history of the patient, along with laboratory tests, especially electrophysiology, can provide crucial information and a deeper understanding of the pathological mechanisms underlying disease in selected cases.
Methods: We conducted a retrospective study on 131 combined sural nerve-gastrocnemius muscle biopsies performed and processed in Colentina Clinical Hospital between 2014-2018, to investigate the sensitivity of nerve biopsy by evaluating the main pathological features that enabled us to identify various PN types, using histological, histochemical, enzyme histochemical techniques on cryosections, routine and special stains on paraffin-embedded tissue, resin semithin and ultrathin sections, fiber teasing and morphometric analysis in all cases and electron microscopy in selected ones.
Results: We identified vasculitic, inflammatory axonal and demyelinating PN, some related to connective tissue diseases, hypertrophic PN with onion-bulb formation, amyloid and tomaculous PN and much rarer types like mitochondrial neuromyopathy and a case of Fabry disease. In 3 cases, a motor neuron disease was diagnosed. However, in many cases, a diagnosis of demyelinating, axonal or mixed PN of variable severity could be highlighted, with only nonspecific additional findings.
Conclusion: In the molecular era of medicine, the nerve and muscle biopsy remains a valuable diagnostic tool in carefully selected cases, providing relevant data, mainly in treatable types as vasculitic PN, in amyloidosis and other PN with abnormal deposits, as well as in hereditary PN when genetic tests are unavailable.

PS-11-009

Update of a series of 65 central nervous system "PNETs" according to the 2016 WHO classification

A. Tauziede Espariat[1]
[1] Sainte-Anne Hospital, France

Background & Objectives: The term primitive neuroectodermal tumour (PNET) of the central nervous system (CNS) has disappeared from the 2016 WHO classification. Data from recent literature shows that this ancient nosology corresponds to various histomolecular entities.
The goal is to update the histomolecular diagnosis of 65 CNS PNETs diagnosed between 1993 and 2016 in children, adolescents, and adults.
Methods: After a central review of these tumours, immunohistochemical studies and molecular analyses (FISH, NGS, RNAseq) were performed.
Results: Seven tumours/65 could not be reclassified due to insufficient tissue material. Forty-seven/58 paediatric tumours (81%) were

reclassified: 1 AT/RT, 5 *RELA* fusion positive ependymomas, 21 *C19MC*-altered embryonal tumours with multilayered rosettes, 1 CNS primitive Ewing sarcoma with *EWSR1* fusion, 3 high grade gliomas with *MYCN* amplification, 4 neuroepithelial high grade tumours with *BCOR* alteration, 4 cerebral metastases from medulloblastomas, 1 pineoblastoma, 2 immature teratomas with a primitive neuronal component, 1 pilomyxoid astrocytoma, and 4 IDH- and histone- wild type paediatric high grade gliomas.
One tumour is an ETMR for which there is no more paraffin-embedded material, another ETMR is undergoing molecular confirmation. One glioma, one tumour and one sarcoma are currently being characterised.
Conclusion: This study demonstrates the variety of histomolecular diagnoses grouped within the ancient PNET terminology. The main paediatric tumour is the embryonal tumour with multilayered rosettes, *C19MC* altered. This study shows that histopathological analyses, immunohistochemistry, and classical molecular biology allow for the reclassification of 81% of paediatric former PNETs. Methylome analyses could be useful for the diagnosis of CNS neuroblastoma with *FOXR2* activation and tumours that remain unclassified.

PS-11-010
An integrative radiological, histopathological and molecular analysis of paediatric pontine high-grade gliomas with MYCN amplification
A. Tauziede Espariat[1]
[1] Sainte-Anne Hospital, France

Background & Objectives: Diffuse midline glioma, H3K27M-mutant was recently introduced in the 2016 WHO classification of CNS tumours and represents the main tumoural glial subgroup located in the brainstem. However, 2 rare groups of brainstem gliomas without histone gene mutations have also been described: the *MYCN*-HGG and the silent-subgroups. The aim of this study was to perform a detailed clinicoradiologic and histomolecular study of *MYCN*-HGG of the brainstem.
Methods: A central radiological and pathological review with routine biomarkers assessment was performed. FISH analysis of *MYCN* and whole exome sequencing on cryopreserved tissue were also performed.
Results: All 6 tumours presented as a nodular mass with annular enhancement on MRI. These tumours were morphologically poorly differentiated with spindle cells. They did not express H3K27M, Lin28A, or BCOR. No loss of H3K27me3, INI1 and BRG1 were observed. The immunohistochemical pattern showed no or focal expression of glial markers (GFAP and Olig2) and a constant expression of at least one neuronal marker. Four tumours overexpressed p53. All tumours presented with an amplification of *MYCN* and *ID2* genes. FISH analysis confirmed the presence of a *MYCN* amplification in 4/6 cases.
Conclusion: To conclude, we described detailed clinicoradiologic and immuno-morphologic features of 6 cases of pontine *MYCN*-HGG, thereby highlighting the consistent amplification of *MYCN* and *ID2* genes. This diagnosis must be considered when microscopic features reveal a highly malignant undifferentiated tumour without loss of H3K27me3 trimethylation. Distinguishing this rare neoplasm from diffuse midline glioma, H3K27M-mutant might allow for establishing targeted molecular therapies in the future.

Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-12 | Other Topics

PS-12-001
Live-viewing and video-supplemented teaching modules improve delivery of simulation-based gross pathology education
E. Alcaraz-Mateos[1], K.M. Mirza[2], S. Molina-Valverde[3], I. Turic[4], M. Togkaridou[5], F. Caballero-Aleman[6], M.J. Párraga-Ramírez[7], E. Poblet[8]
[1] University Hospital Morales Meseguer, Murcia, Spain, [2] Department of Pathology and Laboratory Medicine, Loyola University Chicago, USA, [3] Faculty of Medicine, University of Murcia, Spain, [4] Faculty of Medicine, University of Split, Croatia, [5] Faculty of Medicine, University of Thessaloniki, Greece, [6] Department of Internal Medicine, Morales Meseguer University Hospital, Murcia, Spain, [7] Intensive Care Unit, Morales Meseguer University Hospital, Murcia, Faculty of Medicine, Catholic University of Murcia, Spain, [8] Department of Pathology, Reina Sofía University Hospital, Murcia, Faculty of Medicine, University of Murcia, Spain

Background & Objectives: Standardised pathology examinations place enormous emphasis on theoretical pathology content. Consequently, medical students lack knowledge of practical Pathology, especially gross pathology. In order to address this lack of practical skill, we initiated simulation-based practical pathology workshops at our Hospital in 2016. The goal of these gross dissection workshops was to approximate future medical doctors to diagnostic pathology procedures, enhancing the medical student learning experience.
Part of this endeavor was to compare/contrast the utility of supplementing these workshops with different teaching modalities.
Methods: A 1-hour gross-dissection workshop was offered to International Federation of Medical Students' Associations (IFMSA) students.
All participants were provided identical oral and written pre-workshop information. They were then divided into 3 test groups and teaching was supplemented with: fixed pictures (group 1), video (group 2) and live observation of a pathologist while grossing (group 3).
Subsequently, time taken for students to correctly perform gross dissection on handmade silicone tumour simulators was recorded. An OSCE Likert-like checklist was used to assess skills.
Results: 12 students from 8 different countries participated in the workshop-based experiment. Time in performing the simulation was better for group 3 (15'39"), followed by group 2 (16'50") and group 1 (17'52").
Results from the skills assessment showed that grossing was slightly better for group 2 (3.7) in comparison with group 3 (3.4), with group 1 being worst rated (3.1) in this regard.
Conclusion: Although the sample size of this study was small, results reveal that live viewing of gross organ dissection is associated with shorter execution time. However, when quality of skills assessment where evaluated, viewing of a standardised video can improve performance versus the observation of a random surgical specimen. Thus, supplementation of live-viewing with video-viewing would likely have the ideal outcome for gross-pathology simulation education and medical students understanding of practical day-to-day Pathology.

PS-12-002
Communication with pathology evaluated via the pathology requisition using 396,033 pathology reports
M. Bonert[1], A. Naqvi[1], C. Finley[1], R. Juergens[2], P. Williams[2], P. Major[2], A. Kapoor[1]
[1] McMaster University and St. Joseph's Healthcare Hamilton, Canada, [2] McMaster University and Hamilton Health Sciences, Canada

Background & Objectives: Clinical information is often essential for an accurate pathologic assessment. We sought to retrospectively examine communication with pathology by assessing the clinical history (CH) provided on the pathology requisition.
Methods: All in house surgical pathology cases and non-gynaecological cytopathology cases were retrieved within a region for a seven year period (2011-2017). Using custom computer code, the cases were anonymized, categorized into CH present or absent and tabulated by year, hospital, submitting physician/surgeon (SPS), and assigned a tissue group (breast (BR), gastrointestinal (GI),

gynaecological (GYN), head & neck+endocrine (HNE), lung (LUN), miscellaneous (MISC), skin (SK), urologic (URO)) via free text string matching.
Results: Data could be extracted from 396,033 pathology reports. 303,926 (77%) were categorized as clinical history present (CHP). 263 SPSes submitted over 200 cases each (range 201-7119) and had mean/median/stdev/max/min CHP rates of 82%/93%/22%/100%/5%. A linear regression using the submitted volume to predict CHP yielded a Pearson coefficient of -0.32. CHP varied minimally by year (range 75-78%). The CHP of surgicals by hospital (98%, 86%, 85%, 59%) and cytologies by hospital (95%, 87%, 56%) varied significantly. CHP by tissue group was 95%, 92%, 88%, 87%, 84%, 77%, 75%, 63% for GYN, BR, HNE, SK, URO, LUN, MISC, GI respectively.
Conclusion: The tissue type (a surrogate for department of origin), individual SPS, volume submitted and hospital of origin appear to influence physician/surgeon-pathologist communication. CHP data allows one to make inferences about communication and may facilitate evidence based strategies to optimise information flow.

PS-12-003
A method to obtain kappa values for synoptic report parameters applied to data from 1,303 colorectal cancer resections
M. Bonert[1]
[1] McMaster University and St. Joseph's Healthcare Hamilton, Canada

Background & Objectives: In anatomical pathology, inter-rater variation is often assessed with kappa values. The objective of this work is to generate kappa values from rate data via simulation.
Methods: Pathologist diagnostic rate (DR) data was obtained from synoptic reports in a cohort of 1,426 colorectal cancer resections (CRCRs) (accessioned 2012-2017) for tumour deposits present (TD+), margin positive (M+), lymphovascular invasion (LVI+), pN0, LVI+ in pN0, LVI+ in node positive. Virtual pathologists (VPs) (with the obtained DRs) assessed a large virtual CRCR cohort to obtain kappas accurate to 0.01. The calculation made use of the maximal diagnostic overlap assumption (MDOA); this assumes a high DR pathologist calls a diagnosis (e.g. LVI+) in all cases that a lower DR pathologist makes the call. The VPs generated a table of diagnostic assessments (TDA). The TDA was then used to calculate Fleiss' kappa in the usual way.
Results: The DRs of 17 pathologists were available, where each pathologist signed-out >25 specimens and the group together interpreted 1,303. The simulated (in silico) kappas were 0.82, 0.67, 0.59, 0.51, 0.43, 0.33 for pN0, TD+, M+, LVI+, LVI+ in node positive and LVI+ in pN0. The MDOA represents a best case scenario for a given set of DRs; however, the calculated (in silico) kappa values have trends similar to experimental kappas in the literature.
Conclusion: The calculated (in silico) kappas are derived from the assessment of complete cases in a practice setting; they are devoid of study set selection bias and other study associated confounders. The MDOA may approximate diagnostic disagreement patterns in clinical practice. The development of intuitive metrics accessible to pathologists, that can be applied to observational data, may be important to improve care.

PS-12-005
Review of the pattern of traumatic limb lesions sustained in cases of hanging
M. Mc Cabe[1], N. Fyzul[2], L. Mulligan[3]
[1] Cork University Hospital, Ireland, [2] University College Dublin, Ireland, [3] Office of the State Pathologist, Dublin, Ireland

Background & Objectives: Evidence of limb trauma in hanging can raise suspicion of foul play. However, according to the literature, a pattern of trauma on the anterior lower limb and posterior upper limb can be expected in suicidal hanging in 7.4 to 20% of cases. This study sought to identify a pattern of limb bruising which occurs in association with hanging in Ireland, its incidence, and factors which increase its incidence.
Methods: All hanging cases from the years 2005 to 2016 (n = 82) were retrospectively reviewed. Pattern of traumatic limb injury, toxicology, type of suspension and location/scene of hanging were recorded. Patients who had been in physical altercations or accidents prior to the hanging were excluded.
Results: 72% of reviewed cases had traumatic limb lesions, the majority of which occurred on the anterior lower limb and posterior upper limb. The most common lesions were abrasions (56.1%) and bruises (43.9%). Lacerations were rare (3.7%). Positive toxicology was found to increase the incidence of traumatic limb lesions ($p = 0.001449$). Suspension type did not increase the incidence of limb injury.
Conclusion: The pattern of injury identified by our study is in keeping with that found in the literature. However, the incidence is far higher than in previous studies. This could be due to differences in levels of intoxication or location of hanging or in differences in practice of recording limb trauma in cases of hanging. Intoxication increases the likelihood of traumatic limb injury, possibly due to alteration of the agonal sequence.

PS-12-007
Immunohistochemical detection of pan-Tropomyosin Receptor Kinase (pan-TRK) expression in solid tumour specimens: inter-laboratory and inter-reader concordance. Study in progress
S. Stratton[1], J. Feng[1], T. Thorne-Nuzzo[1], M. Kockx[2], F. Penault-Llorca[3], A. Stenzinger[4], F. Lopez-Rios[5,6], G. Viale[7,8], F.A. Soares[9], T. Chou[10,11]
[1] Roche Tissue Diagnostics, USA, [2] HistoGeneX Laboratories, Belgium, [3] Centre Jean Perrin, France, [4] University Hospital Heidelberg, Germany, [5] University HM Sanchinarro Hospital, Spain, [6] CIBERONC, Spain, [7] University of Milan, Italy, [8] European Institute of Oncology, Italy, [9] University of Sao Paolo/D'Or Institute of Research, Brazil, [10] National Yang-Ming University, Taiwan, [11] Taipei Veterans General Hospital, Taiwan

Background & Objectives: Tropomyosin receptor kinase fusions involving *NTRK1*, *NTRK2* and *NTRK3* occur in a diverse set of tumours resulting in the constitutive expression of TRK fusion proteins. Wild-type TRK protein expression in most solid tumours (non-neuroendocrine) is generally minimal with low prevalence. The purpose of this study is to determine the reproducibility of performance of the automated VENTANA pan-TRK (EPR17341) Assay, intended for immunohistochemical detection of the C-terminal region of TRK proteins A, B and C, by assessing interpretations of individual pathologists.
Methods: This is an inter-laboratory reproducibility study using archived specimens, involving 3 replicate tissue sections from each of 50 cases (25 sequencing-confirmed *NTRK* fusion-positive and 25 *NTRK* fusion-negative) for evaluation at seven independent global sites. Sites are blinded to fusion status of the individual specimens, which will be divided among the sites for staining and then collated for interpretation of digital images. Primary endpoints will include between-site and between-reader comparisons of average positive agreement, average negative agreement, and overall percent agreement.
Results: Evaluation of 50 cases (1050 observations) will provide a two-sided, 95% lower confidence bound interval of 87.2% using the Wilson (score) method if a 90% concordance is reached. When completed, this study will verify assay performance across the 7 laboratories, help determine robustness of the assay, and help guide training and education for pathologists. Preliminary results will be presented.
Conclusion: This study design provides a framework to determine the reproducibility of the VENTANA pan-TRK (EPR17341) Assay. Additionally, the results can be used to provide a basis of determination of the presence of TRK protein overexpression using immunohistochemistry.

Monday, 9 September 2019, 09:30 - 10:30, Agora 3
PS-13 | Pulmonary Pathology

PS-13-001
DNA methylation and long non-coding RNA in lung adenocarcinoma
S. Ahn[1], J. Y. Pyo[1], J. Song[1], Y. J. Lee[2]
[1] International St. Mary's Hospital, Republic of Korea, [2] Korea University Anam Hospital, Republic of Korea

Background & Objectives: Exposure to cigarette smoke is powerful environmental modifiers of aberrant DNA methylation, especially in lung carcinogenesis. Thus, smoking induced molecular alteration in lung cancer will provide a range of exposures ideal for the study of smoking-induced carcinogenesis. Herein, we explored the epigenetically regulated long noncoding RNA (lncRNA) and DNA methylation, associated with smoking in lung adenocarcinoma (LUAD).
Methods: TCGA datasets of DNA methylation and mRNA expression profiles were used. LUAD samples were divided into smoker LUAD and never-smoker LUAD. The differentially methylated regions (DMRs) and the differentially expressed lncRNAs (DE-lncRNAs) were screened in smoker LUAD vs. normal, never-smoker LUAD vs. normal, and smoker LUAD vs. never smoker LUAD. Integrated analysis of DE-lncRNAs associated with DMRs was performed. Validation analysis was done in 76 patients with LUAD, using bisulfite sequencing for ADAM6, AGR2, AURBK, BUB1B, CAV1, CCNB1, FOXP3, HMGA1, MMP13, and SBSN.
Results: We identified that epigenetic regulated lncRNAs (HOTAIR, SYN2, MALAT1, H19, CYP4A22-AS1 and Lnc-MUC2-1) were significantly differentially expressed in smoker LUAD. The most significantly related category of GO analysis was LPS/IL-1 Mediated Inhibition of RXR Function. In validation analysis, four CpG sites of ADAM6, AURBK, FOXP3 and HMGA1 showed borderline significance.
Conclusion: Our study indicated that epigenetic regulated lncRNAs were significantly and differentially expressed in smoker LUAD. They may exert a significant epigenetic role in lung cancer development and could be potential targets for future treatment of LUAD.

PS-13-002
SuperARMS EGFR mutation detection kit vs. qPCR in detecting EGFR mutations in tumour tissue and plasma cell-free DNA of lung cancer patients
M.K. Zerna[1], M.S. Aguilera[1], V. Dy[1], J.J. Andal[1], D. Ang[1]
[1] St. Luke's Medical Center, Philippines

Background & Objectives: Filipinos with lung adenocarcinoma has a reported EGFR mutation rate of 49.4%. The SuperARMS EGFR mutation detection kit has been reported to detect 41 EGFR somatic mutations, with a sensitivity (0.2% mutant) higher than qPCR. We aim to compare SuperARMS with RocheCobasv2 (RC), which is the currently used platform in our hospital, in the detection of EGFR mutation status using both tissue and plasma samples.
Methods: A total of 42 lung adenocarcinoma patients (22 tissueDNA and 20 plasmaDNA) were tested using the RC and SuperARMS (AmoyDX) kits. Concordance rate of EGFR mutation status between the two detection kits was analysed. Kappa value was calculated for concordance analyses.
Results: Of 22 lung adenocarcinoma tissue DNA samples, 12 (54%) had EGFR mutations, detected by both platforms. SuperARMS detected an additional S768I and a T790M mutation. Of the 19 lung adenocarcinoma plasma DNA samples, 9 (47%) were positive for EGFR mutations in both platforms; three cases had concurrent T790M mutations. There is one case positive for T790M by RC but negative by SuperARMS kit. Using the cobas test as the reference, the overall percent agreement is 91%, kappa value was 0.8.
Conclusion: SuperARMS EGFR assay is highly sensitive and specific method to detect tissue and plasma EGFR mutations in lung cancer patients. Its performance is comparable to the cobas EGFR kit.

PS-13-003
Comparison of ddPCR and qPCR for detection of EGFR mutations in plasma cell-free DNA in Lung Adenocarcinoma.
J. Uyboco[1], M.S. Aguilera[1], J.J. Andal[1], V. Dy[1], M.V. Cruz-Ordinario[1], R. Li[1], D. Ang[1]
[1] St. Luke's Medical Center, Philippines

Background & Objectives: Circulating tumour DNA (ctDNA) is a promising, non-invasive method for epidermal growth factor receptor (EGFR) mutations detection in lung cancer patients. In this pilot study, we evaluated and compared the performance of digital droplet PCR (ddPCR) vs. real time PCR (qPCR) in detecting EGFR mutations in plasma ctDNA from patients with advanced lung adenocarcinoma. The possibility of the implementation of ddPCR platform in the detection of EGFR mutation in samples with low mutation rates, was assessed.
Methods: In this study, ddPCR (BIORAD, QX200) and qPCR (Roche Cobas v2) were used to analyse 39 plasma ctDNA from lung adenocarcinoma patients, in detecting EGFR exon 19 deletion (E19del), exon 21 L858R (L858R), and exon 20 T790M (T790M).
Results: Both platforms detected EGFR E19del, L858R, and T790M, in 27% (9/34), 29%(11/38), and 23% (9/39) respectively. One (3%) L858R, one (3%) E19del and three (8%) cases of T790M were detected with qPCR but not by ddPCR. On the contrary, one (3%) case of E19del and nine (23%) cases of T790M were detected by ddPCR but not by qPCR. The concordance of the two platforms in detecting E19del, L858R and T790M are as follows: 94% (k=0.86, 95%CI 0.67-1.0), 97% (k=0.94, 95%CI 0.81-1.0), and 70% (k=0.4, 95% CI 0.09-0.065), respectively.
Conclusion: This study demonstrates the feasibility of using ddPCR in detecting EGFR mutations in ctDNA of lung adenocarcinoma patients. It also highlights the advantage of utilizing ddPCR especially in the detection of T790M resistance mutation, for patients with low mutation burden, enabling early detection and appropriate clinical management.

PS-13-004
Ciliated muconodular papillary tumours of the lung, an increasingly recognised entity in surgical lung resection specimen
K. Argyropoulos[1], N. Narula[1], A. Moreira[1], F. Zhou[1], M. Bannan[1], J. Melamed[1]
[1] New York University School of Medicine, Department of Pathology, USA

Background & Objectives: Ciliated muconodular papillary tumour (CPMT) is a rare benign lesion, which occurs in the periphery of the lung and is characterised by papillary architecture, intra-alveolar mucin and the presence of non-atypical ciliated-columnar, basal and mucous cells. Since its introduction in 2002 by Ishikawa et al, this entity counts a few reports in the literature, which have primarily occurred in East Asia. Although not in the 2015 WHO classification, CPMT represents a frank neoplastic process, harbouring genetic alterations including BRAF and EGFR mutations. The goal of this study was to characterise the clinicopathologic features of CPMT diagnosed at a tertiaty care institution in the U.S.
Methods: Nine cases with characteristic features of classic and non-classic CPMT from New York University Tisch Hospital and Bellevue Hospital from 2016 to 2019 were identified. Clinical and pathologic data were reviewed.

Results: CPMTs were identified in 3 Male and 6 Female patients, whose age ranged from 47 to 82 years old. The lesions were predominantly found in the right lung and had a median size of 6 mm. Six (6) cases represented classic CPMTs, while 3 cases lacked the full spectrum of CPMT diagnostic features, and were classified as non-classic CPMTs. While in 7 cases, surgical resection was performed due to radiologic diagnosis of a peripheral nodule, in 2 cases, small CPMTs were incidental findings in resections performed for a dominant lesion, which was either adenocarcinoma, non-mucinous type (case 2) or atypical carcinoid (case 8). All lesions showed the characteristic immunohistochemical TTF-1 stain of columnar cells and p63 or p40 stain of basal cells. Two out of four (2/4) cases stained for BRAF-V600E showed uniform staining of all 3 cellular components of the lesion. The data are summarized on Table 1.

Table 1 Clinicopathologic features of CPMT diagnosed at tertiary care institution in 2016-2019

Case	Age(y)/ Sex	Site	Size (greatest dimension, mm)	Specimen	Classic (C) vs Non-classic (NC)	Concomitant pathologies in same (s) or other (o) resection site	Immunophenotype
1	73/Male	RLL	8	Wedge	C	No	TTF-1(+) p63(+)
2	66/Female	RUL	1	Segmentectomy	C	Multifocal non-mucinous adenocarcinoma (s), Respiratory Bronchiolitis (s)	TTF-1(+), p40(+)
3	82/Male	RLL	6	Lobectomy	C	Bronchiolar Metaplasia (s), Adenocarcinoma (o)	TTF-1(+), p40(+)
4	82/Female	RML	2	Wedge	C	Neuroendocrine hyperplasia (s), Chronic Bronchiolitis (s), Squamous cell carcinoma (o)	TTF-1(+), p40(+), BRAF-V600E (-)
5	71/Female	RLL	20	Wedge	C	Resolving pneumonia (s)	TTF-1(+), p63(+), BRAF-V600E (+)
6	80/Male	LUL	13	Wedge	NC	No	TTF-1(+), p40(+), EGFR-L858R (-), EGFR-E746_ A750del (-), ALK (-), BRAF- V600E (-)
7	59/Female	RLL	4	Wedge	NC	No	TTF-1(+), p40(+)
8	71/Female	RUL	2	Lobectomy	C	Atypical carcinoid (s), Neuroendocrine hyperplasia (s), Atypical adenomatous hyperplasia (s)	TTF-1(+), p40(+)
9	47/Female	RLL	20	Lobectomy	NC	No	

Conclusion: CPMTs although infrequent are now increasingly recognized and their incidence appears higher than reported in western literature. Interestingly, this self-limited tumour shares similar driver mutations with lung adenocarcinoma. Further studies will include a comprehensive immunohistochemical and molecular characterization of these nine cases and comparison with morphologically similar non-neoplastic processes, like bronchiolar metaplasia.

PS-13-005

Prognostic value of the 7th and 8th edition of the TNM classification and pathologic and radiologic regression in non-small cell lung cancer resected after neoadjuvant treatment

C. Bello[1], P. Zens[2], A. Scherz[3], J. Koenigsdorf[4], A. Pöllinger[5], R.A. Schmid[6], A. Ochsenbein[7], I. Zlobec[2], C. Neppl[2], S. Berezwoska[2]

[1] Institute of Pathology, University of Bern, Switzerland, [2] Institute of Pathology, University of Bern, Switzerland, [3] Department of Medical Oncology Inselspital, University Hospital Bern, Switzerland, [4] Department of Diagnostic, Interventional and Paediatric Radiology, University Hospital Bern, Switzerland, [5] Department of Diagnostic, Interventional and Paediatric Radiology, Inselspital University Hospital Bern, Switzerland, [6] Department of Thoracic Surgery, Inselspital University Hospital Bern, Switzerland, [7] Department of Medical Oncology, Inselspital University Hospital Bern, Switzerland

Background & Objectives: Adaptations for non-small cell lung cancer (NSCLC) in the 8th edition of the UICC/AJCC TNM classification (TNM8) were informed on data from large international patient cohorts. Notably, patients treated with neoadjuvant chemotherapy were excluded. We aimed at comparing TNM8 to the 7th edition (TNM7) and regression staging in neoadjuvantly treated patients in a single-center retrospective study.

Methods: We analysed 131 consecutive patients with NSCLC resected after neoadjuvant (radio)chemotherapy, 2000-2016. The pathological slides, clinical records and CT-scans were reevaluated assessing tumour-size according to current IASLC-recommendations, TNM7, TNM8, histological and radiological regression.

The cohort consisted of 59 squamous cell carcinomas, 65 adenocarcinomas and 7 others. Applying TNM8 staging criteria led to down-staging 2/131 (1.5%) and an up-staging 32/131 (24.4%) patients. Median progression free survival (PFS) was 13 months (95%CI=4.3-70.5 months). Median overall survival (OS) was 16 months (95%CI=4.1-88.5 months).

Results: Higher stage as assessed by both TNM8 and TNM7 was significantly associated with shorter PFS (p=0.002, p<0.001), but only applying TNM8 with shorter OS (p=0.002; p=0.439). Pathological regression grading alone (<1%, <10% or ≥50% viable tumour cells) was associated with PFS (p=0.037), even stronger if combined into a score including ypT and ypN (p=0.005), but not OS. There was no correlation between CT-assessed and pathological tumour size. Radiological regression using RECIST criteria alone lacked significant association with OS or PFS.

Conclusion: In conclusion, we document a prognostic value of the TNM8 staging system and histopathological regression grading in NSCLC patients treated with neoadjuvant (radio)chemotherapy.

PS-13-006

PD-L1 expression in 1051 non-small-cell lung cancer samples of a tertiary hospital in 2017-2018 and concordance in paired samples

L. Blasco Santana[1], S. Hernández-Bonilla[1], A. Rodríguez Garcia[1], R.M. Regojo-Zapata[1], R. Rosas[2], C. Rodríguez-Antolín[3], I. Esteban-Rodríguez[1,2]

[1] Pathology Department, La Paz University Hospital, Madrid, Spain, [2] Biomarkers and Experimental Therapeutics in Cancer, IdiPAZ, Madrid, Spain, [3] Cancer Epigenetics Laboratory, INGEMM, La Paz University Hospital, Madrid, Spain

Background & Objectives: Programmed Death Ligand 1 (PD-L1) is an important biomarker in lung cancer. Our objective is to describe our findings in non-small-cell lung cancer (NSCLC) patients in 2017-2018 in our centre and analyse concordance between paired samples (cytology, diagnostic biopsy and surgical piece).

Methods: We retrieved PD-L1 expression (%) and histological subtype from 1051 cases of NSCLC diagnosed in 2017-2018 in our centre. 621 samples (59.1%) were external consult cases. Our cases (430) were 206 diagnostic biopsies, 154 surgical pieces and 70 cytology specimens (50 cell block and 20 liquid cytology samples). Fifteen surgical pieces were paired with biopsy (12) or cytology (3), and 12 diagnostic biopsies with cytology.

Results: PD-L1 was evaluable in 993 cases (94.5%). PD-L1 expression was negative [<1%] in 378 cases (37.9%), it had low expression [1-49%] in 330 patients (33.1%), and high expression [≥50%] in 289 cases (29.0%). We found a higher proportion of PD-L1≥1% in squamous cell carcinoma (68.8%) than in adenocarcinoma (57.8%). Biopsy-surgical piece concordance was poor with Kappa=0.28 and an Intraclass Correlation Coefficient (ICC) of 0.04, while cytology-biopsy concordance was moderate with Kappa=0.50 and ICC=0.60. Epidermal Growth Factor Receptor (EGFR) mutations were associated with a lower level of PD-L1 expression, as 15 (68.2%) EGFR mutated cases were PD-L1 negative (P=0.005).

Conclusion: Our PD-L1 expression prevalence is similar to that described in current literature. Despite having only a few paired cases, we believe that poor to moderate concordance is caused by tumour heterogeneity and not by the type of sample chosen. Besides, EGFR mutations may affect PD-L1 expression profile.

PS-13-007

Expression of pluripotency factors Oct4 and LIN28 in lung adenocarcinoma

P. Bosgana[1], F. Dimitrakopoulos[2], F. Sampsonas[3], H. Kalofonos[4], V. Zolota[5]

[1] Department of Pathology, University Hospital of Patras, Greece, [2] Department of Oncology, University Hospital of Patras., Greece, [3] Department of Respiratory Medicine, University Hospital of Patras, Greece, [4] Department of Oncology, Medical School, University of Patras, Greece, [5] Department of Pathology, Medical School, University of Patras, Greece

Background & Objectives: Lung adenocarcinoma is a leading cause of cancer mortality worldwide despite recent therapeutic advances. Cancer stem cells (CSCs) have gained an increasing attention, due to their ability to generate new tumour through their self-renewal potential and differentiation into multiple cell lineages.OCT4 and LIN28 (homolog A and B) have been identified as key regulators of pluripotency in mammalian embryonic and induced stem cells and are proven to be crucial for cancer development, but our knowledge concerning their exact role in lung adenocarcinoma is limited.

Methods: The present study investigates the immunohistochemical expression of pluripotency factors (OCT4, LIN28A, B) and their association with clinicopathological data and survival in 98 cases of human lung adenocarcinoma patients.

Results: Higher OCT4 expression was related to improved 5-year overall survival (OS) (p<0,001).Patients with N2 disease were found to have lower LIN28A expression compared to patients with N0 and N1 disease (p<0,01).Nuclear LIN28B expression was lower in stage I and II tumours (p<0,05).LIN28B cytoplasmic expression was associated with 5-year OS not only in univariate (p<0,005),but also in multivariate analysis (age, gender, histological subtype and stage were used as cofactors, p<0,01 HR=2.592).In particular, patients with lower expression showed improved 5-year OS.

Conclusion: The results suggest that OCT4 and in particular LIN28B are promising prognostic biomarkers and could serve as future therapeutic targets in lung adenocarcinoma.

PS-13-008

EGFR mutations in Fez population: about 69 patients

S. Boukansa[1], S. El Bardai[2], Z. Benbrahim[3], N. Mellas[3], H. El Fatemi[4,5]

[1] Medical Centre of Biomedical and Translational Research, Faculty of Medicine and Pharmacy Fez, Morocco, [2] Anatomy and Cytopathological Department, CHU HASSAN II Fez, University Sidi Mohamed Ben Abdellah, Morocco, [3] Department of Oncology, CHU HASSAN II Fez, University Sidi Mohamed Ben Abdellah, Morocco, [4] Department of Pathology, Hassan II University Hospital, Fez, Morocco, [5] Faculty of Medicine and Pharmacy of Fez, Morocco

Background & Objectives: EGFR mutations in NSCLC, dysregulate various oncogenic mechanisms, including proliferation, increased malignant cell survival, invasion and metastasis. The management of NSCLC has envolved with the use of driver mutation in tumours samples toward selecting the right agent for a patients treatement. EGFR mutations is a predictive marker of tumour response to EGFR tyrosine kinase inhibitor treatment. The aim of this prospective study is to define the frequency and predictive value of EGFR mutations in Fez population with NSCLC.

Methods: 69 formalin-fixed paraffin-embedded tumours from patients diagnosed with NSCLC were included. The presence of EGFR mutations was determined by three methods according to percentage of tumour cells. For tumours with high percentage of tumour cells> 30%, PCR amplification followed by automatic direct sequencing was performed. The therascreen EGFR RGQ PCR Kit which is designed to detect the most commonly reported EGFR 29 mutations, was performed in samples with tumour cells< 30%. All mutations obtained by QPCR were comfirmed by Pyrosequencing.

Results: 17 mutations were detected in the serie of 69, more frequently in womens(52.9%) and non smokers(70.5%). The main types were in-frame deletions in exon19 (58.8 %), followed by the missense substitution in exon21 (23.5%), three patients had exon20 mutations (17.6%). 8patients were excluded due to lost to follow-up or death. 7patients demonstrated a marked response to afatinib with stable disease. One patient devellop a resistance after 12 month on afatinib therapy, a T790M mutation is thought to cause this resistance.

Conclusion: Consistent with what has been reported in other studies, EGFR mutations were more common in womens, non smokers and lung adenocarcima histology. This preliminary results of EGFR mutations in Fez population reveals an overall prevalence of 24.6%, wich is somewhat higher than north america (22%), higher than Europe (15%), but lower than Asia Pacific (47%).

PS-13-009

Optimal diagnostic algorithm for morphological diagnosis and management of patients with NSCLC lung tumours: 4 years experience of one center

M. Byakhova[1], L. Gurevich[2], V. Ashevskaya[1], V. Byakhova[3]

[1] M.F. Vladimirskiy Moscow Region Research Clinical Institute, Moscow, Russia, [2] The State Budgetary Healthcare Institution of Moscow Area Moscows regional research clinical Institute n.a. M.F. Vladimirskiy, Moscow, Russia, [3] Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Background & Objectives: At present, it is necessary to divide lung cancer (LC) before surgery not only into variants, but also to determine their histological and molecular subtype, as this significantly changes the prognosis of the course of the disease and the management tactics of a treatment patient. The aim of our study was to determine the histogenesis, immunophenotypic and genetic characteristics of the neoplasm for the development of optimal therapeutic approaches in each case.
Methods: Since January 2014 to July 2018 morphological and immunohistochemical (IHC) and genetic research of 326 samples of lung tumours was carried out. For IHC studies a panel of markers was used: cytokeratins (CK) 7, 5/6, TTF-1, napsin A, p63). Also determined mutations in the genes EGFR.
Results: In 148 cases, the diagnosis was made on hematoxylin/eosin-coloured glasses (highly and moderately differentiated cases of adenocarcinomas (AK) (72cfse) and squamous cell carcinoma (SCC) (73case)). With poorly differentiated tumours, a panel of 3 markers (CK7, TTF-1, Napsin A) was placed at the first stage. It made possible to differentiate AK. 25 patients (31%) with abnormalities in the EGFR gene were prescribed targeted therapy. The second stage delivered markers p63 and CK5/6 to confirm cases of SCC, they went to polychemotherapy and radiation.
Conclusion: Accurate morphological diagnosis plays a key role in choosing the optimal treatment strategy and determining the prognosis for patients with various lung tumours.

PS-13-010
Aquaporin-3 expression profile in malignant mesothelioma
S. Carnevale[1], G. Ferrario[2], U. Laforenza[3], P. Morbini[1]
[1] Section of Anatomical Pathology, Department of Molecular Medicine, University of Pavia, Italy, [2] PhD in Experimental Medicine, Department of Molecular Medicine, University of Pavia, Italy, [3] Department of Physiology, University of Pavia, Italy

Background & Objectives: Aquaporins regulate water transport in normal and neoplastic cells. They also play a role in cell migration, proliferation and adhesion. Preliminary data have shown AQP-1 upregulation in MM, but other aquaporin such as AQP-3 could present disregulation and be used as potential therapeutic targets: AQP-3 (an aquaglyceroporin expressed in the stratum corneum of the skin) was found to be overexpressed in colorectal, cervical, lung, oesophageal, gastric, skin and tongue (squamous) carcinomas and in hepatocarcinomas.
Methods: Supported by preliminary biochemical results, a consecutive series of ten MM samples was evaluated with immunohistochemistry (Sigma Aldrich anti-AQP3 antibody) and AQP-3 expression was compared with adjacent non-neoplastic mesothelium. We evaluated only the positivity or negativity, regardless of the intensity of the staining.
Results: Expression of AQP-3 was observed in 7 out of 10 cases, with a membrane (62%) or cytoplasmic (25%) pattern of expression in up to 70% of MM cells, while expression in non-neoplastic mesothelium was not significant. The only case of sarcomatoid malignant mesothelioma in our series was found to be negative for AQP-3.
Conclusion: AQP-3 appears to be upregulated in 70% of our series of MMs, with a prevalent expression on the membrane surface, where the protein can play its natural role in water (and glycerol) exchange. The cases where a cytoplasmatic pattern was observed, suggest us that protein can play a pathogenetic role not only if correctly exported to the cellular membrane, but also if accumulated in the cytoplasm.

PS-13-011
The optimal use of image analysis in the assessment of PD-L1 immunostaining in non-small cell lung cancer
J. Fay[1], A. O'Grady[1], K. Sheehan[1], M. Redmond[2], B. Doyle[1]
[1] Department of Pathology, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland, [2] Department of Histopathology, Beaumont Hospital, Dublin, Ireland

Background & Objectives: The immunohistochemical analysis of PD-L1 in non-small cell lung cancer (NSCLC) is an important diagnostic test to assess the potential response of the tumour to immunotherapy. The assignment of PD-L1 staining into categories (<1% tumour proportion score (TPS), 1-49% TPS and ≥50% TPS) is the current benchmark for treatment decisions, with only those with ≥50% TPS eligible for first-line immunotherapy treatment in Ireland.
The aim of this study was to assess if image analysis of PD-L1 immunostaining alone or alongside immune cell markers correlated with manual interpretation.
Methods: We compared the TPS as assessed by two pathologists to the positive percentage score using QuPath software in 20 NSCLC cases.
Results: When using image analysis to measure the level of positive membrane staining alone only 5/20 (25%) cases were in agreement. However when a minimum nuclear size was added in an attempt to eliminate non-tumour cells 13/20 (65%) cases were in agreement. The addition of CD4 and CD68 immunostaining to the analysis to help eliminate PD-L1 positive immune cells did not improve the number of cases in agreement. The analysis of cases close to the ≥50% TPS score (40-60%) using PD-L1 positive membrane staining and nuclear size showed that 6/8 (75%) cases were in agreement.
Conclusion: Image analysis may be a useful tool to support the pathologist in assessing PD-L1 TPS in NSCLC, especially for cases close to the ≥50% threshold for treatment

PS-13-012
Bronchial-pulmonary carcinomas actin and fibroelastotic stroma: suggestion for routine report
J. Fraga[1], V. Sousa[1,2], L. Carvalho[1,2]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal, [2] Faculdade de Medicina da Universidade de Coimbra, Portugal

Background & Objectives: American Thoracic Society/European Respiratory Society (ATS/ERS) defined in 2013 Idiopathic Pleuroparenchymal Fibroelastosis as «rare condition that consists of fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes, with elastotic fibrosis, intraalveolar fibrosis and commonly associated to recurrent infections».
Methods: This disease may not be rare but its characteristics may help to understand tumoural stroma as an important element for targeted therapy as epithelial malignant cells. Then tumoural stroma demands reporting/scoring containing either its quality or relative percentage. Currently, bronchial-pulmonary carcinoma presents four main patterns concerning lymphoid, fibrolymphocytic, predominantly fusiform celled stroma-with smooth α-actin/elastin deposition, and bronchioloalveolar pattern, validated by immunohistochemistry/histochemistry for α-actin and elastin, respectively.
Results: Searching for smooth α-actin/elastotic fibers in pulmonary diseases, also raises understanding of a new repair cascade in chronic collagenizing pleuritis, young men non-smokers/smokers spontaneous pneumothorax with sub-pleural triangular infancy infarcts scars and in peripheral adenocarcinomas stroma, under two delineated patterns: basal membrane type and/or well defined elastotic stroma, with variable smooth α-actin positivity - emphasized in surgical specimens, where stromal heterogeneity commits with malignant epithelial heterogeneity.
Conclusion: Pancreatic ductal adenocarcinoma prognosis is an example of α-SMA mRNA expressed by activated stromal regulating malignant

behaviour of pancreatic cancer cells; high density of stromal myofibroblasts identified with α-smooth muscle actin may contribute to poor survival in patients with solid cancers (Sinn 2014/ Fujita 2010/Liu 2016/Nishishita 2018). Fibroelastotic stroma stands without clinical commitment and it might be related with better prognosis, demanding search in either tumoural/non-tumoural pulmonary disease.

PS-13-013

A standardised structured training of pathologists to improve inter- and intra-reader reproducibility for scoring PD-L1 expression levels in non-small cell lung cancer: results of a worldwide training programme

B. Jasani[1], R. Oberthür[1], G. Bänfer[1], R. Diezko[1], G. Kumar[1], J. Rüschoff[1], H. Schildhaus[2]
[1] Targos Molecular Pathology GmbH, Germany, [2] University of Essen, Germany

Background & Objectives: Immunohistochemical diagnostic testing for programmed cell death-ligand 1 (PD-L1) has been approved for targeted treatment of several major cancer types including non-small cell lung cancer, NSCLC. However, the semi-quantitative scoring of PD-L1 expression is complex and requires training of pathologists to reduce inter- and intra-reader variability. Here we present our data for a worldwide, expert-led training in PD-L1 interpretation and scoring of NSCLC cases, conducted over a two-year period, 2016-2017, using glass slides or equivalent digital images
Methods: Tissue slides representative of NSCLC resected specimens with differing PD-L1 expression levels enriched around the relevant clinical cut-offs, were stained with the PD-L1 IHC pharmDx 22C3 assay. After initial training and a self-assessment exercise, the participants (n=751) were given 20 cases on Day 1, followed by a further 25 cases on Day 2, including 15 slides already seen on Day 1. From the data obtained, inter-reader overall percentage agreement (OPA), and the intra-reader OPA were calculated.
Results: The inter-reader OPA for PD-L1-stained NSCLC were calculated to be 95.6% (Cohen kappa, CK = 0.84) for TPS ≥1%, and 87.3% (CK = 0.74) for TPS ≥50% cut-off, respectively. The corresponding intra-reader OPA were calculated to be 95.9% (CK = 0.87) and 91.4% (CK = 0.83) for the ≥1% and ≥50% cut-offs.
Conclusion: The consistently high inter- and intra-reader agreements observed are promising, given: a) the complexity of scoring tumour cells especially with heterogeneous PD-L1 staining pattern; b) the varied background in terms of expertise and experience of the participants; and c) the use of digital images in addition to glass slides to manage the worldwide training programme.
Background Biotechnological Support from Dako/Agilent & MSD.

PS-13-014

High expression of Carboxyl terminus of Hsp70-interacting protein (CHIP) is a favourable prognostic factor in Non-small cell lung cancer

J. Kim[1], J. Chung[2], Y.S. Park[1], S.J. Jang[1], C.M. Choi[3], H.R. Kim[4], J.S. Song[5]
[1] Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [2] Experimental Pathology Laboratory, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA, [3] Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [4] Department of Cardiovascular and Thoracic Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [5] Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Republic of Korea

Background & Objectives: Carboxyl terminus of Hsp70-interacting protein (CHIP) is a negative regulator of necroptosis via inhibition of Receptor-interacting serine/threonine-protein kinase 3 (RIPK3). Necroptosis, a form of caspase-independent programmed cell death, promotes cancer progression and metastasis in a few cancer types although anti-tumour effects of necroptosis have been reported. However, the clinicopathologic role of CHIP expression in non-small cell lung cancer (NSCLC) is still poorly characterised. Herein, we aimed to evaluate the prognostic implication of CHIP expression in NSCLC.
Methods: Immunohistochemistry (IHC) for CHIP was performed on tissue microarray in 404 NSCLC patients. The cytoplasmic expression was assessed by semi-quantitative H-score (range 0-300) using image analyser. CHIP was subdivided into positive and negative using optimal cut-off point (score 242) and was correlated with clinicopathologic features.
Results: Eighty-nine patients (22.2%) showed high expression for CHIP by IHC. High CHIP expression was associated with squamous histology ($p < 0.001$) and the lower stage ($p = 0.010$), but other parameters including smoking ($p = 0.178$), tumour size ($p = 0.120$) and adjuvant treatment ($p = 0.280$) were not statistically significant. In univariate analysis, high CHIP expression was associated with the longer overall survival (OS) (log-rank test, $p = 0.044$). In multivariate analysis, high CHIP expression was an independent favourable prognostic factor for OS [HR 0.477, (95% CI, 0.235-0.966), $p = 0.040$], but not disease-free survival (log-rank, $p = 0.321$).
Conclusion: High CHIP expression is an independent favourable prognostic factor in NSCLC, suggesting the potential role of CHIP as the novel therapeutic target for NSCLC.

PS-13-015

The prognostic significance of lung adenocarcinoma grading

P. Kisialeu[1]
[1] N.N. Alexandrov National Cancer Centre of Belarus, Belarus

Background & Objectives: WHO 4th classification of lung tumours introduced the changes concerning the histological assessment of lung adenocarcinoma and it's grading in particular. The aim of the research was to establish the predictive value of new histological features in comparison with the previous classification system.
Methods: We investigated the clinical, histological and follow-up data of the retrospective group of 100 patients (64 males, 36 females, mean age 64,6 years old) with primary lung adenocarcinoma. The group included 47% of cases with the clinical stage I, 23% – stage III, 21% – stage II and 9% – stage IV. All the patients underwent treatment in the N.N. Alexandrov National Cancer Center of Belarus in 2012.
Results: Depending on the predominant histology subtype of the tumour, all cases have been classified as three grades: G1– lepidic and minimal invasive carcinoma (19%), G2 – acinar (39%) and papillary (9%) carcinoma, G3 – solid (19%), micropapillary (8%) and invasive mucinous (6%) carcinoma. The statistical analysis showed the significant difference in 5-year survival between G1, G2 and G3 groups (100,0% vs 61,9% vs 8,0%, Kaplan-Meier, $p<0.001$). Unfavourable prognostic value of such factors as the presence of foci of necrosis ($p<0.001$) and desmoplasia ($p=0.02$) in the tumour tissue were established.
Conclusion: The study confirms that the new principles of diagnosis and grading of lung adenocarcinoma described in the WHO classification have a high prognostic value.

PS-13-016

Validation studies of PD-L1 IHC 22C3 pharmDx (Dako Omnis) for human non-small cell lung carcinoma (NSCLC) tissues

L. Kramer[1], G. Toland[1], J. O'Brien[1], C. Roach[1], R. Welcher[1], K. Kulangara[1]
[1] Agilent Technologies, Inc., USA

Background & Objectives: PD-L1 IHC 22C3 pharmDx is indicated as an aid to identify NSCLC patients for treatment with KEYTRUDA® (pembrolizumab) monotherapy. The assay is currently approved by the FDA for use on the Autostainer Link 48 (ASL48) instrument. The intent of these studies was to validate the assay for the Dako Omnis, an automated staining platform offering continuous delivery of patient slides. In addition to precision studies, an important element was to show performance equivalence between staining platforms for NSCLC specimens.
Methods: The comparison study investigated the performance of PD-L1 IHC 22C3 pharmDx (Dako Omnis) staining equivalence to the FDA-approved PD-L1 IHC 22C3 pharmDx assay on ASL48. The same set of NSCLC specimens (n=84) was stained on both instruments, and then certified pathologists evaluated all specimens at the 1% and 50% cut-offs. In addition to the comparison study, NSCLC specimens were stained with PD-L1 IHC 22C3 (Dako Omnis) and were also evaluated for combined precision (inter-lot, inter-instrument, inter-day).
Results: The results from the comparison study demonstrated comparable staining between the ASL48 and Dako Omnis. At the 1% cut-off the point estimates for Negative Percent Agreement (NPA), Positive Percent Agreement (PPA), and Overall Agreement (OA) were 99.0%, 98.5%, and 98.8%, respectively. The results for 50% cut-off were: NPA was 95.5%, PPA was 91.6%, and OA was 93.7%. At the 1% and 50% cut-offs, the combined precision study resulted in an OA of 97.9% and 100.0%, respectively.
Conclusion: Results from the comparison and combined precision studies indicate equivalent staining performance between PD-L1 IHC 22C3 pharmDx (Dako Omnis) and PD-L1 IHC 22C3 pharmDx on Autostainer Link 48 at the clinically significant cut-offs.

PS-13-017

Best practice session on lung cancer molecular diagnostics in the Netherlands to enhance testing proportions nationwide

C. Kuijpers[1], M. van den Heuvel[2], A. van Lindert[3], R. Damhuis[4], S. Willems[1]
[1] Department of Pathology, University Medical Centre Utrecht, The Netherlands, [2] Department of Lung Disease, Radboudumc, Nijmegen, The Netherlands, [3] Department of Respiratory Medicine, University Medical Centre Utrecht, The Netherlands, [4] Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands

Background & Objectives: Adequate and timely testing for genetic alterations in lung cancer is necessary to consider targeted therapy. Previously, we demonstrated that in the Netherlands molecular testing was suboptimal in 2015, as 25% (EGFR/KRAS and ALK) to 50% (ROS1) of patients were not tested according to guidelines, and notable laboratory variation was present. Results were fed back to laboratories. In a best practice session, we aimed to identify a process for best possible flow and highest possible testing proportions.
Methods: We invited pathologists, molecular biologists, pulmonologists, and technicians from six laboratories/hospitals with highest testing proportions to join a best practice session. Ultimately, four laboratories, two academic and two non-academic, joined. Following a questionnaire, we discussed their work flow and why they think their laboratory/hospital performs well.
Results: We identified several stimulatory factors for molecular testing: 1. discuss all metastatic lung cancer patients at multidisciplinary meetings; 2. dedicated/specialized professionals; 3. short communication lines and clear agreements; 4. work culture of critical openness and honesty; 5. awareness and feedback on performance; 6. comprehensive request by the pulmonologist of all genes to be tested; 7. to obtain sufficient tumour tissue: a. perform CT-scan earlier in process, making it possible to collect larger biopsies in case a metastasis is detected, and b. embed cytological material. Costs, without reimbursement, were seen as a prohibitive factor.
Conclusion: Several elementary steps (such as good communication) to improve adequate molecular testing were revealed. Initiatives will be taken to implement the outcomes nationwide, by starting a dialogue with health care professionals at a regional level.

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PS-13-018

Primary pleuropulmonary synovial sarcoma: clinico-pathological features of 55 cases from a single tertiary care oncology centre

R. Kumar[1], T. T. Nair[1], V. Rao[1], G. Hardas[1], A. Janu[2], B. Rekhi[1], K. Prabhash[2], C. Pramesh[3]
[1] Department of Pathology, Tata Memorial Centre, India, [2] Tata Memorial Centre, India, [3] Department of Thoracic Surgery, Tata Memorial Centre, India

Background & Objectives: Primary pleuropulmonary synovial sarcoma (PPSS) is an extremely rare intra-thoracic malignancy, characterised by specific chromosomal translocation[t(X;18)(p11.2,q11.2)]. The objective of this study is to evaluate the clinicopathological features of PPSS from a single tertiary care oncology centre
Methods: PPSS diagnosed between 2007-18 were retrieved from pathology archives. Cases with known extra-thoracic primary were excluded. Clinico-radiological details were recorded and histopathological features were reviewed.
Results: A total of 55 cases of PPSS were identified, with age range 16-80 years(mean age 39 years) and male: female ratio of 1.75:1. The tumour was located in lung primarily{35(63.6%)}, while others were either pleural based(n=11) or infiltrating the chest wall(n=9) and mean tumour size was 12cms(range: 3.3-20 cms). Monophasic variant was the commonest histological subtype(43/48). Diffuse sheets or fascicles of the uniform spindle/ovoid cells with scanty cytoplasm and indistinct borders was seen in most of the cases. In addition hemangiopericytomatous vasculature [77%], necrosis[44%] and focal myxoid change[23%] was also seen. On immunohistochemistry(IHC), Mic2(44/46) and Bcl2(41/45) were consistently expressed along with focal expression of epithelial markers[pan CK(19/31) and EMA(16/28)]. Desmin and CD34 were consistently negative. Molecular confirmation was performed in 10 cases. Chemotherapy was the main treatment modality and 8 underwent surgery. 5 patients died of disease and 22 had metastatic disease.
Conclusion: We present one of the largest series on clinicopathological features of PPSS, from this region. Establishing the diagnosis can be challenging, in the small biopsy specimen. Increasing awareness amongst pathologist, characteristic hemangiopericytomatous pattern and judicious use of IHC and molecular tests helps to ascertain the diagnosis.

PS-13-019

Usefulness of detection of amplification of PIK3CA and YEATS2 genes using FISH in SqCC of lung

E. Lee[1], H. Kim[2], C. Kim[2]
[1] Naeun Hospital, Republic of Korea, [2] Korea University Guro Hospital, Republic of Korea

Background & Objectives: One of the characteristic of squamous cell carcinoma (SqCC) of lung is amplification of distal portion of Chromosome 3q. Our previous study using whole genome microarray for comparative genomic hybridization (CGH) and then NanoString nCounter assay (NanoString) revealed that, among the genes located at distal portion of 3q, only *PIK3CA* and *YEATS2* gene gains were associated with poor prognosis. The aim of study is to investigate the usefulness of detection of amplification of *PIK3CA* and *YEATS2* genes using fluorescence in situ hybridization (FISH) in SqCC of lung.
Methods: We performed FISH in tissue microarray (TMA) block of 90 cases of SqCC of lung. RP11-12L14 and RP11-245C23 (Empire Genomics, US) probes covered the locus of *YEATS2* and *PIK3CA,* respectively with orange colour was used. It was considered amplification

when there were ≥5 signals in each cell and more than 5 cells. The FISH results were compared to NanoString nCounter analysis results.
Results: *YEATS2* and *PIK3CA* gene were amplified in 37 (41%) and 29 (32%) cases, respectively. SqCC of lung can be subdivided by 3q amplified status using FISH, but amplified group didn't show statistically significant survival difference.
Conclusion: FISH is easily accessible method to detection of amplification of specific chromosome locus. We developed new FISH biomarker to define *YEATS2* or *PIK3CA* gene amplification status. However, using FISH, amplified subgroup of SqCC of lung didn't show clinically different prognosis. It is necessary further study to confirm clinical meaning of *PIK3CA* or *YEATS2* genes amplified group of SqCC of lung.

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PS-13-020

Classic driver oncogene mutations in EGFR, ALK, ROS1 and PD-L1 expression in chemonaive lung adenocarcinoma specimens: clinico-pathological correlations

F. Lunardi[1], F. Pezzuto[1], F. Fortarezza[1], S. Vuljan[1], G. Comacchio[1], G. Pasello[2], F. Rea[1], F. Calabrese[1]
[1] University of Padua, Italy, [2] Veneto Oncology Institute - IOV, Italy

Background & Objectives: Target somatic genome analysis (EGFR, ALK and ROS1) and PD-L1 tumour proportion score (TPS) are used for selection of first-line therapies in advanced lung cancer; however their frequency and significance in early stages in relation to the main morphological and clinical characteristics is poorly reported.
Methods: The study population included 100 patients consecutively resected for primary pulmonary adenocarcinoma (stages I-II in 80% of cases) without any neoadjuvant therapy in the period January 2017 - January 2018, followed for a mean follow-up time of 15.7 months. EGFR mutational status and tissue immunohistochemical expression of PD-L1 (clone: E1L3N), ALK (clone: D5F3) and ROS1 (clone: D4D6) biomarkers were correlated with the main clinical and morphological characteristics (histological pattern, proliferation index, lymphnode invasion, extension of necrosis and inflammatory infiltrate).
Results: 27% of patients showed PD-L1 expression (12% with TPS ≥ 50%), 4% of patients were positive for ALK and 2% for ROS1 (score 3). PD-L1 expression was significantly associated with the solid histological pattern and the proliferation index ($p = 0.009$ and $p = 0.030$). The positivity for PD-L1 was also related to a higher frequency of recurrence ($p = 0.035$). For ALK and ROS1, no significant differences emerged, except for a greater predisposition of females to express ROS1. EGFR mutations were more frequent in non-smoker patients ($p = 0.002$).
Conclusion: The present study highlights PD-L1 as an intriguing predictive biomarker: its expression seems to be associated with increased tumour proliferation and aggressiveness as well as a higher risk of recurrence.

PS-13-021

Indoleamine 2,3-dioxygenase 2 immunohistochemical expression in a resected non-small cell lung cancer series

M. Mandarano[1], G. Bellezza[2], C. Volpi[3], J. Vannucci[4], I. Ferri[2], G. Mondanelli[3], L. Cagini[4], F. Puma[4], M.L. Belladonna[3], A. Sidoni[2]
[1] Department of Experimental Medicine, Section of Anatomic Pathology and Histology, Medical School, University of Perugia, Italy, [2] Department of Experimental Medicine, Section of Anatomic Pathology and Histology, Medical School, University of Perugia, Italy, [3] Department of Experimental Medicine, Section of Pharmacology, University of Perugia, Italy, [4] Department of Thoracic Surgery, Medical School, University of Perugia, Italy

Background & Objectives: Indoleamine 2,3-dioxygenase 1 and 2 (IDO-1 and IDO-2) are both implicated in immunomodulatory functions. Although several studies exist on the role of IDO-1 in human tissues, little is still known about IDO-2 functions and particularly about its involvement in non-small cell lung cancer (NSCLC) immunescape. [1,2]
Methods: IDO-2 immunohistochemical expression was evaluated on 193 formalin-fixed and paraffin-embedded resected NSCLC, both in neoplastic cells and in normal adjacent lung parenchyma. Correlations with clinical-pathological data, tumour-infiltrating lymphocytes (TILs), IDO-1, programmed cell death ligand-1 (PD-L1) and patients' prognosis were analysed.
Results: IDO-2 was chiefly enlightened at the interface between tumoural cells and tumoural stroma and at cell to cell junction; almost always normal bronchial epithelium expressed IDO-2. Moreover, IDO-2 overexpression is closely related both to high PD-L1 among squamous cell carcinomas ($p=0.012$) and to adenocarcinoma histotype ($p<0.001$). Considerably, IDO-2 overexpression correlates with a worse NSCLC prognosis ($p=0.027$), particularly in case of concurrent overexpression of IDO-1 ($p=0.030$) or high density of TILs ($p=0.045$), regardless of histotype.
Conclusion: Our preliminary results have improved the knowledge about IDO-2 in lung tissue and NSCLC, suggesting a function both in immune system modulation and in tumoural invasiveness. The abovementioned interactions of IDO-2 with other microenvironmental molecules and their relationship with patients' prognosis could support both the assessment of their status on pathological report and the introduction of combined immunotherapies as clinically useful. Nevertheless, further studies are needed to better understand IDO-2 role as potential biomarker in NSCLC.
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PS-13-022

Gender differences of nuclear morphometric and texture features in small cell neuroendocrine carcinoma of the lung

K. Metze[1], A. Castro de Mattos[1], R. L. Adam[1], J. B. Florindo[1]
[1] State University of Campinas, Brazil

Background & Objectives: Some neoplasms show subtle differences of the nuclear architecture between male and female patients. The aim of this study was to compare morphometric and texture features of nuclei of small cell neuroendocrine lung cancers (SCLC) between both genders.
Results: The most striking finding was a difference of the nuclear area. When comparing group means, tumour nuclei of male patients were about one third larger than those of female patients ($p < 0,005$). There were no significant differences of the mean values of the Shannon entropy of chromatin, but a small significant difference for the 75th percentile of the fractal dimension obtained by differential box counting (men: 2,174; women: 2,187; $p = 0,001$)
Methods: We selected from our archive 49 consecutive SCLC patients with complete clinical data and follow-up. Routinely HE-stained brush cytology slides obtained at diagnosis were digitalized. After segmentation of the nuclei, morphometric and nuclear texture features were measured by in-house developed software.
Conclusion: Our investigation suggests that in male SCLC patients larger tumour nuclei are more frequent, whereas chromatin texture featreus show only very subtle differences between men and women. A possible explanation for our findings could be the presence of different SCLC subtypes with varying proportions between both genders.

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PS-13-023

Immune-profilling depends on immunogenic collagen and mismatch proteins to predict death and therapy in malignant mesothelioma

G. Morgantetti[1], M. Balancin[2], V. Martins[3], J. T. De Miranda[4], A. K. Assato[3], N. A. de Souza[5], A. P. Pereira Velosa[6], W. Rosolia Teodoro[7], G. A. de Medeiros[8], R. Falzoni[9], A. M. Ab'Saber[3], V. Capelozzi[3]
[1] University of Sao Paulo, Brazil, [2] Department of Pathology, Faculty of Medicine, University of São Paulo, Division of Pathology, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil, [3] Department of Pathology, Faculty of Medicine, University of São Paulo, Brazil, [4] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [5] Division of Pathology, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil, [6] Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [7] Faculdade de Medicina, Universidade de Sao Paulo, Rheumatology Division, Brazil, [8] Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil, [9] Division of Pathology, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil

Background & Objectives: Malignant mesothelioma (MM) is a highly fatal disease with limited therapeutic options. The role played by microenvironment is evident, although unknow for Type V collagen (Col V) and mismatch repair (MMR) proteins. These elements have been evaluated as well as the cross-talking as predictive and prognostic factors.
Methods: Ninety MM patients were enrolled, located in pleural and peritoneal serosae. We quantified through image analysis and employed immunofluorescence to evaluated Col V and immunohistochemistry to detect programmed death ligand 1 (PD-L1) expression in malignant cells (MCs), cells expressing the immune markers CD4, CD8 and CD20,BAP1, and MMR proteins (MLH1, PMS2, MSH2, MSH6).
Results: MCs-PD-L1 expression was 7/mm2,inflammatory cells expressing PD-L1 2.94/mm2,CD4+ 60/mm2, CD8+ 301/mm2and CD20+ 186/mm2. Loss of BAP1 occurred in 61 (59%) cases. Col V fibers mean density were 2.67/mm3. The mean MMR protein expression in tumour cells was MLH1 (713/mm2), PMS2 (957/mm2), MSH2 (1306/ mm2) and MSH6 (855/mm2). A Cox multivariate model reliably predicted high risk of death for MM with necrosis (p=0.01), high nuclear grade (p=0.003), low MCs-PD-L1 (p=0.002), and inflammatory cells expressing PD-L1 (p=0.006), loss of BAP1 expression p=0.005),low CD4+ (p=0.008), high MLH1 expression (p=0.002), and MSH2 (p=0.01), and high Col V fibers (p=0.004). There was no significant difference between pleural and non-pleural disease.
Conclusion: PD-L1 depends on the cross-talk between Col V and tumour mutation burden to promote cold-hot immunogenic switching and to predict death and target therapy in MM in pleural and non-pleural MM.

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PS-13-024

Immunohistochemical staining of PD-L1 using 22C3 laboratory developed test (LDT) for Ventana platform: real-life statistical validation

T. Neuman[1], G. Vainer[1]
[1] The Hebrew University - Hadassah Medical Center, Jerusalem, Israel

Background & Objectives: Immunotherapy is a novel treatment in oncology. Pembrolizumab (MSD) is a monoclonal antibody against programmed cell death [1] that has been approved for use in many indications. In some indications a companion diagnostic by Dako (22C3 clone) for patient stratification is required. Ventana's BenchMark immunohistochemistry (IHC) platform is widely used around the world. Our group described a 22C3-based LDT for the Ventana platform, and showed its reliability and reproducibility (2016). However, real-time data about the reliability is lacking.
Methods: Between July 2016 and March 2019, 1084 NSCLC patients were evaluated at the Hadassah Medical Center for PD-L1 by immunohistochemistry. All patients were evaluated using the clone 22C3 LDT.
Results: The overall PD-L1 tumour proportion score (TPS) of ≥50%, 49-1%, and <1% of the keynote-010 trial and our cohort is 28.48%, 37.89%, 33.63%, and 29.05%, 33.16%, 37.79%, respectively. Tumours with a PD-L1 TPS of ≥50% were not associated with patient gender, ethnicity, or biopsy type.
Conclusion: Our 22C3 LDT for the Ventana platform and the Keynote 001/010 display similar scoring distribution in NSCLC. Our cohort represent a real-time, heterogenic group, outside of clinical trial setup. This support the notion that the LDT is clinically effective in NSCLC.

PS-13-025

Lung cancer in young adults in Ceará Brazil

D. Nunes Oliveira[1], P. V. Pereira Motoyama[2], V. M. Maia Amorim de Morais[2], R. Teófilo Parente Prado[2], L. Matias Marques[2], G. Bitu dos Santos Ponte[2], S. Capelo Barroso Garcia[2], S. Andrè de Souza Júnior[2], J. Carneiro Melo[1], R. L. Freitas de Almeida[3], A. Rolim Campos[3], F. Rocha Fernandes Távora[4], J. Benoit Sabourin[5]
[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil, [3] Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [4] Federal University of Ceara, Brazil, [5] Department of Pathology, Rouen University, France

Background & Objectives: Lung cancer (LC) has become one of the most lethal neoplasm in the world. Smoking is its main cause. Histologically it is divided into four types: squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma. In Brazil, there is a shortage of information about LC histology, gender differences and epidemiological tendencies. However, it is known that adenocarcinoma has become the most common histological subtype in the last 30 years especially among women. Concerning LC in young subjects studies show that there is a decreasing tendency in smoking prevalence, but also that an early onset of smoking hampers its cessation during adulthood. The goal of this study is to analyse the prevalence of LC among young people (≤ 40 years old) in the state of Ceara, Brazil.
Methods: This is a descriptive study. Data was collected from the website of Brazilian National Institute of Cancer (INCA). We selected cases of LC in young patients recorded in Ceara between 2012 and 2016.
Results: Twenty-nine cases of LC in young patients occurred in Ceara during the selected period. 20 (69%) of them were in the metropolitan region of Fortaleza, 3 (10.3%) in the countryside of the state, 2 (6.9%) in the Vale do Jaguaribe and Northeast regions of the state each, and 1 (3.4%) for the North and Mid-south regions each. There were 20 (69%) cases of LC in young women and 9 (31%) in young men. Regarding the histological subtypes, 18 (62.1%) cases did not report their subtype, 5 (17.2%) were adenocarcinomas, 2 (6.9%) were small cell carcinomas and mesenchymal tumours each, 1 (3.4) undifferentiated/large cell carcinoma and non-specified carcinoma. Thus, there was a predominance of non-small cell carcinoma (NSCC) (82%) in the analysed population.
Conclusion: We concluded that there is predominance of females among young people with LC and that NSCC is the most common subtype of LC as already described in the literature. Therefore, we found a need of more multicentric studies that analyse other risk factors for the early development of LC besides smoking and the prognosis for those patients that is still controversial in the literature.

PS-13-027

Pulmonary metastases of gynaecological tumours

A. Ok Atilgan[1], M. Tepeoglu[1], B. Ozdemir[1]
[1] Baskent University Faculty of Medicine Pathology Department, Turkey

Background & Objectives: The purpose of this study was to investigate the clinicopathological features of pulmonary metastasis of gynaecological tumours.
Methods: This is a retrospective study of forty-nine cases with pulmonary and/or pleural metastases were diagnosed between 2003 and 2018. Clinical, pathological and survival data of these cases were reviewed.
Results: Serous carcinomas were the most histological type of primary tumour (53%), followed by leiomyosarcoma (24%). Eighteen patients (36,7%) had metastasis at the time of primary tumour diagnosis. The remaining 31 patients were diagnosed with metastasis after initiation of primary cancer treatment, with a median presentation interval of 39 months after primary cancer diagnosis. The pulmonary and pleural metastasis presented synchronously in 7 patients, only pulmonary metastasis in 22 patients, only pleural metastasis in 20 patients. Among patients with pulmonary metastasis, 10 patients had a tru-cut biopsy from lung, 5 had wedge resection, 8 had a lobectomy. Among patients with pleural metastasis, seventeen patients had pleural cytology, 5 pleurectomy, 4 pleural biopsy for diagnosis of metastasis The average size of the largest pulmonary nodules was 3,1 cm and the number of nodules was 3,6. The median follow-up time was 47,8 months. Thirty-three patients (67,3%) had died after metastasis. The Kaplan-Meier estimated overall survival at 2 years was 68% and disease-free survival at 2 years was 40%. We found that primary tumour stage, number of metastatic nodules, the diameter of nodules were identified as a prognostic factor for disease-free survival ($p \leq 0,05$).
Conclusion: Complete surgical resection of metastasis is the most beneficial treatment which determines the outcome in these patients.

PS-13-028

Pulmonary sclerosing pneumocytoma: a comprehensive study of the molecular features of a series of six cases in Western (non-Asian) patients

A. Panizo[1], I. Amat[1], L. Nova[1], I. Fernandez[1], T. Labiano[1], M. Gomez-Dorronsoro[1]
[1] Complejo Hospitalario de Navarra, Spain

Background & Objectives: Pulmonary sclerosing pneumocytoma (PSP) is a rare benign tumour. The molecular profile of these tumours is not well known.
Methods: We performed a clinicopathological, IHC, and molecular study in six PSP. IHC was performed: beta-catenin, ALK, BRAF V600E, ROS1, HER2, and PD-L1. Molecular tests included *EGFR*, *KRAS,* and *BRAF.* FISH tests included *ALK*, and *ROS1* rearrangement.
Results: All patients were women: median age of 50 yrs. (range: 29-73). Mean size was 26 mm (range 15-45 mm). All tumours were located within the right lung, and presented as single pulmonary nodule. Frozen sections (n=4): accurate diagnosis was 25%, 25% deferral rate and 50% were misdiagnosed as malignancy. All tumours were composed of more than two growth patterns. EMA, TTF1, and PR were observed in both cells type. The surface cells showed also CK7, Napsin-A, and surfactant-A. IHC showed aberrant nuclear and cytoplasmic accumulation of beta-catenin in the cuboidal cells in 3 cases, with even a significantly decreased or lack of expression in polygonal cells. Mutational analysis of *EGFR*, *KRAS*, *BRAF* and IHC/FISH for HER2, ALK, BRAF V600E and ROS1 did not reveal molecular alterations. All cases were negative for PD-L1. All patients were alive and well without recurrence at the time of last follow-up.

PS-13-029

Role of autoimmunity and interleukin-17 expression in acute and chronic lung allograft rejection: an experimental rat model

F. Pezzuto[1], F. Lunardi[1], S.E. Vuljan[1], F. Fortarezza[1], E. Cozzi1, F. Rea[1], F. Calabrese[1]
[1] University of Padua, Italy

Background & Objectives: Lung transplantation represents the treatment strategy for many end-stage pulmonary diseases. Chronic lung allograft dysfunction (CLAD) remains the major limit for long-term survival and its risk is increased by the occurrence of acute cellular rejection. A key role of IL-17 in the pathogenesis of lung alloimmune-induced rejection has already been demonstrated, reporting T-lymphocytes as the principal source of this cytokine. The aim of the study was to investigate IL-17 expression in different cell components of acute and chronic lesions occuring after lung transplantation in grafts of two different rat strains.
Methods: An orthotopic lung transplantation (OLT) was performed in 50 rats (37 inbred Lewis into Fisher and 13 Sprague Dawley outbred rats). Histological features of primary graft dysfunction (PGD), acute and chronic rejection (AR, CR) (according ISHLT grading system) were evaluated and tissue IL-17 immunostaining was expressed as score (from 0 to 3) in different cell types: lymphocytes, macrophages, airway epithelial and stromal cells. IL-17 mRNA expression was also carried out in the bronchoalveolar lavages (BALs).
Results: PGD, moderate-severe AR and CR were detected in 16%, 30% and 22% of rats, respectively. IL-17 expression was higher in AR and CR than PGD. IL17 expression was similar for AR and CR in macrophages (median score value: 3), lymphocytes and epithelial cells (median score value: 2), while it was different in stromal cells (median score value: 0.5 in AR and 3 in CR). A significant increase of IL-17 mRNA was observed in AR than CR (4-fold). No differences were detected between the two experimental model strains.
Conclusion: IL-17 is overexpressed in allograft rejection, mainly in more severe grade of AR and CR. Airway and stromal cells other than inflammatory cells represent an important source of this cytokine, particularly in CR. Both rat strains seem viable animal models to study and further investigate the role of IL-17-mediated pathway in lung transplantation.

PS-13-030

STK11 mutations are associated with lower PDL1 expression in lung adenocarcinoma and is a candidate biomarker to predict the response of immunotherapy

N. Piton[1], L. Claude[1], F. Marguet[1], E. Colasse[1], A. Lamy[1], F. Guisier[1], M. Salaün[1], L. Thiberville[1], J. Sabourin[1]
[1] Rouen University Hospital, France

Background & Objectives: The tumour expression of PDL1 is an imperfect predictive biomarker of response to immunotherapy in lung cancer. *STK11* is frequently associated with *KRAS* mutation. Experimental data suggest that *STK11* impacts PDL1 expression, and that an impaired *STK11* is associated with lower PDL1 expression. To improve the selection of eligible patients for immunotherapy, we explored in further detail *STK11* as a predictive biomarker of PDL1 expression and the association between the *KRAS* status of *STK11* mutated tumours and PDL1 expression.
Methods: Lung adenocarcinomas harbouring a *STK11* mutation were consecutively included in the study group, while a control group lacking a *STK11* mutation was randomly selected using a 26-gene panel with high throughput sequencing. The effects of *STK11* mutations were predicted in silico. Tumours were immunostained for PDL1 using the E1L3N and SP263 clones. The percentage of PDL1 positive tumour cells was evaluated.
Results: Fifty-two *STK11* mutated tumours, including 28 with a *KRAS* mutation, were compared to 42 *STK11* wild-type tumours, including 17 with a *KRAS* mutation. Mean percentage of PDL1 positive tumour cells in the *STK11* mutated group was 9%, while 25% in the control group ($p = 0.044$). There was no statistically significant association between a *KRAS* mutation and the expression of PDL1 in the *STK11* mutated group. Five tumours expressing PDL1 harboured a *STK11* mutation described as pathogenic.

Conclusion: We confirmed that PDL1 expression is dramatically lowered in *STK11* mutated lung adenocarcinomas compared to *STK11* wild-type tumours. In addition, we did not observe any association between PDL1 expression and *KRAS* mutation. Despite the mechanism between *STK11* activity and PDL1 expression remains unclear, it seems that *STK11* is a good candidate biomarker to predict the response of immunotherapy.

PS-13-031

Microfluidic immunohistochemistry for rapid detection of diagnostic and predictive biomarkers on non-small cell lung carcinoma

M. Procopio[1], S. Brajkovic[2], A. Leblond[1], D. Dupouy[2], A. Soltermann[3]
[1] University Hospital of Zurich, Switzerland, [2] Lunaphore Technologies SA, Switzerland, [3] Institute of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland

Background & Objectives: Lung cancer is the most lethal tumour world-wide. Immunohistochemistry (IHC) is an essential tool in oncologic pathology. Considering the increasing cancer incidence, a concomitantly accurate and time-efficient IHC is clinically highly relevant.
The automated microfluidic staining device enables for a precisely controlled immune-reaction to take place in an extremely short incubation time; typically, a complete microfluidic IHC lasts less than 12 minutes on frozen tissue section.
We aimed to develop and validate a microfluidics IHC for fast and accurate biomarkers detection on formalin fixed paraffin-embedded (FFPE) non-small cell lung carcinomas (NSCLC) - the most common lung cancer type. Here, we focus on the first part of the study aiming at optimizing the microfluidic protocols.
Methods: Each protocol step - from antigen retrieval to counterstaining - was automatized and optimised on the microfluidic device for all biomarkers on representative FFPE NSCLC specimens to reach high-quality staining equivalent to a routinely used benchmark autostainer.
Results: The optimised microfluidic IHC protocol achieved an analytical performance comparable to standard staining on NSCLC for (i) differential diagnosis into adenocarcinoma (TTF1/CK7) or squamous cell carcinoma (p40/CK5-6) and (ii) prediction of immuno-therapy response (PD-L1). Concomitantly, the total process time was shortened to less than thirty minutes including the antigen retrieval pre-staining step, with a time reduction up to nine folds.
Conclusion: The microfluidic IHC resulted in fast automated high-quality staining for all assessed markers on NSCLC. Subsequent clinical validation on a large cohort will provide a diagnostic tool for biomarkers detection in a turnaround time far beyond the existing autostainers.

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PS-13-032

Immunisation with type V collagen promotes fibrotic interstitial pneumonia of human systemic sclerosis in C57BL/6 mice via IL-17 immune response

Z.A. Queiroz[1], A.P. Pereira Velosa[2], S. Catanozi[1,3], A. dos Santos Filho[2,4], S. de Moraes Fernezlian[1,5], E. Ministene Eher[1,5], I. Begalli Mendes[1,4], J.T. De Miranda[1], E.R. Parra[1,5], V.L. Capelozzi[1,5], W. Rosolia Teodoro[1,4]
[1] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [2] Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [3] Department of Endocrinology, Brazil, [4] Rheumatology Division, Brazil, [5] Department of Pathology, Brazil

Background & Objectives: The immunogenic type V collagen (Col V) and the proinflammatory interleukin (IL)-17 have been implicated in the pathogenesis of multiple autoimmune diseases. Because IL-17 and Col V are key contributors to Systemic Sclerosis (SSc) pathogenesis, in this report on SSc pathology, we have investigated IL-17 and Col V expression in a murine model Col V immunized–induced lung injury and human SSc.
Methods: Histology, immunofluorescence, histomorphometry and qRT-PCR in lungs of C57BL/6 mice (n=19) immunized with human Col V in Freund´s adjuvant was assessed and associated to surgical lung biopsy of patients with SSc (n=14) and controls (n=5).
Results: Lungs of Col V immunized animals showed a fibrotic interstitial pneumonia. RT-PCR on whole lung mRNA confirmed overexpression of genes which encoding chains of Col I [COL1A1, COL1A2] and Col V [COL5A1 and COL5A2] thus resulting in abnormal and increased deposition of the correspondent collagen fibers in tissue compared to controls [Col I, 25.90 ± 3.315 vs. 5.571±0.5929, p=0.0003) and Col V, 7.53±0.41vs18.53 ±1.05, p<0.0001)]. Patients lung biopsies showed a SSc histologic pattern and so demonstrated comparable abnormal and increased deposition of Col I (44.49±0.93 vs. 30.62±1.34; p=0.01) and Col V (40.62±0.70 vs. 16.06 ±1.39, p=0.002). Compared to normal lung, overexpression of IL-17 was detected in lung lesions of the murine model (20.86±3.21 vs. 0.56±0.20; p<0.0001) and patients lung biopsies (3.455±0.36 vs. 1.72±0.19, p=0.01).
Conclusion: Our findings highlight an overexpression of IL-17 and Col V in lung associated fibrotic injury, thus providing one possible link between autoimmunity and SSc.

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PS-13-033

Automating tumour proportion score computation for lung cancer immunohistochemistry images

H. Qureshi[1], P. O'Reilly[2], J.P. Maxwell[3], A. Kennedy[2], A. Serag[2], A. Ionmargineanu[2], J. Diamond[2], M. Saint Martin[2], R. McMillan[2], M. Salto-Tellez[4], P. Hamilton[2]
[1] Philips Digital & Computational Pathology, United Kingdom, [2] Philips Digital & Computational Pathology, United Kingdom, [3] Queens University, Belfast, United Kingdom, [4] Queen's University Belfast, United Kingdom

Background & Objectives: PD1-PD-L interaction (referred to as PD-L1) prevents the immune system from attacking tumour cells. Immunohistochemistry is used to detect PD-L1 as a guide for drug therapy. Detecting PD-L1 presence identifies patients that are likely to respond to anti-PD-1 therapy. In Non-Small Cell Lung Cancer (NSCLC) PD-L1 is assessed using the Tumour Proportion Score (TPS). TPS is computed as the ratio of the number of PD-L1 positive tumour cells to the total population of tumour cells.
Methods: We used a deep neural network (UNET) ensemble to distinguish between the PD-L1 positive and negative tumour cells from the non-tumour cells. UNETs are used to discriminate between complex tissue types in the presence of PD-L1 immuno-reactivity. We employed nuclei level as well as tissue structural level information to differentiate between cell types. The detected PD-L1 positive and negative tumour cells are counted and the TPS score is computed.
Results: The technique provides reliable predictions of cell types with heat maps showing the classification of different cells. TPS scores provided by expert are compared with the TPS computed using our technique. Highly accurate results are obtained with good concordance with expert scores i.e. ≥ 85% (also Pearson Correlation of 0.855).
Conclusion: We present a deep learning based technique for classification of cell types. Our technique offers a mechanism for screening of large numbers of cases thus relieving pressure on the pathologist and also offers an opportunity for double scoring.

PS-13-034

Sclerosing pneumocytoma: pulmonary tumour in the last ten years

F. Ramalhosa[1], M.B. Pimentão[1], M.J. Martins[1], L. Carvalho[2]

[1] Centro Hospitalar e Universitário de Coimbra, Portugal, [2] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal

Background & Objectives: Sclerosing Pneumocytoma-Sclerosing Hemangioma, type II pneumocytes origin, very rare benign lung tumour, accounting 3% - 5% of benign rare lung lesions, usually without clinical symptoms, incidentally found (Lovrenski A *et al*, 2019), has been diagnosed as 1/10 years - University Hospital of Coimbra. The last case reported in March 2019.
Methods: Fifty-years-old woman, out-patient for tobacco cessation, with morning cough related to smoking habits. Very well circumscribed lesion was detected by X-Ray and MRI, with both pulmonary bronchoscopy and bronchial aspirate negative for tumoural cells. Sample received for frozen diagnosis and postponed for ffpe. The patient was submitted to surgical resection afterwards.
Results: Left Lower Lobe surgical biopsy - 20g and 4,5x3,6x2cm – cut surface revealed a well-circumscribed red-whitish haemorrhagic lesion. After the whole section and paraffin embedding, the histopathology revealed two predominant histological patterns: sclerotic and solid architecture. However, papillary and haemorrhagic regions were also present. The tumour was composed by two cellular components: luminal cuboidal cells and round "basal" cells, without cytological/nuclear atypia. The bulk of the tumour consisted of either haemorrhagic spaces delineated by the two cellular components and sclerosing heterogeneous stroma. Stromal cells expressed vimentin and SMA and epithelial cells TTF1, CAM 5.2, CK7 and EMA; PR focally.
Conclusion: Surgical resection is the curative treatment that has been assuring the benign behaviour of the tumour. Although, the follow-up remains necessary due to lymph node metastasis possibility, as referred by Chien NC *et al.* (2009), who reported metastasis to the regional lymph nodes in an 18-years-old male.

PS-13-035

PCR-based analysis of MET exon 14 skipping mutations in Russian lung cancer patients

G. Raskin[1], M. Kholmatov[2], N. Mitiushkina[2], V. Tiurin[2], A. Romanko[2], E. Imyanitov[2]
[1] Academic A.M. Granov Scientific Center for Radiology and Surgical Technology, Russia, [2] N.N. Petrov Institute of Oncology, Russia

Background & Objectives: MET exon 14 skipping (exon 14Δ) mutations are associated with tumour sensitivity to a number of tyrosine kinase inhibitors, however clinical testing for MET gene status remains complicated.
Methods: 1415 EGFR mutation–negative lung carcinomas (LCs) were tested for MET exon 14Δ using newly developed allele-specific PCR cDNA-based method.
Results: MET exon 14Δ was identified in 35 LC cases, being associated with elderly age and non-smoking status. 34 (97%) out of 35 tumours carrying MET exon 14Δ showed preferential expression of the mutated allele coupled with absence of the wild-type transcript. Sanger sequencing revealed genomic MET mutation in 24/35 (68.6%) cases with the exon 14Δ allele detected by PCR. In contrast to published data, none of LCs with MET exon 14Δ allele carried mutation in PIK3CA gene.
Conclusion: MET exon 14 skipping occurs in 2.5% of EGFR-negative LCs. Several methodological issues should be taken into account in order to ensure the reliable diagnosis of MET exon 14 skipping.

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PS-13-036

Incorporating CTLA-4, CD274 and LAG3 single nucleotide polymorphisms (SNPs) to immune profile improves prediction of risk of brain metastases and death in a Brazilian cohort of advanced non-small cell lung carcinoma

J. Machado-Rugolo[1], A. Fabro[2], C. Aparecida Rainho[3], C. Farhat[4], V. Karen de Sá[4], A. Carolina Scintini Herbst[5], V. Cláudio Cordeiro de Lima[6], E. Parra[7], W. Rosolia Teodoro[8], V. Luiza Capelozzi[9]
[1] Clinicas Hospital, Faculty of Medicine, São Paulo State University, Botucatu, Brazil, [2] Department of Pathology and Legal Medicine, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil, [3] Department of Genetic, São Paulo State University, Botucatu, Brazil, [4] Department of Pathology, University of São Paulo Medical School, São Paulo, Brazil, [4] Department of Pathology, University of São Paulo Medical School, São Paulo, Brazil, [5] Department of Thoracic Surgery, A.C. Camargo Cancer Center, São Paulo, Brazil, [6] Medical Oncology Department and Translational Immune-Oncology Group, A. C. Camargo Cancer Center, São Paulo, Brazil, [7] Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Houston, USA, [8] Faculdade de Medicina, Universidade de Sao Paulo, Rheumatology Division, [9] Faculdade de Medicina, Universidade de Sao Paulo, Department of Pathology, Brazil

Background & Objectives: To investigate whether polymorphisms of immune checkpoints genes is associated with the tumour immune cell profile and risk of brain metastases and death in Brazilian patients with advanced stage NSCLC.
Methods: Seventy-five NSCLC patients were enrolled (37 adenocarcinomas, 25 squamous cell carcinomas and 13 large cell carcinomas). Using multiplex immunofluorescence and image analysis, we evaluated programmed death ligand 1 (PD-L1) expression in malignant cells (MCs), CD68+ macrophages, and cells expressing the immune markers CD3, CD8, CD57, CD45RO, FOXP3, PD-1, and CD20. We used high-throughput next-generation sequencing (NGS) to evaluate single nucleotide variants in immune checkpoints genes CD274 (PD-L1), CTLA-4, PDCDL1LG2 (PD-L2), LAG3 and B7H4 (VTCNI) in NSCLC by TruSeq Custom Amplicon Panel. A total of five single nucleotide polymorphisms (SNPs) were selected: rs2297136G/A (PD-L1), rs231775A/G (CTLA-4), rs7854303C/T (PD-L2), rs870849T/C (LAG3) and rs10754339G/A (B7H4).
Results: Brain metastases was observed in 10% of patients and 31% of them received adjuvant therapy. MCs-PD-L1+ expression was: <1% (40%), 1-10% (40%) and >10% (20%). Cells expressing the immune markers CD3+ (330/mm2), CD3CD8+ (110/mm2), CD3-PD1+ (85/mm2), CD68+ (58/mm2), CD68-PD-L1+ (2.5/mm2), CD3CD45RO+ (260/mm2), CD3CD45FOXP3+ (260/mm2) and CD20+ (46/ mm2). The frequency of genotypes was: CTLA-4 rs231775A/G (AA=40%; AG=25%; GG=10%), CD274 rs2297136G/A (AA=32%, GA=26, GG=17%), PDCDL1LG2 rs7854303C/T (CC=100%), LAG3 rs870849T/C (TC=32%, CC=31%, TT=12%) and VTCN1 rs10754339G/A (AA=57%, GA=13%, GG=5%). A significant association was found between PD-L1 and VTCN1 rs10754339 XX genotype (R=0.26; p=0.02) and PD-L1 rs2297136 GA genotype and MCs-PD-L1 (R=0.26; p=0.04). Cox Regression analysis, controlled for age, histologic types and adjuvant treatment, predicted low risk of brain metastases and death for patients in N1 stage (p=0.01), CTLA-4 rs231775 AG genotype (p=0.04), CD274 rs2297136 GA genotype (p=0.03), LAG3 rs870849 TC genotype (p=0.04), low density of MCs-PD-L1 (p=0.04) and high density of CD3+CD8+ lymphocytes (p=0.04).
Conclusion: Incorporating immune checkpoints genes polymorphisms ito immune profile score improves prediction of brain metastases and death in a Brazilian cohort of NSCLC and may be promise as combining target therapy.

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PS-13-037

Cicatricial lung fibrosis is not a variant of organising pneumonia

M. Samsonova[1], A. Cherniaev[1], K. Mikhajlichenko[1]
[1] Pulmonology Scientific Research Institute, Russia

Background & Objectives: Recently variant labelled "cicatricial" organizing pneumonia (CiOP) has been described by Yousem (2017) and Churg et al (2018), which characterised with a combination of ordinary organizing pneumonia (OP) and dense fibrous tissue. The aim of our research was to describe 5 cases of CiOP.
Methods: 5 patients (4 male, 1 female) with the age ranged 41-57 yrs with histologic pattern of CiOP were included.
Results: Patient complaints were cough, dyspnea (5/5), weakness (2/5). On CT scans of the chest, there were ground glass opacities with fibrosis and cavities (1/5), perilymphatic dissemination (2/5), a cavity with perifocal infiltration (1/5) or interlobular septal thickening with ossification (1/5). Histological examination revealed linear masses or nodules of dense fibrous tissue, some of them were ossified. Recognizable OP with prominent eosinophilic infiltration was found only in 1 case which looked like organizing eosinophilic pneumonia. In two cases with perilymphatic dissemination on CT, there were loose perivascular granulomas composed of histiocytes and lymphocytes. In two cases we saw atypical adenomatous hyperplasia and mucous hyperplasia of alveolar epithelium. And in one case dendriform ossification was more prominent than fibrous masses, in this case, there was progression on CT during the half of year.
Conclusion: In cases of CiOP we did not always see granulation plugs in the lumen of respiratory bronchioles and alveolar ducts. Ossification is the most common feature of CiOP. We propose that CiOP is a reparative reaction which could be the result of various lesions. Dendriform ossification previously described by many authors could be the variant or the end stage of CiOP.

PS-13-038

Exhaled breath condensate proteome profiling for lung cancer diagnostics by high resolution mass-spectrometry

V.Sergeeva[1], A. Yusupov[2], N. Zakharova[3], M. Indeykina[3], A. Bugrova[3], K. Fedorchenko[4], A. Ryabokon[4], M. Kushaeva[5], E. Anaev[5], V. Barmin[6], O. Pikin[6], A. Kononikhin[7]
[1] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia, [2] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Moscow Institute of Physics and Technology, Russia, [3] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia, [4] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Lomonosov Moscow State University, Russia, [5] Research Institute of Pulmonology, Federal Biomedical Agency of Russia, Pirogov Russian National Research Medical University, Russia, [6] Herzen Moscow Oncology Research Institute, Russia [7] V.L. Talrose Institute for Energy Problems of Chemical Physics, Russian Academy of Sciences, Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia

Background & Objectives: The main cause of high mortality from lung cancer is late diagnosis because early symptoms may be absent or non-specific (e.g. cough and shortness of breath). Timely diagnosis significantly increases the life expectancy of patients. Invasive methods of investigation of the lungs (bronchoscopy, aspiration ultrasonic transbronchial needle, etc.) can not be fully used for screening. Computed tomography is an encouraging, but rather expensive and resource-intensive method of diagnosis. Exhaled air and exhaled breath condensate (EBC) analysis become popular and relevant. The aim of the study is to developed and optimise methods for EBC sample collection for further proteome profiling by high resolution mass spectrometry. Comparative EBC proteome analysis is performed for patients from different groups (COPD, lung cancer, smokers and non smoking healthy individuals) to identify EBC proteins specific for lung cancer.
Methodes EBC was collected using RTube™ (Respiratory Research, Inc., Austin, TX, USA), ECoScreen® (Erich Jaeger GmbH, Hoechberg, Germany) and cooling trap from Lenz Laborglas Instrumente (Wertheim, Germany) placed to a thermos with a cooling agent. EBC samples were collected from patienta (12 - COPD, 16 - NSCLC) and 31 healthy volunteers (12-smokers/19-nonsmokers).
EBC sample (~1 mL) was transferred into polypropylene low temperature-resistanttest-tubes with a low protein-absorbing surface and lyophilized up to complete dryness and reconstituted in 0.05 M NH4HCO3 buffer (pH 8.0) to final protein concentration 1 mg/mL. Then EBC samples were hydrolysed with modified porcine trypsin (Promega, USA). All samples (injection volume 2 L) were analysed in triplicate on a nano-HPLC Agilent 1100 system (Agilent Technologies, Santa Clara, CA, USA) combined with a 7-T LTQ-FT Ultra mass spectrometer (Thermo Electron, Bremen, Germany) using a nanospray ion source (positive mode, high voltage +2.1 kV).
Results: Proteomic analysis of the EBC revealed more than 200 different proteins groups. Cytoskeletal keratins type II and type I were confirmed as an invariant part of EBC proteome for all the samples from patients (COPD and lung cancer). Also cytoskeletal keratins are the major protein components of the EBC for smokers, as well as for non smoking healthy individuals. It is shown that EBC proteome analysis was significantly deeper for samples collected with washing step from the tube walls. The optimised collection was performed with both commercial devices (RTube™, ECoScreen®) and laboratory built cooling trap. Comparative EBC proteome analysis was performed for patients from different groups (COPD, lung cancer, smokers and non smoking healthy individuals). The approach enable us to identify additional set of EBC proteins (POTE, NUCKS 1 and other) specific for lung cancer.
Conclusion: An optimised method for EBC sample collection for further proteome profiling by high resolution mass spectrometry was developed. It is shown that the results of the proteome analysis significantly differ for samples collected with and without washing step. Both protocols should be used for more deep EBC proteome profiling from patient. Comparative EBC proteome analysis with an optimised sample collection protocol enable us to reveal EBC proteins specific for lung cancer.

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PS-13-039

Specific morphological features of pulmonary adenocarcinoma in plutonium production workers

G. Sychugov[1], E. Kazachkov[1], T. Azizova[2], A. Sychugov[1]
[1] South Ural State Medical University, Russia, [2] Southern Urals Biophysics Institute, Russia

Background & Objectives: Epidemiological studies prove increased risks of lung cancer and chronic obstructive pulmonary disease in workers exposed to internal alpha-radiation. However various mechanistic, morphological and pathogenetic aspects of radiation-induced pulmonary diseases are still insufficiently investigated.
Examination of autopsy tissues from deceased workers internally exposed to alpha-particles revealed that 'hot particles' were distributed in the lungs inhomogeneously. The highest carcinogenic risk per 1 Gy of alpha-radiation was found for adenocarcinoma (AC) which is the most common histological type of lung cancer in plutonium production workers.
Previously it was demonstrated that ALK rearrangements, expression Ki-67 and oncogene c-Myc are predictive tumour markers.
Methods: We investigated morphological characteristics of pulmonary AC based on autopsy specimens collected from 22 Mayak PA workers (group 1) taking into account total lung absorbed dose from internal alpha-radiation and duration of radiation exposure. Group 2 included 15 AC cases found in individuals who had never been working at the Mayak PA.
The tissue sections were incubated with monoclonal antibodies against Ki67 proliferating cell nuclear antigen (clone MIB-1), ALK (clone D5F3, Ventana) and oncogenic antibody c–Myc (clone EP121).

Results: ALK gene rearrangement and c-Myc expression were negative in 100% cases of group 1.
Considerable decrease of proliferative cell activity in tumour specimens of group 1 compared to group 2 was found.
Conclusion: No significant associations with ALK and c-Myc biomarkers were observed for lung cancer.
The specific Ki-67 expression in AC cells suggest specific biological mechanisms involved in lung cancerogenesis following prolonged internal radiation exposure.

PS-13-041
Raman-fluorescent characteristics of bleomycin-induced pulmonary fibrosis
I. Chernov[1], E. Malysheva[2], S. Timofeev[2], V. Kukushkin[3], Y. Kirillov[1]
[1] Tyumen State Medical University, Russia, [2] City Hospital of Moscow #40, Russia, [3] Institute of Solid State Physics Russian Academy of Sciences, Russia

Background & Objectives: Raman spectroscopy is used to diagnose different diseases, including benign and malignant neoplasms. The method uses a laser beam which interacts with the tissue and scatters light, creating a fluorescent effect. This is then detected by a spectrometer and captured in graph form.
Methods: The study was performed on 30 male rats, under protocol, where they were injected intratracheally with a single dose of bleomycin 10 mg / kg body weight. The control group consisted of 10 rats which were injected the same way with the same quantity of saline. The lungs were examined through histology and spectroscopy, using a specific device, on days 7, 14, and 30 after the administration of bleomycin and saline.
Results: Day 7: the initial fluorescence (9.5 thousand units), the maximum (14 thousand units) and residual fluorescence, similar to the control group.
Day 14: the spectrum of initial fluorescence in the range of 20.0- 29.1 thousand units with a gradual increase in the values of fluorescence and a high level of its local maximum (32.5 thousand units)
Day 30: two local maxima of fluorescence (70.0 and 83.0 thousand units), high values of initial (49.2 thousand units) and residual fluorescence.
Conclusion: This study suggests that there is a correlation between changes in Raman fluorescent characteristics and pulmonary tissue remodelling in the course of an experiment, which is expressed in the progression of sclerosis.

PS-13-042
Malignant pleural mesothelioma with TRAF7 gene mutation
T. Tsujimura[1], A. Sato[1], M. Yuki[1], Y. Shinohara[1], J. Takeshita[2], H. Aburatani[2], Y. Sekido[3]
[1] Hyogo College of Medicine, Japan, [2] University of Tokyo, Japan, [3] Aichi Cancer Center Research Institute, Japan

Background & Objectives: It has been recently reported that the *tumour necrosis factor receptor-associated factor 7*, *TRAF7*, gene was frequently mutated in adenomatoid tumour and well differentiated papillary mesothelioma of the peritoneum, but no mutations were found in malignant mesothelioma of the peritoneum. Although the analysis of *TRAF7* gene mutation may be useful to differentiate these tumours of the peritoneum, the abnormality of the *TRAF7* gene has not been well investigated in malignant pleural mesothelioma, MPM.
Methods: The *TRAF7* gene in 61 cases of either clinical samples or established cell lines of MPM was analysed by next generation sequencing. The expression of TRAF7 and L1 cell adhesion molecule, L1CAM, which is a molecule in the NF-kB pathway activated by TRAF7 mutation was immunohistochemically examined.
Results: *TRAF7* gene mutations were found at the WD40 domain of the C-terminus in 2 of 61 (3.3%) MPM cases. Immunohistochemistry clearly showed loss of TRAF7 expression and high expression of L1CAM at least in 1 of 2 MPM cases with *TRAF7* gene mutation.
Conclusion: The abnormality of the *TRAF7* gene may be involved in the development of MPM, unlike malignant mesothelioma of the peritoneum. Immunohistochemistry of TRAF7 and L1CAM would be useful for detection of such MPM with *TRAF* gene mutation.

PS-13-043
Correlation of predominant type of lung adenocarcinoma with TNM stage of disease
L. Vučković[1], M. Miladinovic[1], F. Vukmirovic[1], M. Golubovic[1]
[1] Medical Faculty, University of Montenegro, Clinical Center of Montenegro

Background & Objectives: Tumour staging is essential to patient care, reasrch and control of the disease. The stage of disease at the time of diagnosis is a reflection of the rate of growth, extension of the neoplasm, type of tumour and the tumour-host relationship. Since the TNM staging system is one of the most important prognostic factor, we analysed whether there is a statistically significant difference in distribution of predominant histological type of lung adenocarcinoma (AD) compared to the TNM stage of disease.
Methods: We analysed 148 patients with invasive AD of the lung. We defined the predominant type using the IASLC / ATC / ERS criteria (solid, acinar, papillary, micropapillary, lepidic and enteric type). The stage of the disease was determined according to the eight edition of TNM classification.
Results: The most common types of AD were solid (35.1%), acinar (31.1%) and papillary (16.9%). The most of patients were in T2a stage of disease. Metastases in lymph nodes were found in 51 patients. Distant metastases were found in 16.2% of patients. Using Fisher's nonparametric test ($p = 0.009$) there was no statistically significant difference in the distribution of types of lung AD in relation to T and N status. Statistically significant difference in relation to M status was confirmed.
Conclusion: Determination of TNM stage of cancers is considered as the most important prognostic factor. According to our results there are no statistically significant differences in the distribution of prevalent types of lung AD in relation to T and N status, while metastases in distant organs most common are given by solid and acinar types.

PS-13-044
Expression of Carbonic Anhydrase IX as a novel biomarker for differentiating pleural mesothelioma from non-small cell lung carcinoma
B. Xu[1], T. Zou[1], Z. Liu[2]
[1] Roswell Park Cancer Center, USA, [2] State University of New York at Buffalo, USA

Background & Objectives: Malignant mesothelioma (MM) is an aggressive tumour with poor prognosis. Histological diagnosis of MM with limited tissue can be challenge, particularly for epithelioid type of MM. Immunohistochemical (IHC) stains with panel of antibodies are useful for confirmatory diagnosis of MM. Carbonic anhydrase IX (CAIX) is a transmembrane protein and is overexpressed in variety solid tumours. In our routine IHC work-outs for tumour of unknown origin, we discovered a robust cytoplasmic membrane expression of CAIX in pleural MM. In this study, we further investigate the sensitivity and specificity of CAIX expression in large scale by using tissue microarrays of mesothelioma and non-small cell lung carcinoma (NSCLC), respectively.
Methods: Unstained TMA slides composed of 56 cases of pleural MM (38 epithelioid type and 16 sarcomatoid type) and 79 cases of lung cancerNSCLC (including 42 lung adenocarcinoma, 37 lung squamous cell carcinoma) from year 1993-2013 were used for IHC stains performed on DAKO Omnis platform using pre-diluted mouse anti-human Ab

against CAIX (Bio-SB). CAIX IHC staining was graded semi-quantitatively by two independent surgical pathologists.
Results: All 38 cases of epithelioid MM (including epithelioid component of biphasic MM) are positive for CAIX, 89% (34/38) cases displayed diffuse and strong reactivity in tumour cells. Two sarcomatoid MM and most of sarcomatoid component in biphasic MM (5/16) were negative and remaining showed low to moderate expression level of CAIX. There is no distinction in terms of expression level and patterns between MM and benign mesothelial cells. Among NSCLC, 76% (32/42) adenocarcinomas and 57% (21/37) squamous cell carcinoma are completely negative, whereas the remaining cases show focal weak to moderate expression of CAIX.
Conclusion: Our study demonstrate that expression of CAIX has high sensitivity (100%) in detecting pleural EM, which is equal or better than that of current commonly used mesothelioma markers. The specificity of CAIX is at compatible ranges to that of common mesothelial markers for differentiating epithelioid MM from lung adenocarcinoma, but is much higher for differentiating lung squamous cell carcinoma. Therefore, we believe that CAIX can be an additional useful marker for immunohistochemical work ups of MM, particularly for epithelioid mesothelioma.

PS-13-045
Diagnostic value of TTF-1, CK5/6, CK7, CD56, Chromogranin A and Synaptophysin expression in differential diagnosis of small cell and non-small cell lung carcinomas in biopsies
L. Zakhartseva[1], O. Guz[1], G. Chytaieva[1], Y. Zakhartsev[2]
[1] National Medical Bohomolets University, Ukraine, [2] Kiev City Oncology Center, Ukraine

Background & Objectives: Nowadays lung carcinomas are most often verified on small biopsies that causes some difficulties in routine diagnostics. Immunohistochemistry (IHC) plays a key role, but IHC markers significance varies in different types of lung carcinomas. Purpose of the study is diagnostic value estimation of antibodies panel (Thyroid transcription factor-1 (TTF-1), Cytokeratin 5 (CK5/6), Cytokeratin 7 (CK7), Cluster of Differentiation (CD56), Chromogranin A, Synaptophysin) for accurate verification of different lung carcinomas.
Methods: Patients' mean age was 58.01±2.09, ranged from 30 to 79. Biopsy samples of 121 lung carcinomas have been studied: 56 (46.28%) adenocarcinomas, 36 (29.75%) squamous cell carcinomas, and 29 (23.97%) small cell carcinomas. In 76 (62.81%) cases there was an additional verification on aftersurgery samples. Standard IHC methods were applied: tumour's immunophenotype was defined in all samples using TTF-1, CK5/6, CK7, CD56, Chromogranin A, and Synaptophysin.
Results: 54 (96.43%) adenocarcinomas were CK7-positive, 50 (89.29%) were TTF-1-positive. 5 (17.24%) small cell lung carcinomas were TTF-1-positive, 9 (31.03%) tumours – CK7-positive, and 3 (10.34%) – CD56-positive. All squamous cell carcinomas were TTF-1-negative, most of them expressed CK5/6. Chromogranin A or Synaptophysin was expressed in 15 (51.72%) samples of small cell lung carcinoma, both neuroendocrine markers – in 12 (41.38%),
none – in 2 (6.89%) cases. Morphological and ICH features were identical in biopsy and aftersurgery samples in 96.69% observations.
Conclusion: Lung biopsy studies allow accurate diagnostics of different pulmonary carcinomas. IHC antibodies panel (TTF-1, CK 5/6, CK7, CD56, Chromogranin A, and Synaptophysin) is the most appropriate. The use of some individual markers may lead to diagnostic errors, since IHC expression in non-differentiated tumours may vary significantly.

Tuesday, 10 September 2019, 09:30 - 10:30, Agora 3
PS-14 | Cytopathology

PS-14-001
Performance assessment of Multiplex Ligation-dependent Probe Amplification (MLPA) in malignant pleural effusions (MPE)
L. Antonangelo[1,2,3], C. Silvèrio Faria[2,4], R. Oliveira da Rocha[5,4,6], A. Mendes Nascimento[7,4,6], G. Francisco da Silva Carvalho[5,4,6], A. Torchio Dias[5,4,6], L. Domenici Kulikowski[5,4,6]
[1] Hospital das Clinicas, Brazil, [2] Faculty of Medicine, University of São Paulo, SP/Brazil - Laboratorio de Investigacao Medica - LIM 03, Brazil, [3] Department of Patology, Brazil, [4] Department of Pathology, Brazil, [5] Hospital das Clinicas - Laboratorio de Investigacao Medica - LIM 03, Brazil, [6] Universidade de Sao Paulo, Brazil, [7] Hospital das Clínicas - Laboratorio de Investigacao Medica - LIM 03, Brazil

Background & Objectives: Malignant pleural effusion (MPE) is a common occurrence in medical practice, and its diagnosis is a challenge for clinical laboratories. It is known that most of metastatic tumours to pleura presents chromosomal gains and losses, which can be detected by cytogenomic techniques. The aim of this study was to evaluate the performance of Multiplex Ligation-dependent Probe Amplification (MLPA) to identify genomic abnormalities of tumour cells in pleural effusions (PE).
Methods: We evaluated a total of twenty-eight pleural effusion samples: 17 samples from patients with MPE and 11 samples with effusions of benign etiology. DNA was extracted using QIAMP DNA Blood kit (QIAGEN, Valencia, California) and cytogenomic investigation was performed using MLPA with P175-B1 Tumour Gain kit (MRC-Holland®, Amsterdam, The Netherlands), searching for pathogenic CNVs and *BRAF* specific point mutations. The results were analysed with GeneMarker® software (SoftGenetics, LLC, State Collage, PA).
Results: From the 17 cases of MPE, MLPA identified genomic changes in 5 cases: 2 cases with *BRAF* (7q34) p.V600E (c.1799T> A) point mutation; 1 case with *MYC* duplication (8q24); 1 case with *BRAF* p.V600E (c.1799T> A) point mutation and *MDM2* (12q15) duplication and 1 case with concomitant duplications in *CDK4* (12q14), *MDM2* (12q15) and *CCND1* (11q12). Control group presented normal results in MLPA investigation.
Conclusion: MLPA technique was efficient to detect several different genomic abnormalities in 5 MPE samples with at least 30% of tumour cells in the cytological results and provides a valuable tool to detect pathogenic variants especially in MPE cases.

Supported by FAPESP and LIM 03.

PS-14-002
Usefulness of type V collagen and α2β1-integrin in the cytological diagnosis of pleural liquid biopsy
L. Antonangelo[1,2,3], W. Rosolia Teodoro[4,5], C. Silvèrio Faria[2,6], Z.A. Queiroz[4], L. Ramos da Silveira[7,8], A.P. Velosa[7,8], V. Capelozzi[9]
[1] Hospital das Clinicas, Brazil, [2] Faculty of Medicine, University of São Paulo, SP/Brazil - Laboratorio de Investigacao Medica - LIM 03, Brazil, [3] Department of Patology, Brazil, [4] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [5] Rheumatology Division, Brazil, [6] Department of Pathology, Brazil, [7] Faculty of Medicine, University of São Paulo, SP/Brazil, Brazil, [8] Laboratorio de Investigacao Medica - LIM 17 - Rheumatology Division, Brazil, [9] Department of Pathology, Faculty of Medicine, University of São Paulo, Brazil

Background & Objectives: The identification of metastatic cells in serous effusions has prognostic and therapeutic implications, thus leading to permanent investigation to improve the usual diagnostic procedures, including immunofluorescence. Collagen type V (Col V) is a fibrillar collagen up-regulated in the stroma of different malignant tumours, which promotes cell migration and motility. The aim of the study was to evaluate the usefulness of Col V and its receptor α2β1-integrin, in detecting metastatic cells in samples of pleural effusion.

Methods: Malignant pleural effusion (MPE, n=12) and benign pleural effusion (n=4) were processed in a cytospin cytocentrifuge, fixed in 95% ethanol and stained for Papanicolaou. Diagnoses were established by clinical, cytological and histological evaluation. Immunofluorescence double staining and image analysis were employed to detect and quantify Col V and Integrin expression.
Results: From MPE, eight patients were men (median age, 50y) and 4 patients were women (media age, 45y). The cellular composition of MPE included nucleated total cells (mean, 1937/mm^3), neutrophils (mean, 65.54/ mm^3), macrophages (mean, 32.54/mm^3) and mesothelial cells (mean 1.90 / mm^3). Tumour cells from all MPE showed a strong red and green birefringence respectively from Col V and Integrin coinciding with an increased expression when compared to negative reactive mesothelium (mean 24.15 and 12.11 px, respectively). A similar expression of Col V and Integrin was found among tumours originated from breast (n=5), gastrointestinal tract (n=3), kidney (n=1) and lung cancer (n=3) (mean, 18.31 and 13.10; mean 26.54 and 11.78; mean 25.18 and 11.79 ± 0.14 and mean 24.14 and 12.11, respectively, p>0.05).
Conclusion: Collagen V and α2β1-integrin were useful in detecting single-tumour cells dispersed among inflammatory reaction and might be a promising biomarker for the identification of malignant cells in pleural liquid biopsy.

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PS-14-003
Urinary cytology suspicious for urothelial carcinoma (2015): re-evaluation, according to the Paris System for reporting urinary cytology (2016) and correlation with follow-up
D. Argyropoulou[1], C. Dahlstedt Ferreira[1], H. Oliveira Coelho[1], N. Ramos[2], M. Carvalho[2], M. Brito[1]
[1] Department of Pathology, Hospital Garcia de Orta, Portugal, [2] Department of Urology, Hospital Garcia de Orta, Portugal

Background & Objectives: Urinary cytology remains a pertinent, non-invasive method to patient care and monitoring. The introduction of a more precise terminology with the Paris System allows a standardised reporting way and a better correlation with clinical parameters. Our aim was to re-evaluate the urinary cytology specimens reported during 2015 in our Institution as "suspicious for urothelial carcinoma", according to The Paris System for Reporting Urinary Cytology and correlate those with patients' follow-up.
Methods: All (n=378) the 2015 urinary cytology slides of liquid based urinary cytology, reports and clinical follow-up data were retrieved from the files. 61 urinary cytology slides previously classified (2015), as "suspicious for urothelial carcinoma" were blindly reviewed by two different pathologists. A diagnosis was given based on the Paris System for Reporting Urinary Cytology and the results were analysed.
Results: The 61 urinary cytology specimens previously classified (2015) as "suspicious for urothelial carcinoma" were re-classified (Paris System,2016) as: High Grade Urothelial Carcinoma (HGUC-16), Atypical Urothelial Cells (AUC-5), Other malignancies (OM-1), Low Grade Urothelial Neoplasm (LGUN-21) and Negative for High Grade Urothelial Carcinoma (NHGUC-18).
When correlated with clinical follow up (cystoscopy + cytology/biopsy) the new re-classification (Paris System,2016) displayed a sensitivity of 87.2% for urothelial carcinoma and a specificity of 92% for HGUC.
Conclusion: In our series, the implementation of the Paris System for Reporting Urinary Cytology provided a more specific diagnosis in all specimens that had been previously classified just as "suspicious for urothelial carcinoma", with a sensitivity of 87.2% for urothelial malignant lesions and a specificity of 92% for HGUC.

PS-14-004
Rapid on-site evaluation by imprint cytology for liver core-needle biopsies, is it really needed?
A. Armutlu[1], O.C. Taskin[1], L. Oguzkurt[2], P. Firat[1]
[1] Koc University Hospital, Department of Pathology, Turkey, [2] Koc University Hospital, Department of Radiology, Turkey

Background & Objectives: Rapid on-site evaluation (ROSE) of core-needle biopsies by imprint cytology is used to increase diagnostic adequacy. This study aimed to document the efficacy of ROSE for liver core-needle biopsies.
Methods: Archieved records of our department between January 2017 and April 2019 were retrospectively reviewed. Clinicopathological features, patient demographics, number of passes and final diagnoses were retrieved from the pathology reports and hospital database.
Results: 119 cases with core-needle biopsies of liver were retrieved. Male/female ratio was 1.3/1, with a mean age of 61.8 (range 20-89) years. ROSE was performed in 72 cases. Mean number of passes was 3,8 for cases with ROSE (vs. 2,6 without ROSE).Final diagnoses were malignant in 64 [6 hepatocellular carcinoma (HCC), 58 other], benign in 6, and non-diagnostic in 2 cases (%2,7) with ROSE [vs. 44 malignant (2 HCC, 42 other), 2 benign and 1 non-diagnostic (%2,1) without ROSE].Two cases with ROSE were non-diagnostic due to abundant necrosis, whereas non-diagnostic case without ROSE represented sampling error. Two of three non-diagnostic cases were diagnosed as HCCs with repeat biopsies, one did not have histologic follow-up, but was clinically suspicious for recurrent HCC.
Conclusion: Advantage of ROSE for liver biopsies was not remarkable in this study, because no significant difference was observed in terms of diagnostic adequacy between both groups, except for one case with sampling error. All of the non-diagnostic cases were primary hepatocellular lesions, biopsied with or without ROSE. High number of passes may be explained with selection bias. Further studies with larger series and prospective design are needed to draw sharper conclusions.

PS-14-005
Evaluation of the selective study of BRAF V600E mutation in thyroid fine needle aspirative cytology
M. Bella-Cueto[1], C. Padilla[1], P. Serret[1], M.C. Ramos[1], R. Carrera[1], C.M. Blazquez[1], M.I. Agustín[1], M. Escoda[1], V. Perez[1], F.X. Guirao[1], I. Capel[1], M. Rigla[1], N. Combalia[1]
[1] Parc Taulí Hospital Universitari. Institute d'Investigació i Innovació Parc Taulí. Universitat Autònoma de Barcelona, Spain

Background & Objectives: *BRAF* p.V600E is a known mutation of thyroid papillary carcinoma (PTC), with variable frequency according to the subtype. In our centre, its determination has been incorporated to fine needle aspirative cytology (FNAC) by pyrosequencing (PSQ) in cases of Bethesda III category with cytological atypia and of Bethesda V category suspicious of PTC. Currently, immunohistochemical study is also available. Objective: To determine the feasibility, suitability and contribution to the diagnosis of *BRAF* p.V600E determination in these selected thyroid FNAC.
Methods: Retrospective review of the frequency and results of the *BRAF* p.V600E study by PSQ in thyroid FNAC performed in our centre, from January 2015 to August 2018, with diagnoses of Bethesda III with atypia or Bethesda V, and with histological correlation. Immunohistochemical study with VE1 antibody was performed in cases with surplus available material.
Results: 1092 thyroid FNAC were performed in 895 patients, 47 of which met the inclusion criteria. In 25 cases the study was discarded because the atypia observed was not suggestive of PTC or the material was follicular-patterned. Of the 22 remaining, only 16 had enough material, resulting in 6 mutated cases (37.5%), 4 of them with a confirmed PTC in the subsequent thyroidectomy, and the other 2 pending surgery. Positive results with VE1 were obtained in the 4 surgical specimens and in two FNAC cell blocks.

Conclusion: We estimate that the study of *BRAF* p.V600E mutation in selected thyroid FNAC (Bethesda III with atypia and Bethesda V) can improve the diagnostic accuracy in 6/16 cases (37.5%) of our series.

PS-14-006

Diagnostic value of the European Thyroid imaging reporting and data system in stratifying the malignancy risk of Bethesda category III nodules

I. Dimitrova[1], A. Shinkov[1], R. Kovatcheva[1], R. Ivanova[1]
[1] Department of Endocrinology, Medical University of Sofia, Bulgaria

Background & Objectives: Ultrasound-guided fine-needle aspiration (US-FNA) with cytology is the pivotal method for differentiating malignant from benign thyroid nodules. Nevertheless, Bethesda category III remains a clinical challenge. Ultrasound has an essential role in detecting malignant nodules and recently the most eminent thyroid societies published ultrasound malignancy risk stratification systems. We aimed to evaluate prospectively the diagnostic value of the Thyroid Imaging Reporting and Data System established by the European Thyroid Association (EU-TIRADS) in a series of Bethesda category III thyroid nodules.
Methods: For a period of one year 1000 nodules in 783 patients were prospectively evaluated according to EU-TIRADS and then submitted to US-FNA. Cytological reports were based on the Bethesda system and nodules classified in category III were included in this study. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy of EU-TIRADS were calculated compared to histology. We used the high risk category (EU-TIRADS 5) as a cut off for test positivity.
Results: Seventy one nodules were classified in Bethesda category III. The mean nodule diameter was 13.83±10.28 mm. Thirty three nodules underwent surgery and 12 (36.3%) were malignant. Eleven (91.7%) of the malignant nodules were classified in EU-TIRADS 5. Sensitivity, specificity, NPV, PPV and accuracy of EU-TIRADS were 91.66%, 42.8%, 90.0%, 47.8% and 60.6%, respectively. Between the four equally weighted ultrasound characteristics of EU-TIRADS microcalcifications had the highest sensitivity and specificity.
Conclusion: EU-TIRADS is reliable in the malignancy risk stratification of Bethesda category III nodules and can rule out malignancy with high certainty.

PS-14-007

Small volume biopsy in the diagnosis of myxoid liposarcoma

H. Domanski[1], J. Köster[1]
[1] Department of Genetics and Pathology, Division of Laboratory Medicine, Lund, Sweden

Background & Objectives: An increasing use of minimally invasive diagnostic procedures and the growing availability of diagnostic ancillary tests has resulted in better acceptance of small volume biopsies such as fine needle aspiration (FNA) and core needle biopsy (CNB) as the first-line approach in the diagnosis of soft tissue lesions. Myxoid liposarcoma accounts for 15% to 20% of liposarcomas. The most common site of involvement is in the deep soft tissue, preferably of the thigh. This neoplasm carries a specific cytogenetic abnormality which helps to render a correct diagnosis.
Methods: Seven patients were admitted to the Sarcoma Center in Lund underwent FNA and CNB of deeply seated soft tissue masses. Examination of routine stained FNA smears and histological sections was completed by fluorescence in situ hybridization (FISH) analysis on FNA specimen.
Results: Six tumours were located in the thigh and 1 in the lower leg. All of the examined small volume samples were correctly diagnosed as myxoid liposarcoma. Clusters and sheets of small, round to ovoid cells with scant cytoplasm embedded in the myxoid matrix and prominent branching capillary network were seen in all FNA smears and in all corresponding sections of CNB. FISH analysis disclosed rearrangement involving FUS gene in 5 cases, and was inconclusive/borderline in 2 cases.
Conclusion: This study illustrates that characteristic cytological and histologic features of myxoid liposarcoma together with specific cytogenetic abnormality allows definitive diagnosis in small volume biopsies. Compared to open biopsy, small volume biopsies are most cost-effective, outpatient procedures with negligible risks for serious complications.

PS-14-008

Breast hemangioma: malignant neoplasm simulator in breast cancer screening

J. Fraga[1], F. Ramalhosa[1], A. Lai[1], C. Faria[1], B. Pimentão[1], H. Moreira[1], R. Almeida[1], V. Almeida[1], C. Oliveira[1], G. Fernandes[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal

Background & Objectives: Hemangiomas are benign vascular tumours that arise from malformation of mature blood vessels, and are usually incidental findings. They are usually microscopic lesions, discovered in 1.3% of mastectomies for carcinoma and in 4.5% of biopsies for benign breast lesions and rarely manifest clinically as palpable lesions.
Methods: We present an 81-year old woman which screening mammography revealed a circumscribed lobulated nodule. Ultrasound located the lesion on the periphery of the right upper quadrant of the right breast, with 19x11mm, hypoechogenic and heterogeneous, with a slight increase in size from previous imaging study 2 years ago. Physical examination of her breast and axilla were normal. Given the suspicion of malignant lesion, cytological evaluation was performed.
Results: It was performed a Fine Needle Aspiration Cytology (FNAC) which smear revealed a sample with hematic background and rare cellular elements, raising the question of the lesion being of vascular nature given the imagiological correlation. After inclusion in paraffin of the product obtained by aspiration, a vascular neoplasia was observed, consisting of thin and branched vessels, coated endothelial cells with positivity to CD34 and CD31 and negativity to podoplanin.
Conclusion: Benign or malignant mesenchymal tumours of the breast are rare. Breast hemangiomas are rare, and usually appear as well-delimited round or oval nodules at mammography, as case presented. On ultrasonography, hemangiomas might present as solid, hypoechoic or cystic areas with small bright echoes due to calcification and fibrous septations. Given the clinical–pathological difficulty of diagnosing vascular lesions in the breast, extensive excisional biopsy is recommended.

PS-14-009

Retrospective analysis of pap smears in patients diagnosed with endometrial carcinoma: a 5-year study from an emergency university hospital in Romania

T.A. Georgescu[1], A.C. Lisievici[2], A. Dumitru[3], M. Sajin[4,5]
[1] Department of Pathology, Bucharest Emergency University Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [4] SUUB, Romania, [5] UMF Carol Davila, Romania

Background & Objectives: Babes-Papanicolaou test (often abbreviated Pap smear) has proven to bean efficient screening method for potentially precancerous and cancerous lesions of the uterine cervix. In the aftermath of its success, endometrial cancers are

showing a rising trend worldwide and several attempts have been made in order to establish a potential role of this analysis in the early diagnosis of endometrial carcinoma. However, detection of glandular lesions can be limited by issues related to both sampling and interpretation.
Methods: This is a 5-year retrospective study undertaken within the Pathology Department of the Emergency University Hospital in Bucharest Romania, in which we aim to rescreen the initial Pap smears of patients already diagnosed with endometrial carcinoma on biopsy or hysterectomy specimens, for the detection of normal, atypical or malignant glandular cells. Our goal was to correlate the presence of glandular cell abnormalities on conventional Pap smears with the histopathological type, grade, stage and clinical outcome of endometrial carcinoma.
Results: Among the total of 183 patients who underwent hysterectomy for endometrial carcinoma, 32.79% had a Pap result 1-3 months prior to surgery. Cervical cytology was reported as follows: 31.67% patients had atypical endometrial cells, 21.67% patients had atypical glandular cells and 46.66% patients had no glandular cells abnormalities. The presence of glandular cell abnormalities was more strongly associated with serous carcinoma (85.71%) than with endometrioid carcinoma (55.76%). Almost all patients with no glandular cell abnormalities (95.83%) had low-grade tumours.
Conclusion: Although not even remotely as sensitive for screening endometrial carcinoma, identification of atypical glandular cells on Pap smears warrants further investigations in order to rule out neoplasia. Our study revealed that higher-grade tumours (especially serous carcinomas) are strongly associated with atypical glandular cells, while lower-grade tumours either lack any glandular modifications or featureminor cellular changes with high inter-observer variability.

PS-14-010
Correlation between initial and consensus cytology review of "STAT" thyroid surgical pathology cases: a 5-year experience
N. Javakhishvili[1], B. Hunt[2], K. Arispe[2], A. Farooq[2], T. Giorgadze[2]
[1] David Tvildiani Medical University, Tbilisi, Georgia, [2] Medical College of Wisconsin, USA

Background & Objectives: In our academic Institution, clinically challenging thyroid lesions and lesions with indeterminate preoperative fine needle aspiration (FNA) diagnoses are triaged by overnight "STAT" processing with final diagnosis provided the next day. Completion thyroidectomy is performed the day after surgery if needed. We evaluated if the diagnostic accuracy of FNAs can be improved by consensus review.
Methods: Twenty-eight consecutive FNA specimens from this cohort of challenging cases (2011-2015) were blindly reviewed by 2 cytopathologists with consensus Bethesda category diagnosis obtained and compared to the original diagnosis. Both diagnoses were correlated with final surgical pathology findings. All discrepant cases were re-reviewed to determine the cause of discrepancy.
Results: Twenty-eight FNA specimens were obtained from twenty-six separate nodules of twenty-two patients. Initial diagnoses were discrepant in 7 cases (4 due to interpretation, 3 from sampling). Consensus diagnoses were also discrepant in 7 cases (3 due to interpretation, 4 from sampling). Discrepant cases included 2 cases of PTC, 6 cases of NIFTP and 1 case of follicular adenoma.
Conclusion: No difference in discordance rate between initial and consensus cytology and follow-up histology diagnoses were found in this cohort of challenging thyroid lesions. Discrepancies were all "undercalls" associated with scant cellularity, minimal microfollicular component or background lymphocytic thyroiditis. The cases of PTC did not show diagnostic cytologic features on review. Consensus review did not offer any significant benefit in this cohort of unique and challenging thyroid FNA specimens in our academic setting.

PS-14-011
Alveolar rhabdomyosarcoma in adults: cytological evaluation
K. Ikemura[1], S. El Hussein[2], L. Hakima[2], S. Khader[2]
[1] Montefiore Medical Center, USA, [2] Montefiore Medical Center/Albert Einstein College of Medicine, USA

Background & Objectives: Rhabdomyosarcoma (RMS) is an aggressive and extremely rare soft tissue malignant neoplasm in the adult population. Fine needle aspiration biopsy (FNA) is often performed to diagnose primary and metastatic tumours. Cytological evaluation of FNAs can be challenging due to overlapping morphologic features of various entities and limited biopsy material available. The objective of this study is to highlight the cytomorphologic features of RMS and raise awareness of the differential diagnostic difficulties.
Methods: A 28-year-old otherwise healthy female presented with a 2.0 x 1.5cm polypoid mass in the right nasal ala. FNA and follow-up surgical biopsy were performed. There was no imaging done prior to the FNA.
Results: The FNA smears showed dispersed and loosely cohesive aggregates of hyperchromatic cells with uniform round-oval nuclei, inconspicuous nucleoli, and scant cytoplasm. Marked crushing artifact and nuclear karyopyknosis were also noted. Immunohistochemical stains were positive for myogenin and MyoD1, while negative for AE1/3, CD45, S100, MelanA, HMB45, CD99, Synaptophysin and Chromogranin. FISH analysis showed a translocation in (1;13)(p36;q14) (*FOXO1A*), which established the diagnosis of alveolar RMS.
Conclusion: RMS is rare and often clinically misdiagnosed in the adult population. The cytomorphologic features of "small round blue cells" raise a wide differential diagnosis and the distinction between alveolar and embryonal RMS can also be challenging. It is essential for cytopathologists to be aware of the differential diagnosis and integrate morphologic, immunohistochemical, and cytogenetic analysis to accurately classify these tumours.

PS-14-012
Solid papillary neuroendocrine carcinoma of the breast - cytopathological features in 36 cases
T. Kawasaki[1,2], R. Katoh[3,4], T. Kondo[3], K. Horibe[2], H. Nagai[2], M. Takahashi[5]
[1] Saitama Medical University International Medical Center, Japan, [2] National Hospital Organization Nagoya Medical Center, Japan, [3] University of Yamanashi, Japan, [4] Ito Hospital, Japan, [5] Nagoya University, Japan

Background & Objectives: The purpose of this study was to clarify the cytological profiles of solid papillary/neuroendocrine mammary carcinoma *in situ* (SP/NE-CIS).
Methods: We cytopathologically analysed 26 fine needle aspiration (FNA) smears and 17 nipple discharge smears obtained from 36 Japanese patients with SP/NE-CIS.
Results: The background of the FNA smears was clear in 17 cases (65%), mucoid in five cases (19%), hemorrhagic in three cases (12%) and necrotic in one case (4%). Cellularity was high in 25 cases (96%) and low in one case (4%). Characteristically, SP/NE-CIS cells were loosely arranged in three-dimensional, solid clusters or singly dispersed. Well-developed vascular cores with or without cancer cells were occasionally recognized. Cancer cells were polygonal or spindle-shaped with a fine-granular, abundant cytoplasm. Nuclei with finely granular chromatin were round or ovoid and often eccentrically located (plasmacytoid appearance). Mitotic figures were infrequent. Nuclear grade was estimated to be low in 88% (23/26) of the samples. Most nipple discharge smears had fairly-low cellularity with poorly-preserved cell clusters in markedly hemorrhagic backgrounds, although two (12%) were extremely cellular with cytological characteristics similar

to those of the FNA smears. Preoperative cytological cancer diagnoses were made in 46% (12/26) of FNA smears and 0% (0/17) of nipple discharge smears. Immunohistochemistry for neuroendocrine markers (chromogranin A and synaptophysin) confirmed the neuroendocrine nature of this tumour in adequate cytological specimens as well as histological specimens.
Conclusion: SP/NE-CIS has distinctive cytopathological features and can, therefore, be diagnosed as a carcinoma with neuroendocrine features in most FNA and some nipple discharge smears by cytologic examination employing immunohistochemical techniques. We stress that a breast lesion with these features may be *in situ* and not invasive, and also that there is a risk of under-diagnosis.

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PS-14-013

Risk of malignancy in salivary gland lesions using the Milan system for reporting salivary gland cytopathology: a single Institution experience

S. Lajara[1], C. Castrodad[1], D. Guerrero[1], S. El Hussein[1], S. Khader[1], A. Colanta[1], L. Hakima[1]
[1] Montefiore Medical Center/Albert Einstein College of Medicine, USA

Background & Objectives: Fine needle aspiration (FNA) is a routine part of the initial evaluation of salivary gland lesions. Most published literature report high sensitivity, specificity and accuracy, but the results vary greatly, which is likely due to study design variations and lack of uniform reporting. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) aims to standardize reporting and serve as a guide for pathologists and clinicians.
This study investigated the utility of the MSRSGC by evaluating its ability to predict the risk of malignancy (ROM).
Methods: A total of 383 salivary gland FNA reports over a three-year period were reviewed and reclassified blindly according to the MSRSGC categories. The ROM was determined by comparing the corresponding surgical resections in 181 cases.
Results: The ROM for the corresponding categories were: 3.8% for Non-Diagnostic, 20% for Non-Neoplastic, 42.9% for Atypia of Undetermined Significance (AUS), 1.6% for Benign Neoplasm, 17.9% for Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP), 91% for Suspicious for Malignancy and 100% for Malignant. The sensitivity, specificity, positive and negative predictive values were: 91.7%, 98.5%, 97.1%, and 95.8%, respectively, similar to published data.
Conclusion: These ROMs are within the wide range of reported values in literature. The comparatively high ROM for AUS (42.9%) can be attributed to the cases of low-grade mucoepidermoid carcinomas and lymphomas, which provide diagnostic challenges on cytology. The low resection rates (26/102 for non-diagnostic and 10/62 for non-neoplastic) likely account for the relatively low and relatively high ROMs for non-diagnostic (3.8%) and non-neoplastic (20%) categories, respectively.

PS-14-014

Application of liquid base cytology to bronchopulmonary cytology

P. Lewitowicz[1], Y. Sleiman[2], A. Horecka-Lewitowicz[1]
[1] JKU University in Kielce, Poland, [2] St. Raphael Memorial Specialistic Hospital in Czerwona Gora, Poland

Background & Objectives: Conventional approach based on direct smear possesses many restrictions which could be dissolved by LBC. Another type of fixation with lysis of erythrocytes et mucus diluting provides a cell suspension as a top quality output to followed thin smears, immunocytochemistry or molecular assays. Noteworthy, all used agents have a full validation to immunocytochemistry and molecular analysis.
Purpose: We pointed to implement that method to pulmonary cytology and to assess its diagnostic efficiency and quality of immunocytochemistry.
Methods: All mucous rich or bloody specimens were Cyto Rich Red fixed and watery pleural effusions were Cytospin Collection Fluid fixed. After centrifuging a supernatant was removed and a sediment were rinsed again. LBC smears were performed with BD Thin Prep, then were stained H&E, Papanicolau, Giemsa and 2 unstained slides were stored in fridge. Immunohistochemistry was based on Benchmark XT Roche Diagnostics. We applied concurrent double immunostaining for CD4 and CD8 using two separate chromogens (DAB/Red) and other conventional antibodies.
Results: LBC approach provided clear, thin smear with steadily dispersed cell allowing easy counting of cell fraction. High quality smear helped in diagnosis of cancer cases in bronchial washings and also pleural effusion. Bronchial brushing specimen granted vortexing and sedimentation provided high quality material. We met CD4 positive reactivity in alveolar macrophages what hampered counting of CD4/CD8 ratio but that observation, especially small macrophages meaning, shed a new light on CD4 positive cells ratio in flow cytometry.
Conclusion: LBC method is a good solution improving quality of pulmonary cytology and providing a foundation for immunocytochemistry.

PS-14-015

PD-L1 IHC 22C3 pharmDx expression on cytology preparations from non-small cell lung carcinoma (NSCLC): precision and inter-observer analysis

J. Musser[1]
[1] Agilent Technologies, USA

Background & Objectives: Background: PD-L1 expression is required by a companion diagnostic test (PD-L1 IHC 22C3 pharmDx) for identification of Pembrolizumab-responsive NSCLC patients, currently approved for resected biopsy or core specimens. Cytology material may be the only specimen available in advanced NSCLC malignancies and is emerging as a useful specimen type for PD-L1 assessment.
Objective: Precision of PD-L1 IHC 22C3 pharmDx on formalin-fixed, paraffin-embedded (FFPE) cytology specimens, including fine-needle aspirates (FNA), bronchial wash (BW), and pleural fluid (PF).
Methods: A blinded and randomized Intra-site study was designed for testing variables on 48 cytology specimens, with 3 operators each operating a unique autostainer instrument immunostaining with PD-L1 IHC 22C3 pharmDx assay over 3 non-consecutive days.
Inter-observer precision was evaluated using the same assay on 103 cytology specimens and scored by multiple observers.
Tumour Proportion Score (TPS) was utilized for determining PD-L1 positive/negative agreement for ≥1% and ≥50% tumour thresholds.
Results: Positive, negative and overall agreements were determined by Bootstrap method. All bootstrapped 95% confidence interval lower bound values met an acceptance criterion of ≥85%. Overall agreement values for both studies, analysed for both diagnostic cut-offs, ranged from 93% to 97.7%.
Conclusion: FFPE cytology preparations from NSCLC can be successfully stained and scored for PD-L1 expression using PD-L1 IHC 22C3 pharmDx assay. There was very high overall agreement for both studies.

PS-14-017

Anal carcinoma screening strategy based on cytology, hrHPV biomarkers testing and conventional anoscopy

O. Ondic[1], J. Nemcova[2], K. Cerna[3], J. Smahelova[4], F. Rob[5]
[1] Medical Faculty Pilsen, Czech Republic, [2] Biomedical Center of the Faculty of Medicine in Pilsen, Czech Republic, [3] Sikl's Department of Pathology, Faculty Hospital in Pilsen, Czech Republic, [4] National

Reference Laboratory for Papillomaviruses and Polyomaviruses, Czech Republic, [5] 2nd Medical Faculty Charles University in Prague and Bulovka Hospital, Czech Republic

Background & Objectives: The anal carcinoma (AC) screening is warranted in high-risk populations, particularly in HIV positive men having sex with men (HIV-MSM). In the absence of high-resolution anoscopy, a cytologically-based approach is possible. Sensitivity and specificity of anal cytology are limited. Co-testing of high-risk human papillomaviruses (hrHPV) biomarkers could triage patients harbouring high-grade anal lesion (HGAIN) for further examination (conventional anoscopy) and treatment more precisely. We tested this combined screening approach in Czech HIV-MSM.
Methods: Anal LCB (liquid-based cytology) samples were collected from 172 HIV-MSM. Upon cytology reading, hrHPV transcription activity was studied together with HPV genotyping and DNA methylation of selected tumour suppressor genes (TSG) associated with HPV induced carcinogenesis. Some patients complied with recommended follow-up anoscopy.
Results: 93 samples rendered abnormal cytology (ASC-US, LSIL, ASC-H, and HSIL). Transcription activity of hrHPV was detected in 55 patients. HPV 16/18/45 was detected in 53 patients. Methylation silencing of TSG was present in 38 patients. ASC-H or HSIL cytology was found in 12 patients paired with hrHPV transcriptional activity in 10 with simultaneous DNA methylation of TSG in 4 patients. Anoscopy detected no visible lesion in any of 75 patients (including 9 with ASC-H or HSIL cytology).
Conclusion: 1. The results indicate an increased efficiency of AC screening based on cytology - hrHPV biomarkers co-testing. 2. No AC case was identified using conventional anoscopy. 3. Also, no precancerous lesion was found in any of the patients with ASC-H/HSIL cytology result. 4. In those patients digital anorectal examination is warranted.

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PS-14-018

Predictive value of dual stain P16/Ki67 for detection of high-grade cervical intraepithelial lesions

P. Mentzelopoulou[1], A. Magkana[1], M. Magkana[2], M. Sotiropoulou[3], K. Pappa[2], M. Papaefthimiou[1]
[1] Department of Cytology, Alexandra Hospital, Athens, Greece, [2] Department of Colposcopy of 1st Clinic of Gynaecology and Obstetrics of University of Athens, Greece, [3] Department of Histopathology, Alexandra Hospital, Athens, Greece

Background & Objectives: The purpose of this study is to estimate the predictive value of the combined P16/Ki67 dual staining (DS) in high grade squamous intraepithelial lesions.
Methods: We evaluated the performance of P16/Ki67 immunochemistry (Cintec Plus, dual stain) in 64 women with histological diagnoses of high-grade cervical intraepithelial lesions 2/3 (CIN 2/3) in colposcopy-directed biopsies or cone biopsy results. All women had a previous liquid-based cytology specimen (PreservCyt, ThinPrep Paptest). The cytological diagnoses included 10 cases of atypical squamous cells of undetermined significance (ASCUS), 28 cases of low-grade squamous intraepithelial lesion (LSIL) and 26 cases of high-grade squamous intraepithelial lesion (HSIL).
Results: Out of the 64 cases, 48 cases were P16/Ki67 positive (75%) and 16 cases were negative (25%). Out of those 48 cases, DS immunochemistry positive, 22 cases were diagnosed by HSIL cytological diagnoses (PPV 84.62%), 20 were diagnosed by LSIL cytology results (PPV 71.42%) and finally 6 cases had ASCUS cytology results (PPV 60%). The positivity of DS was more frequently expressing in HSIL lesions and decreasing in LSIL lesions.
Conclusion: The rates of the positive predictive value for the DS immunochemistry were directly associated by the severity of the cervical lesions. So, the P16/Ki67 dual stain could be an effective method to assist in the diagnosis of squamous intraepithelial lesions.

PS-14-019

Study of the morphology and reproducibility of brushed colorectal polyps utilising liquid-based cytology

D. Aninos[1], D. Pouloudi[2], N. Kavantzas[2], A.C. Lazaris[2], D. Tranoudakis[1], K. Christina[1], N. Asimaki[1], I. Panayiotides[3], G. Thomopoulou[1]
[1] Department of Diagnostic Cytopathology, General University Hospital of Athens "Attikon", School of Medicine, National and Kapodistrian University of Athens, Greece, [2] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [3] Second Department of Pathology, General University Hospital of Athens "Attikon", School of Medicine, National and Kapodistrian University of Athens, Greece

Background & Objectives: The purpose of this study was to assess the inter- and intraobserver agreement in cytological brushing from colorectal polyps, with the use of ThinPrep® technique, as well as to emphasize cytomorphologic criteria needed for the diagnosis and categorization of colonic adenomas.
Methods: A total of 193 brushing specimens from 118 patients with colorectal polyps were examined with corresponding histopathological diagnosis. ThinPrep slides were evaluated by two skilled cytopathologists. After establishment of the criteria, three additional cytopathologists without relative experience in liquid-based colorectal cytology, examined the same smears to determine interobserver variability. Each reviewer was asked to categorize each slide into the following categories: within normal limits/blunt cytology, adenoma with low grade intraepithelial neoplasia, adenoma with high grade intraepithelial neoplasia and adenocarcinoma. The intraobserver variability was also evaluated by all five observers.
Results: The overall interobserver agreement was nearly perfect with k value of 0.9350 during the checking round and again nearly perfect with k values ranged from 0.8469 to 0.9253 respectively to the other diagnostic rounds ($P<0.0001$). Adenoma with high grade intraepithelial neoplasia was the most difficult category to identify because of minimal deviation from adenocarcinoma. Regarding intraobserver agreement, it was nearly perfect with respective k values ranged from 0.8554 to 1.00 in all diagnostic rounds ($P<0.0001$).
Conclusion: The overall inter- and intraobserver agreement was nearly perfect for brush cytology of colorectal polyps using Thin Prep method. Liquid based cytology appears to be highly accurate and reliable cytological method for diagnostic approach of colorectal polyps and could be added as a complementary technique to biopsy for the improvement of the diagnosis.

PS-14-020

Parathyroid adenoma - fine-needle aspiration cytology correlation with surgical specimens

C. Quadros[1], M. Mendes-de-Almeida[1]
[1] CHULN - Hospital de Santa Maria, Portugal

Background & Objectives: Parathyroid adenoma (PA) is suspected when a single gland is enlarged and hyperfunctioning. The cytological aspects of the PA are very similar to the normal parathyroid tissue and may mimic other non-neoplastic lesions. We present a correlation study between cytologic aspects and the respective resection specimens regarding PA.
Methods: Retrospective data pertaining to the 2016-2018 period were evaluated for fine-needle aspiration cytology (FNAC) in parathyroid tissue and the corresponding specimen diagnosis.
Results: In total 12 samples were obtained pertaining to the referred period. Out of these, in 3 (25%) the diagnosis of parathyroid

tumour more suggestive of PA was made based on the cellularity, architectural patterns, nuclear morphology, immunocytochemistry and clinical data. The respective surgical resection specimens confirmed the diagnosis of PA having a concordance of 100%. In the remaining parathyroid samples, the diagnosis of parathyroid tissue was rendered and no surgery was performed.
Conclusion: Even though FNAC has its limitations in distinguish PA from other lesions, our results seem to show that it may have a role in pre-operatory assessment, avoiding unnecessary overtreatment.

PS-14-021
A follow-up study on thyroid aspirates reports as follicular lesion of undetermined significance (FLUS) in 2017: a retrospective study with histopathological correlation

F. Ramalhosa[1], A.C. Lai[2], R. Almeida[3,4], M.A. Cipriano[5], R.C. Oliveira[2], G. Fernandes[2], M.J. Martins[2]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal, [2] Centro Hospitalar e Universitário de Coimbra, Portugal, [3] Centro Hospitalar e Universitário de Coimbra - Pathology Department, Portugal, [4] Faculty of Medicine in Coimbra, Portugal, [5] Centro Hospitalar e Universitário de Coimbra - Pathology Department, Portugal

Background & Objectives: Thyroid fine-needle aspiration (FNA) is the fastest and minimally invasive technique to tailor patients for surgery. The thyroid nodules cytology is classified accordingly with The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), revised in 2017. Follicular lesion of undetermined significance (FLUS) is a heterogeneous category which includes cases for which the cytological findings are not convincingly benign, with an implied malignancy risk of 5–15%. The objective was to review cytology and histopathology reports, clinical and ultrasound data, for thyroid nodules reported as FLUS, in order to evaluate the malignancy rate and to assess factors associated with malignant outcome.
Methods: A retrospective study of 2.174 FLUS, at Centro Hospitalar e Universitário de Coimbra, was performed to compare with the second FNA cytology and to relate with histological and imaging findings (the type of carcinoma and nodule size), in order to estimate malignancy predictors.
Results: The overall incidence of FLUS in 2017 was 8.9% (191/2.174);19(20.9%) were referred to surgery and 134(70.15%) were followed-up by repeat FNA, in a period of 7-12months.
After the second FNA, a benign result was found in 84 patients (62.7%) and 50(37,3%) had category equal or higher than grade III [22.4% FLUS/III and 14,9% IV-VI]. Forty-nine patients underwent surgery (25.7%) and of these:15 cases (31.3%) had a malignant disease: 84,2% papillary thyroid carcinoma and 29(64.4%) had benign lesions.
Conclusion: The risk of malignancy in FLUS in our study is in accordance with the estimated by TBSRTC. Second FNA following a FLUS diagnosis is useful for better classification since the majority of FLUS are benign.

PS-14-022
Utility of the p16/Ki67 dual stain in equivocal Liquid Based Cervical Cytology (LBC) in everyday practice

H.E. Razafindrafara[1], E. Pacevicius[1], A. Mendibourg[1], S. Blaise[1], P. Le Van Quyen[1], G. Lang-Averous[1]
[1] University Hospital Strasbourg, France

Background & Objectives: The aim of this study was to evaluate the utility of p16/Ki67 dual staining (CINtec®PLUS) in equivocal cytology, to identify CIN 2+ in everyday practice.
Methods: This retrospective study included equivocal cervical (BD SurePath®) LBCs of 149 women with a mean age of 43,8 years that were dual stained for p16/Ki67 between 2015 and 2018. HSILs and WNLs served as controls. Results were correlated with HPV-HR test (CEPHEID®), histological and cytological follow-up data.
Results: Equivocal cytology concerned ASCUS (n=23), LSILs (n=11), ASC-H (n=31) and AGCs (n=9). HSILs (n=44) and WNLs (n=31) served as controls. Follow-up data was available for 145 patients: 63 histologies and 82 cervical smears. Sensitivity, specificity, PPV and NPV of p16/Ki 67+ for CIN2+ ASCUS was 66%, 85%, 40% and 100% for LSIL, it was 66%, 75%, not accessible, and 75%, for ASC-H it was 100%, 36,3%, 69,5% and 100%, and for HSILs it was 100%, 100%, 100% and 100%. Among AGCs one p16/Ki67 negative smear showed CIN2 on biopsy and 4 had WNL cytology. Among WNLs only one case was p 16/Ki67+ without follow-up data.
In smears of women over 40, the interpretation of hyperchromatic crowded cell groups due to atrophy is often challenging. High sensitivity and specificity of p16/Ki67 dual staining allows the detection of underlying CIN2+ even in equivocal and atrophic smears with ASCUS and ASC-H cytology.
Conclusion: Thanks to its good NPV p16/Ki67 dual staining represents an excellent triage tool in patients with atrophic smears.
Keywords: CINtec®OLUS, ASCUS, LSIL, ASC-H.

PS-14-023
P16/ki67 immunostaining in the triage of postmenopausal women with ASCUS and LSIL cytology Results:

A. Repse Fokter[1], S. Šramek Zatler[1], N. Irgel[1], L. Salobir[1], B. Antolovič[1], D. Podgoršek[1], A. Dovnik[2]
[1] Department of Pathology and Cytology, Celje General Hospital, Slovenia, [2] Department of Gynaecological Oncology and Oncology of the Breast, University Clinical Centre Maribor, Slovenia

Background & Objectives: Interpretation of postmenopausal smears and gynaecological treatment of these patients can often be difficult and time consuming. The objective of this study was to assess the performance of p16/Ki-67 dual-stained cytology as a triage of ASCUS and LSIL cytology results in postmenopausal women.
Methods: All consecutive ASCUS and LSIL smears in one-year period were collected and p16/Ki-67 immunostaining was performed retrospectively. The results were compared with histology results or long-term cytology follow-up in cases with no biopsy.
Results: Among 269 cases in the study there were 239 (88.5%) with ASCUS and 30 (11.5%) with LSIL diagnosis. Dual p16/Ki67 staining was positive in 18 (8%) and 6 (20%) of ASCUS and LSIL patients, respectively (chi-square=5.100; p=0.024). Out of 24 patients with positive p16/Ki67 staining, 14 (58.3%) had HSIL detected on subsequent follow-up. Out of 245 patients with negative p16/Ki67 staining, 235 (95.9%) had low grade/normal histology or normal follow-up (chi-square=101.074; p<0.001).
Conclusion: Dual p16/Ki67 staining is a useful additional method in postmenopausal patients with low grade cytology.

PS-14-024
Cyto-hystologic correlation in anal samples. Two years experience

J.M. Suárez Gómez[1], A. Lopez Janeiro[1], A. Rodriguez Garcia[1], E. Senda Gorta[1], M.J. Beato Merino[1], P. Lopez Ferrer[1] and B. Vicandi Plaza[1]
[1] Hospital Universitario La Paz, Spain

Background & Objectives: Anal Intraepithelial Neoplasia (AIN) is a precancerous condition that can be detected with cytology. We aimed to examine the correlation between cytological findings and biopsy diagnosis.
Methods: We selected cases from our center of patients undergoing anal cytology and posterior anal biopsy during the years 2016 and 2017. From 1503 anal cytologies consulted, 239 met inclusion criteria. We recorded cytological and biopsy diagnoses, Human Papilloma Virus (HPV) status, and gender. We determined prevalence of cytological and biopsy lesions, concordance between them, HPV infection prevalence, as well as sensitivity and specificity of anal cytology. Analysis was performed using R (3.5.2).

Results: We analysed 239 patients, 91% were male, 40% were infected by HPV 16, 10% were infected by HPV 18, and 88.5% were infected by other types. There were no differences between the prevalences of HPV infection among sexes. In our study, 13% of cytologies and 27% of biopsies were negative. High grade lesions represented 4% and 30% of all cytological and biopsy diagnoses respectively. Prevalence of concordance between cytological and biopsy diagnosis was poor (Weighted Kappa =0.19). Sensitivity and specificity of cytology in relation with biopsy lesion was 89.3% and 21.5% respectively.

Conclusion: Anal cytology is sensible for the detection of precancerous lesions, especially in high-grade lesions, and less specific in ASCUS and LSIL. Our results suggest that cytological and biopsy diagnostic categories are non-overlapping. In literature, when periodic sampling can be done, it increases sensibility. The high prevalence of HPV infection in our population limits its clinical utility as a risk stratifier.

PS-14-025

Squamous cell carcinoma metastasis in pleural and pericardial effusions

E. Sunnetcioglu[1], C. Aydin[2], O. Hurdogan[1], D. Yilmazbayhan[1], P. Firat[2], Y. Ozluk[1]

[1] Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Turkey, [2] Koc University Hospital, Department of Pathology, Turkey

Background & Objectives: Squamous cell carcinoma (SqCC) is rarely diagnosed in effusion cytology. In this study, we aimed to document effusion samples diagnosed as SqCC and evaluate the efficacy of p16 immunostaining for determination of the primary site.

Methods: We retrospectively reviewed archive records of two medical centers for pleural and pericardial effusions diagnosed as SqCC between 2009-2018. Clinicopathological features were retrieved from the pathology reports and hospital database. Eighteen cases with adequate cell blocks were included. We performed p16 immunohistochemical stain on cell blocks. Cutoff level for positivity was 90% diffuse, nuclear or nuclear and cytoplasmic staining.

Results: There were 16 pleural and 2 pericardial effusions. Male to female ratio was 3.5:1 with a mean age of 63.5 (range 38-85) years. The primary sites were lung (10), uterine cervix (2), head and neck (1), oesophagus (1), and larynx (1). Three cases were of unknown primary. Out of 13 cases with poorly differentiated morphology, 5 (1 lung, 1 uterine cervix, and 2 unknown origin) showed signet-ring like appearance. All cases showed positivity with at least one of the squamous cell markers (p63, p40). P16 positivity was observed in only 2 patients with a previous history of cervical cancer.

Conclusion: SqCC in effusion cytology poses diagnostic difficulties, especially due to variations in histomorphological appearance. Albeit low number of cases, our case series show that p16 immunostaining can be an efficient diagnostic marker for HPV-induced uterine cervical cancer metastases. Further studies in larger number of series are needed to confirm our finding.

Tuesday, 10 September 2019, 09:30 - 10:30, Agora 3
PS-15 | Ophthalmic Pathology

PS-15-001

Biodegradable collagen matrix as a subconjunctival and intrascleral implant: an animal model

T. Demura[1], N. Fisenko[2], E. Kogan[1]

[1] First Moscow State Medical University (Sechenov University), Russia, [2] Research Institute of Eye Diseases, Russia

Background & Objectives: To assess the biocompatibility and biodegradation of porous, bioengineered collagen matrices (hemostatic collagen sponge and iGen) in case of subconjunctival and intrascleral implantation.

Methods: 32 eyes of 16 adult rabbits underwent translimbal microdrainage. Group 1 included 16 eyes of 8 adult rabbits with hemostatic collagen sponge implanted subconjunctivally and intrasclerally. Group 2 included 16 eyes of 8 adult rabbits with iGen subconjunctival and intrascleral insertion. Rabbits were sacrificed on day 7, 30, 60, 90. Enucleated eyes were fixed in 10% formaldehyde and stained with methylene blue and fuchsine for general histological observation. Morphometric analysis of conjunctiva, sclera and matrix was performed.

Results: Hemostatic collagen sponge and iGen showed good biocompatibility as subconjunctival and intrascleral implants. The biodegradation rate of both materials was higher in scleral tunnel than under conjunctival flap. Hemostatic collagen sponge had resolved by 60 days, iGen - by 30 days. Strong negative correlation between angiogenesis and extracellular matrix fibrosis in both groups during the whole period was revealed. The decrease of conjunctival and scleral angiogenesis was noted on day 90 in group 1, on day 60 in group 2.

Conclusion: Hemostatic collagen sponge and iGen are biocompatible for conjunctiva and sclera. The longer period of angiogenesis in case of hemostatic collagen sponge implantation decreases the risk of subconjunctival and scleral scar formation following glaucoma surgery.

PS-15-002

The use of hemostatic collagen sponge as a matrix for tissue bioengineering: animal model of full-thickness bulbar conjunctivalesion

T. Demura[1], N. Fisenko[2], E. Kogan[1]

[1] First Moscow State Medical University (Sechenov University), Russia, [2] Research Institute of Eye Diseases, Russia

Background & Objectives: To study the healing processes of full-thickness wounds in the adult rabbit conjunctiva after grafting with hemostatic collagen sponge (a porous biodegradable matrix comprising collagen (98%), boric acid (1.25%) and furacilinum (0.75%).

Methods: A 6-mm trephine was used to create a full-thickness lesion of bulbar conjunctiva. Wounds were grafted with hemostatic collagen sponge (right eyes of 10 rabbits) or remained ungrafted (left eyes of 10 rabbits). Rabbits were sacrificed on day 7, 15, 21, 30. Enucleated eyes were fixed in 10% formaldehyde and stained with hematoxylin-eosin. The healing of conjunctiva was evaluated by immunohistochemistry and scanning electron microscopy. The expression of TGFβ, αSMA, VEGF in the wound was scored from 0.5 to 6.

Results: Biodegradation of hemostatic collagen sponge passed from periphery to the center of the wound. By 30 days collagen sponge had degraded and grafted wounds had closed with conjunctival stroma and stratified squamous epithelium. Moderate (4) expression of VEGF, αSMA expression and low (2) level of TGFβ reflected this process. By 30 days, ungrafted wounds had closed by contraction and formation of fibrous tissue covered with stratified squamous epithelium. VEGF, αSMA expression was equal to 0.5, TGFβ expression was moderate (4).

Conclusion: Hemostatic collagen sponge serves as a scaffold for cell migration and proliferation and can promote the formation of nearly normal conjunctiva in case of full-thickness wounds.

Tuesday, 10 September 2019, 09:30 - 10:30, Agora 3
PS-16 | Paediatric and Perinatal Pathology

PS-16-001

Expression of Sox2 and its regulation in the cells of residual respiratory epithelium in foetal pulmonary aplasia

A. Apostolou[1], M. Joubert[2], C. Piolat[1], B. Poreau[1], P. Jouk[1], C. Coutton[1], F. Arbez Gindre[3], E. Brambilla[1], H. Sartelet[1]
[1] CHU Grenoble, France, [2] CHU Nantes, France, [3] CHU Besançon, France

Background & Objectives: Pulmonary agenesis is defined by a total absence of bronchi, pulmonary parenchyma and pulmonary vessels. Normal embryonic lung development is the result of a complex reciprocal induction between the endoderm and mesoderm involving proteins and transcription factors, in particular SOX 2. The regulation of SOX 2 is essential for the morphogenesis of the bronchial tree. The main objective of this work is to study the expression of SOX 2 in the residual respiratory epithelium of pulmonary agenesis/aplasia.
Methods: Six cases of pulmonary agenesia/aplasia aged between 12 and 25 week of gestation and 6 controle cases age matched of normal foetal bronchi, trachea and oesophagus were studied. An immunohistochemical study was performed using primary antibodies against SOX2, BMP4, FGF9, FGF10, TTF1, Shh et Bcatenin.
Results: The residual epithelium presents a high expression of Sox 2 and an absence of expression of BMP4 while in control cases, there is an absence of expression Sox 2 and a expression of BMP4. The squamous epithelium of the oesophagus presents a high nuclear expression of Sox 2 and an absence of expression of BMP4. No differences between our control cases and our pathological cases concerning the expression of FGF 9, FGF10, SHH, TTF1 and βcatenin.
Conclusion: The presente study observed a continuous expression Sox 2 associated with an absence of BMP4 in epithelium of bronchi or trachea bud in agenesis and pulmonary aplasia at different gestational ages. Thus, BMP4 seems regulate tissue specific proliferation activity during lung development.

PS-16-002

Testicular juvenile granulosa cell tumour: a case report in a newborn

L. Barona García[1], B. Ferri Ñíguez[2], M.I. Oviedo Ramírez[1], A. Salazar Nicolas[1], M.I. Ortuño Moreno[1], A. Caballero Illanes[1], E. Martínez Barba[1]
[1] Servicio de Anatomía Patológica. Hospital Clínico Universitario Virgen de la Arrixaca., Spain, [2] Hospital Clínico Universitario Virgen de la Arrixaca, Spain

Background & Objectives: Neonate 10 days age with an enlarged descended right testis, smooth and firm to palpation. There was no other abnormalities on physical exam. Alpha-fetoprotein was slightly increased. Scrotal ultrasound revealed a multicystic mass with internal vascular flow that replaced the testicle. The patient underwent a right radical inguinal orchiectomy without complications.
Methods: Gross pathologic examination revealed a 2.2 × 1.5 × 1.0 centimeter gray–white ovoid mass with multiple cysts containing light yellow glistening fluid.
Results: Histologically there were variably shaped and sized follicles lined by bland- looking oval to round cells arranged in single and multiple layers, with basophilic fluid in the lumen. The stroma was fibrous with bland spindle cells positive for actine around the follicles. Tumour cells showed positive immunoreactivity for inhibin, WT1 and calretinin, while negative for panCK, alpha-fetoprotein (AFP), CD30, CD117, PLAP, D2-40 and OCT3/4. Diagnosis of Juvenile granulosa cell tumour (JGCT) was made.
Conclusion: Even though JGCT is the most common testicular tumour in infants < 6 months, there are few cases described in the literature. Its importance lies in the differential diagnosis with other neoplasm with worse prognostic, like yolk sac tumour or other sex cord-stromal tumours. The clinical context may be useful. However, certain cases may present histological findings that may pose a diagnsotic challenge.

PS-16-003

Liver mesenchymal hamartoma, a report of a case

A. Bdioui Thabet[1], C. Pierre[2], H. Busby[2], N. Mhammedi[2]
[1] Georges Pompidou Hospital Paris France, [2] Brabois Hospital, Nancy, France

Background & Objectives: Mesenchymal hamartoma of the liver is a benign tumour of infancy characterised by an admixture of epithelial structures in a loose connective tissue stroma with fluid accumulation suggestive of lymphangiomatous channels. The differential diagnosis includes other paediatric hepatic masses, in particularly hepatoblastoma.
Methods: A 9-month–old female infant, with history of incidentally discovering of intra-abdominal large anechoic cyst, during antenatal ultrasound. Postnatal examination of the baby revealed a palpable cystic mass in the right hypochondrium. No other congenital abnormalities were noted. A computed tomographic scan similarly showed a large complex multiloculated cystic. Laparotomy was performed at 2 months. The lésion was removed with a clear margin.
Results: In gross, the lesion measure 12 cm, having numerous cysts, each approximately 4 to 7 cm in size, containing clear fluid.
The histopathology showed solid areas mixed with multiloculated cysts. The solid areas consist of loose myxoid stroma containing dilated ducts lined by cuboidal epithelium. The cysts are surrounded by a layer of loose mesenchyme without an identifiable epithelial lining and appear to be bounded by the mesenchyme itself. The child is well on follow-up with a normal appearing liver.
Conclusion: Hepatic mesenchymal hamartoma is a benign tumour that is typically diagnosed in childhood; its etiology has not been completely elucidated. Complications of an enlarging hepatic mesenchymal hamartoma stem from compression of adjacent vital organs and structures. Prognosis is excellent with complete resection.

PS-16-006

Gorham-Stout disease: a French series

S. Boudjemaa[1], J. Donadieu[2], S. Fraitag[3], E. Angot[4], H. Sartelet[5], S. Valamary-Degano[6], I. Pommepuy[7], G. Leverger[2], S. Heritier[2]
[1] Sorbonne Université- APHP6, Hôpital Armand Trousseau, Service d'Anatomie et Cytologie Pathologiques, Paris, France, [2] Hôpital Armand Trousseau, France, [3] Enfants Malades Necker Hospital, France, [4] CHU de Rouen, France, [5] CHU de Grenoble, France, [6] CHU de Besançon, France, [7] CHU de Limoges, France

Background & Objectives: Gorham Stout disease (GSD) is a rare idiopathic disorder with about 200 reported cases in children and adults. GSD is characterised by spontaneous and progressive osteolysis of one or more skeletal bones, related to proliferation of thin-walled vascular channels. Typical radiographic finding is represented by intramedullary and subcortical radiolucency, hence the name of "phantom bone" or "vanishing bone disease".
Methods: We retrospectively reviewed 13 GDS cases collected over a 28-year period (1990-2018).
Results: There is a male predominance (10 males and 3 females, sex ratio 3,3). Patient age varied from 1 month to 18 years (median age 7.9 years). As reported in the literature, maxillofacial involvement represented about 30% in our series (5/13). Other locations included: 2 vertebral, 2 costal, 2 multifocal, 1 peritoneal and 1 unknown. Clinical manifestations were variable, but the more frequently reported were bone pain and local swelling.
Histological diagnosis was usually challenging, showing nonspecific vascular proliferation intermixed with fibrous connective tissue and

sometimes inflammatory component in bones or adjacent soft tissues. In some cases, fibrous tissue completely replaced resorbed bone, without vascular proliferation. On immunohistochemistry, D2-40 was usually expressed with variable expression of vascular markers.
Pathogenesis of GSD is still unknown and up to now, no somatic mutation that could drive this vascular abnormality has been highlighted.
The best therapeutic management is undefined and patients frequently received bisphosphonate therapy, and/or sirolimus or interferon alpha therapy.
Conclusion: Multidisciplinary discussion based on clinical, radiological and histological criteria is key in establishing this usually challenging diagnosis.

PS-16-008

Foetal mediastinal teratoma: misinterpretation as congenital cystic lesions of the lung on prenatal diagnosis

S. Darouich[1], N. Taamallah[2], H. Bellamine[3]
[1] Unitè de Pathologie Foetale et Placentaire, CHU Habib Bougatfa, Universitè de Tunis El Manar, Facultè de Mèdecine de Tunis, LR99ES10 Laboratoire de Gènètique Humaine, Tunis, Tunisia, [2] Clinique Raouabi, Tunisia, [3] Service d'Anatomie et Cytologie Pathologiques, Hôpital Menzel Bourguiba, Tunisia

Background & Objectives: Teratomas are among the most common congenital tumours and frequently reported to be associated with foetal hydrops. The thoracic teratomas are commonly misinterpreted on prenatal ultrasound, being confused with congenital adenomatoid malformation of the lungs, diaphragmatic hernia or bronchopulmonary sequestration. The aim of this case report is to document this challenge.
Methods: In the present case, we correlated prenatal diagnosis with autopsy findings of mediastinal teratoma complicated by severe hydrops foetalis.
Results: The ultrasound revealed severe hydrops foetalis, placentomegaly and multiple pulmonary cysts that were suggestive of cystic adenomatoid malformation of lung. Autopsy of the 24-weeks gestation stillborn male foetus showed a 54.3g, 6.1 x 4.4 x 2.8-cm, large and well encapsulated polycystic mediastinal teratoma with thymic, cardiac and pulmonary hypoplasia, and moderate post-hemorrhagic hydrocephalus. Histological study confirmed that the tumeral mass was consistent with immature teratoma and revealed placental diffuse chorangiomatosis and chorangiosis.
Conclusion: This case emphasizes that congenital mediastinal teratoma should be considered in the differential diagnosis of non-immune hydrops, particularly if a thoracic cystic lesion is detected on ultrasonography.

PS-16-009

Candida glabrata chorioamniotitis: a cause of premature rupture of membranes and foetal loss without identifiable risk factors

S. Darouich[1], H. Bellamine[2]
[1] Unitè de Pathologie Foetale et Placentaire, CHU Habib Bougatfa, Universitè de Tunis El Manar, Facultè de Mèdecine de Tunis, LR99ES10 Laboratoire de Gènètique Humaine, Tunis, Tunisia, [2] Service d'Anatomie et Cytologie Pathologiques, Hôpital Menzel Bourguiba, Tunisia

Background & Objectives: Chorioamnionitis is a major cause of premature rupture of membranes and foetal loss. It commonly results from an ascending bacterial or fungal infection. Candida glabrata is the second most common commensal yeast of the vagina, the pathogenicity of which is limited in healthy hosts. It is reported to be associated with chorioamnionitis in pregnancies with history of in vitro fertilization or cervical cerclage. We aim to show that Candida glabrata chorioamnionitis may occur in pregnancy without any identifiable risk factor.
Methods: We report a well-documented case of Candida glabrata chorioamnionitis that occurred in second trimester pregnancy and resulted in foetal loss.
Results: A 24-year-old woman, gravida 2, para 0, with a history of premature rupture of membranes in the second trimester due to a probable fungal infection, was referred to our Institution because of the recurrence of premature rupture of membranes. She delivered a non-macerated female foetus at 17 weeks gestation. At autopsy, examination of the stillborn revealed normal growth and didn't demonstrate any malformation. The placenta weighed 84g (normal ranges: 120-135g) and histological examination of the foetal membranes showed a severe polymorphic inflammatory infiltrate and large fungal colonies of yeast-like microorganisms which stained positively with periodic acid-Schiff. The histological features in conjunction with the positive vaginal cultures enabled to identify Candida glabrata as the etiologic agent of the severe chorioamnionitis.
Conclusion: Although Candida glabrata has been considered saprophyte of the normal vaginal flora and only pathogenic in pregnancies with history of vitro fertilization or cervical cerclage, it can cause chorioamniotits in healthy woman with no clear risk factors.

PS-16-010

Hepatic phenotypes of HNF1B mutations: a foetal case of renal cysts and diabetes syndrome and literature review

S. Darouich[1], H. Bellamine[2]
[1] Unitè de Pathologie Foetale et Placentaire, CHU Habib Bougatfa, Universitè de Tunis El Manar, Facultè de Mèdecine de Tunis, LR99ES10 Laboratoire de Gènètique Humaine, Tunis, Tunisia, [2] Service d'Anatomie et Cytologie Pathologiques, Hôpital Menzel Bourguiba, Tunisia

Background & Objectives: Hepatocyte nuclear factor 1-β (HNF1B) defects cause renal cysts and diabetes syndrome (RCAD syndrome), but little is known on liver pathology in patients. We aim to illustrate the most severe hepatic phenotype of *HNF1B* mutation in a fetus presenting with RCAD syndrome with review of the literature.
Methods: We described the autopsy findings in a female foetus presenting with RCAD syndrome with a special focus on the liver abnormalities.
Results: Pregnancy was terminated in a 28-year-old woman because of plymalformative syndrome at 20 weeks gestation. Macroscopic examination showed foetal hypotrophy, facial dysmorphism, hypoplastic Perineum, lower limb amyotrophy, major pancreatic hypoplasia, bilateral nephromegaly with moderate pelvicalyceal dilation, hepatomegaly with multiple large subcapsular cysts, short gut, heart-shaped uterus and severe enlargement of lateral ventricles. Histological examination demonstrated bilateral renal medullary cysts and hepatic periportal fibrosis, and confirmed the presence of multiple subcapsular liver cysts that appeared to be lined by a cuboidal or squamous epithelium. A review of the previously published foetal and paediatric cases with well-documented liver histology allowed distinguishing various hepatic lesions associated with HNF1β defect including paucity or proliferation of the bile ducts, severe biliary stasis, mild to severe periportal fibrosis and extramedullary hematopoiesis. Subcapsular hepatic cysts were not previously reported.
Conclusion: Our study demonstrates that the histological liver lesions associated with *HNF1B* mutations are of variable severity. The documented foetal case is the most severe hepatic phenotype. There is, however, no clear genotype-phenotype correlation.

PS-16-011

Hydrops foetalis associated with Wolf-Hirschhorn syndrome and large foam cells on bone marrow: a fortuitous association with lysosomal storage disorder

S. Darouich[1], I. Lariani[2], M. Kharrat[2]
[1] Unitè de Pathologie Foetale et Placentaire, CHU Habib Bougatfa, Universitè de Tunis El Manar, Facultè de Mèdecine de Tunis,

LR99ES10 Laboratoire de Gènètique Humaine, Tunis, Tunisia, [2] Universitè de Tunis El Manar, Facultè de Mèdecine de Tunis, LR99ES10 Laboratoire de Gènètique Humaine, Tunis, Tunisia

Background & Objectives: Hydrops foetalis has a wide range of possible etiologies, providing a diagnostic challenge for the physician. It may be a presentation of the lysosomal storage disorders including mucopolysaccharidosis VII and IVA, type 2 Gaucher disease and infantile sialic acid storage disease. Thus, all cases of unexplained hydrops foetalis should be investigated for these disorders by histological and biochemical or molecular methods in order to provide the family with an appropriate genetic counselling. We document a challenging case of non-immune hydrops foetalis associated with 4p deletion
Methods: We described pertinent autopsy findings that were consistent with a lysosomal storage disorder in a hydropic fetus and discussed the available genetic test results.
Results: Prenatal ultrasound detected hydrops foetalis in a 38-year-old woman at 17 weeks gestation. Amniocentesis was performed. The pregnancy was terminated and subsequent autopsy was performed. The male fetus weighed 77.35 g with a crown to heel length of 16 cm and foot length of 1.6 cm, which were consistent with a gestational age of 15-16 weeks. He presented with ankyloglossia, hypospadias, club feet, subcutaneous edema, ascites and pericardial and pleural effusions. The liver weight was in normal range. There were no heart defects. The lengths of the long bones were consistent with 13-14 weeks gestation. The placenta was not received. On histological examination, multiple and large storage cells, involving the chondrocytes and osteoclasts, were found in bone marrow. The cells were filled with abundant closely packed small vacuoles which were weakly stained positive for PAS. In the other foetal tissues, similar vacuolized cells could not be identified. Karyotype showed partial deletion of the short arm of chromosome 4 with chromosomal formula 46 XY,del(4)(p14;pter). Mucopolysaccharidosis type IVA was suspected. The NGS-based sequencing and copy number variation analysis did not detect any mutation or deletion/duplication of the GALNS and GLB1 genes. Whole exome sequencing was considered.
Conclusion: Diagnosis of hydrops foetalis that cannot be explained by a chromosomal aberration should encourage the pathologist to search for storage cells in the foetal tissues, especially the bone marrow. Further biochemical and genetic investigations, that have impact on genetic counselling and prenatal diagnosis, may then be considered.

PS-16-012

Congenital eventration of the diaphragm due to early-onset muscular dystrophy: an unusual cause of neonatal respiratory distress

S. Darouich[1], H. Bellamine[2]
[1] Unitè de Pathologie Foetale et Placentaire, CHU Habib Bougatfa, Universitè de Tunis El Manar, Facultè de Mèdecine de Tunis, LR99ES10 Laboratoire de Gènètique Humaine, Tunis, Tunisia, [2] Service d'Anatomie et Cytologie Pathologiques, Hôpital Menzel Bourguiba, Tunisia

Background & Objectives: Congenital diaphragm eventration is a developmental abnormality characterised by hypoplasia of the diaphragm due to severe early-onset muscular dystrophy. It may result in lung hypoplasia and neonatal respiratory distress. We aim to illustrate such a case.
Methods: We described the autopsy findings of a female newborn dying from respiratory failure due to congenital muscular dystrophy related diaphragm eventration.
Results: This female infant was born to a 26-year-old G3P2 woman. Pregnancy was complicated by polyhydramnios. Premature rupture of membranes occurred at 35 weeks gestation with subsequent vaginal delivery of a 1931.55g girl with body length of 44cm and head circumference of 32cm. The newborn was hypotonic and made no spontaneous breathing movements. She died after 15 min of resuscitative efforts. On physical examination, she had club feet. Gross autopsy examination showed a very thin diaphragm which was strikingly elevated into the thoracic cavity. The intercostal muscles were also markedly thinner than normal. The lungs were severely hypoplastic with a combined weight of only 12.35g (expected for dates 26.8, lung weight/body weight ratio 0.006). The Neuropathological examination was normal. Microscopically, the skeletal muscle showed dystrophic rearrangements including small muscle fibers with centrally placed nuclei resembling foetal myotubes, large areas of muscle degeneration and abundant endomysium. The severe alterations in the dystrophic skeletal muscles without involvement of the central nervous system were suggestive of mutation in *LAMA2*-gene. Molecular analysis was considered.
Conclusion: This case report emphasizes that diaphragm eventration can be the manifestation of an underlying muscular or neuromuscular disorder. Therefore, examination of the central nervous system and muscle tissues is necessary in any neonatal death due to unexplained respiratory distress.

PS-16-013

Cystic teratoma of the face - report of a rare case

S. Foreid[1], J.M. Dias[1]
[1] Synlab Pathology Porto, Portugal

Background & Objectives: Teratomas are among the most common germ cell tumours in children. These are true neoplasm's composed of tissues derived from the three blastodermic layers (ectoderm, mesoderm and endoderm), that are capable of independent growth in tissues foreign to the body part in which they arise.
The most frequent locations are the sacrococcygeal region and gonads. Extragonadal sites are less frequent. Presentation in the neck and head area is exceptionally rare, representing 2-5% of all cases (2). Here we present a case of a facial teratoma in a 4 year old children.
Methods: This case is about a 4 year old children with a cystic mass in the face. By image exams, a diagnosis of lymphangioma was made. Surgery was not recommended, instead, the aspiration of the cystic contents for management. After the first aspiration, the cyst grew back in a couple months. Because at this time there was facial disfigurement and a concern that the facial nerve could be affected, surgery was done.
Results: The gross specimen measured 5x4, 5 x 3,5cm. The cut section revealed a biloculated cyst, with a macroscopic appearance resembling an intestinal bowel loop.
Microscopic examination revealed that the cyst wall was composed of structures similar to the ones found in the intestinal wall.
Immunostains with CDX-2, CD10, Chromogranin, synaptophysin, cytokeratinAE1/AE3, smooth muscle actin, desmin, protein S100 and calretinin stained the same structures expected in a normal intestinal wall.
Conclusion: Because of its rare location, teratomas of the face are often misdiagnosed as lymphangiomas and cystic hygromas, when they are predominantly cystic. Definitive diagnosis usually cannot be confirmed until the histopathologic analysis of the specimen. Needle aspiration may provide temporary relief, but does not represent a definitive measure given the propensity for recurrence, and surgery should be considered.
In our case, we document the presence of mature tissue derived from all three germ layers allowing us to make the diagnosis of teratoma.
Unlike adults, most teratomas presenting in early childhood are congenital and benign, rarely turning malignant. The histopathological examination in our case had shown only mature tissue components, with no evidence of immature tissue or malignant transformation, compatible with a benign nature.

PS-16-014

Foetal autopsy unveiling the death: a rare congenital central nervous system neoplasia

J. Fraga[1], A. Lai[1], C. Cerdeira[1], M. Silva[2], A. Alarcão[2], O. Rebelo[1], R. Pina[1], L. Carvalho[1,2]

[1] Centro Hospitalar e Universitário de Coimbra, Portugal, [2] Faculdade de Medicina da Universidade de Coimbra, Portugal

Background & Objectives: Glioma is the leading Central Nervous System (CNS) tumour in children. Low-grade gliomas are the leading paediatric CNS tumours overall and responsible for 1/3 of cases. Higher grade gliomas occur less often (7–11 %) of cases of CNS malignancy beyond infancy.
Methods: We present a medical pregnancy termination at 37 weeks of gestational age, of a female foetus, due to cerebral hemorrhage and hydrocephalus (normal anterior echography).
Results: Autopsy revealed asymmetric brain with 345g. In section, there was a left, paramedian nodular formation with 4.3x3.8cm, with extensive hemorrhage appearance, friable, located in the frontal lobe with extension to the corpus callosum, leading to deviation of the midline structures. It corresponded to a glial neoplasia with hemorrhagic necrosis, with hypercellular areas consisting of cells of clear, ill-defined cytoplasm, nuclear atypia and rare mitosis. Immunohistochemistry study showed positivity of tumour cells for GFAP and WT1 and negativity to IDH1, OLIG2, MAP2, synaptophysin, EMA, p53 or H3K27M. Genetic evaluation demonstrated absence of EGFR and IDH mutations and 1p/19q codelection.
Conclusion: Autopsy diagnosed an unpredicted congenital CNS neoplasia: diffuse astrocytoma, IDH-wild type, without mutations in the IDH genes: a rare neoplasia that most likely constitute a variety of entities which can follow a broad range of clinical courses and could be reclassified in adults as other tumours with additional genetic analyses. Astrocytoma is the commonest glial tumour of infancy and childhood, frequently outside the posterior fossa and typically as an intracranial mass and it tends to causing hydrocephalus, macrocephaly and intracranial hemorrhage.

PS-16-015

Neonatal mortality due to congenital candidiasis in low birth weight infants: a 5-year retrospective study from an Emergency Unit in Romania

T.A. Georgescu[1], A.C. Lisievici[2], S. Barbu[3], V.A. Dumitru[3,4], R. Bohiltea[5,6], M. Costache[7,4], M. Sajin[8,9]
[1] Department of Pathology, Bucharest Emergency University Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania, [4] Department of Pathology, Emergency University Hospital Bucharest, Romania, [5] Department of Obstetrics and Gynaecology, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania, [6] Department of Obstetrics and Gynaecology, Emergency University Hospital Bucharest, Romania, [7] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [8] SUUB, Romania, [9] UMF Carol Davila, Romania

Background & Objectives: Congenital candidiasis is an extremely rare and severe cause of early-onset sepsis, usually caused by an ascending infection from the maternal genital tract. The condition manifests within the first few days of life and involves a high mortality rate (35%). It may be localized (congenital cutaneous candidiasis), presenting as an extensive skin rash which eventually results in widespread desquamation, or generalized (congenital systemic candidiasis), resulting in respiratory distress, meningitis, sepsis and death.
Methods: In this 5-year retrospective study developed within the Pathology Department of the Emergency University Hospital Bucharest Romania, we aim to evaluate the clinical and histopathological aspects of fatal candidiasis in infants and correlate the results with literature data. We reviewed slides from foetal autopsies and extracted clinical information from archived medical files. Cases confirmed by culture in Sabouraud agar were selected. Additional Periodic acid-Schiff and Grocott's methenamine silver stains were performed from archived tissue blocks.
Results: Four cases of fatal neonatal candidiasis have been identified between 2014 and 2019. Median gestational age was 27 weeks. All mothers presented spontaneous rupture of membranes and abnormal vaginal discharge. Median weight of the infants was 900g. One infant was stillborn and the other 3 died after 3-8 days due to candidemia, with respiratory arrest and multiorgan failure. Histopathological examination revealed angioinvasive hyphae in the lung (n=4), brain (n=2), liver (n=3), spleen (n=2), kidney (n=2) and gastrointestinal tract (n=3).
Conclusion: Preterm infants are predisposed to Candida infections mainly due to the immaturity of their immune system. Congenital candidiasis is rare and must be distinguished from other conditions presenting with pustular lesions at birth. Central venous catheterisation and parenteral nutrition are significant risk factors for developing candidemia, which can be fatal or lead to severe complications with lifelong repercussions.

PS-16-017

PD-L1 and PD-L2 mutations in paediatric Hodgkin Lymphoma: do they have any prognostic significance?

G. Gul[1], D. Ince[2], N. Olgun[2], E. Özer[3]
[1] Tepecik Training and Research Hospital, Department of Pathology, Izmir, Turkey, [2] Dokuz Eylul University Faculty of Medicine Department of Paediatric Oncology, Turkey, [3] Dokuz Eylul University Faculty of Medicine Department of Pathology, Turkey

Background & Objectives: Reed-Sternberg cells are able to escape from the immune system by multiple mechanisms including the enhancement of the expression of programmed cell death-1 ligands (PD-L1 and PD-L2). We aimed to investigate *PD-L1* and *PD-L2* gene mutations in childhood Hodgkin Lymphoma's (HL) and their relationships with clinical and prognostic parameters.
Methods: The study included 39 paediatric HL patients treated with a standard protocol. *PD-L1* and *PD-L2* mutations were determined by whole exome Sanger sequencing. Clinicopathological parameters including age, sex, histological subtype, bone marrow and lymph nodes with involvement, clinical stage, bulky disease, EBER positivity, LDH level, erythrocyte sedimentation rate and event-free survival were obtained from patients' records. Statistical analyses were performed to address the relationship between mutation profile and both clinical and pathological variables.
Results: Eight cases (20,5%) showed p.R260C mutations, and three (7,7%) pR234L in the exome 5 of *PD-L1* gene. None of the cases had *PD-L2* mutations. In statistical analysis, p.R260C mutation exhibited a significant relationship with older age and nodular sclerosing (NS) histological type (P=0.04 and P=0.04, respectively). *PD-L1* mutation did not statistically correlate with other variables.
Conclusion: Although *PD-L1* mutation did not show statistically significance with well-established prognostic factors, based on our findings indicating significance with NS histology and older age, we speculate that *PD-L1* gene mutations may be associated with better prognosis in paediatric HL. This conclusion can be explained by amino acid sequence change affecting the PD1 / PD-L1 interaction, and thereby preventing malignant cells from escaping the immune system.

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PS-16-018

Morphometric analysis of vascular clefts in children with symptoms of acute appendicitis and negative appendectomy

B. Jurić[1], M. Kirigin[1], R. Ivelj[2], A. Čizmić[2], I. Pezelj[3], B. Krušlin[1,4]
[1] Department of Pathology and Cytology, Sestre Milosrdnice University Hospital Center, Croatia, [2] Children's Hospital Zagreb, Croatia, [3] Clinic of Urology, Sestre Milosrdnice University Hospital Center, Croatia, [4] School of Medicine, University of Zagreb, Croatia

Background & Objectives: Acute appendicitis is one of the most common causes of abdominal emergency surgical procedures. Many cases of clinically suspected acute appendicitis showed no microscopic signs of acute inflammation. Negative appendectomy rate differs greatly, partly due to various criteria different Institutions use to define acute appendicitis. Prominent vascular clefts, frequently found in negative appendectomy specimens, could be implicated in the pathophysiology of acute appendicitis and might be one of the early signs of inflammation.
Methods: We conducted a retrospective study by searching for patients who had negative appendectomy at Children's Hospital Zagreb (January 1st 2014-March 31st 2019). 124 patients were identified, aged 1-18. Their histologic slides were re-examined. Vascular clefts, if present, were measured microscopically. Other abnormalities were also noted, such as the presence of fecaliths. Statistical analysis was carried out.
Results: Out of the 124 patients included in the study, 50,8% were female (n=63), and 49,2% were male (n=61). Mean age of patients was 11,5 and median was 12 years. 94 of 124 (75,8%) negative appendectomy specimens showed prominent vascular clefts. Vascular clefts width varied between 140 and 1751 μm. 12 specimens (9,7%) showed no signs of vascular clefts, and 18 specimens had partial vascular clefts which did not penetrate the muscular wall of the appendix and consequently could not be measured. 63,7% (n=79) of appendices contained fecaliths in their lumina.
Conclusion: Our results suggest that widened vascular clefts as sites of weakness in the muscular layer of the appendiceal wall may be one of the first signs of acute appendicitis.

PS-16-019

Role of immunohistochemistry on differential diagnosis of paediatric renal tumours: expression of Cyclin D1, PTEN, PDGFR-alfa and Beta-catenin

Z. Ecem Kain[1], G. Gokturk Ozcan[1], R. Ozcan[2], S. Emre[2], T. Tiraje Celkan[2], N. Comunoglu[2]
[1]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Pathology, [2] Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Paediatric Surgery, Istanbul, Turkey

Background & Objectives: Paediatric renal tumours overlap histomorphologically, and may cause misdiagnosis. Blastemal component of Wilms tumour (WT) may mimic clear cell sarcoma (CCS) and Ewing sarcoma, while stromal component of WT mimics CCS and mesoblastic nephroma (MN). Recent studies suggest several immunohistochemical markers to differentiate between these overlapping features. In this study, we aimed to determine the role of immunohistochemical staining patterns of Cyclin D1, PTEN, beta-catenin and PDGFR alfa, on paediatric renal tumours.
Methods: A total of 34 paediatric and 2 adult renal tumours (16 Wilms Tumour,10 clear cell sarcoma, 2 congenital mezoblastic nephroma (CMN),3 cellular mesoblastic nephroma (CeMN),2 rhabdoid tumours (RT), 1 solitary fibrous tumour (SFT),1 Ewing sarcoma (ES),1 diffuse large B-cell lymphoma (DLBCL)) cases were included in the study. Four blocks of paraffin tissue microarray were constructed. Cyclin D1, PTEN, beta-catenin and PDGFR-alfa were performed on all cases. Staining intensity was graded from weak to strong, the extensity was graded as percentages.
Results: All cases of CCS and epithelial components of WT showed positivity for Cyclin D1 but blastemal and stromal components of WT were negative. All cases of CCS and CMN, and most cases of WT consisting of blastemal and stromal components demonstrated loss of expression with PTEN. Most cases of CCS and all components of WT showed cytoplasmic, weak staining with beta-catenin,while rhabdoid components showed strong positivity. ES, CMN, and rhabdoid components of WT were negative with PDGFR-alfa. The other cases showed variable positivity.
Conclusion: Cyclin D1 is not a specific immunohistochemical marker due to its strong and diffuse positivity in CCS cases. It may be useful to differentiate CCS from blastemal and stromal components of WT. Staining patterns of PTEN, beta-catenin and PDGFR-alfa indicate the tumours using these pathways. Other markers except cyclin D1 do not have a role in differential diagnosis.

PS-16-020

Angiogenesis and apoptosis in human placentas with aneuploidies - trisomies 21, 18 and 13

A. Kolobov[1], V. Karev[2], O. Kolobova[3]
[1] Saint Petersburg University, Russia, [2] Children's Scientific and Clinical Center of Infectious Diseases, Saint Petersburg, Russia, [3] Saint Petersburg Paediatric Medical University, Russia

Background & Objectives: Trisomies 21, 18 and 13 are the frequent aneuploidies in live newborns. The aims of this study were to compare CD31, bFGF and FasL expressions in placentas with normal and trisomic karyotype and to associate differentially expressed with concrete biological pathways.
Methods: The placentas were collected from four groups of patients: 1) placentas from foetuses of gestation 19-21 weeks with trisomy 21 (10 placentas); 2) placentas from foetuses of gestation 19-21 weeks with trisomy 18 (10 placentas); 3) placentas from foetuses of gestation 19-21 weeks with trisomy 13 (10 placentas); 4) placentas from foetuses of gestation 19-21 weeks without any congenital defects and abnormal karyotype (control group – 20 placentas). CD31, bFGF and FasL expression was studied immunohistochemically.
Results: In placentas with trisomy 21 the expression CD31 was 1.52 ±0.54% (in control group – 6.8±1.54%, $p<0.05$); the expression bFGF was 11.27±1.75% (in control group – 3.28±0.26%, $p<0.01$). In placentas with trisomy 13 the expression CD31 was 2.7±0.84%. The expression FasL in group with trisomy 21 (1.22±0.77%) and trisomy 13 (0.16 ±0.08%) in comparison with control group (4.43±0.79%) statistically significant decreased. The expression of FasL was the highest in placentas from foetuses with trisomy 18 (11.74±0.09%).
Conclusion: Thus, in placentas with trisomies 21 and 13 is disturbance of branching and vascularization of villi. In placentas with trisomy 18 the activation of apoptosis is noted.

PS-16-021

9-years-old male with isolated mucormycosis of trachea and bronches: a case report

N. Korchagina[1], T. Vorozhbieva[2], E. Tumanova[3], D. Zhakota[3]
[1] N.F. Filatov Children's City Hospital of Moscow Healthcare Ministry, Russia, [2] Moscow City Oncology Hospital №62, Russia, [3] Pirogov Russian National Research Medical University, Russia

Background & Objectives: We report the case of isolated mucormycosis of trachea and bronches of 9-year-old patient with diabetes for 1 month. Mucormicosis is a rare complication of diabetes mellitus, which usually occurs with long-term experience of this disease.
Results: 9-year-old male with diabetes for 1 month came to the our clinic with complaints of cough, dyspnea. On the same day, there was a drop SaO2 to 60%, respiratory arrest, after resuscitation vital functions were restored. In bronchoscopy in the lower third of the trachea is black, the lumen is narrowed by 50%, with fibrinous overlay, and granulations. Lumen of right main bronchus was spot, covered with floating portion of the right wall of the trachea. During the study, the material was taken for histological examination.
The biopsy spicement consisted on the necrotic tissue with non-septate hyphae branching at wide angles, that allowed to conclude about the presence of the patient mucormycosis. The patient's condition was

progressive deterioration, respiratory failure was increased, necrotic changes in the trachea were progressed, which required VA-ECMO and traditional lung ventilation. Despite the ongoing therapy, the patient died on the 20 day of his stay in the clinic.
The autopsy confirmed an isolated mucormycosis of the lower third of the trachea and the main bronchi, thrombosis of the pulmonary arteries.
Conclusion: We found only 5 articles in the last 50 years with similar pathology in Scopus and RSCI databases. All of these cases was in the elder patient with minimal 5-years experience of the diabetes mellitus and episodes of ketoacidosis.

PS-16-022
Segmental absence of intestinal musculature in infant with Hirschprung disease

B. Krsteska[1], B. Ilievski[2], L. Spasevska[3], V. Janevska[3], P. Zdravkovski[2], V. Stojkovski[2], V. Naunova[4], V. Filipovski[5], M. Bogdanovska-Todorovska[2], G. Petrushevska[3]
[1] Institute of Pathology, Medical Faculty, Republic of North Macedonia, [2] Institute of Pathology, Medical faculty, Skopje, Republic of North Macedonia, [3] Institute of Pathology, Medical Faculty, Skopje, Republic of North Macedonia, [4] University Clinic for Paediatric Surgery, Skopje, Republic of North Macedonia, [5] Acibadem Sistina Hospital, Laboratory for Histopathology and Cytology, Skopje, Republic of North Macedonia

Background & Objectives: Segmental absence of intestinal musculature (SAIM) is a rare histopathologic entity with a few published cases in neonatal pathology and has uncertain pathogenesis. It is classified as primary congenital or secondary acquired. Clinical manifestations usually are intestinal obstruction and perforation. Majority of reported cases are neonates, children, but it can affect adults also.
Methods: We present a case of male, 6 months old baby, with previously diagnosed Hirschprung disease when multiple colorectal biopsies were taken and colostomy was made. After 1 month he develops fever and vomits with poor clinic evolution. Intraoperativelly there was diffuse peritonitis and intestinal adhesions due to perforation. A 75cm long segment of small intestine was resected. The wall of intestine was thinned (paper-like) with massive hemorrhage and peritonitis. Many specimens were taken for pathohistologic analysis along the whole length of the intestinal segment. The tissue sections were formalin fixed and paraffin embedded and routinely stained with HE. Additional immunohistochemical analysis was performed with SMA.
Results: All specimens revealed absence of intestinal muscular layer with intact mucosa, muscularis mucosae, submucosa and serosa. There was transmural diffuse acute inflammatory infiltrate and hemorrhage with fibrinopurulent peritonitis. Immunohistochemically SMA confirms the absence of muscularis propria and marks muscularis mucosae. Resection of the affected segment is curative. Up to now the baby is in good condition.
Conclusion: There is no published case of SAIM associated with Hirschprung disease. As etiopathogenesis remains unclear and there is a spectrum of published histopathologic morphologic elements there is a need of homogenous classification for further comparative studies.

PS-16-023
Possible involvement of endocannabinoid receptor CB1 expression in the pathogenesis of preeclampsia: immunohistochemical study

M. Lambropoulou[1], E. Karantzali[2], V. Papadatou[1], M. Simopoulou[3], S. Tologkos[1], T. Deftereou[1], T. Alexiadis[1], S. Alexopoulou[2], I. Koukourakis[1], G. Tripsianis[4], S. Meditskou[5], O. Pagonopoulou[6]
[1] Histology-Embryology Lab., Medical Department, Democritus University of Thrace, Greece, [2] Histology-Embryology Lab. Medical Department, Democritus University of Thrace, Greece, [3] Physiology Lab., School of Medicine National & Kapodistrian University of Athens, Greece, [4] Medical Statistics Lab., Medical Department, Democritus University of Thrace, Greece, [5] Histology-Embryology Lab., Medical Department, Aristotle University of Thessaloniki, Greece, [6] Physiology Lab., Medical Department, Democritus University of Thrace, Greece

Background & Objectives: Pre-eclampsia is a particularly serious disorder expressed during pregnancy, which is usually expressed in the clinical triptoma: proteinuria, hypertension, edema. The endocannabinoid receptor CB1 is known to be a G protein that acts in synergy with delta-9-tetrahydrocannabinol (THC), which is the major psychoactive agent of cannabis. We aimed to assess the expression of CB1 endocannabinoid receptor in histological placental samples with a characteristic pre-eclampsia disorder during foetal development.
Methods: Forty (40) samples from pre-eclamptic placentas as well as normal ones were used. We performed indirect immunohistochemistry using anti-CB1 antibody. Immunohistochemical staining was evaluated using a Nikon Eclipse 50i optical microscope and antibody expression was graded with a semi-quantitatively four scale scoring system (0-3).
Results: The results demonstrated increased expression of the CB1 receptor in pathological samples relative to normal ones. Preeclamptic women over the age of 35, as well as those in higher gestational weeks had higher levels of receptor expression. It is also demonstrated that pre-eclampsia is an independent factor that correlates directly with high levels of CB1 expression. In contrast, low levels of CB1 expression were observed in normal placentas.
Conclusion: To conclude, increased expression of the CB1 receptor appears to correlate with the pathogenesis of preeclampsia. Eventually, the receptor could be considered a valuable prognostic marker when it comes to this disorder. However, it is always proposed to review the hypotheses and outcomes of this research work, as well as to elucidate the underlying reasons and mechanisms that lead to these outcomes.

PS-16-024
Molecular investigation and identification of apoptotic and inflammatory factors involved in normal and abnormal pregnancies

M. Lambropoulou[1], T. Deftereou[1], S. Tologkos[1], V. Papadatou[1], I. Koukourakis[1], C. Alexiadi[1], P. Tsikouras[2], T. Alexiadis[1], G. Tripsianis[3], O. Pagonopoulou[4], M. Simopoulou[5], N. Papadopoulos[1]
[1] Histology-Embryology Lab., Medical Department, Democritus University of Thrace, Greece, [2] Obstetrics & Gynaecology Dep., Medical Department, Democritus University of Thrace, Greece, [3] Medical Statistics Lab., Medical Department, Democritus University of Thrace, Greece, [4] Physiology Lab., Medical Department, Democritus University of Thrace, Greece, [5] Physiology Lab., School of Medicine National & Kapodistrian University of Athens, Greece

Background & Objectives: The aim of this study was to evaluate apoptosis in placentas coming from pathological and normal pregnancies, as well as inflammation and viral infections markers expression. Furthermore, we tried to uncover a possible link between the level of apoptosis and inflammation, the outcome of the pregnancy and viral presence.
Methods: We examined 68 placentas from pathological pregnancies and 24 from normal pregnancies. Immunohistochemistry was applied to analyse apoptotic expression using M30 and TUNEL method, whereas antibodies against TNF-a and NF-kβ were used for inflammation detection. Furthermore, we used anti-CMV and anti-HSV antibodies to evaluate viral presence. Antibodies expression was graded in terms of the proportion of positively stained cells according to a semi-quantitatively four scale scoring system (0-3).
Results: Our analysis showed that inflammation and apoptosis markers were found in higher expression patterns in the study group compared with the control group with statistical significance. Regarding the viral infection, only 10 positive cases were found, all among patients with adverse pregnancy outcomes. Furthermore, when we focused in the study group, all the markers showed a statistically significant correlation between high expression and increased mother's age as well as higher

gestational weeks. Moreover, the presence of viral infections has also been correlated with higher inflammation and apoptosis levels.
Conclusion: Our results established a clear correlation between adverse pregnancy outcomes, viral placental infection and higher inflammation and apoptosis levels. However, the underlying mechanisms involved in these procedures need further clarification.

PS-16-025
Paediatric diffuse myocardial fibrosis: a case report
C. Makni[1], M. Ksentini[1], N. Zneidi Sabbegh[1], Z. Ghorbel[1], R. Aloui[1], I. Boubaker[1], A. Trahore[1], A. Blel[1], H. El Mokh[1], I. Ben Romdhane[1], L. Hadj Kacem[1], M. Ben Khelil[2], M. Hamdoun[2], S. Rommani Rammeh[1]
[1] Pathology Department, Charles Nicole Hospital, Tunisia, [2] Forensic Medicine Department, Charles Nicole Hospital, Tunisia

Background & Objectives: Etiologies of myocardial fibrosis vary according to age, medical history, clinical presentation and histological findings. The aim of this case report is to discuss the etiologies of diffuse myocardial fibrosis among paediatric population.
Methods: We present a rare case of diffuse myocardial fibrosis resulting in a child's sudden death.
Results: An 8-year-old boy was victim of a sudden death while at school. He had no known personal medical history or family history of sudden death at a young age. Necropsy findings revealed slightly hypertrophic myocardium, with pale and fibrous appearance. All the other organs were congestive without other abnormalities. Histological examination revealed an important hypertrophy of myocardial fibers in both right and left ventricles associated with fibrosis of the interstitial tissue. There was no significant myocardial fibers disorganization, nor inflammatory reaction. Pulmonary non inflammatory alveolar edema was noticed, as well as lesions of chronic hepatitis. Toxicological tests were reported negative. Myocardial fibrosis is rare in paediatric population. The etiologies can be divided in two groups: chronic heart failures occurring on congenital cardiac malformations and those occurring on structurally normal hearts. The pathologies occurring on a structurally normal heart can be either primary cardiomyopathy (dilated, hypertrophic or restrictive) or secondary (arythmogenic, ischemic, toxic, infiltrative or infectious). In view of the association with the hepatic lesions, we concluded that myocardial fibrosis would be probably secondary to myocarditis. No virological investigations were done.
Conclusion: Diffuse myocardial fibrosis is rare in paediatric population. Histological examination establish the diagnosis and can help in the etiological orientation.

PS-16-026
Utility of foetal autopsy for the characterisation of Glutaric Aciduria type II
A.P. Martinez Aracil[1], A. Perez-Rodriguez[1], I. Llano-Rivas[2], A. Sagasta[1]
[1] OSI Araba University Hospital, Spain, [2] Genètica Clinica- Servicio de Genetica, Hospital Universitario Cruces, Biocruces-Vizcaya Health Research Institute, Spain

Background & Objectives: Glutaric aciduria is a rare and lethal disorder that affects metabolism of fatty acids. Lipid accumulation is observed in the tissues. Enlarged, polycystic kidneys and hepatomegaly with steatosis are common findings and can be prenatally detected. Therefore we wanted to pathologically and genetically characterise a foetus of 15 weeks, from a consanguineous couple, carrier of a novel *ETFDH* variant, with 4 previous perinatal deaths.
Methods: Due to the medical history, prenatal echography and a chorial biopsy for ETDFH-associated glutaric aciduria analysis was ordered. The gestation was interrupted and the foetal autopsy performed.
Results: Sanger sequencing confirmed the presence of the homozygous familiar probably pathogenic variant in the *ETFDH* gene (c.706dupG + c.706dupG) that codifies for a truncated protein (p.Glu236Glyfs*5 + p.Glu236Glyfs*5). Autopsy findings revealed a prominent forehead, flat nasal bridge, malformed ears, intrauterine growth retardation, as well as polycystic kidneys and steatosis in the liver, confirming the diagnosis of glutaric aciduria type II.
Conclusion: The foetal autopsy allowed the characterisation of the novel variant (c.706dupG at ETDFH) as pathogenic**.** Genotype-phenotype relationship is important in the study of rare genetic disorders such as glutaric aciduria type II, as variants are usually familiar-specific leading to a difficulty in the characterisation of their pathogenicity.

PS-16-027
Infantile-onset lysosomal acid lipase deficiency
O. Mishnev[1], A. Talalaev[1,2], L. Leonova[1,2], Y. Semina[2]
[1] Pirogov Russian National Research Medical University (RNRMU), Russia, [2] Morozovskaya Children's Clinical Hospital, Russia

Background & Objectives: Lysosomal acid lipase deficiency (LAL-D), Wolman disease is a rare autosomal recessive lysosomal storage disease characterised by progressive accumulation of cholesterol esters and triglycerides in the liver, spleen and other. The goal is to show the importance of genetic expertise for clinical and full autopsy diagnosis of LAL-D.
Methods: LAL-D was diagnosed in two full-term sisters from the same family, who died at the age of two months and three months respectively. Similar clinical manifestations of the disease were rapidly progressing in the sibs from birth, complicated by viral and bacterial infections and led to the death caused by multiple organ failure. Intravital molecular genetic and morphological expertise of the autopsy material was carried out using basic histological methods with hematoxylin-eosin, Pas-reaction and Masson's trichrome stain.
Results: Clinically: appetite decrease, hypotrophy, reflexes decrease, hepatosplenomegaly, jaundice, dyslipidemia, hypoalbuminemia, increase in blood acid phosphatase, coagulopathy, anasarca. The activity of LAL was reduced. Molecular genetic research has revealed compound-heterozygote c.442del & c.817_818del. Specific enzyme replacement biological therapy with Kanuma (Sebelipase alpha) was carried out without effect. The autopsy research revealed typical LAL-D changes: microvesicular steatosis with the outcome of micronodular liver cirrhosis, lipids and calcifications in the adrenal glands, accumulation of lipids in lymph nodes and intestine mucosa.
Conclusion: Classic LAL-D diagnostic is based on typical clinical and morphological symptoms: reduction of the LAL activity, elevated blood acid phosphatase levels and histological findings of microvesicular steatosis on liver tissue, accumulation of lipids in internal organs and calcifications in the adrenal glands. Molecular genetic expertise of the child and his parents is key method of successful diagnosis of the disease.

PS-16-028
Shwachman-Diamond Syndrome in a child of 11 months
O. Mishnev[1], A. Talalaev[1,2], L. Leonova[1,2], Y. Semina[2]
[1] Pirogov Russian National Research Medical University (RNRMU), Russia, [2] Morozovskaya Children's Clinical Hospital, Russia

Background & Objectives: Shwachman-Diamond syndrome (SDS), or Shwachman–Bodian–Diamond syndrome, is a rare congenital multisystemic disorder characterised by exocrine pancreatic insufficiency, bone marrow dysfunction with aplasia or leukemic transformation, skeletal dysplasia and abnormalities. The syndrome was named for doctors Harry Shwachman and Lois Diamond (1964). The goal is to show the importance of genetic expertise for clinical and complete pathologic diagnosis of SDS.

Methods: Invitrial molecular genetic research and morphological examination of the autopsy material was conducted for a full-term child who died 11 months old, using hematoxylin-eosin and immunohistochemical reactions with monoclonal antibodies such as Insulin, Glucagon and CD 15. Since birth, the clinical manifestations of the disease were progressing rapidly and led to the death caused by bacterial infection.
Results: The blood test revealed: neutropenia, anemia, thrombocytopenia. By Sanger's method of sequencing the gene SBDS (ex 1-5): **c.201A>G (p=), genotype A/G (rs1061695)** was detected. An autopsy examination revealed: pancreatic lipomatosis, chronic inactive pancreatitis, fatty degeneration of the liver and single myeloid and granulocyte cells in the bone marrow, nesidiodysplasia, cortical dysplasia of the kidneys and a cleft of the soft palate was revealed. Immunohistochemically: positive reactions with Insulin, Glucagon; lack of the reaction in the bone marrow with CD 15.
Conclusion: The peculiarity of the observation was the defect of the exocrine and endocrine pancreas and kidney dysplasia. The child's disease was quickly progressing with febrile fever, steatorrhea, the loss of appetite, hepatosplenomegaly, hypotrophy, necrosis of soft tissues of face and extremities. Molecular genetic expertise of the child and his parents is a key to a successful diagnosis of the disease.

PS-16-029
High-grade foetal vascular malperfusion is associated with diffuse chorionic haemosiderosis
E. Mooney[1], E. Crotty[1], M. Culliton[1]
[1] National Maternity Hospital, Ireland

Background & Objectives: Diffuse chorionic haemosiderosis (DCH) is an abnormality of the placental membranes, characterised by the deposition of iron pigment. It is usually secondary to recurrent venous bleeding from early pregnancy. In many papers, it is associated with pre-term delivery. Foetal vascular malperfusion (FVM) is an abnormality of the fetoplacental circulation that may be seen at any gestational age, but often in the third trimester. No link has been identified in the placental literature, but we have noted the two conditions co-existing. This study examined the association of these two entities.
Methods: Laboratory records were searched for singleton cases diagnosed as DCH on H&E stain over a 5 year period. These were classified as showing high-grade FVM (HGFVM), low-grade FVM (LGFVM) or no FVM. Controls were gestational-matched cases without DCH. Cord length, coiling, insertion, or other abnormalities were noted. Membranes were classified as normal or circumvallate. Results were analysed using Graphpad.
Results: There were 66 cases of DCH between 16 and 41 weeks gestation and 130 controls. 14/66 (21%) cases of DCH showed HGFVM and 2/66 (3%) showed LGFVM. 16/130 (12%) controls showed HGFVM and 20/130 (15%) had LGFVM. Where FVM is present, high-grade FVM is significantly associated with DCH versus controls ($P<0.0031$ Fischer's Test).
Conclusion: HGFVM occurs significantly more often in placentas with DCH. Histologic correlates of FVM have been under-explored to date. We have previously shown that FVM occurs four times more commonly in placentas with maternal vascular malperfusion (MVM) (Cooley et al JOG 2011). Both FVM and DCH are among 9 lesions significantly increased in placentas from infants with neurologic injury, and both are independently related to neurologic injury (Redline & ORiordan Arch Pathol Lab Med 2000). Whether iron in high quantities causes or contributes to vascular damage in the developing placenta requires further study.

PS-16-030
Abernethy syndrome - a case report
C. Padrao[1], A. M. G. Pereira[1], F. Galante Pereira[1], R. Theias Manso[1]
[1] Hospital Prof. Doutor Fernando Fonseca, EPE, Portugal

Background & Objectives: Abernethy syndrome is an eponym for congenital extrahepatic portocaval shunt. It can be divided in two types depending if liver is perfused (type II: partial shunt) or not (type I: total shunt) with portal blood. It is a rare condition and causing hepatopulmonary syndrome is even rarer. Here, we present a suspect case in an autopsy of a male child with 19 months old.
Methods: Imagiologic studies in the context of acute respiratory distress raised the suspicion of an extrahepatic portocaval shunt. The patient died and to verify the cause of death and to confirm the extrahepatic shunt, an autopsy was performed using the Letulle *(en mass)* method to preserve the vascular supply and relationships between organs. The block of thoracic and abdominal organs was immersed in formalin and evaluated after fixation. Samples for histologic evaluation were collected.
Results: The autopsy showed that the main causes of death were recent myocardial infarct, acute lobar bronchopneumonia, diffuse alveolar lesion and hemorrhagic diathesis. Hypoplasia of portal vein was verified, together with intra-abdominal, intrahepatic and also pulmonary vascular malformations. Chronic effects of the partial portal shunt were also found like oesophageal varices, severe pulmonary hypertension and *cor pulmonale*.
Conclusion: The Abernethy type II malformation was confirmed and caused in this child an hepatopulmonary syndrome, along others vascular malformations, promoting a cascade of events that lead to death.

PS-16-031
Wilms' tumour arising from nephrogenic rests located inside a tubular colon duplication adherent to the kidney: an exceptional case
C. Picard[1], G. Schneider[1,2], J. Pracros[1,3], S. Collardeau-Frachon[1,4], P. Leblond[5,6], F. Hameury[1,2], F. Dijoud[1,4]
[1] Hospices Civils de Lyon, France, [2] Dèpartement de chirurgie viscèrale pèdiatrique, France, [3] Service d'imagerie mèdicale, France, [4] Institute de Pathologie Multisite, France, [5] Institute d'Hèmatologie et de Cancèrologie Pèdiatrique, France, [6] Service de cancèrologie pèdiatrique, France

Background & Objectives: Colonic duplication is the less common reported congenital duplication of the gastrointestinal tract and is characterised by multiple clinical presentations. Renal adhesion of a duplication at an early stage may induce the infiltration of the digestive wall by embryonic nephrogenic tissue, which could give rise to neoplasia.
Methods: This 2-year old child without significant medical history was referred to the emergency for mild abdominal bloating and fever. Imaging found a tubular communicating sigmoid colon duplication, ending in a retroperitoneal extra-renal and extra-adrenal cystic calcified collection, thought to be part of the malformation. Pre-operative procedures 2 months later showed a growing palpable colon duplication.
Results: Surgery found the duplication ending in a large cystic mass, adherent to the upper pole of kidney. Cyst rupture during surgical manipulation revealed a suspect tissue, compatible with a Wilms' tumour (WT) in frozen section. The duplication resection was completed by a left nephrectomy. Final histological examination confirmed the diagnosis of WT. Colonic wall of the duplication end was infiltrated by immature glomeruli associated with islands of blastema evocative of nephrogenic rests (NRs) that were continuous with the malignant tumour.
Conclusion: We report a case of WT arising from diffuse NRs located inside a colon sigmoid duplication adjacent to the kidney in a child. This exceptional case demonstrates the potential of heterotopic NRs to evolve into primary WT. The adhesion between the digestive duplication and the kidney may have taken place at an early stage of embryogenesis in this child.

PS-16-034
Extravillous trophoblast peculiarities in pregnancies under circulatory hypoxia conditions
O. Reshetnikova[1], L. Rudiuk[2,3]

[1] Immanuel Kant Baltic Federal University, Russia, [2] Immanuel Kant Baltic Federal University, Kaliningrad, Russia, [3] Regional Clinical Hospital of the Kaliningrad Region, Kaliningrad, Russia

Background & Objectives: Pregnancy, complicated with circulatory hypoxia may cause placental dysfunction, which results in immediate and lifelong consequences for a mother and child. Failures in adapting blood flow in mother-placenta-fetus system under congenital heart disease (CHD) conditions can have a negative impact in oxygen and nutrient transport to the developing fetus. Placental extravillous trophoblast (PEVT) is associated with immune and hormonal interactions in feto-placental complex.
The aim of present study was to evaluate the PEVT peculiarities in cases, when pregnancy was complicated with CHD and when surgical intervention preceded pregnancy.
Methods: Morphological study of 54 placentas was carried out according to the standard scheme. They were divided into groups: I - 20 cases of CHD non-operated, II - 19 cases of CHD operated and 15 cases of physiological pregnancy (control group). Histological slides, stained with hematoxylin and eosin, were studied microscopically, then they were analysed by point count method and using the computer morphometry. The immunohistochemical staining protocol with monoclonal mouse antibodies to SMA (Dako, 1:500) for placental tissue samples has been developed. Morphological and immunohistochemical data were studied in parallel with clinical information. Differences between groups were elucidated by non-parametric Mann-Whitney. Reliability established at $p<0.05$.
Results: Results have shown that PEVT volume fractions had no significant differences in both CHD groups and controls. However, histological investigation of the first group placentas revealed PEVT cells dystrophy, cysts formation, accompanied with decreased SMA expression. Morphological peculiarities of the second group PEVT, as well as SMA expression were close to the control parameters.
Conclusion: Structural remodelling and immunohistochemical features of PEVT are considered in the aspect of hormonal and immune adaptation of placentas to circulatory hypoxia under CHD conditions in operated and non-operated patients.

PS-16-035
Placental pathology and foetal thyroid gland peculiarities in late spontaneous abortions

O. Reshetnikova[1], O. Zinchenko[2], I. Goryanikova[2]
[1] Immanuel Kant Baltic Federal University, Russia, [2] Saint Luka Lugansk State Medical University, Lugansk, Lugansk People's Republic, Ukraine

Background & Objectives: Adequate endocrine homeostasis within foetus-placental system is crucial for normal child growth and development. Placental pathology may influence in utero thyrogenesis and impair newborn thyroid function. Therefore, we investigated the association between placental morphology and thyroid histogenesis in cases, when pregnancies terminated with late spontaneous abortions.
Methods: Thyroid gland of 38 foetuses from the late spontaneous abortions material were compared with 34 foetal glands in cases of induced abortions due to psychological reasons (control group). Tissue samples were immersion-fixed in 10% buffered formalin solution, embedded in paraffin wax. Histological slides were stained routinely with hematoxylin and eosin. Microscopical examination was performed on magnification x 10 and x 40. Morphometry of thyroid gland histology was conducted by point-count method. Volume fractions (VF) of pathological accumulations, placental membrane components, etc. were revealed. All data were compared with control parameters. The differences were analysed with the help of Student's t-test.
Results: Results have shown morphological changes in placental structures in cases from the late spontaneous abortions. The intervillous space had smaller VF due to fibrinoid accumulations, extremely close arrangement of chorion villi with zones of fibrinoid 'glued' villi and ischemic infarcts. Placental membrane thickness increased as a result of increased connective tissue and syncytiotrophoblast VF, smaller number of the capillaries per villi. Foetal vessels mainly located within the central area of villi. It also contributed to the increase of the distance between maternal and foetal blood circulations. General architecture of thyroid glands in late abortions group followed the pattern similar to controls. Connective tissue fascicles between follicles were wider than in controls and VF of follicles clusters were smaller. The foci of immature structural units of the thyroid gland occupied wider zones, divided with loose, poorly cellular, fibrous stroma.
Conclusion: Placental structural and functional disorder may cause thyroid grand growth and maturation restriction.

PS-16-036
Retrospective analysis of the mortality rate in children with cystic fibrosis in the industrial region of Donbas

O. Reshetnikova[1], E. Burgelo[2], O. Teleshova[2]
[1] Immanuel Kant Baltic Federal University, Russia, [2] Saint Luka Lugansk State Medical University, Lugansk, Lugansk People's Republic, Ukraine

Background & Objectives: Cystic fibrosis (CF) is a lethal genetic disorder caused by mutations in the transmembrane conductance regulator (CFTR) gene on chromosome 7. CFTR impaired function results in abnormal ion transport at the apical membrane of airway epithelial cells which cause hyperviscous airway mucus formation. CF is variable in clinical expressions, but lung disease is the major cause of mortality in patients with CF. Scientific data suggests that risk factors for lethal outcome of CF have different impact on individuals in countries of different income. Therefore the aim of the study was to investigate the information about the mortality rate in children with cystic fibrosis in the industrial region of Donbas, which for few years has suffered due to civilian military conflict.
Methods: 10 autopsy reports of children who died from CF and its complications for the period 2010-2018 have been studied. The diagnosis was made on the basis of clinical data, pathological and bacteriological examinations. The following indicators were also taken into account: age, gender, type of bacterial infection, the form of CF and its complications. According to the age of the child three groups were formed: I – 0 – up to 6 months; II - 6 months- up to 1 year, III - 1 -3 years.
Results: Results have shown that 50 % of CF lethal cases were established in the 0-6 month's age group. The minimal indicators were in the III group - 20%. No prevalence by gender was found. Most of the children had a mixed form of the disease and only one had an intestinal form of CF. A microbiological study of the lung tissue revealed P. Aeruginosa and Staphylococcus Aureus in majority of cases.
Conclusion: Late diagnosis and severe course of the disease, the development of purulent bronchopneumonia, multi organ failure syndrome led to the death of CF.

PS-16-037
Maternal factors and foeto-placental peculiarities in cases of the IUGR

O. Reshetnikova[1], O. Kononenko[2], A. Antonova[2]
[1] Immanuel Kant Baltic Federal University, Russia, [2] Saint Luka Lugansk State Medical University, Lugansk, Lugansk People's Republic, Ukraine

Background & Objectives: Intrauterine growth restriction (IUGR) is an important reason of perinatal complications and high mortality.
The aim of present study was to investigate maternal-foetal and placental relationships in late gestation, as well as to establish possible imbalances in the development of the foetus and placenta.
Methods: 21 placentas from the late medical abortions at 20-22 weeks of gestation (wg) due to psychotherapeutic reasons were divided in two groups: I – 11 cases of IUGR and II group (comparison) - 10 cases with

no foetal IUGR. The material of study included the results of a survey of women aimed at the medical termination of pregnancy. Foetuses and placentas were investigated at pathology department. Volume fractions (vf) of the major placental components were determined by computer morphometry of H&E stained slides. The differences were analysed with the help of Student's t-test.

Results: Results revealed feto -placental growth discordance in cases of the IUGR. Placental-foetal ratio in the IUGR group increased to 0,42+ 0,05 (II group -0,27+0,01,<0.01). The weights of the foetal liver, kidney, and heart were lower than in the II group. The relative indicators of the foetal organs to the placentas weights were also lower in cases with IUGR. Poor placental vascularity and immaturity of the villous tree were common findings in IUGR cases. Placental membrane thickness here increased compared with II group of investigation. In parallel terminal villi vessels occupied smaller area, while the area of the connective tissue stroma increased. Patient's survey showed that in the group I mothers were older, with lower educational level and more frequent drinking alcohol. They were less involved in sports activity.

Conclusion: On the basis of these results, it was estimated that maternal factors as well as inadequate remodelling of placental structures may contribute to the development of clinical and morphological signs of placental insufficiency and IUGR emergence.

PS-16-038

Paediatric extragonadal germ cell tumours: a single center experience

A. Sassi[1], N. Boujelbene[1], R. Doghri[1], L. Charfi[1], I. Abbes[1], H. Houari[1], K. Mrad[1], M. Driss[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Extragonadal germ cell tumours (EGCT) are uncommon paediatric tumours with particular clinical behaviour. Our aim is to report epidemiological, histopathological and prognosis characteristics of EGCT.

Methods: We performed a retrospective study of EGCT diagnosed at our department over a period of 20 years (1999–2019). Patients aged under 16 years old were included. Three age groups were defined with the following ranges: congenital/neonatal (birth-6 months), childhood/ prepubertal (7 months-12 years) and postpubertal (12 – 16 years). Dermoid cysts were excluded.

Results: A total of 30 patients were included. Mean age was 4.5 months (2 days – 11 years old). The congenital/neonatal group encompassed 57% of patients and the childhood/prepubertal 43% of patients. There was a female predominance (63%). Specimen integrity was mainly intact (87%). The most common tumour site was sacrococcygeal (53%). Tumour mean size was 9 cm and mean weight 250 gr. All EGCT were teratomas of which 63% were mature. Immature teratomas were mostly grade 3 (44%). Nonteratomatous components were not reported. For the sacrococcygeal location, coccyx was not removed in 56% of the cases. When removed, it was statistically associated with negative margins (p=0.036).

Conclusion: Sacrococcygeal teratomas are the leading paediatrician EGCT. In these tumours, the presence of immature neuroglial elements is not predictive of malignant behaviour. Coccygectomy has to be performed for a complete surgical resection. Recurrence often occurs in the form of a yolk sac tumour.

PS-16-039

Congenital abnormalities as a cause of perinatal death

A. Shchegolev[1], U. Tumanova[1], M. Shuvalova[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: Congenital abnormalities account for a significant proportion of the causes of perinatal death. The type and frequency of their development differ in the Federal districts of the Russian Federation. Improving prenatal examination of the fetus is the main reserve for reducing mortality from congenital abnormalities.

Objective: to conduct a comparative analysis of congenital abnormalities frequency as the cause of stillbirth and early neonatal death in the Russian Federation.

Methods: The statistical analysis of Rosstat on the causes of stillbirth and early neonatal death in the Russian Federation in 2012-2016 was performed.

Perinatal losses were: 58298 stillbirths and 27367 early neonatal deaths. Congenital abnormalities as the initial cause of death figured in 7846 cases (9,8%). They were the cause of stillbirth in 5.6% and early neonatal death in 16.8%.

Results: Most often (39.3%), the causes of stillbirth were abnormalities from the "Other types of congenital abnormalities" group, which include multiple abnormalities. The second and third places were nervous system (25.7%) and heart (17.3%) congenital abnormalities, respectively. Digestive system congenital abnormalities as the initial cause of death were the least common (2.9%). At early neonatal death, abnormalities from the "Other types of congenital abnormalities" group were also observed most often (44.2%). The heart (31.9%) and circulatory system (7.7%) congenital abnormalities were second and third, respectively.

Conclusion: The type and frequency of lethal congenital abnormalities detection differed in the Russian Federation Federal districts. The largest share of stillborn from congenital abnormalities was registered in the North-West Federal District (7.6%), and of early neonatal death - in the Central Federal District (22.6%).

PS-16-040

Comparative characteristics of the villi vascularisation in monochorionic diamniotic twin pregnancies with selective birth weight discordance

A. Shchegolev[1], U. Tumanova[1], V. Lyapin[1], V. Sakalo[1], N. Tetruashvili[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: Monochorionic twin gestations are associated with a high risk of poor pregnancy and perinatal outcome, including the development of foetal growth retardation.

Objective: to study the degree of vascularization of the villi in monochorionic diamniotic twin placentas selective birth weight discordance.

Methods: Complex morphological study of 12 placentas from monochorionic diamniotic twin placentas in selective birth weight discordance was performed. Morphometric indices of terminal villi vascularization was determined on CD31 immunohistochemical preparations. The area and perimeter of the terminal villi, as well as the number, area and perimeter of their capillaries were determined. Calculated the vascularization degree indexes of villi (the ratio of the total area of the capillaries of the villus to the cross-sectional area of corresponding villus).

Results: The average weight of the larger newborn significantly exceeded the weight of the smaller newborn (2167±131.4g vs 1626±194.6g, p<0,05). At morphometric analysis of placenta preparations, the average area and perimeter of terminal villi in the placenta of a foetus with a larger weight (2099.2±188.1mkm² and 168.1±8.5mkm) did not differ much from similar indicators of the foetus with a lower weight (2081.4±93.2mkm² and 166.7 ±3.6mkm). The average area and perimeter of terminal villi capillaries were larger in the placenta of the foetus with less weight (85.0±7.8mkm² and 33.7±1.5mkm vs 100.1±15.3mkm² and 35.9±2.4mkm).

Conclusion: When studying microscopic specimens of monochorionic diamniotic twin placentas, different degree of the terminal villi vascularization were established depending on the weight of the foetus. The calculated vascularization index of the terminal villi was higher in the placenta with a lower weight (36.2% vs 27.2%), which reflects the development of compensatory processes in placental hypoxia.

PS-16-041

Features the glycome of syncytiotrophoblast in the placental terminal villi during early-onset and late-onset foetal growth restriction

G. Kulikova[1], M. Ziganshina[1], A. Shchegolev[1], V. Sinitsyna[1], E. Yarotskaya[1], N. Kan[1], V. Tyutyunnik[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: Syncytiotrophoblast is an interface between maternal blood and foetal extracellular fluid, responsible for hormone production and nutrient exchange. Various molecular and functional changes in syncytiotrophoblast are detected during pregnancy complications. Today there is limited data on syncytiotrophoblast glycopathology in foetal growth restriction (FGR). The aim of the study was to characterise the glycome of syncytiotrophoblast in the placental terminal villi by lectin histochemistry in healthy women and in patients with early-onset (EO) and late-onset (LO) FGR.
Methods: Streptavidin-biotin-peroxidase labelling technique was used to localize the binding sites for ten lectins (Con A, UEA-I, ECL, VVL, GSL-I, GSL-II, MAL-II, SNA, SBA, DSL) in combination with enzymatic treatments. Lectin binding patterns were analysed in 36 formalin-fixed paraffin-embedded samples of placental tissues in early-onset FGR (n=12), late-onset FGR (n=12) and normal pregnancy (n=12). Quantitative analysis of histochemical reactions was performed by Nikon Eclipse E 80 computer program. The intensity of staining was assessed in 10 visual fields in each observation.
Results: Lectin-binding patterns of syncytiotrophoblast in FGR showed increase of terminal residues of αGal-, αGalNAc- (GSL-I) and sialoglycans with α (2,3)-linked sialic acids (MAL-II); and decrease of mannose-containing glycans (ConA), compared to healthy patients. Content of terminal Fucα- (UEA-I) was increased, and contents of terminal Galβ- (ECL) residues and sialoglycans with α (2,6)-linked sialic acids (SNA) were decreased in EO FGR only.
After treatment with neuraminidase the altered subterminal glycans (Galβ- (ECL) and αGalNAc- (GSL-I) residues) decreased in LO FGR only.
Conclusion: Changes in the glycome of syncytiotrophoblast appear to the terminal residues of glycans in early-onset FGR. Subterminal glycan structures mainly modified in late-onset FGR. It is likely that the modified glycome of syncytiotrophoblast may play an important role in pathogenesis of early-onset and late-onset FGR.

PS-16-043

MRI lung volume in living and dead newborns: evaluation and comparison

U. Tumanova[1], V. Lyapin[1], V. Bychenko[1], A. Shchegolev[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: MRI allows to non-invasive assessment of the lungs size and volume in life and postmortem. Data on postmortem lung volumes are necessary for differential diagnosis of intravital and postmortem processes.
Objective: to study and compare the volume indices of the lungs of living and dead newborns without lung pathology using magnetic resonance imaging (MRI).
Methods: Group-I -5 bodies of newborns who died from multiple congenital malformations, without lung pathology. Group-II -4 live newborns. Postmortem MRI was performed 6–15 hours after death before the autopsy. In 3D reconstructions of MR-tomograms, the volume of each lung, the volume of the thoracic cavity and specific volume of the lungs in each observation were calculated. Conducted a comparison and evaluation of the obtained values. Diseases and cause of death verification in the dead newborns carried out at the autopsy.
Results: The smallest volume of the right lung (48.7 ml), left lung (32.8 ml) and both lungs volume (81.5 ml) were observed in Group-I, and the largest - in Group-II (61.6, 44.9 and 106.5 ml, respectively). The average volume of the right lung in Group-I was 1.3 times less than in Group-II, the left - 1.4 times, and both lungs 1.3times, respectively. The highest average volume of the thoracic cavity was observed in Group-I (193.7ml), which exceeded Group-II by 1.06 times.
Conclusion: The ratio of right and left lungs in Group-I was 1.67, and in Group-II - 1.37. The highest value of the specific volume of the lungs was in Group-II (58.4%) and exceeded the corresponding value in Group-I by 1.4 times.

PS-16-044

Opportunities of postmortem MRI at autopsy for the diagnosis of non-immune hydrops foetalis

U. Tumanova[1], V. Lyapin[1], V. Bychenko[1], A. Shchegolev[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: With NHF, pathological fluid accumulations was found in 2 or more cavities, THI-value in all studied areas indicates a generalized edema of the skin, at our research.
Objective: to identify and assess the severity of non-immune hydrops foetalis (NHF) using postmortem MRI.
Group-I -7 died newborns from NHF; Group-II -7 died newborns with signs of general edema syndrome in NHF absence; Group-III -10 dead newborns with no signs of edema. 6-15hours after death, 3T MRI was performed before the autopsy.
Methods: The volume of fluid and its specific volume in serous cavities were determined at 3D tomography reconstructions. The T1- and T2- signal intensity of the skin (T1siS, T2siS) in the body areas and fluid (T1siF, T2siF) were measured. The skin edema was determine by the formula of tissue hydration index (THI)=T2siS*T1siF/T1siS*T2siF*100.
In Group-I hydrothorax was detected in 100%, ascites -in 85.7%, hydropericardium -in 42.9%. In Group-II hydrothorax was in 57,1%, ascites -in 85.7%, hydropericardium -in 42.9%. In Group-III hydrothorax and ascites was in 30%.
Results: The average value of hydrothorax specific volume was the maximum in Group-I, exceeding the values of Group-II and Group-III by 2.2 and 5.1 times, respectively ($p<0.05$). The average specific volume of ascites prevailed in Group-I and exceeded the values of the Group-II and Group-III by 1.5 and 4.1 times, respectively ($p<0.05$).
Conclusion: The maximum average THI-value is installed in the anterior chest wall in Group-I (77), exceeding that by 3.4 and 1.7 times in the Group-III and Group-II ($p<0.05$). The THI average value in the anterior abdominal wall in Group-I (66) higher than in Group-III and Group-II by 3.01 ($p<0.05$) and 1.84 times ($p>0.05$), respectively.

PS-16-045

Virtopsy possibilities in the diagnosis of the VACTER association in a newborn: a case report

U. Tumanova[1], V. Lyapin[1], V. Bychenko[1], A. Kozlova[1], A. Shchegolev[1]
[1] NMRCOGP, Russia

Background & Objectives: Postmortem CT and MRI allowed for a non-invasive, objective and clear analysis of the pathology.
We report on the Virtopsy of the deceased newborn with VACTER Association.
We investigated the body of a male newborn born at gestational age 40weeks. Fetus ultrasound at gestational age of 20weeks revealed the left kidney agenesis; on 30weeks - ventricular septal defect, aortic coarctation, anus atresia, open atrioventricular canal. After birth, the newborn underwent surgery: elimination of the tracheooesophageal fistula and unnatural anus imposition.
Methods: 3T-MRI and CT with contrast were performed 10 hours after death before the autopsy. The analysis of tomograms and 3D-reconstructions were performed. Virtopsy data were compared with the autopsy results.
Results: When the complex Virtopsy identified: Vertebral anomalies (C7 cervical right rib, posterior segments of left ribs I-II and III-V fusion, 12 left rib hypoplasia, deformation of C7 and Th1-5 vertebral bodies);

Cardiovascular anomalies (aortic isthmus hypoplasia, superior vena cava absence, right and left brachiocephalic veins flowing into the right atrium, occipital-parietal subcutaneous angiodysplasia); Renal defects (left kidney agenesis, right kidney vicarically enlargement). Anal atresia and Tracheooesophageal fistula –were operated. Bilateral focal pneumonia, brain edema, anasarca, bilateral hydrothorax, ascites were identified.
Conclusion: VACTERL association occurs with a frequency of 1:10000-40000 live births and is a congenital anomalies combination: Vertebral anomalies, Anal atresia, Cardiovascular anomalies, Tracheo-Oesophageal fistula, Renal defects and Limb defects.
Based on Virtopsy and autopsy data, the VACTER association in the deceased newborn was diagnosed at our research case.
Virtopsy of newborns is recommended for multiple congenital abnormalities.

Tuesday, 10 September 2019, 09:30 - 10:30, Agora 3
PS-17 | Uropathology

PS-17-001
PTEN, ERG, SPINK1 and TFF3 status and relationship in a prostate cancer cohort from an Arab population
S. Al Bashir[1], M. Alorjani[1], N. Aldauod[2], O. Halasheh[2], M. Al Hamad[3], I. Matalka[2]
[1] King Abdullah University Hospital, Jordan University of Science and Technology, Jordan, [2] Jordan University of Science and Technology, Irbid, Jordan, [3] Dammam University, Saudi Arabia, Jordan

Background & Objectives: Prostate cancer (PCa) is the most common malignancy in men, and is associated with high morbidity and mortality rates. Phosphatase tensin homologue (PTEN) deletions, ETS-related gene (ERG) rearrangements, serine protease inhibitor Kazal type 1 (SPINK1) and trefoil factor 3 (TFF3) overexpression are proposed prognostic biomarkers in prostate cancer (PCa). However, their relations and patterns of expression in prostate cancer in a Middle Eastern population are not well studied.
Methods: A cohort of 110 PCa specimens from the archives of King Abdullah University Hospital (Jordan) and Aldammam University Hospital (Saudi Arabia), spanning a period from 2005 to 2018. These cases included 45 radical prostatectomies (RP), 63 transurethral resections of prostate (TURP), and 2 enucleation cases. Tissue microarray (TMA) of prostate cancer patients was constructed. PTEN, ERG, SPINK1 and TFF3 expression status was assessed by immunohistochemistry and correlated with each other.
Results: PTEN loss,ERG and TFF3 expression were observed in 43.6 %, 62.8 % and 44.6 % of PCa cases, respectively. SPINK1 expression was observed in 6 out of 110 PCA cases (5.4%). In all PCa cases, 3.6% of the cases showed SPINK1+/ ERG+ phenotype, 1.8% showed SPINK1+/ ERG- phenotype, 59% showed SPINK1-/ERG+ phenotype, and 35.4% showed SPINK1-/ERG- phenotype. SPINK1 expression was observed exclusively in a subgroup of cancers that expressed TFF3 (6/6). There was an increased PTEN loss and TFF3 expression from Gleason score 6 (Grade group 1) to Gleason score 9-10 (Grade group 5), the association was statistically significant with P values of 0.002 and 0.0365, respectively.
Conclusion: In this first study to address the question of PTEN loss, ERG, SPINK1 and TFF3 gens status in a predominantly Arab population, we documented that PTEN loss and TFF3 expression are associated with more aggressive prostate cancers with higher Gleason scores/ Grades. SPINK1 expression was observed exclusively in a subgroup of cancers that expressed TFF3. These findings support a rationale of screening for these biomarkers for prognostic purposes and molecular subtyping of the disease.

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PS-17-003
Assessment of tumour different architecture compounds through fractal analysis in prostate adenocarcinoma in correlation with Gleason and Srigley grading systems
M. Bara[1], M.-. Serbanescu[2], R.M. Plesea[3], V. Ciovica[3], A.M. Istrate-Ofiteru[4], G.C. Rosu[4], L. Iovan[4], F. Simionescu[5], V.T. Moldovan[6], I.E. Plesea[7,6,3]
[1] University Emergency Hospital in Bucharest, Romania, [2] Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy, Craiova, Romania, [3] Doctoral School, University of Medicine and Pharmacy, Craiova, Romania, [4] Department of Histology, University of Medicine and Pharmacy, Craiova, Romania, [5] Department of Pathology, University Emergency Hospital, Bucharest, Romania, [6] Department of Pathology, "Victor Babes" National Institute of Pathology, Bucharest, Romania, [7] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Background & Objectives: The aim of the study is to assess the different constitutive elements of tumour architecture in correlation with two different grading systems of prostate adenocarcinoma using the fractal dimension (FD) analysis.
Methods: 433 fields with different patterns of prostatic adenocarcinoma according to Gleason and Srigley grading systems were selected and stained on four serial sections with: H&E for grading and Gömöri technique, Goldner's trichrome, and CD34 immunomarker to assess: tumour cells architecture (GO), tumour stroma (TC) and vascular network (VN) respectively. Images were binarized using different approaches, with colour focus for Goldner's and CD34 stainings and intensity focus for Gömöri staining. The FD was computed for each binary image using a box-counting algorithm. The three computed values were used for clustering and classification, k-nearest neighbour proving to be a good choice with a classification rate, due to the irregular distribution of cases in different patterns.
Results: GO had a more ordered smooth ascending trend towards “area like” type of distribution (with FD>1.5in Srigley system than in Gleason system. TC had almost the same type of distribution – between “linear-like” and “area-like” (FD~1.5) in both grading systems. VN had a more “linear-like” type of distribution (FD<1.5), with a descending trend towards high-grade patterns in both systems.
GO had a direct correlation with TC and VN (“p” value of Pearson’s test <0.001) while TC and VN proved no correlation (“p” value of Pearson’s test >0.05), irrespective of grading pattern.
Conclusion: FD analysis proved that Srigley system is more accurate in grading prostate adenocarcinoma than Gleason system.

PS-17-005
Small cell carcinoma of the urinary bladder: clinicopathological and immunohistochemical features of 11 cases
D. Beypinar[1], M.F. Acikalin[1], D. Arik[1], F. Kaya[1], A. Ozen[2], C. Can[2]
[1] Eskisehir Osmangazi University, Department of Pathology, Turkey, [2] Eskisehir Osmangazi University, Department of Urology, Turkey

Background & Objectives: Most of the bladder cancers are urothelialcarcinoma (UC) which are over 90% percent of diagnosed patients. Small cell carcinoma (SmCC) of the urinary bladder is a rare and highly aggressive tumour. It accounts for less than 1% of all malignant bladder tumours and has a poor prognosis.
Methods: We searched the electronic database of Eskişehir Osmangazi University Hospital from 2010 to 2019 and found 11 cases of SmCC of the urinary bladder. The demographic data, clinical presentation and follow-up information were extracted from the medical charts.
Results: The patients consisted of seven men and four women with a meanage of 70.1years (range, 51-83years). There were 9 cases with transurethral resection of the bladder and 2 radical cystectomy specimens. Three patients had pure SmCC while 8 of the tumours were mixed with

other histology. Five of the specimens had also carcinoma in situ. Ten of the tumours had at least muscularis propria invasion and the other had at least lamina propria invasion. Expression of synaptophysin, chromogranin, CD56, and TTF-1 proteins was found in 10/11 (90.9%), 7/11 (63.6%), 8/8 (100%), and 7/11 (63.6%) cases, respectively. Nine of the patients were metastatic either at the time of diagnosis or during follow-up.
Conclusion: SmCC of the urinary bladder is an aggressive tumour characterised by advanced stage at presentation and a propensity for metastasis. SmCC has a poorer clinical outcome than pure UC even if it is a small component in mixed tumours.

PS-17-006
What may influence biochemical recurrence in organ-confined (pT2) prostate cancer, Gleason score ≤6, and negative surgical margins?
A. Billis[1], L. Freitas[2], L. Costa[2], I. Barreto[2], A. Botega[2], J. Costa[2], N. Almeida[2], T. Rotta[2]
[1] State University of Campinas - Unicamp, Brazil, [2] Dep. Anatomic Pathology, School of Medical Sciences, State University of Campinas (Unicamp), Brazil

Background & Objectives: Detect clinicopathological findings associated with biochemical recurrence (BR) in patients who usually have very-low risk for BR following radical prostatectomy (RP).
Methods: Step-sectioned and completely processed specimens of 88 consecutive patients considering BR >0,2 ng/mL. Assessed: age, prostate weight, presence of benign prostatic hyperplasia (BPH), preoperative PSA, PSA density, tumour extent evaluated by a semi-quantitative method, clinical stage, and number and percentage of quadrants showing benign glands at the inked margin (BGIM).
Results: 71/88 (80.7%) patients had no BR, and 17/88 (19.3%) had BR; 17/17 (100%) patients with BR and 36/71 (50.7%) patients without BR had BGIM. Patients with BR had significantly higher number ($p<0.001$) and percentage ($p<0.001$) of quadrants with BGIM, higher prostate weight ($p=0.004$), higher frequency of BPH ($p=0.035$), higher level of preoperative PSA ($p=0.044$), and less extensive tumours ($p=0.050$). Considering percentile 95, cases with >8 and/or >20% positive quadrants showing BGIM almost always were associated with BR.
Conclusion: Benign glands at the inked margin may possibly explain postoperative PSA elevation following RP. In step-sectioned and completely processed specimens pathologists should report BGIM in cases with organ-confined cancer (pT2), Gleason score < 6, and negative surgical margins. BGIM in >8 and/or >20% positive quadrants, urologists should consider this possibility and avoid immediate treatment unless presence of cancer is documented.

PS-17-007
Granulomatous orchitis: how often mimics a testicular tumour? A study in Brazil
A. Billis[1], L. Freitas[2], L. Costa[2], I. Barreto[2], D. Losada[2], B. Zaidan[2], A. Costa[2], A. Herculiani[2], K. Araujo[2]
[1] State University of Campinas - Unicamp, Brazil, [2] Department Anatomic Pathology, School of Medical Sciences, State University of Campinas (Unicamp), Brazil

Background & Objectives: There are several causes for granulomatous orchitis. The pathologic features may be challenging for a proper diagnosis and in some cases clinically mimic a testicular tumour resulting in orchiectomy.
Methods: We describe the pathologic findings of 17 patients submitted to biopsy or orchiectomy and the frequency of cases misdiagnosed clinically as malignant testicular tumour.
Results: Frequency according to cause: 1. Schistosomiasis 6/17 (35.3%); 2. Malakoplakia 4/17 (23.5%); 3. Idiopathic 3/17 (17.6%); 4. Paracoccidioidomycosis 2/17 (11.8%), 5. Syphilitic gumma 1/17 (5.9%); and, 6. Tuberculosis 1/17 (5.9%). The patient with syphilitic gumma in this series was HIV positive. In 6/17 (35%) patients the testicular lesion was misdiagnosed clinically as malignant tumour resulting in orchiectomy. In these patients the cause was: malakoplakia (2 patients), idiopathic (2 patients), schistosomiasis (1 patient), and syphilitic gumma (1 patient).
Conclusion: Schistosomiasis and paracoccidioidomycosis are the most frequent infectious diseases causing granulomatous orchitis in Brazil. The pathologist must be aware of the pathologic features of syphilitic gumma due to increase in frequency of syphilis associated with or not with HIV. Unfortunately, in our series, 35% of patients were clinically misdiagnosed as having malignant tumour being submitted to orchiectomy.

PS-17-008
A comparison of grading by summary score and highest grade in 2,090 biopsy sets with prostate cancer
M. Bonert[1], M. Carvalho[2], B. Shayegan[1], S. Salama[1], A. Kapoor[1], I. El-Shinnawy[1]
[1] McMaster University and St. Joseph's Healthcare Hamilton, Canada, [2] Hamilton Health Sciences, Canada

Background & Objectives: Prostate cancer biopsy grading may include a summary score (SS) that is based on assessing the biopsy set as one piece of tissue, and may differ from the highest grade (HG) in the biopsy set. Biopsy-prostatectomy comparisons are confounded by selection bias. We sought to assess the concordance of the SS and HG in biopsies.
Methods: In house prostate biopsy reports at two Institutions from 2011 to 2017 were extracted and the SS retrieved. A previously validated hierarchical free text string matching algorithm (HFTSMA) established the HG.
Results: The study period has 4,477 biopsies and 2,090 had a SS. The HFTSMA had a 1% error based on pathologists auditing of 700 reports. This was corroborated by a 1% deviation in the ISUP/WHO grade group 1 (WHO1) or Gleason score 6 (GS6); there were 625 WHO1/GS6-SS cases and 620 WHO1/GS6-HG cases. The 780 WHO2/GS3+4-SS cases were by HG 81%WHO2, 15%WHO3, 3%WHO4. WHO3/GS4+3-SS (346 cases) were by HG 66%WHO3, 33%WHO4. WHO4/GS8-SS (166 cases) were by HG 1%WHO3, 93%WHO4, 6%WHO 5. WHO5/GS9&10-SS (173 cases) were by HG 1%WHO4, 99%WHO5. The grade by HG and SS was concordant in 86% of cases.
Conclusion: The HG in relation to the SS upgrades 18% WHO2 and 33% WHO3 cases. Understanding the significance of this is complicated by possible biases associated with grading practices. Adoption of the SS would result in a downgrade migration and could cause a reverse Will Rogers Phenomenon. Consensus on prostate cancer grading/reporting should be established in conjunction with unbiased outcome data.

PS-17-009
Slug regulating epithelial-mesenchymal transition is associated with aggressive tumour features, recurrence and reduced survival in prostate cancer
A. Børretzen[1], K. Gravdal[1], S.A. Haukaas[2], C. Beisland[2], L.A. Akslen[3,4], O.J. Halvorsen[1]
[1] Centre for Cancer Biomarkers CCBIO, and Gade Laboratory for Pathology, Department of Clinical Medicine, University of Bergen, Norway, Department of Pathology, Haukeland University Hospital, Bergen, Norway, [2] Department of Clinical Medicine, University of Bergen, Norway, Department of Urology, Haukeland University Hospital, Bergen, Norway, [3] Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, Section for Pathology, University of Bergen, Norway, [4] Department of Pathology, Haukeland University Hospital, Bergen, Norway

Background & Objectives: Epithelial-mesenchymal transition (EMT), important for tumour cell invasion and metastasis, is a feature of aggressive carcinomas. We studied the EMT-regulator Slug in different human prostatic tissues focusing on EMT, clinico-pathologic phenotype, recurrence and survival.
Methods: Sections from 338 radical prostatectomies (Haukeland University Hospital, Norway, 1986–2007), 33 castration resistant prostate cancers, 33 non-skeletal metastases, 13 skeletal metastases, and 41 prostatic hyperplasias were immunohistochemically stained for Slug.
Results: Slug was strongly expressed in localized prostatic carcinomas and skeletal metastases. In localized carcinomas, strong Slug was associated with adverse clinico-pathologic features, such as extraprostatic extension, seminal vesicle invasion, high pathologic stage and lymph node infiltration. Strong Slug was also associated with strong expression of the EMT transcription factors Twist, Snai1 at tumour-stromal border and FOXC2, as well as strong HIF-1α and high Ki-67. In univariate survival analyses, strong Slug was associated with shorter time to biochemical recurrence, clinical recurrence, loco-regional recurrence and cancer-specific death. By multivariate Cox' survival analysis, strong Slug was an independent predictor of time to biochemical and loco-regional recurrence. Among E-cadherin low carcinomas, strong Slug independently predicted shorter time to clinical recurrence, skeletal metastases and cancer-specific death (HR 2.3-3.3, $p<0.04$), together with Gleason grade groups (≥GG3 vs. ≤GG2).
Conclusion: The EMT-regulator Slug was associated with aggressive tumour features, recurrence and cancer-specific death in prostate cancer. Slug and other EMT-regulating transcription factors can be useful as prognostic biomarkers and are potential targets for cancer therapy.

PS-17-011
Praja2 expression in non-invasive and muscle invasive urothelial carcinoma of the bladder
R. Cepurnaite[1], M. Fuggi[1], E. Guadagno[1], S. Pignatiello[1], S. Varricchio[1], L. Insabato[1]
[1] Department of Advanced Biomedical Science of the University of "Federico II" in Naples, Italy

Background & Objectives: Urinary bladder cancer is the seventh most common cancer worldwide. The most common histological type is urothelial carcinoma. It is usually diagnosed at non-invasive or early invasive stage, has a high risk of a reoccurrence (50-70%) and progresses only in 15-25% of cases.
Praja 2 (PJA2) is an enzyme, that is involved in growth regulation of various tumours. Our aim was to analyse the expression of PJA2 in muscle invasive and non-muscle invasive urothelial carcinoma of the bladder.
Methods: We analysed 21 different tumours of non-muscle invasive (high grade) urothelial carcinoma, which in a period of 6 months or more progressed into muscle invasive carcinoma. We built 2 tissue microarrays (TMA) from representative areas of each tumour: first TMA contained non-muscle invasive specimens, second TMA was composed of muscle invasive specimens.
Immunohistochemical staining with PJA2/Praja2 antibody was performed.
Results: In first TMA (non-muscle invasive tumours) 15 samples from 13 patients were evaluable, in second TMA (muscle invasive tumours) 26 samples from 21 patients were evaluable. PRAJA2 was expressed in all of them and was scored from 0 (negative) to 3+ (very strong and diffuse positivity). In first TMA 27% of tumours were scored as 3+, 60% as 2+ and 13% as 1+. In second TMA 46% of tumours were scored as 3+, 35% as 2+ and 19% as 1+.
Conclusion: PRAJA2 was expressed in all samples of high grade urothelial carcinoma of the bladder with higher percentage of 3+ score (very strong positivity) cases in muscle invasive tumours. Next step in our research will be to compare these results with PRAJA2 expression in low grade urothelial carcinoma of the bladder and in normal bladder tissues.

PS-17-012
Oncocytic papillary renal cell carcinoma reveals K-RAS mutation
C. Choi[1], S.S. KIM[2], J. KIM[3], Y.M. CHO[4], H.S. KIM[5], K.M. KIM[6], K.H. KEE[7]
[1] Chonnam National University, Republic of Korea, [2] CNUH, Republic of Korea, [3] CNUHH, Republic of Korea, [4] Ulsan University, Republic of Korea, [5] Wonkwang University, Republic of Korea, [6] Jeonbuk University, Republic of Korea, [7] Chosun University, Republic of Korea

Background & Objectives: Oncocytic papillary renal cell carcinoma (OPRCC) is a recently described subtype of papillary renal cell carcinoma (PRCC) characterised by voluminous and intensely eosinophilic cytoplasm, uniform nuclei and low nuclear grade, and indolent biological behaviour. However, there is still an overlap of histology between OPRCC and type 2 PRCC. In this study we aimed to define the clinicopathologic and molecular features of OPRCC by comparing to type 2 PRCC using morphology assessment, immunohistochemical stain, and targeted next-generation sequencing.
Methods: A cohort of 33 OPRCC and 30 type 2 PRCC was used. Tissue microarray (TMA) was made using 3 cores per tumour. They were stained with CK7, racemase, EMA, E-cadherin, vimentin, CD10. Targeted sequencing of 90 cancer-related genes was performed in 28 OPRCC using MiSeqDx. PNA-mediated clamping PCR of KRAS was also performed in paired normal and tumour DNA of 33 OPRCC and 30 type 2 PRCC cases.
Results: OPRCC revealed distinct clinocopathologic features: small tumour size, lower pathologic T stage, and no disease-specific death. Morphologically, they showed peritumoural lymphoid aggregation, prominent papillary architecture (>80% of tumour), edematous or hyalinized papillae, inverted nuclear location, and lower nuclear grade. Immunohistochemically, they are usually positive for CK7, racemase, EMA and E-cadherin, but not for vimentin and CD10. Recurrent mutations in *KRAS* were detected in 26 of 33 OPRCC. However, there was no *KRAS* mutation in any of the type 2 PRCC.
Conclusion: OPRCC reveals distinct clinicopathologic profiles with indolent behaviour and unique molecular profiles, which are different from type 2 PRCC.

PS-17-013
The relationship between epithelial mesenchymal transition with Galectin-3 expression in low and high grade urothelial carcinomas of bladder
M. Cin[1], A. Igdem Akyildiz[2], S. Bektas[2], S. Cin[3], E. Kimiloglu[2], Ö. Gündogar[2], N. Komut[2], N. Dursun[1]
[1] University of Health Sciences, Istanbul Health Practice and Research Hospital, Department of Pathology, Turkey, [2] University of Health Sciences, GOP Taksim Health Practice and Research Hospital, Department of Pathology, Turkey, [3] Istanbul University Cerrahpaşa Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Our aim was to evaluate the relationship between clinicopathological parameters and epithelial mesenchymal transition (EMT) by immunohistochemical analysis (E-cadherin and Vimentin) and how EMT interacts with Galectin-3 immunoreactivity in bladder urothelial carcinomas.
Methods: Transurethral resection (TUR) materials of 223 bladder urothelial carcinomas were included. Hematoxylin&eosin stained preparations were reevaluated. Three groups were formed; T1 stage low grade, T1 stage high grade and T2 stage high grade. E-cadherin, Vimentin and Galectin-3 antibodies were applied immunohistochemically to the selected paraffin blocks. The staining percentage score and the staining intensity score were obtained for each marker. The relationship between age, sex, carcinoma in situ, lymphovascular invasion, tumour grade, tumour stage were evaluated with these three markers.
Results: There was no significant relationship between age, gender, carcinoma in situ and lymphovascular invasion. Additionally, there was no

significant correlation between age, gender, carcinoma in situ and expression of E-cadherin, Vimentin and Galectin-3 antibodies. Increased histologic grade and stage, presence of lymphovascular invasion showed decreased E-cadherin expression and increased Vimentin expression. There was no significant relationship between Galectin-3 expression and histological grade. But in high grade carcinomas Galectin-3 expression rate was higher for T1 stage compared with T2 stage. There is a significant correlation between E-cadherin and Vimentin expression. However Galectin-3 was not significantly associated with both markers.
Conclusion: The relationship between prognostic parameters and E-cadherin / Vimentin expression is significant. There was no correlation between E-cadherin / Vimentin expression and Galectin-3 immunoreactivity. Galectin-3 and EMT do not show a clear relationship with these results.

PS-17-014
Clinical and morphological characteristics of prostate cancer in Western Romania
A. Dema[1], S. Taban[2,3], C. Lazureanu[4], D. Herman[1], D. Anderco[2], M. Iacob[5], M. Botoga[4], R. Minciu[4], A. Croitor[6], V. Dema[6]
[1] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania, [2] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania, [3] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Pathology, Romania, [4] The Victor Babes University of Medicine and Pharmacy, Timisoara, Romania, [5] Department of Pathology, Emergency County Hospital Timişoara, Romania, [6] Emergency Clinical County Hospital Timisoara, Romania

Background & Objectives: Prostate cancer (PC) continues to represent, mainly in countries that do not benefit from a screening program, a major health problem because of delayed diagnosis that, consequently, involves considerable treatment efforts and costs afterwards. This paper analyses the main clinical and pathological characteristics of patients with PC diagnosed in Timisoara County Hospital – a reference center for the western part of Romania.
Methods: The inclusion criteria were: patients with PC diagnosed on core-needle biopsies (CNB) specimens, during a three-year period (2015 - 2017); the exclusion criteria were: secondary tumours of the prostate and treated PCs. The following data were collected: patient age, PSA serum level and histological characteristics of the tumours.
Results: 486 patients were diagnosed on CNB specimens with PC, having a mean age of 70 years. The most affected age group was 60-69 years (40%). The mean serum PSA level was 68 ng/ml. Tumours had an average Gleason score of 7.6. Intraductal carcinoma was associated with invasive carcinoma in 15.8% of cases, in a group of patients with the mean age of 72.8 years, mean serum PSA of 163 ng/ml, mean Gleason score of 8.14, mean WHO/ ISUP grade of 4.
Conclusion: In the Western part of Romania, patients diagnosed with prostate cancer are younger, but with more advanced stage of the disease. It is necessary to standardize the activities in the services directly involved in the diagnosis and treatment of these patients.

PS-17-015
The expression of TROP2 in the urothelial carcinomas of the upper urinary system
S. Ekmekçi[1], Y. Dere[2]
[1] Izmir Tepecik Training and Research Hospital, Department of Pathology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Upper urinary system urothelial carcinomas (UUSUC), including renal pelvis and ureteral tumours, are rare tumours. Many prognostic and predictive factors are defined in UUSUCs. The transmembrane glycoprotein Trop2 is highly expressed in many cancers, and has different expression profile in certain normal tissues. Trop2 overexpression is associated with decreased patient survival, tumour aggressiveness and metastasis in many cancers. We aimed to determine the characteristic features of UUSUCs and to evaluate the relation of clinicopathological parameters with TROP2 expression.
Methods: A total of 45 cases of UUSUC were included from two different centers. Demographic data and histopathological features obtained from the hospital records were evaluated retrospectively. One demonstrative block of each case was stained with TROP2 antibody. Histopathologic prognostic features such as grade, perineural invasion, lymphovascular invasion, tumour necrosis, and surgical margin status were assessed for their relation with TROP2 expression.
Results: Among 45 cases; 39 were male whilst 6 were female. The mean age was found as 65,64. TROP2 expression was positive in 38(84.4.%) cases. Age, grade, stage, localization, differentiation, lymph node metastasis, necrosis, lymphovascular invasion, perineural invasion, surgical margin positivity, depth of invasion and metastasis showed no significant relation with TROP 2 staining.
Conclusion: Trop2 was first discovered in trophoblast cells which is overexpressed by various human carcinomas including, breast, cervix, colorectal, oesophagus, lung, many lymhomas. Trop2 overexpression appears to correlate with poor patient prognosis in these studies, leading to the suggestion that Trop2 could be a therapeutic target for various carcinomas. Although we found no relation of TROP2 expression with any clinicopathologic factors; our results need to be supported by larger studies with higher number of cases.

PS-17-016
Trop-2 overexpression may indicate tumour aggressiveness among prostatic adenocarcinomas
Y. Dere[1], Ţ Akarken[2], O. Ilhan Celik[1], S.Y. Celik[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Urology, Turkey

Background & Objectives: Prostatic adenocarcinoma is the most common cancer among men worldwide which has many prognostic and predictive factors. The transmembrane glycoprotein, TROP2, which is firstly described on trophoblastic cells is variably being expressed in many cancers. In general TROP2 overexpression was found as associated with worse prognosis and tumour aggressiveness. In this study, we aimed to evaluate the relation of clinicopathologic parameters with TROP2 expression.
Methods: A total of 101 prostatic adenocarcinomas were included. Demographic data and histopathological features obtained from the hospital records and pathology reports retrospectively. One demonstrative block of each case was stained with TROP2 antibody. Histopathologic prognostic features such as grade group, tumour localization, extraprostatic extension, perineural and lymphovascular invasion, surgical margin and lymph node status and degree of inflammation were assessed for their relation with TROP2 expression.
Results: The mean age was found as 64,11. TROP2 was stained over 10% of the tumoural cells in 64 (63.4.%) cases. Gleason grade group, perineural invasion, lymphovascular invasion, ganglionic and seminal vesicle involvement, lateral and basal surgical margin positivity showed significant relation with TROP 2 staining.
Conclusion: TROP2 is overexpressed in various human cancers TROP2 overexpression appears to correlate with poor prognosis leading to the suggestion that TROP2 could be a therapeutic target for various carcinomas. Our results suggest that TROP2 expression is higher in advanced tumours and these results need to be supported by larger studies.

PS-17-017

GATA-3 expression in urothelial carcinoma and its correlation with prognosis

A. Dixit[1], K. Sahu[1], P. Suresh[1], J. Kini[1], S. Sreeram[1] and G.G.L. Prabhu[2]
[1] Department of Pathology, Kasturba Medical College, Mangalore, India, [2] Department of Urology, Kasturba Medical College, Mangalore, India

Background & Objectives: According to Indian statistics, Urothelial Carcinoma is the ninth most common cancer constituting 3.9% of all malignancies. Markers like GATA-3, CK 5/6, and Cyclin D1 are helpful in subtyping Urothelial Carcinoma into 'luminal' and 'basal'. GATA-3 is a sensitive and relatively specific marker for 'luminal' subtype of Urothelial Carcinoma.
The aim of the study was to gain an understanding of the immunohistochemical expression of GATA-3 in Urothelial Carcinoma and correlate it with the grade and stage to evaluate the prognosis.
Methods: It was a retrospective and prospective cross- sectional observational study and included 50 cases. All TURBT specimens of patients morphologically diagnosed as Urothelial Carcinoma and all specimens of radical cystectomy of those patients who haven't received neoadjuvant chemoradiotherapy were included. Variants of bladder carcinoma, other than Urothelial Carcinoma and recurrent cases were excluded. Further clinical details were analysed. Immunohistochemistry scoring for GATA-3 was evaluated by the intensity and percentage of nuclear positivity in tumour cells.
Results: Most Urothelial Carcinomas expressed presence of GATA-3 but some high- grade muscle invasive and basal subtype reflected absence. Loss of GATA-3 expression was associated with a poorer prognosis.
Conclusion: Molecular subtyping of Urothelial Carcinoma using GATA-3 immunohistochemical analysis helps in tailoring the therapy based on the molecular signature of the tumour. The reason for the researcher's keenness on presenting the study in Europe is the fact that the highest incidence of Urothelial Carcinoma has been reported in the continent.

PS-17-019

Angiogenesis assessment in transrectal ultrasound guided prostate biopsy

G. Dordevic[1], M. Bembic[2], K. Božić[3], R. Oguić[4], E. Mustać[3]
[1] Department of Pathology Medial Faculty, University of Rijeka, Croatia, [2] Istrian Health Centers, Hungary, [3] Department of Pathology Medical Faculty, University of Rijeka, Hungary, [4] Urology Clinic, Clinical Hospital Centre Rijeka, Hungary

Background & Objectives: Prostate cancer screening and diagnosis is guided by PSA serum levels and angiogenesis assesment as a new wave of prostate cancer biomarkers could be complementary diagnostic tool. The aim of the study was to evaluate the usefulness of microvessel density (MVD) as a diagnostic parameter in early detection of prostate cancer and to compare the blood vessels count in pathohistological samples among the most common prostate diseases.
Methods: This retrospective study included clinical and pathohistological data and samples from the Urology Clinic and the Department of Pathology Medical faculty, Rijeka. Prostate cancer biopsies (n = 20), benign prostatic hyperplasia (n = 21) and prostatitis and nonspecific findings (n = 28) were treated immunohistochemically with CD31 antibodies. MVD (the number of vessels per high-powered field) was determined by Weidner method.
Results: Comparison of the MVD in patients with cancer diagnosis with other diagnoses did not show significant correlation (p=0.097). ROC analysis suggested the cut-off values for MVD (>19.7) and > 6.07 for PSA for the prostate cancer diagnosis. Diagnostic model using both parameters provided 70% sensitivity and 85% specificity. Logistic regression analysis model that included both parameters showed significance (p<0,0001) with high AUC value of 0.809 and p = 0.05. Multivariate model correctly classifies 80% of patients, in compare to univariate model (PSA) that correctly classifies 70% of patients.
Conclusion: MVD is not good diagnostic predictor for prostate cancer, but due to its relatively high specificity, it represents a good complementary data to PSA value. Study represents a different approach and contribution to the improvement of prostate cancer diagnostic methods.

PS-17-020

Abnormal/wild type p53 immunohistochemistry shows high specificity and positive predictive value for p53 mutation status: time to reassess p53 thresholds in bladder cancer

M. Downes[1], A. Hodgson[2], S. Kim[3], C. Ding[3], R. Saleeb[3], D. Vesprini[4], S. Liu[4], B. Xu[5], G. Yousef[6]
[1] Sunnybrook Health Sciences Centre, Canada, [2] Sunnybrook Health Sciences Centre, Canada, [3] St. Michael's Hospital, Canada, [4] Radiation oncology, Sunnybrook Health Sciences Centre, Canada, [5] Memorial Sloan Kettering Cancer Center, USA, [6] Sick Kids Hospital, Canada

Background & Objectives: p53 immunohistochemistry is often used as a surrogate for *TP53* mutation status. A 10% staining cut off has traditionally been used in the evaluation of high grade urothelial carcinoma (HGUC) for designation as p53 positive/negative, however recent work has shown that an alternate method (0% or >50% - abnormal or 1-49% - wild type) has significant correlation with oncologic outcome. *FGFR* mutations are frequent in the low grade pathway of UC and should be virtually mutually exclusive of HG pathway *TP53* mutations. We hypothesized that the alternate method of p53 assessment would show better correlation with *TP53* and/or *FGFR* mutation status than the traditional 10% cut off.
Methods: Tissue microarray sections from a HGUC cohort (cystectomy, ≥pT2) were stained with p53 and scored by two blinded reviewers (n=206). Both 10% and abnormal/wild type cut offs were applied. Fifty cases (30 abnormal, 20 wild type) were subsequently examined for p53 and FGFR status using NEBNext Direct custom ready panel on the Illumina NextSeq 550 sequencer. The BaseSpace programme was used for alignment and variant interpretation. Fisher's exact test, sensitivity, specificity and positive/negative predictive values (PPV/NPV) were calculated.
Results: 122 cases (59%) showed abnormal p53 staining and 84 (41%) showed wild type. Using the 10% p53 threshold, 145 were positive (70%) and 61 were negative (30%). Cases that were p53 abnormal (n=30) had 15 with p53 mutations, 3 with FGFR mutations and 12 with neither. The wild type group had 1 with p53 mutation, 6 with FGFR mutations and 13 with neither. When the 10% cut off was used, >10% cases (n=32) had 11 p53 mutated cases, 7 FGFR and 14 with neither. <10% group (n=18) had 4 with p53 mutations, 3 FGFR and 11 with neither. Using abnormal/wild type p53 assessment showed correlation with p53 mutation status (p=0.0007). Using the 10% p53 cut off did not (p=0.523). Neither showed a significant correlation with FGFR status. Employing abnormal/wild type scoring had a specificity of 95% and sensitivity of 50% compared with specificity of 78% and sensitivity 34% using the 10% cut off for p53 mutation status. The PPV/NPV for abnormal/wild type was 94% and 56% respectively versus 73% and 40% for the 10% cut off.
Conclusion: Abnormal/wild type p53 staining in HGUC shows significant correlation with *TP53* mutation status and outperforms the traditionally employed 10% cut-off.

PS-17-021

Tumour immune microenvironment drives prognostic relevance correlating with bladder cancer subtypes

M. Eckstein[1], P. Strissel[2], C. Pfannstiel[3], K. Chiappinelli[4], D. Sikic[5], S. Wach[5], H. Taubert[5], B. Wullich[5], B. Keck[5], R. Wirtz[6], J. Breyer[7], M. Burger[7], W. Otto[7], N. Fuhrich[3], C. Geppert[3], V. Weyerer[8], S. Bertz[9], R. Stoehr[3], F. Erlmeier[3], A. Hartmann[3], R. Strick[2]

[1] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, [2] Department of Gynaecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany, [3] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany, [4] Department of Microbiology, Immunology, and Tropical Medicine, The George Washington University School of Medicine and Health Sciences, Washington D.C., USA, [5] Department of Urology and Paediatric Urology, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany, [6] STRATIFYER Molecular Pathology, Cologne, Germany, [7] Department of Urology, Caritas Hospital St. Josef, University of Regensburg, Germany, [8] Insitute of Patholoy, University Hospital Erlangen, Friedrich-Alexander University Erlangen, Germany, [9] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Background & Objectives: Muscle-invasive bladder cancer (MIBC) represents approximately two thirds of invasive urothelial bladder cancers (UBC) and has high morbidity and mortality. Despite intensive efforts to improve patient treatment and outcome, two thirds of patients with UBC will have a recurrence or disease progression within 5 years. We conducted this study to gain further insights in the immunological tumour microenvironment (TIME).
Methods: sTILs were scored continuously on HE slides in a cohort of 135 patients with MIBC treated by radical cystectomy (adjuvant chemotherapy n= 34) according to current recommendations (Salgado et al, 2015). In parallel, we assessed intrinsic subtypes by 21-gene Nanostring signature adapted from the MDACC-subtyping approach. Tertiary lymph structures were assessed by whole slide immunohistochemistry of CD3, CD8, CD68, and CD79a. Spatial immune profiling was carried out on regionally (tumour center, invasive margin) designed TMAs by CD3, CD8, CD56 (NK-Cells), CD68, PD-1 and PD-L1 and revealed spatial organized immune phenotypes. Results were validated in 407 MIBC of the TCGA cohort by hierarchical clustering analysis, immune cell population analysis via CIBERSORT and sTIL-scoring on digitalized HE-slides. Furthermore, tumour mutational burden, neoantigen load and mutational patterns as well as mutational signatures were correlated with immune phenotypes in the TCGA cohort.
Results: We demonstrate that quantity and spatial distribution of stromal tumour infiltrating lymphocytes (sTILs) within the tumour immune microenvironment (TIME) predict stages of tumour inflammation, subtypes, patient survival and correlate with expression of immune checkpoints in an analysis of 542 MIBC. High sTILs indicate an inflamed subtype with 80% 5-year disease-specific survival. A lack of immune infiltrates identifies an uninflamed subtype with a survival rate of less than 25%. A separate immune evading phenotype with upregulated immune checkpoints associated with poor survival. Within the TIME are tertiary lymph node structures (TLS), which can mediate anti-tumour activity via active immune cells. High TLS amounts and close tumour distance correlated significantly with an inflamed phenotype and favourable survival. The uninflamed and evasion phenotypes showed lowest TLS numbers and farthest tumour distances and shortest survival. High inflammation also correlated with increased neoantigen load, high TMB and specific mutational patterns (TCGA-MSig1, TCGA-MSig3/4). Patients treated with adjuvant chemotherapy showed a favourable prognosis dependent on high sTILs.
Conclusion: Determination of sTILs and tumour subtypes may stratify therapy success and patient survival. Considering sTILs can easily be quantified using simple morphological parameters, like hematoxylin-eosin, sTILs can be implemented for predicting patient survival and outcome after adjuvant platinum containing chemotherapy in a routine manner.

PS-17-022

Preventative effect of Omega-3 polyunsaturated fatty acids (n-3 PUFAs) against induction of bladder cancer (BC) in rat model

Y. Elshennawi[1]
[1] Urology and Nephrology Center Mansoura University, Egypt

Background & Objectives: The available data in urological literature regarding the role of n-3 PUFAs in the field of BC chemo-prevention are scarce and conflicting. The present work aims to test the chemo-preventative effects of n-3 PUFAs against BC induction in a rat model and the potential anti-neoplastic mechanisms of the drug.
Methods: Ninety male Fisher rats were divided into 3 groups during a 22-week protocol: group 1 (control), group 2 (Placebo+ N-butyl-N-4-hydroxybutyl nitrosamine (BBN) for induction of BC) and group 3 received n-3 PUFAs at a daily dose of 1200 mg/kg/day + BBN. At the end bladder tissues were collected and checked for the presence of malignancy , markers of angiogenesis (CD34 expression and VEGF relative gene expression), inflammation (IL-6), proliferation (KI-67 expressions), redox status (serum MDA) and epigenetic control (miRNA-145 level).
Results: Survival was [30/30 rats (100%) ,18/30 (60%) and 26/30(86.6%)] for group (1,2 and 3 respectively).There was significant weight loss among rats in group 2(carcinogen) when compared with n-3PUFAs rats(group 3) P.value <0.001.The frequency of neoplastic and paraneoplastic lesions was less in group 3 when compared with group 2 Staining for CD34 expression and KI-67 were less in group 3 when compared with group 2.There were significant up regulation of miRNA-145 expression in group 3 when compared with group 2.
Conclusion: The n-3 PUFAs at our modified dose were able to inhibit tumour growth in the BBN induced rat model of BC, which might be due to anti-inflammatory, antioxidant, anti-proliferative, and anti-angiogenic properties together with epigenetic control.

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PS-17-023

PRMT1 expression is associated with tumour grade, stage, and survival of the patients with clear cell renal cell carcinomas

J. Filipović[1], M. Bosić[1], S. Ćirović[1], M. Životić[1], D. Dunđerović[2], D. Đorđević[3], S. Živković-Perišić[4], I. Filipović[1], J. Marković-Lipkovski[1]
[1] Institute of Pathology, Faculty of Medicine, University of Belgrade, Serbia, [2] Institute of Pathology, Faculty of Medicine, University of Belgrade, Serbia, [3] Clinic for Urology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia, [4] Institute of Public Health "Dr. Milan Jovanovic Batut", Belgrade, Serbia

Background & Objectives: Protein arginine methyltransferase-1 (PRMT1) is associated with the progression of various tumour types. However, the expression of PRMT1 in renal cell tumours (RCT) is unknown.
Methods: We evaluated PRMT1 immunohistochemical expression on tissue microarray of 194 specimens of RCT, including 120 clear cell renal cell carcinomas (ccRCC), 7 papillary RCC type I and 16 type II, 28 chromophobe RCC (chRCC), 11 renal oncocytomas (RO), 7 collecting duct carcinomas and 5 multilocular cystic renal cell neoplasms of low malignant potential (MLCRN-LMP). PRMT1 expression in carcinomas was compared to the tumour grade, stage, age, gender and patient's survival.
Results: PRMT1 immunoreactivity was observed in the majority of ccRCC, RO, all MLCRN-LMP, but in a minority of chRCC (p=0.044). Loss of PRMT1 expression was associated with high-nuclear grade, and high-tumour stage ccRCC (p=0.014; p=0.044, respectively).Kaplan–Meier survival analyses revealed that PRMT1 expression in ccRCC, as well as low-nuclear tumour grade and low-tumour stage were significantly associated with better cancer-specific survival (p=0.029, p<0.001, and p<0.001, respectively).

Conclusion: Loss of PRMT1 may be characteristic of high grade and high stage ccRCC. PRMT1 expression could be associated with better survival of the patients with ccRCC.

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PS-17-024

RBM10-TFE3 renal cell carcinoma characterised by paracentric inversion with consistent closely split signals in break-apart fluorescence in situ hybridization: study of ten cases

M. Furuya[1], I. Kato[1], M. Baba[2], Y. Nagashima[3]
[1] Yokohama City University, Japan, [2] Kumamoto University, Japan, [3] Tokyo Women's Medical University, Japan

Background & Objectives: Renal cell carcinomas (RCC) associated with Xp11 rearrangement harbors fusion genes involving transcription factor E3 (*TFE3*) on chromosome Xp11.2. Dual-colour break-apart fluorescence *in situ* hybridization (FISH) is recommended to confirm histological diagnoses. Recently, RNA binding motif protein 10 (*RBM10*), on chromosome Xp11.3, was identified as a chimeric partner of *TFE3*; thus, *RBM10-TFE3* fusion results from paracentric inversion. It is known that *RBM10-TFE3* RCC may have false-negative results for *TFE3* FISH.
Methods: We investigated the clinicopathological features of 10 patients with *RBM10-TFE3* RCC. Histological analysis, immunostaining, dual-colour break-apart FISH for *TFE3*, RT-PCR and sequencing were done.
Results: *RBM10-TFE3* RCCs showed strong nuclear immunoreactivity for TFE3. FISH displayed consistent closely spaced split signals in RCCs of four patients, and polysomic signals with occasional closely spaced split signals in RCCs of six patients. In the latter six patients, five had renal failure and four developed tumours in hemodialysis kidneys. Five patients experienced recurrences including the two who died of metastases.
Conclusion: The present study suggests that the carcinogenesis of *RBM10-TFE3* RCC in some, but not all, patients may be associated with chronic kidney disease.

PS-17-025

Is presurgical biopsy accurate in grading prostatic adenocarcinoma? A comparison of ISUP Grade Groups and Gleason Scores in a tertiary Institute's cohort of paired needle biopsies and prostatectomies

D. Gigliano[1], S. Petronilho[1], A. Rodrigues[1], R. Henrique[1]
[1] IPO-Porto, Portugal

Background & Objectives: Following clinical suspicion of prostatic adenocarcinoma, most patients undergo needle biopsy. Apart from confirming the diagnosis, it provides the substrate for evaluating essential therapeutic and prognostic parameters. Among these, the Gleason Score (GS) is widely used. Additionally, since the last WHO classification (2016), reporting the new set of ISUP Grade Groups (ISUP-GG) is recommended. We aimed to assess the concordance of presurgical needle biopsy and radical prostatectomies (RP) in regard to GS and ISUP-GG.
Methods: We retrospectively identified a cohort of 209 patients, with both needle biopsy and corresponding RP diagnosed at IPO-PORTO by one of our two Uropathologists, between Jan/2009 and Dec/2018. Exclusion criteria included known preoperative neoadjuvant treatment and incomplete pathologic data. We defined overgrading as a biopsy-based GS/ISUP-GG higher than the RP-based GS/ISUP-GG. Undergrading was defined correspondingly. Descriptive statistics were used to compare GS and ISUP-GG between biopsies and RPs.
Results: Biopsy-based GS and ISUP-GG were identical to their RP-based counterparts in 70% (147) and 57% (118), respectively. GS undergrading/overgrading occurred in 24% (50)/6% (12) of cases, while ISUP-GG undergrading/overgrading in 35% (73)/9% (18) of cases, respectively. When considering the clinically relevant cut-off of ISUP-GG ≤2, the biopsy-based ISUP-GG more often undergraded [25% (36/143)] than overgraded [12% (8/66)] the RP-based ISUP-GG.
Conclusion: Biopsy-based ISUP-GG ≤2 is a frequently used criterion for including patients in active surveillance programs. Unsampled high-grade carcinoma is a recognized cause of active surveillance failure. In our cohort, 25% of patients with an initial biopsy-based ISUP-GG of 1-2, had a final RP-based ISUP-GG ≥3. Recognizing this group of patients is vital to avoid undertreatment.

PS-17-026

Chromophobe renal cell carcinoma with potential aggressive behaviour. Histologic and clinicopathologic analysis of 7 cases

M.L. Gomez Dorronsoro[1], I. Fernadez de los Reyes[2], A. Zabalo[3], M. Asiain[4], M. Bronte[2], M. Mercado[2], A. Panizo[2]
[1] CHNavarra. Pamplona. Dpt. Pathology, Spain, [2] CHN. Pamplona. Dpt. Pathology, Spain, [3] CHN. Pamplona Dpt. Urology, Spain, [4] CHN. Pamplona. Dpt. Urology, Spain

Background & Objectives: Chromophobe renal cell carcinoma (ChRCC) is a tumour of low malignant potential, but large scale studies have described 7% recurrence/metastases and tumour-related death happening in 6%-12% (5-10 years) of them.
In a retrospective study, gross and microscopic characteristics of ChRCC, recurrences, metastases and survival were evaluated in an attempt to identified those pathologic features that might display aggressive behaviour.
Methods: ChRCC treated with nephrectomy at our Department from 1996 to 2018 with available material for examination were reviewed.
In aggessive ChRCC, clinical, gross and microscopic features such as histologic type, microscopic necrosis, vasculo-lymphatic invasion, renal vein involvement, perinephric or sinus involvement and TNM were documented
Results: Thirty ChRCC were detected, seven cases with an adverse outcome (6 men/1 woman). Except for one case, all showed macro/microscopic necrosis and that one case presented tumour renal vein trombosis. Three cases had lymph node and distant metastases at diagnosis.
Four patients died from tumour. One patient with sarcomatoid differentiation died after 4 months. The other suffered from local recurrences or lymph node metastases with a median survival of 64 months (7-179). Old cases did not include the renal sinus among their variables, so two cases showing T1 stage were probably underestimated.
Conclusion: Microscopic necrosis was a common finding in these aggressive ChRCC.
Sarcomatoid differentiation was associated with a more aggressive behaviour.
The specific study of the renal sinus involvement is indispensable for an adequate staging.
Despite the appearance of metastasic disease, succeeding surgical or oncologic treatment, resolve in longer survival times.

PS-17-028

A clinicopathological analysis of synchronously multifocal renal cell neoplasms

G. Gümrükçü[1], E. Sayman[1], O. Yuksel[2], F. Aker[1], D. Ertoy Baydar[3]
[1] Haydarpasa Numune Hospıtal, Pathology, Turkey, [2] Haydarpasa Numune Hospital, Urology, Turkey, [3] Koc Unıversity, Pathology, Turkey

Background & Objectives: We conducted a retrospective analysis of nephrectomies performed in a single clinic to evaluate the incidence of synchronous multifocality of RCC and its relation to the stage, grade, size and histology.
Methods: Between 2005 and 2018, we examined 647 kidneys after partial/radical nephrectomy for renal cell carcinoma (RCC).

Results: Of 613 RCCs, 27 (4.4%) contained multifocal malignant or benign nodules. 6 patients had predisposing genetic syndrome (5 VHL, 1 tuberosclerosis). In 19 cases, multifocality was evident radiologically whereas it was detected after pathologic evaluation in the rest. The number of nodules ranged from 2 to innumerable. The average size of the lesions was 6.22 (range 0.5-13) cm. Tumours in 19 kidneys were the same histological type:12 clear cell (CCRCC), 2 clear cell papillary (CCPRCC), 1 papillary-type II, 1 sarcomatoid chromophobe (ChRCC),1 oncocytic papillary, 1 unclassified RCC and 1 oncocytoma. Careful histologic examination and immunohistochemistry showed that the ChRCC, PRCC and 8 of CCRCCs had intrarenal lymphovascular spread which lead to formation of intraparenchymal satellite multinodules giving the impression of multifocality. Median pT stage and WHO/ISUP grade were both 3 in this group of 10 cases. Discordant histologic subypes were found in 8 cases (2CCRCC+Oncocytoma, 1 CCRCC+PRCC, 1 CCPRCC+ChRCC, 1 ChRCC+Oncocytoma,1 ChRCC+AML,1 CCRCC+Low grade oncocytic unclassified RCC,1 tuberosclerosis-associated PRCC+AML)
Conclusion: RCCs with lower stage and grade have a higher tendency of multifocal nodules with dissimilar histologic subtypes. It seems that in the case of large infiltrative tumours, the presence of multiple foci may be the result of intrarenal metastasis from the main tumour lesion.

PS-17-029
Stromal lymphoid response is significantly lower in micropapillary urothelial carcinomas than in conventional urothelial carcinomas
E. Hacihasanoglu[1], K. Behzatoglu[2], E.R. Bozkurt[3]
[1] Sirnak State Hospital, Turkey, [2] Acibadem Health Group, Turkey, [3] Istanbul Training and Research Hospital, Turkey

Background & Objectives: Micropapillary urothelial carcinoma (MPUC) is an aggressive urothelial carcinoma (UC) variant. Stromal lymphoid response (SLR) status in MPUCs may be responsible for this and has not been studied before.
Methods: Electronical database was scanned for 'invasive UC' in bladder transurethral resection materials (B-TUR) between January 2010-March 2017. Hematoxylin-Eosin stained slides were re-examined. Cases with ≥5% MPUC were included and evaluated for age, gender, grade, stage, accompanying conventional UC/UC variants, in situ UC/MPUC, lymphovascular invasion (LVI), necrosis and SLR. SLR was scored semiquantitatively as 0-1-2-3. All parameters were also evaluated in 50 pure invasive conventional UC cases for comparison.
Results: Among 1440 B-TURs, 47 had ≥5% MPUC. Mean age was 69; 87% were male. pT1/pT2 was 23/24. All cases had high-grade features. Six were pure MPUC, 13 had other UC variants. Thirty-two had in situ UC, 2 in situ MPUC. LVI was present in 8, necrosis in 9. SLR score was 0 in 15, 1 in 18, 2 in 9 and 3 in 5 cases. Advanced stage and LVI were higher and SLR was lower in MPUCs than conventional UCs.
Conclusion: MPUC shows significantly lower levels of SLR than conventional UC. Our study shows that low levels of SLR correlates with advanced stage and high frequency of LVI. Status of SLR may be one of the factors responsible for the aggressive clinical outcome and also have an important role in impaired therapy response in MPUCs.

PS-17-031
Mucinous tubular and spindle cell carcinoma: a report of 8 cases from a tertiary center
O. Hurdogan[1], H. Karatay[2], S. Erdem[3], I. Kilicaslan[2], Y. Ozluk[4]
[1] Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Turkey, [2] Istanbul Faculty of Medicine, Department of Pathology, Turkey, [3] Istanbul Faculty of Medicine, Department of Urology, Turkey, [4] Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare variant of renal cell carcinoma (RCC). This entity shows female preponderance and displays favourable prognosis. We aimed to document histopathological characteristics and clinical course of this rare neoplasm.
Methods: We retrospectively reviewed our archive between 2009-2018 and identified 8 cases diagnosed as MTSCC.
Results: There were 4 male and 4 female patients with a mean age of 52.9 (27-72) years. Six patients underwent radical nephrectomy and 2 patients partial nephrectomy. Two were consultation cases. Gross examination was performed at our Institution in 6 cases. Mean tumour size was 82.5 mm (45-150). In all cases histopathological examination revealed spindle cells with bland nuclei, tubular structures in myxoid stroma and extracellular mucin. Along with classical MTSCC morphology, one case demonstrated sarcomatous differentiation, scattered papillary structures as well as solid areas. Another case showed large areas of hemorrhage and necrosis accompanying a clear cell component along with typical areas for MTSCC. Mean follow-up time was 48.3±36.8 (range 10-112, median 51.5) months. Only two patients with histologically aggressive tumour areas were lost to disease due to metastases within post-surgical 10th and 112th months. No evidence of recurrence or metastasis was reported in the remaining 6 patients.
Conclusion: MTSCC is a unique renal tumour, generally with an excellent prognosis subsequent to surgical treatment and should be considered in the differential diagnosis of spindle cell renal tumours. Adequate sampling and thorough histopathological evaluation is essential for proper classification.

PS-17-032
Detection of AHNAK overexpression in bladder urothelial carcinoma cells using quantitative proteomics analysis and immunohistochemical stain
C. Hyun[1], S. Song[2]
[1] Department of Pathology, Jeju National University Hospital, Republic of Korea, [2] Jeju National University, Republic of Korea

Background & Objectives: Cytological examination of urine is the most widely used non-invasive pathologic screen for bladder urothelial carcinoma (BLCA); however, inadequate diagnostic accuracy remains a major challenge.
Methods: We performed high-throughput proteomic analysis of ten paired BLCA and benign urothelial lesion (BUL) samples to identify ancillary proteomic markers for use in liquid-based cytology (LBC). Samples were analysed mass spectrometry to identify differentially expressed proteins (DEP) between the two groups. A total of 4,839 proteins were identified and 111 DEP were confirmed as expressed at significantly different levels between the BLCA and BUL groups. Independent proteomic data generated from tissue samples (7,916 identified proteins and 784 DEP), along with comparative mRNA expression profiles from The Cancer Genome Atlas were analysed for biomarker discovery.
Results: Six proteins, AHNAK, EPPK1, HSP90AB1, MYH14, OLFM4, and TUBB, were thereby identified as putative candidate and analysed by immunostaining. To determine their immunocytochemical expression levels in LBC, protein expression was screened using data from The Human Protein Atlas and five proteins were finally selected for immunoreactivity validation in two independent LBC cohorts. These analyses confirmed AHNAK as a unique intracellular protein differing in immunohistochemical expression and subcellular localization between tumour and non-tumour cells.
Conclusion: this study identified a new biomarker, AHNAK, applicable to discrimination between BLCA and BUL by LBC. To our knowledge, the present study provides the first identification of a clinical biomarker for LBC based on in-depth proteomics.

PS-17-033
Teratoma prepubertal-type of the testis. 20-year experience of La Paz University Hospital, with 19 cases
N. Ibarra[1], E. García Fernández[1], M. Nistal[1], P. González-Peramato[1]
[1] Hospital La Paz, Spain

Background & Objectives: Our aim was to review all the teratomas prepupertal-type (TPT) (WHO 2016) and assess the age of presentation, histological findings and their behaviour.
Methods: We searched in our database all teratomas in the last 20 years, selecting for review those without germ cell neoplasia in situ (GCNIS).
Results: We found 72 cases of teratoma. Of them, 19 (26%) were TPT. In TPT cases, the patients´ age ranged from 10 months to 58 years, being 8 (42%) older than 15 years. The histological diagnosis was epidermoid cyst in 12 cases (63%), dermoid cyst in 2 cases (11%) and TPT in 5 cases (26%). All cases lacked GCNIS, dysgenetic changes (microlithiasis or Leydig cell hyperplasia), atypia or regressive changes in the adjacent testicular parenchyma. One case showed Sertoli cell-only. Six cases (31%) had an organoid pattern. No case showed recurrence or metastasis. The follow-up was between 5 and 19 years. Eight cases (42%) underwent radical orchiectomy and 11 (58%) underwent tumour enucleation.
Conclusion: TPT represented 26% of all teratomas. It stands out that 42% were older than 15 years. The histological diagnosis was: epidermoid cyst (63%), dermoid cyst (11%) and TPT (26%). The surrounding testicular parenchyma lacked alterations and, except for one case, all adults showed complete spermatogenesis. Teenagers showed pubertal maturation and children normal tubule fertility index and normal germ cell maturation. No case had recurrence or metastasis. TPT has benign behaviour so testis-sparing surgery could be a valid option in these cases.

PS-17-034

Neuropeptide Y and its receptors (NPY system) in prostate cancer - immunohistochemical study

W. Wesolowski[1], E. Iżycka-Świeszewska[2], A. Gruszecka[2], J. Gulczyński[3], D. Sigorski[2], E. Szwed[4], J. Kitlinska[5]
[1] EL PAT Co, Poland, [2] Medical University of Gdansk, Poland, [3] Medical University of Gdańsk, Department of Pathology and Neuropathology, Poland, [4] Copernicus Hospital Gdansk, Poland, [5] Georgetown University, USA

Background & Objectives: Prostate cancer (PCa) is one of most common malignancies in men, with high morphological and clinical heterogeneity, from clinically insignificant to advanced, incurable cases. Despite many prognostic factors and nomograms, there is no effective tool to predict disease outcome and cure disseminated cancer. Therefore it is necessary to search for novel biomarkers and possible future therapeutic targets. One of new directions in oncology are neuropeptides and relations cancer cells - neural microenvironment.
Methods: The material comprised of 51 primary prostate cancer cases and 11 bone metastases. The patho-clinical data: age, pT feature, Gleason score and Grade Group were considered. Microarray technique was performed on 0.5cm tissue cores, with supplement of full slides in some of the cases. Among NPY system (NPY, Y1R, Y2R, Y5R) strength of reaction, expression index (EI) as well as distribution of reaction in cell and tissue were evaluated. Perineural invasion and extraprostatic extension areas were assessed separately. In the same time NPY system were explored in PIN and benign prostate (BP). ERG status and proliferative index Ki67 was also assessed. Statistical analysis was performed.
Results: Performed study reveal expression of NPY in PCa and BP with quality differences: homogeneous membrane-cytoplasm pattern in cancer cells and membranous with apical accentation in BP.
EI and expression intensity h of NPY receptors were higher in PCa then in BP with correlation among Y2R and Y5R. Moreover PIN, bone metastases and PCa displayed similar EI of all NPY system elements. Interestingly, zonal distribution of immunohistochemical reaction in reference to all system were seen with markedly higher strength of signal in perineural invasion and EPE areas. There were no statistically significant differences between NPY system and clinico-pathological features.
Conclusion: The observations indicate activation of NPY system in PCa and its possible auto and paracrine role, participation in perineural invasion and extraprostatic extension. Similar reactivity of NPY elements in PIN and PCa speaks for its universal character and early event in prostate cancerogenesis.

PS-17-035

Both cytoplasmic and nuclear immunohistochemical staining for AMP-activated protein kinase is associated with prognosis of clear cell renal cell carcinoma and with expression of Smads proteins

M. Jung[1], C. Lee[2], J.H. Park[3], K.C. Moon[4]
[1] Department of Pathol, Seoul National Univ. Hosp., Republic of Korea, [2] Department of Pathology, Seoul National University Hospital, Seoul, Republic of Korea, [3] Department of Pathology, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea, [4] Seoul National University, Republic of Korea

Background & Objectives: AMP-activated protein kinase (AMPK), an intracellular energy sensor protein, was known for its tumours-suppressive functions against various cancers, including clear cell renal cell carcinoma (ccRCC). In addition, AMPK was reported to downregulate TGF-β/Smad pathway partly by suppressing phosphorylation of Smad2/3 proteins. We aimed to evaluate the prognostic significance of immunohistochemical (IHC) staining for pAMPK and its association with the expression of Smads proteins in ccRCC.
Methods: IHC staining for pAMPK (Thr-172), pSmad2 (Ser-467), and Smad4 was performed on 455 resected ccRCC samples using tissue microarray. Cytoplasmic and nuclear IHC staining for pAMPK was measured respectively, in semiquantitative manner. Nuclear reaction to Smads proteins was counted with digital analyser. Kaplan-Meier and cox-regression survival analyses were performed. Nuclear expression of Smads proteins were compared between pAMPK-high and -low tumours. In addition, the change of pSmad2 of human ccRCC cell Caki-1 was investigated with AMPK activator (5-aminoimidazole-4-carboxamide-1β riboside) treatment.
Results: High cytoplasmic and nuclear expression of pAMPK was observed in 263 (59.1%) and 241 (54.2%) tumours, respectively. High pAMPK expression was predictive of longer progression-free (both, $p<0.001$) and cancer-specific survival (cytoplasmic, $p=0.003$; nuclear, $p<0.001$). Furthermore, high cytoplasmic expression of pAMPK was an independent favourable prognostic factor of progression-free survival ($p=0.013$, hazard ratio=0.563) when adjusted to grade and stage. pAMPK-high tumours showed higher pSmad2 and Smad4 nuclear expression than pAMPK-low tumours ($p<0.001$). Consistently, pSmad2 was elevated with pAMPK activation *in vitro*.
Conclusion: We identified that IHC staining for pAMPK, in either cytoplasmic or nuclear manner, was significantly associated with prognoses of ccRCC. High cytoplasmic expression of pAMPK was independently associated with favourable outcome of ccRCC. Positive association between expression of pAMPK and Smads proteins was observed both *in vivo* and *in vitro*, which may be a novel finding of ccRCC.

PS-17-036

Bladder urothelial carcinoma patients under the age of 40 years; clinical and pathological characteristics and outcomes

Ö. Kaya[1], S. Ekmekçi[1], E. Kısa[2], Ü. Küçük[1]
[1] Izmir Tepecik Training and Research Hospital, Department of Pathology, Turkey, [2] Izmir Tepecik Training and Research Hospital, Department of Urology, Turkey

Background & Objectives: Urothelial carcinoma (UC) is the most common tumour of the urothelial tract. Urothelial carcinoma of the bladder (UCB) is rare in younger adults and occurs more commonly in older individuals. Objective of this study is to analyse clinical and pathological characteristics of UCB in patients under the age of 40.
Methods: Nineteen patients who were diagnosed less than 40 years old as UBC in our hospital between 2007-2019, and who had clinical follow-up

were included in this study. Age, gender, symptoms, tumour stage, recurrences, disease progression, the postoperative follow up period and survival time of the patients were obtained from the patients files. Hematoxylin and eosin stained sections of the tumours were re-evaluated. Tumour growth pattern, tumour grade, pT stage, tumour differentiation were documented.
Results: The study consisted of 16 (84.2%) male and 3 (15.8%) female patients. The mean age at diagnosis was 32,95 years. One cases (5.3%) died, 18 cases (94.7%) were alive. Nine (47.4%) cases showed papillary growth pattern, 6 (31.6%) cases papillary and inverted growth pattern. The pathologic tumour stages were 8 (42.1%), 7 (36.8%), 2 (10,5%) and 2 (10,5%) for Ta low grade, Ta high grade, T1 high grade and T2 high grade respectively.
Conclusion: Bladder UC is a very rare condition in young patients. Studies have suggested that younger patients with urothelial tumours are related to more favourable outcomes. Our results supported that the younger patients usually present with low-grade bladder cancer. So clarifying this relationship, further studies including larger patient cohorts are needed.

PS-17-037

Expression of 34betaE12, D2-40, and P504S immunohistochemical markers in atypical small proliferation and prostate adenocarcinomas

E. Kazachkov[1], A. Dub[1], I. Cheter[1], D. Voropaev[1]
[1] South Ural State Medical University, Russia

Background & Objectives: Atypical small acinar proliferation (ASAP) is a problematic diagnostic category, the essence of which should be clarified by determining its immunohistochemical phenotype.
Methods: We used prostate biopsy samples obtained from 90 patients, which were divided into 6 groups according to the morphological diagnosis: ASAP and the carcinomas of Grade Groups 1-5. Normal prostate tissue samples served as controls. We performed an immunohistochemical staining method using 34betaE12, D2-40, and P504S antibodies. We applied non-parametric statistical methods.
Results: In the control group, the marker 34betaE12 expression [Me = 13% (3 - 36)] was noted in 100% of cases. In ASAP and Grade Group 1-5 adenocarcinomas, there was a complete absence of 34betaE12 in all cases. P504S expression was significantly less in the group of patients with ASAP [Me = 10 % (5-15)] than in adenocarcinomas of Grade Groups 1-5 and was not registered in the controls. The lower was the degree of carcinoma gradation the higher were the index and intensity of P504S expression by atypical epithelial cells of the prostate tumour. The level of D2-40 expression in the basal epithelial cells was discovered only in the control samples (Me = 37.5% [14-47]). In ASAP and Grade Group 1-5 adenocarcinomas, D2-40 was not expressed.
Conclusion: Therefore, 34betaE12, D2-40, and P504S markers make it possible to determine the predominant phenotype of ASAP as the following: D2-40 (−), 34betaE12 (−), and P504S (+). This phenotype indicates the presence of prostate adenocarcinoma with high probability.

PS-17-038

Immunohistochemical evaluation of the lymphatic vessels in atypical small acinar proliferation and adenocarcinomas of the prostate

E. Kazachkov[1], A. Dub[1], I. Cheter[1]
[1] South Ural State Medical University, Russia

Background & Objectives: Currently, there is a lack of a reliable algorithm for differential diagnosis of nonneoplastic, premalignant processes, and prostate adenocarcinomas. Moreover, atypical small acinar proliferation (ASAP) is a problematic diagnostic category, therefore its immunohistochemical phenotype should be clarified.
Methods: We divided prostate biopsy samples of 90 patients into 6 groups according to morphology (ASAP and the carcinomas of Grade Groups 1-5). Normal prostate tissue samples served as controls. We performed immunohistochemistry using 34betaE12, D2-40, and P504S (AMACR) antibodies and applied non-parametric statistical methods.
Results: The expression of 34betaE12 [Me = 13% (3 - 36)] was noted in every control sample and absent in the other groups. AMACR expression was significantly less in ASAP [Me = 10 % (5-15)] than in adenocarcinomas and was not registered in the controls. The lower was the degree of carcinoma gradation the higher were the index and intensity of AMACR expression by atypical epithelial cells of the prostate tumour (from [Me = 42% (28-47)] to [Me = 64% (55-69)]). D2-40 expression was noted in the controls only (Me = 37.5% [14-47]).
Conclusion: The 34betaE12, D2-40, and AMACR antibodies make it possible to determine the predominant phenotype of ASAP as the following: D2-40 (−), 34betaE12 (−), and P504S (AMACR) (+). This phenotype determines prostate adenocarcinoma with high probability. The absence of 34betaE12 and D2-40 expression in ASAP, along with the identification of its AMACR-positive phenotype, may be used to identify neoplastic transformation of the epithelium and to consider the early prostate rebiopsy.

PS-17-039

Tertiary Gleason, grade groups and biomarkers for prostate cancer risk stratification: models and algorithms

G. Kharaishvili[1], Z. Kolar[2], J. Bouchal[3], M. Kral[4]
[1] Department of Clinical and Molecular Pathology, Faculty Hospital in Olomouc, Czech Republic, [2] Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic, [3] Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Olomouc, Czech Republic, [4] Department of Urology, Faculty Hospital in Olomouc, Czech Republic

Background & Objectives: Tertiary Gleason patterns are reported with increasing frequency in relation with disease recurrence (Epstein et al 2012, Trock et al 2009). A new contemporary prostate cancer grading system was proposed in 2014 for accurate grade stratification (Egevald et al 2016). We have previously reported association between periostin, Skp2 and Slug in aggressive prostate cancer. We decided to verify association of tertiary Gleason and ISUP contemporary grade groups with expression of these and other selected proteins in our patients using mashine learning tools.
Methods: Formalin fixed paraffin embedded tissues of 101 prostate carcinomas were stained immunohistochemically for PSA, periostin, versican, E-cadherin, beta-catenin, vimentin, Skp2, Slug, Ki67, p53, androgen receptor, and scored. Slides were reviewed for the presence of tertiary Gleason (worse than the primary and secondary grade, usually pattern 4 and 5). Carcinomas were classified into localized, advanced and metastatic groups, and ISUP 2014 Gleason grade groups (GG1-5 [1=GS≤6; 2=GS3+4; 3=GS4+3; 4=GS8, 5=GS9-10], Pierorazio et al 2013 and Epstein et al 2016). Statistical analysis was performed by SPSS and STATISTICA softwares. Hierarchical cluster analysis (average linkage, within groups) was done to identify subgroups based on protein expression. Kohonen importance network was generated for accurate clustering and associations.
Results: Tertiary Gleason was recognized in 22% of radical prostatectomy cases, it was more frequent in advanced and metastatic tumours ($p<0.001$). It also positively correlated with total preoperative PSA (Rs 0.303, $p=0.003$), Ki67 (Rs 0.209, $p=0.045$) and periostin stromal expression (Rs 0.276, $p=0.008$) while negative correlation was observed for membrane-localized beta-catenin (Rs -0.211, $p=0.035$). Gleason grade groups were in negative association with E-cadherin (Rs -0.203, $p=0.045$) while with nuclear Skp2 and periostin stromal expressions showed positive association (Rs 0.338 and 0.269, $p=0.001$ and 0.008, respectively). Periostin stromal positivity correlated with versican stromal expression (Rs 0.368, $p<0.001$) and stromal versican correlated with stromal vimentin (Rs 0.332, $p=0.001$). Chi-square test based correlation network showed significant relationships between AR, GS groups, stage and clusters ($p<0.001$, $=0.006$, $=0.004$, respectively). Kruskal-Wallis Anova test revealed significant differential expressions of stromal periostin ($p=0,017$), stromal versican ($p<0.001$), as well as Skp2 ($p<0.03$) and AR ($p<0.001$), in different clusters. Models for conditional high risk groups identified Ki67 as an important predictor.

Conclusion: For the first time, we showed significant association of grade groups GG4/5 and tertiary Gleason with periostin, Ki67, Skp2 and beta-catenin. Cluster analysis revealed significant differences of versican, periostin, AR, tertiary Gleason and Grade Groups between patients clusters. Larger cohorts are further needed to accurately identify potentially aggressive prostate cancer using selected models.

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PS-17-040

Renal cell carcinoma in patients 40 years of age or under: a single-center experience

M. Kilic[1], S. Ekmekci[2], E. Kisa[3], U. Kucuk[4]
[1] Tepecik Education & Research Hospital, Department of Pathology, Turkey, [2] Izmir Tepecik Training and Research Hospital, Department of Pathology, Turkey, [3] Tepecik Education & Research Hospital, Department of Urology, Turkey, [4] Izmir Tepecik Education and Research Hospital department of Pathology, Turkey

Background & Objectives: Early-onset Renal Cell Carcinoma (RCC) patients differ in survival, stage and tumour type compared to older patients. In this study, stages, histopathological features and their relationship with survival at early-onset RCC are evaluated.
Methods: Twenty-one patients who were diagnosed as RCC in our hospital between 2008-2018 and who were aged 40 or under were included in this study. Age, gender, tumour size, tumour stage, histological subtype, Fuhrman grade, renal capsule invasion (RCI), perinephric fat invasion (PNFI), renal sinus fat invasion (RSFI), necrosis, survival status were documented.
Results: The study consisted of 10 male,11 female patients. One of the male patients had Von Hippel Lindau Syndrome. The mean follow-up period was 43.8 months. Three of the patients died because of the disease. Nine (42.8%) cases were clear cell RCC (CCRCC), 5 (23.8%) Chromophobe RCC, 2 (9.5%) Translocation RCC, 3 (14.2%) RCC, Not Otherwise Specified, 1 (4.7%) RCC Papillary type 1, 1 (4.7%) RCC Papillary type 2. Eighteen cases were stage 1, 3 were stage 3. Necrosis was present in 3, PNFI in 2, RSFI in 2, RCI in 6 cases. Statistical analysis revealed that PNFI, RSFI, RCI, necrosis, stage were significantly associated with survival (respectively, $p=0.003$, $p=0.009$, $p=0.017$, $p=0.047$, $p<0.01$).
Conclusion: In young adults under 40 years RCC is seen in a very low ratio. In the English literature that approximately 80% of RCCs in young adults are CCRCC, and most of them are low stage. Most of the cases in our series were low stage CCRCC with good prognosis as in the literature.

PS-17-041

Stem cell markers in urothelial carcinomas and their prognostic value

E. Kogan[1], Y. Osmanov[1], S. Demura[1]
[1] First Moscow State Medical University (Sechenov University), Russia

Background & Objectives: The question of the presence of cancer stem cells (SC) in urothelial carcinomas (UC) of various immunophenotypes is currently open. The possibilities of a number of potential markers of stem in tumour cells for the determination of cancer SCs in urothelial carcinomas and their prognostic significance are discussed. The purpose of the study is a comparative assessment of the expression of stem markers in different immunophenotypes of UC and the determination of their prognostic significance.
Methods: Material and methods. The study was performed on surgical material from 196 patients with UC of the renal pelvis and bladder. Immunohistochemistry was performed on paraffin sections using a standard protocol. The antibodies used were: ALDH1A1, CD133, CXCR4, NANOG, OCT4, SOX2 ("Abcam"), CD24, CD105 ("Invitrogen"), CD31, CD34 ("Novocastra").
Results: It was established that the frequency and intensity of expression of SC markers correlated with the tumour stage and the degree of cellular anaplasia. The SC markers used in the study expressed in all types of UC and did not differ in both frequency and expression intensity.
Conclusion: Tumour cells of different UC can maintain SC markers, reflecting the degree of their immaturity. The number of stemless tumour cells correlates with the stage of the tumour progression and the prognosis. The revealed features of the expression of SC markers will make it possible to develop new approaches to the treatment of urothelial carcinomas.

PS-17-042

Pathology of testes in male addicts

N. Krupnov[1], A. Astrakhantsev[2]
[1] Bureau of Forensic Medicine, Ryazan, Russia, [2] Central Clinical Hospital №2 named after N.A. Semashko, Moscow, Russia

Background & Objectives: Drug use causes the development of not only mental dependence, but also damage to internal organs.
Objective: Morphological analysis of testicular structural changes in men with drug addiction.
Methods: The testicles of 42 patients aged 20–35 years who suffered from inject opioid (desomorphine) addiction and dead from accidents were studied. The control group consisted of 18 healthy testicles from men of the same age who died from accidents. Macroscopic, histological and morphometric studies of testicular tissue were performed.
Results: In macroscopic examination, the testicular mass in drug addicts (32.35 ± 1.22 g) on 26.9% less than the value of control group. When morphometric analysis of histological preparations of drug addicts testicles, the volume of the tunica albuginea (2.67 ± 0.37 cm^3) is less than the values of the control value by 13%. The volume of the testicular network (0.39 ± 0.09 cm^3) is less than the control by 31.6%, and the volume of the convoluted seminiferous tubules (7.50 ± 1.59 cm^3) - less by 55%. Along with the lesion of the canalicular apparatus, at drug addiction revealed focal necrosis of the seminiferous tubules and an increase of interstitial connective tissue volume (6.10 ± 1.13 cm^3) by 20.0% compared to the control group.
Conclusion: In male-drug addicts, a decrease in testicular mass and violation of their structure, mainly in the form of a decrease in the absolute volume of the seminiferous tubules and interstitial connective tissue has been found.

PS-17-043

Performance of an AI-based cancer diagnosis system in France's largest network of pathology Institutes

D. Laifenfeld[1], J. Sandbank[1], C. Linhart[1], L. Bien[1], D. Raoux[2]
[1] Ibex Medical Analytics, Israel, [2] Medipath, France

Background & Objectives: Prostate cancer is the second leading cause of cancer-related deaths, compounded by complexity of diagnosis, insufficient diagnostic reproducibility, and a growing shortage in pathologists. Ibex Medical Analytics, focusing on AI-based cancer diagnostics, has developed an algorithm that identifies various cell types, tissue structures and morphological features within whole slide images of prostate core needle biopsies (PCNBs), such as cancerous glands (of Gleason patterns 3, 4 and 5), high-grade PIN, and inflammation. The algorithm utilizes state-of-the-art Artificial Intelligence (AI) and Machine Learning techniques and was trained on hundreds of thousands of image samples, the majority taken from hundreds of manually annotated PCNBs from Maccabi Healthcare Services centralized pathology lab. Medipath is the largest network of pathology Institutes in France, servicing 370000 patients including 5000 prostate biopsies annually. The goal of this study was to assess the performance of the algorithm on benign slides from 4 different labs within the network, and to assess the error rate in these labs.

Methods: 150 anonymized cases with pre-specified features were used for calibration of the prostate algorithm to the Medipath preanalytic processes. Upon calibration, 100 consecutive anonymized benign cases were scanned with a Philips UFS Scanner, uploaded to the Ibex cloud and analysed by the prostate algorithm.
Results: The performance of the algorithm on the benign cases will be discussed, including details on the confidence levels and identification of various features within the cases/slides.
Conclusion: AI-based algorithms such as developed by Ibex can be used in various stages of the diagnostic process, to enable higher accuracy in a fraction of pathologist effort and time, enabling faster turn-around-time and the diversion of resources to increase lab throughput.

PS-17-044

PDL1 protein expression and mRNA expression in TFE3 translocation renal cell carcinoma are associated with poor prognosis

H.J. Lee[1]
[1] Pusan National University Yangsan Hospital, Republic of Korea

Background & Objectives: Renal cell carcinoma (RCC) is widely recognized as a heterogeneous disease with various histological subtypes. Xp11.2 translocation RCC (tRCC) is a rare subtype, recognized as a distinctive pathological entity in the 2004 WHO renal tumour classification and it shows poor prognosis. Due to its chemoresistant phenotype, the mainstay of therapy for advanced RCC had been systemic immunotherapy. In this study, we tried to evaluate the result of PDL1 expression in tRCC, and examined lymphocyte infiltration with relation of prognosis.
Methods: Immunohistochemistry (IHC) for PD-L1, FOXP3 and CD8 expression in FFPE tissue sections were cut in 5-mm slices. IHC analysis was performed on tumour samples using antibodies against PD-L1 (E1L3 and SP142) and T cell proliferation for FOXP3 and CD8. TIL density score based on a 0–3 scale as follows: 0, no TILs; 1 (mild), <5% of the tumour area with TILs; 2 (moderate), 5–50% of the tumour area with TILs; and 3 (diffuse/marked), >50% of the tumour area with TILs.
Results: We did western blot for PDL1 expression in ASPL-TFE3 translocation RCC cell line and clear cell RCC cell line. ASPL-TFE3 translocation RCC cell line expressed PDL1 strongly in western blot. Patients with PD-L1+ tumour cells were significantly more likely to progress disease from tRCC compared with patients without PD-L1+ tumour cells ($P < 0.02$). In Kaplan- Meier survival analysis, TILs high groups were correlated with progression free survival ($p<0.001$).
Conclusion: We found that PDL1 expression and TILs with CD8+ proliferation in tRCC were correlated with poor prognosis. Overall, the current findings indicated that the expressions of PD-L1 protein and mRNA PD-L1 may serve as a potential marker of invasiveness and prognosis. Also, the high expression of PD-L1 in tRCC would be possible to clinically adopt the immunotherapy for targeting PD-L1.

PS-17-045

The clinicopathologic significance of long non-coding RNA urothelial cancer associated 1 via Hippo pathway in prostate cancer

H. Oh[1], Y.J. Lee[2]
[1] Korea University Anam Hospital, Republic of Korea, [2] Korea University Anam Hospital, Republic of Korea

Background & Objectives: Although overexpression of long noncoding RNA Urothelial Cancer Associated 1(UCA1) has been involved in several human cancers, its biological functions in prostate cancer have not been identified. Yes-associated protein 1(YAP1), a transcription cofactor, is a key component of Hippo pathway. When YAP1 is translocated into the nucleus, it promotes cell proliferation, inhibits apoptosis, and plays an oncogenic role. The aim of this study is to assess the clinicopathologic significance of UCA1 and determine their association with YAP1 in prostate cancer.
Methods: Seventy Paraffin embedded prostate cancer tissue specimens were retrospectively collected from 2009 to 2013 at Korea University Anam Hospital. All of the specimens were samples of radical prostatectomy with pathologically proven acinar adenocarcinoma. The expression of YAP1(anti-YAP1, diluted 1:1000) was determined by immunohistochemistry, scored by sum(0-8) of proportional score(0-5), and intensity score(0-3), and the expression of UCA1 were determined by RNA in situ hybridization according to the manufacturer's instructions, scored from 0 to +3.
Results: The expression of UCA1 was significantly correlated with the presence of extraprostatic extension, seminal vesicle invasion, pathologic T stage, and high or very high risk group according to the NCCN guideline. ($p<0.05$) On the other hand, it did not show significant correlation with lymphatic invasion, prognostic group, Gleason's score, recurrence, resection margin involvement, and disease free survival. Importantly, we found that UCA1 overexpression is correlated to increased nuclear YAP1 expression.
Conclusion: The present study revealed increased UCA1 in prostate cancer with poor clinicopathologic factors, supporting evidence of potential diagnostic and therapeutic efficacy. Also, we can propose new insight into the role of UCA1 through Hippo pathway in prostate cancer pathogenesis.

PS-17-046

The prognostic value of PD-L1 and CTLA-4 immunoexpression in immune cells and in tumour cells of testicular germ cell tumours

J. Lobo[1], A. Rodrigues[1], R. Guimarães[1], M. Cantante[1], P. Lopes[1], C. Jerónimo[1], R. Henrique[1]
[1] IPO Porto, Portugal

Background & Objectives: Novel less toxic treatments for testicular germ cell tumour (TGCT) patients are needed. Immunotherapy is on the brink, but has been scarcely explored in TGCTs, which naturally contain prominent immune infiltrate, especially seminomas. We aimed to assess the immunoexpression of immune-checkpoints PD-L1/CTLA-4 in a cohort of TGCTs and seek for clinicopathological correlates.
Methods: A total of 162 consecutively diagnosed patients (2005-2017) were included. In mixed tumours immunostaining was evaluated individually for each tumour component (total of 271 tumour samples). CTLA-4 and PD-L1 (clone 22C3) immunoexpression were assessed both in immune cells (ICs) and tumour cells (TCs), considering both intensity/proportion of positive cells. In the 109 seminoma samples the immune infiltrate was further characterised by CD20/CD3/CD4/CD8/CD56/CD68.
Results: 156/162 (96.3%) and 136/160 (85.0%) TGCTs exhibited CTLA-4- and PD-L1-positive ICs, with no significant differences among seminomas/non-seminomas. Patients with <20% CTLA-4-positive ICs showed significantly more *rete testis*/lymphovascular invasion ($p=0.0474$,$p=0.0312$) and pT2-3 stage ($p=0.0325$); those with absent PD-L1-positive ICs showed significantly more relapse and Intermediate/Poor IGCCCG ($p=0.0078$,$p=0.0300$). 235/262 (89.7%) and 65/262 (24.8%) samples showed TCs positive for CTLA-4 and PD-L1, respectively. Teratomas, choriocarcinomas and yolk sac tumours exhibited significantly higher intensity staining in TCs for CTLA-4 ($p<0.01$). Choriocarcinomas and teratomas displayed significantly more and less frequent PD-L1-positive TCs, respectively ($p<0.05$).
Conclusion: These preliminary results demonstrate the prognostic value of immunoexpression assessment of immune-checkpoints in TGCTs and point towards a possible clinical benefit of agents targeting PD-L1/CTLA-4.

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PS-17-047

Programmed Death Ligand-1 (PD-L1) immunohistochemical assessment using QR1 clone in muscle-invasive urothelial carcinoma: a comparative study with 22C3 clone

A. Loghin[1], A. Nechifor-Boila[1], A. Borda[1], I.A. Nechifor-Boila[2], S. Voidazan[3], E. Dee[1], M. Decaussin-Petrucci[4]
[1] Department of Histology, UMFST Targu-Mures, Romania, [2] Department of Anatomy, UMFST Targu-Mures, Romania, [3] Department of Epidemiology, UMFST Targu-Mures, Romania, [4] Department of Pathology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Universite Lyon 1, Pierre Benite, France

Background & Objectives: PD-L1 immunohistochemistry (IHC) is used to guide treatment decision regarding the use of checkpoint immunotherapy in urothelial carcinoma (UC). QR1 (Quartett) is a novel PD-L1 IHC assay with proven efficiency in lung cancer, but no data in UCs. The aim of our study was to compare the performances of QR1 PD-L1 IHC expression to 22C3 clone (Dako) (one of the approved antibody for UCs), in a cohort of muscle-invasive UCs.
Methods: Our study included 69 UC cases. PD-L1 IHC status was assessed using both QR1 and 22C3 clones. Combined Positive Score (CPS), percentage of positive tumour cells (TC) and tumour-infiltrating immune cells (IC) were determined. The positivity cutoffs were set at CPS ≥10, TC and/or IC ≥25%. Cohen's kappa statistics were used to compare scoring methods.
Results: Among all the 69 cases, 28(40.6%) were considered positive when using CPS assessment for both QR1 and 22C3 clones, with a kappa agreement factor of 0.880 ($p<0.001$). When the percentage of positive TC and/or IC ≥25% was considered as positive for QR1 and CPS≥10 for 22C3, respectively, the corresponding kappa factor was 0.791 ($p<0.001$).
Conclusion: Our study is the first one demonstrating that QR1 clone can be used to evaluate PD-L1 status in UCs, with a very good agreement rate compared to 22C3 clone. The best agreement factor was obtained when CPS was applied for QR1 evaluation. Consequently, QR1 clone could be an alternative antibody in PD-L1 IHC status assessment to guide treatment decision regarding the use of checkpoint immunotherapy in UC.

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PS-17-048

Genomic instability in morphologically normal urothelium in patients with low grade (LG) and high grade (HG) urothelial carcinoma (UC)

T. McHale[1], K. Gilligan[2], R. Dwyer[2], S. Bastacky[3]
[1] HSE/NUIG, Ireland, [2] NUIG, Ireland, [3] UPMC, USA

Background & Objectives: In this study we examine the level of genomic instability in background normal urothelium at the time of presentation of patients with low grade and high grade urothelial carcinoma.
Methods: Using loss of heterozygosity analysis (LOH), we compared the level of fractional allelic loss (FAL) in microdissected and anatomically separate samples of normal urothelium and matched tumour samples in LG and HG UC patients. A panel of 20 microsatellite (MS) markers was used. FAL was calculated as the number of loci with LOH / the number of informative markers. 22 LG and 12 HG (all pT0) cases were analysed.
Results: The mean FAL for LG and HG UC was 0.48 and 0.44, respectively (not significant). FAL for normal urothelium in patients with LG and HG carcinoma was 0.49 and 0.41, respectively (not significant). For LG UC patients at first presentation, mean FAL of tumour was 0.49 and of normal urothelium was 0.5. Mean concordance between tumour and normal urothelium for pattern of LOH across all MS markers was 0.56 for LG and 0.62 for HG UC.
Conclusion: The level of genetic instability by LOH in normal urothelium in patients with UC is similar to that present in tumour tissue, even for patients at first presentation of LG UC. The development of molecular-based testing of urine samples for tumour diagnosis and surveillance will need to take account of this finding.

PS-17-049

Is intraoperative frozen section consultation during nephron sparing surgery really warranted? An audit from a tertiary oncology center

S. Menon[1], G. Bakshi[2], G. Prakash[3], A. Joshi[4], S.B. Desai[5]
[1] Department of Pathology, Tata Memorial Hospital, Mumbai, India, [2] Tata Memorial Centre Mumbai India, India, [3] UroOncology, Tata Memorial Centre, India, [4] Tata Memorial Centre Mumbai India, India, [5] Pathology, Tata Memorial Centre, India

Background & Objectives: Small renal masses are now amenable to be treated by nephron sparing surgery. Our aim was to retrospectively analyse the pathologic characteristics of nephron sparing surgery (NSS) seen at our Institute with emphasis on intraoperative frozen section margin assessment.
Methods: A 10-year retrospective clinico-pathologic analysis of NSS seen at our Institute was done. The histopathology slides were reviewed and frozen section data was recorded. Patient demographics and follow-up was obtained from electronic medical records.
Results: 115 cases of NSS patients were identified. 105 cases had a malignant diagnosis of which the commonest was conventional renal cell carcinoma (81 cases). 81 cases had pathologic stage 1 (pT1) tumours with median tumour size of 3.2 cm. Intra-operatively frozen margin was positive in 18 /74 cases (24.3%) of which 10 were revised. The mean margin for all cases was 2.1mm. Only two patients of Type 2 papillary renal cell carcinoma, developed recurrence during the period of follow-up.
Conclusion: Intraoperative frozen section consultation has a minimal role in evaluation of margins of NSS as even close/positive margins are not associated with an increased risk of local recurrence in small renal tumours. Mini margins of even less than 5mm are associated with excellent loco-regional control of disease.

PS-17-050

Collecting duct carcinoma of kidney: a clinicopathologic and immunohistochemical study of 12 cases from a single tertiary oncology centre

S. Menon[1], G. Bakshi[2], A. Joshi[2], S. Desai[2]
[1] Department of Pathology, Tata Memorial Hospital, Mumbai, India, [2] Tata Memorial Centre Mumbai India

Background & Objectives: Collecting duct carcinoma (CDC) comprises less than 1% of all renal tumours. Our objective was to study the clinicopathological and immunohistochemical (IHC) features of collecting duct carcinoma of kidney at our Institute.
Methods: Cases of collecting duct carcinoma were searched on the electronic pathology database over a period of six years. The histopathology slides and immunohistochemistry (IHC) were reviewed. The clinical details and follow up of these patients were obtained from electronic medical records and case files.
Results: Twelve cases of collecting duct carcinoma of kidney were retrieved. Ten were males and two patients were female. Median age was 50 years. Six cases were Stage III and 2 were stage IV. The tumour cells were variably arranged in cords, trabeculae, and tubulo-papillary pattern. Desmoplasia, necrosis and wreath- like periglomerular tumour spread was noted (100% cases). IHC for CK19, CK7 and HMWCK was positive in 91% cases. Two patients developed metastasis locoregional and distant metastasis within 2 years.
Conclusion: Collecting duct carcinoma of kidney is a rare renal cancer. The morphological characteristics are variable and careful gross, microscopy and ancillary immunohistochemical marker evaluation is necessary for correct diagnosis and patient management. The prognosis is dismal and research is needed to develop better therapies for this aggressive subset of renal cancer.

PS-17-051

Analysis of tumour depth invasion with Smoothelin antibody in equivocal TURBT surgical specimens

I. Mihai[1], B. Nataras[2], D. Herman[2], G.E. Olteanu[1,3], A. Gheju[1], A. Jurescu[1], O. Vita[4], A. Cumpanas[5], R. Bardan[5], A. Dema[2]
[1] Department of Pathology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, [2] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania, [3] Centre for Gene and Cellular Therapies in Cancer - Oncogen, Romania, [4] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [5] Department of Urology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania

Background & Objectives: The aim of our study was to evaluate some immunohistochemical (IHC) markers which can be of value in determining tumour depth infiltration in transurethral resection of urinary bladder tumour (TURBT) specimens.
Methods: Representative sections from 15 cases were selected: 5 cases of urinary bladder tumours with equivocal invasion of the muscularis propria (MP) diagnosed on TURBT specimens, 5 cases of the normal urinary bladder wall (UB) obtained from total cystectomy specimens with other malignancies and 5 cases with normal intestinal wall. The cases were analysed IHC with Smooth muscle actin (SMA) antibody and Smoothelin antibody. The positivity of the smooth muscle structures from the muscularis mucosae (MM) and MP was assessed.
Results: The reactivity for Smoothelin in the normal UB cases was: heterogeneous (4moderate, 1weak) in MP and predominantly negative in the MM. The staining pattern for Smoothelin in the intestinal wall cases was: moderate, diffuse (3cases) and weak, heterogeneous (2cases) in the MP; negative in the MM. All cases presented a strong and diffuse positivity for SMA in the MM and MP. Subsequently, the association of SMA and Smoothelin antibodies in the equivocal cases facilitated the classification of 4cases-pT1 and 1case-pT2.
Conclusion: Although the value of the study is limited by the few numbers of cases analysed, the association of Smoothelin and SMA can represent an attractive and useful combination of markers in the interpretation of problematic cases of TURBT specimens.

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PS-17-052

Expression profile and cellular localisation of GLI3 and PTCH1 proteins in healthy and tumour prostate tissue

I. Stefanac[1], M. Mrcela[2], D. Trnski[3], M. Sabol[3], V. Musani[3], P. Ozretić[3], S. Levanat[3]
[1] Primary Health Care Center Osijek, Croatia, [2] Medicinski Fakultet Osijek, Croatia, [3] Division of Molecular Medicine, Ruđer Bošković Institute, Zagreb, Croatia

Background & Objectives: The Hedgehog-GLI (HH-GLI) signalling pathway is primarily associated with embryonic development but its role in carcinogenesis has being intensely studied in the last two decades. Recent research indicates that HH-GLI pathway could be a key player in prostate cancer (PC) development and progression, as well as therapeutic resistance. The main objective of this study was to investigate the HH-GLI pathway activity in PC in comparison with healthy prostate and prostate inflammation.
Methods: Around 30 formalin-fixed paraffin-embedded tissue samples per group were collected from PC patients (Grade Groups I-V) and two controls groups (benign prostate tissue and prostate inflammation). Expression profiles of GLI3 and PTCH1 proteins was detemined immunohistochemically. The level of protein staining was expressed by multiplying percentage of positive stained cells and staining intensity (histoscore), separately for prostate epithelium and stroma. Cellular localization of protein staining (nuclear and/or cytoplasmic) was also determined.
Results: GLI3 and PTCH1 were overexpressed in epithelium ($P<0.0001$ for both), but not in stroma. GLI3 localization in epithelium was mostly diffuse (nuclear and cytoplasmic), while cytoplasmic GLI3 localization in stroma was negatively associated with Grade Group ($P<0.0001$). Same was observed for PTCH1 localization in epithelium and stroma ($P<0.0001$ for both). In prostate inflammation samples prevails cytoplasmic PTCH1, while in benign prostate diffuse. All HH-GLI patway components were expressed in androgen-dependent PC cell line LNCaP. Interestingly, androgen-deprived conditions significantly upregulated GLI3.
Conclusion: Our study has determined an increased activity of HH-GLI pathway in PC and potential role of GLI3 in androgen-independent growth. However, its relation to PC progression and mechanisms of sustaining androgen-independent growth has yet to be determined. Observation of higher nuclear localization of GLI3 in higher Grade Group could indicate an increased paracrine HH-GLI signalling, from tumour cells toward stroma.

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PS-17-053

Differential proteomic profiles in ASCL1-positive prostate cancer

F. Naples[1], I. Rapa[1], B. Pergolizzi[1], C. Barbero[1], D. Tota[1], A. Rigutto[1], E. Bollito[2], M. Volante[1]
[1] University of Turin, Italy, [2] AUO San Luigi Gonzaga, Orbassano (TO), Italy

Background & Objectives: Neuroendocrine differentiation (NED) in prostatic cancer is a frequent phenomenon, dynamically induced by androgen deprivation therapy. Over-expression of *ASCL1* has been demonstrated to be a pivotal mechanisms of NED, but the pathways impaired by its activation in prostate cancer cells are unknown.
To identify novel protein biomarkers associated with the transcriptional activation of *ASCL1* in prostatic cancer.
Methods: LNCaP cell line was transfected with *ASCL1* and empty vector, as control. Protein extracts were analysed by bi-dimensional electrophoresis and quantitative expression of the protein spots was evaluated with PDQuest Advanced software. Differentially expressed proteins were identified by mass spectrometry using MALDI ToF. Selected proteins were validated by means of immunohistochemistry in a series of 50 prostate cancer tissues segregated according to levels of *ASCL1* gene expression.
Results: 97 proteins were differentially expressed in LNCaP-*ASCL1* transfected as compared to control cells, and 29 additional proteins were exclusive of one or the other cell model. Of them, 30 were identified by mass spectrometry and regulate a variety of biological processes revealed by means of bioinformatics analysis. In addition, three of them, peroxiredoxin, calreticulin and alpha-enolase were selected for tissue validation according to their impact on cancer biology and availability of commercial antibodies for immunohistochemistry. In agreement with proteomic data, expression of calreticulin was increased whereas expression of peroxiredoxin and alpha-enolase was reduced in *ASCL1*-positive prostate cancer samples.
Conclusion: Our data identified specific proteomic profiles and novel tissue biomarkers associated with *ASCL1* transcriptional activation in prostate cancer.

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PS-17-054

Clear cell sarcoma of the kidney

R. Narjess[1], G. Sahraoui[2], R. Doghri[3], R. Sellami[2], O. Chakir[2], K. Mrad[3], L. Charfi[3], M. Driss[3]
[1] Institute of Carcinology Salah Azaïez Institute, Tunis, Tunisia, [2] Salah Azaïez Institute, Tunis, Tunisia, [3] Department of Pathology, Salah Azaïez Institute, Tunis, Tunisia

Background & Objectives: Clear cell sarcoma of the kidney (CCSK) is an uncommon malignant paediatric renal neoplasm. It has a propensity for aggressive behaviour and late relapses.
Our aim is to perform a clinicopathological study of CCSK.
Methods: Retrospective study of 7 cases of CCSK diagnosed at our department between January 2005 and December 2018.
Results: Our series included 4 male and 3 female patients. Mean age was 19 months (6 months-4 years old).
Right kidney was affected in 2 cases, the left in 1 case. In other cases, the side was not specified.
Diagnosis was made on a piece of nephrectomy in 6 cases.
The mean size of these tumours was 13 cm (6.5–24 cm). The cut surface was heterogeneous, with mucinous glistening appearance and cystic foci, in 3 cases.
Histologically, nests or cords of cells separated by regularly spaced fibrovascular septae was found in 6 cases.
Immunohistochemistry, including vimentin, CD34, cytokeratin, desmin, actin and CD99, was performed in 6 cases. Vimentin was positive in all these cases.
Abdominal lymph node metastases were present in 3 cases and distant metastases in 2 cases. Tumour recurrence was observed in 2 cases (after 2-3 years).
Conclusion: CCSK is notorious for mimicking virtually every other paediatric renal neoplasm, particularly nephroblastoma. The importance of distinguishing it from Wilms tumour lies in its poor prognosis. Immunochemistry is used to exclude differential diagnosis. Recently, molecular biology is regaining its place in the diagnosis of CCSK.

PS-17-055

PDL-1 in urothelial carcinoma: can clinical and pathological factors predict the immunohistochemical expression status?

I.A. Nechifor-Boila[1], A. Nechifor-Boilă[2], M. Decaussin-Petrucci[3], A. Loghin[4], C. Chibelean[5], A. Ruffion[6], S. Voidăzan[7], A. Borda[8,9]
[1] Department of Anatomy, UMFST Targu-Mures, Romania, [2] Department of Histology, UMFST Târgu Mureş, Romania, [3] Department of Pathology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Universite Lyon 1, Pierre Benite, France, [4] Department of Histology, UMFST Targu-Mures, Romania, [5] Department of Urology, Mureş County Hospital, Târgu-Mureş, Romania, [6] Department of Urology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Universitè Lyon 1, Pierre Bènite, France, [7] Department of Epidemiology, UMFST Targu-Mures, Romania, [8] Department of Histology, University of Medicine, Pharmacy, Science and Technology Târgu-Mureş, Romania, [9] Department of Pathology, Târgu-Mureş Emergency County Hospital, Romania

Background & Objectives: PDL-1 (Programmed Death Ligand -1) expression assessment is compulsory for anti-PDL1 chemotherapy in cisplatin-unfit urothelial carcinoma (UC) patients. We aimed to assess if current clinical and pathological factors could predict PDL-1 status in a transversal cohort study.
Methods: We included 69 patients with radical cystectomy performed for muscle-invasive UC in the Urology Department, Târgu-Mureş County Hospital (România) and Urology Department, Centre Hospitalier Lyon Sud (France). PDL-1 status was immunohistochemicaly assessed using the 22C3 clone (DAKO). The Combined Positive Score (CPS) was applied with the positive cut-off value set at ≥10.
Results: The majority of patients were men (57/82.6%). Pure classic UC was present in 36 cases (52.2%), followed by UC variants (n=33, 37.8%). PDL-1 CPS score was positive in 28 cases (40.6%). No statistically significant differences were observed between PDL-1 positive, versus PDL-1 negative cases in relation to patients' age (p=0.22), sex (p=0.33), carcinoma in situ (p=0.3), positive surgical margins (p=0.13), T (p=0.72), N (p=0.67) or M stages (p=0.86). However, UC variants were associated with a positive PDL-1 expression status (p=0.048), especially the squamous variant (p=0.0007), compared to classic UC.
Conclusion: No positive correlation was found between PDL-1 expression and the studied demographic and pathological factors, making the prediction of its expression unlikely. Presence of an UC variant could be associated to a positive PDL-1 expression but broader studies are required. PDL-1 immunohistochemical status assesment remains imperative for all patients requiring anti-PDL-1 targeted chemotherapy.

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PS-17-056

Evaluation of the true incidence of RCC in a large pathology department

G.E. Olteanu[1,2], I. Mihai[1], A. Jurescu[1], A. Gheju[1], D. Herman[3], A. Dema[3]
[1] Department of Pathology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, [2] Centre for Gene and Cellular Therapies in Cancer - Oncogen, Romania, [3] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania

Background & Objectives: Renal cell carcinoma (RCC) has an estimated incidence of approximately 1940 per 100000 people in Romania (GLOBOCAN), regrettably, no countrywide database exists to evaluate the true incidence of this pathology. The aim of our study was to retrospectively evaluate the incidence of renal cell carcinoma diagnoses in our pathology department over a period of 40 months (01.09.2015 - 01.01.2019) and to provide a starting point in collecting and evaluating the true incidence of RCC in Romania.
Methods: Our indexed database was searched for diagnoses of renal cell carcinoma in renal biopsy specimens, tumourectomy, partial nephrectomy, and total nephrectomy surgical specimens. The age range was established between 20 and 90 years of age. Exclusion criteria were a diagnosis of non-renal cell neoplasm arising in the kidney and the pathological evaluation of a metastatic lesion. Our indexed database was searched for diagnoses of renal cell carcinoma in renal biopsy specimens, tumourectomy, partial nephrectomy, and total nephrectomy surgical specimens. The age range was established between 20 and 90 years of age. Exclusion criteria were a diagnosis of non-renal cell neoplasm arising in the kidney and the pathological evaluation of a metastatic lesion.
Results: In the 40 months of retrospective data examined, 28.820 surgical specimens of non-tumour and tumour cases were examined in our pathology department. Out of 28.820 surgical specimens, 726 surgical specimens and biopsies of the kidney (non-tumour and tumour) were selected, out of which a total of 65 diagnoses of RCC were identified representing 8.95% of the cases. The results were further stratified based on sex, age, urban or rural residence, associated pathology, type of surgical specimen, and RCC type.
Conclusion: Our results provide an opening perspective of the true incidence of RCC in Romania in a large pathology department-based study and the prospects and implications of knowing the true incidence of a malignancy.

PS-17-057

Comparing the performance of three PD-L1 antibodies for PD-L1 expression in renal cell carcinoma

S. Park[1], Y.C. Wi[1], S. Shin[1], K. Jang[1]
[1] Department of Pathology, College of Medicine, Hanyang University, Seoul, Republic of Korea

Background & Objectives: Immunotherapies targeted against programmed death ligand 1 (PD-L1) and its receptor (PD-1) have improved survival in patients with advanced cancer. PD-L1 protein

expression has emerged as a biomarker that predicts which patients are more likely to respond to immunotherapy. For more effective immunotherapy for renal cell carcinoma (RCC), comparing the performance of PD-L1 antibodies has been necessary.
Methods: Three PD-L1 antibodies (SP142, SP263, and E1L3N) expressions in tumour and immune cells were immunohistochemically evaluated in 252 RCC patients. All PD-L1 immunohistochemistry assays were performed using Ventana Benchmark platforms. Each slide was estimated percentage of malignant and immune cells expressing PD-L1. Samples were defined as a positive when 10% or more PD-L1 expression of tumour cells and 1% or more of immune cells.
Results: Among 252 samples, the SP142 assay was an outlier, with a significantly lower positive rate in tumour cells (clear cell RCC, 3.3%; papillary RCC, 13.6%). The positive rate of E1L3N tests was higher than that of SP263 test in clear cell RCC (SP263, 7.2%; E1L3N, 18.2%). The positive rate of SP263 tests was higher in papillary RCC (SP263, 68.18%; E1L3N, 40.9%). There was no significant difference among three antibodies expression of immune cells (SP142, 59.1%; SP263, 72.6%; E1L3N, 71.0%).
Conclusion: The assay using the SP142 antibody is detected significantly less PD-L1 expression in tumour cells. The assay for antibody SP263 and E1L3N showed significantly different staining results among tumour subtypes.

PS-17-058
Review of collecting duct carcinomas in a tertiary hospital: 20 year review

A. Pezzella Risueño[1], I. Ruz-Caracuel[1], C. Ballesteros[1], E. Linares[1], E. Garcia-Fernandez[2], P. Gonzalez-Peramato[1]
[1] Hospital Universitario La Paz, Spain, [2] Hospital Universitario La Paz, Argentina

Background & Objectives: Collecting duct carcinoma (CDC) is a rare but very aggressive variant of kidney carcinoma. It´s frequency is less than 1%. Our objetive was to evaluate clinical aspects, histological (updated tp WHO 2016 classification) and immunohistochemical findings in CDC in a tertiary hospital.
Methods: We reviewed at the Department of Pathology 783 specimens of nephrectomy specimens between 1996 and 2017. Seventeen cases were diagnosed of CDC. After review of all the cases by two expert uropathologists and ancillary studies, 9 were admitted as CDC (1.15%).
Results: Median age was 68 (age range 48-82) years. Average size tumour was 7.4 (5-18) cm. The 50% of the patients had metastatic disease at diagnosis. After histological review 8 cases were re-classified as papillary carcinoma (4), urothelial carcinoma (3), morphological fumarate hydratase deficient carcinoma (1). We did immunohistochemistry, and all our cases of CDC were positive for PAX-8.
Of our CDC cases, 4 showed a predominant papillary pattern, the other cases had a tubular, tubulo-papillary, or tubulocystic morphology with an invasive ductal pattern and an associated desmoplastic response in the adjacent stroma.
At clinical follow-up all of them had metastasis, the lung the most frecuent organ, followed by liver and bone.
Overall survival after surgery was 7.3 months (1.5-23), 6 patients died of cancer related causes, 1 after surgery, 1 unkown and 1 alive.
Conclusion: CDC is a very rare, malignant epithelial tumour, with a bad prognosis. Half our cases had metastasis at diagnosis with an overall survival of 7 months. PAX8 helps in the differential diagnosis.

PS-17-059
Intraluminal inclusions in prostate cancer: association with level of inflammation

A. Piddubnyi[1], A. Romaniuk[1], R. Moskalenko[1]
[1] Sumy State University, Ukraine

Background & Objectives: Intraluminal inclusions (IIn) are found in 30% of prostate cancer (PCa) biopsies.
Objective: to estimate the influence of IIn on the level of inflammation in the PCa tissue.
Methods: 30 PCa samples with IIn (prostatic calculi and/or corpora amylacea) and 30 PCa control samples were used for the study. All samples were examined histologically (hematoxylin-eosin staining) and by immunohistochemistry (detection of CD68-positive and MPO-positive cells). All data was analysed by Shapiro-Wilk test, Mann-Whitney U-test and Student's t-test.
Results: Inflammation in PCa tissue was presented as diffuse or focal inflammatory infiltrates. PCa with IIn had 37.48±3.39 SD68-positive cells in the field of view with diameter 1 mm. Their localization was associated with IIn. Control PCa samples had 92.14±4.12 ($p<0.001$) CD68-positive cells. In the PCa with IIn 31.5±1.71 MPO-positive cells were detected. Their localization corresponded to areas of necrosis and tissue around the IIn. PCa without IIn had 13.89±1.26 ($p<0.001$) MPO-positive cells.
Conclusion: The presence of intraluminal inclusions in the prostate cancer tissue is accompanied by intense inflammation. This may lead to disease progression, increased invasive growth and metastasis development.

PS-17-060
The micronucleus frequency in urothelial exfoliated cells as possible additional test for early detection of urothelial cell carcinoma

A. Podrimaj-Bytyqi[1], S. Manxhuka-Kerliu[1,2], G. Gashi[1,2], L. Shahini[1,2], A. Borovecki[3]
[1] Faculty of Medicine, University of Pristina, Albania, [2] Institute of Pathology, University Clinical Center of Kosovo, Albania, [3] Institute of Pathology "Enge", Zurich, Switzerland

Background & Objectives: Bladder urothelial cell carcinoma (UCC) is an increasingly prevalent cancer worldwide. It has a higher incidence rate in men than in women; in people exposed to arsenic, cigarette smoking, alcohol, and so on. Cystoscopy is the gold standard for the detection of bladder tumours, followed by urine cytology and the UroVysion™ FISH test. Except for cytology, other methods, although they have high detection rates, are expensive, time consuming and uncomfortable.
Methods: Overall forty first-diagnosed and non-smoker patients (men) with UCC and twenty controls were enrolled in the study. Patients were divided according to tumour grade in low grade UCC (N=20) and high grade UCC (N=20), and according to tumour muscle invasion in non-muscle-invasive UCC (N=16) and muscle-invasive UCC (N=24). Micronucleus (MN) assay was used to evaluate the genetic instability levels in urine derived urothelial cells, expressed as the number of micronucleated cells per 1000 counted cells. All microscopic slides were analysed by a second observer.
Results: Our results show that the MN frequency in UEC is significantly higher in patients with UCC than in controls ($p<0.001$), as well as between subgroups according to tumour grade ($p<0.049$) and tumour muscle invasion ($p<0.044$).
Conclusion: Although further studies are needed for standardization, our findings indicate that the MN frequency in UEC may be a potential biomarker for the early detection of bladder cancer and for patient surveillance. We recommend it as a possible triage-test that might be used prior to the UroVysion™ FISH testing. This cost-effective method could reduce the number of unnecessary tests.

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PS-17-061
Penile squamous cell carcinoma – a 15-year long series with p16 correlation

C. Quadros[1], D. López-Presa[1]
[1] CHULN - Hospital de Santa Maria, Portugal

Background & Objectives: Squamous cell carcinoma (SCC) represents the majority of the malignant epithelial penile tumours. The newest WHO classification of the tumours of the Urinary System and Male Genital Organs, subclassifies SCC according to HPV status. We present our casuistic data throughout a 15 year-long series with p16 correlation.
Methods: An experienced pathologist subclassified the specimens of penile SCC pertaining to the 2004-2018 period, according the WHO classification; p16 examination was performed.
Results: A total of 39 specimens were assessed with an average diagnosis of 2,4 SCC/year. Age ranged from 35 to 103 years (mean 71 years). The non-HPV-related carcinomas were more frequent (79%), with the usual subtype being predominant (56%), followed by mixed (13%), pseudohyperplastic (5%) and verrucous subtypes (5%). The HPV-related carcinomas were led by the warty-basaloid variant (10%), followed by the warty (8%) and the basaloid subtypes (3%). Regarding p16, there was 97,4% concordance of HPV-related carcinomas and p16 positivity - particularly noteworthy is one case of SCC usual type and one SCC mixed type with sarcomatoid component that showed p16 expression.
Conclusion: The high concordance between p16 status and histological subtyping demonstrates that p16 status is a reliable stratification method that may have diagnostic and prognostic implications, yet, some exceptions to that concordance may punctually be found.

PS-17-062

Specific miRNA profiles are associated with the development of neuroendocrine phenotype in prostate cancer patients undergoing androgen deprivation therapy

I. Rapa[1], C. Barbero[1], C. Buttigliero[1], S. Izzo[1], D. Tota[1], F. Naples[1], E. Bollito[2], M. Tucci[3], A. Berruti[4], G.V. Scagliotti[1], M. Volante[1]
[1] University of Turin, Italy, [2] A.U.O. San Luigi Gonzaga, Orbassano Turin, Italy, [3] S.C. Oncologia Ospedale Cardinal Massaia, Asti, Italy, [4] University of Brescia, Italy

Background & Objectives: The onset of neuroendocrine differentiation (NED) is associated with resistance to androgen deprivation therapy (ADT) in prostate cancer, but the mechanisms responsible for its dynamic modulation are unclear.
We analysed *in vivo* and *in vitro* the association of miRNA expression with NED as a consequence of ADT in prostate cancer.
Methods: 1066 human miRNAs were arrayed in LNCaP cells at basal conditions and cultured under androgen withdrawal and in tumour tissue samples before and after ADT, and correlated with the onset of NED after treatment. Tissue samples were grouped as follows: group A, prostate cancer tissues negative for NED after ADT; group B, prostate cancer tissues developing NED after ADT; group C, pure neuroendocrine prostate cancers, untreated.
Results: Unsupervised cluster analysis of global miRNAs profiling in pre-treatment samples segregated prostate cancer patients according to the presence or absence of NED after treatment, clustering group B together with pure neuroendocrine carcinomas (group C), with 218 miRNAs differentially expressed between group A and group B. Global miRNA profiling in matched samples before and after ADT showed a significant dynamic modulation of subsets of miRNA in group A (38 miRNAs) and B (117 miRNAs), all but one different in the two groups. 27 miRNAs (21 up-modulated and 6 down-modulated) were common in group B and in LNCAP cells developing NED under androgen withdrawal, and regulate up to 2500 genes, involved in more than 60 pathways.
Conclusion: Specific miRNA signatures are associated to the development of NED in prostate cancer undergoing ADT.

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PS-17-063

An immunohistochemical analysis of HIF1 alpha and VEGFR1 in high grade T1 bladder cancer

A. Ristic-Petrovic[1], D. Stokanovic[2], S. Stojnev[1], M. Potic-Floranovic[1], I. Djordjevic[1], L. Jankovic-Velickovic[1]
[1] University of Nis, Medical Faculty, Department of Pathology, Serbia, [2] University of Nis, Medical Faculty, Department of Pharmacology, Serbia

Background & Objectives: Hypoxia-inducible factor 1 alpha (HIF1 alpha) is known to induce transcription of more than 60 genes, including vascular endothelial growth factor (VEGF) and VEGF receptors that are involved in angiogenesis, which assist in increasing oxygen delivery to hypoxic regions of tumour. It has been determined that overexpression of hypoxia-inducible factor 1-alpha (HIF1 alpha), and vascular endothelial growth factor receptor 1 (VEGFR1) correlates with tumour grade, recurrence and progression of the bladder cancer, as well as poor overall survival.
Methods: The immunohistochemical expression of HIF1 alpha, and VEGFR1 was evaluated in 135 high grade T1 bladder cancer samples, incorporated in tissue microarrays. HIF1-alpha was assessed through nuclear staining, while for VEGFR1 cytoplasmic expression was declared as positive.
Results: After a mean follow-up of 50 months, in 135 patients diagnosed with high grade T1 urothelial bladder cancer, we found that patients who had concomitant carcinoma in situ had worse overall survival ($p<0.05$), furthermore, those tumour samples less expressed HIF1 alpha ($p<0.05$), and VEGFR1 ($p<0.05$). We found nuclear HIF1-alpha expression to be an independent prognostic factor for both recurrence-free survival ($p<0.001$) and overall survival ($p<0.01$) in all high grade T1 samples. Patients with positive VEGFR1 had longer disease-free ($p<0.01$) and overall survival ($p<0.01$).
Conclusion: Estimation of HIF1 alpha and VEGFR1 expression could be diagnostic supplement, selecting the high grade T1 bladder cancer patients that require an intensive follow-up, especially if concomitant CIS is present, considering this entity as additional obstacle in treatment high grade T1 urothelial cancer.

PS-17-064

Evaluation of two important prognostic factors related to the biochemical progression after radical prostatectomy in a series of 530 patients: staging and surgical margins. A study in Brazil

A. Rolim da Paz[1], A. Billis[2]
[1] University Hospital Lauro Wanderley/EBSERH/UFPB, Brazil, [2] State University of Campinas - Unicamp, Brazil

Background & Objectives: The data provided by radical prostatectomy (RP) on staging (extraprostatic extension - EPE) and surgical margins (SM) allow us to evaluable the risk of neoplasia progression, determined by recurrence/biochemical progression. The objective of this study is correlate the factors related to the morphological findings in the surgical specimen of RP with the biochemical progression after radical prostatectomy (PSA>=0.2): a) surgical margins (SM) and b) extraprostatic neoplastic extension (EPE).
Methods: In this retrospective study, we used the information obtained from the anatomopathological reports and EXCEL table containing the corresponding morphological and clinical-laboratory data of 530 sequential RP over the 20-year period (1997 to 2017). The statistical study was performed through the Kaplan-Meier estimator for the biochemical recurrence time using the Log-Rank test for comparison between groups.
Results: The Kaplan-Meier estimator and the Log-Rank statistical test ($p<0.001$) showed for both variables that the focal EPE bahaves closer to the patients without EPE and the focal SM closer to the SM negative patients. Both EPE and SM when non-focal behave statistically significant in relation to cases without EPE and SM negative.

Conclusion: This study highlights the importance of the evaluation of surgical margins and staging (EPE) as influencing factors in the biochemical progression of prostate carcinoma. It also allows the comparison with international series and construction of guidelines for post-RP prognostic evaluation.

PS-17-065

The features of p53 and Ki-67 expression during Gleason's grade increase in prostate cancer

M. Lyndin[1], A. Piddubnyi[2], V. Sikora[3], O. Romaniuk[4], O. Kravtsova[5], A. Romaniuk[4]

[1] Sumy State University, Medical Institute, Department of Pathology, Ukraine, [2] Sumy State University, Ukraine, [3] Sumy State University, Medical Institute, Pathology Department, Ukraine, [4] Sumy State University, Ukraine, [5] Sumy State University, Department of Pathology, Ukraine, Ukraine

Background & Objectives: Prostate cancer is the most common malignant tumour of the male reproductive organs. Its course depends on the histological and immunohistochemical characteristics of neoplasias. In view of this, the purpose of study was to investigate the influences of prostate cancer differentiation on peculiarities of Ki-67 and p53 expression.

Methods: The research was conducted on acinar prostate cancer cases which were graded according to Gleason Score. The presence of p53 (SP5–1μg/ml) and Ki-67 (SP6–0.5μg/ml) receptors was detected by the immunohistochemistry.

Results: Immunohistochemically in prostate cancer tissues it was revealed different p53 and Ki-67 expressions in tumours. Despite the strong correlation between them, they didn't depend on the Gleason's grade. It should be noted, that significantly higher their expression was found in 5th Gleason's grade comparing with others. Moreover, in 5th grade group there are two kinds of tumour tissue: 1. with over-expression of p53/Ki-67 and significant cellular atypia; 2. with low level of p53/Ki-67 expression and without cellular polymorphism.

Conclusion: The increase of Gleason's grade in prostate cancer tissue is not accompanied by the direct enhance of Ki-67 and p53 expression. The morphological evaluation of cancer tissue should include as Gleason's grade as cellular atypia due to different expression of these proteins for 5th Gleason's grade tumours.

PS-17-066

Low frequency of mismatch repair protein expression in a series of bladder carcinoma

T. Sanhueza[1], M.C. Gómez[2], E. Musulèn[3], A. Font[4], N. Malats[5], J.P. Fernández[2], J.L. Gago[6], E. Grande[7], D. Castellano[8], M.î Climent[9], N. Lainez[10], M. Sáez[11], E. González[12], M. Lázaro[13], M. Guix[14], M. Lopez-Brea[15], N. Sala[16], I. Duran[15], I. García[17], S. Vazquez[18], B. Mellado[19], F.X. Real[20], P.L. Fèrnandez[2], C. Carrato[2]

[1] Pathology Department, Hopsital Germans Trias i Pujol, Barcelona, Spain, [2] Pathology Department, Hospital Germans Trias i Pujol, Barcelona, Spain, [3] Pathology Department, Hospital General de Cataluyna, Barcelona, Spain, [4] Institute Català d'Oncologia, Barcelona, Spain, [5] Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Ciberonc, Madrid, Spain, [6] Urology Department, Hospital Germans Trias i Pujol, Barcelona, Spain, [7] Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain, [8] Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain, [9] Instituteo Valenciano de Oncología, Valencia, Spain, [10] Medical Oncology Department, Complejo Hospitalario de Navarra, Navarra, Spain, [11] Medical Oncology Department, Hospital Clínico de Málaga, Málaga, Spain, [12] Medical Oncology Department, Hospital Morales Messeguer, Murcia, Spain, [13] Medical Oncology Department,Hospital Universitario de Vigo, Vigo, Spain, [14] Medical Oncology Department, Hospital del Mar, Barcelona, Spain, [15] Medical Oncology Department, Hospital Universitario Marquès de Valdecilla, Santander, Spain, [16] ICO Josep Trueta, Girona, Spain, [17] Medical Oncology Department, Hospital Virgen de la Salud, Toledo, Spain, [18] Medical Oncology Department, Hospital Universitario Lucus Agusti, Lugo, Spain, [19] Medical Oncology Department, Hospital Clínic i Provincial De Barcelona, Barcelona, Spain, Spain, [20] Epithelial Carcinogenesis Group, Spanish National Cancer Research Centre (CNIO), CIBERONC, Madrid; Department de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Barcelona, Spain

Background & Objectives: Lynch syndrome (LS) patients develop upper tract urothelial carcinoma (UTUC) in 4-6% of cases and urothelial bladder carcinoma (UBC) in 0-5%. Although it is well documented that 1-3% of all UTUCs are associated with LS, the frequency of LS among UBC cases is not well known. This study assessed the frequency of mismatch repair (MMR) protein expression loss (as a LS screening test) in a large series of cases with muscle-invasive UBC (MI-UBC).

Methods: Review of medical records from 16 Spanish hospitals identified 540 muscle-invasive UBC cases. Sixteen tissue microarrays (TMAs) were built and immunostained for MSH2, MSH6, MLH1 and PMS2. TMAs were built with tumour specimens obtained by either radical cystectomy without prior neoadjuvant therapy (n=404) or diagnostic transurethral resection (TUR) (n=136). TMA negativity for PMS2 and MSH6 staining was confirmed on whole sections. Two expert pathologists (CC, EM) reviewed all slides.

Results: Only one out of 536 evaluable UBC cases showed loss of expression for both MMR proteins. The patient was a 40-year-old man whose LS diagnosis (confirmed by sequencing, with a germline *MSH2* mutation) was known at the time of UBC TUR.

Conclusion: As shown in the literature, frequency of MI-UBC in the context of LS is very low. Our results indicate that implementation of a universal LS testing algorithm to detect such an uncommon occurrence is not necessary in patients with MI-UBC cases. Nevertheless, MMR protein expression analysis is recommended for younger patients or those suffering from a LS-related condition.

PS-17-067

Incidental prostate adenocarcinoma with prostate transuretral resection, 8 years experience

C. Sayar[1], S. Ekmekci[1], O. Cakmak[2], U. Kucuk[1]

[1] Izmir Tepecik Training and Research Hospital, Department of Pathology, [2] Izmir Tepecik Training and Research Hospital, Department of Urology

Background & Objectives: Patients with benign prostatic hyperplasia (BPH) and transurethral resection of the prostate (TURP) are able to detect incidental early stage prostate cancers (PrCa), which can not be detected by clinical examination and / or imaging. In our study, we investigated whether there was a significant difference in the PrCa detection rate, age between tumour detection and non-detection, histopathologic examination of prostate tissue volume and serum PSA levels after TURP for BPH in our study.

Methods: Between 2011 and 2018, 391 patients who underwent TURP due to BPH in our hospital were included in the study.

Results: After histopathological examination, 17 of 391 patients (4.3%) had incidental PrCa. The mean age was 69.5 (26-93) in cases with no tumours and the mean age was 74,5 (54-93) in cases with PrCa. When the tumours were classified according to age groups, two cases between 50-60 years, two between 61-70 years, eight between 71-80 years, 5 cases over 80 years were observed. Preoperative serum PSA levels were measured and mean PSA level was 5.05 ng / mL in 226 of the non-tumour cases. Pre-operative serum PSA levels of 15 cases with tumour were measured and the mean value was 4.46 ng / mL (0.40-28.5).

Conclusion: In our study, incidence of incidental PrCa detection (<5%) in TURP materials for BPH was found to be in parallel with the literature.

In these cases, it was noticed that preoperative PSA levels were lower than those of untrained cases. It has been observed that the incidence of coincidental PrCa detection is higher, especially in patients over 70 years of age. This is thought to be important in avoiding tumours, especially if the pre-operative PSA levels and BPH pre-diagnosis were used, especially if all of the TURP materials of advanced age were processed.

PS-17-068

Concordance and predictive factors of prostate cancer upgrade and downgrade from multiparametric-magnetic resonance imaging prostate guided biopsy to radical prostatectomy using 2014 ISUP Gleason grade group

A.Y. Setiasti[1], D. van Midden[2], C. Hulsbergen van-de Kaa[3], J.A. Schalken[4]

[1] Radboud University Medical Center, Urology Department, Experimental Lab, RIMLS, Nijmegen, The Netherlands, [2] Radboud University Medical Center, Pathology Department, RIMLS, Nijmegen, The Netherlands, [3] Laboratorium Pathologie Oost-Nederland (LabPON), Hengelo, The Netherlands, [4] Radboud University Medical Center, Urology Department Experimental Lab, RIMLS, Nijmegen, The Netherlands

Background & Objectives: The discrepancy between biopsy and radical prostatectomy (RP) Gleason score (GS) results remains a challenge in the management of prostate cancer (PC). The use of multiparametric-MRI prostate guided biopsy (mp-MRGB) may play role in increasing PC detection and could improve the concordance by solving some of the upgrade and downgrade problems. The study aimed to assess the concordance and to determine the predictors related to upgrade and downgrade occurrence between mp-MRGB to RP results using 2014 ISUP GG.
Methods: Ninety five eligible patients who performed both RP and coresponding mp-MRGB prior to RP from January 2006 to December 2014 at Radboud University Medical Center, Nijmegen, The Netherlands have been selected and reviewed using 2014 ISUP GG. The association of upgrading and downgrading and the predictive factors between mp-MRGB and RP GG were analysed.
Results: The concordant diagnosis occurred in 51.6% cases. The downgrade rate (14.7%) was lower than upgrade rate (33.7%). The discriminative power of upgrade and downgrade models showed satisfactory area under ROC curve (AUC) results (upgrade=0.747; downgrade=0.867). An upgrade was associated with increasing pre-operative serum PSA level (OR=1.098; p=0.0005). Increasing mp-MRG GG (OR=0.379; p=0.002) and total tumour percentage biopsy cores (OR=0.984; p=0.08) reduced upgrading possibility. Downgrade was related to increasing mp-MRGB GG (OR=2.363; p=0.001). Increased biopsy cores decreased the downgrade (OR=0.571, p=0.001).
Conclusion: We concluded that the concordance rate between biopsy and RP was good. The upgrading rate was higher than the downgrading. Predictor for upgrading was pre-operative serum PSA (prostate specific antigen) level. A combination of high biopsy Gleason grade and higher percentage of tumour in biopsy core reduced the upgrade. Sufficient number of biopsy core reduced the downgrade.

PS-17-069

Comparative analysis of programmed cell death ligand 1 (PD-L1) assays in renal cell carcinoma

B. Shim[1], K.S. Lee[1], S. Yun[2], K. Lee[3], S. Moon[1], G. Choe[1,4]

[1] Department of Pathology, Seoul National University Bundang Hospital, Republic of Korea, [2] Department of Diagnostic Pathology, Samkwang Medical Laboratories, Republic of Korea, [3] Department of Pathology, Kangwon National University Hospital, Republic of Korea, [4] Department of Pathology, Seoul National University College of Medicine, Republic of Korea

Background & Objectives: The importance of programmed cell death ligand 1 (PD-L1) expression has recently emerged in renal cell carcinoma (RCC). The aim of this study was to compare the PD-L1 assays in four major subtype of RCC.
Methods: We compared PD-L1 expression by two FDA-approved assays (22C3 and SP142) and one research use-only antibody (E1L3) in a retrospective cohort of 591 RCC patients. PD-L1 positivity on the tumour cell (TC), immune cell (IC), and combined positive score (CPS) was evaluated.
Results: At a cut-off of ≥ 1%, 132 (22.3%), 120 (20.3%), and 65 (11.0%) cases stained positively for 22C3, SP142, and E1L3 on IC, respectively. Meanwhile, 22C3, SP142, and E1L3 expression on TC ≥ 1% was observed in 24 (4.1%), 12 (2.0%), and 16 (2.7%) cases, respectively. The score of PD-L1 expression between the three assays yielded moderate to high positive correlation ($\rho = 0.599$ to 0.835, $P < 0.001$). The three assays appeared largely similar, although E1L3 was less frequent in staining in IC. Notably, 22C3 showed highly frequent positivity in TC. PD-L1 expression on TC was positively associated with papillary type 2 RCC ($P < 0.001$) and expression on IC was predominantly found in clear cell and papillary type 1 RCC ($P < 0.05$). Kaplan–Meier analysis showed a correlation between PD-L1 expression on IC and tumour recurrence ($P \leq 0.001$), but not on TC ($P > 0.05$).
Conclusion: The present study shows that expression of PD-L1 varies depending on the type of antibody and histologic subtype in RCC.

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PS-17-070

Assessment of tumour cells specific features in prostate adenocarcinoma in correlation with Gleason and Srigley grading systems

F. Simionescu[1], M. Şerbănescu[2], R.M. Pleşea[3], V. Ciovica[3], M. Bara[4], A. Stefan[5], A. Gradinaru[5], M.O. Leavitt[6], V.T. Moldovan[7], I.E. Pleşea[8,7,3]

[1] Department of Pathology, University Emergency Hospital, Bucharest, Romania, [2] Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy, Craiova, Romania, [3] Doctoral School, University of Medicine and Pharmacy, Craiova, Romania, [4] Department of Pathology, University Emergency Hospital, Bucharest, Romania, [5] Themis Pathology SRL, Bucharest, Romania, [6] Leavitt Medical Inc, Orem, Utah, USA, [7] Department of Pathology, "Victor Babes" National Institute of Pathology, Bucharest, Romania, [8] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Background & Objectives: The aim of this study is to assess the expression of some of the main biological behaviour parameters of the tumour cells in correlation with two different grading systems of prostate adenocarcinoma.
Methods: A series of 435 fields with different patterns of prostatic adenocarcinoma according to Gleason (GlS) and Srigley (SgS) grading systems were selected and immunomarked on four serial sections with: MMP9, MMP2, E-CAD and PTEN in order to assess: the capacity to degrade extracellular matrix, intercellular adhesion and aggressiveness degree. Images were assessed through a proprietary computational algorithm that marked the pixel where the red channel was more intense than the other channels. Then the overall colour intensity of the previously selected mask was inverted and considered as the value for the intensity of the IHC staining, larger values meaning more intense staining.
Results: MMP9 and MMP2 expressions were almost constant irrespective the degree of differentiation in both systems, the former having

around twice higher values than the latter. E-CAD had a smooth descending trend towards poor differentiated patterns, more pronounced in SgS. PTEN expression was almost constant, irrespective the degree of differentiation. However, there was a direct correlation between MMP9 and E-CAD, MMP9 and PTEN, MMP2 and E-CAD, and E-CAD and PTEN and no correlation between MMP9 and MMP2 and MMP2 and PTEN expressions irrespective the degree of differentiation.
Conclusion: Our results suggest that expressions of tumour cells behaviour parameters correlated with each other in almost all cases, but not with the degree of differentiation irrespective of grading system.

PS-17-071
Primary urethral clear cell carcinoma: clinical and pathologic implification and characterisation of molecular aberrations
B. Song[1]
[1] Kangbuk Samsung Hospital, Republic of Korea

Background & Objectives: Primary clear cell carcinoma of the urethra is very rare and known to occur predominantly in women. It has been reported to have poor prognosis with low 5-year survival. A number of clinicians and pathologists may be unfamiliar with this rare entity. And even molecular abberations of this rare neoplasm has not yet been fully studied. In this study, we presented clinical, histopathlogical findings and molecular characteristic of this rare neoplasm.
Methods: A total of 5 cases diagnosed as primary clear cell carcinoma of the urethra was included. We assessed immunohistochemical profile and the mutational spectrum of the neoplasm evaluated by whole exome sequencing (WES).
Results: All 5 patients were female and the mean age of the patients was 61.8 yrs. Two of these patients had history of breast cancer.
Immunohistochemical staining revealed CK7 and PAX8 strong positivity and CK20, PSA, ER, PR negativity with variable SMAD4, p53 and Ki-67 index.
The molecular abberation analysed by whole exome sequencing was variable and revealed no overlapping common mutation between patients. Genetic alteration of PBRM1, LAMC2, KRAS, KEAP1, AMER1, PIK3R, ARID1A, NKD1, CAPN2, CHD4 were identified. Germline mutation of BRCA gene was not found in two cases with concurrent breast cancer.
Conclusion: In this study, primary urethral clear cell carcinoma showed diverse mutational spectrum and no common pathogenic mutation. Futher studies of molecular characteristics is needed to advance our understanding of the pathogenesis of the neoplasm.

PS-17-072
Crypto-1 in the microenvironment of the prostate cancer
S. Stifter[1], F. Grizzi[2], A. Cescato[3], M. Crncic[4], E. Ahel[4], G. Dordevic[5]
[1] Department of Pathology, Clinical Hospital Centre Rijeka, Croatia, [2] Humanitas Clinical and Research Center, Milano, Italy, [3] Laboratori Riuniti Trieste, Italy, [4] Medri UNIRI, Croatia, [5] Department of Pathology Medial Faculty , University of Rijeka, Croatia

Background & Objectives: Goal was to investigate the cancer cells microenvironment in prostate cancer (PCa) to target molecular marker Crypto-1, which might have been potentially significant in PC progression. Crypto-1 is among the embryonic genes that regulate the function of stem cells and is found to be over-expressed in human tumours. Immunosuppressive tumours associated with macrophage (TAMs) are associated with poor clinical outcomes. The function of macrophage against antitumour phenotypes and immune response in the prostate microcirculation remain to be further elucidated. Further investigation of macrophage polarization status in the prostate microcirculation and its colocalization within the angiogenic properties of tumour neovascularization and Crypto-1 were analysed. We assume that crosscutting multiple path activation could be responsible for progression, PC architecture change in the broader sense observed morphologically visible Gleason score progression.
Methods: We used a tumour model on the entire tissue cut of tumour tissue and tissue microarrays obtained by radical prostatectomy. Quantitative analysis of immunohistochemically detected Crypto-1 was performed. For descriptive analysis of microenvironment CD34, CD68, CD206 and VEGF were used.
Results: Preliminary data evaluation showed statistically significant correlation ($p< 0.01$) of Crypto-1 immunohistochemical expression with progression from non-malignant – prostatic intraepithelial neoplasia (PIN)-adenocarcinoma; correlation of Crypto-1 expression and TAMs of M1 phenotype and in the group of adenocarcinoma with leading Gleason pattern ($p<0.05$), respectively.
Conclusion: Study showed that Crypto-1 assures more precise detection of poorly differentiated and undifferentiated subpopulations of cells that are gaining properties similar to embryonic and stem cells. Therefore, future targeting signalling pathway Crypto-1 has potential to become an attractive target for unresponsive cancer cases treatment.

PS-17-075
Prostate cancer in young adults
S. Teoran[1], A. Dema[2], R. Bardan[3], L. Daminescu[3], A. Cumpanas[3], B. Suciu[1]
[1] Spitalul Clinic Judetean de Urgenta "Pius Brinzeu" Timisoara, Romania, [2] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania, [3] Spitalul Clinic Judetean de Urgenta "Pius Brinzeu" Timisoara/"Victor Babes" University of Medicine and Pharmacy, Romania

Background & Objectives: Prostate cancer represents the appanage of old age, the majority of patients with this neoplasia being diagnosed between the ages of 70 and 80 years old. However, the number of young adults diagnosed with prostate cancer has increased during the last two decades.
The present paper aims to analyse, from the perspective of some clinical and morphological characteristics, prostate cancer in young men.
Methods: The Pathology Department of SCJUPBT database provided the cases of prostate cancer corresponding to the following inclusion criteria: patients under the age of 55, histopathological diagnosis in our department; the cases with secondary involvement of the prostate were excluded. For the selected cases, the following data was collected: age, Gleason score, the specimen on which the diagnosis was established, PSA levels and other relevant data.
Results: 23 patients that correspond to the study's inclusion criteria have been identified, with ages between 48 and 55 years old (average age of 53.3). The average PSA level was 169 ng/ml, ranging from 4.2 ng/ml to 1971 ng/ml. 19 cases were diagnosed in core-needle biopsy, 2 in prostatectomy specimens and 2 in transurethral resection specimens. The cases had Gleason scores between 6 and 10 (average score of 7.8).
Conclusion: The number of prostate cancer cases in young men had an ascending trend in the analysed period. Our results suggest that prostate cancer in young adults represents an aggressive neoplasia, which imposes a revision of the diagnosis strategy and adapted management.

PS-17-076
Application of Raman-fluorescence spectroscopy for diagnosis of prostatic cancer
S. Avraamova[1], N. Aleksandrov[1], S. Timofeev[2], Y. Kirillov[3]
[1] I.M. Sechenov First Moscow State Medical University, Russia, [2] City Hospital of Moscow #40, Russia, [3] Tyumen State Medical University, Russia

Background & Objectives: Evaluate the effectiveness of the Raman-fluorescence spectroscopy method for the diagnosis of prostate cancer (PC).

Methods: The prostate gland or fragments were removed from 64 patients during a radical prostatectomy or transurethral resection because the suspicion on cancer or benign prostatic hyperplasia. Before carrying out a histological study, Raman-fluorescence spectroscopy of tumour tissue samples was performed. InSpectr R532 software and hardware complex was used.
Results: Spectral characteristics of samples with benign hyperplasia (n = 25) characterised by the maximum intensity (>40000 AU) of fluorescence at a 550 nm wavelength due to oxidized flavoproteins. Tissue samples affected by a malignant tumour (n = 39), differed by the intensity of fluorescence both in high and low intensity regions (25 to 80 000 AU) depending on the degree of tumour differentiation, and characterised by the presence of porphyrins (600 nm). Tumour was confirmed in 93,7% by traditional histological and immunohistochemical study.
Conclusion: The results of the investigation showed that Raman fluorescence spectroscopy can be used as an accurate and early method of prostate cancer detection. Being safe and inexpensive, RFS is used on-line and takes only several minutes. It enables to interactively identify tumourous regions pre- and intraoperative and define the volume of surgical intervention with maximum precision.

PS-17-078
Correlation between CD 10 and TIMPs expression in urothelial bladder carcinoma on TUR-V specimens
L. Tutuianu[1], L. Nichita[1,2], M. Cioplea[3], A. Vrâncianu[3], V. Mitroi[3]
[1] Colentina Clinical Hospital, Bucharest, Romania, [2] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [3] Colentina Clinical Hospital, Romania

Background & Objectives: Prognosis in urothelial bladder carcinoma depends on the histological grade and stage of the tumour at diagnosis; however these parameters are difficult to appreciate on TURV specimens and there are no reliable parameters predicting the risk of progression or recurrence. The aim of this study is to evaluate CD10 and TIMPs markers expression in urothelial bladder carcinoma and correlate their imunnohistochemistry intensity with histological grade and tumour staging.
Methods: We examined retrospectively 96 TURV specimens submitted in our department (we selected 48 non-invasive, low grade carcinomas and 48 infiltrating high grade carcinomas). Multitissue blocks (which incorporated 6 specimens /block) were prepared and slides were immunohistochemically stained for CD10, TIMP 1, TIMP 2 and TIMP 3.
Results: Non-invasive low grade cases were negative or showed focally CD10 stromal positivity. Tumour cells were also negative or showed positivity in rare cells. All cases of infiltrative, high grade cases showed CD 10 positivity in both stromal and intratumoural compartment.
TIMP 1 showed both stromal and intratumoural positivity with a significant difference in staining between the two lots (more intense in infiltrative high grade carcinomas).
TIMP2 and TIMP3 expression were inconclusive.
Conclusion: CD 10 and TIMP1 expression in urothelial bladder carcinoma correlates with histological grade and their detection in routine specimens may improve estimation of individual prognosis.

PS-17-079
Mast cells in prostate cancer: potential prognostic marker?
A. Vilaia[1], A. Vrancianu[2], A. Toma[3], A.I. Savin[4], M. Cioplea[5,4], C. Socoliuc[2,6], V. Mitroi[2], L. Nichita[2,7]
[1] Colentina Clinical Hospital, Bucharest, Romania, [2] Colentina Clinical Hospital, Bucharest, Romania, [3] Pathology Department, Colentina University Clinical Hospital, Romania, [4] Colentina University Hospital, Pathology Department, Bucharest, Romania, [5] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [6] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [7] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Background & Objectives: Mast cells (MC) are found in various tumour types, but their pro or antitumoural role in prostate carcinoma is still debated. There are divergent opinions regarding MC correlation with prognostic factors. There are also contradictory findings regarding correlations between MC number and Gleason score (GS) in needle biopsy samples and radical prostatectomy. Our aim was to evaluate the MC distribution and its correlation with prognostic factors.
Methods: Ninety patients who underwent transurethral resection of the prostate (TURP) at Colentina Clinical Hospital between 2016-2018 were selected for this study. We generated multi-tissue blocks and stained mast cells immunohistochemically with tryptase. We evaluated the mast cells infiltrate density in peritumoural and intratumoural areas and correlate the data with GS.
Results: The ages of patients ranged from 53 to 91 (median 71 years). There was no correlation between age and MC count. We found that higher MC counts correlate with lower prognostic group ($p<0.05$), similar to studies conducted on prostatectomy and in contrast with needle biopsy samples. We found a difference in MC counts from intratumoural areas comparative to peritumoural areas. GS was negatively correlated with intratumoural MC number ($p<0.001$).
Conclusion: Higher MC number correlates with better prognosis suggesting that MC can be a reliable prognostic marker in prostate cancer. Differences in MC number in needle biopsy versus prostatectomy and TURP may be due to smaller stromal areas identified in the biopsies. MC may play a role in the relationship between stromal microenvironment and tumour cells and can be a potential target of effective antitumour strategies.

PS-17-080
Evaluation of angiogenesis in benign prostatic hyperplasia and prostatic carcinoma, with correlations to Gleason Score
A. Vrancianu[1], A. Vilaia[2], L. Tutuianu[3], D. Costache[1], M.D. Cioplea[3,4], L. Sticlaru[3], V. Mitroi[3], L. Nichita[3,4]
[1] Pathology Department, Colentina University Clinical Hospital, Bucharest, Romania, [2] Colentina Clinical Hospital, Bucharest, Romania, [3] Colentina Clinical Hospital, Bucharest, Romania, [4] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Background & Objectives: Prostate cancer is the second most common cancer worldwide and tumour growth is strongly related to angiogenesis. The aim of this study was to evaluate the correlation between stromal and tumoural VEGF expression, microvessel density (MVD) and the severity of prostatic carcinoma (PCa), and whether these can differentiate it from benign prostatic hyperplasia (BPH).
Methods: We reviewed 90 transurethral prostatic resection specimens – 45 cases PCa, 45 cases BPH. We performed immunohistochemistry for VEGF and CD34 and recorded the Gleason score (GS), prognostic group and investigated the correlation between them. MVD was measured in intratumoural, peritumoural and non-tumoural stromal areas (three high-power fields/area). We evaluated the intensity of stromal and tumoural VEGF expression.
Results: The BPH resection specimens were slightly larger than those with PCa -27g and 20g, respectively, on average-, from patients aged between 57-91 years (median age-73).
Most cases with high GS presented prominent VEGF expression in the tumour areas.
Specimens with PCa showed tumour positivity for VEGF more frequently than BPH (most PCa showed strong positivity, whereas BPH cases showed at most moderate positivity). 25% of BPH and 75% of PCa were negative for VEGF in the stroma.
CD34 immunohistochemical stain revealed increased MVD correlated to GS, especially in peritumoural areas. In BPH nodules, MVD was higher than in PCa.
Conclusion: The present findings may support the assumption that VEGF could be significant in predicting the PCa, as well as the MVD.

Moreover, VEGF expression level showed intense staining in cases with higher GS, which reveals its importance as prognostic marker.

PS-17-081

Large nested variant of urothelial carcinoma: a prime example of a FGFR3-mutated, luminal tumour

V. Weyerer[1], M. Eckstein[2], E. Compèrat[3], H. Juette[4], Y. Allory[5], R. Stoehr[6], B. Wullich[7], M. Roupret[8], A. Hartmann[6], S. Bertz[9]
[1] Insitute of Patholoy, University Hospital Erlangen, Friedrich-Alexander University Erlangen, Germany, [2] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, [3] Hôpital Tenon, HUEP, Sorbonne University, Paris, France, [4] Institute of Pathology, Ruhr-University Bochum, Germany, [5] Department of Pathology, Hôpital Foch, Universitè Versailles-Saint-Quentin-en-Yvelines, Universitè Paris-Saclay, Suresnes, France; Institute Curie, CNRS, UMR144, Paris, France, [6] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany, [7] Department of Urology and Paediatric Urology, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany, [8] Service d'Urologie, Hôpital La pitiè- Salpetrière, Sorbonne University, Paris, France, [9] Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Background & Objectives: Urothelial carcinoma (UC) of the bladder may present with distinct histomorphological features and rare histologic subtypes have been defined. Since 2016 large nested urothelial carcinoma (LNUC), has been included within the World Health Organization Classification among the nested type UC. Little is known about LNUC. However, the very limited reports with mainly small case numbers confirm the fully malignant and life-threatening behaviour despite the bland morphological appearance. In this study we evaluated*FGFR3*mutational status as well as the molecular subtype of this specific variant by using a simplified panel of immunohistochemical markers.
Methods: 26 cases diagnosed as LNUC were collected and histomorphologically reevaluated. DNA was extracted after manual microdissection of the tumour, including separation of morphologically distinct areas. SNaPshot analysis of the hot spot regions of the *FGFR3*gene was done. Immunohistochemical basal and luminal markers CK14, CK5, CD44 FOXA1, GATA3, CK20 and Uroplakin were tested to elucidate the molecular subtype.
Results: Of 26 cases eight were pure LNUC, 12 showed an additional exophytic (non-invasive) papillary component, four presented areas of classical nested type variant and three a component of conventional UC. 7/7 evaluable pure cases were *FGFR3*-mutated. 8/10 LNUC with papillary component were mutated in both areas. No mutations were found in 3/3 LNUC combined with classical nested type UC. LNUC cases showed predominantly high protein expression levels of luminal markers.
Conclusion: LNUC either pure or combined with a papillary component is a prime example of a luminal, *FGFR3*mutated tumour. However, LNUC combined with classical nested type UC seems to represent a different molecular pathway. Regarding the unique molecular features our findings are of particular interest since FGFR-pan inhibitors are currently tested in clinical trials.

PS-17-082

Expression of molecular biomarkers in the cribriform pattern of prostate cancer and PIN

V. Zakharava[1], T. Liatkouskaya[1], E. Cherstvoy[1], I. Masansky[2], M. Ivanovskaya[3], L. Sagalchik[4], S. Kuralenya[5]
[1] Belarusian State Medical University, Belarus, [2] Minsk Municipal Center for Clinical Oncology, Belarus, [3] Belarusian Medical Academy of Postgraduate Education, Belarus, [4] Urology Center of Minsk Municipal Outpatient Clinic № 6, Belarus, [5] Minsk Consulting and Diagnostic Center, Belarus

Background & Objectives: Intraductal proliferation in form of cribriform structures can be found in intraductal carcinoma (IDC) and prostatic intraepithelial neoplasia (PIN). The aim of the study was to establish expression of PTEN, AMACR, ERG, p53, chromogranin A (ChrA), androgen (AR) and estrogens (ERa and ERß) receptors, aromatase (Arom), adhesion molecules (E Cadherin, ß-catenin, CD44), growth factors (TGF-ß, EGFR and VEGF), proliferation (Ki-67, CyclinD1, TopoIIα) and apoptotic (Bax, Bcl2) markers in the cribriform pattern of the IDC and PIN.
Methods: The material under study comprised 90 radical prostatectomy specimens (including 30 specimens of IDC adjacent to invasive adenocarcinoma and 60 specimens of PIN located remotely from cancer). U-test was applied, $p<0.05$.
Results: In IDC cytoplasmic PTEN loss was found in 93% of cases (28/30) and expression of ERG in 67% (20/30). In PIN no cytoplasmic PTEN loss was found, whereas ERG expression was found in 7% of cases (4/60). In the cribriform foci of IDC the expression of AMACR ($p<0.001$), p53 ($p=0.026$), ERa ($p=0.023$), Arom ($p=0.015$), TGF-ß ($p<0.001$), EGFR ($p<0.001$), Ki-67 ($p=0.0016$), CyclinD1 ($p<0.001$) and Topo IIα ($p=0.018$) was significantly higher than in PIN. Reduced expression of AR ($p=0.0016$), Erß ($p<0.001$), E-Cadherin ($p=0.007$), ß-catenin ($p<0.001$) and Bax ($p<0.001$) was also found in IDC. No difference in expression of ChrA, CD44, VEGF, Bcl2 was found between the cribriform patterns of IDC and PIN.
Conclusion: The cribriform pattern of IDC and PIN differ reliably by the level of expression of PTEN, ERG, AMACR, p53, ERa, Arom, TGF-ß, EGFR, Ki-67, CyclinD1, TopoIIα, AR, Erß, E-Cadherin, ß-catenin and Bax, which may prove significant for differential diagnosis and for explanation of the aggressive biological nature of IDC.

PS-17-083

Comparison of morphological examination techniques for surgical material from radical prostatectomy in staging and prognosis of prostate cancer

V. Zakharava[1], T. Liatkouskaya[1], E. Cherstvoy[1], A. Muradkhanau[1], N. Rudishkin[1], L. Sagalchik[2]
[1] Belarusian State Medical University, Belarus, [2] Urology Center of Minsk Municipal Outpatient Clinic № 6, Belarus

Background & Objectives: Screening measures aimed at certain types of cancer undertaken in the course of last years resulted in considerable increase in prostate cancer (PCa) detectability. Current protocols of morphological examination of biopsy and surgical specimens from PCa patients include a number of prognostic parameters, informativeness of which may decrease depending on the technique of morphological examination.
Objective: Assessment of informativeness of morphological characteristics of PCa depending on the method of radical prostatectomy sampling.
Methods: Surgical material from 111 patients having undergone radical prostatectomy (RPE) was investigated. PCa staging was based upon the pTNM classification of prostate carcinomas (8^{th} Edition TNM), and the tumour histological type was determined based on the WHO classification of prostate gland tumours (WHO, 2016). The data were processed using the Statistica 8.0, $p<0.05$.
Results: All the prostate cancer cases included into this study were those of various grades of acinar carcinoma (ISUP GG1 – 30.7%, GG2 – 36.8%, GG3 – 19.3%, GG4 – 6.2%, GG5 – 7%) with local stage prevailing (pT2c – 62.3%, pT3a – 19.3%, pT3b – 18.4%).

Two techniques of prostatectomy sampling were used within the framework of this study: that of partial sampling of the material from the prostate base, its middle third (mostly in the are on visually detectable prostate cancer) and the prostate apex and the technique of complete sectioning of RPE. A direct relationship has been revealed between the volume of the material under study and the probability of detecting extraprostatic extension (focal and non-focal EPE ρ=0.31 и ρ=0.34 respectively, bladder neck invasion ρ=0.32 и SVI ρ=0.22) and positive margins (multifocal PMs ρ=0.27, including posterolateral surface ρ=0.18* and prostate base ρ=0.15). Dispersion analysis also showed a significantly higher proportion of cases of EPE and PMs in the group of patients, where the RPE material was submitted to complete sectioning, $p<0.05$. The number of cases with a positive surgical margin was low, with predominant localization in the apex region (55%) and posterolateral surface of the prostate (25%, mostly in the zone of EPE), and also the bladder neck (15%) and SVI (5%).
Conclusion: Notwithstanding the fact that the technique of complete sectioning of RPE material enhances dramatically the workload of the pathology service, it makes it possible to increase detectability of pT3a stage of PCa and, accordingly, to optimise the management of this category of patients. The parameters of the PMs, which are subject to morphological evaluation, in turn provide an opportunity of improving the surgical technique for the most problematic locations and also of securing personalised approach to management of patients with prostate cancer in the postoperative period.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-18 | Autopsy Pathology

PS-18-001
Drug-related and toxic myocarditis - histopathologic findings
C. Amalinei[1], V. Jitaru[2], A. Grigoras[3], L. Riscanu[4,2]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] Institute of Legal Medicine Iasi, Romania, [3] Department of Morphofunctional Sciences I-Histology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania, [4] "Grigore T. Popa" University of Medicine and Pharmacy, Romania

Background & Objectives: Myocarditis is a relatively frequent diagnosis in forensics. Beside idiopathic (viral) and infectious myocarditis, hypersensitivity, drug-induced, and toxic variants may be relatively rare in practice. The aim of our study is to report two necroptic cases, one being referred for multidrug voluntary intoxication, in a 44 years-old man, with a history of toxic liver cirrhosis, mitral failure, alcoholic cardiomyopathy, and secondary pulmonary hypertension and the second beeing a 90 years-old female who has been suspected of accidental carbon monoxide intoxication.
Methods: Routine hematoxylin-eosin and Masson's trichrome stainings have been performed.
Results: Microscopy revealed, in the first case, a drug-related myocarditis, exhibiting a predominant mononuclear inflammatory infiltrate, correlated with renal nephrotoxicity, associated with benign nephroangiosclerosis and nephrocalcinosis, along with hepatotoxicity, on a background of liver cirrhosis, in the context of Aminophylline voluntary intoxication. Toxic myocarditis, exhibiting a mixed inflammatory infiltrate, containing frequent neutrophils, on a background of coronarian atherosclerosis and ischaemic myocardial fibrosis, along with an incidental thyroidian papillary carcinoma, follicular variant have been diagnosed in the second case.
Conclusion: The diagnosis of myocarditis is of great relevance, since the histopathological features may favour drug-related or toxic myocarditis against other common conditions, such as infections. In our reports, the medical history and the circumstances of death have been suggestive of aminophylline-related and carbon monoxide toxicity, respectively.

PS-18-002
Umbilical cord hemangioma - case report
C. Amalinei[1], D. Bulgaru Iliescu[2,3], L. Riscanu[2,3], A. Grigoras[4]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] "Grigore T. Popa" University of Medicine and Pharmacy, Romania, [3] Institute of Legal Medicine Iasi, Romania, [4] Department of Morphofunctional Sciences I-Histology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

Background & Objectives: Umbilical cord hemangioma is a very rare entity and may be missed during prenatal investigation. This tumour tends to occur at the placental end of the cord and may arise from one or more umbilical vessels. It should be considered in differential diagnosis with other umbilical masses because it may result in significant morbidity. We report a case of an umbilical cord hemangioma associated with chorangiosis in a stillborn, of 41 weeks gestational age.
Methods: Tissue fragments have been harvested in autopsy for microscopic examination. Routine hematoxylin-eosin (HE) and trichrome Masson staining have been performed.
Results: Autopsy revealed the presence of a cerebral edema, along with kidney, heart, thymus, liver, and adrenal gland hyperemia. Lung parenchyma revealed capillary congestion associated with foetal squames in alveolar spaces, along with alveolar and interstitial hemorrhages. Microscopically, chorangiosis associated with fibrinoid deposits, syncytial knots, and intervillositary haemorrhages have been noticed in the placenta. Umbilical cord sections revealed a proliferation of large vascular spaces lined by endothelial cells and foci of haemorrhages in Wharton's jelly.
Conclusion: A high perinatal morbidity rate is associated with hemangiomas of the umbilical cord due to impaired umbilical circulation. This condition may be correlated to premature delivery, severe foetal haemorrhage, intrauterine growth restriction, and intrauterine death, as reported in the current case. The differentials with varices, aneurysms, thrombosis, and tumours need a careful examination of representative and adequate number of samples.

PS-18-003
Seronegative autoimmune encephalitis presenting with a new-onset refractory status epilepticus: a post-mortem study
J. Duarte Santos[1], H. Pereira[1], L. Bento[2], A. de Sousa[3], C. Pontinha[1], M. Honavar[4], M. Melo-Pires[5], R. Taipa[5]
[1] Serviço de Anatomia Patológica, Centro Hospitalar Universitário de Lisboa Central, EPE, Lisboa, Portugal, [2] Unidade de Urgência Mèdica, Centro Hospitalar Universitário de Lisboa Central, EPE, Lisboa, Portugal, [3] Serviço de Neurologia, Centro Hospitalar Universitário de Lisboa Central, EPE, Lisboa, Portugal, [4] Pathology Department - Hospital Pedro Hispano, Portugal, [5] Neuropathology Unit and Portuguese Brain Bank, Centro Hospitalar Universitário do Porto, Porto, Portugal

Background & Objectives: Autoimmune encephalitis can be triggered by infections, paraneoplastic disorders or it may be idiopathic, and present by variety of clinical manifestations, which can be acute or subacute. We report the case of a 53-year-old patient, with no history of epilepsy or other neurological disorder, presenting with acute onset aphasia and disorientation that rapidly evolved to altered mental status, generalized tonic-clonic seizures, respiratory difficulty and evolving to refractory status epilepticus, prompting admission to the intensive care unit.
Methods: The patient had a personal history of essential thrombocythemia and insulin-treated diabetes mellitus. Following extensive investigation, vascular, paraneoplastic, infectious and metabolic aetiologies were excluded. Cerebral CT and MRI, and cerebrospinal fluid analysis were normal. Serum and CSF evaluation of neuronal cell-surface antibodies (NMDA, AMPA,

GABA, VGKC) was negative. Thyroglobulin antibodies and thyroid peroxidase antibodies were elevated in serum and negative in the cerebrospinal fluid.
Results: Despite aggressive immunomodulatory treatment there was no clinical improvement and after 46 days the patient died of a medical condition (septic shock). The main findings of the post-mortem neuropathologic examination were inflammatory lesions, namely microglial nodules, distributed in the limbic region (hippocampus, entorhinal cortex and periamygdaloid cortex) and brainstem, particularly in the pons. No inclusions suggestive of viral infection were identified.
Conclusion: Although the patient had high serum thyroid autoantibodies, the lack of response to high-dose corticosteroid therapy along with the neuropathological examination favour the diagnosis of seronegative limbic and brainstem encephalitis and do not support the hypothesis of Hashimoto's encephalopathy. We highlight the importance of neuropathological examination in refractory status epilepticus and further CSF studies are still being performed.

PS-18-004

Previously undiagnosed malignant tumours found in adult autopsy: a 12-year retrospective study

F. Galante Pereira[1], A. M. G. Pereira[1], C. A. Padrao[1], J. Palla Garcia[1], R. S. S. Oliveira[1]
[1] Hospital Prof. Doutor Fernando Fonseca, EPE, Portugal

Background & Objectives: Autopsy is a valuable tool in evaluating diagnostic accuracy in oncologic disorders. Many studies have drawn attention to the level of concordance between the clinical evaluation and the autopsy diagnosis of neoplasia. Our purpose was to determine the incidence of unsuspected neoplasia, the concordance of the clinical evaluation and neoplasia, and the concordance of previous histologic diagnosis with neoplasia that were present in autopsies.
Methods: A retrospective, 12-year review of consecutive adult hospital autopsies done between January 2007 and December 2018, were divided in three groups. One where the malignant cancer found corresponded to the patient's confirmed diagnosed disease; another group with a suspected diagnosis of cancer through clinical and radiological criteria but without histologic confirmation; and a final group where there was no clinical suspicion of malignant disease. Each group was analysed according to cancer site and histologic characterization.
Results: On a total of 372 autopsies, 67 cases (18.0%), one or more malignant neoplasms were found. The average patient age on these cases was 68.8 years, with the highest prevalence in males (59.7%). The malignant diagnosis that corresponded with the previous histological diagnosis were 9 (12.7%), the number of clinically suspicion of malignancy without definitive tissue diagnosis was 24 (33.8%), and the number of patients with undiagnosed malignant tumours was 38 (53.5%) of the 71 diagnosis.
Conclusion: Although the numbers of autopsies performed have deceased in hospitals, this retrospective study shows the importance of the autopsy as a mean for the medical quality. Even though the recent advances in medical diagnostic, a great number of malignant tumours were found only at the autopsy.
Conclusion: Age at diagnosis (> 60 years), higher tumour size, presence of LN metastases and absence of oncologic treatment are all negative factors influencing prognosis, but the only statistically significant unfavourable independent prognostic parameters in multivariate analyses are axillary LN status (p=0.005) and triple negative molecular profile (p=0.05). Further research is needed to better understand the factors that affect this disease and appropriate screening may be warranted.

PS-18-005

Dynamics of the number of melanocytes in the hair follicle during ontogenesis

M. Kostyaeva[1], I. Kastyro[1], D. Grosu[1], E. Doroginskaya[1]
[1] Peoples' Friendship University of Russia (RUDN University), Russia

Background & Objectives: Features of the origin and cytophysiology of melanocytes are of increased interest. In clinical practice, there is a high mortality rate from melanomas due to their early metastasis and difficulties associated with their diagnosis.
Objective: to follow the growth dynamics of the number of melanocytes in different age groups.
Methods: The study was performed on 30 autopsy samples no later than 15 hours after death: a fragment of the hairy scalp of women was studied from 15 weeks of gestation to 50 years, the preparations were stained with H&E. The number of melanocytes in each of the 30 hair follicles (HF) of one autopsy sample was counted.
Results: In HF the number of melanocytes was min. 2.6±0.6 shit per bulb($p<0.005$). In postnatal ontogenesis, this indicator increased by 10.1±1.9 units in adolescents($p<0.01$) and women 20–25 years old 18.5 ±1.6($p<0.01$). However, in women 48-60 y.o., the number of melanocytes decreased to 6.6±0.9 ($p<0.005$). At the same time, the number of melanosomes in melanocytes and their surrounding keratinocytes decreased. In the skin of the foetus the hair had a downy structure, but even this type of hair had melanocytes with melanosomes.
Conclusion: Age-related changes in the quantitative composition of melanocytes in the hair follicles were established. The maximum number of melanocytes was noted in the period of 20-25 years. Already the 15-week foetus has melanocytes with melanosomes. This study showed that the content of melanocytes in the hair follicles of the scalp of women changes in ontognosis. Since there has been a rise in the number of melanocytes, the question remains: from which cell sources do new melanocytes come from?

PS-18-006

Pseudocarcinomatous hyperplasia of the lung: a pathological diagnostic challenge

R. Machado-Neves[1], J. dos Santos[1], D. Carvalho[2], R. Araújo[2], T. Amaro[1]
[1] Pathology Department - Hospital Pedro Hispano, Portugal, [2] Intensive Care and Emergency Department - Hospital Pedro Hispano, Portugal

Background & Objectives: Pseudocarcinomatous hyperplasia of the lung is a rare, reactive response to an underlying inflammatory or neoplastic process. It is a benign condition that mimics a malignant neoplasm. A correct diagnosis of this entity is important to avoid radical treatment.
Methods: A 83 year-old man, an ex-smoker with ischemic cardiomyopathy, had an active autonomous life. He was seen in the emergency room with dry cough and dyspnea, which was interpreted as a community acquired pneumonia and given antibiotics.
He returned with severe respiratory insufficiency and bilateral pulmonary infiltrates after two weeks and died a week later.
Results: The lungs (right-1122g; left-944g) had irregular pleura, especially over the lower lobes, and compact congested parenchyma. Histologically, lungs had diffuse alveolar damage (DAD) with hyaline membranes formation, fibrin deposition, septal thickening, pneumocyte hyperplasia, fibroblastic proliferation and intralveolar fibrin plugs. There was extensive proliferation of metaplastic squamous epithelium with cytological atypia and many mitotic figures. There were some small vessels with thrombi. Pleura was thickened with fibrosis, muscular hyperplasia and osseous metaplasia.
The final diagnosis was acute and organizing diffuse alveolar damage with extensive atypical squamous metaplasia.
Conclusion: DAD may involve injury and necrosis of bronchiolar epithelium, which is subsequently replaced by regenerative squamous epithelium spreading from the bronchioles over contiguous alveolar septae and producing a bronchiolocentric pattern. The metaplastic cells can display an alarming degree of cytologic atypia, leading to misdiagnosis as carcinoma. Patient's clinical history, can provided important clues to the reactive nature of the atypical squamous cells.

PS-18-009

Fulminant hepatitis associated with sevoflurane after arthroscopic lavage of right knee, suspected of septic arthritis. An Authopsy case

J. Martinez Martinez[1], S. Saez Alvarez[2]
[1] Complejo Asistencial Universitario de Leon (CAULE) / CITOCLINIC, Spain, [2] Complejo Asistencial Universitario de Leon (CAULE), Spain

Background & Objectives: Volatile anesthetics are drugs that are widely used in surgical interventions. These Halothane-derived drugs present a bundle of adverse effects, including drug-induced liver injury (DILI). Most recent volatile anesthetics, such as Sevoflurane, show less incidence of DILI. Sevoflurane-associated DILI is not clearly defined in the bibliography, without knowing its frequency. There are some case reported, which can oscillate from chronic to fulminant hepatitis.
We present a case of fulminant hepatitis associated with sevoflurane diagnosed by autopsy study.
Methods: We were requested to perform the autopsy study of a 59-year-old patient with a personal history of arterial hypertension and Friedreich's ataxia, who entered via emergency trauma department due to pain and joint inflammation in the right knee, suspected of septic arthritis. Arthroscopic lavage was performed in the operating theatre, using sevoflurane, propofol and fentanyle as anesthetics. Subsequently, the patient presented a rapid deterioration in his state of health, showing coma and dying within 3 days despite CPR. Microbiological cultures of blood and synovial fluid were negative. No liver enzyme analytics were performed.
Results: The autopsy study showed, among other findings, a necroinflammatory lesion of the liver, with perivenular predominance, affecting approximately 70% of the organ parenchyma. This injury was characterised by hepatocellular necrosis with ceroid material deposit and without bilirubin accumulations. No signs of virus infection were observed. Bacterial and fungal techniques were negative
Conclusion: Given the results of the microscopic study, and after dismissing other causes of hepatic damage, a diagnosis of DILI was performed. After studying each administered drug, and contemplating chronologic and morphologic characteristic of this case, we considered that the liver injury was probably caused by sevoflurane.
We compare with, and review the literature

PS-18-010

HHV8+ Lymphoproliferative disease and Kaposi sarcoma in an HIV- immunosupressed patient. An autopsy case

J. Martinez Martinez[1], S. Saez Alvarez[2], F.M. Izquierdo Garcia[2]
[1] Complejo Asistencial Universitario de Leon (CAULE) / CITOCLINIC, Spain, [2] Complejo Asistencial Universitario de Leon (CAULE), Spain

Background & Objectives: A 83 year old female, followed in our institution for reumathoid artritis treated with immunosupresors was diagnosed at 2013 of Kaposi Sarcoma with lessions afecting skin and soft palate and followed thereafter. HIV tests were allways negative
By summer 2017 an axilary lymphadenopathy was biopsied, finding reactive-inespecific changes with some HHV8+ cells. Last september, she was admited with anemia and fever. CT discovered generalized lymphadenopathy, great splenomegalia with lesser hepatomegalia and a 5 cm cardicac mass. An haemophagocytic síndrome was diagnosed and related with an active EBV infection. Clinical course was bad and the patient died. Autopsy was performed
Methods: We were requested for autopsy study, skipping the central nervous system
Results: Kaposi Sarcoma was reactivated with skin and colonic mucosa lessions
Lymph nodes show a distorted microanatomy with effacement of germinal centers, presence of "plasmablastic cells" and other HHV8+ cells
Splenomegaly of 1136 gr was massively affected by a lymphoproliferative mass with extensive necrosis
The cardiac mass observed in the right atrio-ventricular sulcus adipose tissue was infiltration by the same lymphoproliferative lesion observed elsewhere
Hepatic iron overload was observed with severe Kupffer cells hemosiderosis secondary to hemophagocytic process
The lymphatic process is HHV8 +, CD20, CD79a and CD138 negative, MUM1/IRF4+coexisting with an small amount of EBER+ cells
Conclusion: The histology of the lymphoproliferative lesion does not strictly fits in a single WHO 2017 classification item.
A full description of our case and review of the literature is presented with suggestion that more than separate entities HHV8+ related lymphproliferative lesions may be a spectrum sharing in the same patient features of separate categories.

PS-18-011

Gossypiboma in the abdominal cavity and its clinical implications: an autopsy report

J. Melo[1], G. Ribeiro Pontes[2], H. Moita Mota[2], G. Nobre Cavalcanti Lucas[2], D. Nunes Oliveira[1], I. Texeira de Souza[3]
[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil, [3] Morphofunctional Laboratory, Faculty of Medicine, University of Fortaleza, Brazil

Background & Objectives: The oblivion of surgical compresses during abdominal operations can lead to serious complications, such as gossypiboma. To report a case of a patient with gossypiboma.
Methods: A 59-year-old woman, previously submitted to appendectomy and videolaparoscopic cholecystectomy. It evolved postoperatively with flank obstruction. She underwent exploratory laparotomy for lysis of the flanges and adhesions. She sought care two days after hospital discharge with distention and severe abdominal pain, nausea and vomiting. Autopsy was made.
Results: At the autopsy, a large amount of purulent fluid and a surgical compress adhered to the intestinal loops were seen in the abdominal cavity. Adjacent to this dressing, reddish areas with blackened foci were noted. The body was then referred to the Institute that performs medical-legal autopsies.The oblivion of foreign bodies during abdominal operations represents a serious complication, estimating an incidence of 1 for every 1000-1500 laparotomies and generates inflammatory tissue activity in its environment which can culminate in septic / exudative or aseptic / fibrinous reaction. Most of the time, the diagnosis is only established during the operative procedure for intestinal clearing or during the autopsy.
Conclusion: In summary, it was possible to observe that the forgetting of foreign bodies during surgeries leads to significant harm to the patients, often culminating in death. However, there are simple and effective mechanisms to avoid this event, such as adherence to the protocol of safe surgery whose one of the principles is the counting of the surgical material before the patient leaves the operating room.

PS-18-012

Maternal mortality by Hellp Syndrome: an autopsy report

J. Melo[1], J. Barreto Alves Melo[2], G. Van Der Linden Fialho[2], A. de Andrade Cavalcante[2], M. Albuquerque Montenegro[2], M.C. Netherlands Lima[2], I. Veras Beleza[2], L. Dantas Sampaio Leite[2], F.D. Barreto milk[2], A. Santos Correia[2], A.C. Sampaio Braga[2], D. Nunes Oliveira[1]
[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil

Background & Objectives: HELLP syndrome (HS) is a serious complication in pregnancy. Report an autopsy of HELLP syndrome.

Methods: Pregnant woman, 27 years old, with loss of colorless fluid of thin consistency and then thick for 3 weeks and abdominal pain. She presented no heart beat upon her admission to the hospital. In the immediate postoperative, she evolved with vomiting, headache, tingling in lower limbs and profuse bleeding. Laboratory tests: anemia, thrombocytopenia and coagulopathy. She died by hypovolemic shock refractory to vasoactive drugs.
Results: At the autopsy, focal cerebral, oesophageal and tracheal hemorrhages, pulmonary congestion and anthracosis, areas of hepatic hemorrhage, cholesterosis, discrete cardiac hypertrophy, focuses of ischemia and petechiae in the intestine, clear renal corticomedular delimitation and petechiae in the pelvic region. Microscopic indicates hepatocellular necrosis, hepatic steatosis, biliary stasis, chronic cholecystitis and acute tubular necrosis. We present a case of acute postpartum HS complicated by disseminated intravascular coagulation that caused rapid maternal death in the immediate postoperative period after a cesarean section of an uncomplicated pregnancy.
Conclusion: HELLP syndrome is associated with severe maternal morbidity, especially when it occurs in the postpartum period. Early diagnosis and an effective therapeutic approach are essential for better prognosis and prevention of complications. Further studies are needed to provide a better understanding of its pathophysiology and evolution.

PS-18-013
Association between haemophagocytic lymphohistiocytosis syndrome with a Kikuchi-Fujimoto linfadenitis with fulminant clinical evolution
N. Papaleo[1], A. Puche[1], M. Gonzalez[1], J. Gimeno[1], L. Naranjo Hans[1], L. Colomo[1] and B. Lloveras[1]
[1] Hospital del Mar, Spain

Background & Objectives: 48-year-old female patient from China, presenting clinical history of left hemithyroidectomy and Sjögren's syndrome (SS) causing ocular xerostomia, referred to our Institution due to detection of multiple lymph nodes during a concurrent episode of acute bacterial pyelonephritis. CT revealed multiple and bilateral axillary and iliac lymphadenopathies suggesting an inflammatory, infectious or tumoural disease. Multiple serological tests as well as axillary lymph node core-biopsy and bone marrow and peripheral blood smears were performed, without achieving a precise diagnosis. As complications, the patient presented persistent febrile syndrome due to Pneumocystis jirovecci pneumonia, thrombocytopenia and transaminitis with high bilirubin levels. After unfavourable clinical evolution, with progressive respiratory failure, the patient died seven days after the admission
Methods: None
Results: Clinical autopsy was performed. Lung parenchyma showed a diffuse alveolar damage (DAD), consistent with an adult respiratory distress syndrome. Lymph nodes presented nonprominent follicles with depleted cellularity and areas of necrotizing lymphadenitis, containing karyorrhectic debris and histiocytic cells (with myeloperoxidase and TIA-1 positive staining), with a pattern similar to a Kikuchi-Fujimoto (KF) lymphadenitis. Splenic and bone marrow examination revealed diffuse hemophagocytosis, with macrophages containing rests of red blood cells and platelets. Special and immunohistochemical stains performed in necrotic areas did not detect microorganisms. 'In situ' hybridization revealed an increased number of lymphoid cells containing Epstein Barr virus RNA
Conclusion: The autopsy shows the coexistence of a KF-type necrotizing lymphadenitis with histological and clinical findings consistent with an hemophagocytic lymphohistiocytosis syndrome. This relationship has been previously reported, in patients with some acute viral infections (as a possible trigger), and presenting poor clinical course. This association suggests an eventual alteration of the immune system, especially considering that these patients usually present autoimmune diseases, such as lupus erythematosus or SS, as in the present case

PS-18-014
Multicentric Castleman disease associated with HHV-8 in a HIV patient
D. Pereira de Melo[1], J. Pacheco[2,3], E. Fonseca[1,4], R. Portugal[1]
[1] Centro Hospitalar Universitário de São João, Portugal, [2] Department of Pathology, Centro Hospitalar de São João, Porto, Portugal, [3] Department of Pathology, Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal, [4] Faculdade de Medicina da Universidade do Porto, Portugal

Background & Objectives: Castleman disease has three recognized variants, hyaline-vascular variant, plasmacytic variant and the multicentric variant associated with HHV-8, the latter can have a fatal outcome, mostly due to sepsis with multiorganic failure and/or lymphoma.
Methods: We report a case of a 36-year-old man with a 8-year history of HIV infection, without treatment in the last 7 years.
In January 2018 he was admitted at our Institution due to persistent cough and fever, and began treatment with Clarithromycin. On physical examination multiple cervical and axillary lymph nodes were identified with associated splenomegaly. Biopsy of a cervical lymph node revealed Castleman disease associated with HHV-8 with hyalinized vessels,plasmacytoid, concentrically organized plasmablasts around depleted follicular germ centers.
Rituximab and HAART were initiated.
The symptoms persisted, and the lung disease progressed, with associated liver dysfunction. The patient died 3 days later, and an autopsy was requested.
Results: Autopsy revealed: icteric skin; enlargement of multiple chains of lymph nodes with extensive follicular depletion, with focal HHV-8 positivity; lungs with bilateral and multifocal acute pneumonia; splenomegaly with red pulp congestion; kidney acute tubular necrosis; adrenal necrosis.
Conclusion: Multicentric Castleman's disease associated with HHV-8 can progress to a fatal outcome, in this case due to Streptococcus pneumoniae pneumonia and sepsis.
Resection of the lymph node is the most effective treatment in limited disease, in multicentric disease CT, antiretroviral therapy and, specially, Rituximab are the best options for treatment.
In the current case, pneumonia progressed with sepsis, and there was no response to Rituximab or antibiotherapy, leading to the fatal outcome.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-19 | Cardiovascular Pathology

PS-19-001
Anti-apoptotic role of Galectin-3 at 24-hour post myocardial infarction
S.N. Al-Salam[1], S. Hashmi[2]
[1] College of Medicine & Health Sciences-UAEU, United Arab Emirates, [2] Agha Khan University, Pakistan

Background & Objectives: Galectin 3 (GAL-3) is a beta galactoside binding lectin that has different roles in normal and pathophysiological conditions. It is up-regulated in animal models of Heart Failure (HF) even before the development of HF. We have investigated left ventricular myocardial changes associated with high levels of GAL-3 at 24-hour following myocardial infarction (MI) and before the development of HF symptoms and signs. We have studied if raised GAL-3 has any role in apoptotic mechanisms in the heart after MI.
Methods: Male C57B6/J mice and GAL-3 knockout (KO) mice were used for permanent ligation of the left anterior descending artery of the heart to create infarction in the anterior myocardium.

Heart and plasma samples were collected 24 hours after the induction of MI and were used for immunohistochemistry, western blot and ELISA.
Results: Our results show that there was a significant increase in GAL-3 levels in the left ventricle at 24-hour following MI. Our results show that proapoptotic proteins like cleaved caspase-3 and cytochrome c were significantly higher in GAL-3 KO mice as compared to GAL-3 wild mice. We also found a significant higher level of BCL2 in GAL-3 wild mice as compared to GAL3 KO mice.
Conclusion: GAL-3 is highly expressed in left ventricular myocardium at 24-hour following myocardial infarction and mediating antiapoptotic activities.

PS-19-002
Comparison of the damage to aorta wall in aortitis versus non-inflammatory degenerative aortic diseases

K. Amemiya[1], E. Mousseaux[1], H. Ishibashi-Ueda[2], M. Ochiai[3], P. Bruneval[1]
[1] Hopital Europeen Georges Pompidou, France, [2] National Cerebral and Cardiovascular Center, Osaka, Japan, [3] Department of Cardiology Showa University Northern Yokohama Hospital, Japan

Background & Objectives: Frequently aortits is firstly identified by histopathological analysis of surgical aorta specimens from aneurysms or dissections in the absence of clinical evidence of systemic inflammatory disease emphasizing the importance of histology for the diagnosis of aortitis. Histology can be confusing since medial degenerative changes (MDC) can be prominent in a background where inflammation is limited. This raises the question of the role of aging or other degenerative process versus the role of inflammation in the damage to aorta wall.
Methods: In this retrospective single center study we retrieved 719 ascending aorta surgical specimens for treatment of aneurysms or dissections from 2010 until 2018. Aortitis was pathologically diagnosed in 66 patients (9.2%). MDC [elastic fiber fragmentation and/or loss (EFFL), smooth muscle nuclei loss (SMNL), mucoid extracellular matrix accumulation intralamellar or translamellar (MEMA-I or -T, respectively)] was scored according to the consensus statement. Aortitis (n=66) versus age-matched non-inflammatory degenerative aortic diseases (n=66) were compared. Aorta diameter was assessed by cardiovascular imaging.
Results: In 66 aortitis patients; mean age 65 years, 47 patients (71%) were identified pathologically prior to the clinical diagnosis. MDC score was higher in aortitis than in non-aortitis; EFFL and SMNL scores were the most severe in aortitis than in non-aortitis ($p<0.0001$). Moreover higher MDC scores were observed at all aortic size in aortitis versus non-aortitis, especially EFFL and SMNL.
Conclusion: Aortitis was remarkably associated with severe damage to the aorta wall resulting in advanced MDC scores. Inflammatory process in the aorta wall is responsible for increased MDC over aging.

PS-19-004
Histopathological evidence of aortopathy in newborns and infants with Tetralogy of Fallot at the time of surgical repair

O. Fabian[1], R. Gebauer[1], L. Hornofova[1], M. Koblizek[1], J. Janousek[1]
[1] Motol University Hospital, Czech Republic

Background & Objectives: We evaluated microscopic structural abnormalities of the ascending aorta in infants with Tetralogy of Fallot (ToF) and compared them with aortic samples from children that died of other diseases. We aimed at identification of specific histopathological changes associated with ToF and correlation of their severity with time to surgery and mean levels of saturation in the ToF group, and age at death in the second group.
Methods: The ascending aortic wall samples from 23 children with ToF at the time of surgical reconstruction (2 to 19 months) were evaluated by microscopy. Corresponding samples were taken from 16 cadaverous cases of children with other diseases (0 to 76 months). The assessed variables included: elastic fiber fragmentation/thinning/disorganisation, laminar medial necrosis, mucoid matrix accumulations, smooth muscle alterations and grade of overall medial degeneration.
Results: No difference was found between the groups in the individual variables. However, there was a significant difference in the distribution of the grades of the overall medial degeneration ($p=0.016$). ToF group showed uniform mild degenerative changes, whereas second group harboured spectrum of changes ranging from normal to moderate. The presence and severity of those changes were associated neither with age at surgery or mean levels of saturation in ToF group, nor with the age at death in the second group.
Conclusion: This study emphasizes the histopathological assessment of the ascending aorta during the surgical repair of ToF, since the patients demonstrating moderate or severe degenerative changes already in early childhood may be in increased risk of the subsequent late complications.

PS-19-005
New histopathologic grading system in surgical aortic specimens: three year experience

T. Paavonen[1], E. Niinimäki[2], A. Mennander[3], I. Kholová[4]
[1] Department of Pathology, Fimlab Laboratories and Department of Medicine and Life Sciences, University of Tampere, Finland, [2] Department of Anesthesiology, Southern Carelian Central Hospital, Lappeenranta, Finland, [3] Department of Cardiothoracic Surgery, Heart Hospital, Tampere University Hospital, Tampere, Finland, [4] Department of Pathology, Fimlab Laboratories and University of Tampere, Finland

Background & Objectives: Histology for aortic aneurysms and dissections are procured during surgery for these diseases. They are consequences of a spectrum of underlying pathologies, syndromes and age-related degenerative processes. Several partially overlapping histopathological terms have been developed to describe the histopathological changes. A new consensus document was published by Halushka et al (Cardiovasc Pathol 2016) to cover overarching themes: a.unify the nomenclature of histopathological changes in the noninflammatory degenerative aorta; b.provide a new grading scheme to better and more consistently classify aortic lesions. Gradually we have gathered information on the document´s practical applicability in clinical and research context.
Methods: We analysed and scored all aortic samples processed at our pathology department within three years (2016-2018). A total number of 240 samples were scored using both analogue and digital microscopy methods. All samples were scored with the extended version of the scoring system and tabled as a part of our routine pathology reports.
Results: Overall degeneration score distribution: mild degeneration in 20% cases, moderate degeneration in 53%, and severe degeneration in 27% cases. The histopathological scoring results can with ease be correlated to most important clinical patient records.
Conclusion: Interestingly one fourth of patients were scored as severe degeneration, which leads to more careful clinical follow up. The grading system was quickly learned and adopted by pathologists. The new type of histopathology report was appreciated by the clinicians and it ameliorated the communication between clinicians and pathologists. Future prospects include a detailed analysis in correlation to clinical data.

PS-19-006
Histopathology of systemic amyloidosis with cardiac involvement

M. Rybakova[1], V. Baykov[1], I. Kuznetsova[1], M. Vlasova[1]
[1] Pavlov First Saint Petersburg State Medical University, Russia

Background & Objectives: To characterise subtypes and histopathological distribution of amyloid deposits in the myocardium

Methods: Heart specimens from 25 autopsies with systemic amyloidosis were included in the study. We measured heart weight, left (LV) and right ventricular (RV) diameter and wall thickness. For histology H&E and congo red stained slides with subsequent polarization microscopy were used. Finally, we performed IHC for P-component, κ-chain, λ-chain, A-amyloid and prealbumin (substitute for transthyretin).

Results: The mean age of patients was 61±3years (nearly equal in males and females). The average heart weight was 421 g with heart chambers dilated in all patients. The thickness of the LV wall was 1.5 cm, RV wall - 0.4 cm. AL-lambda was diagnosed in 80%, AL-kappa – in 5%, mixed type (AL lambda + ATTR) - in 10%, AA - in 5% of cases. Classical gross presentation (density, fragility, rigidity, increased weight and thickness of the myocardium) were seen only in 13% of cases. All of them contained AL deposits with intermuscular/diffuse and perivascular localization. Nodular forms of heart involvement were documented in 5% - these were AL cases with focal perivascular deposits, diffuse involvement of the myocardium was seen in 82% - these were AL, AA, mixed forms with diffuse pericollagen deposition of amyloid. Microscopically focal deposits appeared as scars with hyaline-like material.

Conclusion: The morphological signs of heart involvement in systemic amyloidosis in most patients are non-specific and may be mistaken for coronary heart disease or dilated cardiomyopathy.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-20 | Digestive Diseases Pathology – GI

PS-20-001

Preliminary study (in conjunction with KWF Budding Consortium, Radboud UMC, NL) regarding standardised approach to detection of tumour budding in diagnostic cancer biopsies and correlation with tumour regression grade of post-neoadjuvant resections

S. Aherne[1], D. Gibbons[1], D. Winter[1], E. Ryan[1], B. Creavin[1], R. Kennelly[1], S. Martin[1], I. Nagtegaal[2], K. Sheahan[1]
[1] St Vincent's University Hospital, Dublin, Ireland, Ireland, [2] Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands

Background & Objectives: Tumour budding (TB) is a histological biomarker of tumour aggressiveness and an independent prognostic factor in colorectal cancer (CRC). TB in biopsies may predict poor pathological response to radiochemotherapy. We aimed to correlate the presence of TB (for biopsies intra-tumoural budding {ITB}) in pre-neoadjuvant therapy rectal cancer biopsies with outcome using tumour regression grade (TRG) of the corresponding post-neoadjuvant resection specimens as a surrogate for survival.

Methods: 106 cases of rectal cancer having both pre-therapy biopsies containing invasive cancer and post-therapy resection specimens were selected from one centre's colorectal cancer database. Each biopsy contained at least one complete/full face of invasive carcinoma at 200x magnification in at least one tissue fragment for inclusion. The biopsies were assessed for ITB on haematoxylin and eosin slides using 20x objective/per eye piece diameter of 0.785mm^2. Assessable field number was also noted.

Results: 34 cases (32%) contained ITB. The median ITB for TRG 1 (complete response) was 1.3 and median ITB for TRG2 and TRG3 (partial/no response) combined was 0.95. 23% of ITB negative cases had a TRG of 1 as opposed to 17% of ITB positive cases. 77% of ITB negative cases had partial/no response (TRG2/TRG3) as opposed to 83% of ITB positive cases. Median ITB/assessable field was 1; median ITB/case was1.3.

Conclusion: Study demonstrates that ITB is manually assessable on biopsies (in preparation for digital analysis) and assessable field number/biopsy is more important than tissue fragment number. Predictive power of biopsy ITB needs larger numbers to assess it's potential in a clinical setting.

PS-20-003

Pathology of intestinal wall and gut microflora translocation in rats during disruption of the mesenteric blood flow and reperfusion

D. Amanova[1], M. Tusupbekova[1], P. Ivachyov[1], S. Kuanyshev[1], Y. Turgunov[1]
[1] Karaganda Medical University, Kazakhstan

Background & Objectives: The aim is to study intestinal morphology during gut microflora translocation in different periods of ischemia and reperfusion in rats.

Methods: 30 male rats were divided into 3 groups: I (n=10) - with ischemia duration 30 min and reperfusion for 60 min, II (n = 10) - with 30 min ischemia and 2 hours reperfusion, III (n=10) -sham (only laparotomy and follow-up 3 hours). The model of ischemia was performed under general anesthesia by clipping superior mesenteric artery, reperfusion was restored by removing the clips. The translocation was determined by injecting a suspension of fluorescent *E.coli* and further microbiological examination of organ crops. The morphological study was performed by using of "Leica DM 1000" microscope.

Results: In group I the translocation was detected in 8(80%) of cases, while morphologically the plethora of vessels was expressed to the maximum, local hemorrhages of the surface mucosal epithelium, weak cellular infiltration of the submucosa were observed. In 5(62,5%) of cases, bacteria are found in the mesentery. In group II after 2 hours of reperfusion, translocation was observed in 7(70%) of rats, of which the most frequent 5(71,4%) were in the spleen and liver. In this group morphologically a plethora of capillaries, focal hemorrhages of the submucosa, diffuse mesentery edema were revealed. In the sham group, the intestinal and mesentery morphology is intact.

Conclusion: With an increase in the period of reperfusion, the translocation of bacteria is more pronounced in the internal organs, the severity of morphological changes is maximal after 2 hours of reperfusion.

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PS-20-004

The spectrum of CKIT and PDGFRA mutations in gastrointestinal stromal tumours in Filipino patients

J.A. Arceño[1], A.J. Dumasis[1], C.K. Obong[1], I.J. Uy[1], L.K. Cabral[1], J.J. Andal[1], G.L. Pua[1], R. Lo[1], R. Li[1], D. Ang[1]
[1] St. Luke's Medical Center, Philippines

Background & Objectives: Gastrointestinal stromal tumours (GIST) diagnosis in the Philippines relies purely on immunohistomorphology. However, with the advent of molecular testing, the classification, diagnosis and targeted-therapy for GIST has greatly evolved. The spectrum of mutations in gastrointestinal stromal tumours is still unknown among Filipino patients. This study aims to determine the prevalence of CKIT and PDGFRA mutations in our population diagnosed with GIST.

Methods: Fifty eight cases of GIST were retrospectively analysed and subjected to mutational analysis (Sanger sequencing) for exon 9, 11, 13, and 17 of KIT and Exons 12, 14, and 18 of PDGFRA genes.

Results: The mean age of diagnosis is 59 years (29 to 86 years), with equal gender distribution. The most common tumour site is gastric (63.79%), followed by the small intestine (22.41%). Immunoreactivity to CD117, DOG1 and CD34 are high at 94.48%, 92.31% and 67.65%, respectively. Majority are diagnosed at larger sizes (>10 cm.); however, mitotic count remains low (<5 mitosis/50HPF) in most cases. Mutational analysis of the GISTs showed a predominant mutation involving KIT

Exon 11 (47.83%) followed by CKIT Exon 9 (13.04%) and PDGFRA Exon 18 (10.87%). Wild type GIST comprise 47.83% of our cohort.
Conclusion: This data is important in the management of Filipinos with GIST. The high prevalence of KIT Exon 11 and PDGFRA exon 18 mutation connotes a higher risk of tumours and predicted resistance to targeted therapy, respectively. There is also a need to test for additional genes to better categorize the wild type GISTs.

PS-20-005
Expression of Wingless-related integration site-3A and Olfactomedin4 in pseudopyloric metaplasia of small intestine in patients with Crohn disease
M. Antolic[1], A. Ognjenovic[1], V. Erakovic Haber[1], I. Glojnaric[1], G. Aralica[2,3], M. Banic[3], S. Cuzic[1]
[1] Fidelta Ltd., Croatia, [2] School of Medicine, University of Zagreb, Croatia, [3] Clinical Hospital Dubrava, Zagreb, Croatia

Background & Objectives: Crohn disease is a chronic inflammatory disease that can discontinuously affect different parts of the human digestive tract. Most commonly affected are small intestine and colon, with pseudopyloric metaplasia as a most prolific feature. Wnt signalling pathway has an important part in intestinal epithelial stem cell proliferation. The aim of the study was to explore changes in Wingless-related integration site–3A distribution and expression of Olfactomedin4 protein, which is a WNT3A target gene and marker for crypt base columnar stem cells.
Methods: A study was performed on formalin-fixed paraffin-embedded intestinal tissue, obtained by resection either from Crohn patients or carcinoma patients (controls). Out of these, three patients had pseudopyloric metaplasia. One micron control and affected small intestine sections were stained using immunofluorescence (WNT3A antibody, Biorbyt, orb49054) or immunohistochemistry (Anti-OLFM4 antibody, Abcam, ab85046). Stained small intestine tissue samples were scored semiquantitatively according to signal intensity.
Results: In the non-IBD small intestine, Wingless-related integration site–3A (WNT3A) is secreted by at least two types of intestinal epithelial secretory cells; Paneth and enteroendocrine cells. In fulminant Crohn disease, elongated crypts showed an increased number of WNT3A positive Paneth cells within crypt stem cell niche and in ectopic position. Olfactomedin4 (OLFM4) labelled enlarged stem cell crypt zone. Most of the cells in pseudopyloric gland metaplasia were strongly WNT3A positive, while a small number of cells were OLFM4 positive.
Conclusion: In this study, we have shown that cells of pseudopyloric gland metaplasia share some characteristics with intestinal stem cells by secreting WNT3A and expressing its target protein OLFM4.

PS-20-006
Tumour budding and poorly differentiated clusters in colorectal carcinoma. Correlation with lymph node total tumour load
I. Archilla Sanz[1], S. Diaz-Mercedes[2], I. Gorostiaga[3], J.J. Aguirre[3], J. Guerrero[4], N. Castrejon[2], J. Tarragona[5], J. Camps[6], I. Aldecoa[1], M. Cuatrecasas[2]
[1] Pathology Department, Hospital Clinic de Barcelona, Spain, [2] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic of Barcelona, Spain, Spain, [3] Pathology Department, Hospital Txagorritxu, Vitoria, Spain, [4] Pathology Department, Hospital Clinic. University of Barcelona, Spain, [5] Pathology Department, Hospital Arnau de Vilanova, Lleida, Spain, [6] IDIBAPS - Barcelona, Spain

Background & Objectives: Tumour budding (TB) and poorly differentiated clusters (PDC) are related to an aggressive behaviour in colorectal carcinoma (CRC). Molecular detection of CK19 mRNA in lymph nodes (LN) of early stage CRC by One Step Nucleic Acid Amplification (OSNA) is an alternative LN staging method to the standard H&E. We aimed to evaluate the correlation between TB and PDCs with LN total tumour load (TTL), defined as the sum of CK19 mRNA/μL copies present in the LNs of CRC specimens.
Methods: 5931 LNs were freshly isolated from 342 CCR from 3 Spanish hospitals. All LNs were analysed with H&E and OSNA. A TTL> 250 copies / μL was considered positive. TB and PDC were evaluated with H&E and CK19 immunohistochemistry.
Results: OSNA was positive in 38.3% cases; TB was low (Bd1) in 45%, intermediate (Bd2) in 25% and high (Bd3) in 30% of cases. PDC was low grade in 53%, intermediate in 32%, and high in 15% of cases. A positive correlation was observed between TB and PDC with TTL ($r = 0.249$, $p < 0.001$ for TB, $r = 0.266$, $p < 0.001$ for PDC), which was higher with immunohistochemistry evaluation. TB and PDC also correlated with high histological grade, lymphovascular and perineural invasion, pT and pN stages ($p < 0.001$)
Conclusion: In early CRC, molecular LN staging is a promising approach and an alternative to H&E staining. The correlation between TTL, TB and PDC would imply a more precise LN staging compared to H&E and hence for the detection of patients at risk of recurrence.

PS-20-007
Gene mutation profile in metastatic colorectal cancer of Egyptian patients
A. Ayach Salem[1], H. Khalil[2], E. Anis Ishak[1]
[1] Kasr El Aini Cairo University, Egypt, [2] Theodor Bilharz Research Institute, Egypt

Background & Objectives: Colorectal cancer is the 4th most common cancer and the second cause of mortality worldwide. Recent improvement in understanding the molecular mechanisms involved in colorectal cancer carcinogenesis allowed the development of targeted therapy and the selection of the patients that will most benefit from these therapies.
The purpose of this study is to investigate the mutation status of different driver oncogenes (KRAS/NRAS/BRAF/PIK3CA) and tumour suppressor genes (TP53, PTEN) in a cohort of Egyptian patients with metastatic colorectal cancer.
Methods: 156 cases of histologically proved metastatic colorectal cancer were collected from a private pathology lab during a period of 3 years (2015-2018). All cases were submitted to a gene mutation study using the next-generation sequencing-based biomarker study to detect KRAS, NRAS, BRAF, EGFR, TP53, PIK3CA and PTEN mutation.
Results: Among the 156 cases included in this study, 97 cases (62.179%) harbouring gene mutation were detected. TP53 was the most common mutation detected (61 cases, 41.780%) followed by RAS genes mutation (60 cases, 38.461%). NRAS and BRAF mutations were significantly less common than KRAS mutation. A single mutation was detected in 53 cases (33.974%) with TP53 the most common one detected in 29 cases (18.589%). 44 cases (28.205%) showed combined mutations, with {KRAS, TP53} being the most common association.
Conclusion: To the best of our knowledge, this is the first study of gene mutation profile in metastatic colorectal cancer of Egyptian patients. Our results were similar to the data reported in previous studies with TP53 and RAS gene being the most commonly detected mutations, but the incidences in our study were lower than what was commonly reported.

PS-20-008
An immunophenotype-based molecular classification of colorectal carcinomas
L. Banias[1], I. Jung[2], T. Bara[3], Z. Fülop[3], S. Gurzu[1]
[1] University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania, [2] University of Medicine, Pharmacy, Sciences and

Technology, Targu Mures, Romania, [3] University of Medicine, Pharmacy, Sciences and Technology of Tirgu Mures, Romania, Surgery Department, Romania

Background & Objectives: Colorectal carcinoma (CRC) remains the third most common cancer worldwide, a large number of these patients being diagnosed in late stages. Molecular subtyping of CRC may improve the case management and selection of cases for targeted therapy. The aim of the paper was to propose a molecular classification based on epithelial-mesenchymal transition (EMT) related immunophenotype.
Methods: 84 consecutive CRC cases, without preoperative radio-chemotherapy, were included. Based on the EMT-related markers, three molecular subtypes were defined: epithelial (positive for E-cadherin and membrane β-catenin and negative for vimentin), mesenchymal (loss of E-cadherin positivity and vimentin positivity or nuclear β-catenin), and hybrid cases (epithelial core and mesenchymal buds). AE1/AE3 cytokeratin and subcellular expression of Maspin (cytoplasmic versus nuclear) were used for buddings counting, whereas microsatellite status was evaluated with MLH1, MSH2, PMS2, and MSH6.
Results: There were 31 females and 53 males with ages ranging from 33 to 88 years old. Most of the cases were diagnosed as moderately-differentiated adenocarcinomas (78.57%) in pT3 (70.24%) stage. Majority of carcinomas were hybrid-type (48.81%), followed by epithelial (35.71%) and mesenchymal (15.48%). Maspin nuclear expression was correlated with the budding-degree (p=0.0328) and was more frequently seen in both tumour center (p=0.0385) and buds (p=0.0502), in hybrid and mesenchymal carcinomas, compared with the epithelial-subtype CRCs, which mostly expressed cytoplasmic maspin.
Conclusion: Nuclear maspin positivity represents an indicator of EMT transition of CRC cells.

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PS-20-009

Neuroendocrine tumours in children and young adults, experiece in the University Hospital Fundación Santa Fe de Bogotá

R. Lopez[1,2], L.E. Barrera-Herrera[3]
[1] Department of Pathology and Laboratories, Hospital Universitario Fundación Santa Fe de Bogotá, Colombia, [2] School of Medicine, Universidad de los Andes, Bogotá, Colombia, [3] Department of Pathology and Laboratories, Hospital Universitario Fundación Santa Fe de Bogotá, Colombia

Background & Objectives: Despite the significant increase in the incidence of neuroendocrine neoplasms, they are still considered rare tumours. In children and young adults its true incidence is not known, most of the published information correspond to case reports and in Latin America there are no data of its true incidence. In the centers of paediatric oncology, the proportion of these neoplasms is 16%, representing 0.1% of all paediatric tumours. The most frequent location is the cecal appendix and is usually associated with acute appendicitis. Extra-appendicular tumours are even more infrequent and course with uncertain malignant potential, slow growth, high recurence risk and can metastasize even several years after the initial diagnosis.
Methods: We present a cross-sectional descriptive retrospective study in patients diagnosed with neuroendocrine neoplasms in the Department of pathology and laboratories of the University Hospital Fundación Santa Fe de Bogotá between October 2003 and October 2018, we present the demographic, clinical and pathological variables of these patients.
Results: In the database of our hospital in a period of 15 years, we found 48 patients (average age, 17.8 years range: 10 - 24); 20 men and 28 women. 60% (n = 29) located in the cecal appendix, 100% with acute appendicitis, 2 of them with lymph node metastasis. 22.9% were metastatic tumours to liver (n = 4), lymph nodes (n = 6) and mesentery (n = 1), in these cases primary origin was found in the bile duct / common bile duct, small intestine, appendix, pancreas. Other primary sites were lung / bronchus, cervix, anterior mediastinum, rectum and skin / soft tissues. WHO 2010 classification prevalence: NET Grade 1: n=26, Grade 2: n=14, Grade 3: n=5 and Pulmonary / Bronchial Carcinoid: n=3.
Conclusion: We calculate in our Institution an average rate of 1,914 cases per 100,000 patients / year.

PS-20-010

Assessment of tumour buds in colorectal cancer. A large-scale international digital observer study

J. Bokhorst[1], H. Dawson[2], A. Blank[2], A. Lugli[2], I. Zlobec[2], L. Rijstenberg[3], M. Vieth[4], R. Kirsch[5], m. Urbanowicz[6], S. Brockmoeller[7], J. Flejou[8], J. van der Laak[3], F. Ciompi[3], I. Nagtegaal[3]
[1] Radboud University Medical Center, The Netherlands, [2] University of Bern, Switzerland, [3] Radboud University Medical Center, The Netherlands, [4] University Bayreuth, Germany, [5] University of Toronto, Canada, [6] EORTC Translational Research Unit, Belgium, [7] Pathology & Data Analytics, Leeds Institute of Medical Research at St. James's, School of Medicine, University of Leeds, United Kingdom, [8] APHP Sorbonne Université, France

Background & Objectives: Tumour budding (TB) is a promising and cost-effective biomarker with strong prognostic value in colorectal cancer. We previously found moderate agreement between two pathologists scoring TB using the International Tumour Budding Consensus Conference (ITBCC) guidelines, while considerable discrepancy in identifying individual tumour buds was observed. To explore this issue further, we performed a large-scale international digital observer study on the assessment of individual tumour buds.
Methods: We extracted 3000 tumour bud candidates by application of digital image analysis algorithms. For every candidate, an image patch (size 256x256um) was extracted from pan-cytokeratin-stained whole-slide images of 36 patients with reported TB. Members of a tumour budding consortium were invited to categorize each individual object as (1) tumour bud, (2) poorly differentiated cluster, or (3) none of the previous, based on best practice and current definitions. Agreement was assessed with Cohen's and Fleiss Kappa.
Results: Cohen's and Fleiss Kappa showed a fair to moderate overall agreement between observers (range 0.24-0.65 and 0.37 respectively) when asked to score 3000 individual objects.
Conclusion: Despite adequate agreement between observers in the assessment of TB on patient level, the agreement on individual tumour bud level using immunohistochemistry is only fair. To better understand the causes of this disagreement, more research is needed involving H&E stained images. A machine learning approach may prove especially useful for a more robust assessment of individual tumour buds.

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PS-20-011

The use of Stochastic Optical Reconstruction Microscopy (STORM) in formalin fixed paraffin embedded tissue

S. Brockmoeller[1], K. Kouvidi[1], H. Slaney[1], R. Hughes[2], A. Curd[2], M. Peckham[2], P. Quirke[1]
[1] Pathology & Data Analytics, Leeds Institute of Medical Research at St. James's, School of Medicine, University of Leeds, United Kingdom, [2] Faculty of Biological Sciences, University of Leeds, United Kingdom

Background & Objectives: Colorectal cancer (CRC) with amplification/over-expression of cell surface receptors or ligands

are specifically targetable (e.g. HER2 and anti HER2 therapy, EGFr and anti EGFr therapy) but most patients selected for these therapies fail to respond due to unknown mechanisms of resistance. Developments in advanced fluorescence microscopy have made it possible to resolve protein localisation at up to 5nm resolution. In this pilot study we aimed to develop a robust routine methodology for Formalin Fixed Paraffin Embedded tissue (FFPE) that exploits this technology and explore its potential for visualisation of ligand-receptor pathways in CRC to increase our understanding of resistance mechanisms at a cellular level.
Methods: To establish the protocol on FFPE tissue we selected colorectal cancer cases with strong HER2 and negative HER2 receptor expression. Previously described cell culture protocols (Creech et al. 2017) were modified, optimised and imaged by confocal microscopy using HER2 (1:250) with affinity purified secondary antibody (1:500). The optimised protocol was used in 3D dSTORM on FFPE.
Results: Protocols for HER2, EGFR, RAB5 and RAB11 expression on FFPE samples were determined using the confocal microscope. In 3D dSTORM, high levels of HER2 were localised to aggregates in the membrane and lower levels in the cytoplasm. Further work will focus on imaging and quantification of further components of the MAPK/ERK pathway in 3D dSTORM and imaging multiple proteins in combination to assess ligand-receptor and receptor-adapter interactions as well as receptor cycling.
Conclusion: STORM microscopy opens up subcellular microscopy in FFPE to Histopathologists.

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PS-20-013

Helicobacter pylori infection: a comparative prospective study of histochemical stains versus real-time diagnosis with EndoFaster® test

A. Caminoa-Lizarralde[1], I. Carretero-Barrio[1,2], T. Rodajo-Fernandez[1,2], E. Romio[1,2], E. Sanchez-Rodriguez[1,3], E. Vazquez-Sequeiros[1,3], C. Perna-Monroy[1,2]
[1] Hospital Universitario Ramon y Cajal. IRYCIS., Spain, [2] Department of Pathology, Spain, [3] Department of Gastroenterology, Spain

Background & Objectives: Helicobacter pylori (HP) infection has been implicated in a number of malignant and non-malignant conditions. The confirmatory diagnosis of HP requires an endoscopic biopsy, followed by histopathological examination using haemotoxylin and eosin stain or special stains such as Diff-Quick (DQ) stain and/or Warthin-Starry (WS) stain. EndoFaster® is a novel device able to perform real-time ammonium and pH measurement in gastric juice, allowing HP diagnosis during gastro-duodenal endoscopy. This study aimed to validate the accuracy of EndoFaster® for real-time HP detection.
Methods: Consecutive patients who underwent upper endoscopy in our centre were prospectively enrolled from July to August 2017. During the endoscopy procedure, gastric juice was aspirated to perform automatic analysis by EndoFaster®, and HP was considered positive (>67 ppm/ml) or negative (<57 ppm/ml). Accuracy was measured using histology as gold standard, with two histochemistry determinations (DQ and WS stains). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for EndoFaster® test and DQ stain, using WS as gold standard.
Results: Overall, 80 patients were enrolled, and 86 aspirated gastric juices were studied. In 19 cases (24%) the histology was normal. In the remaining cases, varying degrees of inflammation were found. Compared with pathology and WS, sensitivity, specificity, PPV, and NPV were 73%, 84%, 73% and 84% for EndoFaster® test; and 63%, 100%, 100% and 82% for DQ stain, respectively.
Conclusion: Biopsy remains the gold standard test in HP infection. However, this new technique is useful in monitoring HP eradication or to select patients in whom biopsy could be avoided.

PS-20-014

Clinicopathologic features of radiation-induced enteritis: a monocentric surgical study of 41 patients with outcome correlations

D. Cazals-Hatem[1], J. Didier[1], J. Cros[2], N. Guedj[1], Y. Panis[1], F. Joly[1]
[1] Hopital Beaujon, France, [2] Beaujon University Hospital / Pathology Department, France

Background & Objectives: Surgery is required in patients with symptoms of radiation-induced enteritis (RE) resistant to medical therapies. The study aimed to describe and correlate histopathological features of RE to the initial clinical presentation and to postoperative outcome.
Methods: All patients with a small bowel resection performed for RE between 2006 and 2017 in our center were studied. Histological data were retrospectively correlated to initial clinical data at radiation and to recurrence of RE symptoms observed during a median postoperative follow-up of 32 months (occlusion, need for reoperation, prolonged parenteral nutrition).
Results: Forty-one patients were studied (39F/2M), median age 62yo at time of radiation for pelvic cancer (80% gynaecological). Median time to surgery for RE after radiation was 3 years [1-41]. Ileocaecal resections (80% of patients) removed a median small bowel length of 60 cm [10-220]. Histologically, diffuse obliterative arteriopathy was present in 24 (59%) patients, significantly associated to amyotrophy, villous atrophy and ulceration observed in 66, 63 and 34% of patients respectively. The 17 (41%) patients left presented all with serosal sclerosis with adhesions responsible for occlusion. Arteriopathy was uncorrelated with age and vascular risk factors present at time of radiation (active tobacco, diabetes, hypertension, dyslipidemia, combined chemotherapy). Median time to surgery after radiation was longer in patients with arteriopathy (13 years *vs* 2.6 years, p=0.0002). During the postoperative follow-up, 50% of patients had recurrence of RE symptoms, uncorrelated to the radiation-induced arteriopathy.
Conclusion: The radiation-induced arteriopathy is observed in RE with ischemic features and occurs very late after the radiation indicating a slow progressive and long-standing vascular injury. It does not influence the postoperative outcome. In our series, half of the patients was wounded by the surgery.

PS-20-015

Prognostic perspectives of PD-L1 combined with tumour-infiltrating lymphocytes, Epstein-Barr virus infection, and microsatellite instability in gastric carcinomas

M.S. Chang[1], E. Choi[2], S. Byeon[2], S. Park[2]
[1] Seoul National University Boramae Hospital, Seoul National University College of Medicine, Republic of Korea, [2] Seoul National University Boramae Hospital, Republic of Korea

Background & Objectives: The prognostic potential of PD-L1 is currently unclear in gastric carcinomas, although the immune checkpoint PD-1/PD-L1 inhibitors have produced promising results in clinical trials. The purpose of this study was to define the prognostic implications of PD-L1 and immunomodulatory tumour-infiltrating lymphocytes (TILs), and further to provide guidance regarding the selection of patients for whom PD-1/PD-L1 blockade immunotherapy would be advantageous.
Methods: We explored the prognostic implications of programmed death ligand 1 (PD-L1) in 514 consecutive surgically-resected gastric carcinomas. Overall survival and recurrence-free survival were evaluated. Immunohistochemistry for PD-L1, CD8, FOXP3, and PD-1, and molecular grouping by *in situ* hybridization for Epstein-Barr virus (EBV)-encoded small RNAs and multiplex PCR for microsatellite instability (MSI) markers were performed.
Results: PD-L1(+) tumour cells and PD-L1(+) immune cells were observed in 101 patients (20%) and 244 patients (47%), respectively. Tumoural PD-L1(+)/immune cell PD-L1(-)/$CD8^{+/low}$ TILs, and late-stage tumours were associated with unfavourable clinical outcomes in

the entire cohort using a Cox proportional hazards model. Tumoural PD-L1(+)/FOXP3$^{+/low}$ TILs were associated with worse clinical outcomes in the entire cohort, EBV-positive carcinomas, and MSI-high carcinomas through univariate analysis. Tumoural PD-L1(+) alone was an adverse prognostic factor in the entire cohort and EBV-positive carcinomas.
Conclusion: The prognostic impact of PD-L1 may depend on the tumour microenvironment. The combination of PD-L1 expression and CD8^{+} TILs may serve as an independent prognostic factor. Tumoural PD-L1(+)/immune cell PD-L1(-)/CD8$^{+/low}$ TILs showing a worse prognosis may be beneficial for combinatorial therapies of anti-PD-L1/PD-1 and anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA4) that would promote effector T cells, thus attack the tumour.

PS-20-017

Immunogenic phenotype of EBV-negative mismatch repair proficient gastric cancer

B. Dislich[1], N. Blaser[1], B. Gloor[2], K. Mertz[3] and R. Langer[1]
[1] Institute of Pathology, University of Bern, Switzerland, [2] Department of Visceral Surgery and Medicine, Inselspital University Hospital Bern and University of Bern, Switzerland, [3] Cantonal Hospital Liestal, Switzerland

Background & Objectives: EBV-positive and mismatch repair deficient (MMRd) Gastric Cancers (GC) show higher levels of tumour infiltrating lymphocytes (TILs) and increased PD-L1 expression and thus are more likely to respond to immunotherapy. The majority of GC, however, are EBV-negative and MMR proficient (MMRp). We systematically analysed PD-L1 expression and immune infiltrates in EBV-negative MMRpGC in comparison to EBV-positive and MMRdGC to evaluate whether additional tumours may harbor an immunogenic phenotype that would make them eligible for immunotherapy.
Methods: A next generation tissue microarray of 401 primary resected GC was analysed by EBER in situ hybridization, MSH1, PMS2, MSH2, MSH6, PD-L1 and CD8 immunohistochemistry. PD-L1 positivity was defined as tumour proportion score >1%. CD8+TILs and their proximity to cancer cells were analysed on the HALO™ image analysis platform. The total number of CD8+TILs and their tumour proximity was dichotomized using the median as cut-off.
Results: Twelve cases were EBV-positive, 48 cases MMRd and 341 cases EBV-negative MMRpGC. EBV-positive and MMRdGC were more often PD-L1-positive (73%, 19%), demonstrated increased numbers of CD8+ TILs (92%, 81%) and increased proximity of CD8+TILs to tumour cells (83%, 74%) compared to EBV-negative MMRpGC (5%, 43%, 46%, p<0.001 each). PD-L1-positive EBV-negative MMRpGC demonstrated increased numbers of CD8+TILs with increased proximity to tumour cells compared to PD-L1-negative tumours (80% vs 42%; 80% vs 45%; p<0.01). Further tumour subgroups showed high CD8+TILs or tumour proximity despite being PD-L1-negative (n=126 and n=134).
Conclusion: PD-L1 and CD8 immunohistochemistry, supplemented by digital image analysis, may be helpful to identify probable candidates for immunotherapy in EBV-negative MMRpGC.

PS-20-018

Mis-match repair protein antibodies and their performance in the UK National External Quality Assessment Scheme for Immunocytochemistry and In-Situ Hybridisation (UK NEQAS ICC & ISH)

A. Dodson[1], S. Parry[1]
[1] UK NEQAS ICC & ISH, United Kingdom

Background & Objectives: UK NEQAS ICC & ISH carries out external quality assessment of mis-match repair (MMR) immunohistochemistry (IHC) at quarterly intervals and has done so since 2011. Participating laboratory's stained slides are assessed for technical quality; data are collected on primary antibodies used and other methodological parameters. We examined our data, looking for trends over time and associations between assessment score achieved and methodological parameters.
Methods: For each of four MMR proteins (MLH-1, MSH-2, MSH-6, PMS-2), data were collated from the Scheme's database and analysed in respect of performance of primary antibody clones, detection methods and staining platforms.
Results: Between 2011-19, 28 assessments were conducted (4,447 submissions). Median number of laboratories subscribed at each run was 169 (range: 134 – 228). These comprised laboratories located in 30 different countries; UK-based laboratories contributed 44.0% of submissions.
The mean pass-rate for each MMR protein on samples provided by UK NEQAS was, MLH-1: 88.9%; MSH-2: 87.7%; MSH-6: 81.8%; PMS-2: 86.8%.
Improvement in proportions of submissions obtaining a pass over time was seen in all groups (P<0.05, Cochran–Armitage test for trend).
Conclusion: Performance of different primary antibodies against all four MMR proteins showed very large variations. Staining platforms supplier was not associated with performance differences.

PS-20-019

Is there an optimal definition for positive circumferential resection margin in oesophageal cancer?

C. Dufour[1], B. Brac[1], H. Behal[1], M. Messier[2], E. Leteurtre[3,4], C. Mariette[3,4], G. Piessen[3,4], F. Renaud[3]
[1] CHU Lille, France, [2] CHU, Inserm UMRS 1172, Lille, France, [3] CHU, Univ. Lille, France, [4] Inserm UMRS 1172, Lille, France

Background & Objectives: Positive circumferential resection margin (CRM) is a major prognostic factor in resected oesophageal carcinoma. The Royal College of Pathologists (RCP) defines a positive CRM (R1) as the presence of tumour cells within 1 mm of the circumferential margin and the College of American Pathologists (CAP) as the presence of tumour cells at the cut margin of resection. The aim of this study was to evaluate the clinical impact of a positive CRM (R1) according to the RCP and CAP definitions.
Methods: Patients who underwent radical oesophageal resection for adenocarcinoma or squamous cell carcinoma of the oesophagus (pT3 or pT4) were selected from 2007 to 2016. They were secondarily excluded if CRM was macroscopically incomplete (R2) or if longitudinal resection margins were positive. CRM was histologically reassessed using an ocular micrometer. Overall survival (OS) and disease-free survival (DFS) were estimated with uni and multivariate analysis.
Results: 283 patients were included. CRM was measured as follows: CRM=0mm (n=48), CRM within 1 mm (n=123) and CRM>1mm (n=112). R1 resection, according to both definitions was significantly associated with poor OS (CAP: p<0.001; RCP: p=0.008). Interestingly, CRM=0mm was the optimal definition to predict global and locoregional recurrence.
Conclusion: R1 is a poor prognostic factor in resected oesophageal cancer according to the CAP and the RCP definitions. However, CAP definition appears more accurate to predict prognosis and recurrence.

PS-20-020

Gastric signet ring cell carcinoma: a comparative analysis of clinicopathologic features

B. Efared[1], J. Nshizirungu[2], N. Hammas[2], H. El Fatemi[2], L. Chbani[2]
[1] Department of Pathology, Hassan II University Hospital, Fez, Morocco, [2] CHU Hassan II de Fès, Morocco

Background & Objectives: Signet ring cell carcinoma (SRC) is a distinct histological type of gastric carcinoma. The aim of our study is to investigate differential characteristics between gastric SRC and other non SRC carcinomas (nSRC).

Methods: It was a retrospective study including 166 patients diagnosed with gastric carcinoma over a period of 4 years (2014-2017), at the department of pathology of Hassan II university Hospital, Fès, Morocco. We have performed statistical comparison of clinicopathological features between patients with SRC and those with nSRC.
Results: 111 patients (66.9%) had nSRC and 55 had SRC (33.1%). Patients with SRC were younger (mean age of 50.53 *versus* 59.78, P=0.014). SRC tends to be located in the fundus and in the antropyloric region (P=0.007). Patients with SRC present more often with pT3 tumours (P<0.001), with lymph node metastasis (P=0.003). Perineural invasion was more frequently found in patients with SRC (P=0.005). The median overral survival time was 38.8 months. Patients with nSRC live longer than those with SRC (P=0.284).
Conclusion: Signet ring cell carcinoma is a histological subtype of gastric carcinoma with characteristic clinicopathologic features (younger age, lymph node and perineural invasion). The clinical management of patients should take into account these particular features.

PS-20-022
Expression of FAP-1 in colorectal adenocarcinoma associated fibroblasts
C. Ercan[1], M. Coto-Llerena[2], V. Kancherla[1], G. Nicolas[3], L. Terracciano[1], S. Piscuoglio[1], M. Fani[4]
[1] Institute of Pathology, University Hospital Basel, Switzerland, [2] Department of Biomedicine, University of Basel, Switzerland, [3] Division of Nuclear Medicine, University Hospital Basel, Switzerland, [4] Division of Radiopharmaceutical Chemistry, University Hospital Basel, Switzerland

Background & Objectives: FAP-1 is expressed on tumour-associated fibroblasts in the majority of epithelial cancers and has been associated with tumour growth. In this study, we aim to investigate the expression of FAP-1 in colorectal cancers and correlate its expression with clinicopathologic features.
Methods: FAP-1 mRNA expression and clinico-pathologic information were obtained from 622-CRC patients and 51 non-tumoural tissue from The Cancer Genome Atlas dataset. FAP-1 protein expression was evaluated in a cohort of 92 CRCs and 19 non-tumoural tissues by immunohistochemistry. FAP-1 expression was scored in cytoplasm of stromal cells based on percentage of positive cells (0=<1%; 1+=1-10%; 2+=11-50% and 3+=>51%) and intensity (0= none; 1= weak; 2=intermediate; 3=strong). Statistical analysis was performed using log-rank test (Survival) and X^2 or Fisher's exact tests.
Results: FAP-1 mRNA was significantly upregulated in tumours and high expression in tumours was significantly associated with poor survival (p<0.005). Results obtained at the mRNA level were further corroborated at protein level. FAP-1 expression was detected in stromal cells in 90% of the tumours but not in the non-tumoural mucosa. Among those positive, 24% tumours showed a high-intensity stain while 25% and 41% of tumours showed a weak and intermedia intensity stain, respectively. Semiquantitative staining was scores 1+ in 18%, 2+ in 31%, and 3+ in 41% of the tumours. Low expression of FAP-1, both at mRNA and protein level, was found to significantly correlate with stage I tumours (p<0.005).
Conclusion: Colorectal tumours with high levels of stromal FAP-1 are more likely to have aggressive disease progression and survival.

PS-20-023
Development of a mismatch repair immunohistochemistry clinical trial assay and novel BRAF V600E antibody
H. Finkelstein[1], V. Tennant[1], C. Mayhew[1], S. Soleimani[1], S. Tabuena-Frolli[1], J. Lee[1], T. Haase[2], F. Aidt[2], E. Oroudjev[2]
[1] Agilent Technologies, USA, [2] Agilent Technologies, Denmark

Background & Objectives: Loss of function of any of the four MMR proteins (MLH1, PMS2, MSH2, MSH6) results in MMR deficiency (dMMR) and is associated with the hereditary disease Lynch syndrome. It's been shown that dMMR patients respond well to immunotherapy, therefore MMR proteins are important emerging biomarkers.
Agilent is validating Dako Omnis MMR Immunohistochemistry (IHC) Panel as a predictive diagnostic assay for OPDIVO® treatment. To support a Lynch syndrome intended use, Agilent is also developing a novel anti-BRAF V600E antibody.
Methods: Analytical testing for Dako Omnis MMR IHC Panel and anti-BRAF V600E antibody includes sensitivity, specificity, precision, robustness, and stability. Testing was performed on human formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissues using Dako Omnis automated staining solution with EnVision FLEX visualization system. Biomarker status was evaluated as intact or loss for MMR and positive or negative for BRAF V600E.
Results: Sensitivity testing of 179 commercially procured FFPE specimens resulted in a dynamic range of staining intensities for all antibodies. MMR antibodies showed an expected bimodal distribution. When evaluating 60 specimens for biomarker status by multiple observers, inter-observer reproducibility agreement was ≥ 93.3 % and intra-observer reproducibility agreement was ≥ 99.0 %. Robustness testing produced staining variation less than 0.5 intensity grade for the eight most critical parameters. Reagent stability testing using an accelerated model resulted in stability of 24 months.
Conclusion:
Analytical testing indicates Dako Omnis MMR IHC Panel plus anti-BRAF V600E antibody is a sensitive, precise, robust, and stable assay for detecting target proteins in CRC.

PS-20-024
Eosinophil counts in colon biopsies can predict treatment response to vedolizumab in Inflammatory Bowel Disease
R. Gabriëls[1], A.R. Bourgonje[1], G. Trentadue[1], K.N. Faber[2], G. Dijkstra[1], G. Kats-Ugurlu[3]
[1] Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, The Netherlands, [2] Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands, [3] Department of Pathology University of Groningen, The Netherlands

Background & Objectives: Vedolizumab, an antibody against α4β7-integrin capable of blocking the migration of several immune cells across endothelium expressing MAdCAM-1, is a second-line biological treatment for moderate-to-severe inflammatory bowel disease (IBD). Because of moderate response rates to this drug, there is an urgent need for predictive markers to identify patients who would benefit from vedolizumab. Our hypothesis is that the number of mucosal eosinophils can predict therapy response to vedolizumab.
Methods: We analysed inflamed and non-inflamed colon biopsies of IBD patients before the start of vedolizumab therapy using hematoxylin-eosin staining. We selected hot spots of eosinophils at low magnification from digitally-scanned slides. Two independent researchers counted manually the number of eosinophils in three high power fields (HPF, 0.24 mm²). Results above 60/HPF were grouped together. Clinical response to vedolizumab was defined at 14 weeks of treatment by using HBI and SCCAI scoring methods.
Results: Baseline median eosinophil count in non-inflamed colon ascendens mucosa (n=24, Crohn's disease n=10, ulcerative colitis n=14) was significantly higher in responders compared to non-responders (60 ± 12 vs. 25 ± 7,5 eosinophils/HPF, P<0.001, Mann Whitney U test). Patients with >30 eosinophils/HPF achieved clinical response in 83,3% of cases (n=12), whereas only 8,3% of patients with <30 eosinophils responded (n=12). Eosinophil count in inflamed tissue was excluded because of differences in inflammation severity.

Conclusion: Based on our results, eosinophilic count can be used to predict response to vedolizumab in IBD patients. Our method should further be validated in a larger cohort.

PS-20-026

The influence of the genetic and immunologic context in the development of colorectal adenoma

D. Garcia[1], I. Gullo[2,3,4], L. Spaans[5], S. Miranda[6], J. Reis[6], J.L. Costa[6], F. Carneiro[7], J.C. Machado[8]
[1] Medical Faculty of the University of Porto, Portugal, [2] Department of Pathology, Centro Hospitalar de São João, Porto, Portugal, [3] Department of Pathology, Faculty of Medicine of the University of Porto (FMUP), Portugal, [4] Institute of Molecular Pathology and Immunology at the University of Porto (Ipatimup), Instituteo de Investigação e Inovação em Saúde (i3S), Portugal, [5] Maastricht University, The Netherlands, [6] I3S/Ipatimup, Portugal, [7] I3S/Ipatimup; Centro Hospitalar de São João; FMUP, Portugal, [8] Institute of Molecular Pathology and Immunology of the University of Porto (Ipatimup), Portugal

Background & Objectives: Overcoming immunosurveillance is a major step in the progression of many types of tumours. Several immune escape strategies have been identified, including immunoediting and the establishment of an immune suppressive microenvironment. The aim of the present study was to determine whether the hereditary or sporadic context has any influence in the relationship between immune surveillance and tumour development, using sporadic and familial adenomatous polyposis (FAP) related colorectal adenomas as a model.
Methods: The immune tumour-infiltrating cells of a total of 58 low-grade and 18 high-grade colorectal adenomas were examined and compared, using immunostaining for CD3, CD4, CD8, CD57, CD68 and FoxP3. The mutational burden was evaluated by Next Generation Sequencing and was compared between sporadic and FAP adenomas.
Results: FoxP3 and CD68 counts were significantly higher in sporadic low-grade dysplasia (p=0.0003 and p=0.0103, respectively), and FoxP3 and CD4 counts were found to be significantly higher in high-grade sporadic dysplasia (p=0.0008 and p=0.0018, respectively) when compared with corresponding lesions in FAP patients. The mutational burden was found to be significantly higher in FAP samples (p=0.0040), when compared with sporadic samples.
Conclusion: This study suggests that the immune microenvironment of sporadic and hereditary lesions is different. Sporadic lesions contain a higher number of immune suppressive Treg cells and a lower mutational burden, hinting at a stronger immune selective pressure. In contrast, hereditary lesions seem to benefit from a more tolerant immune microenvironment, allowing for the development of lesions with a higher mutational burden and lower immune cell infiltration.

D. Garcia and I. Gullo are first authors in equal proportions.

PS-20-027

Assessment of colorectal resection specimens for the predictor features of presence of tumour deposits and lymph node characteristics: importance of mucinous tumour histology

G. Kir[1], R.B. Girgin[1], T. Soylemez[1], S. Gundogdu[2], I. Tosun[3], A. Gapbarov[4], G. Bas[4], O. Alimoglu[4]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, School of Medicine, Turkey, [3] Umraniye Training and Research Hospital, Department of Pathology, Turkey, [4] Istanbul Medeniyet University, Department of General Surgery, Turkey

Background & Objectives: The presence of tumour deposits (TDs), number of harvested lymph nodes (LNs), LN positivity, positive LN number, and LN ratio (LNR) are well-known prognostic factors in colorectal carcinoma.
Methods: The relationship between clinicopathological parameters and the presence of TDs, number of harvested LNs, N stage, positive LN number, and LNR was investigated in 278 consecutive patients who underwent surgery for colorectal adenocarcinoma.
Results: Binary logistic regression analysis revealed that mucinous tumour histology and lymphovascular invasion (LVI) were independent risk factors for the presence of TD (p=0.014 and p=0.001, respectively). Age, tumour localisation, and pT stage were statistically significant parameters affecting harvested LN number (p=0.002, p=0.032, and p=0.015, respectively). Only LVI was an independent risk factor for LN metastasis (p=0.000), whereas age, mucinous tumour histology, and LVI were independent risk factors for higher LNR (p=0.003, p=0.001, and p=0.042, respectively). On univariate analysis, only LVI was significantly correlated with a positive LN number ≥ 5 (p=0.016).
Conclusion: Mucinous tumour histology and LVIwere independent predictive factors for the presence of TDs and higher LNR. Also older age influenced LNR. Younger age, right tumour location and advanced pT stage increased independently the number of harvested LNs. These results have to be proven in larger cohorts.

PS-20-028

Plasmacytoid carcinomas of the stomach: the immunoprofile highlights the potential targeted therapy of these rare histological variants

S. Gurzu[1], C. Molnar[2,3], L. Banias[1], M. Sincu[3], Z. Kovacs[4], I. Jung[4]
[1] University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania, [2] University of Medicine, Pharmacy, Sciences and Technology, Targu-Mures, Romania, [3] Clinical County Emergency Hospital, Targu Mures, Romania, [4] University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania

Background & Objectives: Plasmacytoid carcinoma is known as a rare and aggressive tumour of the urinary bladder. Its occurrence in the gastrointestinal tract is extremely rare and the proper therapeutic management is still unknown. The aim of the paper was to reveal the immunoprofile of these rare tumours. Besides the markers used for differential diagnosis, we aimed to emphasize the microsatellite status, epithelial mesenchymal transition (EMT), and angiogenic immunophenotype. Predictive biomarkers such HER-2, c-Kit, and c-MET were also used.
Methods: In order to elucidate the molecular background of these rare tumours, we performed a complex molecular examination and checked the immunoprofile of five gastric plasmacytoid carcinomas (surgical specimens, primary tumours of the stomach) diagnosed by our team in the last three years. The possibility of metastatic tumours were excluded. A panel of 39 diagnostic and predictive biomarkers have been used.
Results: All of the patients, aged between 67 and 83 years, died below 6 months after surgery. The diagnosis was based on double positivity for AE1/AE3 Keratin and CD138. The tumour cells proved to be negative for VEGF-A, S100, HER-2, c-KIT, etc. All of the cases showed a microsatellite stable (MSS) status and presented EMT features: E-cadherin negative, SLUG positivity, β-catenin nuclear positivity and focal positivity for vimentin. The c-MET diffuse positivity was also emphasized.
Conclusion: Patients with gastric plasmacytoid carcinoma can benefit by a targeted therapy based on anti-c-MET drugs but their molecular profile suggest lack of response to antiangiogenic (anti-VEGF), anti-HER-2 drugs or immunotherapy. The agressivity seems to be induced by the EMT of tumour cells.

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PS-20-029

Tumour budding in 3D: a novel approach to visualisation and characterisation

T. Haddad[1], N. Farahani[2], D. Treanor[3], M. Hale[3], F. Doubrava-Simmer[4], J. Bokhorst[1], M. Goodman[5], J. van der Laak[4], I. Nagtegaal[6]
[1] Radboud University Medical Center, The Netherlands, [2] 3Scan, USA, [3] University of Leeds, United Kingdom, [4] Radboud University Medical Center, The Netherlands, [5] 3Scan, USA, [6] Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands

Background & Objectives: Scoring tumour budding at the invasive front of a colorectal carcinoma is primarily performed on slides using two-dimensional diagnostic visualization. This limits our understanding of this powerful and independent prognostic biomarker. To better understand the invasive front, we set out to explore the infiltrative margin in three-dimensions by deploying three distinct visualization modalities to quantitatively assess their feasibility and efficacy in characterizing tumour budding.
Methods: Immunofluorescence Confocal Microscopy: Thick sections (up to 90 microns) of formalin-fixed paraffin-embedded (FFPE) colorectal carcinoma tissue were stained using a free-floating immunostaining protocol and imaged via confocal microscopy.
Knife-Edge Scanning Microscopy: Technology developed by 3Scan involves high-precision serial slicing (5 micron) and simultaneous scanning of a whole-mount H&E stained FFPE colorectal carcinoma tissue block.
3D Digital Pathology: Serially sliced (4 micron) FFPE colorectal carcinoma tissue blocks are mounted on glass, scanned and registered to create a virtual 3D reconstruction.
Results:

Technique	Advantages	Disadvantages
Immunofluorescence Confocal Microscopy	-Single-cell imaging -Multiplexed staining	-Time-intensive -Limited tissue thickness -Antibody specific complications
Knife-Edge Scanning Microscopy	-Converts entire block into high quality, serially sliced and registered data -Provides complete visualization of entire tissue	-Consumes tissue -Near single cell resolution
3D Digital Pathology	-High quality, single-cell resolution data -Similar to diagnostic whole slide images -Preserves tissue	-Involves manual work-up of tissue slicing, staining, and scanning -Limited thickness due to technician's capabilities for exact serial slicing

Conclusion: Each platform for 3D visualization displays a unique perspective with clearly defined advantages and disadvantages at visualizing the invasive margin of a colorectal carcinoma. When used synchronously, these methods provide an un-paralleled view with novel insights into the morphological, molecular and micro-environmental features of tumour budding, thereby furthering our understanding of tumour heterogeneity and cancer invasion.

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PS-20-030

Gastric cancer with neuroendocrine differentiation and tumour development

M. Hadzhi[1], K. Dinkova[2], J. Ananiev[2], M. Gulubova[2]
[1] Medical Faculty, Trakia University, Bulgaria, [2] Department of General and Clinical Pathology, Medical Faculty, Trakia University, Bulgaria

Background & Objectives: About 50% of gastric cancer (GC) has focal neuroendocrine differentiation. The neuroendocrine cells in GC could be predictive for patient's survival and treatment.
Human gastric mucosa contains chromogranun A (CHA) endocrine cells (ECs) distributed mainly in gastric body and very small number in the antrum. Serotonin (SER)+ECs are less far numerous thought stomach. Somatostatin (SOM)+ECs are located mainly in gastric body intermingled with ghrelin (GHR)+ECs. The gastrin (GAS)+cells are located mainly in gastric antrum. Presence of GHR+ECs in GC is documented by Tian and Fan, 2012 and it is stimulating the proliferation of GC cells.
The aim of the study is to determine EC presence in GC tissue and in the overlying mucosa, and their prognostic value for the patients.
Methods: Surgical biopsy specimens from 95 GC patients (n=56 males, n=39 females) are investigated immunohistochemically with anti-CHA, anti-SOM, anti-GAS, anti-SER and anti-GHR antibodies. Immunofluorescence co-localization studies are done using anti-GHR, anti-SER, anti-SOM and anti-CHA antibodies in order to assess co-expression of SER and SOM with GHR.
Results: GC patients in stage I-II are 27 and in stage III-IV are 68. GCs contains mainly SOM+ECs and about twice lower values of GAS, CHA, SER and GHR. The overlying mucosa shows increased EC number and microendocrine cell nests mainly with CHA and GAS.
Survival analysis show that increased numbers of GAS+ECs and of SER+ECs in tumour tissue are associated with longer survival
Conclusion: The presence of ECs in tumour tissue of GC is related to patient's prognosis.

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PS-20-031

Epithelial budding: a promising morphological biomarker in colorectal adenomas?

A. Handra-Luca[1], E. Papagianni[2], C. Magkou[2]
[1] APHP University Paris Nord, France, [2] Evangelismos Hospital Athens, Greece

Background & Objectives: Endodermal budding is considered a basic process which leads to primitive tube development (gastrulation). Epithelial budding and ramification of primitive tubes result in tubular branching in colorectal adenomas (CRA). Beta-catenin is more frequent in epithelial budding zones of CRA (Kirchner and Brabletz, 2000).
We aimed to study the relationships of epithelial budding to baseline morphological features of CRA, to the stem phenotype protein CD133 and to PTEN.
Methods: Baseline morphological features were assessed for a series of colorectal adenomas (n=127). These results were analysed with regard to presence of epithelial budding and to immunohistochemical expression of CD133 and PTEN (as evaluated on tissue microarrays constructed from the adenoma tissues).
Results: Epithelial budding (81%) correlated to extent of the epithelial adenomatous component (as compared to stromal component), adenoma size, presence of high grade dysplasia, left colon location, as well as to presence of glandular kysts (defined as a 3-fold increase in glandular lumina) ($p<0.05$ for all comparisons). Presence of glandular cysts was a significant predictor of epithelial budding (logistic regression model, $p=0.01$). Epithelial budding correlated to lack of cytoplasmic CD133 and to cytoplasmic PTEN ($p<0.05$ for both comparisons).
Conclusion: In conclusion, epithelial budding in colorectal adenomas, predicted by presence of glandular cysts, correlated to large adenoma size, to left colon location as well as to high grade dysplasia.

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PS-20-032

The expression profile of EPHB3 during colorectal cancer progression and the prognostic impact of EPHB3 in colorectal cancer patients

S. Song[1], C. Hyun[2]
[1] School of Medicine, Jeju National University, Republic of Korea, [2] Department of Pathology, Jeju National University Hospital, Republic of Korea

Background & Objectives: Ephrin type-B receptor 3 (EPHB3) is a protein that in humans is encoded by the *EPHB3* gene. The Eph family of receptors are divided into two groups based on the similarity of their extracellular domain sequences and their affinities for binding ephrin-A and ephrin-B ligands. Ephrin receptors make up the largest subgroup of the receptor tyrosine kinase (RTK) family. We aimed to investigate the expression profile of EPHB3 during colorectal cancer (CRC) progression and determine the prognostic impact of EPHB3 in a large cohort of CRC samples.
Methods: We examined EPHB3 expression in 610 Formalin-fixed Paraffin-embedded colorectal cancer tissue specimens using immunohistochemistry. The relationships between EphB3 expression and clinicopathological parameters, *KRAS* mutations, *BRAF* mutation, MSI and survival were evaluated using Spearman's rank correlation and Kaplan–Meier survival analyses, respectively
Results: EPHB3 expression was higher in CRCs than in normal mucosa and was associated with intestinal stem cell markers (EPHB2, OLFM4, LRIG1) and CD44, a candidate cancer stem cell marker. EPHB3 positivity was observed in 24% of 610 CRCs and showed negative correlations with differentiation, lympho-vascular invasions and TNM stages. Enhanced EPHB3 expression significantly declined during the adenoma-carcinoma transition and invasion into deeper layers. In particular, a substantial reduction of EPHB3 was observed in the budding cancer cells at the invasive fronts. Notably, EPHB3 was positively associated with microsatellite instability phenotype but was not associated with CpG island methylator phenotype, KRAS and BRAF mutations.
Conclusion: EPHB3 positivity was a prognostic marker for better clinical outcomes in CRC patients. Taken together, our data suggest the suppressive role of EPHB3 in the late stage of CRC progression.

PS-20-033

IL-6/STAT3 immune cell interactions in the immunosuppressive tumour microinvironment of CRC

K. Ivanova[1], D. Chonov[2], K. Dinkova[1], M.M. Ignatova[3], T. Vlaykova[4], M. Gulubova[1]
[1] Trakia University, Medical Faculty, Department of General and Clinical Pathology, Bulgaria, [2] Medical Faculty, Trakia University, Department of Surgery, Bulgaria, [3] Trakia University, Medical Faculty, Bulgaria, [4] Medical Faculty, Trakia University, Department of Chemistry and Biochemistry, Bulgaria

Background & Objectives: IL-6/STAT3 induces and maintains mainly pro-tumour microenvironment (TME) and IL-6 trans-signalling is observed in inflammatory cells. IL-6 inhibits dendritic cell (DC) maturation and induces generation of Th17 cells.
The aim of the present study is to enumerate IL-6$^+$ and STAT3$^+$ immune cells, Treg and Th17 cells in colorectal cancer (CRC) and to find an association with microsatellite instability/stability (MSI/MSS) status and with DCs.
Methods: Surgical biopsy specimens from 104 patients (n=53 males, n=51 females) are MSI tested and the immune cells positive for IL-6, STAT3, IL-17, FoxP3 and for DCs (CD1a, CD83, CD11c and CD123) are immunostained. Non-parametric analysis (Mann-Whitney) is used.
Results: IL-6$^+$, STAT3$^+$ and IL-17$^+$ immune cells are more in number in MSS patients as compared to MSI patients. Only FoxP3$^+$ cells are less in number in MSS patients. All investigated immune cells are more in number in stages I+II CRC as compared to stages III+IV CRC. IL-6$^+$ immune cells correlated positively with CD1a$^+$ DCs in the invasive front (IF) (Rho=0.262, p=0.008); with CD123$^+$ DCs in the tumour stroma (TS) (Rho= 0.275, p=0.013); and with CD83$^+$ DCs in TS (Rho=0.269, p=0.006).
Conclusion: In conclusion we may state that IL-6 released from immune cells (macrophages or T lymphocytes) in TME modulate DC-induced T cell polarization in direction of Th17 and Th22 cell development. MSS patients show increased number of immunosuppressive factors in TME such as IL-6, STAT3 and IL-17. The early stages of CRC show increased numbers of as IL-6, STAT3 and IL-17 that maintain immunosuppressive TME promoting cancer development.

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PS-20-035

Development of immunohistochemistry based molecular classification of colorectal carcinomas; correlation between transcriptome analysis and immunohistochemical study

M. Jang[1]
[1] Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea

Background & Objectives: Colorectal cancer (CRC) is the third most common cancer worldwide, with a 5-year overall survival of 65%. There is an urgent need to establish the classification strategy to identify the patient group who may benefit from adjuvant therapy. Several studies on molecular heterogeneity in CRCs have used gene expression-based data to assess disease stratification. However the practical approach to classify the molecular subtype is in need. This study aimed to investigate and establish algorithms for immunohistochemical assessment of molecular subtypes.
Methods: The gene expression data of training cohort of a total 101 CRCs were used to classify into the consensus molecular subtypes (CMSs). We selected thirteen markers available for IHC that overexpressed >1.5 folds in one subtype to that of the other 3 subtype, and included another 19 previously proposed as molecular markers. We finally constructed IHC classifier using 9 factors. The validation cohort (n=416) was classified into CMSs using the IHC classifier and the clinicopathologic characteristics were evaluated.
Results: Using SNAI1, MUC2, SPINK4, KIT, CDX2, ZMYND8, TFF3, MUC5AC, and MSI status by MMR markers, IHC classifier was constructed (the accuracy: 0.825, 95% CI=0.737-0.825, AIC: 134.771, 95% CI = 134.507-160.549). Application to validation cohort (n = 416) revealed that similar subtype specific characteristics with training cohort and poor prognosis of CMS4. Using the IHC classifier, we found that CMS3 and CMS4 are bad prognostic group from FOLFOX chemotherapy
Conclusion: This study proposes the practical IHC classifier predicting the prognosis of CRCs.

PS-20-036

Isolated tumour cells in regional lymph nodes of patients with adenocarcinoma of the ooesophagogastric junction representing part of a true metastasis

D.N.M. Jepsen[1], A.K. Fiehn[1], M.P. Achiam[2], H. Ugleholdt[1], B. Federspiel[3]
[1] Department of Pathology, Rigshospitalet, Denmark, [2] Department of Surgical Gastroenterology, Rigshospitalet, Denmark, [3] Department of Pathology Copenhagen University Hospital Rigshospitalet, Denmark

Background & Objectives: Regional lymph node metastases in patients with carcinoma of the oesophagogastric junction (EGJ) is an important

prognostic factor. The impact of lymph nodes with isolated tumour cells (ITCs) is not completely clarified. The aim of this study was to determine the prevalence of regional lymph nodes with ITCs and to examine how often ITCs in fact represent part of a true metastasis.
Methods: The study included surgical specimens of 126 patients with adenocarcinoma of the EGJ. Lymph nodes with ITCs were identified. Supplementary sections were performed and stained with HE and cytokeratin. All slides were evaluated for the presence of tumour cells and it was determined whether the criteria for a metastasis was met on the additional sections.
Results: ITCs were detected in 59 (1.7%) of 3454 lymph nodes and in 41 (32.5%) of 126 patients. In 29 (49.2%) lymph nodes with ITCs on the primary slide further sections resulted in a changed status from ITC to a metastasis. In 7 (5.6%) of the 126 patients the pN category was changed.
Conclusion: In patients with adenocarcinoma of the EGJ the presence of ITCs in regional lymph nodes is a common observation. ITCs often represent a real metastasis. To obtain a correct pN category we strongly recommend thorough examination with additional levels when ITCs are observed.

PS-20-037

The prognostic significance of tumour budding and poorly differentiated clusters in colorectal carcinomas

A. Jurescu[1], A. Gheju[1], A. Văduva[1], I. Mihai[1], O. Vița[1], R. Cornea[1,2], M. Cornianu[1,2], F. Lazăr[3,4], S. Tăban[1,2], A. Dema[1,2]
[1] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [2] Department of Pathology, Emergency County Hospital Timişoara, Romania, [3] Surgery Department II, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [4] Surgery Department II, Emergency County Hospital Timişoara, Romania

Background & Objectives: The aim of our study was to assess the tumour budding (TB) and the poorly differentiated clusters (PDCs), as additional grading tools in the evaluation of colorectal carcinomas (CRC). According to the International Tumour Budding Consensus Conference (ITBCC) from 2016, based on the presence of budding differentiation (BD), the TB grading system comprises BD1- low budding, BD2- intermediate budding, and BD3- high budding. The PDCs-grading system (PDCs-G), as proposed by Ueno et al, includes PDCs-G1, PDCs-G2, and PDCs-G3.
Methods: We performed a retrospective study on a group of 21 CRC patients that underwent robotic surgery between 07/2015-07/2016, at the Emergency County Hospital "Pius Brinzeu" from Timisoara, Romania. The CRC cases were classified, on H&E scanned slides, using the TB grading system and the PDCs-G. We analysed the associations between TB/PDCs grades with other factors: gender, the location of the tumour, the degree of differentiation, depth of invasion (pT), tumour border configuration, lymphovascular invasion (LVI) and lymph node metastases (LNM).
Results: Using TB grading system, 9% of the cases were BD1, 24% BD2 and 67% BD3, while in the PDCs-G, 14% cases were PDCs-G1, 48% PDCs-G2 and 38% PDCs-G3. In multivariate analysis, BD3 was significantly associated with rectal location (71.43% cases), pT3-4 (64.29%) and with infiltrative and mixed tumour border configuration (92.86%, p = 0.0251). Moreover, PDCs-G3 presented significant correlation with pT3-4 (87.50%), LNM (62.50%) and especially with LVI (62.50%, p= 0.0139).
Conclusion: High TB and PDCs grades correlate with other negative prognostic parameters in CRC cases. These new parameters/methods of classifications could be helpful for risk stratification and seem to present prognostic significance for CRC patients.

PS-20-038

Clinicopathological features of primary colorectal carcinomas correlated with lymph node and distant metastases

A. Jurescu[1], A. Gheju[1], S. Tăban[1,2], M. Cornianu[1,2], A. Mureșan[1,2], C. Lăzureanu[1,2], R. Cornea[1,2], E.G. Olteanu[1], V. Lupu[1], C. Duță[3,4], A. Dema[1,2]
[1] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [2] Department of Pathology, Emergency County Hospital Timişoara, Romania, [3] Surgery Department II, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [4] Surgery Department II, Emergency County Hospital Timişoara, Romania

Background & Objectives: The therapeutic management for colorectal cancer (CRC) depends on various factors. The aim of this study was to identify the possible parameters which correlate with lymph node metastasis (LNM) and distant metastasis (M) in CRC patients.
Methods: We performed a retrospective study on a group of 150 patients diagnosed with CRC at the Emergency County Hospital "Pius Brinzeu" from Timisoara, Romania. The study group comprises three subgroups of 50 patients each (local, nodal and distant disease). Associations between the clinicopathological variables including gender, age, tumour location, mucinous differentiation, tumour grade (G), depth of tumour invasion (pT), lymphovascular invasion (LVI) with the three CRC patients' subgroups were analysed using the Chi-square and Fischer exact test.
Results: The CRC cases with evidence of LVI had a significantly higher risk of nodal and distant disease than those without LVI. In multivariate analysis the rectal location (p = 0.0430), low differentiation (G3-G4, p = 0.0013), depth of invasion (pT3-T4, 0.0443), and LVI (p < 0,0001) were significantly related to tumour spread, while the independent risk factor for distant metastasis was LVI (p < 0,0001) only.
Conclusion: In our study, several risk factors correlate highly with nodal disease, while for the distant disease only the LVI plays an important role. The potentials prognostic factors for CRC patients must be well known and all the important parameters for the therapeutic management must be standardised and included in the pathological report.

PS-20-039

Combined positive score measured by pathologists and digital image analyses are not significantly different in predicting responses for immune checkpoint blockade therapy in gastric cancer patients

H. Kim[1], H. Jung[2], Y. Jang[1], S.T. Kim[3], J. Lee[3], W.K. Kang[3], K. Kim[2]
[1] Department of Pathology and Translational Genomics, Samsung Medical Center, Republic of Korea, [2] Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [3] Division of Haematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background & Objectives: Programmed death ligand-1(PD-L1) immune checkpoint blockade is one of emerging methods for cancer immunotherapy. PD-L1 immunohistochemistry is used to predict likelihood of response to ***anti***-PD-1 or ***anti***-PD-L1 therapy. However, intra- and inter-observer variability influence the results of PD-L1 expression. Unlike non–small cell lung cancer using PD-L1 expression determined by tumour proportion score, gastric cancer uses combined positive score. We aimed to compare the results of digital image analysis and interpretation by pathologists predicting responses for pembrolizumab in gastric cancer patients.
Methods: Either primary or metastatic gastric cancer tissue consisting of biopsy (22) and resected specimens (17) from 2013 to 2017, and enrolled for pembrolizumab clinical trial at Samsung Medical Center were reviewed. Among them, 39 cases were finally selected based on the availability of tissues and clinical responses for pembrolizumab. The PD-L1 22C3 PharmDx (Dako) immunohistochemistry slides were interpreted by digital image analysis software and two pathologists for PD-L1 combined positive score, and the results were compared to the clinical responses for pembrolizumab.

Results: With the combined positive score cutoff of 1 for pembrolizumab approval, 33 (84.6%) out of 39 cases showed concordant results by digital image analysis and pathologists' interpretation. In 6 (15.4%) cases, discordant results were caused by weak staining of PD-L1 (n=2), anthracotic pigments deposition (n=1), decalcification artifacts (n=1), and unknown reasons (n=2). In statistical analyses, PD-L1 combined positive score measured by pathologists and digital image analysis did not show significant difference in predicting responses for pembrolizumab (p=0.1856).
Conclusion: For PD-L1 combined positive score, digital image analysis and pathologists' interpretation showed concordant results in most cases and the prognostic predictabilities were not significantly different. Digital evaluation PD-L1 would reduce scoring variability and may facilitate stratification of cancer patients in clinical practice.

PS-20-040
When physicist helps pathologist: fluorimetry for differentiation between high-grade dysplasia and early colonic adenocarcinoma on hystologycal sections
Y. Korneva[1], V. Maryakhina[2], A. Dorosevich[1]
[1] Smolensk Regional Institute of Pathology, Russia, [2] Kumertau Branch of Orenburg State University, Russia

Background & Objectives: Currently there is no objective method to distinguish the early onset of invasive adenocarcinoma within adenomatous colonic polyps with high-grade dysplasia.
Aim: To create objective method for differentiation on histologycal sections high-grade dysplasia form early adenocarcinoma, basing on biochemical changes in the tissues, cased by malignant transformation.
Methods: Autofluorescence excitation of unstained dewaxed histological sections from our sample groups were measured on a spectrofluorimeter (SOLAR CM-2203). The wavelength of registration was 410 nm after its excitation in the UV region. Our sample groups consisted of 11 cases of invasive adenocarcinomas (AC), 51 were adenomas with various grades of dysplasia (41 tubular adenomas / 10 tubulovilllous adenomas) and 13 were normal colonic mucosa.
Results: All the measured spectra have 2 maxima – 1st at 260-270 nm (defined by tryptophan-containing peptides) and the 2nd at 330-340 nm (defined by collagen and NADH), but the relation between this maxima depends on the type of pathological process. The greatest maxima ratio has normal mucosa (1,46 and more), ratios for tubular and tubulo-villous adenomas are almost the same (1,35-1,45 and 1,26-1,35 respectively) and depend on grade of dysplasia. The smallest ratio is for AC (1,13-1,25).
Conclusion: If the ratio between maxima of the spectra of autofluorescence excitation form the histologycal section of colonic tumour is more than 1,26, the case is considered to be adenoma with high dysplasia, if 1,25 and less – as AC, that may help to objectify the diagnostic of early malignant transformation of the adenoma on histologycal sections.

PS-20-041
Stabilising and upregulating Axin by Tankyrase inhibitior reverses 5-fluorouracil chemoresistance through inhibition of WNT/Caveolin-1 in colorectal cancer cells
K. Liu[1], J. Li[1]
[1] Department of Pathology, the Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan, Guangdong, China

Background & Objectives: Colorectal cancer (CRC) is a common malignant tumour, 5-Fluorouracil (5-Fu) and its derivatives are commonly used in the chemotherapy of CRC, but resistance to chemotherapy is one of main obstacles for CRC treatment. In present study, we evaluated effects and mechanisms of WNT/β-catenin/Caveolin-1 signalling pathway on drug resistance of CRC.
Methods: The activity of β-catenin in CRC cells were activated/inhibited by small molecule compounds GSK-3 inhibitor BIO and tankyrase inhibitor XAV939. The downstream target genes of WNT/β-catenin signalling pathway were screened by cDNA microarray. Apoptosis induced by 5-Fu, cell cycle distribution and expression levels of β-catenin/TCF12/Caveolin-1 and multidrug resistance proteins (MRPs) were elucidated after β-catenin activation/inhibition and Caveolin-1 overexpression/interference. The effect of XAV939 on proliferation and apoptosis induced by 5-Fu in xenograft tumours of nude mice were evaluated.
Results: BIO increased β-catenin expression, accompany with upregulation of TCF12, Caveolin-1, MRPs and downregulation of apoptosis induced by 5-Fu in CRC cells. Conversely, XAV939 decreased β-catenin, accompany with downregulation of TCF12, Caveolin-1, MRPs and upregulation of apoptosis induced by 5-Fu in CRC cells. Caveolin-1 was identificated as an important downstream gene of WNT/β-catenin signalling pathway. Caveolin-1 regulated the β-catenin, MRPs and apoptosis induced by 5-Fu. XAV939 reduced β-catenin and Caveolin-1, increased apoptosis induced by 5-Fu and repressed xenograft tumour growth.
Conclusion: WNT/β-catenin regulates chemoresistance of CRC cells by targeting the downstream gene Caveolin-1. The inhibition of WNT/β-catenin/TCF12/Caveolin-1 provides a new promising therapeutic strategy for CRC treatment.

PS-20-042
Predictive value of the high-risk histopathological criteria in appendiceal neuroendocrine tumours and their correlation with lymph node status in additional right hemicolectomy
R. Loveikyte[1], B. van Etten[2], P. Hemmer[2], A. Walenkamp[3], G. Kats-Ugurlu[1]
[1] Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands, [2] Department of Surgery, University of Groningen, University Medical Center Groningen, The Netherlands, [3] Department of Medical Oncology, University of Groningen, University Medical Center Groningen, The Netherlands

Background & Objectives: Appendectomy is the standard treatment for appendiceal neuroendocrine tumours (aNETs). The recent European Neuroendocrine Tumour Society (ENETS) guidelines advocate additional right hemicolectomy for aNETs with high-risk for lymph node metastasis based on their size, grade, location, resection margin, (lympho-)vascular invasion, and mesoappendiceal invasion.
Our aim was to evaluate the ability of the current ENETs histopathological criteria to indicate patients with high-risk aNETs in the appendectomy specimens, and to predict the presence of lymph node metastasis in additional right hemicolectomy specimens.
Methods: We conducted a retrospective database pilot study. Using Laboratorium Management System we identified thirteen patients with well-differentiated aNETs with high-risk histopathological features who underwent both appendectomy and right hemicolectomy. There was no age restriction.
Results: Three of the 13 patients had lymph node metastasis. All 3 primary tumours were <2cm (range: 1.3 – 1.7cm) and showed >3mm mesoappendiceal invasion. One patient without metastasis showed > 3mm mesoaappendiceal invasion. Five other patients had tumours ≥2cm (range: 2 – 3.6cm) and none of them had positive lymph nodes. (Lympho-)vascular invasion was found in patients with and without lymph node metastasis. The positive predictive value of the current histopathological criteria is 23%.
Conclusion: This retrospective analysis indicates that the current ENETS histopathological criteria may not be the best predictor of lymph node metastasis in the additional right hemicolectomy. Among the high-risk criteria mesoappendiceal invasion of >3mm was the best predictor of lymph node metastasis. Further studies are needed to evaluate if mesoappendiceal invasion could be used as an independent high-risk criterion.

PS-20-043

c-Myc as a key-marker in the colorectal cancer resistance to EGFR inhibitors

M. Martini[1], A. Strippoli[2], A. Cocomazzi[3], T. Cenci[3], M. Basso[2], L.M. Larocca[3]

[1] Institute of Pathology, Italy, [2] Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy, [3] Institute of Pathology, Università Cattolica del Sacro Cuore, Rome, Italy

Background & Objectives: Despite the outstanding success of EGFR inhibitors in the treatment of metastatic colorectal cancer (mCC), targeted therapy (TT) leads inevitably to the acquired resistance stemming from various molecular mechanisms such as activation of compensatory kinases. Alterations in the transcriptional factor c-Myc, a downstream effector of several kinase pathways, could be also involved in the TT resistance.
Methods: The expression of c-Myc was assessed in 121 RAS and BRAF wild type mCC samples before treatment with anti-EGFR+Folfiri therapy and in 33 subsequent metastases collected during TT or in TT resistance phase. In this cohort, and in two cancer cell lines, we also analysed the expression of miRNA143 and miRNA145, using real-time assay, and we performed a c-Myc Targets PCR Array. Results were correlated with clinical and pathological features.
Results: Low c-Myc expression patients showed a significant higher PFS and OS respect to those with high c-Myc expression (HME). HME pattern was significantly associated to the anti-EGFR molecular resistance alterations. Moreover, restoring miRNA143 and miRNA145 expression in two KRAS mutated cancer cell-lines, determined a c-Myc downregulation with a reduction of the cell proliferation and migration after exposure to cetuximab. Several altered genes expression in HME mCC highlighted the role of c-Myc in CC-related cell cycle, apoptosis and cell growth pathways.
Conclusion: HME in anti-EGFR treated mCC might discriminate patients with a lower PFS and OS. Moreover, the significant c-Myc association to anti-EGFR resistance, also through some miRs alteration, and the individuation of c-Myc activated genes suggest the c-Myc pathway blockade to prevent the kinome reprogramming mechanism.

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PS-20-044

Eosinophilic oesophagitis: standardised diagnosis with digital pathology platform

C. Molnár[1], T. Micsik[2], Á. Patai[1]

[1] Semmelweis University, Hungary, [2] 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

Background & Objectives: Eosinophilic ooesophagitis (EoE) is a chronic, antigen-mediated disease causing severe dysphagia. Diagnosis relies on clinical symptoms and eosinophil leukocytes (EoL) per High Power Field (HPF), thought histology samples may not fill the whole objective and there is an almost 2,5-fold difference in HPF-area of different microscopes. Thus, a standardised number of EoL/mm^2 may decrease diagnostic discrepancies and help towards better diagnostic rate.
Methods: 45 EoE and matched GERD cases were selected retrospectively from the archives of the Pathology Departments of Semmelweis University, Budapest, Hungary. Clinicopathological data were collected, slides were digitized using *Pannoramic™ P250 Flash* digital slide scanner (3DHISTECH Ltd., Budapest, Hungary). Epithelial and subepithelial compartments and EoLs were annotated digitally with *CaseViewer*.
Results: The 45 EoE patients were 66% males; mean age was 23.5 ± 19.7 years. Most common endoscopic EoE-manifestations were rings (36.8%), longitudinal furrows (21.1%). Histopathologic EoE-findings were: eosinophilic cell degranulation 86.6%, spongiosis 75.5%, eosinophilic aggregate formation 66.7%. Average sample areas were similar in both groups, whereas digital image analysis showed significantly higher EoL/mm^2 count in both epithelial (171.2±177.2 vs 3.3±11.6) and subepithelial (61.01±67.1 vs 4.5±13.2) compartments of EoE versus GERD patients. ROC-analysis found a reliable threshold for differentiating EoE from GERD at 33 EoL/mm^2 in epithelial and 16 EoL/mm^2 in subepithelial compartment.
Conclusion: Last October an international guideline firstly suggested, instead of EoL/HPF, an estimated 60 EoL/mm^2 threshold for diagnosing EoE. Our study with numerical counting of EoLs on a digital platform found that lower, 33EoL/mm^2 threshold reliably detects EoE.

PS-20-045

Assessment of gastric mucosal atrophy: from consensus estimation to the development of a decision support system

S. Mozgovoi[1], A. Shimanskaya[1], A. Kononov[1], M. Parygina[1], I. Ostroglyadova[1]

[1] Omsk State Medical University, Russia

Background & Objectives: Atrophic gastritis increases the risk of intestinal-type gastric cancer (adenocarcinoma). Semi-quantitative assessment of the level of atrophy is subjective, inappropriate endoscopic technology makes it impossible to use traditional approaches.
Methods: 98 diagnostic cases of chronic gastritis were selected. Analysis of the reproducibility of the assessment (inter-rater agreement) between 41 pathologists was carried out using kappa statistics (Cohen's kappa) by pair-wise comparison. The validity (sencitivity and specificity) of histochemical techniques and biomolecular markers of atrophy and intestinal metaplasia (metaplastic atrophy) were assessed by special stains and immunohistochemistry. 50 selected cases with kappa=1 between authors were used as a "gold standard".
Results: General unweighted κ before training was 0.23 (fair agreement). The level was maximal when marked atrophic changes was revealed. Low values of the validity criterion in assessing routine histochemical characteristics were identified (confidence interval 0,53-0,85 for sensitivity). Three molecules with high validity as markers of metaplastic atrophy are identified: CDX-2 - nuclear transcription factor associated with intestinal differentiation, CD10 - a membrane mucin brush border and MUC2 - intestinal type mucin (confidence interval for all three markers 70-94, but up to 100% at metaplastic athrophy). The algorithm for using markers to assess the grade of atrophy and the stage of chronic gastritis was proposed.
Conclusion: The data obtained in our pilot study demonstrate the problem of recognition and interpretation of atrophic changes detected in biopsy specimens. At the same time, the introduction of a marker evaluation method can significantly increase the degree of consistency in decision making.

PS-20-046

Expression of miR-21 and its target protein PDCD4 in intestinal type gastric cancer

S. Mozgovoi[1], E. Pomorgailo[1], A. Shimanskaya[1], A. Kononov[1], V. Rubtsov[1], J. Fedotova[1]

[1] Omsk State Medical University, Russia

Background & Objectives: The participation of miR-21 and its target protein PDCD4 in key molecular mechanisms in carcinogenesis. The mail purpose was assessment of the level of oncogenic miR-21 and its target - PDCD4 regulatory protein in gastric cancer.
Methods: The subjects of the study were 40 biopsy specimens with a histological features of chronic atrophic gastritis and fragments of 45 stomachs resected for intestinal type adenocarcinoma. The assessment of the PDCD4 protein was carried out by semi-quantitative immunohistochemical scale. The amount of miR-21 was determined by stem-loop real-time PCR in paraffin sections using specific miR-21 primers.

Descriptive statistics of groups are presented in the form of a median and interquartile latitude.
Results: The expression of miR in chronic gastritis within the distant zone of gastric cancer (225.69; from 101.05 to 280.67), adenocarcinoma stomach (378.65; from 103.16 to 375.12) were increased. The difference between the distant zone of gastric cancer and samples with a similar histological pattern, but without association with gastric cancer, was significant ($p = 0.00046$). PDCD4 was showed decrease ($p = 0.00001$) in the level of PDCD4 in the tissues of intestinal adenocarcinoma (4; from 2 to 6) compared to the distant zone group (9; from 9 to 12). , There was no statistically significant difference after comparing chronic gastritis in biopsy specimens (10; from 9 to 10) with a group of chronic gastritis in the distant zone of gastric cancer.
Conclusion: The study shows that miR-21 and its target protein PDCD4 are promising markers for assessing the risk of development, early diagnosis of intestinal type gastric cancer.

PS-20-047

Detection of tissue patterns, their immunohistochemical signatures and biomarkers of inflammation in the gastric mucosa as a system of personalised prediction of sporadic gastric cancer

S. Mozgovoi[1], A. Shimanskaya[1], A. Kononov[1], E. Pomorgailo[1], V. Rubtsov[1], L. Panyushkin[2], M. Parygina[1]
[1] Omsk State Medical University, Russia, [2] West Siberian Medical Center FMBA of Russia

Background & Objectives: Correa's cascade is fundamental basis of gastric cancer prevention, and stomach mucosal atrophy in conjunction with intestinal metaplasia will be considered as a non-return point in the cascade of carcinogenesis.
Methods: The problem is that the detection of atrophy by the international system requires scrupulous adherence to the protocol for obtaining biopsy specimens from 5 points of the gastric mucosa, which turns out to be a problem for the practitioner. According to our data, the protocol is observed in 4.0% of endoscopic studies. Therefore, we need a search for other ways to personalize the risk of gastric cancer.
Results: Immunohistochemical detection of intestinal differentiation proteins allows for earlier and more reliable determination of metaplastic atrophy in the gastric mucosa. The immunohistochemical signature of metaplastic atrophy with the calculation of the sensitivity and specificity of immunohistochemical markers reliably identifies atrophy, which determines the risk of developing gastric cancer, and not by 5, but by 2-3 biopsy specimens.
In order to increase the predictability of the system by molecular profiling of miRNAs that regulate the physiological manifestation of genes from both the inflammatory response and those involved in carcinogenesis, molecules were selected. Their aberrant expression rom superficial gastritis to atrophic background of sporadic cancer in increased. The level of research in this direction is still pilot.
Conclusion: The results suggest that combinations of a panel of biomarkers of inflammation and tissue pattern monitoring can be a valid system for personalised assessment of the risk of developing gastric adenocarcinoma.

PS-20-048

Looking for an immunohistochemical / molecular predictor of recurrence in the surveillance colonoscopy after resection of colorectal high-risk adenomas

D. Naranjo-Hans[1], M. Iglesias[2], G. Navarro[1], J. Gimeno[3], J. Masso[1], L. Carot[4], C. Alvarez-Urturi[4], X. Duran[5], M. Andreu[4], B. Lloveras[3]
[1] Pathology Department. Hospital del Mar, Spain, [2] Pathology Department, Hospital del Mar, Spain, [3] Hospital del Mar, Spain, [4] Gastroenterology Department. Hospital del Mar, Spain, [5] Institute Hospital del Mar d'Investigacions Mèdiques, Spain

Background & Objectives: Screening for early detection of colorectal malignancies has demonstrated efficacy in reducing disease-specific mortality. Current surveillance guidelines recommend a 3-year follow-up colonoscopy after resection of high-risk adenomas (HRA), defined by multiplicity (three or more) or advanced lesions (>1cm in diameter, villous component and/or high-grade dysplasia. However, this recommendation is exclusively based on endoscopical and histological criteria.
Methods: The aim of this study was to evaluate immunohistochemical expression of different markers, to perform a molecular analysis in HRA of a large cohort of patients whom underwent surveillance colonoscopy, and to determine their association with recurrence. Serrated lesions and adenomas with high-grade dysplasia were excluded in this cohort to be further analysed. Among 638 patients with a prior diagnosis of HRA, a total of 518 underwent a 3-year follow-up colonoscopy in our Institution. We selected the biggest lesions in those cases with multiplicity and created a tissue micro-array with 479 samples. Immunostains for p53, MLH-1, beta-catenin, CDX-2, Ki-67, keratin 7 and keratin 20 were performed and evaluated. There was enough remaining material in 389 cases to perform mutational analysis. A sampler library was generated from the DNA extracted with a QIAseq Targeted DNA panel (Qiagen) containing the coding region of genes *KRAS, NRAS, BRAF, APC, TP53, FBXW7, CTNNB1* and *SMAD4*. The resulting library was sequenced on a NGS platform MiSeq® (Illumina).
Results: As expected, the molecular analysis revealed a high prevalence of different pathogenic mutations involving APC and other genes, althought no significant statistical association was observed between any of the immunomarkers and neither with the genes evaluated. Only advanced age was statistically associated with higher risk of recurrence in the follow-up colonoscopy ($p < 0.05$). Remarkably, trend was observed between the risk of recurrence in the surveillance colonoscopy and the presence of partial loses of immunohistochemical expression of MLH-1 and the detection of *SMAD4* mutations.
Conclusion: No distinct immunohistochemical nor genetic patterns related to recurrence of HRA in the surveillance colonoscopy were identified in our study. However, we identified some immunohistochemical and molecular trends that might become an independent variant for individualized surveillance strategies in the future, although further investigation in required.

PS-20-049

Prognostic value of CD8 Immunogradient indicators in tumour-stroma interface zone of colorectal cancer

A. Nestarenkaitė[1,2], A. Rasmusson[1,2], D. Zilenaite[1,2], R. Augulis[1,2,3], A. Laurinaviciene[1,2], V. Ostapenko[4], T. Poskus[5], A. Laurinavicius[1,2]
[1] National Center of Pathology, affiliate of Vilnius University Hospital Santaros Clinics, Lithuania, [2] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences of the Faculty of Medicine of Vilnius University, Lithuania, [3] Institute of Biosciences, Life Sciences Centre, Vilnius University, Lithuania, [4] National Cancer Institute, Vilnius, Lithuania, [5] Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Lithuania

Background & Objectives: The immune response within the tumour microenvironment assessment methods were proposed to predict patient survival and therapy outcomes in colorectal (CRC) and other cancers; nevertheless, automated operator-independent approaches are lacking. We present a new image analysis method to automatically extract *Immunogradient* indicators and their prognostic value in CRC patients.
Methods: Surgically excised CRC samples from 101 patients were stained for CD8, scanned, and analysed by *Indica Labs'* HALO™ software. The image analysis data was then subsampled by a hexagonal grid which was used to extract and rank the tumour interface zone (IZ) according to distance to the tumour edge. Lastly, a set of novel *Immunogradient* indicators representing CD8 cell density profiles across

the IZ were computed. The prognostic value of the indicators was tested by univariate and multiple survival statistics.
Results: The *Immunogradient* indicators Immunodrop (ID) and Centre of Mass (CM) for the CD8 cells, as well as CD8 cell densities within tumour and stroma aspects of the IZ and their factor scores provided significant stratifications of CRC patients into prognostic groups ($p<0.05$). Multiple Cox regression analyses of extracted indicators along with conventional clinicopathologic characteristics revealed ID and the Aggregated IZ CD8 cell response factor as strong independent predictors of worse (HR: 2.41, $p=0.0126$) and better (HR: 0.41, $p=0.0196$) 5-year overall survival, respectively.
Conclusion: The proposed automated, data-driven digital image analysis method for the IZ immune infiltrate assessment provides strong independent prognostic biomarkers of anti-tumour immune response in CRC. The method is operator-independent and is based on single CD8 immunohistochemistry slides.

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PS-20-050

Epithelial-mesenchymal transition markers, MMP2 and MMP9 - comparative study in poorly cohesive versus intestinal type gastric adenocarcinoma

M. Niculae[1], A. Ienea[2], M. Farcas[2], C. Popp[2,3]
[1] Spitalul Clinic Colentina Bucuresti, Romania, [2] Spitalul Clinic Colentina Bucuresti, Romania, [3] UMF Carol Davila Bucuresti, Romania

Background & Objectives: Multiple epithelial-mesenchymal transition (EMT) molecules, as well as different matrix metalloproteases are involved in gastric tumourigenesis and evolution. Epithelial-mesenchymal transition, intercellular adhesion and proteolytic processes are associated with normal and pathological migration of cells, having a significant impact on gastric adenocarcinoma patients' outcome. The aim of this study is comparative analysis of E-cadherin, N-cadherin, SNAIL, MMP2 and MMP9 in poorly cohesive versus intestinal type gastric adenocarcinoma, in order to identify immunohistochemical patterns for stratifying patients in different prognosis groups.
Methods: We conducted a retrospective study including 50 consecutive cases of gastric tumours (25 poorly cohesive and 25 intestinal type). We performed SNAIL, E-cadherin, N-cadherin, MMP2 and MMP9 on representative samples from gastrectomy specimens included in multi-tissue blocks.
Results: SNAIL was expressed in about 65% of poorly cohesive and in only 10% of intestinal type gastric adenocarcinomas, correlated with loss of expression for cadherins. MMP2 and MMP9 were more frequent and intensely expressed in poorly cohesive adenocarcinomas, a significant difference being observed for MMP9 (80% in intestinal type versus 40% in poorly cohesive type).
Conclusion: Expression of SNAIL and MMP2 and 9 was higher in poorly cohesive gastric adenocarcinomas than in intestinal type ones, correlated with a loss of cell adhesion markers. These data are indicating the importance of EMT and MMP evaluation in gastric cancer, as well as the potential of these molecules to become therapeuthical targets (as MMP9 is already used) for adjuvant treatments.

PS-20-051

Co-expression analysis of microRNA-21 and TNF-alpha mRNA in budding cancer cells in colorectal cancer

B. Nielsen[1], T. Møller[1], J. P James[1], K. Holmstrøm[1], F. B Sørensen[2], J. Lindebjreg[3]
[1] Molecular Histology, Bioneer AS, Denmark, [2] University Institute of Pathology, Aarhus University Hospital, Denmark, [3] Department of Clinical Pathology, Vejle Hospital, Part of Lillebaelt Hospital, Denmark

Background & Objectives: MicroRNA-21 (miR-21) is upregulated in many cancer types including colorectal cancers (CRC) and is a prognostic indicator of recurrence and poor prognosis. In CRC, miR-21 is highly expressed in stromal fibroblastic cells and more weakly in a subset of budding cancer cells. Exploration of the expression of inflammatory markers in CRC using RNAscope probe technology, revealed tumour necrosis factor alpha (TNF-α) in cancer cells with characteristics of both branching and budding. We hypothesized that miR-21 may protect both fibroblasts and cancer cells from cell death directed by TNF-α. The aim of this study was therefore to analyse the presence of miR-21 and TNF-α mRNA expression at the invasive front of CRC.
Methods: We established an automated multiplex procedure on a Ventana instrument for the co-staining of miR-21, TNF-α mRNA and cytokeratin in frozen CRC samples (n=4) with evident cancer cell budding. Digital whole slides were obtained using a Pannoramic confocal slide scanner.
Results: In all of four cases, TNF-α mRNA was seen in a small subset of cancer cells at the invasive front. Both co-expression and lack of co-expression of miR-21 and TNF-α in the branching and budding cancer cells was noted, suggesting non-correlated expression. miR-21-positive fibroblastic cells were all TNF-α negative and not always associated with TNF-α positive cancer cells.
Conclusion: miR-21 and TNF-α mRNA are often co-expressed, but not co-regulated, in a subset of cancer cells with branching or budding characteristics. The implications of these findings for the local tumour growth at the invasive front will be discussed.

PS-20-052

Altered linkage pattern of N-glycan sialic acids in pseudomyxoma peritonei

P. Nummela[1], A. Heiskanen[2], H. Leinonen[1], C. Haglund[3,4], A. Lepistö[3], T. Satomaa[2], A. Ristimäki[1,5]
[1] Applied Tumour Genomics Research Program, Faculty of Medicine, University of Helsinki, Finland, [2] Glykos Finland Ltd., Helsinki, Finland, [3] Department of Surgery, Helsinki University Hospital, Finland, [4] Translational Cancer Medicine Research Program, Faculty of Medicine, University of Helsinki, Finland, [5] Department of Pathology, HUSLAB, Helsinki University Hospital and University of Helsinki, Finland

Background & Objectives: Cancer cells often show glycosylation alterations, such as increased sialylation and fucosylation, which may provide new biomarkers and therapy targets. We have recently reported highly increased N-glycan fucosylation in pseudomyxoma peritonei (PMP), but could not identify alteration in overall sialylation. Here, we utilized more detailed analyses to study the linkage pattern of N-glycan sialic acids in PMP as compared to normal appendices.
Methods: We extracted acidic N-glycans from formalin-fixed, paraffin-embedded tissue specimens of normal appendices, low-grade appendiceal mucinous neoplasms (LAMNs), and low-grade and high-grade PMPs (n=4 in each group), and analysed their sialic acid linkage pattern by ethyl esterification or sialidase digestion (alpha2,3- vs. total sialidase) combined with mass spectrometry.
Results: Sialylation was the predominant acidic modification (>90%) of the analysed N-glycans. With the used methods, we could further divide the sialylated glycan structures into two subclasses: alpha2,3- or alpha2,6-sialylated, according to the sialic acid linkage type. When comparing these subclasses, the N-glycans of PMP tumours showed higher proportion of alpha2,6- than alpha2,3-sialylated glycans, whereas control appendices and LAMNs had the opposite pattern.

Conclusion: Although overall sialylation seems to be unchanged in PMP tumours, they contain increased proportion of alpha2,6-linked sialic acids. Previously, increased alpha2,6-sialylation has been reported in several cancers, and has been associated with cancer cell adhesion, migration, invasion and therapeutic resistance.

PS-20-053

Gastrointestinal carcinomas with rhabdoide features: clinicopathologic, immunohistochemical, and molecular study of a series of 9 cases

A. Panizo[1], C. Llanos[1], M. Garcia-Martos[2], D. Guerrero[1], Y. Rodriguez[1], M. Gomez-Dorronsoro[1]
[1] Complejo Hospitalario de Navarra, Spain, [2] Hospital Universitario de Torrejon, Spain

Background & Objectives: Neoplasms with rhabdoid features (RF) have been reported in many sites. Gastrointestinal (GI) cancers with RF are extremely rare.
Methods: We studied 9 GI carcinomas with RF. Clinicopathological and IHC analysis: cytokeratins, vimentin, myogenic markers, mismatch repair proteins (MMRp), CDX2, SMARCB1-INI1, p53, and Ki-67. KRAS mutations were studied by real-time PCR.
Results: Four patients male and 5 female: mean age 70 yrs. (range 50-81 yrs.). Location: stomach (2), duodenum (1), and colon (right: 3; left: 1; sigma: 2). Mean size: 7,5 cm. All but two tumours were pT4 (remaining: pT3). All cases revealed a glandular component (6 poorly-differentiated, 2 moderate, and 1 signet-ring). Rhabdoid areas ranged from 30% to 80%. All but one case had lymph node metastasis (pN1: 5; pN2: 2; and pN3: 1). One case: liver metastasis at presentation. Rhabdoid areas were positive for cytokeratin, and vimentin, and negative for CDX2, myogenic markers. Ki-67 and p53 in the RF were higher than in the non-rhabdoid. All cases had intact nuclear expression for MMRp. One case had KRAS mutation at codon 13 exon 2. One case had loss of SMARCB1-INI1 protein expression. Follow-up available in 8 cases (median follow-up: 3,5 months; range 0,1-181): 3 patients were alive and well, 2 died without disease, and 3 died due to progression.
Conclusion: We described 9 new GI neoplasms with RF with co-expression of vimentin and cytokeratin, and no relationship with microsatellite-instability. The RF represents a distinctive pathway of dedifferentiation. Recognition of RF in GI tumours is important because of their aggressive clinical course.

PS-20-054

Faecal microbiota transplantation and hydrocortisone ameliorate intestinal barrier dysfunction and improve survival in a rat model of cecal ligation and puncture-induced sepsis

I. Papadopoulou[1], D. Bantouna[2], I. Maroulis[3], C. Gogos[4], V. Zolota[5], S. Assimakopoulos[6]
[1] Department of Gastroenterology, Metaxa Cancer Hospital of Piraeus, Greece, [2] Department of Pathology, Medical School, University of Patras, Greece, [3] Department of Surgery, Medical School, University of Patras, Greece, [4] Department of Internal Medicine, Medical School, University of Patras, Greece, [5] Department of Pathology, Medical School, University of Patras, Greece, [6] Department of Internal Medicine, Medical School, University of Patras, Greece

Background & Objectives: Sepsis is associated with high mortality and intestinal barrier failure motors the systemic inflammatory response. Early administration of low dose hydrocortisone in septic shock has been shown to increase survival, while faecal microbiota transplantation reverses intestinal barrier dysfunction.
Methods: Forty adults male Wistar rats were randomly divided into four groups: I=sham(n=10), II=cecal ligation and puncture(CLP)(n=10), III=CLP + hydrocortisone(n=10)(2.8 mg/kg/d, intraperitoneally single dose at 6 hours) and IV=CLP + faecal microbiota transplantation(FMT from healthy donors at 6 hours by nasogastric tube)(n=10). At 24 hours, ileal tissues from experimental animals were harvested for histological analyses (mucosal/villous architectural characteristics, mitotic/apoptotic counts, occludin expression and lymphocytic infiltration). In a second experiment the same groups were observed for seven days for mortality, with daily administration of hydrocortisone (group III) and FMT (group IV) in surviving rats of these groups.
Results: Compared to sham, the septic rats(group II) showed reduced mucosal thickness ($P<0.05$), villous density and height ($P<0.001$), mitotic/apoptotic ratio ($P<0.001$) and increased apoptosis ($P<0.001$), lymphocytic inlfiltration and intraepithelial CD3+T-lymphocytes ($P<0.001$). Hydrocortisone(group III) or FMT(group IV) significantly ameliorated 7 days survival ($P<0.001$), mucosal atrophy ($P<0.001$), villous blunting ($P<0.001$ and $P<0.01$), intraepithelial T-lymphocytes ($P<0.001$) and apoptosis ($P<0.05$ and $P<0.001$), while increased paneth cells ($P<0.05$, $P<0.01$) and mitotic/apoptotic ratio ($P<0.05$, $P<0.001$). In the CLP group occludin expression in intestinal cells was significantly decreased ($P<0.01$ vs group I) while increased in groups III and IV ($P<0.01$ vs group II).
Conclusion: Faecal microbiota transplantation and low dose hydrocortisone administration ameliorate gut barrier dysfunction in polymicrobial sepsis in rats leading to improved survival.

PS-20-055

Immune Checkpoint Inhibitors (ICPIs)-induced granulomatous colitis

D. Pouloudi[1], D. Kamberoglou[2], H. Gogas[3], S. Sakellariou[1]
[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Greece, [2] Deptartment of Gastroenterology, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Greece, [3] First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Greece

Background & Objectives: Among immune checkpoint inhibitors (ICPIs), anti-PD1 regimens are the immunomodulating treatment of choice for malignant melanoma. Ipilimumab, an anti-CTLA-4 ICPI, is currently administrated in combination schemes or as second-line treatment. ICPIs can cause serious immune-related side effects such as severe colitis, dermatitis, thyroiditis, hypophysitis and hepatitis.
Methods: A 63-year-old female patient on anti-PD1 and ipilimumab for metastatic melanoma presented with fever and persistent diarrhea. Biopsies from endoscopically edematous, hyperemic and eroded sigmoid colon mucosa revealed many small epithelioid granulomas within the crypts with partial or complete destruction of crypt epithelium. A moderate degree of lymphoplasmacytic inflammation with few eosinophils and neutrophils and rare crypt abscesses coexisted. Histological findings were compatible with granulomatous colitis probably related to ICPIs therapy.
Results: ICPIs-induced colitis usually presents as active colitis characterised by lymphoplasmacytic lamina propria expansion accompanied by neutrophils with cryptitis and crypt microabscesses. Significant apoptosis at the crypt base, intraepithelial lymphocytosis resembling lymphocytic colitis and progression to active chronic colitis mimicking inflammatory bowel disease have also been reported.
Current literature refers to granulomas associated with ruptured crypts in 5-18% of anti-PD1 but not anti-CTLA-4 related colitis. Additionally, post-immunotherapy sarcoid-like reaction in lymph nodes and skin, granulomatous interstitial nephritis and hepatic fibrin ring granulomas have been reported. It seems that ICPIs can induce a cell-mediated immune granulomatous reaction.
Conclusion: Awareness of this rare histologic manifestation of ICPIs-induced colitis can help to avoid misdiagnosis. The diversity of histological subtypes points towards complex immune mechanisms and possible synergistic factors and may reflect treatment response.

PS-20-057

Syntaxin - a novel robust neuroendocrine marker

A. Sejben[1], S. Turkevi-Nagy[1], Z. Fekete[1], B. Kővári[1]
[1] University of Szeged, Hungary

Background & Objectives: Although typical neuroendocrine tumours (NET) and neuroendocrine carcinomas (NEC) have characteristic morphology, considering the specific clinical management of neuroendocrine neoplasms (NEN) immunohistochemistry is needed to confirm the diagnosis. For this purpose synaptophysin and chromogranin-A are most frequently used. The sensitivity and specificity of these classic neuroendocrine markers are not perfect. Syntaxins are a family of membrane-integrated proteins involved in neuromediator release. So far syntaxin expression was only reported in neuronal tissues, therefore syntaxin immunohistochemistry is potentially a highly specific method to demonstrate neuroendocrine differentiation.
Methods: Syntaxin-1A, synaptophysin and chromogranin-A expression were analysed by immunohistochemistry in gastroenteropancreatic NETs and NECs. To investigate the specificity of this novel marker, a variety of carcinomas including gastrointestinal, pulmonary, breast, female genital, skin, liver, kidney, thyroid, parathyroid, and adrenocortical tumours were also tested.
Results: Strong and diffuse membranous syntaxin-1A expression was observed in 59/60NETs, while moderate to strong membranous expression was documented in 15/15 NECs. In all NECs at least 50% of tumour cells were labelled (average: 80%). The sensitivity of syntaxin-1A (98%) in NETs was similar to synaptophysin (96%) and chromogranin-A (93%), whereas syntaxin-1A (100%) had somewhat higher sensitivity in NECs compared to synaptophysin (91%) and chromogranin-A (89%). The various types of non-neuroendocrine neoplasms were uniformly negative for syntaxin-1A.
Conclusion: Syntaxin-1 is a robust neuroendocrine marker with excellent sensitivity and specificity. Syntaxin-1 is expressed regardless of tumour grade, with usually a diffuse positivity even in NECs and rectal L-cell tumours. Compared to classic cytoplasmic markers, the membranous staining pattern can be more reliably interpreted in routine histopathology.

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PS-20-058

Clinicopathological significance of claspin overexpression and its association with spheroid formation in gastric cancer

K. Sentani[1], G. Kobayashi[2], T. Imai[1], N. Oue[1], N. Sasaki[2], W. Yasui[1]
[1] Department of Molecular Pathology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan, [2] Department of Pathology, Kure-Kyosai Hospital, Federation of National Public Service Personnel Mutual Aid Associations, Japan

Background & Objectives: Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide. Spheroid colony formation is a useful method to identify cancer stem cells (CSCs). The aim of this study was to identify a novel prognostic marker or therapeutic target for GC using a method to identify CSCs.
Methods: We analysed the microarray data in spheroid body-forming and parental cells and focused on the *CLSPN* gene because it is overexpressed in the spheroid body-forming cells in both the GC cell lines MKN-45 and MKN-74.
Results: RT-PCR analysis revealed that *CLSPN* mRNA expression was upregulated in GC cell lines MKN-45, MKN-74, and TMK-1. Immunohistochemistry of claspin showed that 94 (47%) of 203 GC cases were positive. Claspin-positive GC cases were associated with higher T and N grades, tumour stage, lymphatic invasion and poor prognosis. In addition, claspin expression was co-expressed with CD44, human epidermal growth factor receptor type 2 (HER2) and p53. *CLSPN* small interfering RNA (siRNA) treatment decreased GC cell proliferation and invasion.
Conclusion: These results indicate that the expression of claspin might be a key regulator in the progression of GC and might play an important role in CSCs of GC.

PS-20-059

Influence of histopathological factors on cancer-specific survival of patients with stage II colorrectal carcinoma that later became stage IV

A. Sobrino Prados[1], R.I. Bermudez Cameo[1], C. Hörndler Argarate[2], E. del Valle Sánchez[2], A. Puertas Canteria[2], M.Á. Trigo Cebrián[2], L.A. Ligorred Padilla[2], M.J. Viso Soriano[1], J.I. Franco Rubio[2], S. Bakali Badesa[1], H.P. Almanzar Comas[1], Á. Arellano Álvarez[1], N. Estrada Mallarino[1]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain, [2] Hospital Universitario Miguel Servet, Spain

Background & Objectives: Patients with colon carcinoma (CC) may develop recurrence/metastasis, even in a stage II. We consider necessary to identify histological findings related with tumour progression.
Methods: Patients with CC operated in stage II between 2008 and /2012 were evaluated. Patients with change from stage II to IV were compared by Kaplan-Meier curves. Several histopathological factors were analysed, including the level of invasion, the presence of "tumour budding" and peritumoural desmoplastic stroma. For statistical analysis we used Student-t test, Fisher test and Mann-Whitney U. Univariate and multivariate analysis were also performed using Cox regression. We found 147 patients with CC operated in stage II, and 30.3% had tumoural progression from stage II to IV. The conditions that we found related to adverse prognosis were high histological grade ($p=0.04$), lympho-vascular invasion ($p<0.001$), perineural invasion ($p=0.04$), tumour budding ($p=0.02$) and the presence of marked peritumoural stroma ($p=0.004$).
Results: When comparing the characteristics of patients with CC who changed from stage II to stage IV, besides the advanced level of invasion worsening the prognosis, we found the overall 5-year survival of patients with presence of pronounced peritumoural stroma and high "tumour budding" was significantly lower than those patients without any of these histological factors. The prognostic factors described can help to recognize which patients at high risk of recurrence could benefit from chemotherapy.
Conclusion: Some histopathological factors, like tumour budding and peritumoural desmoplastic stroma, may have a great relevance in patients' evolution. Therefore, further research is needed to provide the best treatment options according to these characteristics.

PS-20-060

The role of additional stainings in the assessment of the Peritoneal Regression Grading Score (PRGS) in peritoneal metastasis from gastric origin

W. Solass[1], D. Nann[1], J. Steinke[1], D. Westerwick[1], G. Nadiradze[2], K. Thiel[2], P. Horvath[2], R. Archid[2], H. Bösmüller[1]
[1] Institute of Pathology and Neuropathology, University Hospital Tuebingen, Eberhard-Karls-University Tuebingen, Germany, [2] Department of General and Transplant Surgery, University Hospital Tuebingen, Eberhard-Karls-University Tuebingen, Germany

Background & Objectives: The Peritoneal Regression Grading Score (PRGS), proposed in 2016 by a group of European pathologists, is a 4 tied regression grading score for peritoneal metastasis (PM) of various origins. Reproducibility of PRGS has been validated in a multicentric comparative study. As other regression scores, PRGS is based on the evaluation of HE-stained biopsies. A potential added value of supplementary stainings or immunohistochemistry (IHC) is unclear.
Methods: Retrospective analysis of 339 biopsies obtained during 76 laparoscopies in 33 patients with PM of gastric origin. PRGS

was determined based on HE-staining by an independent pathologist. In a 2nd round all biopsies classified as PRGS 1 (no residual tumour) or "uncertain" were re-evaluated in PAS-stain. In a 3rd round all PRGS1 and "remaining uncertain" cases were scored in IHC with BerEP4-stain.

Results: After HE staining, 95/339 biopsies (28%) were classified as PRGS1. Additional PAS staining confirmed scoring in 74/95 biopsies, in 10/95 biopsies were upgraded to PRGS 2 and 11/95 classified as "uncertain". After further BerEp4 staining, score was confirmed in 6/11 biopsies but in 5/11 biopsies score was upgraded to PRGS 2. In the "PAS confirmed PRGS1" group an additional BerEp4-staining confirmed in 65/74 the PRGS 1 and lead to an upgrading of the score to PRGS 2 in 9/74 biopsies.

After HE staining, 50/339 biopsies (15%) were classified as "uncertain". After additional PAS staining, 26/50 biopsies were classified PRGS 1, 18/50 biopsies classified PRGS 2 and 6/50 "remaining uncertain". After further BerEp4 staining, 1/6 biopsies were classified PRGS1 and 5/6 PRGS 2. In the group of 26/50 PRGS1 further BerEP4-staining lead in 3/26 to an upgrading of the score to PRGS 2 and confirmed in 23/26 biopsies the PRGS 1.

Conclusion: In this cohort of patient with PM of gastric origin, additional staining with PAS and/or BerEp4 showed residual tumour cells in 15/95 (15.8%) biopsies initially classified PRGS1. The number of "uncertain" biopsies could be reduced from 50 to zero and residual tumour cells were shown in 23 of these 50 biopsies (46%). Supplementray stainings showed the presence of residual tumour cells not only in uncertain cases but also in formerly (HE-based) tumour-free classified biopsies.

PS-20-061

Tumour microenvironment: tumour-stroma ratio and cancer-associated fibroblasts

R.M. Souza da Silva[1], E. Pedra Dias[1]
[1] Federal Fluminense University, Brazil

Background & Objectives: Current research focuses on the study of tumour microenvironment, especially the stroma. Fibroblasts, which are the major components of cancer stroma, are called cancer-associated fibroblasts (CAFs) and are similar in morphology to myofibroblasts. CAFs are fundamental regulators of tumour progression (tumour-stroma crosstalk and cancer cell migration) and influence response to therapeutic treatments. To describe the clinical profile of patients with colorectal adenocarcinoma (CRA), determine the tumour-stroma ratio (TSR), determine the presence of CAFs and investigate associations between these variables.

Methods: Retrospective study, paraffin-embedded CRA fragments from patients at the Lauro Wanderley University Hospital, Paraíba, Brazil. Excluded patients with neoadjuvant treatment. Variables analysed: age; sex; anatomopathological variables, TSR and the presence of CAFs. The TSR determined based on histological sections, on the T-status determining slide. TSR were separated into two categories: stromal poor - TSR ≤ 50%; rich in stromal – TSR > 50%. CAFs were defined as stromal spindle cells with cytoplasmic immunostaining for α-SMA (high expression defined as positive immunostaining > 10% of cells), observed in the estimated area of TSR, in the tumour front and around tumour cells.

Results: Thirty-five patients participated in this study, 60.0% male, mean age of 58.94 years. The T3 status was found in 71.4% of patients.A stromal-rich tumour was observed in 54.3% of the cases. Well differentiated tumours presented the lowest stromal proportion(p=0.048). Stromal-rich tumours was observed when perineural invasion occurred(p=0.023), angiolymphatic invasion(p=0.019) and tumour budding (p=0.008). Fibroblasts with high expression of α-SMA were identified in all cases, therefore CAFs, with high frequency for all the topographies observed (ranging from 88.2%-97.1%).

Conclusion: The TSR is associated with prognostic factors of aggressiveness, showing a strong and independent prognostic parameter. CAFs (myofibroblasts) are present in high frequency in the tumour microenvironment. Indicating that in a tumour microenvironment, the surrounding stromal tissue can be transformed, acquiring an abnormal phenotype with modification of the metabolism of resident cells.

PS-20-062

Interobserver concordance of tumour-stroma ratio estimative

R.M. Souza da Silva[1], E. Moreira Queiroga[2], A. Rolim da Paz[3], E. Pedra Dias[1]
[1] Federal Fluminense University, Brazil, [2] Alcides Carneiro University Hospital of the Federal University of Campina Grande, Brazil, [3] University Hospital Lauro Wanderley/EBSERH/UFPB, Brazil

Background & Objectives: The tumour stroma plays an important role in the initiation and progression of neoplasia, rich stroma in a tumour tissue can promote tumour invasion and aggressiveness. Tumour-stroma ratio (TSR) is a histological feature, reflecting the value of the stromal component that surrounds cancer cells. In different studies, the TRS stands out as a potential prognostic factor. Outline the clinicopathological profile of patients diagnosed with colorectal cancer and evaluate the interobserver agreement in the estimation of TRS.

Methods: Colorectal adenocarcinoma fragments, paraffin-embedded, from patients of the Napoleão Laureano Hospital Paraíba, Brazil, between 2017-2018.Excluded patients with neoadjuvant treatment. The analysed variables were: age; sex; anatomopathological features and TSR.TSR was determined based on histological sections stained, routine HE, on the T-status determining slide. TSR were separated into two categories: stromal percentage ≤ 50%-stromal poor; stromal percentage> 50%-rich in stroma. The interobserver concordance in the estimation of the TSR was observed among three pathologists: two pathologists with more than 10 years of professional experience and one trained pathologist (e-learning training in TSR determination), with less than 5 years.

Results: Ninety-eight patients participated in this study, 54.1% male, with a mean age of 61.9 years. The left colon was the most common topography (75.5%). Perineural invasion was frequent in 40.8%, angiolymphatic in 31.6% and lymph node metastasis in 40.8%. The T3 status was found in 75.5% of the patients. The concordance between the TSR percentages of the three pathologists was almost perfect (ICC above 0,8). There was greater agreement among pathologists in the estimation of stromal-poor tumours.

Conclusion: The TSR estimate is simple, based on routine histological material, without the need for additional special techniques or extra costs, easy to detect and has high agreement among pathologists.

PS-20-063

Quantitative morphometry of colorectal cancer vascularity

A. Stanek-Widera[1], M. Biskup-Frużyńska[1], J. Młynarczyk-Liszka[1], R. Lamch[1], D. Lange[1]
[1] Tumour Pathology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Background & Objectives: Multifactor morphometric evaluation of vascular network in colorectal cancer primary tumour to identify and assess prognostic factors and markers of metastatic potential in untreated patients.

Methods: Samples of tumours from 80 cases of untreated colorectal cancer in stage pT1-pT4 were used as material for immunohistochemical assays. Morphometric parameters of vessels (density, average surface area, perimeter, elongation ratio, compactness and fullness) were estimated by Factor VIII and Podoplanin stains in tumours with metastases versus those without metastases. Vessels characteristics assessed using Factor VIII staining were compared with Podoplanin estimates and correlated with T and N stage.

Results: The study shows that average density of lymphatic vessels in colorectal carcinoma is substantially higher in cases with nodal metastases and suggests that the intensity of lymphangiogenesis in colorectal cancer can be considered a negative prognostic factor. The examined vessel shape factors showed statistically significant differences between study groups. It may reflect deformation of lymphatic vessels in cases with metastasis. Also, it indicates the possibility of using the discussed morphometric features as prognostic factors.
Conclusion: Present study shows that Podoplanin assay provides more precise and significant estimates of vascular morphometric parameters than Factor VIII and therefore is recommended for further studies. Tumour vascularity characteristics of colorectal cancer might be used as prognostic factors in combined treatment strategy planning and in treatment outcomes. Studies in this field are in progress.

PS-20-064
Morphological features of acute appendicitis in elderly patients
I. Strumfa[1,2], S. Lapsa[1], R. Uljanovs[1], I. Fridrihsone[1,2], A. Ozolins[1], J. Gardovskis[1]
[1] Riga Stradins University, Latvia, [2] Department of Pathology, Latvia

Background & Objectives: Acute appendicitis in the elderly population is less frequent than in young patients but can follow a more severe course. The aim of our study was to compare the morphology of appendicitis and background changes in elderly *versus* young patients undergoing appendectomy.
Methods: Consecutive, retrospective cases of surgically treated acute appendicitis were identified. Two cohorts were defined by age: young (18-35 years) *versus* elderly (>65 years) patients. Tissues were evaluated for presence and stage of appendicitis (early *versus* phlegmonous *versus* gangrenous); occurrence of perforation; presence and type (eccentric *versus* concentric) of chronic vascular stenosis in *a.appendicularis*, small mesenteriolar and submucosal arteries and arterioles; any combined pathologies.
Results: Archive search yielded 59 elderly and 97 young patients subjected to appendectomy for suspected acute appendicitis. Elderly patients were characterised by significantly more frequent gangrenous appendicitis ($p<0.0001$) and perforation ($p<0.0001$). Chronic vascular stenosis was more frequent in elderly cases (69.8% [95% confidence interval 56.4-80.6] *versus* 17.1% [9.9-27.8] of young patients; $p<0.0001$); in these patients it showed concentric pattern contrasting with focal eccentric stenosis in the young ($p < 0.0001$). In addition, appendicitis in elderly patients was characterised by more frequent co-occurrence of apical diverticula ($p=0.0383$) and tumours ($p < 0.0001$), mainly serrated adenomas.
Conclusion: Morphologically, acute appendicitis in elderly patients is more severe and frequently accompanied by significant background changes that can have pathogenetic significance and underline the role of surgical treatment.

PS-20-065
Histology-based microRNA profiles do not predict Barrett's oesophagus progression to oesophageal adenocarcinoma
L. Suzuki[1], A. Gillis[1], L. Dorssers[1], J. Henriquez[1], A. Koch[1], M. Bruno[1], M. Spaander[1], L. Looijenga[1], K. Biermann[1]
[1] Erasmus MC, The Netherlands

Background & Objectives: This study aims to identify and validate microRNAs (miRs) that are differentially expressed in non-dysplastic Barrett's oesophagus (NDBE) samples from progressors compared to non-progressors as potential prognostic biomarkers to identify BE patients at risk for oesophageal adenocarcinoma (EAC), prior to histological changes.
Methods: BE samples of patients from a Dutch multicenter prospective cohort study (PROBAR) were investigated (n=34). NDBE of 16 patients who developed high grade dysplasia (HGD) and/or EAC (cases) was compared to NDBE of 18 patients that did not progress (controls) after a long-term follow-up. Patients were divided in a discovery and validation set. In addition to NDBE samples, HGD/EAC samples of 9 patients in the discovery set were studied as well. Both high throughput miR-profiling (Taqman Low Density MicroArray cards; TLDA) and individual assays were used.
Results: The discovery set revealed eleven upregulated miRs in NDBE tissues from cases compared to controls. Thirteen miRs showed higher expression levels in HGD/EAC versus NDBE samples from controls. Of these, three were similarly upregulated in NDBE and HGD/EAC from cases compared to NDBE samples from controls (i.e., miR-18a, 93, 331-5p), potentially serving as informative biomarkers for high progression risk. No significant differences were found between paired NDBE and HGD/EAC samples. However, these results were not confirmed in the validation set.
Conclusion: Early identification of BE patients at risk for progression remains challenging. This study shows that NDBE samples of progressors and non-progressors do not differ in the expression of miRs.

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PS-20-066
PDL-1 expression in colorectal cancer is associated with microsatellite instability
P. Tziakou[1], T. Marinis[2], E. Arkoumani[1], A. Zizi-Sermpetzoglou[1]
[1] Department of Pathology of Tzaneio General Hospital of Piraeus, Greece, [2] 1st Department of Surgery of Tzaneio General Hospital of Piraeus, Greece

Background & Objectives: PD-L1 expression on tumour cells may be induced by the immune microenvironment, resulting in immune escape and an adverse prognosis in many malignancies. The role of PD-L1 expression in colorectal carcinoma is less clear, with some published studies reporting conflicting results as to whether PD-L1 expression indicates a better or worse prognosis.
Methods: We investigated immunohistochemical expression of PD-L1 in 95 paraffin-embedded colorectal carcinoma tisuue samples with known microsatellite instability and its correlation with clinicopathologic parameters and survival.
Results: The 19 (18%) CC specimens displayed a positive membranous staining reaction for PD-L1, while 81 (72%) had a negative staining. PD-L1 expression on tumour cells was evaluated using a three-tiered grading system: 0=<5% of the tumour cells; 1=5-49% of tumour cells; and 2=≥50% of tumour cells with membranous staining of any intensity. PD-L1 expression was only seen in resections of the primary tumour ($P=0.010$), mostly in cases without neoadjuvant therapy. Histologically, the PD-L1 positive tumours were more likely to be poorly differentiated ($P<0.001$) with a medullary phenotype. Angiolymphatic and perineural invasion had no bearing on PD-L1 expression. In the cases without neoadjuvant therapy, the 3-year disease- specific survival rate for the PD-L1 positive ($n=13$) and negative ($n=47$) groups were 73% and 68% respectively ($P=0.1786$). Interestingly, among the microsatellite-instability-positive patients, PD-L1 expression was associated with reduced disease-specific survival.
Conclusion: PD-L1 may serve as a useful molecular marker because it is considered as poor prognostic factor for survival. Furthermore, it may be useful in prognostic stratification of high microsatellite-instability colorectal carcinoma.

PS-20-067
Impact of tumour budding in gastric carcinoma
D. Ulase[1], S. Heckl[2], H. Behrens[3], S. Krüger[3], I. Strumfa[4,5], C. Röcken[3]
[1] Department of Pathology, Riga Stradins University, Latvia, [2] Department of Internal Medicine I, University Hospital Schleswig-

Holstein, Kiel, Germany, [3] Department of Pathology, Christian-Albrechts-University, Kiel, Germany, [4] Riga Stradins University, Latvia, [5] Department of Pathology, Latvia

Background & Objectives: Gastric carcinoma (GC) is a heterogeneous disease with high mortality and variable histological features and genotypes. Presence of distant metastases, the depth of invasion and lymph node involvement have traditionally been recognized as important factors predicting outcome. Tumour budding (TB) has been shown to be predictive of lymph node metastasis, lymphatic and venous invasion, distant metastasis, and local recurrence in various cancers. However, its significance in GC is unclear yet. Therefore, the study aim was to assess TB and correlate it with clinicopathological parameters in GC.
Methods: TB was evaluated (according to ITBCC 2016 recommendations) in the invasive front of the tumour using the hotspot method, counted at 200x magnification per 0.785 mm^2 field and scored as Bd0 (no buds), Bd1 (1-4 buds), Bd2 (5-9 buds) or Bd3 (≥10 buds). Cases with TB present were divided into low-budding (Bd1/Bd2) and high-budding (Bd3) groups, and associations between TB score and clinicopathological parameters were analysed by Kendall's tau test.
Results: Among 456 consecutive, surgically treated GCs, 115 (25.2%) had no TB, 104 (22.8%) had low TB, and 237 (52.0%) – high TB. A statistically significant association was observed between TB score and pT ($p<0.001$), pN ($p<0.001$) and M categories ($p<0.001$), tumour grade ($p<0.001$), lymphatic invasion ($p<0.001$), perineural invasion ($p<0.001$), but not venous invasion ($p=0.119$).
Conclusion: In GC, higher tumour budding is significantly associated with higher invasion depth, lymph node metastasis, distant metastasis, higher grade, lymphatic and perineural invasion. Thus, the presence and extent of tumour buds could be a useful predictive marker in GC.

PS-20-068
A prospective analysis of endoscopic colonic biopsies to differentiate intestinal tuberculosis and Crohn's Disease on histology
J. Varshney[1], R. Chaturvedi[1], A. Joshi[1], D. Gupta[2]
[1] Department of Pathology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, India, [2] Department of Gastroenterology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai 400012, India

Background & Objectives: Crohn's disease (CD) and intestinal tuberculosis (ITB) are chronic granulomatous diseases of the intestine with overlapping clinico-pathological features. Differentiating the two poses a dilemma to the clinicians as well as the pathologists. The limited tissue available in biopsies makes it even more challenging. But this is essential for appropriate management as misdiagnoses can cause flare up or delayed appropriate treatment. Due to limited literature available on this, we conducted a study aimed at analysing their differentiating histological features along with clinical correlation.
Methods: This was an eighteen months prospective study of 50 clinically suspected ITB or CD cases. Endoscopic colonic biopsies (2-5 per patient) were taken and cases re-grouped as ITB and CD, based on minimum 6 months follow-up with Anti Tuberculosis Treatment (ATT) response and/or culture. Histological features (size, number, location of granulomas, giant cells, hyalinization, follicular hyperplasia, pyloric metaplasia, epithelial regeneration etc.) were studied and clinically correlated.
Results: Large (>400 microns) confluent granulomas, suppuration/caseation, giant cells and deep ulcers favoured ITB while small discrete granulomas, mucosal fibrosis, chronic and discontinuous inflammation favoured CD on histology. A new parameter- 'biopsy area occupied by granulomas' was introduced which alone covers two variables (used in previous studies), i.e. size as-well-as number of granulomas/low-power-field, with an advantage of nullifying the error caused by variation in field size of different microscope brands. Occupied area>10% in any biopsy favoured ITB and was statistically significant.
Conclusion: Differentiating ITB and CD is possible on biopsy, especially on mapping. As caseation is not always seen in TB, other features need careful observation. Submucosal granulomas otherwise described in CD can also be seen in ITB while discontinuous inflammation, hyalinization and epithelial regeneration can be features of CD too. We also recommend use of a new parameter for better differentiation.

PS-20-069
Cardiac-type epithelium development after ooesophagectomy: assessment of its origin and implications
D. Vinha Pereira[1], J. Castela[2], S. Mão de Ferro[3], R. Fonseca[4], A. Dias Pereira[3], P. Chaves[4,5]
[1] Pathology Department, Instituteo Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [2] Gastroenterology Department, Instituteo Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisbon, Portugal, [3] Gastroenterology Department, Instituteo Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisbon, Portugal, [4] Pathology Department, Instituteo Português de Oncologia de Lisboa Francisco Gentil E.P.E., Lisbon, Portugal, [5] Faculdade de Ciências da Saúde da Universidade da Beira Interior, Covilhã, Portugal
Background & Objectives: The congenital *versus* metaplastic origin of cardiac epithelium (CE) is under debate. Gastrooesophageal anastomosis seems ideal to study the development of CE, reproducing its natural history. Our aim was to evaluate the prevalence of CE at different time-points post-oesophagectomy.
Methods: We developed a prospective study of patients who undergone oesophagectomy with gastric pull-up in our Institution during one year. Upper gastrointestinal endoscopy was performed 3 and 15 months after surgery; anastomosis was evaluated with white-light, Narrow band Imaging and Near Focus; targeted biopsies from mucosa different from squamous-oesophageal or gastric-corpus mucosa (non-native mucosa - NNM) and protocoled biopsies from oesophagus, stomach and anastomosis were performed. Histology was evaluated by GI pathologists.
Results: 19 patients were included and 15 were eligible for the 15^{th} month endoscopy. NNM was identified in 17/19(89,5%) at 3 months, and in all patients (15/15) at 15 months. CE was histologically confirmed in all NNM areas in both time-points, but also in 33% of endoscopically non-recognized areas - NNM has a sensitivity, specificity, positive and negative predictive value for CE's diagnosis of 84%, 100%, 100% and 67%, respectively. Intestinal metaplasia was identified in 2/19 patients (10,5%), at 3 months.
There was a significant increase of NNM length between the first and second endoscopic evaluation ($p=0,011$). The presence of endoscopic oesophagitis was statistically associated with increased CE extension ($p=0,016$).
Conclusion: CE development after oesophagectomy is an almost universal and extremely rapid metaplastic reflux-induced phenomenon, with good endoscopic-histological correlation. The congenital nature of CE should be re-evaluated.

PS-20-070
Mucin 16 expression in colorectal carcinomas: a predictor for peritoneal dissemination?
B. Yeni[1], U.O. Idiz[2], E. Yarikkaya[3], M. Cin[4], H. Dincer[3], G. Usul[3], N. Dursun[4]
[1] University of Health Sciences, Department of Pathology, Turkey, [2] Istanbul Training and Research Hospital, General Surgery, Turkey, [3] Istanbul Training and Research Hospital, Pathology, Turkey, [4] University of Health Sciences, Istanbul Health Practice and Research Hospital, Department of Pathology, Turkey

Background & Objectives: Colorectal carcinoma(CRC) is one of the most frequent cancer in men and women. Pathologic tumour stage is the strongest prognostic factor in patients with CRC. The presence of peritoneal carcinomatosis (PC) is critical and can change the stage of disease. Carbohydrate antigen 125(CA125) also known as Mucin 16(MUC16) is a glycoprotein found on tumour cells that reacts with mesothelial cells.
Although there are plenty of studies investigating CA125 expression in ovarian carcinoma and in some degree gastric adenocarcinoma, there is insufficient data for CRC. We aimed to investigate MUC16 expressions in colorectal tumours in our series and crosscheck the results with patients' prognostic factors, especially PC.
Methods: Total of 30 patients' HE stained slides (13 PC positive, 17 PC negative) diagnosed with CRC were retrieved from our archive and re-examined. We applied immunohistochemistry (MUC16) to both groups' tumours and PC positive omentums.
Results: In our PC positive group, five cases had both positivities in tumour and peritoneum (5/13). Only two cases showed positivity in peritoneum but no reaction in tumour (2/13). None of our PC positive cases were positive with MUC16 in tumour together with negativity in peritoneum. In PC negative group, six cases showed positive staining with MUC16 (6/17). These six cases had adverse prognostic factors like; distant metastasis, high histologic grade, circumferential tumour, lymphovascular and perineural invasion. In 13 MUC16 positive cases, nine had either lymphovascular or perineural invasion (9/13) and nine had lymph node metastasis (9/13). pT1 and pT2 tumours showed no reaction with MUC16.
Conclusion:MUC16(CA125) may predict PC in CRC and can be used as a prognostic tool. Using such marker while diagnosing the patient may change the therapy options and result in a better survey.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-21 | Digestive Diseases Pathology – Liver / Pancreas

PS-21-001
Pure and mixed gallbladder neuroendocrine neoplasms: rare and orphan lesions
N. Ahmed[1], F. Pedica[2], F. Falcinelli[1], F. Sanvito[2], I. Sassi[2], C. Doglioni[2,1]
[1] Vita-Salute San Raffaele University, Milan, Italy, [2] Pathology Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background & Objectives: Neuroendocrine differentiation in the neoplasms of the gallbladder are rare since they represent around 0,5% of all gallbladder cancers. Mixed adeno-neuroendocrine carcinomas (MANEC) are combined neoplasms in which both components represent at least 30% of the tumour. In the last 2 years we found 2 MANEC of the gallbladder, so we retrospectively investigated our Archive to define their frequency in our Hospital and estimate the incidence of the disease.
Methods: We searched for gallbladder "MANEC" in our database from January 2009 to March 2019, and then we defined how many gallbladders were neoplastic in these last 10 years.
Results: Of the 8087 sampled gallbladders, 200 were neoplastic (2,4%). In particular, 4 of them were diagnosed as MANEC (0,05%), the others were dysplastic (1% low-moderate grade, 0,4% high grade), adenocarcinomas (1,4%) and a pure moderately differentiated NEC (0,012%).
All MANECs displayed a poorly differentiated adenocarcinoma plus a neuroendocrine carcinoma with Ki67 higher than 30%. Two cases presented well distinct counterparts with numerous Paneth cells CDX-2+ in the neuroendocrine population, whilst in the other cases the two populations were deeply intermingled.
Conclusion: The neuroendocrine neoplasms of the gallbladder are very rare and only a few reports are found in the literature (pure NEC = around 500, MANEC= 33 cases). Since they are frequently aggressive lesions, the collections and characterization of these neoplasms could help in better defining prognosis and treatment.

PS-21-002
HIV hepatic biopsy, what else?
D. Argyropoulou[1], T. Robalo Nunes[2], S. Boavida[2], H. Oliveira Coelho[1], M. Brito[1]
[1] Department of Pathology, Hospital Garcia de Orta, Portugal, [2] Department of Infectiology, Hospital Garcia de Orta, Portugal

Background & Objectives: The purpose of this work is to report a case of a 56-year-old female HIV positive patient, with the diagnosis of amyloidosis performed at the liver biopsy. Amyloid is defined as an amorphous, eosinophilic proteinaceous tissue deposit, with typical green birefringence in polarized light after Congo red staining. There are over 25 different proteins acknowledged and can affect any organ and tissue. Their enigmatic clinical presentation ranges from clinically insignificant to life-threatening.
Methods: The patient was a retired seamstress, with background of chronic osteomyelitis under antibiotic therapy, fistulizing perianal disease, HIV positive under medical treatment that was admitted in the Emergency with fever, abdominal pain and nausea followed by diarrhoea and haematochezia. She presented weight loss of 7kg in a month. The physical examination showed hepatosplenomegaly. The blood analyses revealed microcytic anemia, leucocytosis, neutrophilia, high inflammatory markers and a high alkaline phosphatase. TC-scan revealed a small nodular single hepatic lesion and a liver biopsy was performed.
Results: The liver biopsy revealed a perivascular and peri-sinusoidal deposition of an amorphous, hyaline substance that stained positive with Congo red and showed green birefringence in polarized light. The diagnosis of amyloidosis was given. There are 26 patients with amyloidosis in our hospital; this was the first in a liver biopsy.
Conclusion: The diagnosis of amyloidosis at liver biopsy is rare. This diagnosis was crucial for the adequate patient management. In our Institution there are documented, in the past 10 years, 3 cases of amyloidosis secondary to a chronic inflammation state due to HIV infection.

PS-21-003
Grading neuroendocrine neoplasms of the pancreas according to the new 2017 World Health Organization grading system: a retrospective study of 18 cases
S. Ben Khalifa[1], N. Abdessaied[1], T. Zahmoul[2], S. Chaeib[2], O. Belkacem[2], A. Ben Abdelkader[1], M. Mokni[1]
[1] Pathology Department of Fattouma Bourguiba Hospital, Monastir, Tunisia, [2] Department of Pathology; Farhat Hached Hospital; Sousse, Tunisia

Background & Objectives: Pancreatic neuroendocrine neoplasms (PanNENs) are a rare and heterogeneous disease comprising only 2% of all pancreatic neoplasms, but have increased significantly in incidence over the past few decades. The aim of the current study is to review updated grading system of the pancreatic NEN.
Methods: We retrospectively analysed the clinical and pathologic data of 18 patients diagnosed at our Institution from 2010 to 2018. Age, Sex ratio and tumour size were recorded. All slides for each case were reviewed. Tumours were graded according to the number of mitoses and/or Ki-67 index, using the 2017 WHO Classification.
Results: There were 12 men and 6 women with a mean age of 59 years (34-80 years). The average tumour size was 8 cm (2 to 18 cm). PanNENs were well-differentiated in 83,3% (n=15) with 40% of PanNET G1 (n=6), 53,3% of PanNET G2 (n=8) and % 6,6 of PanNET G3 (n=1). Poorly-

differentiated PanNEM (PanNE carcinomas) represented 16,6 % of cases (n=3).
Conclusion: The WHO classification released in 2010 led to a significant change in the grading system of NENs of the digestive system. However, there are a number of remaining issues. In the revised version of the "WHO Classification of Tumours of Endocrine Organs" published in 2017, to solve the problems of high-grade (grade 3) neuroendocrine neoplasms, they are divided into PanNET G3 and neuroendocrine carcinomas, grade 3 (PanNEC G3) depending on their histo-morphologic characteristics. The PanNEC G3 category is associated with a better prognosis and does not significantly responds to cisplatin-based chemotherapy.

PS-21-004
SOX9, a highly sensitive and specific marker to discriminate hepatocellular carcinoma from intrahepatic cholangiocarcinoma
X. Ding[1], B. Trac[1], X. Duan[1]
[1] Loyola University Medical Center, USA

Background & Objectives: Hepatocellular carcinoma (HCC) and Intrahepatic cholangiocarcinoma (ICC) are two most common primary liver cancers. The differential diagnosis between these 2 entities is relatively straightforward if the tumour exhibits typical histological features. However, a differential diagnosis between ICCs and HCCs could be challenging, particularly in cases of poorly differentiated carcinoma. Immunohistochemical markers that are commonly used in current clinical practice include arginase-1, HepPar-1, glypican-3, and CK19. However, none of these are sensitive enough to distinguish high grade HCC from poorly differentiated cholangiocarcinoma. Sex-determining Region Y box 9 (SOX9) has been shown to be a tumour stem cell marker as well as be dysregulated in certain cancer. In this study, we examined the expression of SOX9 in HCCs, CCs and combined HCC and cholangiocarcinoma.
Methods: We herein examined the immunohistochemical expression of SOX9 in HCCs (n=20), ICCs (n=18), combined HCC and cholangiocarcinoma (n=7) in surgical resection specimen. A nuclear staining of SOX9 was treated as positive and was scored for intensity (weak, moderate and strong staining). Cytoplasmic staining was considered nonspecific. Fisher's exact test with two tails was performed using the GraphPad statistical software.
Results: Benign hepatic bile duct epithelium exhibits diffuse moderate to strong SOX9 nuclear staining while benign hepatocytes are completely negative for SOX9 expression. 20 HCC cases tested are all negative for SOX9 expression. 7 of 18 CC cases show diffuse strong nuclear staining of SOX-9 while 11 of 18 CC cases exhibit diffuse moderate SOX-9 nuclear expression. For combined HCC and cholangiocarcinoma cases tested, the cholangiocarcinoma component is diffusely positive for SOX-9 while the HCC component is completely negative.
Conclusion: SOX-9 is a highly specific and sensitive marker to distinguish cholangiocarcinoma from hepatocellular carcinoma. Positive SOX-9 staining could be used to exclude hepatocellular carcinoma. Further study will be conducted to elucidate SOX-9 expression in different hepatic metastatic tumours from other organs.

PS-21-005
Mechanism of action of modulated electro-hyperthermia in resolving radio-resistance of pancreas adenocarcinoma and improving gemcitabine efficacy
G. Forika[1], T. Vancsik[1], A. Balogh[2], Z. Benyó[2], T. Krenács[1]
[1] 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Hungary, Hungary, [2] Semmelweis University, Institute of Clinical Experimental Research, Budapest, Hungary, Hungary

Background & Objectives: Pancreatic adenocarcinomas are among the worst to respond to oncotherapy with 5-year survival rate under 10% thus more effective therapies are required for. Modulated electro-hyperthermia (mEHT) is a non-invasive therapy which can generate selective heat (≤42°C) in cancer based on its elevated glycolysis, ion concentration and permittivity.
Methods: Panc1 pancreas adenocarcinoma cells were treated *in vitro* using mEHT for 60 min; 10 μM/ml gemcitabine for 24 h (G); irradiation using 2Gy for 2.5 min (137Cs, R); and with combinations of mEHT and G (mEHT+G) or R (mEHT+R). Samples were tested 24 h post-treatment for cell stress, DNA double-strand brakes, tumour viability, apoptosis and ALDH1+ progenitor/stem cells.
Results: mEHT treatment alone resulted insignificant tumour cell apoptosis detected by morphology and flow cytometry, which was more pronounced after combined therapies (mEHT+G and mEHT+R). Immunocytochemistry revealed significant upregulation of γH2AX and cleaved/activated caspase-3 positive cell fractions, while pAKT and the ALDH1+ cells were reduced in the mEHT, G, mEHT+G, mEHT+R groups, compared to controls. In contrast, irradiation alone did not significantly affect tumour cell viability and apoptosis.
Conclusion: mEHT treatment alone can induce cell stress, DNA double-strand breaks and apoptosis in pancreas adenocarcinoma cells. Combined with radiotherapy, it can reduce pAKT and tumour stem cell ratio in Panc1 cell cultures, thus improves the efficacy of radiotherapy. Combined with gemcitabibne mEHT is as efficient as chemotherapy, and can induce also cell stress and apoptosis which leads to tumour destruction.

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PS-21-006
Liver adenomatosis and NAFLD developed in the context of hereditary fructose intolerance: a case report
L. Ghannem[1], A. Beaufrère[2,3], A. Montasser[4,5], F. Cauchy[6], G. Couchy[7], J. Zucman-Rossi[7], O. Soubrane[6], V. Paradis[2,3]
[1] Pathology Department, Beaujon University Hospital, AP-HP, Clichy, France, [2] Pathology Department, Beaujon University Hospital, AP-HP, Clichy, France, [3] INSERM U1149, Beaujon University Hospital, Clichy, France, [4] Pathology Department, Beaujon University Hospital, AP-HP, Clichy, France, [5] Pathology Department, Theodor Bilharz Research Institute, Giza, Egypt, [6] Department of HPB and Pancreatic Surgery, Beaujon University Hospital, AP-HP, Clichy, France, [7] INSERM, UMR 1162, Gènomique Fonctionnelle des Tumeurs Solides, Institute Universitaire d'Hèmatologie, Paris, France

Background & Objectives: Hereditary fructose intolerance (HFI) is an autosomal recessive metabolic disorder resulting from a deficiency in fructose-1-phosphate aldolase activity. This deficiency induces postprandial hypoglycemia after fructose ingestion. Association between HFI and non-alcoholic fatty liver disease (NAFLD) has rarely been described. The aim of this study was to report an observation of NAFLD and hepatic adenomatosis genotypically typed developed in the context of HFI.
Methods: We report the case of a 35-year-old female with HFI, referred to our hospital after the discovery of twelve hepatic nodules in both lobes. The patient had no history of diabete or obesity. A right hepatectomy was realized. The surgical specimen was fixed in 10% neutral buffered formalin and was adequately sampled. Paraffin sections from tumours and non-tumoural liver were histologically examined. Liver tumours were phenotypically (immunohistochemistry) and genotypically typed (Targeted next generation sequencing).
Results: Macroscopically, three tumours were observed, well-limited and red-brownish. Microscopically, all lesions corresponded to hepatocellular adenoma and the non neoplasic liver displayed moderate macrovacuolar steatosis without features of steatohepatitis. Immunohistochemical analysis showed an overexpression of C-reactive protein and serum amyloid-

associated antibodies in tumours. L-FABP and β-catenin antibodies were normally expressed in tumour cells and glutamine synthetase staining was negative. Molecular analysis confirmed the diagnosis of inflammatory hepatocellular adenoma with gp130 mutation.
Conclusion: We report here a case of liver adenomatosis associated with NAFLD developed in a patient with HFI, that may suggest a possible link between these pathologies**.** Thus, a specific clinical and radiological follow-up should be advised in patients with HFI for screening NAFLD and development of liver tumours.

PS-21-007
Heterogeneous ALCAM expression in pancreatic ductal carcinoma
S. Giusca[1], I.D. Caruntu[1], D. Ciobanu[1], A. Rusu[1]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Background & Objectives: In pancreatic tumour pathology, the Activated Leucocyte Cell Adhesion Molecule (ALCAM) role as prognostic factor is poorly investigated, with contradictory results. Within this context, our study aims to analyse the ALCAM expression in pancreatic ductal carcinoma and associated preneoplastic lesions.
Methods: 46 cases of pancreatic ductal carcinoma, 28 of them presenting associated preneoplastic lesions, were immunohistochemically investigated. ALCAM expression was assessed at membranous and cytoplasmic level, by using an immunoscore based on the percentage of positive tumour cells and the intensity of reaction. Relationship between ALCAM expression and clinico-pathological characteristics was statistically analysed.
Results: ALCAM expression was strongly membranous in all low-grade preneoplastic lesions, with progressive loss in high-grade ones; no cytoplasmic staining was noted. In 40 of 46 cases of pancreatic ductal carcinoma, ALCAM was expressed both at membranous and cytoplasmic level, with a heterogeneous distribution: 5 cases had moderate membranous and low cytoplasmic expression; 20 cases registered low membranous staining with moderate cytoplasmic expression; 5 cases showed low membranous and cytoplasmic staining; 10 cases displayed moderate membranous and cytoplasmic expression. In 6 cases, ALCAM immunostaining was completely absent. Statistical analysis revealed no significant differences between membranous, respectively cytoplasmic ALCAM expression, and clinico-pathological parameters defined for pancreatic ductal carcinoma (tumour extension, tumour grade, lymph node metastasis, lympho-vascular invasion).
Conclusion: From preneoplastic pancreatic lesions to tumour proliferation, ALCAM loses its membranous expression and gains a cytoplasmic one. The low or absent membranous ALCAM expression does not seem to influence an aggressive behaviour in pancreatic tumours, as in other malignancies.

PS-21-008
Comparison of two different approaches for pancreatoduodenectomy by ductal adenocarcinoma of pancreas: pathological features
M.L. Gomez Dorronsoro[1], M. Mercado[2], I. Fernandez de los Rios[3], P. Sanchez Acedo[4], I. Eguaras[5], R. Beloqui[6], I. Amat[7]
[1] CHNavarra. Pamplona. Dpt. Pathology, Spain, [2] CHN.Pamplona. Dpt. Pathology, Spain, [3] CHN. Pamplona. Dpt.Pathology, Spain, [4] CHN.Pamplona. Dpt.Surgery, Spain, [5] CHN. Pamplona. Dpt. Surgery, Spain, [6] CHN.Pamplona. Dpt Pathology, Spain, [7] CHN. Pamplona Dpt. Pathology, Spain

Background & Objectives: To analyse the pathological differences related to survival between two types of surgical approach to cephalic duodenopancreatectomy (DPC) by ductal adenocarcinoma. Two types of surgical approach are compared: classic approach (CA) and mesenteric artery approach (MAA). The later includes CA and extends towards mesopancreas, a structure that extends from posterior face of pancreatic head behind mesenteric artery and vein.
Methods: 173 patients underwent DPC between 1994 and 2017 at our Institutsion: 59 AC (from 1994 to 2008) and 114 with MAA (2008 onwards). MAA specimens were examined by the same two pathologists and a standarized pathological protocol was applied, whereas previous reports (AC) were randomly assigned to any staff member.
Results: Both groups differ in T stanging, more advanced staging was observed in MAA approach (>T3 86%) versus CA (>T3 76,6%). The number of isolated lymph nodes was much higher in the modified approach (23,9 MAA versus 7,95 CA) and consequently the lymph node ratio (metastatic lymph nodes/total lymph nodes,LNR) was lower in the AMS group (0,07 MAA versus 0,16 AC). Complete resection rate (R0) were 73,3% in CA and 67,5% in MAA. Specific survival rates were 24,4 months for AC group and 32,8 months in MAA patients.
Conclusion: MAA allows isolating a greater number of lymph nodes and obtaining a lower LNR, a good prognostic factor. But, we have not shown a significative increase in global survival with this approach, probably because more advanced stages have been selected in this group.

PS-21-009
ARX expression and alternative lengthening of telomeres identify insulinomas that develop liver metastasis
W. Hackeng[1], W. Schelhaas[2], F. Morsink[1], C. Heidsma[2], S. van Eeden[2], M. Vriens[1], G. Valk[1], E. Nieveen van Dijkum[2], J. Offerhaus[1], K. Dreijerink[1], L. Brosens[1]
[1] University Medical Center Utrecht, The Netherlands, [2] Amsterdam University Medical Center, The Netherlands

Background & Objectives: Liver metastases are the leading cause of death in patients with pancreatic neuroendocrine tumours (PanNETs). PanNETs are called "functional" if symptomatic by excess hormone production; functional "insulinomas" rarely metastasize and are generally considered benign. The primary treatment of insulinomas is surgery; if successful and symptoms resolve, patients are discharged from hospital follow-up. Nevertheless, some insulinomas do give liver metastases. The value of prognostic markers to identify malignant sporadic insulinomas was investigated, since these patients might benefit from more extensive follow-up.
Methods: Tissue-microarrays were constructed from 36 insulinomas. Data on functionality and clinical follow-up were collected. Expression of several recently described prognostic markers and endocrine hormones and transcription factors (ATRX, DAXX, ARID1A, H3K36me3, Insulin, PDX1, Glucagon and ARX) was determined by immunohistochemistry. *CDKN2A* loss and the alternative lengthening of telomeres phenotype (ALT) were determined by fluorescence in situ hybridization. Slides were scored blinded for follow-up.
Results: Insulin, PDX1, glucagon and ARX were expressed in 100%, 100%, 61% and 11% (4/36) of insulinomas, respectively. No allelic *CDKN2A* loss; or loss of ATRX, DAXX, or ARID1A expression were observed. H3K36me3 was uniformly strong. 6% (2/36) showed ALT. 3 patients developed liver metastasis after resection. All 3 metastatic PanNETs showed ARX expression, and 2 also had the ALT phenotype.
Conclusion: ARX expression and ALT mark malignant behaviour of insulinomas. ALT has not been reported previously in insulinomas specifically. ARX expression which is normally absent in islet beta-cells suggests endocrine dedifferentiation. These markers might change the standard of care in pancreatic insulinoma patients, but further validation is necessary.

PS-21-010
Histomorphological and immunophenotypical subtypes of pancreatic ductal adenocarcinoma
L. Haeberle[1], L. Ingenhoff[1], M. Schlensog[1], S.A. Safi[2] and I. Esposito[1]
[1] Institute of Pathology, Heinrich Heine University and University Hospital, Düsseldorf, Germany, [2] Department of General and Visceral Surgery, Heinrich Heine University and University Hospital Düsseldorf, Germany

Background & Objectives: Prognostically relevant molecular subtypes of pancreatic ductal adenocarcinoma (PDAC) can partly be recapitulated by immunohistochemistry. CK81 positivity and loss of UTX expression seem to correlate with the more aggressive "squamous" subtype, while HNF1A positivity is a suggested marker for the less aggressive non-"squamous" PDAC. However, the link between molecular/immunohistochemical subtypes and histomorphological subtypes is unclear. The aim of this study is a detailed histomorphological and immunohistochemical analysis of PDACs from a well-characterised cohort.
Methods: Tumour samples of patients resected for PDAC (n=223) were analysed regarding histomorphology and immunoprofile. A detailed histomorphological analysis of whole slides has been completed in 157 cases so far. Immunohistochemistry for HNF1A, CK81, UTX, p40 and p53 was performed on tissue microarrays of all cases. HNF1A and CK81 were assessed according to previously published criteria. For HNF1A and UTX, an immunoreactive score (IRS, 0-12) was (also) used.
Results: 124/157 (79%) conventional PDACs, 6/157 adenosquamous PDACs (3.8%) and 27/157 (17.2%) other histomorphological subtypes were found. CK81 or HNF1A positivity were not correlated with other immunohistochemical markers or classical prognostic features such as grading. Low UTX-IRS was correlated with poorer grading (p=0.002, Mann-Whitney-U), but not with other markers. Neither CK81 nor HNF1A status correlated with survival in this cohort. Patients with UTX-negative (IRS 0-1) PDACs showed significantly worse survival than patients with UTX-positive PDACs (p=0.0005, log rank).
Conclusion: Our preliminary results confirm that PDAC is a highly heterogeneous entity both morphologically and regarding its immunoprofile. So far, there appears to be no clear relationship between CK81-positive/UTX-negative "squamous" subtype and histomorphological features.

PS-21-011
The evaluation of HER2 discordance and heterogeneity in pancreas adenocarcinoma
S. Han[1]
[1] Department of Pathology, Dong-A University College of Medicine, Republic of Korea

Background & Objectives: HER2 (ERBB2) amplication and overexpression are reported in 30-100% of pancreas carcinoma (PC). However, impacting treatment effects of trastuzumab for PC remain largely undefined. In this study, we evaluated HER2 status associated with gene copy number (GCN) gain and amplification and protein overexpression comparing the results of the tissue microarray (TMA) and the matched whole tissue section (WTS), respectively.
Methods: Dual-colour siver-enhanced in sity dybridizaiton (SISH) and immunohistochemistry (IHC) for HER2 were performed in TMA and the paired WTS of 73 primary PC patients. The amplification status (GCN ratio>2), and GCN gain (average GCN>4) data were obtaind. The GCN variation and IHC results were evaluated by the 2018 CAP/ASCO guidelines for HER2 assessment.
Results: Among the 73 PC cases, HER2 IHC staining showed that 47 cases was negative, and 25 cases were equivocal and 1 case was positive in both TMA and the matched TWS, respectively. Amplification and GCN gain of HER2 showed in 21.9% (16) and 23.3% (17) in TMA, and 15.1% (11) and 19.2% (14) in WTS, respectively. Analysing the patterns of HER2 protein and gene status, 16 patients showed HER2 discordance. HER2 heterogeneity was recognized in 38 cases (52.1%). Patients with HER2 discordance had significantly worse survival than concordance (p<0.05). The group of HER2-Heterogeneity had significantly worse survival than the non-heterogeneous (p<0.05).
Conclusion: Through the evaluation of HER2 status, we identified the importance of discordance and heterogeneity in PC. And in term of treatment effects, even if the alteration of HER was minor portion, the targeting of HER2 in PC may be alternate or complementary approach to establish a precision medicine based on tumour characterisation.

PS-21-012
HER2 status of biliary tract cancer
N. Hiraoka[1], H. Yoshida[1], H. Nitta[2], A. Ohba[1], C. Morizane[1], T. Okusaka[1]
[1] National Cancer Center Hospital, Tokyo, Japan, [2] Roche Tissue Diagnostics, USA

Background & Objectives: Human epidermal growth factor receptor 2 (HER2)-targeted therapy improves clinical outcomes in cases of HER2-positive breast and gastric cancers, although ineffective or recurrent cases also exist. One reason is assumed to be the heterogeneity of HER2 expression in cancer cells. Herein, we investigated HER2 amplification or overexpression in biliary tract cancer (BTC), which is one of the most devastating cancers.
Methods: We examined HER2 protein expression using immunohistochemistry, HER2 gene amplification using fluorescence in situ hybridization, and both protein and transcript levels simultaneously using a gene–protein assay. These tests were performed using samples from 459 cases of BTC surgically resected in National Cancer Center Hospital, which included 110 intrahepatic cholangiocarcinomas (ICCs), 187 extrahepatic cholangiocarcinomas (ECCs), 80 gallbladder carcinomas (GBCs), and 82 ampullary carcinomas (AVCs). HER2 status was assessed according to the guideline for HER2 testing in gastrooesophageal adenocarcinoma.
Results: HER2 positivity was found in 3.8% of ICC, 7.0% of ECC, 26.9% of GBC, and 12.7% of AVC cases. More than 80% of these showed heterogeneity of HER2 expression, and 70% of papillary adenocarcinomas and 10% of non-papillary adenocarcinomas expressed HER2 homogenously. Reductions in HER2 expression were often found in deeper invasive areas with reductions in the differentiation status of cancer cells. There was sometimes a collision of two different types of cancer in HER2 expression.
Conclusion: These results suggest that a significant subgroup of HER2-positive BTC cases can be considered for HER2-targeted therapy.

PS-21-013
MET amplification was associated with adverse prognostic factors in gallbladder cancers
Y. Kim[1], S. Bang[1], S. Jee[1], S. Park[2], S. Shin[2], S.S. Paik[1], K. Jang[2]
[1] Department of Pathology, Hanyang University College of Medicine, Seoul, Republic of Korea, [2] Department of Pathology, College of Medicine, Hanyang University, Seoul, Republic of Korea

Background & Objectives: Mesenchymal epithelial transition (MET) is a proto-oncogene which encodes a heterodimeric transmembrane receptor tyrosine kinase for the hepatocyte growth factor. Aberrant MET signalling has been described in a number of solid tumours, especially non-small cell lung cancer, and is associated with tumour progression and adverse prognosis. Since MET is a potential treatment target, knowledge of its prevalence and clinicopathological relevance is crucial.
Methods: We investigated MET expression and gene amplification in 116 gall bladder cancers using tissue microarray. Immunohistochemistry was used to evaluate c-MET overexpression, silver in situ hybridization to assess gene copy number.
Results: The prevalence of MET overexpression and amplification was 27.6% and 10%. MET protein expression was not correlated with MET gene copy numbers. MET amplification was associated with higher histologic grade (p = 0.029), advanced pT stage (p = 0.026), lymph node metastasis (p = 0.008), AJCC stage (p = 0.018), and perineural invasion (p = 0.018). MET overexpression was not associated with any clinicopathological parameters. No

survival difference was found according to the MET overexpression and amplification status.
Conclusion: Our data suggest that MET might be an interesting molecule for targeted therapy in gallbladder cancer, because MET amplification was found in a subset of tumour and associated with adverse prognostic factors. MET amplification might be a more useful stratification biomarker than MET protein overexpression.

PS-21-014
Granulocytic Epithelial Lesion (GEL)-Positive Pancreatitis of Heterotopic Pancreas
S. Jun[1], S.J. Kim[2], G. Yoon[3], S. Hong[4,5]
[1] Department of Pathology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea, [2] Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea, [3] Department of Pathology, Kyungpook National University School of Medicine, Republic of Korea, [4] Department of Pathology, Asan Medical Center, Republic of Korea, [5] University of Ulsan College of Medicine, Republic of Korea

Background & Objectives: Autoimmune pancreatitis (AIP) was formally recognized based on the histologic features. Especially, type 2 AIP has the definitive diagnostic feature, called granulocytic epithelial lesion (GEL). GEL is characterised by periductal neutrophilic infiltration showing clustered neutrophils underneath the ductal epithelium and within the lumen. Clinically, type 2 AIP seems to be associated with inflammatory bowel disease (IBD).
Methods: We analysed clinicopathological features of GEL-positive pancreatitis among 165 resected heterotopic pancreas (HPs) [57 gastric (35%), 56 duodenal (34%), 30 omental (18%), and 22 jejunal (13%)]. GEL-positive pancreatitis was seen in 9% (15/165) of HPs, including ductal epithelial (5/15, 33%) and acinar (4/15, 27%) neutrophilic infiltrations and neutrophils in duct lumen (8/15, 53%). Abdominal pain was commonly observed in patients with GEL-positive pancreatitis of HPs (11/15, 73%).
Results: GEL-positive pancreatitis was more commonly observed in HPs having symptoms (P=0.038) and showing larger size (P=0.027), infiltrative growth pattern (P=0.036), interstitial fibrosis (P=0.007), and lymphoid cuffs (P=0.001). Periductal lymphoplasmocytic infiltration and fibrosis ($P < 0.001$, both), acinar-ductal metaplasias (ADMs; P=0.013), and pancreatic intraepithelial neoplasia/intraductal papillary mucinous neoplasms (PanIN/IPMN; P=0.004) were more commonly seen in HPs with GEL-positive pancreatitis than those without GEL-positive pancreatitis. IBD was present only in one patient without GEL-positive pancreatitis in HP.
Conclusion: In conclusion, GEL can be seen in HPs without clinical evidence of AIP, so this is not specific diagnostic criteria of type 2 AIP.

PS-21-015
Prognostic impact of the modifications of the 8th versus 7th edition of AJCC staging system, regarding hepatocellular carcinoma
C. Satala[1], S. Gurzu[2], Z. Kovacs[3], L. Banias[2], I. Jung[3]
[1] Clinical County Emergency Hospital, Targu Mures, Romania, [2] University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania, [3] University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania

Background & Objectives: Representing the 4th cause of cancer-related death worldwide, hepatocellular carcinoma (HCC) represents a global health problem. The aim of our study was to emphasize the prognostic impact of differences between the 8th vs. 7th edition of AJCC staging system of HCC.
Methods: All consecutive HCCs diagnosed in the Pathology Department of Clinical County Emergency Hospital of Targu-Mures Romania, during 2009-2017, were retrospectively evaluated. We analysed the clinicopathological parameters such patient's age and gender and histopathological parameters such grade of differentiation and pTNM stage, based on both 7th and 8th edition of AJCC Cancer Staging Manual. The overall survival rate was estimated after a period of follow-up ranging between 10 and 60 months.
Results: There were 36 HCCs included in the study. According to 7th edition of AJCC, 20 cases were staged as pT2- and 16 HCCs were diagnosed in pT1 stage. After restaging, 10 pT2 cases were under-staged to pT1b. The 16 pT1-HCCs were re-staged as pT1a. We did not find a correlation between overall survival rate and patient's age (p=0.21) or grade of differentiation (p=0.55). Independently by the used staging system, the survival rate was not influenced by the pT stage (p=0.18 for 8th edition and p=0.92 for the 7th edition). The survival curve linearly decreased at 3 years after diagnosis, for both pT1 and pT2 cases.
Conclusion: Compared with the 7th edition of AJCC Staging System book, in the 8th edition, there is a tendency of under-staging HCCs, which do not influence the overall survival rate. The prognostic impact of the 8th edition changes should be estimated in a larger number of cases.

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PS-21-016
CAMTA-1 expression in 24 cases of hepatic epithelioid hemangioendothelioma in a single Institute: diagnostic utility for differential diagnosis from hepatic angiosarcoma
H. Jung[1], S. Ha[1]
[1] Department of Pathology and Translational Genomics, Samsung Medical Center, Republic of Korea

Background & Objectives: Epithelioid hemangioendothelioma(EHE) of liver is a rare vascular tumour having variable clinical course, from stable disease to fatal outcome. Although histologic features are distinctive, EHE with marked cytologic atypia can mimic epithelioid angiosarcoma. EHEs have been known to have chromosomal translocations involving 1p36.3 and 3q25, resulting WWTR1-CAMTA1 fusion gene. Nuclear expression of CAMTA1 by immunohistochemistry was reported in about 90% of EHEs in multi-organ. Our study aims to validate diagnostic utility of CAMTA1 expression for EHEs, especially in liver.
Methods: Pathology database of Samsung Medical Center, Seoul, Korea, was queried for all biopsy and resected specimen of hepatic EHEs from June 2000 to December 2018. A total of 24 EHE patients were found including 9 surgical resections and 20 biopsy specimens (5 of which underwent both procedures). For control, 13 hepatic angiosarcomas were selected. Immunohistochemistry was performed using anti-CAMTA1 antibody (Novus Biologicals, Littleton, CO, USA) in total 37 tumours (24 hepatic EHEs and 13 angiosarcomas).
Results: 22 of 24 (91.6%) hepatic EHEs showed nuclear staining for CAMTA1. One of two CAMTA1-negative cases showed TFE3 positivity. The other one case was negative for TFE3. Meanwhile, all 13 angiosarcoma cases showed negativity for CAMTA1.
Conclusion: CAMTA1 can be helpful in differential diagnosis of hepatic vascular tumours, especially in a small biopsy specimen, that have overlapping morphology between EHE and angiosarcoma.

PS-21-017
Evaluation of the American Joint Committe on Cancer (AJCC) 8th edition staging system for hepatocellular carcinoma in 1,034 patients with curative resection
H. Jung[1], S. Ha[1]
[1] Department of Pathology and Translational Genomics, Samsung Medical Center, Republic of Korea

Background & Objectives: Recently, 8th edition staging system of the American Joint Committee on Cancer (AJCC) was released with change in T stage. We validated the prognostic value of the new AJCC staging system in comparison to the previous 7th edition.
Methods: Total 1,034 patients who had undergone curative resection as the initial treatment for hepatocellular carcinoma at Samsung Medical Center, between 2008 and 2012, were enrolled. Pathology T stage was determined as AJCC 7th and 8th edition, respectively. Recurrence free survival (RFS) was estimated using the Kaplan-Meier method and compared by log-rank test. The analysis of the time dependent receiver-operating-characteristic (ROC) curves for censored survival data was used to compare the capability of the two models to predict tumour recurrence.
Results: Stage migration was observed in 63 patients (6.3%); from T2 to T1a in 45 patients and from T3 to T4 in 20 patients. For solitary tumours ≤2cm(T1a by 8th), those with microvascular invasion had shorter RFS(p=0.016). Tumours involving a major branch of portal vein or hepatic vein(T4 by 8th and T3b by 7th, n=20) showed shorter RFS than multifocal tumours at least one of which is >5cm(T3 by 8th and T3a by 7th, n=40)(p=0.017), supporting the change in 8th edition.
Conclusion: The AJCC 8th edition staging system for HCC showed comparable predictive performance to the 7th edition. It is desirable in future revision to consider sub-stratification of solitary tumours ≤2cm(T1a) depending on the presence of vascular invasion, which is not included in 8th edition. Further studies are required to validate these findings.

PS-21-018
Role of liver biopsy in the management of liver diseases following the end of interferon era: experience of a tertiary referral center
N. Ehsan[1], D. Sweed[1], E. Karman[2], E.A. Abdelsameea[1], A. Mohamed[1], M. Elsabaawy[1]
[1] National Liver Institute - Menoufia University, Egypt

Background & Objectives: Liver biopsy is the cornerstone for the management of patients with liver diseases. During the interferon era for the treatment of chronic hepatitis C patients, liver biopsy was mandatory for evaluating the degree of necroinflammation activity and the stage of fibrosis. The development of direct acting antiviral agents for hepatitis C virus made liver biopsy less required. The purpose of this study was to explore the role of liver biopsy related to adult liver disease following the end of the interferon era.
Methods: Pathology and medical records of patients who had underwent needle liver biopsy from January 2015 through December 2018 were collected. Liver biopsy taken for evaluation of donor liver histology, post liver transplant or focal lesion was excluded from the study.
Results: A total of 275 liver biopsies were collected, 191 males and 84 females with mean age 41.22±13.36. The pathological diagnosis was as follows 48 drug induced liver injury, 38 Non-alcoholic fatty liver disease, 34 chronic hepatitis B or hepatitis C with cholestasis, 29 autoimmune hepatitis, 26 primary sclerosing cholangitis, 8 primary biliary cholangitis, 7 autoimmune overlap syndrome, 13 ascending cholangitis, 13 active bilharziasis, 10 Wilson's disease, 11 sarcoidosis, 10 cytomegalovirus/ Epstein-Barr virus infection, 7 Dubin Johnson syndrome, 6 liver abscess, 4 resolving acute hepatitis. Solitary cases of latent congenital hepatic fibrosis, amyloidosis, hemochromatosis, hepatic amoebiasis, malaria, polyarteritis nodosa, myeloproliferative disease were noticed. Four cases of non-specific hepatitis were also seen. Initial diagnosis was made by liver biopsy and confirmed by laboratory investigations.
Conclusion: Liver biopsy remains to be an integral component for the hepatologist's diagnostic decision.

PS-21-019
Prognostic immunhistochemical parameters of pancreatic neuroendocrine neoplasms (PanNETs)
B. Keskin[1], E. Bozkurtlar[1], P. Bagci[1]
[1] Marmara University, Turkey

Background & Objectives: ATRX and SSTRs have been defined as prognostic and therapeutic markers for PanNETs. We examined these markers in our data set, along with the markers for organ of origin.
Methods: TMAs prepared from thirty consecutive resection specimens between 2013-2019. SSTR2A, ATRX, Islet 1, CDX2, and TTF1 were applied with immunohistochemistry. Membranous and/or cytoplasmic staining for SSTR2A, and nuclear staining for the other markers were noted.
Results: F/M: 19/11. Mean age: 52. Mean survival: 29 mos (6-70). 11 were G1, 18 were G2, and 1 was a G3(NEC). ATRX lost in 18, SSTR2 negative in 3, CDX2 positive in 7, Islet-1 negative in 5 cases, and TTF1 negative in all. The mean diameter in ATRX lost ones was 5 cm, and 2 cm in ATRX retained cases (p:0.01). 3/7 CDX2 positive cases were R1. ATRX lost in 9/11 with node metastasis, 7/9 with LVI, and 7/10 with PNI. NEC case lost ATRX, was positive with SSTR2 and Islet1. 2/3 SSTR2 negative cases had long survivals (59 & 70 mos). Death seen in 1/30 with loss of ATRX, positive SSTR2 and negative Islet1, and CDX2.
Conclusion: Even though no significant statistical results were found, loss of ATRX seems to be common in cases with worse pathological prognostic parameters such as larger tumours, lymph node metastasis, lymphovascular and perineural invasion. SSTR2 was positive in almost all cases and even the negative ones had long survivals. One should not count on Islet1 and CDX2 to prove the pancreatic origin.

PS-21-020
Incidental diffuse hepatic angiosarcoma in a liver explant - a case report of an uncommon presentation of a rare liver neoplasia
N.J. Lamas[1], M. Oliveira[1], L. Ferreira[1], C. Fleming[1], R. Amorim[2], B. Fernandes[2], J.R. Brandão[2], A. Coelho[1], J.R. Vizcaíno[1]
[1] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Portugal, [2] Centro Hospitalar do Porto, Portugal

Background & Objectives: Primary angiosarcoma of the liver, although rare, is the most common malignant mesenchymal hepatic tumour, with aggressive behaviour and dismal prognosis. It is a high-grade malignant neoplasm of endothelial cells of blood or lymphatic vessels, affecting more men than women, with peak incidence in the 6th-7th decades of life.
Methods: We report the case of a 54-year-old male diagnosed with alcohol-related hepatic cirrhosis. The computed tomography scan showed a dysmorphic liver with lobulated contours and heterogeneously diffuse density, without focal lesions. After several episodes of clinical deterioration, the patient underwent liver transplantation.
Results: A liver specimen weighing 1273g and measuring 25x13x11,5 cm was received. The external surface was smooth and lobulated. Upon section, the liver was globally multinodular with multiple nodules of small size. Throughout the liver parenchyma, within the nodular regions, there were some vague greyish areas, the largest measuring 4,5x3 cm; and numerous ill-defined reddish areas, the largest measuring 4x3 cm. A 0,5 cm lymph node was isolated from the peri-hilar region. The histological analysis revealed a cirrhotic liver with fibrous bridges containing ductular proliferation and linfomononuclear infiltrate. In the greyish and reddish areas one observed multiple foci of marked proliferation of atypical large sized endothelial cells, with hyperchromatic nuclei and increased pleomorphism. Mitosis were frequent and atypical. Focally, the lesion conditioned atrophy and destruction of the neighboring hepatic parenchyma. In other areas, there were dilated sinusoids filled with blood and containing small aggregates of neoplastic cells with papillary-like morphology. The lymph node isolated from the peri-hilar region was unremarkable. The immunohistochemistry study showed neoplastic cells positive for Factor VIII, ERG, CD31, p53 (aberrant overexpression) and c-Myc. The estimated proliferative index (%Ki-67) was above 50%. A diagnosis of hepatic angiosarcoma was made.

Conclusion: This case reports an incidental presentation of a rare aggressive liver neoplasm.

PS-21-021

Large tumour size, lymphovascular invasion, and synchronous metastasis are associated with recurrence of solid pseudopapillary neoplasm

G. Lee[1], Y. Sung[1,2], J.H. Lee[3,2], K. Song[3,2], D.W. Hwang[3,2], S.S. Lee[4,2], D. Seo[4,2], S.K. Lee[4,2], S.C. Kim[3,2], E. You[1], S. Hong[1,2]
[1] Department of Pathology, Asan Medical Center, Republic of Korea, [2] University of Ulsan College of Medicine, Republic of Korea, [3] Department of Surgery, Asan Medical Center, Republic of Korea, [4] Department of Gastroenterology, Asan Medical Center, Republic of Korea

Background & Objectives: Solid pseudopapillary neoplasms (SPNs) of the pancreas have low malignant potential. However, our understanding of malignant SPNs is limited. The purpose of this study was to 1) to identify the proportion of malignant SPNs after removing non-relevant malignant factors, and 2) to identify factors investigate risk factors of recurrence in malignant SPNs.
Methods: To evaluate risk factors affecting malignant potential, 376 surgically resected SPN cases were reviewed and compared with clinicopathologic features.
Results: Mean patient age was 35.1±13.5 years-old with a male to female ratio of 0.25. SPNs were predominantly located in body and tail (261 cases, 69.6%) with mean size of 4.6±2.8 cm. Forty-eight cases (12.8%) were malignant SPNs, and 26 of which (54.2%) had perineural invasion and 19 (40.0%) had lymphovascular invasion, respectively. Invasion to adjacent organs was noted in 11 cases (22.9%). Three (6.3%) had synchronous liver metastasis, one (2.1%) had lymph node metastasis, and one (2.1%) had omentum metastasis. Recurrence was observed in 9 cases (18.8%), and was associated with higher pT category (p=0.02), lymphovascular invasion (p<0.01), and synchronous metastasis (p<0.001). Patients with malignant SPNs had significantly worse recurrence-free survival (10 year survival rate, 73.2%) than those with benign SPNs (96.3%, p=0.01). Other factors, including higher pT category (p=0.02), synchronous metastasis (p<0.01), and lymphovascular invasion (p<0.01) also showed worse recurrence-free survival by univariate analysis. Worse prognostic factor for recurrence was lymphovascular invasion (p=0.02).
Conclusion: Malignant SPNs were observed in 13% of SPNs. Even SPNs were malignant, they had far better 10 year recurrence-free survival than other malignant pancreatic tumours. Recurrence of SPNs was associated with increased tumour size, lymphovascular invasion, and synchronous metastasis. Lymphovascular invasion was a worse prognostic factor in malignant SPN patients.

PS-21-022

The prognostic value of the RON expression in the periampullary cancers

S. Lee[1], Y. Kim[1], C. Cho[1], H. Oh[1], W. Sung[1]
[1] Department of Pathology, Catholic University of Daegu School of Medicine, Republic of Korea

Background & Objectives: With an increase in the knowledge of recepteur d'origine nantais (RON) receptor tyrosine kinase function in different types of human cancers, it is becoming clear that RON has prominent roles in both cancer cells and associated microenvironment. These understandings of this oncogene make it an exciting therapeutic target. In this study, we investigate the expression pattern of RON in human periampullary cancer and correlate the findings with the clinicopathologic parameters.
Methods: 72 cases of totally resected specimen for periampullary cancer from January 2003 to December 2014 were reviewed. Tissue microarrays of 68 cases of periampullary cancers were assembled. The expression of total RON, c-MET and PD-L1 protein has been analysed by immunohistochemistry. The association between a positive expression of RON and clinicopathologic features was analysed.
Results: 24 cases showed dominant expression of RON protein in the cancer relative to adjacent normal epithelium. Another 23 cases showed aberrantly decreased expression and the other 20 cases showed unremarkable expression of RON protein between cancer tissue and normal one. An association was identified between the poor prognostic factors and the expression of RON. No significant association was identified between RON overexpression and c-MET or PD-L1 overexpression. There was significant association between the expression of RON and patient survival. (p=0.034)
Conclusion: We suggest that RON plays an important role in aggressive behaviour of periampullary cancers. This finding provides additional understanding of the biology of the RON in periampullary cancer and has have implications for therapeutic strategies to target RON activity.

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PS-21-023

Sinusoidal platelet obstruction is associated with portal hypertension in myeloid metaplasia of the liver

A. Normand[1], Y. Le Bris[2], E. Frampas[3], J. Gournay[4], J. Mosnier[1]
[1] Hotel Dieu de Nantes, Department of Pathology, France, [2] Hotel Dieu de Nantes, Haematology Laboratory, France, [3] Hotel Dieu de Nantes, Department of Radiology, France, [4] Hotel Dieu de Nantes, Department of Gastroenterology, France

Background & Objectives: To study liver histological lesions associated with portal hypertension (PH) in myeloid metaplasia (MM).
Methods: Between 2012 to 2018 liver biopsies with MM were retrieved from Pathology Department. Clinical, hematological and imaging data were collected. All biopsies were reviewed and lesions described in portal hypertension without cirrhosis were studied: peri-sinusoidal fibrosis (PF), sinusoidal dilatation (SD), obliterative portal venopathy (OPV), nodular regenerative hyperplasia (NRH). Immunostaining for CD31 expression and *JAK2/CALR/MPL* mutations detection was performed.
Results: We have included 17 patients with MM among them 10 patients (59 %) with PH (oesophageal varices, ascites or raised portal gradient). In this sub-group we observed SD (n=10), PF (n=9), NRH (n=5), OPV (n=3) and CD31+ sinusoïdal platelet obstruction in 3 patients. Myeloproliferative neoplasm (MPN) was diagnosed in 6 patients with PH and all of them showed PF, 3 cases showed extrahepatic portal vein thrombosis, 3 NRH, 1 OPV and 2 sinusoidal platelet obstruction. *JAK2V617F* mutation was detected in 83% of MPN patients. All mutated patients have portal vein thrombosis or NRH. Chronic myelomonocytic leukemia-2 was diagnosed in one case with PH. Sinusoidal platelet obstruction was detected in this patient and in another. The latter had PH but neither portal vein thrombosis (PVT) nor proven MPN. No *CALR* or *MPL* mutations were found in this series.
Conclusion: MM is not constantly associated with PH which is explained by other causes: in these patients, PH is frequently associated with extra-hepatic PVT or NRH. In lacking of these anomalies, intra-hepatic sinusoidal platelet obstruction might explain PH.

PS-21-024

Non-alcoholic fatty liver disease (NAFDL) - a retrospective study in paediatric liver biopsies

T. Oğuzsoy[1], H. Sahin Ozkan[2], C. Celikel[3]
[1] Marmara University Training and Researching Hospital, Turkey, [2] Marmara University Faculty of Medicine, Department of Pathology, Turkey, [3] Marmara University Faculty of Medicine, Turkey

Background & Objectives: Non-alcoholic steatohepatitis(NASH) is a morphological pattern of liver injury that is characterised by hepatocellular steatosis, ballooning and lobular inflammation. Our aims were to evaluate the distribution of morphological features, to determine NAFLD activity score (NAS) and SAF score, and to observe the effect of morphological changes on fibrosis, in paediatric age group.
Method : The biopsies of patients diagnosed as NAFLD under 18 years of age, between 2014 and 2016, were retriewed from the archives of the Marmara University School of Medicine.
Methods: The biopsies of patients diagnosed as NAFLD under 18 years of age, between 2014 and 2016, were retriewed from the archives of the Marmara University School of Medicine.
Results: We analysed 45 liver biopsies. Due to insufficient biopsy, 3 cases were excluded from the study. Among 42 patients, the mean age was 11.9 and 28(%66.6) were male. The degree of steatosis was scored as 1 for 10, 2 for 8, and 3 for 24 cases. The distribution of steatosis were panacinar in 14(%33.3), azonal in 11(%26.1), peri-portal in 8(%19), pericentral in 8(%19) and limited to zone 2 in 1 case. The lobular inflammation score was 0 in 4 cases, 1 in 17 cases, 2 in 12 cases and 3 in 9 cases. Ballooning degeneretion were evident in 21 patient, being mild or prominent in 18 and 3 of biopsies, respectively. No fibrosis was observed in 16 cases, whereas 15 were stage 1c, 7 were stage 2 and 4 were stage 3. In statistical analysis fibrosis was statistically related to the distribution of steatosis ($p< 0.01$), NASH score ($p<0.001$) and lobular inflammation ($p<0.01$), but not with the degree of steatosis and/or ballooning.
Conclusion: Although ballooning degeneration is accepted as the hallmark feature of NASH, in our study it was not related to the degree of fibrosis. In contrast, the distribution but not the degree of steatosis and lobular inflammation w ere both correlated with the degree of fibrosis.

PS-21-025

Histochemical techniques applied in freezing cuts during intraoperative biopsies in liver transplantation

A. Salazar Nicolas[1], M.I. Ortuño Moreno[1], L. Barona Garcia[1], A. Caballero Illanes[1], N. Villa Lorente[2], M.A. Menárguez Arnaldos[3], M.D. Perez Caparros[4], G. Ruiz Garcia[1], M.I. Oviedo Ramirez[5], E. Martinez Barba[1]
[1] Servicio de Anatomía Patológica. Hospital Clínico Universitario Virgen de la Arrixaca., Spain, [2] Servicio de Anestesia y Reanimación. Hospital Clínico Universitario Virgen de la Arrixaca., Spain, [3] Servicio de Urgencias. Hospital Clínico Universitario Virgen de la Arrixaca., Spain, [4] Servicio de Ginecología y Obstetricia. Hospital de Mèrida., Spain, [5] Servicio de Anatomía Patológica. Hospital Clínico Universitario Virgen de la Arrixaca., Spain

Background & Objectives: The introduction of more extended clinical criteria when considering the suitability of a donor has led to an increase in the number of transplants, especially kidney transplants, and this implies a rise in intraoperative biopsies performed in the pathology department. Given this growth in transplants from "not ideal donors" makes the histological study should be more precise, optimal and objective.
Methods: 18 cases of intraoperative biopsy of liver transplantation between the months of December and January of 2018-2019 were studied. The samples were stained with Hematoxylin-Eosin and 2 histochemical techniques were applied: Chromotrope Aniline Blue to enhance fibrosis and Sudan III- IV for the study of hepatic steatosis, comparing the results obtained in each of boths techniques.
Results: In the study of fibrosis comparing HE and Aniline Blue, 4 cases showed a greater lesion in their study with Aniline (22.2%), 6 cases with a diagnosis of lesion of lesser degree (33.3%) and 8 presented similar lesions between HE and Anilina (44.4%). Regarding the study of macrovesicular steatosis with HE and Sudan III-IV, 5 cases showed a greater injury with the Sudan technique (27.78%), 4 cases with lesion of lesser degree (22.2%) and 9 showed a similar injury (50%).
Conclusion: The introduction of the techniques of Aniline Blue and Sudan III-IV in the intraoperative study in liver transplant allows a more objective and sensitive study to detect possible alterations that show the organs, being specific techniques enhance the fibrous lesions and steatotic lesions that we must study and its application does not significantly increase the time of histological study and in case of diagnostic doubt are techniques that can offer a more reliable diagnosis.

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PS-21-026

Diagnostic accuracy of an immunohistochemical panel to distinguish intrahepatic cholangiocarcinoma from bile duct adenoma

L. Nicolè[1], S. Sarcognato[1], R. Cappellesso[1], T. Sanavia[2], C. Luchini[3], C. Mescoli[1], P. Capelli[3], A. Fassina[1], M. Guido[1]
[1] University of Padua, Italy, [2] Harvard Medical School, USA, [3] University of Verona, Italy

Background & Objectives: Differential diagnosis between intrahepatic cholangiocarcinoma (ICC), an aggressive liver tumour, and bile duct adenoma (BDA), an indolent lesion, is fundamental but sometimes challenging, particularly for well-differentiated ICC. Morphological analysis alone is often not sufficient to achieve a correct diagnosis. Several immunohistochemical markers have been proposed to improve the diagnostic performance, but all of them, taken singularly, showed a low sensitivity and are not used in clinical practice. Moreover, only a few studies focused on the differential diagnosis between ICC and BDA, so far.
The aim of this study was to investigate the diagnostic performance of a 3-marker panel, including p53, $p16^{INK4a}$, and S100P, to evaluate whether their combination might help to distinguish ICC from BDA.
Methods: Fifty-two surgically resected liver nodules (30 ICCs and 22 BDAs) were retrospectively selected and stained with p53, $p16^{INK4a}$, and S100P. p53 was considered positive when a strong nuclear immunoreaction was observed, while $p16^{INK4a}$ and S100P positivity was both nuclear and cytoplasmic. An algorithm was built and its diagnostic performance analysed.
Results: As expected, despite their perfect specificity (100%), all the evaluated markers showed a low sensitivity when considered singularly (56.7%, 26.6%, 23.4%, for p53, $p16^{INK4a}$, S100P, respectively). On the contrary, the algorithm based on the sequential use of p53, $p16^{INK4a}$, and S100P, showed a sensitivity of 73.4%, a specificity of 100% and an overall accuracy of 84.6%.
Conclusion: The adopted 3-marker algorithm is helpful in differentiating ICC from BDA. Further larger studies are needed to validate the proposed algorithm.

PS-21-027

Pancreatic neuroendocrine microadenomatosis: clinicopathologic features of 5 cases

D. Unal Kocabey[1], E. Cakir[1], F.H. Dilek[1], I. Aydin[1]
[1] Izmir Katip Celebi University Ataturk Training and Research Hospital Department of Pathology, Turkey

Background & Objectives: The presence of multiple small neuroendocrine tumours (NET) in pancreas measuring less than 0.5 cm in greatest dimension has been referred to as pancreatic microadenomatosis (PMA). PMA has been considered the precursor of NET. PMA can occur sporadically or be associated with syndromes such as multiple endocrine neoplasia type 1 syndrome (MEN1) and von Hippel-Lindau (VHL) disease. We report the clinical and histopathological features of 5 cases diagnosed as PMA.
Methods: Five cases diagnosed as PMA at our Institution over a 2-year period were analysed retrospectively. Clinical and demographic data were retrieved from the hospital records.

Results: The patients included two male and three female. Patient age ranged from 52 to 74 years. All patients underwent pancreaticoduodenectomy. One of 5 patients exhibited MEN1 and had well-differentiated NET in duodenum and parathyroid adenoma. Two patients presented with accompanying well-differentiated NET in pancreas. One patient exhibited accompanying well-differentiated adenocarcinoma in ampullary region. The remaining patient had no concomitant tumour and suffered from an insulinoma syndrome. Histopathologically, all PMA displayed a trabecular or mixed solid-trabecular growth pattern. Two of accompanying well-differentiated NET were G1 with the size of 1.3 cm and 0.4 cm and one was G2 with the size of 2.5 cm.
Conclusion: PMA is a rare entity and may be detected as an incidental finding in patients with pancreatic tumour. It is not restricted to genetic syndromes such as MEN1; it may also occur independently from this inherited condition. Further studies with larger case series are needed to elucidate the etiopathogenesis of these lesions.

PS-21-028
Hepatocellular carcinoma in non-cirrhotic liver: a retrospective clinicopathological study of 55 cases
M. Varela dos Santos[1], A. Figueiredo[2], A.M. Carvalho[2], S. Silva[3]
[1] Serviço de Anatomia Patológica - Centro Hospitalar e Universitário de Lisboa Central, E.P.E., Portugal, [2] Serviço de Anatomia Patológica - Hospital Curry Cabral, Centro Hospitalar e Universitário de Lisboa Central, E.P.E., Portugal, [3] Serviço de Cirurgia Geral - Hospital Curry Cabral, Centro Hospitalar e Universitário de Lisboa Central, E.P.E, Portugal

Background & Objectives: Liver cirrhosis is the main risk factor for Hepatocellular Carcinoma (HCC), but a smaller number of HCCs arise in non-cirrhotic livers (NCL): albeit some etiological factors have been described, the development of HCC without cirrhosis has been a subject of debate, and its pathophysiology is still largely unknown.
The main goal of this study was to investigate the clinical and pathologic features of HCC in NCL.
Methods: A retrospective medical record and pathological review was conducted for all cases of HCC in NCL that were subjected to liver surgery in our Medical Centre between January 2013 and December 2017. Demographic data, clinical course pre and post treatment, laboratory results and pathologic findings of all cases were analysed. We used nonparametric tests for statistical analysis, and a p value ≤ 0.05 was considered statistically significant for all tests.
Results: Age ranged from 19 to 96 years (median 74) and 76,36% were male. Alcoholism (27%), diabetes (25%) and HCV-infection (16%) were the most common clinical factors. Steatosis (27,3%), chronic viral hepatitis (21,8%) and steatohepatitis (5,45%) were the most frequent pathological findings in non-tumoural liver. The neoplasms had the usual histology. 7,27% of all HCCs were fibrolamellar carcinomas. Recurrence occurred in 27 patients (49%), but showed no significant association to vascular invasion, histological grade or TNM staging.
Conclusion: HCC in NCL is still a poorly understood and heterogeneous neoplasm: in our series, these tumours were mostly found in elderly male individuals, and had the usual morphological features of HCC. Most patients had normal non-tumoural parenchyma. HCV-hepatitis and alcohol consumption may be risk factors for this neoplasm. Recurrence was common but nondependent of any of documented variables.

PS-21-029
Angiomyolipoma of the gallbladder. A case report with 10-year follow-up
F. Liberati[1], L. Ventura[2]
[1] Division of Pathology, San Camillo De Lellis Hospital, Rieti, Italy, [2] Division of Pathology, San Salvatore Hospital, L'Aquila, Italy

Background & Objectives: Angiomyolipomas were reported in many different locations. In the gallbladder, only one case of "edematous angiomyolipoma-like polyp", 3 primary malignant PEComas and 1 metastasis from malignant PEComa have been described in literature. We report a case of gallbladder angiomyolipoma, with long follow-up.
Methods: A 58-year-old woman was admitted with abdominal pain, nausea and vomiting. Ultrasound scan showed a distended gallbladder with a suspect stone embedded in the neck region. A laparoscopic cholecystectomy was performed. The gallbladder measured 6.5 cm in length and presented a 2.0x1.5x1.2 cm white-grayish nodule in the neck region wall. No stones were found.
Results: A well-circumscribed, unencapsulated tumour, was composed by sheets of spindle and plump epithelioid cells with abundant pale eosinophilic cytoplasm, and a rich vascular network. Tumour cells were positive for HMB-45, actin and desmin; negative for CD117 and CD34. S100 was positive in rare mature fat cells within the neoplasm. Ki67 proliferation index was 1%. A diagnosis of extrarenal angiomyolipoma was made. Chronic cholecystitis and pseudopyloric metaplasia were also present. No additional lesion was identified after a subsequent CT scan, and the patient remains free of disease ten years after the diagnosis.
Conclusion: Mesenchymal tumours of the extrahepatic bile ducts may show PEC (perivascular epithelioid cell) differentiation. The identification of an angiomyolipoma in the gallbladder is not surprising because similar lesions are described in liver, pancreas and, occasionally, in the common bile duct. The presence of a stenosing tumour in the neck region may have induced the symptoms in absence of obstructing stones.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
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PS-22-001
Adrenal myelolipomas: case series
E. Gun[1], A. Avci[1], S.D. Altindag[1], D. Etit[1]
[1] Izmir Katip Celebi University Ataturk Training and Research Hospital, Department of Pathology, Turkey, and Research Hospital, Department of Pathology, Turkey

Background & Objectives: Adrenal myelolipomas are rare, benign neoplasms consisting of mature fat tissue and hematopoietic elements resembling bone marrow. They constitute approximately 2,5% of all primary adrenal gland tumours. They are usually unilateral with regular borders and variable in size. We aimed to review these cases we encounter in our daily practice.
Methods: All the patients with adrenal myelolipomas who were operated in our hospital between January 2008 and July 2018 were evaluated retrospectively. Demographic characteristics, size, laterality and other associated lesions were recorded.
Results: A total of 21 adrenal myelolipoma cases were detected, accounting for 4,9% of all adrenal lesions. Sixteen (76,2%) of the cases were female and 5 (23,8%) were male. The mean age was 50,4 (23-70). While 15 (71,4%) of the cases were localized in the right adrenal gland, 6 (28,6%) were localized on the left side. The mean diameter of the lesions was 6 (1-17) cm. The most common accompanying lesion was adrenal cortical adenoma with 3 cases, followed by adrenal hyperplasia, adrenal endothelial cyst and pheochromocytoma with 1 case. Macroscopically, the lesions consisted of whitish, fibrotic areas within mature adipose tissue-like areas. Histopathologically, the dominant component was lipoma in the majority of cases.
Conclusion: Adrenal myelolipomas are very rare lesions, often seen as small tumoural foci accompanying other tumours or as space-occupying masses alone. Although these tumours do not need to be removed in the treatment because there is no mass effect, we have reviewed all of the cases we have encountered since they are observed more frequently than expected.

PS-22-002

The evolving understanding of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) - lessons from surgical pathology and cytopathology series from Asia

A. Bychkov[1], C.K. Jung[2,3], H. Vuong[4], Z. Liu[5], K. Kakudo[6]
[1] Department of Pathology, Kameda Medical Center, Kamogawa City, Chiba, Japan, [2] Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3] Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [4] Department of Pathology, University of Yamanashi, Chuo, Yamanashi, Japan, [5] Department of Pathology, School of Basic Medical Sciences, Cheeloo College of Medicine, Shandong University, Shandong, China, [6] Department of Pathology, Kindai University Nara Hospital, Japan

Background & Objectives: The introduction of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was initiated by pathologists. The Asian Working Group (WG) in Thyroid Pathology performed several NIFTP projects based on data collected from Japan, Korea, China, India, and several ASEAN countries. The original surgical pathology (26,604 thyroid cancers) and cytopathology (11,372 thyroid nodules) series from the Asian WG and meta-analysis of existing literature are the core datasets of this study.
Methods: Our original data and the results of a meta-analysis suggest that the initial rate of NIFTP was overestimated, averaging 8.5% (95% CI 5.8–11.6%) of all thyroid cancers worldwide. We found that the incidence of NIFTP in the Asian cohorts (2.6%, 11 studies) is significantly lower than that reported in American (12.2%, 26 studies), European (11.5%, 9 studies) or combined non-Asian series (11.9%, 35 studies). We identified several contributing factors to such discrepancy.
Results: Difference in the prevalence is due to various histological diagnostic thresholds, different biology of tumours, and distinct management strategies (e.g., active surveillance for indeterminate nodules and NIFTP). The lower prevalence of NIFTP in Asia indicates a low impact on malignancy risk in cytopathology. Our original series and further meta-analysis (14 studies, 14,153 resected nodules) found decrease in risk of malignancy after NIFTP reclassification for most of the Bethesda diagnostic categories, which was more significant in Western than in Asian practice.
Conclusion: The incidence of NIFTP was higher in Institutions where surgical resection rates for cytologically indeterminate nodules were high ($r = 0.83$; $p = 0.02$). Recent Asian studies added new knowledge to aid a better understanding of NIFTP.

PS-22-003

Hyalinising trabecular tumour of the thyroid. A molecular study

J.M. Cameselle-Teijeiro[1], M. Sanchez-Ares[1], J. Caneiro-Gómez[1], T.Y. Rico-Rodríguez[1], R. Pèrez-Becerra[1], A. Vázquez-Boquete[1], I. Abdulkader-Nallib[1]
[1] Clinical University Hospital of Santiago de Compostela, Spain

Background & Objectives: Hyalinizing trabecular tumour (HTT) is a rare follicular derived neoplasm. The prognosis is extremely good with only very rare documented cases of distant metastasis. There is controversy surrounding its relationship with papillary thyroid carcinoma (PTC), and malignant potential. Since EWRS1 rearrangements have recently reported in PTC, and TERT promoter (TERTp) mutations are a major indicator of poor outcome in differentiated thyroid carcinomas, we investigate these alterations in a series of HTT.
Methods: Five cases of HTT were studied from 5 patients, 4 female and 1 male, with a mean age of 56 years (range 25-66). All the studies were performed on 4-ηm paraffin embedded tissue sections of HTT without histological or clinical data of malignancy. Fluorescence in situ hybridization (FISH) was carried out using Vysis EWSR1 Break Apart FISH Probe Kit (Abbott Molecular). Cases were considered positive for EWSR1 rearrangement when 5% or more of the nuclei with the break-apart signal were detected. Analysis of the presence of TERTp mutations (-124C>T and -146C>T) was performed by Sanger sequencing in a CEQ8000 Beckman Coulter Sequencer.
Results: No recurrence, metastases or death occurred in any of the patients followed during an average of 33.4 months (range 12-72). EWRS1 rearrangements were detected in the four cases tested (one case not tested for EWSR1). In only one of the five patients (a 66 year-old female) was a TERTp mutation (-124C>T) detected.
Conclusion: Our results suggest the participation of EWSR1 rearrangements in the tumourigenesis of HTT. TERTp mutations are not always associated with malignant tumours.

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PS-22-004

Eighteen-year history of medullary thyroid carcinoma at Centro Hospitalar Universitário de São João, Porto, Portugal (2000-2018)

T. Cardoso Lima da Costa Pereira[1], D. Pereira de Melo[1], J. Magalhães[1]
[1] Centro Hospitalar Universitário de São João, Portugal

Background & Objectives: Medullary thyroid cancer (MTC) is a neuroendocrine tumour of the parafollicular or C cells of the thyroid gland. Most MTCs are sporadic, however, approximately 25 percent are familial, mostly as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome. Also, in most patients, the disease was already metastasized at the time of diagnosis. We wanted to compare the experience in our Instituteion with the literature and determine how many cases were sporadic, which were associated with MEN2 syndrome and how many had metastases at the time of diagnosis.
Methods: All cases with diagnosis of MTC registered in our center, from 2000 until 2018, were collected for review and the following variables were analysed: gender, age at diagnosis, size of primary tumour, presence of RET germline mutation and presence of lymph node metastasis.
Results: A total of thirty-nine cases were reviewed (n=39), twenty-two were female, the mean age was 57,22 years. Average tumour size was 21,26 mm. Six cases had RET mutation (n=6) and ten had lymph node metastasis (n=10).
Conclusion: An eighteen-year review at our center demonstrated that most MTC occurred in female patients and were neither associated with MEN2 syndrome or with lymph node metastasis.

PS-22-005

Surgical treatment of adrenal gland metastasis: a single centre experience

S. Cerovic[1], B. Kovacevic[1], V. Skuletic[1], J. Dzambas[1], D. Mikic[1]
[1] Military Medical Academy, Serbia

Background & Objectives: Adrenal glands (AG) are often the site of various malignant metastases, especially lung, breast, melanoma, gastrointestinal and kidney cancer. In 30%-70% of patients, changes in AG represent incidental findings – incidentalomas, as there is usually unknown primary malignancy. The average period between diagnosis of malignancy and the metastases occurring in AG is about 2.5 years
Methods: In 205 patients treated in Military Medical Academy in 2004-2018, adrenalectomy and/ or adrenalectomy with nephrectomy (due to renal cell cancer- RCC) were performed. The basic macroscopic and microscopic parameters were analysed. From the clinical and pathohistological protocols, the time from the beginning of the primary malignancy treatment to the adrenalectomy has been established. Statistical analysis was done in the IBM SPSS 24.0 software program, with statistical significance for values $p<0.05$.

Results: AG metastases were diagnosed in 37 (17.96%) patients, and 54.05% were incidental. Statistically significant difference in AG mass was in patients with RCC compared to other malignancies ($p<0.002$). RCC metastases were the most common, 43.24%, and 35.13% patients were with lung cancer (LC) metastases. Among 17 (47.95%) patients with treated malignancies, adrenalectomy was done averagely after 14.71 months. The shortest time for the occurrence of AG metastases was related to LC statistically significant ($p=0.00131$).
Conclusion: The results of our analysis show that over 50% of patients with unknown primary malignancies have diagnosed metastases in AG. The high prevalence of metastases in AG in patients with known extrarenal malignancies of 47.95% indicates the need for intensive clinical monitoring.

PS-22-006
Genomic landscape of pulmonary carcinoids with high grade progression

J. Cros[1], N. Thèou-Anton[2], V. Gounant[2], R. Nicolle[3], C. de Reyes[4], A. Guyard[2], L. de Mestier[5], S. Brosseau[2], Y. Castier[2], D. Gentien[4], P. Ruszniewski[5], G. Zalcman[2], A. Couvelard[2], A. Cazes[2]
[1] Beaujon University Hospital / Pathology Dpt, France, [2] APHP- Bichat University Hospital, France, [3] CIT - Ligue Contre le Cancer, France, [4] Institute Curie, France, [5] APHP- Beaujon University Hospital, France

Background & Objectives: High grade lung carcinoids have been recently reported. While they appear to be the thoracic counterparts of grade 3 neuroendocrine tumours of the digestive tract, there is no molecular data on such lesions. We aimed to study their genetic landscape including analysis of tumoural heterogeneity.
Methods: Six patients with a high grade (>20% Ki-67 and/or >10 mitoses) thoracic carcinoid were included. We analysed copy number variations, somatic mutations and protein expression in 9 tumour samples (2 samples in 3 patients allowed to study spatial/temporal heterogeneity).
Results: We identified most frequent loss of chromosome 13 (5/6 tumours), 11 (4/6 tumours) and 3 (4/6 tumours). LOH of tumour suppressor genes involved different pathways including chromatin remodelling (*POLQ, ATR, ARID1A, SETD2, SMARCA2, BAP1, PBRM1, KAT6A*), DNA repair (*MLH1, ATM*), cell cycle (*RB1, TP53, LATS2, CDKN2A, CTNNB1, GSK3B*), metabolism (*MEN1, VHL*). We found somatic mutations of *ARID1A* in one tumour and of *ATM* in another tumour. Comparison of low/high grade areas and of initial/recurrent tumours identified an additional mutation of *RB1* in high grade area in a patient; an additional heterogeneous deletion of chromosome 17 with loss of TP53 and a new fusion transcript (EIF3E-RSPO2) in recurrent tumour in another patient; a *TP53* mutation with an additional homozygous deletion of *RB1* and loss of Rb protein expression in the high grade area of a third patient.
Conclusion: These data confirm the importance of chromatin remodelling genes in pulmonary carcinoids and highlight the potential role of TP53 and RB1 to drive the transformation in more aggressive high grade tumours.

PS-22-007
Histopathological features in risk stratification of phaeochromocytoma and paraganglioma patients - comparison of the PASS and GAPP score

J. Dušková[1], Z. Musil[2], K. Novák[3], D. Michalský[3], T. Zelinka[3]
[1] 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2] 1st Fac.of Medicine, Czech Republic, [3] 1st Fac. of Medicine, Czech Republic

Background & Objectives: To compare the two risk stratification systems: PASS (Phaeochromocytoma of the Adrenal Gland Scaled Score) and GAPP (Grading System of Adrenal Phaeochromocytoma and Paraganglioma) evaluated in parallel in a subgroup of patients of a large ongoing study.
Methods: Phaeochromocytomas from 60 patients operated in 2014-19 and examined in parallel by both evaluation systems.
The group of patients monitored over the five-year period was gender-balanced (M28 / F32).
The mean age at diagnosis was 52 years with a wide range (22-79); the average tumour size (by largest dimension) was 59 mm. These characteristics did not differ significantly by gender. Side representation was without obvious predilection.
We used image analysis to accurately assess tumour proliferation activity and tumour cellularity.
Results: In the PASS score, only a small proportion of tumours were below the arbitrary threshold of minimal risk of malignancy, these tumours were slightly more frequent in men (PASS <4 [%]: ALL 11.6; M 17.8; F 6,25).
The mean GAPP score was 3.15 (0-9) with no significant gender difference (M 3,39 (0-9); F 2,94 (1-8)). The vast majority of tumours in this scoring system were well and moderately differentiated.
There were no major categorization differences between the two systems.
Conclusion: In a time-defined probe of 60 patients, we did not find significant differences in the use of PASS and GAPP score in stratification of morphological risk. We prefer GAPP score for a broader definition including extraadrenal paragangliomas. The advantage is lower number of evaluated parameters. The inclusion of functional assessment in the GAPP score links the clinical-morphological evaluation of patients.

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PS-22-010
Clinicopathological features of Warthin-like papillary thyroid carcinoma: a case series from a tertiary center

B. Güçlüer[1], T. Soylemez[1], G. Kir[1], A.I. Ozemir[2], I. Akalın[3]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, Department of General Surgery., Turkey, [3] Istanbul Medeniyet University, Head, Department of Medical Genetics, Turkey

Background & Objectives: The Warthin-like variant of papillary thyroid carcinoma (WLPTC) is a rare variant of papillary thyroid carcinoma. The aim of the study was to analyse the clinicopathological characteristics of Warthin-like papillary carcinoma of the thyroid gland.
Methods: A total of 176 patients underwent surgical treatment and were histologically confirmed to have papillary thyroid carcinoma (PTC) at Goztepe Training and Research Hospital between 2017 and 2019. Of these, 5 (3%) were diagnosed as WLPTC and 4 patients (2%) had varying proportions of Warthin-like features. Demographic features, gross and microscopic findings were recorded. Mutation analysis of KRAS, NRAS and BRAF genes was studied in seven cases.
Results: Median patient age was 47years (range: 25–74 years). All cases were female (100%). Mean tumour size was 14.4 mm (range: 8–21 mm). Lymphovascular and perineural invasion was noted in one case and only lymphovascular invasion was detected in another case. Ipsilateral central neck lymph node dissection was performed in two cases and lymph node metastasis was detected in one case. Extrathyroidal extension was not observed. All of them associated with lymphocytic thyroiditis (100%). Multifocal tumours were found in seven cases. The BRAF mutation detected in four patients, KRAS mutation was present in two patients and one patient has both BRAF and NRAS mutation.
Conclusion: The WLPTC is an uncommon subtype of papillary thyroid carcinoma. In the current small series WLPTC has similar histopathologic features to classic papillary carcinoma.

PS-22-011

Comprehensive DNA methylation profiling identifies novel diagnostic biomarkers for thyroid cancer

C.K. Jung[1,2], J. Park[3,4,5], S. Jeon[6], E. Seo[3,4], D.H. Bae[3,4], Y.M. Jeong[7], Y. Kim[1], J.S. Bae[8], S. Kim[5] and Y.S. Kim[3,4]

[1] Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2] Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3] Genome Editing Research Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon, Republic of Korea, [4] Department of Functional Genomics, University of Science and Technology, Daejeon, Republic of Korea, [5] Personalised Genomic Medicine Research Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon, Republic of Korea, [6] Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Republic of Korea, [7] Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [8] Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background & Objectives: There are no reliable biomarkers to accurately differentiate indolent thyroid tumours from more aggressive thyroid cancers. This study aimed to develop new DNA methylation markers for diagnosis and recurrence risk stratification of papillary thyroid carcinoma (PTC).

Methods: Thyroid tumour-specific DNA methylation profiling was investigated in 34 fresh frozen tumour tissues which included non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP, n = 11) and PTC (n = 23), using the Illumina Human EPIC array. We performed a genome-wide assessment of thyroid tumour-specific differentially methylated CpG sites, then validated the top candidate markers in 206 paraffin tissue samples comprised of follicular adenomas (n = 46), NIFTPs (n = 57), and PTCs (n = 103), by pyrosequencing.

Results: Three selected markers differentiated non-malignant (NIFTP and follicular adenoma) tumours from PTCs with area under the Receiver Operating Characteristic (ROC) curve of 0.88, 0.88 and 0.87, respectively. PTC patients with low DNA methylation levels of two or three markers more frequently had tall cell variants, extrathyroidal extension, lymph node metastasis, *BRAF* V600E mutations, and high recurrence risk than those with low levels of zero or one methylation marker. All patients who developed disease recurrence had low DNA methylation levels for three markers.

Conclusion: DNA methylation levels of three markers can be useful for differentiating PTC from non-malignant follicular thyroid lesions, and for selecting high-recurrence risk PTC patients.

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PS-22-013

Increased oxyphil cell ratio, parathyroid gland volume and weight correlate with the localisation of parathyroid adenoma on Technetium-99m MIBI scintigraphy scan

E.T. Durmuş[1], M. Kefeli[2], D. Bayçelebi[2], A. Atmaca[1], R. Çolak[1], C. Polat[3], O. Mete[4,5,6]

[1] Department of Endocrinology and Metabolism, Ondokuz Mayis University, Samsun, Turkey, [2] Ondokuz Mayıs University, Department of Pathology, Turkey, [3] Department of General Surgery, Ondokuz Mayis University, Samsun, Turkey, [4] Department of Pathology, Laboratory Medicine Program, University Health Network, Toronto, Canada, [5] Department of Laboratory Medicine & Pathobiology, University of Toronto, Canada, [6] Endocrine Oncology Site, The Princess Margaret Cancer Centre, Toronto, Canada

Background & Objectives: Technetium-99m MIBI Parathyroid Scintigraphy (Tc-Scan) has been used to localize abnormal glands in patients with primary hyperparathyroidism (PHPT). This series aimed to identify the biochemical and histopathological correlates of Tc-Scan findings in patients with parathyroid adenomas.

Methods: A total of 378 patients with parathyroid adenoma were included. The results of Tc-Scan, histopathological (gland volume, weight, oxyphil cell ratio) and biochemical (blood and 24 hr urine calcium, creatinine and GFR, PTH, ALP, vitamin D3) variables were recorded. Positive Tc-Scan status was referred to adenomas that were localized. A cut-off of 30% is applied to define adenomas with low (<30%) and high (≥%30) oxyphilic cell content. Statistical analyses were performed to assess the relationship among variables.

Results: Tc-Scan localized the abnormal gland in 306 patients. Parathyroid gland volume and weight, and oxyphil ratio were significantly higher in Tc-Scan positive group. Among the biochemical variables, only PTH was found to be significantly increased in Tc-Scan positive group. Binary logistic regression models identified statistically significant cut-offs for the gland volume (1700 mm^3), gland weight (1.3 gr) and PTH levels (170 pg/ml) that can be used to predict Tc-Scan positivity.

Conclusion: In addition to PTH levels, this series underscored the impact of cellular composition along with gland volume and weight in the prediction of Tc-Scan positivity in patients with uniglandular benign parathyroid disease.

PS-22-014

Prevalence of papillary thyroid carcinoma is significantly higher in Graves' disease with synchronous nodular thyroid tissue

M. Kefeli[1], H. Gücer[2], E.T. Durmuş[3], A. Atmaca[3], R. Çolak[3], O. Mete[4,5,6]

[1] Ondokuz Mayıs University, Department of Pathology, Turkey, [2] Department of Pathology, Recep Tayyip Erdogan University, Rize, Turkey, [3] Department of Endocrinology and Metabolism, Ondokuz Mayis University, Samsun, Turkey, [4] Department of Pathology, Laboratory Medicine Program, University Health Network, Toronto, Canada, [5] Department of Laboratory Medicine & Pathobiology, University of Toronto, Canada, [6] Endocrine Oncology Site, The Princess Margaret Cancer Centre, Toronto, Canada

Background & Objectives: The role of autoimmunity-related tissue injury in development of thyroid cancer remains an area of interest. Evidence suggests that patients with Graves' disease may have an increased risk for differentiated thyroid cancer. Multicenter studies are needed to gain insights into the correlates of papillary thyroid carcinoma (PTC) identified in this particular group of patients. This study investigated the prevalance of PTC and synchronous thyroid nodules in thyroidectomy specimens of Graves' patients originating from an endemic goiter region.

Methods: A retrospective review of Institutional pathology records at two tertiary-care centers identified 173 surgically treated Graves' patients. Patients were grouped as GN when coexistent nodular thyroid was noted, and those with no synchronous thyroid nodules were grouped as G. The prevalence of PTC and its histopathological correlates, and demographic characteristics were recorded. These were compared between groups GN and G.

Results: Ninety-five and seventy-eight patients were assigned to groups GN and G. The mean age was significantly higher in group GN when compared to group G. The overall frequency of PTC was 31% (53/173). The rates of PTC were 45% (43/95) and 13% (10/78) in groups GN and G($p<0.0001$). Papillary microcarcinomas accounted for around 80% of all PTCs in both groups. Group G was enriched in BRAF-like tumours whereas group GN had a balanced RAS- and BRAF-like tumours.

Conclusion: This series underscored most PTCs encountered in patients with Graves' disease are papillary microcarcinomas. Furthermore, the biology and prevalence of PTC vary depending on the presence of underlying nodular thyroid tissue.

PS-22-015

IGF-1 splice variants' expression in adrenal gland neoplasms - possible role in adrenal tumourigenesis

G. Kyriakopoulos[1], N. Nasiri-Ansari[1], A. Angelousi[2], A. Philippou[3], A. Karapanagioti[1], G. Zografos[4], C. Aggeli[4], T. Choreftaki[5], D. Tiniakos[6,7], D. Rontogianni[8], G. Dimitriadis[9], G. Kaltsas[10], A.G. Papavassiliou[1], E. Kassi[1,2]

[1] Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Greece, [2] 1st Department of Internal Medicine, Laiko University Hospital, National and Kapodistrian University of Athens Medical School, Greece, [3] Department of Physiology, Medical School, National and Kapodistrian University of Athens, Greece, [4] 3rd Department of Surgery, General Hospital of Athens "G. Gennimatas", Greece, [5] Department of Pathology, General Hospital of Athens "G. Gennimatas", Greece, [6] Department of Pathology, Aretaieion Hospital, National and Kapodistrian University of Athens Medical School, Greece, [7] Institute of Cellular Medicine, Newcastle University, United Kingdom, [8] Department of Pathology, Evaggelismos Hospital, Athens, Greece, [9] Division of Translational and Experimental Medicine-Metabolic and Vascular Health, Warwick Medical School, University of Warwick, Coventry, United Kingdom, [10] 1st Department of Propaedeutic Internal Medicine, Laiko University Hospital, National and Kapodistrian University of Athens Medical School, Greece

Background & Objectives: IGF-1Ea, IGF-1Eb and IGF-1Ec isoforms are differentially regulated in neoplasms. Moreover IGF-1Ec and IGF-1Eb overexpression has been positively associated with cell survival and proliferation in tumourigenesis. We aimed to examine the expression of IGF-1 isoforms in human adrenocortical carcinomas (ACCs), adrenocortical adenomas (ACAs), pheochromocytomas(Pheo) and compare to normal adrenal gland(NAG). Additionally, we investigated the role of IGF1-Ec and IGF1-Eb peptides in ACC cells proliferation/migration.
Methods: The mRNA and protein levels of IGF-1 isoforms were evaluated by qPCR and immunohistochemistry respectively. SW-13, H295R cells were incubated with IGF-1Ec and IGF-1Eb peptides. Cell proliferation and scratching assays were performed.
Results: IGF-1 isoforms mRNA levels were increased in adrenal cortex neoplasms compared to medulla. Additionally, the mRNA levels of IGF-1Ec and IGF-1Eb were significantly higher in ACCs as compared to ACAs. Immunohistochemistry revealed that 100%of ACCs, 73.3%of ACAs and 70%of NAGs expressed IGF-1Ec, 67% of ACCs, 25% of ACAs and 75% of NAGs expressed IGF-1Eb. IGF-1Ea was detected only in ACCs (58%) and ACAs (66%). IGF-1Eb protein expression levels were higher while IGF-1Ec expression levels were reduced in NAGs compared to ACCs. No IGF-1 isoforms were detected in the Pheo. A borderline negative correlation between IGF-1Eb protein levels and IGF-1Eb/IGF-1Ea ratio with Ki-67 was observed in ACCs. Incubation of SW-13 and H295R cells with IGF-1Ec resulted in a significant increased in cell proliferation and migration.
Conclusion: Expression of IGF-1Ec is related to malignant behaviour of adrenal neoplasms. IGF-1Ec appears to play a causative role while higher expression of IGF-Eb may have a protective effect in ACC tumourigenesis.

PS-22-016

May lesion size impact recognition of biologically aggressive non-invasive follicular thyroid neoplasm with papillary-like nuclear features? Meta-analysis

I. Laklouk[1], R. Fazeli[1], S. Cerda[1], R. Gedik[1]

[1] Boston University Medical Center, USA

Background & Objectives: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) represents a special cohort of encapsulated thyroid neoplasm that has been unanimously distinct as biologically indolent neoplasm. Lymph node/distal metastasis, however, occurs occasionally in these biologically indolent tumours. The impact of tumour size as risk factor of metastasis remain unknown. Therefore, this study aimed to determine impact of including sub-centimeter lesions under NIFTP entity on the reported prevalence of metastasis attributed to NIFTP based on systemic review followed by meta-analysis.
Methods: The literature search was conducted using Pubmed/MEDLINE databases searching for original NIFTP articles up until Feb 2019. A proportion meta-analysis calculation was used to obtain the pooled prevalence of the adverse event (lymph node and/or distal metastasis) in lesion size subgroups (sub-centimeter, centimeter and larger, or both). Using the random-effects model to pool weighted proportions were reported with stander error (SE), and 95% confidence intervals (CI). The significant the heterogeneity was defined as an I^2 >50%.
Results: Ultimately, 16 studies were included for meta-analyses, 44/1361 (3.2%) NIFTPs had adverse events. In 8 studies included sub-centimeter lesions, 35/800 NIFTPs associated with metastasis compromised 2% [CI 0%-6%] pooled prevalence with significant heterogeneity (I^2 80%, p<0.001). 6 studies excluded sub-centimeter lesions, 8 /494 NIFTPs with the adverse events with negligible pooled prevalence of metastasis [CI 0%-2%] without the heterogeneity (I^2 49.81%, p=0.06). Two studies evaluated only sub-centimeter lesions, 1/60 lesions had metastasis, with negligible pooled prevalence [CI 0%-3%].
Conclusion: Among the majority of "indolent" NIFTP, lymph node/distal metastasis occurs occasionally at 3.2 %. The pooled prevalence of metastasis was negligible in the studies excluded sub-centimeter lesions compared to 2% in the others included sub-centimeter lesions. Further risk factors studies should be conducted to evaluate the utility of establishing size criteria to predict a higher possibility of biologically aggressive NIFTP.

PS-22-017

PD-L1 expression in normal endocrine tissue

T. Neuman[1], M. Kagan[1], R. Dresner-Pollak[1], R. Pollack[1]

[1] The Hebrew University - Hadassah Medical Center, Jerusalem, Israel

Background & Objectives: Immune checkpoint inhibitor (ICI) therapy, including cytotoxic T-lymphocyte-associated protein 4 (CLTA-4) and programmed cell death 1 (PD-1) inhibitors, is revolutionizing cancer treatment. However, these agents are associated with immune-related adverse events (irAEs), most commonly endocrine-related. Hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus and primary adrenal insufficiency have been reported as irAEs due to ICI therapy. The reasons why endocrine irAEs are so common in ICI treatments are unkonwn. In this study, we evaluated patterns of programmed cell death ligand 1 (PD-L1) expression in normal endocrine tissues to determine whether increased expression may explain the predilection of endocrinopathies in patients treated with PD-1 inhibitors.
Methods: Immunohistochemical (IHC) analysis using the Ventana 22C3 PD-L1 IHC platform was performed on normal thyroid, parathyroid, adrenal and pancreatic FFPE endocrine tissue samples stored in our hospital pathology tissue archive. Pituitary tissue samples were obtained from non-functioning pituitary adenomas.
Results: Five samples from each organ including pituitary, thyroid, parathyroid, adrenal and pancreas were examined.
Focal membranous PD-L1 positivity was noted in the pituitary adenomas consistent with previous data, but was negative in normal thyroid, parathyroid, adrenal and pancreatic tissues.
Conclusion: The majority of normal endocrine tissues do not demonstrate increased PD-L1 expression.
Our preliminary data so far does not support the hypothesis that increased PD-L1 expression in endocrine tissues is associated with endocrine irAEs following anti PD-1 therapy. The increased predilection of endocrinopathies in patients treated with anti PD-1 inhibitors seems to be via alternate pathways.

PS-22-018

The use of FTIR spectroscopy for search of a biomolecular pattern differentiating adrenal gland tumours

M. Ulatowska-Białas[1], J. Dudała[2], K. Okoń[1]
[1] Jagiellonian University, Collegium Medicum, Chair of Pathomorphology, Poland, [2] AGH University of Science and Technology, Faculty of Physics and Applied Computer Science, Poland

Background & Objectives: In recent years, there has been a growing interest in the FTIR microspectroscopy as a complementary diagnostic method. Investigations are carried out to find biomolecular markers of pathological states, including neoplastic changes. For method validation the wide-range population studies should be done. In case of rare disease it would be convenient to use the formalin-fixed paraffin-embedded (FFPE) tissue samples. In presented study we tried to explore the possibilities of using the archival deparafinized cortical part of adrenal gland tissue samples.
Methods: An archival FFPE tissue samples (5 normal adrenal cortex - N, 8 adrenocortical adenoma - ACA, 8 adrenocortical carcinoma - ACC) were used (approval number KBET/113/B/2014). The Fourier Transformed Infrared Spectroscopy (FTIR) was applied in the measurements. To avoid the interference from paraffin on IR spectra, samples were de-waxed under standard local histological protocol. The averaged spectra for each group were used for general comparison. The spectra second derivative were used to determine the main absorption bands as well as to perform the semi-quantitative analysis of the biomolecular composition. The non-parametric Mann-Whitney U test was used for statistical analysis.
Results: The analysis was based on the "fingerprints" spectral region 1710 – 900 cm-1. The main absorption bans were find at around ~1643 cm -1, 1537 cm -1, 1454 cm -1, 1394 cm -1, 1310 cm-1, 1237 cm-1 as well as between 1180 and 1140 cm-1. The differences in the position of the dominant absorption band within the 1700-1600 cm -1 spectral range of amide I were find. The biggest difference were found within the region 1135 - 980 cm -1 (attributed to carbohydrates and nucleic acids).
Conclusion: The presented results show that it is possible to compare IR spectra of the deparaffinised samples from adrenal gland tissues but the differences are not so evident. The spectral region which could be taken into differentiation procedure is connected with absorption band attributed to DNA (1237 cm -1) and the whole massif related mainly with carbohydrates between 1130 and 980 cm -1.

PS-22-019

Biologic significance of Insulinoma-associated protein 1 (INSM1) expression in medullary thyroid carcinoma

O. Semerci[1], H. Gucer[1], D. Baycelebi[2], M. Kefeli[2], O. Mete[3,4,5]
[1] Recep Tayyip Erdogan University, Department of Pathology, Turkey, [2] Ondokuz Mayıs University, Department of Pathology, Turkey, [3] Department of Pathology, Laboratory Medicine Program, University Health Network, Toronto, Canada, [4] Department of Laboratory Medicine & Pathobiology, University of Toronto, Canada, [5] Endocrine Oncology Site, The Princess Margaret Cancer Centre, Toronto, Canada

Background & Objectives: Clonal tumour progression can lead disruption of cellular differentiation in malignancy. INSM1is a transcription factor implicated in neuroendocrine differentiation and has been shown to be positive in various neuroendocrine neoplasms including medullary thyroid carcinomas (MTCs). However, the impact of INSM1 in the biology of MTCs remains largely unknown. This study aimed to investigate the biological significance of INSM1 expression in MTCs by comparing its expression profile with conventional clinicopathological parameters.
Methods: Thirty-six MTCs were stained with INSM1 (Clone A-8, 1:200 dilution, 37°C, 30 min. incubation, Santa Cruz) and assessed using an automated image analysis nuclear algorithm. A histoscore (H-score) (max: 300) was given to each tumour based on an integrated formula [H-score = 1×(1+ cells%) + 2×(2+cells%) + 3×(3+ cells%)]. The H-scores were correlated with clinicopathological parameters including age, gender, tumour size and multifocality, angioinvasion, lymphatic invasion, perineural invasion, extrathyroidal extension, nodal metastasis, and tumour stage.
Results: All MTCs except one with a widely invasive growth were INSM1 positive. The mean H-score was 136.75±59.08 (range: 0-251.24). Among clinicopathological variables, angioinvasion (mean: 94.8±53.3), extrathyroidal extension (86.4±43.3), and tumour multifocality (116.5±51.5) were associated with significantly reduced H-scores (p=0.001, p=0.038, p=0.039, respectively). While H-scores were decreased in tumours with advanced stage, this observation did not yield a statistical significance (p=0.067). There was no correlation with INSM1 and other variables.
Conclusion: Reduced nuclear INSM1 expression in a subset of MTCs with adverse histological features (angioinvasion and extrathyroidal extension) maybe due to cellular mechanisms that result in disruption of embryonic transcription of INSM1-mediated neuroendocrine differentiation in these tumours. Further translational studies are required to explore the underlying biology of INSM1 in neuroendocrine tumourigenesis.

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PS-22-020

Reassessing primary thyroid tumours according to the new WHO classification: A five-year retrospective study

S. Tzorakoleftheraki[1], C. Poulios[1], S. Arelaki[1], O. Kazarli[1], G. Karayannopoulou[1]
[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece

Background & Objectives: The latest WHO classification introduced new entities regarding follicular neoplasms with low risk of recurrence or metastasis. The scope of the present study was to reevaluate archival cases of primary thyroid tumours according to this classification, with emphasis on diagnoses that could modify the follow-up of the patients.
Methods: We retrieved cases of primary thyroid tumours from the archives of the Department of Pathology, Aristotle University of Thessaloniki, collecting a period of five years (2013-2017) prior to the incorporation of the latest WHO classification. We recorded the diagnosis along with complete histological data, including tumour size, presence of full capsule (with or without invasion), tumour architecture, cellular and nuclear features. The aim was to identify all the cases that would have a different diagnosis according to the new classification.
Results: A total of 518 cases of primary thyroid tumours were retrieved. We disclosed up to 15 cases that had a different diagnosis. These cases were encapsulated neoplasms, mostly with follicular architecture. The updated diagnoses included well-

differentiated tumour of uncertain malignant potential, non-invasive follicular thyroid neoplasm with papillary nuclear features and minimally-invasive follicular carcinoma.
Conclusion: The incorporation of new classification systems reflects the ongoing changes in patient management, which in this case is based on the histopathological report, making it essential for pathologists and clinicians to be up-to-date with the latest WHO classification.

PS-22-021
PD-1 and PD-L1 expression in pulmonary carcinoid tumours
T. Vesterinen[1], T. Kuopio[2], M. Ahtiainen[3], A. Knuuttila[4], K. Salmenkivi[1], H. Mustonen[5], J. Arola[1], C. Haglund[5]
[1] HUSLAB, Department of Pathology, University of Helsinki and Helsinki University Hospital, Finland, [2] Department of Biological and Environmental Science, University of Jyväskylä and Department of Pathology, Central Finland Health Care District, Finland, [3] Department of Education and Research, Central Finland Central Hospital, Finland, [4] Department of Pulmonary Medicine, Heart and Lung Center, and Cancer Center, University of Helsinki and Helsinki University Hospital, Finland, [5] Department of Surgery, University of Helsinki and Helsinki University Hospital, Finland

Background & Objectives: Pulmonary carcinoid (PC) tumours are rare tumours that account for approximately 1% of all lung cancers. The primary treatment option is surgery, while there is no standard treatment for metastatic disease. As the number of PCs diagnosed yearly is increasing, there is a need to establish novel therapeutic options for these patients. This study aimed to investigate programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) in PC tumours since blocking of the PD-1/PD-L1 pathway is a promising therapeutic option in various other malignancies.
Methods: A total of 125 consecutive PC patients operated on in the Helsinki University Hospital between 1990 and 2013 were included. Patient records were retrospectively reviewed. Expression of PD-1 and PD-L1 was evaluated immunohistochemically and correlated with clinical parameters.
Results: After re-evaluation of the tumours, 93 (74%) were classified as typical carcinoid (TC) and 32 (26%) as atypical carcinoid (AC) tumours. Expression of PD-1 was detected in 7% of the tumours. PD-L1 expression was detected in 8% of TC tumours; all AC tumours were PD-L1 negative. PD-L1 expression was associated with mediastinal lymph node metastasis at the time of diagnosis (P=0.014). Neither PD-1 nor PD-L1 expression was associated with survival.
Conclusion: Our data suggest that PD-1/PD-L1 is expressed in 7-8% of PC tumours. PD-L1 expression seems to be associated with increased malignancy. Thus, targeting of the PD-1/PD-L1 pathway may offer a treatment option for a small subset of PC patients.

PS-22-022
Association of thyroid pathology to primary hyperparathyroidism requires complex investigations prior to treatment
O. Vita[1], A. Văduva[1], R. Cornea[1,2], C. Lăzureanu[1,2], A. Mureşan[1,2], G. Oprişan[2], M. Iacob[2], E.G. Olteanu[1], I. Golu[3], M. Cornianu[1,2]
[1] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [2] Department of Pathology, Emergency County Hospital Timişoara, Romania, [3] Department of Endocrinology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania

Background & Objectives: Primary hyperparathyroidism (PHPT) is often accompanied by thyroid pathologies. Nowadays, there is an increased rate of performing minimally invasive parathyroidectomy, thus thyroid diseases can be missed.
Methods: We performed a retrospective histopathological study on PHPT cases diagnosed between 2011 and 2018 at the Emergency County Hospital Timisoara, Romania. We aimed to assess the rate of concurrent PHPT and thyroid diseases.
Results: We identified 66 cases of PHPT (54 women and 12 men, mean age 54.16) diagnosed as: 39 adenomas, 1 carcinoma, 25 nodular hyperplasia, 1 nodular hyperplasia associated with parathyromatosis. 30/66 (45.45%) cases presented associated thyroid pathologies: 17/66 (25.75%) nodular and diffuse goiters, 1/66 Basedow disease (1.51%), 8/66 (12.12%) carcinomas (1 isolated papillary microcarcinoma, 6 papillary microcarcinomas associated with nodular goiter and 1 papillary carcinoma – follicular variant), 2/66 (3.03%) follicular adenomas and 2/66 (3.03%) autoimmune lymphocytic thyroiditis.
Conclusion: The association between PHPT and thyroid pathologies is not uncommon in our study group. Therefore, in the case of minimally invasive parathyroidectomy, the possibility of coexisting thyroid pathology should be considered and steps towards its diagnosis must be taken.

PS-22-023
Predictive factors for recurrence in poorly differentiated thyroid carcinomas
E.-A. Zahan[1], A. Nechifor-Boilă[2], D. Piciu[3], A. Borda[4]
[1] Department of Histology, University of Medicine, Pharmacy, Science and Technology of Targu Mures, Romania, [2] Department of Histology, UMFST Târgu Mureş, Romania, [3] Department of Nuclear Medicine, "Ion Chiricuță" Institute of Oncology, Cluj-Napoca, Romania, [4] Department of Histology, UMFST Targu-Mures, Romania

Background & Objectives: Poorly differentiated thyroid carcinoma (PDTC) is a rare and aggressive tumour. The aim of our study was to assess the predictive factors for persistent-disease and recurrence of PDTC in our Institution.
Methods: We performed a retrospective study on 34 PDTC cases from the Department of Pathology, Targu-Mureş Emergency County Hospital between 1990-2015. Pathological data were retrieved from database registers and pathological reports, whereas follow-up data were obtained from the Department of Nuclear Medicine, "Ion Chiricuță" Institute of Oncology, Cluj-Napoca.
Results: In our study the prevalence of PDTC was 3,9% (34 PDTCs/869 thyroid cancers). All patients were treated by total thyroidectomy followed by ^{131}I ablation. The mean follow-up period was 75 months (available data for 25 cases). At the last clinical assessment, the disease-free survival-rate at 5 years was 83% and the 5-year recurrence-free survival was 48.3% By univariate and multivariate analysis, following risk factors were predictive for persistent disease and recurrence: age (older than 55 years-old) (OR) 5.97, p-0.001), tumour size ≥ 4mm (OR 9.97, p-0.001), extrathyroid extension (OR 12.66 p<0.005) and lymph node involvement (OR 17.66 p<0.005). This parameter influencing the disease-free survival rate. Six (28%) patients developed metastases (lung and bones), during the follow-up period.
Conclusion: PDTCs is an aggressive tumour, with high rates of persistent disease and recurrence. Age (older than 55 years-old), extrathyroid extension, lymph node involvement and tumour size ≥ 4 mm were found to be risk factors for recurrence. Careful clinical monitoring of patients with these factors for early detection of metastasis is necessary.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-23 | History of Pathology

PS-23-001
Professor Leo Taussig - an underestimated pioneer of complex investigation of cerebrospinal fluid
J. Dušková[1], O. Sobek[2]
[1] 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2] Topelex, s.r.o., Czech Republic

Background & Objectives: To trace back the history of CSF fluid knowledge and investigation.
Methods: Comprehensive review of international and national databases and archive materials. During the studies of cognition and the function of CSF, a large, 440 page, comprehensive monograph by Prof. Leo Taussig (1884 – 1944) published in Czech in 1926, was discovered. Its content represents a valuable resource and a basis for the tradition of complex CSF investigation still respected today.
Professor Taussig was a teacher of the Czech part of Charles University.
Results: Professor Taussig was an excellent specialist, healthcare organizer and chess player. He was unfortunately also Jewish. That is why his fate unfolded in the tragic times of the Protectorate of Bohemia and Moravia in the same way as the fate of the Jewish professor of the German part of Charles University in Prague, Oscar Fischer - the author of priority articles on dementia later called Alzheimer's. Neither man survived the Holocaust and their scientific work remained unfinished.
Conclusion: Leo Taussig's outstanding work printed in Czech remains unknown internationally. Cultivation of national culture and language should run in parallel with communicating outstanding works to the international scientific community. The problem of racial intolerance has regrettably not disappeared. Scientific and educational careers discontinued in such an untimely way serve as a warning sign of losses to the scientific community.

PS-23-002
50 shades of H&E: sexually transmitted diseases (STDs) in the pathology collection of Turin
L. Ferrari[1]
[1] Division of Pathology Cardinal Massaia Hospital Asti, Italy

Background & Objectives: The Pathology Collection of Turin houses around 300 wet specimens dating back to end of XIX century and beginning of the XX century. The Sexually Transmitted Diseases were really common in Turin at the time shown on the autopsy reports. The most common disease was surely syphilis both congenital and acquired. However HPV related infections were also widespread. The wet specimens of STDs cases in the Collection were selected to investigate these old diseases epidemiologically and morphologically.
Methods: The choice of the cases was based on the original diagnosis reported on the label. The most representative cases were sampled by conservative approach and a diagnostic re-evaluation with modern techiniques was performed.
Results: There are a total of 29 cases of STDs: 24 cases of tertiary syphilis, 4 cases related to HPV infections and a case of blenorrhagia. In the sampled cases the morphology allows the diagnostic re-evaluation. Immunohistochemistry showed incostant results but thanks to the positivity for Cytokeratin MNF 116 and p63 a case of vulvar "adenocarcinoma" was re-evaluated as squamous carcinoma, probably related to HPV infection.
Conclusion: The most common disease in this collection was syphilis. Some other STDs were present so as those related to HPV infection. The morphology of these diseases seems to be comparable to the modern one. The absence of preventive healthcare and of modern therapies often caused death even if these diseases were preventable and treatable.

PS-23-003
Pathological findings of the 1918-1920 Spanish influenza from the autopsy report of the University of Turin
L. Ferrari[1]
[1] Division of Pathology Cardinal Massaia Hospital Asti, Italy

Background & Objectives: The ancient catalogs kept at the Pathology Department of Turin report autopsies of all deceased in city hospitals. These reports describe the most relevant pathological findings and the final cause of death. An archive search was carried out to investigate the pathological findings of the Spanish flu from autopsy descriptions.
Methods: The cases with the diagnosis of "flu bronchopneumonia" were selected. Cases of " hemorrhagic bronchopneumonia" have also been selected since 1918. They were probably also due to the flu, although the initial censorship prevented mentioning it directly.
Results: The first case of flu was that of a 23-year-old male who died on 24th November 1918. There was a first pandemic wave between October 1918 and April 1919. Subsequently there are no reported cases until January 1920 which was the month with the greatest number of death, 16 in all. Among them only 4 people were over 40 years. The last reported case was that of a 22-year-old female who died on 7th February 1920.The reports describe a hemorrhagic bronchopneumonia, splenic reactive hyperplasia and blood congestion of kidney and liver. The report also show that there was no particular concern for post-mortem infectivity, in fact an autopsy was performed during the autoptic technique lessons.
Conclusion: The autopsy reports of the University of Turin confirm the prevalence of the Spanish flu in young people and the temporal distributions of deaths reflects the pandemic trend. The pathological findings are comparable to those described in the literature often referable to bacterial pneumonia following viral infection.

PS-23-004
Necropsy reports and anatomo-pathological observations from the archives of the grand ducal Medici family of Florence (16th-18th century)
R. Gaeta[1], V. Giuffra[1]
[1] University of Pisa, Italy

Background & Objectives: During the Renaissance and Early Modern Age, dissection began to be practiced for medico-legal purposes, in order to investigate the causes of death. In particular, during the 15th century evidences of autopsies performed by doctors on their private patients emerge. These dissections were requested by those families who can afford the expenses, in order to search the possible presence of hereditary diseases and to predispose a prevention and cure. The diffusion of this practice is attested also by the work of Antonio Benivieni (1443-1502), who is considered a pioneer of the pathological anatomy.
Methods: The extremely rich documentary archives of the Medici family, one of the most important family of the Italian Renaissance, report several description of necropsies carried out on the bodies of the members of the Grand Ducal family. It was possible to analyse the original documents and, in some cases, to compare them with

the skeletal remains studied during the exploration of the Medici tombs in the Basilica of San Lorenzo in Florence.
Results: The analysis of the autoptic reports offers important direct information on the autopsy practices performed by court surgeons of the members of an aristocratic class in a period comprised between the 16th and the first half of the 18th century, and allows in some cases also to propose a retrospective diagnosis on the diseases that afflicted the Medici.
Conclusion: The analysis of the documents relating to the autopsy investigations proves to be of great interest and importance. These archives are in fact a very valuable source of information about the state of health of past populations and reveal which diseases were present and how they were treated.

PS-23-005
Exhumation and anthropological study of the skeletal remains attributed to Liutprand, King of the Longobards (690 ca AD-744 AD)
R. Gaeta[1], S. Minozzi[1], A. Fornaciari[3], V. Giuffra[1], G. Riccomi[1], G. Fornaciari[1]
[1] University of Pisa, Italy, [2] Division of Paleopathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy

Background & Objectives: Liutprand, one of the greatest Longobard sovereign, was born in the early 90s of the 7th century and died in 744 at the age of about 55 years. According to the *Historia Longobardorum* of Paolo Diacono, he was King of Italy from 712 to 744.
Methods: We performed the exhumation and the anthropological study on the skeletal remains attributed to Liutprand in the Church of San Pietro in Ciel d'oro (Pavia, Italy). We selected bone fragments and two teeth in order to make imaging studies (CT and RX), 14C dating, chemical and molecular analyses.
Results: Anthropological examination highlighted the presence of bones attributable to at least three individuals. Most of the remains belonged to a robust male individual with an age to death between 40 and 50 years. We found a left tibia with the diaphysis completely enlarged due to a severe form of osteomyelitis. Bone repair is evident and the presence of a circular depression with a diameter of about 10 mm could represent the trace left by a pointed object that caused the perforation of the bone and the subsequent infection. 14C dating provide a range from 430 to 640 for the first subject, 600-770 for the second and 530-670 for the last male. Isotopic data show a rather high nutritional status for the time.
Conclusion: Currently it is not possible to define the identity of the three individuals for lack of archaeological data and for the fragmentary nature of the bones. The age of the subjects, the robust constitution and the nutritional data suggest a belonging to a middle-high social class devoted to war activity. Future molecular studies may reveal a degree of kinship between the individuals and clarify the identity of the subjects.

PS-23-006
The short history of non-existing procedure - teratological autopsy
J. Gulczyński[1], S. Goertz[2], W. Grajkowska[3], E. Izycka-Swieszewska[1,2]
[1] Department of Pathology and Neuropathology, Medical University of Gdansk, Poland, [2] Pathomorphology Department Copernicus Hospital, Gdansk, Poland, [3] Pathology Department The Children's Memorial Health Institute, Warsaw, Poland

Background & Objectives: The objective was to describe the type of autopsy, which though performed since ages, never had been distinguished as a separate entity and properly appreciated. Teratology as a term was introduced by Etienne Geoffroy Saint-Hilaire (1772-1844) and Isidore Geoffroy Saint-Hilaire (1805–1861) in the 19th century, but first images of deformed fetuses and newborns date around 15.000 years back. Hippocrates was one of the first trying to find the mechanisms and causes of different deformations. Despite all this long history the first noted autopsy concluded with a post mortem report dates from 1533. For several centuries it was rather performed as a curiosity than real anatomical and pathological procedure for medical and scientific research. Even today with subspecialties as molecular or neuropathological autopsy it is still put aside, though the demands to perform it, especially in most rare cases, are extremely high.
Methods: We performed critical review of the available articles and researches published in the databases (PubMed, Researchgate and Academia.edu) focusing on perinatal autopsies with reported deformations and malformations dating form the ancient to present times. The literature was confronted with personal experience of researchers from our team.
Results: The vast range of variations that can be found during the perinatal autopsy with deformations requires skills and knowledge far from the usual. In some cases the procedures are performed on such scale that magnifier may be applied. The post mortem reports are connected with perinatal counselling, but what is more important with consecutive decisions about parenting. Therefore it is even more appropriate to quote "Hic est locus ubi mors gaudet succurrere vitae" - this is the place (or case) where death gladly helps the living. What is more - it helps those who just might have the chance to be born in the nearest future.
Conclusion: The teratological autopsy should be distinguished as a separate subtype of post mortem examination with full stress on the technical skill demands and proper preparation to it.

PS-23-007
Unexpected heart dwellers
R. Henriques de Gouveia[1], T. Ferreira[2], L. Carvalho[3]
[1] INMLCF & FMUC & CHLO, Portugal, [2] FMUC, Portugal, [3] FMUC & CHUC, Portugal

Background & Objectives: Heart involvement by *Echinoccocus* is rare (0.02-2% or 0.5-3% in the worldwide literature), although – when present – may be responsible for relevant morbidity or mortality (namely arrhythmias, anaphylactic shock, sudden death). The authors present a specimen from an historical museum.
Methods: A liquid-fixed heart specimen from a 19th century European Pathology Museum was analysed.
Results: Multiple *Hydatid Cysts* were observed, involving / damaging various cardiac structures.
Conclusion: This presentation testify a type of zoonotic pathology in this European country in the 19th century and highlight the teaching mission of University Museums, since with globalization and interexchange programs, medical students/residents/young doctors may face diverse disease contexts – in their home country or abroad –, namely unexpected parasitosis.

PS-23-008
History of teaching pathological anatomy (pathology) at Moscow State University
P. Mailkov[1], N. Danilova[1], N. Oleynikova[1], N. Gaifullin[1], I. Mikhailov[1]
[1] Lomonosov Moscow State University, Russia

Background & Objectives: Pathology is a fundamental discipline that has traditionally been the bridge between science and medicine.

Pathology teaching is important discipline of the training of qualified MD specialists which is traditionally carried out in the departments of pathology of the Medical Faculties of classical Universities.
Methods: The collection of history data was carried out by archival search.
Results: The Moscow University was founded in 1755. Teaching of pathology began in 1769 (Veniaminov P.D.). Further development Pathology in Russia is associated with Polunin A.I., Klein I.F., Abrikosov A.I. In 1930, Medical Faculty was transformed into the 1stMoscow Medical Institute and to which university clinical campus builded in 1897 was transferred. Medical education in Moscow University was restored 62 years later (1992). Currently, a course of pathological anatomy is taught at the University Clinic on basis of Clinical Pathology Department.
Conclusion: The University Clinic has qualified specialists and modern equipment. Biopsy and surgical materials, modern histological, histochemical, immunohistochemical, molecular, genetic, ultrastructural methods are widely used both for education and science purposes which ensures the implementation of the unity of education, science and clinical practice.

PS-23-009
The history of research of placenta
T. Pavlova[1], A. Selivanova[1], A. Kaplin[1], A. Nesterov[1], L. Zemlianskaia[1]
[1] Belgorod State University, Russia

Background & Objectives: The history of research of placenta is important aspect in obstetrics
Methods: Work with archive, materials, textbooks and monographs
Results: The first mention of placenta was revealed in archives of Egyptian pharaoh Amenhotep IV. T. Langhans explored histological structure of placenta and the microscopic period of placenta's research was begun. Active research of this organ was in the end of XIX century (Schatz F., V. Becker Bar P., Wilson T.). The ultramicroscopic period in the research of placenta begun in the second part of XX century. The separate science called "placentology' was formed.
Conclusion: The study of placenta allows to make a basis for correct diagnosis, correction and treatment of pathological conditions in obstetrics for preservation.

PS-23-010
Renal stone disease in an XVIII century mummy from Popoli, central Italy
L. Ventura[1], A. Fornaciari[2], A. Calabrese[3], L. Arrizza[4], G. Fornaciari[2]
[1] Division of Pathology, San Salvatore Hospital, L'Aquila, Italy, [2] Division of Paleopathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy, [3] Division of Radiology, Santissima Trinità Hospital, Popoli, Italy, [4] Centre of Microscopies, University of L'Aquila, Italy

Background & Objectives: A natural, well-preserved mummy belonging to an anonymous 35-40 years old male was found in a crypt beneath the Church of the Holy Trinity in Popoli, central Italy. Fine clothes and burial location suggested high social status and an important role in the church community. Probably, he was a nobleman, member of the congregation of the Holy Trinity. Artifacts helped in dating back the individual to the early 1800's.
Methods: The body was secured to a cardboard layer by a plastic film and recovered from the crypt to be submitted to visual inspection, X-ray examination, and CT scanning. A left abdominal stone was removed by videoendoscopy and investigated with binocular stereomicroscopy, microcomputed tomography, scanning electron microscopy with microanalysis, and X-ray diffraction analysis.
Results: The ovoidal mass measured 22x16x15 mm. External surface showed small superficial spherical buds, whereas internal structure detail revealed a central nucleus of sharp-edged crystals and concentric laminations of similar density values. Chemical elements were: C, O, N, Ca, P, K, S, Cl, Na with different distribution within inner and outer surfaces of the stone. Compositional analysis revealed calcium oxalate monohydrate (whewellite) (90%) and calcium phosphate (hydroxylapatite) (10%).
Conclusion: The stone composition supports the hypothesis of high animal protein intake by the subject, confirming that he belonged to high social class. The co-existence of significant dental pathologies, without major arthritic changes confirmed a life free from extensive labor. The cause of death could be related to infectious complications of renal urolithiasis and hydronephrosis.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-24 | Pathology in Favour of Developing Countries

PS-24-001
Comparison of HER2 status in breast cancer using fluorescent in situ hybridisation and immunohistochemistry at National Hospital Abuja, Nigeria - a case for alternate testing in developing countries
A.N. Ado Wanka[1], S. Amin[1], P. Taniere[2], P. Jibrin[1], A. Shaaban[2]
[1] National Hospital Abuja, Nigeria, [2] Queen Elizabeth Hospital, Birmingham, United Kingdom

Background & Objectives: Breast cancer patients that are positive for *HER2* will benefit from targeted therapy. Most centres in Nigeria utilise only immunohistochemistry (IHC) in determining *HER2* status, as it is cheaper, quicker and more widely available. Cases that are IHC equivocal present a treatment dilemma, as there is currently no centre in the country that provides alternate test to assess these tumours. The objective is to compare HER2 expression by IHC with *HER2* gene amplification by fluorescence ISH (FISH).
Methods: Clinical information was obtained from request form. Haematoxylin and Eosin stained slides were evaluated for histologic type and tumour grade. Dual probe FISH and standard HER2 IHC were performed on formalin fixed paraffin embedded tissue blocks at a UK laboratory and scored as per UK guidelines.
Results: Immunohistochemistry was done on 91 samples. The HER2 +3 tumours accounted for 10% (n=9), the +2 (equivocal) tumours were 11% (n=10) and the negative 0/+1 tumours were 79% (n=72). FISH was done on 20 samples (19 +3 and +2 tumours by immunohistochemistry and 1 negative sample), however the test failed in 5 cases. By FISH,74% (n=11) of the tumours were amplified, with 83% (n=5) of the IHC +3 cases and 75% (n=6) of the +2 IHC tumours showing gene amplification.
Conclusion: This study shows that by FISH, a significant percentage of equivocal cases on IHC had gene amplification and these cases should benefit from anti-HER2 therapy. Further work into improving the pre-analytical factors such as fixation is needed to minimise the test failure rate.

PS-24-002
Pathology services in a low resource setting: University of Abuja Teaching Hospital, Abuja, Nigeria experience
O. Oluwole[1]
[1] University of Abuja, Nigeria

Background & Objectives: The practice of pathology in the developing world, where the majority of the earth's population lives, presents special challenges for the Western-trained physician accustomed to the high standard of living, long life expectancy, and predictable disease patterns that are prevalent in the developed world.
ObjectiveTo highlight how pathology services in a low resource setting is been used to meet the health needs of our populace, teach medical students and getting involved in international collaborative studies.
Methods: The use of specimen accessioning, gross specimen examination and automatic tissue processing to produce quality microscopic slides using routine, haematoxylin and eosin (H&E) stain. Fine needle aspiration cytology services, a low-cost and reliable diagnostic technique is available in our laboratory. This also contribute significantly to the number of specimens processed in the laboratory. As we speak there is no immunohistochemistry services in our facility, but we can access it in sister hospitals close to us.
Results: In a year, we received and processed around 4000 surgical specimens and around 2500 fine needle aspiration cytology specimens including Papanicolau smears. We diagnosed around 200-300 cancer cases that comprises of cervical, breast, prostate, ovarian, gastrointestinal tract, endocrine, lymphoid and some from the central nervous system.
We have been involved in the following international research collaborative studies; African Collaborative Microbiome and Genetic Research: PI, Clement Adebamowo; AIDS-Malignancies study: PI, Clement Adebamowo; Sub-Saharan Africa Lymphoma study: PI, Leona Ayers.
Conclusion: Pathology services in low resource setting may be rudimentary, but it is undergoing gradual transformation in spite of the challenges that has bedeviled it and there is room for much development. Pathologists from the developed world can play a critical role in providing support for locally adapted services in low-resource nations, acting in cooperation with local medical and government Institutions.

PS-24-003
Physicians satisfaction with cytopathology services; an experience at a tertiary care hospital in Lahore
S. Mahmood[1], S. Sarwar[1], S. Shahid[2], F. Rehman[1], S. Ahmad[1], M.Z. Sarwar[1]
[1] King Edward Medical University, Lahore, Pakistan, [2] CMH Medical College, Lahore, Pakistan

Background & Objectives: Physicians are an integral part of the cytopathology services in determining the quality of laboratory work. Their feedback is a useful quality indicator in determining the standard of laboratory procedures and parameters towards the improvement in the service delivery. Aim of this study is to evaluate the satisfaction level of requesting medical practitioners regarding cytopathology services so that the issues can be addressed appropriately.
Methods: A cross sectional study was conducted through a self-designed questionnaire by distributing it to 375 physicians of mayo hospital, Lahore which is a tertiary care hospital affiliated with King Edward Medical University, Lahore. Ethical approval for this study was taken from ethical review board of the Institution. Data was analysed by using SPSS 22.
Results: The overall respondents were 285 (76%) in which 78.6% were male and only 21.3% were females with a mean age of 38.18 ±11.87. They had an average satisfaction level of 46.31%, 31.57%, 18.24%, 52.63%, 46.31% and 38.24% in turnaround time, diagnostic accuracy, notification of critical alerts, laboratory test ordering system, appropriate result reporting system and courtesy of staff respectively. Responsiveness of laboratory staff turned out to be 69.47%. Physicians were most dissatisfied (18.24%) with reporting of critical alerts in cytology.
Conclusion: As the satisfaction of physicians towards cytopathology services was average in most of the parameters, therefore, appropriate measures should be taken and implemented effectively to improve the service quality and standards of specialized cytopathology services with professional ethics. Efforts should be made at both individual and organizational level to provide best possible services to our valuable customers.

PS-24-004
Potential and utility of YouTube for teaching and learning in surgical pathology; resident's perspective from Pakistan
S. Mahmood[1], F. Rehman[1], F. Iqbal[1], S. Ahmad[1], M.Z. Sarwar[1], A. Momina[1]
[1] King Edward Medical University, Lahore, Pakistan

Background & Objectives: A biggest dilemma in training of the surgical pathology residents of third world countries is lack of skilled and trained supervisors, insufficient technical support, provision of ancillary studies and low quality reagents and limited exposure to all specialties. Aim of this study was to determine effectiveness and utility of various video logging & channels available on YouTube in the education and training of surgical pathology residents working in public sector laboratories of Lahore.
Methods: A cross sectional survey analysis was done and the data collected from 77 surgical pathology residents working at both public & private sector laboratories. A questionnaire was designed covering different aspects of usefulness and practicality of social networking sites in surgical pathology. Students were asked to fill the questionnaire after the written informed consent is taken. The questionnaire consists of 25 survey questions on the potential use of Youtube for teaching and education of surgical pathology residents. A 5-point Likert scale was used as follows: 1- Strongly agree; 2- agree; 3 – unsure; 4 – disagree; 5 – strongly disagree.
Results: The findings show that YouTube can be used as an instructional tool in surgical pathology in line with current trends of collaboration and social networking in pathology education. The analysis shows that the instructional videos for teaching and learning especially through live streaming of slide sessions, case series, gross cutup of surgical specimens and various advanced techniques can be effectively channelled through YouTube. The YouTube is also beneficial for providing information, as well as for teaching and learning in the surgical pathology.
Conclusion: With an increasing tendency to use social networking sites in the recent decade, YouTube has played a pivotal role in the training of surgical pathology residents. Video blogging is an effective strategy to teach residents using a combination of supporting text, images, live streaming and other metadata. Core knowledge is currently less represented in you tube content. The findings of this study indicate the integration of information technology in learning and teaching the surgical pathology can be done using YouTube. In the context of teaching and learning, YouTube is used as a video repository to assist both lecturers and students.

Wednesday, 11 September 2019, 09:30 - 10:30, Agora 3
PS-25 | Soft Tissue and Bone Pathology

PS-25-001

Identification of SRF-STAT6 fusion transcript in a cellular myofibroma of the forearm in a 15 years-old boy: expanding the molecular spectrum of the recently described entity

C. Bouvier[1], H. Nihous[2], F. Le Loarer[3,4], J. Massière[5], N. Macagno[1], F. Tirode[6], J.L. Jouve[7], J.C. Gentet[8], D. Figarella Branger[9]
[1] Service d'anatomie pathologique et de neuropathologie Hopital de la Timone, France, [2] Service d'anatomie pathologique et de neuropathologie hopital de la Timone, France, [3] Department of Biopathology, Institute Bergonie, Bordeaux, France, [4] University of Bordeaux, Talence, France, [5] INSERM U1812, Institute Bergoniè, Bordeaux, France, [6] INSERM 1052 centre Lèon Bèrard, France, [7] Service de chirurgie orthopèdique Hopital d'enfants de la Timone, France, [8] Service d'oncologie pèdiatrique Hopital d'enfants de la Timone, France, [9] Service d'Anatomie pathologique et neuropathologie Hopital de la Timone, France

Background & Objectives: The spectrum of mesenchymal tumours keeps increasing with the input of NGS. Recently myofibroblastic tumours arising within deep soft tissue with high cellularity and a more differentiated immunophenotype towards myoid lineage have been described harboring a recurrent *SRF-RELA* fusion.
Methods: We report the case of a 15 years old patient who presented with a calcified soft tissue mass of the forearm.
Results: Histological examination showed a moderately cellular fascicular proliferation mainly composed of spindle cells with variable eosinophilic cytoplasm. However areas of higher cellularity with more basophilic cells were also seen giving a biphasic appearance. Tumour stroma contained calcifications. There was no necrosis and mitotic index was 1 mitosis/50HPF. Cells stained for alpha smooth actin, H-caldesmon and desmin but were negative for myogenin, MyoD1, CD34. CGH-array showed no copy number alteration. As a cellular myofibroma/myopericytoma with *SRF-RELA* fusion was suspected, whole RNA-sequencing was performed leading to identify *SRF-STAT6* fusion that joined SRF exon 5 to STAT6 exon 17. Tumour cells diffusely stained for STAT6 by immunohistochemistry. Tumour profile clustered with classical *SRF-RELA* tumours.
Conclusion: Our case of myogenic soft tissue tumour with *SRF-STAT6* fusion expands the morphological and molecular spectrum of the SRF-rearranged lesions.

PS-25-002

Immunohistochemical TP53 expression in atypical fibroxanthoma and their mimics

R. Erber[1], A. Hartmann[1], A. Agaimy[1]
[1] Institute of Pathology, University Clinics Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Germany

Background & Objectives: Atypical fibroxanthoma (AFX) is a cutaneous neoplasm composed of spindle and pleomorphic cells, mainly arising in the sun-damaged skin of head and neck sites. Differential diagnosis comprises pleomorphic dermal sarcoma (PDS), undifferentiated pleomorphic sarcoma (UPS), spindle cell und desmoplastic squamous cell carcinoma (SCC), smooth muscle neoplasms, nerve sheath tumours, angiosarcoma, spindle cell und desmoplastic melanoma and atypical fibrous histiocytoma (AFH).
Methods: Cases of AFX, PDS, UPS and AFH were searched in our diagnostic archive database. We retrieved clinical and pathological characteristics from the original reports and reviewed all cases and slides in order to confirm diagnosis and to assess morphological and immunohistochemical (IHC) features. Main focus was on p53 (TP53), p63 (TP63) and CD10 IHC.
Results: We reviewed 141 cases (64 AFX/PDS, 6 UPS, 70 AFH, 1 sarcoma ex AFH). 21.9 % of AFX/PDS patients were female (AFH: 47.1 %); mean age was 80 years (AFH: 42 years). AFX/PDS and AFH expressed CD10 in 98.3 % and 100 %, whereas p63 was negative in 92.3 % (AFX/PDS) and 100 % (AFH). Of 21 AFX/PDS tested for TP53 IHC, all showed aberrant expression (13/21 positive, 8/21 null-type). In contrast, 11/13 AFH stained for TP53 had wildtype expression.
Conclusion: While CD10 does not separate AFX/PDS and head and neck AFH, aberrant TP53 immunostain seems to be specific for AFX/PDS versus AFH.

PS-25-003

A challenging diagnosis in paediatric pathology: BCOR-CCNB3 sarcoma

I. Gullo[1,2,3], K. Mazzocco[4], F. Buffelli[4], A. Zin[5], A.R. Sementa[4]
[1] Department of Pathology, Centro Hospitalar de São João, Porto, Portugal, [2] Department of Pathology, Faculty of Medicine of the University of Porto (FMUP), Portugal, [3] Institute of Molecular Pathology and Immunology at the University of Porto (Ipatimup), Instituteo de Investigação e Inovação em Saúde (i3S), Portugal, [4] IRCCS Istituto Giannina Gaslini, Italy, [5] Institute of Paediatric Research (IRP), Fondazione Città della Speranza, Italy

Background & Objectives: Breast metastases are rare. They represent 0.4 to 6% of all breast cancers. Our aim is to discuss their clinicopathological features.
Methods: We report a retrospective survey of 12 cases of breast metastases diagnosed over a period of 23 years (1992—2016) in the department of pathology of the university hospital of Sfax (TUNISIA).
Results: The diagnosis was carried on a material of cytoponction in two cases, a needle biopsy in seven cases and a surgery specimen in three cases. The primary tumours understood two cases of small cell non-Hodgkin lymphoma, a case of nasopharyngeal carcinoma, a case of retroauricular melanoma, a case of leiomyosarcoma, a case of uterine choriocarcinoma, a case of rectal neuroendocrine carcinoma, a case of *small cell lung carcinoma,* three cases of gastric adenocarcinoma and one case of a hematological malignancy of underminated origin. All patients were women with a middle age of 37 years. In only one case the mammary metastasis revealed the primary tumour. Clinically, the size average of tumours was 2.9 cm. Bilateral mammary involvement was noted in three cases.
Conclusion: A confrontation of clinical and pathological data with immunohistochemical study is recommended for an accurate diagnosis of breast metastasis.

PS-25-004

Inflammatory myofibroblastic tumour: a case series and immunohistochemical work-up and prognostic follow up study

Ü. Kutlu[1], P.G. Ergun[1], Û Batur[1], N. Kepil[1], N. Çomunoğlu[1]
[1] Istanbul University Cerrahpasa-Cerrahpasa Medical Faculty Department of Pathology, Turkey

Background & Objectives: Inflammatory myofibroblastic tumour (IMT) is a mesenchymal neoplasm that may arise in soft tissues of nearly every organ and it is usually seen in paediatric population. IMT is characterised by the presence of myofibroblasts and inflammatory cells within a fibrous stroma. Screening of the literature revealed the fact that all studies based their research on one anatomic location. In this study we share our IMT experience by presenting 32 cases, comparing their immunohistochemical (IHK) staining pattern, and follow up data.
Methods: The patients archives of Pathology Department of Istanbul University –Cerrahpaşa Cerrahpaşa Medical Faculty was inspected retrospectively. Immunohistochemical stains that were applied to all cases are: SMA, ALK and p53. The cases which lack one or more of those stains in their original IHK panel were completed afterwards, the blocks which were used in the original immunohistochemical work-up were used.
Results: Total of 32 IMT cases were detected. Female to male ratio was 1.4:1 (19/13). The mean value of age is 32 (2-86). The mean of tumour diameter is 7.5 cm (0,5-23 cm). Lungs were the most frequent location (7/32), followed by bladder (6/32). Rare locations of ovary, orbita and femoral bone were detected, 1 case for each. 25/32 of the cases were stained positively for SMA, 18/32 for ALK, 15/32 for p53. 6/32 cases reoccurred during follow up.
Conclusion: Our case series is the only large series of IMT's occurring in different locations, and it investigates differences in histopatholgic appearance, immunohistocemical staining properties and clinic behaviour in correspondence with tumour location. Rare localisations for IMT were seen in our series, such as long bone, ovary and heart. 6 out of 32 cases presented with recurrence. Only one case was treated with chemotherapy, other cases were treated with surgery only.

PS-25-005
Synovial chondromatosis - a retrospective review
M. Sezak[1], O. Oz[2], E. Buyuktalanci[3], E. Kaya Bicer[4], B. Doganavsargil[5]
[1] Ege University Faculty of Medicine Department of Pathology, Turkey, [2] Bergama Hospital, Department of Pathology, Turkey, [3] Ege University Faculty of Medicine Department of Pathology, Turkey, [4] Ege University Faculty of Medicine Department of Orthopaedics, Turkey, [5] Ege University Faculty of Medicine, Department of Pathology, Izmir, Turkey

Background & Objectives: Synovial chondromatosis is a benign nodular cartilaginous proliferation arising in the synovium of joints, bursae or tendon sheaths. Grossly round or oval shaped loose bodies-like nodules ranging 0.1-3 cm are seen. It is frequently encountered in adults and in larger joints as knee and shoulder. Histologically it is characterised with sy\novial lined cartilaginous nodules with varying degree of cellularity, especially at the periphery of nodules, therefore can be mistaken for a chondroid malignancy in biopsy specimens.
Methods: We retrospectively reviewed the cases diagnosed in a single center between 1986-2016 years. Cellularity (1=enchondroma-like, 2=Slightly appearent, 3=appearent), nuclear pleomorphism (focal/diffuse), presence of calsification- Ossification were evaluated and correlated with clinicopathological features.
Results: Thirty-nine cases were identified with an equal gender distribution (male/female ratio:0.95) Median agewas 54 ±16.7years-old (Range: 12-86 years). Most common localizationS were knee (53.8%, n=21) followed by hip (15.4%), ankle (12.8%) and elbow (10.3%), rare localisations were wrist, shoulder, and metatarsophalangeal joint (2.6% for each). No correlation was found between histological features and localization of lesions, age and gender of cases.
Conclusion: Most of our cases were located around knee joint, consistent with the literature. However we observed rare localizations as ankle, hand and foot joints. Synovial lining over the nodules was not a constant feature and the nodules showed increased cellularity, nuclear pleomorphism and hyperchromatism which can be mistaken for a low grade chondrosarcoma if the exact localization of cases are not known.

PS-25-006
Distinct histologic and genetic characteristics of round cell sarcoma with CIC-DUX4 or BCOR-CCNB3 fusion and comparison with Ewing sarcoma
M.J. Song[1], J.S. Song[2], K. Cho[2]
[1] Department of Pathology, Kyung Hee University Hospital at Gangdong, Republic of Korea, [2] Department of Pathology, Asan Medical Center, Republic of Korea

Background & Objectives: *CIC-DUX4* and *BCOR-CCNB*3 fusion gene associated sarcoma is a new emerging subgroup of round cell sarcoma with Ewing sarcoma-like morphology. Distinguishing these tumours from Ewing sarcoma family tumour (ESFT) is still challenging. The present study 1) investigated *CIC-DUX4* or *BCOR-CCNB3* fusion in small round cell sarcoma, 2) examined clinicpathologic and immunohistochemical characteristics of *CIC-DUX4* or *BCOR-CCNB3* sarcoma, and 3) evaluated diagnostic parameters.
Methods: Seventy patients diagnosed with undifferentiated round cell sarcoma or Ewing–like sarcoma in Asan Medical Center were investigated. The inclusion criteria were as follow: 1) *EWSR1* translocation was negative or non-informative by molecular test and 2) available tumour tissue for molecular analysis. *EWSR1* FISH was performed to exclude ESFT. *CIC-DUX4* and *BCOR-CCNB3* gene fusion was investigated by RT-PCR. The clinical and histologic phenotypes were reviewed. CD99, NKX2.2, Caveolin-1, BCOR and NUT immunohistochemical stains were performed and assessed the diagnostic value to differentiate Ewing sarcoma.
Results: We identified six cases of *CIC-DUX4* sarcoma but *BCOR-CCNB3* sarcoma was not detected. Compared to ESFT, they demonstrated short event-free survival (P=0.034) and poor response to treatment (P=0.007). Histologically, heterogeneous round, plasmacytoid, and spindle cells were observed. Unlike Ewing sarcoma, severe cytologic pleomorphism, multinucleated cells and myxoid stroma were common. CD99 and NKX2.2 combination test may be helpful to differentiate *CIC-DUX4 / BCOR-CCNB3* sarcoma from Ewing sarcoma.
Conclusion: *CIC-DUX4* sarcomas have distinct histologic features and poor prognosis compared with ESFT. Therefore, molecular analysis to detect the distinctive genetic alteration is mandatory in small round cell tumours with atypical histologic, immunohistochemical and/or clinical presentation.

Poster Sessions One-Day CPS and Two-Day MDS

Sunday, 8 September 2019, 09:30 - 10:30, Agora 3
PS-CP-01 | 1-Day Computational Pathology Symposium

PS-CP-01-001
Can image recognition techniques on whole slide images of colorectal polyps help in the identification of areas of high grade dysplasia?
P. De Paepe[1], J. Van Huysse[2], A. Driessen[3], P. Niville[4], W. Van Laer[4], K. De Wolf[4]
[1] AZ Sint-Jan, Brugge-Oostende, Dept of Pathology, Belgium, [2] AZ St Jan Brugge-Oostende, Dept of Pathology, Belgium, [3] University Hospital Antwerp, Dept of Pathology, Belgium, [4] Ixor, cvba Schuttersvest 75 2800 Mechelen, Belgium

Background & Objectives: Colorectal screening programs have resulted in a significant increase in the number of colorectal polyps in daily pathology practice. The aim of the study is to design a model, based on deep learning techniques, that recognizes and indicates major zones of interest on whole slide digital images (WSI) of colorectal polyps. The zones of interest are: normal mucosa, zones with low grade dysplasia and zones with high grade dysplasia as defined by the WHO criteria.
Methods: With a digital drawing tool three pathologists identified the zones of interest on 73 WSI. Only zones indicated by all three were used to design and train a first deep learning model focusing on pattern recognition. Each WSI was subdivided into tiles, 256x256 pixels.
Next 9804 tiles, clearcut examples of the zones of interest, were selected to retrain the model. These tiles were subdivided into a training set (8656), a validation set (786) and a test set (362).
Results: The final model reached a 75% accuracy on recognizing high grade dysplasia with a recall of 90% on the test set, 93% accuracy and 84% recall on low grade dysplasia and 77% accuracy and 81% recall on normal tissue.
Conclusion; Our study demonstrates the possibility to develop a machine learning model that indicates zones of major interest in WSI's. Improving our model among other by increasing the number of WSI for training, will allow us to develop a pre-diagnostic tool that offers support to the pathologist and may help to provide an accurate pathology report at appropriate time.

PS-CP-01-002
Low discordance rate of digital diagnostics of histopathology compared to conventional microscopy - results from 1048 cases in a validation study
S. Jarkman[1], A. Bodèn[1,2], B. Williams[3,4], J. van der Laak[5], D. Treanor[4]
[1] Department of Pathology, Linkoping University Hospital, Sweden, [2] Department of Clinical and Experimental Medicine, Linkoping University, Sweden, [3] Histopathology Department, St James University Hospital, Leeds, United Kingdom, [4] University of Leeds, United Kingdom, [5] Radboud University Medical Center, The Netherlands

Background & Objectives: Since 2011 the Department of Anatomical Pathology in Linköping, Sweden, is routinely digitizing all histopathological glass slides. Implementation of a novel diagnostic modality requires careful validation. Our validation model is designed in cooperation with Leeds University Hospital, UK, and is adapted to the local circumstances. This validation study, ongoing since 2016, aims to investigate if diagnoses made digitally are concordant with traditional microscopic diagnoses.
Methods: The validation model consisted of diagnosing sets of slides from different topographic areas with one training-step and one validation-step. The pathologist first read the cases digitally and directly afterwards using a microscope. Diagnostic discrepancies were recorded, as well as cases deferred to traditional microscopy. The training step consisted of approximately 20 slides. The validation step used a minimum of 60 cases. For pathologists validating more than one set, a minimum of 30 cases was used in subsequent sets.
Results: We collected 18 sets (10 pathologists, 8 areas) corresponding to 1058 cases in the validation step. A total of 10 cases was excluded. Included were 1048 cases (approx. 10711 slides), while 24 cases (2.3%) were deferred to traditional microscopy. In 5 cases, a diagnostic discrepancy was recorded. The diagnostic concordance (deferred cases excluded) was 99.5%. Frequently commented discrepancies (not diagnosis-altering) regarded scanning- and tissue quality, cell details, mitoses, small objects and dysplasia.
Conclusion: The diagnostic concordance of 99.5% between digital diagnostics and microscope indicates that digital microscopy is a safe alternative to traditional microscopy.

Monday, 9 September 2019/Tuesday, 10 September 2019, 09:30 - 10:30, Agora 3
PS-MD-01 | 2-Day Molecular Diagnostics Symposium

PS-MD-01-001
Expression of Transient Receptor Potential Vanilloid-1 in gliomas vs medulloblastomas
M. Assimakopoulou[1], A. Moutafidi[1], V. Zolota[2], G. Gatzounis[3]
[1] Department of Anatomy-Histology and Embryology, School of Medicine, University of Patras, Greece, [2] University of Patras, School of Medicine, Greece, [3] Department of Neurosurgery, University Hospital of Patras, Greece

Background & Objectives: The non-selective cation channels Transient Receptor Potential Vanilloid (TRPV) of TRP superfamily are activated by numerous stimuli and thus, may mediate downstream signalling. Previous data implicates alterations of TRPV1 expression in growth and progression of gliomas. Additionally, low or absent $TRPV1_{v3}$ variant expression has been strongly correlated with short survival in glioblastoma multiforme (WHO, grade IV) patients. The aim of this study was to investigate the expression levels of TRPV1 channel in gliomas and compare with embryonal tumours such as medulloblastomas.
Methods: Immunohistochemistry was performed in formalin-fixed, paraffin-embedded tissue sections from 81 human brain tumours and samples from normal brain, using specific primary antibody against TRPV1. Analysis of immunoexpression was defined as the percentage of positive (labelled) cells out of the total number of tumour cells counted in ten non-overlapping fields (Labelling index, LI). The results were confirmed by immunofluorescence and qRT-PCR.
Results: TRPV1 cytoplasmic localization was detected in tumour cells of gliomas and in neurons and a few glial cells of normal brain specimens. All medulloblastomas were TRPV1-immunonegative. In contrast, TRPV1-immunopositive gliomas (LI≥10) included 62.50% of diffuse fibrillary astrocytomas (WHO, grade II), 71.42% of anaplastic astrocytomas (WHO, grade III), 53.33% of glioblastomas multiforme (WHO, grade IV), 14.28% of oligodendrogliomas, and 33.33% of ependymomas. No significant association between TRPV1 channel expression and patients' clinicopathological characteristics was found.
Conclusion: Given the cellular heterogeneity, and the distinct cells of origin of different brain tumours, further functional studies would clarify the role of TRPV1 in biological behaviour of these tumours.

PS-MD-01-002

Validation of a novel approach for molecular breast cancer classification

S. Baldacchino[1], J. Debattista[2], C. Saliba[3], C. Scerri[4], G. Grech[1]
[1] Department of Pathology, University of Malta, Malta, [2] Applied Biotech Ltd, Malta, [3] Centre for Molecular Medicine and Biobanking, University of Malta, [4] Department of Physiology and Biochemistry, University of Malta

Background & Objectives: The current breast cancer diagnostic workflow is subject to pre-analytic variables, interpretation and defined thresholds. Despite updated guidelines, equivocal and inter-laboratory disconcordance persist in current methodologies for HER2 assessment. The validation process for a novel molecular breast cancer classification method is outlined.
Methods: 660 breast cancer specimens were cored (0.5mm) and arranged into a TMA. Cases selected were equally distributed as HER2 positive, negative or equivocal by immunohistochemistry. The TMA was assessed for HER2, ER and PR immunohistochemistry and HER2 FISH. TMA cores were then retrieved, lysed and analysed using a bead-based Quantigene assay. Data was controlled for quality and processed using a developed algorithm to classify molecular breast cancer subtypes.
Results: In a pilot study (N=108) the Quantigene assay showed a 100% sensitivity and 93.5% specificity for HER2 detection. Considering the non-equivocal HER2 cases, Quantigene showed a 100% sensitivity and 100% specificity concordant with HER2 immunohistochemistry. Equivocal cases (2+) (n=35) tested by Quantigene show 100% Specificity and 80% Sensitivity compared to the HER2 FISH confirmatory result.
Conclusion: A new molecular pathology tool has been developed for the classification of breast cancer using a diagnostic-ready approach with control material, minimal turnaround time and low cost.

Supported by Project "Accurate Cancer Screening Tests" (ACT) financed by the Malta Council for Science & Technology through FUSION: The R&I Technology Development Programme 2016.

PS-MD-01-003

Characterisation of genetic mutation spectra and identification of gene amplification and fusion variants in cell-free nucleic acid from cultured cancer cell media and liquid biopsy specimens using Oncomine™ pan-cancer cell-free assay

R. Cao[1], K. Lea[1], J. Schageman[1], K. Hanif[1], Y. Li[1], J. Gu[1], V. Bagai[1], P. Kshatriya[1], A. Luchetti[2], L. Quagliata[1], H. Wikman[3], S. Loges[3], K. Bramlett[1]
[1] ThermoFisher Scientific, USA, [2] Thermo Fisher Scientific, Italy, [3] Department of Tumour Biology, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf, Germany

Background & Objectives: Currently the standard practice in tumour biomarker research still relies on invasive tumour biopsy following by molecular testing or NGS assay. However, this only provides limited characterization of tumour composition. Recent studies in non-invasive biomarker research have demonstrated the potential advantages of using cell-free nucleic acids isolated from blood plasma to study genetic heterogeneity of tumour population and dissect the complex cancer clonal architecture.
Methods: Recently developed Oncomine™ Pan-Cancer Cell-free Assay employs an amplification-based approach from Ion Torrent NGS technology and achieves exceptional sensitivity and specificity with input as little as 20 ng. It includes comprehensive genetic content to simultaneously interrogate both cfDNA and cfRNA.
Results: In this study, cancer cell lines harboring multiple variant types were selected for evaluation. Using Pan-Cancer Cell-free Assay, we successfully detected all the expected variants in these cancer cell lines including gene amplification (MET, ERBB2, CDK4) and fusion variants (ALK fusion and MET exon skipping). Subsequently, we applied this assay to a set of liquid biopsy samples collected from a human subject with NSCLC during the course of 15 months. The results showed that a well-known TP53 mutation R248Q was consistently detected in the longitudinal samples. Interestingly, additional gene amplifications including MET, CDK4 and FGFR3 were identified at late time points, which were also confirmed by digital PCR and showed concordant with FISH analyses in solid tumour.
Conclusion: Overall, this study demonstrates that Pan-Cancer assay provides a unique and complete NGS solution for comprehensive genetic mutation assessment using *in vitro* and *in vivo* liquid biopsy models.

PS-MD-01-004

Case report: NGS of cell-free DNA from blood and bile as a follow-up strategy in a patient with metastatic pancreatic adenocarcinoma

K. Ebner[1], C. Driescher[2], W. Goering[3], L. Haeberle[2], V. Keitel[1], D. Haeussinger[1], I. Esposito[2]
[1] Department of Gastroenterology, Hepatology and Infectious Diseases, Heinrich Heine University and University Hospital, Germany, [2] Institute of Pathology, Heinrich Heine University and University Hospital, Germany, [3] Institute of Pathology, Heinrich Heine University and University Hospital, Germany

Background & Objectives: A 65-year-old patient initially presenting to our clinic with jaundice and weight loss was diagnosed with metastasized pancreatic ductal adenocarcinoma. After undergoing ERCP for biliary stent implantation, chemotherapy with Gemcitabin/nabPaclitaxel was initiated. After initial therapy response, we aimed at monitoring disease development by using a liquid biopsy approach with NGS analysis of cell-free DNA (cfDNA) extracted from serially collected blood and bile samples.
Methods: Blood samples were collected at study inclusion and during outpatient-visits after 4, 7 and 14 weeks. Bile was collected at study inclusion and 7 weeks later during routine ERCP for biliary stent replacements. After cfDNA extraction and quantification, panel-based NGS analysis was performed using Ion-S5 next generation sequencing platform. Additionally, results were compared to mutation profiles obtained from tissue samples of the primary tumour.
Results: During tumour progression, primary tumour mutations in *TP53* and *KRAS* were detected in blood with rising allele frequencies (AF) from 13.9% and 13.2% after 4 weeks to 25% and 19.7% after 7 weeks. Bile-derived cfDNA after 7 weeks showed *TP53* and *KRAS* mutations with AF of 5.5% and 4.4% compared to 0.3% and 0.2% at study inclusion. After modification of the chemotherapy-regimen, ultrasound-based detection of regression of liver metastases was accompanied by decreasing AF of *TP53* and *KRAS* mutations in blood-cfDNA to 1.1% and 1.0%.
Conclusion: This report suggests that mutation profiles of cfDNA from blood as well as bile might be useful in monitoring tumour development and therapy response. Larger cohort studies remain necessary to investigate the potential of this method for therapy-surveillance and possible benefits over routine biomarkers.

PS-MD-01-005

Effect of radio-wave and molecular resonance surgery on rat neck skin regeneration

I. Kastyro[1], P. Pryanikov[2], A. Alsufev[1,3], V. Popadyuk[1], A. Kovalenko[1], A. Sedelnikova[1], N. Kamanina[1]
[1] Peoples' Friendship University of Russia (RUDN University), Russia, [2] Pirogov Russian National Research Medical University (RNRMU), Russia, [3] Greenberg City Clinical Hospital Perm, Russia

Background & Objectives: Presently, modern methods of electrosurgery are necessary for conducting surgeries, especially in emergency conditions, such as when tracheostomy is performed in patients with tumour laryngeal stenosis. The aim of the work was to compare the effects of radio-wave (RW) and molecular resonance (MR) surgery on rat neck skin regeneration.

Methods: Cuts were made with a microsurgical RW generator (1group) and a MR generator (2group) on neck skin of 10 rat's. Cytological study of preparations obtained using the superficial biopsy method (May-Grünwald stain). Cytograms were determined for 5 types according to M.F.Kamaev. After surgery at 1,2,4,6,8,10&12 days rats were scored 2 from each group and a histological study of postoperative wounds (H&E, toluidine blue stain). In assessing morphological changes we evaluated necrosis,the severity of inflammatory changes, edema, proliferative changes, epithelization.
Results: Cytological examination showed that from day 2 the number of neutrophils decreased in gr.1 ($p<0.01$), and from day 5 the number of fibroblasts increased, compared with gr.2 ($p<0.005$). In gr.1, the thickness of the necrosis is less than in gr.2 (87.5+8.1 against 112±6.5), from day 3, edema ($p<0.005$), the mast cells number ($p<0.005$) and neutrophilic infiltration of the wound edges were more in group 2 ($p<0.005$), proliferative changes and epithelialization were better in gr.1 ($p<0.001$).
Conclusion: RW exposure is a more effective way of transforming electric energy in the vibration of tissue molecules, which allows to achieve the dissection at lower power output, as compared to the MR method. This studies have revealed that the inflammatory response and the healing time for wounds are significantly less after RW exposure compared to MR method.

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PS-MD-01-006

Up-converting nanoparticles as a tool for histopathological tissue evaluation with multiplexing and machine learning potential

K. Krawczyk[1], S. Andersson-Engels[2], A. Sjögren[1]
[1] Lumito AB, Sweden, [2] Biophotonics@Tyndall, Tyndall National Institute, Cork, Ireland

Background & Objectives: In the field of histopathology, a risk for misdiagnosis is a serious issue. A standard way to visualise cell morphology is through H&E staining often combined with DAB chromogenic stain. However, this method suffers from narrow dynamic range, problems with quantitation and difficulties with multiplexing and co-localisation. Fluorescent IHC techniques generate a more quantitative readout but suffer from photobleaching. Here we present that the use of up-converting nanoparticles (UCNPs) allows to overcome problems associated with commonly used imaging techniques.
Methods: Novel luminescent UCNPs were used together with a prototype instrument to image selected markers, e.g. Her2, in the human tissue. Formalin-fixed paraffin-embedded human colon and breast cancer tissues were sectioned and stained using autostainer. UCNP fluorescence imaging of the human tissue sections was compared with a standard DAB based IHC. Pulsed excitation and gated detection were explored to improve the scanning speed. UCNP and H&E co-staining and co-imaging were also investigated.
Results: Images obtained with our novel device clearly show that developed by us antibody-UCNP conjugates can be used to successfully stain the human tissues. Brightfield images show that UCNPs are not visible in white light and hence do not interfere with standard tissue evaluation by a pathologist. Additionally, brightfield and luminescent images can be merged to provide better understanding of tissue morphology.
Conclusion: Emerging field of UCNPs opens up new possibilities. Staining solutions and a novel device developed by us give hope for more accurate diagnosis by keeping the advantage of H&E staining and combining it, in one image, with luminescent data, ideal for generating ground truth for machine learning algorithms.

PS-MD-01-007

Pathohistological characteristics of breast cancer in BRCA-positive and BRCA-negative women

S. Ramic[1], I. Kirac[1], T. Oresic[1], T. Zigman[1], V. Musani[2], P. Ozretic[2], O. Vugrek[3], I. Milas[1]
[1] Genetic Counseling Unit, University Hospital for Tumours, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia, [2] Lab. for Hereditary Cancer, Div. of Molecular Medicine, Institute Rudjer Boskovic, Zagreb, Croatia, [3] Lab. for Advanced Genomics, Div. of Molecular Medicine, Institute Rudjer Boskovic, Zagreb, Croatia

Background & Objectives: Our Hospital introduced Genetic counseling and testing for patients affected with breast/ovarian cancer or healthy individuals from hereditary breast and ovarian cancer families. BRCA1/2 gene testing was indicated in individuals who met the criteria according to the Clinical Practice Guidelines.
Methods: BRCA1/2 germline mutations were analysed in whole blood samples using next-generation sequencing, Sanger sequencing and quantitative PCR methods. We compare pathohistological characteristics of breast cancer in BRCA-mutation carriers and non-carriers.
Results: BRCA1/2 was tested in 153 women, and 20 of them carry germline BRCA1/2 mutation: 16 in the BRCA1 gene, 4 in BRCA2 gene and 3 had a BRCA2 variant of *unknown* significance. We collected data on 57 breast cancer patients, of which 12 were BRCA mutation carriers. BRCA-positive women with BC were younger at the time of diagnosis than women without BRCA mutations (median 38.5 years *vs.* 45.5 years). Among BRCA-positive patients, 75% had triple-negative breast cancer (TNBC), 16.7% had Luminal/HER2 positive BC and 8.3% with Luminal/HER2 negative BC. Among BRCA-negative patients, only 9.5% had TNBC, 66.7% had Luminal/HER2 negative BC, 16.7% had Luminal/HER2 positive and 7.1% had HER2 enriched BC. Patients with BRCA2 variant of unknown significance had Luminal/HER2 negative breast cancer. Although the average size of the tumour was larger in BRCA positive patients (25 mm *vs.* 18 mm), there is no difference in median size of the tumour (15mm).
Conclusion: Detection of family members with germline BRCA1/2 mutations may play a vital role in breast cancer risk assessment and surveillance/treatment plan.

PS-MD-01-008

Comparison of four microsatellite instability testing methods in endometrial cancer- reliability, handling, cost effectiveness

J. Siemanowski[1,2], B. Schömig-Markiefka[1,2], W. Dietmaier[3,4], N. Arens[5], T. Buhl[1,2], R. Büttner[6], S. Merkelbach-Bruse[7]
[1] University Hospital Cologne, Germany, [2] Institute of Pathology, Germany, [3] University Regensburg, Germany, [4] Institute of Pathology, Germany, [5] Molecular Pathology Trier, Germany, [6] Institute for Pathology, Cologne, Germany, [7] Institute of Pathology University Hospital of Cologne, Germany

Background & Objectives: Microsatellite instability (MSI) is a common alteration in endometrial cancers caused by aberrations in the DNA mismatch repair system and recently designated as a predictive biomarker for response to immune checkpoint therapy. Differences in MSI profiles between endometrial and colorectal cancers enable the possibility of false negative results in routine diagnostic. This study compares four different PCR based testing approaches initially designed for the detection of MSI in colorectal cancer.
Methods: 25 endometrial tumours with immunohistochemically diagnosed stable, instable and uncertain microsatellite status were selected. Tumour and paired normal tissue DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) material. MSI testing was performed by fragment length analysis with an in-house Bethesda-Panel and the MSI Analysis system (Promega) as well as parallel sequencing with a custom GeneRead V2 panel (Qiagen). 10 μm slices of the same FFPE tumour tissues were taken for the Idylla MSI assay (Biocartis).
Results: All four methods showed a high overall concordance and could clarify uncertain MSI status due to inaccurate IHC. Analysis and interpretation of results was more time consuming with the Bethesda-, Promega-Panel and the parallel sequencing Approach.

Conclusion: This study showed that all MSI testing methods provided reliable results for MSI testing albeit dealing with difficulties during interpretation of results. The Idylla MSI assay seems to be a suitable alternative to the other assays due to easy result interpretation and cost effectiveness caused by short hands on time without the need of normal tissue.

PS-MD-01-009

Association between KRAS, NRAS, BRAF mutation status and clinicopathological prognostic factors in colorectal carcinoma in Turkish population

D. Unal Kocabey[1], E. Cakir[1], F.H. Dilek[1], B. Bolat Kucukzeybek[1], A. Calli[2]
[1] Izmir Katip Celebi University Ataturk Training and Research Hospital Department of Pathology, Turkey, [3] Dokuz Eylul University Molecular Medicine, Turkey

Background & Objectives: *KRAS*, *NRAS and BRAF* mutations have prognostic and predictive value in colorectal carcinoma (CRC). The aim of this study is to investigate frequency of *KRAS*, *NRAS*, *BRAF* mutations in Turkish CRC patients and to evaluate their relationship with clinicopathological prognostic factors.
Methods: All CRC patients who underwent surgical resection from 2008 to 2018 and tested for *KRAS*, *NRAS*, *BRAF* mutation at our Institution were analysed retrospectively. The association between *KRAS*, *NRAS, BRAF* mutation status and clinicopathological prognostic factors including age, sex, tumour site, tumour size, histological grade, pT stage, pN stage, lymphovascular invasion, perineural invasion, tumour deposit were compared statistically.
Results: A total of 137 patients with CRC were retrieved. *KRAS*, *NRAS* and *BRAF* mutations were detected in 34.6% (47/136), 13.2% (12/91) and 3.6% (2/56) of tumours, respectively. We identified *KRAS* mutations in codon 12, 13, 59 and 146 in 70.2% (33/47), 21.3% (10/47), 6.4% (3/47) and 2.1% (1/47), respectively. Also, we found *NRAS* mutations in codon 12, 61, 13, 59 in 41.7% (5/12), 25% (3/12), 16.7% (2/12), 16.7% (2/12), respectively. While absence of *KRAS* mutation was significantly associated with perineural invasion ($P = 0.002$), there was no significant association between *KRAS* mutation status and other clinicopathological features. Similarly, there was no significant association between *NRAS* and *BRAF* mutation status and clinicopathological features.
Conclusion: The effect of *KRAS*, *NRAS* and *BRAF* mutations on clinicopathological features is unclear. Future studies with larger patient groups can help to clarify the association between *KRAS*, *NRAS*, *BRAF* mutations and clinicopathological features.

PS-MD-01-010

Results of the Belgian ring trial for liquid biopsy testing in non-small cell lung cancer show variety in the interpretation of the test result

K. Van Casteren[1], K. Dufraing[1], P. Pauwels[2], N. D'Haene[3], E. Dequeker[1]
[1] Biomedical Quality Assurance Research Unit, KU Leuven, Leuven, Belgium, [2] Laboratory of Pathological Anatomy, Antwerp University Hospital, Edegem, Belgium, [3] Department of Pathology, Erasme University Hospital, Brussels, Belgium

Background & Objectives: The use of liquid biopsies for detecting resistance mutations after disease progression in patients with non-small cell lung cancer has been introduced into routine. This study aimed to evaluate how well laboratories interpret and report test results.
Methods: Laboratories participating in the Belgian *EGFR* ctDNA Ring Trial 2018 (N=17) received 3 mock requests and test results from fictional patients for which they had to submit reports resembling their daily routine. Reports were assessed based on pre-defined scoring criteria. Marks were given for the test result (0.75), clinical interpretation (0.625), patient name (1.00), date of birth (1.00), the assay used (0.125), targeted aberrations (0.25) and the reference sequence (0.25). For other items only individual feedback was given.
Results: The average reporting score was 3.12/4 (N=17) based on the presence of 7 elements. Interpretations received average scores of 67%, 50% and 44% for cases 1, 2 and 3, respectively. In case 3, a resistance mutation was detected but not the activating mutation because not targeted by the test method. The latter was recommended to be clearly stated in the interpretation. Elements like the sampling date (59%), reason for testing (59%), DNA extraction method (47%), method sensitivity (53%) and reference sequence (18%) were only present on a limited number of reports.
Conclusion: This ring trial showed that there is still room for improvement regarding reporting molecular pathology results. As liquid biopsy testing has only recently entered daily practice, a clear and correct report might further educate prescribing oncologists. Further initiatives on improvement are currently being set-up.

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PS-MD-01-011

Establishment of a 3D histopathology platform for precision tumour diagnosis

J. Yang[1], Y. Lin[2,3], A. Chiang[2,4], I. Wang[5], S. Wu[6], M.D. Chang[7], J. Lee[8], J. Ko[9], S. Liang[9], J. Guo[10], X. Song[10], H. Huang[10], M. Chao[11], C. Lin[12]
[1] Department of Life Science, National Tsing Hua University, Hsinchu, Taiwan, [2] Brain Research Center, NTHU, Taiwan, [3] JelloX Biotech, Hsinchu, Taiwan, [4] Institute of Systems Neuroscience, NTHU, Taiwan, [5] Institute of Biotechnology, NTHU, Taiwan, [6] Department of Engineering and System Science, NTHU, Taiwan, [7] Institute of Molecular and Cellular Biology, NTHU, Taiwan, [8] Oncology Department, National Taiwan University Hospital Hsin-Chu Branch, Taiwan, [9] Internal Medicine Department, National Taiwan University Hospital Hsin-Chu Branch, Taiwan, [10] Pathology Department, National Taiwan University Hospital Hsin-Chu Branch, Taiwan, [11] Surgery Department, National Taiwan University Hospital Hsin-Chu Branch, Taiwan, [12] Oncology Department, National Taiwan University Hospital, Taipei, Taiwan

Background & Objectives: Rapid and accurate evaluation of full picture of histopathological biopsy has clinic unmet need. We thus aim to establish an automated 3D histopathology platform that emerges comprehensive pathologic images in support of quantitative data analyses and standardised digital format to overcome technology limitation of current 2D image diagnosis tools.
Methods: The platform offers an innovative optical tissue clearing immersion system with high-resolution of 3D image technology, employing alternative scanning and slicing processes reliable depth control of continuous automatic images and digital suture parallel multi-stack images, and thus panoramic 3D digital images of a complete histopathological sample are produced.
Results: The platform allows detection in-depth and comparative analysis of normal and pathological organization. Moreover, our innovative database stores high resolution images of deep tissues that are suitable for building up artificial intelligence algorithms. The 3D-AI assisted pathological modules in detecting malignant cancer cells in mouse lung cancer model and in clinical metastatic breast to lymph nodes model will be demonstrated in ECP 2019.
Conclusion: Our automated 3D histopathology platform could provide intact deep tissue histopathological database for practical application of AI auxiliary precision medicine.

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E-Posters

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-01 | Autopsy Pathology

E-PS-01-001
Pulmonary fibrosis as a manifestation of connective tissue disease
E. Malysheva[1], S. Timofeev[1], E. Startseva[1], N. Zharkov[1]
[1] City Hospital of Moscow, Russia

Background & Objectives: Pulmonary fibrosis is a complex issue, so much so that determining the true causes of this disease has been a stumbling block for pulmonologists and pathologists for many years. More recently, however, our understanding of pulmonary fibrosis has developed to such an extent that researchers have discovered that there are similarities between patients with pulmonary fibrosis and those with a connective tissue disease.
Methods: A 48-year-old woman was admitted to hospital and diagnosed with pneumonia. Her medical history informed us of childhood asthenia and hypermobility of the joints. Despite treatment, her condition worsened and she died. The cause of death was pulmonary heart disease. The autopsy revealed deformation of the chest, sometimes seen in patients who suffer from a connective tissue disease. Lungs had pleural and perivascular fibrosis. The lumen of the alveoli had a mixture of desquamated epithelium with macrophages and hyaline membranes.
Results: Epithelium cells of the alveolar lining and stroma cells had a positive reaction with plasminogen activator inhibitor type 1 (PAI-1), "dot like" cytoplasmic staining.
Stroma cells, perivascular spaces and walls of blood vessels were markedly positive with antibodies to type IV collagen and positive with CD117 / c-kit.
The lumen of the alveoli and the interstitial spaces had a significant amount of HLA-DR and CD68-positive cells, which formed clusters in the cavity of the alveoli.
Conclusion: Despite the patient suffering from symptoms related to connective tissue disease, including weight loss, chest deformation and hypermobility of the joints, the main manifestation of the disease was actually pulmonary fibrosis.

E-PS-01-002
Incidental adrenal tumours in forensics
C. Amalinei[1], L. Lozneanu[1], B. Ioan[1,2], L. Riscanu[1,2], A. Grigoras[3]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] Institute of Legal Medicine Iasi, Romania, [3] Department of Morphofunctional Sciences I-Histology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

Background & Objectives: Adrenal masses are rare, incidental findings in forensic pathology. The aim of our study is to report the particular features of four cases, occurred in 50-69 years old subjects, two females and two males.
Methods: Routine hematoxylin-eosin, along with immunohistochemistry using synatophysin, chromogranin, S100, MelanA, and inhibin, in two selected cases, have been performed.
Results: Gross findings were variable. Microscopy revealed, in two cases, circumscribed areas of alveolar growth pattern and cytologic vacuolar degeneration, synaptophysin+, chromogranin+, S100+ (focal), MelanA-, and inhibin-, characteristics of pheocromocytoma. One of them had vascular invasion, and multiple tumoural implants, being diagnosed as metastatic malignant pheocromocytoma. In another case, islands of metastatic implants of a lung adenocarcinoma have been detected. In the last case, an adrenal nodule with alveolar growth pattern of slightly enlarged cells was diagnosed as a cortical adenoma.
Conclusion: Although rare in necropsy, adrenal masses should be investigated as they may reveal potential severe diseases and tanathogenesis significance. Immunohistochemistry may be useful to discriminate specific types of tumours, in correlation with the clinical information, gross findings, and microscopic features in routine staining.

E-PS-01-003
Secondary meningo-cerebral tumours with unknown lung primaries - necroptic features
C. Amalinei[1], A. Grigoras[2], C. Teodorescu[3], L. Riscanu[1,3], L. Lozneanu[1]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] Department of Morphofunctional Sciences I-Histology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania, [3] Institute of Legal Medicine Iasi, Romania

Background & Objectives: Most common central nervous system tumours represent metastases and the primary tumour has usually been already diagnosed. Metastases of unknown primaries may be discovered in forensic pathology. The aim of our study is to report the particular features in eight cases of meningo-cerebral metastases diagnosed during the last three years, in our Department, in subjects with age range between 55 and 80 years old, five men and three women.
Methods: Routine hematoxylin-eosin and Masson's trichrome staining, along with immunohistochemistry using a panel of markers (CK7, TTF1, CK5, p63, AE1/AE3, CK20, and HepPar1) have been performed.
Results: Gross appearance was that of sharply delimited lesions, mainly disposed at the gray-white matter junction, of 1-2 cm diameter, containing variable necrosis and haemorrhage. Microscopy revealed multiple lesions with variable location: cerebrum, brainstem, cerebellum, meninges, along with meningeal carcinomatosis (in three cases). Liver metastases have been also found in two cases and have been excluded in a case with an ectopic adrenal gland. The primary tumours have been identified as seven cases of lung adenocarcinomas and one squamous cell carcinoma.
Conclusion: Metastases of lung carcinomas have to be considered in meningo-cerebral malignancies. Differentials should include primary meningo-cerebral tumours and the final diagnosis has to be certified by corroboration of comparative size between primaries and secondaries, characteristic multiple, secondary lesions, including the possibility of additional liver metastases, along with specific expression of immunohistochemical markers and microscopic features.

E-PS-01-004
Post-mortem diagnosis of metastatic male breast cancer with fulminant evolution
D. I. Enea[1], M. Ceausu[2], A. Tita[2], G. Roman[2], M. Bosa[2], L. Luca[2], O. Neagu[1], L. Tomescu[1]
[1] University Emergency Hospital, Bucharest, Romania, [2] "Mina Minovici" National Institute of Legal Medicine, Bucharest, Romania

Background & Objectives: Male breast cancer is a rare form of malignancy which develops from the small amount of residual breast tissue found in men. It usually affects older men with a background of hormonal imbalances, but the risk factors are not entirely known.
Methods: This report describes an unusual case of breast cancer in a 60-year-old man with obesity and vertebral algic symptoms. MRI exam highlighted multiple lytic lesions of the spine, including T12-L2 pathological fractures. Subsequent clinical examination revealed a left breast mass. Due to rapid deterioration of the patient's condition, followed by exitus (<1 month), any further investigations couldn't be performed and

the diagnosis remained uncertain. The autopsy detected cirrhosis, a left breast tumour and metastasis in the spine.
Results: Microscopically, there was an invasive carcinomatous proliferation composed of pleomorphic cells arranged in nests, trabeculae, cords, with desmoplastic stroma, located in the breast, lungs and liver. By means of immunohistochemistry, the tumour cells showed positive reaction for AE1-AE3, ER (~ 1-5 %) and a high proliferation rate (PCNA ~ 80-90%). The histopathological findings suggested a poorly differentiated, highly aggressive, invasive ductal carcinoma of no special type (NST) of the breast with liver, lung and bone metastasis.
Conclusion: The particularity of this unusual case resides in rapid evolution of an aggressive, metastatic, male breast cancer, with a high rate of proliferation, on a background of a delayed diagnosis due to a misleading tumour appearance, in the context of hormonal imbalance caused by cirrhosis and obesity.

E-PS-01-005
Multi-organic infiltration by anaplastic large celllymphoma, ALK positive, diagnosed in autopsy
A. M. G. Pereira[1], F. Galante Pereira[1], C. A. Padrão[1], A. T. Alves[2]
[1] Hospital Prof. Doutor Fernando Fonseca, EPE, Portugal, [2] Instituto de Anatomia Patológica da Faculdade Medicina Universidade de Lisboa, Portugal

Background & Objectives: ALK-positive (ALK+) anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma that accounts for approximately 3% of adult non-Hodgkin lymphomas and frequently involves both lymph nodes and extranodal sites, most commonly the skin, bone, soft tissue, lungs, and liver.
Methods: Diagnosing lymphoma is not easy, and the clinical presentation of this 64 years old man we are presenting was challenging and misleading with high fever, heterogeneous hepatomegaly and diarrhea. Clinical presentation suggested an infectious disease and a possible consumptive process supported by a story of weight loss. Empiric antibiotic therapy was started and the CT-scan report found multiple adenomegalies and hepatomegaly with areas of nodular hipocaptation suggestive of small abscesses. Blood tests also revealed acute renal and liver failure.
Results: With rapidly progressive health deterioration, the man died after three days and, without a definitive diagnosis, an autopsy was requested. An extensive infiltration by ALK+ ALCL was documented, involving all the lymph nodes that were observed plus the liver, lung, bone marrow, spleen, kidneys, adrenal glands and the myocardium.
Conclusion: We present this case to highlight how even an extensive and advanced stage ALCL can "fly under the radar" and involve some less common and rare extranodal sites.

E-PS-01-006
Anaplastic Carcinoma Thyroid in a cervical trauma: an autopsy report
J. Melo[1], E. Ribeiro de Lemos[2], M.C. Carneiro da Ibiapaba[2], T. Guimaraes do Nascimento[2], L. Camelo Oliveira[2], L. Macedo Pinto[2], D. Nunes Oliveira[1], D. Nunes de Melo[3]
[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil, [3] State Secretary of Health, Brazil

Background & Objectives: Anaplastic thyroid carcinoma (ATC) is one of the most aggressive cancers Report a case of Anaplastic thyroid cancer which symptoms were triggered after a car accident.
Methods: Autopsy was made in Legal Medical Institute. Male, 51 years old, victim from a car accident three months ago suffered a anterior cervical trauma steering wheel injury. A few days later, he evolved with a bulky anterior cervical mass, hoarseness, an obstructive respiratory insufficiency and was submitted to an urgent tracheostomy. After, there was a food leakage from the tracheostomy, so it was put a nasoenteral tube. He evolved with dyspnea, bulky tracheostomy bleeding and death.
Results: Macroscopy: a surgical specimen measuring 10x8x7cm where we identified proximal portion of the trachea, larynx, thyroid and related structures, compromised by tumour lesion of ill defined, grayish and friable limits. Microscopy, an undifferentiated malignant neoplasm with pleomorphic giant cells, parts of them fusiform, with sarcomatous aspect, presenting vesiculous nucleus with macronucleolus, many bizarre mitosis figures, extensive areas of necrosis and hemorrhagic focus. Tumour cells are arranged in solid blocks and infiltrate widely the thyroid parenchyma, skeletal muscle adjacent, larynx and trachea, which causes complete luminal obstruction. Also compromises angiolymphatic structures and perineural spaces adjacent.
Conclusion: The case shows a rare episode of anaplastic thyroid cancer in which the symptoms appeared after a trauma. Therefore, it is necessary a fast identification and establishment of a effective therapeutic, looking after a better care for the patient.

E-PS-01-007
Giant intraventricular thrombi as a complication of chronic abuse of cocaine-levamisole
K. Metze[1], N. Biagioni de Lima[1], R. Lanaro[1], C.A. de Lima[1]
[1] State University of Campinas, Brazil

Background & Objectives: Giant intraventricular thrombi in the heart are a rare phenomenon. They can be caused by different conditions such as antiphospholipid syndrome, heparin-induced thrombocytopenia, malignant neoplasias, Takotsubo cardiomyopathy, hypereosinophilic syndrome or aluminium phosphide poisoning. An important pathophysiological mechanism for many different conditions seems to be an endothelial dysfunction. The aim of this case report was to show that chronic cocaine-levamisole abuse can also cause giant ventricular thrombi.
Methods: A 44-year old man with a history of chronic cocaine abuse was admitted to hospital with necrosis of the toes. Angiography revealed multiple arterial and venous thrombi in both legs and pulmonary thromboemebolism. Echocardiography suggested biventricular giant thrombi of the heart. Although submitted to anticoagulation treatment with heparin and symptomatic therapy, the patient evolved to hemodynamic instability and expired on the sixth day. An autopsy was performed.
Results: Autopsy revealed widespread veonous thrombosis in both legs, recurrent pulmonary thrombembolism with infarcts and giant thrombi in both cardiac ventricles as well as gangrene of the distal parts of all fingers and toes due to thrombotic arteritis. Toxicologic hair analysis showed chronic abuse of cocaine mixed with levamisole for at least 6 months.
Conclusion: Levamisole, an antihelminth and immunomodulatory adjuvant, is an adulterant in cocaine worldwide. Widespread venous thrombosis and thrombotic arteritis suggest generalized endothelial dysfunction as the leading pathophysiological mechanism which might also eplain the genesis of the giant thrombi.
In summary, we describe cocoaine–levamisole intoxication as a new predisposing condition for intracardiac giant thrombi most probably related to a generalized endothelial dysfunction.

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E-PS-02 | Breast Pathology

E-PS-02-001
Squamous cell carcinoma of the breast with apocrine features: a rare variant of metaplastic breast cancer
C. Taverna[1], A.G. Naccarato[2], C. Scatena[3]

[1] Division of Pathological Anatomy, Department of Health Sciences University of Florence School of Human Health Sciences Florence, Italy, [2] University of Pisa, Italy, [3] Division of Pathology, Department of Translational Research and of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background & Objectives: Small-cell neuroendocrine carcinoma of lung is one of the most frequent types within endobronchial biopsies. Although it shows characteristic histopathological finding, immunohistochemistry is necessary in many cases due to the variety of possible differential diagnoses. The expression of the different markers usually employed as CKAE-1AE3, TTF-1 and neuroendocrine markers varies according to the literature. In particular, it is very important to know that these neoplasms can show negative immunostain for epithelial markers and even for TTF-1.
Methods: The archive were reviewed between the years 2009-2014, obtaining 110 cases. There were 97 mens and 13 women.The median age was 72 (range betwen 41 to 90 year old). We studied 78 biopsies and we also included 32 cases of lung FNA.
Results: From 110 cases we found 7.27% that were negative for TTF1 immunostain, 1.8% with negative immunostain for CKAE1-AE3. The rest of performed neuroendocrine markers were chromogranin, synaptophysin and CD56, which were negative in 11.92%, 22% and 2.75% respectively.
Conclusion: There are few bibliographical references to the percentage of negativity for TTF1 and CKAE1-AE3 in this tumour. The negativity for CKAE1-AE3 and TTF-1 is considered extremely rare. This study contributes important information, since it characterises immunoprofile of small-cell carcinoma. This information is useful in cases that show a usual morphology of small cell neuroendocrine carcinoma but with unusual immunohistochemical expression.

E-PS-02-002
Sebaceous carcinoma of the breast in a male patient with a BRCA2 germline mutation: case report and literature review

J. Lobo[1], P. Lopes[1], R. Henrique[1], î Rodrigues[1]
[1] IPO Porto, Portugal

Background & Objectives: Sebaceous carcinoma (SC) is an overall uncommon neoplasm. Its occurrence on the breast is very rare. We aim to present a case of primary SC of the male breast in the context of a BRCA2 mutation.
Methods: A 79-year-old man complained of a breast lump detected on self-examination. Core-biopsy reported "grade 2 invasive carcinoma with secretory pattern". He was referred to our Institution and underwent left total mastectomy was performed. Macroscopically, a hard, well-circumscribed and lobulated, yellowish, 1.9cm nodule was depicted. It was centered in breast parenchyma and the overlying skin/nipple-areolar complex were unremarkable.
Results: Histologically, it corresponded to an invasive carcinoma, with nested architecture and no evidence of cutaneous origin. >80% of the tumour displayed large clear cells, with microvacuolated cytoplasm, admixed with smaller basophilic cells. Intraductal carcinoma with same features was present. It was diffusely positive for ER/PR/AR/EMA, and negative for HER2/GCDFP15. A diagnosis of SC of the breast was made. The patient's daughter had been diagnosed with breast cancer at age 44 and the patient was found to carry a BRCA2 mutation.
Conclusion: Compliance with strict criteria proposed in WHO 2012 is necessary for clearly discriminating this entity from breast cancer with sebaceous differentiation and from SC of the overlying sebaceous glands. This is the first case of SC of the breast in a male patient with a germline BRCA2 mutation.
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E-PS-02-004
Case report: a 56-year-old woman with primary neuroendocrine carcinoma of the breast

M. Dieaconu[1], D. Ferariu[2]
[1] Regional Institute of Oncology, Iasi. Romania, [2] Department of Pathology, Regional Institute of Oncology, Iasi, Romania

Background & Objectives: Primary neuroendocrine carcinomas of the breast represent a rare entity, with incidence under 0.1% from all breast carcinomas and under 1% from all neuroendrocrine carcinomas. We present the case of an 56-year-old woman with a single solid nodule in the right breast, admitted to the surgical oncology department of Regional Institute of Oncology Iasi, Romania. Five days prior to the admission the lesion was discovered during a routine screening mammogram. The patient has no significant past medical history.
Methods: The routine screening mammogram revealed a well circumscribed homogeneous nodule of 12/10 mm situated in the lower inner quadrant of the right breast, considered low-risk. No additional abnormalities were found. It was performed a core-biopsy, and two fragments of tissue of 7 and 4 mm were fixed with formalin 10%, paraffin embedded and analysed using hematoxylin and eosin staining and immunohystochimical tests.
Results: Microscopy revealed uniform small cells separated by delicate fibrovascular stroma. Tumour cells have round nuclei with granular chromatin, scant cytoplasm, mitosis and apoptosis. Cells were positive for synaptophysin, chromogranin and TTF-1, negative for estrogen and progesterone receptors. HER2neu was 0 (negative). After immunohistochemical analysis the differential diagnosis was made with a metastasis from another primary neuroendocrine tumour. PET/CT and abdominal ultrasound excluded a non-mammary primary site. The patient received chemotherapy and radiotherapy.
Conclusion: Primary neuroendocrine carcinoma of the breasts is a rare tumour, classified as a type of invasive mammary carcinoma with distinctive histopathological features. It exhibits morphological features similar to those of neuroendocrine tumours of the gastrointestinal tract and the lung, therefore it is crucial to make an accurate diagnosis and first exclude a metastasis in the breast.

E-PS-02-005
Low grade breast adenosquamous carcinoma: a clinicopathological and genetic study

R. Ondruššek[1]
[1] CGB laboratory a.s., Czech Republic

Background & Objectives: Low grade adenosquamous carcinoma (ASC) of the breast is an unusual and rare variant of metaplastic triple-negative carcinoma with excellent prognosis. Tumour is characterised by small well-developed glandular formations intimately admixed with solid nests of squamous cells in a spindle-cell background. Triple negative carcinomas are included in heterogenous group of tumours with therapeutic limitations. Specific changes in several genes can help to offer targeted therapy.
Methods: In 2018 we diagnosed mammary ASC in three female patients in the segmentectomy specimens. We evaluated clinical data, pathological features and genetic profiling retrospectively. *TP53, EGFR, PTEN, CDKN2A* genes were investigated by fluorescence in situ hybridization (FISH).
Results: The median age of patients was 74 years (ranging from 70 to 79), tumour diameters 0.2 – 2.7cm, TNM stage pT1a - pT2. Sentinel lymphatic nodes were available for their evaluation in 2 out of 3 patients and no metastases were found. FISH did not demonstrate amplification *EGFR* gene (7p11), deletion *PTEN* gene (10q23), deletion *TP53* gene (17p13) deletion *CDKN2A* gene (9p21). All cases showed typical histopathological features of low grade ASC with conspicuous stromal lymphocytic aggregates.
Conclusion: This study confirms excellent prognosis of ASC of the breast without sentinel lymphatic nodes involvement and where available genetic testing turns out to be negative. We suggest that lymphocytic aggregates might be useful and significant morphological feature to improve diagnosis in breast low grade ASC.

E-PS-02-006

Breast adenomyoepithelioma: potential pitfalls in the diagnosis

S. Aviel-Ronen[1], J. Simon[2], M. Papa[3], G. Gitstein[4]
[1] Department of Pathology, Sheba Medical Center, Tel-Hashomer, Israel, [2] Institute of Diagnostic Radiology, Meuhedet Health Maintenance Organization, Rehovot, Israel, [3] Surgery Department, Assuta Medical Center, Tel Aviv, Israel, [4] Pathology Department, Sourasky Medical Center, Tel Aviv, Israel

Background & Objectives: Adenomyoepithelioma of breast is a rare benign tumour of the epithelial-myoepithelial group of lesions. This tumour is characterised by proliferation of myoepithelial cells surrounding small epithelium-lined spaces. Here we describe a case of adenomyoepithelioma and discuss the potential pitfalls in the diagnosis.
Methods: The medical records, imaging tests and pathological findings of a 64 patient have been studied and are presented. A suspicious left breast semi-cystic lesion, 1 cm in diameter, was identified on screening mammography. The core needle biopsy that was performed showed unusual and non-conclusive histological characteristics, therefore a complete excision of the lesion was advised. Subsequently, lumpectomy was performed.
Results: On lumpectomy, a cellular multi-lobulated lesion was identified. The lesion showed proliferation of bland spindle cells occasionally surrounding gland-like structures. Neither nuclear atypia nor mitotic activity were identified. Many myoepithelial cell markers including p63, calponin, caldesmon, podoplanin and CD10 were negative. However, CK 5/6, S100 and SMA stained diffusely the tumour cells, while ER stain highlighted the epithelium-lined spaces. In spite of the partly contradicting immunostain results, it was concluded that the lesion is a benign adenomyoepithelioma.
Conclusion: Myoepithelial cells show diverse appearance with their various immunostain markers and demonstrate differences in their staining sensitivity in different lesions. Therefore, it is crucial to use a broad panel approach and address the morphological features in order to reach an accurate interpretation of epithelial-myoepithelial lesions.

E-PS-02-007

Prognostic value of proliferation marker assessments in patients with different biological subtypes of breast cancer

L. Rudiuk[1,2], O. Reshetnikova[3], S. Korenev[1]
[1] Immanuel Kant Baltic Federal University, Kaliningrad, Russia, [2] Regional Clinical Hospital of the Kaliningrad region, Kaliningrad, Russia, [3] Immanuel Kant Baltic Federal University, Russia

Background & Objectives: Breast cancer (BC) is the most common cancer and the second leading cause of cancer-related death among women. BC remains an important health issue worldwide.
The aim of this study was to correlate tissue expression of proliferation biomarker Ki-67 with different immunohistochemical (IHC) subtypes of breast cancer and to assess the relationship of Ki-67 to tumours histological grading.
Methods: This was a retrospective study including 220 female patients with breast cancer. The histological diagnosis was performed on formalin-fixed and paraffin-embedded breast tissue blocks from pretreatment biopsies and mastectomies. Tumour grading was determined according to Elston&Ellis. IHC analyses were carried out with the help of following monoclonal mouse antibodies: to ER (RTU, Bond 6F11), PgR (RTU, Bond 16), HER2 (Novocastra, CB11 1: 250). Ki67 expression was tested with monoclonal mouse antibodies (RTU, MM1) and then proliferation activity was determined as a percentage of the stained parenchymal component of an invasive breast carcinoma of a no special type (in 10 microscopic fields of view per 1000 cells at magnification x400). Relation between the tumour grade and proliferative activity in biological subgroups of the BC were assessed by Spearman's rank correlation coefficient. High correlation between the two variables got rank 1 (r=1).
Results: Molecular subgroups of the BC cases were distributed as follows: luminal A -45.91%; luminal B HER2- positive - 25.46%; luminal B HER2- negative -18.64%; triple negative-18.18%; HER2- positive - 10%.The majority of cancer samples had histological grade (G) 2, to a lesser extent G1 and G3 were recognized. Luminal B group, both positive and negative, a statistically significant positive correlation was established between the indicators (Spearman correlation coefficient: 0.410521 and 0.403631, respectively). Luminal B group, both positive and negative, had a high correlation between G and Ki67 expression (Spearman correlation coefficient: 0.410521 and 0.403631, respectively). Other molecular subgroups of the BC had a low correlation between mentioned variables.
Conclusion: In order to assess the biological aggressiveness of a breast cancer, a further IHC study of apoptosis and intercellular adhesion needed.

E-PS-02-008

Maligant phyllodes tumour cum CDIS: case report

W. Michej[1], W. Olszewski[2], J. Owczarek[2]
[1] Cancer Centre Instytute Warsaw, Poland, [2] Cancer Centre Instytute, Poland

Background & Objectives: Malignant phyllodes tumour is a rare case end develops in older women. The recognition demands macroscopic, microscopic end immunuhistochemical description. The characteristic whorled pattern, curved clefts is seen in the most lesions. Histologically - a combination of marked nuclear plemorphism of stromal cells, mitotic activity, permeative margins. The aim of this case report is to highlight characteristic details to make a good recogniction of phyllodes tumour and differentiate from metaplastic carcinoma. It is important for futher treatment after surgical removing.
Methods: A 50 years old woman was operated due to 3,0cm tumour of breast. Grossly well defined, grey tumour was revealed. H-E examination showed many pleomorphic cells, necrosis and unregular mitotic figures. Between such pictures the structures of CDIS NG1 were also present. The question was: is it a malignant phyllodes tumour with CDIS or metaplastic carcinoma? Many of immunohistochemical reactions were done. The final diagnosis was - malignant phyllodes tumour (pleomorphic sarcoma) with CDIS low grade.
Results: The woman was observed in our institute. After two years she developed a small lump in the same breast. Histologically it had only a pattern of pleomorphic sarcoma identical to the primary tumour. The component of CDIS was absent. It confirmed our diagnosis that it was a malignant phyllodes tumour.
Conclusion: This case shows the possibility of coexistence of malignant transformations two components in phyllodes tumour. It is important to make a good diagnosis because of futher treatment. The recogniction of metaplastic carcinoma implicates more aggresive treatment after surgery i.e. chemotherapy. After diagnosis of malignant phyllodes tumour with CDIS low grade, excision within healthy limits until recurrence is recommended.

E-PS-02-010

Interobserver agreement between pathologists assessing tumour-infiltrating lymphocytes in breast cancer by applying international TILs Working Group recommendations

R. Ayadi[1], D. Bacha[2], O. Belkacem[2], R. Yaiche[2], A. Ben Amor[3], S. Gharbi[2], A. Lahmar[2], S. Bouraoui[2]
[1] Pathology Department, Military Hospital, Tunis, Tunisia. University of Tunis El Manar, Faculty of Medicine of Tunis, Tunisia, [2] Pathology department, Mongi Slim Hospital, University Tunis El Manar, Medicine Faculty of Tunis, Tunisia, [3] Department of Gynaecology-Obstetrics, Mongi Slim Hospital, University Tunis El Manar, Medicine Faculty of Tunis, Tunisia

Background & Objectives: Several studies highlighted the prognostic and predictive values of tumour-infiltrating lymphocytes (TILs) in breast cancer (BC).
The aim of this study was to determine interobserver agreement between pathologists using the International TILs Working Group recommendations for the assessment of stromal TILs (sTILs) in BC.
Methods: We retrospectively analysed 53 hematoxylin and eosin stained slides of invasive BC, obtained from 26 core needle biopsies and 27 surgical resections. Three pathologists independently reviewed each slide and evaluated sTILs. We used Fleiss's kappa statistics to calculate the overall proportion of interobserver agreement.
Results: The average age was56.5 years.The kappa statistic for sTILs assessment was 0, 55 with15 discrepancies cases.Discordances were mostly noted in surgical resection specimens (37%) compared to micro-biopsies (19%) and interested mainlyTILs proportions in intervals (5-10%) and (40-50%).Discrepancies reasons included the difficult distinction between carcinomatous cells and lymphocytes or granulocytes.In all samples, there has been a tendency to increasingTILs average rates in the presence of a focal hot spot zone.Artefactual retraction spaces helped to distinguish carcinomatous clusters from stromal inflammatory infiltrate.
Conclusion: Acceptable agreement in sTILs assessment was noted when applying the international TILs Working Group recommendations. Sample fixation quality, which is better in micro-biopsies specimen, and a suitable contrasting staining, play an important role in the distinction between cell types.

E-PS-02-011
Comparative evaluation of immunological micro-environment in the study of trepanobiopsy specimens and operational material of invasive breast carcinoma
A. Semenova[1], O. Isaeva[1], A. Vagenin[1], M. Bogatyreva[1]
[1] Chelyabinsk Oncology Clinic, Russia

Background & Objectives: To assess differences in the representation of lymphocyte subpopulations in the biopsy and surgical specimens of breast carcinomas by routine morphological diagnostics; to determine by means of immunohistochemistry if the amount of tissue material is adequate for a reliable study of tumour-filtering lymphocytes (TILs) in breast carcinoma.
Methods: The object of the study was trepanobiopsy specimens and surgical material taken from 60 patients with breast carcinoma with malignancy of various degrees (from G1 to G3). In the surgical material, the central zone of the tumour and the zone of active tumour growth (peritumoural) were evaluated and compared with the biopsy specimen (one tissue sample was taken). Subpopulations of T and B lymphocytes were investigated immunohistochemically using CD4 (Clone 4B12) (Dako), CD8 (Clone SP57) (Ventana), CD56 (Clone 123C3) (Ventana).
Results: The study showed that regardless of the tumour malignancy degree, a significantly smaller number of CD4 positive T-lymphocytes and CD56 positive natural killer cells was observed in the surgical material and biopsy specimens taken from central and peritumoural zones of breast carcinomas. The representation of CD8 positive T-cytotoxic lymphocytes in all studied groups was comparably identical both in the biopsy specimens and in the surgical material, regardless of tumour malignancy degree.
Conclusion: To assess the representation of CD8 positive T-cytotoxic lymphocytes in breast carcinomas, one standard core biopsy specimen is sufficient, regardless of tumour malignancy degree. To assess the infiltration of CD4, CD56 by positive breast carcinoma lymphocytes correctly, comparable to the surgical material, more samples are required, one specimen is not enough.

E-PS-02-012
Primary leiomyosarcoma of the breast: a rare case report
P. Tziakou[1], V. Papamichail[2], E. Delliou[3], A. Zizi-Sermpetzoglou[1]
[1] Department of Pathology of Tzaneio General Hospital of Piraeus, Greece, [2] Laboratory of Pathology "ISTODOMI" - Piraeus, Greece, [3] Laboratory of Pathology - Xanthi, Greece

Background & Objectives: Malignant mesenchymal tumours of the breast, other than angiosarcomas, are rare and comprise <0,5% of breast tumours. Primary leiomyosarcoma of the breast is an extremely rare tumour with <40 cases reported till date. We present a case of primary leiomyosarcoma of the breast.
Methods: A 55-year-old female presented to our hospital complaining for pain with a large lump in her left breast for the last 6 months. Mammography and ultrasonography revealed a well-circumscribed tumour measuring 9x7cm in size, located in the upper quadrant of the left breast. FNA revealed evidence of malignancy and the patient underwent total mastectomy of the left breast and axillary lymph node dissection.
Results: Microcopically, the tumour was composed of pleomorphic spindle cells arranged in intersecting fascicles and bundles, showing frequent mitoses and necrosis. On immunohistochemistry the tumour cells were positive for SMA and desmin and negative for S100p and CD117. Based on the immunomorphological features, the tumour was diagnosed as leiomyosarcoma.
Conclusion: Leiomyosarcoma of the breast may originate from the smooth muscle of the lactiferous ducts of the nipple and the surrounding blood vessels. Differential diagnosis includes leiomyoma, spindle cell myoepithelioma and spindle cell sarcomatoid carcinoma. The prognosis is better than that of other breast sarcomas. The prognostic factors are not fully known because of the limited number of studies. The benefits of chemotherapy, radiotherapy and hormonal therapy are still controversial. However, there is a need for further studies to determine the prognostic factors.

E-PS-02-013
Peptidil argenin deiminase typ 4 level in blood samples of women with different molecular-genetic subtypes of breast cancer
A. Semenova[1], O. Tereshin[1], A. Vagenin[1], I. Dolgushin[2]
[1] Chelyabinsk Oncology Clinic, Russia, [2] South-Ural Medical University, Russia

Background & Objectives: Elevated peptidyl arginine deiminase type 4 (PAD-4) enzyme activity in breast cancer is a well-documented fact, but little is known in connection with molecular – genetic subtypes of breast carcinoma.
Methods: PAD-4 level was determined in serum samples of 98 women with primary breast cancer in period January 2017 – april 2018. They were divided in 5 subgroups based on standart IHC data: group 1 – luminal A cancer, 2 - luminal B Her-2 negative, 3 - luminal B Her-2 positive, 4 - non-luminal Her-2 positive, 5 - triple negative cancer. Samples were obtained before initiation of any oncologic treatment and in 41 cases again 15-24 days after definitive surgery. Also 20 samples were taken from 20 healthy women. PAD-4 level was determined with Human PAD-4 ELISA Kit n automatic analyser ADALTIS Personal LAB. Statistical analysis performed by means of IBM SPSS Statistics 19.
Results: Median PAD-4 level before treatment was 9,0 ng/ml, with the same 9,0 ng/ml median level after surgery. Median enzyme levels for cancer subgroups were as follows: group 1 - 11,05 ng/ml., group 2 - 11,9 ng/ml., group 3 -10,8 ng/ml., group 4 - 7,99 ng/ml., group 5 - 9,9 ng/ml. Median PAD-4 level for healthy women was 1,5 ng/ml (Q1=0,0; Q3=2,0) ng/ml, which is significantly different from cancer group (Mann –Whitney U test, U=38,500, p<0,001).
Conclusion: PAD-4 level was higher in luminal cancer, but further research is needed to make definitive conclusions.

E-PS-02-014
Breast cancer subtypes - single institution results of 11754 consecutive cases
P. Drev[2], O. Blatnik[2], J. Blazina[2], J.A. Bandres Contreras[2], G. Gasljevic[1], M. Gjidera[2], B. Grcar Kuzmanov[2], A. Klevisar Ivancic[2], S. Pavlovic[2], B. Gazic[2]

[1] Department of Pathology, Institute of Oncology Ljubljana, Slovenia,
[2] Institute of Oncology Ljubljana, Slovenia

Background & Objectives: Invasive breast carcinoma (IBC) is a heterogenous disease consisting of a number of subtypes with different prognostic and predictive characteristics. Assessment of breast carcinoma subtypes (BCS) is a crucial factor for management of IBC. Published large-series, long-term, single-institution data on observed frequencies of BCS are scarce.
Methods: Institutional database was searched for IBCs in the period 2006-2018. BCS were classified using molecular tumour biomarkers. ER and PR were assessed immunohistochemically. Cut-off was 1%. HER2 was assessed with both IHC and FISH. Cut-off set according to valid ASCO guidelines. IHC and FISH protocols were EQA monitored. Analysis was performed to obtain data (average and annual variation) on predictive factors (PF) ER, PR, HR, HER2 and BCS.
Results: 11754 consecutive IBC were identified. PF results:87.3% ER, 75.6% PR, 87.7% HR and 13.3% HER2 positive. BCS results: 78.3% luminal-A, 9.3% luminal-B, 3.9% HER2-positive and 8.5% triple-negative (TN). Annual variation was minimal in all PF and BCS, however there is a slight increase in both luminal subtypes and a slight decrease in HER2-positive and TN.
Conclusion: Observed proportions of luminal A (78.3%) and B (9,3%) subtypes are in line with latest reports but slightly higher compared to majority of reports, while proportions of HER2-positive (3,9%) and TN (8,5%) are slightly lower compared to reported values.
Observed slight increase of frequencies of luminal subtypes and decrease in HER2-positive and TN are in line with recently published population studies that show increasing incidence of ER-positive and decreasing incidence of ER-negative IBC.

E-PS-02-015
In situ lobular carcinoma involving the sclerosing adenosis: a report of two case
G. Kir[1], H. Gunel[1], A. Aydin[1]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey

Background & Objectives: Sclerosing adenosis is a common lesion in the breast. Sclerosing adenosis may rarely contain lobuler carcinoma in situ (LCIS) foci and may cause diagnostic challenge.
Methods: We report the first case of a 44-year-old premenopausal women and the second case of a 55-year-old postmenopausal women, both presented with breast pain. On ultrasonography of the first case demonstrated a 8 mm solid isoechoic mass which is a well contoured lesion including milimetric calcification. The second patient's ultrasonography showed a 12 mm solid hypoechoic noduler lesion. Both mammographies were unremarkable (BIRADS 0). The patients underwent core-needle biopsy.
Results: On the microscopic evaluation of both cases revealed stromal fibrosis and expanding solid tubules which preserved lobular architecture.LCIS morphology was seen in most of the tubules. The dyscohesive cells in this tubules were uniform with peripheral round nuclei. On immunohistochemical analysis, myoepithelial cells were observed with p63, CK14, E-kadherin and β- catenin stains. E kadherin and β-catenin staining were lost in the epithelial cells filling the tubulus. Diffuse ER and PR expression were observed. The diagnosis were consistant whit lobular carcinoma in situ involving the sclerosing adenosis.
Conclusion: The presence of LCIS in sclerosing adenosis is rare and may be misdiagnosed as invasive mammary carcinoma. Immunohistochemical staining may be used to resolve this confusion.

E-PS-02-016
No special type invasive breast carcinoma transformed to metaplastic carcinoma after neoadjuvant chemotherapy
G. Kir[1], Z.C. Olgun[1], O. Alimoglu[2]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey,
[2] Istanbul Medeniyet University, Department of General Surgery, Turkey

Background & Objectives: Metaplastic breast carcinoma is a rare and aggressive type of breast carcinoma. Here, we report a case of metaplastic breast carcinoma which transformed from Invasive Breast Carcinoma, No Special Type (NST) following neoadjuvant chemotherapy (NAC).
Methods: 46 year-old woman presented with a palpable mass which was diagnosed with tru cut biopsy as invasive breast carcinoma, NST. The patient received 4 cycles of NAC with anthracyclin and taxane
Results: The patient underwent a segmental mastectomy after NAC. Microscopically the tumour was arranged in a diffuse pattern. Tumour cells had large vesicular, irregular nuclei with prominent nucleoli and abundant cyoplasm. Necrosis was detected in large areas. The neoplastic cells of the excised tumour were estrogen receptor (ER), progesterone receptor (PR), and HER-2 negative whereas on previous biopsy tumour cells were diffusely positive for ER and PR and negative for HER-2. After NAC tumour showed diffuse positivity for EGFR and vimentin, scattered cells stained with P63 and HMWCK. EMA was patchy and weakly positive at neoplastic cells. Tumour was negative for PANCK, CAM 5.2, Cytokeratin 5/6, Cytokeratin 14, and CD34. So the tumour was consistent with metaplastic carcinoma.
Conclusion: Immunhistochemical changes after NAC is not an uncommon finding but morphologic transformation is very rare entitiy. This is the third case of transformation to metaplastic carcinoma after NAC as far as we know from English literature.

E-PS-02-017
The distribution of morphomolecular subtypes of breast cancer in patients who recieved neoadjuvant therapy and breast-conserving surgery
M. Urezkova[1], A. Kudaybergenova[1], E. Turkevich[1], V. Klimashevsky[1], P. Krivorotko[1]
[1] N.N. Petrov National Medical Research Center of Oncology, Russia

Background & Objectives: Beginning with the B-14 NSAB study, the concept of neoadjuvant (pre-operative) therapy for breast cancer is in common use with oncologists. According to P. Cortazar, the frequency of pre-operative therapy is up to 80% in different biological subtypes. The aim of our study is to determine the proportion of BCS after pre-operative therapy, distribution of biological subtypes in this patients and proportion cases achieved complete pathological response (pCR).
Methods: The study included 1016 cases of breast cancer treated with neoadjuvant therapy and subsequent surgery in our center in 2013-2018.
Results: BCS after neoadjuvant therapy was 206 cases (20,2% of patients treated with neoadjuvant therapy and 16% of BCS in total). The distribution of biological subtypes in the group of patients receiving neoadjuvant therapy and BCS:

- "All luminal subtypes"- 119 (57.7%);
- "HER2-positive"- 21 (10%);
- "Triple-negative (TNBC)" - 58 (28%);

In the BCS group pCR was recorded in 23% of cases. Distribution in this group:

- "All luminal subtypes" – 13 (27%);
- "HER2-positive" – 10 (20,8%);
- "TNBC" – 25 (52,2%).

Conclusion: The proportion of BCS after neoadjuvant therapy in our study is significantly less than that described in international studies nevertheless in TNBC we achieved maximal response to pre-operative therapy and can avoid surgery as option for this group.

E-PS-02-018

Androgen receptor expression in non-metastatic breast cancer: has it go any prognostic and predictive value?

D. Lokuhetty[1], B.I. Ruiz[2], H. Wijesinghe[3], V. White[2], I. Cree[1]
[1] International Agency for Research on Cancer, France, [2] IARC/WHO, France, [3] University of Colombo, Sri Lanka

Background & Objectives: Androgen receptor (AR) is emerging as an useful prognostic and predictive marker in breast carcinoma (BCa). Evidence points towards different AR signalling pathways in molecular BCa subtypes with different oncogenic roles. Several studies document AR to have prognostic value in early, non-metastatic BCa, but subtype is less evaluated. The predictive role of AR for targeted therapy has not been evaluated extensively.
This systematic review protocol plans to summarize the prognostic and predictive value of AR expression in non-metastatic breast cancer.
Methods: Electronic databases (PubMed, EMBASE, Cochrane Library, WOS) will be searched. Data base specific search terms related to the review question, such as "breast neoplasm", "androgen receptors", but also other expressions "breast cancer"or "AR expression" will be combined into a tailored search strategy that will include all references from 1980 to March 2019 in English, Spanish, German or French. Studies will be included if they analyse the relation between the AR and its prognostic or predictive value in women with non-metastatic breast cancer, reporting on outcome measures, such as overall survival, disease free survival, progression free survival or median survival.
Results: Results will be screened by two independent reviewers and the initial selection full-text assessed applying eligibility criteria. Data from included papers will be extracted into standardised forms including participant and prognostic factor information, outcomes and effect size. Risk of bias of studies will be assessed using the Quality Prognostic Studies tool and quantitative synthesis of results performed. A narrative synthesis of results will include description of strength and consistency of outcomes, as well as the methodological quality of the studies.
Conclusion: This review will synthesize available evidence for the prognostic and predictive value of AR expression in non-metastatic BCa considering subtypes. Research gaps will be identified and recommendations drafted. The results will update to the 5th series of WHO Classification of Tumours. Review title will be registered and protocol will made available.

E-PS-02-022

Suspicious microcalcifications associated to Xanthogranulomatous Mastitis

L. Campos Clemente[1], L. de Medeiros Reis[1], M.L. Balancin[1], M. Abrantes Giannotti[1]
[1] Department of Pathology, University of Sao Paulo, Brazil

Background & Objectives: Xantogranulomatous Mastitis (XM) is benign, usually self-limited inflammatory condition of the breast. No clear etiology has been established, electing it as an exclusion diagnosis: special stains and cultures should be negative and differentials as histiocytic diseases should be excluded, as well as malignancy. In this series we have reported a cohort of XM cases and evidenced a distinct group of calcification-associated XM. The main objectives of this study were to build an exploratory case series on XM cases from a Brazilian Cohort of patients and describe associated findings.
Methods: Data was extracted from pathology report of our institutional pathology files after an extensive systematic retrieval from the laboratory informatics system on patients subjected to breast biopsies (including core biopsies) and resection specimens from the last 10 years.
Results: 37 women subjected to breast biopsy or resection were retrospectively reviewed from our institutional pathology files. 32 (89%) were biopsy specimens, while 5 (11%) were resection; 17 were located on the right breast (46%) and 20 on the left (54%). Superior quadrants (24, 65%) were followed by retroareolar (14%) and other breast regions. Clear steatonecrosis criteria was evidenced in 9 cases (24%), calcifications, including distrophic and microcalcifications, were evidenced in 11 cases (30%). Other findings reported were usual ductal hyperplasia (2), atypical ductal hyperplasia (1), collunar cell changes (3) and pseudoangiomatous stromal hyperplasia and fibroadenomatoid changes (2). In a subgroup analysis, microcalcification was statistically distinct from other grouped features (p= 0.004, IC (-0.799 - -0.221)). Special stains were performed and resulted negative.
Conclusion: XM is an exclusion diagnosis, usually directly made after special stains result negative. In this series, the presence of a microcalcification group associated to XM in biopsies performed to exclude malignant microcalcifications reveals that this diagnosis should be considered more often as a differential in the breast microcalcifications workup. We have presented a summary of findings for XM and reviewed the most common associated findings, especially the association to microcalcifications, suggesting the important of relying in this differential diagnosis during a microcalcifications workup.

E-PS-02-023

New about the "natural history of cancer"

V. Danilenko[1], V. Onufrieva[1], A. Filin[1]
[1] Voronezh State Medical University named after N.N. Burdenko, Department of Pathological Anatomy, Voronezh, Russia

Background & Objectives: The aim of the study was to clarify ideas about the «natural history of cancer», particularly breast cancer.
Methods: 765 cases of surgical material of breast cancer were studied (protocols of gross-descriptions and microslides). The dynamics of changes in the tumour volume were determined.
Results: The average volume of breast cancer nodes in five decades of women's lives did not differ significantly. Similar was the frequency of occurrence of nodes with cancer-stages double the volume (<1cm^3 ~2sm^3, ~4sm^3, ~8sm^3, >8sm^3). By fluctuating in the zone of small volumes, the cancer nodes reached stable maximum in the region of linear dimensions of about 2.5 cm (>8 cm^3).
Conclusion: The obtained data shows that the nodes of breast cancer grow unevenly, sharply slowing the growth rate as its volume increases. Hence, the single data on the doubling of the volume of specific nodes of breast cancer for some time intervals cannot be extrapolated to the entire «natural history of cancer», as it was postulated before.

E-PS-02-024

Profile of Adenoid Cystic Carcinoma (ACC) of the breast: A 17 year-histopathological review of 13 cases

L.L. Sousa Veras[1], M. Alvares Leão[1], A. Uema Watanabi[1], N. Soares de Menezes[2,1]
[1] Barretos Cancer Hospital, Brazil, [2] European Society of Pathology, Brazil

Background & Objectives: Adenoid cystic carcinoma (ACC) of the breast is a rare subtype. It occurs in less than 0.1% of patients with breast cancer. The objective of this study was to determine the clinical, histological and immunohistochemical features of these tumours.
Methods: A retrospective review between January 2002 and March 2019 was performed using the cancer registry database in a single reference center for cancer treatment in Brazil.

Results: Thirteen patients were diagnosed with ACC. The mean age of the patients was 63.8 years (52-87 years). There was only one male patient. Only 3 patients reported a familial history of breast cancer. There was one case of intraductal carcinoma in the contralateral breast. The size of tumour ranged from 2.0 to 7.5cm. 46% of the patients underwent mastectomy with sentinel lymph node biopsy. The nodal status was positive in just one case. All cases were HER-2 negative. There was only one case in which estrogen and progesterone receptors were positive. Follow-up was done in 53% of patients with 85% patients being free of disease in the last follow-up. There was only one case of distant metastasis for the lung.
Conclusion: Adenoid cystic carcinoma is a rare special subtype of breast cancer with good prognosis despite being a triple-negative tumour.
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E-PS-02-025
HER positivity in breast cancer is not associated with Ki67 of <5% and 50% of HER2 positive breast cancer are PR negative
S. Javidparisijani[1], I. Kim[1], S. Pambuccian[2], P. Tang[1]
[1] Loyola University Medical Center, USA, [2] Loyola Univeristy Medical Center, USA

Background & Objectives: HER2 over-expression or amplification is a poor prognostic factor for breast cancer, It has been suggested to associate with younger patients, higher grades and higher Ki67 expression. ASCO/CAP guidelines recommend all primary breast cancer being tested for HER2 by either IHC or FISH as the primary test, and reflexed to the other test if IHC is equivocal (2+) or FISH is inconclusive. It has been our institutional policy that all HER2 IHC 1+ to 3+ cases reflexed to FISH analysis. Taking the advantage of our available data set, we investigated the relationship between HER2 positivity and these clinico-pathological features, and with a focus on Ki67 and PR expression levels.
Methods: We have reviewed our archival data for primary breast cancer between Jan 2015 and June 2018, and identified 278 cases with both HER2 IHC and FISH analysis. The clinico-pathologic features including patient age, histologic type, histologic grade, and expression of ER, PR and Ki-67 were documented, and the evaluation of positive HER2 with tumour grade, patient age, and ER, PR and Ki67 expression were conducted.
Results: Among the 278 cases studied, 71 cases are HER2 positive, included 3%, 31% and 66% as grade 1, 2, and 3 tumours, respectively; and 4%, 41% and 55% of tumours are in <40 years of age, 40-60 years of age, and >60 years of age groups, respectively. 1) As in relation to Ki-67 expression levels (<5%; 5-10%, 11-20%; and >20%), no tumour with <5% Ki67 expression has positive HER2 regardless of its histologic grade. 2) HER2 positivity is noted in between 5-11% in ER negative and 44-57% in PR negative Grade 2 and grade 3 tumours. 3) There is no significant age difference among different age groups noted between HER2 positive and HER2 negative tumours, even within the same histologic grade.
Conclusion: Ki-67 expression of <5% is not associated with HER2 positive; and over 50% of HER2 positive tumours are PR negative. Larger studies are warranted to confirm these finding; so it could provide guidance to pathologists in perform HER2 reflex test.

E-PS-02-026
Sequential multiplex immunohistochemistry and virtual image reconstruction using a single slide for quantitative Ki67 proliferation index measurement in breast cancer: method development and validation
G. Serna[1], S. Simonetti[1], R. Fasani[1], F. Pagliuca[2], P. Gallego[1], L. Alonso[1], X. Guardia[1], J. Jimenez[1], P. Nuciforo[1]
[1] Molecular Oncology Group, Vall d'Hebron Institute of Oncology (VHIO), Spain, [2] Department of Advanced Biomediacal Sciences, Pathology Unit, University of Naples "Federico II", Italy

Background & Objectives: Immunohistochemical (IHC) stain of Ki67 is a prognostic and predictive marker in breast cancer (BC). However, manual scoring (MS) is semiquantitative at best and suffers from high inter-observer variability which limits its clinical value.
Methods: We developed an innovative digital image analysis (DIA) workflow which uses sequential Ki67 and cytokeratin (for precise automatic tumour cells recognition) IHC staining on the same section. Ki67 proliferation index was determined by DIA and MS in 4 tissue microarrays containing 257 breast cancer tissue cores divided in training (n=140, HR+) and test (n=117, HER2+ and TNBC) sets. Agreement between DIA and MS was calculated using intraclass correlation coefficient (ICC) and Bland-Altman (BA) plot.
Results: In the training set, 124 and 121 cores were evaluable for DIA and MS, respectively. ICCs were 0.928 and 0.807, depending if a cytokeratin mask was used or not. When applied to the test set (115 evaluable cores for DIA and 100 for MS), ICCs were 0.821 with mask and 0.727 without the mask. BA plot revealed that the distance between DIA and MS increased with the magnitude of Ki67 measurement and positively correlated with analysed tumour area.
Conclusion: Sequential multiplex IHC combined with DIA represent a valid alternative to MS for Ki67 measurement. The observed increase in difference between the two methodologies with increasing Ki67 values does not directly impact on clinically relevant thresholds, but points to the poor quantitative nature of MS. Additional data on DIA reproducibility and agreements across different cut-offs will be presented.

E-PS-02-027
Lymphoepithelioma-like carcinoma of the breast: a case report
C. Gkogkou[1], E. Baliou[1], E. Koniaris[1], E. Gioti[1], E. Moula[1], G. Kafiri[1]
[1] "Hippokratio" General Hospital of Athens, Greece

Background & Objectives: Lymphoepithelioma-like carcinoma (LELC) is an exceptionally rare tumour of the breast with only a few cases reported in the literature. It mimics its nasopharyngeal counterpart and its possible correlation to HPV is still being investigated.
Here we present a case of LELC of the breast because of its rarity and the diagnostic challenges it poses on histological level.
Methods: A 57 year-old woman presented with a tumour located in the left breast. Lumpectomy was performed and the surgical specimen was submitted for histological examination. Sectioning of the excised specimen revealed a white, solid, firm tumour measuring 1.6cm and irregular, stellate border.
Results: Microscopically the tumour was composed of large cells with eosinophilic cytoplasm and pale stained nuclei with prominent nucleoli. The cells were arranged in solid nests and small trabeculae, separated by a dense inflammatory infiltrate, composed of small lymphocytes. Lymphoid follicles were also evident. The periphery of the tumour was frankly invasive and no syncytial growth pattern was observed. There was no evidence of necrosis. Mitotic activity was increased. Neoplastic cells were immunoreactive for CK8/18 and e-Cadherin. They didn't stain for ER, PR and Her2. Ki-67 proliferation marker was positive in approximately 30% of the malignant cells.
Based on the above findings, the diagnosis of LELC was established.
Conclusion: The main differential diagnosis of LELC of the breast is medullary carcinoma. The lack of circumscription and the absence of syncytial growth pattern will aid to the correct diagnosis. Pathologist awareness is required to avoid possible diagnostic pitfalls.

E-PS-02-028
Uncommon metastasis of invasive lobular breast cancer to the endometrium,an endometrial polyp, the cervix and a leimyoma: a case report and review of the literature
G. Benkhedda[1], I. El Hafaia[2]
[1] University Algiers, Algeria, [2] EHS Centre Pierre et Marie Curie, Algeria

Background & Objectives: Although it is known that breast cancer can metastasize to many organ sites, metastasis to the uterus is uncommon and usually occurs during widespread metastatic disease. Lobular carcinoma is not the most common histological subtypes of breast carcinoma, but it is the most frequent histologic type that causes gastrointestinal, ggynaecological and peritoneal metastases.When an extragenital tumour metastasizes to the uterus, it is predominantly located in the myometrium; in a minority of cases, the metastasis is confined to the endometrium. The main symptoms of the uterine metastasis depend on the anatomic involvement site. Abnormal uterine bleeding is by far the most important symptom. Uterine metastases account for approximately 4% of genital tract metastases, with 47% of cases involving the breast as the primary site.
Methods: A 50-year-old woman was complaining of postmenopausal uterine bleeding and leucorrhea. Her medical history revealed that she was diagnosed with breast carcinoma 4 years ago. At that time she enderwent a radical mastectomy associated with axillary lymph node dissection pathological examination of the tumour revealed Grade 3 infiltrating lobular carcinoma; stage IIIa (T2 N2 M0).A diagnostic work-up was initiated to detect possible causes of vaginal bleeding. She underwent transvaginal ultrasound, which revealed endometrial thickening (13 mm). A hysteroscopic examination revealed an endometrial polyp in the uterine cavity, which was resected. The morphology and immunohistochemical studies confirmed the diagnosis of metastasis of lobular breast carcinoma to an endometrial polyp.
The patient then underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and partial colectomy.
Results: The hysterectomy measuring (8x5x4). The section slice showed an intramural leiomyoma measuring 3 cm. The cervix presents a white thickening in some places.
Pathology results demonstrated that the endometrium,the uterine leiomyoma and the cervix shared the same histopathological features as those presented by the primary lobular breast carcinoma.
Conclusion: Uterine metastases of breast cancer are very rare; the presence of abnormal bleeding symptoms in a patient with a history of breast cancer should be suggestive of endometrium metastatic disease especially in case of invasive lobular carcinoma.
The current review presents the second reported case of lobular breast carcinoma metastasizing to an endometrial polyp, the cervix and a leiomyoma simultaneously.

E-PS-02-029
Immunohistochemical analysis of cancer stem cell markers CD 133 and ALDH1 expression in carcinoma breast
J. Kini[1], K. Jeepalem[1], H. Kini[1], K. Sahu[1]
[1] Department Of Pathology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India

Background & Objectives: Carcinoma breast is the most commonly diagnosed malignancy, accounting for 22% of all malignancies in women. In India, breast cancer ranks second to cervical cancer with increasing incidence in both developed and developing countries. Carcinoma breast encompasses numerous histological sub-types with unique molecular features and therapeutic response. The aim of the study was to analyse and correlate the expression of cancer stem cell markers CD133 and ALDH1 in carcinoma breast with that of size, stage, grade of tumour, lymphovascular invasion and lymph node status.
Methods: Immunohistochemistry was performed with CD133 and ALDH1 on 130 retrospectively and prospectively collected cases of carcinoma breast. The study samples included mastectomy specimens of breast cancer. Clinical details were retrieved from the case files. Histopathology findings and ER, PR, Her-2 neu status were noted.
Results: A total of 53 cases (40.8%) stained positive for CD133 marker. Similarly, 30 cases stained positive for ALDH1. In the study, more than half of the cases were negative for both CD133 and ALDH1 cancer stem cell markers (55.4%, n=72), whereas about 20% of the cases stained positive for both CD133 and ALDH1 expression. The expression of CD133 had a highly significant correlation with the grade of tumour (p=0.0005). Increased expression was seen in grade 3 tumours. Expression of ALDH1 had a significant correlation with the size of tumour (p=0.0005). Combined expression of CD133 and ALDH1 had a statistically significant correlation with the grade of tumour (p=.0005) and size of tumour(p=0.008).
Conclusion: In our study, we analysed the expression of CD133 and ALDH1 CSC markers in carcinoma breast. CD133 was significantly associated with increased tumour grade. There was significant correlation between ALDH1 expression and tumour size. In combination both the markers correlated significantly with grade and size of the tumours. Identification of cancer stem cells and early intervention with targeted therapy might be of clinical use for a better patient prognosis.

E-PS-02-030
Immunohistochemical evaluation of the possible prognostic significance of MTA-1 protein in breast cancer
M. Lambropoulou[1], A. Maroudas[1], V. Papadatou[1], S. Tologkos[1], O. Pagonopoulou[2], I. Balgkouranidou[1], N. Xenidis[3], G. Tripsianis[4], L. Yorkas[1], S. Meditskou[5], N. Papadopoulos[1]
[1] Histology-Embryology Lab., Medical Department, Democritus University of Thrace, Greece, [2] Physiology Lab., Medical Department, Democritus University of Thrace, Greece, [3] Dep. of Clinical Oncology, Medical Department, Democritus University of Thrace, Greece,
[4] Medical Statistics Lab., Medical Department, Democritus University of Thrace, Greece, [5] Histology-Embryology Lab., Medical Department, Aristotle University of Thessaloniki, Greece

Background & Objectives: Breast cancer is the most common type of cancer in women and the major type responsible for their mortality. For that reason, new cancer prognostic biomarkers are being developed, such as the gene of MTA-1 protein. This particular protein belongs to the metastasis associated proteins family (MTA) and is encoded by the corresponding gene located on chromosome 14q32.33. High expression levels of MTA-1 are observed in cases of tumours and its levels are directly related to cancer aggression and the possibility of metastasis. Expression of MTA-1 has been observed in various types of cancer, such as liver, gastric and ovarian cancer. This research work aims at the immunohistochemical study of the expression of MTA-1 protein in breast cancer and its correlation with clinical-histopathological parameters.
Methods: We used 26 breast tissue specimens derived from patients with various cancer subtypes. Of these 26 patients 24 were women and 2 were men. Indirect immunohistochemistry was performed, using anti-MTA-1 antibody and the expression levels of MTA-1 were then tested and correlated with clinical-histopathological parameters.
Results: Positive expression of MTA-1 was observed in 20 of 26 patient samples. Furthermore, the presence of lymph node metastases was correlated with high MTA-1 levels with statistical significance ($p < 0.001$).
Conclusion: Based on the results of this study, we concluded that MTA-1 protein is a potential effective prognostic marker for this disease and can possibly be used as a therapeutic target. However, due to small sample pool further investigation is required.

E-PS-02-031
Role of protein P66 SHCA in programs epithelial-mesenchimal transition in invasive carcinoma of no special type
T. Bezuglova[1], A. Erzieva[1], T. Bezuglova[1], L. Kaktursky[1], M. Mnikhovich[1], A. Asaturova[2], V. Kometiva[3], I. Vasin[4], S. Snegur[4], K. Bunkov[4], D. Kushch[5], N. Malyugin[5]
[1] Research Institute for Human Morphology, Russia, [2] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation, Russia, [3] National Medical Research Center of Obsterics, Gynaecology and

Perinatalogy, Russia, [4] Ryazan Reginal Clinical Hospital, Russia, [5] Pirogov Russian National Research Medical University (Moscow), Russia

Background & Objectives: Protein P66 SHCA can act as a suppressor and stimulator of carcinogenesis in different types of tumours.p66Shc is involved in the regulation of individual types of cell death and it also participates in the pathogenesis of malignant tumours..p66Shc is involved in the regulation of individual types of cell death and it also participates in the pathogenesis of malignant tumours.
Methods: Researched material of 35 patients with ICNst after radical mastectomy.30 patients (n =30) with metastases in regional lymph nodes, liver, lungs and brain, 5 patients (n = 5) without metastatic lesion. Age of patients was 35-85 years .Patients before the operation did not receive neoadjuvant therapy. The diameter of the tumour site is 0.8-4.0 cm. The degree of malignancy ICNST is G 2- G 3. The research was carried out by using light microscopy and IHC method with the protein p66ShcA (Abcam) and E-cadherin (Dako , LabVisionFlex)with a semi-quantitative estimate.
Results: Expression ofp66ShcAproteinis higher in invasive carcinoma of no special type (ICNST)with confirmed metastases (n= 30) in lymph nodes, liver and brain, than in breast cancer without metastases (n= 5). The severity of the cytoplasmic membrane expression was (+++) in the anaplastic component of tumours (epithelial-mesenchymaltransition zone), unlike fields with a more differentiated tumour component in parallel with changes in expression of E-cadherin (reduced expression of change, until complete disappearance).
Conclusion: The high expression level of p66shccorrelateswith an unfavourable prognosis for breast cancer, which was shown by us in the areas of invasive growth (epithelial-mesenchymaltransition zone) innon-specificcarcinoma.Proteinp66ShcA is one of the first diagnostic biomarkers for identifying malignant tumours with an unfavourable prognosis and aggressive course, regardless of the molecular subtype.

E-PS-02-032
Fibromatosis-like spindle cell lesion occurring after breast reconstruction with omental flap: a case report
S.G. Song[1], J.H. Moon[1], M. Jung[1], Y.J. Hwang[1], J.H. Kim[2], H.S. Ryu[2], I.A. Park[2]
[1] Department of Pathol, Seoul National Univ. Hosp., Republic of Korea,
[2] Department of Pathology, Seoul National University College of Medicine, Republic of Korea

Background & Objectives: Recently, omental flap has been widely used as one of the autologous breast reconstruction methods after surgery. Some complications related to omental flap were reported, including short-term regional problems and recurrence of breast cancer.
Methods: Here, we report a case of fibromatosis-like proliferative lesion in a patient with intraductal breast carcinoma who had a nipple-sparing mastectomy and reconstruction with omental flap.
Results: The patient was a 54-year-old woman who was diagnosed with metachronous intraductal carcinomas in the bilateral breasts. She received breast-conserving surgery for the left breast and eight months later, she undergone nipple-sparing mastectomy and immediate reconstruction using omental-flap for the right breast . Three years later, she complained of palpable mass in reconstructed right breast. Needle biopsy of the mass revealed atypical spindle cells lesion showing focal positivity to cytokeratin in immunohistochemistry stain. She received total mastectomy under a suggestion of metaplastic carcinoma. However, the histologic analysis of the mastectomy specimen showed infiltrative bland-looking spindle cell proliferation resembling fibromatosis or nodular fasciitis and expressed β-catenin in the nuclei. Cytokeratin expression was observed only in a few cells. She was finally diagnosed as fibromatosis-like proliferative lesion.
Conclusion: To the best of our knowledge, this is the first case report of tumour occurrence other than recurrence of carcinoma in omental flap. The diagnosis of the newly occurred lesion with positive staining of cytokeratin in reactive fibroblasts in the harvested omentum was difficult because the possibility of breast cancer recurrence, especially fibromatosis-like metaplastic carcinoma should be ruled out.

E-PS-02-033
Elastic fibers in microenvironment of invasive ductal carcinomas of breast
S. Rjabceva[1], I. Siamionik[1], M. Derevyanko[1]
[1] Institute of Physiology of National Academy of Sciences of Belarus, Belarus

Background & Objectives: Collagen components in the tumour microenvironment substantially influence cancer pathogenesis and progression. Nevertheless, status of elastic fibers and its prognostic role remain unclear. The aim of this study is to estimate the changes of stromal elastic fibers in breast invasive ductal carcinoma.
Methods: Forty-seven slides from 42 female patients were investigated in this prospective study (median 1 slide/case). Histochemical studies for Russell-Movat pentachrome stain was done.
Results: The mean age of the patients was 66.5 (range 30-86). The mean of tumour size was 2.1 cm (range = 0.9-3.0 cm). 25 (59.5%) of the patients had low grade cancer, 14 (33.3%) – medium grade and 3 (7.1%) of the patients had high grade. Lymph node metastases was detected in 21 (50.0%) cases. Thickened elastic fibers was found in tumour tissue in 37/88.1% of patients: around vessels (37/88.1%), in stroma (24/57.1%) and around ducts (15/35.7%). Gamma`s correlation analysis revealed the associations between an increasing of thickness of elastic fibers around vessels and tumour grade ($r=-0.35$, $p<0.05$).
Conclusion: This study showed that the change in the thickness of the elastic fibers in breast invasive ductal carcinoma microenvironment is related to tumour grade. Low grade breast carcinoma of no special type characterised by formed of thickened elastic fibers around vessels often than high grade carcinoma.

E-PS-02-034
Expression of oestrogen receptor, progesterone receptor, and HER2 between primary breast carcinomas and metastatic carcinomas to the lung
H. Lee[1], W. Han[2], S. Im[3], J.H. Kim[4], H.S. Ryu[4], I.A. Park[4]
[1] Department of Pathology, Chungbuk National University College of Medicine, Republic of Korea, [2] Department of Surgery, Seoul National University College of Medicine, Republic of Korea, [3] Department of Internal Medicine, Seoul National University College of Medicine, Republic of Korea, [4] Department of Pathology, Seoul National University College of Medicine, Republic of Korea

Background & Objectives: Estrogen receptor (ER), progesterone receptor (PR), and HER2 are major immunohistochemical (IHC) markers of breast carcinoma. We analysed the difference of IHC markers among primary breast carcinoma specimen without prior chemotherapy (PBC1), post-neoadjuvant chemotherapy specimen of primary breast carcinoma (PBC2), and metastatic carcinoma to the lung (MCL).
Methods: One hundred cases were selected in which paraffin blocks of MCL and PBC1 and/or PBC2 were available. All PBC1, PBC2, and MCL specimens were available in 31 cases. Expression of ER, PR, and HER2 was studied in the PBC1, PBC2, and MCL. McNemar test was used for the changes of the markers among the groups.
Results: There was a tendency of loss of PR expression between PBC1 and MCL ($p=0.095$). This tendency was also shown between PBC1 and

PBC2 (p=0.074). However, there was no difference between PBC2 and MCL. Changes of ER and HER2 were not significant among the groups. Subtype was changed in seven of 87 cases (8.04%) between PBC1 and MCL, three of which were changed from luminal into triple negative and two of which were from HER2 and triple negative subtype. Three cases showed differences in subtype among PBC1, PBC2, and MCL: Subtype of PBC2 in these cases was all triple negative subtype. Subtype of MCL was the same as PBC1 in one case and as PBC2 in two cases, respectively.
Conclusion: IHC studies for ER, PR, and HER2 should be assessed in the resection specimen or metastatic lesion after neoadjuvant or adjuvant chemotherapy for establishing the further treatment plans.

E-PS-02-035
Invasive cribriform carcinomas of the breast: histopathological and prognostic features
S. Demir[1], A. Akder Sari[1], B. Bolat Kucukzeybek[1], S. Yigit[1], D. Etit[1], A. Yazici[1], Y. Kucukzeybek[2]
[1] Izmir Katip Celebi University Ataturk Training and Research Hospital, Department of Pathology, Turkey, [2] Izmir Katip Celebi University Ataturk Training and Research Hospital, Department of Oncology, Turkey

Background & Objectives: Invasive cribriform carcinoma (ICC) is a rare type of invasive breast cancer which has three histological forms: the *pure invasive type* (>90% of cribriform pattern); *the invasive type*, predominant invasive cribriform pattern accompanied by a component of tubular carcinoma; *the mixed type* (except tubular carcinoma). Our aim is to evaluate histopathological and prognostic features of ICC of the breast.
Methods: ICC of the breast diagnosed between 2008-2019 in our department was included in our study.
Results: The study population consisted of 40 female patients (n=16 pure-ICC and n=24 mixed-ICC). Invasive ductal carcinoma was the predominant accompanying component (n=18/24, 75%). No invasive type was identified. The median age was 46,5 years (min43-max53) for pure ICC, and 59 years (min53-max65) for mixed-ICC. The median size of the tumour was 2 cm in both types. Low grade tumours were more frequent in pure-ICC (35.7% vs %21) whereas high grade tumours were more common in mixed-ICC (17.4% vs 7%). Lymph node metastases were present in 42.9% of pure-ICC and 50% of mixed-ICC. All of the tumours were ER and PR positive. Of all tumours, only one case of mixed-ICC was positive for CERB-B2.
Ki67-index was <14% in all tumours except for 6 cases of mixed-ICC and 1 case of pure-ICC. The follow-up time for pure-ICC was 2 to 127 months (with a median of 81 months), and no recurrences/progression was identified.
Conclusion: Pure-ICC of the breast is a very rare type of breast carcinoma, seen in younger patient population and has a very good prognosis.

E-PS-02-036
Metastasis of extramammary malignancies to the breast - report of two cases
S. Foreid[1], J. Lopes[2,1], J.M. Dias[1]
[1] Synlab Pathology Porto, Portugal, [2] Centro Hospitalar São João, Portugal

Background & Objectives: Metastases of extramammary malignancies to the breast are a rare event, representing about 0,2%-1,3% of all mammary malignancies. Excluding hematological malignancies, the number drops well below 1%. The most common reported sites of origin include lung, skin, stomach and ovary.
Due to the high frequency of primary breast cancer and the rarity of metastasis of non-mammary cancers to the breast, a new palpable mass in the breast is usually presumed to be a primary breast tumour.
Recognition of a non-mammary breast metastasis is very important, as treatment and prognosis is very different.
Here we report two cases of metastasis to the breast with primary origin in the colon and lung.
Methods: Patients presented with a firm palpable mass in the breast, suspicious for neoplasia on image studies.
Biopsy reveled an invasive carcinoma, G3 solid pattern with necrosis in one case, and an invasive carcinoma, G2 with papillary features on the other, both triple negative.
No previous malignancy was known.
Results: Specimens revealed well circumscribed tumours, with an unusual morphology, and absence of in situ carcinoma and calcifications, what made the pathologist suspect of metastasis.
Immunohistochemistry helped make the correct diagnosis: metastasis of colon adenocarcinoma and metastasis of papillary lung carcinoma.
Conclusion: Metastasis on extramammary carcinoma are rare in the breast. Some histological features help make the right diagnosis: unusual morphology, well-circumscribed lesion and absence of in situ carcinoma and calcifications.
Immunohistochemistry is particularly helpful, if no previous history of malignancy is known.
Making the right diagnosis is important as to avoid unnecessary procedures and treatment of these patients.

E-PS-02-037
Immunohistochemical evaluation of stromal component of invasive carcinoma of no special type (IC NST)
T. Bezuglova[1], V. Kometova[2], M. Mnikhovich[1], L. Kaktursky[1], A. Asaturova[3], A. Erzieva[1], I. Vasin[4], S. Snegur[4], K. Bunkov[4], D. Kusch[5], N. Malyugin[5], A. Romanov[5]
[1] Research Institute of Human Morphology (Moscow), Russia, [2] Institution National Medical Research Center of Obstetrics, Gynaecology and Perinatology Ministry of Healthcare of the Russian Federation (Moscow), Russia, [3] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation, Russia, [4] Ryazan Reginal Clinical Hospital, Russia, [5] Pirogov Russian National Research Medical University (Moscow), Russia

Background & Objectives: We aimed to evaluate stromal component of invasive carcinoma of no special type (IC NST) using qualitative and quantitive immunohistochemical study.
Methods: We have assessed the post-operative specimens of 118 patients (aged 40-80 years with mean age of 61 year old) with IC NST. Expression of smooth muscle actin, desmin, collagen IV and VEGF was studied.
Results: In invasive carcinomas of solid type basement membrane was absent or disrupted, in scirrhus fragments of basement membrane were absent. Vimentin expression in stroma manifested as presence of fine cytoplasmatic granules, as well as staining of cells' membranes. Most prominent smooth muscle actin expression was detected in invasive scirrhus. Expression VEGF was present in all forms of breast cancer, although in scirrhus it was minimal and was present in 16,3% of all cases. For breast cancer there is a pronounced topographical and quantitive relations between expression of these markers and growth patterns, tumour grade and stages of progression; myofibroblast-like markers (actin, vimentin) are not infrequently situated in the parenchyma and stroma. Collagen IV expression are lowered. Desmoplastic changes in scirrhus manifest with minimal expression of VEGF, other markers are expressed predominantly by stroma regardless to tumour stage.
Conclusion: Our results signify importance of further studies of tumour stroma.

E-PS-02-039
Cystic neutrophilic granulomatous mastitis - the importance of histological diagnosis
C. Dahlstedt-Ferreira[1], R. Rosas[1], D. Gonçalves[1]
[1] Hospital Garcia de Orta, EPE, Portugal

Background & Objectives: Cystic Neutrophilic Granulomatous Mastitis (CNGM) is a rare breast pathology that is believed to arise from *Corynebacterium spp* infection. We present a case of CNGM, a rare disease that clinically is a cancer mimicker.
Methods: A 48 year old woman, multiparous, presented with a mass on her right breast on January 2018 and was thus submitted to antibiotics, without resolution. A year later, she underwent a mammogram, breast ultrasound and magnetic resonance, revealing a mass on her right breast, highly suspicious for a malignant lesion.
Results: The core needle biopsy revealed a stromal mixed inflammatory infiltrate and numerous granulomas formed by epithelioid histiocytes, with cystic spaces on the inside, lined by a rim of neutrophils, with occasional multinucleated gigantic cells. In some cystic spaces we were able to identify gram positive bacilli.
Conclusion: This mastitis is treated through surgical resection or lipophilic antibiotics, and can take weeks or months to be fully resolved. Through this case report, we want to show the distinctive histologic pattern of this rare entity, which is frequently highly suspicious for malignancy by radiology.

E-PS-02-040
Breast metastasis: clinicopathological study of 11 cases
M. Mellouli[1], M. Triki[1], R. Kallel[1], I. Saguem[1], W. Ghribi[1], T. Sallemi Boudawara[1], S. Charfi[1]
[1] Department of Pathology, Habib Bourguiba Hospital, Sfax, Tunisia

Background & Objectives: Breast metastases are rare. They represent 0.4 to 6% of all breast cancers. Our aim is to discuss their clinicopathological features.
Methods: We report a retrospective survey of 12 cases of breast metastases diagnosed over a period of 23 years (1992—2016) in the department of pathology of the university hospital of Sfax (Tunisia).
Results: The diagnosis was carried on a material of cytoponction in two cases, a needle biopsy in seven cases and a surgery specimen in three cases. The primary tumours understood two cases of small cell non-Hodgkin lymphoma, a case of nasopharyngeal carcinoma, a case of retroauricular melanoma, a case of leiomyosarcoma, a case of uterine choriocarcinoma, a case of rectal neuroendocrine carcinoma, a case of small cell lung carcinoma, three cases of gastric adenocarcinoma and one case of a hematological malignancy of underminated origin. All patients were women with a middle age of 37 years. In only one case the mammary metastasis revealed the primary tumour. Clinically, the size average of tumours was 2.9 cm. Bilateral mammary involvement was noted in three cases.
Conclusion: A confrontation of clinical and pathological data with immunohistochemical study is recommended for an accurate diagnosis of breast metastasis.

E-PS-02-041
Unexpected metastatic axillary node in a high grade DCIS
S. Khalid[1], M.W.A. Mangat[1], A. Arnaout[1]
[1] St George's University Hospital NHS Foundation Trust, United Kingdom

Background & Objectives: Axillary node metastasis in pure DCIS is rare and has been reported in literature varying from 2-13%[1].
Methods: A 68 year old female, known to have an intermediate grade DCIS on the right breast treated by complete wide local excision two years ago, was found to have calcifications on the left breast. The biopsy showed high grade DCIS. She underwent left mastectomy and Sentinel Lymph Node Biopsy (SLNB). The frozen section of the SLN showed a 16mm macrometastatic tumour deposit.
Results: Despite extensive sampling, sections from the left breast revealed an intermediate to high grade DCIS (ER and HER2 positive) and a 4.5mm focus of Grade 1 invasive ductal carcinoma, ER positive but HER2 negative. The macrometastatic tumour deposits in the sentinel node however had a completely different morphology and resembled the DCIS as both expressed HER2 receptor gene. All the other axillary nodes were negative. Radiological assessment of the right breast showed no abnormality.
Conclusion: The morphology of the macrometastatic sentinel node was different from the Grade 1 IDC in the mastectomy, in fact it closely resembled the high grade DCIS and that's why we labelled the IDC as an incidental finding. There is evidence of underestimation of invasive carcinoma on initial diagnosis in patients undergoing axillary node dissection for DCIS[2]. But there is no documentation about the possibility of high grade DCIS metastasising in the presence of small low grade focus of invasive cancer. This case is unusual and raises a challenge in the management of these patients.

E-PS-02-042
Solid papillary carcinoma of the breast: an unusual carcinoma involving the breast
R. Ayadi[1], N. Boujelbene[2], M. Driss[2], L. Charfi[2], I. Abbes[2], H. Azaiez[3], K. Mrad[2], R. Doghri[2]
[1] Pathology Department, Military Hospital, Tunis, University of Tunis El Manar, Faculty of Medicine of Tunis, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia, [3] Department of Pathology, Salah Azaïez Institute, Tunis, Tunisia

Background & Objectives: Solid papillary carcinoma of the breast (SPCB), a newly defined entity, is defined as a "distinctive form of papillary carcinoma characterised by closely apposed expansive, cellular nodules." This uncommon tumour frequently demonstrates neuroendocrine differentiation. To date, a few cases have been reported in the literature.
We aimed to report a new case of SPCB and to describe its histopathological and immunohistochemical features.
Methods: We report, a case of a 58-year-old female presented with a mass in the left breast.
Results: A chirurgical biopsy was done and showed a well-circumscribed proliferation typically composed of solid papillary nodules.The diagnosis of SPCB was suggested. Based on these findings,a radical mastectomy with axillary lymph node excision were performed.The gross specimen identified a circumscribed tumour measuring 15 mm with predominantly solid components. Microscopy showed solid encapsulated tumour, with well-defined pushing borders, arranged in lobules with compactly arranged papillary fronds and branching networks of the fibrovascular cores.The tumour cells were bland-looking with low-grade atypia and few mitoses (< 5/10 HPF). On immunohistochemistry, tumour cells are positive for synaptophysin and negative for chromogranin and CD56. P63, a myoepithelial cell marker, is negative along the epithelial-stromal interface of the tumour.The final diagnosis of SPCB was established.
Conclusion: SPCB is an unusual entity with distinctive clinicopathological features and an excellent prognosis.It should be distinguished from conventional breast carcinoma to avoid over-treatment.

E-PS-02-043
Clinicopathological and genetic risk factors of regional metastasis in breast cancer patients
V. Kometova[1], O. Bourmenskaya[1], M. Rodionova[1], M. Dardyk[1], Y. Dergunova[2], P. Borovikov[1], I. Balashov[1], V. Rodionov[1]
[1] National Medical Research Center of Obstetrics, Gynaecology and Perinatology named after acamician V.I.Kulakov, Russia, [2] Ulyanovs Regional Clinical Oncological Center, Russia

Background & Objectives: In 60–70% of breast cancer patients invasive axilla surgery appears to be unnecessary as pathology examination reveals no regional metastases. The aim of our study was to identify the predictors of lymph node involvement in breast cancer patients according to clinicopathological and genetic features of the primary tumour, which could help to avoid unnecessary lymph node dissection.
Methods: Pathological reports of 175 breast cancer patients who underwent breast surgery in V.I.Kulakov RC for OGaP were retrospectively reviewed. Univariate analysis and multivariate logistic regression were used to analyse the correlation between lymph node metastasis and clinicopathological and molecular characteristics of the primary tumour. The included patient age, multi/unifocal growth, laterality and quadrant localization, tumour size, histological type, grade, Integrated Pathological Index (IPI), number of resected lymph nodes, ER- and PR-status, HER2-status, Ki67 index, molecular subtypes and 48 genes.
Results: Tumour size (p=0.0026), IPI (p‹0.001), CCND1 (p=0.021), SCGB2A2 (p=0.022), FOXA1 (p=0.025), FGFR4 (p=0.027), AR (p=0.048), PTEN (p=0.049), TMEM45B (p=0.049), CCNE1 (p=0.05) were the most powerful predictors of axillary lymph node metastases. There was no statistically significant correlation between regional lymph node metastasis and age, tumour localization, molecular subtypes, hormone receptor- and HER2-status and other 40 genes. Multivariate logistic regression of significant variables was used to create a nomogram.
Conclusion: Size of the primary tumour, IPI and 8 genes (CCND1, SCGB2A2, FOXA1, FGFR4, AR, PTEN, TMEM45B, CCNE1) are independent predictive risk factors of axillary metastasis in breast cancer.

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E-PS-02-044

Mucoepidermoid carcinoma of the breast with MAML2 gene rearrangement: a case report

D. Gigliano[1], M. Farinha[1], J. Vieira[1], N. Coimbra[1], C. Leal[1]
[1] IPO-Porto, Portugal

Background & Objectives: Mucoepidermoid carcinomas (MEC) are the most common malignant neoplasms of both major and minor salivary glands. Occasionally, they may occur in other sites such as lacrimal glands, thyroid and, very rarely, breast tissue, with less than 40 cases of breast MEC described in literature. Given their rarity, grading and management are frequently controversial.
Methods: We report the case of a 15-years-old female with long-standing serosanguineous nipple discharge and a 9mm hypoechoic breast nodule detected by ultrasound. The core biopsy of the nodule, performed in another hospital, resulted in a diagnosis of invasive carcinoma, with features of secretory carcinoma. Once transferred to our Institution, an MRI scan detected a smaller additional nodule. A second core biopsy was performed in this smaller nodule, while the slides from the first biopsy were reviewed.
Results: The morphological features of the two nodules were overlapping, both being evocative of salivary gland-like breast carcinomas. Our main diagnostic hypotheses were MEC and secretory carcinoma. Immunohistochemical characterization revealed a ER-, PR-, HER2-, p63+, CK14+ and CK5/6+ phenotype. FISH analysis revealed MAML2 gene rearrangement in 76% of the cells, while no translocations involving the ETV6 gene were found. Based on these findings, a diagnosis of low-grade MEC was rendered. Three years after conservative surgery, the patient is healthy and disease-free.
Conclusion: MEC of the breast is an exceedingly rare neoplasm with distinct morphological and molecular features. Genetic studies, along with morphology and immunohistochemistry, are an essential aid in the differential diagnosis of salivary gland-like breast carcinomas.

E-PS-02-045

Male breast carcinoma in a Romanian series of cases

O.C. Voinea[1], A. Dumitru[2,3,4], T. Georgescu[2,3,4], M. Sajin[2,3,4]
[1] CCSMM, Romania, [2] SUUB, Romania, [3] UMF Carol Davila, Romania, [4] European Society of Pathology, Romania

Background & Objectives: Breast malignancies are the most important generators of morbidity and mortality among women worldwide. Considering its frequency, impresive advances in diagnostic and therapeutic options were made. Being sporadic among male's oncologic lesions, no standardised protocol exists, either for diagnostic, follow up or treatment. All these aspects are borrowed from pathology and oncology guidelines dedicated to female breast cancer. Since the importance of hormonal expression in this type of lesions is universally recognized, we believe that male breast lesions, taking into account it's much worst prognostic and stage at presentation than in women, deserves further studies for a superior approach.
Methods: We present our experience with male breast cancers in a retrospective review series of cases from Pathology Department of University Emergency Hospital Bucharest. Histopathological examination was completed with clinical information and the immunohistochemical expression of several markers was assed.
Results: We identified 6 male breast carcinomas, four of which were encountered in 5th, 6th and 7th decade and the other 2 in young adults (35 and 40 years old). In a single case 2 different breast carcinoma histotypes were found. All of them were G2, with tumoural stages varying between IB to IV. Several hormonal receptors, Ki 67 and HER2 were tested and expressed in each case, in different percentages.
Conclusion: Male breast carcinoma is a rare entity with a poor prognostic, with a diffuse and profound invasion of adjacent structures, with a high expression of hormone receptors and with no histologic relation to gynecomastia, considering that no associated benign lesions were found.

E-PS-02-046

Characterisation of fluorescence signals chromosome 17 centromere in epithelial cell breast ducts

D. Chuglova[1], A. Murashkina[1], A. Kudaybergenova[1], V. Kushnarev[1]
[1] N.N. Petrov National Medical Research Center of Oncology, Russia

Background & Objectives: Normal epithelial cells used as internal control for HER2 in situ hybridization tests for its validity. This study aimed to investigate the morphology of nucleus and fluorescent signals of chromosome 17 centromere (CEP17) in adjacent to invasive carcinoma breast ducts in patients with intermediate (2+) HER2 cases.
Methods: We randomly selected 5 cases of invasive breast cancer without any treatment with non-cancer adjacent ducts on slides and performed fluorescent in situ hybridization (FISH) assay for HER2 amplification. Slides were scanned by Pannoramic 250 (3D Histech) and were assessed by manual tool selection of nuclei and fluorescence signals by annotations on whole slide images.
Results: We quantified 200 non-overlapping nuclei. Mean area of non-cancer nuclei by DAPI was 46,25± 11,5 μm2 (compare 78,4±.16,08 μm2 in cancer cells). Distribution of the fluorescent signals from HER2 gene and CEP17 in non-tumour breast duct epithelium were to red signal: 1,9 ±0,4; to green signal: 2,1±0,3.
Conclusion: Normal distribution of CEP17 and parameters of fluorescent signals of gene HER2 is a key feature for analysis of diagnostic test. Pathologist has to know basic morphological parameters of probe and nuclei.

E-PS-02-047

Programmed death-ligand 1 expression in triple negative breast cancer

M. Bogdanovska Todorovska[1], G. Petrushevska[1], V. Janevska[1], L. Spasevska[1], S. Kostadinova Kunovska[1], R. Jovanovic[1], B. Krsteska[1], A. Eftimov[2], S. Komina[1], P. Zdravkovski[1]

[1] Institute of Pathology, Medical Faculty, Skopje, Assistant professor, Republic of North Macedonia, [2] Pharmacist/ Institute of Pathology, Medical Faculty, Skopje, Republic of North Macedonia

Background & Objectives: Triple negative breast cancer (TNBC) account for 10-20% of all breast subtypes and are associated with poor prognosis. There is no approved targeted therapy for these patients, yet. Programmed death-ligand 1 (PD-L1) expression has been identified in different cancers achieving good results with immunotherapy. There is limited data reporting the PD-L1 expression in TNBC. The aim of this study is to evaluate the expression of PD-L1 in TNBC patients and to analyse the relationship between PD-L1 expression and clinicopathological features of the patients.
Methods: Paraffin tissue blocks from 19 TNBC patients were used. PD-L1 immunohistochemistry was performed using monoclonal mouse anti-PD-L1, Clone 22C3. Expression of PD-L1 was correlated with clinicopathological features. Tumours were defined as PD-L1 positive if there was membranous expression in ≥ 1% of tumour cells.
Results Median age at diagnosis was 56 (range 33-74). PD-L1 was expressed in 7 (36, 8%) of the patients. Six of the patients showed low PD-L1 expression (3-20%) and only one patient showed high expression (>50%). The PD-L1 expression showed no significant correlation with clinicopathological parameters. Although statistically not significant (p>0,05), PD-L1 was more often expressed in high grade tumours with larger size, high clinical stage and mutated p53.
Conclusion: Expression of PD-L1 was found in more than one third of TNBC and correlated with poor prognostic factors. PD-L1 may be a significant marker for predicting prognosis of TNBC patients. These data need to be confirmed in larger study group.

E-PS-02-048

Adenomyoepithelioma of the breast: a case report with review of literature

L.E.B.F. Luísa Brochado Ferreira[1], M. Marques Oliveira[1], R. Amorim[1], C. Estima Fleming[1], B. Fernandes[1], J.R. Brandão[1], N. Lamas[1], J. Raposo Alves[1], J. Ramon Vizcaino[1]

[1] Centro Hospitalar e Universitario do Porto, Portugal

Background & Objectives: Adenomyoepithelioma of the breast is an uncommon tumour characterised by biphasic proliferation of myoepithelial cells around epithelial-lined spaces. A spectrum of histologic patterns may be present, even in different areas of the same tumour. Because of this heterogeneity, these lesions can be diagnostically challenging. Although most tumours usually behave indolently, rare cases have a more aggressive course. For this reason, failure to recognize this entity may lead to inappropriate diagnosis and management. Hence, accurate diagnosis, and adequate excision followed by close follow-up is mandatory.
Methods: A healthy 25-year-old woman, without family history of breast cancer, had a palpable right breast mass. The mammogram showed a heterogeneous nodule, predominantly solid, with cystic areas, and apparently surrounded by a capsule, with 26.7x14.8 mm in greatest dimensions. A 35×25×15 mm nodule was removed. The nodule was composed by areas of elastic tissues with vaguely multinodular appearance and microcystic/ cystic areas.
Results: Histologically, the tumour was constituted by a proliferation of myoepithelial cells, surrounding small epithelial ducts, and presented paucicellar estroma. The myoepithelial cells were cuboid, with abundant, clear and foamy cytoplasm, bulky nuclei with fine chromatin and small nucleolus. About 12 mitoses / 10 large magnification fields were documented, essentially in the myoepithelial component. No significant atypia, infiltrative growth pattern, desmoplasia or necrosis was identified.
Conclusion: Adenomyoepitelioma is a relatively rare benign breast tumour with potential for recurrence, malignant transformation and metastasis. The lesion may be morphological heterogeneous, and has potential to mimic other benign or malignant lesions of the breast, therefore posing a diagnostic challenge.

E-PS-02-049

Pathological features of the structure of the endoprosthesis capsule. Complications reconstructive breast surgery. Look at the pathologist

N. Volchenko[1], I. Shirokih[1], M. Yudakova[2], V. Surkova[1]

[1] Moscow Oncology Research Institute - Branch of the National Medical Radiology Research Centre of the Ministry of Health of the Russian Federation, Russia, [2] Multidisciplinary Medical Center of the Bank of Russia, Russia

Background & Objectives: The installation of a tissue expander or implant immediately after a mastectomy is the most often used method of breast reconstruction. According to American Society of Plastic and Reconstructive Surgeons, currently The share of simultaneous breast reconstruction is more than 70%. In Australia it increased by 9.9% from 1982 to 2000, in Denmark by 14% from 1999 to 2006, in England - by 16.5% from 2006 to 2009 (Platt J., Baxter N., Zhong T. Breast reconstruction after mastectomy for breast cancer. CMAJ 2011).
In our work, we analysed the complications of breast reconstruction:
• Textured endoprostheses
• Polyurethane endoprostheses
• Simultaneous reconstruction of the endoprosthesis with additional shelter
mesh implant
• Simultaneous reconstruction of the endoprosthesis with additional shelter acellular dermal matrix (ADM) Permacol (porcine)
Methods: In our study, 79 (50.31%) observations used an implant with polyurethane coating, 78 (49.68%) used an implant with a textured coating. Morphological study of the formed endoprosthesis capsule was held in terms of 12 months. after operation. (Pic.1,2,3,4)A morphological assessment of the endoprosthesis capsules with various variants of the endoprosthesis coating (ADM and mesh implant). Installed 30 endoprostheses with a sheath of ADM flap, 2 flaps were examined. Morphological examination of the formed endoprosthesis capsule using ADM, as well as net implant was performed for 14 months. after surgery sharp extrusion of the endoprosthesis (Fig. 5, 6).
ADM (cell-free dermal matrix)
Biological implants, or cell-free dermal matrix (ADM) - donor skin flap, by special treatment, devoid of its antigenic properties In Russia it is allowed to use ADM Permacol pork.
Mesh implants (Fig. 7, 8).
• Strengthening the lower slope of the reconstructed chest
• Creation of additional space for a muscle pocket
• Full endoprosthesis shelter
• reasonable material cost
Results: 1. Using polyurethane endoprostheses has several advantages.
• During healing, dense connective tissue grows into the surface. The implant is held firmly in place preventing it from dropping • Eliminates the displacement outward, as well as the rotation of the anatomical implant.

• Netting of a fiber capsule similar to a grapevine (with smooth and textured fiber implants arranged in parallel surface). The structure of the capsule in the form of a lattice prevents its reduction, thereb reducing the occurrence of capsular contracture
Microscopic view of the capsule:
• A characteristic microscopic feature is the presence of triangular polyurethane crystals, which are formed over time during resorption polyurethane foam endoprosthesis. (Fig. 9)
• The fibrous capsule consists of a set of tightly bound tissues that randomly intertwined. (pic.10)
• According to our histological data, despite the claimed advantage polyurethane coating, in the form of reducing the occurrence of contractures, polyurethane triangular structures cause productive inflammatory the reaction with the presence of giant multi-core cells "type of foreign body", which leads to fibrosis and hyalinosis of the capsule tissue, thereby increasing percentage of occurrence of contracture. (fig.11,12)
2. Microscopic view of the capsule of a textured endoprosthesis:
• The fibrous capsule is constructed of dense connective tissue, the fibers of which are located relatively parallel to the surface of the implant, which reduces its extensibility and increases the percentage of fibrous contracture (fig. 13,14)
• In the fibrous capsule along the inner surface, the pseudo-synovial membrane, as it turned out, it occurs twice as often, of varying degrees of severity, in contrast to capsules with polyurethane implants. Psevdosinovialny overlay leads to the formation of fluid between the implant and the fibrous capsule (seroma). (Fig.15,16)
• Inflammatory changes in the fibrous capsule of a textured implant. Severe lymphoid infiltration with the presence of xanthoma cells, which also results to the expressed fibrosis and hyalinosis of the tissue of the capsules and, as a result, to contracture. (Fig.17,18)
3. ADM (cell-free skin matrix)
• Microscopic examination of the endoprosthesis capsule with ADM did not reveal pronounced formation of pseudo-synovial membrane, productive
• The inflammatory reaction was found mainly in the thinned skin. flap (in the reticular and papillary dermis), and in the ADM flap itself is productive inflammation markedly weak. The synovial membrane in the flap examined is not detected (fig. 19, 20).
4. Mesh implants:
• Morphological assessment of endoprosthesis capsules with the presence of a mesh implant in patients after extrusion of the endoprosthesis Rapid germination (large-pore the mesh design fills a three-dimensional collagen fiber mesh, which reduces risk of contracture) (Fig. 21,22)
Conclusion: Complications occurring in patients after endoprosthetics depend on the type capsules formed around the implant, which in turn depends on the type of endoprosthesis or additionally covering it. In the case of polyurethane endoprostheses, complications such as pronounced productive inflammation ("red syndrome"), appear in the first place, contractures are formed in second place, and the third place is the formation of seroma. With a textured implant: the formation of contractures, seroma different severity, inflammatory changes. When using additional ADM closing valves and nets, complications such as contractures and formation of seromas are extremely rare. This technique is used, as a rule, with a small pinch test, the most frequent A complication in this group of patients is the protrusion of the implant and the addition of pronounced nonspecific inflammation.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-03 | Cardiovascular Pathology

E-PS-03-001
Hydatid cyst of the heart, fatal evolution, a case report
Z. Merad[1]
[1] CHU Sidi Bel Abbes, Algeria

Background & Objectives: The hydatid disease remains a public health problem. However, the cardiac hydatid cyst is rare (0.5-2%).
The objective of the work: is to report the rarity of this lesion
Methods: We report a case of cardiac hydatid cyst for a man of 50 years, presented with syncope clinically
Results: A chest roentgenogram showed big enlargement of the cardiac silhouette with deformation of the left arch. The electrocardiogram revealed the presence of the complete right bundle branch block. The ultrasound cardiac showed a cystic mass fluid in the left ventricle. The extracardiac locations were excluded after completion of a comprehensive review. The patient died after refusing the surgical treatment. The macroscopic and microscopic study has confirmed the diagnosis of cardiac hydatid cyst
Conclusion: Cardiac localisation of hydatidosis is rare. Polymorphism Clinical, latency and severity of complications are the essential features. The treatment is essentially surgical. Medical treatment is limited to disseminated and non-operable forms. The eradication of this condition in endemic countries requires effective prevention.

E-PS-03-002
Morphological features of the peripheral arterial occusive lesions in diabetic patients with critical limb ischemia
B. Magrupov[1], S. Temirov[2], V. Ubaydullaeva[3,1], T. Kamalov[4], B. Tursunov[2]
[1] Tashkent Institute of Postgraduate Medical Education, Uzbekistan,
[2] Central hospital of the ministry of internal affairs, Uzbekistan,
[3] Republican Research Center of Emergency Medicine, Uzbekistan,
[4] Republican specialized scientific and practical medical center of endocrinology, Uzbekistan

Background & Objectives: Critical limb ischemia (CLI) is one of the severe complications of diabetes mellitus (DM). An assessment of the morphological changes of the arteries may help clarify the causes of the aggressive course of the process in the peripheral arteries in patients with DM.
The object of this work was to study the morphological changes in the peripheral arteries in the diabetic patients with critical ischemia.
Methods: A morphological analysis of the arteries of the amputated lower limbs was carried out in 14 patients with DM. Specially prepared fragments of arteries were studied under a light microscope, and their morphometric study was also conducted.
Results: In 12 cases of 14 the calcification of the middle layer of anterior tibial artery occurred in different severity, in 6 there was a thickening of the intimal due to the accumulation of cholesterol and proliferation of smooth muscle cells.
In the posterior tibial artery, in 11 cases, calcification of the middle layer in different severity was detected. In 5 cases, an intimal artery thickening due to the atheromatosis was observed and similar lesions were observed in the peroneal artery.
Conclusion: Peripheral arterial lesions in patients with DM are not a purely atherosclerotic process. Considering the presence of middle layer calcification, it probably necessary to review the algorithm of pharmacological therapy in diabetic patients with peripheral arterial occlusive lesions, taking into account the disturbance of mineral metabolism.

E-PS-03-003
Giant cell myocarditis associated with immune checkpoint inhibitor treatment for metastatic renal cell cancer
A. Bdioui[1], K. Amemiya[1], P. Bruneval[1]
[1] Hopital Europeen Georges Pompidou, France

Background & Objectives: Myocarditis represents a severe complication of cancer immunotherapy. Lymphocytic-type myocarditis has been constantly reported in this setting. Giant cell myocarditis (GCM) is rare and characterised

by a specific histopathology showing giant cells and by inexorable outcome leading to cardiac failure whatever the treatment. We report a case of GCM occurring during immune checkpoint inhibitor treatment.
Methods: A 53-year old male patient had nephrectomy for renal cell carcinoma in October 2013. From December 2017 to January 2019, he received 27 cycles of nivolumab, an anti-PD1 antibody, inducing partial metastasis regression without complications. In January 2019 he was admitted for rapidly progressive cardiac failure (Normal coronary angiography; Ejection fraction at 36%, global hypokinetic left ventricle, and edema at echocardiography and MRI; Troponin T at 5,800 □g/L).
Results: Endomyocardial biopsy showed GCM with extensive myocyte necrosis. Viral molecular study was negative. Nivolumab was stopped. Intravenous methylprednisolone pulses were given, followed by tapered oral. Cardiac failure, imaging, and biological parameters improved in a few weeks allowing discharge from the hospital. Although we cannot definitely rule out coincidence of immunotherapy and occurrence of a rare type of myocarditis, this case of GCM is very unusual since cardiac failure, biological and imaging parameters improved under steroid treatment and withdrawal of nivolumab.
Conclusion: This suggests two hypothesis: 1- GCM could be a second type of myocarditis complicating immune checkpoint inhibitors besides lymphocytic myocarditis; 2- Autoimmunity could be involved in this puzzling type of myocarditis in which so far no viral or immune mechanisms had been documented.

E-PS-03-004
Atresia of common pulmonary vein (ACPV) of fetus: an autopsy analysis
D. Chen[1,2], J. Shang[1,3], W. Fang[1,3]
[1] Department of Pathology, China, [2] Beijing Anzhen Hospital, Capital Medical University, China, [3] Beijing Anzhen Hospital, Capital Medical University, China

Background & Objectives: Objective to investigate pathologic manifestations of atresia of common pulmonary vein (ACPV) of fetus by autopsy.
Methods: Three pathological specimens of atresia of common pulmonary vein of fetus were studied and who had been found by using echocardiography.
Results: Of the 3 casesone was of complete and two were of incomplete atresia of common pulmonary vein. 3 cases were associated with total anomalous pulmonary venous drainage (TAPVD). They also had other complex congenital heart disease and associated with visceral heterotaxy and asplenia. It was different from infant that the fetus was not associated with pulmonary lymphangiectasis.
Conclusion: ACPV is an extremely rare congenital heart disease. It is even more difficult to establish a diagnosis of ACPV if not associated with pulmonary lymphangiectasis.

E-PS-03-005
Complex characteristics of various of the heart different forms myocardial infarctions
V. Ubaydullaeva[1,2], B. Magrupov[2]
[1] Republican Research Center of Emergency Medicine, Uzbekistan,
[2] Tashkent Institute of Postgraduate Medical Education, Uzbekistan

Background & Objectives: Coronary heart disease remains one of the topical diseases of medicine, connected mortality its prevalence and a stable first place in the structure of the able-bodied population in most countries of the world. Currently more than 20 risk factors of coronary heart disease have been identified. Atherosclerosis is one of the main causes of coronary artery disease.
Methods: A complex morphological and morphometric study of the heart muscle in 247 patients who died from various forms of myocardial infarction (MI) was carried out. Myocardium for morphological investigation from the following area was taken the necrosis zone border zone 2 cm from the necrosis area, opposite to the necrosis of the left ventricle (LV) and the right ventricle (RV) walls. Sections were stained with hematoxylin and eosin, pikrofuksinom, Schiff's reagent. Frozen sections were stained with Sudan III.
Results: The zone of necrosis expanded during the first 72 hours. In the zone bordering the infarction, changes interstitial to the necrosis zone were with observed 8-12 hours delayed. At a distance of 2 cm. there were dystrophic, edema. Perivascular edema, vascular plethora were noted in the opposite of the infarction wall of the LV, RV.
Conclusion: At recurrent and continuous recurrent MI a pathological process is more extensive and dystrophic changes along the periphery are more apparent. An increase of the heart with a predominance of width over length, an increase in mass by more than 200 grams, and a restructuring of the cardiac tracts corresponding should be considered as the risk limit for MI development.

E-PS-03-006
Myocardium: structure-functional relationship
V. Zakharova[1,2], E. Trembovetskaya[2], A. Balabai[3], E. Rudenko[2], T. Savchuk[3]
[1] Ukrainian Society of Pathologists; International Academy of Pathology, Ukraine, [2] Amosov National Institute of Cardiovascular Surgery, Ukraine, [3] Bogomolets National Medical University, Ukraine

Background & Objectives: The Torrent-Guasp theory about unique myocardial band contradicts the data of histological and functional studies. In 2018 a group of authors from 10 universities published 2 articles in which they debunked this concept. But the question, how the myocardium provides a complex trajectory of heart movement, needs further study.
Objective: to study the role of myocardial architecture in the formation of a complex trajectory of the heart left ventriculum (LV) movement.
Methods: Macroscopy: 10 boiled prepared pig hearts. Microscopy: serial histological sections of 16 fetal hearts (abortion at 20-21 weeks of gestation due to medical reasons, not related to the heart pathology): 10 hearts were cut across, 3 - in the frontal and 3 - in the sagittal planes.
LV mechanics were studied in 35 healthy young volunteers using speckle tracking echocardiography. The longitudinal displacement, rotation angles and degree of myocardial deformation were evaluated for each of 17 myocardium segments.
Results: The apex of the heart rotates counterclockwise by 12,5±1,1°, the basal segments – clockwise by 8,3±1,4°. The median LV part doesn't rotate, but moves most of all radially. Basal segments show the maximal longitudinal displacement, apical – minimal, apex - maximal deformation. Myocardium is 3D-cardiomyocytic network, the compact layer of which at the base and apex turn into trabeculae, forming a closed contour. There are bundles in it, the direction of which corresponded to the segmental trajectories of LV movement.
Conclusion: Systolic movement of LV myocardium is provided by a consolidated contraction of its different segments in the longitudinal, radial and circulatory directions. The motion vector of each myocardial segment depends on the orientation of its muscle fibers and their contractions sequence. Trabeculae contract first of all and therefore they are initial fulcrum for cardiomyocytes of the compact myocardium.

E-PS-03-007
HSP70 overexpression in calcified aorta affected by atherosclerosis
A. Romaniuk[1], I. Radomychelski[2], M. Lyndin[3], A. Piddubnyi[1], V. Sikora[3], M. Baumann[4], R. Moskalenko[1]
[1] Sumy State University, Ukraine, [2] Sumy State University, Department of Pathology, Ukraine, [3] Sumy State University, Medical Institute, Department of Pathology, Ukraine, [4] Internistische Fachklinik Dr. Steger Ag, Germany

Background & Objectives: High levels of HSP70 appear to have atheroprotective effect. It was reposted, that antibodies to HSP70 were increased in patients with vascular disease. Also HSP70 levels correlate with lesion severity. Aim of the investigation was to study the HSP70 expression in aortic tissue with calcifications affected by atherosclerosis.
Methods: We examined 30 samples of mineralized aorta with calcifications (group I) and 10 samples of aorta wall tissue without any signs of biomineralization (group II). The group II was considered to be a control group. Histological and immunohistochemical methods were used during the study. Samples were fixed, embedded in paraffin, and analized for HSP70 accumulation using the anti-HSP70 antibody, followed by DAB detection substrate and counterstained with Mayer's hematoxylin.
Results: HSP70 expression was increased in aortic tissues with calcifications (23.4±1.28 cells per 1 mm2) in comparison to those without them (11.5±1.14, $p<0.001$, Student test). HSP70 was mostly localized in cells cytoplasm of macrophages, fibroblasts, endothelial cells and smooth muscle cells, also in the tissue around the calcifications.
Conclusion: Overexpression of HSP70 was found in several cell types in aortic mineralized tissue affected by atherosclerosis may be regarded as its involvement in the formation of such biominerals.

E-PS-03-009
Angiosarcoma developing in dialysis-related arteriovenous fistulae: two cases with review
R. Almeida[1,2], H. Moreira[1], J. Fraga[1], B. Pimentão[1], A. Lai[1], V. Almeida[3], C. Faria[1], F. Ramalhosa[1], R.C. Oliveira[1], V. Sousa[3], M. Julião[1], M.A. Cipriano[1]
[1] Centro Hospitalar e Universitário de Coimbra - Pathology department, Portugal, [2] Faculty of Medicine in Coimbra, Portugal, [3] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, Universitário

Background & Objectives: Arteriovenous fistula (AVF) is the first method considered for vascular access in patients with renal failure, who require or may require renal dialysis. Recent studies suggest that AVF should not be ligated post-transplant, except in cases of ischemia, infections or aneurysms.
Angiosarcoma in AVF is a very rare complication in non-functioning fistulae, usually after transplant. Typically, presents as an enlarging painful lesion of several months duration, and such conditions should raise concern about this entity.
Methods: A retrospective research at Coimbra Hospital and Universitary Center, over a period of 15y, revealed two cases of angiosarcoma in AVF. A 82y-old male under hemodialysis, presenting a 4,5cm painful mass in the right arm, growing over a non-functioning AVF. A 54y-old female with history of renal transplant 15y before, with a pulsatile subcutaneous lesion in the left arm, 9,5cm, clinically diagnosed as an aneurysm of a non-functioning AVF. Both patients were submitted to excisional surgery.
Results: Histology showed ulcerated neoplasias with deeply infiltrating borders, compromising the surgical margins, composed of epithelioid cells, with solid growth and focal vascular-like pattern. Neoplastic cells were vimentin and vascular markers - CD31, CD34, ERG and Fli-1 - positive, without staining for keratins. The male patient died 6 weeks after surgery, and the female patient has no known relapse until the moment of submission (1 month after surgery).
Conclusion: Angiosarcoma is a rare mesenquimatous neoplasia, deeply invasive with a very aggressive behavior, and a low disease-free survival. The aim of this work is to warn physicians about the developing of angiosarcoma in AVF, particularly in immunosuppressed patients, commonly after transplant.

E-PS-03-0010
Mitral valve caseous calcification with interventricular involvement: presentation of two cases
S. Papadodima[1], J.R. Stone[2]
[1] Department of Forensic Medicine and Toxicology, National and Kapodistrian University of Athens, Greece, [2] Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA USA

Background & Objectives: Caseous calcication of the mitral annulus (CCMA) is a rare variant of mitral annular calcification. Extension of mitral caseous calcification along the fibrous skeleton of the heart is extremely rare. We report two cases in which an extensive involvement of the interventricular septum was revealed during the pathological examination.
Methods: A retrospective analysis of the pathology database of Massachusetts General Hospital during the period 2010-2015 was performed in order to identify cases with CCMA with interventricular septum involvement.
Results: Two cases were identified. **Case 1.** An 83-year-old man underwent surgical aortic valve replacement. During the surgery, the bicuspid aortic valve was found to be heavily calcified. A large amount of calcium with an area of liquefaction within the interventricular septum was observed, and a septal myectomy was performed. Pathologic examination of the interventricular septum revealed patchy calcification with areas of caseous calcification. **Case 2.** A 70 year old female died on the third postoperative day after aortic and mitral valve replacement, left atrial appendage amputation, and decalcification and pericardial patch repair of the mitral annulus. Gross examination of the heart revealed two well-circumscribed, soft, white mass lesions in the interventricular septum focally abutting the mitral valve, which upon histology showed caseous calcification.
Conclusion: CCMA is often considered a benign process; it is usually asymptomatic and an incidental finding. However, in the case of interventricular septum involvement, it may cause several conduction system disorders. Such interventricular septum involvement may be misinterpreted as a neoplasm on imaging, prompting unnecessary surgery.

E-PS-03-011
Cardiac Fibroma in 4-month-old infant: a case report
D. Anestakis[1], I. Leonida[1], E. Petrou[1], C. Leonida[1], E. Chatzifotiou[1], E. Zagelidou[2]
[1] Department of Autopsy Histopathology, Lab. of Forensic Medicine and Toxicology, Aristotle University of Thessaloniki, Greece, [2] Thessaloniki Forensic Service, Thessaloniki, Greece

Background & Objectives: Cardiac Fibromas are benign primary tumours of connective tissue, situated in the heart; especially in the ventricles or in the interventricular septum. The frequency of Cardiac Fibromas is higher in Paediatric population and ranges from 0.03-0.032% in the general population. We report a case about a sudden death of an infant with cardiac fibroma.
Methods: The 4-month-old female passed away unexpectedly at home without previous hospitalization. There were no symptoms, but the autopsy examination of the cardiac tissue revealed three white-grey mattered masses composed of fibroblasts located in the ventriclescovering the largest part of the cavity.
Results: According to the histological findings, in some parts of the masses were found homomorphous atractoid cells, disseminated and intertwined among collagen fibrils. There were rare inflammatory cell-clumpingsnear healthy tissue, elements of autolysis, median swelling, places of median fibrosis around vessels. There were places of fibrotic connective tissue inside the myocardium, locally myocardial fibers have waveform morphology, layout disorder, while there are inflammatory

cells and capillaries with varying degree-thickened walls. There are locally ischemic lesions and presence of neoplasm, which looks like fibrosis.
Conclusion: The diagnosis of primary cardiac fibroma is of great importance, because although is benign it might be fatal. The prognosis is poor if the fibroma is not surgically resectable. There is no prediction depended on sex or race. Cardiac fibrosis may cause heart failure, cyanosis, arrhythmias, syncope, chest pain or sudden death.

E-PS-03-012
A rare cardiac benign tumour case report: papillary fibroelastoma
T. Bolme Savli[1], H.E. Pasaoglu[2], T.C. Savli[3], F. Emre[1]
[1] Bagcilar Training and Research Hospital, Turkey, [2] Clinical Pathology, Turkey, [3] Istanbul Training and Research Hospital, Turkey

Background & Objectives: Papillary fibroelastomas are the third most common cardiac tumours after myxoma and lipoma. Papillary fibroelastoma is the most common tumours located on cardiac valves. Surgical resection should be offered to all patients who have symptoms and to asymptomatic patients who have pedunculated lesions or tumours larger than 1 cm in diameter.
Methods: We report a 75-year-old male patient. A routine echocardiogram revealed small pericardial effusion, patent foramen ovale and 1.3x1.2x1 cm sized mobile cardiac mass attached to the aortic valve.
Results: The tumour was surgically removed and histopathological examination confirmed the diagnosis to be a cardiac papillary fibroelastoma.
Conclusion: Although cardiac papillary fibroelastomas are commonly detected incidentally, they can cause embolization and mortality. Since our papillary fibroelastoma case causes pericardial effusion and patent foramen ovale, we found it worth to present.

E-PS-03-013
Leiomyosarcoma of the inferior vena cava and renal vein: a case report
A. Ok Atilgan[1], E. Yilmaz Akcay[1], B. Ozdemir[1]
[1] Baskent University Faculty of Medicine Pathology Departmant, Turkey

Background & Objectives: Leiomyosarcoma of the inferior vena cava is a rare mesenchymal tumour originated from smooth muscular fibers of the tunica media. They grow slowly and extend to the adjacent tissue.
Methods: A 57-year-old-woman had developed an abdominal distention and pain during the last one year. Radiological imaging revealed a large mass in the left renal vein extend to inferior vena cava, suprarenal vein, and ovarian vein.
Results: The patient underwent a left nephrectomy and resection of the vena cava inferior. Macroscopic analysis revealed a 13x7x6 cm diameter mass which was grown up an intraluminal extension of inferior vena cava, renal vein, suprarenal vein, and ovarian vein. Extraluminal extension into renal parenchyma, renal sinüs, renal pelvis was not seen. Cut surface of the tumour was gray-white, firm and whorled. In microscopic examination, the tumour showed hypercellular spindle cell with moderate to severe nuclear atypia, tumour cell necrosis, increased mitotic activity. Tumour originating from the wall of the renal vein and inferior vena cava was also observed. Immunohistochemistry showed strong positive staining for caldesmon, smooth muscle actin, and negative staining for CD117, DOG-1, S-100, CD34, Fli-1.
Conclusion: Leiomyosarcoma of vascular origin was located in the larger vein, especially vena cava. The differential diagnosis includes angiosarcoma, leiomyosarcoma, intravenous leiomyomatosis, sarcomatoid renal cell carcinoma invasion, clinically and pathologically. Total surgical resection with negative margins of the tumour is the main treatment for leiomyosarcoma.

E-PS-03-014
Calcified amorphous tumour of the heart: a case report
C. Gkogkou[1], V. Lozos[1], E. Koniaris[1], E. Nikolopoulos[1], K. Tsiardis[1], G. Kafiri[1]
[1] "Hippokratio" General Hospital of Athens, Greece

Background & Objectives: Calcified amorphous tumour (CAT) is an exceptionally rare endocardial non-neoplastic mass of unknown pathogenesis that was first described in 1997. Since then less than fifty cases were reported in the literature.
Here we present a case of CAT because of its rarity and the diagnostic challenges it poses predominantly on clinical level.
Methods: A 75 year-old woman presented with recurrent ischemic strokes. Echocardiographic examination revealed a pedunculated mass attached to the posterior leaflet of the tricuspid valve. The lesion was excised and it was submitted for histological examination in three pieces. Grossly the pieces were whitish, solid and hard, with diameter ranging between 0.8-1.3cm.
Results: Microscopically the lesion was composed of connective tissue and masses of fibrin with extensive calcification. The connective tissue lacked hypercellularity and cytologic atypia. A moderate number of foreign body multinucleated giant cells were also focally evident. There were no epithelioid granulomas, fungal hyphae, parasites or other cellular elements.
Based on the above findings, the diagnosis of CAT was established.
Conclusion: Patients with CAT are reported to present with non-specific symptoms, like dyspnea, arrhythmias or syncope. Clinical awareness of this rare entity is required, since its non-neoplastic nature may allow for a conservative management in some, mainly elderly patients. Excised masses should be thoroughly sampled to exclude the possibility of underlying granulomatous or neoplastic processes.

E-PS-03-015
Brachial artery fusiform aneurysm with intimomedial mucoid degeneration in a young child - a case report of a rare entity
N.J. Lamas[1], M. Oliveira[1], L. Ferreira[1], C. Fleming[1], R. Amorim[2], J.R. Brandão[2], B. Fernandes[2], F.E. Costa[1], D. Tente[1], J.R. Vizcaíno[1]
[1] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Porto, Portugal, [2] Centro Hospitalar do Porto, Portugal

Background & Objectives: Intimomedial mucoid degeneration (IMMD) is an extremely rare vascular disorder characterised by mucin deposition in both the tunica intima and media of arterial walls, with associated elastic tissue degeneration of both internal and external elastic lamina, leading to aneurysm formation.
Methods: We report the case of a 4 year-old male child who had two bilateral brachial artery and right common iliac artery fusiform aneurysms detected at 12 months of age through magnetic resonance imaging. The patient has been under surveillance for nearly 3 years and recently underwent vascular surgery to remove the right brachial artery aneurysm since the presence of a thrombus was suspected.
Results: A two centimeter tubuliform specimen was received, with fusiform morphology, having 3 mm diameter in the surgical ends and 8 mm diameter in the middle region. The external surface and the internal lining were smooth. The histological analysis showed a large caliber arterial wall with marked expansion of the intimal and specially medial layer secondary to the extensive extracellular deposition of mucin-like material (colloidal iron and PAS/Alcian blue positive stainings), with accompanying fragmentation of both the internal and external elastic lamina (emphasized using the Van Gieson elastin staining). Furthermore, we could not observe thrombus formation, inflammatory infiltrate, degenerative cysts, fibrotic areas or amyloid deposition in the wall (absence of congophilic areas or apple-green pigment under polarized light after Congo Red staining). A diagnosis of intimomedial mucoid degeneration of the brachial artery was made.

Conclusion: This case illustrates the main features of this extremely uncommon cause of aneurysm formation.

E-PS-03-016

A rare case of sudden arrhythmic cardiac death

R. Henriques de Gouveia[1], C. Cordeiro[2], F. Corte Real[2]
[1] INMLCF & FMUC & CHLO, Portugal, [2] INMLCF & FMUC, Portugal

Background & Objectives: Among Sudden Cardiac Deaths, Arrhythmic ones may be difficult to explain. The authors present a case with an unexpected cause.
Methods: A 32 year-old male – with medical history of arrhythmia [suspicion of Wolf-Parkinson-White (WPW) Syndrome] for 12 years –, died suddenly during sleep, after a previous physical effort.
Results: A thorough *postmortem* examination revealed cardiac pathology – "*Persistent Left Superior Vena Cava* and *Coronary Sinus Orifice Atresia*".
Conclusion: This congenital cardiopathy is rare, with 99 known cases reported, and may be associated to other cardiac malformations and/or rhythm / conduction disturbances, namely WPW Syndrome type. Being aware of these associations may facilitate *antemortem* diagnosis and directed therapeutic intervention.

E-PS-03-017

Dystrophin Cardiomyopathy

R. Henriques de Gouveia[1], R. Anjos[2], J.P. Neves[2], S. Ramos[2]
[1] INMLCF & FMUC & CHLO, Portugal, [2] CHLO, Portugal

Background & Objectives: Cardiomyopathy is a phenotypic manifestation of *Dystrophinopathies*. The authors present such a case.
Methods: A 23 year-old male, with family and personal medical history of Dystrophinopathy, was submitted to heart transplantation due to cardiac failure. The native heart specimen was sent to anatomo-pathological examination.
Results: Macroscopic and microscopic evaluation (complemented with histochemistry and immunohistochemistry) revealed a "Dilated Cardiomyopathy Dystrophin-Deficient".
Conclusion: The present case intends to draw attention to Dystrophin Cardiomyopathy, since with increased survival of dystrophinopathies' affected persons due to therapy improvements and classic complications control, cardiac involvement (25% to 90%) has become an important cause of morbidity and mortality.

E-PS-03-018

IgG4 related disease in heart valves

T. Paavonen[1], E. Niinimäki[2], A. Mennander[3], I. Kholová[4]
[1] Department of Pathology, Fimlab Laboratories and Department of Medicine and Life Sciences, University of Tampere, Finland,
[2] Department of Anesthesiology, Southern Carelian Central Hospital, Lappeenranta, Finland, [3] Department of Cardiothoracic Surgery, Heart Hospital, Tampere University Hospital, Tampere, Finland, [4] Department of Pathology, Fimlab Laboratories and University of Tampere, Finland

Background & Objectives: Immunoglobulin G4 (IgG4) related disease is a systemic disease involving various organs as well as vascular structures like aorta. There is rather limited data on IgG4-related disease in other vascular tissues for example heart valves.
Methods: Sixty surgically resected heart valves were included (48 aortic and 12 mitral valves). There were 44 males and 16 females with a mean age of 60 years. There were 24 valves with endocarditis (19 acute endocarditis, 3 chronic endocarditis, and 2 healed endocarditis). Degeneration was the main diagnosis in 36 cases, of which 17 had significant inflammation without full criteria of endocarditis. Immunohistochemistry was performed using Ventana Lifesciences Benchmark XT Staining module. CD38/CD138, IgG and IgG4 were used as antibodies to identify IgG/IgG4 positive plasma cells.
Results: Increased IgG4 positive cell infiltration was found in four patients. Two degenerative heart valves with IgG4 positive plasma cells fulfilled the generally accepted criteria of >50 IgG4 positive cells/HPF, one mitral and one aortic valve. However, also two other valves had >20 IgG4 positive cells/HPF.
Conclusion: IgG4-related disease may impact heart valves and heart can be be the first presenting organ of systemic disease.

E-PS-03-019

Structural changes in the myocardium in cases of sudden cardiac death in young males

A. Sapargaliyeva[1], K. Ospanova[2], T. Zhakupova[2], F. Galitskiy[2]
[1] Pathology Bureau of the city of Almaty, Kazakhstan, [2] Department of Forensic Medicine, Astana Medical University, Kazakhstan

Background & Objectives: Mast cells (MC) are found in various tumour types, but their pro or antitumoural role in prostate carcinoma is still debated. There are divergent opinions regarding MC correlation with prognostic factors. There are also contradictory findings regarding correlations between MC number and Gleason score (GS) in needle biopsy samples and radical prostatectomy. Our aim was to evaluate the MC distribution and its correlation with prognostic factors.
Methods: Ninety patients who underwent transurethral resection of the prostate (TURP) at Colentina Clinical Hospital between 2016-2018 were selected for this study. We generated multi-tissue blocks and stained mast cells immunohistochemically with tryptase. We evaluated the mast cells infiltrate density in peritumoural and intratumoural areas and correlate the data with GS.
Results: The ages of patients ranged from 53 to 91 (median 71 years). There was no correlation between age and MC count. We found that higher MC counts correlate with lower prognostic group ($p<0.05$), similar to studies conducted on prostatectomy and in contrast with needle biopsy samples. We found a difference in MC counts from intratumoural areas comparative to peritumoural areas. GS was negatively correlated with intratumoural MC number ($p<0.001$).
Conclusion: Higher MC number correlates with better prognosis suggesting that MC can be a reliable prognostic marker in prostate cancer. Differences in MC number in needle biopsy versus prostatectomy and TURP may be due to smaller stromal areas identified in the biopsies. MC may play a role in the relationship between stromal microenvironment and tumour cells and can be a potential target of effective antitumour strategies.

E-PS-03-020

Hydrophilic polymer cardiac emboli: postmortem case report

F. Filipello[1], N. Ahmed[1], C. Doglioni[2,1], F. Sanvito[2]
[1] Vita-Salute San Raffaele University, Milan, Italy, [2] Pathology Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background & Objectives: Hydrophilic polymer emboli (HPE) are a possible complication of intravascular procedures and have been reported in heart and other organs.
We describe two postmortem examinations of sudden cardiac arrest with histological features of HPE in myocardium.
Methods: The first case (A) was a 44 year-old man, arriving in Emergency Department (ED) in cardiac arrest. He received cardiac catheterization with coronary stenting due to thrombosis of the anterior interventricular artery (IVA). No evidence of cardiac function recovery was recorded and, 24 hours later, expired. The second case (B), a 52 year-old man pacemaker assisted, arrived in ED with cardiac arrest in suspected

myocardial infarction and died before any treatment was given or any clinical history was taken.
Results: Postmortem examination of case A: the metal stents in the IVA were in place and patent. Acute infarction with prior ischemic events of the left ventricle were detected. Basophilic, amorphous material was present in the small vessels of the myocardium.
Case B revealed two bare metal stents in the IVA occluded by thrombi and microscopic evaluation displayed amphophilic to basophilic, amorphous material in the intramyocardial vessels associated with inflammatory cell infiltrate with foreign-type giant cells in the left ventricle.
Conclusion: Although HPE may not have been the ultimate cause of death, it is possible that they contributed to the clinical outcome of patients. At present, attention has been focused on this issue, nevertheless the role and the complications of myocardial HPE are poorly understood by clinicians and pathologists.

E-PS-03-021
The new concept of the interstitium explains the microscopic features and pathogenesis of a case of hypertensive pneumopericardium
K. Metze[1], N.B. de Almeida[1], F.A. Borges da Silva[1]
[1] State University of Campinas, Brazil

Background & Objectives: Recently a new concept of the interstitial space has been created (Scientific Reports, 2018,8:4947). In this autopsy report of a patient with hypertensive pneumopericardium we want to show how this new theory helps to explain the morphologic findings and the pathogenesis of this disease.
Methods: A girl of two months was hospitalized due to respiratory distress provoked by viral bronchiolitis. During mechanical ventilation she suffered a sudden decrease in oxygen saturation followed by cardiac arrest. Resuscitation attempts were unsuccessful. An autopsy was performed.
Results: Macroscopic inspection revealed mediastinal emphysema. When opening the pericardium under water hypertensive pneumopericardium was seen.
Microscopic examination showed many confluent "empty" spaces in the peritracheal and mediastinal connective tissue, as well as in thymus and lymph nodes, creating smaller or larger tissue islands. We interpreted these spaces as channels of air propagation.The pericardium revealed also these channels connected to those of the other mediastinal organs and terminating in myriads of microscopic submesothelial bubbles.
Conclusion: The new concept of the interstitium postulates a widespread fluid-filled pre-lymphatic space within and between different tissues. We believe, that after a microscopy tracheal rupture mechanic ventilation injected pulsating air into the interstitium, until reaching the pericardial space. There the alignment of the interstitial space (parallel or oblique to the mesothelial surface) created and air-trapping mechanism, which caused the lethal hypertensive pneumopericardium.

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E-PS-03-022
Secondary cardiac lymphoma with unusual clinical presentation: a case report
A. Saidi[1], I. Msakni[1], R. Hedhli[2], N. Mansouri[1], F. Gargouri[1], A. Bouziani[1], B. Laabidi[1]
[1] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia, [2]Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: Cardiac lymphoma is an extra nodal lymphoma usually secondary to a disseminated disease. Primary cardiac lymphoma is a very rare malignancy defined as involving only the heart and/or pericardium or with limited extra cardiac involvement. It affects more frequently adult men and carries an overall poor prognosis. Cardiac lymphoma is predominately of B cell lineage with diffuse large B-cell lymphoma being the most common histological type. Cardiac lymphoma often involves the right heart, especially the right atrium. Epicardial and pericardial infiltration with pericardial effusion is typical. Clinically, and contrarily to primary cardiac lymphoma, generalized lymphoma involving the heart is rarely initially revealed by cardiac manifestations. When present, cardiac symptoms are most commonly associated with pericardial effusion and congestive heart failure. Arrhythmias and sudden heart death are not uncommon.
We report a new case of cardiac lymphoma in a young female adult with an unusual clinical presentation.
Methods: In a case of secondary cardiac lymphoma, the clinical and pathological parameters are studied and discussed.
Results: We report a case of a 32 year-old female reporting dyspnea and multiple episodes of syncope. Echocardiography, CT scan and MRI reveal an ill-defined, myocardial infiltrating mass localized in the right atrium and associated with moderate pericardial effusion, bilateral ovarian involvement. However, no mediastinal adenopathy was seen. A suspected meningeal involvement was confirmed on cerebrospinal fluid pathological analysis. Grossly, the surgically removed cardiac lesion presented as a 5 cm large whitish firm multinodular mass. Histological examination revealed an undifferenciated malignant proliferation composed of diffuse sheets of large and atypical immunoblast-like cells. Multiples areas of tumour necrosis were found. The proliferation's immunophenotype was characterised by CD20 positivity and the negativity of CK, CD3, CD30, CD117 (c-kit) and CD99. Thus, the diagnosis of cardiac diffuse large B-cell lymphoma was established. Treatment included systemic and intrathecal rituximab-based chemotherapy followed by autologous peripheral blood hematopoietic stem cell transplantation. The patient had however a lethal outcome.
Conclusion: Although our patient was affected by generalized malignant lymphoma involving her heart, she had only cardiac symptoms at initial presentation which is unusual with this type of malignancies. Like the majority of cardiac lymphomas, diffuse large B cell lymphoma was the histological type encountered in our case. Even though being sensitive to chemotherapy, cardiac lymphoma keeps carrying a poor prognosis as attested by this observation.

E-PS-03-023
On application of cardiac fish preparations in education and research of pathology
E. Neu[1], B. Rattel[2], M. Michailov[1], T. Plattner[1], P. Birkenbihl[1], T. Senn[1], V. Foltin[3], G. Weber[4], D.G. Weiss[5]
[1] Inst. Umweltmedizin c/o ICSD/IAS e.V. Muenchen, Germany, [2] Amgen Res. Munich (Exec. Dir.) & IUM c/o ICSD/IAS e.V., Germany, [3] St. Elisabeth Univ., Bratislava, Slovakia, [4] Univ. Lxbg. and Vienna, Fac. Psychology (Dean), Austria, [5] Univ. Rostock, Inst. Physiology (Dir.a.D.), Germany

Background & Objectives: In medical education&research are till today usual cardio-vascular preparations of frog, rat, rabbit,etc. An essential part of experiments with isolated angio-cardiac preparations could be replaced by fish organs. About pharmaco-physiological reactions of fish heart of *salmo gairdneri* is reported [1,3]. Now is given information about effects of xenobiotics leading to pathophysiological reactions.
Methods: Isolated fish heart (atrium, ventriculus cordis) from rainbowtrout: Registration of spontaneous contractions (isotonic rec.) in Krebs-Henseleit-solution (n=120, $p<0.05<0.01$) [1].
Results: Atrium & ventriculus cordis generate spontaneous regular&uniform contractions (6-24°C). Ethanol (0.01-0.5%) and butanol (0.001-0.01%) transform regular contractions of atrium into burst-like ones. $HgCl_2$ 10nmol/l also induce similar transformation with very long burst-duration. Inotropic effect is not changed. Cypermethrin 10µmol/l has similar effect, but with strong negative inotropic effect. Their differences in effects in fish ventriculus cordis are observed.

Conclusion: Fish cardiac preparations could be used as sensitive indicator for xenobiotics in water. Further, fish preparations could reduce enormous application of animal organs in academic education&research (universities) as well as in pharmacological industry, leading to large animal protection.

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Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-04 | Cytopathology

E-PS-04-001
Antigen stability of cells stored in in-house liquid-based cell medium

U. Klopcic[1], A. Kuhar[1], N. Nolde[1], V. Kloboves-Prevodnik[1]
[1] Institute of Oncology Ljubljana, Slovenia

Background & Objectives: Our study was designed to test how long the antigen properties of cells stored in our in-house liquid based cell medium are retained and immunocytochemical (ICC) reactions for estrogen receptor (ER), MOC-31, CK AE1/AE3, CD45, Calretinin and Melanoma triple cocktail can safely be performed.
Methods: Each of the ICC markers was tested on ten different cell samples. For each sample cytospins were prepared and fixed in methanol on the day of the sampling and then subsequently on the second, fourth, fifth and eight day of the sampling. Percentage of positive cells, intensity of ICC staining, background, counterstaining and morphology were evaluated on 300 tested slides. Each tested slide had its respective negative control. Assessment criteria were adopted from UK NEQAS ICC scheme.
Results: Percentage of positive cells and intensity of ICC staining of CK AE1/AE3, MOC-31, CD 45, ER and Melanoma triple cocktail were similar even after eight days storage of cell sample in in-house liquid based cell medium, while the percentage of positive cells in Calretinin ICC stained slides dropped significantly after the fourth day. Background, morphology and counterstaining changes did not affect the percentage of positive cells and intensity of ICC staining.
Conclusion: Cells stored in in-house liquid-based cell medium retained unchanged antigen immunoreactivity for at least four days in our series. The time period in which antigen immunoreactivity of cells stored in in-house liquid medium is still retained should be tested for each ICC marker individually.

E-PS-04-002
Reliability of fine needle aspiration of thyroid gland

A. Ilic[1,2], D. Miljkovic[1], M. Panjkovic[1], J. Ilic Sabo[1,2], Z. Vrekic[2], M. Miladinovic[3,4] and T. Lakic[1,2]
[1] University of Novi Sad, Faculty of Medicine, Serbia, [2] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia,
[3] University of Montenegro, Faculty of Medicine, Montenegro, [4] Clinical Center of Montenegro, Podgorica, Center for Pathology, Montenegro

Background & Objectives: Fine needle aspiration cytology of thyroid gland (FNAC) is a generally accepted, minimally invasive, fast and economical procedure that determines algorithm for treating nodular thyroid lesions. FNAC routine application has reduced the number of thyroidectomies.
We analysed performed thyroidectomies and presence and reliability of preoperative FNAC of nodular thyroid lesions.
Methods: Retrospectively, pathohistological reports (PH) of patients who underwent partial/total thyroidectomy in the period 2014-2018 were analysed at the Center for Pathology and Histology of the Clinical Center of Vojvodina. Patients with preoperative FNAC were marked and analysed.
Results: In five-year-period, 395 thyroidectomies were performed with female predominance. The average age was 51. The preoperative FNAC was found only in 10.9% of the total number. The positive correlation of FNAC and PH findings was registered in 84.7% of cases with 73.3% sensitivity. False positivity was present in 26.6% cases, while false negativity in 42.9%. Positive predictive value was registered in 47.8% and negative predictive value in 80% cases. AUS category consisted of 20% malignant and 80% benign PH diagnoses.
Conclusion: FNAC of thyroid gland is accurate method which remarkably reflects the biological nature of thyroid lesion providing faster, less expensive and more reliable diagnosis of thyroid solitary nodes than any other clinical and laboratory tests. The main problems are caused by inadequate or borderline aspirates of the thyroid node and taking inadequate material without the diagnostic cells in the smear.

E-PS-04-003
Pleomorphic carcinoma of the lung: diagnostic utility of fine needle aspiration

K. Kuan[1], S. El Hussein[1], S. Khader[1]
[1] Montefiore Medical Center/Albert Einstein College of Medicine, Department of Pathology, USA

Background & Objectives: Pleomorphic carcinoma of the lung is an exceedingly rare tumour that has only been recognized recently and classified by the World Health Organization in 2015. As its incidence only makes up to 0.4% of all lung malignancy, few studies are done on this entity. Here we present a case of metastatic pleomorphic carcinoma diagnosed with fine needle aspiration (FNA). This case report aims to highlight the cytologic features of this tumour and correlate them to its histological counterparts.
Methods: A 70-year-old, female who is chronic smoker was found to have a mass in the right lung and subsequently underwent right pneumonectomy. Histological examination revealed the tumour to be pleomorphic carcinoma of the lung. Despite being on intense adjuvant chemotherapy, the disease still progressed. An ultrasound-guided FNA was performed later on an enlarged peri-pancreatic lymph node. Diagnosis of the FNA was made based on the cytomorphology of specimen and ancillary studies including immunohistochemical (IHC) stains and genetic testing were performed.
Results: The tumour cells from both the surgical specimen and the FNA biopsy showed poorly differentiated glandular structures admixed with undifferentiated epithelioid cells and giant cells. Although the IHC stains of surgical specimen were positive for TTF-1, Napsin 1, they were not expressed in the cell block from FNA. Follow-up molecular study, however, identified the same EGFR mutation at exon 18 (719 G>X) in both sample. This finding greatly supported the diagnosis of metastatic pleomorphic carcinoma from the known lung primary.
Conclusion: Pre-operative diagnosis of pleomorphic carcinoma of the lung can be very challenging, in part because of the scarcity of cases describing this entity on surgical biopsies or FNA biopsies. This case beautifully highlights and correlates the cytologic and histologic features of pleomorphic carcinoma of lung, emphasizing the crucial role that FNA plays in providing adequate assessment of unusual cases.

E-PS-04-004

Pulmonary adenocarcinoma with enteric differentiation: a diagnostic pitfall

K. Kuan[1], S. El Hussein[2], S. Khader[2]
[1] Montefiore Medical Center/Albert Einstein College of Medicine, Department of Pathology, USA, [2] Montefiore Medical Center/Albert Einstein College of Medicine, USA

Background & Objectives: Lung cancer is the second most common malignancies in the United States. Much work has been put into classifying and characterizing various types of pulmonary malignancies in order to optimise treatment plans. Recently, an uncommon variant of lung cancer that resembles colorectal adenocarcinoma is recognized by different scholar bodies and the term pulmonary adenocarcinoma with enteric differentiation (PAED) is coined to this subtype. Here, we present a case report of PAED that is diagnosed with fine needle aspiration (FNA).
Methods: An 85-year-old male with a remote history of prostate adenocarcinoma presented to the emergency department complaining of persistent abdominal pain. Except for an increase in CEA level, laboratory work-up was otherwise unremarkable. Imaging studies revealed multiple pulmonary nodules, with a predominant mass measuring 5.7 cm. Hence, biopsies were performed on the largest mass via CT-guided fine needle aspiration (FNA) and core needle biopsy. Diagnosis was made based on the cytomorphology and immunochemical (IHC) stains were used for confirmation.
Results: The cells collected from FNA demonstrated gland-forming, columnar carcinoma cells, with vacuolated cytoplasm and basally oriented nuclei. The core needle biopsy finding was in congruence with the FNA biopsy, revealing an adenocarcinoma arising from the alveolar lining, with bland enteric-like columnar cells. Furthermore, IHC stains of the cell block were positive stain for CK7, TTF-1, and CEA-M. As such, these findings along with the IHC results were consistent with a primary lung adenocarcinoma with enteric differentiation.
Conclusion: Pulmonary adenocarcinoma with intestinal features is a newly recognized, uncommon entity that we have limited understanding of its pathogenesis. As this case illustrates, the cytomorphology of PAED can be very misleading. The use of IHC stains and the clinical correlation is crucial for making this diagnosis in order to avoid diagnosing this as metastatic disease of colorectal adenocarcinoma.

E-PS-04-006

Primary synchronous bilateral breast carcinomas: correlation between cytopathologic and radiologic findings

V. Skuletic[1], S. Cerovic[2], B. Kovacevic[2], D. Mikic[1], J. Dzambas[1], N. Stepic[2], M. Elez[2], I. Zenilo[2], M. Zaric[2]
[1] Military Medical Academy, Serbia, [2] Military Medical Academy, Belgrade, Serbia

Background & Objectives: Synchronous bilateral breast cancers (SBC) are rare entities with incidence of 2-5% of all breast malignancies. Physicians consider a synchronous contralateral cancer which are diagnosed within 1 month to 1 year of each other. The second tumour is generally considered to be an independent lesion (rather than metastasis) if it contains an in situ component, has a different histology from the first tumour, or possesses a different degree of differentiation from the first tumour.
Methods: A 46 year old female presented with 8 cm firm mass in upper outer and inner quadrant of right breast and 1,5 cm tumour felt in the left breast, on the border of upper outer and lower outer quadrant. Mammography and corresponding ultrasound of the right breast revealed malignant-appearing with a contralateral benign-appearing suspect on fibroadenoma.
Results: Ultrasound-guided core needle biopsy with imprint cytology of the right breast showed ductal carcinoma while FNA of the left breast lump suggested mucinous carcinoma which was confirmed on histopathology after later core needle biopsy. The pathological examination revealed positivity of both tumours using immunostaining: estrogen and progesterone receptors, HER2 and E-cadherine.
Conclusion: We report a rare case of contralateral infiltrating ductal carcinoma and mucinous carcinoma diagnosed during the initial presentation. This highlights importance of fast and minimal invasive cytologic examination in detecting potential pitfall in the diagnostic imaging of the setting of benign-appearing lesions, especially if there is more lesion. It is also possible to differentiate histological types of breast carcinoma and instruct that these are different primary ones and not metastatic tumours, as well as to confirm these are synchronous tumours. Meticulous histology diagnosis and appropriate management helped to improve the longevity with an improved quality of life.

E-PS-04-007

Neoplastic pleural effusion involvement and ggynaecological tumour: a rare association

J. Fraga[1], F. Ramalhosa[1], C. Faria[1], B. Pimentão[1], A. Lai[1], H. Moreira[1], V. Almeida[1], R. Almeida[1], C. Oliveira[1], G. Fernandes[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal

Background & Objectives: The thorax is a frequent site of metastasis from non-pulmonary cancers. Intrathoracic metastatic disease may manifest in many forms. There are a limited number of studies giving the incidence of pleural metastasis from female genital tract tumours.
Methods: We present a 62 year old woman with progressive worsening of general condition, with clinical information of two pulmonary nodules in right lung and pleural effusion. Posterior dissection of previous clinical history revealed a diagnostic of an endometrial adenocarcinoma four years ago.
Results: Inclusion in paraffin of the sediment obtained after centrifugation of pleural effusion, resulted fibrin imprisoning irregular glandular structures constituted by cells with accentuated nuclear pleomorphism, hyperchromasia and high nuclear/cytoplasm ratio. This cells had cytoplasmic membrane immunoexpression for BerEp4, cytoplasmic positivity for Ck7 and vimentin and nuclear positivity for p53, Pax8 and p16 and negativity for GATA3 and TTF1.
Conclusion: Due to the ambiguous clinical history, our study was conditioned by the multiple possible origins of the neoplastic cells. Cytological diagnosis was a pleural involvement by of high grade serous adenocarcinoma of endometrium. Only 2%–4% of tumours of the female genital are disseminated at the time of presentation, usually, spreading to pelvic and para-aortic nodes by the lymphatic system or to distant organs by the hematogeneous system. Thoracic metastases from ggynaecologic malignancies exhibit various imaging patterns. Metastases from endometrial cancer typically manifest as pulmonary nodules and lymphadenopathy, whereas ovarian cancer often manifests with small pleural effusions and subtle pleural nodules.

E-PS-04-008

Significance of nuclear morphometry in fine needle aspiration from benign tumours and invasive carcinomas of breast

H. Sheikh Alard[1]
[1] Damascus University, France

Background & Objectives: Fine-needle aspiration of breast masses is a safe and cost-effective technique for the diagnosis but this diagnosis is still aubjective. The nuclear morphometry can reduce this subjectivity when it is applied on the aspiration of breast masses.
Objectives: measuring the nuclear area and perimeter then
- comparing these values between the benign masses and invasive carcinomas.
- studying if there is a relation between those values and a) carcinoma's grade evaluated on aspirations, b) carcinoma's grade evaluated on

histolofical sections, c)status of lymph nodes in the same side, d)size of mass, and e)degree of cohesion of carcinoma's cells.
- evaluating the average of variations in the values of nuclear area and perimeter between the group of benign masses and invasive carcinomas.
Methods: 101 masses sent to the department of surgical pathology in the two hospitals of damasuc university for frozen sections, between 2015-2017.
The aspiration had been performed on these masses (G210). The smears have been fixed with ethanol 90% and stained with hematoxyline eosin. The slids of aspirations and the slids of histological sections have been scanned by NIKON (HDCE-10C). The nuclear area and nuclear perimeter have been measured by an open source image processing program (Image J).
The nuclear grade of invasive carcinoma has been evaluated by using the Robinson's system.
The histological grade of invasive carcinomas has been evaluated by using the Nottingham modification of Bloom-Richardson system.
Abbraviations: Nuclear area NA, Nuclear perimeter NP.
Results: - There is a statistical significance for the difference between:
a) NA, NP and the average of variations of these values of isolated cells in benign masses and those in invasive carcinomas.
b) NA and NP of cohesive cells in clusters and this of isolated cells in the group of invasive carcinomas.
c) NA of cohesive cells in clusters and the nuclear area of isolated cells in the group of invasive carcinomas.
d) NA and NP of the group of invasive carcinoma with nuclear grade 1 and those with nuclear grade 2 and 3.
e) NA and NP of cohesive cells and this of isolated cells in the group of invasive carcinoma with N+.
f) NA and NP of cohesive cells and isolated cells and also mean nuclear morphometry in the group of invasive carcinoma with histological grade 2 and those in the group of invasive carcinoma with histological grade 3 (the specimen of invasive carcinoma grade 1 is not sufficient for statistical study)
- No statistical significance for the difference between:
a) NA and NP of cohesive cells and mean nuclear morphometry in benign masses and those in invasive carcinomas.
b)the average of variations in the values of NA of cohesive cells in benign masses and those in carcinomas.
c) NA and NP of cohesive cells in clusters and this of isolated cells in the group of benign tumours.
d) NA and NP in the 4 groups of lymph nodes status of invasive carcinomas
e) NA and NP of the group of invasive carcinoma with N+ and this of N-.
f) NA and NP of cohesive cells and this of isolated cells in the group of invasive carcinoma with N-.
g) NA and NP of the 4 groups of invasive carcinoma's size.
h) NA and NP in the three degrees of cohesiveness of carcinomatous cells.
- NA: benign tumours (64.14 +/-18.68)um^2, invasive carcinomas (109.69+/-39.53)um^2.
- NP: benign tumours (28.41+/-6.67)um^2, invasive carcinomas (43.87 +/-3.89)um.
Conclusion: -The NA and NP play an important role in distinguishing the benign tumours from invasive carcinomas, specially isolated cells (values of isolated cells in invasive carcinomas are bigger than those of isolated cells in benign tumours).
-The difference between the NA and NP of cohesive cells in clusters and those of isolated cells is bigger in the group of invasive carcinomas than in the group of benign tumours with statistical significance.
-the average of variations in NA and in NP in the group of invasive carcinomas are more important than the average of variations of these values in the group of benign tumours.
-The values of NA, NP and mean values in the group of invasive carcinoma with histological grade 3 are bigger than those in the goup with histological grade 2.
-The variations in the values of NA and N are more important in the group of invasive carcinomas grade 3 than in the group of invasive carcinomas grade 2.
-The NA in the group of invasive carcinomas with nuclear grade 3 evaluated on FNA are bigger than those of invasive carcinomas with nuclear grade 2and 1.
-The difference between NA and NP of cohesive cellls in clusters and those of isolated cells has a prognostic value for the metastases in lymph nodes but the nuclear morphometry itself doesn't have a prognostic significance for the metastases in lymph nodes.
-No relation between nuclear morphometry (NA and NP) and the size of invasive carcinomas.

E-PS-04-009
Cytological and histological aspects of tall cell and hobnail variant of papillary thyroid carcinoma: 3 cases
U. Aykutlu[1], C. Uzun[1], M. Ozsen[1], Y. Cakir[1]
[1] Erzurum Regional Training and Research Hospital, Turkey

Background & Objectives: Papillary thyroid carcinoma (PTC) is the most common tumour among the thyroid malignancies. This presentation aim to present the clinicopathological features of tall cell and hobnail variant of PTC cases.
Methods: We report three cases diagnosis with tall cell and hobnail variant of PTC by fine needle aspiration and total thyroidectomy procedure.
Results: One of the 2 cases diagnosed with Tall cell variant of PTC is 65 years old male. The other case is 48 years old, female. Microscopic examination of fine needle aspiration (FNA) material show numerous intranuclear inclusions and atypical thyrocytes with long cytoplasm aligned near basal nucleus alignment. Histopathological evaluation revealed a tumoural lesion with the features of distinct restrictive papillary thyroid carcinoma, which consisted of long cylindrical cells, of which heights are at least 2-3 times their width.
The case, which is diagnosed as Hobnail variant of PTC, is 51 years old male. Microscopic examination of FNA material showed atypical thyrocytes with papillary thyroid carcinoma characteristics, as well as dyscohesive cells with loss of polarity and isolated cells with eccentric nucleus and teardrop-shaped cytoplasm. Histopathological evaluation revealed a tumoural lesion composed of complex papillary and micropapillary structures with nuclear cells that have features of papillary thyroid carcinoma. Apical localised nuclei of the tumour cells show typical hobnail pattern.
Conclusion: Most of the PTC variants have good prognosis, however tall cell variant, hobnail variant, columnar cell variant are associated with poor prognosis. It is important to distinguish these variants from the classical variant for better patient management.

E-PS-04-010
Parotid gland metastasis from endometrial cancer: first reported case with cytologic description
S. Lajara[1], R. Balakrishnan[1], C. Castrodad[1], A. Colanta[1], S. Khader[1]
[1] Montefiore Medical Center/Albert Einstein College of Medicine, USA

Background & Objectives: Endometrial adenocarcinomas are the most common ggynaecologic malignancies in the USA. Type 1 is associated with low stage at diagnosis and better prognosis, while type 2 is associated with increased intraperitoneal and metastatic spread. Typical metastatic sites include regional lymph nodes and lungs; uncommon sites are the liver, adrenals, soft tissue, bone and brain.
Our aim is to describe an unusually widely metastatic well-differentiated endometrial adenocarcinoma and the cytologic findings of a fine needle aspiration (FNA) of the parotid gland, a rare site of metastasis.

Methods: We report a case of a 65-year-old female with a past medical history of well-differentiated, FIGO stage IB endometrioid endometrial adenocarcinoma, presenting with a necrotic intraparotid lymph node. Two years prior to presentation, she was diagnosed with multiple brain lesions, managed as cancer of unknown primary site. Her endometrial cancer was considered as an unlikely primary because the brain is an uncommon metastatic site. However, pathology revealed metastatic endometrial adenocarcinoma. A gingival nodule, identified during dental extraction, also revealed metastatic adenocarcinoma.
Results: FNA of her left parotid gland revealed scattered clusters of large pleomorphic cells with prominent nucleoli and moderate to abundant pale, sometime clear cytoplasm compatible with metastatic endometrial adenocarcinoma.
Conclusion: An aggressive clinical course with extensive distant metastasis is peculiar for low-stage, well-differentiated endometrial adenocarcinomas. Brain involvement is extremely uncommon, and is usually seen in high grade and high stage tumours. Gingival metastasis is also vanishingly rare. To our knowledge, there is no reported case of endometrial carcinoma involving the parotid gland in literature.

E-PS-04-012
Cytologic features of gastric type mucinous carcinoma of the uterine cervix
K. Suh[1], K. Kim[1]
[1] Chungnam National University Hospital, Republic of Korea

Background & Objectives: Gastric type mucinous carcinoma (GMC) of the uterine cervix is difficult to recognize in cytologic specimens. These tumours are characterised by bland nuclear features and abundant mucin or goblet cell differentiation, but clinically aggressive. GMC is not associated with human papillomavirus (HPV) infection. We analysed cytologic features of GMC of the uterine cervix compared to usual type endocervical adenocarcinoma.
Methods: We reviewed the cervical and ascites fluid smears from 3 patients with a pathologic diagnosis of GMC. All slides were conventionally smeared or liquid-based prepared (ThinPrep) and stained with papanicoloau stain.
Results: Among three cases, the cytologic diagnoses were atypical glandular cells, favor neoplastic in two cases and adenocarcinoma in one case. High risk-HPV testing in these 3 cases was negative. Histologically, the tumours consist of irregular angulated glands invading the cervical stroma. These cells were positive for MUC6 and p53, but negative for p16. Cytologically, the tumour cells had bland nuclear morphology with low nuclear to cytoplasmic ratios and abundant mucinous cytoplasm. The characteristic features of GMC were honeycomb sheets, vacuolar or foamy cytoplasm with yellowish brown hue due to mucin, intracytoplasmic neutrophil entrapment, and occasional small nucleoli, compared to usual type endocervical adenocarcinoma.
Conclusion: Even though the case numbers are small, GMC may be recognized by cytologic features, such as honeycomb sheets of bland tumour cells with abundant foamy cytoplasm with yellowish brown hue due to mucin.

E-PS-04-013
Colonic adenocarcinoma presenting with supraclavicular lymph node metastasis: a rare case report
H. Seneldir[1], G. Kir[1], B. Gucluer[1], N. Ozbay[1], A. Gapbarov[2], O. Alimoglu[2]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey,
[2] Istanbul Medeniyet University, Department of General Surgery, Turkey

Background & Objectives: In colorectal cancers, the most common sites of metastasis are liver, lung and peritoneum. Non-regional lymphatic involvement in colon primary is an uncommon finding.

Methods: A 69-year-old female patient was admitted to our hospital with a progressively enlarging swelling of the left supraclavicular region for approximately 4 weeks. Ultrasonography of the neck revealed multiple nodules, with rounded and heterogenic echo parenchyma which suggested metastasis. An ultrasound-guided fine needle aspiration biopsy was performed from the largest mass of the left supraclavicular region. Cytology revealed carcinoma metastasis. Immunohistochemical examination showed the tumour cells at the cell block to be positive for CK20 and CDx2 and negative for CK7 and p40 expression. The positron emission tomography (PET) of the patient, which was investigated for etiology and origin, was observed hypermetabolic area that about 6x3 cm at the transverse colon. Upon this the patient was performed right hemicolectomy and excisional biopsy of left supraclavicular lymph node.
Results: Macroscopic examination of the right hemicolectomy showed a infiltrating mass measuring 4x4 cm on the transvers colon and the tumour extended into the pericolic fat. Histologically the appearance was moderately differentiated colonic adenocarcinoma. Histopathologic examination of the left supraclavicular lymph node again confirmed as metastasis from colonic adenocarcinoma.
Conclusion: Supraclavicular lymph node metastases are common occurrence in breast cancer, lung cancer, gastro-oesophageal cancer and lymphoma. Colonic cancer represents an unusual primary for supraclavicular lymph node metastases.

E-PS-04-014
Rosai-Dorfman disease: cases report
Y. Gulyaeva[1], T.I. Nabebina[1], A.T. Dubrovskij[1]
[1] National Cancer Centre, Belarus

Background & Objectives: Rosai–Dorfman disease is a reactive histiocytic proliferation of unknown etiology characterised by a proliferation of histiocytes with distinctive cytologic and immunophenotypic features.
Methods: We describe here two: one - with damage to the soft tissues and bones of the face and lymph nodes, the second - with damage to the CNS and lymph nodes.
Results: Histologically, lymph nodes are significantly enlarged. At low-power magnification, the overall nodal architecture is generally maintained, and sinuses are distended by a proliferation of large histiocytes associated with small lymphocytes and plasma cells. The lymph node parenchyma is characterised by follicular hyperplasia and plasmacytosis in interfollicular areas. Mitotic figures are rarely identified. the histiocytes are large and characterised by abundant eosinophilic cytoplasm, distinct cell borders, and a central round nucleus with a prominent nucleolus. These histiocytes also exhibit emperipolesis. At extranodal sites there are large histiocytes and emperipolesis, the lesions are accompanied by fibrosis. Tumour cells demonstrated the following immunoprofile: S-100+, CD68+, CD1a-.
The patients with damage to the CNS received surgical treatment, both patients are under observation for six months after diagnosis.
Conclusion: The Rosai–Dorfman disease prognosis is excellent, with most patients being free of disease or with stable disease. However, some patients may develop recur-rent disease in the original site or other body sites.

E-PS-04-015
Pitfall in urinarycytology - are non-neoplastic findings not relevant at all? - crystals versus parasites
A.M.G. Pereira[1], C. Padrao[1], F. Galante Pereira[1], R. S. S. Oliveira[1], A.T. Alves[2]
[1] Hospital Prof. Doutor Fernando Fonseca, EPE, Portugal, [2] Instituto de Anatomia Patológica da Faculdade Medicina Universidade de Lisboa, Portugal

Background & Objectives: In an era so focused on cancer, sometimes we tend to disregard non-neoplastic findings that are important to

diagnosis, treatment and clinical outcome of the patients. With these cases we pretend to raise awareness for non-neoplastic findings in urine cytology specimens namely the differential diagnosis between uric acid crystals and parasites.

Methods: We report two cases of urinary cytology specimen's analysis. One, referring to 77-years-old male patient in the context of follow up of high grade urothelial cancer, and the other, referring to 86-years-old-female patient, on etiological investigation of a non-lithiasic hydronephrosis.

Results: Both cytologies had similar findings. On microscopic examination, we identified some elliptical structures that seemed to be parasitic in nature. The objects were considerable smaller than eggs of Schistosoma haematobium, lacked a single terminal spine and had no miracidium which raised suspicion of a different structure. These objects appeared to have a spine on both ends and were highly birefringent under polarized light, making it possible to identify them as uric acid crystals.

Conclusion: Crystals in urine cytology can present in various shapes and sizes and uric acid crystals are one of the most variable, sometimes with pointy extremities and multiple colors that be confused with parasite eggs, exogenous material or artifacts. It is especially important to avoid pitfalls and clarify the diagnosis of Schistosoma's eggs because of its relation with squamous cell carcinoma of the bladder.

E-PS-04-016

Collecting duct carcinoma of the kidney diagnosed on fine needle aspiration with distinctive cytomorphology: a case report with histological correlation and literature review

D. Pinto[1], X. Qian[2,3]

[1] Centro Hospitalar de Lisboa Ocidental, EPE, Portugal, [2] Brigham and Women's Hospital, USA, [3] Harvard Medical School, USA

Background & Objectives: Collecting duct carcinoma (CDC) of the kidney is a rare high-grade adenocarcinoma of the renal medullary region. Its diagnosis is based on criteria proposed in the WHO 2016. Cytologic features, however, are considered mostly non-specific. We report on a case of CDC diagnosed by fine needle aspiration (FNA) cytology and perform a literature review.

Methods: A relevant case was selected from our routine. Literature review was performed.

Results: 58-year-old man with history of collecting duct carcinoma of the kidney and follicular thyroid carcinoma. A mass of the left humerus was detected and submitted to FNA. Smears were moderately cellular and contained epithelial cells forming acinar clusters. Fragments of a paucicellular fibroconjuctive tissue were identified. Cytology was high-grade. Tumour cells were positive for CK7, CKAE1/AE3, FH, PAX8 and SMARCB1 and negative for AMACR, AR, CK20, ERG, OCT3/4 and TTF1. A diagnosis of metastatic CDC was made.

Conclusion: The observed fibroconjunctive fragments are compatible with a desmoplastic stroma. Previous publications have shown these are part of the morphologic spectrum of CDC on FNA cytology, but not specific. To make a specific diagnosis, we followed an algorithmic immunohistochemistry approach, excluding different primary locations, namely urothelial carcinoma, and other distal nephron tumours showing a high-grade adenocarcinoma morphology with a desmoplastic stroma. Diagnosing a specific entity is important not only to enable future studies of tumour genetics and pathogenesis, but also to allow for appropriate therapy. This is possible on FNA cytology.

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E-PS-05-001

Hepatitis C-related liver cirrhosis associated with mixed cryoglobulinemia

M. Rolon[1], M. Tapias[2], L. Barrera[3], J. Alvarez-Figueroa[3]

[1] Department of Pathology and Laboratories, Hospital Universitario Fundación Santa Fe de Bogotá. Bogotá, Colombia, [2] Transplant and Hepatobiliary Surgery Service, Hospital Universitario Fundación Santa Fe de Bogotá. Bogotá, Colombia, [3] Department of Pathology and Laboratory Medicine, Hospital Universitario Fundación Santa Fe de Bogotá. Bogotá, Colombia

Background & Objectives: Cryoglobulinemia is a disease defined by the presence of abnormal proteins in blood that accumulate and become insoluble at low temperatures. Clinically, it is a multisystemic entity with cutaneous involvement due to purpuric lesions. It is classified as type I (monoclonal) with the presence of intravascular deposits of cryoglobulin and type II (mixed) with acute vasculitis. We present a patient with a mixed cryoglobulinemia associated with hepatitis C virus infection.

Methods: A 56-year-old male with a diagnosis of decompensated cirrhosis due to chronic Hepatitis C infection, hepatic encephalopathy, portal hypertension, refractory ascites and renal dysfunction. During his hospitalization presented hemorrhagic purpuric and painful lesions compromising the lower limbs associated with decreased distal perfusion and blister on the right leg.

Results: The skin biopsy revealed areas of necrotic epithelium, superficial perivascular mononuclear inflammatory infiltrate associated with abundant extravasated erythrocytes, karyorrhexis around small vessels in the upper and middle dermis with fibrinoid necrosis of vascular walls, abundant interstitial hemorrhage, deposits of hyaline material inside the vascular structures or fibrin thrombi. Such findings where compatible with necrotizing hemorrhagic leukocytoclastic vasculitis due to mixed cryoglobulinemia. Patient received pulses of methylprednisolone, plasmapheresis improved of skin lesions; however, with posterior anuria, and despite hemodialysis he died.

Conclusion: In the presence of an acute vasculitis, although there is no presence of hyaline thrombi, it is important to raise the suspicion of mixed cryoglobulinemia. We presented a case of Hepatitis C virus-related mixed cryoglobulinemia.

E-PS-05-002

Cutaneous adenoid cystic carcinoma metastasizing to the lung 10 years after the initial diagnosis

S. Sotiriou[1], M. Bobos[2], D. Hatzibougias[2], E. Michalopoulou-Manoloutsiou[2], E. Athanasiou[2], E. Goupou[2], I. Boukovinas[3], S. Galanis[4], I. Kostopoulos[1], T. Koletsa[5]

[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece, [2] "Microdiagnostics" Ltd., Thessaloniki, Greece, [3] Bioclinic Thessaloniki, Greece, [4] "G. Papanikolaou" General Hospital, Thessaloniki, Greece, [5] Pathology Department, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background & Objectives: Cutaneous adenoid cystic carcinomas (CACCs) are rare neoplasms, that most commonly arise in the scalp and metastasize to the lungs, even many years after the initial diagnosis. The aim of this case report is to raise awareness regarding this entity and to point the importance of the differential diagnosis, especially in the context of metastatic disease.

Methods: In 2008 a 66-year-old man has undergone resection of a skin nodule of the scalp, and ten years later (2018) has undergone a biopsy of a pulmonary lesion.

Results: Microscopically, the cutaneous lesion represented an infiltrating carcinoma. The neoplastic cells were immunoreactive for AE1/AE3 and CD117, and arranged in tubular and cribriform formations, with an inner luminal (highlighted with EMA) and an outer basal/myoepithelial cell layer (highlighted with SMA). Perineural infiltration was prominent. The pulmonary lesion represented a carcinoma with similar morphology. Based on the histological and immunohistochemical findings, but also on the absence of other lesions, our final diagnosis was that of a CACC with pulmonary metastasis.

Conclusion: CACC must be differentially diagnosed from metastatic ACC, but also from primary cutaneous neoplasms with similar morphology, such as secretory, cribriform and adenoid basal cell carcinoma. A high level of suspicion is recommended whenever a patient with a history of CACC presents a second lesion. Clinicopathological correlation is of paramount importance in the differential diagnosis between primary and secondary ACCs.

E-PS-05-003

Eccrine angiomatous hamartoma - a seemingly benign lesion with an unpredictable behaviour

A.C. Lisievici[1], T.A. Georgescu[2], A. Zota[3], T. Tebeica[4]
[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Bucharest Emergency University Hospital, Romania, [3] Department of Dermatovenerology, Dr. Leventer Centre, Bucharest, Romania, [4] Department of Pathology, Dr. Leventer Centre, Bucharest, Romania

Background & Objectives: Eccrine angiomatous hamartoma (EAH) represents a rare nevocytic malformation composed of sweat gland and mesenchymal elements including blood vessels and smooth muscle, which usually occurs in children. Most cases of EAH reported in the literature had an indolent behavior and did not recur, except for 2 cases from a retrospective study. Another case report presented a patient with localized severe pain, which warranted partial amputation of the affected finger.
Methods: We report the case of a 22–year-old male who presented a few years ago in another center with a red plaque on his inner thigh, that incresed in size and became tender in the past few months. The lesion was surgically excised and diagnosed as cavernous hemangioma. Two years later, the lesion recurred and the initial histopathological specimen was referred to our clinic for second opinion.
Results: Histopathological examination revealed a proliferation of blood vessels in close relation with the epidermis, focally mimicking angiokeratoma. However, a significant number of sweat glands and smooth muscle fibers were intermingled between the vascular structures. The lesion was diffusely infiltrating both reticular dermis and hypodermis and was covered by hyperplastic epidermis with verrucous features. Lateral excision was incomplete.
Conclusion: EAH is a rare lesion with unusual behavior, which can be easily misdiagnosed due to the bland appearance of its components. Simple excision is usually curative, but recurrences, although rarely reported in the literature, are possible and warrant increased awareness for practicing pathologists and clinicians. Therefore, in such lesions, close follow up is recommended.

E-PS-05-004

Dedifferentiated melanoma with rhabdomyosarcomatous transdifferentiation - a rare case report

J. Soukup[1,2], M. Manethova[1,2], L. Krbal[1,2]
[1] The Fingerland Department of Pathology, University Hospital Hradec Kralove, Czech Republic, [2] Charles University Faculty of Medicine in Hradec Kralove, Czech Republic

Background & Objectives: Dedifferentiation in melanoma is an unusual phenomenon, characterised by loss of normal immunohistochemical profile and morphology. Some of these tumours may show a divergent differentiation including rhabdomyosarcomatous. Such cases are exceedingly rare, with less than 12 cases reported. Here we present an additional case.
Methods: 84-year-old male presented with a skin tumour of a right arm. Excision measuring 55 x 35 x 12 mm with the tumour measuring 35 x 35 x 8 mm was retrieved. Histopathologic evaluation and immunohistochemical staining for SOX10, S100, HMB45, MelanA, CD30, CD45, CD56, CD117, CK AE1/3, CK18, CK20, BER-EP4, p63, SMA, INI1, synaptophysin, ERG, desmin, myoD1, myogenin and BRAF V600E was performed.
Results: The tumour was situated in superficial dermis and composed of solid sheets of atypical rhabdoid cells with vesicular nuclei and nucleoli. Mitoses were conspicuous. Tumour cells expressed INI1 and desmin in diffuse and strong fashion with focal expression of myoD1 and myogenin. All other immunohistochemical melanoma markers (SOX10, S100, HMB45, MelanA) were negative. In the surrounding epidermis, remnants of a junctional and lentiginous atypical melanocytic proliferation with pagetoid spread were identified, consistent with melanoma in situ, with maintained SOX10 expression.
Conclusion: Melanoma with rhabdomyosarcomatous differentiation is a rare tumour that must be considered in differential diagnosis when dealing with rhabdomyosarcoma of the skin, especially in elderly.
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E-PS-05-005

A case of sebaceous carcinoma arising on the wrist - an atypical location for an uncommon neoplasm

M. Kilmpasani[1], I. Karafoulidou[1], A. Baliaka[1], N. Pastelli[1], Z. Tzimorota[2], S. Papaemmanouil[1]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Plastic, Reconstructive and Hand Surgery, General Hospital of Thessaloniki "G. Papanikolaou", Greece

Background & Objectives: Sebaceous carcinoma is an uncommon cutaneous malignant neoplasm, often misdiagnosed as a benign lesion or a basal cell carcinoma. It is most commonly found on head and neck, mainly at periocular sites. The extremities are an atypical location for an extraocular sebaceous carcinoma. We report the case of a 78-year-old patient with a tumour on the right wrist, reportedly existent for at least 2 years.
Methods: Following excision, the protruding tumour measured 2.3cm, and demonstrated a tan-pink cut surface. It was examined in FFPE sections with hematoxylin-eosin and immunohistochemical stains.
Results: The neoplasm consisted of cells with multivacuolated, clear cytoplasm and oval nuclei. They formed well-demarcated, solid nests in a desmoplastic, highly vascularized stroma, with the presence of comedotype necrosis and vascular neoplastic emboli. A high mitotic activity was prominent, including mainly atypical mitoses.
The overlying epidermis showed areas of low-grade dysplasia with hyperkeratosis and parakeratosis, while the adjacent epidermis demonstrated independent foci of full-thickness, dysplastic epithelium, with evident parakeratosis.
The final diagnosis was sebaceous carcinoma of the skin, grade I, with coexisting, multiple foci of in situ carcinoma in the adjacent skin.
Conclusion: An intraepidermal growth pattern is seen more often in periocular sebaceous carcinoma and less commonly at extraocular sites. A grading system based on growth pattern has been proposed; moreover, vascular invasion, persistence of symptoms longer than 6 months and size larger than 10mm, among others, also seem to be related with an adverse prognosis. Given the above, our case demonstrates some interesting features.

E-PS-05-007

The curious case of an anal polyp that turned out to be lymphangioma circumscriptum: a case report

A.D. Plopeanu[1], A. Dema[2], S. Olariu[3], S. Taban[1,4]
[1] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania, [2] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania, [3] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Surgery, Romania, [4] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Pathology, Romania

Background & Objectives: Lymphangioma circumscriptum is a rare benign tumour consisting of abnormal ectatic lymph vessels involving the upper part of the dermis. This infrequent lesion appears with predilection on the extremities, trunk and axilla. The best course of treatment is not well established. Although considered the most effective, surgery is associated with a high risk of complications. The aim of this case report is to highlight the possibility of diagnosing an uncommon lesion with a localization rarely mentioned in the specialty literature.
Methods: We report the case of a 35 years old woman who was operated on for external hemorrhoids and an anal polyp. The microscopic examination revealed the polyp to be a benign vascular tumour and further immunohistochemistry tests were performed in order to confirm the diagnostic.
Results: The histopathological examination revealed an achanthotic and hyperparakeratotic epithelium, with numerous dilated vessels in the papillary dermis, vessels that in hematoxylin-eosin staining appeared to be lymphatic. In order to confirm the diagnosis, further immunohistochemical examination were carried out. The vessels were proven to be lymphatic by being positive for D2-40 and CD31 antibodies, allowing us to give a positive diagnostic for lymphangioma circumscriptum.
Conclusion: Lymphangioma circumscriptum is a rare tumour involving the lymphatic vessels in the dermis and despite its infrequent nature, it must be taken into account for differential diagnosis, even when appearing in an unusual topographic area.

E-PS-05-008

A 3-year retrospective study demonstrating an important histopathologic clue for diagnosing cutaneous Rosai-Dorfman disease

A.C. Lisievici[1], T.A. Georgescu[2], A. Rizoiu[3], A.M. Stanciu[4], T. Tebeica[5]
[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Bucharest Emergency University Hospital, Romania, [3] Department of Dermatovenerology, MEDINVEST, Bucharest, Romania, [4] Department of Dermatovenerology, Dr. Leventer Centre, Bucharest, Romania, [5] Department of Pathology, Dr. Leventer Centre, Bucharest, Romania

Background & Objectives: Cutaneous Rosai-Dorfman disease is a rare non-lymphoid cutaneous infiltrate of unknown etiology. It is currently acknowledged that skin lesions may represent the sole manifestation of Rosai-Dorfman disease, although involvement of both skin and lymph nodes is much more frequently encountered. Histologically, it is characterised by an abundant inflammatory infiltrate, in which numerous histiocytes are identified, some of them showing classic emperipolesis. Immunohistochemically, the large histiocytes express both S100 and CD68, but are negative for CD1a.
Methods: This is a retrospective study including all cutaneous Rosai-Dorfman diseases that were diagnosed in our Dermatopathology unit during a period of three years (2016-2018). Clinical information was retrieved from the virtual database. We thoroughly re-examined all Hematoxylin-Eosin and immunohistochemically stained slides, aiming to establish clinico-pathological correlations. Ancillary studies included: S100, CD68, CD1a, CD79a, CD30.
Results: Clinically, the face and the trunk were involved equally often, while the extremities and the buttocks were less affected. 50% of all cases presented as nodules, 25% presented as indurated plaques with subcutaneous nodules and 25% cases mimicked a panniculitis. 62.5% of all patients had solitary lesions, while 37.5% presented with multiple nodules. Histologically, all cases presented an inflammatory reaction in which plasmocytes abounded and bordered the infiltrate. This feature was more than once, the first clue to this diagnosis.
Conclusion: In our opinion, an abundant plasma cell infiltrate that surrounds a diffuse lympho-histiocytic infiltrate is highly suggestive for this entity and an important clue that should warrant a thorough analysis of the slide, in order to find characteristic emperipolesis. This sign can be especially useful when dealing with atypical lesions, like those limited to the hypodermis and mimicking a panniculitis.

E-PS-05-009

ALK-positive atypical spitz tumour: report of two cases and brief review of the literature

C. Ricci[1], A. De Leo[2], G. Santandrea[3], B. Corti[2]
[1] Department of Biomedical and Neuromotor Sciences, Bellaria Hospital, Bologna, Italy, [2] University of Bologna, Department of Surgical pathology, Italy, [3] Pathology Unit, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Background & Objectives: Spitz tumours (STs) are a subgroup of melanocytic neoplasms ranging from Spitz nevus (SN) to atypical Spitz tumours (ASTs) and spitzoid melanoma (SM), the latter with capacity of metastasis and lethal outcome. In the last years molecular investigations played a central role in the sub-characterization of STs. In particular, ALK fusion has been noticed in 10% of STs, including 5% of ASTs and 1% of SMs. Herein, we report two cases of ALK-positive ASTs (ALK-ASTs) arose during adolescence.
Methods: The first patient was a 16-year-old boy with a lesion on the right leg; the second one was a 14-year-old boy with a lesion on the right foot over the previous months. Immunoistochemistry (IHC) for HMB45, MART1, S-100, Ki67, ALK, p16 and BAP1 was performed.
Results: In both cases, histology revealed a wedge-shaped proliferation of atypical spindle, epithelioid and multinucleated melanocytes, arranged in a plexiform pattern in deep dermis. Mitoses were present ($\leq 4/mm^2$), even deep/marginal. Tumour cells were strongly positive for S-100, p16 and ALK1; Ki-67 was low and BAP-1 maintained. A diagnosis of ALK-AST was rendered. Both patients underwent a sentinel lymph-node biopsy and, in the first patient, we found subcapsular ALK-positive tumour clusters. In both cases, no recurrence or disease progression were detected.
Conclusion: Our report confirms that ALK expression identifies a biologically and morphologically distinct subcategory of ASTs, unrelated to the other variants. Further investigations are needed to clarify the prognostic meaning of these findings.

E-PS-05-010

The role of the pathologist in the Mohs micrographic surgery: a retrospective study

I. Español[1], I. Trias[1], M. Alegre[2]
[1] Hospital Plató. Pathology DP, Spain, [2] Hospital Plató. Dermatology, Spain

Background & Objectives: Transplant glomerulitis is a key feature of antibody-mediated rejection. Leukocytes occluding the glomerular capillaries define its morphological pattern. It is difficult to recognize and its scoring only has a fair interobserver agreement. We aimed to determine and validate a well reproducible immunohistochemical marker for glomerulitis, and looked at its prognostic value.
Methods: Receiver operator curves (ROC) using CD3, CD45, or CD68 positive cell counts in the glomeruli of kidney transplant biopsies with glomerulitis or without relevant pathology were used to determine cut-offs. Findings were independently validated, tested for interobserver agreement, and compared to other rejection patterns. The prognostic value was investigated in a cohort of patients (n=95) transplanted in the presence of donor-specific antibodies (DSA).
Results: A cut-off >5.5 CD68 positive cells in the most affected glomerulus ($CD68_{max}$) resulted in an area under the curve (AUC) of 0.966. $CD68_{max}$ correlated with the percentage of glomeruli with CD68 counts above the cut-off ($\rho = 0.875$). Three risk groups (baseline, low, high) with prognostic impact on graft survival were established using ROC comparing cases with glomerular Banff scores 0 vs. 1 (AUC = 0.891, cut-off >

3.9 % of glomeruli) and 1 vs. 2-3 (AUC = 0.867, cut-off >64.4 %). Interobserver agreement was good and independent of the level of expertise. In the DSA positive cohort, the risk groups proved to be an early and independent prognostic marker of poor graft function.
Conclusion: Addition of a CD68 stain to the routine analysis of kidney transplant biopsies provides additional diagnostic and prognostic information.

E-PS-05-011
Cutaneous microcystic/reticular schwannoma determined incidentally in pilonidal sinus specimen: a case report
R. Bedir[1], S. Orhan[2], F.G. Gülname[2]
[1] Recep Tayyip Erdogan University Deparment of Pathology, Turkey,
[2] Department of Pathology, Recep Tayyip Erdogan University, Medical Faculty, Turkey

Background & Objectives: Schwannoma is a common, slow-growing, encapsulated and usually asymptomatic benign peripheral nerve sheath tumour. Microcystic/reticular schwannoma (MRS) is a very rare histological variant of schwannoma. MRS is a recent addition to this group of tumours, which have a predisposition for visceral organs. Unlike typical morphology of schwannomas, it shows no Antoni A, Antoni B areas or Verocay bodies. Here, we present the case of a 28-year-old male who has an incidentally detected cutaneous MRS in pilonidal sinus specimen.
Methods: The specimen was fixated with 10% buffered formalin and were processed by conventional histopathological methods using paraffin embedding, sectioning and Hematoxylin-Eosin staining.
Results: A 28-year-old male patient presented with anintermittent painful swelling in the anogenital region. The clinical impression was a pilonidal sinus and it is surgically removed. Macroscopic examination revealed a sinus tract and nearby mass under the skin with a gray-white solid cut surface showing focal myxoid appearance which is found incidentally. Mass measured 2x1.5 cm, and it was well circumscribed with lobular appearance. Microscopic examination revealed spindle-shaped neoplastic cells which have scant eosinophilic cytoplasm and bland hyperchromatic round to oval nuclei. There is no mitotic figures, cytological atypia or necrosis. The tumour cells were forming lace-like, retiform or pseudoglandular structures containing abundant basophilic myxoid material. The tumour showed strongly diffuse positivity for S-100 protein, vimentin, and GFAP while negative for CD34, pan-CK (AE1/AE3), HMB-45 and EMA in immunohistochemical staining. Finally the case was diagnosed as cutaneous MRS.
Conclusion: Schwannomas are benign tumours which arise from the cells of Schwann that form the neural sheath. There are several morphologic variants of schwannoma, including cellular schwannoma, ancient schwannoma, plexiform schwannoma, epithelioid schwannoma, glandular schwannoma, melanotic schwannoma, hybrid schwannoma/perineurioma and microcystic/reticular schwannoma. MRS is a very rare variant of schwannomas with benign biological behaviour. Both surgeons and pathologists should consider MRS in the differential diagnosis of soft tissue tumours with a reticular growth pattern.

E-PS-05-012
Primary cutaneous myxoid spindle cell squamous cell carcinoma of the scalp: a case report
M. Suntur[1], O. Semerci[1], R. Bedir[1]
[1] Recep Tayyip Erdogan University, Department of Pathology, Turkey,

Background & Objectives: The primary cutaneous squamous cell carcinoma (SCC) is the second most common skin cancer. Primary cutaneous myxoid spindle cell squamous cell carcinoma (MSC SCC) is an extremely rare variant of SCC with only 7 cases reported in the literature. Here, we present an MSC SCC case located at the scalp of a 78-year-old male patient and its differential diagnosis with immunohistochemical results.
Methods: A 78-year-old male patient presented to the clinic with the ulcerated nodular lesion at the parietal region of the scalp. The lesion was totally excised. In microscopic findings, we identified a tumour which showing infiltration as single cells and cell groups in the myxoid stroma of dermis and also causes ulceration in the epidermis. The depth of invasion of thetumour was 0.3 cm and the diameter of the tumour was 0.7 cm (stage pT1). In immunohistochemistry tumour cells showed positivity for pan-cytokeratin (AE1/AE3), p40, vimentin and negativity for S-100, HMB-45, MART1, SMA, desmin.
Results: The diagnostic criteria of MSC SCC in the literature are the significant myxoid stromal changes, observing these changes onmore than half of the lesion, positive staining of neoplastic spindle (and squamous) cells with minimum one cytokeratin and negative staining with melanocytic and mesenchymal markers. Based on these results, the case was diagnosed with MSC SCC. The myxofibrosarcoma, malign peripheral nerve sheath tumour, spindle cell atypical fibrocarcinoma and spindle cell melanoma should always be considered in the differential diagnosis of MSS SCC.
Conclusion: The differential diagnosis of MSC SCC's should be made by using melanocytic and mesenchymal markers in order to distinguishit from all other potential tumours. The diagnosis should be confirmed by using epithelial markers.

E-PS-05-013
Minimal deviation melanoma: a rare case study report
D. Anestakis[1], M.I. Givannakis[2], P. Konstantinidou[1], F. Louka[1], E. Zagelidou[3]
[1] Department of Autopsy Histopathology, Lab. of Forensic Medicine and Toxicology, Aristotle University of Thessaloniki, Greece, [2] Surgical Department , General Hospital "AHEPA", Thessaloniki Greece,
[3] Thessaloniki Forensic Service, Thessaloniki, Greece

Background & Objectives: Minimal deviation melanomas, also called borderline melanocytic lesion, are uncommon nevomelano-cytic tumours of indeterminate risk that appear as pigmented or non-pigmented skin nodules. They are typically lesions that satisfy the requisites for vertical growth. In borderline variants, they form an expansile nodule that is confined to a widespread papillary dermis. If they form an expansile nodule and infiltrate the reticular dermis, they are minimal deviation melanomas without the borderline qualification. They differ cytologically from the common aggressive melanomas.
Methods: This report describes a case of minimal deviation melanomas involving on the scalp in a 72-year-old man. The patient presented with a skin nodule of scalp, simple excision of the tumour was performed.
Results: Histological and the immunophenotype findings were compatible with minimal deviation melanoma. In the follow-up, after three years no recur or metastasis appeared. In the follow-up, after three years no recur or metastasis appeared.
Conclusion: In our experience, they may rarely recur or rarely metastasize. These tumours are mostly observed in young adults and older children and are clinically diagnosed as Spitz nevi, hemangiomas, or malignant melanomas. It may originate from a pre-existing mole, or from normal skin (a new growth type). Minimal Deviation Melanoma of Skin tumours is said to have a 'borderline' behaviour. The most common treatment is surgery. Tumour metastasis is not observed very often and recurrences are uncommon after surgery.

E-PS-05-014
Muir-Torre Syndrome: a rare hereditary condition
C. Faria[1], M.J. Julião[1], V. Almeida[2], F. Ramalhosa[1], J. Fraga[1], A. Lai[1], R. Almeida[3,4], M.B. Pimentão[1], H. Moreira[3], R.C. Oliveira[1], M.A. Cipriano[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal, [2] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the

University of Coimbra, Portugal, [3] Centro Hospitalar e Universitário de Coimbra - Pathology Department, Portugal, [4] Faculty of Medicine in Coimbra, Portugal

Background & Objectives: Muir-Torre syndrome, a rare autosomal dominant condition, is caused by germline mutations in the DNA mismatch repair (MMR) genes, MLH1, PMS2, MSH2 and MSH6 genes. This syndrome is considered a phenotypic variant of hereditary nonpolyposis colorectal carcinoma syndrome (HNPCC, Lynch syndrome) and is characterised by the association of at least one sebaceous skin tumour and/or keratoacanthoma and at least one visceral malignancy.
Methods: We describe the case of a 49-year-old woman with a previous diagnosis of pancreatic carcinoma in 2015 and with a right inferior palpebral lesion of rapid growth developed three years later.
Results: Histopathological examination revealed a sebaceous skin neoplasia with lobulated pattern, composed by two cellular populations, one central with a clear cytoplasm and a monotonous nucleus, and a second population of peripheral basaloid cells. The stroma is scant and edematous with congestive blood vessels. The mitotic activity is low and there were not areas of tumour necrosis.
Immunohistochemistry study showed positivity for EMA and negativity for CEA; with immunoreaction for Ki67 limited to the basal cell layer. The neoplastic nucleus also retained positivity for MLH1 and PMS2 and had complete loss of MSH2 and MSH6.
Conclusion: The diagnosis is a sebaceous adenoma with microsatellite instability that is related to germline mutation of Muir-Torre syndrome. Particularly this patient was previously diagnosed with a pancreatic ductal carcinoma although the internal malignancies most frequently associated with this syndrome are colorectal, ggynaecological and urothelial cancers. So genetic testing and preventive cancer screening program alongside clinical criteria should be studied for these patients.

E-PS-05-015

A rare lesion of ear; Merkel Cell Carcinoma

S.Y. Celik[1], O. Ilhan Celik[1], Y. Dere[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Merkel Cell Carcinoma(MCC) is a rare, aggressive, cutaneous neuroendocrine neoplasia with a high mortality rate. It is generally seen in sun-exposed skin of head, neck and extremities in older adults with light skin. It may present at an earlier age in immunocompromised individuals like HIV-infected patients, organ transplant recipients and patients with hematologic diseases.
Methods: A 71-year-old male suffering from a rapidly growing, 5cm, fixed, subcutaneous, nodular mass on his left auricle was referred to oto-rhino-laryngology clinic. An incisional biopsy demonstrated a necrotic tumour composed of small, uniform, round cells with high nucleus-to-cytoplasm ratio, round vesicular nuclei with 'salt and pepper' chromatin, scarce cytoplasm and high mitotic index.
Results: Tumour cells were positive for Cytokeratin20, chromogranin A, Neuron-specific-enolase and synaptophysin and negative for Cytokeratin7, CD45, TTF-1, s100, Desmin, Myogenin, p63, Melan A. Ki67 index was about 50%. The lesion was diagnosed as MCC. Later the tumour is completely excised and ipsilateral lymph nodes of the neck were dissected. Three of the lymph nodes were metastatic. Radiotherapy was added to the surgical treatment.
Conclusion: MCC is a very rare, aggressive tumour of epithelial and neuroendocrine origin that usually presents as a painless, exophytic nodul with a poor prognosis, including high rates of metastasis, recurrence and mortality. As it forms a banal-appearing lesion, the diagnosis of MCC is rarely suspected at the time of biopsy. The treatment of it is surgical excision and sometimes adjuvant radiotherapy and/or chemotherapy. Immunotherapy and targeted therapies are the other treatment methods which have been investigated.

E-PS-05-016

Cutaneous infiltrate of a B chronic lymphocityc leukemia in two patients with an atypical fibroxanthoma and squamous cell carcinoma: two case reports and review of the literature

A. Sobrino Prados[1], C. Yus Gotor[2], N. Torrecilla Idiope[2], M.J. Viso Soriano[1], J.I. Franco Rubio[2], H.P. Almanzar Comas[1], S. Bakali Badesa[1], R.I. Bermudez Cameo[1], î Arellano Álvarez[1], N. Estrada Mallarino[1], B. Cazaña Pèrez[2], M. Pastor Adiego[2]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain, [2] Hospital Universitario Miguel Servet, Spain

Background & Objectives: Cutaneous infiltrate of a B chronic lymphocityc leukemia (B-CLL) is an infradiagnosed condition, in which clinical data and a methodic sample analyse is needed for making a correct diagnosis. Reviews in the literature suggest neoantigens and cytokines recognition and an immunosupressive microenvironment might explain the cause of the association of B-CLL and cutaneous neoplasms.
Methods: Two 82-and-83-years-old-patients presented two lesions (0,9 and 1,2 cm size) in sun-exposed skin, which were completely excided, in 2018 in Hospital Universitario Miguel Servet in Zaragoza. Both suffered from a B-CLL for years, with lymphocytosis as the only clinical manifestation.
Results: The H-E sections showed an atypical fibroxanthoma (AFX) and a squamous cell carcinoma (SCC) surrounded by an homogeneous infiltrate of mature B lymphocytes, which stained for CD20, CD79 a, CD5 and CD23. Therefore, patients were diagnosed of an AFX and SCC respectively with a cutaneous infiltration by B-CLL.
Patients with B- CLL have an increased risk of devoloping neoplasms, probably due to the immunosupresive environment caused by the B-CLL. Besides, neoplasic lymphocytes infiltrate more frequently tumours or other inflammatory conditions taking place in the skin. The most common neoplasms associated with B-CLL are SCC, basocelular carcinoma and actinic queratosis. These have a higher risk of recurrences and it is recommended the surgical margins to be wider.
Conclusion: Further research is necessary for improving our knowledge about the etiopathogenic mechanisms and the prognosis they may have and therefore, provide the best treatment options to patients.

E-PS-05-017

Stepwise progression of proliferating pilar tumour and trichilemmal carcinoma from pilar cysts is associated with p53 loss: a case report

L. Ahmed[1], R. Hejmadi[1], M. El-Shafie[1], K. Kok[2], O. Cain[1]
[1] University Hospitals of Birmingham NHS Trust, Cellular Pathology Queen Elizabeth Hospital, United Kingdom, [2] University Hospitals of Birmingham NHS Trust, Plastic and Burns department, Queen Elizabeth Hospital, United Kingdom

Background & Objectives: Pilar (trichilemmal) cysts are commonly encountered specimens in routine diagnostic practice and only very rarely show atypical features. There is some debate as to whether stepwise molecular changes accumulating in pilar cysts gives rise to proliferating pilar tumour and trichilemmal carcinoma, or whether these tumours develop de novo in the absence of a pre-existing pilar cyst.
Methods: We present a case of a patient with seventeen scalp cysts removed in one large surgical excision. Histologically all showed trichilemmal differentiation, ranging from benign pilar cyst, through proliferating pilar tumour to trichilemmal carcinoma.
P53 immunohistochemistry was performed on the tumour.
Results: We were able to demonstrate loss of p53 expression on immunohistochemistry specifically in the malignant element. In contrast, non-malignant elements showed patchy wild-type staining.

Conclusion: This case supports the hypothesis that stepwise molecular changes result in the development of proliferating pilar tumour and trichilemmal carcinoma from pilar cysts. In keeping with previous studies, p53 mutation may well be a critical step in this progression detectable by routine immunohistochemistry.

E-PS-05-018

Aleukemic neonatal leukemia cutis preceding monocytic leukemia with a favourable outcome

B. Sirine[1], J. Pourchet[1], S. Fraitag[2], N. Sturm[1], H. Gil[1]
[1] Grenoble Alpes University Hospital, France, [2] Enfants Malades Necker Hospital, France

Background & Objectives: Leukemia cutis(LC)is defined by cutaneous infiltration by leukemic cells.In aleukemic LC,the invasion of the skin happens at least 1 month before the acute leukemia.The neonatal form of LC which occurs within 4 weeks of life is less frequent than adult LC.Neonatal leukemia has a poor prognosis usually fatal.We report an exceptional case of complete remission after aleukemic LC preceding acute leukemia with main objectives to describe epidemiologic,clinical,histological,molecular and prognostic features of aleukemic neonatal LC.
Methods: A female newborn presented at birth for a few firm red-violaceous papulo-nodular lesions in the face and the trunk.Physical examination didn't reveal other abnormalities.CBC and coagulation tests of umbilical cord blood and in the first 24 hours were normal.Cutaneous biopsy performed on 3rd day of life showed a dense dermal infiltrate composed of a monomorphous undifferentiated blast cells with nuclear dust. These cells stained positively for CD4,CD15,CD68,CD43,HLA-DR.Myeloperoxidase was negative.Molecular testing revealed rearrangement of the MLL gene with translocation t(9;11).
Results: We concluded to a cutaneous monocytic leukemia cutis (AML-M5).Thirteen days later,cerebrospinal fluid examination and bone marrow aspirate were normal, however, the peripheral blood smears showed the presence of monoblasts(14%).A close biological follow-up was mandatory.On the 31th day of life,the patient presented anemia, hyperleukocytosis(54,6x10^9/L),elevated blasts(28%)and monocytes(18%).Urgent administration of multiple drug induction chemotherapy(ELAM 02 protocol)was followed by complete remission and clearance of cutaneous lesions on day 28 of life.
Conclusion: LC is common in the ALM-M5 leukemia but its neonatal form has very rarely been described.Neonatal LC without other clinical signs has been reported in a few patients.Cutaneous biopsy and molecular testing is mandatory for diagnosis and typing of the disease.The favourable outcome of our patient is exceptional.

E-PS-05-019

Pseudovascular squamous cell carcinoma: case report of an elusive entity and potential diagnostic pitfall

T.A. Georgescu[1], A.C. Lisievici[2], A. Dumitru[3], M. Sajin[4,5,6], M. Costache[3,7]
[1] Department of Pathology, Bucharest Emergency University Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [4] SUUB, Romania, [5] UMF Carol Davila, Romania, [6] European Society of Pathology, Romania, [7] Department of Pathology, Emergency University Hospital Bucharest, Romania

Background & Objectives: Pseudovascular squamous cell carcinoma was initially described in 1992 by Nappi, Barnejee and their collaborators, as a rare variant of cutaneous acantholytic squamous cell carcinoma which occurs on sun-exposed areas of middle-aged or elderly patients and can easily be mistaken histologically for angiosarcoma or an ulcerated metastasis of adenocarcinoma.
Methods: We present the case of a 78-year-old male presenting to our clinic with an exophytic tumour of 12/7/5mm with extensive surface erosion, located on the left thigh. After clinical examination, the patient was subjected to surgical excision and the specimen was sent to the Department of Pathology for histopathological examination.
Results: Microscopically, the tumour was composed of interanastomosing cord-like sheets of plump epithelial cells with vesicular and hyperchromatic nuclei forming pseudolumina and hobnail aspects. No foci of squamous differentiation or clear derivation from the surface epithelium were observed. Tumour cells were diffusely positive for AE1/AE3, CK5/6, p63 and Vimentin and completely negative for SMA, desmin, myogenin and S-100. In contrast to angiosarcoma, the tumour cells were also invariably negative for endothelial cell markers such as factor VIII-related antigen, CD31 and CD34.
Conclusion: Based on the clinical, morphological and immunohistochemical aspects, the final diagnosis of pseudovascular squamous cell carcinoma has been established. Although the general outcome of this particularly rare variant is not very well studied, its recognition is extremely important due to the potential confusion with angiosarcoma, which yields a completely different clinical outcome.

E-PS-05-021

Subcutaneous atypical ossifying fibromyxoid tumour with dermal involvement and mosaic loss of INI-1 expression: a case presentation

P.I. Stinga[1], A. Cioroianu[1], S. Iacob[2]
[1] Colentina University Hospital, Romania, [2] Personal Genetics, Romania

Background & Objectives: Ossifying fibromixoid tumour(OFT) is a rare soft tissue tumour with unusual dermal involvement, of uncertain lineage of differentiation, harboring particular histological and immunohistochemical features, as well as newly discovered molecular signatures. Three subtypes have been described-typical,atypical,malignant, based on cellularity,nuclear grade,mitotic index. Owing to its rarity,this entity poses vexing diagnostic challenges.
Methods: We present the case of a 48 year-old male patient with a 7 years clinical course of a 60mm superficial subcutaneous mass of the trunk(subscapular region), diagnosed elsewhere as extraskeletal myxoid chondrosarcoma.
Microscopy revealed a well-circumscribed,multinodular proliferation, arising in the subcutis, focally extended into the deep dermis, compound of small,round to spindle-shaped, mild pleomorphic cells with vesicular nuclei, eosinophilic cytoplasm, arranged in cords/trabeculae/clusters, imbedded in an fibromyxoid matrix, surrounded by a peripheral shell of lamellar bone;the cellularity was classified as intermediate and the mitotic index was 3/50HPFs. The immunohistochemical study revealed S100 diffuse positivity and focal GFAP, SMA,NSE,CD56 positivity; others markers performed(CD34,EMA,Desmin) were negative. INI-1 stain showed mosaic pattern staining. A diagnosis of an atypical OFT was made.
Results: Molecular testing was elsewhere done, the result sustaining the diagnosis of OFT.On subsequent follow-up, the patient is alive and well, without signs of recurrence or metastasis after 1 year from the surgery.
Conclusion: OFT is a peculiar neoplasm, often located in the superficially soft tissue, with infrequent dermal involvement and potentially aggressive behavior, recently included in the group of translocation-related lesions; the entity should be taken in consideration in the differential diagnosis of the superficial soft tissues tumours, often encountered in dermatopathology practice.

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E-PS-05-022

Melanocytic matricoma: a case report of a rare entity

G. Morgantetti[1], G.A. Medeiros[1], S.B.G. Hosseini[1], M.L. Balancin[1], M.E.d.A.S. Yamashita[2]
[1] University of Sao Paulo, Brazil, [2] Barretos Cancer Hospital, Brazil

Background & Objectives: Melanocytic matricoma is a rare form of pigmented follicular neoplasm with both matrical and melanocytic components, first reported in 1999 by Carlson et al. Since its first publication, few cases have been published in the current scientific literature. Usually associated with hyperpigmented lesions appearing at sun-damaged skin of adults, melanocytic matricoma is rarely listed as the most probable diagnosis based on clinical examination alone, due to its very low incidence and lack of pathognomonic epidemiologic, clinical or dermathoscopic aspects. Microscopically, the lesion consists of a well circumscribed hypercellular nodule composed of a biphasic cell population: an epithelial phase composed of both matrical and supramatrical cells with clustered shadow cells and a melanocytic one, composed of dendritic melanocytes. The main clinical differential diagnoses are hemangioma, pigmented basal cell carcinoma and melanoma, while the main histopathological pitfall resides in the differentiation of melanocytic matricoma with matricoma or pigmented pilomatricoma. The present report aims to contribute with the current clinical, histological and immunohistochemical knowledge of the disease.
Methods: A 42 year old female patient presented to the Ribeirão Preto Clinics Hospital (HCFMRP-USP) Dermatology Outpatient Clinic with a 0,9 cm forearm pigmented nodule. It showed no ulceration or irregular pigmentation. Excisional biopsy was performed under the clinical hypothesis of pigmented basal cell carcinoma. The biopsy material was submitted for histopathological examination, fixed in buffered formalin, embedded in paraffin and routinely stained with hematoxylin-eosin. Immunohistochemical study was performed with antibodies targeted to CEA, Chromogranin, CK5/6, HMB45, MelanA, p63, S100 and Synaptophysin.
Results: Microscopically the lesion consists of a pigmented nodular tumour of well-defined borders composed of biphasic celullar components: (1) matrical cells that contain ovoid nuclei and frequent conspicuous nucleoli, with an intermediate nuclear-cytoplasmic ratio; (2) dentritic melanocytic cells that are elongated and pigmented (Figure 1). Clusters of ghost cells can be found dispersed through the lesion (Figure 2). Cysts that contain hyaline proteinaceous fluid are sparse. There is no necrosis or mitotic figures. The adjacent dermis show solar elastosis and a mild dermal mononuclear inflammatory infiltrate. The immunohistochemical profile of the neoplasm showed positivity to p63, with focal expression of high molecular weight cytokeratins (CK5/6) of the epithelial matrical component (Figure 3). MelanA, HMB45 and S100 stained positive in the dendritic melanocytes (Figure 4). There was no reactivity of CEA, CK20, Chromogranin or Synaptophysin antibodies.
Conclusion: Melanocytic matricoma is a very rare biphasic neoplasm composed of matrical cells admixed with dendritic melanocytes, with few case reports and series of cases presented in current scientific literature. With the present case, we expect to contribute with useful clinical and pathological data to the current scientific knowledge of this rare entity.

E-PS-05-023
Mycosis fungoides bullosa: a case report
Î Yalçın[1], A. Dobral[1], S. Yıldırım[2]
[1] Istanbul Okmeydani Training and Research Hospital, Turkey, [2] Istanbul Maltepe University- Medical School, Turkey

Background & Objectives: Mycosis fungoides is the most common type of cutaneous T-cell lymphoma which can be presented with different clinical and histological forms. Mycosis fungoides bullosa is a rare variant of mycosis fungoides. Therefore we report a case of mycosis fungoides bullosa and review the relevant literature.
Methods: We present a case of mycosis fungoides in a 75-year-old man who presented with erythematous plaques on all extremities histologically diagnosed as mycosis fungoides bullosa which is incompatible with the clinical apperance.
Results: Histopathology revealed extensive lichenoid changes with intraepidermal bullae. Atypical lymphocyte infiltration was present at the dermoepidermal junction, in bulla.
Conclusion: Although mycosis fungoides bullosa is extremely rare, it is regarded as an important clinical subtype of cutaneous T-cell lymphoma. Mycosis fungoides bullosa represents an aggressive form of mycosis fungoides and is associated with a poor prognosis.
Mycosis fungoides bullosa is a rare occurance which is always manifested in vesiculobullous eruptions. We describe a 75-year old man with histopathologic diagnosis of mycosis fungoides bullosa who developed plaques lacking blister formation on normal appearing skin.Our case is rare in the literature with the incompatible clinical and histological diagnosis of the rare variant 'mycosis fungoides bullosa'.

E-PS-05-024
Cutaneous biphasic sarcomatoid basal cell carcinoma: report of a rare entity and review of the literature
M. Mellouli[1], S. Graja[1], S. Makni[1], N. Gouiaa[1], A. Ben Mabrouk[1], Z. Lajmi[1], M. Zghal[1], M. Walha[1], T. Sallemi-Boudawara[1]
[1] Department of Pathology, Habib Bourguiba Hospital, Sfax, Tunisia

Background & Objectives: Biphasic sarcomatoid carcinoma is an uncommon biphasic neoplasm that has been reported in diverse anatomical sites. The tumour is composed of a malignant epithelial component intimately associated with a malignant mesenchymal component, which may be homologous or heterologous. Only 47 cases of primary cutaneous biphasic sarcomatoid basal cell carcinoma (BSBCC) have been reported in the English literature. We report a further one case of BSBCC of the scalp and include the clinical, histological and immunohistochemical features.
Methods: The histological and immunohistochemical features of BSBCC of the scalp are described with a review of the related literature.
Results: A 65-year-old man presented with an elevated and ulcerated lesion on the scalp measured 20×15×6 mm. The lesion was surgically excised. Histology showed basal cell carcinoma intimately admixed with a sarcomatous component composed of spindle and oval atypical cells with vesicular nuclei and quit high mitotic count. There was no heterologous stroma. Immunohistochemical analysis showed these cells to be positive for vimentin and negative for keratin and HMB45. The diagnosis of BSBCC was made. In our case, tumour was completely resected with no recurrence or metastases.
Conclusion: The histogenesis of BSBCC has been extensively debated. Four main theories have emerged, the most widely accepted was that the sarcomatous component is a metaplastic transformation of the carcinomatous component which would confer an increase in aggressive potential to the tumour. In view of this potential, complete resection is recommended.

E-PS-05-026
Morphological and immunohistochemical studies of Kaposi sarcoma
V. Filatov[1], J. Omarova[1], T. Bezuglova[2], M. Mnikhovich[3], A. Asaturova[4], V. Kometova[4]
[1] Pirogov Russian National Research Medical University, Russia,
[2] Research Institute of Human Morphology, Russia, [3] Research Institute of Human Morphology (Moscow), Russia, [4] Federal State Budget Institution National Medical Research Center of Obstetrics, Gynaecology and Perinatology Ministry of Healthcare of the Russian Federation (Moscow), Russia

Background & Objectives: The differential diagnosis of Kaposi sarcoma (KS) includes many tumours such as dermatofibroma, histiocytoid hemangioma, kaposiform hemangioendothelioma, angiosarcoma.
Methods: Biopsy material from 7 HIV negative patients (age 45-75 years), 3 women (51, 32%) and 4 men (48, 68%), was studied. In 6 cases

(72,37%) patients complained of skin tumours. In 1 case (27,63%) diagnosis was established post mortem.
Results: Immunohistochemical studies have shown monomorphic expression of CD34 by endothelial cells while expression of von Willebrand factor was heterogeneous, cells were generally negative for CD31. Endothelial cells and myofibroblast-like cells have shown focal intensive nucleocytoplasmatic expression of HHV8. Myofibroblast-like cells demonstrated intensive Ki-67 positivity. Additional markers (IgL(lambda), IgL(kappa), CD38, CD3, CD79a, CD30) were used. Cells demonstrate intensive IgL(lambda), IgL(kappa), CD38 cytoplasmatic expression, CD3, CD30 membrane and cytoplasmatic expression and membrane expression of CD79a.
Conclusion: Pathomorphological diagnostics of KS should include histological study with consideration of chaotic character of angiogenesis, proliferation of spindle cells with endothelial markers, mononuclear cell infiltration, and immunohistochemical study with CD34, CD36, CD31, Von Willebrand factor, and Ki-67. Additional markers (IgL(lambda), IgL(kappa), CD38, CD3, CD79a, CD30) in pathomorphological practice for differential diagnosis.

E-PS-05-027
Infundibulocystic basal cell carcinoma: an unusual variant at an unusual age in sun protected skin
M. Mc Cabe[1], J. Fitzgibbon[1]
[1] Cork University Hospital, Ireland

Background & Objectives: Infundibulocystic basal cell carcinoma (BCC) is a rare variant with a distinct underlying mutation which contains elements of follicular differentiation. <1% of BCC occurs in the vulva. Two previous cases of vulval infundibulocystic BCC have been described in the literature. The first was a woman with widespread BCCs due to a germline mutation in a gene downstream from Sonic Hedgehog. The other was an elderly woman with concurrent Paget's disease.
Methods: We present the case of a 28-year-old woman who presented with a left upper labial cyst which, on histological examination, was revealed to be an infundibulocystic BCC. The specimen was received labelled as "Tiny left labial cyst.".
Results: Grossly, the specimen was a pale, round, smooth piece of tissue measuring 6x4x3mm. The entire mass was embedded. At low magnification, a well-circumscribed, palisading tumour was seen, consisting of infundibular-like structures with keratin plugs and anastomosing nests of basaloid cells, and tumour–stroma retraction. The tumour was superficially located and at the margin. At higher magnification, the tumour cells had a high nuclear:cytoplasmic ratio with pleomorphism, hyperchromatic nuclei, and inconspicuous nucleoli.
Conclusion: Infundibulocystic BCC is a less aggressive subtype whose underlying mutation differs from that found in more common forms. This case highlights the heterogeneity of BCC and in contrast with the previous reports, occurred in isolation in a young woman.

E-PS-05-028
Combined cutaneous tumours with melanoma component. Case report and literature review
A. Abuomar[1]
[1] Hospital General universitario de Elda, Alicante, Spain

Background & Objectives: Combined cutaneous tumours (CCTs) with a melanoma component are very rare with only 49 cases in the literature up to our knowledge. Squamomelanocytic CCTs are the most frequent followed by basomelanocytic CCTs and trichoblastomelanoma. We present a case of malignant basomelanocytic tumour and a literature review.
Methods: A 37 years old woman with brown eyes and skin phenotype III, a medical history on hypothyroidism and frequent sunburns. Patient arrived to our hospital complaining of that his year old left thigh nevi changed its color and size in the last week. Dermatology examination revealed a 5x5 mm with skin lesion on the anterior face of the left thigh with suspected signs on dermatoscope. Skin melanoma was suspected. elliptical incision of the lesion with narrow margins was performed.
Results: We received a skin elips of 10x5x5 mm with a pigmented lesion of 5x5 mm. Microscopic examination showed a skin with a neoplastic proliferation of basaloid epithelial cells with mild atypia admixed with severely atypical large melanocytes colonized the epitelial component and showing lentiginous and inflitrative growth pattern. Melanocytic component showed positive stain for S100, Melana A and HMB45, while epithelial component showed CK AE1-3 expresion. Cells with double expression of S100 and CK were observed.
Conclusion: The histogenesis of CCTs is not clear. 11q13 amplification in both components supports the theory of dual differentiation from a common progenitor cell. Studies showed that CCTs have better prognosis in comparison to melanomas with the same pathological stage.

E-PS-05-029
Sweet syndrome like neutrophilic dermatosis as an initial presentation of new-onset bullous systemic lupus erythematosus: a case report
M. Zivanovic[1], A. Vizjak[1]
[1] Insitute of Pathology, Medical Faculty Ljubljana, University of Ljubljana, Slovenia

Background & Objectives: To report a case of bullous systemic lupus erythematosus (SLE) that presented initially as a neutrophilic dermatosis (ND) in an adult male patient with antiphospholipid syndrome.
Methods: 30-year-old male presented with annular erythematous skin eruptions on his trunk and thighs that clinically raised suspicion of urticarial vasculitis. We examined the skin lesion from right thigh by light microscopy and direct immunofluorescence, followed by indirect immunofluorescence (ELISA).
Results: Histopathological examination revealed diffuse mild to moderate interstitial and perivascular dermal infiltrate composed predominantly of neutrophils, without accompanying fibrinoid necrosis of vascular walls or other histological features of presumed vasculitis. Direct immunofluorescence showed so called »full house« deposition of IgA, IgG, IgM, C3 and C1q along dermo-epidermal junction, in vascular wall of small blood vessels and also along conective tissue fibers in dermis. These findings were suggestive of SLE but also of possible hipocomplemented urticarial vasculitis. Indirect immunofluorescence testing on blood sample was negative for the presence of anti-C1q antibodies. Serological findings were highly suggestive of SLE. Less than one month after the initial symptoms patient developed widespread vesiculobullous skin eruption.
Conclusion: While the association of ND and autoimmune connective tissue diseases is well recognized, Sweet syndrome like ND as a presenting sign of SLE is reported only in a handful of cases, mostly in women. Even tough ND often presents in idiopathic fashion, it is important to think about possibility of underlying SLE, especially in younger patients.

E-PS-05-031
Cladophialophora Immunda: an extremely unusual infectious agent for chromoblastomycosis
J.I. Franco[1], A. Sobrino[2], N. Torrecilla[2], C. Yus[2], P. Cerro[3], R. Baldellou[3], C. López[4], M.I. Millán-Lou[4]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain, [2] Anatomía Patológica. Hospital Universitario Miguel Servet, Spain,
[3] Dermatología. Hospital Universitario Miguel Servet, Spain,
[4] Microbiología. Hospital Universitario Miguel Servet, Spain

Background & Objectives: Chromoblastomycosis, described for the first time in 1911, with few cases reported in Spain, is a deep mycotic infectious disease, resulted from inoculation of dermatiaceous fungi

after a traumatic injury, specially in males with a wide range of age. It is a slow-course disease, predominantly reported in tropical or subtropical areas. Clinically, it can simulate a malignant lesion, such as squamous cell carcinoma. It is a disease with an easy diagnosis that needs microbiological correlation in order to stablish a specific treatment.

Methods: We report the case of a 56-year-old male with history of kidney transplant, with a fastly-growing verrucous lesion, asymptomatic, located on the right foot. An incisional biopsy was performed and a sample for microbiological culture was taken.

Results: Histological examination of the biopsy showed an ulcerative lesion, with pseudoepitheliomatous hyperplasia and superficial granulomatous process, with multinucleated giant cells containing small, from 6 to 12 μm, round dark-coloured structures, evidenced without any special stain. Subsequent microbiological culture allowed typify the microorganism as Cladophialophora Immunda.

Conclusion: Chromoblastomycosis,is a very uncommon disease in a non-tropical country and Cladophialophora Immunda is an extremely unfrequent microorganism among the dermatiaceous fungi, causal agents of this entity. The posibility of this diagnosis should be taken in consideration in a verrucous and ulcerated lesion, from a tropical or subtropical climate country-native patient, specially in situation of immunosupression. Microbiological cultures should be granted in order to typify the microorganism and stablish the best treatment.

E-PS-05-032

Epidermolytic ichthyosis: study of a family with skin fragility and palmoplantar keratoderma

A. Sobrino Prados[1], N. Torrecilla Idiope[2], C. Yus Gotor[2], P. Cerro[2], Y. Gilaberte[2], J. Forteza[2], J.I. Franco Rubio[2], M.J. Viso Soriano[1], S. Bakali Badesa[1], H.P. Almanzar Comas[1], R.I. Bermudez Cameo[1], N. Estrada Mallarino[1], î Arellano Álvarez[1]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain, [2] Hospital Universitario Miguel Servet, Spain

Background & Objectives: Epidermolytic ichthyosis (EI) is a rare autosomal dominant genodermatosis, affecting the keratinization and suprabasal maduration of keratinocytes and is generally associated with mutations in the keratin 1 and 10 genes. Symptoms in newborns are bullous lesions, erythroderma and desquamation, followed by different degrees of skin fragility in adulthood and sometimes, palmoplantar keratoderma. Although in newborns there is an increased risk of infections or sepsis, the prognosis is usually good, but it depends also on the severity of each case.

Methods: One-month-old male presented bullous lesions in buttocks, thighs and perioral area since birth. His mother, grandmother and uncle have a history of palmoplantar keratoderma along with skin fragility with a tendency to suffer bullous and ulcerative lesions. Two biopsies, an ultraestructural and genetical study were necessary to reach the diagnosis.

Results: Newborn biopsies showed a subcorneal blister with eosinophils and negative immunofluorescence. In the second biopsy of the mother, a characteristic perinuclear cytoplasmic vacuolization of keratinocytes of higher strata was observed. Ultraestructural study had images of epidermolysis of the epidermocytes, being compatible with the EI. Massive sequencing revealed a mutation in gen KRT1, p.Val198Glu; c.593>A, not described before in literature, and usually associated with palmoplantar keratoderma.

Conclusion:

- EI is a rare genodermatosis with a broad clinical, histological and prognostic spectrum, due to the different mutations in KRT1 and KRT10.
- KRT1 alterations are associated with palmoplantar keratoderma.
- Further research is needed to improve our knowledge of this entity.

E-PS-05-033

Epidermodysplasia verruciformis: an unusual diagnosis

S. Yacoub[1], S. Mistiri[1], N. Abdessayed[1], B. Sriha[1], M. Mokni[1], D. Chiba[1]
[1] Department of Pathology Farhat Hached Hospital, Tunisia

Background & Objectives: Epidermodysplasia verruciformis (EV) is a very rare genetic dermatologic condition, HPV related, causing an increased risk of cutaneous dysplasia and malignancy. The lesions of EV tend to exhibit a characteristic histopathologic appearance.

We describe a rare case of EV.

Methods: A 23 year-old female presented for management of a 3 cm waxy-brown verrucous plaque on the forehead that appeared 1 year before. A biopsy of the lesion was performed.

Results: The resected specimen was fragmented. Histopathologic examination of these lesions showed a thickened epidermis with a verruciform architecture. The epidermis was aconthotic, covered by a marked orthokeratosis. Numerous koilocytic cellular atypia was present associated to cluster of vacuolated cells with bubbly bluish cytoplasm. The superficial dermis showed a mild dermis infiltrate.

Conclusion: EV is a premalignant entity, that needs a close dermatologic monitoring.

E-PS-05-034

Erithema Elevatum Diutinum - a rare and often misdiagnosed entity

D. Vinha Pereira[1], J. Ferreira[1], A. Robson[1] and J. Costa Rosa[1]
[1] Pathology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal

Background & Objectives: Erythema (red) elevatum (elevated) diutinum (persistent) - EED is a rare middle-age chronic cutaneous vasculitis of unknown etiology associated with autoimmune, infectious and hematological diseases. Many clinical and histological mimics can be recognized, such as inflammatory conditions, in early stages (e.g.: granuloma faciale, Sweet´s syndrome) or neoplasias, in later stages (e.g.: dermatofibroma, myxoinflammatory fibroblastic sarcoma).

Methods: We report two cases clinically diagnosed as a neoplasia (first case) and epidermal cysts/keloid scars (second case).

Results: Two women (aged 42 and 50) with no relevant medical history presented with slowly developing multiple cutaneous limb nodules (first case) and facial papules (second case).

Histologically, both cases revealed superficial and deep dermal mixed inflammatory infiltrates (more prominent on the second case), with abundant neutrophils and scattered eosinophils; neutrophilic vasculitis and leucocytoclasis were present; fibrosis was particularly dense on the first case. Special stains for fungi and mycobacteria were negative. A diagnosis of EED was performed (later and early stages, respectively).

Although the first patient had a history of recurring limb nodules (outside our institution), 15 months after this excision, she remains disease free. The second patient developed similar lesions at the same location after 6 years. There is no evidence of other systemic diseases in both cases.

Conclusion: EED diagnosis is challenging and requires histological and clinical correlation, because of its strong association with systemic diseases. Isolated cases can also exist.

E-PS-05-035

A non-scalp neurocristic cutaneous hamartoma with malignant transformation - a case report and review of literature

C. Costa[1], I. Gullo[1,2,3], J. Pacheco[1,2], J.M. Lopes[1,2,3], E. Rios[1,2,3]
[1] Department of Pathology, Centro Hospitalar de São João, Porto, Portugal, [2] Department of Pathology, Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal, [3] Institute of Molecular

Pathology and Immunology at the University of Porto (Ipatimup), Instituto de Investigação e Inovação em Saúde (i3S), Porto, Portugal

Background & Objectives: Neurocristic cutaneous hamartoma (NCH), a rare hamartomatous-type lesion of neural crest origin, characteristically unveils fibrogenic, melanocytic, and/or neuro-sustentacular differentiation. NCH displays predilection for the scalp, and may be congenital or sporadic. Despite few reported cases, up to 35% NCH (~40% congenital) developed malignant transformation. Herein we report a sporadic NCH with melanoma transformation and lymph node metastases.
Methods: A 55-year-old-male with giant "bathing-trunk"-type pigmented lesion since his adolescence, which displayed recent rapid growth. Resection of two indurated subepidermal nodules was performed, then margins widening/sentinel node/inguinal lymph node dissection.
Results: Histology revealed a complex lesion comprising cellular blue nevus-like and neurofibroma-like components, in a background of congenital intradermal nevus. One of the nodules disclosed nodular melanoma area without ulceration of epidermis. Five out of eleven lymph nodes dissected (including sentinel node) disclosed metastases. Immunohistochemistry revealed common features of neurofibroma and melanocytic components. Diagnosis: NCH with melanoma transformation. No *BRAF* mutations were detected. The patient was proposed for adjuvant chemotherapy/radiotherapy (recent case).
Conclusion: NCH is rare and can develop melanoma over variable time course (15 to 67 years), due to etiopathogenesis that differ from low degree of cumulative sun damage skin melanomas. So far, 11 cases of malignant transformation (all as melanoma) NCH were reported (excluding the present case), 5 (~45%) of which developed metastases.

E-PS-05-036
Quinquaud's decalvans folliculitis: a case report
S. Ben Khalifa[1], N. Abdessaied[1], S. Chaieb[1], Z. Nfikha[1], A. Ben Abdelkader[1], M. Mokni[1]
[1] Pathology Department of Fattouma Bourguiba Hospital, Monastir, Tunisia

Background & Objectives: Folliculitis decalvans (FD) of Quinquaud is a rare chronic follicular inflammatory process, extremely resistant to treatment, causing follicular atrophy and subsequent hair loss. The etiology is still unknown.
Methods: We report a case of FD diagnosed in the department of pathology of Farhat Hached hospital.
Results: A 31-year-old man presented to dermatology department with a tumoural lesion on the scalp of 2 years duration, with progressive loss of hair. He had no medical history. Physical examination revealed a nodular alopecic lesion of the scalp, 2cm in size. Bacteriological and mycological findings were negative. Complete removal of the lesion was performed, and histopathological examination revealed a FD of Quinquaud.
Conclusion: FD is a chronic form of deep folliculitis that usually occurs on the scalp as oval patches of scarring alopecia at the expanding margins of which are follicular pustules. Any or all of the hairy areas of the body may be involved. The etiology is unknown, although Staphylococcus aureus is sometimes cultured from the lesions. Initially there is a folliculitis; this is followed by disruption of the follicular wall and liberation of the contents of the follicle into the dermis. The dermis adjacent to the destroyed follicle contains a mixed inflammatory cell infiltrate. Plasma cells are sometimes present in the infiltrate, particularly in resolving lesions. Foreign body giant cells may form around the hair shafts lying free in the dermis. FD sometimes responds to oral antibiotics but usually relapses after interruption of therapy, sometimes with severe scarring.

E-PS-05-037
Pretibial myxedema- a case report
S. Jakovljević[1,2], A. Fejsa Levakov[3,2], L. Djurdjev[4], V. Zečev[5], L. Vujanović[1,2], J. Sekulić[4]
[1] Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, [2] Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia, [3] Pathology and Histology Center, Clinical Center of Vojvodina, Novi Sad, Serbia, [4] General Hospital 'Đorđe Joanović', Zrenjanin, Serbia, [5] General Hospital 'Dr Radivoj Simonović' , Sombor, Serbia

Background & Objectives: Pretibial myxedema is a form of cutaneous mucinosis. It is a rare, chronic dermatosis, caused by thyroid dysfunction.
Methods: We present a 79-year-old female patient with chronic, symmetric, pretibial edematous, erythematous, yellowish plaques with affected skin resembling *'peau d'orange'* followed by feeling of the weight in the legs. The anamnestic data revealed the presence of thyroid dysfunction and diabetes mellitus, cholelithiasis and nephrolithiasis, as well as arterial hypertension and ischemic cardiomyopathy. In order to determine the etiology of pretibial edema and accurate diagnosis, a skin biopsy was done and histopathological findings confirmed the diagnosis of pretibial myxedema.
Results: The haematoxylin and eosin (H&E), Periodic Acid Schiff (PAS), Gomori and Giemsa staining were performed. Pathology analysis presented a diffuse atrophic and distinctly hyperkeratotic epidermis with flattened rete ridges. Dermis was expanded with granular appearance in lower two thirds due to abundant deposits of mucin widely separating collagen bundles. Capillary blood vessels were dilated, while sweat glands were of regular shape and distribution.
Conclusion: Our report confirms association between pretibial myxedema and thyroid endocrinopathy. Histopathology is of crucial significance in differentiating pretibial myxedema from other clinically similar conditions such as stasis dermatitis. Due to prompt diagnosis and conduction of recommended therapy, the skin remission and good quality of life could be accomplished.

E-PS-05-038
Merkel cell carcinoma, diagnostic experience in a reference hospital
R. Lopez[1,2], D.A. Suarez-Zamora[1], L.E. Barrera-Herrera[3], M. Rolon[1]
[1] Department of pathology and laboratories, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia, [2] School of Medicine, Universidad de los Andes. Bogotá, Colombia, [3] Department of Pathology and Laboratories, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia

Background & Objectives: Merkel Cell Carcinoma (MCC) is a poorly differentiated neuroendocrine tumour with very low frequency, usually is located on the exposed skin and classically manifests with aggressive behavior and high recurrence and metastatic risk. We present the largest series of MCC to date in Latin America focusing on understand and clarify essential concepts for prompt diagnosis and management of this not well known and aggressive disease.
Methods: We present a cross-sectional descriptive retrospective study in patients diagnosed with MCC at our University Hospital between October 2003 and October 2018, we present the demographic, clinical and pathological variables of these patients.
Results: 36 patients with histopathological diagnosis of MCC, 20 (55.6%) were men and 16 (44.4%) were women, male: female ratio of 1.25: 1. The median age was 71.5 years and the age range was 17.0 to 87.0 years. 88.9% (32/36) of the patients were older than 50 years. The most frequent location was facial skin (27.8%), followed by metastasis with unknown primary site (25.0%) and skin of the lower limbs and hip (13.9%).
The incidence rate of Merkel cell carcinoma at our university hospital was 0.72 cases per 100 000 people between October 2003 and October 2018.
Conclusion: This is the largest series of MCC to date in Latin America, we conducted a complete histopathological analysis, our information is consistent with what is referred to worldwide regarding the clinical and histopathological characteristics.

E-PS-05-039

Malignant complex (composite) adnexal cutaneous tumour mistaken for basal cell cancer: a case report

E. Delic[1], J. Redzepagic[2], D. Spirtovic[1], T. Ramovic[1], N. Bilalovic[1]
[1] Clinical Center University of Sarajevo/ Clinical Pathology and Cytology, Bosnia and Herzegovina, [2] Clinical Center University of Sarajevo, Bosnia and Herzegovina

Background & Objectives: Adnexal tumours of the skin are rare, heterogeneous group of tumours. Malignant tumours are even rarer than their benign counterparts. Here, we describe a metastatic complex malignant adnexal tumour of the skin in the axillary lymph node.
Methods: Case presentation.
Results: A 46-year-old male patient is sent from another hospital in our institution due to an enlarged lymph node in the right axilla and multiple masses in both lungs radiologically. Before this, the patient had the lesion on the face skin, which was surgically removed 5 years ago, diagnosed as basal cell cancer. Core needle biopsy of the lymph node is performed and histological examination reveals microscopic picture suspicious for metastatic skin cancer. The revision of the primary skin biopsy has been obeyed and the diagnosis of the malignant complex adnexal tumour with follicular, trichilemmal, sebaceous and ductal differentiation is established. During the diagnosis process, the patient died.
Conclusion: Many histological subtypes of malignant adnexal tumours been described. These tumours are rare, locally aggressive, and have the potential for nodal involvement and distant metastasis, with a pore clinical outcome. Patients age under 50 requires a higher degree of suspicion for the diagnosis of basal cell cancer. The complex histology of the presented case emphasizes the importance of histopathological examination in the diagnosis and therapeutic management of malignant cutaneous adnexal tumours.

E-PS-05-040

Dermal clear cell sarcoma: a very rare and confusing diagnosis

A. Saidi[1], R. Jouini[2], F. Khanchel[2], I. Hell[2], W. Koubaa[2], E. Ben Brahim[2], A. Chedli-Debbiche[2]
[1] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia, [2] Pathology Department; Habib Thameur Hospital, Tunisia

Background & Objectives: Clear Cell Sarcoma (CCS) is a rare and aggressive tumour with melanocytic differentiation. It was first described by Enzinger as a tumour that mainly involves the tendons and fasciae of the distal extremities of the young- to middle-aged woman. It is characterised by the frequency of local recurrences and late metastases that explain its poor prognosis. Dermal location is much rarer.
We report a new case of dermal CCS and discuss its anatomoclinical features
Methods: Standard Histological study of the tumour with immunohistochemical analysis targeting the markers: Melan A, HMB45, P16, Pancytokeratin, Ki67, PS100, CD68, Fact13a, EMA, Calponin, Caldesmone.
Results: We report the case of a 65-year-old female patient consulting for a 1.5 cm large pedunculated tumour with a smooth surface arising in the inner side of her right thigh. The mass has gradually increased in size since 8 months. After excision, histological examination shows that the dermis is entirely occupied by an ill-defined proliferation arranged in cellular bundles and clusters surrounded by collagen bands. Tumour cells are spindle shaped or epitheloid with often vesicular nuclei, otherwise hyperchromatic. The figures of mitosis are numerous.
The tumour cells exhibit only a weak and focal positive PS100 staining with a proliferation index (Ki67) estimated at 5%. The diagnosis of dermal clear cell sarcoma was additionally confirmed by Prof. Mentzel (Germany).
Conclusion: Dermal CCS is a rare, highly malignant soft tissue tumour, usually affecting young women and occuring most commonly in the extremities. Due to its rapid and aggressive evolution, it should always be considered in front of a fast-growing and rapidly ulcerating, cutaneous nodular lesion.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-06 | Digestive Diseases Pathology – GI

E-PS-06-001

Arylsulfatase B as prognostic marker in colorectal cancer

Z. Kovacs[1], L. Banias[1], I. Jung[1], S. Gurzu[1]
[1] University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania

Background & Objectives: Arylsulfatases are lysosomal enzymes with role in several metabolic processes. In normal colonic mucosa, Arylsulfatase B (ARSB) is present in the cell membranes. Few aspects are known about ARSB in colorectal adenocarcinoma (CRC). The aim of the paper was to evaluate the possible correlation between ARSB and clincopathological aspects of CRC.
Methods: ARSB immunohistochemical expression (polyclonal, Abcam, dilution 1:50) was prospectively quantified in 45 CRCs. As membrane to cytoplasmic translocation was seen in tumour cells, compared with normal mucosa, cases were divided into three groups, based on cytoplasmic expression intensity and number of positive cells.
Results: ARSB was more expressed in young versus old patients ($p=0.0095$) and slightly higher in cases with ulcero-infiltrative aspect, compared with polypoid tumours ($p=0.0088$). As regarding microscopic aspect, the ARSB intensity increased with tumour dedifferentiation, all of the G3/G4 cases showing high expression ($p=0.041$). It was also directly correlated with presence of lymph node metastasis ($p=0.026$) and lymph node ratio (14 cases out of 34 with a lymph node ratio <0.1 had low ARSB expression, $p=0.026$).
Conclusion: In CRC, compared with normal mucosa, membrane to cytoplasmic translocation is characteristic. High ARSB intensity was correlated with increasing aggressiveness of CRC cancer, which underlines the possible role of this enzyme as a prognostic maker of CRC.

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E-PS-06-002

AA Amyloidosis of the gastrointestinal tract associated with Waldenström´s Macroglobulinemia

M. Garcia Martos[1], C. Perna Monroy[2], C. Prada Puentes[3]
[1] University Hospital Gregorio Maraño, Spain, [2] Univ. Hosp. Ramon y Cajal, Spain, [3] Univ Hosp Torrejon, Spain

Background & Objectives: AL amyloidosis is a well-known complication of Waldenström´s macroglobulinemia (WM). AA amyloidosis is commonly associated with chronic inflammatory disorders. We present a case of gastrointestinal AA amyloidosis and WM. We show the importance of Congo red staining in bowel biopsies in patients with unexplained gastrointestinal tract symptoms.
Methods: A 59-year-old male with WM and several months' history of profuse diarrhea. He did not have fever, lymphadenopathy, or any other systemic manifestations, neither autoimmune nor connective tissue disorders. The patient underwent a colonoscopy and multiple colonic biopsies.
Results: Biopsy specimens from colon and rectum showed marked eosinophilic acellular material in the lamina propia and submucosa, with variable inflammatory infiltrated. This material was Congo red positive

(showed apple-green birefringence under polarized light). Immunohistochemistry showed strong positivity for AA deposits, confirmed by immunoelectron microscopy. It was also detected high serum monoclonal IgM levels. Disease progressed with renal, pulmonary, cardiac, hepatic and bone marrow involvement. He began Rituximab therapy but he had a lower digestive hemorrhagic episode and die.
Conclusion: Amyloidosis is a well-known complication of IgG related gammapathy but it is rare in IgM related gammapathy, including WM, and even rarer AA amyloidosis. Only a few cases have been reported of AA amyloidosis associated with WM. This association is seen in 5% of all gammapathy cases. Since each subtypes of amyloidosis requires different therapy, amyloid subtyping is crucial.

E-PS-06-003
Clinical and morphological features of eosinophilic oesophagitis in patients with asthma

L. Mikhaleva[1], V. Golovanova[1], V. Pechnikova[1], O. Vasyukova[1], E. Akopyan[1], K. Midiber[1], M. Gushchin[1]
[1] Research Institute of Human Morphology, Russia

Background & Objectives: Eosinophilic esophagitis (EoE) is an immune-mediated condition, characterised by oesophageal dysfunction and eosinophil-predominant inflammation. Patients with EoE are more likely to suffer from atopic conditions such as asthma than others. The accepted threshold for eosinophil density for the EoE diagnosis is 15 eos/hpf. The research goal was to show EoE clinical and morphological features in patients with asthma.
Methods: We observed 81 patients, 46 of which had controlled asthma of different severity and the rest of them represented the comparison group. Moreover, 15 autopsy cases were used in this study. Imaging (esophagogastroduodenoscopy), morphological (light microscopy), immunohistochemical and morphometrical methods were used.
Additional EoE histological criteria are eosinophil microabscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, papillary elongation, and lamina propria fibrosis.
Results: Morphometrical study showed mucosal layer atrophy. The active role of macrophages and NK-cells and an SE4+ and CB8+ cells imbalance (SE4/SE8 <1) in the mucous membrane atrophy and sclerosis in the oesophagus and stomach were proven unlike the comparison group. EoE infiltration evaluation revealed a significant number of macrophages and NK-cells which correlates with the subepithelial sclerosis prevalence, as well as earlier mucosa atrophy and lamina propria sclerosis in the oesophagus than in the stomach and the duodenum.
Conclusion: In conclusion, it is necessary to conduct a timely differential EoE diagnostics in patients with asthma, taking into account its frequency and EoE early development in these patients and its disabling complications.

E-PS-06-004
A case of MiNEN arising in the rectum with metastases in a benign tumour

I.A. Ungureanu[1], A. Dumitru[2], L.A. Ursache[1], D.I. Enea[1]
[1] University Emergency Hospital Bucharest, Romania, [2] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Background & Objectives: Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) are rare entities defined by the presence of two morphologically different neoplastic components (each at least 30% of the tumour), including a neuroendocrine one. High-grade MiNEN are usually aggressive neoplasms with poor prognosis and the metastatic risk is correlated to the grade of the neuroendocrine component. In this paper we present the first case of a high-grade MiNEN metastasized in an ovarian serous cystadenofibroma.
Methods: A 63 year-old female was hospitalized with a mass in the rectosigmoid junction, liver metastases and an ovarian mass. The patient underwent surgery and the primary tumour and the ovarian mass were both sent to gross examination. The microscopic analysis was performed on paraffin-embedded tissue samples stained with hematoxylin-eosin. Immunohistochemistry was performed for the following markers: ki-67, CK7, CK20, Chromogranin A, Synaptophysin, CD56, CDX2.
Results: Microscopy revealed a malignant population with 40% adenocarcinoma differentiation and 50% neuroendocrine component. The neuroendocrine cells exhibited organoid and cribriform structures with rosettes-arrangements. Squamous differentiation was present. Surprisingly, the examination of the ovarian mass revealed a serous cystadenofibroma with malignant cells invading both the cystic wall and the normal ovarian stroma. Immunohistochemistry showed positivity for CK20, CDX2, Chromogranin A and Synaptophysin and negativity for CK7. The proliferation rate was 70%. All these features were consistent with a MiNEN.
Conclusion: MiNEN is a rare entity and we highlight the importance of the pathological exam considering both immunohistochemistry and classic stain examination. Based on its aggressive behavior we recommend an optimal strategy of management and close supervision by a multidisciplinary team. Unexpected microscopical features and locations of metastases, as presented in this case, should always be considered as a possibility.

E-PS-06-005
Columnar-lined oesophagus less than 1 cm above gastro-oesophageal junction and Barrett's oesophagus: morphological features

L. Mikhaleva[1], K. Voytkovskaya[2], E. Fedorov[2], A. Shidii-Zarkua[3]
[1] Research Institute of Human Morphology, Russia, [2] Moscow University Hospital No. 31, Russia, [3] Pirogov Russian National Research Medical University, Russia

Background & Objectives: Barrett's oesophagus (BE) is well known risk factor for oesophageal adenocarcinoma, though columnar-lined oesophagus (CLE) less than 1cm above gastro-oesophageal junction (GEJ) is not well characterised.
The aim of our study was to perform a comparative morphological analyse of BE and CLE less than 1 cm above GEJ.
Methods: We examined endoscopic biopsies of 60 patients: 23 with CLE less than 1cm above GEJ and 37 with BE, stained with haematoxylin-eosin. Combined PASD/Alcian Blue stain was used for detection of goblet cells (GC). Each group of patients with GS was subdivided into groups with single GS, low density GC (LDGC, count of GS <50%) and high density GC (HDGC, count of GS >50%).
Results: In patients with CLE <1 cm above GEJ cardiac-type metaplasia was found in 7 (30,43%), acid-producing metaplasia – in 4(17,39%) and intestinal – in 12 cases (52,17%): SGC – in 4 (17,39%), LDGC – in 6 (26,09%) and HDGC – in 2 patients (8,7%).
Cardiac-type metaplasia was found in 4 cases of BE (10,8%), acid-producing metaplasia – in 6 (16,22%) and intestinal metaplasia – in 27 patients (72,97%): SGC in 8(21,62%), LDGC in 7(18,92%) and HDGC in 12 patients (32,43%).
Conclusion: Reactive changes of epithelium presented in 34,78% CLE cases and in 56,76% BE cases.
The frequency of intestinal metaplasia was 1,4-folds higher and the frequency of reactive changes was 1,6-folds higher in BE compared with CLE less than 1 cm above GEL. Reactive changes were associated with presence and density of GC.

E-PS-06-006
Invasive adenocarcinoma case in the background of intracholecystic tubulopapillary neoplasia originated from adenomyoma of gallbladder

T.C. Savli[1], N. Dursun[2], T. Bolme Savli[3]

[1] Istanbul Training and Research Hospital, Turkey, [2] University of Health Sciences, Istanbul Health Practice and Research Hospital, Department of Pathology, Turkey, [3] Bagcilar Training and Research Hospital, Turkey

Background & Objectives: The malignant potential of adenomyomas of gallbladder has controversy. Neoplastic transformation potential in literature is reported as 3%. Intracholecystic tubulopapillary neoplasms (ICPN) are defined as preinvasive neoplasms, which form prominent protuding mass in gallbladder mucosa. There are no publications in the literature about intracholecystic tubulopapillary neoplasms originating from adenomyoma. We present our case because it has adenomyoma and intracholecystic tubulopapillary neoplasm and also invasive carcinoma foci in the same lesion.
Methods: A 75-year-old male presented with abdominal pain. MRI revealed 2.1x2.1cm sized lesion with heterogeneous contrast enhancement containing suspected millimetric invasion areas at fundus of gallbladder. On PET-CT scan there was intense FDG uptake in the same area, consequently cholecystectomy was performed.
Results: We encountered sized of 6.5x3x2cm polypoid lesion extending to lumen which was located at gallbladder fundus. Histopathological examination revealed a lesion within adenomyoma. This lesion protruded from superficial mucosa with a pattern similar to ICPN. There were also millimetric invasive tumour foci which was confined to adenomyoma. The tumour was extended to perimuscular connective tissue, as it was in the adenomyoma (pT2). After two year follow-up the patient had disease free survival.
Conclusion: ICPN arising in an adenomyoma with invasion is a rare condition. In addition, although there was pT2 invasion in the lesion; it was confined to adenomyoma; so the expected survival will be better than other pT2 tumours. As a matter of fact, our case has been living without disease for two year.

E-PS-06-007
Mixed acinar endocrine carcinoma presenting as a polyp in stomach
T.C. Savli[1], N. Dursun[2], B. Yeni[3], T. Bolme Savlı[4]
[1] Istanbul Training and Research Hospital, Turkey, [2] University of Health Sciences, Istanbul Health Practice and Research Hospital, Department of Pathology, Turkey, [3] University of Health Sciences, Department of Pathology, Turkey, [4] Bagcilar Training and Research Hospital, Turkey

Background & Objectives: Although, pancreatic neoplasms can occur in any of the sites where heterotopic pancreatic tissue is present, the incidence of extra pancreatic pancreatic type neoplasms is very rare.Mixed acinar endocrine carcinoma (MAEC) is a rare clinical entity, with 30 or so cases of pancreas reported in the English literature.
Methods: The patient is a 58-year-old woman who presented with epigastric pain applied to another clinic. Endoscopic investigation was done and 5x4,5x3,7 cm measured polip at the region of corpus in the stomach was seen. Polipectomy was performed succesfully.
Results: This case was diagnosed as a well differantiated neuroendocrine tumour, grade 3 and than consultated to our clinic. Microscopic examination showed a malignant neoplasm with morphologic features of mixed acinar endocrine pancreatic tumour. Immumohistochemistry revealed diffuse and strong positivity with trypsin, chromogranin A and synaptophisin that consistent with exocrine and endocrine differention. There was no clinical or radiologic evidence of primary pancreatic tumour. After our diagnosis PET-CT scan was performed and there was no metastatic lymph nodes or distant metastasis.
Conclusion: Heterotopic pancreatic tissue in the stomach is relatively common when we compare with another heteropias.Mixed tumours of the pancreas are extremely rare and their clinical features and pathogenesis remain unclear.Our case is originated from heterotopic pancreatic tissue in the stomach and the first case in literature.If not carefully examined, either the acinar or endocrine component may be overlooked and misdiagnosed.

E-PS-06-008
A case of gastrointestinal stromal tumour, mimicking signet ring cell carcinoma
A. Dobriakov[1], K. Opalenov[1], M. Antonov[1], N. Shvets[1], E. Poputchikova[1], V. Salaeva[1], A. Tokmakov[1], J. Cherkasova[1]
[1] City Clinical Hospital of the Bahrushin Brothers, Russia

Background & Objectives: Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour originating in the digestive tract. Stomach is the most frequently affected anatomic site.
Methods: A 31-year-old female was admitted to the Emergency Department with weakness, vomiting blood, and emission of dark black stools. Her hemoglobin was 8.6 g/dl. Esophagogastroduodenoscopy showed a submucosal tumour that protruded into the prepyloric antrum with a central ulcer.
Wedge resection of gastric tumour was performed. The histopathology of the gastric specimen showed a firm submucosal tumour measuring 4.5x3.5 cm in size, without margin involvement. Overlying mucosa was focally ulcerated.
Results: Microscopically, the tumour was seen in the submucosa and was composed of solid sheets of tumour cells with hyperchromatic nucleus and clear cytoplasm. The periphery of the tumour contained a little spindle cell component. Morphology of tumour cells had a striking resemblance to gastric adenocarcinoma with signet ring cell morphology. However, immunohistochemistry for epithelial markers (AE1/AE3, EMA, CEA) were negative. DOG-1, CD34, CD117 were positive; and Ki67-index was 3%. The tumour was diagnosed as GIST in the very low-risk category.
Conclusion: We report the case of gastric GIST, mimicking gastric adenocarcinoma with signet ring cell morphology.

E-PS-06-009
Distinguishing palisade veins as a histologic marker of oesophageal origin in endoscopically resected specimens
J. Aida[1], K. Takubo[1], T. Arai[2], T. Ishiwata[1]
[1] Tokyo Metropolitan Institute of Gerontology, Japan, [2] Tokyo Metropolitan Geriatric Hospital, Japan

Background & Objectives: Palisade veins (PV) are considered markers of the oesophagogastric junction endoscopically. In cases of endoscopic resection, the oesophageal or gastric origin of small cancers is determined solely on histologic information. In the previous study, we revealed the PV corresponds to the intramucosal veins with a minor axis exceeding 100 μm. In the present study, we measured the lengths of PVs to allow determination of tissue origin, in various conditions such as cutting with longitudinal direction or artificial venal dilatation.
Methods: We defined the intramucosal veins as reside in the proprial mucosal lamina and also lying horizontally. We measured the lengths of intramucosal veins in H&E stained specimens in totally 30 ESD specimens from each 10 of the lower oesophagus, upper or middle oesophagus, and gastric body not including the oesophagogastric junction.
Results: The median lengths of intramucosal veins in the lower oesophagus, upper or middle oesophagus and gastric body were 1880 μm, 1074μm, and 848 μm, respectively. Those in the lower oesophagus were significantly longer than the others. The veins in the lower oesophagus were significantly longer than the others, and oesophageal veins were significantly longer than those in the gastric body (maximum length in the latter, 902 μm).
Conclusion: In the lower oesophagus, intramucosal veins 100 μmwide or 1000 μmlong correspond to PVs. Histologically evident PVs can be used as a marker of oesophageal origin.

E-PS-06-010

Adenosquamous carcinoma of gallbladder: a case report of an uncommon neoplasm

I. Kourtesis[1], A. Tsavari[1], K. Koulia[1], T. Vasilakaki[1], G. Sotiropoulou[2], K. Manoloudaki[1]

[1] Tzaneio General Hospital of Piraeus, Greece, [2] General Hospital of Korinthos Greece

Background & Objectives: Primary gallbladder adenosquamous carcinoma (GBASC) is an uncommon neoplasm, which accounts for 0,5%-12,7% of all malignancies (in the literature, it has been represented mostly as individual case reports). Females are affected most frequently, with a male to female ratio of 1:3. It has an aggressive behavior and a poorer prognosis than adenocarcinoma. Here, we present a case of a male patient with GBASC.

Methods: An 85-year-old male presented with pain in right hypochondriac region. Ultrasound and CT-scan revealed an enlarged gallbladder with thickened wall and multiple calculi occluding the lumen. Cholecystectomy was performed. Macroscopically, it was an enlarged gallbladder measuring 8x3x2cm, with a wall thickness of 0,7cm and a firm tumour measuring 1,5cm in diameter in the region of the fundus. The rest of the mucosa was of grayish tan color.

Results: Microscopically, a superficially ulcerated malignant epithelial neoplasm was revealed, which comprised two main components:

a) a squamous moderately differentiated and mildly keratinizing carcinoma which represented the majority (90%) of the tumour extent. The tumour invaded two thirds of the muscle wall thickness and was associated with foci of squamous metaplasia, as well as squamous dysplasia.

b) a moderately differentiated intestinal type adenocarcinoma, focally invading half of the muscle wall thickness and growing on a background of high-grade biliary intraepithelial neoplasia (BilIN-3).

Conclusion: GBASC is a rare, aggressive malignant tumour. Reporting this tumour adds to the literature and helps in better understanding the biological nature and pathological characteristics of this uncommon entity.

E-PS-06-011

Morphological and immunohistochemical features of neuroendocrine tumours in gastroenteropancreatic tract

Z. Vrekic[1], T. Lakic[1,2], J. Ilic Sabo[1,2], A. Ilic[1,2], M. Panjkovic[1], M. Zivojinov[1,2]

[1] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia, [2] University of Novi Sad, Faculty of Medicine, Serbia

Background & Objectives: Neuroendocrine tumours (NETs) result from neoplastic proliferation of neuroendocrine cells, with both characteristics of endocrine and nerve cells. NETs can be different localizations but the most common site is the gastrointestinal including pancreas. We evaluated the morphology and frequency of NETs in our hospital as well as correlation between lymph node status and Ki67 proliferative index.

Methods: Retrospectively, we analized NETs pathohistological reports of patients who underwent surgical excision of gastroenteropancreatic tumours in Clinical Center of Vojvodina in Novi Sad, in the period 2011-2018. The descriptive and correlation statistics was done.

Results: It was registered 78 surgical specimens, average age of patients 58.88(±17),whereby 53.8% were male.The most frequent site was the pancreas (29.5%),followed by large intestine (26.9%).The mean tumour size was 3.71(±3.13)cm. Chromogranin A, Synaptophysin, CD56 and Ki67 were usually used immunohistochemical markers.Lymph node metastases were found in 47.44%.Positive correlation between the Ki67 index and the percentage of positive lymph nodes was determined ($r = 0.343$, $p = 0.046$ $p < 0.05$),so tumours with higher Ki67 index gave much more lymph node deposits.

Conclusion: Most NETs lymph node metastases originated from high grade tumours, with high Ki67 index. All mentioned above suggest that the proliferative index Ki67 can be used as prognostic marker for the presence of metastases, disease progression and prognosis for neuroendocrine tumours.

E-PS-06-012

Demographic characteristics, histological types and complications of appendicitis operated in the clinical center of Vojvodina in 2015

Z. Vrekic[1], T. Lakic[1,2], A. Ilic[1,2], A. Lovrenski[2,3], J. Amidzic[1,2], J. Ilic Sabo[1,2]

[1] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia, [2] University of Novi Sad, Faculty of Medicine, Serbia, [3] Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia

Background & Objectives: Appendicitis is one of the most common surgical emmergencies of abdominal surgery. The treatment is routine procedure and includes removal of the appendix. However, appendicitis is still interesting subject for research because its etiology and pathogenesis remain unknown. The goal was to determine incidence of the most common types of appendicitis, distribution by age and gender, incidence of periappendicitis as appendicitis associated pathology and to determine perforation rate of the appendix.

Methods: The analysis is carried out using documents from the Center for Pathology and Histology of Clinical Center Vojvodina. Pathohistological samples were analysed with microscope and photographed. The results were processed in Microsoft office Excel and displayed in tabular and graphical form.

Results: A total of 626 cases of appendicitis from 2015 were analysed. Appendicitis affects patients from all age groups but more often occurs at a young age. It affects equally men and women. Acute forms of appendicitis occur far more frequently than chronic. The results showed that a total of 306 patients had periapendicitis (48.88%). Perforation was present in 2.72% patients.

Conclusion: Appendicitis is a disease predominantly of young population. The most common form of appendicitis is acute phlegmonose appendicitis. Chronic appendicitis is more common in elderly people. Perforation of the appendix is present in a very small number of cases.

E-PS-06-013

Coccidioides SPP in the cystic ganglion

M. Mejia[1], J.D. Hernandez[2], M. Rolon[1], M. Baldión[1], L.E. Barrera-Herrera[1], J. Alvarez-Figueroa[1]

[1] Department of Pathology and Laboratory Medicine, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia, [2] Department of Surgery, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia

Background & Objectives: Coccidioides are soil-dwelling found in southern portions of California and southwestern United States, disseminated infection affects skin, skeletal system, and meninges. Classic spherules measure up to 250 μm in diameter and contain endospores (2-5 μm in size). Tissue response to Coccidioides is granulomatous, with and without caseation, spherules are found in macrophages and multinucleated giant cells and classicaly endospores.

Methods: A 45-year-old female with a recent trip to the United States presented to emergency service with 5-hour evolution of constant, burning abdominal pain located in the epigastrium, 9/10 intensity and associated with 1 soft stool, bilateral upper limb paresthesias, asthenia and adynamia. Bile duct ultrasound revealed nonspecific diffuse thickening of the gallbladder walls, without evidence of stones inside. Cholecystectomy was performed.

Results: The gallbladder presented changes due to acute and chronic cholecystitis with cholesterolosis. Cystic ganglion exposed the presence of round micotic microorganisms with presence of spherules containing endospores inside, positive with PAS, negative for gomory and mucicarmine. Coccidioides infection was recognized.
Conclusion: Intraabdominal coccidioidomycosis is a very rare entity, to our knowledge, this is the first described cystic ganglion compromise due Coccidioides.

E-PS-06-014
Correlation of E-Cadherin with pathological features in colorectal cancer
I. Msakni[1], R. Hedhli[2], N. Mansouri[1], F. Gargouri[1], A. Saidi[1], A. Bouziani[1], B. Laabidi[2,3]
[1] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia, [2] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia, [3] Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: An important mechanism of Colorectal cancer progression is the Epithelial-mesenchymal transition. It is responsible for promoting the migratory phenotype of cancer cells through inhibition of adhesion molecules and stimulation of mesenchymal markers. The main marker is the loss of membrane E-cadherin expression. Many studies showed that colorectal cancer with low E-cadherin expression tend to have poor prognosis.
Our objectives were to analyse the expression of E-cadherin in colorectal cancer and its correlation with histopathological parameters.
Methods: It was a retrospective and monocentric study of 68 patients with colorectal cancer, collected at the Department of Pathology between 2011 and 2014.
Results: The median age of the patients was 62 years (27-87 years). 74% of patients were males with a sex ratio of 2.9. Immunohistochemical study showed 38 E-cadherin positive and 30 E-cadherin negative tumours. The expression of E-cadherin was inversely proportional to the degree of differentiation ($p = 0.001$). There was no statistically significant correlation between the expression of E-cadherin and other histopathologic parameters.
Conclusion: the expression of E-cadherin protein in colorectal cancer is correlated with histopathological parameters like in our study. Identification of regulators of gene expression involved in the Epithelial-mesenchymal transition process is critical for understanding tumourigenic mechanisms and therefore facilitate the development of novel therapies.

E-PS-06-015
Carcinosarcoma of the ampulla of Vater: a case report
S. Batur[1], C. Turker[1], Z.E. Kain[1], N. Kepil[1]
[1] Istanbul University Cerrahpasa-Cerrahpasa Medical Faculty Department of Pathology, Turkey

Background & Objectives: Carcinosarcomas are rare malignant tumours that are composed of both carcinomatous and sarcomatous elements that grow intermingled with each other. This tumour type has been detected in many different organs. However, carcinosarcoma of the ampulla of Vater is extremely rare.
Methods: The patient was a 47 year-old woman, She complained of discomfort in the upper abdomen. Abdominal magnetic resonance imaging indicated nodular lesion at the head of pancreas and pancreaticoduodenectomy with lymph node dissection were performed. Macroscopically, the well-demarcated, polypoid, infiltrative tumour was identified in the ampulla of Vater. The tumour was 7x3,8x2,5cm in diameter.
Results: The histological examination revealed that the tumour consisted of two components. One was an adenocarcinoma, exhibiting tubulary and cribriform architecture while the other was a sarcoma containing atypical mesenchymal cells. Immunohistochemically, the sarcomatous atypical cells were diffusely positive for vimentin, S100 and focally positive for α-smooth muscle actin; these cells are also negative for pancytokeratin and desmin. It did not contain heterologous elements. The tumour was therefore diagnosed as a carcinosarcoma. There was four lymph node metastasis.
Conclusion: Carcinosarcoma of the ampulla of Vater has a poor prognosis, and lymph node metastases are often seen. We have presented an extremely rare case of carcinosarcoma of the ampulla of Vater.

E-PS-06-016
Cecal mucinous adenocarcinoma with heterotopic ossification: a case report and review of the literature
A. Podrimaj-Bytyqi[1], M. Hashani[1,2]
[1] Faculty of Medicine, University of Pristina, Albania, [2] Institute of Pathology, University Clinical Center of Kosovo, Albania

Background & Objectives: Heterotopic ossification is a very rare event in the gastrointestinal tract tumours, being less than 0.4% among them. The mechanism of ossification is still unclear. It's usually observed in tumours associated with mucine extravasation, subsequent calcification of which it is thought to be a predisposing factor. Furthermore, osteoblastic metaplasia of cancer cells and pluripotent mesenchymal cells, both under the influence of factors generated by the cancer cells, are proposed as possible mechanisms.
Methods: We present a case of a 25 years old male, who was admitted to surgical clinic with acute intestinal obstruction due to the presence of a cecal mass. The computed tomography scan and ultrasonography showed an irregular cecal mass with signs of calcification or ossification. Patient underwent surgery, where a right hemicolectomy with regional lymphadenectomy was undertaken.
Results: Macroscopically, tumour was located on the upper part of the cecum, near the ileo-cecal valve, it perforated the wall and caused cecal ischemic necrosis due to the total obstruction. Tumour was exophytic, 5 cm in diameter, with hard/osseal consistency. Histologically, well differentiated mucinous adenocarcinoma with heterotopic ossification was diagnosed. In the resected specimen, six negative lymph nodes were found. Immunohistochemistry for Ki67 showed a low index of proliferation; CK20 and CEA were positive, while CK7 and p53 were negative.
Conclusion: Heterotopic bone formation in colon is a rare phenomenon, especially in young patients. Colon cancer and other benign lesions of the colon which are presented with heterotopic ossification, needs to be differentiated from carcinosarcoma, which has a similar clinical presentation, but worse prognosis.

E-PS-06-017
A rare soft tissue tumour of the stomach
I. Dumitru[1], M.A. Bani[1], X. Sastre Garau[1], T. Lons[1]
[1] CHI Crèteil, France

Background & Objectives: Glomus tumour is a rare benign menchymal neoplasm derived from the glomus body witch is an arteriovenous anastomosis. The stomach is an exceptional site for those tumour. Their diagnosis may pose a real challenge for the pathologist especially in small gastric biopsies.
Methods: A 56 –year-old man with no history referred for a microcytic anemia. The endoscopy revealed an ulcerated lesion of the greater curvature of 34 mm. The diagnostic of a stromal tumour was presumed and a biopsy performed. Histologically the tumour was composed of uniform

round cells with regular nuclei and pale eosinophilic cytoplasm. Immunohistochemistry expression for smooth muscle actine and absence of staining for S100 proteine and CD117. The retained diagnosis was gastric glomus tumour.
Results: Glomus tumours are rare. The first case of gastric glomus tumour was reported in 1951, since then only 34 cases have been reported in the literature. The tumour is generally benign however in one case metastasis have been reported. Malignant behaviour may be associated with the size, localization, high nuclear grade and atypia. The diagnosis can be challanging with endoscopic and radiologic findings witch are nonspecific for such tumours. Immunohistochemistry is mandatory to rule out other differential diagnoses.
Conclusion: We think that the diagnosis of a glomic tumour on a biopsy is challanging. It raises a large spectrum of differential diagnoses. The pathological asses may pose the diagnosis but their prognostic factors are still to be proven.

E-PS-06-019
CD44 expression in dysplastic glands of colorectal adenomas
G. Cerrone[1], V. Aimola[1], G. Senes[1], R. Murru[1], G. Faa[1,2]
[1] Division of Pathology, Department of Medical Science, University Hospital San Giovanni di Dio, AOU Cagliari, University of Cagliari, Cagliari, Italy, [2] Temple University, Philadelphia, Pennsylvania, USA

Background & Objectives: CD44 is an ubiquitous transmembrane glycoprotein that interacts with different components of the extracellular matrix. Different isoforms of CD44 exist since the mRNA encoding for this protein may undergo alternative splicing. CD44 isoforms have been related to multiple cancers, being considered stem cell markers of many tumours.
CDX-2 is a fundamental regulator of intestinal development and oncogenesis, which is considered a prognostic biomarker.
In this study we evaluated CD44 and CDX-2 immunohistochemical expression in polyps and adenomas of the colorectum.
Methods: We evaluated 7 cases of polyps/adenomas of the colorectum. At histology 2 adenomas with high grade dysplasia (A/HGD), 4 adenomas with low grade dysplasia (A/LGD) and 1 sessile serrated polyp without dysplasia (SSPwD) were identified. Immunohistochemical evaluation for CDX-2 and CD44 was performed.
Results: All cases analysed showed diffuse and intense nuclear immunoreactivity for CDX-2. All adenomas showed membrane strong and diffuse immunostaining for CD44, except for one A/LGD that revealed a focal immunoreactivity. CD44 immunostaining was mainly localized in dysplastic glands. Areas with high grade dysplasia showed stronger reactivity for CD44 than those with low grade dysplasia. Only SSPwD showed no evidence of CD44 expression.
Conclusion: Our preliminary data show that the stem cell marker CD44 is expressed in colorectal adenomas. The reactivity for CD44 is stronger in high grade than in low grade dysplasia. Further studies are needed to better clarify the role of CD44 expression in colon carcinogenesis.

E-PS-06-021
The value of subtyping of intestinal metaplasia for the risk stratification of gastric cancer
S. Savcenko[1], S. Isajevs[2,3], I. Bogdanova[1,3], I. Liepniece-Karele[1,3], M.B. Piazuelo[4], M. Leja[1,3]
[1] Institute of Clinical and Preventive Medicine; Faculty of Medicine, University of Latvia, Riga, LV-1586, Latvia, [2] Department of Pathology, University of Latvia, Faculty of Medicine, Riga, Latvia, [3] Centre of Pathology, Riga East University Hospital, Riga, Latvia, Latvia, [4] Division of Gastroenterology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, 37232, USA

Background & Objectives: The use of Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Assessment based on Intestinal Metaplasia (OLGIM) staging system is recommended to identify subjects at risk for developing gastric cancer, generally high-risk lesions are considered only stages III and IV. Accumulating evidence is suggesting that incomplete IM is of importance in developing gastric cancer.
Our aim was to identify the prevalence of incomplete IM in patients with low-risk OLGA/OLGIM stages in a high-risk general population.
Methods: Healthy adult volunteers aged 40-64 years were invited to undergo upper endoscopy within a regional GISTAR pilot study in Kazakhstan (n=166). Five gastric biopsies according to the updated Sydney system were obtained from each study subject. High iron diamine-alcian blue (HID-AB) was used for the subtyping of IM.
Results: Overall 46.0% IM prevalence was revealed. Incomplete IM was present in 48.0% (type II in 22.0% and type III in 26.0%), whereas complete IM was found in 52.0% of individuals. The prevalence of OLGIM I and II stage was 85.0% and 10.0%, respectively, whereas OLGIM III was observed in 5.0%. The prevalence of incomplete IM in patients with OLGIM I was 32.0% (type II in 18.0% and type III in 14.0%).
Conclusion: High prevalence of incomplete IM was revealed not only in subjects with extensive IM, but also in those stratified OLGIM I stage. Without IM subtyping, up to 32.0% of the patients with high risk of gastric cancer development would be missed for surveillance.

E-PS-06-022
Gastric glomus tumour: a case report
Z.E. Kain[1], S. Batur[1], N. Kepil[1], O. Aydın[1], N. Comunoglu[1]
[1] Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine, Pathology Department, Turkey

Background & Objectives: Glomus tumour (GT) is a rare mesenchymal tumour of stomach,arising from glomus bodies.Peripheral soft tissues and extremities are the major sites of involvement. Case series revealed that GT is 100 times rarer than gastric GIST. It is known as benign, and wedge resection with tumour-free margin is adequate for treatment. Since first case reported in 1951, there are less than 100 case reports in English literature up-to-date. Clinically and histopathologically, differential diagnosis includes gastric GIST, leiomyomas and neuroendocrine tumours.
Methods: A 60-year-old female was admitted to the hospital with a pain in the left upper abdomen. A computed tomography (CT) scan of the abdomen demonstrated well-defined lesion, measuring 24x22 mm in close relation to the anterior wall of the stomach. The patient underwent laparoscopic wedge resection of the gastric mass with a preliminary diagnosis of gastrointestinal stromal tumour. Surgical resection revealed a 2x1,5x1cm well circumscribed submucosal tumour, extending into the subseroza.
Results: Microscopically,the tumour showed submucosal infiltration by solid sheets of round cells having a nodular pattern of growth,separated by fibrous bands. The neoplastic cells were uniform with round nucleus,clear to eosinophilic cytoplasm,and a distinct cell border separated by dilated vascular channel lined with flat endothelium. There were no mitosis,cytomorphological atypia or necrosis. The proliferative index (Ki-67) was 1%. Immunohistochemically, the tumour cells were stained positive for alpha-smooth muscle actin, beta catenin, vimentin, collagen type IV and synaptophysin. The tumour cells were negative for CD117, CD34, pancytokeratin,HMB-45,S-100,CD56 and chromogranin.
Conclusion: GT is a rare entity that clinicians and pathologists may not come across in their lifelong career. It can be easily misdiagnosed as neuroendocrine tumour and may cause pitfalls. Recent imaging techniques or endoscopic biopsy are not reliable differentiating from other

mesenchymal tumours. We have presented an extremely rare case of GT of the stomach.

E-PS-06-023

Leishmaniasis of duodenum: a case report

G. Sotiropoulou[1], O. Abazis[1], C. Vasileiou[1], E. Axioti[1]
[1] General Hospital of Korinthos, Greece

Background & Objectives: Leishmaniasis is a disease caused by an intracellular protozoan parasite (genus Leishmania) transmitted by the bite of female phlebotomine sandfly (genus Phlebotomus). The disease is divided into 3 clinical forms: cutaneous,mucocutaneous and visceral. Visceral leishmaniasis (kala-azar) is a potentially lethal widespread systemic disease characterised by fever, weight loss, hepatosplenomegaly, darkening of the skin, pancytopenia and hypergammaglobulinemia.The prognosis is poor without special treatment(70%-90%).In Greece are recorded 30-70 cases of visceral and about 10 cases of cutaneous leishmaniasis annually.
Methods: A 32 year old foreign male shepherd presented in the outpatient department with anemia. The patient also reported malaise, weakness and anorexia. CBC count demonstrated microcytic hypochromic anemia, leukopenia with decreased neutrophils and relative lymphocytosis. Prothrombin time was prolonged and biochemical studies were within normal range. US showed splenomegaly. An upper GI endoscopy was perfomed - with no essential findings - and biopsies were taken from the stomach and duodenum for the investigation of anemia.
Results: Histological examination showed a dense lymphoplasmatic population with participation of neutrophil granulocytes, as well as plenty of macrophages, which in their cytoplasm contained the baseophilic Leishman Donovan bodies. The amastigotes were confirmed by Giemsa stain.
Conclusion: Leishmaniasis cases are increasing in numbers favored by changing immigration conditions. The disease should be included in the differential diagnoses of various infectious parasitic disorders . Serological studies and PCR are less invasive methods for the detection of the disease.Early diagnosis , treatment and informing the population are the main measures for controlling leishmaniasis.

E-PS-06-024

A unique renal cell carcinoma solitary colonic metastasis. An atypical metastatic presentation

E. Koniaris[1], I. Nikolopoulos[1], E. Gioti[1], K. Tsiardis[1], E. Moula[1], G. Kafiri[1]
[1] "Hippokratio" General Hospital of Athens, Greece

Background & Objectives: Our aim was to present a rare and atypical metastastasis of a renal cell carcinoma(RCC), eosinophilic type, to the cecum. RCCs are tumours with strong prevalence to metastasize, virtually to all organs, but most frequently to lung, bone, brain and liver, with a 30-40% recurrence, after resection and a 10% risk of metastasis after 5 years. The gastrointestinal tract and especially the colon is a very unusual site.
Methods: Our patient referred to our hospital for a regular check up, 6 months after a total nephrectomy for a RCC , a tumour mass was found endoscopically on the cecum. He underwent right colectomy and we received cecum of 20cm in length, with a protruding, ulcerated tumour m.d.: 7cm, 6cm from the ileocecal valve. Due to the previous history immunohistochemistry was performed with the following: AE1/AE3 (+), CK7 (+), CK20(-), S100 (-), LCA (-), Chromogranin (-), Synaptophysin (-), HMB45 (-), Alcian blue (-), PAS (-).
Results: Histologically, the tumour was a high grade carcinoma, with mainly solid growth pattern, with tumour islands with delicated fibrovascular cores between them. The tumour cells had high nuclear atypia and pleomorphism, with presence of bizarre cells with multilobular and multinucleated forms, high mitotic index and bright eosinophilic cytoplasm. Necrosis and inflammatory elements as well as foci of abscess formation were also noted.
Conclusion: The colon and particularly the cecum, is a highly uncommon site of RCC metastatic involvement. In general, this atypical presentation occurs many years after the initial kidney resection, although in our patient this occurred only a few months after the initial resection.

E-PS-06-025

Nosologic structure of gastric pathology in cases of endoscopic mucosal resections

M. Shushval[1], L. Volkova[2,3], G. Lyashenko[4], L. Nyzhnik[4], A. Antishina[2], A. Musatov[2], K. Abdujabborov[1]
[1] Baltic Federal University, Russia, [2] Immanuel Kant Baltic Federal University, Kalinigrad, Russia, [3] Lab. of Immunohistochemistry and Pathology Diagnostics, Russia, [4] Regional Hospital, Pathoanatomical, Kaliningrad, Russia

Background & Objectives: Gastrointestinal endoscopic mucosal resection (EMR) is one of methods of diagnostics and treatment of exophytic epithelial lesions of the stomach. Our study is aimed to evaluate nosological structure and morphological peculiarities in EMR stomach specimens.
Methods: The study was performed on 62 stomach samples of patients of Kaliningrad Regional Hospital after EMR during 2016-2018. Characteristics of the study group with epithelial lesions of the stomach: sex (M:F) - 10:52, age: 36-75 years.
Results: Pathologic process location in the stomach: 1) body - 69.2%; 2) pylorus - 12.5%; 3) antrum - 12.1%; 4) cardia - 7.1 %. 49 cases of hyperplastic polyps with following histological appearances were revealed: 1) low grade intraepithelial neoplasia – 2; 2) intestinal metaplasia of the colonic type - 1; 3) inflammation - 6; 4) ulceration - 9; 5) cystic glandular hyperplasia – 3. Tubulovillous adenomas (9) were found: 1) 7 cases – with low grade intraepithelial neoplastic changes; 2) 2 specimens - with high grade intraepithelial lesions. Diagnosis in 1 patient - Menetrier's disease. 3 cases of malignancy were observed: 1) high grade adenocarcinoma in hyperplastic polyp - 1; 2) high grade adenocarcinoma in tubulovillous adenoma - 2.
Conclusion: The predominance of benign pathology of the stomach among EMR samples was demonstrated (79.0%), but in some patients the intraepithelial neoplastic changes (14.5%) and superficial adenocarcinomas (4.8%) were found. Diagnosis of epithelial lesions of the stomach in EMR specimens is necessary for early diagnostics and effective treatment of benign processes and early stages of malignancy.

E-PS-06-026

Ossified gastric tumour with tumour trombus - case report

I. Guvendir[1], K. Altundag[1], I. Tosun[2], I.E. Zemheri[1], K. Ozdil[3]
[1] Health Sciences Health Sciences University Umraniye Eduation and Training Hospital Pathology Department, Turkey, [2] Umraniye Training and Research Hospital, Department of Pathology, Turkey, [3] Health Sciences Health Sciences University Umraniye Eduation and Training Hospital Gastroenterology Department, Turkey

Background & Objectives: Glomus tumours of the stomach are very rare, mesenchymal neoplasms, account for nearly 1% of all gastrointestinal soft tissue tumours. The most common involvement of stomach is antrum. Gastric glomus tumours are submucosal tumours that lack specific clinical and endoscopic characteristics and are often mistaken for gastrointestinal stromal tumours.
Methods: A 62-year-old female presented with upper gastro-intestinal bleeding for 15 years. Endoscopic ultrasound revealed a 3.5x2.7 cm-sized, round, hyperechoic mass with a central ulcer and focal calsification at the gastric wall. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was applied.

Results: Cytologic examination revealed a losely cohesive, uniform, small, round to oval cells with scant cytoplasm, indistinct cell borders and hyperchromatic nuclei with homogeneous chromatin. After that, local resection was performed. Macroscopically, 4.5x3x1.5 cm nodular mass arising submucosa and muscular layer was observed. Microscopic and immunohistochemical findings were consistent with a gastric glomus tumour with ossification and vascular tumour trombus. Mitosis was 1/50Hpf. After the diagnosis, the patient underwent systemic examination, metastasis was not found despite vascular tumour trombus. There was no evidence of recurrence 6 months after the resection.
Conclusion: Gastric glomus tumour is very rare and ossified glomus have not been yet reported in English literature. We reported this case because of rarity and distinctive features.

Key words Stomach, Glomus tumour; ossification, Endosonography; Biopsy, fine-needle; Cytology

E-PS-06-027

Precancerous and background processes in carcinomas of the stomach

M. Shushval[1], L. Volkova[2,3], A. Antishina[2], L. Nyzhnik[4], K. Abdujabborov[1]
[1] Baltic Federal University, Russia, [2] Immanuel Kant Baltic Federal University, Kalinigrad, Russia, [3] Lab. of Immunohistochemistry and Pathology Diagnostics, Russia, [4] Regional Hospital, Pathoanatomical, Kaliningrad, Russia

Background & Objectives: Revealing of precancerous and background processes for gastric carcinomas is very important for prophylaxis and early diagnostics. The aim of the study investigation of pathological processes associated with various types of gastric carcinomas.
Methods: The study group - 29 patients with arcinomas of the stomach after gastrectomy, sex (M:F) - 19:10, age: 42-75 years. Specimens from the tumours and at the different distance were investigated for evaluation of morphological peculiarities of the background and precancerous processes in the mucosa.
Results: Location of gastric cancer (cases): 1) body – 14; 2) cardia – 8; 3) antrum – 4; 4) pylorus – 1. The main cancer type - adenocarcinoma (23 cases) of different Grade: G3 - 11; G1 - 10; G2 – 2. Precancerous and background processes in the subgroup of adenocarcinomas: 1) chronic gastritis of different activity - weak (8), moderate (7), severe (5); 2) intestinal metaplasia (17); 3) epithelial hyperplasia (13); 4) low grade (9) and high grade (3) dysplasia; 5) glandular atrophy (6). Precancerous and background processes in the subgroup of diffuse cancer (total -5): 1) chronic gastritis (5) of different activity - weak (0), moderate (4), severe (1); 2) intestinal metaplasia (2); 3) epithelial hyperplasia (2); 5) glandular atrophy (3). Mucinous adenocarcinoma (1) was revealed with association with severe active chronic gastritis and intestinal metaplasia.
Conclusion: It was revealed that the main background pathology in gastric carcinomas of different types is chronic gastritis, the most common precancerous processes - intestinal metaplasia and dysplasia.

E-PS-06-028

CD1a$^+$ DCs and CD83$^+$ DCs number is associated with MSI status of CRC patients

M. Gulubova[1], K. Ivanova[1], T. Vlaykova[2]
[1] Trakia University, Medical Faculty, Department of General and Clinical Pathology, Bulgaria, [2] Trakia University, Medical Faculty, Department Chemistry and Biochemistry, Bulgaria

Background & Objectives: About 15% of colorectal cancers (CRC) display a deficiency in the DNA mismatch repair (MMR) system. MSI CRCs are associated with intense by lymphocyte infiltrate. Dendritic cell (DC) infiltration in CRC is investigated in CRC patients. The tumour tissue contains most S100$^+$ and CD1a$^+$ DCs and very few numbers of all other CD types. The aim of our study is to evaluate DC numbers in CRC patients tested for MSI/MSS and to assess their significance for association with MSI and with patients' survival.
Results: MSI patients have statistically significantly greater number of CD1a$^+$ DCs in tumour stroma (TS) (p=0.001) and in the invasive front (IF) (p=0.002). In patients with stage II CRC CD1a$^+$ DCs in TS (p=0.001) and in IF (p=0.021) are statistically significant increased number. The same dependence is observed for CD83$^+$DCs. CRC MSI patients having increased number of CD1a$^+$DCs both in TS (p=0.028) and IF (p=0.045) show a tendency for longer survival as compared to those with lower numbers of CD1a DCs in MSS patients. There was a tendency for longer survival of patients having increased number of CD11c$^+$ DCs in TS (p=0.106).
Conclusion: CD1a$^+$ DCs number and CD83$^+$ DCs number are associated with MSI status of CRC patients. They could be used as predictive immunohistochemical marker for MSI.

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E-PS-06-029

Appendiceal intussusception secondary to benign lymphoid hyperplasia in appendix and cecum: report of two cases

M.E. Kara[1], E. Uzun[1]
[1] Gaziantep University Medical Faculty Hospital, Department of Pathology, Turkey

Background & Objectives: Benign lymphoid hyperplasia in the wall of intestines is usually located in the terminal ileum and it occurs in children and young adults. Intussusception is a common cause of acute abdomen in infancy. Here we present two appendiceal intussusception cases developed due to benign lymphoid hyperplasia.
Methods: Case 1: An 11-month-old baby girl was presented with discomfort, vomiting, abdominal pain and blood in feces. Abdominal ultrasonography (USG) examination revealed the appendiceal intussusception. During the operation intussusception was detected, appendix and cecum wall were found thickened. Right hemicolectomy was performed. Microscopically; there was extensive benign lymphoid hyperplasia both appendix and cecum wall. It has been verified with immunohistochemistry.
Results: Case 2: A 10-month-old baby boy referred to our hospital with vomiting, abdominal pain, and blood in feces. In abdominal USG, appendiceal intussusception was detected. The patient was treated surgically. Intraoperatively, the appendix was wide and cecum wall was thickened. In additionally; small lymph nodes and thinned wall cyst were found in the mesenterium. Histological examination revealed benign lymphoid hyperplasia in appendix and cecum. The diagnosis was supported by immunohistochemically.
Appendiceal intussusception is a very rare entity which has been many pathological conditions such as fecalith, foreign body, parasites, and rarely benign lymphoid hyperplasia. In the gastrointestinal tract, lymphoid hyperplasia leads to confusion, while it is induced by allergy, parasites, immunological diseases or no cause is detected. In infancy, appendiceal intussusception secondary to lymphoid hyperplasia is rare. The diagnosis is difficult preoperatively, histological examination is necessary.

E-PS-06-030

Case report of a signet ring cell carcinoma of the ampulla of Vater

A. Dimitriadi[1], C. Karambogias[1], G. Koutsonikas[2], C. Zorzos[1], A. Kostopoulou[1], A. Koliopanos[3], T. Choreftaki[1]
[1] Department of Surgical Pathology/General Hospital of Athens "G. Gennimatas", Greece, [2] Department of Cytology/General Hospital of Athens, "G. Gennimatas", Greece,[3] 2nd Department of Surgery/General Hospital of Athens "G.Gennimatas", Greece

Background & Objectives: We present a case of signet ring cell carcinoma (SRCC) of the ampulla of Vater of a 68 year old man, submitted for obstructive jaundice.
Methods: Endoscopic Retrograde Cholangiopancreatography (ERCP) highlighted oedematus and brittle ampulla of Vater with constriction at the lower end of common bile duct. Biopsy was performed, positive for a primary poorly differentiated adenocarcinoma. A Whipple procedure was performed. We received a pancreatoduodenectomy.
Results: A tumour was located at the ampulla of Vater with maximum diameter 1.5cm. Microscopically, the tumour consisted of, mostly, diffusely arranged, poorly differentiated cells, with signet ring cell morphology, infiltrating the duodenal wall, with lymphatic invasion and without infiltration of adjacent pancreas or peripancreatic soft tissue. Fourteen lymph nodes were identified with no metastases (pT2N0M0, according to AJCC 8th ed.).
Immunohistochemical staining showed that the tumour cells were positive for CK19, CK7, MUC1, MUC5AC, and focally for CK20, MUC2, TTF1, MUC6 and negative for SYP, CgA and b-catenin. Thus, the diagnosis was a mixed type SRCC with intestinal, pancreatobiliary and gastric differentiation.
Conclusion: Ampullary SRCC is an extremely rare neoplasm with only 38 cases described so far, from which only 3 were mixed type. Some studies indicate that mixed type SRCC, especially with gastric differentiation, has worse prognosis. Furthermore, coexpression of E-cadherin and b-catenin may show poorer prognosis.

E-PS-06-031
Histologic description of cytopathic effects of Human Herpes Virus 6 (HHV6) enteritis
S. Renne[1], C. De Carlo[1], T. Brambilla[1], M. Sollai[1], J. Mariotti[1], E.C. Ferrara[1], L. Di Tomaso[2,3], M. Roncalli[2,3], P. Spaggiari[1]
[1] Humanitas Clinical and Research Center - IRCCS, Italy, [2] Department of Pathology, Humanitas Clinical and Research Center - IRCCS, Rozzano (MI), Italy, [3] Department of Biomedical Sciences, Humanitas University, Rozzano (MI), Italy

Background & Objectives: Patients undergoing bone marrow transplantation (BMT) often require gastrointestinal (GI) biopsies to rule out viral infections or Graft Versus Host Disease (GVHD). HHV6 is a very prevalent infection affecting 95% of the general population, and it remains latent in most of the cases, but it represents a common pathogen in immunocompromised hosts. However, a histological description of its cytopathic effect in GI tract is missing. We here provide the first histologic description of HHV6 enteritis.
Methods: A 53 years-old man with a 31 years-long history of Hodgkin's lymphoma and previous reactivation of HHV6 infection, underwent to BMT. He developed grade 3 mucositis, sepsis, diarrhea, nausea and vomiting. GI biopsies were performed to rule out GVHD: duodenum showed cytopathic alterations suggestive of viral infection; cytomegalovirus infection was excluded, and polymerase chain reaction analysis revealed the presence of HHV6 DNA. Lower-GI biopsies showed atrophy and apoptosis, compatible with GVHD. The patient was thus treated with Ganciclovir and Methylprednisolone-Etanercept. Four months later, the patient developed a severe anemia and a lethal Aspergillus pneumonia.
Results: Duodenal biopsy showed atrophy and mild subacute inflammation of lamina propria; few apoptotic enterocytes were identified; epithelial and stromal cells showed marked cytomegaly and nuclear inclusions.
Conclusion: To our knowledge this is the first histological description of cytopathic effects of HHV6 enteritis. Histology is of paramount importance in the management of patients undergoing BMT. HHV6 should be considered in presence of cytopathic effects and CMV negativity.

E-PS-06-032
Intracholecystic papillary-tubular neoplasm (ICPN) with high grade dysplasia: a case report
Y. Ozerdem[1], B. Koca[1], S. Kulacoglu[1]
[1] Ankara Numune Training and Research Hospital Department of Pathology, Turkey

Background & Objectives: The histological, clinical and prognostic aspects of the neoplastic gallbladder polyps were not well-described historically. ICPN terminology is defined recently, for mass forming exophytic gallbladder lesions distinct from adjacent mucosa, measuring ≥1 cm and showing dysplasia. ICPNs are seen predominantly in women and mean age is 61.
Methods: A 65-year old male with abdominal pain underwent an abdomen CT which revealed a heterogenous nodular mass in the gallbladder. Grossly a 1.4x1x1 cm green, pedinculated, friable polypoid lesion was seen at gallbladder corpus.
Results: Microscopic sections showed a papillary neoplasm composed of tightly packed glandular epithelium with foci of tubulary configuration. The morphologic appearance of the glands were variable consisting of biliary epithelium, clear cells with broad cytoplasm and hyperchromatic epithelium accompanying intestinal metaplasia. High grade dysplasia is observed at %30 of the glands. Immunohistochemical staining showed the predominant cell type to be pancreatobiliary with diffuse and strong MUC1 and CK7 staining. The gastric foveolar type glands showed MUC5AC staining and the foci of intestinal differentiation were CK20 and CDX2 positive. Apart from the lesion, high grade dysplasia was also consistent in the fundus, corpus and neck extensively, with cytoplasmic pCEA staining.
Conclusion: ICPNs are rare neoplasms with remarkable cell lineage diversity and biliary pattern is the most common. Although gallbladder carcinomas arise mainly from flat dysplasia, extensive evaluation is essential to exclude invasion. Reporting histopathological, immunohistochemical and clinical aspects of polypoid preinvasive gallbladder neoplasms will contribute to our knowledge about ICPNs.

E-PS-06-033
Gastric adenosquamous carcinoma: A case report
S. Batur[1], R. Akpinar[1], N. Kepil[1]
[1] Istanbul University Cerrahpasa-Cerrahpasa Medical Faculty Department of Pathology, Turkey

Background & Objectives: Adenosquamous carcinoma, a rare malignant tumour of the stomach, is characterised by two different cell components, one adenomatous and the other squamous component. It amounts to less than one percent of all gastric carcinomas and its clinical and endoscopic findings are similar to the adenocarcinoma. It occurs more frequently in the proximal stomach and tends to be found in advanced stages at diagnosis, with a worse prognosis than adenocarcinoma.
Methods: A 56-year-old male was admitted to the hospital with a pain in the left upper abdomen. An upper gastrointestinal endoscopy had revealed an extensive ulcer of the gastric antrum. The patient underwent a distal subtotal gastrectomy. Grossly specimen revealed an ulceroinfiltrative lesion occupying most of the antrum, measuring 8×5×3cm, and infiltrating his gastric wall to the serosal layer. On cutting the liver fragment, a tumour was identified as a whitish nodular subcapsular lesion of well-defined limits with a major diameter of 0.5cm.
Results: A pathological exam revealed a poorly-differentiated malignant epithelial neoplasia of solid pattern and focally glandular with expansive growth. Venous, lymphatic and perineural invasion were identified. There was metastatic neoplasia in four of the ten identified lymphatic nodes, as well as in her liver fragment. Immunohistochemically, the tumour cells were stained positive for CK7, CK5-6 and p40. The tumour cells were negative for CK20, synaptophysin and chromogranin. The tumour was diagnosed as adenosquamous carcinoma.
Conclusion: Primary gastric adenosquamous carcinoma is a rare malignancy. Its clinicopathologic feature and prognosis are quite different from

the ordinary adenocarcinomas. We have presented an extremely rare case of adenosquamous carcinoma of the stomach.

E-PS-06-034

Carcinoid tumour and Cystoisospora belli infection of the gallbladder: a case report

B. Koca[1], Y. Ozerdem[1], S. Kulacoglu[1]
[1] Ankara Numune Training and Research Hospital Department of Pathology, Turkey

Background & Objectives: Carcinoid tumour of the gallbladder is a rare entity comprising less than 1% of all carcinoid tumours. *Cystoisospora belli*, formerly known as *Isospora belli* is an intracellular parasite which is mostly associated with gastrointestinal disease in immunocompromised patients. Gallbladder cystoisosporiasis in immunocompetent individuals is also described.
Methods: A 84 year old woman was hospitalized with nausea and abdominal pain in the right upper quadrant. She had no remarkable prior history. Abdominal ultrasound showed multiple gallstones with signs of cholecystitis and cholecystectomy was performed. 0,4 cm polypoid mass was found in the neck of the gallbladder at gross examination.
Results: Histological examination revealed that the polypoid tumour was composed of small uniform cell nests with round to oval nuclei invading the mucosa extensively, and penetrating the superficial muscular layer in a small focus. No mitoses, lymphovascular and perineural invasion were seen. Tumour cells showed positive reaction for chromogranin and synaptophysin. This lesion was proved to be neuroendocrine tumour grade 1 (carcinoid) of the gallbladder. There was also an area in corpus with eosinophilic intraepithelial parasites consistent with *C. belli*. Intestinal metaplasia and follicular cholecystitis were also seen.
Conclusion: Carcinoid tumour and cystoisosporiasis of the gallbladder are extremely rare entities. Most of the cases are incidental. To our knowledge this is the first case report of a patient with carcinoid tumour accompanying *C. belli* infection. Although being relatively uncommon, these two entities should be considered in the differential diagnosis of gallbladder diseases.

E-PS-06-035

Spindle cell lipoma of the appendix: a rare incidental finding

R. Griffiths[1], A. Arnaout[1]
[1] St. George's University Hospitals NHS Foundation Trust, United Kingdom

Background & Objectives: Spindle cell lipoma is a benign form of lipoma typically found in soft tissues. They show a male predominance and the majority are diagnosed between 45 to 65 years of age. Most have a characteristic distribution with up to 80% of cases arising on the posterior neck, shoulders, and back. Less frequently lesions arise intradermally or in the head and neck region, including in the oral cavity, face and orbit. Individual case reports have documented occurrences in the mediastinum, labium majus and perineum.
Methods: We present a case of an 84 year old female with weight loss and anaemia. She underwent an extended right hemicolectomy for an adenocarcinoma detected on CT scan. Macroscopically an incidental 8mm firm white nodule was identified at the tip of the appendix.
Results: Histological examination showed a spindle cell tumour consisting of mature adipose tissue merging with spindle cells displaying pale eosinophilic cytoplasm and uniform wavy nuclei. The spindle cells showed strong and diffuse positivity for CD34 and were negative for CD117 and DOG1. S100 highlighted mature adipocytes but was negative in the spindle cells. Histological features confirmed a spindle cell lipoma of the appendix.
Conclusion: Spindle cell lipoma is a rare lipomatous tumour and to our knowledge has never before been reported in the appendix. The behaviour of spindle cell lipomas arising at unusual sites is not well known and therefore, for treatment purposes, they should be considered as similar to that of atypical lipomatous tumour.

E-PS-06-036

Rapid detection of mismatch repair proteins by immunohistochemistry in colorectal cancer patients

K. Kubelka-Sabit[1,2], V. Filipovski[1,2], B. Dimova[1], D. Jasar[1]
[1] Clinical Hospital Acibadem Sistina, Department of Histopathology and Cytology, Republic of North Macedonia, [2] Medical faculty, University Goce Delchev, Republic of North Macedonia

Background & Objectives: Lynch syndrome is an inherited disorder that increases the risk of many types of cancer, particularly colorectal and endometrial cancer. Therefore, all newly diagnosed colorectal cancers should be screened for Lynch syndrome. New immunohistochemistry (IHC) based tests which detect mismatch repair (MMR) proteins offer quick and reliable identification of patients with probable Lynch syndrome.
Methods: In this prospective study, we evaluated 50 cases of colorectal cancer patients using the Ventana MMR IHC Panel. The panel contains five primary mouse or rabbit monoclonal antibodies: MLH-1 (M1), PMS2 (EPR3947), MSH2 (G219-1129), MSH6 (44) and BRAF V600E (VE1). The analysis was performed on automated platform Ventana Bench Mark GX, using 4μ thin tissue sections from representative tumour tissue paraffin blocks.
Results: Of the 50 analysed cases, 3 cases showed absence of positivity for MLH1 and PMS2 markers. Two of these cases had MLH1 promoter hypermethylation and were classified as sporadic cancers. One case was negative for PMS2 marker and one case was negative for MSH6 marker. In total, 3 of the 50 cases analysed were sent for further Lynch syndrome testing. Two of these three patients were female and also had a history of endometrial cancer prior to the diagnosis of colorectal cancer. One case was positive for BRAF V600E antibody.
Conclusion: Immunohistochemical detection of MMR proteins enables quick detection of patient with probable Lynch syndrome. Further identification of the syndrome in patients and family members may result in early detection and possible cancer prevention in these patients.

E-PS-06-037

Primary extra-ampullary duodenal adenocarcinoma: a rare case report

H. Seneldir[1], G. Kir[1], E. Apaydin Arikan[1], T. Soylemez[1], O. Ekinci[2]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey,
[2] Istanbul Medeniyet University General Surgery Department, Turkey

Background & Objectives: Tumours arising in the non-ampullary segment of the duodenum are rare and considered true duodenal cancers. These malignant neoplasms, accounting for 0.5% of all gastrointestinal malignancies and 33–52% of small bowel adenocarcinomas.
Methods: A 87-year-old male patient was admitted to our general surgery clinic with complaints of abdominal pain, nausea and vomiting. Upper gastrointestinal endoscopy was performed for diagnostic purposes. In the endoscopic imaging, a submucosal mass was observed between the 3rd and 4th segment of the duodenum causing ulceration in the mucosa. Two repetitive endoscopic biopsies showed regenerative changes in the duodenum. As the patient's complaints persisted, duodenectomy was performed.
Results: Macroscopically, a 2 cm diameter tumoural lesion was found in the submucosa of the duodenum. The mucosa in this area was regular in appearance. Histologic examination revealed that the submucosal lesion was a well- moderately differentiated adenocarcinoma with clear cells.

The tumour invaded the mucosa, muscularis propria and serosal fatty tissue. No dysplasia was found in the surrounding tissue. Immunohistochemistry was diffusely positive for Cam5.2, MUC-6, MUC 5AC, MUC 1, DPC4, CEA-P, negative for CK7, CK20, CDX2, MUC2, NKX2, PAX8, PSAP, SALL4, TTF-1, NAPSİN A, HMB45, TFE-3. Secondary involvement was excluded by extensive immunohistochemical panel and PET screening.
Conclusion: Extra-ampullary duodenal adenocarcinomas are divided into two major subsets, intestinal type and gastric type, are associated with distinct histopathologic features and clinical behavior. Our case was evaluated as extra-ampullary duodenal adenocarcinoma originating from Brunner glands or gastric heterotopia.

E-PS-06-038
CD4+ and CD8+ lymphocytes in the immune microenvironment of gastric cancer: evaluation in Tumour Tissue (TT) and Adjacent Areas of Unchanged Mucosa (AAUM)
I. Mikhailov[1], N. Danilova[1], P. Malkov[1], N. Oleynikova[1]
[1] Lomonosov Moscow State University, Russia

Background & Objectives: The assessment of tumour immune microenvironment in AAUM isn't enough studied. This is an important direction in gastric cancer research because immune cells in AAUM may contribute in epithelial-mesenchymal transition and tumour metastasis. CD4+ and CD8+ lymphocytes are the main component of antitumour immunity which controls all other cellular reactions. It is known that high density of intratumour CD4+ and CD8+ infiltration is associated with better prognosis in gastric cancer patients but it is not well known in AAUM.
Methods: 55 cases of gastric cancer (surgical material) were included in our study. Lymphocytes identification was performed by immunohistochemical staining on markers CD4 (clone 4B12) and CD8 (clone C8/144B). Cell counting was performed in three fields of view (magn. x200) separately in TT and AAUM. These results were compared with classic tumour characteristics: depth of invasion (T), number of nodes metastases (N), distant metastases (M), grade (G).
Results: CD4+ infiltration in TT (median=37,8 cells) was higher than in AAUM (median=19,5 cells) in samples with N3 tumours (p=0,6148); CD4+ infiltration in AAUM in samples with N3 tumours was significantly higher than in samples with N2 tumours (median=11,33). CD8+ infiltration in TT (median=105,79 cells) was higher than in AAUM (median=72,21 cells) in samples with T4a tumours (p=0,7123); CD8+ infiltration in AAUM (median=74,33 cells) in samples with T4a/T4b tumours was significantly higher than in samples with T1a/T1b tumours (median=48,33).
Conclusion: High density of CD4+ and CD8+ infiltration in AAUM in gastric cancer is associated with greater depth of invasion and large number of lymph modes metastases which is opposite to intratumour infiltration. This indirectly confirms the hypothesis that CD4+ and CD8+ in AAUM may be involved in tissue restructuring that conduct to the tumour progression.

E-PS-06-039
Coexistence of intrahepatic bile duct adenoma and colorectal adenocarcinoma
D. Anestakis[1], C. Tsompanidou[2], P. Konstantinidou[1], M.I. Givannakis[3], I. Fountos[4], P. Pavlidis[5]
[1] Department of Autopsy Histopathology, Lab. of Forensic Medicine and Toxicology, Aristotle University of Thessaloniki, Greece, [2] Department of Pathology, General Hospital of Thessaloniki "Agios Dimitrios" , Greece, [3] Surgical Department, General Hospital "AHEPA", Thessaloniki Greece, [4] Forensic Service of West Republic of North Macedonia, Kozani, Greece, [5] Lab. of Forensic Medicine, Medical School, Democritus University of Thrace, Greece

Background & Objectives: Bile duct adenomas are benign proliferations of intrahepatic bile ducts usually encountered as an incidental finding. They are usually located on the surface of the liver and are <1 cm in diameter. These rare lesions should be included in the differential diagnosis of hepatic masses in addition to metastatic tumours if the patient has another malignancy.
Methods: A 70 year old woman with a diagnosis of colorectal adenocarcinoma was undergoing surgery when a small nodule was discovered on the surface of the left lobe of her liver. Thought to be possible metastatic disease this lesion was excited and sent for pathologic evaluation. The diagnosis of this nodule was benign in frozen sections intraoperatively and colectomy was performed during the same operation.
Results: Macroscopically the nodule of the liver was well circumscribed but not encapsulated, gray-white nodule measuring 1 cm in diameter. The microscopic study of the lesion showed an increased number of small, normal appearing bile ducts lined with a single layer of cuboidal cells which were positive to cytokeratin 7, negative to cytokeratin 20 and had a ki67 proliferation index of 1%. The morphology, immunophenotype and ki67 proliferation rate were consistent with a bile duct adenoma. The tumour of the colon was a pTNM stage II adenocarcinoma.
Conclusion: Recognition of this unusual co-existence of tumours could help to elaborate the appropriate therapeutic strategy for these patients.

E-PS-06-040
A rare case of acute abdomen in a pregnant woman – deciduosis of the appendix
F. Galante Pereira[1], A. M. G. Pereira[1], C. A. Padrão[1], J. Palla Garcia[1], R. S. S. Oliveira[1]
[1] Hospital Prof. Doutor Fernando Fonseca, EPE, Portugal

Background & Objectives: Ectopic decidua reaction or deciduosis is a physiological phenomenon that results from the effects of progesterone on extrauterine mesenchymal cells during pregnancy. In rare cases, ectopic decidual tissues can develop in the appendix. This case report pretends to raise the awareness of this uncommon finding.
Methods: A 30-year-old primigravida in her 17st week of an uncomplicated pregnancy, presented with nausea, right lower abdominal pain, positive Blumberg sign, slightly increased inflammatory markers, and a positive ultrasound for acute appendicitis. Following the diagnosis of appendicitis, the patient was later submitted to an appendicectomy. Hematoxylin-eosin, vimentin, calretinin and AE1/AE3 stain were performed.
Results: On specimen handling, there were white plaques and small nodules on the serosa. Histologically, the lesion was composed by haphazardly distributed sub-mesothelial decidualized cells, occasionally forming nodules. The vimentin was positive and the vimentin, calretinin and AE1/AE3 stain were negative.
Conclusion: It is important to be aware of less frequent causes of acute abdomen in a pregnant woman. All these diseases can present with similar clinical and imagiologic findings, highlighting the role of the pathologist in the final diagnosis.

E-PS-06-041
Evaluation of reproducibility of the diagnosis of gastric intraepithelial neoplasia/dysplasia: possibility of using mathod as a part of continuous professional education for pathology
S. Mozgovoi[1], A. Kononov[1], A. Shimanskaya[1], M. Parygina[1], M. Keruchenko[1]
[1] Omsk State Medical University, Russia

Background & Objectives: There is a need to introduce optimally reproducible classification approaches into the practical activity through the system of continuous education. The purpose of this study was to assess the level of consistency of the pathology diagnosis of gastric intraepithelial neoplasia / dysplasia on the consensus model.
Methods: A collection of 45 histological slides from the material of gastrobiopsy was compiled. All diagnostic categories of the Modified

Vienna classification of gastrointestinal neoplasia were showed on these data. Histological slades were stained with hematoxylin and eosin and then were photographed to obtain 216 representative images.Only the unambiguously evaluated cases were included (26 cases corresponding to 98 images). An analysis of the agreeement of the diagnostic evaluation was performed by peer review using the Cohen's kappa.
Results: The kappa level ranged from 0.2 (poor agreement, unweighted kappa) to 0.47 (average level of agreement, linear weighted) and 0.66 (good agreement, quadratic weighted). A simplified assessment method was used to record individual expert opinion in the binary evaluation format in regard to neoplasia/dysplasia diagnosis (yes/no). The application of this approach led to 0.47 unweighted kappa, which corresponds to average level of agreement.
Conclusion: The analysis showed average degree of agreement. The difficulties of introducing modern definitions of intraepithelial neoplasia/dysplasia such as a large number of diagnostic categories, an insufficient level of agreement in evaluating the signs of intraepithelial neoplasia/dysplasia, the lack of full follow-up to recommendations were identified.

E-PS-06-043
Cystic lymphangioma of the sigmoid colon: a case report
A. Jurescu[1], A. Dema[1,2], S. Tăban[1,2], M. Cornianu[1,2], A. Mureşan[1,2], C. Lăzureanu[1,2], R. Cornea[1,2]
[1] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [2] Department of Pathology, Emergency County Hospital Timişoara, Romania

Background & Objectives: Lymphangiomas are considered benign malformations of the lymphatic system but still, their pathogenesis is poorly understood. They are occasionally found in the abdomen, being generally cystic in type in this area. Colon cystic lymphangiomas are infrequently, the sigmoid segment being the least common location. At the same time, they are very rare in adulthood only a few cases being reported in the elderly. They usually are incidentally detected on colonoscopy or in colonic resection for other pathology.
Methods: We report the case of a 62 years old male, admitted in the outpatient clinic of County Hospital with hemorrhoidal disease and rectoragy. A colonoscopy examination was performed which showed multiple sigmoidal polyps. For this reason, he was referred to the Surgery Department for surgical intervention. A sigmoid segmentary colectomy was performed and sent to the Pathology Department.
Results: Grossly, a 5 cm soft polypoid lesion was identified, with a smooth surface, on cross-section having a multicystic appearance and clear fluid content. Histologically, a submucosal multilocular cystic lesion was observed, with overlying normal colonic mucosa. The cystic spaces, separated by variable thickness fibrous septa, were lined by a single layer of endothelial cells, positive immunohistochemically for D2-40. Focally we observed a cuboidal cell and giant multinucleated cells lining, positive for CD68 marker.
Conclusion: We present a unique case found in our Department. The particularity of the case consists of the fact that colon cystic lymphangiomas are extremely rarely found in the elderly, especially in the sigmoid colonic segment. Also, to our knowledge, this is the second study to describe the histiocytic replacement of endothelial lining as a sign of spontaneous resolution.

E-PS-06-044
Hepatoid adenocarcinoma of the colon: a case report and literature review
S.A. Postolache[1], M. Svrcek[1], Y. Parc[2], R. Cohen[3]
[1] Department of Pathology, Saint-Antoine Hospital, Paris, France, [2] APHP Sorbonne Universitè, France, [3] Department of Oncology, Saint Antoine Hospital, Paris, France

Background & Objectives: Hepatoid adenocarcinoma (HA) is a rare and highly aggressive tumour, firstly described in the stomach, morphologically characterised by hepatocellular and adenomatous differentiation. HA can occur in other organs including the colon, where less than 20 cases have been reported.
Methods: We present the case of a 49-year-old female patient taken into medical care for rectal bleeding. The colonoscopy revealed a sigmoid tumour for which biopsies confirmed a poorly differentiated adenocarcinoma. A CT scan excluded any distant lesion and the patient underwent sigmoidectomy with lymph node resection.
Results: Pathological examination revealed cuboidal atypical cells with eosinophilic cytoplasm, arranged in a solid or trabecular fashion, resembling that of HA. The tumour cells were positive for hepatocellular markers (alpha-fetoprotein, HepPar-1, Glypican 3 and Arginase) and also for gastrointestinal origin marker (CDX-2). The tumour was finally staged pT3N1b (2 positive lymph nodes, including the pedicular lymph node) with a mismatch repair proficient status. The patient was treated with a cytotoxic regimen of FOLFOX (oxaliplatin, leucovorin, 5-fluorouracil) during 3 months, with stable results being achieved after 5 months.
Conclusion: The HA is a rare type of primary colon cancer, that carries a very poor prognosis. It is essential to exclude a primary hepatocellular carcinoma. Because little is known about the pathogenesis of this unusual tumour, further studies are needed to identify a potentially guided standardised management.

E-PS-06-045
Analysis of gastrointestinal (GI) tract pathology frozen sections (FS) in tertiary referral cancer hospital in India: an audit of 3 years (1/1/2016 to 31/12/2018)
K. Deodhar[1], A. Jadhav[2], R. Kumar[2], M. Bal[2], M. Ramadwar[2]
[1] European Society of Pathology, International Academy of Pathology-Indian Division, India, [2] Department of Pathology, Tata Memorial Hospital, Mumbai, Homi Bhabha National University, India

Background & Objectives: We aimed to analyse the distribution, sensitivity, specificity, positive and negative predictive values of frozen sections in GI pathology in our institution for a period of 3 years.
Methods: Between 1st Jan 2016 to 31st Dec 2018, 1704 frozen sections (FS) were carried out in gastrointestinal oncosurgery, out of overall total 14740 FS; constituting 11.6% of total workload. The frozen section diagnoses and their paraffin section diagnoses are noted from the records.
Results: Cholecystectomy specimen for primary diagnosis and common bile duct cut margin (402 cases;23.6%) was the commonest FS; followed by gastrectomy margins (318cases;18.66%), followed by margins of colorectal resection specimen(300cases,17.60%). Other FS requests included Whipple surgery for margin, peritoneal nodule biopsy, liver biopsy, lymph node biopsy etc. (constituting approximately 684cases;40.14%). However, if all organ surgeries are considered, (colorectal, stomach, pancreas, extrahepatic bile duct excision), margin assessment was the most frequent (41.8%) FS request (713 out of 1704).
The accuracy of FS when compared with paraffin report was 96.77% (35 discordant cases out of total 1704 cases; 91.71% sensitivity, 99.69% specificity, positive predictive value of 98.84%, negative predictive value of 97.68%). Commonest discrepancies were in peritoneal biopsy interpretation and primary diagnosis of gall bladder.
The reasons for discrepancies included superficially cut tissue, scanty tissue, sampling error and interpretation error due to freezing and crushing artefacts.
Conclusion: Cholecystectomy for primary diagnosis and cut margins are the commonest FS requests in GI pathology. We can attempt to avoid discrepancies by studying deep cuts, careful sampling and being cautious of the artefacts.

E-PS-06-046

Comparison of clinicopathological and molecular features between left-sided and right-sided colon adenocarcinoma

E. Cakir[1], D. Unal Kocabey[1], N. Ekinci[2], A. Avci[2], A. Akder Sari[2]
[1] Izmir Katip Celebi University Ataturk Training and Research Hospital Department of Pathology, Turkey, [2] Izmir Katip Celebi University Ataturk Training and Research Hospital Department of Pathology Izmir Turkey

Background & Objectives: Colon cancer is among the leading causes of cancer-related deaths all over the world. Recent data suggest that right-sided colon cancer (RSCC) and left-sided colon cancer (LSCC) have different clinicopathological and biological features and should be considered as two distinct disease entities. This study aimed to compare the clinicopathological parameters and molecular features between right and left-sided colon adenocarcinomas.
Methods: We reviewed resected colon adenocarcinoma cases from our institutional database; 40 cases of right-sided (cecum, ascending colon, hepatic flexure, transvers colon) and 54 cases of left-sided (splenic flexure, descending colon, sigmoid colon). Parameters including age, gender, histological grade, tumour size, pT stage, pN stage, lymphovascular invasion, perineural invasion, presence of tumour deposit, mutations of KRAS and NRAS were analysed.
Results: The patients with RSCC were older and their tumour size were larger than LSCC but the differences were not statistically significant. KRAS and NRAS mutations were identified respectively in 43.6 % and 16% of RSCC compared with 25.9 % and 7.5% of LSCC (P=0.118 and p=0.415). Right-sided colon cancers more frequently displayed higher histological grade (27% vs 14.9%) compared with LSCC (p=0.185). There was no statistically significant differences between RSCC and LSCC according to gender, lymphovascular ainvasion, perineural invasion, pT stage, pN stage and presence of tumour deposit.
Conclusion: Right-sided colon adenocarcinomas tend to show relatively larger tumour size, frequent KRAS and NRAS mutation and higher histological grade when compared with left sided colon adenocarcinomas.

E-PS-06-047

A rare case of synchronous double cancer in the oesophagus and stomach

C. Ciora[1], M. Cornianu[2], S. Taban[3,4], G. Oprisan[1], M. Iacob[5], A. Ghiughici[6]
[1] Department of Pathology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, [2] V. Babes University of Medicine and Pharmacy, Romania, [3] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania, [4] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Pathology, Romania,
[5] Department of Pathology, Emergency County Hospital Timişoara, Romania, [6] Department of Gastroenterology and Hepatology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania

Background & Objectives: Squamous cell carcinoma of the oesophagus is occasionally associated with other malignancies, particularly of the respiratory tract and the head and neck. Presentation of synchronous diffuse gastric carcinoma is rare but important to be investigated, because stomach is the main organ used for reconstruction of the alimentary tract after esophagectomies. In cases where there are synchronous gastric tumours, the colon becomes an option for transit reconstruction.
Methods: A 66-year-old man, with a medical history of accidental caustic ingestion, had presented with appetite loss, dysphagia, epigastric pain and reflux symptoms for several months.
Results: Oesophagogastroscopy showed an oesophageal stenosis and a mucosal edema of the gastric angle. Abdominal and thoracic CT scan with contrast showed strong and regularly thickness in the middle third of the oesophagus due to an oesophageal stenosis longer than 6 cm.
The oesophagus and gastric biopsy revealed an invasive non-keratinized squamous cell carcinoma of the oesophagus (nuclear expression for p63) and a diffuse gastric carcinoma - signet-ring cell carcinoma (tumoural cells positive for pancytokeratin, AE1/AE3 and mucin stain - PAS-AA).
Conclusion: During the initial study, physicians should consider the possibility of a double cancer. Therefore, reporting such cases in the future, will increase our knowledge to avoid misdiagnosis and delayed therapy for the double cancer cases.

E-PS-06-048

Adenosquamous carcinoma of perianal region: an unusual site of occurence

G. Sahraoui[1], L. Bouzidi[1], L. Charfi[1], R. Doghri[1], K. Mrad[1], M. Driss[1]
[1] Salah Azaiez Institute, Tunisia

Background & Objectives: Perianal carcinoma is rare accounting for less than 2% of all gastrointestinal malignancies. It may arise de novo or from a fistula or abscess cavity. This is an aggressive cancer often misdiagnosed clinically as benign pathology.
We report a case of perianal adenosquamous carcinoma to highlight its epidemiologic, clinical and pathological features.
Methods: A 53-year-old woman with no chronic history of perianal fistulas or abscesses was referred to our hospital for management of melena with alternating diarrhea and constipation.
Results: Clinical examination and particularly digital rectal examination was normal. Colonoscopy did not reveal a rectal or colic tumour. The pelvic enhanced magnetic resonance imaging revealed perianal infiltrating tumour. Histopathological evaluation of abdominoperineal resection revealed an adenosquamos carcinoma arising from perianal glands. The continuity between the anal gland epithelium and the tumour was evident. Lymphovascular and perineural invasion was frequent. Surgical margins were tumourous.
The absence of associated abscess or fistula was microscopically confirmed. Tumour was positive for CK7 and negative for CK20.
Conclusion: Carcinoma of the perianal region is an oncologic rarity posing a diagnostic and therapeutic dilemma due to very few reported cases without definite therapeutic guidelines.

E-PS-06-049

Colorectal cancer: age dynamics of tumour volume

A. Filin[1], A. Sizov[1], V. Danilenko[1]
[1] Voronezh State Medical University named after N.N. Burdenko, Department of Pathological Anatomy, Voronezh, Russia

Background & Objectives: Despite the improvement of early diagnosis methods, late-stage colorectal cancer is diagnosed in more than 25% of patients, and tumours of stage I–II are detected in less than half of patients. The aim of the study was to analyse the dynamics of tumour volume in patients of different age groups.
Methods: 527 patients (238 men, 289 women, average age was 64,7 years old) suffering from colorectal cancer, underwent primary resection of the tumour. Based on the data obtained from the description of the removed intestinal fragments, the tumour volume was calculated.
Results: Volume of the tumour varied considerably from 0,1 cm^3 to 1650 cm^3 (the average volume was 37,3 cm^3). The largest tumours were found in the youngest patients (up to 40 years). In all the studied age periods the incidence of different volume tumours was similar. Most often, in every 5 cases (on average 21.5%) in all age groups there are tumours with a volume of 16-32 cm^3. Tumours with smaller volumes are less common, with approximately the same pattern. The largest and smallest tumours are less common, in 3.5% and 4.6% of cases, respectively. It can be assumed that

tumours with a small volume are not common because of their rapid progression, and after reaching a certain volume (16-32 cm^3, the diameter of such foci varies within 2.5-3.5 cm), their growth is significantly inhibited and only in a few cases the tumours grow to giant sizes.
Conclusion: The change in tumour volume in colorectal cancer is non-linear, which can explain the low rates of detection of the tumour in the early stages.

E-PS-06-050
Digestive lymphomas
G. Sahraoui[1], N. Redissi[1], R. Doghri[1], L. Charfi[1], K. Mrad[1], M. Driss[1]
[1] Salah Azaiez Institute, Tunisia

Background & Objectives: Gastrointestinal tract is the most common extra nodal site of lymphomas accounting for 5%-20% of all cases with a majority of non-Hodgkin type. The most frequent sites are the stomach followed by small intestine and ileocecal region. Almost 90% of these lymphomas are of B cell lineage. Our aim was to report clinical and histopathological features of digestive lymphomas.
Methods: We identified cases of digestive lymphomas between January 1999 and December 2018.
Results: Our series included 143 cases of digestive lymphomas. The sex ratio was 2.3. The average age was 55 years (3-84 years). The most frequent location was gastroduodenal (86%) followed by rectocolic location (10%). Concomitant gastric and colonic localization was found in 2% of cases. Ileal site was noted in 1% of cases and anal site in 1% of cases. Marginal-zone lymphoma was diagnosed in 56 % of cases, large cell B lymphoma in 39% of cases and Burkitt Lymphoma in 3% of cases. Two per cent of cases were difficult typing. Evolution was marked by a transformation of MALT lymphoma into large cell lymphoma in two cases and recurrence in 21 cases.
Conclusion: There has been a tremendous leap in the diagnosis, staging and management of these lymphomas attributed to a better insight into molecular aspect and the knowledge about its critical signaling pathways.

E-PS-06-051
Somatostatin-producing neuroendocrine tumours of the duodenum: clinical aspects, histological features and immunohistochemical profile - two case reports
A. Cohn[1], G. Terinte-Balcan[1], M. Manuc[2], V. Enache[3], C. Iosif[3], G. Becheanu[3]
[1] Emergency University Hospital, Bucharest, Romania, [2] Fundeni Clinical Institute, Bucharest, Romania, [3] Victor Babes National Institute of Pathology, Bucharest, Romania

Background & Objectives: Somatostatinoma is a rare neuroendocrine tumour, derived from the delta-cells of the pancreas or the endocrine cells of the digestive tract. We report two cases of sporadic well-differentiated duodenal somatostatinoma, one of them with pancreatic invasion and multiple hepatic metastases, diagnosed at Victor Babes National Institute of Pathology.
Methods: We present two somatostatin-producing endocrine tumours of a 42-year-old male and a 50-year-old female, which were evaluated according to location, morphology and immunohistochemical profile. Stains for synaptophysin, chromogranin, somatostatin, Ki-67 and SSTR2 were performed.
Results: The female patient underwent upper endoscopy for abdominal pain, which evidentiated a duodenal ulcerated lesion with infiltrative pattern. Imagistic exams revealed a tumoural mass of 47/37/32 mm situated near the ampullary region, invading the head of the pancreas, hepatic metastases and lymph node enlargement. tumoural markers CA 125, CA 15-3 and CA 19-9 were increased. Two months later, the patient started chemotherapy. There was no evidence of neurofibromatosis type I. No clinical data were available for the male patient.
Microscopically, the tumours exhibited tubular and glandular architectural pattern, with focal islets and trabeculae. One case presented psammoma bodies in glandular spaces. Tumours were positive for synaptophysin, chromogranin and somatostatin and presented a low Ki-67 index (<10%). SSTR2 reaction was negative.
Conclusion: Given the low incidence of this tumour, its malignant potential and the differential diagnosis with adenocarcinoma, somatostatinoma represents a clinical and morphopathological challenge. tumoural size may predict the rate of metastasis, but a correlation between a low Ki-67 index and extensive metastases must be further investigated.

E-PS-06-052
A single center experience in subepithelial oesophageal lesions (2000-2018)
T. Cardoso Lima da Costa Pereira[1], D. Pereira de Melo[1], J. Magalhães[1]
[1] Centro Hospitalar Universitário de São João, Portugal

Background & Objectives: Subepithelial oesophageal lesions (SELs) are frequently clinically assymptomatic and the vast majority are incidental findings. The differential diagnosis includes a number of benign and malignant nonepithelial tumours.
Methods: All cases with diagnosis of SELs registered in our center, from 2000 until 2018, were collected for review, and six variables were chosen for analysis: age, gender, type of surgical specimen , type of SEL, concomitant lesion and follow-up.
Results: Sixty-four cases were reviewed, fifty-eight of which were from female patients. The mean age at the time if diagnosis was 52,77 years. The majority had no concomitant lesion (n=51) and had been clinically discharged during follow-up (n=41). Leiomyoma (n=37), followed by granular cell tumour (n=10) and GIST (n=6) were the most common findings and biopsy (n=30) was the most common type of surgical specimen.
Conclusion: An eighteen-year review at our center demonstrated that most SELs occurred in female patients and had no associated lesions. Leiomyoma was the most frequent lesion, wich is compatible with the data described in the literature.

E-PS-06-053
The effect of pathological changes in the intestinal wall on the translocation of microorganisms in rats with strangulation intestinal obstruction
M. Tusupbekova[1], D. Amanova[1], P. Ivachyov[1], A. Lavrinenko[1], Y. Turgunov[1]
[1] Karaganda Medical University, Kazakhstan

Background & Objectives: The aim is studying the effect of histological changes in intestinal wall on the microbial translocation in strangulated intestinal obstruction (SIO).
Methods: 30 male rats were divided into 3 groups: I (BT+) - 12 rats with SIO model and present bacterial translocation, II (BT-) – 12 rats with model SIO and absence of translocation, III- 6 rats of the sham group (laparotomy without model). The SIO model was created under general anesthesia by clipping the loop of small intestine and feeding mesentery for 60 min with a further reperfusion for 2 hours. Translocation detection was carried out after injection of suspension of fluorescent *E. coli* with further microbiological examination of homogenized organs. Morphological study of intestine and mesentery was performed by the "Leica DM 1000" microscope. The significance of differences was determined by Fisher's exact test.
Results: In 10(83.3%) cases of BT+ group histologically in the intestinal wall was observed desquamation and necrosis foci in all layers of the intestine up to muscular, vascularization of mesentery, perivascular lymphocytic

infiltration, in 2 (16,65%) the process is also organic with a submucosal layer with point foci of necrosis of the muscular layer. In the BT- group morphological picture in 11(91.6%) is represented by damage to the layers of intestinal wall to submucosal and intact muscular layer, edema of mesentery. Morphologically changes were not found in the sham group.
Conclusion: Thus, the fact of the BT is associated with the depth of defeat of intestinal wall, the presence of muscle necrosis leads to bacterial translocation ($p<0.05$).

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E-PS-06-054
Long term survivor of ampullary undifferentiated carcinoma with osteoclast like giant cells
S. Giusca[1], I.D. Caruntu[1], D. Ciobanu[1], A.D. Timofte[1], A. Rusu[1]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Background & Objectives: Undifferentiated carcinoma with osteoclast-like giant cell (UCOGC) is a rare heterogeneous tumour defined by the presence of two populations, the mononuclear pleomorphic tumour cells and non-tumour multinucleated giant cells (MGC), with a recently accepted good prognosis. It was described in numerous organs, more frequently in pancreas; few cases located in Vater ampulla are reported.
Methods: We report a case of a 45 years old male patient, admitted for jaundice in a surgical department in February 2009. Abdominal ultrasound revealed a solid mass and dilated distal common bile duct leading to periampullary tumour suspicion. Subsequently, Whipple procedure was performed by surgeons.
Results: Gross examination of the pancreatoduodenectomy specimen revealed a focally ulcerated intestinal mucosa and a solid, white tumour of 2 cm diameter, involving the ampullary area, duodenal wall and adjacent pancreas. Histopathological exam showed an epithelial proliferation composed from individual pleomorphic spindle or round-ovoid cells forming trabeculae or discrete duct-like structures chaperoned by scattered MGC with benign appearance, mainly located intraampullary with limited pancreatic invasion (<0.5 cm). Immunohistochemically, the pleomorphic tumoural cells were positive for CK AE1/AE3 and Vimentin; MGC cells were positive for CD68 and Vimentin, and negative for CK AE1/AE3; immunostaining for LCA, CK7, CK20, and CDX2 was negative. The final diagnosis was ampullary UCOGC, stage III A. The patient had a good clinical course with no metastasis or local recurrence till July 2017, qualifying as a very long term survivor.
Conclusion: Our case report confirms the good clinical course of ampullary UCOGC, and completes the limited data available on this entity.

E-PS-06-056
Liver metastases of gastrointestinal stromal tumour (GIST): a case report and literature review
V. Caamaño[1], E. Camacho[1], R. Ruiz[1], B. Atares[1], I. Saenz de Santamaria[1], J. Aguirrre[1], A. Perez[1], I. Gorostiaga[1], A. Martinez[1], N. Barriobero[1], L. Lorente[1]
[1] Araba University Hospital, Spain

Background & Objectives: Gastrointestinal stromal tumour is the most frequent mesenchymal tumour in the gastrointestinal tract, accounting for 1% to 3% of all gastrointestinal neoplasms following gastric and colorectal cancer.
Methods: 72 years old woman with a history of abdominal discomfort for and weight loss over the last two months. Physical exam showed abdominal pain at abdominal palpation. The resonance magnetic images (MRI) demonstrated a 13cm mass on the stomach and also 0,7cm on the liver. A fine needle aspiration biopsy of the gastric mass was performed and it was diagnosed as: Gastrointestinal stromal tumour (GIST).
Results: The patient underwent surgery of the gastric and liver masses. Pathology report showed in both lesions: A proliferation of monotonous spindle cells arranged in fascicles. Immunohistochemistry showed positivity for: DOG1, CD117 and CD34 and negativity for: SMA, S100 and desmin; Ki67: 10%.
The final Diagnoses was: Gastrointestinal stromal tumour of the stomach (13cm) with liver metastases.
Conclusion: Approximately 40% to 50% of gastrointestinal stromal tumour (GIST) patients will have recurrence or metastases after surgical removal of the primary lesion. The most common affected sites are liver and peritoneum.Imatinib has been propose as the first line therapy for metastatic GIST, however surgery for metastases should be considered when is possible. The long –term outcome of GIST patients with liver metastases remain unknown.

E-PS-06-057
High grade appendiceal mucinous neoplasm
M. Chantziara[1], X. Grammatoglou[1], S. Pappa[2], D. Mpouklas[1], A. Kostopoulou[1], E. Gettimis[3], T. Choreftaki[1]
[1] Department of Surgical Pathology/General Hospital of Athens, "G.Gennimatas", Greece, [2] Department of Cytology/General Hospital of Athens, "G.Gennimatas", Greece, [3] 1st Department of Surgery/ General Hospital of Athens, "G.Gennimatas", Greece

Background & Objectives: We present the case of a 63-year-old male patient with high grade appendiceal mucinous neoplasm.
Methods: The patient presented to the emergency department complaining of severe pain on his right lower quadrate (RLQ) of the abdomen with duration of 12 hours. Standard laboratory examination showed mild leukocytosis. The radiological examinations revealed a dilated appendix. The patient underwent appendectomy.
Results: Microscopic examination revealed replacement, focally, of the normal appendiceal epithelium by mucin-producing columnar epithelium with low or high grade dysplasia in a micropapillary or cricriform growth pattern, loss of lamina propria and muscularis mucosae with submucosal fibrosis and pushing invasion into the muscularis propria. The remnant epithelium was ulcerative. Pools of acellular mucin were found into the muscularis propria and mesoappendix.
Conclusion: High-grade appendiceal neoplasms (HAMNs) are rare tumours that resemble LAMN in lacking destructive invasion, but show high-grade cytologic features. This term has been recommended in a recent consensus publication and has been included in the AJCC 8th edition.

E-PS-06-058
HER2 status in paired of gastric biopsies and resection specimens: is biobsy reliable for prediction of HER2?
M.E. Kara[1], E. Uzun[1]
[1] Gaziantep University Medical Faculty Hospital, Department of Pathology, Turkey

Background & Objectives: In breast and stomach cancer, HER2 oncoprotein overexpression is very important for prognosis and treatment. HER2 protein overexpression is thought to increase that proliferation activity and suppress apoptosis of the malign cells. Therefore Trastuzumab/HER2 treatment is a choice for patients with advanced stage/metastatic gastric cancer. Since these patients are usually inoperable at diagnosis, it is important to accurately and reliably determine HER2 status. For HER2 analysis, sometimes the only available material can be small biopsies. The aim of this study is to determine the reliability of HER staining applied to biopsy materials for the decision of HER2 treatment in patients with gastric cancer.
Methods: HER2 status in paired of 35 gastric biopsy and resection materials were examined. The HER2 stained cases were confirmed by silver in situ hybridization (SISH). The result of resection specimens was considered as a gold standard.

Results: The concordance of HER2 status between biopsy and gastrectomy materials was 91%. In biopsy materials, there was no false positive case, while three cases showed false negativity. The positive predictive value of biopsy material was 100% and the negative predictive value was 91.8% in determining HER2 status.
Conclusion: In determining the HER2 status, the biopsy materials provide accurate and reliable data. In discordant cases, the tumour heterogeneity is accepted as the main cause.

E-PS-06-059
Prevalence of oesophageal squamous papillomas (ESPs) in Romania: a 12 year multicentric retrospective study
A. Evsei[1], C. Rosianu[1], N. Copca[1], C. Gheorghe[2], M. Diculescu[2], M. Dumbrava[2], B. Codruta[2], I. Bancila[2], V. Herlea[2], V. Enache[3], S. Enache[3], F. Vasilescu[3], F. Andrei[3], A. Birceanu[4], C. Iosif[4], A. Dumitru[5], M. Sajin[5], G. Becheanu[3]
[1] CESITO Center, Saint Mary Clinical Hospital, Bucharest, Romania, [2] Gastroenterology and Hepatology Center, Fundeni Clinical Institute, Bucharest, Romania, [3] Victor Babes National Institute, Bucharest, Romania, [4] Pathology Department, Saint Mary Clinical Hospital, Bucharest, Romania, [5] Pathology Department, Emergency University Hospital, Bucharest, Romania

Background & Objectives: Oesophageal squamous papillomas (ESPs) are rare epithelial tumours with an uncertain etiology and a variable reported incidence. Chemical, mechanical and viral agents have been proposed as a mechanism of pathogenesis with recent reports arguing in favor of malignant transformations, but so far there is little information on a direct cause for this lesion.
Methods: We reviewed all patients who underwent an upper gastrointestinal endoscopy as part of a multicentric retrospective study which comprised four clinical and research institutions. We collected a total of 123 cases of microscopically confirmed ESPs over a period of 12 years (2006-2018). Our purpose was to establish a more precise incidence of this lesion in Romania and to find evidence for a possible link to tumour progression.
Results: According to our data, clinical and pathological diagnosis of ESP was highest in 2013 (18,69%) in all four centers. Female patients were more affected than male patients with a 1,3:1 sex ratio. More than 90% of lesions were under 5 mm and the age category most often affected was between 26 and 50 years old. 88% of cases were single lesions and their typical location was found in the distal third of the oesophagus (71 cases). 20,32% cases associated lesions in other locations such as Helicobacter pylori associated chronic gastritis, reactive gastritis, gastric hyperplastic polyps etc.
Conclusion: ESPs are unusual, frequently benign lesion that are still under debate regarding their mechanism of pathogenesis. Despite their rarity, their potential for malignant transformation warrants an attentive approach to endoscopic, pathological and clinical management.

E-PS-06-060
Multifocal small bowel adenocarcinoma which is developed in the setting of Crohn's disease: a case report
C. Ozturk[1], T.B. Ozcan[1], H.E. Pasaoglu[1]
[1] Bagcilar Training and Research Hospital, Turkey

Background & Objectives: Small bowell adenocarcinoma occurs very rarely in patients with Crohn's disease (CD). Here multifocal small bowel adenocarcinoma developed in the setting of CD is presented.
Methods: 62 year old male admitted to our hospital with persistent abdominal pain after an hernia operation. In clinical history the patient had intermittant abdominal pain that migt related with inflammatory bowel disease but colonoscopic examination was not performed before. Small bowell perforation was detected in emergency laparotomy. Ileum resection was performed. Macroscopically ten polypoid lesions were seen throughout the ileal mucosa. The polpys' sizes varied between 1 cm to 3cm. The mucosal surface' colour was brown. Ulcerated areas between the polyps and deep fissur-like ulcers were also seen.
Results: Histopathologic examination of the polypoid lesions revealed poorly differentiated adenocarcinoma containing mucinous component on the background of Crohn's disease. 8 of the polyps were high grade tubulovillous adenoma which were complicating with adenocarcinoma. Some of them were inflammatory pseudopolyps There were also deep lineer fissurs, pyloric metaplasia, cyript distortion, thickened muscularis mucosa, neuronal hyperplasia, submucosal fibrosis, linear arranged lymphoid follicules in submucosa and in subseroza in nonneoplastic bowel compatible with Crohn's disease.
Conclusion: Crohn's disease may be presented as adenocarcinoma first. In the case of adenocarcinoma of small bowell, adjacent mucosa should evaluated for CD carefully.

E-PS-06-061
Stomach: an unusual presentation of glomus tumour; a case report
E. Apaydin Arikan[1], A.N. Yildirim[1], R.B. Girgin[1], I.M. Leblebici[2], O. Alimoglu[2], G. Kir[1]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey,
[2] Istanbul Medeniyet University, Department of General Surgery, Turkey

Background & Objectives: Glomus tumour is a mesenchymal tumour usually occurs in the peripheral soft tissue, especially in subungal region. Although gastric glomus tumours are extremely rare, it is important to be aware of this entity because of involving in the differential diagnosis of gastric submucosal tumours.
Methods: We report a 42-year-old women presenting with anemia.
Results: Endoscopy revealed a submucosal mass at the antrum, but endoscopic biopsy taken from the lesion was nondiagnostic. A computed tomography showed a well-demarcated solid mass and a gastric wedge resection was performed with the initially diagnosis of gastrointestinal stromal tumour (GIST). In macroscopic examination, underlying the normal appearing mucosa, a 2.8x2.7x2 cm mural mass was observed. Microscopically, it was composed of solid sheets and island of small, round to oval uniform cells with very suspicious for neuroendocrine tumour. Immunohistochemically, tumour cells were strongly positive with smooth muscle actin and focally positive with CD34. Neuroendocrine tumour and GIST were excluded based on the negativity of chromogranin, synaptophysin, CD117 and DOG1. S100, HMB45, melan-A, desmin and caldesmon were also negative.
Conclusion: Pre-operative diagnosis of gastric submucosal lesions can be challenging and glomus tumour should be considered in the differential diagnosis. The light microscopic findings of glomus tumour may mimic neuroendocrine tumour, epithelioid GİST and leiomyoma. Combination of histological and immunophenotypic findings is crucial for proper diagnosis.

E-PS-06-062
Duodenal gastrointestinal stromal tumour: clinical, histopathological and immunohistochemical features - a series of 5 cases
G. Terinte-Balcan[1], A.M. Cohn[1], S. Enache[2], V. Herlea[3], G. Becheanu[3]
[1] Emergency University Hospital, Bucharest, Romania, [2] Victor Babes National Institute of Pathology, Romania, [3] Fundeni Clinical Institute, Bucharest, Romania

Background & Objectives: The term "gastrointestinal stromal tumour" (GIST) was first used by Mazur and Clark in 1983. They represent the most common mesenchymal neoplasm of the gastrointestinal tract. They are usually found in the stomach (50-60%) and in the small intestine (30-40%). Duodenal GISTs represent less than 5% of all cases.

Methods: We conducted a retrospective study of the duodenal GIST diagnosed at Victor Babes Institute of Pathology, Histopathology and Immunohistochemistry Department between 2015 - 2019 and selected 5 cases. We used the following criteria in order to evaluate them: age, sex, macroscopy, histology and presence of metastases. Furthermore, we performed a large panel of immunohistochemical markers, which included at least DOG1, CD34, CD117 and Ki67.
Results: Of the 5 cases, one of them was male. The median age was 64.2 years (range 48 – 80 years). The size of the tumours varied between 1 and 9 cm, with an average size of 2.9 cm. All cases were described as a proliferation of spindle cells, organized in whorls or short intersecting fascicles. The mitotic count was less than 5/50 HPF. The tumours were positive for CD117, DOG1 and CD34, except for one case that was positive only for CD34.
Conclusion: GISTs located in the duodenum represent a very rare entity and require a high level of suspicion in order to be correctly diagnosed. The prognosis of this tumour is uncertain, mainly because of the small number of cases that have been reported so far.

E-PS-06-063
24 neuromas of the appendix: a study of retrospective appendectomy specimens in King Chulalongkorn Memorial Hospital
D. Thirabanjasak[1], L. Sansopha[2]
[1] Department of Pathology, Faculty of Medicine, Chulalongkorn University and Chulalongkorn Hospital, Thailand, [2] Department of Pathology, Chulalongkorn Hospital, Faculty of Medicine-Chulalongkorn University, Thailand

Background & Objectives: Neuromas of the appendix or so-called fibrous obliteration, the common benign finding of appendectomy specimen that is not harmful but charming to the pathologist. Neuromas of the appendix is a unique pathologic lesion. The lesion is composed of proliferation of S-100 positive spindle cells, admixed with benign adipocytes and fibrous stroma. The lesion is commonly found in both appendectomy specimens and surgically removed specimens. Awareness of neuromas of the appendix should be helpful for surgery planning in eldery or related risky patients.
Methods: Retrospective study for appendix specimen was examined, during 2014-2018. Archives in Department of Pathology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital found 1,641 cases of appendix. 24 cases of neuromas of the appendix, 24 cases of mucinous neoplasm of appendix, 9 cases of diverticulum of the appendix, 6 cases of neuroendocrine tumour of the appendix, 3 cases of endometriosis at the appendix, 1 Kaposi Sarcoma at the appendix, 1 lymphoma at the appendix, minority of metastatic carcinoma and the rest is about the inflammation of the appendix (both appendicitis and periappendicitis). 24 neuromas of the appendix were studied, with IHC for S-100 and NSE.
Results: Patients with neuromas of the appendix is majority female (Sixteen female and eight male). The minimum age is 21 and the maximum age is 87. Mean age is 56.75. Diameter and length of the appendix were studied (Length : min 3.0 cm, max 7 cm, and mean 4.3 cm) (Diameter : min 0.3 cm, max 0.7 cm, mean 0.44 cm). The spindle cells are stained for NSE and S-100.
Conclusion: Neuromas of the appendix are common and benign finding. It is one of the most common finding in the appendix that is not harmful. In case there is periappendicitis, it should be precaution for surgeon to look for any other accompanying condition that can lead to appendicitis-like pain.

E-PS-06-064
Microsatellite instability in gastric cancer
G. Setdikova[1], I. Tin'kova[1], O. Paklina[1], D. Rotin[1,2]
[1] Botkin Clinical hospital, Russia, [2] Hospital Haim Sheba, Tel-ha-Shomer, Ramat Gan, Israel

Background & Objectives: Gastric cancer is the most common malignant tumour. Males are affected 1.3 times more than women, and the age of patients is usually 50 years and older. MMR definition in gastric cancer plays important prognostic role.
Methods: The study based on material obtained after surgery in Moscow Botkin hospital, and the group was 107 patients (age range 31-82) with surgical gastric resection during 2018, where MMR was evaluated. IHC panel of 4 antibodies was used including MLH1, MSH2, PMS2, MSH6.
Results: MMR was identified in 14 out of 107 cases. Type of MMR was MLH1-/PMS2- (11/14), PMS2- (3/14). No cases was negative both proteins MSH2 and MSH6, or MSH2 or MSH6. Histologically was significant predominance of Adenocarcinoma (total -12, G1-1, G2-2, G3-9), 2 cases belonged to signet ring cell carcinoma. 11 of 14 of MMR+ tumours had pT3 stage, 1 - pT2 , 2 - pT4a stage.
Conclusion: In our study of gastric cancer MMR was 13% cases. There were no cases of Lynch Syndrome or other family abnormalities.

E-PS-06-066
Gastric plexiform fibromyxoma - a mimicker of GIST: a case report
E. Caranfil[1,2], D.G. Ciobanu Apostol[1,2], D.I. Franciug[2]
[1] "Grigore T.Popa" University of Medicine and Pharmacy, Iasi, Romania, [2] Emergency County Hospital Spitalul Sfântul Spiridon Iaşi, Romania

Background & Objectives: Gastric plexiform fibromyxoma is a rare and unique tumour of the stomach located mainly in the antrum. Up to date less than 100 cases have been reported. Most patients present with anemia, melena, hematemesis, abdominal pain and distension. We present a case of a 34-year old woman, admitted to the emergency department for melena and moderate anemia. Endoscopy followed by CT scan revealed an antral mass suspected to be a GIST. Gastroduodenostomy (Bilroth I) was subsequently performed.
Methods: Tissue samples were routinely processed. HE stains and immunohistochemical tests were performed.
Results: Grossly the gastric fragment presented a nodular intramural tumour (5,1x4,7x2,6 cm) with mucosal ulceration. Microscopically, the tumour presented multiple submucosal and intramural nodules, with plexiform growth, composed of bland spindle cells, with low mitotic activity situated in an occasionally collagenous fibromyxoid stroma, with proeminent small vessels and lymphoplasmacytic inflammatory infiltrate. The adjacent gastric mucosa presented features of chronic gastritis and incomplete intestinal metaplasia.
The tumour cells were diffusely positive for SMA, H-caldesmon, focally positive for Desmin, CD10. DOG1, CD117, CD34, ALK 1 stains were negative.
Conclusion: Plexiform fibromyxoma is a rare entity with good prognosis and follow-up data of cases do not report recurrence or metastases. It should be distinguished from GIST which could have an aggresive course and requires a different follow-up and treatment.

E-PS-06-067
Poorly differentiated gastrooesophageal carcinoma with trilineage differentiation
D. Vinha Pereira[1], G. Y. Lauwers[2], K. Jiang[2]
[1] Pathology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [2] Pathology Department, H Lee Moffitt Cancer Center, Tampa, Florida, 33612 USA

Background & Objectives: Gastroesophageal junction (GEJ) is an anatomical controversial location with neither consensual definition nor universally reproducible landmarks. Neoplastic lesions of this location are particularly challenging. Regardless the precise anatomical site of origin and ethiopathogenic process, carcinomas of GEJ have similar histomorphology and behavior of the correspondent counterparts in

oesophagus and stomach. Poorly differentiated carcinomas could include a variety of lineages of differentiation, with distinct prognoses. The identification of each component could be challenging (histopathologically and immunophenotypically), and rarely more than two lineages have been reported.

Methods: We describe the case of a 56-year-old patient presented for second opinion regarding his recently diagnosed GEJ tumour. The outside diagnosis stated poorly-differentiated adenocarcinoma.

Results: Review of the outside biopsy identified a poorly-differentiated tumour with definitive adenocarcinoma histomorphology and peculiar features suggestive of neuroendocrine differentiation; indeed, both were confirmed (positive CDX2, synaptophysin and chromogranin immunostains performed at our institute). Remarkably, P40 was also positive in foci of cells. The histomorphology and immunophenotypes are most consistent with trilineage differentiation, a rare and poorly described entity.

Conclusion: To our knowledge this is the first GEJ carcinoma identified in a biopsy with unequivocal simultaneous trilineage differentiation (adenoneuroendocrine and squamous differentiation) without a collision tumour pattern. We believe that meticulous histomorphological evaluation and systemic immunohistochemistry are essential in reaching an accurate diagnosis, particularly in the setting of poorly differentiated carcinomas in this location. The impact of this subclassification on the clinical management and patient outcome awaits further investigation.

E-PS-06-068

Desmoplastic tumour reaction, inflammatory infiltrate and colorectal cancer: how it works?

R.I. Bermudez Cameo[1], A. Sobrino Prados[1], C. Hondler Argarate[1], J.I. Franco[1], M.J. Viso Soriano[1], H.P. Almanzar Comas[1], S. Bakali Badesa[1], A. Arellano Alvarez[1], N. Estrada Mallarino[1], L. Ligorred Padilla[1], V. Vazquez Alvarez[1], M.A. Nasarre Perez[1], A. Perez Ibañez[1], L. Lazaro Villanua[1], E. Del Valle[1], A. Puertas[1], M.A. Trigo Cebrian[1]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain

Background & Objectives: A pronounced desmoplastic tumour reaction (DTR) was associated with a reduced immune response, and has been related to be a poor prognosis indicator in colorectal cancer and cancer recurrence. However, CRC with a prominent inflammatory infiltrate, which is composed of intraepithelial (TIL) and peritumoural (PTL) lymphocytes, is predictive of a better prognosis. This study sought to investigate the relation between DTR with low rate of TIL and high rate of PTL in CRC.

Methods: The study included 109 patients with CRC who had undergone surgery from 2009 to 2011 at a single institution (University Hospital 'Miguel Servet' of Zaragoza (Spain)). They were categorized according to: TNM protocols of the American Joint Committee on Cancer (AJCC) as pT3 N0 M0, DTR, TIL and PTL status. Adjustment was made for relate low rate of TIL and high rate of PTL with a pronounced DTR. All biopsies were examined with Hematoxylin and Eosin and TIL and PTL were controlled by CD3 and CD8 immunohistochemistry (Polyclonal Rabbit anti-human CD3- Dako Omnis; Monoclonal Mouse anti-human CD8-Dako Omnis).

Results: The 51% of the patients were men (56/109) and 49% were women (53/109). Also 33% (36/109) of the total group were death by the end of this study. Low rate of TIL was present in the 61% of the patients with a DTR, in comparison with the 18% with high rate of TIL (25/41 and 7/41 respectively). Also 22% had moderate rate of TIL (9/41). About PTL, only 20% of patients with DTR and low rate of TIL were high rate of PTL.

Conclusion: Low rate of TIL was more frequent in patients with desmoplastic tumour reaction, which can be explained because of the resistance wielded by the tumour reaction in the stroma. However, our sample was not big enough to conclude with a high impact result, indicating the need of further investigations.

E-PS-06-070

Uncommon metastatic disease of colon carcinoma - report of two cases

R. Caetano Oliveira[1], V. Sousa[2], î Jesus[1], P. Teixeira[1], R. Vieira[3], M.J. Julião[1], J.G. Tralhão[4], M.A. Cipriano[1]
[1] Pathology Department, CHUC, Coimbra, Portugal, [2] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, [3] Dermatology Department, CHUC, Coimbra, Portugal, [4] Surgery Department, CHUC, Coimbra, Portugal

Background & Objectives: Signet ring cell carcinoma (SCRC) of the colon is a rare entity, sometimes in association with a mucinous component, which possesses an aggressive potential and even in cases with complete resection justify a long-term follow-up.

We report two cases of a SCRC with uncommon cutaneous metastases.

Methods: Two male patients, one with 70-year-old referred to the Dermatology department for suspicion of perioribitary sweat gland adenocarcinoma and other with cutaneous lesions in the lower right leg. Both were previously subjected to colectomy for PCCC of the colon 10 and 15 years ago, respectively. None had previous records of metastatic disease.

Results: Both lesions exhibited a diffuse and poorly cohesive cell neoplasia, with wide fatty tissue infiltration, without microsatellite instability. After six months, both patients are alive but with disseminated cutaneous lesions and under chemotherapy.

Conclusion: Cutaneous metastases of colorectal carcinoma are uncommon and usually reflect advanced disease. The SCRC have a diffuse pattern of dissemination, without boundaries respect, avoiding the usual routes of colorectal metastases – lung and liver, motivating a tight follow-up.

E-PS-06-071

De novo colorectal carcinoma after renal and hepatic transplantation

R. Caetano Oliveira[1], H. Antunes[2], A.M. Abrantes[3], E. Tavares Silva[2], R. Martins[4], J.G. Tralhão[4], E. Furtado[5], M.F. Botelho[6], M.A. Cipriano[1]
[1] Pathology Department, CHUC, Coimbra, Portugal, [2] Urology Department, CHUC, Coimbra, Portugal, [3] Biophysics Institute, FMUC, Coimbra, Portugal, [4] Surgery Department, CHUC, Coimbra, Portugal, [5] Hepatic Transplantation Unit, CHUC, COimbra, Portugal, [6] Biophysics Unit, FMUC, Coimbra, Portugal

Background & Objectives: Solid organ transplantation (SOT) is effective for the treatment of certain diseases, however has some risk associated, namely development of neoplasias. Immunosuppression has been appointed as higher risk for colorectal cancer (CCR) development.

Our objective is to study the incidence as well as the clinical and pathological characteristics of *de novo* CCR after renal and hepatic transplantation.

Methods: Retrospective study of patients with CCR diagnosis at ours institution between Jan/2004 and Dec/2016, previously submitted to renal/hepatic SOT.

Results: 12 patients (10M:2F), median age 60.54±13.41years, from which 9 were submitted to surgery – CCR in the right colon in 5 patients (41.7%) and in the left colon on 7 patients (58.3%), none on rectum.

5 patients were previously subjected to hepatic SOT – incidence 1:151. CCR developed after a median of 55.2±26,13months after SOT, with a median of 58±10,19years.

7 patients were submitted to renal SOT – incidence de 1:380. CCR developed after a median of 117.85±76.97months, with a median of 61.43 ±16.65years. After a median of 16.9±6,7months all the patients are dead. Tumours were mainly of higher stages (N=7), especially in the renal SOT cohort and revealed overexpression of cancer stem cells (CD133, CD44, ALH1). There were large areas of necrosis and low density of immune population. There was no expression for PD-L1 and through CD56 expression there were no NK cells. 4 patients were MSI and 5 were P53 mutated.

Conclusion: CCR after SOT has an aggressive behavior. Selected cases may benefit from individualized therapy; however, surgery and early detection seem to be the key.

E-PS-06-072

High grade appendiceal mucinous neoplasm; a new classification is obligatory

R.B. Girgin[1], T. Soylemez[1], E. Apaydin Arikan[1], H. Seneldir[1], G. Kir[1]
[1] Istanbul Medeniyet Universitesi, Department of Pathology, Turkey

Background & Objectives: Epithelial tumours of appendix range in a wide spectrum and their nomenclature has been a subject of debate for many years. Here we present a case of high grade mucinous appendiceal neoplasm (HAMN) and we want to discuss this entity through this case.
Methods: A 41 years old male patient was admitted to emergency service with symptoms of acute abdominal pain. Computerized tomography revealed that a dilated cystic lesion of 6 cm diameter compatible with appendiceal lesion and the radiologists mentioned that they could not rule out a tumoural process . Thus the patient underwent surgery.
Results: Intraoperative examination revealed that there was no mucinous material in the abdominal cavity. Macroscopically appendix was cystically dilated, creamy white and measured 6x6x4 cm. Microscopic evaluation revealed that this cystic lesion was lined by papillary and cribriform arranged epithelium. These epithelial cells displayed loss of polarity, full thickness nuclear stratification and high grade cytologic atypia. The appendix was totally submitted and did not exhibit infiltrative invasion.
Conclusion: The current WHO classification has no definition that corresponds to this entity. Whereas in the litterature, the use of the term "high grade appendiceal mucinous neoplasms" is encouraged.

E-PS-06-073

Colorectal cancer screening: the center of Portugal stands up with 4,6% incidence in 10 years of experience

V. Almeida[1], A. Alarcão[1,2,3], A.F. Ladeirinha[1,2], M. Reis Silva[1,2,3], T. Ferreira[1,2], A.I. Rodrigues[1], V. Sousa[1], L. Carvalho[1]
[1] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, [2] CIMAGO - Research Center for Environment, Genetics and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [3] Centre of Pulmonology, Faculty of Medicine of the University of Coimbra, Portugal

Background & Objectives: In Portugal, as in other European countries, the recommended primary screening test for colorectal cancer starts with the guaiac-based Faecal Occult Blood Test (gFOBT) directed to asymptomatic population with no risk factors between 50 and 74 years-old. This strategy is followed by total colonoscopy in positive gFOBT cases. Screening implementation had a previewed raise of colorectal carcinomas diagnosed without symptoms.
Screening of 10 years-period and synchronous lesions were reviewed.
Methods: The registry between 2008 to 2018 corresponded to polypectomies of 1576 patients submitted to a colonoscopy following the positive gFOBT as part of the colorectal cancer screening programme.
Colorectal adenocarcinomas and concomitant polyps were reviewed.
Results: From the 1576 patients/cases tested, 4,63% (78) were diagnosed with adenocarcinoma, which is under the 10% recognizes by European Union Recommendation on cancer screening (2017).
From those 78 cases, 51 belonged to men. The median age of affected patients was 64.
The most frequent localization was the sigmoid colon. The diagnosed carcinomas were alone in 33 cases and the other 45 endoscopic examinations revelled synchronous polyps, and all were biopsied or submitted or polypectomy. The most common type was tubular adenomas followed by tubulovillous adenomas. The serreated morphology was the least prevalent.
Conclusion: The screening program is not yet homogenously implanted in all territory, but the actual sampling is relevant to recognize the favourable prevention and Health Minister commitment.
Data from other studies revealed that the percentage of positive CCR for work-up of a positive gFOBT is around 4%, which is in line with our results.

E-PS-06-074

Sall4 expressing gastric carcinoma with high serum afp level; is it possible to rule out a burned out yolk sac tumour metastasis?

R.B. Girgin[1], T. Soylemez[1], A.N. Yildirim[1], E. Apaydin Arikan[1], G. Kir[1]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey

Background & Objectives: SALL4 has been identified as a diagnostic marker of germ cell tumours. Recent studies showed that SALL4 may act as an onco-fetal or carcinoembryonic molecule İN some neoplasms of extragonadal organs. AFP-producing gastric carcinomas accounts for 2.7%-5.4% of all gastric carcinomas with some of them containing germ cell components which explains retrograde differentiation of neoplastic cells.
Methods: 60 years-old male patient was investigated for abdominal pain. Endoscopic examination revealed an ulcerous lesion at the corpus-antrum junction and the serum AFP level was >20000 ng/mL. No mass was detected in testis nor a previous tumour was present.
Results: Microscopic examination revealed a poorly differantiated tumour with focal trabecular areas and with clear cell areas which lacked mucin and glycogen accumulation with Alcian blue and PAS stain, respectively. Tumour cells were diffusely positive for CDX2, SALL4, Glipycan 3, AFP and EMA. No mass was detected in testis nor a previous tumour was present. PET scan was unremarkable except stomach.
Conclusion: It should be kept in mind that AFP-producing gastric carcinoma and yolk sac tumour share similar morphologic and immunhistochemical features. EMA positivity support the diagnosis of gastric carcinoma based on the knowledge that germ cell tumours are negative for EMA.

E-PS-06-075

Clear cell sarcoma of the digestive tract: a case report

R. Narjess[1], N. Boujelbene[2], I. Abbes[2], R. Doghri[2], L. Charfi[2], N. Kcherem[2], K. Mrad[2], M. Driss[2]
[1] Institute of carcinology Salah Azaiz Tunis, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Clear cell sarcoma (CCS) of the gastrointestinal tract is a rare malignant neoplasm that occurs in the wall of the small bowel, stomach, or large bowel, predominantly in young adults. It is an aggressive neoplasm that frequently presents with metastatic disease and has a high mortality rate. Herein we report a case of CCS with description of the pathological and molecular features of this rare entity to make pathologists aware of this entity.
Methods: A 27-year-old patient with a history of retinoblastoma consulted for dysphagia.
Results: Fibroscopy shows a bulging formation of the middle 1/3 of the oesophagus. Histological examination of a biopsy shows a densely cellular tumour consisting of rounded monomorphic cells disposed in a vaguely fasciculate pattern. Tumour cells have a round or oval nucleus with a reduced eosinophilic clarified cytoplasm. The immunohistochemical study

show that these cells are Pancytokeratin (-), PS100 (+), SOX10 (+), HMB45 (-), MelanA (-), Desmin (-), RB1 (+), C-kit (-), DOG1 (-), CD99 (+), SMARCB1 (+).
Molecular study identified a EWSR1-ATF1 fusion transcript, which confirmed the diagnosis of a clear cell sarcoma of the digestive tract.
Conclusion: The lack of familiarity of pathologists with the features of this neoplasm may have previously contributed to its under recognition, but the finding of an epithelioid or spindle cell neoplasm in or around the gastrointestinal tract with S100 protein expression should always warrant molecular assessment for EWSR1 rearrangement and for EWSR1-CREB1 and EWSR1-ATF1 fusion transcripts.

E-PS-06-076
Ceacal adenocarcinoma arising from huge Traditional Serrated Adenoma located in appendix and ceacum: a case report
H.E. Pasaoglu[1], E. Erel[1], N. Okkabaz[2], T.B. Ozcan[1], T. Cay[1], N. Erdogan[1]
[1] Clinical Pathology, Turkey, [2] Gastrointestinal Surgery, Turkey

Background & Objectives: Traditional serrated adenomas are uncommon, making –up <%1 of all colorectal polyps. They are usually found in the distal colon . Appendix and ceacum are very rare locations for TSA. The majority of TSAs are protuberant lesions smaller than 2cm. Here, we presented a case of ceacal adenocarcinoma arising from a huge, broad based traditional serrated adenoma located in appendix and ceacum.
Methods: 75 year old female was admitted to clinic with abdominal pain and distention. Physical examination was normal. The patient had undergone breast conserving surgery for breast cancer four years ago. Colonoscopy revealed a 5 centimeters broad based polypoid lesion in ceacum. Intramucosal carcinoma arising from an adenoma with serrated pattern was seen in colonoscopic biopsy. Right hemicolectomy was performed.
Results: Macroscopically 5,5x4 cm polypoid mass in ceacum was detected. Diameter of the appendix was 1,7 cm . Polypoid lesion was connected with the appendiceal orifice. Longitidinal section was performed from the orifice to the tip of the appendix and fingerlike projections troughout the appendix mucosa were seen. Histopathologically the lesion had a villiform growth pattern and serrated luminal surface. The cells lining the villi were tall and columnar with eosinophilic cytoplasm and pencillate nuclei. Small, abortive ectopic crypts were also seen. These features were consistent with TSA. The lesion exhibited high grade dysplasia in some areas . An adenocarcinoma containing mucinous component was detected in deep portion of the adenoma in ceacum, which was infiltrating the subseroza. Immunhistochemically MUC-2, MUC 5AC were positive, MUC-6 negative and DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) were diffusely expressed in nuclei in both adenoma and invasive carcinoma areas.
Conclusion: The diagnosis of TSA may be difficult in small endoscopic biopsies. Furthermore, carcinoma in the deep portion of the polyp may not be detected in endoscopic biopsies . Total excision with intact surgical margin should be done.

E-PS-06-077
Adenocarcinoma of anal glands with apocrine differentiation: a case report and a literature review
O.B. Popescu[1], O. Cerezo-Aranda[1], J.M. Barria Castro[2], L. G. Pastrián[1], E. Palacios Lázaro[1]
[1] Hospital Universitario La Paz, Spain, [2] Complejo Hospitalario Dr. Arnulfo Arias Madrid, Panama

Background & Objectives: Apocrine carcinoma is a rare skin appendage tumour that shows apocrine-type decapitation secretion. It occurs in the body sites where apocrine ducts are normally located.
Methods: An 88-year-old male presented with a sessile polypoid lesion in the anal region. It was 2,5 cm wide, white and firm, and was surgically resected.
Results: Lesion was an expansive mass of variable-sized nodules, located in lamina propria, growing in solid and cribriform patterns with eosinophilic acellular secretions. Cells had large eosinophilic cytoplasm with pleomorphic nuclei and prominent nucleoli. Numerous mitotic figures were identified. The overlying epithelium showed pagetoid spread of atypical cells, but was not intraepithelial dysplasia. Lymphovascular invasion was present and the resection margin was positive. A few mammary-type glands were seen, affected by an analogue intraductal lesion. The immunophenotype of the tumour cells was strongly and diffusely positive for CK7, GCDFP-15, androgen receptor and Her2 (3+), and negative for CK20, CK 5/6, CDX2, p63 and p40.
Conclusion: Adenocarcinoma with apocrine differentiation arising from anogenital glands is uncommon and only a few cases have been published. Both genders are equally affected. Pathogenesis is unknown, but it seems to arise from apocrine hyperplasia or adenoma of anogenital mammary-like glands. Differential diagnosis includes metastatic breast cancer, benign apocrine tumours, colorectal adenocarcinoma and mucinous carcinoma. Treatment is wide excision.

E-PS-06-078
PDL-1 expression is poor prognostic factor in gastric carcinomas?
S. Erdamar[1], S. Bahsi[1], Ļ Yıldız[1]
[1] Acibadem University Medical College, Turkey, College, Turkey

Background & Objectives: PDL1 expression and Microsatellite Instability (MSI) is getting more important gastric carcinoma to get benefit from immunotherapy. In this study, we aimed to investigate the MSI status and the frequency of PD-L1 expression in gastric cancer cases and the relationship between this frequency and clinicopathological features and overall survival.
Methods: The patients diagnosed with gastric cancer between the years 2010-2017 at Acibadem University Hospitals were retrospectively analysed and 86 patients were included in the study. Patients were evaluated of age, sex, tumour location, tumour size, tumour histological subtype, clinical and pathological tumour stage, HER-2 staining status, preoperative treatment status, lymphovascular and perineural invasion, resection status. Tumour sections were immunostained with MMR proteins and PD-L1 (22C3 clone). Analytical statistical methods, survival analysis was performed. Factors affecting survival were determined by univariate and multivariate analysis.
Results: The incidence of MSI was 11.6% (n:10), the presence of PD-L1 expression in tumour cells was 34.9% (n:30) and the presence of PD-L1 expression in immune cells with Combine tumour score (≥1%) was 57% (n:49). PD-L1 positivity was found to be statistically higher in patients with node positive, adenocarcinoma subtype, microsatellite instability, preoperative treatment, and chemotherapy response.
Conclusion: In our study, the impact of MSI status on survival was not demonstrated, but PD-L1 expression positivity was associated with short survival in both tumour cells *(p:0.008)* and in immune cells *(p:0.027).*

E-PS-06-079
Synchronous presence of epithelial and stromal tumours in the stomach - characterization of molecular pathways
E. Kocsmar[1], G. Papp[2], I. Kocsmar[1], L. Szalai[3], I. Kovalszky[2], G. Lotz[1]

[1] 2nd Department of Pathology, Faculty of Medicine, Semmelweis University, Hungary, [2] 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Hungary, [3] 2nd Department of Pathology, Semmelweis University, Hungary

Background & Objectives: Gastrointestinal stromal tumours (GISTs) are the most common tumours in the digestive tract arising from the mesenchymal components of the tissue. Small GISTs (GIST tumourlets) are usually asymptomatic and most frequently found in gastric surgical specimens incidentally. Our aim was to assess prevalence of incidental GISTs among gastrectomy specimens of gastric adenocarcinoma patients and to obtain data about molecular mechanisms of these synchronous tumours.
Methods: Gastrectomy specimens obtained between 2002-2018 were selected from the institutional register of the 2nd Department of Pathology. Incidence of incidental GISTs was also assessed separately according to the method of resection (partial or total). Patients with adenocarcinoma and synchronous GIST were selected and CD117 (c-kit), CD34 and DOG1 immunohistochemical stainings were performed on both tumours. KIT exon 9, 11, 13, 4, 17 mutations were analysed by Sanger sequencing.
Results: 1,027 gastrectomy specimens were analysed in the study period, including 665 cases of patients operated due to adenocarcinoma. Synchronous incidental GIST was found in ten cases (1.5% of 665). All of the GIST tumourlets were of spindle cell variant and immunohistochemically positive with CD117, CD34 and DOG1. Positive DOG1 immunostain was detected in four adenocarcinomas as well. KIT mutation was found in four GISTs, but in none of the synchronous adenocarcinomas.
Conclusion: Incidence of incidental GISTs in gastrectomy specimens was lower in our cohort than in other studies. Although a common carcinogenic effect cannot be ruled out, our data suggest that distinct mechanisms play role in the development of synchronous GISTs and gastric adenocarcinomas.

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E-PS-06-081

Correlation between different histopathological indices and clinical parameters in children with ulcerative colitis

J. Jevtic[1], R. Jankovic[2], S. Strizovic[2], D. Obradovic[1], N. Ristic[3], N. Dragutinovic[3], I. Milovanovic[3], M. Radusinovic[3]
[1] Faculty of Medicine, University of Belgrade, Serbia, [2] Institute of Pathology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [3] University Children's Hospital, Serbia

Background & Objectives: A diagnosis of ulcerative colitis (UC) requires multidisciplinary approach. Among wide variety of diagnostic modalities histopathology still stands as the diagnostic gold standard. Since the histological remission is the main goal in treatment of UC, assessment of disease activity during endoscopy and histopathological examination is of paramount importance. The aim of the study is to determine the correlation between different histopathological scores (Geboes and Nancy) in biopsies of the children with UC, endoscopic Mayo score (EMS) and clinical overview.
Methods: Colonic biopsies of children with UC from the Institute of Pathology, Medical Faculty, University of Belgrade were retrospectively analysed, as well as clinical data and endoscopic characteristics collected from University Children's Hospital in period of three years (2016-2018).
Results: We analysed 243 endoscopic biopsies of 41 children with newly diagnosed UC as well as specimens after treatment. The average age of patients was 12.8±4.39 years. Majority of patients were male (53.66%). Twelve percent of patients had extraintestinal manifestations of the disease with the primary sclerosing cholangitis as the most common. Statistical analysis showed significant moderate correlation between histopathological scores and EMS, and significant strong correlation among histopathological scores. We found slightly stronger correlation between histopathological scores and EMS in children with newly diagnosed UC than after treatment.
Conclusion: There is strong statistically significant correlation between histopathological scores (Geboes and Nancy). Therefore both of the histopathological scores can be successfully applied in estimation of disease severity.

E-PS-06-083

Correlation of tumour budds, epidermal growth factor 2 and exspression of E-cadherin with overall survival of patients with advanced gastric adenocarcinoma

M. Cuk[1], R. Gajanin[2], S. Kulic[1], M. Vasic Milanovic[3]
[1] University of East Sarajevo, Faculty of Medicine Foca, Department of Pathology, Bosnia and Herzegovina, [2] University of Banja Luka, Faculty of Medicine, Department of Pathology, Bosnia and Herzegovina, [3] Public Health Hospital, Department of Pathology, Zvornik, Bosnia and Herzegovina

Background & Objectives: Adenocarcinoma of the stomach is very aggressive biological behavior and has a poor prognosis in patients in an advanced stage of the disease. Testing new prognostic parameters and discovering new therapeutic targets is a long-standing challenge for pathologists and oncologists.
Methods: Tumour buds were determined on the invasive edge of the tumour and defined as individual or groups of less than five tumour cells. Paraffin-embedded tumour samples were examined for E-cadherin, CK20 and HER2 using immunohistochemistry. Additionally, gene amplification was examined using fluorescent in situ hybridization (FISH) for HER2.
Results: The minimum follow-up period was 6 months and a maximum follow-up period of 87 months. The survival rate of patients after 12 months was 80.2%, after 24 months 51%, after 36 months 28.5%. Budding was present in 76 of 96 cases and was associated with decreased overall survival (OS) (Log Rank=32,805, $p<0.001$). Reduced expression of E-cadherin was identified at the frequency of 74% and was associated with decreased overall survival (Log Rank=23,80, $p<0.001$). There was a significant difference in OS between HER2-positive and HER2-negative patients [median, 17.0 vs. 26.0 months; $p < 0.01$]. Multivariate analysis showed that high grade of tumour budding was an independent prognostic factor for overall survival [hazard ratio, 1,46 (95 % confidence interval, 1,25 – 1,69); $p<0.01$], but HER2 and E-cadherin did not show themselves as independent prognostic parameters.
Conclusion: Tumour budding is significant and independent predictors of poor outcomes in patients with advanced gastric adenocarcinoma.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-07 | Digestive Diseases Pathology – Liver / Pancreas

E-PS-07-001

Hepatocellular adenoma like associated with vascular obstructive disease secondary to alcohol consumption

A. Vera-Torres[1], L. Barrera[2], M. Tapias[1], J. Alvarez-Figueroa[2]
[1] Transplant and Hepatobiliary Surgery Service, Hospital Universitario Fundación Santa Fe de Bogotá Colombia, [2] Department of Pathology and Laboratory Medicine, Hospital Universitario Fundación Santa Fe de Bogotá, Colombia

Background & Objectives: Hepatocellular nodules are commonly observed in hepatic vascular disorders and the lesions that resemble a hepatocellular adenoma share the same characteristics as a conventional hepatocellular adenoma. We present a lesion that resembles a hepatocellular adenoma associated with a hepatic vascular disorder secondary to alcohol consumption.
Methods: 64-year-old man with history of alcohol consumption, diabetes mellitus and variceal bleeding. The CT scan show liver with normal contours and diminish of size with prominence of the caudate lobe, permeable vascular structures and focal poorly defined 25 mm lesion.
Results: Liver examination revealed micronodular surface and microscopically heterogeneous architecture, both severe and slight nodular areas, significant sinusoidal dilatation, hemorrhage and blood vessels destruction associated with hepatocellular lesions with cholangiolar proliferation, chronic inflammation and telangiectasia with CD34, FVIII and SAA reactivity, with low cell proliferation index and negativity for glutamine synthetase and Betacatenin. The reticular pattern was preserved without presence of malignant hepatocellular lesion.
Conclusion: Obstructive vascular disease can be seen in alcoholic patients. Fibrosis after abstinence may improve and steatohepatitis characteristics would be lost. Lesions similar to hepatocellular adenoma (inflammatory/telangiectasic adenoma morphology) present with an immunophenotype similar to the observed on conventional hepatocellular adenoma. This lesion associated with hepatic vascular disorders, may increase the risk of malignant transformation compared to a conventional hepatocellular adenoma.

E-PS-07-002
Adult hepatic Langerhans cell histiocytoris associated with chronic colangiopaty
M. Rolon[1], M. Romero[1], C. Saavedra[1], D. Cañon[1,2], L. Barrera[1], A. Vera-Torres[3], M. Tapias[3], J. Alvarez-Figueroa[1]
[1] Department of Pathology and Laboratory Medicine, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia, [2] Universidad de los Andes. Bogotá, Colombia,
[3] Transplant and Hepatobiliary Surgery Service, Hospital Universitario Fundación Santa Fe de Bogotá. Bogotá, Colombia

Background & Objectives: Langerhans cell histiocytosis (LCH) is a rare neoplasm characterised by the presence of positive CD1a histiocytes. Predominates in the paediatric age with cutaneous lesions as the first manifestation. We present a case of an adult with hepatic involvement associated with chronic damage of the bile duct without cutaneous manifestations.
Methods: 47-year-old male with history of diabetes insipidus and one year of multiple episodes of acute cholangitis associated with abdominal pain, jaundice, high bilirubin direct levels, transaminases and alkaline phosphatase. AMA negative. The cholangioresonance reveled global hepatomegaly with alteration of parenchymal intensity and stenosis of the intrahepatic bile duct.
Results: Liver biopsy showed architectural distortion, portal fibrosis, portal spaces with inflammatory infiltrate composed by histiocites, lymphocites, plasma cells, foamy histiocytes and abundant eosinophils, granulomas and bile duct damage with aberrant expression of cytokeratin 7 at periportal level and ductular reaction with acute cholangiolitis. Hepatocanalicular cholestasis, xanthomatous change with periportal copper deposits. CD1a and s100 positivity in the portal histiocytes. The patient was subjected to chemotherapy and with morphologic remision pending for trasplantion.
Conclusion: Although adult presentations of LCH is described in the literature this patient's age is unusual. As a morphological finding, we shown that the presence of granulomas with histiocytes and eosinophils in biopsies should be considered as a suspicious finding for LCH and Hodgkin lymphoma and Mastocytosis should, however, be consider in the differential diagnosis.

E-PS-07-003
Intracranial meningeal hemangiopericytoma metastatic to the liver
J. Alvarez-Figueroa[1], L. Barrera[1], A. Vera-Torres[2], E. Jimenez-Hakim[3], P. Escalante[1]
[1] Department of Pathology and Laboratory Medicine, Hospital Universitario Fundación Santa Fe de Bogotá. Bogotá, Colombia, Colombia, [2] Transplant and Hepatobiliary Surgery Service, Hospital Universitario Fundación Santa Fe de Bogotá, Colombia, [3] Department of Surgery, Hospital Universitario Fundación Santa Fe de Bogotá, Colombia

Background & Objectives: Solitary fibrous tumour/The hemangiopericytoma is a mesenchymal central nervous system tumour of uncommon fibroblastic origin, when the phenotype corresponds to a hemangiopericytoma there is an increased risk of extracranial metastases, which usually occur several years after the initial diagnosis. We present a case of metastatic meningeal hemangiopericytoma to the liver.
Methods: A 42-year-old female patient with a history of recurrent extra-axial tumour, who presented abdominal induration sensation 9 years after the initial diagnosis. Multiple solid hepatic lesions with heterogeneous cystic components and peripheral enhancement were documented on CT scan. Patient was submited to right hepatectomy and segmental resection of lesions in the left lobe.
Results: Histopathological study reveladed a malignant, hypercellular mesenchymal neoplasm, consisting of cells with rounded to oval nuclei, vesicular and condensed chromatin, some cells with epithelioid appearance, arranged in a disorganized architectural pattern, thin-walled blood vessels cells and up to 8 mitosis in 10 HPF. Immunohistochemical showed diffuse and strong positivity of neoplastic cells for CD34, BCL-2, CD99 and Vimentin, with focal and weak positivity for Progesterone Receptors and negativity for EMA and Desmin.
Conclusion: These findings correspond to a meningeal mesenchymal tumour of hemangiopericytic morphology, which is part of the solitary fibrous tumour/hemangiopericytoma spectrum, and it is classified as WHO 2016 grade III, metastatic to liver. These tumours should be considered as potentially malignant in all cases and hepatic metastases are rare.

E-PS-07-004
Solitary fibrous tumour hepatic: case report and review of current knowledge
R.M. Souza da Silva[1], E. Moreira de Queiroga[2], A. Rolim da Paz[3], Á. Regina Gouveia[4]
[1] Federal Fluminense University, Brazil, [2] Alcides Carneiro University Hospital of the Federal University of Campina Grande, Brazil, [3] University Hospital Lauro Wanderley/EBSERH/UFPB, Brazil, [4] Faculty of Medical Sciences, Brazil

Background & Objectives: Solitary fibrous tumours (SFTs) are a rare type of spindle cell neoplasm, composed of cellular and collagenous components, predominantly arise from the pleura. SFT of the liver (SFTL) are uncommon

with little number of cases reported in English literature. The diagnosis is based on histological and morphological characteristics, associated with immunohistochemical markers and molecular analysis. The rarity of this tumour makes it difficult to evaluate its prognosis and natural course. Surgical resection remains the mainstay of treatment.
Methods: The present study reports a new case of SFTL and has the main purpose of updating the current knowledge.
Results: 42-year-old woman, with right hypochondrial discomfort and postprandial fullness. Magnetic nuclear resonance showing nodular expansive formation with well-defined contours, located in left hepatic lobe. Macroscopically, a nodular mass, white color, firm and elastic, measuring 3,2 cm x 3,0 cm.. Microscopic examination evidenced fusocellular proliferation, hypocellular and hypercellular areas (mild atypia), with predominance of a sclerotic pattern. The immunohistochemical study revealed ki-67 1%, positivity for STAT 6, CD 34 and Bcl-2. The diagnosis was of Solitary Fibrous Tumour Hepatic.
Conclusion: The SFTL is rare, with only 85 cases reported in the English Literature including the present case. The clinical presentation is habitually indolent. The diagnosis is histopathological e immunohistochemical. SFTL because due to its rarity, its clinical presentation, study, treatment, and prognosis are not well known.

E-PS-07-005
Chylous ascites, induced by a pancreatic carcinoma
A.C. Tinca[1], Tivadar Bara[1], Ioan Jung[1], Simona Gurzu[1]
[1] Department of Pathology, Clinical County Emergency Hospital, Tîrgu Mureş, Romania Department of Pathology, University of Medicine, Pharmacy, Sciences and Technology, Tîrgu Mureş, Romania

Background & Objectives: Chylous ascites is an uncommon condition of peritoneal cavity. The aim of the paper was to describe the case of a patient with ductal adenocarcinoma of the pancreatic body that presented as acute abdomen and chylous ascites.
Methods: A 76-year old previously healthy male presented with acute abdomen and suspicion of pancreatic body cancer, with associated ascites, was done. Emergent surgery consisted on splenopancreatectomy with dissection of the peripancreatic lymph nodes. The fluid from abdominal cavity had a milky aspect and was proved having lymphatic origin.
Results: The 50x40x20 mm pancreatic tumour involved the pancreatic body and tail and showed direct infiltration of the spleen hilum, being diagnosed as pT3N1 ductal adenocarcinoma. Most of the lymph vessels showed tumour emboli, which induced blockage of the lymphatic flow. The patient died at three weeks after surgery.
Conclusion: In patients with pancreatic cancer, chylous ascites can indicate an aggressive carcinoma with lymphatic flow blockage.

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E-PS-07-006
Synchronous pancreatic stromal tumour and granulous T-cell leukemia
A. Bdioui Thabet[1], C. Pierre[2], H. Busby[2], N. Mhamedi[2]
[1] Georges Pompido Hospital Paris, France, [2] Brabois Hospital, Nancy, France

Background & Objectives: Coexistence of stromal tumours with other malignancy is rarely reported, it has been described for digestive stromal tumour with adenocarcinoma, either MALT or Hodgkin lymphoma. Extra digestive stromal tumour are rare counting less than 5%, Their association with other synchronous tumours is furthermore exceptional, the case of our patient.
Methods: 59-year-old man, consulting for chronic abdominal pain, radiological investigations showed a large exophytic pancreatic tumour. The patient underwent surgery, he has had caudal spleno-pancrectectomy. In gross, there was a voluminous exophytic pancreatic tumour, well limited, firm, appended to the tail; and presenting an heterogeneous cut surface.
The spleen was increased in size, 20 cm of large, with homogeneous appearance.
Results: Histological examination of the pancreatic mass and the immunohistochemical study concluded to a gastrointestinal stromal tumour of moderate risk of malignancy, expressing DOG 1 and CD 117.Examination of the spleen showed an infiltration by large granular T lymphocytes, with large nuclei, these cells expressed in immunohistochemistry T markers: CD2, 3, CD7 and 8 and show a loss of CD4 expression. . The molecular biology study confirms the diagnosis by showing a clonal rearrangement of the TCR gamma and betta genes.
Conclusion: The association of stromal tumours with other neoplasia must search for common carcinogen or genetic predisposition, multicenter studies involving a large number of cases are necessary to confirm or refute this hypothesis.

E-PS-07-007
The analysis of mortality at gallstone disease according to autopsy studies
T. Vervekina[1,2], B. Magrupov[2]
[1] Republican Research Center of Emergency Medicine, Uzbekistan, [2] Tashkent Institute of Postgraduate Medical Education, Uzbekistan

Background & Objectives: The problem of gallstone disease in the structure of the morbidity grows steadily. Surgical activity at this pathology surpassed the number of other abdominal interventions including appendectomy. Complicated forms of the disease and combined pathology increase the level of cholelithiasis in the structure of mortality.
Methods: We performed analysis of 2674 patients' case histories with various forms of cholecystolithiasis. Fatalities were recorded in 18 patients at the age of 41-60 years, 13 of them were 51-60 years old men. Analysis of lethal outcome was carried out according to the results of autopsy studies.
Results: We found that in 89% of cases an unfavorable outcome occurred at the combination of various forms of cholecystitis and choledocholithiasis. In the gallbladder were diagnosed: destructive forms of inflammation (11 cases), chronic cholecystitis (4), chronic recurrent cholecystitis (3). The third part of the lethal outcomes was in patients with a combined pathology, such as liver cirrhosis, myocardial infarction, peptic ulcer, and heart disease. The death cause in most cases was sepsis, as well as complications of combined diseases.
Conclusion: The analysis showed that deaths are more often recorded in 51-60 years old men with destructive forms of cholecystitis at a lesion of the gallbladder and choledoch. Combined pathology of the digestive organs and cardiovascular systems has a significant impact on the disease outcome.

E-PS-07-008
A rare case of signet-ring cell carcinoma of the gallbladder, presenting as Krukenberg tumours of the ovaries
M. Kilmpasani[1], I. Matzarakis[2], A. Baliaka[1], I. Dimitriadis[2], N. Pastelli[2], I. Karafoulidou[2], S. Despina[2], V. Penopoulos[2], S. Papaemmanouil[2]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, Thessaloniki "G. Papanikolaou", Greece, [2] 2nd

Surgery Department, General Hospital of Thessaloniki "G. Papanikolaou", Greece

Background & Objectives: Signet-ring cell carcinomas of the gallbladder are very rare and considered to have an aggressive behaviour. Krukenberg tumour of the ovary may be the first manifestation of a malignancy, and is associated with poor prognosis. We report the case of a 49-year-old woman, admitted with bilateral ovarian tumours, without any known gallbladder-related symptoms.
Methods: During the surgical oophorectomy, a simultaneous cholecystectomy was performed, due to suspected metastasis to cystic duct lymph nodes.
The surgical specimens were examined in FFPE sections with hematoxylin-eosin and immunohistochemical stains.
Results: Two white-tan lesions of the gallbladder mucosa were observed, each measuring 1.5cm. The microscopic examination revealed a signet-ring cell carcinoma, beginning from the overlying epithelium and infiltrating the gallbladder wall. Two cystic duct lymph nodes showed metastasis from the carcinoma.
Both ovaries demonstrated nodular, solid, white-tan tumours, measuring 10cm (right) and 2cm (left). The microscopic findings were similar to the aforementioned carcinoma in the gallbladder. Among others, the neoplastic cells stained positive for Ck7 and Ck19, and negative for Ck20, vimentin, CD15 and a-fetoprotein.
Consequently, the ovarian tumours were diagnosed as metastases of the carcinoma of the gallbladder.
Conclusion: It is a challenge to differentiate primary from metastatic carcinoma of the ovaries. Krukenberg tumours are ovarian tumours of metastatic origin, with a diffuse infiltration by signet-ring cells. A primary malignancy in the gallbladder is rarely encountered. Only few cases of primary signet-ring cell carcinoma of the gallbladder are described in the literature, and they are frequently associated with locally infiltrative behaviour and distant metastases.

E-PS-07-009

Immunohistochemical study of cell proliferation in hepatocellular carcinoma

R.A. Barna[1], M. Cornianu[2], D. Lazar[3], N. Basa[4], S. Taban[5,6], A. Dobrescu[7], F. Lazar[8,9]
[1] Department of Pathology, University of Medicine and Pharmacy „Victor Babes", Timisoara, Romania, [2] V. Babes University of Medicine and Pharmacy, Romania, [3] Internal Medicine Department IV, University of Medicine and Pharmacy „Victor Babes", Timisoara, Romania, [4] Internal Medicine Department I, University of Medicine and Pharmacy „Victor Babes", Timisoara, Romania, [5] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania, [6] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Pathology, Romania, [7] Surgery Department II, University of Medicine and Pharmacy „Victor Babes", Timisoara, Romania, [8] Surgery Department II, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [9] Surgery Department II, Emergency County Hospital Timişoara, Romania

Background & Objectives: The aim of this study was to evaluate the proliferative activity of neoplastic and non-neoplastic hepatocytes, to identify possible correlations between histopathological features of HCC and its proliferation rate and to establish the role of Ki-67 as a prognostic factor in patients with radical surgery of HCC.
Methods: Assessment of the proliferative activity was made using monoclonal Ki-67 antibody, clone MIB-1 ready-to-use. To appreciate the proliferation index of Ki-67 (PI Ki-67), it has been used the semi-automated method of counting the nuclei on digital images.
The study included 32 surgically removed liver carcinomas. In order to compare results, it was included a group of non-tumour lesions obtained by liver biopsy.
Results: Mean value of Ki-67 index was 0.4% ± 0.2% in normal liver, 3.52% ± 0.2% in non-tumour liver lesions and 13.4% ± 7.7% in HCC ($p<0.001$). Mean value was 5.2% in portal chronic hepatitis and 5.5% in active chronic hepatitis with cirrhotic evolution.
66.6% of HCC associated with HBV infection and 66.6% of HCC developed from a cirrhotic lesion had a high Ki-67 score. High proliferation rate was correlated with presence of intrahepatic metastasis ($p<0.001$) and with vascular invasion ($p<0.001$).
Conclusion: Differences between the proliferation rate of HCC and non-tumour liver lesions ($p<0.001$) show that the uncontrolled division of tumour cells can play an important role in the development of HCC.
Ki-67 expression as a prognostic factor can be used to select the right therapy for hepatocellular carcinoma and may be a future target for molecular therapy.

E-PS-07-010

Epstein Barr Virus-associated smooth muscle tumour: a case report

C. Fumagalli[1], E. Chenu[1], S. Novelli[1], J.C. Pernas[1], A. Mozos[1], J. Szafranska[1]
[1] Hospital de la Santa Creu i Sant Pau, Spain

Background & Objectives: Epstein Barr virus associated smooth muscle tumour (EBV-SMT) is an under-recognized entity that usually occurs in immunosuppressed patients. Herein, we present a case of EBV-SMT affecting a post-transplant female.
Methods: The patient, an 18-year-old female with a history of T-cell lymphoproliferative disorder, was treated with bone marrow transplant in 2012. In CT scan, a well-defined mass (44 mm) was found in the liver and, due to its hypervascular pattern, a tru-cut biopsy was performed. Histological examination showed a neoplasm consisting of spindle cells arranged in small fascicles with elongated cigar-like nuclei and an eosinophilic cytoplasm. No cytological atypia was found and the mitotic activity was low (Ki67<5%).
Results: Immunohistochemistry highlighted that tumoural cells expressed smooth muscle actin and caldesmon. In situ hybridization for Epstein-Barr virus (EBV) was strongly positive, while the EBV protein late membrane protein 1 (LMP1) was negative. Based on these findings, EBV-SMT was diagnosed. A conservative management was established and the patient was treated with Sirolimus. A control performed five months later showed persistence of active EBV infection and stability of the lesion. Nonetheless, due to collateral effects, immunosuppressive therapy was retrieved.
Conclusion: EBV-SMT has been described in patients infected with HIV, in the posttransplant setting, and in those with congenital immunodeficiency. In the present case it affected the liver of an immunosuppressed patient. Due to its rarity, it might inadvertently be misdiagnosed as a leiomyoma. There isn't an established treatment for this tumour, but a correct diagnosis would avoid overtreatment.

E-PS-07-011

Histological features and dynamics of colorectal metastasis in the liver

C. Fumagalli[1], E. Chenu[1], B. Martin[1], I. Gich[1], D. Paez[1], J.C. Pernas[1], V. Artigas[1], J. Szafranska[1]
[1] Hospital de la Santa Creu i Sant Pau, Spain

Background & Objectives: Colorectal cancer (CRC) is the third most prevalent cancer worldwide and liver is the most common site of CRC metastases (CRCLM).Hepatic resection of CRCLM remains the standard of treatment, sometimes associated with neoadjuvant chemotherapy (NC). Aim of the study was to analyse histological features within the metastases, in the tumour-liver interface (TLI) and in the non-tumoural liver parenchyma, in order to identify how the metastases modify the liver histology.

Methods: The clinical history and histologic parameters were revised of 131 CRCLM resected at our institution during the period 2010-2017. The study included 95males and 48females with a median age of 67yrs and a tumour median size of 2,9cm.Among them, 82(62,6%) received NC.The histological features studied were: mucinous component, vascular-perineural-biliar invasion, growth pattern, fibrous capsule, ductular proliferation and chronic inflammation with/without lymphoid follicles in TLI and presence of portal-centrilobular-lobular inflammation, hepatocyte ballooning-acidophilic bodies, fibrosis, colestasis and rosette formation in liver parenchyma.
Results: Statistical analysis was performed dividing the patients in group A (who received NC) and B (without NC).It was found that NC was associated with replacement growth pattern, absence of chronic inflammation and fibrous capsule in TLI ($p < 0.005$),while in group B surgical hepatitis and rosette formation ($p < 0.005$) in the no-tumoural liver parenchyma were observed. No differences in overall survival were found when comparing the growth pattern or the use of NC.
Conclusion: Both CRCLM and NC could induce liver changes.In this study, it was found replacement growth pattern, absence of chronic inflammation and fibrous capsule in TLI in pts who received NC, while more prominent surgical hepatitis was curiously found in pts who didn't receive NC. However, further research is required to understand de complex mechanisms taking place within the metastatic liver.

E-PS-07-012

The conclusive utility of cell-block procedure in diagnosing rare pancreatic neoplasms through EUS-FNA approach

O. Neagu[1], M. Dumbrava[2], B. Cotruta[2], I. Bancila[2], V. Herlea[2], C. Gheorghe[2], G. Becheanu[2,3]
[1] University Emergency Hospital Bucharest, Romania, [2] Fundeni Clinical Institute, Bucharest, Romania, [3] "Victor Babes" National Institute of Pathology, Bucharest, Romania

Background & Objectives: EUS-FNA has become the gold standard in preoperative pancreatic masses assessment. Nevertheless, rare pancreatic neoplasms display indefinite morphology on routine cytologic smears, even for experienced cytopathologists. Adding the cell-block procedure increases the diagnosis accuracy by enabling the use of ancillary tests.
Methods: We report two cases of isthmus and body pancreatic neoplasms detected during abdominal sonography in a 23-year-old and 66-year-old women, respectively. An EUS-FNA was performed and the cytologic material obtained was used for routine cytologic smears and one cell-block.
Results: The rapid-HE stained smears showed loose clusters and single cells with finely granular cytoplasm and hyperchromatic nuclei with fine chromatin, resembling neuroendocrine cells, with minimal to moderate atypia, insufficient for diagnosis. The cell-block cellular material revealed a solid pattern with thin vessels throughout, scattered rosette-like or intact papillary structures with fibrovascular components. The cells were displayed in a perivascular fashion. In one case, we also identified fragments of liver tissue and gastric mucosa with normal architecture. Positive immnunohistochemistry reactions for beta-catenin, CD56, androgen-receptor, vimentin and negative reactions for E-cadherin, AE1/AE3 and chromogranin confirmed the diagnosis of a solid pseudopapillary pancreatic neoplasm (SPN).
Conclusion: SPN is a rare entity, comprising less than 2.7% of all pancreatic tumours. It mainly affects young women and the common location is the tail of the pancreas. In the reported cases, presentation and cytology appearance weren't conclusive for this pathology. The aid of a cell-block procedure lead to the correct diagnosis, giving the possibility of immunohistochemistry tests and haematoxylin-eosin staining equivalent to histological slides.

E-PS-07-013

A rare case of primary inferior vena cava leiomyosarcoma mimicking hepatocellular carcinoma presentation

O. Neagu[1], M. Grasu[2], M. Dumbrava[2], R. Cerban[2], V. Herlea[2], G. Becheanu[2,3]
[1] University Emergency Hospital Bucharest, Romania, [2] Fundeni Clinical Institute Bucharest, Romania, [3] "Victor Babes" National Institute of Pathology, Bucharest, Romania

Background & Objectives: Primary leiomyosarcoma of the inferior vena cava (IVC) is a rare malignant tumour, with less than 400 cases reported so far. It has a slow progression and becomes symptomatic at an advanced stage, justifying its poor prognosis once detected. Clinical presentation depends on tumour location along the IVC, divided into three segments by Kulaylat.
Methods: We report a case of a 61-year-old male, diagnosed 6 months prior with an IVC thrombosis, who was admitted for a liver tumour evaluation. CT examination revealed a 65/50 mm tumour, involving the VI-VII segments, the IVC and the abutting right atrial wall. Another similar small lesions were also noted in the right lobe, highly suggesting a hepatocellular carcinoma.
Results: The liver biopsy showed a spindle cell proliferation with eosinophilic fibrillary cytoplasm and large pleomorphic nuclei with scattered atypical mitoses. Ancillary immunohistochemistry tests showed positive tumour cells reactions for smooth muscle markers (SMA, desmin, H-caldesmon) and negative reaction for CD117, DOG1 and CD34, advocating for a leiomyosarcoma. Thoroughly systemic investigation didn't find any other conceivable primary site for the liver tumour. Considering the aforementioned findings, the conclusive diagnosis was a leiomyosarcoma of the third segment of the IVC with extra- and intraluminal growth.
Conclusion: Although IVC leiomyosarcoma is more common among women and usually affects the first two segments, the presentation herein was distinctive. The mainstay treatment is complete surgical resection with a customized approach. Given the tumour extension in our reported case, a palliative chemotherapy scheme is currently administered, with no tumour progression so far.

E-PS-07-014

Solid and pseudopapillary neoplasm of the pancreas: pathological characteristics of 5 cases with Imaging correlation

A. Bdioui Thabet[1], A. Fourati[2], N. Mhammedi[3], S. Benkhlifa[3], M. Mokni[3]
[1] Georges Pompido Hospital Paris, France, [2] Sahloul Hospital of Sousse, Tunisia, [3] Farhat Hached Hospital of Sousse, Tunisia

Background & Objectives: Solid pseudopapillary neoplasm of the pancreas is a rare tumour often detected initially on imaging. Of uncertain histogenesis, it has a low-grade malignant potential with excellent post-surgical curative rates and rare metastasis. Pathological evaluation remains the gold standard in reaching a definitive diagnosis. On morphology alone, other primary pancreatic tumours pose a diagnostic challenge. Recent advances in immunohistochemical characterization have made the histopathologic diagnosis more specific and, shed light on the likely histogenesis of this rare tumour.
Results: 5 patients included 4 females and 1 male, with a median age of 48.5 years. CT scan was performed showed a pancreatic well limited mass measuring between 4 and 17 cm. A peripheral capsule was seen and some calcifications were detected and none of the patients was found to have hepatic and lymph nodes metastases. In one case an hemorrhagic content was noticed. Microscopic examination and the immunohistochemestry study confirmed the diagnosis of solid pseudopapillary neoplasm in all cases.

E-PS-07-015

Hepatocellular adenomas in a cirrhotic liver: report of an unusual case

C. Araújo[1], J. Cristóvão[2], A. Figueiredo[3], A. Carvalho[4]
[1] Centro Hospitalar Universitário Lisboa Central, Portugal, [2] NOVA Medical School, Lisboa, Portugal, [3] Serviço de Anatomia Patológica - Hospital Curry Cabral, Centro Hospitalar e Universitário de Lisboa Central, E.P.E., Portugal, [4] Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Portugal

Background & Objectives: Hepatocellular adenoma (HCA) is a liver tumour usually presenting in young females undergoing oral contraception. HCA occurs mostly against the background of healthy and disease free liver. Herein, we report a case of a 73-year-old male patient with multiple HCA-like lesions in the setting of a cirrhotic liver.
Methods: A 73-year-old male with a past history of arterial hypertension, dyslipidemia, type 2 *diabetes mellitus* and oesophageal varices was investigated for anemia and cholestasis and performed a computed tomography that revealed four nodules in the IV and V hepatic segments, the largest one with 4cm.
Results: The liver biopsy showed a cirrhotic liver, but the definite diagnosis of the hepatic nodules was not possible. The patient was submitted to a hepatic bissegmentectomy. Histology revealed nodules of hepatocellular proliferation with preserved reticulin framework, normal thickness of the trabeculae, unaccompanied arteries and absence of portal tracts. CD34 expression was patchy, glutamine synthetase confined to perivenular hepatocytes and no nuclear expression of beta-catenine , p53 or HSP70. The final diagnosis was compatible with hepatocellular adenoma-like nodules in a background of cirrhosis with features of steatohepatitis. A close follow-up of the patient was recommended.
Conclusion: Nodules that deviate in appearance, size and behavior from the conventional spectrum of large regenerative nodules, dysplastic nodules and hepatocellular carcinoma in cirrhotic livers are very rare and only a handful of cases of HCA in the background of cirrhosis have been described. Despite this, this possibility needs to be considered, in order to avoid the risk of misdiagnosing and subjecting patients to incorrect treatments. Extensive sampling and immunohistochemistry are fundamental to achieve a correct diagnosis.

E-PS-07-016

Foregut origin ciliated cyst of the gallbladder

H. Dincer[1], E. Yarıkkaya[1], N. Dursun[2]
[1] University of Health Sciences, Department of Pathology, Turkey, [2] University of Health Sciences, Istanbul Health Practice and Research Hospital, Department of Pathology, Turkey

Background & Objectives: Foregut origin ciliated cysts of the gallbladder are very rare, benign, cystic lesions. They are usually located above the diaphragm but they can also arise in relation to the liver, gallbladder and pancreas.
Methods: A 62-year-old women was referred to our hospital's surgery clinic with symptoms of chronic abdominal pain. On abdominal ultrasonography and computed tomography, multiple calculi was found. The gallbladder was resected through laparoscopic cholecystectomy.
Results: Grossly, the cystic lesion, measuring 0,6x0,6x0,3 cm, was located in the neck of the gallbladder. The cyst had no communication with the lumen. Microscopically the histopatology showed that the cyst was lined by pseudostratified ciliated columnar epithelium. These findings led us to diagnosis of ciliated foregut cyst.
Conclusion: Ciliated foregut cysts are rare anomalies due to aberrant embryological development. Characteristically, most of the cases are middle-aged females and unilocular lesions. Ultrasound is an efficient method of imaging for hepatobiliary masses. There are a few reports of squamous cell carcinoma arising in the ciliated foregut cyst, however there is no reports in the gallbladder. Foregut cysts requires surgical removal because of the frequent occurrence of squamous metaplasia and possibility of squamous cell carcinoma.

E-PS-07-017

Inflammatory myofibroblastic tumour of the pancreas - case report

R. Gajanin[1], V. Gajanin[1], I. Sladojević[1], M. Cuk[2]
[1] University of Banja Luka, Faculty of Medicine, Bosnia and Herzegovina, [2] University of East Sarajevo, Faculty of Medicine, Bosnia and Herzegovina

Background & Objectives: Inflammatory myofibroblastic tumours (IMT) are rare mesenchymal proliferative lesions, built of myofibroblasts and inflammatory cell infiltrate in the stroma, of unknown etiology and prognosis. They can be found in all anatomical regions, most commonly in the lungs, and very rarely in the pancreas.
Methods: We report a case of a 51 years old woman with IMT localized in the pancreatic head. Clinical manifestations included abdominal pain, nausea, yellowing of the skin and mucous membranes, and newly diagnosed diabetes. Using MRCP, we saw a dilatation of the intrahepatic and extrahepatic bile ducts and a soft tissue change with unclear boundaries, localized in the pancreatic head, 9 cm in diameter. The surgical treatment included pancreatectomy and splenectomy.
Results: Macroscopically, the tumour change was located in the pancreatic head, had a yellow-whitish color, sized 9.5 x 4.5cm. Morphologically, it was built by spindle cells with storiform and fascicular arrangements and mixed stromal inflammatory infiltrate. Immunohistochemical analysis showed positive staining for SMA, Calponin, Desmin, and ALK, and negative for Myogenin, S-100, H Caldesmon, and CD117. The diagnosis of IMT in the pancreas with peripancreatic extension in the connective tissue was established, with negative resection margins. The patient is 18 months without recurrence of the disease.
Conclusion: IMT is rare in the pancreas. So far, 32 cases were published in the English language literature. Presurgical differentiation from other neoplastic lesions is difficult and usually requires resection and histological analysis. Morphologically, it is necessary to differentiate IMT from fibrosarcoma, adenocarcinoma, lymphoma and chronic pancreatitis.

E-PS-07-018

Mixed adenocarcinoma and neuroendocrine carcinoma of the gallbladder: next generation sequencing suggests a monoclonal origin

F.M. Sta. Ines[1], A.L. Anceno[1], R.A. Salamat[1], N. Navarro Jr.[1], G.L. Pua[1], J.J. Andal[1], D. Ang[1]
[1] St. Luke's Medical Center, Philippines

Background & Objectives: Mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder is a rare tumour that is defined by the presence of a neuroendocrine carcinoma or neuroendocrine tumour, admixed with an adenocarcinoma, each component constituting at least 30% of the neoplasm. MANEC's histogenic classification remains unclear. We present a case of a 74 year-old Filipino woman who presented with right upper abdominal pain and fever. Whole abdominal CT scan demonstrated a distended multiseptate gallbladder and a 1.1 cm. non-enhancing faintly hyperdense ovoid focus (*suggestive of cholelithiasis versus sludgeball*) within the body. She subsequently underwent open cholecystectomy.
Methods: Histopathologic examination of the cholecystectomy specimen revealed two morphologic and immunophenotypic components: a mixed well-differentiated adenocarcinoma (30%) and a poorly differentiated large cell neuroendocrine carcinoma (70%). The adenocarcinoma and neuroendocrine tumour components were carefully microdissected separately, and next-generation analysis was performed on both components, using Illumina Trusight 15 Tumour (TST) kit and sequenced on Illumina MiSeq.

Results: The tumour showed a high mitotic rate of 83 mitosis per 10 high power fields and extensive necrosis. Immunohistochemical studies showed the neuroendocrine component to be reactive to synaptophysin and chromogranin. Mutational analysis of selected targeted regions of 15 cancer associated genes identified a TP53 missense mutation that leads to a stop codon (c.273G>A, p.Trp91Ter) in both components.
Conclusion: The molecular genetic similarities of the two morphologically different components of the tumour supports the hypothesis that MANEC arises from a common precursor stem cell capable of divergent phenotypic differentiation.

E-PS-07-019
Splenic vein leiomyosarcoma: a case report
F. Filipello[1], G. Fiorentini[2], C. Doglioni[3,1], M. Schiavo Lena[3]
[1] Vita-Salute San Raffaele University, Milan, Italy, [2] Pancreatic Surgery Division, IRCCS San Raffaele Hospital, Milan, Italy, [3] Pathology Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background & Objectives: Leiomyosarcoma (LMS) is an aggressive mesenchymal tumour originating from smooth muscle. Primary pancreatic LMS has been reported in the literature, nevertheless it is a rare entity. Venous origin for LMS is an extremely uncommon site of origin of LMS, mostly affecting the inferior vena cava and only five cases arising from the splenic vein have been described. We present a case of primary splenic vein LMS.
Methods: We report the case of a 51 year-old women who presented to San Raffaele Scientific Institute with non-specific abdominal pain. Abdominal computed tomography showed a 27x15 mm solid tumour in the body of the pancreas, in proximity to the splenic vein. Afterward, the patient underwent ecoendoscopy with cytological examination that indicated the mesenchymal nature of the lesion. Distal pancreatectomy and splenectomy were performed and subsequent histopathological examination.
Results: Morphological and immunohistochemical investigations showed a moderately differentiated LMS originating from the splenic vein, infiltrating the pancreatic parenchyma with three lymph nodes involved by contiguity.
Conclusion: Venous splenic LMS is a rare entity, nevertheless it can be a difficult differential diagnosis from other pancreatic mesenchymal tumours. In order to make a correct diagnosis, care must be taken for the anatomical localization of the tumour from early diagnostic steps. Careful macroscopic evaluation and exhaustive sampling are fundamental to identify the structure of origin, to be confirmed microscopically.

E-PS-07-020
Acinar cell cystadenoma of the pancreas
G. Setdikova[1], O. Paklina[1], A. Karpov[1], M. Tavobilov[1]
[1] Botkin Clinical Hospital, Russia

Background & Objectives: Acinar cell cystadenoma is a rare, benign cystic lesion of the pancreas that can affect almost any age group. First described in 2000 by Klöppel using the term acinar cell cystic transformation, the term acinar cell cystadenoma was first proposed by Albores-Saavedra, as the lesion was postulated to be the benign precursor of acinar cell cystadenocarcinoma.
Methods: We present a case of acinar cell cystadenoma in a 67-th men.
Results: A 67-year-old man was admitted to our hospital complaining of abdominal distension. He had no history of alcohol intake, acute pancreatitis, or trauma. Serum carbohydrate antigen (CA) 19.9 and carcinoembryonic antigen (CEA) was normal. Computed tomography (CT) showed a cystic mass with an irregularly thickened wall of up to 43 mm. No pancreatic duct dilatation or peripancreatic inammatory changes were identied. Enucleation was remarkable for a 40 mm pussy uid-lled, thin-walled, unilocular cyst. The cyst was lined by a single layer of cuboidal to columnar cells, with uniform, round nuclei with occasional small nucleoli and eosinophilic, granular cytoplasm, which formed small acinar structure with eosinophilic PAS-positive cytoplasmic granules. The cyst wall was collagenous with no evidence of ovarian-type stroma. Immunohistochemical stains showed the cyst-lining cells were trypsin and chymotrypsin, Muc6 positive. These findings confirmed the cytological diagnosis of an acinar cell cystadenoma.
Conclusion: We report an unusual case of a cystic lesion of the pancreas lined by acinar cells with mucinous metaplasia, consistent with the diagnosis of acinar cell cystadenoma. Acinar cell carcinoma is an uncommon malignant tumour accounting for 1% to 2% of all exocrine pancreatic neoplasms. This lesion can be added to the list of unilocular cystic neoplasms of the pancreas.

E-PS-07-021
Cystic neuroendocrine tumour of the pancreas: a misleading variant
D. Chiba[1], S. Chaieb[2], S. Mestiri[2], O. Belkacem[2], S. Yacoub[2], N. Abdessayed[2], B. Sriha[2], M. Mokni[2]
[1] Department of Pathology Farhat Hached Hospital, Tunisia, [2] Farhat Hached Hospital, Tunisia

Background & Objectives: Pancreatic neuroendocrine tumours (PanNETs) are rare neoplasms that comprise up to 5% of pancreatic malignancies. Cystic PanNETs are a distinctive subgroup with unique clinical and pathological features.
Because of their cystic nature, preoperative radiological diagnosis of this entity continues to be a challenge to differentiate them from others pancreatic lesions like cystic neoplasms.
The clinical and histopathologic characteristics of cystic PanNETs are poorly defined which motivated us to present this case report.
Methods: We present a 54-year-old man with no significant history in whom we found incidentally a tumour in the tail of the pancreas, by abdominal ultrasonography.
Computed tomography revealed a well-defined cystic lesion in the tail of pancreas measuring 45 mm of diameter.
A mucinous cystic lesion was suspected and considering the malignat potential of this tumour, the patient had a distal pancreatectomy without prior cytological diagnosis.
Results: Macroscopically, the surgical specimen was constituted of a distal pancreatectomy measuring 10 X 6cm, containing on cut section a multilocular cystic mass with a hemorrhagic content.
A definite diagnosis of neuroendocrine neoplasm was confirmed by microscopic and immunohistochemical findings using synaptophysin , chromogranin. Grading of the tumour was based on mitotic index and ki67, and the tumour was classified according to the ENETS2010/OMS 2017, as G1 well differentiated neuroendocrine tumour with cystic component.
Conclusion: Cystic PanNETs are a distinctive subgroup of PanNETs with unique clinical and pathologic features. Because of their cystic nature, these neoplasms often present a radiologic preoperative diagnostic dilemma.
Recently, endoscopic ultrasonography guided fine needle aspiration (EUS-FNA) was reported to be useful for preoperative definitive diagnosis. But until now; the definitive diagnosis remains only histological reinforced by immunohistochemistry.

E-PS-07-022
Intestinal immunophenotype in pancreatic cancer: true or fall?
G. Setdikova[1], O. Paklina[1]
[1] Botkin Clinical hospital, Russia

Background & Objectives: To study the immunophenotype ducts of the pancreas in embryogenesis and taking into account the data obtained to analyse the immunophenotype of pancreatic ductal adenocarcinoma.

Methods: We examined the expression of MUC1, 2,5AC, CK8, CK7, CK20, CDX2 by immunohistochemical analyses in pancreas ducts at different weeks of gestations (fron 6 to 21 weeks).
Results: At 3-7 weeks in pancreas the expression of PanCK, CK7, CK20, CDX2 and MUC1,2,5AC types was negative. We found only expression CK8 in foregut epithelium. At 13-14 weeks we found expression CK20 in goblet cells and epithelial cells of the foregut epithelium. At 20-21 weeks for the first time, we found the cytoplasmic expression with CK7 and MUC1 in the epithelium of the pancreatic ducts, which may indicate the onset of specialization. Expression of CK 20 was found not only in the goblet cells, but throughout the entire foregut epithelium.
Conclusion: Pancreatobiliary type of epithelium is more specialized. Substrate for the development of the pancreas is the foregut epithelium , which at the embryogenesis, differentiates into specialized organs and tissues; Based on this statement and comparing the available morphological data in PDA with intestinal immunophenotype, we found only incomplete intestinal metaplasia of the epithelium can be asserted, leading to further development of cancer, but not the appearance of true intestinal differentiation of the tumour.

E-PS-07-023
Comparison of the results of the calculation of the liver volume of cadavers on the basis of linear dimensions obtained with sonography and measurements ex vivo
I. Stepanyan[1], V. Izranov[2], S. Stepanyan[2], K. Abdujabborov[2], M. Shushval[2], V. Gordova[2]
[1] Baltic Federal University; Infectious Diseases Hospital of the Kaliningrad region, Russia, [2] Baltic Federal University, Russia

Background & Objectives: We set a goal to find out whether the three linear liver sizes used in formula J.T.Childs are sufficient to get an objective parameter of an organ volume before and after its dissection from the abdominal cavity.
Methods: Liver sonography was performed before an autopsy with measurements of the anteroposterior (AP) of the left and right lobes and oblique vertical size (OVS) of the right lobe. The left lobe was measured without view of the inferior vena cavae, the right lobe from the anterior axillary line (AAL) and the midclavicular line (MCL). The similar to sonography sizes of both lobes were measured by a ruler on the dissected liver. The linear dimensions obtained from sonography and dissection results were substituted into the J.T. Childs formula.
Results: After dissection the liver from the abdominal cavity, the average linear dimensions significantly change: AP size of the left lobe decreases 2.27 times, AP size of the right lobe decrease 1.9 times, OVS of the right lobe increases 1.15 times. Due to changes in linear dimensions, the volume is according to the formula J.T.Childs after liver dissection from cadavers, decreases 2.2-2.3 times ($p \leq 0.05$).
Conclusion: With a direct dependence of the volume of the liver on the above dimensions, they are not enough to obtain an objective parameter. It is required either to add additional linear dimensins to the formula or to introduce a non-linear correlation coefficient of these linear dimensions.

E-PS-07-024
The dependence of the results of the calculation of the volume of the liver according to the formula J.T.Childs on the choice of access points and depth of breathing
I. Stepanyan[1], V. Izranov[2], V. Gordova[2], M. Beleckaya[2], S. Stepanyan[2]
[1] Baltic Federal University; Infectious Diseases Hospital of the Kaliningrad Region, Russia, [2] Baltic Federal University, Russia

Background & Objectives: We noticed that the linear dimensions of the liver depend on the access points and the depth of breathing. Study objective is to determine the effect of these parameters in an ultrasound study on the volume of the liver, calculated according to the formula J.T. Childs.
Methods: The measurements of the left and right lobe carried out by two ultrasound diagnostics doctors on 26 healthy volunteers with quiet breathing and with a breath hold on a deep breath, for the left lobe with and without an inferior vena cava (IVC) in sight, for the right lobe from access via the anterior axillary line (AAL) and midclavicular line (MCL). The volume of the liver was calculated by the formula J.T.Childs: 343.71+ 0.84*(oblique vertical size (OVS)*anterior-posterior (AP) of the right lobe*anterior-posterior(AP) of the left lobe) / 1000.
Results: The maximum sizes of the volumes of the liver are obtained with quiet breathing without capture in the field of view of the IVC for left lobe, and at the level of AAL and MCL for the right liver lobe, the average values are comparable ($p \leq 0.05$).
Conclusion: To obtain objective resultes of possible calculations of the liver volume by different specialists, we recommended measuring the linear dimensions of the liver with quiet breathing, when measuring the left lobe without IVC in view, when measuring the right lobe of AAL of MCL.

E-PS-07-025
Hepatitis C: the importance of non-invasive diagnostic methods in the development of liver fibrosis
I. Stepanyan[1], V. Izranov[2], S. Stepanyan[2], I. Ashtarkhanova[2], V. Gordova[2], I. Ivanov[1], E. Konopleva[2]
[1] Baltic Federal University; Infectious Diseases Hospital of the Kaliningrad Region, Russia, [2] Baltic Federal University, Russia

Background & Objectives: Liver fibrosis is the inevitable outcome of hepatitis C and detecting it in the early stages makes it possible to adjust the therapy in such a way as to improve the quality and increase the life expectancy of the patient. It is important to understand how much the changes in elastometry and blood tests of patients are proportional to the stages of development of fibrosis.
Methods: The results of liver 2D SWE (shear wave) elastometry on the Aixplorer (France) and the results of blood tests (indices Aspartate aminotransferase to platelete ratio (APRI) and Fibrosis-4 (FIB-4)), were compared in 56 patients with hepatitis C.
Results: The results of the liver 2D SWE elastometry with the assessment of the stage of fibrosis according to the conventional Metavir scale showed that 25 patients had 0-1 fibrosis stage; 11 patients had stage 1-2; 7 patients had stage 2-3; and 13 patients had stage 3-4, respectively. At the same time, with fibrosis of the 0-1 and 1-2 stages, no changes in blood parametes (APRI and FIB-4) were observed.
Conclusion: Comparison of the results of 2D SWE elastometry with the results of laboratory blood tests show that elastometry reveals fibrosis with 0-1 stage, and methods APRI and FIB-4 starting from 2-3 stages. Therefore, 2D SWE elastometry is a more sensitive method for diagnosing fibrosis in its early stages than APRI and FIB-4 in hepatitis C.

E-PS-07-026
Detection of human polyomavirus 6 and 7 in the human cholangiocarcinoma tissues
F. Klufah[1], E. Chteinberg[2], G. Mobaraki[1], R.A. Alharbi[3], A.K. Kurz[4], V. Winnepenninckx[2], E. Speel[2], A. zur Hausen[2]
[1] Department of Pathology, Maastricht University Medical Center, The Netherlands, [2] Maastricht University Medical Centre+, The Netherlands, [3] Faculty of Applied Medical Sciences, Albaha University, Saudi Arabia, [4] University Hospital RWTH Aachen, Germany

Background & Objectives: Cholangiocarcinoma (CCA) is a rare biliary duct neoplasm with poor prognosis. Recently, the presence of HPyV6 has

been reported in the bile hepatobiliary diseases including the bile of CCA patients. Here, we investigated the prevalence of HPyV 6 and 7 in CCA by using diverse molecular techniques to assess their possible role in neoplastic hepatobiliary diseases.
Methods: We tested 61 FFPE tissues of 21 CCA patients. PCR screening for HPyVs were conducted using a pair of degenerated HPyV primers. Specific-PCRs for HPyV6 and 7 and MCPyV were performed. All PCR products were sequenced. FISH, RNA(ISH) and immunohistochemistry (IHC) were used to assess the presence of HPyV6 and 7 on the DNA, transcriptional and transitional level.
Results: Degenerated primers revealed the presence of HPyV7 in 4 out of 21 CCAs (19%) and HPyV6 in 2 CCAs (9.5%). The presence of HPyV7 and 6 DNA was confirmed by specific FISH. RNA-ISH confirmed the presence HPyV6 and 7 on the single cell level. IHC using monoclonal antibodies (HPyV7 2T10 and HPyV6 1T1, both kindly supplied by Dr. C. Buck, NCI, Bethesda, USA) revealed the specific nuclear expression of viral proteins within these tissues.
Conclusion: HPyV6 and 7 are hepatotropic and can be specifically found in peritumoural non-neoplastic hepatocytes and to a lesser extent in neoplastic CCA cells. In our patient cohort, HPyV7 was found to be more prevalent than HPyV6. Based on our results, HPyV6 and 7 are yet unlikely to play an important role in the etiopathogenesis of CCA.

E-PS-07-027
Solid-pseudopapillary neoplasm of the pancreas: a (not so) rare diagnosis

C. Alves-Vale[1], R. Brodbeck Ilgenfritz[1], P. Borralho[1]
[1] CUF Descobertas Hospital, Department of Pathology, Lisbon, Portugal

Background & Objectives: Solid-pseudopapillary neoplasm (SPN) is an extremely rare entity, corresponding to 0.9-2.7% of all exocrine pancreatic tumours, mostly affecting young women. We aimed to review the clinical and histopathological features of the SPNs diagnosed in our department.
Methods: This retrospective analysis collected all cases of SPN diagnosed between January 2009 and March 2019. Clinicopathological data was analysed.
Results: The diagnosis of SPN was made in four patients: one after fine-needle aspiration and three after surgery, corresponding to 5.1% (3/59) of all surgically resected pancreatic neoplasms in our institution. The group includes one male and three female patients, with a mean age of 36.5 years (SD±14.7). The three patients undergoing surgery in our hospital presented with a single mass located in the pancreatic tail, with a mean size of 105.0 mm (SD±20.0). The lesion was associated with nausea in one patient and it was incidentally found in imaging studies in the remaining two cases. Gross examination revealed an encapsulated lesion, with both solid and/or cystic components. Microscopic analysis showed solid areas and pseudopapillae covered by epithelial cells positive for beta-catenin, CD56, CD10 and vimentin. Complete excision of the lesion was achieved in all cases. No evidence of relapse has been detected (follow-up period: 3 months-6 years).
Conclusion: A correct morphological analysis supported by ancillary studies allows the diagnosis of SPN. Our series adds to the list of this singular entity while reminding us of its possibility in male patients.

E-PS-07-028
Mature cystic teratoma of the liver: a case report

M. Varela dos Santos[1], A. Figueiredo[2]
[1] Serviço de Anatomia Patológica - Centro Hospitalar e Universitário de Lisboa Central, E.P.E., Portugal, [2] Serviço de Anatomia Patológica - Hospital Curry Cabral, Centro Hospitalar e Universitário de Lisboa Central, E.P.E., Portugal

Background & Objectives: Teratomas are germ cells tumours, which must contain more than one of the three germ layers: ectoderm, endoderm and mesoderm. They are usually located on the ovaries and testis. Liver teratomas are extremely rare and comprise less than 1% of all teratomas. Pathological diagnosis is crucial to confirm radiological suspicion along with the assessment of immature component, which has implications in further management of these patients.
Methods: The present study is a case report of a liver teratoma in an adult, diagnosed and treated in 2019.
A 27-year-old woman, with no relevant prior medical history, was admitted in our Medical Centre in March 2019 after the incidental discovery of a hepatic lesion on a CT-scan: there were distinctive imaging characteristics suggesting liver teratoma, and based on this information the patient was electively submitted to a mesohepatectomy for the centrally located hepatic lesion.
Results: Gross pathological examination showed a cystic tumour with 21cm: cut section revealed multiple cystic areas with sebaceous material, hair and calcifications. Microscopic examination showed a mixture of various tissues, including skin and appendages, bone, adipose tissue and respiratory epithelium: the final diagnosis was Mature Liver Teratoma, fully resected. The patient had a gradual post-operative recovery phase without major complications and was discharged after 9 days of hospitalisation. 2- and 4-weeks follow-up confirmed absence of symptoms and a full recovery.
Conclusion: Liver Teratomas are extremely rare, even more in adults, with only a small number of cases described in the literature. Albeit they harbour some extremely distinctive imagiological features, pathological examination is vital to the correct diagnosis and characterization of teratomas. Complete resection of the lesion remains, to this day, the best treatment option.

E-PS-07-029
Unique cystic neoplasm of liver in child-undifferentiated embryonal sarcoma

Z. Yusifli[1], M. Kazimi[1], K. Beydullayev[1]
[1] Central Customs Hospital, Azerbaijan

Background & Objectives: Undifferentiated embryonal sarcoma of the liver (UESL) is a unique and rare malignant mesenchymal neoplasm. We report a case of UESL observed in a 14 year old boy. The patient underwent liver resection for cyst hydatid. The intraoperative frozen section technique was used during operation and was reported as fibrinous tissue, no malignancy. Grossly 14 x 11cm encapsulated mass were seen in liver parenchyma. The cut surface was soft with necrosis and haemorrhage areas.
Methods: Specimens were fixed in 10% formalin solution and embedded in paraffin. Sections were stained with Haematoxylin eosin and special immunohistochemical stains. Staining was considered positive when >10% of cells showed positive staining with appropriate pattern.
Results: Microscopic examination showed tumour with hypocellular and myxoid stroma. In some areas tumour was highly cellular with marked pleomorphism. Bizarre hyperchromatic giant cells, cytoplasmic hyaline eosinophilic globules and entrapped benign bile ducts were present. Immunohistochemical staining showed positivity for CD56, desmin, SMA, CD68 and were negative for pan-cytokeratin, Heppar-1. The MIB-1 proliferation index was 20-25% in neoplastic cells. Based on these findings, a diagnosis of UESL was confirmed.
Conclusion: UESL is a rare and aggressive mesenchymal neoplasm which occurs almost exclusively in children and adolescents. Intraoperative frozen sections technique is not usefull, because cysts, necrosis and haemorrage areas may occupy up to 80-90% of the cut surface. Early correct diagnosis and complete resection are necessary for a favorable outcome. This entity should keep in mind in all cystic liver masses in children.

E-PS-07-030
Cystic lymphangioma in pancreas

M. Chantziara[1], D. Mpouklas[1], G. Theodoropoulou[1], S. Roditis[2], X. Grammatoglou[1], A. Kostopoulou[1], I. Margaris[3], T. Choreftaki[1]

[1] Department of Surgical Pathology/General Hospital of Athens, "G.Gennimatas", Greece, [2] 3rd Department of Surgery/General Hospital of Athens "G. Gennimatas", Greece, [3] 2nd Department of Surgery/General Hospital of Athens "G. Gennimatas", Greece

Background & Objectives: We present the case of a 50-year-old male patient with cystic lymphangioma in pancreas.
Methods: The patient presented to the surgery department complaining of atypical abdominal pain the last six months. An abdominal computerized tomography (CT) scan was performed and a cystic neoplasm with a maximum diameter of 18.6 cm was seen at the pancreatic body and tail. The mass had not invaded any adjacent organs. The lesion was aspirated using the EUS-FNA needle. Cytology felt to be consistent with the diagnosis of pancreatic serous cystadenoma. The patient underwent peripheral pancreatectomy and spleenectomy.
Results: On gross sectioning, the cystic neoplasm had a honeycomb appearance with single space filled with haemorrhagic yellowish fluid. Microscopic examination revealed cystic lesions of variable size, separated by fibroconnective septa, containing irregular smooth muscle fascicles, adipocytes and mature lymphocytes. These cystic spaces were lined by flattened and slightly elevated endothelial cells. No cell atypia was found. Immunohistochemistry (IHC) labeling for endothelial markers, factor VIII-R antigen and CD 31 was positive while CD 34 was focally weakly positive. Furthermore, immunohistochemistry for Inhibin-a, EMA, CK19, CKAE1/AE3, MUC-1 was negative. So, the diagnosis of pancreatic lymphangioma was made.
Conclusion: Cystic lymphangioma of the pancreas is extremely rare, accounting for less than 1% of pancreatic tumours but should be taken into consideration as a differential diagnosis of a pancreatic cystic lesion.

E-PS-07-031
Adenosquamous carcinoma of the ampulla of Vater: report of two cases

M.E. Kara[1], E. Uzun[1]
[1] Gaziantep University Medical Faculty Hospital, Department of Pathology, Turkey

Background & Objectives: Primary adenosquamous carcinoma of the ampulla of Vater is rare. There are few reports about its clinicopathological features. Here, we report two adenosquamous carcinomas of the ampulla of Vater.
Methods: CASE 1
A 62 years-old male presented with abdominal pain and jaundice. The laboratory examination revealed alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), amylase and total bilirubin levels elevated. CA 19-9 level was 242 U/mL. Computed tomography (CT) revealed a solid mass in the periampullary region. Pancreatoduodenectomy was performed to the patient. Grossly infiltrative, solid mass, measuring 4.2x3x3 cm, was detected in the ampulla of Vater. Histopathologically; the tumour was comprised both of adenocarcinoma and squamous cell carcinoma elements. The retroperitoneal margin was involved, pancreas invasion and lymph node metastasis were present. The patient has received chemoradiotherapy and had no tumour recurrence or metastasis until 48 months after surgery.
Results: CASE 2
A 49 years-old female patient presented with abdominal pain and jaundice. The laboratory examination revealed ALT, AST, LDH, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), amylase and total bilirubin levels elevated. CA 19-9 level was 560 U/mL. Computed tomography revealed a solid mass in the periampullary region. Whipple procedure was performed. Grossly; solid mass, measuring 2.5x1.5 cm, was observed in the ampulla of Vater. Duodenum wall was involved by tumour. Microscopic examination revealed that the tumour comprised both adenocarcinoma and squamous cell carcinoma components. The patient has received chemoradiotherapy and had no tumour recurrence or metastasis until 25 months after surgery.
Conclusion: Adenosquamous carcinoma is defined as a tumour which has both adenocarcinoma and squamous cell carcinoma components. Its histogenesis is not clear. While it has been reported in the oesophagus, stomach, small intestine and colorectum, rare in the ampulla of Vater.

E-PS-07-032
Ductal adenocarcinoma of the pancreas with extensive hyaline globules: a case report

M.E. Kara[1], E. Uzun[1]
[1] Gaziantep University Medical Faculty Hospital, Department of Pathology, Turkey

Background & Objectives: Ductal adenocarcinoma is the most common type of pancreatic cancer (constitutes %90 of all pancreas cancers) and it is a type of exocrine pancreatic cancer. In the world; ductal adenocarcinoma of the pancreas is the fourth most common cause of death from cancer in both men and women. Early recognition of these precursor lesions is important to improve the treatment and prognosis of PDAC.
Methods: Case report: A 58 years old female patient was presented with weight loss and fever. Laboratory examination revealed that alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and amylase levels were elevated. CA19-9 level was 896 U/mL. Contrast-enhanced computed tomography (CT) revealed a solid mass in the head of the pancreas, measuring 25x20 mm. Pancreatoduodenectomy was performed. Grossly; the infiltrative, solid tumour was detected in the head of the pancreas which was infiltrating duodenal wall.
Results: Histologically; tumour had ductal adenocarcinoma morphology with extensive hyaline globules. Immunohistochemically; the tumour was positive with CK7, CK19, MUC1, MUC5, and Maspin. Lymph node metastasis, lymphovascular and perineural invasion were present. Margins were uninvolved. After surgery patient is receiving chemoradiotherapy for 2 months.
Conclusion: Hyaline globules in the pancreas are usually seen in solid pseudopapillary carcinomas. While Neuroendocrine carcinomas can also have hyaline globules focally, it is uncommon in ductal adenocarcinomas. Because of its rarity; there is no data about the meaning of hyaline globules in pancreatic ductal adenocarcinomas.

E-PS-07-033
Unusual localisations of hydatid cyst and its clinicopathological features

M.E. Kara[1], E. Uzun[1]
[1] Gaziantep University Medical Faculty Hospital, Department of Pathology, Turkey

Background & Objectives: Hydatid cyst is a zoonotic parasitic disease caused by Echinococcus granulosus larva. It is endemic in Turkey and is a big health problem in farming areas. The hydatic cyst is mostly seen in the liver and lung, it can rarely occur in atypical localizations.
Methods: In this study 550 hydatid cysts which were diagnosed in Gaziantep University Medical Faculty Hospital between 2012-2019, were evaluated based on criteria such as sex, age, cyst localization, liver or lung involvement for atypical localized cysts, Echinococcus granulosus indirect hemagglutination antigen (IHA) test status.
Results: 232 of (%42.2) 550 cyst hydatids were localized in lung, while 231 (%42) were in liver. 87 of 550 cyst hydatids were localized outside of liver and lung. 16 of these cysts were in the kidney, 13 were intraabdominal, 13 were in the spleen, 9 were in the heart, 7 were in the brain, 2 were in the ovary, 1 was in the pancreas, 1 was in diapraghm, 1 was in the gallbladder and 23 were in the musculoskeletal system. 24 of (%27,5) 87 unusually localized cyst hydatids showed lung or liver

involvement. Right lower lobe and left upper lobe were most involved lobes by cyst hydatid at 39% and 25%, respectively.
Conclusion: Although its typical localizations are liver and lung, hydatid cyst can be seen in unexpected organs/tissues. It should be evaluated in differential diagnosis because of its tumour mimicry in imaging studies.

E-PS-07-034
Pancreatic mixed neuroendocrine- nonneuroendocrine neoplasm: a case report
S. Batur[1], î Kutlu[1], K. Ozcan[1], G. Ozcan[1], N. Kepil[1], T. Ozturk[1]
[1] Istanbul University Cerrahpasa-Cerrahpasa Medical Faculty Department of Pathology, Turkey

Background & Objectives: The WHO classification of the tumours of endocrine organs, published 2017, has introduced significant changes in the classification of pancreatic neuroendocrine tumours. The previous term mixed adeno-neuroendocrine carcinoma (MANEC) is substituted by the term mixed neuroendocrine-non neuroendocrine neoplasm (MiNEN). MiNEN are neoplasms with two distinct neuroendocrine and non-neuroendocrine cell populations. Pancreatic MiNEN represent 0.5% of all pancreatic adenocarcinomas and 5% of all pancreatic NEN.
Methods: A 63-year-old man presented with jaundice and was referred to our hospital for further examination. Abdominal contrast-enhanced computed tomography revealed a mass of 4,3 cm in size in the pancreas head with portal vein narrowing. Pancreatoduodenectomy and regional lymph node dissection were performed. Macroscopically, the ill defined infiltrative tumour was identified at the head of the pancreas. The tumour was 7x3,8x2,5cm in diameter.
Results: Histological examination revealed that the tumour consisted of two cell populations.: well differentiated ductal adenocarcinoma (%60), and neuroendocrine tumour cells arranged in a nest, with round nuclei, abundant cytoplasm, and coarse chromatin. Immunohistochemically, the adenocarcinoma cells were positive for MUC1 and MUC5AC, while the neuroendocrine tumour cells were positive for chromograninA, synaptophysin and CD56. Based on the findings, a diagnosis of MiNEN of the pancreas was made. Metastasis of the two components of the tumour was observed in the lymph nodes.
Conclusion: We reported an extremely rare case of a MiNEN derived from the pancreas. The clinical features and effective treatment of such tumours have not been well-described due to their rarity. Therefore, more reports of cases of pancreatic MiNEN are necessary for a complete analysis.

E-PS-07-035
Incidental IgG4-related autoimmune pancreatitis in a middle-aged patient with suspected pancreatic neoplasia - a case report of an uncommon entity
N.J. Lamas[1], M. Oliveira[1], L. Ferreira[1], C. Fleming[1], R. Amorim[2], B. Fernandes[2], J.R. Brandão[2], F.E. Costa[1], J.R. Vizcaíno[1]
[1] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Porto, Portugal, [2] Centro Hospitalar do Porto, Portugal

Background & Objectives: IgG4-related disease (IgG4-RD) is a fibroinflammatory pathology with either synchronous or metachronous multi-organ involvement. Patients develop focal or diffuse organ enlargement with mass-forming or nodular lesions containing abundant infiltration by IgG4-positive plasmocytes and fibrosis. In pancreas, these lesions frequently mimic neoplasia on imaging studies.
Methods: We report the case of a 66-year-old male with a computed tomography scan showing dilated intra-hepatic biliary tree and common bile duct thickening in a 30mm extension in its final portion. A pancreatic head neoplasia was suspected, and the patient underwent cephalic duodenopancreatectomy.
Results: A surgical specimen comprising a 7,5x5,5x2,5cm pancreatic head, a 7cm stomach piece and an 11cm duodenal segment was received. Upon section, centered on the pancreatic duct, there was a firm and whitish area, with ill-defined limits, measuring 6x4x4cm. The histological analysis showed a pancreatic parenchyma extensively involved by an intense interlobular fibro-inflammatory process, containing an abundant inflammatory infiltrate rich in plasmocytes, lymphocytes and eosinophils. This process extended to the peri-pancreatic adipose tissue and was close to the mesenteric vein bed. Multiple lesions of obliterative venulitis and phlebitis (highlighted using the Van Gieson elastin staining) were present. The immunohistochemistry study confirmed the presence of numerous CD38+/CD138+/IgG+ plasmocytes and more than 75% were IgG4-positive plasmocytes (beyond 100 IgG4-positive plasmocytes per high-power field). A diagnosis of IgG4-related type 1 autoimmune pancreatitis was made. The ensuing immunological study revealed serum IgG4 levels (1240 mg/dL) nearly 14 times above normal.
Conclusion: This case reports an incidental presentation of a pathology less frequent than pancreatic cancer, but which can mimic it on imaging studies. The IgG4-related autoimmune pancreatitis is treated with corticosteroids for at least 3 months, or rituximab in patients with steroid intolerance. A better correlation between serum IgG4 levels, imaging features and biopsy findings could help to avoid pointless surgical approaches and complications.

E-PS-07-036
Acinar cell cystadenoma of the pancreas: report of a case and a comprehensive review of the literature
C. Vestrup Rift[1], J. Preuss Hasselby[1], C. Palnæs Hansen[2], B. Federspiel[1]
[1] Department of Pathology Copenhagen University Hospital Rigshospitalet, Denmark, [2] Department of Surgery Copenhagen University Hospital Rigshospitalet, Denmark

Background & Objectives: Acinar cell cystadenoma (ACC) is a rare cystic lesion of the pancreas. We hereby present a case of ACC and a review of the literature to characterise the patient population.
Methods: A systematic review was performed using PubMed and the keywords “acinar cell cystadenoma” and “acinar cystadenoma”, yielding a total of 24 publications.
Results: A total of 75 cases including our case report has previously been described in the literature. The patients are primarily female with presenting symptoms of abdominal pain. The cysts are located in the head of the pancreas, and are often multilocular on cross section with a mean size of 53,2 mm. Microscopically the cysts are lined by a PAS positive acinar epithelium, often with abortive acinar formations. The cells are immunohistochemically positive in stains for trypsin, chymotrypsin and CK7. The Ki67-index is reported low, 1-2%. No malignant transformation has been reported, and the mean follow up time is 37,4 months.
Conclusion: ACC is a rare cystic lesion with no malignant potential, primarily affecting women. The indication for surgical intervention should be based on the symptoms of the patients, as no risk of malignancy has been reported.

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E-PS-07-037
Acinar cell carcinomas of the pancreas: report of 4 cases
E. Ben Hadj Khalifa[1], A. Bdioui[1], z. Nfikha[1], A. Baccouche[1], T. Zahmoul[2], B. Sriha[1], M. Mokni[1]
[1] Cytology and Pathology Department CHU Farhat Hached, Sousse-Tunisia, [2] Cancer Registry of the Tunisian Center, Tunisia

Background & Objectives: Acinar cell carcinoma is a rare malignant tumour of the pancreas, accounting for only 1 to 2% of pancreatic tumours. The diagnosis is based on the pathological examination and immunohistochemistry study. The main differential diagnosis is the

neuroendocrine tumours. The treatment is based on surgical resection and chemotherapy. The prognosis is reserved and the average survival does not exceed 18 months.The purpose of this work is to report, from 4 clinical cases and a review of the literature, the clinico-pathological, therapeutic and progressive features of pancreatic acinar cell carcinoma.
Methods: Our study was retrospective, descriptive, dealing with 4 cases of acinar cell carcinoma, collected in the laboratory of pathological anatomy and cytology of Sousse, during a period of 10 years.
Results: The mean age of the patients was 60 years, with extremes of 50 to 65 years, the sex ratio was 1. The most common clinical sign was abdominal pain. Morphological examinations revealed a pancreatic tumour, which was cephalic in 2 cases and caudal in 2 cases; the size varied from 3 to 15 cm with a solid-cystic aspect, well circumscribed, with presence of foci of necrosis, in the most voluminous tumours. On histological examination, the tumour cells were cubo-cylindrical, with strongly nucleated monomorphic nuclei, organized into small glands and spans. The mitotic activity was variable and the stroma was fibrous. Foci of necrosis were observed. The IHC study showed diffuse expression of trypsin and pancytokeratin (CK). Anti-CK7, CK20, CD10 and C-KIT antibodies were negative. The treatment was surgical corresponding to a spleno-pancreatectomy in one case, and a double diversion with cholecystectomy in another. The other two patients had palliative treatment. The decline ranged from 3 months to 7 years. The evolution was marked by the appearance of hepatic metastases in 2 patients, one with an adrenal metastasis.
Conclusion: Pancreatic acinar cell carcinoma is a rare tumour, diagnosed at a late stage, given its clinical latency. Due to the rarity of this neoplasm, its therapeutic approach is still not codified. Surgical treatment with carcinologic resection seems to be the standard treatment.

E-PS-07-038
Rare pancreatic tumours: about four cases
B. Laabidi[1,2], R. Hedhli[3], R. Yaich[1,2], N. Mansouri[4], F. Gargouri[4], A. Saidi[4], A. Bouziani[4], I. Msakni[4]
[1] Tunis El Manar University, Medicine School of Tunis, Tunisia,
[2] Military Hospital of Tunis, Department of Pathology, Tunisia, [3] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia, [4] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia

Background & Objectives: The pancreas harbors a wide array of diseases. It involves many uncommon non-neoplastic and neoplastic conditions. As for the rare pancreatic tumours, they can vary from solid to cystic features, ranging from benign to low-grade malignant ones.We report here four cases of three rare histological types of tumours that occur in the pancreas.
Methods: The first case is of a 45-year-old female who presented with abdominal pain. The second case concerned a 25-year-old female who was diagnosed with a painful cystic mass of the pancreatic tail. The third case is of a 41-year-old man who presented with a solid epigastric mass. The fourth case reported a 69-year-old male who was diagnosed with a pancreatic tail tumour.
Results: In the first and second case, histopathological examination and immunohistochemistry on biopsy led to the diagnosis of solid pseudopapillary pancreatic tumour. Both patients underwent respectively pancreatoduodonectomy and distal pancreatectomy. In the third case, the diagnosis of Solitary fibrous tumour was concluded on histological and immunohistochemical findings on biopsy. The patient was treated surgically. The operative follow-up was marked by a diffuse hemorrhagic syndrome leading to the patient's death on the 3rd post-operative day. In the last case, microscopic features on lumpectomy confirmed the diagnosis of pancreatic lymphangioma.
Conclusion: The pancreas may be involved with a large variety of unfrequent solid or cystic neoplasms. Therefore, operative exploration is the treatment of choice of these rare lesions to provide the correct diagnosis based on histological examination and initiate adequate surgical therapy.

E-PS-07-039
Latent pancreatic metastasis, 13 years after renal cell carcinoma - a case report
M. Danciu[1], C.E. Andriescu[2]
[1] Grigore T. Popa UMF Iasi, Romania, [2] Sf. Spiridon Emergency County Hospital Iasi, Romania

Background & Objectives: Pancreatic metastasis represent less than 4% of all pancreatic tumours, about 1-4% originating from renal cell carcinomas (RCC). We present the case of a solitary pancreatic metastasis occurring 13 years after nephrectomy, in a 69-year-old female patient.
Methods: The surgical resection specimen was submitted for intraoperative consultation (frozen sections). HE staining and immunohistochemical tests were performed after routine processing of the whole sample.
Results: Gross examination revealed a well circumscribed yellow 2.2 cm nodule, in the pancreatic isthmus. On frozen section examination, the tumoural nodule consisted of isles and trabeculae of large round cells with central hyperchromatic nuclei surrounded by finely vacuolar cytoplasm. Lacking the relevant clinical information regarding patient history, a diagnosis of malignancy was provided. The histological examination of the paraffin embedded tissue yielded new morphological details of the tumour population: polygonal cells with clear cytoplasm and moderate pleomorphism, inconspicuous mitotic activity, sparse vascular stroma, peripheral fibrosis. The suspicion of pancreatic metastasis of RCC was advanced based on tumour morphology and patient's history of nephrectomy (provided upon request). Immunohistochemical tests (positive for RCC, CK7, CD10; negative for CK20) confirmed the diagnosis.
Conclusion: In absence of the oncological history of the patient, a solitary pancreatic nodule may raise difficulties on frozen section examination in differentiating a primary pancreatic tumour from a metastasis. As about 70% of pancreatic metastasis originates from RCC, one should always consider this scenario, even if the RCC was resected more than one decade ago, as in our patient.

E-PS-07-040
A rare case of pancreatic carcinosarcoma with unique histological pattern
I.A. Spiridon[1], S. Lunca[1,2], D. Ferariu[3]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] Second Clinic of Surgery, Regional Institute of Oncology, Iasi, Romania, [3] Department of Pathology, Regional Institute of Oncology, Iasi, Romania

Background & Objectives: Carcinosarcoma is a rare biphasic tumour with epithelial and mesenchymal features, most commonly arising in the uterus. The pancreatic location of this neoplasm is an extremely rare finding, with few cases recorded in literature. We report the occurrence of a pancreatic carcinosarcoma in a 63-year-old male patient.
Methods: Multiple samples from the complex surgical resection specimen were routinely processed. HE staining and immunohistochemical tests were performed.
Results: On gross evaluation, the resection specimen revealed a tumoural mass apparently originating in the pancreas and engulfing several other organs (duodenum, colon, left kidney, spleen). The histological examination identified two distinct areas, a tumoural population of epithelial origin, forming microlobular to trabecular aggregates, with abundant eosinophilic cytoplasm and marked nuclear pleomorphism, in collision with a highly cellular proliferation of spindled cells, with sarcomatous morphology and notable pleomorphism, often with bizarre, multinucleated cells. Mitotic activity was increased in both of the tumoural populations, with an associated Ki-67 index of over 90%. Immunohistochemistry confirmed the epithelial component as neuroendocrine carcinoma (positive CKAE1/AE3, Chromogranin, Synaptophysin), while the spindled area was classified as undifferentiated pleomorphic sarcoma, with negativity

for CKAE1/AE3, EMA, CK7, CD117, CD34, SMA, Desmin and positivity for Vimentin.
Conclusion: This is, to our knowledge, the first reported case of a pancreatic carcinosarcoma associating a malignant neuroendocrine component with an undifferentiated pleomorphic sarcoma component. While with recent studies argue for the monoclonal origin of this tumour, its prognosis remains dismal, with otherwise limited consensus regarding surgical management and postoperative treatment.

E-PS-07-041
Glycogenic hepatopathy - an underrecognised clinicopathological entity
A. Baltan[1], I. Simionov[1], A. Constantinescu[1], G. Becheanu[1]
[1] Fundeni Clinical Institute, Romania

Background & Objectives: We present the case of a 21-year-old male with type 1 diabetes mellitus, who complained of weight loss and fatigue, having elevated transaminase, gamma glutamyl transferase and glucose blood levels. Abdominal ultrasound showed hepatomegaly and diffuse liver hyperecogenicity, which was considered to represent mild steatosis. Autoimmune hepatitis was suspected and serologic tests showed slightly increased anti-nuclear antibodies levels and absence of a viral liver infection.
Methods: The sampled liver tissue was immediately immersed and fixed in 10% neutral buffered formalin solution, 3 μm thick sections were obtained and H&E, Perls and van Gieson stains were performed.
Results: The liver biopsy had a total length of 10 mm. The lobular architecture was preserved and the portal spaces were unremarkable. The hepatocytes were diffusely enlarged, with abundant clear cytoplasm and visible cytoplasmic margins. Rare steatotic macrovesicles and relatively frequent megamitochondria were present. The hepatocyte nuclei varied slightly in size and some of them were glycogenated. No inflammation was noted, except for a few intralobular neutrophils, and fibrosis was not identified. The histopathological diagnosis was glycogenic hepatopathy. The pacient received a adequate insulin regimen and is currently on follow-up, with clinical improvement.
Conclusion: Glycogenic hepatopathy is a rarely reported entity, with an unspecific clinical pattern. It should be suspected in diabetic patients, particularly with type 1 diabetes mellitus, and liver abnormalities. Liver biopsy exammination is needed for a definitive diagnosis.

E-PS-07-042
Alpha-smooth muscle actin and vimentin expression in primary liver carcinomas may relate with epithelial-mesenchymal transition carcinogenesis
L. Carvalho[1], A.F. Ladeirinha[1,2], A. Alarcão[1,2,3], L. Neves[1], R. Santos[4], J. Espírito Santo[5]
[1] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, [2] CIMAGO - Research Center for Environment, Genetics and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [3] Centre of Pulmonology, Faculty of Medicine of the University of Coimbra, Portugal, [4] Internal Medicine Department A, Coimbra Hospital and Universitary Centre, Portugal, [5] Adult and Paediatric Liver Transplantation Unit, Coimbra Hospital and Universitary Centre, Portugal

Background & Objectives: Hepatocellular carcinoma (HCC) represents 85-90% and intrahepatic cholangiocarcinoma (iCC) 10-25% of all primary liver carcinomas (PLC), where epithelial-mesenchymal transition (EMT) may play a key role in hepatocarcinogenesis. Thought to be associated with the acquisition of aggressive traits by tumour cells, alpha-smooth muscle actin (αSMA) and vimentin may be specific markers of epithelial - mesenchymal origin. αSMA and vimentin expression was evaluated in HCC and iCC.
Methods: One-hundred and thirteen epithelial malignant liver lesions were studied, from 52 consecutive patients undergoing resection or liver transplantation. Pathological review was performed and tumours were classified according to World Health Organization 2010. αSMA actin and vimentin expression was considered positive when single tumour cells or tumour cell clusters showed immunoreactivity, whereas negative expression was defined as no detectable expression.
Results: From the 18 early HCC studied, 6 (33,3%) had αSMA expression and 10 (55,6%) were vimentin-positive, 12 (66,7%) showed perinodular αSMA positive hepatocytes and 12 (66,7%) perinodular vimentin positive hepatocytes; of the 56 advanced HCC, 19 (33,9%) expressed αSMA and 30 (53,6%) had vimentin positive cells, 26 (46,4%) presented perinodular αSMA in hepatocytes and 26 (46,4%) perinodular vimentin positive hepatocytes; none from the 6 iCC expressed αSMA and 4 (66,7%) had vimentin expression, perinodular hepatocytes expressed αSMA in 4 (66,7%) iCC and perinodular hepatocytes expressed vimentin in 5 (83,3%).
Conclusion: αSMA and vimentin expression either in tumour cells of HCC and iCC may correlate with EMT. Dedifferentiation of liver epithelial benign/malignant cells reflects the importance of tumour microenvironment in PLC development, which may retain clinical specificities.

E-PS-07-043
An unusual case of metastatic liver melanoma in a patient with chronic lymphocytic leukemia
A. Sykaras[1], A. Paraskevas[1], D. Sampaziotis[1], K. Pavlou[1], K. Roidou[1], C. Kouvidou[1]
[1] Department of Pathology, Evangelismos General Hospital, Athens, Greece

Background & Objectives: The major hematologic conditions in patients with multiple malignancy are multiple myeloma, myelodysplastic syndromes, non-Hodgkin's lymphoma (NHL) and chronic lymphocytic (CLL) or myelogenous leukemia. Specifically, patients with a history of CLL or NHL have a higher incidence of melanoma. If they are synchronous the patient's prognosis may be adversely affected.
Methods: We present a 69 years old man with a history of CLL treated with chemotherapy three years ago. The patient presented to haematology department with fever, weight loss and anorexia. The CT scan revealed multiple foci in the liver and a needle biopsy was performed.
Results: The needle biopsy showed two distinct neoplastic populations. The first consisted of small to medium size lymphocytes with immunophenotype CD20+, Pax-5+, CD5+, CD23+ and LEF-1+ suggesting liver infiltration from CLL cells. A second population of epithelioid cells with visible nucleoli and immunophenotype Melan-A+, HMB45+, S100+, MITF-1+, BRAF V600E- established the diagnosis of malignant melanoma. Our patient has not a known melanoma in skin or gastrointestinal tract.
Conclusion: The coexistence of CLL with melanoma has been reported in lymph nodes but not in the liver, to our knowledge. It has been suggested that in CLL the dysfunctional lymphocytes are unable to elicit an antitumour response, thereby contributing to the increased incidence of carcinomas and melanomas in these patients. Moreover, the immunosuppressive effect of chemotherapeutic agents and irradiation used to treat NHL increase the risk of cancer in these patients.

E-PS-07-044
A rare case of granular cell tumour in the biliary tract
A. Sykaras[1], S. Pantelakos[1], D. Sampaziotis[1], K. Botsakis[2], C. Stamou[1], N. Stavrinou[1], C. Kouvidou[1]
[1] Department of Pathology, Evangelismos General Hospital, Athens, Greece, [2] Department of Surgery, Evangelismos General Hospital, Athens, Greece

Background & Objectives: Granular cell tumours (GCT) are rare usually benign neoplasms although some of them may be focally aggressive and <2% are malignant. GCTs may be found in the tongue, skin, gastrointestinal tract, lung, urinary bladder, breast and thyroid. Biliary GCTs represent <1% of all the GCTs and are rarely diagnosed preoperatively, <90 cases have been reported in the literature and no cases of malignant GCT has been published.
Methods: A 57 years old woman was presented to surgical department with jaundice, mild pruritus and abdominal pain. Ultrasound imaging, CT scan and MRI revealed excessive dilation of the endohepatic and extrahepatic biliary tree and an ovoid solid mass of 13mm located in the common bile duct. The endoscopic needle biopsy were not performed due to the location of the tumour and a whipple procedure was performed due to the suspicion of cholangiocarcinoma.
Results: The gross examination revealed a yellow solid tumour 1mm causing thickness of the wall and partly obstruction of the duct. The histopathological features and the immunohistochemistry (S100+, CD68+, inhibin a +, actin-, desmin-, CD117-) were consistent with a benign granular cell tumour. No necrosis, no atypia, no increased mitosis were seen. Radiation or chemotherapy were not recommended. 16 months postsurgically the patient showed no signs of disease.
Conclusion: GCTs of biliary tree are commonly found in the common bile duct (58-49%) and in common hepatic duct (23%). Myoblasts, histiocytes, fibroblasts, undifferentiated mesenchymal cells and schwann cells have been implicated but the histogenesis still remains unknown.

E-PS-07-045
Correlation between radiologic diagnosis and pathological results in resectable pancreatic neoplasms
G.M. Parini[1], M.T. Rodrigo Calvo[1], M. González Farrè[1], C.V. Martinez Stocker[2], F.F. Díaz Rojas[2], M. Pumar Perez[2], G. Aguilar Sanchez[2], X. Duran[3], A. Radosevic[2], B. Lloveras Rubio[1,4,3], M. Iglesias Coma[1,4,3]
[1] Pathology Department. Hospital del Mar, Barcelona, Spain,
[2] Radiodiagnostic Department. Hospital del Mar, Barcelona, Spain,
[3] Institut Hospital del Mar d'Investigacions Mèdiques, Spain,
[4] Universidad Autónoma de Barcelona, Spain

Background & Objectives: Diagnostic imaging is important to evaluate pancreatic neoplasms. Accurate detection and staging are essential for ensuring appropriate treatment. The radiologic diagnosis includes the macroscopic appearance, neoplastic type, staging and atrophy, among others. Pathological reports include also these variables. We want to establish the correlation between the pre-surgical radiologic diagnosis and the final pathological report.
Methods: We reviewed the radiological and pathological report of 120 surgical pancreatic lesions (2014-2018, Hospital del Mar). The variables collected were: location, macroscopy, diagnosis, staging, lymph nodes and atrophy. We use the Cohen's kappa coefficient statistical test to find the correlation.
Results: The correlation between radiological and pathological diagnose is 71,43% (k of 0,58). The differences in diagnosis are mostly related to neoadjuvant treatment, malignant cystic lesions without cystic component in surgical specimens and NET-like in radiology consistent with clear cell renal carcinoma metastasis. There is 97,17% in agreement in location and 60,5% in macroscopy. The correlation drops in relation with affected lymph nodes (58,47%) and with atrophy (50%).
Conclusion: We found an optimal correlation between radiological and pathological diagnoses, which is important in order to establish a possible surgical treatment and behaviour, and also with location. In addition, we are able to explain the cause of the discrepancy in the majority of un-correlated cases.

E-PS-07-049
Solid-pseudopapillary neoplasm of the pancreas: an institution's experience and literature review
G. Gerardo[1], R. Veiga[1], A. Catarino[1]
[1] Hospital da Luz Lisboa, Portugal

Background & Objectives: The rare solid-pseudopapillary neoplasm of the pancreas (SPNP) occurs predominantly in young females; after complete surgical resection, about 85-95% of patients are cured. Long disease-free periods have been recorded even in patients with local spread or metastasis. We present a patient with an unusual clinical picture of SPNP, and a review of the literature.
Methods: A 27-year-old female with complaints of abdominal pain and nausea had a CT-scan that depicted a mass of possible pancreatic origin in her left flank. Multiple nodules were reported in the abdominal and pelvic cavities. A core biopsy was performed and the lesion was classified as SPNP.
Results: The tumour was excised and the diagnosis of SPNP was confirmed, based on the morphological pattern and immunocytochemistry studies. A CTNNB1 mutation was found. Regarding the seven cases of SPNP we retrieved from our files, between 2011 and 2018, the male: female ratio was 1:6 and the age ranged between 18-68. This case was the only one showing disseminated disease at the time of diagnosis. A follow-up was available in 5 cases (from 1-8 years) and all the patients are well and asymptomatic.
Conclusion: SPNP can display abdominal widespread disease in a minute number of cases, with no apparent prognostic implications. This clinical picture does not seem to correlate with a particular histological pattern. Our patient has a follow up time (12 months) free of symptoms and with minimal residual disease at second look MRI.

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E-PS-08-001
Alveolar echinococcosis of the adrenal, accidental discovery
Z. Merad[1]
[1] CHU Sidi Bel Abbes, Algeria

Background & Objectives: We repport a case of alveolar echinococcosis confirmed histologically discovered in bilan of extension at a woman presented a cancer of the endometrium and discuss the differential diagnosis.
Methods: 75-year-old woman, followed in gynaecology for a cancer of the endometrium to whom the realized abdominal ultrasound found a mass in the right adrenal heterogeneous of 6 cms on 4 cms of size. The biological examinations were normal (17 ketostéroïd, 17 hydroxycortisone, metanephrine and acid vanillyl-mandelic). The abdominal CT objectified an adrenal mass heterogeneous right of 6 cms on 4 cms. This mass adrenal is not functional who raised a problem of natural diagnosis.
Results: A coelioscopy explorer was practised with an extemporaneous examination which showed a fibrous fabric reshaped by the necrosis and the beaches microphone - abscess which did not end in a diagnosis of certainty. A right adrenalectomy was practised. The histologically adrenal gland was completely erased by alveolar architecture, of many cavities of variable sizes which contained fragments of cuticle with presence in their lights of proto scolex.
The evolution after operating were simple and patient went out one week later.
Conclusion: Alveolar hydatid disease of the adrenal is an exceptional pathology it will raise with any cystic tumour of the adrenal, especially in endemic countries. However, the definitive diagnosis remains the prerogative of the pathological examination, especially as prevention is difficult given the parasitosis cycle takes place in nature.

E-PS-08-003
Case report: co-existance of papillary thyroid carcinoma and follicular carcinoma as a rare collision tumour
M. Shariati[1]
[1] Surgical Pathology Laboratory, Iran

Background & Objectives: The simultaneous occurrence of different types of thyroid carcinoma in a single patient is a rare event.Synchronization of PCT and follicular thyroid carcinoma (FCT) is very rare.So far a few cases (less than 5 cases) of the simultaneous occurrence of the papillary thyroid carcinoma and follicular thyroid carcinoma have been reported.This article introduces a rare thyroid malignant case in the world that shows bilateral collision tumour of Papillary thyroid carcinoma and Follicular thyroid carcinoma in a 66 year-old iranian female.
Methods: In macroscopic examination, total thyroid weight was 30 g and measured(right: 4.5 * 3.0 * 2.0 centimetres and 1.2 cm 3.0 * 2.2 * 1.5 centimetres).Also, the gross evaluation of specimen showed encapsulated thyroid without macroscopic capsular invasion.Serial cutaways revealed several nodules with different size and calcification which were filled the whole right thyroid lobe.The largest one was 3.5 cm in dimension.One the other side,there were two nodule without calcification in the left lobe(the great dimension was 3.0 cm).
Results: Microscopic histopathological examination of right nodule confirmed papillary thyroid carcinoma with complex branching papillae, fibrovascular cores and characteristic nuclear features: nuclei show overlapping, optically clear chromatin, nuclear longitudinal grooves and eosinophilic intra-nuclear inclusions.And left nodule slides revealed encapsulated follicular carcinoma with capsular invasion. Solid pattern of small and normal size follicles without nuclear features of papillary thyroid carcinoma.ΩCapsular invasion were noted in two sites. One site: full thickness penetration through the capsule and the other: mushroom-like invasion through the capsule.
Conclusion: Our presentation expresses the presence of two distinct types of thyroid carcinoma (papillary and follicular carcinoma) in two different lobes, which in turn is very rare in the world.
We discussed some hypothesis for explaining the simultaneous occurrence of thyroid carcinomas in this case report article.

E-PS-08-005
Concomitant pheochromocytoma and adrenal adenoma in the same adrenal gland
T.M. Costa[1], C. Albuquerque[1], R. Sampaio[1]
[1] Centro Hospitalar Lisboa Ocidental, Portugal

Background & Objectives: Both adrenal adenoma and pheochromocytoma in the same adrenal gland concomitantly is a rare pathology, to our knowledge with only 6 reported cases until now.
Methods: A 61-year-old female, presented with primary hyperaldosteronism and a left adrenal gland mass on the CT scan which was consistent with adrenocortical adenoma. Her past medical history was resistant arterial hypertension, type 2 Diabetes Mellitus and hypercholesterolemia. The biochemical tests showed hyperaldosteronism, strongly suggesting the diagnosis of adrenal gland adenoma, and so she underwent surgical removal. The pathological gross examination of the suprarenalectomy specimen revealed two separate tumours: one yellow cortical nodule 1x0.9x0.7cm and a greyish medullary one with 0.6x0.6x0.5cm.
Results: On microscopic examination we identified an adrenocortical adenoma and a pheochomocytoma. There has been reported cases associating essential hypertension and pheochromocytomas to cause adrenal hyperplasia and consequent adrenal adenoma formation. In fact the incidence of adrenal adenomas in patients with essential hypertension is increased. So there is a chance that our adrenal adenoma could be resultant of an undetected pheochromocytoma.
Conclusion: We think that this case is noteworthy in highlighting the importance of biochemical tests studying an adrenal mass to rule out pheochromocytoma prior to surgery, especially due to possible dangerous intra-operative hemodynamic consequences, as well to understand the hypertension ethiology.

E-PS-08-006
Familial paraganglioma and morphologic criteria importance
T.M. Costa[1], C. Albuquerque[1], R. Sampaio[1]
[1] Centro Hospitalar Lisboa Ocidental, Portugal

Background & Objectives: Paraganglioma is a rare neuroendocrine tumour that arise from neural crest cells. Despite of great importance, there is still no consensual morphologic prognostic criteria for these tumours.
Methods: A 46-year-old woman presented to our emergency department due to tension headache followed by nausea, sweating and syncope associated with extreme arterial hypertension. After exclusion of neurological and cardiogenic causes it was found an intra-abdominal mass; Adherent to left renal vein, limited superiorly by the spleen, laterally by the left kidney and adrenal gland, and posteriorly adherent to the thoracic vertebra. The laboratory workup showed elevation of methanephrines, and with high suspicion of a paraganglioma she underwent surgical removal.
Results: On gross examination was a nodule with 39g and 6,5x4,5x3cm, in section yellow with central cystic area of hematic content. Histologically was a paraganglioma, with large and irregular cell nests, moderate cellularity, pseudorosettes, vascular invasion, Ki67 3-5% and capsular infiltration. According to Grading System of the Adrenal Phaeochromocytoma and Paraganglioma (GAPP) the tumour was classified as moderately differentiated.
Conclusion: The immediate follow-up was benign; however, 3 months later, the patient is having symptomatology recurrence. Genetic testing disclosed a familial paraganglioma, with a germline mutation in succinate dehydrogenase-subunit B gene, which has worse prognosis. The pathological report in this case was crucial to identify an uncommon paraganglioma and alert the clinicians for patient vigilance, genetic testing and evaluation of relatives.

E-PS-08-007
Morphological features of the parathyroid glands in rats under heavy metal salts influence
O. Tymakova[1], N. Hryntsova[1], O. Romaniuk[1], Y. Kuzenko[2], A. Korobchanska[3], I. Kravtsova[1], A. Romaniuk[1]
[1] Sumy State University, Ukraine, [2] Sumy State University, Department of Pathology, Ukraine, [3] Kharkiv National Medical University, Kharkiv, Ukraine

Background & Objectives: The aim of this study was to explore the morphological features of the parathyroid glands in the experimental animals under the heavy metal salts influence.
Methods: The experiment was conducted on 18 mature male albino rats, which were divided into 3 groups. The first group (C) was the intact animals. During 30 days the rats of the second group (HMS 30), as well as the animals of the third group (HMS 90) during 90 days got the water solution of heavy metal salts mixture (Zn,Cu,Fe,Mn,Pb,Cr). The functional activity of the parenchymatous glands structures was immunohistochemically assessed, the expression of the chromogranin in cells was determined.
Results: On the 90th day the capsule thickness was nearly twice thicker, the connective-tissue layers in the parenchyma were increased in 3.8 times. The hypertrophy, as well as cytoplasm vacuolization were observed in the parathyrocytes. The parathyrocytes area in experimental animals was twice increased, on the 90th day – in 1.9 times. The cell nucleus area increased in 2.3 times on the 90th day. The immunohistochemical study revealed the suppression of the chromogranine expression in the parathyrocytes.
Conclusion: The toxic action of heavy metal salts was the most significantly expressed on the 90th day by the proliferation of the connective-tissue capsule. The increased area of parathyrocytes and cell nucleus area was observed. The most significant increase in the cell nucleus was observed on 90th day. The chromogranine expression decreased under the heavy metal salts influence.

E-PS-08-008

Clinical presentation of medullary thyroid carcinoma as "triple negative" breast cancer: case report and literature review

M. Mchedlishvili[1], N. Kekelidze[2], K. Khachapuridze[2], E. Imerlishvili[2]
[1] A. Natishvili Institute of Morphology, TSU, Georgia, [2] TSU, Georgia

Background & Objectives: Medullary Thyroid Carcinoma is a malignant tumour of C-cells, which can be manifested in different organs as a metastatic disease. The most common metastatic sites are - bones (45%), lungs (33%), brain (1-5%) skin and rarely in breast. According to the literature only 25 cases of medullary thyroid cancer metastasis in breast are described. None of them was primarily manifested in breast involving axillary lymph nodes as well.
Methods: The article describes clinical cases of two patients with medullary thyroid carcinoma.The first case describes 71 years old man with medullary thyroid carcinoma in breast, lesion localization - in the upper-lateral quadrant of the breast, tumour size was 3.2 x 2.0 x 1.8 cm (the first patient). The second patient was 13 year-old boy with thyroid medullar-microcarcinoma. The both patients were examined by immunohistocemistry. Examination was done with surgical samples of tissue.
Results: The first patient - negative expression of ER,PR,HER-2. Expression of proliferation marker Ki67 was very low. S100 (+) – expressed in tumour cells; Calretinin - strongly positive; Post surgical thyroid ultrasound examination revealed 1.7 cm tumour in the left lobe. Calcitonin level in blood was 1037. 4pg/ml. The multiple metastasis caused patient death within three years. The second patient - following our recommendation patient's grand-child examined and 0.4 cm thyroid medullary carcinoma of the left lobe was diagnosed.
Conclusion: There are extremely rare cases of Medullary Thyroid Carcinoma with clinical manifestation in breast as a "classical" breast cancer. "Triple negative"malignant lesions of breast need carefully examination to exclude tumour metastasis in breast. In order to verify malignancy at an earlier stage, screening of patient's family members is very important.

E-PS-08-009

Value of Cytokeratin 7 expression to determine the origin of metastases of neuroendocrine tumours

L. Gurevich[1], V. Ashevskaya[1], E. Bondarenko[1], I. Voronkova[1], M. Byakhova[1]
[1] The State Budgetary Healthcare Institution of Moscow Area Moscows Regional Research Clinical Institute n.a. M.F. Vladimirskiy, Moscow, Russia

Background & Objectives: Recently, the problem of determining the localization of a primary neuroendocrine tumour (NET) on the material of diagnostic biopsies of metastases of NET of unknown origin has become increasingly urgent.
Methods: The expression of cytokeratin 7 (CK7) was analysed 271 NETs of various localization: 14 NET pancreas, 36 stomach (22 G1, G2; 8 G3: 4 small cells neuroendocrine carcinomas(SCNEC), 4 large cells(LCNEC)), 6 NET duodenum, 214 - lungs (100 typical (TC) and atypical carcinoids(ATC); 85 SCNEC, 19 LCNEC), 6 - mediastinum, 14 - medullary thyroid cancers(MTC), 8 - breast, 4 – kidneys, 2 - tracheas, 2 - nasopharynx.
Results: The expression of CK7 was detected in 100% of MTC, breast, trachea, and was completely absent in all NETs of the pancreas, duodenum, Merkel carcinomas, nasopharyngeal carcinoids and kidney. Expression of CK7 was detected in 22.7 (5/22) gastric carcinoids G1, G2, and in 75% (6/8) and NEC G3, in 17% (9/53) TC and 54.4% (27/47) ATC of lung, in 51.6% (49/95) of SCNEC and 68.4% (13/19) of LCNEC of lung, 16.7% (1/6) of mediastinal carcinoids.
Conclusion: Expression of CK7 in diagnostic biopsies of NET metastases of unknown origin allows to exclude the localization of primary tumours in the pancreas, intestines, skin, nasopharynx, kidney; suggests their origin from the thyroid gland, breast, trachea and for CK7-positive SCNEC and LCNEC the probability of their localization in the lung and stomach is very high.

E-PS-08-011

Thyroid angiosarcoma in a non-alpine country. A case report and review of the literature

P. Ravazoula[1], D. Koumoundourou[1], E. Mpota[1]
[1] University Hospital of Patras, Greece

Background & Objectives: Thyroid angiosarcoma is a malignant neoplasm which is reported in Alpine region countries of central Europe. It is manifested as a 'cold nodule" most often in eldery female patients. We present a case of thyroid angiosarcoma in a non-alpine country.
Methods: A 69 years old woman presented with a right lobe thyroid nodule measuring 2,2cm. in greatest diameter. Ten years ago she had underwent a total mastectomy and had recieved radiotherapy. Fine needle aspiration cytology revealed "epithelioed malignant cells". Histological examination showed a malignant neoplasm with areas of necrosis and anastomosing channels lined by medium size cells with abundant eosinophilic cytoplasm, large nucleus with prominent nucleoli and numerous typical and atypical mitoses. There was invasion of sternoyoid muscle.
Results: Immunocistochemically tumos cells were positive for CD31, CD34 and Vimentin, focally positive for low molecular weight keratins and S-100 protein and negative for thyroglobulin, calcitonin, galectin, TTF-1, Melan A, HMB45, ER, PR, CEA. The diagnosis was that of an angiosarcoma.
Conclusion: We described a case of thyroid angiosarcoma in a patient living in a non-alpine region with a history of radiation therapy. Thyroid angiosarcomas are rare malignant tumours mainly with poor prognosis and most patients die in less than six months. Differential diagnosis includes anaplastic thyroid carcinoma with angiomatoid feature.

E-PS-08-012

Primary paraganglioma of thyroid gland: a rare case report with clinicopathologic and immunohistochemical analysis

R.A. Barna[1], M. Cornianu[2], A. Faur[3], G. Oprisan[1], A. Dobrescu[4], F. Lazar[4,5]
[1] Department of Pathology, University of Medicine and Pharmacy „Victor Babes", Timisoara, Romania, [2] V. Babes University of Medicine and Pharmacy, Romania, [3] Anatomy and Embryology Department, University of Medicine and Pharmacy „Victor Babes", Timisoar, Romania, [4] Surgery Department II, University of Medicine and Pharmacy „Victor Babes", Timisoara, Romania, [5] Surgery Department II, Emergency County Hospital Timişoara, Romania

Background & Objectives: Primary thyroid paraganglioma (PTPG) is a rare and unusual neuroendocrine tumour, most of the times it can be mistaken for other thyroid neoplasms.
This study reports a case of PTPG accompanied with euthyroidism, which mimics medullary thyroid carcinoma, from a 44-year-old woman who presented with dyspnea and dysphonia caused by an anterior cervical lesion.
Methods: Physical examination revealed a painless, well-circumscribed thyroid nodule of 3 cm within the left lobe, with normal mobility and without palpable cervical lymphadenopathy.
Ultrasonography (US) of the thyroid gland showed a nodule in the left lobe measuring 30 mm, hypoechoic, with increased intranodular vascular flow. The laboratory examination results were in normal range. US and

computed tomography had no diagnostic value. Later, the patient underwent surgical resection of the left thyroid lobe.
Results: PTPG diagnosis was determined by histopathological features and confirmed by immunohistochemical staining. The specimen showed positivity for chromogranin A (CgA), synaptophysin (Syn), neuron-specific enolase (NSE) and CD56, whereas it was negative for TTF-1, calcitonin and carcinoembryonic antigen (CEAm); S-100 protein was positive in sustentacular cells located at the periphery of the tumour cell nests.
After performing surgical resection as a curative approach, at 36 months of follow up there is no local recurrence or metastasis.
Conclusion: Becoming aware of the existence of PTPG and recognizing its histological characteristics is essential for the diagnosis and treatment of the lesion. Even though it is hard to diagnose, PTPG seems to have a favourable prognosis and preferred treatment option is total thyroidectomy with long-term follow-up.

E-PS-08-013
Neuroendocrine tumours: an observational study
V. Tudorache[1]
[1] Universitatea de Medicina si Farmacie Targu Mures, Romania

Background & Objectives: Neuroendocrine tumours (NETs) predominantly affects the gastrointestinal tract but other organs can also be involved. The aim of the paper was to perform a retrospective evaluation of NETs diagnosed in our department in the last years.
Methods: Consecutive cases of NETs diagnosed during 2009-2017 in Department of Pathology of University of Medicine, Pharmacy, Sciences and Pathology, were retrospectively evaluated.
Results: There were 175 cases diagnosed in 9 years, with a median number of 19.44±5.27 cases per year (range 11-28) and a M:F ratio of 1.18:1. The median age of patients was 59.09±15.75 years (range 8-92 years). The predominant locations were appendix (34%), stomach (17%) and pancreas (16%), followed by tumours of colorectal segments (9%), small intestine (7%), lung (7%) and adrenal glands (3%). The other cases (7%) were diagnosed in genital organs, head and neck area, and gallbladder. Most of the tumours (n=132) were carcinomas (36 out of 132 cases showed lymph node metastases), the other 43 tumours being diagnosed as G1- (n=33), G2- (n=5) or G3-NETs (n=5).
Conclusion: Most of the NETs are localized in the gastro-entero-pancreatic area and show a malignant behavior.

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E-PS-08-015
Multiple solid cell nests accompanying amyloid goiter: a rare case report
Î Kaya[1], S. Ekmekci[2], Ţ Sert[3], Î Küçük[1]
[1] Izmir Tepecik Education and Research Hospital, Department of Pathology, Turkey, [2] Izmir Tepecik Training and Research Hospital, Department of Pathology, Turkey, [3] Izmir Tepecik Education and Research Hospital Department of General Surgery, Turkey

Background & Objectives: Amyloid goiter is a disease that results in diffuse growth of the gland due to the accumulation of amyloid protein in the thyroid gland. In systemic amyloidosis, all the organs as well as thyroid glands can be infiltrated with amyloid.This report presents a new case of amyloid goiter with diffuse fat deposition which may be confused with other pathological conditions of the thyroid gland.
Methods: A 32-year-old male patient, had undergone renal transplantation 5 years ago due to chronic renal failure, was admitted to our endocrinology department with a rapidly increasing mass localized in front of his neck and hypothyroidism findings. In the macroscopic examination of the patient who underwent total thyroidectomy, thyroid gland was lobule, solid appearance. Microscopic examination of the thyroid revealed diffuse infiltration of the parenchyma by mature fat tissue and atrophic thyroid follicles. An eosinophilic amorphous material consistent with amyloid substance infiltrated these fat tissue. This material stained intensely with Congo red and was apple green in color under polarized light. Most of the areas of the thyroid gland consisted of solid cell nests between these fat tissue.
Results: Amyloidosis is results from the deposition of insoluble, fibrous amyloid proteins, nearly always in the extracellular spaces of organs and tissues. Amyloid deposition in the thyroid parenchyma is rare and usually accompanies medullary carcinomas.
Conclusion: The origin of adipose tissue accompanying amyloid goiter is unknown.Diffuse accumulation of metaplastic fat tissue should be differentiated from diffuse thyrolipomatosis of thyroid gland. Amyloid stains can be helped us for the differential diagnosis.

E-PS-08-016
Neuroendocrine cells relevant to endocrine mammary and cutaneous carcinomas: nature and significance
T. Kawasaki[1,2], T. Kubota[2], R. Katoh[3,4], T. Kondo[3], S. Ichihara[2], K. Horibe[2], H. Nagai[2], M. Takahashi[5]
[1] Saitama Medical University International Medical Center, Japan,
[2] National Hospital Organization Nagoya Medical Center, Japan,
[3] University of Yamanashi, Japan, [4] Ito Hospital, Japan, [5] Nagoya University, Japan

Background & Objectives: The developmental mechanisms of neuroendocrine carcinomas (NECs) of the breast and the skin have not been sufficiently analysed and are not well understood. The aim of this study was to investigate neuroendocrine (NE) cells in the background tissues surrounding mammary and cutaneous NECs.
Methods: Four Japanese cases (four breasts and one eyelid) having solid papillary NECs accompanied by many NE cells were identified. These patients were, respectively, 28-, 31- and 38-year-old women (breasts) and 51-year-old man (eyelid) with no familial history of NE tumour. The totally resected breasts and excised skin of the eyelid were serially studied by immunohistochemistry for specific NE markers and the morphologies and/or localization of NE cells were investigated.
Results: Immunohistochemical examination showed extensively-distributed NE cells in the background terminal duct-lobular units or sweat ducts of NECs. These NE cells reactive for chromogranin A and/or synaptophysin were classifiable into three emerging patterns: isolated/scattered, clustered and circumferential. NE cells were morphologically polygonal, oval or columnar with sometimes eosinophilic and/or fine-granular cytoplasm and round-to-ovoid nuclei lacking atypia. Some cells were located between epithelial and myoepithelial cells. Apical snouts were occasionally observed in NE cells forming luminal structures.
Conclusion: Benign-looking NE cells in the parenchyma of a skin as well as a breast with NEC could be regarded as hyperplastic from their emerging patterns and distribution; this "NE cell hyperplasia" may be associated with the histogenesis of NEC as a precancerous condition. These observations might raise questions about the treatment for NEC. (*J Clin Pathol*, 2012 & *Pathology*, 2018).
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E-PS-08-017
Bone metastases of unknown primary in a patient with bilateral ovarian tumour and thyrotoxicosis - an unusual case of highly differentiated follicular carcinoma of ovarian origin (HDFCO) [malignant struma ovarii]
O. Stanowska[1], O. Kuczkiewicz-Siemion[1], J. Gałczyński[2], E. Bakuła-Zalewska[3]

[1] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland, [2] Department of Oncological Endocrinology and Nuclear Medicine, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [3] Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland

Background & Objectives: Struma ovarii (SO) is a monodermal teratoma with preponderance of thyroid tissue.
Rarely, it undergoes malignant transformation, most often to papillary or follicular thyroid-type carcinoma.
SO may present as HDFCO, which histologically resembles normal thyroid tissue or follicular adenoma but displays malignant behavior.
We present a case of HDFCO with bone metastasis.
Methods: 68-year old woman with thyrotoxicosis and hypertension presented with pelvic mass palpated per rectum during evaluation for constipation.
Radiology tests demonstrated bilateral bulky ovarian tumours with multiple bone metastases. The patient underwent total hysterectomy and adnexectomy with histopathological examination that was not conclusive for metastases' site of origin.
Subsequent spine biopsy was prompted which resulted in detection of metastatic thyroid tissue.
Total thyroidectomy was required.
Results: Histopathological assessment of bilateral oophorectomy specimens revealed strumal carcinoid in mature teratoma of the left ovary (SC) and giant SO in the right ovary.
Entirely submitted thyroid gland demonstrated only papillary microcarcinoma (PMC).
Reevaluation of the bone biopsy excluded papillary carcinoma metastasis.
Diagnosis of HDFCO was made based on microscopic appearance of bone metastasis [degenerative thyroid tissue, Thyroglobulin (+), TTF-1(+)] coexisting with struma ovarii, without presence of eutopic follicular carcinoma.
PMC of the thyroid gland and SC were recognized as incidental findings.
The patient remains stable under adjuvant radioactive iodine therapy with antithyroid treatment.
Conclusion: Our case supports the previous reports of malignant potential of histologically benign SO and confirms that tumour with size >10 cm, thyroid tissue >80%, adhesions, peritoneal fluid and ovarian serosal rent should be evaluated as HDFCO.

E-PS-08-020

Composite phaeochromocytoma with a differentiating neuroblastic component in a 71-year-old man

C. Masaoutis[1], A. Sykaras[2], F. Dolkiras[1], K. Stefanaki[3], I. Provatas[1], T. Choreftaki[4], A. Angelousi[5], G. Kyriakopoulos[6]
[1] Evaggelismos General Hospital of Athens, Greece, [2] Department of Pathology, Evangelismos General Hospital, Athens, Greece,
[3] Aghia Sofia Children's Hospital, Greece, [4] Department of Pathology, General Hospital of Athens "G. Gennimatas", Athens, Greece, [5] 1st Department of Internal Medicine, Laiko University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece, [6] Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background & Objectives: A 71-year-old man was subjected to right adrenalectomy due to an asymptomatic adrenal tumour measuring 3,7 cm in greatest diameter.
Methods: Light microscopy and immunohistochemistry.
Results: Microscopy revealed a biphasic tumour, resembling a typical phaeochromocytoma to the greater extent (~80%) and a neurogenic tumour to a lesser extent (~20%). The neurogenic component consisted of centrally located nodules of ample neuropil with rare (<10%) foci of schwannian stroma and dispersed neuroblastic elements, mostly ganglion cells and neuroblasts of intermediate differentiation. Immunohistochemically, the schwannian stroma was highlighted with S100 and neuropil with synaptophysin; the neuroblastic elements stained consistently with PHOX2B, mostly with VIP, and variably with S100, synaptophysin, chromogranin and CD56; the phaeochromocytoma was positive for synaptophysin, chromogranin, CD56 and PHOX2B. Ki67/MIB-1 was detected in 1% of the nuclei of both components.
Conclusion: These features are diagnostic of composite phaeochromocytoma with a differentiating neuroblastic component. The neurogenic component is usually a ganglioneuroma or a ganglioneuroblastoma; a neuroblastic component is very rare, mostly undifferentiated. The (ganglio)neuroblastic component is usually identified reliably on morphological grounds. Immunohistochemically, PHOX2B is considered the best marker for the peripheral autonomic nervous system. VIP highlights neuronal elements and its expression may be associated with functional manifestations. Surgery is curative in most cases, even with an extensive neuroblastic component.

E-PS-08-021

Molecular profiling of follicular-patterned thyroid tumours in a Romanian population highlights distinct clinical, pathological and follow-up features between BRAFV600E versus RAS positive genotypes

A. Nechifor-Boila[1], A. Cota[1], C. Banescu[2], V. Moldovan[2], F. Descotes[3], M. Decaussin-Petrucci[4], D. Piciu[5], A. Borda[1]
[1] Department of Histology, UMFST Targu-Mures, Romania,
[2] Department of Genetics, Center for Advanced Medical and Pharmaceutical Research, UMFST Targu-Mures, Romania,
[3] Department of Biochemistry, Molecular Biology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Benite, France,
[4] Department of Pathology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Universite Lyon 1, Pierre Benite, France,
[5] Department of Nuclear Medicine "Ion Chiricuta" Institute of Oncology, Cluj-Napoca, Romania

Background & Objectives: The aim of our study was to assess in a Romanian population the prevalence of *BRAF*^{V600E} and *RAS* mutations in follicular-patterned thyroid tumours, and to correlate the molecular results to the clinico-pathological and follow-up data.
Methods: All cases of papillary (PTC) and follicular (FTC) thyroid carcinomas registered at the Targu-Mures Pathology Department between 2008-2015, with available follow-up data were reviewed by two pathologists and re-classified into one of the following categories: conventional PTC (CPTC), follicular variant PTC (FVPTC), other variants PTC, FTC and NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features). All cases were subjected to RT-PCR amplification targeting the *BRAF*^{V600E} and *RAS (KRAS, NRAS, HRAS)* somatic mutations.
Results: Our study included 165 cases: 80(48.5%) CPTCs, 14(8.5%) FVPTCs, 20(12.1%) PTC other variants, 5(3%) FTCs and 46(27.9%) NIFTPs. Among these cases, 55(33.3%) were *BRAF*^{V600E} and 31(18.8%) *RAS* positive. The majority of *BRAF*^{V600E} positive cases (92.7%) were CPTCs. Any NIFTP case was associated with *BRAF*^{V600E} mutation. Compared to *RAS*, *BRAF*^{V600E} positive tumours revealed a higher rate of multifocality (p=0.023), extrathyroidal extension (p=0.002) and lymph node involvement (p=0.001). All patients with *RAS* positive tumours were disease free at the last clinical assessment, compared to *BRAF*^{V600E} positive patients (only 85.5%, p=0.026).
Conclusion: In our study *BRAF*^{V600E} and *RAS* positive tumours revealed distinct clinical, histo-pathological and follow-up features. Assessment of tumours' molecular profile could play a role in a better risk-stratification of the patients in need for additional post-surgery treatment.

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E-PS-08-022

Angioinvasive, poorly differentiated thyroid carcinoma developed on an oncocytic follicular carcinoma: report of a challenging case

A. Nechifor-Boila[1], S. Cristina[2], R. Catana[1], C. Carasca[3] and A. Borda[1]
[1] Department of Histology, UMFST Targu-Mures, Romania, [2] Department of Pathology, Targu-Mures Emergency County Hospital, Romania,
[3] Department of Forensic Medicine, UMFST Targu-Mures, Romania

Background & Objectives: Poorly differentiated thyroid carcinoma (PDTC) is a rare, but clinically significant entity because it accounts for most fatalities from non-anaplastic follicular cell-derived thyroid cancer.
Methods: We report the case of a 68-years-old male admitted to the hospital for a large, compressive thyroid goiter. Total thyroidectomy was performed and the specimen was sent to the Pathology Department.
Results: On gross examination, the left thyroid lobe was almost entirely replaced by a gray- whitish nodule of 105-mm with extensive necrosis. On microscopy, the nodule was surrounded by a thick capsule, with capsular and extensive vascular invasion. The architectural pattern was solid or trabecular, with large tumour sheets or tumour cords/ribbons, separated by thin, fibrovascular septa. Extensive foci of endocrine-type necrosis were present in the centre of the tumour sheets. The tumour was composed entirely of oncocytic cells, with abundat eosinophilic cytoplasm and small, slightly irregular, centrally placed nuclei, with prominent nucleoli. The mitotic index was 6 mitosis/10HPF. A minor component of well-differentiated oncocytic follicular carcinoma was also observed. Immunoreactivity for Thyroglobulin was restricted to isolated tumour cells (mainly in a perinuclear dot-like pattern) or in few residual microfollicles. Immunostainning for CEA, Chromogranin and Synaptophisin were negative. A final diagnosis of angioinvasive PDTC developed on an oncocytic follicular carcinoma was set.
Conclusion: The diagnosis of PDTC can be challenging, especially in oncocytic tumours. The presence of a co-existent well-differentiated component is an important morphological aid that helps and must be searched for the correct assessment of the final diagnosis.

E-PS-08-023

Karyometric analysis of thyroid gland tumours

D. Mihailovic[1], Ů Mijović[1]
[1] Institute of Pathology, Medical Faculty, University of Nis, Serbia

Background & Objectives: Papillary carcinoma is the most commonly diagnosed malignant tumour of the thyroid gland and makes 85% of all tumours of the thyroid gland. The aim of this study was karyometric analysis of papillary carcinomas and follicular adenomas of the thyroid gland.
Methods: This study includes 23 tumours, 13 follicular adenomas, and 10 papillary carcinomas. The material was obtained by thyroidectomy in the Clinical Center of Niš from 2000-2017. All thyroid tumours were analysed immunohistochemically using monoclonal MIB-1 antibodies for Ki-67 antigen, and "ImageJ" software was used for karyometric analysis. After manual editing of binary images, seven nuclear parameters were estimated: nuclear area, optical density, perimeter, circularity, Feret's diameter, integrated optical density (IOD) and Ki-67 index. For statistical analysis of the data MANOVA and t-test were used. The probability of less than 0.05 was considered statistically significant ($p<0.05$).
Results: Nuclear size (area, perimeter, and Feret's diameter) and IOD were significantly lower in papillary carcinoma than in follicular adenoma ($p<0.05$). Ki-67 index was higher in papillary carcinoma, but this difference was not statistically significant. Similarly, other differences were not statistically significant ($p>0.05$).
Conclusion: Our results indicate that nuclear size and IOD can be useful parameters in diagnostic pathology of thyroid tumours.

E-PS-08-024

Hobnail variant of papillary thyroid carcinoma

J. dos Santos[1], R. Machado-Neves[1], T. Amaro[1], M. Honavar[2]
[1] Pathology Department - Hospital Pedro Hispano, Portugal, [2] Unidade Local de Saúde de Matosinhos - Portugal

Background & Objectives: Hobnail variant of papillary thyroid carcinoma (HVPTC) is a rare and aggressive tumour defined as a papillary carcinoma (PTC) with > 30% of tumour cells with hobnail features. We report a case of HVPTC.
Methods: Clinical history, macroscopic and histological features have been reviewed.
Results: A 72-year-old woman with 40 mm nodule in the right thyroid lobe was submitted to fine needle aspiration: the result was papillary carcinoma. She underwent thyroidectomy: in the right lobe was a 45 mm encapsulated nodule with cystic and solid areas, yellowish and friable. Histologically, the lesion had a complex papillary and micropapillary architecture with prominent vascular cores (sometimes with foamy histiocytes) and areas with cellular discohesiveness. These papillary structures were lines by cuboidal/columnar cells with eosinophilic cytoplasm and high N/C ratio. Nuclei were apically placed, sometimes with grooves and pseudoinclusions, producing a surface bulge. These hobnail/micropapillary features were present in approximately 75% of the lesion. Microcalcification was observed. Vascular invasion was identified; there was no capsule invasion. Necrosis was absent and mitosis was scant. Immunohistochemically: TTF-1 and p53 (focal) positive. Patient was diagnosed with HVPTC pT3a Nx R0; no distant metastasis was identified. BRAF, NRAS and TERTp mutations were negative. Patient was treated with radioiodine; she is well and under clinical surveillance (10 months follow-up).
Conclusion: HVPTC is a particularly aggressive and invasive tumour. Patients with this diagnosis should be observed closely for recurrent disease.

E-PS-08-025

Hobnail variant of papillary thyroid carcinoma associated with a tall cell component: report of an unusual, rare case

A. Borda[1], B. Nagy[2], E. Szasz[1], R. Catana[1], A. Cota[1], A. Nechifor-Boila[1]
[1] Department of Histology, UMFST Targu-Mures, Romania, [2] Department of Pathology, Targu-Mures Emergency County Hospital, Romania

Background & Objectives: The hobnailvariant of papillary thyroid carcinoma (HVPTC) is recognised as a new variant of PTC in the fourth edition of the WHO 2017 Classification Tumours of Endocrine Organs.
Methods: We report the case of a 65-years-old female admitted to the hospital for suspicion of a thyroid malignant neoplasm. Total thyroidectomy with lymph node dissection was performed and the specimen was sent to the Pathology Department.
Results: On gross examination, both the right and left lobe of the thyroid were entirely replaced by a gray-whitish tumour mass. On microscopy, the tumour exhibited complex papillary structures, lined by cells with abundant, eosinophilic cytoplasm, apically located nuclei with proeminant nucleoli and loss of cellular cohesion. This distinctive hobnail feature was associated with a "tall-cell" component: elongated, ribbon-like structures, lined by cells with abundant, eosinophilic cytoplasm, three times as tall as wide and having typical nuclear features of PTC. The tumour cells stained positive for Thyroglobulin and TTF1, which confirmed the primary origin of the tumour in the thyroid. A diagnosis of HVPTC associated with a tall-cell component was set. Extensive extrathyroid extension into strap muscles was documented. Multiple lymph node metastases, some with extra capsular extension revealing both hobnail and tall-cell-like PTC features were described.
Conclusion: Although rare, HVPTC is histologically unique and important to be recognised due to its very aggressive behaviour. It can be found isolated, but more frequently associated with other aggressive histologic types of thyroid cancers, like tall-cell variant as in this case.

E-PS-08-026

Testicule feminisation: a case report

B. Laabidi[1,2], R. Hedhli[3], R. Yaich[1,2], N. Mansouri[1,2], F. Gargouri[4], A. Saidi[1,2], A. Bouziani[4], I. Msakni[4]
[1] Tunis El Manar University, Medicine School of Tunis, Tunisia, [2] Military Hospital of Tunis, Department of Pathology, Tunisia, [3] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia, [4] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia

Background & Objectives: Testicule feminisation is an X-linked disease characterised by variable defects in virilization of 46,XY individuals due to resistance to the actions of the androgen hormones, which in turn stops the forming of the male genitalia and gives a female phenotype. It occurs in one out of 20,000 births. We report the clinical and pathlogic findings in a rare case of testicular feminization.
Methods: A 32-year-old woman presented with primary amenorrhea and infertility.
Results: The clinical examination showed a female phenotype with normally developed breasts, normal vulva and a short vagina. Ultrasonography of pelvis showed absent uterus and hypo-echoic structure with internal vascularity in bilateral inguinal region. Testosterone was 6ng/ml. Laparoscopy showed absent uterus and presence of two pelvic masses reminiscent of ovarian structures. Bilateral gonadectomy was performed. Histologic examination of the nodules revealed two testes, with atrophy of the seminiferous tubules, insufficient development of the germinal cells with hyperplasia of the Leydig cells. No signs of testicular cancer and neither ovarian tissue were identified. Karyotyping was 46 XY. Estrogen replacement therapy was introduced.
Conclusion: Testicular feminization is a rare disease that must be diagnosed and treated through collaborative interaction between gynecologists, geneticians and pathologists. Role of pathologists is to confirm the presence of atrophic tests and absence of malignancy.

E-PS-08-027

Elastic fibers in papillary thyroid carcinoma microenvironment

S. Rjabceva[1], M. Derevyanko[1], I. Siamionik[1], M. Vorobel[1]
[1] Institute of Physiology of National Academy of Sciences of Belarus, Belarus

Background & Objectives: The tumour microenvironment, composed of non-cancer cells and their stroma, was recognized as a one of major factor of cancer growth. The aim of this study is to estimate the changes of stromal elastic fibers in papillary thyroid carcinoma (PTC).
Methods: Review of hematoxylin-eosin slides of 44 cases PTC followed by stratification into groups based on tumour size. Histochemical studies for Russell-Movat pentachrome stain was done.
Results: According to tumour size all patients distributed as follows two groups: with tumour size < 1.0 cm (1st group, 16/40.1%) and with tumour size > 1.0 cm (2nd group, 18/52.9%). Thickened elastic fibers in capsule of thyroid glands was found in 13/85.3% patients of the first group and in 11/61.1% – of the 2nd group (Manna-Whitney test, p>0.05). Thickened elastic fibers around vessels was found in 6/37.5% cases of the first group and in 3/16.7% – of the 2nd (Manna-Whitney test, p>0.05). Thickened elastic fibers in tumour microenvironment were detected in 7/47.8% patients of the first group and in 2/11.1 % – of the 2nd group (Manna-Whitney test, p=0,036). Gamma`s correlation analysis revealed the associations between an increasing of thickness of elastic fibers and tumour size (r=-0.37, p <0.05).
Conclusion: This study showed that the change in the thickness of the elastic fibers in PTC microenvironment is related to tumour size. Papillary thyroid microcarcinoma characterised by formed of thickened elastic fibers in tumour stroma often than PTC with more tumour size.

E-PS-08-028

Searching for Hodgkin - discovering a carcinoma ex pleomorphic adenoma

C. Dahlstedt-Ferreira[1], J. Nogueira[1], A. Galzerano[1], J. Oliveira[1]
[1] Hospital Garcia de Orta, EPE, Portugal

Background & Objectives: Carcinoma ex pleomorphic adenoma (Ca ex PA) is an entity arising from a benign pleomorphic adenoma, either primary or recurrent. It is a rare tumour, comprising 3,6% of all salivary gland neoplasms, more predominant in women in the sixth to eighth decades of life, affecting more often the major salivary glands.
Methods: A 42 year-old male, with known classical Hodgkin lymphoma (HL) diagnosis, presented with a mobile and painless mass on his right parotid gland, which had been growing for 5 years, previously to the HL diagnosis. The subject underwent computerized tomograph, which described an intraparotideal adenomegaly, with necrosis. He was submitted to aspiration cytology and total parotidectomy.
Results: Grossly, the mass measured 4x2x3cm and appeared solid, with white and yellow colour, with expansive growth. Microscopically, it presented as a biphasic tumour, having myoepithelial cells and epithelial cells with squamous differentiation and keratinization, within a condroid stroma. It had intraglandular extension and was minimally invasive, although the surgical margins were not involved by the lesion.
Conclusion: Pleomorphic adenoma in the parotid gland is a benign and common entity. However, in rare cases, it can undergo malignant transformation, having an aggressive behavior, with potential to metastize in 70% of cases. However, if it is intracapsular or minimally invasive, it has a more favourable outcome, hence the importance of surgical resection of a pleomorphic adenoma before it undergoes malignant transformation.

E-PS-08-029

Mixed medullary and follicular thyroid carcinoma: a rare and challenging case

I. Fridrihsone[1,2], I. Briede[1,2], A. Abolins[1,2], I. Strumfa[1,2], G. Bahs[1,3]
[1] Riga Stradins University, Latvia, [2] Department of Pathology, Latvia, [3] Department of Internal Diseases, Latvia

Background & Objectives: Mixed medullary and follicular carcinoma is a rare thyroid malignancy. To set the diagnosis, tumour must show both follicular/thyroid and medullary/C-cell differentiation by morphological features and immunophenotype. In addition, mixed pattern should be retained in metastases.
Methods: Medical documentation, pathology slides and radiologic investigations were reviewed in the context of up-to-dated scientific literature.
Results: A case of mixed medullary and follicular thyroid carcinoma in a 42-year-old-female is reported. TI-RADS 5 lesion by ultrasonography was suspected. Total thyroidectomy with right-sided lateral lymphadenectomy was performed. At grossing, white, firm, ill-defined lesion involved right lobe and isthmus. By histology, polygonal cells with round nuclei, coarse chromatin and amphophilic cytoplasm as well as amyloid deposits in stroma were observed. Cells were growing in nests; pseudopapillary architecture was evident focally. Both entrapped and neoplastic follicles were present, showing markedly different nuclear features. Immunohistochemically, neoplastic cells were reactive to calcitonin, CEA and synaptophysin. Expression of TTF-1 was heterogeneous by intensity, correlating with follicular morphology. Metastases in lymph nodes (12/33) showed mixed medullary and follicular morphology with marked TTF-1 expression in follicular component and positive calcitonin, CEA and low level of TTF-1 in medullary component, hence leading to diagnosis of mixed medullary and follicular thyroid carcinoma.
Conclusion: Mixed medullary and follicular thyroid carcinoma is a rare thyroid tumour; thus it can be challenging, especially for young pathologist. To reach the diagnosis, awareness of the entity is important. Morphology, tumour heterogeneity and immunohistochemical findings must be considered by integrated approach, looking for correlations between morphology and immunophenotype.

E-PS-08-030

Prevalence of atypical adenomas in an Algerian series of pituitary tumours

F. Terkmani[1], S. Bakhti[2], Z.C. Amir[3], S. Mimouni[4]
[1] Hospitalo University Center Mustapha, Algeria, [2] EPH Ait Idir, Algeria, [3] CHU Mustapha, Algeria, [4] CPMC, Algeria

Background & Objectives: Pituitary adenomas (PA) are defined as a group of slow-growing tumours. They are most often benign controlled by surgical resection and / or specific medical treatment, nevertheless the aggressive pituitary adenoma which is characterised by an extension to adjacent structures and pituitary adenomas recurrent or resistant to medical treatment is a problem major care in current practice.
The pathological classification (OMS 2017) of pituitary adenomas distinguishes the "typical" pituitary adenomas; pituitary carcinomas whereas the term of atypical adenoma is no longer recommended nevertheless it remains important to identify them with some criteria including a Ki67 □ 3% and a strong nuclear positivity for p53.
Methods: The aim of this study is to evaluate the histopronotic value of Ki67 and P53 nuclear staining performed on a series of 42 atypical PA.
Results: According to our results, we noted a female predominance (80%).
The age of the patients in our series varies between 16 to 77 years old. The most affected age group is between 25 to 40 years old. According to the size we note a predominance of macroadenoma (64%).
In our series Ki-67 revealed a degree of proliferation ≥3% in 26% of cases with a positive p53 in 20% control.
Conclusion: The WHO classification (2017) took into account the "risk" presented by a pituitary adenoma with regard to recurrence or aggressiveness by integrating at the same time the size, the phenotype and the histological and / or molecular markers essential to a better stratification of this type of adenoma.

E-PS-08-031

Rectal neuroendocrine tumour G2 with multiple metastatic lesions (case report)

B. Güçlüer[1], G. Kir[1], T. Soylemez[1]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey

Background & Objectives: Primary neuroendocrine tumours (NETs) are common and neuroendocrine carcinomas (NECs) are rarely seen in the rectum. It is reported that Rectum NETs exhibit different histopathological features and clinical behaviour than other GIS NETs. A case of NET with a bland morphology showing aggressive clinical behaviour was reviewed with current data.
A 71-year-old man without medical/surgical history presented with lower urinary system symptoms and rectal bleeding. Rectal examination and prostate needle biopsy was unremerkable. Colonoscopic examination revealed a 15 mm, polypoid mass in rectum. Colonoscopic biopsy was performed.
Results: The tumour composed of uniform cells, arranged in alveolar pattern and with a ribbon-like pattern on microscopy. Tumour cells have round nuclei and stippled chromatin. The mitotic count was low and Ki-67 proliferation index was 3%. Necrosis was absent. The differential diagnosis inclues prostatic adenocarcinoma and NETs. The immunoprofile of this tumour showed diffuse strong positive staining for Synaptofisin, CD56, PSAP and negative staining for PSA, NKX3.1, CK7, CK20, CDX2, TTF-1, chromogranin A, calcitonin. These morphological findings and immunohistochemistry results supported a diagnosis of well differentiated NET. Metastatic foci were found in the liver, adrenal gland and iliac lymph nodes.
Conclusion: In many organ systems, NETs are graded as G1, G2, or G3 based on mitotic count and/or Ki-67 labeling index, NECs are considered high grade by definition. This conceptual approach can form the basis for the next generation of NEN classifications and will allow more consistent taxonomy to understand how neoplasms from different organ systems inter-relate clinically and genetically.

E-PS-08-032

Adrenocortical adenomas with concurrent adrenal myelolipomas: a single unit experience

D. Di Nanni[1], A. De Leo[2], F. Ambrosi[3], G. Di Dalmazi[4], G. Zavatta[4], V. Vicennati[4], S. Selva[4], C. Ceccarelli[5], D. Santini[1]
[1] Pathology Unit, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy, [2] 1)Pathology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Italy, [3] Pathology Unit, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy, [4] Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy, [5] Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Background & Objectives: The aim of the study was to analyse the clinico-pathological characteristics of the adrenocortical adenomas combined with myelolipomas.
Methods: We identified 10 cases over 222 adrenalectomies collected between 2015 and 2019. For each case we reported: clinical data, macroscopic and histological features including Weiss score.
Results: Among 10 cases collected, 7 were women; the patients' age ranged from 47 to 69 years (on mean of 62 years). About clinical symptoms, 9 cases were functional adenomas (with hyperproduction of glucocorticoids in 6 cases and aldosterone in 2, mixed secretion in 1).
At gross examination, the median size of the nodules was 3.8 cm (from 1.5 to 10 cm). Almost all nodules were yellowish, mostly with cystic or hemorrhagic changes. Microscopically, the tumours were composed of cords and nests of clear and / or eosinophilic cells which included adipose tissue with scattered islands of myelopoietic elements. The Weiss Score range was from 1 to 4 (median of 1.5). The median value of Ki-67 was 4.6 (from 2.5 to 5.6).
Conclusion: In summary, the combination of adrenocortical adenoma with myelolipoma is not so rare as reported in literature. In the present study, it occurred mainly in adult females with clinical presentation of cortisol excess. Moreover, considering the separate embryologic origin of the adrenal cortex and medulla, these lesions could represent a form of collision tumour.

E-PS-08-033

Medullary thyroid carcinoma - giant cell type

S. Loxha[1], R. Limani[2], O. Blatnik[3], B. Gazic[4], I. Loxhaj[5]
[1] Institute of Pathology Kosovo, Kosovo, [2] Institute of Pathology Kosovo, Albania, [3] Institute of Oncology Ljubljana, Slovenia, [4] Institute of Oncology Ljubljana, Slovenia, [5] Institute of Pathology Kosovo, Kosovo

Background & Objectives: Medullary thyroid carcinoma is a rare agressive tumour of the neuroendocrine origine, that arises from parafollicular C-cell.
Methods: Case report
Results: A 61-year-old woman with surgical spicemen of total thyroidectomy and clinical diagnosis tumour glandulae thyroidae. FNAC of the patient was malignant. Histopathology confirmed encapsulated nodular tumour 7x6.5x3.5cm, showed nests and sheets of cells with moderate to abundant cytoplasm, round and oval nuclei, large giant cells with bizarre nuclei surrounded by dense hyalinized stroma. Mitotic activity, necrosis, vascular invasion and calcifics presents. The tumour was limited to thyroid capsule. Imunichemistry examination: Calcitonin positive, CEA, Chromogranin i TTF1 positive.
Conclusion: Medullary thyroid carcinoma is a rare and aggressive tumour, but morbidity and mortality remain high if untreated. It was

difficult to diagnose only with H&E examination, but the appearance of imunochistochemical biomarkers Calcitonin positive, CEA positive and Chromogranin positive ,has helped us in the final diagnosis.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-09 | Gynaecological Pathology

E-PS-09-001
Malignant mixed sex cord stromal cell tumour with unusual histological appearance: a case report
R. Shi[1], C.Y. Chow[1,2], M.A. Gudi[2], S.H. Chew[2], Y.C. Yeo[2]
[1] Singapore General Hospital, Singapore, [2] KK Women's and Children's Hospital, Singapore

Background & Objectives: Sex cord-stromal tumours (SCST) are uncommon primary ovarian neoplasms. Occasionally a sex cord-stromal tumour lacks definitive characteristics of any specific tumour type and may be classified as "SCST, NOS (Not Otherwise Specified)". Here, we report a malignant SCST, NOS, with unusual histological features. Molecular tests on recently discovered gene profiles for SCST were performed.
Methods: A 68-year-old lady presented with pressure symptoms. Ultrasound showed a large hypoechoic abdominopelvic mass with lobulated appearance, coarse calcification and cystic areas measuring 14.3 x 11.1 x 7.9cm. Differential diagnoses included pedunculated fibroid and ovarian tumour.
Results: Microscopically, the ovarian tumour showed a heterogeneous morphology. Focally, areas of fibroma were admixed with areas comprising fascicles of markedly atypical malignant spindle cells with brisk mitotic activity and necrosis resembling fibrosarcoma. Other areas show fibromatous background with clusters and sheets of cells showing nuclear grooves resembling fibromatous AGCT. FOXL2, TERT and DICER2 gene mutations were not demonstrated. The differential diagnoses were between sarcomatous transformation of an adult granulosa cell tumour and a malignant SCST, NOS.
Conclusion: High grade malignant sex cord-stromal tumours are rare and challenging to classify. Recently, several gene mutations have been identified which may help in classification. However, in our case, these mutations were not detected. This may reflect the complex molecular pathogenesis of these tumours, especially when they undergo malignant transformation.

E-PS-09-002
Intermediate vascular tumours of the female genital tract
O. Oluwole[1]
[1] University of Abuja, Nigeria

Background & Objectives: Vascular tumours of intermediate malignancy encompass a broad range of histologic entities. They are characterised clinically by having a high risk of local recurrence and limited risk of regional or distant metastasis. Vascular tumours of intermediate malignancy frequently presented in the skin often with diagnostic difficulty and are very rare in the female genital tract.
Objective was to analyse the distribution of intermediate vascular tumours the female genital tract.
Methods: Materials are derived from private pathology consultations and review of the literature.
Results: Three patients aged (27, 33 and 35) years respectively. The sites of the tumour were two in the ovaries (right and left) and one in the cervix. The tumour was diagnosed based on routine Haematoxylin and Eosin stain as immunohistochemistry facility is not available in our center at the time of diagnosis. All the patients had surgical treatment and there was no recurrence after a year of follow-up by the attending surgeon.
Conclusion: Intermediate vascular tumours in the female genital tract can present with symptoms similar to any gynaecological tumours and can lead to radical surgery. Histopathological examination is obligatory in all such cases to exclude aggressive high-grade sarcoma.

E-PS-09-003
Microcystic stromal tumour of the ovary: a report of 2 cases
C.Y. Chow[1], G. Mihir[2], S.H. Chew[2], Y.C. Yeo[2]
[1] Singapore General Hospital, Singapore, [2] KK Women's and Children's Hospital, Singapore

Background & Objectives: Ovarian microcystic stromal tumour is an uncommon neoplasm which was classified in the 2014 WHO Classification as a pure stromal tumour within the category of ovarian sex cord-stromal tumours. This entity was originally described as an ovarian neoplasm exhibiting a distinctive triad of histologic features with microcysts, solid cellular regions and hyalinized fibrous stroma. This neoplasm presents as a non-functioning pelvic mass. In this study, we report two cases of microcystic stromal tumour of the ovary.
Methods: The first case is of a 49-year-old lady who presented with acute abdominal pain and CT scan revealed a torted right ovarian tumour. She underwent emergency right salpingo-oophorectomy. Macroscopic examination showed a 14.5cm solid-cystic tumour with large areas of haemorrhagic infarction. The second case is of a 66-year-old lady who presented with postmenopausal bleed, incidentally found to have a right ovarian complex mass on ultrasound. A 12cm solid-cystic right ovarian tumour was resected in the subsequent operation.
Results: On microscopy, both tumours showed a multinodular pattern, comprising a monotonous population of tumour cells arranged in microcystic architecture. The tumour cells had bland cytologic features and stained for CD10, WT1 and β catenin, but were negative for common sex cord markers such as inhibin and calretinin. Mutational analysis of both cases revealed a missense point mutation in exon 3 of CTNNB1, as reported in the literature. There was no recurrence at the last follow up date for both cases.
Conclusion: Ovarian microcystic stromal tumours are challenging to recognize due to their rarity and microcystic appearance that may raise a broad differential diagnosis. The characteristic immunophenotype and CTNNB1 mutation could serve as useful ancillary tests. It is important to be cognizant of this entity, as most of the cases are reported to have a benign clinical course to date.

E-PS-09-005
Low grade endometrial stromal sarcoma - case report
A. Mărcuţă[1], M. Aschie[2,1], G.C. Cozaru[1,2], A. Mitroi[2,1], C. Brinzan[2,1], T.S. Nitu[1], R.D. Sora[1]
[1] Pathology Department, Emergency County Clinical Hospital of Constanta, Romania, [2] CEDMOG, "Ovidius" University of Constanta, Romania

Background & Objectives: Endometrial stromal sarcomas (ESS) are rare malignant tumours accounting for about 0.2% of all genital tract malignancies, so the majority of information available in literature is based on small series or case reports. The origin and biology of stromal sarcomas are poorly understood and immunohistochemistry will help in the detection of tumour markers specific for ESS.
We report a case of low-grade ESS in a 32-year-old woman who presented with a four-month history of excessive bleeding per vagina.
Methods: The histopathological examination of the endometrial curettage and cervical biopsy and immunohistochemistry markers (asdesmin, h-caldesmon, oxytocin receptors, CD10, and inhibin which were useful in

distinguishing cellular leiomyoma) showed an endometrial stromal sarcoma. The sample were cytogenetically analysed and the result showed an abnormal karyotype: 46,XX,t(10;17)(q22;p13)[18]/46,XX[5]. Total abdominal hysterectomy, with bilateral salpingo-oophorectomy, omentectomy and elective pelvic lymphadenectomy were then performed as a second radical surgical approach.
Results: Endometrial stromal sarcomas are uncommon and their differential diagnosis from typical submucosal uterine myomas or benign endometrial polyps could be difficult. Our patient presented at 32 years, which is a rarity in itself. The hysteroscopic features of uterine sarcomas are often similar to those of endometrial polyps or submucosal myomas. It is a diagnosis that should only be made after excluding other high-grade tumours with a sarcomatous component.
Conclusion: Total abdominal hysterectomy, bilateral salpingo-oopherectomy with pelvic lymphadenectomy is the optimal treatment in cases of endometrial stromal sarcomas.

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E-PS-09-006
Ovarian Leydig cell hyperplasia - a rare cause of virilisation
T.M. Costa[1], C. Albuquerque[1], R. Sampaio[1]
[1] Centro Hospitalar Lisboa Ocidental, Portugal

Background & Objectives: There are two main causes of female hyperandrogenism: ovarian or adrenal pathology. We aim to report a rare case of ovarian Leydig cell hyperplasia causing hyperandrogenism and consequent virilization of a postmenopausal woman. To the best of our knowledge there are 18 reported cases of this entity, and apart from one, all associated with masculinization symptoms.
Methods: A 60-year-old woman presented increasing hirsutism and androgynous alopecia. Her past medical history included breast carcinoma at age 39, for which she underwent surgery, chemo, radio and hormonotherapy, with consequent premature menopause at age of 42. The laboratory work-up showed hyperandrogenism with total serum testosterone 85 ng/dL (normal range 2.9- 40.8 ng/dL). After exclusion of adrenal causes, a virilizing ovarian tumour was assumed and the patient underwent laparoscopic bilateral oophorectomy.
Results: On gross pathological examination without particular findings. Histologically in both ovaries at the hilar region we observed ill-defined scattered small nodules of cells. These had a granular eosinophilic cytoplasm, round uniform nucleus and distinct nucleolus, consistent with Leydig cell hyperplasia. The distinction between Leydig cell hyperplasia and tumour is based on the pattern and size of the nodules. Two months postoperatively, the serum testosterone was undetectable (<2.5 ng/dL), and there was a clinical improvement.
Conclusion: Besides alerting for other causes of virilization, we aim to emphasize the importance of differential diagnosis between two rare entities: Leydig Cell hyperplasia that is curative with oophorectomy, and Leydig Cell tumour that may be associated with DICER1 syndrome, and its clinical behavior is highly correlated with the histologic grade.

E-PS-09-007
Endometrial stromal tumours: a clinicopathological and immunohistochemical review of three cases in a resource poor setting
K. Adoke[1], Y. Iliyasu[2], A. Umar Adoke[3]
[1] Federal Medical centre Birnin Kebbi, Nigeria, [2] Ahmadu Bello University Zaria Nigeria, Nigeria, [3] Usmanu Danfodio University Teaching Hospital, Nigeria

Background & Objectives: Endometrial stromal tumours (EST) were first described by Norris and taylor as a distinct group of mesenchymal neoplasms of the uterus with morphological resemblance to endometrial stroma. The current WHO classification acknowledges four categories within the endometrial stromal family of tumours namely, endometrial stromal nodule, low grade endometrial stromal sarcoma (LG-ESS), high grade endometrial stromal sarcoma (HG-ESS) and undifferentiated uterine sarcoma (UUS). We review three cases of endometrial stromal tumours.
Methods: Three cases of endometrial stromal tumour diagnosed over a 1-year period (2017-2018) were retrieved from departmental archives. Blocks were stained with H&E. Immunohistochemistry was performed with three antibodies used namely CD 10, ER and PR.
Results: The patient's ages were 48, 50 and 65 years. Diagnoses was endometrial stromal nodule in the 48-year-old, LG-ESS in the 50 years old and HG-ESS in the 65 year old patient. Endometrial stromal nodule shows a circumscribe lesion composed of uniform oval small cells with scanty cytoplasm whorl around arteries. LG-ESS shows areas of myometrial invasion and mitosis was less than 3. HG-ESS showed ares of necrosis, lymphovascular invasion. All were positive for CD10, PR and ER stains.
Conclusion: Endometrial stromal tumours are rare in our society. More studies need to be done to fully understand the mutations and biologic behaviour of these tumours.

E-PS-09-008
Classical gonadoblastoma presenting as huge unilateral ovarian mass: an unusual presentation of a germ cell- sex cord-stromal tumour
K. Adoke[1], A. Umar Adoke[2]
[1] Federal Medical centre Birnin Kebbi, Nigeria, [2] Usmanu Danfodio University Teaching Hospital, Nigeria

Background & Objectives: Gonadoblastoma was first described by Scully in 1953 is a mixture of germ cell tumour and sex-cord stromal tumour. It usually occurs in individuals with abnormal sexual development, indeterminate gonads with 80% been phenotypically normal women and 20% phenotypical men with undescended testicles. About 40% are bilateral. It is believed to be a precursor of germinoma. We present a rare case of gonadoblastoma in a phenotypically normal female who presented with large unilateral right ovarian mass.
Methods: A 20-year-old female who was not yet married presented to the gynaecology clinic with abdominal swelling for 10 years. She was accused by her parents of having been impregnated by her boyfriend when they noticed sudden increase in the abdominal swelling in the last five months. Ultrasound reveal unilateral ovarian cyst measuring 37x32x17cm. Cyst was excised and sent for histology.
Results: Gross examination shows a huge cystic specimen measuring 35x30x15cm, it contains 10 liters of clear fluid, the cyst lining showing coarse granular pale surface. Histology shows islands of germ cells admixed with sex cord stromal elements surrounded by hyalinized basement material and few calcifications. No germinoma focus was seen.
Conclusion: Classical gonadoblastoma can present as a cystic ovarian mass, careful follow up of patients is necessary as the germ cell component may overgrow the stromal component resulting in dysgerminoma.

E-PS-09-009
Synchronous mature teratoma and Sertoli-Leydig cell tumour in the same ovary
S. Aviel-Ronen[1], R. Barenboym[2], B. Czernobilsky[3]
[1] Department of Pathology, Sheba Medical Center, Tel-Hashomer, Israel, [2] Gynaecology Department, Galilee Medical Center, Nahariya, Israel, [3] Patho-Lab Diagnostics, Ness Ziona, Israel

Background & Objectives: Sertoli-Leydig cell tumour (SLCT) is a rare ovarian tumour, comprising less than 0.5% of ovarian neoplasms. Mature teratoma accounts for 20% of ovarian tumours. Both tumours have a wide

age distribution but usually appear in the reproductive years. Their synchronous coexistence has been reported in less than a handful case reports. Here we describe a rare case of ovary containing both mature teratoma and Sertoli-Leydig cell tumour (SLCT).
Methods: The medical records, imaging tests and pathological findings of a 77 years old patient have been studied and are presented. The patient was under ultrasonographic follow-up for about a year due to a small right ovarian cyst, 4 cm in largest dimension. Her blood levels of CA125, CA15.3, CA19.9 and CEA were within normal limit. Both her ovaries were removed laparoscopically.
Results: The right ovary contained a sebaceous material filled cyst with some solid areas, representing a typical mature cystic teratoma. A separate, 1.2 cm sized well circumscribed lesion, was attached. The lesion contained closely packed tubules, surrounded by stroma. The tubule columnar cells had bland nuclei, Sertoli cells morphology and were CK and NSE positive while ER and PAX8 negative. Inhibin and calretinin stains enhanced the stromal Leydig cells surrounding the tubules. Well differentiated SLCT was diagnosed.
Conclusion: Theoretically, well differentiated Sertoli-Leydig cell tissue associated with mature teratoma can reflect differentiation of the teratoma into testicular tissue. Although this possibility cannot be excluded, since the Sertoli-Leydig cell tissue was attached to the teratoma and not within it, we favor the interpretation of a rare synchronous occurrence of mature cystic teratoma and SLCT in the same ovary.

E-PS-09-010
A voluminous well differentiated neuroendocrine neoplasm of the right ovary, with uncertain biological behaviour.
E. Koniaris[1], E. Moula[1], K. Tsiardis[1], C. Gkogkou[1], G. Kafiri[1]
[1] "Hippokratio" General Hospital of Athens, Greece

Background & Objectives: Ggynaecological neuroendocrine tumours (NET) are exceptionally rare lesions, with only very few reported cases in the international literature, accounting for approximately less than 0,1% of all ovarian tumours. They are a heterogenous group of separate entities, which all of them share a common feature, the expression of endocrine differentiation potential. NETs can occur in pure forms or maybe associated with other tumours and cases arising in mature cystic teratomas, have been described.
Methods: A 51-year-old patient referred to our hospital with a mass in the right ovary. She underwent hysterectomy and bilateral oophorectomy. We received uterus measuring 11X8,5X6cm, left ovary m.d.: 3,2cm and right ovary measuring 14X12,5X11cm, with was completely infiltrated by whitish in hue, solid mass, with multiple cysts, mainly in central location. Immunohistochemistry: CD56 (+), Chromogranin (+), NSE (+), Synaptophysin (+/-), AE1 (+). PLAP (-), Inhibin (-), S100 (-), Calcitonin (-), SMA (-), Desmin (-), c-kit (-), ki67 (<3%).
Results: Histologicaly, the tumour cells had a monotonous appearance with round nuclei, without nucleoli and an eosinophilic cytoplasm, without atypia and sparse mitosis. The neoplastic cells were arranged in bands, islands, trabecules and at places in microrossettes, as well as with few cystic spaces. Although hemorrhagic infiltrations were found, necrosis was not observed. The presence of perivascular infiltration, the vascular emboli, the cystic degeneration and the size of the tumour, suggest a degree of uncertain biological behavior related to the tumour.
Conclusion: NETs are rare germ cell tumours, and many scientists classify them as teratomas with a predominance of neuroendocrine features, mainly in peri- or postmenopausal women, incidentally, found usually unilaterally, slow growing and diagnosed in early stages. Four distinct histological subtypes have been described: insular (most common), trabecular, mucinous and strumal. A third of the patients might experience carcinoid syndrome symptoms.

E-PS-09-011
Endometriosis in the abdomen and pelvis
A. Ilic[1,2], M. Panjkovic[1], T. Lakic[1,2], M. Zivojinov[1,2], Z. Vrekic[2], J. Ilic Sabo[1,2]
[1] University of Novi Sad, Faculty of Medicine, Serbia, [2] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia,

Background & Objectives: Endometriosis is the condition characterised by the presence of endometrial tissue outside the uterine cavity. It is predominantly found in ovaries, uterosacral and big ligament, Fallopian tubes and intestinal tract. Intestinal endometriosis prevails in rectosigmoid junction and small bowel, usually affecting subserosa and serosa.
We analysed available data of patohistological verified endometriosis in intestinal tract (age, location, clinical and patohistological diagnosis, other diseases and conditions) and compared results with results from other scientific works.
Methods: Retrospective study contained 16 patient with confirmed patohistological diagnosis of endometriosis in 5 years. Data were presented in table and charts. Patohistological samples were photographed and microphotos were described and enclosed with charts.
Results: The highest incidence of endometriosis (56%) is among the patients between age 31-40, followed by group of patients between age 41-50 with percentage frequency of 25% . When it comes to the most common sites of endometriosis, we talk about anterior abdominal wall (33%) and ovaries (28%), while the intestinal tract is affected in less than 5% of cases. In most cases clinical diagnosis does not match patohistological and endometriosis is not followed by additional diseases or conditions.
Conclusion: Our results concerning age are in line with previous research. On the other hand, there is discrepancy in regard with localization. According to our data, endometriosis predominantly occurs in fibrous and fatty tissue in the front abdominal wall.

E-PS-09-012
Glassy cell carcinoma spreading on a prolapsed leiomyoma with marked lymphatic invasion: case report
S. Nagase[1], K. Ogura[1], K. Ashizawa[1], M. Fukunaga[2], T. Matsumoto[1]
[1] Juntendo University Nerima Hospital, Department of Diagnostic Pathology, Japan, [2] Department of Pathology, Shin-yurigaoka General Hospital, Japan

Background & Objectives: Glassy cell carcinoma is a rare variant of poorly differentiated adenosquamous carcinoma and is considered to have poor prognosis. We report a case of 62-year-old nulliparous Japanese woman who presented with 73mm vaginal mass and abnormal vaginal bleeding. The mass was considered as a prolapsed leiomyoma, but since a few clusters of adenocarcinoma with serous-like morphology was shown in cytology and biopsy specimens, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection were performed.
Methods: We recognized a poorly differentiated carcinoma spreading on the surface of a pedunculated leiomyoma evolving from the uterine isthmus. The tumour cells had enlarged nuclei and nucleoli with glassy eosinophilic cytoplasm reminiscent of glassy cell carcinoma. Moreover, carcinoma displayed prominent lymphatic invasion inside the leiomyoma although metastasis was not detected in the dissected lymph nodes. Based on the pathological findings, she underwent postoperative adjuvant chemotherapy.
Results: Six-months after the operation, she was admitted to our hospital due to bowel obstruction and malignant pleural effusion. Despite the treatment, her status deteriorated and died one month after the admission. An autopsy revealed that her death was due to peritonitis carcinomatosa of glassy cell carcinoma and subsequent septic shock.

Conclusion: This case exhibits an unusual infiltrating pattern of glassy cell carcinoma spreading on a prolapsed leiomyoma with marked lymphatic invasion, and as far as we know, this is the first case to be reported.

E-PS-09-013

Immunohistochemical phenotype of decidual cells during ectopic pregnancy

J. Krylova[1,2], A. Drobintseva[1], I. Kvetnoy[1], V. Polyakova[1], V. Korsak[3]
[1] D.O. Ott. Research Institute of Obstetrics, Gynaecology and Reproductology, Russia, [2] Pavlov First Saint Petersburg State Medical University, Russia, [3] International Centre for Reproductive Medicine, ICRM, Russia

Background & Objectives: The process of decidualization occurs as a result of the reaction of fibroblasts of connective tissue to the action of hormones, prostaglandins, cytokines and various growth factors. Since fibroblasts are essential components of any stroma, it can be assumed that a decidual reaction in case of fertilization can take place in any organ.
Aim of the study: to determine the clinical and morphological features of deciduous cells in ectopic pregnancy.
Methods: Material was divided in two groups: I-decidual tissue revealed by pathohistological examination of ectopic pregnancies (6-8 weeks of gestation), II-decidual endometrial tissue of abortive material of the same gestation period.
Methods. Staining with hematoxylin and eosin was carried out to determine the timing of gestation and assess inflammatory changes. Immunohistochemical reactions were performed with antibodies to Vimentin (DAKO, Denmark), LIF (Abcam, UK), PR (DAKO, Denmark)
Results: Microscopic analysis of the I group in the omentum and in the ovarian cortex determined the foci of decidual transformation as an enlarged polygonal cells with eosinophilic, vacuolated cytoplasm and insignificant infiltration of lymphocytes. Immunohistochemical study revealed a positive staining of the foci of decidualization of the omentum with Vimentin, PR, LIF. The level of expression of all markers, when compared with the decidual endometrium, differed insignificantly, and was expressed mainly in the focal response to LIF.
Conclusion: The omentum cells are positive to PR and can be transformed under influence of progesterone into decidia, with increasing concentration LIF, but not all cells with a decadal transformation were positive for this cytokine. What makes it possible to think about the different directions of differentiation of these cells and their functions.

E-PS-09-014

Primary ovarian haemangioma - a relatively common entity incidentally discovered in an extremely unusual site

A. Dumitru[1], T. Georgescu[1,2], C. Gavan[3], O. Munteanu[4], M. Sajin[5,6,7]
[1] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Emergency University Hospital Bucharest, Romania, [3] 4th Department of General Surgery, Emergency University Hospital Bucharest, Romania,
[4] Obstetrics-Gynaecology Department of the University Emergency Hospital Bucharest, Romania, [5] SUUB, Romania, [6] UMF Carol Davila, Romania, [7] European Society of Pathology, Romania

Background & Objectives: Ovarian hemangiomas are very rare benign tumours of the female genital tract with less than 60 reported cases in the scientific literature, the majority being described as isolated case reports of unusual clinical presentations or particular morphologic findings. These neoplasms occur in both adults and children with the age ranging from infancy to 81 years.
Methods: We report the case of a 31-year-old woman admitted at the Emergency University Hospital in Bucharest due to severe abdominal pain. Ultrasound evaluation revealed a large uterine mass with 17 cm in its longest axis and a synchronous 2 cm cystic lesion of the left ovary. Serum tumour markers were normal. The patient underwent a total hysterectomy with left salpingo-oophorectomy.
Results: Gross examination of the surgically resected specimen revealed a well-defined, intramural mass with myxoid changes and focal hemorrhagic areas located on the posterior wall of the uterine corpus. The ovarian mass was highly suggestive for endometrioma. Microscopic examination revealed an incidental mixed capillary-cavernous hemangioma. Immunohistochemical staining showed strong immunoreactivity for CD31 and CD34. Thus, the final diagnosis of primary ovarian hemangioma was established. The uterine mass was represented by a leiomyoma with myxoid changes.
Conclusion: Although an uncommon entity, awareness of ovarian hemangioma's particular and diverse clinical presentation as well as its potential to imitate more common lesions such as endometriosis and other ovarian neoplasms is extremely important. Surgical removal of the involved areas and a careful clinical examination is advised because it is known that these lesions may occur in a syndromic context.

E-PS-09-015

Intravascular leiomyomatosis: a case report

M. Mrcela[1], D. Milojkovic[2], I. Stefanac[3]
[1] Medicinski fakultet Osijek, Croatia, [2] KBC Osijek, Croatia, [3] Primary Health Care Center Osijek, Croatia

Background & Objectives: Intravenous leiomyomatosis is a rare occurrence of histologically benign smooth muscle proliferation venous spaces.
Methods: A 46-year-old patient underwent hysterectomy with bilateral adnexectomy due to clinical suspicion of ovarian tumour. Tumour masses were located in the area of the parametrium, they looked solid and cystic, the solid parts were nodular, whorled appearance on the cut surface, with a longer diameter of 7 and 4,5 cm.
Results: Worm-like smooth muscle proliferations were found in vascular spaces lined with vascular endothelium positive for CD31 and CD34 and negative for D2-40 both in myometrium and veins of the parametrium, where the biggest tumour masses were found. Vascular endothelial layer also was detected on the surface of smooth muscle intravascular proliferations.
Conclusion: This is an illustration of unusual smooth muscle neoplasm with quasi malignant intravascular growrh. At this point, four years after surgery, our patient is alive and healthy.

E-PS-09-016

Unexpected diagnosis in bilateral ovarian tumour

L. Lozneanu[1], R.A. Balan[2], S.E. Giusca[2], R.E. Avadanei[2], I.D. Caruntu[1], C. Amalinei[1], A. Grigoras[2]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] Department of Morphofunctional Sciences I-Histology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

Background & Objectives: Primary ovarian hydatid disease (HD) is a rare distinct entity, commonly involving liver, lung, kidney, spleen, bones, brain, and thyroid gland. HD is rarely diagnosed in pelvic organs, such as ovaries and genital tract.
We report a postmenopausal female patient hospitalized for a large left ovarian tumour which had been slowly developed, along with a right ovary solid ovarian tumour, being suspected of bilateral ovarian malignancy.
Methods: Routine hematoxylin and eosin, along with PAS staining, and immunohistochemistry, for CK7, CK20, Ki-67, and ER have been performed.

Results: The gross specimen of right ovary showed a smooth surface, with pasty consistency and translucent bands, containing a thick mucoid material. Microscopy showed laminated eosinophilic membrane, pericystic sclerosis, collection of eosinophils, along with focal giant cell reaction, being diagnosed as a hydatid cyst. The left ovary specimen had an intact outer surface, exhibited a multilocular cystic appearance, with few inner papillae, and mucinous fluid content. The microscopic examination along with immunohistochemistry features diagnosed a concomitant mucinous borderline tumour.
Conclusion: The ovarian location of echinococcosis is extremely rare but it should still be considered in any differential diagnosis of a cystic lesion, while it does not exclude a synchronous ovarian tumour. The current case highlights the necessity of a better screening of HD in endemic areas.

E-PS-09-017
Clinicopathological analysis of incidentally detected blue nevi of the uterine cervix in biopsy or curettage specimens. A report of 7 cases
N. Basheska[1], B. Ognenoska-Jankovska[1]
[1] Department of Histopathology and Clinical Cytology, University Clinic of Radiotherapy and Oncology, Ss Cyril and Methodius University Faculty of Medicine, Republic of North Macedonia

Background & Objectives: Blue nevi (BN) of the uterine cervix (UC) are rare incidental lesions; they are often found in hysterectomy specimens from middle-aged women, or rarely in specimens obtained during more conservative diagnostic procedures (e.g. biopsy, curettage). The objective of our study was to analyse the clinicopathological features of 7 incidentally detected cases of the BN of the UC in biopsy or curettage specimens.
Methods: Among a total of 60 BN of the UC diagnosed on operative and biopsy specimens in our Department between 2000-2019, in 7 (7/60, 11.7%) cases BN were found in biopsy or curettage specimens that had been taken for an examination of a clinically or cytologically suspicious cervical lesion (3/7, 42.9%) or a dysfunctional uterine bleeding (4/7, 57.1%), respectively. The mean age of the patients was 44 years (range, 29-57 years). In addition to routine hematoxylin&eosin, histochemical and immunohistochemical stainings were also performed.
Results: Histologically, all cases showed loose aggregates of pigmented, spindle-shaped, dendritic or nevoid, epithelioid cells in the superficial stroma in one (4/7, 57.1%) or $\geq$2 fragments of cervical mucosa (3/7, 42.9%). The lesions ranged in size from 0.5 to 6mm (mean, 2.4mm), while their thickness ranged between 0.5-4mm (mean, 1.5mm). In one case the BN was presenting as an endocervical polyp. The pigmented cells in all tested cases were positive for melanin (Fontana-Masson), S100, Melan-A, as well as for HMB45 in 3 cases.
Conclusion: Although the BN of the UC seem to be lesions of low clinical significance, they require careful differential diagnosis with other pigmented lesions including malignant melanoma, especially because they are rarely detected and might easily be missed or misinterpreted in scanty endocervical curettage or cervical biopsy specimens due to their small size, more frequent endocervical localization and occasional discrete findings.

E-PS-09-018
The new approaches in research of pathomorphological aspects of endocrinopathies in obstetrics
T. Pavlova[1], A. Selivanova[1], A. Kaplin[1], L. Zemlianskaia[1], E. Malutina[1]
[1] Belgorod State University, Russia

Background & Objectives: The research of system mother- placentha-fetus in caases of endocrinopathies are still actual questions.
Methods: The research of bioptates of uterus(endometrium, miometrium), placentha, umbilical cord of women with diabetes mellitus type 1(25), gestational diabetes (30), thyroid pathology(hypotheriosis (40) and diffuse toxic goiter (30)) was carried out with help of Scanning Electron Microscopy with emental analysis and atomic force microscopy.
Results: It was revealed that the square of vessels at pathology was less than in control group, especially at diabetes mellitus and hypothyroidism. Folding of endothelium was significantly violates at diabetes mellitus and diffuse toxic goiter. The number of normocytes was decreased to 40,0 ±4,0 % at diabetes mellitus, to 42,0±5,0 % at diffuse toxic goiter, to 55,0 ±3,0 % at hypothyroidism and to 60,0±3,0 % at gestational diabetes(84,0 ±4,0% in control group). Alternative processes in stroma prevailed at diabetes and diffuse toxic goiter.
Conclusion: SEM and AFM are reliable and resultative methods for research of tissues at pathology of pregnant.

E-PS-09-019
Synchronous case of the primary neuroendocrine cancer of fallopian tube and serous papillary cancer of ovary
N. Hyriavenko[1], M. Lyndin[1], S. Vladyslav[1], O. Kravtsova[2], D. Sumtsov[2], D. Hyriavenko[1], A. Romaniuk[1]
[1] Sumy State University, Medical Institute, Pathology Department, Ukraine, [2] Sumy Regional Clinical Oncology Center, Sumy, Ukraine

Background & Objectives: Neuroendocrine tumours commonly occur in the gastrointestinal tract and lungs. They rarely were found in the genital organs. There are a few data about this neoplasia in the fallopian tubes, which is accidentally identified during the morphological study. The aim of our investigation was to demonstrate the case of the primary neuroendocrine cancer of the fallopian tube in combination with the serous papillary cancer of the ovary.
Methods: The histological and immunohistochemical (CK7, CK20, CA125, ER, chromogranin A, CD56, CDX2, Ki-67) investigations were conducted for the study of the molecular peculiarities of the fallopian tube and ovary tumours.
Results: The tumour growth was found in the fallopian tube wall, which is presented by trabecular structures. Immunohistochemistry showed that it was negative for CK7, CK20, CA125, ER, CDX2 and strong positive for chromogranin A and CD56. Ki-67 expression was observed in 3% of cells. In the ovary, the tumour with the formations of papillary structures, cellular atypia, as well as single psammoma bodies was present. It was CK7, CK20, CA125, ER positive and didn't express chromogranin A, CD56 and CDX2.
Conclusion: Finally, the following diagnosis was made: low-grade neuroendocrine cancer of the fallopian tube and high-grade serous papillary cancer of the ovary. This case demonstrates the possibility of the occurrence of the primary neuroendocrine cancer in the fallopian tube in combination with the serous papillary ovarian carcinoma.

E-PS-09-021
Juvenile granulosa cell tumour or adult granulosa cell tumour - a diagnostic dilemma
M. Kirigin[1]
[1] Department of Pathology and Cytology, Sestre Milosrdnice University Hospital Center, Croatia

Background & Objectives: Juvenile granulosa cell tumour (JGCT) mostly occurs in young women, with wide differential diagnosis including small cell carcinoma of hypercalcemic type, desmoplastic small round cell tumour, germ cell tumours and others; however, JGCT is most commonly confused with AGCT.
Methods: The ultrasound in a 16 year old girl with irregular cycles revealed a 12 cm cyst of the right ovary. The cyst was extirpated, sparing the ovary.

Results: Grossly, the cyst was morselated in 2 to 5 cm fragments, with 0,5 cm thick extremely firm smooth wall. Microscopically, the wall was firm fibrous tissue containing cords and trabeculae of small, relatively uniform cells with some larger cells with clear cytoplasms, showing up to 8 mitoses/10HPF. Immunohistochemistry revealed negativity for epithelial, muscle, germ cell, lymphocytic and neuroendocrine markers. There was strong positivity for vimentin, CD99 and CD56. Inhibin and calretitin were positive only in larger cells. Reticulin fibers encircled groups of tumour cells. The conclusion was that characteristics fit the diagnosis of luteinized granulosa cell tumour. After salpingooophorectomy about 20 samples, 0.5 to 5 cm were received. Cut surface of larger samples was yellowish white with hemorrhage. Microscopically, tumour tissue showed macrofollicular and solid pattern. The immunohistochemical characteristics were the same as at first biopsy. Some solid areas contained 40 mitoses/10HPF with proliferative activity up to 50%. Small area showed classic AGCT morphology.
Conclusion: JGCT and AGCT share some morphologic characteristics, and diagnostic difficulty may result when JGCT contains elements of AGCT, which was the case in our patient.

E-PS-09-022

Immunohistochemical study of p16ink4α, Ki67 in combination with the study of the expression of miR-22, miR-92a and methylation of the promoter region of the WIF1 gene in the diagnosis of SIL and cervical squamous cell carcinoma

E. Kogan[1], T. Demura[1], G. Bajramova[2], V. Chernova[2], L. Fajzullin[2], N. Fajzullina[2], V. Kiselev[2]
[1] First Moscow State Medical University (Sechenov University), Russia, [2] National Medical Research Center for Obstetrics, Gynaecology and Perinatology named after Academician V.I.Kulakov, Russia

Background & Objectives: The purpose of the study is a comprehensive analyses of clinical, morphological, immunocytochemical data in combination with changes in epigenetic markers in the diagnosis of SIL and squamous cell carcinoma of the cervix uterus.
Methods: The study included 101 patients aged 21-49 years. Group 1 - 31 patients with LSIL, group 2 - 26 patients with HSIL, group 3 - 12 patients with cervical cancer (SCC), group 4 - 32 patients with NILM. Liquid-based cytology conducted with immunocytochemical determination p16ink4α, Ki67 (DakoCytomation), histological and immunohistochemical examination of biopsies material, HPV - 21 type virus genotyping by means of RT-PCR, determination of the expression level of miR-22, miR-92a and miR25 by PCR and methylation status of the gene WIF1 bisulfite sequencing method.
Results: It has been established that the complex use of liquid cytology, the double staining method p16ink4α / Ki67 and HPV tests qualitatively,methylation level of WIF1 and miR-92a increase the effectiveness of early diagnosis of SIL and SCC.
Conclusion: Considering our results, a comprehensive study of p16ink4α, Ki67 in combination with the study of miR-22, miR-92a expression and methylation of the promoter region of the WIF1 gene can be considered as a potential diagnostic and prognostic marker for cervical carcinogenesis.

E-PS-09-023

Uterine inflammatory myofibroblastic tumour: report of 2 cases and literature review

A. Rolim da Paz[1], J. Pires de Andrade[2], I. De Castro Gomes[3], S. Furtado Roberto[4], T. Lopes de Medeiros[3], E. Moreira de Queiroga[2], A. Furtado Honório Dornelas[2,3]
[1] University Hospital Lauro Wanderley/EBSERH/UFPB, Brazil, [2] Cancer Hospital Napoleão Laureano, Brazil, [3] University Hospital Lauro Wanderley/EBSERH/UFPB, Brazil, [4] CLIM, Brazil

Background & Objectives: We reported two patients: the first one, 35 years old, previously healthy, sought clinical care in gynaecology to insert an intrauterine device (IUD); during the hysteroscopy examination, there was a nodular image on the right lateral wall of the uterus, suggestive of a polyp, with the size of approximately 1.2 cm. The second patient is 41 years old, at the 40th week of gestation, with a subserosal nodule, measuring 5.3 cm, found during cesarean section.
Methods: We used our two cases to review the current literature on the morphological, immunohistochemical and clinical behavior aspects of uterine myofibroblastic tumours, an uncommon entity in the uterus, in addition to emphasizing the importance of its differential diagnosis with other entities, especially leiomyosarcoma and endometrial stromal sarcoma.
Results: Both lesions were resected and showed, at the macroscopy, white-gray tissue, sometimes elastic, sometimes gelatinous. Histopathological examination was characterised by bundles of spindle-shaped cells with nuclei containing inconspicuous nucleoli, sometimes grouped in storiform arrangements, supported by predominantly myxoid stroma with prominent fine vascular tissue and a variable inflammatory infiltrate. The neoplasia did not present with necrosis or significant mitotic activity. In the immunohistochemical study, the neoplastic cells were positive for ALK-1, HHF-35 and negative for p53 and p16.
Conclusion: The IMT is considered a rare tumour of intermediate biological behavior with a small proportion of cases being able to recur or metastasize and cause death. The frequent positivity for ALK has helped in the differential diagnosis with other mesenchymal tumours, as well as offering new therapies with tyrosine kinase inhibitors for those with aggressive behavior.

E-PS-09-024

Overexpression of ephrin receptor A2 in the ectopic endometrium of patients with deep infiltrative endometriosis

A. Shchegolev[1], S. Muftaydinova[1], N. Fayzullina[1], N. Buralkina[1], L. Fayzullin[1], V. Chuprynin[1]
[1] NMRCOGP, Russia

Background & Objectives: Deepinfiltrativeendometriosis (DIE) ischaracterised by the invasion of endometriosis lesions in tissues and organs to a depth of over 5 mm and high proliferation. Ephrin receptor A2 (EphA2) has been demonstrated to critically regulate tumour cell growth, migration and invasiveness.
The aim of this work was a comparative analysis of the expression level of the EphA2 receptor in the ectopic endometrium of patients with deep infiltrative endometriosis and endometrial carcinoma.
Methods: All material from 22 women aged 28-45 years were studied: 4 cases of deep infiltrative endometriosis, 9 - endometrial carcinoma and 9 - endometrium of healthy women (4 - in the secretory phase and 5 - in the proliferative phase). Immunohistochemical analysis with antibodies to EphA2 (1:100, clone SP169, Abcam, GB) was done to detect receptor expression. The results of staining of the glandular cells in the ectopic or eutopic endometrium were performed on a 4-point scale.
Results: Eph A2 receptor were expressed on the cell surface region of glandular epithelial cells in human endometrium in both the proliferative (1.75 ± 0.4) and secretory phase (1.1 ± 0.1). The expression of marker was higher in ectopic endometrium of patients with deep infiltrative endometriosis (2.9 ± 0.3) than in the eutopic endometrium in the proliferative phase of healthy women ($p < 0.005$) and was not significantly different from the data of patients with endometrial carcinoma (3.1 ± 0.3).
Conclusion: EphA2 receptor is overexpressed in the ectopic endometrium of patients with deep infiltrative endometriosis and in the eutopic endometrium of patients with endometrial carcinoma. The obtained data makes it possible creation targeted therapy for treatment deep infiltrative endometriosis and cancer.

E-PS-09-025

Features of the Vitamin D status and expression of the Vitamin D receptors in the uterine mucosa in patients with endometrial hyperplasia

E. Kazachkov[1], E. Kazachkova[1], E. Voropaeva[1], A. Zatvornitskaya[1]
[1] South Ural State Medical University, Russia

Background & Objectives: Currently, there is no data on the level of serum 25(OH)D and vitamin D receptors (VDR) expression in the uterine mucosa in endometrial hyperplasia (EH). The aim is to compare the levels of serum 25(OH)D and VDR expression in the uterine mucosa in EH.
Methods: We used endometrial biopsy samples obtained from 50 women and divided them into the two following groups: EH and normal uterine mucosa. We determined the level of serum 25(OH)D using chemiluminescent microparticle immunoassay (Architect i2000, USA) and VDR expression using Vitamin D Receptor antibody [C1C2] (Genetex, USA). For a morphometric analysis, we used a computerized image analyser Videotest - Morphology 5.2 (Russia) and applied non-parametric statistical methods.
Results: We found the serum 25(OH)D deficiency in 56.67% of patients with EH, whereas the serum 25(OH)D level was adequate in 95% of patients with normal uterine mucosa ($p = 0.04$).
The differences in the levels of serum 25(OH)D were not significant between groups (26.76±2.05ng/ml vs. 35.76±3.67ng/ml, respectively) ($p = 0.06$). In patients with EH, we noted the following types of endometrial VDR expression: diffuse (10%), focal (23,33%), and single-cell (36.67%). The rest 30% of the samples were VDR negative. In patients with normal uterine mucosa, the negative and single-cell expression types were absent, whereas the diffuse type prevailed over the focal type (70% and 30%, respectively).
Conclusion: Patients with HE had serum vitamin D deficiency and a pronounced decrease in the endometrial VDR level, which possibly enhanced endometrial proliferation.

E-PS-09-026
Vaginal recurrence of endometrial carcinoma could be avoided
S. Stolnicu[1], C. Terinte[2], N. Ioanid[3]
[1] Department of Pathology, UMFST, Targu Mures, Romania,
[2] Department of Pathology, Oncologic Institute Iasi, Romania,
[3] Department of Surgery, Oncologic Institute Iasi, Romania

Background & Objectives: The risk of vaginal recurrence in endometrial cancer ranges from 7% to 13% and has been related to various parameters (age, tumour type and grade, depth and type of myometrial invasion, presence of lympho-vascular invasion). Patients with vaginal recurrence are treated with surgery and radiotherapy. However, little is known regarding the mechanism and how to avoid the development of vaginal recurrences.
Methods: A prospective study involved 7 cases of endometrial carcinoma surgically treated with classic laparotomy. In every case, 2 smears were collected from the proximal vagina around the cervix before surgery and 2 additional smears during surgery, before cutting the upper part of the vagina to remove the uterus. All smears were stained with Papanicolaou and the presence of atypical cells in the smears was corelated with the type of the tumour in every case.
Results: Seven patients (range 47-72 years) presented endometrial carcinoma of polypoid type, of 3-8 cm diameter and all infiltrating the endocervix. Six cases were of endometrioid type with squamous metaplasia, while 1 case was of clear cell type. Six cases presented tumour cells in all PAP smears, while 1 case was negative before surgery, but positive during surgery.
Conclusion: The data from this study suggest that in most cases the vagina is contaminated before surgery due to bleedings however, additional cases may be contaminated during surgery. We propose a change in the surgical procedure which would be easier and less costly than applying postsurgical vaginal radiotherapy.

E-PS-09-027
Steroid cell tumour of ovary: a rare case report
P. Tziakou[1], E. Delliou[2], V. Papamichail[3], A. Zizi-Sermpetzoglou[1]
[1] Department of Pathology of Tzaneio General Hospital of Piraeus, Greece, [2] Laboratory of Pathology - Xanthi, Greece, [3] Laboratory of Pathology "ISTODOMI" - Piraeus, Greece

Background & Objectives: Steroid cell ovarian tumours are uncommon sex cord stromal neoplasms accounting for less than 0,1%. of all ovarian tumours.
Methods: We report a case of a 53-year-old postmenopausal female complaining of hair loss, deepening of voice and an unusual increase of her libido. Testosterone serum level was elevated. Ultrasonography identified a solid left ovarian mass. Bilateral salpingo-oophorectomy was performed, leading to complete resolution of symptoms and normalization of testosterone level within 1-2 months.
Results: Macroscopic examination revealed an ovarian yellow solid tumour replacing almost the whole ovary. Microscopically the diagnosis of a steroid cell tumour NOS type with no cytologic atypia was confirmed.
Conclusion: Stromal cell tumours are rare sex hormone secretory neoplasms, producing symptoms of virilization, particularly hirsutism. They are divided into three subtypes: stromal luteoma arising from ovarian stromal cells, Leydig cell tumour from Leydig cells in the hilum of the ovary and steroid cell tumour not otherwise specified (NOS). The last subtype accounts for 60% of all and has malignant clinical behaviour in 25-45%. Histologically the tumour cells arrange in nests, columns or cords. They are polygonal-round, with eosinophilic, clear or vacuolated cytoplasm, with central nuclei and prominent nucleoli. The absence of Rienke's crystals differentiate the tumour from Leydig cell neoplasms. Sensitive immunohistochemical markers are inhibin and calretinin and positive markers are CD99, cytokeratin, S100p. Hayes and Scully identified five pathological characteristics of malignancy:1) two or more mitoses/10HPF 2) necrosis 3) hemorrhage 4)tumour diameter>7cm and 5)grade 2 or 3 nuclear atypia. Bilateral salpingo-oophorectomy is a safe therapy option.

E-PS-09-028
The role of anti-mullerian hormone in pathogenesis of endometriosis
E. Kogan[1], N. Paramonova[1], T. Semeryuk[1]
[1] First Moscow State Medical University (Sechenov University), Russia

Background & Objectives: Anti-mullerian hormone (AMH) is a significant regulator of a female reproductive function. The study of AMH expression may help to clarify the pathogenesis of several ggynaecological diseases including endometriosis.
Aim. To evaluate expressions of AMH and AMH receptors 2 (AMHR2) in patients with deep infiltrative endometriosis.
Methods: The study was performed on the surgical materials and material of endometrial samples, which were recieved from 36 women diagnosed with infiltrative endometriosis of rectovaginal septum and vagina and from 34 women diagnosed with combined infiltrative endometriosis of rectum, rectovaginal septum and vagina. The control group consists of 20 women with local peritoneal endometriosis. Expression levels of AMH and AMHR2 was identified by immunohistochemistry analysis of epithelium and stroma cells of heterotopic and eutopic endometrium.
Results: Expression of AMH and AMHR 2 was significantly lower in stromal cells of endometriosis than in stromal cells of eutopic endometrium. Decrease in AMH and AMHR2 levels was found in stromal cells of eutopic endometrium as a sign of endometriosis progression.
Conclusion: Reduced expression of proapoptotic substances such as AMH and AMHR2 in eutopic endometrium and local endometriosis creates favorable conditions for spreading and engraftment of heterotopic endometrium as well as for progression of endometriosis. This finding may be one of the important links to pathogenesis of endometriosis.

E-PS-09-029
Clear cell carcinoma of the endometrium: evaluation of eight cases
M. Ozsen[1], F. Oz Atalay[2], Y. Cakir[1]
[1] Erzurum Regional Training and Research Hospital, Turkey, [2] Uludag University Faculty of Medicine, Turkey

Background & Objectives: Clear cell carcinoma (CCC) constitutes 2% of endometrial carcinomas. It is an estrogen-independent histological subtype and included in type II (non-endometrioid) endometrial carcinoma group. The aim of this study is to present the clinicopathological features of these tumours, which are relatively rare in routine pathology practice but should be considered in the differential diagnosis because they have a worse prognosis than endometrioid carcinoma.
Methods: In this study, haematoxylin and eosin stained slides of CCC cases and electronic archive records were reviewed, diagnosed between 2005-2018 in our department. Cases were evaluated retrospectively considering age and clinicopathological features such as tumour size, myometrial invasion depth, infiltration pattern, different pattern of differentiation, lymphovascular invasion, stromal reaction, necrosis, cervical stromal involvement, metastasis, and stage.
Results: A total of eight cases were diagnosed as CCC in hysterectomy specimens. The mean age of patients was found to be 61.3 (range: 52-72). The histopathological evaluation revealed papillary, tubulocystic or solid patterned tumours showing polygonal, cuboidal, hobnail, and flat-shaped cells, some with eosinophilic granular cytoplasms. In one case, carcinoma was observed in endometrial polyp while no relationship was observed with polyps in others.
Conclusion: CCC is a relatively rare type of endometrial carcinoma. It is important in terms of differential diagnosis of serous carcinoma, secretory type endometrioid carcinoma or endometrioid carcinoma with clear cell changes, endometrioid carcinoma with glycogen-rich squamous metaplasia areas, reactive atypia with hobnail cell metaplasia, and Arias-Stella reaction, as well as in terms of treatment and follow-up.

E-PS-09-030
Association of epithelial neoplasias of the uterine cervix with non-neoplastic processes
M. Shushval[1], N. Kozlov[2,3], L. Volkova[2,3], A. Shatilova[2], A. Akimova[2], A. Antishina[2], A. Kapustina[2]
[1] Baltic Federal University, Russia, [2] Immanuel Kant Baltic Federal University, Kalinigrad, Russia, [3] Lab. of Immunohistochemistry and Pathology Diagnostics, Russia

Background & Objectives: Investigations of background and precancerous processes for epithelial neoplasia of uterine cervix are necessary for understanding of mechanisms of tumour transformation and progression. The study aimed to evaluate association between non-tumour pathology and neoplasia of the uterine cervix.
Methods: Retrospective analysis of clinico-morphological characteristics of uterine cervix neoplasia in 205 women (2017-2018 years, surgical material) for evaluation of association between non-tumour pathology and malignancies. Age of patients: 21 -81 years.
Results: The main cervical neoplasias were found: 1) CIN III (95/ 46.3%); 2) carcinoma in situ CIS (37/18 %); 3) invasive squamous cell carcinoma of different grade (73/ 35.7%). The prevalence of age groups of women with cervical neoplasias was found: 1) CIN III - 21-40; 2) CIS – 21-50; 3) invasive carcinoma – 31-60 and more. Anamnesis of women: 1) quantity of abortions – CIN III (non/43.2 %), CIS (1-2/51.4%), ISCC (3 and more/ 40%); 2) inflammatory processes with or without association with cervical erosion/ectopy - CIN III (62.1 %), CIS (54 %), ISCC (73.9 %); 3) ovarian cysts and uterine leomyomas - CIN III (27. 4 %), CIS (35.1 %), ISCC (31.6 %); 4) HIV and hepatitis B or C - CIN III (4.3 %), CIS (10.8 %), ISCC (2.8 %).
Conclusion: Tendency of association between epithelial neoplasias of the uterine cervix and quantity of abortions and labors, inflammatory processes, ovarian cysts and uterine leiomyomas in anamnesis of women with HSIL and invasive squamous cell carcinoma was revealed, in some cases HIV and hepatitis B/C also were described.

E-PS-09-031
Primary peritoneal müllerian adenosarcoma: report of a case
L. Barona García[1], E. Iborra Lacal[2], M.I. Oviedo Ramírez[1], A. Salazar Nicolas[1], M.I. Ortuño Moreno[1], A. Caballero Illanes[1], G. Ruiz García[1], E. Martínez Barba[1]
[1] Servicio de Anatomía Patológica. Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [2] Hospital Clínico Universitario Virgen de la Arrixaca, Spain

Background & Objectives: Mullerian adenosarcoma (AS) is a rare mesenchymal and epithelial neoplasm of low malignant potential typically arising from the uterine corpus in perimenopausal or postmenopausal women. Extra-genital sites such as the peritoneum are extremely rare and are typically found in younger women.
Methods: A 71-year-old woman with abdominal pain, dysuria and palpable abdominal mass. The computed tomography scan (CT) revealed a 20 × 15 cm pelvic mass occupying the right upper pelvic region, probably of adnexal origin. Two biopsies were performed, diagnosed as borderline ovarian serous tumour and mucinous adenofibroma. A laparotomy was performed, and a peritoneal mass arising from Douglas peritoneum was found and resected. The uterus and adnexa appeared normal.
Results: Microscopic examination revealed a biphasic tumour with intimally admixed glands and prominent stroma configuring finger-like projections and imparting a leaf-like (phyllodes-like) architecture. No sarcomatous overgrowth or heterologous differentiation was found. The epithelial component was focally stratified, with mild to moderate atypia, forming a more complex pattern. Primary extrauterine mullerian adenosarcoma with 30% atypical proliferating serous tumour was diagnosed.
Conclusion: The main prognosis factor of AS is the condition referred as "sarcomatous overgrowth", when more than 25% of the tumour is composed of pure high-grade sarcoma. This is associated with aggressive clinical behavior. However, independently of sarcomatous overgrowth, extra-uterine AS has a very poor prognosis. Lastly, the diagnosis of adenofibroma should be made with caution when we have small samples, since distinguishing adenosarcomas can be a challenge.

E-PS-09-032
Analysis of regional peculiarities of intraepitelial neoplastic processes of the cervix
M. Shushval[1], N. Kozlov[2,3], L. Volkova[2,3]
[1] Baltic Federal University, Russia, [2] Immanuel Kant Baltic Federal University, Kalinigrad, Russia, [3] Lab. of Immunohistochemistry and Pathology Diagnostics, Russia

Background & Objectives: The frequency, structure, peculiarities of cervical intraepithelial neoplasia aretaking into consideration for planning of prophylaxis, diagnostics and therapy. The aim of study - to assess the regional specificity of cervical intraepithelial neoplasia characteristics in screening cytology in Guryevsk of Kaliningad Region.
Methods: The study group - examination of cytological smears of 10 511 women (age 29-69 years) in 2017- 2018in Guryevsk Central Hospital.
Results: Among the women of study group following cervical pathologywas revealed: intraepithelial neoplasia- 40 cases (0.399%), squamous cell carcinoma- 2 women of age 44 and 69 years (0.019%). LSIL(23) was the more frequent in comparison to HSIL (total -17, CIN II and CIN III) without significant differencesin average age of patients (40 years).HPV positive results: 1) LSIL (23) - 4 (17.39%); 2) HSIL - 10 (58.82%).2 cases of hyperdiagnostics of HSIL in cytology were found after histological examination (10, 52%). Inqualitative PCR the 14 types of HPV of high oncogenic risk were found: 16, 18, 31, 33, 35, 39, 45, 51, 52 , 56, 58, 59, 66, 68.In some cases in anamnesis of women with LSIL and HSIL the following ggynaecological pathology was marked:cervicitis, erosions, endometritis, salpingo-oophoritis, bacterial vaginosis.

Conclusion: The regional tendencies in characteristics of cervical intraepithelial neoplasia are described, improvement of cytological screening and description of ggynaecological pathologyin anamnesis are necessary forcorrect statistic evaluation and diagnosis and understanding of possible mechanisms of progression of cervical neoplasia.

E-PS-09-033

Carcinosarcoma of the vagina: HPV typing in two malignant components

D. Doutel[1], M. Baiao[2], D. Rosa[1], C. Cardoso[1], G. Fernandez[1], J. Caldeira[1], D. Cochicho[1], A. Felix[3]
[1] Instituto Portugues de Oncologia de Lisboa Francisco Gentil, Portugal, [2] Nova Medical School - UNL, Portugal, [3] Instituto Portugues de Oncologia de Lisboa, Nova Medical School - UNL, Portugal

Background & Objectives: Carcinosarcomas of the vagina are extremely rare neoplasms, with 15 cases reported, 4 of which with squamous-cell carcinoma (SCC) as the epithelial component and leiomyosarcoma as the sarcomatous component. The study of HPV DNA in both components has been used to evaluate a common clonal origin. Multiple HPV types in vaginal SCC are frequently found (11%).
Our aim was to use HPV typing as a tool to identify the same cell of origin of both components.
Methods: A 72-year-old woman with vaginal bleeding, submitted to a hysterectomy with bilateral adnexectomy for "leiomyomas" 30 years before. Vaginal examination found an exophytic tumour with 6 cm. MRI distinguished two components: an outer component that showed restriction in diffusion weighted imaging and also contrast enhancement; and a inner component with signal characteristics of higher cellularity.
Vaginal cytology identified High-Grade Squamous Intraepithelial Lesion and HPV70. A local wide excision was performed and adjuvant chemo and radiotherapy used. She is alive without evidence of disease ten months after.
Results: The histopathological study revealed a biphasic neoplasm with two components: an invasive SCC (predominantly in-situ) and a leiomyosarcoma. Both components were isolated from the paraffin blocks and the HPV typing was done using INNOLipa® separately, which showed HPV70 and HPV16 in the epithelial and mesenchymal component, respectively.
Conclusion: The presence of two different HPV types is puzzeling and it has not been described before in vagina carcinosarcomas, but allows to infer that the sarcomatous component is derived from an epithelial cell as HPV16 strictly infects epithelial cells.

E-PS-09-034

Placental site trophoblastic Tumour: a case report

D. Anestakis[1], C. Tsompanidou[2], M.I. Givannakis[3], E. Chatzifotiou[1], E. Kalyva[4], C. Charalampidis[5]
[1] Department of Autopsy Histopathology, Lab. of Forensic Medicine and Toxicology, Aristotle University of Thessaloniki, Greece, [2] Department of Pathology, General Hospital of Thessaloniki "Agios Dimitrios" , Greece, [3] Surgical Department , General Hospital "AHEPA", Thessaloniki Greece, [4] Thessaloniki Forensic Service, Thessaloniki, Greece, [5] Department of Anatomy, Democritus University of Thrace, Greece

Background & Objectives: Placental Site Trophoblastic Tumour is a rare variant of gestational trophoblastic disease that occur mainly in women who have history of miscarriage, termination of pregnancy or even a normal or pathological ongoing pregnancy. The clinical course is unpredictable.
Methods: A 32-year-old woman eleven months following a prior full term normal pregnancy presented to the hospital with a history of two months of amenorrhea. Ultrasonography and MRI showed an ill-defined mass lesion (4,3x2,5x1,5 cm) invading the anterior wall of the uterus body. PET-CT did not detect the presence of metastasis. Laboratory test showed a slightly high level of b-HCG.
Results: Therapeutic curettage was done and microscopical examination of the endometrial curettage specimen revealed a proliferation of intermediate trophoblasts that showed mild nuclear atypia, low mitotic figures (2/10 HPF) and Ki67 proliferation index 6%. These cells were positive for inhibin-A. In addition, some multinucleated cells are present. Chorionic villi and cytotrophoblasts were not identified. So, the diagnosis of Placental Site Trophoblastic Tumour was elected. Total hysterectomy was performed and microscopical examination from the mass was similar to that described in the curettage specimen with infiltration of 75% of the myometrium.
Conclusion: Recognition of these very rare cases might help surgeons to predict the behaviour of the tumour and to determine the specific therapeutic approach for this patient.

E-PS-09-035

Case report of a Krukenberg tumour during pregnancy

G. Panselinas[1], I. Efstratiou[1], S. Pervana[1], E. Pazarli[1], O. Batsi[1], E. Massa[1]
[1] General Hospital Papageorgiou, Greece

Background & Objectives: Report of a rare case of Krukenberg tumour presenting with virilization during pregnancy
Methods: A 39-year-old woman presented with bilateral adnexal masses, elevated CA-125, ascites and androgenic manifestations during pregnancy. The differential diagnosis included Krukenberg tumour, a sex cord stromal tumour of the ovary and a pregnancy luteoma. Gastric biopsies did not show any evidence of malignancy. The pregnancy was interrupted at 21st week and surgery was performed. Frozen sections from the ovarian tumours showed diffuse infiltration of both ovaries by signet ring cells arranged individually or in clusters.
Results: An intraoperative diagnosis of Krukenberg tumour was made and the patient underwent bilateral salpingoophorectomy which confirmed the diagnosis by the consequent routine histologic and immunohistochemical studies . Gastroscopy following the surgery revealed a signet ring cell adenocarcinoma. The patient was treated with chemotherapy but the tumour relapsed and the patient died one year after the surgery.
Conclusion: Krukenberg tumour can present with androgenic manifestations and mimic a sex cord stromal tumour or a pregnancy luteoma of the ovary. The primary carcinoma is an often occult gastric cancer in about 2/3 of the cases.

E-PS-09-036

The endometrial expression of LIF and LIFR in infertile patients with adenomyosis, myoma, uterine malformations, synechia and polyps during the window of implantation

A. Asaturova[1], I. Kozachenko[2], N. Fayzullina[2], A. Shchegolev[2], L. Adamyan[2]
[1] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation, Russia, [2] FSBI "National Center for Obstetrics, Gynaecology and Perinatology named after V.I. Kulakov" Ministry of Healthcare, Russia

Background & Objectives: Adenomyosis, myoma, uterine malformations, synechia, polyps were found to have negative impact on embryo implantation. Leukemia inhibitory factor (LIF), is a molecular marker for endometrial receptivity, has an effect through the LIF receptor (LIFR) on both the embryo and the endometrium site. The aim of our study was to evaluate the endometrial expression of LIF and LIFR in patients with adenomyosis, myoma, uterine malformations, synechia and polyps during the window of implantation (WOI).

Methods: Endometrium was obtained during the WOI from infertile patients of reproductive age planning IVF with adenomyosis (10 patients), myoma (10 patients), uterine malformations (10 patients), synechia (10 patients) and polyps (10 patients) before and after surgery. In the comparative group were 10 patients with tubal factor of infertility and without any uterine pathology. The LIF and LIFR expressions were measured by immunohistochemistry for protein intensity and localization.
Results: The mean age of the patients was as follows: adenomyosis (35,9±0,5 years), myoma (36,2±5,2), uterine malformations (29,0±5,1), synechia (34,2±0,7) and polyps (32, 8 ±1,7). Patients with adenomyosis, myoma, uterine malformations, synechia and polyps showed significantly and parallel reduced LIF and LIFR expressions in the eutopic endometrium during WOI as compared with the control group. An increase in the level of expression of LIF and LIFR was observed after surgery, which correlated with positive results of IVF.
Conclusion: Significant reduction of LIF and LIFR expression as markers of endometrial receptivity explains the negative impact of adenomyosis, myoma, uterine malformations, synechia and polyps on implantation processes and hence the results of IVF.

E-PS-09-037
Pathology of placental circulation in prolonged pregnance
A. Drobintseva[1], V. Polyakova[1], S. Makarenko[2], J. Krylova[2,3]
[1] D.O. Ott. Research Institute of Obstetrics, Gynaecology and Reproductology., Russia, [2] Saint-Petersburg Medico-Social Institute, Russia, [3] Pavlov First Saint Petersburg State Medical University, Russia

Background & Objectives: The reported frequency of postterm pregnancy is approximately 3-17% . Recent studies shown that postterm delivery is at risk of complications such as hypoxia, birth injury and even stillbirth. As the placenta ages, increased rates of placental infarction and fibrin deposition.
The aim of the study was to examine the circulation system in placental tissue in prolonged pregnancy.
Methods: The object of the study was placenta, the investigated groups were 41 g.w. (n=20), >42 g.w. (n=20) and 38-40 g.w. (n=20). Analysis of morphofunctional state were performed by using clinical data and morphological findings. Primary monoclonal antibodies to KISS1 (1:100, Abcam), KISS1R (1:350, Abcam), CD34 (1:100, Dako) and eNOS (1:150, Abcam) were used for IHC method. Alexa Fluor 488 and 647 (1:1000, Abcam) were taken as secondary antibodies. 3D reconstruction of vessels, analysis of diameter of capillars and comparsion of eNOS expression were made.
Results: The number of placenta infarction and acute circulation injury increase sharply after 41 weeks of gestation. The average area of eNOS expression in placental villi was 2 times lower in group with 42 weeks gestational age compare to control group. Expression of KISS1 and KISS1R was elevated compare to control group.
Conclusion: We assume that circulation injury established in placenta of prolonged pregnancy could lead to severe hypoxia and other fetal and neonatal risks.

E-PS-09-038
Expression of signal molecules associated with generation of chronic pelvic pain in patients with endometriosis
A. Drobintseva[1], J. Krylova[1,2], A. Andreev[1], V. Polyakova[1], I. Kvetnoy[1]
[1] D.O. Ott. Research Institute of Obstetrics, Gynaecology and Reproductology, Russia, [2] Pavlov First Saint Petersburg State Medical University, Russia

Background & Objectives: Chronic pelvic pain (CPP) causes neurological changes in the dorsal horn of the spine, resulting in neurogenic inflammation of multiple pelvic viscera, hyperalgesia, dysreflexia, a lower sensory threshold and, therefore, a greater perception of pain. Endometriosis is observed in 71 to 87 percent of women with chronic pelvic pain.
The aim of the study was to investigate neurotrophins and nerve associated peptides in endometriotic lesions of different localization from patients with CPP.
Methods: For all patients the intensity of the pain symptoms was registered using a Visual Analogue Scale. For IHC staining were used antibodies to NGF, VIP, tyrosine hydroxylase, peripherin and synaptophysin were used. For study of spatial relationship of nerve fibers 3D reconstruction of confocal images of some cases were used.
Results: All endometriotic lesions was classified corresponding to their immunohistochemical profile. We found correlation between expression of neurotrophins and nerve associated peptides and severity of CPP.
Conclusion: New information about neoneurogenesis and growth direction of sensitive nerve terminal were onatained.

E-PS-09-039
Evolution of white conisations at the pathological anatomy's service of the University Clinical Hospital Virgen de la Arrixaca
A. Salazar Nicolas[1], M.I. Ortuño Moreno[1], L. Barona Garcia[1], A. Caballero Illanes[1], M.D. Perez Caparros[2], N. Villa Lorente[3], M.A. Menárguez Arnaldos[4], G. Ruiz Garcia[1], M.I. Oviedo Ramirez[5], M.A. Torroba Carón[1], E. Martinez Barba[1]
[1] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [2] Servicio de Ginecología y Obstetricia, Hospital de Mèrida, Spain, [3] Servicio de Anestesia y Reanimación, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [4] Servicio de Urgencias, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [5] Servicio de Anatomía Patológica. Hospital Clínico Universitario Virgen de la Arrixaca, Spain

Background & Objectives: In many occasions, we can find conization pieces that come to us due to high-grade lesions in previous biopsies but, once the histological study in done, there is no trace of those leions described previouysly. These conizations are calld white conizations. Many studies show that, despite being histologically confirmed in a previous CIN2-3 biopsy, in approximately 10-20% of the conizations there is absence of CIN 2-3 lesion.
Methods: Conizations are analysed in the period of time from 2013 to 2017 (664 total conizations, 521 diagnostic conizations and 141 white conizations), studying the proportion of conizations considered as white before and after incorporating processing and histological improvements in the study of the samples, comparing the incidence of white conizations with respect to the data reflected in the last series published in the bibliography found.
The improvements include the gynaecology and obstetrics service by sending the fresh sample instead of coagulating the piece. In the Pathological Anatomy's service, the remitted piece is spread over a piece of cork and held it with sterile needles to maintain the anatomical position and a systematics of carving by time slots. Regarding the histological study, the LAST terminology and the complementary study with the P16 technique were implanted.
Results: From 2013 to 2014, 248 conizations were made, of which, 75 were white (30.2% of the total). That was very far away from what was published in last publications. Once improvements were established in the obtaining, processing and study of the conizations since 2015, 416 conizations were made between 2015-2017, of which 66 white ones assuming 15.9% of the total,

being an acceptable percentage. If we look at the data per year, we see how the percentage decreases referred to white conizations: 2015 with 133 conizations and 28 white conizations (21%), 2016 136 conizations and 21 white conizations (15.4%) and 2017 were made 147 conizations being 17 considered as white ones (11.4%).

Conclusion:

- Achieving the conizations without electrocoagulation and sending the sample in fresh to the Pathological Anatomy service decreases the architectural distortion.
- A systematic setting and carving improves the study of the piece.
- Unification of the terminology used and usage of P16 technique guarantees a lower incidence of white conizations.

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E-PS-09-040

Ovarian teratomas with somatic malignant transformation: report of two cases

A.P. Rodrigues[1], J. Pardal[1]
[1] Hospital de Braga, Portugal

Background & Objectives: Malignant transformation is a rare phenomenon in ovarian teratomas. Mature cystic teratoma is the most common ovarian neoplasm. Nevertheless, malignancy is described in 1-2% of cases. Struma ovarii is a monodermal teratoma representing 2-5% of all ovarian teratomas. The presence of thyroid cancer in struma ovarii is even rarer, occurring in 0.5-5% of cases. We report two cases of somatic malignant neoplasm in teratomas.

Methods: Case 1– A 45-year-old woman presented with abdominal pain. Ultrasonography and magnetic resonance scanning revealed an abdominal mass with 11x10x8 cm in the left uterine appendage.

Case 2- A 45-year-old woman presented with a left-sided pelvic mass on physical examination. Ultrasonography confirmed the findings, revealing a 13.4x8.7 cm mass in the left uterine appendage.

Both patients underwent surgery.

Results: Microscopic examination showed somatic-type malignant lesions associated with teratomas.

Case 1- A nodular area with prominent papillae was identified within struma ovarii. Histological features of papillary thyroid carcinoma were observed.

Case 2- A trilineage mature cystic teratoma with a component of invasive squamous cell carcinoma was observed. The latter corresponded to a polypoid solid lesion on gross examination.

Image and biochemical surveillance was the established post-surgery approach for both patients. Both patients are alive with no evidence of disease.

Conclusion: We describe two cases of unusual malignancies that can occur in daily practice. A postmenopausal setting, older age, large tumour masses and the presence of solid areas in gross examination are important clues that should raise the possibility of malignant transformation.

E-PS-09-041

Widespread malakoplakia of urogenital and gastrointestinal systems

O. Ilhan Celik[1], S.Y. Celik[1], L. Tekin[1], Y. Dere[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Malakoplakia is a rare, chronic, xanthogranulomatous inflamatory disease usually encountered in urinary and gastrointestinal systems of middle-aged women. It rarely affects female genital tract.

Methods: A 57-year-old woman suffering from lower abdominal discomfort, intermittent vaginal bleeding in the last 6 months was referred to gynaecology clinic. Ggynaecological ultrasound and abdominal computed tomography revealed enlargement of uterus with a heterogeneous endometrium and myometrium corresponding a malignancy. Left adnexa was also seen solid and enlarged. The uterus and the both adnexa were adherent to surrounding soft tissues. The wall of the urinary bladder and sigmoid colon were thickened asymmetrically. Also there were many enlarged lymph nodes in pelvic, mesenteric and paraaortic regions. Uterus and both adnexa were resected for frozen section examination. However, it could not allow an exact diagnosis excluding malignancy. At operation it was revealed that uterus, both adnexa, bladder, sigmoid colon, rectum, omentum were adherent to each other. Samples taken from these organs and lymph nodes were histopathologically examined.

Results: Microscopically the whole uterus, ovaries, tuba uterinas and the samples taken from bladder, sigmoid colon and rectum showed dense foamy histiocytic infiltration, granuloma formations with dispersed lymphocytes, plasmocytes and neutrophils with Michaelis-Gutman bodies diagnosing Malakoplakia.

Conclusion: Whilst the etiology of malakoplakia is uncertain it is believed to be associated with defective macrophage phagocytic function causing overgrowth of microorganisms because of inability of destroying of digested bacteria. Coliform bacteria have been the most common associated microorganism. The treatment includes antibiotics and surgical excision in extensive malakoplakia.

E-PS-09-042

Fibroepithelial stromal polyp of labium minus

O. Ilhan Celik[1], S.Y. Celik[1], Y. Dere[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Fibroepithelial stromal polyp(FSP) is a benign mesenchymal lesion typically seen in women of reproductive age. It is generally site-specific and presents commonly in vulvovaginal region.

Methods: A 38-year-old woman suffering from a mass on her labium minus was referred to gynaecology clinic. It had first been noticed 3 months earlier as a small nodule; however it had grown rapidly during the past 2 months. Physical examination revealed a soft, polypoid, painless mass with a diameter of 7cm on her right labium minus. Total surgical resection of the lesion was performed.

Results: In the histopathological examination, the lesion was composed of bland mesenchymal stellate, spindle shaped cells and multinucleated giant cells in a myxoid, loose fibrous stroma. No nuclear atypia or increased mitotic activity was seen. Immunohistochemical studies revealed that the cells of the lesion were positively stained with Vimentin, Desmin, Estrogene and progesterone receptors. The lesion was diagnosed as FSP. No recurrence was seen in 4 months after the resection.

Conclusion: FSP (formerly known as pseudosarcoma botryoides) is a benign mesenchymal lesion that typically occur in the vulvovaginal region of women in reproductive age. It generally presents as a polypoid or pedunculated mass, usually measuring less than 5cm in diameter. It rarely causes local symptoms such as bleeding or discomfort and is known to be associated with hormonal exposure like pregnancy or usage of hormone replacement therapy. Total excision is the treatment. It rarely recurs and no lymph-node or distant organ metastasis have been reported.

E-PS-09-043

Ovarian gastric type mucinous carcinoma arising in incidentally found mature cystic teratoma: a case report

K.E. Kaçar[1], I.E. Seven[1], F. Eren[1]
[1] Marmara University, Turkey

Background & Objectives: Mucinous carcinoma accounts for %3-4 of all primary ovarian carcinomas. Approximately %5 of mucinous tumours arise in mature cystic teratomas and most of them are benign whereas carcinoma is rare.

Methods: A 26-year-old woman presented with abdominal distention and abdominal pain. A giant 26x22x12cm abdominopelvic mass extending from symphisis pubis to the sternum was palpated. MR imaging revealed a cystic dominant mass with solid component. The patient underwent an exploratory laparotomy. A large ovarian cyst was sent for intraoperative consultation, it was evaluated as borderline mucinous tumour. The tumour was sampled by one section per centimeter. The microscopy revealed mostly borderline mucinous tumour with focal areas of mucinous carcinoma with expansile type invasion. The mucinous epithelium was composed of gastric pyloric type epithelium which was CK 7 and Muc6 positive and CK20 negative. In addition to mucinous tumour one section revealed a teratoma component composed of mature ectodermal elements. Although additional sampes were taken we could not find any more teratoma foci.
Results: With these features the tumour is diagnosed as a gastric type mucinous carcinoma arising in mature cystic teratoma.
Conclusion: The origin of primary ovarian mucinous carcinomas is not very well documented. Although association of teratoma and mucinous tumours are well known, this association could be reported in limited cases. The reason for this could be that the teratoma component may be very focal as in our case, so increasing sample size can be helpful in determining the origin.

E-PS-09-044
Squamous cell carcinoma of the uterine cervix associated with systemic sarcoidosis
O. Ilhan Celik[1], S.Y. Celik[1], Y. Dere[1], L. Tekin[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Squamous Cell Carcinoma of the Uterine Cervix (SCC-C) is one of the most common ggynaecological cancers of women. Sarcoidosis is a systemic disease of unknown etiology characterised by the presence of noncaseating-granulomas in any organ, most commonly the lungs and intrathoracic lymph-nodes. The synchronous of sarcoidosis and a solid tumour is a rare condition.
Methods: A 56-year-old postmenopausal woman complaining from swelling on her neck, vaginal bleeding, spontaneous weight loss of 20kilograms in 4 months was referred to gynaecology clinic. Pelvic examination revealed a haemorrhagic-lesion in her cervix and the histopathologic examination of the incisional biopsy of it exposed moderate-differentiated-SCC-C. The computed tomography revealed a localized lesion in her cervix uteri corresponding a malignancy and many enlarged lymph nodes in pelvic, abdominale, hilar regions of lungs, also solid nodules in lungs and the liver.
Results: Submandibular(3cm) and hilar(5cm) lymph nodes were surgically excised and histopathologically diagnosed as Sarcoidosis. After the radical-hysterectomy, bilateral-salpingo-oophorectomy, pelvic lymphadenectomy, it was seen that the tumour was localized to the cervix uteri and no metastasis was present in the lymph-nodes; however, all of the pelvic lymph-nodes excised were diagnosed as sarcoidosis. She was treated with additional external whole-pelvis irradiation for SCC-C and slight immunsupression for sarcoidosis. Her lymph-nodes, lung and liver nodules regressed and SCC-C hasn't recurred in the following year.
Conclusion: It's important to differentiate this rare coexistence from the localized sarcoid reactions in regional-lymph-nodes of solid tumours(LSR-LN-ST). Because Multisystem Sarcoidosis may need to be treated; however, LSR-LN-ST regress spontanously and don't require treatment.

E-PS-09-045
Low grade serous carcinoma with extensive mucinous differentiation mimicking seromucinous carcinoma of the ovary
G. Kir[1], T. Soylemez[1], A. Aydin[1]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey

Background & Objectives: Low grade serous carcinoma (LGSC) is a rare tumour of the ovary. Most ovarian serous carcinomas are high grade tumours, whereas LGSC accounts for < %10 of all ovarian serous carcinomas.
Methods: A 51-year-old woman with no medical/surgical history presented with lower abdominal pain. She underwent exploratory laparotomy for optimal debulking, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, and appendectomy.
Results: On gross examination, the uterus, omentum, and appendix were unremarkable. Grossly, the left ovary measured 17×15×7.5cm with ruptured capsule, and the cut surface was solid and gray with focally hemorrhagic areas. On microscopic examination, the tumour consisted of elongated aggregates of cribriform glands. Intraluminal and intracytoplasmic mucin was detected. Tumour cells had moderate nuclear atypia. Mitotic index was lower than 12/10 HPF. The immunoprofile of this tumour showed negative staining for CK20, CDX2, CEA and diffuse strong positive staining for estrogen receptor, CK7, PAX8, CA125. Staining for WT1, vimentin, progesterone receptor was patchy with strong intensity and staining for p53 was wild type. We diagnosed as "cribriform pattern of low-grade serous carcinoma with mucinous differantiation".
Conclusion: Silva et al. reported 40 cases with LGSC. Mucin was detected either in intracytoplasmic or between the groups of tumour cells, in 31 cases. The differential diagnosis includes endometroid carcinoma with mucinous differentiation, mucinous carcinoma and seromucinous carcinoma. The morphological findings and immunohistochemistry results supported a diagnosis of cribriform pattern of LGSC with mucinous differantiation.

E-PS-09-046
Uterine leiomyosarcoma and retroperitoneal paraganglioma: sporadic association or genetic syndrome?
B. Simona[1], A.C. Lisievici[2], T.A. Georgescu[3], F. Pop[4]
[1] Spitalul Universitar de Urgenta Bucuresti (SUUB), Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Pathology, Bucharest Emergency University Hospital, Romania, [4] "Dr. Carol Davila" University Hospital of Nephrology, Romania

Background & Objectives: Paragangliomas are rare neuroendocrine neoplasms arising from paraganglia, which can be sympathetic or parasympathetic. In the adrenal medulla they are called pheochromocytoma, but they can also occur in the head and neck, retroperitoneum and bladder. Paragangliomas can be sporadic, or can appear in a variety of familial syndromes: von Hippel Lindau, MEN 2A and 2B, Carney-Stratakis syndrome or associated with SDH mutation. Nonetheless, to our knowledge, there are no reports of the association between extra-adrenal paraganglioma and uterine leyomiosarcoma.
Methods: We report the case of a 65-year-old female, who first presented to our clinic in September 2018 and underwent surgery for uterine leiomyosarcoma. In March 2019, a postoperative control CT scan revealed a retroperitoneal mass in direct contact with the transverse colon and the lesser curvature of the stomach. The tumour had a diameter of 15 cm, but did not encompass large abdominal vessels. The patient underwent surgery and the resected specimen was sent to the Department of Pathology.
Results: Histopathological examination revealed a trabecular and nested proliferation of cells separated by fibrovascular septae, featuring finely granular cytoplasm and stippled nuclear chromatin. We identified areas of hemorrhage and comedonecrosis, but no invasion of lymphovascular spaces, gastric or bowel wall. The tumour revealed a Ki-67 proliferative index of 7% and diffuse reactivity for Chromogranin and NSE. The surrounding sustentacular cells were positive for S-100. SDHA and SDHB were not evaluated due to the lack of these markers in our lab.
Conclusion: Coexistence of paraganglioma with other tumours is usually described in rare syndromes, such as Carney triad, a non-hereditary condition which also encompasses gastrointestinal stromal tumour and pulmonary chondroma. Similar associations with other tumours have also been described. To our knowledge, this is the first case report of extra-adrenal

paraganglioma associated with uterine leiomyosarcoma and we believe that this occurrence may not be fortuitous and worthy of further investigation.

E-PS-09-047

A rare entity; ovarian lipoma

S.Y. Celik[1], O. Ilhan Celik[1], Y. Dere[1], L. Tekin[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Ovarian Lipoma is a very rare lesion. Most of the lipomatous lesions of ovary are reported as a part of teratoma. However, this case was not associated with a teratoma or any other lesions.
Methods: While a 31-year-old woman was in follow up for pregnancy, an exophytic, nodular, 2 cm lesion in the left ovary was identified by ultrasound examination. The other parts of the ovary seemed normal. During the operation of cesarean this lesion was totally excised preserving the rest of the ovary.
Results: In the histopathological examination the lesion was completely composed of benign, mature, monomorphic lipocytes constituting solid sheets. The lesion was encapsulated in the parenchym of the ovary. It did not include any other tissues of different origin. So the lesion was diagnosed as Ovarian lipoma. No recurrence or lymph node, distant organ metastasis were seen in 6 months after the resection.
Conclusion: Lipoma is the most common benign tumour of the soft tissues. It is composed of benign, mature, uniform lipocytes and has a thin fibrous capsule seperating it from the surrounding tissues. However, lipoma of the ovary is a very rare entity. Lipomatous lesions are generally defined as associated with teratomas, lipid cell tumours and lipoleiomyomas. As it is a benign tumour total excision is the treatment. It rarely recurs and no lymph node or distant organ metastasis have been reported. So it is important to recognise it in order to protect the rest of the ovary from excision.

E-PS-09-048

Persistent vaginal melanoma as an unusual mimic in the endocervix

I. Busmanis[1], D. Seow[1]
[1] Singapore General Hospital, Singapore

Background & Objectives: Primary vaginal melanoma of the cervix is exceedingly rare, accounting for <3% of vaginal malignancies and <0.3% of all melanomas.
Methods: Case Report
Results: A 61-year-old Chinese female initially presented with a 3cm vaginal polyp, diagnosed as melanoma, and found to harbour a c-kit mutation. Two years later she presented with recurrent disease manifest as vaginal and vulval melanoma-in-situ, synchronously with gastric bleeding from a biopsy proven 7cm gastric metastasis of melanoma. Ten months later further vaginal bleeding necessitated a THBSO and partial vaginectomy/vulvectomy. Examination revealed multiple nodular metastases within the vaginal wall, up to 1.4cm, associated with vascular emboli, and separate foci of primary vulval melanoma-in-situ, lentiginous type. A unique feature in the cervix was colonisation within intact endocervical glands by highly pleomorphic melanoma cells, situated near to small stromal metastatic deposits. Six months later inexorable disease resulted in eventual death.
Conclusion: Histologically, the most common subtype of primary vaginal melanoma is nodular subtype, followed by mucosal lentiginous. If the tumour is amelanotic, awareness of the possibility must be maintained in order to apply appropriate immunostains, and not misdiagnose a poorly differentiated tumour as squamous, or adenocarcinoma, small cell carcinoma, or leiomyosarcoma. The unique feature of this case is the first known situation of melanoma potentially mimicking endocervical adenocarcinoma-in-situ on solely histologic grounds, but in the background of recurrent multifocal metastatic, and primary disease.

E-PS-09-049

Utility of p16, ER, Vimentin and CEA expression in differential diagnosis between endocervical and endometrial adenocarcinoma

J.H. Nam[1], N.I. KIM[1], Y. CHOI[1]
[1] Chonnam National University Hospital, Republic of Korea

Background & Objectives: When clinical and histopathological examination is not effective in determining the primary endocervical adenocarcinoma (ECAs) and endometrial adenocarcinoma (EMAs), immunohistochemistry (IHC) for ER, Vimentin (Vm), CEA and p16 is regularly used in practice. The aim of this study was to evaluate the performance of these 4 IHC markers in differential diagnosis between ECAs and EMAs.
Methods: IHC for p16, ER, Vimentin (Vm) and CEA was performed on 17 ECAs and 34 EMAs (including 31 EMAs, 2 serous and 1 clear cell carcinomas).
Results: Positivity rates of p16, ER, Vm and CEA in ECAs were 94.1%, 23.5%, 5.9% and 76.5%, respectively; those in EMAs were 16.1%, 67.7%, 71.0%, and 38.7%, respectively; those in serous and clear cell carcinomas were 100%, 0%, 66.7% and 33.3%, respectively. All endocervical adenocarcinomas except for one case demonstrated diffuse and moderate to strong p16 expression. In contrast, grade 1 endometrioid adenocarcinomas exhibited less diffuse and less intense expression with variable staining intensity. Similar to endocervical adenocarcinomas, all serous and clear cell carcinomas showed diffuse and moderate to strong p16 expression. The sensitivity and negative predictive value (96.3% and 94.1%) of p16 expression and the specificity and positive predictive value (95.7%, and 94.1%) of Vm expression in differential diagnosis between ECAs and EMAs were significantly higher than those of ER and CEA expression.
Conclusion: p16 and Vm are more useful IHC markers and two-marker panel is recommended for using in differential diagnosis between ECAs and EMAs.

E-PS-09-050

Morphological substrat and pathogenetic mechanisms of adhesion-related pelvic in endometriosis

J. Krylova[1,2], S. Kruglov[2], V. Bezhenar[2], M. Rybakova[2]
[1] D.O. Ott. Research Institute of Obstetrics, Gynaecology and Reproductology, Russia, [2] Pavlov First Saint Petersburg State Medical University, Russia

Background & Objectives: Endometriosis is one of the most common ggynaecological pathologies with complex pathogenesis and a variety of clinical manifestations. It is prone to high frequency of relapses and development of adhesions. The aim of the study was to determine the potential of the peritoneum in infiltrative forms of endometriosis with development of adhesions.
Methods: The material for the study included peritoneal samples obtained from women with infiltrative endometriosis and without endometriosis. Microscopic examination was conducted using the colors: hematoxylin and eosin, Van Gieson's stain, PAS. For IHC (1: 150, Abcam), VIP (1: 150, Abcam), tyrosine hydroxylase (1: 350, Abcam), Substance P (1: 350, Abcam), CD117 (1: 350 , Abcam), TGF beta 1 (1: 350, Abcam).
Results: Microscopic examination was dominated by active foci, represented by cytogenic stroma and proliferative type glands. Endometrioid lesions had perivascular growth and pronounced neovasculogenesis, as well as perineural growth and inflammatory infiltration from moderate to severe. The immunohistochemical profile of heterotopias corresponded to the profile of the intact peritoneum and demonstrated high levels of neutrophins, proliferative activity of telocytes and fibrotic markers.
Conclusion: Improving understanding of the pathogenesis of endometriosis will contribute to the search for therapeutic goals that can provide the necessary ways to treat endometriosis.

E-PS-09-051

Angiosarcoma arising in recurred mature cystic teratoma of the ovary

J.H. Nam[1], N.I. KIM[1], Y. CHOI[1]
[1] Chonnam National University Hospital, Republic of Korea

Background & Objectives: While the most of mature cystic teratoma is benign, it may rarely undergo malignant transformation. Malignant transformation in this type of neoplasm is mostly represented by squamous cell carcinoma and sarcomas very rarely develop in mature cystic teratoma. To our knowledge, this is the ninth case of angiosarcoma arising in mature cystic teratoma.
Methods: Herein, we also describe the clinicopathologic features of this unique case and the literature is reviewed.
Results: The patient was an 18-year-old female with 1 week duration of repeated abdominal pain and tenderness. Her past medical history included previous bilateral cystectomy and was diagnosed with mature cystic teratoma of both ovaries 8 years ago. On physical examination, the patient had a palpable abdominal mass and was further evaluated with pelvis magnetic resonance images. The examination showed 25cm sized huge cystic mass in left ovary and 8cm sized cystic mass in right ovary. Emergency operation was performed due to left ovarian torsion. Macroscopically the left ovarian tumour consisted of red to brownish cystic mass with extensive hemorrhage and necrotic surface. The tumour measured 20.0 cm in greatest dimension. The right ovarian mass was 7.5 cm at its greatest dimension, both tumours were filled with sebaceous material and matted hair. Cytologic investigation of ascitic fluid was negative. Pathologic evaluation of the right ovarian tumour revealed mature cystic teratoma. The left ovarian mass showed mature cystic teratoma with malignant transformation to angiosarcoma. The teratomatous component consisted of ectodermal derived skin and appendages predominated with squamous epithelium and sebaceous glands. Hair follicles, cerebral cortex, mature bone tissue, adipose tissue were also present in varying proportions. While the most of the tumour demonstrated extensive hemorrhagic necrosis, microscopic examination revealed atypical cells with large hyperchromatic pleomorphic nuclei. The tumour displayed sheet like areas and numerous irregular vascular channels lined by atypical endothelial cells. Initial immunohistochemistry revealed strong membranous positivity for CD34, CD31 and nuclear positivity for ERG, FLI-1 with 80% of Ki-67 index. Diagnosis was rendered as angiosarcoma arising in mature cystic teratoma based on its histologic and immunohistochemical features.
Conclusion: Angiosarcomas arising in mature cystic teratomas of the ovary are extremely rare. We experienced a case with recurred mature cystic teratoma which underwent malignant transformation during an interval of 8 years since its initial surgical treatment. Although mature cystic teratoma is a benign tumour, surgery or regular follow-up needs to be planned after due to consideration of the risk of malignant transformation.

E-PS-09-052

Small cell carcinoma of pulmonary type arising in ovarian mature cystic teratoma. A case report

P. Skoufogiannis[1], S. Divani[1], G. Kalodimos[1], D. Koutsogiannis[1], C. Barda[1], A. Feritsean[1]
[1] General Hospital of Volos, Greece

Background & Objectives: We present a small cell ovarian carcinoma of pulmonary type (SCCOPT) arising in a mature cystic teratoma (MCT) in a 62 year-old woman. SCCOPT arising in MCT is a very rare form of ovarian cancer.
Methods: The patient underwent a primary debulking surgery. An intraoperative cytological examination of 25ml free intraperitoneal fluid and a touch imprint cytological analysis of the left ovarian tumour where performed.The tumour together with the uterus, the cervix and the right ovary were sent for histopathological and immunohistochemical analysis.
Results: The cytology of the fluid showed evidence of metastatic disease whereas the imprint presented a poorly differentiated ovarian malignant neoplasm. The histopathology report revealed a SCCOPT arising in a 31,4 cm MCT of the left ovary. A small synchronous cystic teratoma was also found within the right ovary. Immunohistochemically tumour cells expressed: pankeratin, EMA and CD56. NSE and chromograninA were also focally positive. Synaptophysin, MelanA, calretinin, vimentin, p53, Ca125, CK7, CK20 and ER were negative. Ki67(MIB1) index of cell proliferation was ~ 70%.
Conclusion: Malignant transformation of a cystic teratoma is a rare finding (1,8%). SCCOPT is an extremely rare form of ovarian cancer. Histopathology, Cytopathology as well some specific tumour markers may be useful in diagnosing correctly an unexpected ovarian malignancy.

E-PS-09-053

Cross-talk between epithelial-mesenchymal transition, angiogenesis and natural killers in borderline ovarian tumours complicating pregnancy

A. Asaturova[1], M. Shamarakova[2]
[1] FSBI 'National Center for Obstetrics, Gynaecology and Perinatology named after V.I.Kulakov' Ministry of Healthcare Russian Federation, Russia, [2] Family Planning and Reproduction Center (Moscow), Russia

Background & Objectives: Physiological changes in the mother's body during pregnancy with the primary aim to support the fetus's growth may also suspected to worsen the natural course of various malignancies with even poorer prognosis then in non-pregnant women. Though borderline ovarian tumours generally have an excellent prognosis, the risk of their progression during gestation remain has yet to be investigated. The purpose of this study was to assess the expression of epithelial-mesenchymal markers, angiogenesis and the extent of natural killers in samples of ovarian borderline tumours in pregnant and non-pregnant women.
Methods: Twenty three samples [13 from pregnant (30,5±4,7 years) and 10 from non-pregnant women (33,6±5,8 years)] were investigated morphologically and immunohistochemically with VEGF, CD31, CD105, CD56, E-cadherin, Vimentin, Mann-Whitney test was used for statistics.
Results: Serous borderline tumours were diagnosed more frequently in pregnant and in non-pregnant women. In addition we diagnosed endometrioid and mucinous borderline tumours with well-diffentiated components in both groups. CD31 expression in pregnant women was significantly higher than that in non-pregnant patients ($p<0.05$) with the median number of CD31 positive vessels 28 (range 12 – 68) and 11 (range 4 - 19), respectively. There were no differences in the immunoreactivity of all other markers among both groups ($p>0.05$).
Conclusion: Borderline ovarian tumours in pregnant women were characterised by an enhanced CD31 expression compared with non-pregnant patients. The increase level of CD31 expression in pregnant women is supposed to be enhanced be pregestrone activity through progestin-dependent angiogenesis activation. We speculate that the similarity in VEGF, CD-105, E-cadgerin, Vimentin, CD56 expression in pregnant and non-pregnant women's indicates lack of stimulation in these agents-dependent signal pathways on borderline ovarian tumours progression complicating pregnancy.

E-PS-09-057

Low grade endometrial stromal sarcoma of the uterus metastasis to the right atrium and inferior vena cava as tumour thrombus after 10 years of hysterectomy: a case report

M. Suntur[1], G. Findik Guvendi[1], O. Semerci[1], S. Ozan Karakisi[2], R. Bedir[1]
[1] Recep Tayyip Erdogan University, Department of Pathology, Turkey, [2] Recep Tayyip Erdogan University, Department of Cardiovascular Surgery, Turkey

Background & Objectives: Endometrial stromal sarcoma (ESS) is a rare malignant mesenchymal tumour of the uterus. Endometrial stromal sarcoma of the uterus usually metastasis to the pelvic region. However cases showing intravascular and intracardiac metastasis even after 22 years of hysterectomy has also been reported. Here, we describe a 52-year-old woman who presented with right sided atrial mass and presumed inferior vena cava (IVC) thrombus which turns out to be an endometrial stromal sarcoma.
Methods: Sections of formalin-fixed and paraffin-embedded tumour tissue were stained with hematoxylin and eosin. An immunohistochemistry was performed.
Results: A 52-year-old woman was admitted to our hospital with respiratory distress. Transthoracic echocardiography revealed a mass in the IVC extends into the right atrium which reported as a thrombus. Thoracic and abdominal CT scans were also consistent with thrombus. Clinical and radiological impressions were consistent with thrombus. The patient received anti-coagulant treatment but did not respond to the treatment. A medical history revealed that the patient have had a hysterectomy 10 years ago and diagnosed with low grade endometrial stromal sarcoma. The intravascular and intraatrial mass entirely removed. On the macroscopic evaluation, a 18.5x3.2 cm tumoural mass with a tan-brown and grayish cut-surface and fish-meat like appearance observed. It borrows the shape of the vessels and atrium which it occupies. Microscopically tumour composed sheets of small monotonous cells with eosinophilic cytoplasm, round-to-oval nuclei and fine chromatin. There were concentric arrangement of tumour cells at the perivascular site of vessels. Pleomorphism and necrosis were absent. A prominent myxoid changes in the focal areas of the stroma noted. The mitotic index was low (4 mitoses/10 HPF).
Immunohistochemical stain revealed that the tumour was positive with estrogen receptor, and CD10; and negative with desmin, HHV-8, CD117. Ki-67 proliferation index of the tumour was low (%2-3). With the help of the overall immunohistochemical and morphologic features case diagnosed as a low-grade endometrial stromal sarcoma.
Conclusion: Endometrial stromal sarcoma makes up approximately 0.2% of all uterine malignancies and approximately 10% of all uterine sarcomas. ESS is divided into low grade and high grade on the basis of the frequency of mitoses. IVC and right atrium receives metastasis from renal cell carcinoma is a well-known fact. But ESS has also a potential to spread into IVC and right atrium. A case of ESS reoccurrence and metastasis to IVC 22 years after hysterectomy has been reported in the literature. Our case is also emphasis this important feature ESS. In the differential diagnosis of tumours of IVC and atrium endometrial stromal sarcoma also should be kept in mind both by clinicians and pathologists.

E-PS-09-058

New predictive markers for benign endometrial lesions: platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio

S. Köseoğlu[1], Y. Dere[2]
[1] Mugla Sitki Kocman University Training and Research Hospital, Department of Obstetrics and Gynaecology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Endometrial polyps (EP) and endometrial hyperplasia (EH) are the two of the most common causes of abnormal uterine bleeding. The aim of this study to evaluate the differentiation of EP and EH in patients by using NLR and PLR which are inflammatory markers.
Methods: This retrospective study consists of 108 patients diagnosed with EP and 80 patients diagnosed with EH without atypia. Ten cc of venous blood sample from every patient. Hemoglobin, MCV (mean corpuscular volume), RDW (red cell distribution width), MPV (mean platelet volume), numbers of lymphocytes, neutrophils, platelets, plateletcrit. NLR end PLR values were recorded.
Results: NLR values were found as 2.8□2.79 in EP group and 2.2□1.30 in EH group. (P=0.022). PLR values were 157.74□83.14 in EP group and 139.87□59.20 in EH group (P=0.024). There were significant differences in terms of PLR and NLR values.
Conclusion: EH and EPs can be differentiated before the intervention with NLR and PLR which are simple, easily accessible, repeatable and inexpensive methods.

E-PS-09-059

Fumarate hydratase deficient uterine leiomyoma: a case report

H. Sahin Ozkan[1], T. Oguzsoy[2], S.F. Eren[1]
[1] Marmara University Faculty of Medicine, Department of Pathology, Turkey, [2] Marmara university training anad researching hospital, Turkey

Background & Objectives: Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCCS) is a rare disease caused by germline Fumarate Hydratase (FH) mutation. Here, we report a case of FH-deficient leiomyoma (FHDL) without a previously known personal and/or family history.
Methods: A myomectomy specimen, diagnosed with atypical uterine leiomyoma in another medical center was sent to our pathology department for a second opinion. The patient was 33 years old.
Results: Gross examination revealed two masses: 1) A 4 cm myomatous mass, 2) A myomatous mass measuring 9.5 cm with some small foci of hemorrhage. Microscopic examination of the first mass showed an ordinary leimyoma. The second mass was a smooth muscle tumour consisting of hypocellular areas with alveolar-edema and hypercellular areas. Symplastic atypia, prominent cherry-red nucleoli, peri-nuclear clearing, intracytoplasmic eosinophilic globules, and hemangiopericytomatous vessels were the most notable findings. Mitosis was 1/10 HPF. Atypical mitosis and/or necrosis were absent. Tumour cells were positive for SMA and negative for CD10 antibodies. Complete loss of FH immunexpression was found in the tumour cells. The diagnosis was FHDL. An explanatory note was added to clarify that although the most FHDLs are seen sporadically, genetic testing should be recommended if the other risk factors for HLRCCS are present.
Conclusion: Uterine FHDL is a basic component of HLRCCS. While evaluating atypical leiomyomas, pathologists should bear in mind the typical histomorphological findings of FHDL. Histomorphology is superior to blind immunohistochemical screening. Approximately 1% of all uterine leiomyomas are FH-deficient, usually due to somatic inactivation. Genetic testing for HLRCCS should not be routinely recommended to the patients with FHDL in the absence of other clinical risk factors.

E-PS-09-060

Uterine Mullerian Adenosarcoma: a retrospective study of 13 cases

S. Ben Khalifa[1], N. Abdessaied[1], T. Zahmoul[2], E. BelhajKhalifa[2], S. Chaieb[1], B. Atika[2], M. Mokni[1]
[1] Pathology Department of Fattouma Bourguiba Hospital, Monastir, Tunisia, [2] Department of Pathology; Farhat Hached Hospital; Sousse, Tunisia

Background & Objectives: Uterine adenosarcoma is a rare tumour (8% of uterine sarcomas) with a dual component: a benign glandular compartment and a sarcomatous stroma. The objective of this work is to report the clinical and pathological features of this tumour.
Methods: We retrospectively analysed the clinical and pathologic data of 13 patients, initially diagnosed and treated at our institution from 1993 to 2018. Histological confirmation of the diagnosis was obtained after biopsy of the tumour or after hysterectomy.
Results: The median age at diagnosis was 53 years (range, 21–69 years). The majority of patients presented with abnormal uterine bleeding (69%). On preoperative clinical examination, a polyp prolapsing through the cervix was seen in 6 patients (46%). The average tumour size was 11.2 cm (7,8 to 16 cm). Eight patients (61,5%) had stage I disease, 3

(23%) had stage II disease, 7,6 (4%) had stage III disease, and 7,6 (3%) had stage IV disease. Six patients (46%) had sarcomatous overgrowth, and 7 patients (53.8%) had tumours that contained heterologous elements. Death due to the disease was observed in 53,8% (7/13) of patients.
Conclusion: Uterine adenosarcoma is rare cancer, whose diagnostic and therapeutic management are multidisciplinary as regards gynecologists, pathologists, and oncologists. This tumour is seen especially in postmenopausal patients with a polymorphic symptomatology dominated by metrorrhagia. Its prognosis remains favorable in localized forms, of which the surgery alone seems sufficient, on the other hand for the extended forms which are still controversial; Radiochemotherapy always retains their place.

E-PS-09-061
Agressive angiomyxoma of the vulva: a report case
S. Yacoub[1], S. Mistiri[1], D. Chiba[1], T. Tlili[1], N. Abdessayed[1], M. Mokni[1]
[1] Department of Pathology Farhat Hached Hospital, Tunisia

Background & Objectives: Aggressive angiomyxoma (AA) is a rare, locally aggressive mesenchymal tumour of the perineum, affecting more frequently women. its aggressiveness is local, reflecting its infiltrating character and its tendency to recurrence.
We describe the clinical and pathological characteristics of an aggressive angiomyxoma of the vulva.
Methods: A 40-year-old woman with no previous history, consulted for a swelling of the large right lip of the vulva. A surgical resection was performed.
Results: The resected specimen showed a polypoid tumour of 5 cm long axis fixed to a pedicle of 1.3 cm. The surface was greyish without any ulcer or erosions. Histological examination showed a mesenchymal proliferation, of low to moderate cell density. It was made of stellate or elongated fibroblastic-like cells. The stroma was loose, myxoid full of capillaries and venules of variable size. There were scalloped with regular endothelial lining. The skin surface was regular, non-ulcerated. the surgical boundaries were tumour-free.
Conclusion: AA is a locally aggressive rare mesenchymal tumour of the pelvis, expressing the hormone receptors. Surgical removal is the main treatment. The use of hormonal treatment during recurrences is being evaluated and shows in some cases encouraging results.

E-PS-09-062
Mucinous adenocarcinoma of the uterine cervix: clinicopathological study of 8 cases
M. Manai[2], G. Sahraoui[2], R. Doghri[1], R. Sallami[2], H. Guizani[2], K. Mrad[1], L. Charfi[1], M. Driss[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia, [2] Salah Azaiez Institute, Tunisia

Background & Objectives: Adenocarcinoma is the second type of cervical cancer accounting for 20–25% of all cervical cancers. Mucinous adenocarcinoma was redefined in 2014 WHO classification into different subtypes: gatric type, intestinal type and signet-ring cell type. The aim of this study is to describe the clinicopathological characteristics of these various subtypes of cervical cancer.
Methods: This was a retrospective descriptive study of patients diagnosed between 1 January 2010 and 31 December 2016 in one cancer institute. All the cases of cervical adenocarcinoma were defined as mucinous adenocarcinoma according to 2014 WHO classification. We analysed their clinical and pathological characteristics.
Results: Among the 38 cases of cervical adenocarcinoma, 8 (21%) were diagnosed as mucinous. Five were intestinal type, one was of gastric type, two were signet-ring cell type. The patients' mean age was 48 years and 6 patients were premenopausal. The revealing symptom was metrorrhagia in seven cases and (38%) and pelvic pain whose exploration revealed an ovarian mucinous tumour. No patient had a cervical smear. Six cases were negative for p16(INK4a) in immunohistochemistry. Seven patients had recurrence or metastases after initial treatment.
Conclusion: Mucinous adenocarcinoma is a rare and aggressive form of cervical cancer that can be confused with other pathological types.

E-PS-09-063
Primary ovarian carcinoid arising in mature cystic teratoma: case report
A.C. Lisievici[1], T.A. Georgescu[2], M. Sajin[3,4,5], R. Bohaltea[6]
[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Bucharest Emergency University Hospital, Romania, [3] SUUB, Romania, [4] UMF Carol Davila, Romania, [5] European Society of Pathology, Romania, [6] Department of Obstetrics and Gynaecology, Emergency University Hospital Bucharest, Romania

Background & Objectives: Carcinoids are rare neuroendocrine tumours with an incidence of 1 to 2 cases per 100,000 patients. Primary ovarian carcinoids account for less than 1% of all carcinoid tumours and less than 0.1% of all ovarian neoplasms, being so rare that a clinician may not encounter even one during his or her entire medical career.
Methods: We report the case of a postmenopausal 64-year-old female presenting to the Emergency University Hospital in Bucharest, Romania due to lower abdominal pain. CT examination revealed a large, well-defined, bilobed solid and cystic mass of the left ovary, with no detectable ascites. The patient underwent bilateral salpingo-oophorectomy.
Results: Gross aspect of the left adnexa and subsequently examined frozen sections were suggestive for mature cystic teratoma. Careful postoperative histopathological examination of the solid areas revealed a mixed-type carcinoid (insular and trabecular) arising in the background of a mature cystic teratoma. The tumour was limited to the left ovary, without rupturing the cyst wall (T1a). Ancillary tests revealed immunoreactivity for synaptophysin, chromogranin and a low Ki-67 proliferative index (<1%). ER, PR and CDX2 were negative. The right ovary was unremarkable.
Conclusion: In the absence of other teratomatous elements, primary ovarian carcinoids may be difficult to distinguish from metastatic carcinoids. Carcinoid syndrome may develop in the absence of liver metastases. Diagnosis should always be confirmed by immunohistochemistry and extensive sampling of any solid area within a mature teratoma is emphasized, in order to minimize the risk of missing a focus of carcinoid.

E-PS-09-064
Hormone receptor end p16 immunohistochemical expression in distinction between endometrial and endocervical adenocarcinoma
R. Narjess[1], N. Boujelbene[2], M. Driss[2], R. Doghri[2], I. Abbes[2], H. Azaiz[2], N. Ben Hamida[2], K. Mrad[2], L. Charfi[2]
[1] Institut of Carcinology Salah Azaiz Tunis, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Primary endometrial (EmA) and endocervical (EcA) adenocarcinoma are recognized as distinct entities, with different etiologies, behavior and treatments. Sometimes, distinction between them is often difficult in limited diagnostic specimens such as biopsies or curettage specimens. We investigated the value of a panel of antibodies, to distinguish between primary EmA and EcA.
Methods: We use a panel of immunohistochemical stains including estrogen receptor (ER), progesterone receptor (PR) and p16 in a series of cervical biopsies presenting considerable overlap in the morphological features of adenocarcinoma arising in the two sites mentioned above.
Results: Twenty-eight biopsies were evaluated. They concern 20 EmA and 8 EcA. The great majority of EmA (77.7%) express ER but no case of

EcA express ER (p=0.001). Likewise, PR was expressed in most EmA (73.3%) and no case of EcA (p=0.001).
Seventy-five percent of EmA display variable patchy p16 expression, only 1 case show extensive p16 expression. All EcA show diffuse nuclear p16 expression (p<0.0001).
Conclusion: We conclude that ER, PR and p16 are useful immunohistochemical markers in distinguishing EmA and EcA. The "classic" endometrial adenocarcinoma will be positive for ER, PR and show weak or patchy p16. In contrast, the "classic" endocervical adenocarcinoma will be strongly and diffusely positive for p16 but negative for ER, and PR. This distinction is important to make because the different therapeutic management and prognosis.

E-PS-09-065
Vulvar sarcoma: a single institution experience
M. Manai[1], R. Doghri[2], G. Sahraoui[1], R. Sallami[1], D. Kacem[1], K. Mrad[2], M. Drisse[2], L. Charfi[2]
[1] Institute Salah Azaiez, Tunisia,
[2] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Sarcomas of the vulva comprise approximately 1–3% of all vulvar cancers, with leiomyosarcomas, epithelioid sarcomas, and rhabdomyosarcomas being the most common among them.
The aim of this study is to report our incidence of sarcoma at this site and to emphasize the broad differential diagnosis and the prognostic factors.
Methods: All patients with a diagnosis of vulvar sarcoma at the department of pathology of Salah Azaiez Institue over a period of 25 years (1993 - 2018). Clinical, histopathological and immunohistochemical features were recorded.
Results: Six vulvar sarcomas were diagnosed during this period: rhabdomyosarcoma (n = 2), leiomyosarcoma (n=1), epithelioid sarcoma (n=1), dermatofibrosarcoma (n=1), and carcinosarcoma (n=1). The age ranged from 2 months to 56 years. The rhabdomyosarcomas were of embryonal-type and were diagnosed at early childhood (2-16months). All the cases were clinically present as a non-specific tumour mass. The tumour size ranged from 30 to 80mm. The diagnosis was made on biopsy in all cases. Immunohistochemistry was necessary to classify these sarcomas. A vulvectomy was performed in 3 cases (Dermatofibrosarcoma, epithelioid sarcoma, carcinosarcoma) with negative microscopic margins in only one case (dermatofibrosarcoma). Chemotherapy was indicated in rhabdomyosarcomatous cases.
Conclusion: Sarcomas of the vulva are rare malignant neoplasms that often lead to misdiagnosis.It is important to consider them in the clinical differential diagnosis of non-specific vulvar lesions, in order to establish an early accurate diagnosis and appropriate treatment.

E-PS-09-066
RIG-1 is down regulated in placental tissue in cases of early - and late - onset preeclampsia
N. Nizyaeva[1], M.N. Nagovitsyna[1], E.Y. Amiraslanov[1], N.A. Lomova[1], S.V. Pavlovich[1]
[1] V.I.Kulakov National Research Center for Obstetrics, Gynaecology and Perinatology of Ministry of Healthcare of the Russian Federation, Moscow, Russia

Background & Objectives: The objective was to study in placental samples in cases of early–(EPE) and late – onset (LPE) preeclampsia.
Methods: Groups with PE included 12 women with EPE and 8–with LPE. Control groups consist of 10 women with normal pregnancy, 38-39 gestation weeks (late control–LC), and 10 – 26-30 weeks (early control–EC). We performed histological (hem&eosin) and immunohistochemistry studies on the paraffin-embedded slices of placenta, taking after cesarean section, using RIG-1 primary polyclonal antibodies (1:500;GenTex). The intensity of immunohistochemical reaction was estimated by means of microscope imaging software NIS-Elements.
Results: The immunohistochemical study indicated RIG-1 staining in placental villi: amnion cells, endothelium, decidual cells, cyto-and syncytiotrophoblast, syncytial knots, stroma cells. RIG-1 demonstrated significantly higher expression in syncytiotrophoblast (17+4) in LC group than in the other studied groups EC (8+3), EPE (9+4) and LPE (11+3), (p<0.01). Compare to LC group RIG-1 expression were at 47% higher than in EC, 52.9% higher than in EPE, and 62.7% higher than in LPE group (p<0.01). Decreased RIG-1 expression probably contributes to the development of pro-inflammatory response and PE.
Conclusion: Thus, down regulated in syncytiotrophoblast RIG-1 expression in PE confirmed pro-inflammatory trophoblast phenotype and may be one of the predisposing factor for preeclampsia.

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E-PS-09-068
Morphological effects of chemoradiation therapy on cervical adenocarcinoma
A. Candaele[1], J. Van Dorpe[1], E. De Jaeghere[1], P. Tummers[1], A. Makar[1], P. De Visschere[1], H. Denys[1], K. Vandecasteele[1], K. Van de Vijver[1]
[1] Ghent University Hospital, Belgium

Background & Objectives: The Study group included 10 women with a histological diagnosis of advanced cervical adenocarcinoma, receiving neo-adjuvant chemoradiation therapy followed by radical surgery. The aim for the present study is to evaluate the responsiveness to chemoradiation and to identify pathologic changes that occur during treatment and systems for evaluating response to treatment and its effect on long-term survival.
Methods: Pathological response to treatment was evaluated by the presence of residual neoplastic tissue, fibrosis, calcifications, necrosis, inflammatory infiltrates, foamy macrophages, foreign body-like giant cells, acellular pools of mucin and pleomorphic neoplastic nuclei.
Results: 9 out of 10 women responded partially or well to neo-adjuvant chemoradiation therapy. In the patients that responded we can distinguish 3 groups with different morphological features. A first group showed little response with nearly no fibrosis or inflammation, resulting in expanded network of infiltrating small and angulated glands. The second group having an excellent response, was associated with expanded acellular pools of mucin with little remaining tumour glands. A third group showed a good response with an altered eosinophilic morphology of the remaining tumour nests.
Conclusion: Identification of predictive markers associated with a good survival may prove clinically useful and implement an individualized treatment plan.

E-PS-09-070
A unique presentation of blue nevus: a patient with endocervical location
R. Yilmaz[1], R. Bedir[2], O. Semerci[2]
[1] Sanliurfa Siverek Community Hospital, Turkey,
[2] Recep Tayyip Erdogan University Deparment of Pathology, Turkey

Background & Objectives: Blue nevi, composed of spindle-like dendritic melanocytes, are benign lesions usually located on the reticular dermis of the skin and rarely located on mucous membranes. The endocervical blue nevus is a rare benign lesion which can be incidentally found in hysterectomy specimen. Since this is a very rare condition, we intended to report it in the literature.
Methods: A 54-year-old female patient with a long history of menorrhagia was admitted to Obstetric and Gynaecology clinic. The patient had intramural leiomyoma in the radiologic examination. The patient underwent the surgical procedure of total abdominal hysterectomy.

Results: We observed an endocervical polyp and a hyperpigmented area under this polyp on macroscopic examination. Histological examination revealed benign, pigmented, dendritic spindle cells between endocervical glands in the stroma of the uterus cervix. The dendritic spindle cells were immunoreactive for S100 and HMB45. The pigment showed a positive reaction to Fontana-Masson histochemical stain. Melanin pigment in the basal epithelium was not observed in the endocervix. There was no junctional activity in the endocervix. There were no increased typical-atypical mitotic activity, pleomorphism and necrosis. We reported this case as a blue nevus.
Conclusion: Blue nevi of endocervix are usually found incidentally in hysterectomy specimens, and they are usually located in the stroma of the cervix. When located on the endocervix, the blue nevus might be confused with other benign or malignant lesions. Although the blue nevi seem to be lesions of low clinical significance, they require careful differential diagnosis with malignant melanoma, especially in scanty endocervical curettage or cervical biopsy specimens. Herein, we reported a case with endocervical blue nevus presented as an endocervical polyp, which is a rare phenomenon.

E-PS-09-071
Epithelioid leiomyosarcoma with glandular-like pattern
Y. Rogov[1], N. Kornev[2], A. Syantovich[2], O. Solodkaya[2], Y. Kuzmenka-Maskvina[1], V. Zubovich[2], E. Grigorieva[1]
[1] Belarusian Medical Academy of Postgraduate Education, Belarus,
[2] City Clinical Pathology Bureau, Belarus

Background & Objectives: Epithelioid leiomyosarcoma differs from ordinary spindle cell leiomyosarcoma by rounded or polygonal cells with eosinophilic or clear cytoplasm. They may be arranged in sheets, cords, trabeculae, nests. We report a case of recurrent leiomyosarcoma with unusual glandular-like pattern.
Methods: A 71-year-old female patient was hospitalized with recently appeared abdominal pain. 8 years ago, she underwent combined treatment for uterine leiomyosarcoma. Clinical examination revealed tumour nodes in the greater omentum, mesentery of the small intestine and peritoneum measuring 4.0, 2.0 and 2.0 cm in diameter. They were removed, and tissue samples were investigated histologically and immunohistochemically.
Results: Microscopic evaluation of all tumour nodes revealed an epithelioid leiomyosarcoma with areas of conventional type. Tumour cells were predominantly rounded, with eosinophilic cytoplasm. They focally formed glandular-like structures, lining the gaps in one or several rows. These sites looked like adenocarcinoma. Immunohistochemical staining was positive for SMA, Desmin, WT1 and negative for CK, GLUT1, BerEP4, Calretinin, ERG, CD31, CA125, CD117, DOG1, PAX8. Mitotic activity was high. Epithelioid leiomyosarcoma recurrence with glandular-like pattern was diagnosed.
Conclusion: Epithelioid leiomyosarcoma occasionally can form pseudoglandular structures that can be regarded as adenocarcinoma. Histological signs of myoid differentiation in tumour and immunohistochemistry help make the correct diagnosis. We could not find similar descriptions in the available literature.

E-PS-09-072
Uterin mullerian adenosarcoma: an unusual tumour of the uterus
S. Yacoub[1], M. Sara[1], D. Chiba[1], N. Abdessayed[1], B. Sriha[1]
[1] Department of Pathology Farhat Hached Hospital, Tunisia

Background & Objectives: Uterine Mullerian adenosarcoma is an uncommon biphasic tumour composed of a malignant stromal component and benign epithelial component. It was originally described in 1974 and is considered of low malignant potential. We report 2 rare cases of Mullerian adenosarcoma.
Methods: There were two women of 23 and 43 years old, presented clinically with vaginal bleeding. Clinical examination showed a polypoid mass projecting through the cervix. A polypectomy was performed in both cases
Results: Macroscopic examination showed a fleshy and yellowish polypoid mass measuring 3,3 cm in the first case and 8,5cm in the second. No necrosis or hemorrhage were observed. The two tumours shared the same histological features, of a biphasic tumour, formed by a malignant stroma, with moderate to high density. Mesenchymal cells were elongated myofibroblastic-like with low to moderate atypia. Periglandular cuffing of the stromal cells around compressed or cystically dilated benigne endometrial glands, displaying focally progesterone impregnation. Immunohistochemistry was performed in only one case and showed Smooth muscle actin (SMA) expression by stromal cells and negativity of desmin and H-caldesmon.
Conclusion: Adenosarcoma of uterus is a biphasic tumour of generally low malignant potential. A complete and Monobloc surgical resection is the ideal therapeutic option.

E-PS-09-076
Sex cord-stromal tumours of the ovary: clinicopathological and genetic analysis
C. Bartosch[1], S. Alves[2], M. Pinheiro[3], M. Farinha[1], F. Pereira[2], J. Costa[1], F. Silva[1], R. Santos[3], A. Peixoto[3], S. Sousa[2], A. Petiz[4], M.R. Teixeira[3], D. Pereira[2]
[1] Department of Pathology IPOP, Portugal, [2] Department of Oncology IPOP, Portugal, [3] Department of Genetics IPOP, Portugal, [4] Department of Gynaecology IPOP, Portugal

Background & Objectives: Sex cord-stromal tumours are a heterogeneous group of rare neoplasias, with variable biological behavior. This study aims to describe the clinico-patological features of a series of patients with pure sex cord tumours and mix sex cord-stromal tumours of the ovary.
Methods: Retrospective cohort study of a series of patients with sex cord-stromal tumours of the ovary, managed at Portuguese Oncology Institute of Porto (1994-2018). We collected clinical data, reviewed histological material and performed *FOXL2* gene mutations analysis.
Results: Initially we included 41 patients, but only 34 had available histological material. After histological review, tumour subtype changed in 6 patients and one was excluded. We included in the analysis 33 patients, with a median age at diagnosis of 53 (4-79) years. Histological subtypes included 18 adult granulosa cell tumours (TCGA), 9 Sertoli-Leydig cell tumours (TCSL), 2 Sertoli cell tumours and other (n=4). We identified *FOXL2* gene mutations in 14/29 patients, of which 13/16 (81%) corresponded to TCGA, and 1 TCSL. The majority (87.9%) was diagnosed as FIGO stage I. Ten patients had recurrences and 6 died of the disease.
Conclusion: Our series clinico-pathological features are in accordance with previous studies, emphasizing the variability in clinical presentation and morphology of these tumours. The frequency of *FOXL2* gene mutations is also concordant with that reported in the literature. This study highlights the need for central review and reinforces the diagnostic utility of *FOXL2* gene mutations.

E-PS-09-077
A review of the morphologic features of endometrial hyperplasia without atypia, complex after progesterone therapy
S. Noh[1], E. Shin[2], J. Kim[2], J.Y. Shim[2]
[1] CHA Gangnam Medical Center, CHA University School of Medicine, Republic of Korea, [2] CHA University School of Medicine, Republic of Korea

Background & Objectives: Endometrial hyperplasia without atypia is a precursor of endometrial carcinoma. Well differentiated endometrial carcinoma occurs in 1-3% of women with hyperplasia without atypia. Because of retaining fertility, women with endometrial hyperplasia or early stage endometrial carcinoma want to manage with conservative Progesterone therapy. However, Progesterone therapy changes the endometrial morphology and gives pathologist difficulties. To help determine

the therapeutic effect, we aimed to review and list common morphologic features that can distinguish residual complex endometrial hyperplasia without atypia from Progesterone effect. Because the degreee of nuclear atypia is difficult to make intuitive judgment, we reviewed the complex hyperplasia without atypia with the greatest morphological diversity.
Methods: Endometrial curettage and/or biopsy samples that were diagnosed with complex hyperplasia without atypia and had three or more follow-up curettage and/or biopsy of the uterine endometrium from 2008 to present were searched from the database of the Department of Pathology, CHA Gangnam Medical Center. Fifty-two cases diagnosed with complex hyperplasia without atypia were retrieved, but 12 cases were excluded because material insufficiency due to either therapeutic effect or sampling error. Thus, 40 cases were finally included in the review.
Results: Of the retrieved 40 cases, the most frequent morphologic features of complex hyperplasia without atypia after Progesterone treatment were papillary configuration in all cases. All cases turned into dull and blunt shape on follow-up. The helpful features were residual or new squamous morule. The reasons for misclassification of nuclear atypia were eosinophilic metaplasia, after hormonal therapy, similar to apocrine metaplasia in the breast. Two cases of mucinous metaplasia, similar to endocervical glands of uterine cervix can be misdiagnosed as carcinoma, because of their architectural complexity.
Conclusion: Although advances in medical technology have increased the number of people receiving Progesterone treatment, there are still rare reports of changes in morphology after Progesterone therapy. However, false-positives or false-negative cannot be avoided to some extent. Identifying papillary configuration and squamous morule has a merit in itself in that it often leads to the identification of underlying complex hyperplasia without atypia.

E-PS-09-078
A morphometric study of hypoxic and vascular changes of chorionic villi in maternal vascular malperfusion
D. Obradovic[1], R. Jankovic[1], J. Jevtic[1], D. Opric[1]
[1] Faculty of Medicine, University of Belgrade, Serbia

Background & Objectives: Maternal vascular malperfusion (MVM) represents altered uterine and intervilous blood flow resulting in recognizable hystological pattern of placental hypoxic injury with potential adverse effect on fetus. MVM is frequently found in pregnancies complicated by preeclampsia and intrauterine growth restriction.
Being that MVM is vascular and hypoxic phenomenon affecting fetoplacental exchange we analysed a level of vascularisation of chorionic villi and level of intravillous fibrosis.
Methods: Five placentas with MVM were morphometricaly analysed. Inclusion parameters were syntitial knots present in 30% or more terminal villi, retroplacentar haematoma and weight of placenta under 10th percentile for week of gestation. Materials were obtained from autopsy speciments at Institute of Pathology, Medical Faculty in Belgrade. Formalin fixed paraffin embedded tissues were stained with Masson-Trichrome stain for evaluation of fibrosis and blood vessels were marked with CD34 antibody. All images were analysed using Fiji software. Statistical analysis was performed using Microsoft Excel software.
Results: Results of statistical analysis have shown trend of correlation between higher level of vascularisation of chorionic villi with increase of deposition of intravillous fibrin. Analysis haven't shown statistical significance which may be expected due to small sample.
Conclusion: We believe these observations should shed some light on the way of thinking about fibrosis of chorionic villi. We are of opinion that perhaps deposition of intravillous fibrin shouldn't be observed as strictly degenerative, but instead as positive reactive change as part of adaptation to hypoxia in placenta.

E-PS-09-079
Aggressive angiomyxoma of the uterus: a case report
Y. Rogov[1], N. Kornev[2], Y. Kuzmenko-Moskvina[1], A. Syantovich[2], S. Budanova[2]
[1] Belarusian Medical Academy of Postgraduate Education, Belarus,
[2] City Clinical Pathology Bureau, Belarus

Background & Objectives: Aggressive angiomyxoma is a rare myxoid mesenchymal tumour of the pelvis and perineum, which is not included in the latest WHO Classification of tumours of the uterine corpus since it was found in this location in exceptional cases. Morphological diagnosis may be difficult, since the tumour is similar to various myxoid sarcomas. We report our observation of this neoplasm.
Methods: A 58-year-old woman was hospitalized with complains of acute minor vaginal bleeding for some days. The patient was in menopause for 10 years. The examination revealed a submucous node in the body of the uterus 5,5 cm in diameter. Structures suspected of sarcoma were found in curettage tissue samples. After radical hysterectomy, a macroscopic, histological and immunohistochemical study of this tumour was performed.
Results: The tumour had a soft gelatinous appearance with small hemorrhages on cut sections and predominantly well-defined margins, unencapsulated. Microscopically it was highly myxoid, composed of uniform, small, stellate and spindle shaped cells with indistinct borders, without pleomorphism, necrosis and significant mitotic activity. Cellularity was low to moderate. Vessels of various sizes were regularly present, some of them with thick muscular walls. Immunohistochemical staining was positive for Desmin, Vimentin, ER, PR, weakly positive for CD34 and negative for MyoD1, S100, SMA. Ki67 reached about 5-10% (up to 20% in "hot spots"). An aggressive angiomyxoma was diagnosed.
Conclusion: Aggressive angiomyxoma can sometimes be found in the body of the uterus. The diagnosis of this tumour in the study of curettage biopsies is difficult. It should be considered in the differential diagnosis of uterine myxoid lesions.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-10 | Haematopathology

E-PS-10-001
Angioimmunoblastic T-cell lymphoma in patient with plasm cell myeloma. Case report and review of the literature
A. Abuomar[1], T. Lopez[1]
[1] Hospital General Universitario de Elda, Alicante, Spain

Background & Objectives: Angioimmunoblastic T-cell lymphoma (AITL), a subtype of mature peripheral T cell lymphoma, is a neoplasm of mature T folicular helper characterised by a systemic disease involving lymph nodes (LN). AITL has a typical morphological, immunohistochimical (IHQ) and molecular signature. Usually affects older people with a poor prognosis. Rarely associates with B cell neoplasm, exceptionally with plasm cell myeloma (PCM) with few cases reported in the literature to the best of our knowledge.
Methods: A 72 years old man with PCM with high risk cytogenetics, on treatment, and chronic renal faillure was admitted to our hospital with persisted fever, skin rush, generalized lymphadenopathy and positive polymerase chain reaction (PCR) and immunoglobulin M for Epstein-Barr virus (EBV). No improvement was seen after a few weeks of symptomatic treatment. Lymphadenectomy of an enlarged axillary lymph node was done rule out a possible lymphoproliferative disorder.
Results: LN with total effacement of morphology, prominent vascularity with arborization of high endothelial venuls (HEV), a proliferation of small to medium size atypical lymphocytes with clear cytoplasm and distinct cell membrane in an inflammatory back ground. No cells of Hodgkin or Reed–Sternberg morphology were seen. IHQ: CD3, CD4, BCL6, CD10, ICO, PD1 and CXCL13. Few cells expressed CD20+, CD30+. EBER1+ cells were seen. CD23 revealed a marked folicular dentritic cell proliferation entrapping HEV. TCR gene rearrangement were clonal.
Conclusion: Typical morphological, IHQ and molecular characteristics of AITL are diagnostic in the majority of cases, however, realizing a differential diagnosis with Reactive T Zone Hyperplasia,

Angiofollicular Lymphoid Hyperplasia (Castleman Disease), Plasma Cell Type, Peripheral T Cells Lymphoma NOS, T-cell/histiocyte-rich B-cell Lymphoma and Hodgkin Lymphoma is mandatory. It is recommended to report percent of CD30+ cells since target therapy is available.

E-PS-10-002

Retroperitoneal and kidney infiltration with anaplastic plasm cell myeloma simulating an obstructive acute renal failure. Case report and literature review

A. Abuomar[1]
[1] Hospital General Universitario de Elda, Alicante, Spain

Background & Objectives: Anaplastic plasm cell myeloma (APCM) is a rare, highly aggressive and treatment-resistant subtype of plasm cell myeloma (PCM) with Identical morphological and Immunohistochemical (IHQ) findings to plasmoblastic lymphoma (PL). We report, up to our knowledge, the second case in literature with clinical presentation of an obstructive acute renal failure duo to retroperitoneal and renal infiltration.
Methods: A 67 years old immunocompromised heart transplant man was admitted to nephrology department with a clinical picture of obstructive acute renal failure. CT scan suggested metastatic urethral carcinoma showing multiple retroperitoenal nodular masses with infiltration of left kidney and ureter, dilatation of renal chalices, enlarged retroperitoneal and hiliary adenopathy. Bone marrow aspiration showed sheets of anaplastic plasma cells. Monoclonal serum and urine immunoglobulins were detected. A total nephrectomy was performed as a suspicious of metastatic urtetral neoplasm persisted.
Results: Gross examination showed a multiple perirrenal nodular masses of 1-5cm which extrinsically infiltrated left renal parenquima and proximal ureter simulating intraurethral neoplasm with stenosis.Microscopic study showed a monomorphic diffuse proliferation of large cells with plasmoblastic appearance,multinucleated plasmoblast,multiple mitosis and numerous apoptotic figures were seen, with a starry sky appearance.Small cells with plasmocytoide appearance were seen.IHQ:CD138+,CD79A+,CD56+ ,MUM1+,CD20-,CD10-, LMP1-,PAX5-,CD45-,ALK-,HHV8-, EBER1+ Bone marrow monoclonal aberrant plasm cells with 1q21 amplification and 14q32 IGH rearrangement confirmed the diagnosis of APCM. Patient died duo to gastric cancer.
Conclusion: In the setting of immunodeficiency, APCM and PL can be associated with EBV, thus making differencial diagnosis always challenging and sometimes impossible. The diagnosis of APCM should base on clinico-morphological, IHQ and molecular findings. Serum/urine monoclonal immunoglobulins is vital for the diagnosis, though patients with PCM can develop lymphproliferative disorders including PL.

E-PS-10-003

Cytokeratin expression in acute leukaemia: a potential pitfall

J. Garry[1], E. O'Driscoll[1], R. Werner[1], A. Connolly[1], B. Hayes[1]
[1] Cork University Hospital, Ireland

Background & Objectives: Cytokeratin expression is characteristic of carcinomas but is thought rare in haematological malignancies. While several studies have examined cytokeratins in mature lymphoid neoplasms, and several case reports describe cytokeratin expression in acute myeloid leukaemia (AML), no systematic assessment has to our knowledge been previously reported in AML or in acute lymphoblastic leukaemia (ALL). We aimed to assess expression of cytokeratins by immunohistochemistry in a series of bone marrow trephine biopsies from patients with acute leukaemia.
Methods: Fifty bone marrow biopsy specimens from 2013-2017, SNOMED coded as "acute leukaemia" were selected from our files. Original H&E slides were retrieved, new sections stained with MNF116 and AE1/3, and all slides reviewed by a consultant and a trainee pathologist. Cytokeratin expression in tumour cells was graded semiquantitatively from 0 to 3+. The number of cells staining was recorded as 1-10%, 10-25%, 25-50%, 50-75% or 75-100%. Cases with at least 2+ positivity were further examined with an extended cytokeratin panel.
Results: 41 AML and 9 ALL cases were included. The reproducibility of 1+ staining was very poor (AE1/3 $\kappa = 0.16$, MNF116 $\kappa = 0.13$) and so only 2+/3+ staining was considered positive. Three of the AML cases (7.3%) showed at least 2+ staining with AE1/3 or MNF116, which was cytoplasmic and dot-like in character, involving at least 10% of the tumour cells. One case showed 3+ MNF116 positivity in 50-75% of tumour cells and also had 3+ staining with CAM5.2.
Conclusion: Cytokeratin expression in acute leukaemia is uncommon, but not rare (7.3% of all AML cases in this retrospective study), and can be strong and diffuse. Leukaemia can present at extramedullary sites, where cytokeratins may be included in a broad immunohistochemical panel for work-up of a poorly differentiated malignant neoplasm. Pathologists should be aware of the potential pitfall in this scenario.

E-PS-10-004

Histomorphologic evaluation of bone marrow involvement in mantle cell lymphoma and its correlation with flowcytometric immunophenotyping

S. Sharma[1], S. Yadav[1], K. Rahman[2], M. Murari[1]
[1] Department of Pathology, SGPGIMS, Lucknow, India,
[2] Department of Clinical Haematology, SGPGIMS, Lucknow, India

Background & Objectives: Mantle cell lymphoma (MCL), accounts for approximately 3-10% of Non-Hodgkin lymphomas. It is usually composed of monomorphic small to medium-sized lymphoid cells and needs to be distinguished from other small B - cell lymphoproliferative diseases i.e. CLL, B - PLL, follicular lymphoma and marginal zone lymphomas. The aim of the study was to analyse the prevalence of bone marrow involvement and correlate histomorphologic findings with flow cytometric analysis in a series of patients with MCL.
Methods: We retrospectively analysed 26 consecutive patients of MCL diagnosed over a period of 3 years for bone marrow (BM) involvement. BM involvement was assessed by conventional morphology, IHC and flow cytometry (FC) in BM aspirate and trephine biopsy specimens.
Results: MCL comprised 13.7% of all Non-Hodgkin's lymphomas with BM involvement. BM involvement was identified in 22 trephine biopsies. The extent of lymphomatous infiltration ranged from 10-90%. Diffuse pattern of infiltration was seen in 10 cases. All cases were positive for CD5, CD20, and negative for CD23 on both FC and IHC. Cyclin D1 was positive in all cases on IHC. There was a significant correlation between percentage marrow infiltration on BM histology and FC (Spearman's correlation coefficient 0.67, p-value 0.014).
Conclusion: Bone marrow involvement was found in majority of patients with MCL. Bone marrow involvement was associated with high circulating lymphocyte count and serum LDH levels. The histomorphologic findings in BM trephine correlated with flow cytometric analysis.

E-PS-10-005

Lollipops and onions: Castleman disease-like changes in malignant lymphoma - comparison with true Castleman disease and IgG4-related lymphadenopathy

M. Válková[1], K. Kamaradua[1]
[1] The Fingerland Department of Pathology, Charles University Faculty of Medicine and University Hospital in Hradec Kralove, Czech Republic

Background & Objectives: Morphological features of hyaline vascular type of Castleman disease include atrophic germinal centers, prominent mantles with onion skinning and increased vascularity with penetration of vessels into germinal centers (lollipops). Similar patterns can be seen in a subset of IgG4-related lymphadenopathy and in rare cases of malignant lymphoma causing a possible diagnostic pitfall.
Methods: Eleven cases were retrieved from the archive using keyword search for lymph nodes with Castleman disease-like features. All cases

have been reviewed with focus on distinguishing malignant and benign lesions. Additional testing was performed in all cases including basic immunohistochemical panel (CD20, CD23, bcl-2, CD5, cyclin D1, Ki67, CD10, bcl-6, immunoglobulin light chains and IgG4).
Results: Out of eleven cases, five cases presenting with partial or fully developed Castleman disease-like features were lymphomas including three cases of follicular lymphoma and two cases of mantle cell lymphoma. Immunohistochemistry was crucial for establishment of diagnosis of malignant lymphoma. Four cases fulfilled morphological criteria of probable IgG4-related lymphadenopathy with high numbers of IgG4+ plasma cells. Two cases with prominent fully developed changes were classified as idiopathic multicentric Castleman disease after thorough clinical investigation.
Conclusion: Presence of Castleman disease-like features is not always diagnostic just of Castleman disease. In our series, they were observed more frequently in other disorders, namely malignant lymphoma (where only part of the lymph node is usually involved) or IgG4-related lymphadenopathy. Awareness of these changes is crucial and combination with immunohistochemistry and molecular studies can help to avoid a possible misdiagnosis.

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E-PS-10-006
An unusual case of BCL-2, BCL-6, CD10 & MUM-1 quadruple negative follicular lymphoma

S. Shawash[1], N. Abdullah[1]
[1] King Hussain Cancer Center, Jordan

Background & Objectives: Nodal follicular lymphoma originates in germinal centers as proven by markers such as CD10 and BCL-6. It is renowned for BCL-2 overexpression which results from translocation t (14; 18)/IGH-BCL2. Rarely, especially in high grade cases, one or more immunomarkers might be lost, making accurate diagnosis difficult. We present an unusual case of follicular lymphoma showing loss of BCL-2, CD10, BCL-6 and negative MUM-1.
Methods: Our patient is a 66-year-old female with resected colonic adenocarcinoma (pT3N2b). Serial CT scans showed progressively enlarging lymph nodes despite adjuvant chemotherapy. Excisional biopsy was obtained and revealed multiple lymph nodes, some showing effaced architecture, replaced by large follicles which are composed predominantly of centroblasts with centrocytes. Extracapsular extension was also seen. Three lymph nodes showed extensive necrosis mostly due to previous intervention. Immunohistochemical stains showed tumour cells were positive for CD20 and PAX-5.
Results: However, BCL-2, CD10, BCL-6, CD30, CD15, CD3 and MUM-1 were all negative. CD23 highlighted attenuated dendritic meshwork. Ki67 was up to 40% and highlighted loss of zonation. Flow cytometry failed to show neoplastic process. FISH using dual fusion probe for IGH/BCL-2 gene rearrangement was negative. Finally, PCR showed clonal immunoglobulin heavy chain and kappa light chain gene rearrangement. As a result, a diagnosis of follicular lymphoma grade 3a was made. Bone marrow biopsy revealed minimal para-trabecular involvement.
Conclusion: In conclusion, unusual loss of expression in follicular lymphoma should not preclude accurate diagnosis. Such cases remind us that the histomorphology is our cornerstone to make a diagnosis.

E-PS-10-007
Erdheim-Chester disease co-occurring with cholelithiasis associated Langerhans cell histiocytosis

S. Aviel-Ronen[1], S. Fichman-Horn[2], S. Zoabi[3], R.D. Mazor[4], G. Gitstein[5]
[1] Department of Pathology, Sheba Medical Center, Tel-Hashomer, Israel, [2] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [3] Surgery Department, Holy Family Hospital, Nazareth, Israel, [4] Institute of Haematology, Assuta Medical Center, Tel Aviv, Israel, [5] Pathology Department, Sourasky Medical Center, Tel Aviv, Israel

Background & Objectives: Histiocytoses are rare heterogeneous mononuclear phagocytes derived neoplasms. Two of the more recognized hystiocytoses are Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD). Both entities often harbor the *BRAF*^{V600E} mutation, which may be the link between them. The coexistence of LCH with ECD is infrequent and is referred to as mixed LCH/ECD. Here we describe an unusual case of ECD patient who developed cholelithiasis associated with LCH infiltrate in the gallbladder.
Methods: The medical records, imaging tests and pathological findings of a 34 years old patient have been studied and are presented. The patient went through cholecystectomy due to cholelithiasis. Three years before he was diagnosed with ECD based on characteristic clinical-radiological-pathological features. His presentation included multifocal disease involvement of the hypophysis with central diabetes insipidus, lower appendicular skeleton inducing pain and mesenteric fat infiltrates causing abdominal ache. Imaging revealed the typical "hairy kidney" and bone biopsy supported the diagnosis as well.
Results: The resected gallbladder showed distorted structure with thickened wall and cholelithiasis. Microscopic examination identified prominent mucosal infiltrate of histiocytes having irregular nuclei with occasional grooves, accompanied by numerous eosinophils. On immunostains the histiocytes showed positive staining for CD68, CD1a, S100 and langerin. Overall, the morphological features and immunostain results were consistent with LCH. In contrast, the left tibia biopsy preformed 3 years before showed infiltrate of CD68 positive, CD1a negative and S100 negative histiocytes that supported the diagnosis of ECD.
Conclusion: Altogether features reflect co-occurrence of ECD and LCH, otherwise named mixed LCH/ECD. Not only this is a rare condition, its presentation in association with cholelithiasis has not been described yet.

E-PS-10-008
Follicular dendritic cells sarcoma - two case reports

S. Sotiriou[1], A. Bouzakis[2], I. Kostopoulos[1], V. Tzioufa[1], T. Koletsa[3]
[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece, [2] Histopathology Lab. Serres P, Greece, [3] Pathology Department, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background & Objectives: Follicular dendritic cell sarcomas (FDCSs) are rare neoplasms. The aim of these case reports is to raise awareness regarding this unusual entity and to point the importance of the differential diagnosis.
Methods: A 46-year-old man and a 38-year-old woman presented with right and left cervical lymphadenopathy respectively. The clinical history and examination were otherwise unremarkable. Both have undergone a diagnostic lymphadenectomy.
Results: Microscopically, the lymph nodes were almost entirely replaced from a neoplastic population of ovoid to spindle cells with moderate atypia. The nuclei were elongated or ovoid, occasionally exhibiting clear changes or membrane folding. Giant cells with pleomorphic nuclei with pseudoinclusions were observed in the second case. The neoplastic cells of both lesions showed similar immunophenotype: Vimentin+, CD21+, CD23+, Fascin+, HLA-DR+, S100+/-, CD68+/-, CD45-, AE1/AE3-, MelanA-, HMB45-. Based on the histological and immunohistochemical findings, our final diagnosis was that of FDCSs.
Conclusion: Depending on the location, FDCSs should be differentiated from other histological subtypes of dendritic cell tumours, but also from primary or metastatic neoplasms. If FDCS is not considered in the differential diagnosis, its positivity to nonspecific markers, such as CD68 and S100 protein can lead to misdiagnosis. Clinicopathological correlation and immunohistochemical assays are of paramount importance in the differential diagnosis.

E-PS-10-009

Bone marrow involvement in lymphoma: a histomorphologic and immunophenotypic study

S. Sharma[1], S. Yadav[1], K. Rahman[2], M. Murari[1]
[1] Department of Pathology, SGPGIMS, Lucknow, India, [2] Department of Clinical Haematology, SGPGIMS, Lucknow, India

Background & Objectives: Bone Marrow (BM) evaluation has a key role in workup of a case of lymphoma. BM involvement by lymphoma is a definite evidence of disseminated disease and provides important information for decisions regarding treatment.
The aim of the study was to analyse the prevalence of bone marrow involvement and correlate histomorphologic findings with flowcytometric analysis in a series of patients with lymphoma.
Methods: We retrospectively analysed 254 consecutive bone marrow (BM) biopsies which were performed for evaluation of lymphomatous involvement over a period of 3 years. Bone marrow involvement was assessed by conventional morphology, Immunohistochemistry and flow cytometry (FC) in BM samples. Clinical, biochemical and hematological findings were also reviewed.
Results: BM was involved in 160 (63%) cases. The distribution of some of the common lymphoma subtypes among BM positive cases was: CLL/SLL (39.3%), MCL (13.7%), DLBCL (6.8%), Follicular lymphoma (6%), and Hairy cell leukemia (2.5%). Diffuse (55.6%), mixed nodular+interstitial (17.5%) and interstitial (11.2%) were more common patterns of BM infiltration. Majority (68%) of cases had extensive (>50%) and only 10% cases had minimal lymphoid infiltration. There was a significant correlation regarding percentage lymphomatous involvement between BM biopsy and FC ($p<0.001$).
Conclusion: Morphologic detection of lymphomatous involvement in bone marrow trephine biopsy still remains the "gold standard" In lymphoma staging. The ancillary techniques like IHC and Flowcytometry are important for sub-typing and identifying minimal involvement on histomorphology.

E-PS-10-011

Blastic plasmacytoid dendritic cell neoplasm

J. Ilic Sabo[1,2], T. Lakic[1,2], M. Panjković[1], A. Ilic[1,2], Z. Vrekic[2], D. Ćuk[2]
[1] University of Novi Sad, Faculty of Medicine, Serbia, [2] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia,

Background & Objectives: Blastic plasmacytoid dendritic cell neoplasm was initially described in 1995 as acute agranular CD4-positive natural killer (NK) cell leukemia. It is clinically aggressive tumour derived from the precursors of plasmacytoid cells. It has a high frequency of cutaneous and bone marrow involvement and leukemic dissemination. In 2016 World Health Organization classification of tumours of the hematopoietic and lymphoid tissues it has a current name- blastic plasmacytoid dendritic cell neoplasm.
Methods: We got for the analysis the sample of neck lymph node, after a month sample of bone marrow biopsy, and after a year the biopsy of skin change. The analysis was performed with standard stains and additional immunohistochemistry: CD56, CD123, CD4, CD68, CD43, CD33, CD117, CD15, CD14, TdT, CD2, CD3, CD5, CD7, CD20, CD8, granzyme B, BCL2, BCL6, MPO, CD34.
Results: Lymphadenomegalia colli appears at male 57 years old. In trephine biopsy the morphological finding was acute leukemia. In skin biopsy dermal infiltration (sparing of epiderm and adnexa) with medium sized cells blastoid appearance, irregular nuclei and conspicuous nucleoli. Imunochistohemistry in tumour cells was: CD56+, CD123+, CD4+, CD68+, CD43+, CD33+, CD117-/+, CD15+, CD14-/+, TdT-/+, CD2-, CD3-, CD5-, CD7-, CD20-, CD8-, granzyme B-, BCL2+, BCL6-, MPO-, CD34-. According the clinical data, histomorphology and imunochistohemistry, final diagnosis was: Blastic plasmacytoid dendritic cell neoplasm.
Conclusion: It is very rare (< 100 cases reported), so the main problem is to make a proper diagnosis. The proper diagnoses is very important today, especially we are in the era of highly personalised therapy.

E-PS-10-012

Breast implant-associated anaplastic large cell lymphoma with lymph node metastasis

L. Barona García[1], G. Ruiz García[1], M.I. Oviedo Ramírez[1], A. Salazar Nicolas[1], M.I. Ortuño Moreno[1], A. Caballero Illanes[1], E. Martínez Barba[1]
[1] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain

Background & Objectives: Breast implant-associated anaplastic large cell lymphoma (BI- ALCL) is an extremely rare form of non-Hodgkin's lymphoma. It's a newly recognized provisional entity in the 2017 revision of the World Health Organization Classification of Tumours of Hematopoietic and Lymphoid Tissues that usually occurs at a median of 9 years after the implantation. In most cases, BI- ALCL is a localized disease and complete surgical resection of capsule and implants achieve total remission of the disease.
Methods: A 35-year-old woman with bilateral breast implant 8 years ago, presented with right breast pain, swelling and enlargement and a palpable mass in the right lower inner breast, and axillary and supraclavicular lymphadenopathy. The patient underwent bilateral capsulectomy and prosthetic excision.
Results: Gross exam of the breast implant capsule showed a large tumour mass with extensive infiltration. Histology confirmed features of ALK-negative BI-ALCL of T-cell phenotype. Furthermore, a 2,5 cm-round-shaped lymph node occupied by the same clusters of large-sized and pleomorphic cells with abundant cytoplasm and vesicular nuclei containing prominent nucleoli was found. Immunohistochemically, neoplastic cells were diffusely positive for CD30, CD5, CD43 and negatives for ALK, CD20, PAX5, CD8, CD15, EMA y EBV-LPM.
Conclusion: To the best of our knowledge, only 16 cases of BI-ALCL with axillary lymph node involvement have been reported in literature. We report a rare case of BI-ALCL with agressive behaviour and lymph node metastasis. The patient continues treatment with standard regimens containing cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with poor response until now.

E-PS-10-013

An unusual case of a pure erythroblastic sarcoma diagnosed in a patient with acute megakaryoblastic leukemia (AML M7)

Z. Prouzova[1,2], D. Mikulenkova[3], R. Simeckova[3], V. Campr[4], R. Kodet[4]
[1] Department of Pathology Third Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Czech Republic,
[2] Department of Pathology and Molecular Medicine Second Faculty of Medicine, Charles University and University Hospital Motol, Czech Republic, [3] Institute of Haematology and Blood Transfusion, Prague, Czech Republic, [4] Department of Pathology and Molecular Medicine Second Faculty of Medicine, Charles University and University Hospital Motol, Czech Republic

Background & Objectives: A 62-year-old woman with a 2-year-history of AML M7 (secondary to MDS-RCMD del(5q), which had been diagnosed 6 years before) with a poor therapeutic effectiveness and disease progression, was brought to our hospital for biopsy of a Th12 tumour

mass (clinically susp. sarcoma). At the time of the biopsy the patient was seriously ill and developed severe pancytopenia and coagulopathy, which led to her death. The final diagnosis of the vertebral tumour was made a few days later.
Methods: Tissue from the biopsy was formalin-fixed, sampled and then routinely processed. Immunohistochemistry was performed using a broad panel of myeloid and lymphoid markers.
Results: The tumour was composed of large monomorphic blast cells with basophilic cytoplasm and large round nuclei. Immunophenotypically they were positive for CD71, glycophorin A, E-cadherin and weakly positive for CD45. Other markers (CK AE1/3, CD4, CD5, CD15, CD20, CD30, CD34 CD56, CD61, CD117, CD138, HMB45, Melan A, MPX, MUM1, S100, TdT) were completely negative. The morphology and immunohistochemical profile of the tumour was consistent with a diagnosis of erythroblastic sarcoma.
Conclusion: An erythroblastic sarcoma in a pure form is a very unusual variant of myeloid sarcoma and few cases have been reported, especially in association with an underlying, and also rare, hematologic disease such as was seen in this extraordinary case.

E-PS-10-015
The leukemic cells frequently lose CD10 expression in Follicular Lymphoma with leukemic presentation
S. Chuang[1]
[1] Chi-Mei Medical Center, Taiwan

Background & Objectives: Follicular lymphoma (FL) is a malignant B-cell lymphoma of follicular center B-cell origin and frequently involves lymph nodes, but also spleen, bone marrow, and peripheral blood and Waldeyer's ring. The neoplastic cells of FL nearly always express germinal center B-cell antigens CD10 and bcl-6. FL with leukemic presentation (FL-LP) is uncommon and has not been well characterised from Taiwan yet.
Methods: We retrospectively searched for cases of FL-LP in our institution from January 2000 to October 2018. We characterised the leukemic cells by flow cytometric immunophenotyping and biopsies by immunohistochemistry and fluorescence in situ hybridization (FISH). Clinical history was reviewed.
Results: We identified 13 (6.2%) of 212 cases of FL-LP, all *de novo* neoplasms. All cases had concurrent tumours: 12 (92%) low-grade and one grade 3A. CD10 was expressed in the leukemic cells in 38% (5/13) cases by flow cytometry and in 77% (10/13) cases in the tumour tissues (p= 0.0471, Chi-squared test). Reciprocal translocation of *IGH/BCL2* was identified in 85% (11/13) cases by FISH. The 2- and 5-year survival rates were at 100% (7/7) and 83% (5/6), respectively.
Conclusion: In FL-LP, the lower CD10 expression rate of the leukemic cells might be due to different epitopes used in flow cytometry as compared to immunohistochemistry. Alternatively, loss of CD10 expression might play a role in the pathogenesis of leukemic change. The low CD10 expression rate is a diagnostic challenge if only flow cytometric immunophenotyping is used for diagnosis without biopsy.

E-PS-10-016
The surprise within the cyst
I. Dumitru[1], M.A. Bani[1], A. Bourgogne[1], N. Talhi[1], X. Sastre[1]
[1] CHI Créteil, France

Background & Objectives: Tonsillar cysts are characterised by a squamous epithelial lining with underlying follicular lymphoid tissue, resembling tonsillar crypts. Non-Hodgkin lymphoma of the tonsils accounts for less than 1 % of malignant head and neck tumours as a whole, and commonest histologic type is diffuse large B cell lymphoma. Tonsillar involvement in chronic lymphocytic leukemia (CLL) is rare and has only been reported 7 times in the literature. We herein present another exceptional case.
Methods: A 54-year-old man with no history presented with a complaint of respiratory difficulties. There were no palpable cervical lymph nodes or B symptoms. Pathological examination found a cyst with the surrounding tissue replaced by a diffuse lymphoid proliferation of small lymphocytes with scant cytoplasm, round nucleus, clumped chromatine. The immunophenotype showed leukaemic B cells CD20, CD5, CD23, BCL2 and IgD and absence of CD10, cycline D1 and SOX11.
Results: The retained diagnosis was tonsillar cyst associated with chronic lymphocytic leukaemia (CLL).
Conclusion: The pitfall of the case represents the diffuse replacement of the normal lymphoid tissue and the basic knowledge in small cell lymphoid proliferations. The presence of persistent tonsillar cyst on elderly patients should alert for the possibility of an indolent lymphoma. The present case highlights the difficulty to recognize CLL in tonsillar cysts, and the diagnosis should be supported with immunohistochemistry.

E-PS-10-018
Diffuse large B-cell lymphoma and prognostic significance of immunohistochemical antibodies VEGF and COX2
Z. Nikin[1], L. Popovic[1,2], N. Solajic[1], T. Ivkovic-Kapicl[1], S. Knezevic-Usaj[1], M. Panjkovic[1]
[1] University of Novi Sad, Faculty of Medicine, Serbia, [2] Institute for Oncology of Vojvodina, Serbia

Background & Objectives: Diffuse large B-cell lymphoma (DLBCL) is one of the most common lymphomas in the world and represents up to 30% of all non-Hodgkin lymphomas. It is usually a primary disease but also it can develop secondary as a result of the progression of low-grade lymphomas. In most cases, the disease begins in lymph nodes.
Methods: Our research has included 92 patients who were diagnosed at the Institute for Oncology of Vojvodina from 2003 to 2011. They were treated according to modern standard protocols including Rituximab. We have used immunohistochemical antibodies VEGF and COX2. Sex, age, nodal/extranodal origin, and survival were found in medical files.
Results: VEGF was positive in 27,7%, COX2 in 63,64%. Older patients had significantly less often COX2 expression. There was no significant correlation between the expression of VEGF and age or between the expression of VEGF and COX2 with sex neither with nodal/extranodal origin. VEGF and COX2 as markers of signaling pathways for angiogenesis and inflammation respectively did not have a significant correlation with worse prognosis.
Conclusion: It seems that the use of antibodies VEGF and COX2 is not helpful for prognosis of patients with DLBCL. We should be rational and use only basic antibodies for determination of immunohistochemical subtype and antibodies necessary for differential diagnosis.

E-PS-10-019
Experience with 84 cases of bone marrow amyloidosis - caution advised as deposits are frequently extramedullary and may be associated with non-AL amyloidosis
M. Picken[1]
[1] Loyola University Medical Center, USA

Background & Objectives: Progress in treatment of systemic amyloidoses has created the need for defining organ specific involvement. Thus not only the presence but also the location and the extent of amyloid deposits in various organs has implications for diagnosis and therapy. The situation with bone marrow (BM) has not been addressed. We sought to evaluate the distribution of amyloid in 84 consecutive bone BM specimens positive for amyloid and correlate it with clinical data.
Methods: Out of ~ 800 BM biopsies evaluated with Congo red stain, in 84 patients amyloid was detected. We evaluated the distribution of deposits and correlated with clinical data. The M:F ratio was 1.3:1 and the

mean was 65 years (range 26-94). Plasma cell % ranged from 1-80%, mean 13.4%, median 8%. 29/84 (31%) patients had the first-time diagnosis of amyloidosis on BM biopsy 33/84 patients had >10% plasma cells of which 25 met the criteria for multiple myeloma.
Results: The location of amyloid deposits was variable and included marrow stroma (19), vessel wall (26), periosteal soft tissue (POST, 19); in 19 cases with slides no longer available for review, location of deposits could not be specified. While majority of patients had AL (light chain amyloid), AA and ATTR were also diagnosed in 2 and 4 cases respectively. Marrow stromal deposits were seen exclusively in AL while vascular and/or POST deposits were associated with AL, AA and ATTR.
Conclusion: There is significant heterogeneity of amyloid distribution in patients with AL with extramedullary/periosseous amyloid deposits being more frequent than medullary. In non-AL deposits may be detected in BM specimens. These findings raise the need for development of a consensus definition of what constitutes marrow involvement in amyloidosis in general and in AL in particular and how it should be reported.

E-PS-10-020
An exceptional pathological pattern of T-lymphoblastic lymphoma
I. Msakni[1], H. Raoueh[2,3], N. Mansouri[1], F. Gargouri[1], A. Saidi[1], A. Bouziani[1], B. Laabidi[2,3]
[1] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia, [2] Tunis El Manar University, Medicine School of Tunis, Tunisia, [3] Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: Lymphoblastic lymphoma (LBL) accounts for approximately 2% of all non-Hodgkin'slymphoma (NHL) and the majority (90%) are T- lymphoblastic lymphoma (T-LBL). It commonly involves the mediastinum (thymus), nodal or extranodal sites include skin, tonsils, and spleen. It is most frequent in adolescent males. The infiltration of the lymph node is often diffuse. exceptionally, a pseudofollicular pattern is produced mimicking follicular lymphoma. Our aim was to present a case report of a T-LBL with pseudofollicular pattern.
Methods: We report a case of a 28-year-old man with multiple cervicothoracic lymph nodes.Seven lymph nodes measuring between 8 and 15 mm were received in the Departement of Pathology.
Results: lymph nodes showed complete architectural effacement. They were infiltrated by lymphoid proliferation with multinodular pattern.The cells were of medium size with a high nuclear-cytoplasmic ratio and inconspicuous nucleoli. Mitotic figures were rare (one mitosis / 10 HPF). There was no starrysky pattern, no tumornecrosis and no large cells.Tumour cells were TdT, CD3, CD4 and CD10-positive. They were pancytokeratin, CK5-6, P40, EMA, CD20, CD30 and BCL6-negative. we concluded a T-LBL with pseudofollicular pattern.
Conclusion: Due to the rarity of T-LBL with pseudofollicular pattern, the diagnosis can be difficult presenting problems of differential diagnosis with follicular B-lymphoma or follicular variant of T-NOS lymphoma. The use of an adequate panel of antibodies including tdt especially in young subjects is necessary to make the exact diagnosis.

E-PS-10-021
Unicentric Castleman's disease with mesenteric location: case report
O. Vita[1], M. Cornianu[1,2], A. Gheju[1], A. Văduva[1], A. Jurescu[1], I. Mihai[1], S. Tăban[1,2], A. Dema[1,2]
[1] Department of Pathology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania, [2] Department of Pathology, Emergency County Hospital Timişoara, Romania

Background & Objectives: Unicentric Castleman's disease is a nonmalignant lymphoproliferative disorder that usually occurs in the mediastinum, presenting as a solitary lymph node mass. The location of the disease in the mesentery is rare.
Methods: A 72-year-old man with a history of high blood pressure presents with a palpable, but reducible abdominal mass in the umbilical region, that bulges at coughing. Abdominal CT revealed the presence of a mesenteric tumour. A solid mass, adherent to the ascending and transverse colon, was found during the exploratory laparotomy. Surgical excision of the tumour was performed. Representative slides of the resected specimen were examined using haematoxylin-eosin stain and several immunohistochemical markers: CD20, CD3, CD5, bcl-6, bcl-2 and Ki-67.
Results: Macroscopic examination of the resected tissue showed a well demarcated, encapsulated, brown tumour, 6x4,5x4 cm in size. Histopathologic examination and immunohistochemical findings revealed a lymphoid proliferation with features compatible with Castleman's disease, hyaline-vascular subtype.
Conclusion: This case represents the first unicentric Castleman's disease with mesenteric location reported in our department. In the presence of a mesenteric mass, this rare disease should be considered a possible diagnosis.

E-PS-10-022
ALK-positive Large B-cell Lymphoma (ALK-LBCL) - a diagnostic challenge. Presentation of two cases misinterpreted as carcinoma and sarcoma
G. Rymkiewicz[1], O. Stanowska[2], A. Szumera-Ciećkiewicz[3], A. Borysiuk[1], M. Wągrodzki[1], B. Ziarkiewicz-Wróblewska[4,1], M. Prochorec-Sobieszek[5]
[1] Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland, [3] Institute of Haematology and Transfusion Medicine, Diagnostic Haematology Department, Poland, [4] Faculty and Department of Pathology, Medical University of Warsaw, Warsaw, Poland, [5] Department of Pathology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, str. Wawelska 15 B, 02-034 Warsaw, Poland

Background & Objectives: ALK-LBCL is a rare subtype of diffuse Large B-cell Lymphoma CD20-negative, occurring in young men. Clinical manifestation is usually nodal. Diagnostic challenge for surgical pathologists include cohesive morphology with sinusoidal infiltration, EMA- and occasionally cytokeratin and CD56 positivity, weak or negative staining for CD45/LCA.
Hereby, we present two cases of aggressive ALK-LBCL, misinterpreted initially, clinically and pathologically, as carcinoma and sarcoma.
Methods: Two 40-years old men presented with bulky tumour of few-weeks duration. First was suspected to be poorly differentiated carcinoma of salivary gland with destruction of a mandible and the second: sarcoma of the axilla. Microscopic appearance included epithelioid cell infiltrate with immunophenotype: EMA[+]/CK[-]/S100[-]/desmin[-]/CD45[-]/CD20[-]/CD3[-]. Surgical biopsy specimens were required to secure representative material for broad immunohistochemistry (IHC) panel. Additionally, flow cytometry (FCM) and molecular analysis of the material obtained by fine needle aspiration biopsy (FNAB) was performed.
Results: Both patients were finally diagnosed with nodal ALK-LBCL. FNAB/FCM demonstrated expression of CD45/LCA and pan-B/T/macrophage- cell markers, not/faintly detected by IHC. IHC revealed expression of ALK protein, confirmed by FISH and cytogenetics as presentation of *ALK* gene rearrangement. Patients obtained chemotherapy according to modified GMALL protocol; both achieved complete regression.
Conclusion: We present cases of ambiguous CD45/LCA neoplasms by IHC with epithelioid morphology interpreted as non-haematological malignancy by surgical pathologists. In young men with nodal involvement of aggressive neoplasm, especially with morphological and IHC inconsistency, ALK-positive lymphoma, which can be CD45[-/+dim]/CK[+], should be included in the differential diagnosis. FNAB/FCM show high diagnostic accuracy and effectiveness for lymphomas with plasmablast differentiation.

E-PS-10-023

Variation CD markers of B-cell lymphmas

Y. Gulyaeva[1], T. Nabebina[1], A. Kozubovskaya[1]
[1] National Cancer Centre, Belarus

Background & Objectives: Immunophenotyping of leukocyte subpopulations by the flow cytometry uses for the differential diagnosis of lymphoproliferative diseases, determining the stage and monitoring the residual tumour clone. From 2014 to 2018 we described determination of B- lymphocytes markers of patients with the suspicion of LPD. There were peripheral blood (PB), bone marrow (BM) and lymph nodes (LNs) of 874 patients. The gender distribution was 58.8% of men and 41.2% of women.
Methods: The MoAbs used for labeling in flow cytometry were obtained from Beckman Coulter (BC, USA). The final diagnosis was established after comparing the results of morphology, immunophenotyping and FISH. The evaluation of 874 patients (360 females, 514 males) with mean age of 49±12.8 years revealed.
Results: Of the patients, 615 (70.4%) had CLL/SLL, 59 (6.7%) had MCL, 4.3% with follicular lymphomas (FL) and 126 (14.4%) had reactivation without malignant cells. There were low level intensity or absent CD5 expression on the surface B-cells of 44.7% SLL patients. All cases were examined by addition markers CD200, CD180, bcl-1, bcl-2, bcl-6 to recognize CLL/SLL from another lymphoma types. All cases with strong expression of CD200 were CLL/SLL. Besides we had 2.1% cases of FL (CD10+ $CD23^{-}$) with moderate expression CD5+ . This cases were examined with marker Bcl-6 and FISH analyses.
Conclusion: The variation expression CD markers in different types of material even from one patient confirms to use all tools for diagnosis. However, it is difficult to make a differential diagnosis of CLL/SLL from MCL when immunophenotypic features are not typical. The study of variability markers expression is a fundamental criteria for the diagnosis, the expression of atypical markers will improve diagnosis, understand molecular mechanisms, and evaluate the prognosis of the disease

E-PS-10-024

The kidney as initial presenting site of lymphoproliferative disorders. A 5-year study from a haematopathology referral centre

A. Papanikolaou[1], G. Kanellis[1], E. Economaki[1], E. Pouliou[1], L. Marinos[1]
[1] Haematopathology Department/Evangelismos General Hospital, Athens, Greece

Background & Objectives: Kidney involvement by a lymphoproliferative disorder (LD) is a rare occurrence either as primary (less than 100 cases in the literature) or as a secondary (14% in autopsy cases diagnosed prior to death) site of presentation. Initial presentation of a LD in the kidney is even rarer and frequently leads to unnecessary surgical treatment. With the object of stressing out the importance of early preoperative diagnosis and assessing the relative frequency of various LD in the kidney we present 15 such cases studied in a 5-year period from 2014 to 2018 (Table 1).
Methods: All cases were studied with standard hematoxylin and eosin stains and immunohistochemistry

Results:

Table 1

Gender	Age	Specimen	Diagnosis
1.Female	68	Surgical	MZL
2.Male	70	Surgical	FCL
3. Male	75	Surgical	DLBCL
4.Female	67	Surgical	DLBCL
5.Male	*74*	FNB	MZL
6.Female	*57*	Surgical	DLBCL
7.Female	37	FNB	DLBCL
8.Female	40	FNB	T-ALL/LBL
9. Female	79	Surgical	MZL
10.Male	63	FNB	MZL
11.Male	78	FNB	DLBCL
12.Female	71	Surgical	MZL
13.Male	72	FNB	Waldenstrom`s macroglobulinemia
14.Male	58	FNB	IgG-4 sclerosing disease
15.Female	80	Surgical	DLBL

FNB=fine-needle biopsy, MZL=marginal zone lymphoma, FCL=follicular lymphoma, DLBCL=diffuse large B-cell lymphoma, T-ALL/LBL=T-lymphoblastic leukaemia/lymphoma
Conclusion: Kidney involvement by LD is often underdiagnosed and frequently (shown by the relatively large number of surgical specimens in our study) leads to unnecessary surgical treatment. Therefore, early diagnosis by fine-needle biopsy of all tumour-forming kidney lesions followed by detailed morphological and immumohistochemical study is mandatory.

E-PS-10-025

Histopathologic characteristics of multiple myeloma-institutional experience in Bosnia and Herzegovina

J. Redzepagic[1], D. Udovicic-Gagula[2], E. Delic[3], D. Spirtovic[3], T. Kukuljac[2], N. Bilalovic[3]
[1] Clinical Center University of Sarajevo, Bosnia and Herzegovina,
[2] Department of Pathology, Clinical Center University of Sarajevo, Bosnia and Herzegovina, [3] Clinical Center University of Sarajevo/ Clinical Pathology and Cytology, Bosnia and Herzegovina

Background & Objectives: Multiple myeloma is a rare blood cancer of plasma cells. Data about multiple myeloma in Bosnia and Herzegovina are insufficient.
Methods: We searched medical records for multiple myeloma from years 2017-2018. Pathologic characteristics together with immunohistochemical analysis and demographic characteristics were evaluated trough the medical records from our institution.
Results: There were 46 new cases in 2017/2018. The average year was 65. Men were slightly more affected by the disease (52.2%) than women (47.8%). In both sexes frequent bone marrow infiltration by neoplastic cells was more than 60% (52.2%). The common bone marrow pattern of infiltration was diffuse (45.7%). The kappa clone was frequent (65.2%)

followed by lambda clone (34.8%). Plasmablastic morphology of neoplastic cells was less frequent (28.3%) and was associated with lower infiltration. The women were more affected by diffuse infiltration by clonal population of plasma cells (63.3%). The CD138 and CD38 positive plasma cells were found in 93.5%, followed by CD56 positive cells in 41.3%, CD20 positive in 21.7% and CD117 positive plasma cells in 4.3%.
Conclusion: In everyday practice a diagnosis of multiple myeloma is possible in less than 30% of infiltration of plasma cells together with evaluation of clonal population by immunohistochemical methods. The evaluation of plasma cell morphology together with pattern of infiltration and percentage of infiltration are among important factor contributing to correct diagnosis. Knowing these characteristics can help and provide accurate diagnosis and predict the patient outcome and tailor treatment strategies.

E-PS-10-026
Evaluation of CYCLON as a predictive biomarker of anti CD20 response in diffuse large B-Cell lymphoma
A. Bouroumeau[1], L. Bussot[1], T. Bonnefoix[2], M. Callanan[3,4], R. Gressin[1], A. Emadali[2], H. Sartelet[5]
[1] Grenoble Alpes University Hospital, France, [2] Institute for Advanced Biosciences, France, [3] Plateforme de Gènètique des Cancers solides et des Hèmopathies malignes, CHU Dijon, France, [4] Unitè d'innovation en Gènètique et Epigènètique des cancers, CHU Dijon, France, [5] CHU de Grenoble, France

Background & Objectives: Diffuse Large B-Cell Lymphoma (DLBCL) is a clinically heterogeneous tumour, currently treated, in first line, using R-CHOP (Rituximab, an anti-CD20 immuno-chemotherapy regimen, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine Sulfate, Prednisone). However, about 20 percent of patients will not primarily respond or relapse. In this context, CYCLON, a novel nuclear germline factor, overexpressed in aggressive B-Cell Lymphoma, has been recently identified as involved in Rituximab resistance *in vitro*.
The aim of this study is to validate these results in a clinical setting.
Methods: A retrospective quantitative study was undertaken from 68 DLBCL, in University Hospital of Grenoble, France. Between 2011 and 2018, all patients with a de novo DLBCL (excluding all transformed DLBCL), treated in first line by R-CHOP and having a formalin fixed tumour sample were included.
Using Tissue MicroArrays technique, an immunohistochemical analysis of CYCLON expression was performed. Its level was scored semi-quantitatively (percentage of positive cells and intensity), then correlated with clinical and biological data, previously collected for each patient.
Results: CYCLON was expressed in 55 of 68 DLBCL (81%), but with two significant nuclear staining aspects: one homogeneous and the other, heterogeneous, with a dot-like positivity. The univariate survival analysis did not reveal any association between CYCLON staining intensity, or percentage of positive cells, with survival. But, very interestingly, the homogeneous versus dot-like expression of CYCLON was strongly associated with relapse free survival (p=0.0185). Preliminary multivariate analysis also suggests an opposite role for CYCLON, depending on DLBCL molecular subtypes.
Conclusion: Our preliminary data confirm CYCLON as a predictive biomarker in R-CHOP treated DLBCL. Consistently with *in vitro* conclusions, suggesting a role for CYCLON in chromatin regulation, this is CYCLON accumulation in nuclear sub-structures (dot-like aspect), rather than its expression level, that is associated with bad prognosis. Further investigations will be carried out to study the functional significance of these foci.

E-PS-10-027
Sclerosing angiomatoid nodular transformation of the spleen: a case report of a rare entity
C. Nicolae[1], M. Chivu[1], F. Andrei[1], C. Iosif[2], A. Curte[1]
[1] "Elias" Emergency University Hospital, Bucharest, Romania, [2] "Sfânta Maria" Clinical Hospital, Bucharest, Romania

Background & Objectives: Sclerosing angiomatoid nodular transformation (SANT) of the spleen is a recently described, rare, benign lesion with unknown etiology and female predominance. Most cases are either identified incidentally on imaging, or present with abdominal pain.
Methods: We report a case of sclerosing angiomatoid nodular transformation of the spleen found incidentally on imaging.
Results: A 62-year-old male patient, with history of surgically resected bilateral renal cysts and hypertension, was admitted at 'Elias' Hospital with symptoms of acute cholecystitis. Computed tomography scan incidentally revealed a solitary, well-circumscribed, splenic mass with lobular borders. Both cholecystectomy and splenectomy were performed. The spleen specimen measured 160/80/70mm and presented a solitary, sharply demarcated, solid mass, measuring 60/50 mm. The cut surface showed coalescing red-brown nodules within a dense, white, fibrous stroma, slightly firmer than the normal splenic parenchyma. Microscopically, H&E stain revealed a multinodular proliferation composed of slit-like, round, or irregularly shaped vascular spaces and channels of varying caliber, lined by plump endothelium, with interspersed ovoid and spindle cells. There were numerous extravasated erythrocytes and the intervening stroma was brosclerotic, with scattered myobroblasts, plasma cells, siderophages, and inammatory cells. Mitotic figures, necrosis or significant nuclear atypia were not present. Immunohistochemistry was positive diffusely positive for CD34 in the vascular proliferation, and positive for CD31 in small vessels, with Ki67 positive in 5-10 % of tumoral cells.
Conclusion: The H&E and immunohistochemical findings were characteristic of sclerosing angiomatoid nodular transformation of the spleen. This is a very rare, benign entity, with a good prognosis and no recurrence after splenectomy.

E-PS-10-028
Hepatosplenic T-cell lymphoma - a case series
F. Ultimescu[1], C. Dobrea[1,2,3], S. Badelita[4], B. Ionescu[4], A. Bardas[4], D. Coriu[4,3]
[1] Oncoteam Diagnostic, Romania, [2] Fundeni Clinical Institute, Romania, [3] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [4] Center of Haematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Romania

Background & Objectives: Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive T-cell lymphoma, accounting for less than 1% of all non-Hodgkin's lymphoma. We report three cases of HSTCL over a three-year period (2015–2018).
Methods: Three young male patients (23, 23 and 24-years-old) were admitted to hospital with hepatosplenomegaly without lymphadenopathies, anemia, thrombocytopenia and bleeding gums. All of them underwent bone marrow biopsy and, one of them, splenectomy. Histopathological, immunohistochemical and flow cytometry analysis were performed on each case.
Results: The histopathological evaluation of the bone marrow biopsy revealed increased cellularity by diffuse neoplastic infiltrate composed of small/medium sized lymphoid cells with interstitial and sinusoidal distribution. The splenectomy specimen showed neoplastic cells infiltrating both splenic cords and sinuses. The neoplastic cells were CD3+,

CD7+ and CD20-, CD5-, CD4-, CD8-, Granzyme B-. Flow cytometry revealed tumoral cells that expressed CD45++, CD3, CD2 but lacked expression of CD4, CD8, CD5.
Conclusion: The histopathological, immunophenotypic and flow cytometry findings supported the diagnosis of Hepatosplenic T-cell Lymphoma, with a poor outcome: two of the patients died within first year after diagnosis while the other patient deceased within 26 months (after relapse following hapoidentical hematopoietic stem-cell transplantation). This case series highlights the importance of considering Hepatosplenic T-cell lymphoma as differential diagnosis in the clinical setting of pancytopenia with hepatosplenomegaly, allowing early recognition of these aggressive neoplasms.

E-PS-10-029
HHV8 and EBV - associated lymphoproliferative disorders: a case report of two rare entities in the same patient
J. Duarte Santos[1], N. Lourenço-Silva[2], V. Salvado[3], M. Mafra[1], J. Cabeçadas[4]
[1] Serviço de Anatomia Patológica, Centro Hospitalar Universitário de Lisboa Central, EPE, Lisboa, Portugal, [2] NOVA Medical School, Lisboa, Portugal, [3] Serviço de Medicina 1.2, Centro Hospitalar Universitário de Lisboa Central, EPE, Lisboa, Portugal, [4] Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisboa, Portugal

Background & Objectives: Germinotropic lymphoproliferative disorder (GLPD) and extracavitary primary effusion lymphoma (PEL) are rare human herpesvirus 8 (HHV8) and Epstein-Barr virus (EBV) - associated lymphoproliferative disorders with very few cases described in the literature. To our knowledge this is the second case report of an HIV-negative patient who progressed from GLPD to an HHV8 and EBV-positive high-grade lymphoma.
Methods: We present the case of an 86-year-old immunocompetent woman with a 1-month history of left cervical lymphadenopathy with no other symptoms. A computed tomography scan showed extensive cervical, mediastinal and abdominal lymph node enlargement. Excisional biopsy of a left cervical lymph node demonstrated overall preservation of architecture with neoplastic cells with plasmablastic morphology replacing germinal centers.
Results: Neoplastic cells were positive for HHV8, EBV, MUM1/IRF4, CD30 and EMA, without immunoglobulin light chain restriction and negative for CD20, CD138, BCL-6 and CD10, consistent with a diagnosis of HHV8+ GLPD (EBV-positive). 2 months later she presented with exuberant generalized lymphadenopathy, fatigue and peripheral edema and was readmitted. Surgical excision of a left cervical mass revealed a diffuse lymphoid cell neoplasm infiltrating adipose tissue and skeletal muscle, consisting of medium and large cells with plasmablastic morphology, with one or more nucleoli, apoptotic bodies and necrosis. The immunophenotype of the neoplastic cells overlapped with the previous population. The patient showed a decline in her clinical condition and died two days after the surgery.
Conclusion: We report the case of an HIV-negative patient with GLPD who subsequently developed an extracavitary PEL, strongly suggesting an association between these two conditions.

E-PS-10-030
Prognostic value of Ki67 in chronic lymphocytic leukemia B
G. Sahraoui[1], L. Charfi[1], R. Doghri[1], R. Sellami[1], K. Mrad[1], M. Driss[1]
[1] Institute Salah Azaiez, Tunisia

Background & Objectives: Chronic lymphocytic leukemia B (CLL-B) is the most common lymphoid hemopathy of the elderly. It is characterised by a heterogeneous evolution. Our aim was to study the prognostic value of the proliferation index (Ki67) in B-CLL.
Methods: Twenty six cases of B-CLL were collected from 2011 to 2018. The evolution of each patient had been determined. Were considered: low proliferation index = [0 - 10% [, intermediate [10 - 25%] and high> 25%.
Results: The average was 60 (24-82). Sex ratio was 2. Twenty per cent of patients had a low Ki67, 58% had an intermediate ki67 and 22% had a high ki67. The overall survival rate was 65%. Two patients of the weak Ki67 group, 11 of the intermediate group and 4 of the high group had survived. Relapse was observed in 2 low Ki67 patients and 3 high Ki67 patients. No relapse was noted in the middle group. Transformation into high grade lymphoma was noted in 3 cases of low Ki67, 5 cases of intermediate Ki67 and 3 cases of high Ki67.
Conclusion: Our study reinforces the notion of B-CLL heterogeneity. Prognostic value ofKi67 remains to be determined over larger series.

E-PS-10-031
Diffuse large B cell lymphoma located in the subcutaneous tissue
Y. Dere[1], S.Y. Celik[2], O. Ilhan Celik[3], V. Karakuş[2], Î Dere[3]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Haematology, Turkey, [3] Mugla Sitki Kocman University, Faculty of Medicine, Department of Surgery, Turkey

Background & Objectives: Diffuse large B cell lymphoma is the neoplasm of large B lymphoid cells which generally presents with nodal disease. Extranodal involvement is rare but the most common localizations are bone, testis, spleen, Waldeyer ring, salivary gland, thyroid, liver, kidney and adrenal gland. We herein report a case of large B cell lyphoma located in subcutaneous tissue of the forearm.
Methods: A male patient aged as 71 years applied to our hospital with rapidly growing mass located on the medial of the right forearm near the elbow. In the radiological examination a mass lesion in the subcutaneous adipose tissue containing thin septa with approximately 81x31 mm in size was found at the distal medial level of the humerus with a preliminary diagnosis of fibrosarcoma or liposarcoma. Histopathological diagnosis is recommended.
Results: An incisional biopsy was performed and the microscopic examination revealed the diffuse infiltration of large sized lymphocytes reaching the subcutaneous fat admixed with scattered small lymphocytes. The neoplastic large cells were CD20 (+), LCA(+), bcl6(+), CD10 (-), MUM 1 (-), Bcl2(+) immunohistochemically and Ki67 proliferation index was 55-60%.
Conclusion: Extranodal involvement of diffuse large B cell lymphoma is rare but it is important, for especially clinicians, to keep in mind that it can be seen in even extreme localizations such as subcutaneous tissue.

E-PS-10-032
Two cases of splenic inflammatory pseudotumour-like dendritic cell sarcoma, an EBV related tumour
C. Masaoutis[1], D. Sampaziotis[2], A. Choutri[3], V. Pantelaion[1], E. Patsea[5], L. Abou-Asabeh[5], D. Rontogianni[2]
[1] Evaggelismos General Hospital of Athens, Greece, [2] Department of Pathology, Evangelismos General Hospital, Athens, Greece, [3] Nicosia General Hospital, Cyprus, [4] Metropolitan General Hospital of Athens, Greece

Background & Objectives: A 66-year old woman with a history of breast cancer since 2015 presented with a solitary solid 4 cm splenic mass since 2017. A 72-year old woman presented with a cystic 8 cm splenic mass, grown by ~20% over the last 8 months.
Methods: Light microscopy, immunohistochemistry and in situ hybridization for Epstein-Barr virus (EBV)-encoded small RNAs (EBERs).

Results: Both lesions were circumscribed, partly encapsulated and composed of a mixed population of mature plasma cells, small T- and B-lymphocytes forming few secondary follicles, and bland spindle cells in short fascicles or storiform formations. Immunophenotype: spindle cells were diffusely SMA+, fascin+ and patchily CD35+, but CD21- and CD23-; there was minimal IgG4 production; no ALK was noted. In situ hybridization highlighted EBERs in many inflammatory and spindle cells alike. These findings are consistent with inflammatory pseudotumour-like follicular dendritic cell sarcoma.
Conclusion: This is a probably indolent tumour of the spleen and/or liver, rarely involving the gastrointestinal tract, with a strong female predilection. Despite a somewhat inconsistent terminology in the past literature, the latest WHO classification (2017) adopts the designation "sarcoma" for all inflammatory pseudotumour-like lesions of the spleen, liver and/or gastrointestinal tract with presence of EBV in spindle cells -not only in inflammatory cells-, irrespective of a follicular dendritic cell (FDC) or a fibroblastic reticular cell (FRC) immunophenotype.

E-PS-10-033
Comparison of the low Disulfiram concentrations with or without copper ions on apoptosis and pro-apoptotic gene expressions in myeloma cell lines
D. Hrckova Drozdkova[1], J. Gursky[2], Z. Kolar[3], J. Minarik[1,4], K. Smesny Trtkova[1,2]
[1] Institute of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Palacký University, Czech Republic, [2] Institute of Molecular and Translational Medicine, Palacky University Olomouc, Czech Republic, [3] Department of Clinical and Molecular Pathology, Palacky University and University Hospital Olomouc, Czech Republic, [4] University Hospital, Olomouc, Czech Republic

Background & Objectives: Disulfiram is highly potent against various types of tumours, including hematological malignancies. This agent is known to bind the copper (Cu) in a cell to form the DSF-Cu complex that causes oxidative stress and induces apoptosis. The goal of our study was to detect apoptosis in two RPMI8226 and U266 myeloma cell lines caused by using of different DSF concentrations with or without added copper ions. There was subsequently carried out a comparison of the measured apoptosis with the expression of cyclin dependent kinases CDKN2B, CDKN2A and CDKN1A.
Methods: Myeloma cell lines were affected by various concentrations of DSF with and without Cu added. Cyclin dependent kinase inhibitor JNJ-7706621 and the histone deacetylase inhibitor - SAHA, were used as control pro-apoptotic agents. The RNA was isolated from treated and untreated cells (DMSO) with followed by cDNA preparation. Expression of studied genes was quantified by RT-qPCR and the apoptosis was detected by Flow cytometry analysis.
Results: Used low Disulfiram concentrations without Cu ions show a higher percentage of apoptotic cells in compare to higher DSF concentrations. In the accordance with this finding were expressions of pro-apoptotic genes in treated myeloma cells.
Conclusion: Obtained results indicate a supported effect of already present Cu ions content, which is commonly present in tumour cells. Our described event could play an important role in the apoptosis induction in multiple myeloma disease.
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E-PS-10-034
IgG4-related inflammatory pseudotumour of the spleen associated with pleuritis: a rare case report
D. Bantouna[1], C. Davoulos[2], D. Siagris[2], M. Andreou[2], I.M. Grypari[1], V. Zolota[3]
[1] Department of Pathology, University Hospital of Patras, Greece,
[2] Department of Internal Medicine, University Hospital of Patras, Greece,
[3] Department of Pathology, Medical School, University of Patras, Greece

Background & Objectives: Inflammatory pseudotumor (IPT) is a family of diseases with diverse etiologies and unclear definition. Some IPTs may fall into the spectrum of the IgG4-related diseases (IgG4-RD). Here-in, we report a rare case of a splenic IPT with concomitant pleuritis, with clinicopathological features suggestive of IgG4-RD.
Methods: A 51-year-old man was admitted with fever, rigors and malaise. Abdominal CT-scan revealed splenomegaly and a hypodense splenic mass. Splenectomy was performed, and the histopathologic diagnosis was IPT. After months he was readmitted with similar symptoms. Blood tests revealed elevated IgG4 titers-1020mg/dl(8-140). CT-scan revealed an encapsulated pleural effusion. Open biopsy and surgical drainage were performed and revealed "fibrosing pleuritis". He was discharged home on prednisone.
Results: Grossly, the spleen presents a well-circumscribed, non-encapsulated, solitary, white-grayish, firm, parenchymal nodule. Microscopy demonstrates a fibroinflammatory lesion with myofibroblasts and variable numbers of small lymphocytes, plasma cells, eosinophils and foamy macrophages, without atypia, mitoses, or necrosis. Stroma was fibrosclerotic and storiform with hemosiderin deposition, without obliterative phlebitis. Myofibroblasts were positive for SMA, MSA, Vimentin and negative for HHV-8, LMP-1, ALK, CD34. CD138 highlights abundant plasma cells. The IgG4-positive plasma cell count was 104/hpf and the ratio of IgG4-/IgG-positive plasma cells was 60%. Pleural biopsy demonstrated marked fibrous thickening of the parietal pleura and lymphoplasmacytic infiltration with small lymphoid follicles The ratio of IgG4-/IgG-positive plasma cells was 25%.
Conclusion: The present report indicates that splenic IPT with increased numbers of IgG4+ plasma cells, belongs to the spectrum of organ specific IgG4-RD and may be associated with involvement of other IgG4-related organs.

E-PS-10-036
A case of extramedullary involvement of myeloma: skin
Y. Dere[1], S.Y. Celik[1], O. Ilhan Celik[1], L. Tekin[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Plasma cell myeloma is a bone marrow based multifocal plasma cell neoplasm associated with an M protein. Extramedullary involvement is generally a manifestation of advanced disease. Herein we present a case of myeloma with extramedullary involvement.
Methods: Eighty-six-year-old male diagnosed as myeloma a year ago applied to hospital with nodular lesions in her back for two weeks. On physical examination nodular eytematous lesions were found on the back near the scapula. Ultrasonographically a subcutaneous nodular mass with 2 cm size accompanied with inflammatory changes around was revealed. A punch biopsy was performed to the patient.
Results: Histopathological examination revealed a plasmacytic infiltration with eccentrical nuclei in the subcutaneous tissue. The immunohistochemical study revealed diffuse infiltration of CD138(+) and lambda (+), kappa(-) plasma cells similar with the patient's bone marrow biopsy which was diagnosed as myeloma.
Conclusion: Multiple myleoma patients nay manifest with extramedullary involvements in various organs such as skin. In patients who admitted to the dermatology polyclinic with nodular masses diagnosed with myeloma, an extramedullary involvement of the disease should be considered.

E-PS-10-039

Plasmablastic lymphoma: diagnostic difficulties, report of 5 cases and review of the litterature

E. Ben Hadj Khalifa[1], S. Mestiri[2], Z. Nfikha[1], D. Chiba[4], T. Zahmoul[3], O. Belkacem[4], D. Dao[1], S. Hmissa[1]

[1] Cytology and Pathology Department CHU Farhat Hached, Sousse-Tunisia, [2] Pathology Department, Farhat Hached Hospital, Sousse, Tunisia, [3] Cancer Registry of the Tunisian Center, Tunisia, [4] Pathology Department, Farhat Hached Hospital, Sousse, Tunisia

Background & Objectives: Plasmablastic lymphoma (PL) is a subtype of diffuse large B cell lymphoma characterised histologically by the presence of plasmocytoid differentiation. It is an aggressive lymphoma observed on a particular patients (immunocompromised and / or HIV positive patients) with predominance of extra-nodal forms. It is also characterised by a chemo resistance responsible of a bad prognosis. The aim of this study is to present the clinical, pathological and immunohistochemical characteristics of PL through a series of 5 cases.
Methods: The data were extracted from the records of 5 patients whose diagnosis of PL was made in the pathological anatomy and cytology department of Farhat Hached hospital of Sousse between 2014 and 2018.
Results: The sample includes 4 men and one woman aged between 37 and 63 years old. None of these subjects is known to be positive for HIV. The tumour sites were the stomach, the right colon, the lung, the brain and the axillary region. Microscopic examination showed malignant tumour proliferation of large, non-cohesive cells with abundant eosinophilic cytoplasm and atypical nuclei with a prominent nucleolus. The mitoses are numerous. First-line immunohistochemistry involved epithelial, neuroendocrine and mesenchymal markers that returned negative in 3 out of 5 cases (gastric, pulmonary and colonic). The tumour cells are negative for CD3 and CD20; the CD79a and EMA are expressed in 3 cases. CD138 is intensely and diffusely expressed in all 5 cases. MUM1 was requested on 2 occasions and returned positive. Ki67 was high (≥80%). EBV virus was carried out in only one case using in situ hybridization and the result was positive.
Conclusion: PL is a rare and aggressive lymphoma which is associated with immunodeficiency. The diagnosis is made by histopathological examination, immunophenotyping, and the detection of EBV in the tumour cells.

E-PS-10-040

Primary endometrial marginal zone B-cell lymphoma: a case report

O. Ton Eryilmaz[1], R. Ucak[1], A.A. Ozagari[1], F. Kabukcuoglu[1]

[1] University of Health Sciences Sisli Hamidiye Etfal Hospital, Department of Pathology, Turkey

Background & Objectives: Primary lymphoma of the female genital tract is rare, accounting for approximately 2% of all extranodal lymphomas and less than 0.5% of the gynaecologic malignancies. Primary extranodal marginal zone B-cell lymphoma of the endometrium is exceptionally rare and only 15 cases have been described in English literature.
Methods: We report a case of primary endometrial marginal zone B-cell lymphoma.
Results: A 75-year old woman presented with uterovaginal prolapse and pelvic pain complaints. She underwent vaginal hysterectomy and pelvic floor repair. On gross examination, the endometrium was irregular and a white coloured thickening was observed. Microscopically, the endometrium and superficial myometrium contained a nodular infiltrate of monotonous, small-sized, monocytoid-like lymphocytes with scant clear cytoplasm and round nuclei with fine chromatin. Immunohistochemically the lymphoid cells expressed CD20, CD43 and bcl-2. They were negative for CD3, CD5, bcl-1, CD23, bcl-6, CD10.The plasma cells were monoclonal, showing lambda immunoglobulin light chain restriction. The proliferation marker Ki67 was expressed in approximately 8-10% of the neoplastic cells. Routine laboratory tests (complete blood count, biochemical profile, lactate dehydogenase) were within normal limits. A staging computed tomography scan showed no evidence of extrauterine spread (Stage IE) and the patient was managed conservatively with follow-up only.
Conclusion: Most of the lymphomas occurring in the uterus are due to secondary involvement by systemic lymphoma. Primary extranodal marginal zone B cell lymphoma is extremely rare. These lymphomas are monotonous, nodular and often restricted to the endometrium. They usually do not cause symptoms and are detected incidentally after hysterectomy performed for any other reason. They are associated with excellent prognosis without adjuvant therapy.

E-PS-10-041

Paediatric nodal marginal zone lymphoma - a case report

T. Terzic[1], J. Lazic[2], N. Tosic[3]

[1] Institute of Pathology "Prof. Dr Djordje Joannovic", Faculty of Medicine, University of Belgrade, Serbia, [2] University Children's Hospital, Belgrade, Serbia, [3] Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

Background & Objectives: Paediatric nodal marginal zone lymphoma (PNMZL) is a rare subtype of NMZL with characteristic clinical presentation, pathohistological and molecular features, therapy and prognosis.
Results: A 15-year-old boy with no remarkable past history, presented with painless enlargement of left submandibular lymph node (LN) for three months. Chest radiography and abdominal ultrasound revealed no hepatosplenomegaly and lymphadenopathy elsewhere. Blood count test was normal. Biochemistry showed elevated uric acid 499 umol/l, AST 45U/l, ALT 98U/l, and sedimentation rate (65mm/h). The patient underwent biopsy of LN (47x37x20mm). The histopathological examination revealed partial architectural effacement: follicular hyperplasia and nodular B-cell infiltration with features of progressive transformation of germinal centers (PTGC). A CD20 immunostain shows an abnormal expansion of the marginal zone with infiltration of interfollicular space. These B-cells were negative for CD5, CD23, EBV-LMP1, bcl-6, CD10, EMA, CD30, CD15, MUM-1, and positive for bcl-2 and IgD. CD21 immunostain showed an expanded follicular dendritic cell meshwork. It was concluded that LN likely represent reactive follicular hyperplasia with atypical marginal zone hyperplasia or possible PNMZL, with recommendation of polymerase chain reaction (PCR) analysis. Additional IGH PCR analysis demonstrated biclonal heavy chain gene rearrangement. These findings were consistent with PNMZL. Follow-up was recommended without any treatment. The patient has remained disease free for 34 months since diagnosis.
Conclusion: We presented a rare case of PNMZL with morphological features of PTGC, but immunohistochemistry and additional PCR clonality analysis were crucial for final diagnosis. This case represents a diagnostic challenge because of their rarity in the paediatric population.

E-PS-10-042

PD1 expression in diffuse large B-cell lymphoma: pilot study

V. Oparnica[1], M. Ostojic[1], M. Prvanovic[2], N. Boricic[2], T. Terzic[2]

[1] Faculty of Medicine, University of Belgrade, Serbia, [2] Institute of Pathology "Prof. Dr Djordje Joannovic", Faculty of Medicine, University of Belgrade, Serbia

Background & Objectives: A great number of published papers depict the Hans algorithm as an excellent prognostic criterion in stratifying patients with diffuse large B-cell lymphoma, no other specified (DLBCL, NOS) into groups with a good prognosis (germinal centre B-cell, GCB) and a more aggressive one (non germinal centre, non-GCB). The aim of our pilot study was analysis of PD1 positive tumour infiltrating lymphocytes (TIL) and its expression on the tumour cells of DLBCL, along with determining a difference in the expression profile between the GCB and non-GCB subtype.
Methods: A retrospective study enrolled 39 biopsies from patients diagnosed as DLBCL, NOS. The PD1 positive TIL were counted on five

high-power fields (×400) using Cell Image software, and their average value was calculated. PD1 expression on tumour cells was marked as either positive (≥10% positive cells) or negative.
Results: Out of the 39 DLBCL samples, 18 (46.2) were GCB and 21 (53.6) non-GCB subtype. The median of the analysed values for the PD1+ TIL's was 69. The number of PD1 positive TIL's was significantly different between the GCB (99.3±57.8/HPF) and non-GCB phenotypes (54.9±28.0) (p=0,0125). PD1 tumour positivity is mostly present in the non-GCB subtype (12/21; 57.1%) compared to the GCB (3/18; 16.7%), and this difference was also statistically significant (p=0,0195).
Conclusion: Increased number of PD1+ TIL may imply better prognosis in patients with DLBCL, but PD1 expression on tumour cells was more frequent in aggressive DLBCL and may be considered as a potential therapeutic target.

E-PS-10-044
Indolent NK lymphoproliferative disorder: a case report
L. Vassallo[1], N. Maschio[2], L. Soligo[2], S. Grillo[3], E.S.G. d'Amore[4], A. Scapinello[1]
[1] Anatomical Pathology Department, Castelfranco Veneto Hospital, Veneto Oncology Institute - IOV, IRCC Padua, Italy, [2] Haematology Department, Castelfranco Veneto Hospital, ULSS2 Marca Trevigiana, Italy, [3] Gastroenterology Department, Castelfranco Veneto Hospital, Veneto Oncology Institute - IOV, IRCC Padua, Italy, [4] Department of Pathological Anatomy, San Bortolo Hospital, Vicenza, Italy

Background & Objectives: Indolent NK lymphoproliferative disorder (LPDs) of the gastrointestinal (GI) tract represents an under-recognised and recently described entity easily misdiagnosed as an aggressive disease. This group of rare pathologies has been designated by Takeuchi et al. as lymphomatoid gastropathy and by Mansoor et al. as NK-cell enteropathy. Very few cases have been documented so far. Herein we describe a new case with duodenal localization and a follow-up of 3 years.
Methods: A 56-year-old African female with long-standing dyspepsia underwent endoscopic examination that revealed erythematous areas with superficial erosions in the second portion of the duodenum. Multiple biopsies were performed. Histological study and Immunohistochemical stains were performed and EBV-encoded RNA (EBER) was searched with the in situ hybridisation (ISH) technique. The rearrangement of T cell receptor (TCR) gamma/delta chains genes was analysed.
Results: Histological examination of duodenal tissue revealed a focal and dense atypical lymphoid infiltrate sometimes containing large eosinophilic granules. This was admixed with sparse eosinophils, histiocytes and plasma cells. The infiltrate was displacing the mucosal glands and expanding the lamina propria, with extension to the submucosal layer. No necrosis, epitheliotropism or villous atrophy were seen. The neoplastic cells were positive for CD56, CD2 and cCD3, and negative for CD4, CD5, CD8, CD20, CD30 and EBER ISH. Clonal TCR rearrangement was absent. A diagnosis of NK cell enteropathy was given. No chemotherapy was done. After a follow-up period of three years no progression of diseases was documented.
Conclusion: In this study we report a case of NK-cell enteropathy and we emphasize the importance of recognising this pathology to avoid inappropriate therapies and discuss the spectrum of differential diagnosis.

E-PS-10-045
Clinicopathological study of EZH2 and NSD2 expression in DLBCL
Y. Li[1], Y. Pan[2]
[1] Dali University, China, [2] The First Affiliated Hospital of Dali University, China

Background & Objectives: Diffuse large B cell lymphoma (DLBCL) is a heterogeneous disease with various genetic and epigenetic changes. Both EZH2 and NSD2 (WHSC1/MMSET) are histone methyltransferases, whose mutations and aberrant expression were found in many types of cancer. Study showed that NSD2 worked downstream of EZH2 in prostate cancer tumorigenesis. While EZH2 has been shown to play an important role in DLBCL the role of NSD2 in DLBCL has never been explored. In this study we aim to explore the expression of EZH2 and NSD2 and their prognostic role in DLBCL.
Methods: We performed immunohistochemistry to study the expression of EZH2 and NSD2 in a total of 105 cases of DLBCL and analysed their correlation with different clinicopathological features of these patients and their overall survival status.
Results: We found that both NSD2 and EZH2 were highly expressed in DLBCL. Their expression is highly correlated with each other and with Ki67 level. There is an opposite correlation between NSD2 and BCL2 level. Patients with high NSD2 expression showed a slightly better prognosis.
Conclusion: It is the first study to show correlation of expression of EZH2 and NSD2 in DLBCL. Further studies about their working mechanism may help to clarify the role of NSD2 in DLBCL and its potential as a new drug target.

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E-PS-10-046
SOCS1 expression in B-cell lymphoma-derived cell lines
P. Kuerten[1], S.E. Weissinger[1], M. Zahn[2], R. Marienfeld[2], P. Moeller[2]
[1] Institute of Pathology, University Hospital Ulm, Ulm, Germany, [2] University Hospital Ulm, Institute of Pathology, Germany

Background & Objectives: SOCS1 (Suppressor of Cytokine Signaling 1) is a cytokine-inducible negative regulator of the JAK/STAT signaling pathway. Due to its antiproliferative effect SOCS1 is considered to act as tumour suppressor. It is known, that inactivating *SOCS1* mutations may lead to constitutive activation of the JAK/STAT pathway and subsequently to proliferation and survival of various lymphoma entities. Scope of this work was to investigate SOCS1 protein status and *SOCS1* RNA expression in different, especially B-cell lymphoma-derived cell lines.
Methods: To assess SOCS1 protein status immunoblot experiments were performed. *SOCS1* RNA expression was analysed through semiquantitative real-time PCR. Protein and RNA extracts were obtained from a) HEK 293T cells previously transfected with gradually decreasing amounts of wild-type *SOCS1*-DNA and b) cell lines that either express wild-type (wt) *SOCS1* (LCL ([lymphoblastoid], U-MM1b [multiple myeloma], HBL-1 [ABC-DLBCL], L540 [ns-HL]) or show *SOCS1* mutations (Karpas1106 [PMBL], L428 [ns-HL], MedB1 [PMBL]). Karpas1106 cells served as negative control due to biallelic *SOCS1* deficiency of this cell line.
Results: Discrepancies between RNA and protein abundances occurred in two cell lines: HBL-1 cells (ABC-DLBCL, wt) seem to express large SOCS1 protein amounts and low corresponding *SOCS1* RNA while the L540 cell line (ns-HL, wt) shows strong *SOCS1* RNA expression but no detectable SOCS1 protein band by immunoblot.
Conclusion: We found remarkable differences between *SOCS1* RNA levels and corresponding SOCS1 protein expression especially in HBL-1 and L540 cells. To identify the responsible mechanisms further investigations regarding RNA and protein degradation in these cell lines will be necessary.

E-PS-10-047
Myelodysplastic syndrome with translocation t(2;8)(p13;p22) and secondary progression to acute myeloid leukemia - first case report
F. Ultimescu[1], C. Dobrea[1,2,3], A. Tatic[4], V. Popov[5], D. Vasilache[2], C. Jardan[2], D. Coriu[4,3]
[1] Oncoteam Diagnostic, Romania, [2] Fundeni Clinical Institute, Romania, [3] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [4] Center of Haematology and Bone Marrow Transplantation,

Fundeni Clinical Institute, Romania, [5] Colentina Clinical Hospital, Romania

Background & Objectives: Chromosome abnormalities in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are among the most valuable determinants of prognosis and treatment decisions. We report a case of MDS with t(2;8)(p13;p22) and secondary progression to AML.
Methods: A 50-year-old female presented with anemia and thrombocytopenia (without eosinophilia). She underwent bone marrow biopsy and aspiration. Histopathological and flow cytometry analysis were performed, along with cytogenetics and molecular biology assessments.
Results: The bone marrow biopsy and aspirate at diagnosis were consistent with trilinear MDS: multilineage dysplasia (dyserythopoiesis, ALIP+, dysplastic micro/megakaryocytes with separated lobes), with 5% blasts. Cytogenetics at diagnosis and follow-up identified t(2;8) and monosomy 20: 45,XX,t(2;8)(p13;p22),-20. Molecular biology disclosed negative BCR-ABL p210 and JAK2. At 6-month follow-up bone marrow aspirate revealed blastic infiltration (56% myeloblasts), associated with myelodysplastic features: hipogranular, hypolobated granulocytes, neutrophil pelgerization and pleomorphic megakaryocytes with hyperlobated nuclei or micromegakaryocites. In addition, flow cytometry at follow-up showed a blastic population(35%), positive for CD45, CD34, CD117, CD33, enabling the diagnosis of AML(M1) post-MDS. The pacient is alive, has achived partial response to chemotherapy (10% residual blasts) and has been referred to HCST(hematopoietic stem-cell transplantation).
Conclusion: As far as we know, t(2;8) has previously been reported in myeloid/lymphoid neoplasms with FGFR1 rearrangement, Burkitt lymphoma, chronic lymphocytic leukemia and acute lymphoblastic leukemia. To our knowledge, this is the first case report of MDS with t(2;8)(p13;p22) and secondary AML (M1). Identification of additional cases is needed to determine the prognostic significance and therapeutic importance.

E-PS-10-048

Primary bone ALK-negative anaplastic T cell lymphoma

T. Zablocka[1,2,3], S. Isajevs[1,2,3], J. Nazarovs[4,5], A. Repnikovs[2]
[1] Riga East University Hospital, Pathology Centre, Latvia, [2] The Hospital of Traumatology and Orthopaedics, Latvia, [3] Department of Pathology, University of Latvia, Latvia, [4] P. Stradins Clinical University Hospital, Latvia, [5] Riga East Clinical University Hospital, Latvia

Background & Objectives: Primary malignant lymphoma of bone is rare, accounting for approximately 7% of all bone malignancies and 5% of all extranodal lymphomas.
Methods: The case reported 58 years old patient. Patient underwent clinical examination (MRI) and the bone trepane biopsy and tumorous mass curettage. The tissue samples were stained with haematoxylin-eosin and immunohistochemically.
Results: The 58 years old woman had pain in sacrum area; pain radiated to the right leg, after CT and MR imagining was found suspected osteolytic changes and pathological fracture of the *sacrum* bone. The bone biopsy and tumorous mass excochleation was performed. Macroscopically tumour mass appeared yellowish, smooth consistence with sizes 8x8x3 cm. Histopathological examination showed irregular appeared thickened bone trabecular with atypical diffuse infiltrate with scant basophilic cytoplasm, some cells were binucleated-Reed-Sternberg like forms, some focus of necrosis. Immunohistochemical examination demonstrated Reed-Sternberg like cells which were LCA positive, CD30 positive, vimentin positive, CD99 positive, CD4 and CD5 positive, CD3 negative, CD8 negative, CD79a negative, CD20 negative, CD138 negative, CyclinD1 negative, CD117 negative, Kappa and lambda negative, ALK negative and CKAE1/AE3 negative. Subpopulation represented small shaped T lymphocytes, which were CD3 positive, some CD68 positive histiocytes and multiple leukocytes. Flow cytometry demonstrated activated lymphocytes (CD38) -61% and B lymphocytes (CD19)- 8%. There was no any suspicious infiltrate in inner organs or other bone.
Conclusion: Anaplastic large T cell lymphoma (ALCL) ALK negative of bone is extremely rare malignancy. Clinicians and pathologists should keep in mind that ALCL can present with extensive bone involvement without nodal involvement.

E-PS-10-049

Morphological and clinical characteristics of newly diagnosed primary myelofibrosis patients in Latvia

A. Breiksa[1], J. Nazarovs[1,2], R. Kleina[3]
[1] P. Stradins Clinical University Hospital, Latvia, [2] Riga East Clinical University Hospital, Latvia, [3] Riga Stradins University, Latvia

Background & Objectives: Primary myelofibrosis (PMF) is a rare myeloproliferative neoplasm, which is included at ORPHANET database. PM is diagnosed by bone marrow biopsies and clinical correlation. There is very little data available about epidemiology and morphological and clinical characteristics of this disease in the European Union and no data about this disease in Latvia. The aim of our research was to determine newly diagnosed PM patients' morphological and clinical data in Latvia.
Methods: This study is retrospective. We obtained all patients (n= 130) with PMF from 2010 to 2015 in Riga East Clinical University Hospital's haematology centre. Bone marrow biopsy data, such laboratory tests as red blood cells, white blood cells, platelets, haemoglobin (HGB) and visual diagnostic tests were analysed.
Results: Men were 60 (46.2 %;), women – 70 (53.8%) of all cases. Mean age was 67.08 ± 10.09 years. Disease was diagnosed in fibrotic stage in 56.2% (n= 73) cases. Prefibrotic stage was observed in 43.8% (n= 57) cases. Myelofibrosis grades were as follows: MF0 33, 8%, n= 44; MF1 17, 7%, n= 23; MF2 29, 2%; n= 38 and MF3 19, 2%; n= 25. Splenomegaly was confirmed with imaging studies in 111 cases. Hepatomegaly was diagnosed in 26 cases.
Conclusion: Overall primary myelofibrosis patients' morphological and clinical characteristics are similar to these data worldwide. The disease was diagnosed in the fibrotic stage in more than half patients. Clinical data showed such clinical signs as hepatosplenomegaly, anaemia, and leucocytosis. This research is the first which analyses primary myelofibrosis in Latvian population.

E-PS-10-050

Anaplastic large cell lymphoma: clinical and pathological study

M. Manai[1], R. Doghri[2], G. Sahraoui[1], K. Kacem[3], K. Mrad[2], M. Driss[4], L. Charfi[2]
[1] Institute Salah Azaiez, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia, [3] Service d'hèmatologie, Hôpital Aziza Othmana, Tunisia, [4] Department of Pathology, Salah Azaïez Institute, Tunisia

Background & Objectives: Anaplastic large cell lymphomas (ALCL) represent less than 5% of non-Hodgkin's lymphomas in adults and nearly 35% of paediatric non-Hodgkin's lymphomas. The WHO classification distinguishes two types; ALCL ALK + and ALCL ALK-. The aim was to study anatomoclinical and immunohistochemical profile of ALCL through a Tunisian cohort and to identify prognostic factors.
Methods: Retrospective study of cases of ALCL collected over a period of 22 years (1995-2017), classified according to the WHO classification (2016).
Results: Our series included 52 ALCL: 34 ALK- and 18 ALK +. The median age was 45.4 years (ALK -) and 35 years (ALK +). 73% of ALCL ALK + were in advanced Ann Arbor stage (III or IV) versus 83% of ALCL ALK. ALCL ALK + were of phenotype T in 43% versus 50%

in ALCL ALK-. Overall survival was 56% at 5 years in the ALK + group versus 28.4% at 5 years in the ALK- group.
The factors of poor prognosis in the ALK + group: age> 18 years (P = 0.039), PS score> 2 (P <0.001); in the ALK- group: PS score> 2 (0.022), the presence of B symptoms (P = 0.024) and bone marrow involvement (P = 0.043).
In multivariate analysis, PS score was found to be the only significant independent prognosis factor in the ALK+ group. PS score and presence of B symptoms were both found to be significant independent prognostic factors impacting OS and EFS.
Conclusion: In our study, we highlighted the clinical, immunohistochemical and prognostic differences between ALK+ and ALK- ALCLs.

E-PS-10-051
Biological role of ID3 expression in diffuse large B cell lymphoma (DLBCL)
M. Trujillo Coronado[1], R. Manso Alonso[2], L. Cereceda[2], M. Boiza Sanchez[2], Y. Castro[3], M. Garcia-Cosio[4], F. Camacho[5], J.F. Garcia[6], M.A. Piris Pinilla[2], S.M. Rodriguez Pinilla[2]
[1] Hospital Universitario Fundacion Alcorcon, Spain, [2] Hospital Universitario Fundacion Jimenez Diaz, Spain, [3] Hospital Universitario de Guadalajara, Spain, [4] Hospital Universitario Ramon y Cajal, Spain, [5] Hospital Universitario de Getafe, Spain, [6] Hospital MD Anderson Cancer Center Madrid, Spain

Background & Objectives: Inhibitor of DNA binding 3 (ID3) is a member of the ID family of helix-loop-helix (HLH) proteins that inhibit other HLH proteins-like TCF3. It has been found mutated in Burkitt lymphomas, in these subgroup ID3 point biallelic mutation has been related to complete absence of its expression. Its role in DLBCL has not yet been characterised in depth.
Methods: We have taken advantage of a well-characterised monoclonal antibody recognizing ID3 to analyse its expression pattern in a cohort of 58 DLBCL patients. Clinical features of all patients are known. FISH studies of BCL2, BCL6, MYC genes as well as mutational analysis of this cases have been done. Statistical studies have been performed using SPSS programme.
Results: The series consisted of 31 women and 27 men. Median age at diagnosis was 62,5. 35 and 23 patients had a low-IPI and high-IPI score, respectively. All patients received R-CHOP, 37 (64%) achieved complete remission. The median overall survival was 49 months (0-196), with 13 deaths from disease-related-causes.
ID3 was positive in 35 cases while complete absence of expression was found in 17 cases (30%). Hans's algorithm subclassified cases into 22 germinal-center B-cell (GC) and 22 Activated-B-cell (ABC)-phenotype. Loss of ID3 was directly associated with CD10 expression, absence of MUM1 and GC phenotype. Negative ID3 expression was also related to better outcome (p=0.043) (2 dead patients in ID3- vs 14 in ID3+).
Conclusion: ID3 negative identifies a better prognosis subgroup of DLBCL-GC phenotype.
Validation of this study and correlation with mutational events will be shown.

E-PS-10-052
Primary non-Hodgkin's lymphoma on the colon and rectum
M. Manai[1], G. Sahraoui[1], R. Doghri[2], R. Sallami[1], K. Mrad[2], M. Driss[2], L. Charfi[3]
[1] Institute Salah Azaiez, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Primary non-Hodgkin's lymphoma (NHL) of the colon and rectum is rare representing only 0.5% of all colorectal cancers. Colorectal localization constitutes 15 to 20% of all digestive lymphomas. Our aim was to report histopathological features of these lymphomas.
Methods: We collected cases of colo-rectal NHL between January 1999 and December 2018.
Results: Our series included 20 cases. The average age was 46 years (3-74). Sex ratio was 1.5. MALT lymphoma was identified in 6 cases, followed by large cell lymphoma B (5 cases) and Burkitt lymphoma (5cases) and finally mantle cell lymphoma (4cases). The immunohistochemical study was performed in 14 cases. The panel included variously the following antibodies: CD3, CD20, CD5, CD10, CD30, CyclineD1, Tdt, Bcl2, C-Myc, Ki67, Cytokeratin, with an average of 5 antibodies tested/case. The colon was affected in 17 cases, of which 5 were cecal. The rectum was affected in 3 cases. The involvement was multiple (lymphomatous polyposis) in 2 cases of mantle lymphoma. Rectal lymphomas were in all cases a large cell B-cell. All cases of cecal lymphoma were Burkitt lymphoma. This lymphoma was diagnosed in 4 cases (out of 5) in children (3-9 years).
Conclusion: The favourite site of these lymphomas is the cecum. MALT lymphoma is the most common histological type. Mantle lymphoma is less common but is more frequently diagnosed in the colorectal area than in other segments of the gastrointestinal tract.

E-PS-10-053
Fascin expression in classical Hodgkin lymphoma and anaplastic large cell lymphoma
N. Boujelbene[1], M. Driss[1], R. Doghri[1], I. Abbes[1], N. Ben Hamida[1], D. Kacem[1], K. Mrad[1], L. Charfi[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Fascin is an actin-bundling protein that was involved in the formation of dendritic processes.
We aimed to analyse fascin expression in classical Hodgkin lymphoma (CHL) and to determine its usefulness in discriminating CHL from anaplastic large cell lymphoma (ALCL).
Methods: Formalin-fixed, paraffin-embedded tissue samples from cases of CHL and ALCL were analysed. Fascin expression was compared across each type of lymphoma with additional correlation between fascin positivity and the others antibody expression including CD3, CD20, CD30, CD15 and ALK.
Results: A total of 18 archival cases of CHL (n=15) and ALCL (n=3) from adults and children were studied.
The mean age were 35 years (with extremes of 3 to 78 years old). The sites of involvement included 13 lymph nodes (11 cervical, 1 axillary and 1 inguinal), 1 central (mediastinum) location, 2 hepatic biopsy and 2 Bone morrow. All 15 cases of CHL demonstrated intense positive staining for fascin in the Reed-Sternberg cells including CD15 negative cases. Focal and moderate positivity for fascin was observed in one case of ALCL (33%) that does not express ALK. Fascin expression was correlated significantly to the absence of CD3, CD20 and CD15 expression (p<0.0001).
Conclusion: Fascin is expressed consistently in Reed-Sternberg cells of CHL. It is a very sensitive marker particularly useful when CD15 is negative. Taking into the consideration that some CHL may even express cytotoxic molecules, differential diagnosis between CHL and ALCL may be challenging. Fascin negativity or weak expression may help the exclusion of CHL.

E-PS-10-054
Significance of double expressor lymphomas and association with DNA repair proteins
S. Bozkurt[1], H. Toper[2], T. Elibol[3], T. Tuglular[3]
[1] Marmara University Medical Faculty Pathology Department, Turkey, [2] Dokuzeylul University Graduate School of Health Science Molecular Pathology, Turkey, [3] Marmara University Medical Faculty Haematology Department, Turkey

Background & Objectives: The cases of diffuse large B-cell lymphoma, NOS (DLBCL, NOS) which immunohistochemically exhibit MYC and BCL2 expressions are defined as double-expressor lymphomas (DEL). Several studies demonstrated DELs associated with adverse prognosis. In our study, we aim to detect prognostic role of double-expressor subgroup and association with DNA repair proteins.
Methods: In this study, 90 cases of DLBCL, NOS diagnosed between the dates of 2007 and 2015 have been evaluated retrospectively. Clinical and demographical data including age, sex, localization of tumour, Ann Arbor stage and NCCN-IPI scores belonging to patients were collected and immunohistochemical evaluations as well as overall survival analyses have been carried out. Myc and Bcl2 protein expressions were analysed to determine double-expresor lymphoma group. Additionally, expressions of p53, base excision repair proteins (AID, UNG) and mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) were also assessed.
Results: Median age of the cases was 59, and male/female ratio was 0.95. Eleven cases (12.2%) which exhibited ≥40% Myc and ≥50% Bcl2 immunexpressions were classified as double-expressor DLBCL. Age greater than 60, advanced Ann Arbor stage, high NCCN-IPI scores, ≥40% MYC immunexpression and high Ki-67 proliferation index were all associated with lower overall survival. Although a trend of lower overall survival was observed in the double-expressor lymphoma group, this was not proven to be statistically significant. Also, no significant relation between AID, UNG and P53 immunexpressions with double-expressor lymphoma and overall survival could be detected. It is observed solely correlation between immunexpressions of P53 and Myc. The loss of expression for MLH1, MSH2, MSH6, PMS2 antibodies are not detected in any tumour.
Conclusion: Our study showed that the prognostic value of DEL may not be reliable, so that further studies are needed to confirm. Also, our findings demonstrate that DNA mismatch repair protein loss in DBBHL is not usual and it does not seem to have major role in lymphomagenesis.

E-PS-10-055
Histiocytic sarcoma: a case report of skin involvement
D. Gigliano[1], M. Afonso[1]
[1] IPO-Porto, Portugal

Background & Objectives: Histiocytic Sarcoma (HS) is a rare malignant hematologic neoplasm, accounting for less than 1% of all hematolymphoid neoplasms. The etiology is unknown, shows no age or sex predilection, and is clinically aggressive. It consists of a diffuse proliferation of cells exhibiting the morphology and immunophenotype of differentiated histiocytes. We aimed to raise awareness to such a rare entity.
Methods: We report a case of a 51-year-old woman with unremarkable medical history, referred to our Institution because of a rapidly growing erythematous nodule of the right leg. The MRI scan revealed a 3.5x3.3cm subcutaneous heterogeneous lesion. An initial incisional biopsy followed by complete excision of the nodule was performed.
Results: Microscopically, the neoplasm consisted of sheets of large cells with pleomorphic nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. The lesion was centered in the dermis, ulcerated the overlying epidermis and infiltrated the subcutis. Up to 6 mitoses per 10 high-power fields were encountered. Immunohistochemistry showed diffuse positivity for CD68 and CD4, focal positivity for lysozyme and CD31, while epithelial, melanocytic, lymphocytic, dendritic-cell and Langerhans-cell markers were negative. These findings allowed a diagnosis of HS.
Conclusion: HS is an exceedingly rare hematologic neoplasm, with a very aggressive clinical behavior. Therefore, a correct diagnosis is crucial for an adequate treatment. In spite of its reproducible morphology, the diagnosis of HS requires an extensive panel of immunohistochemical markers for the exclusion of more common malignancies. The patient is currently scheduled for re-excision due to inadequate margins and adjuvant chemoradiotherapy.

E-PS-10-056
Sclerosing angiomatoid nodular transformation of the spleen: 3 cases with different morphology
A. Cakir[1], E. Calis[1], O. Canoz[2]
[1] Istanbul Medipol University, Department of Pathology, Turkey,
[2] Erciyes University, Department of Pathology, Turkey

Background & Objectives: Sclerosing angiomatoid nodular transformation of the spleen (SANT) is a benign and rare vasculary lesion of the spleen with an unknown etiology.
Here, we want to present 3 cases of SANT lesions, one with classic morphology and the others are in the spectrum of SANT.
Methods: All patients were females and had one mass in the spleen. Case 1 was 46 years-old and had a history of breast carcinoma. Splenectomy was performed with a pre-diagnosis of metastasis. Case 2 was 33 years-old with thrombocytopenia and splenectomy was performed for the 11 cm mass with a pre-diagnosis of SANT. Case 3 is 71 years old and the pre-diagnosis for the spleen mass was hamartoma or angiosarcoma.
Results: All of the masses had macroscopically demarcated red-brown lesions from the surrounding spleen; microscopically and immunohistochemically, 3 vessel types can be identified (CD34+, CD31+, CD8- capillaries, CD34-, CD31+, CD8+ sinusoids and CD34-, CD31+, CD8- small veins). Case 1 had a classical SANT lesion with macroscopic santral sclerosis of 4x3 cm mass; microscopically slit-like, round or irregular shaped vascular spaces lined by plump endothelial cells forming micronodules. In case 2, no sclerosis can be identified macroscopically and microscopically for the 11x10 cm lesion. Case 3 had a 7x5 cm lesion with focal sclerosis macroscopically. Interestingly, this case had some degenerative/ancient changes, with pleomorphic nucleous in the stroma. No IgG4 increase can be shown immunohistochemically, all of the cases.
Conclusion: Case 1 was a classic SANT case. Although no detailed information can be found in the literature, we concluded that no/minimal fibrosis can be found in some, probably early SANT lesions and some degenerative changes can also be seen. Splenectomy is cure for SANT.

E-PS-10-057
Intratumoral immune and stromal heterogeneity in follicular lymphoma: an implication in relapses and responses to immunotherapies?
C. Lamaison[1], F. Mourcin[1], K. Tarte[1]
[1] UMR_S 1236, Universitè de Rennes 1, INSERM, Etablissement Français du Sang, Rennes, France

Background & Objectives: Follicular Lymphoma (FL) B cells are strongly dependent on a GC-like microenvironment including immune and stromal cells. FL-B cells display different cytological grades, proliferation rates, phenotypes, and subclonal genetic profiles depending on their localization (LN *versus* BM), suggesting that trafficking within various microenvironments could differentially impact FL pathogenesis and clonal selection. The characterization of specific niches supporting FL B cells proliferation or FL ancestral common precursor clone (responsible for relapse and transformation) remains to be explored. Our objective is to identify if different tumour-supportive niches exist that could in turn support different subclonal evolution and affect responses to immunotherapies.
Methods: We made use of *in situ* approaches by using multiplex IHF, and CLARITY clearing , and functional studies with a 3D co-culture model.
Results: We assessed the heterogeneity of stromal and immune cells and identified two different niches in FL-LN. The first one, with a high FL-B cells proliferation, shows high expression of Cancer Associated Fibroblasts markers (SPARC, periostin and podoplanin) that are

correlated with i) a low number of cytotoxic cells ii) an increase of follicular helper T cells and macrophages iii) an anarchic vascularization. In the second niche, FL-B cells are less proliferative, stromal cells express others markers like Madcam with high expression of CCL21, and few immune cells.
Conclusion: We identified two niches within FL-LN, composed by immune and stromal cells with different phenotypes and functions. These data suggest a different capacity to support B-cells subclones which could be related to drugs resistance.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-11 | Head and Neck Pathology

E-PS-11-001
Hybrid carcinoma of the salivary glands: report of two extremely rare cases
K. Kusafuka[1], S. Miyabe[2], K. Ishibashi[2], T. Nakajima[1], T. Sugino[1]
[1] Shizuoka Cancer Center, Japan, [2] Aichi-Gakuin University, Japan

Background & Objectives: Hybrid carcinoma (HC) is defined as two or more distinct and separable carcinomas in the same topographic area and producing a single tumour mass. HC is extremely rare in the salivary glands. We report two additional case of HC.
Methods: We selected two HC cases from our pathology file during 2002-2018, and examined them, clinically, histologically and immunohistochemically.
Results: Case 1 was an 87-year-old Japanese male. Salivary duct carcinoma (SDC) was observed in the most area, whereas squamous cell carcinoma (SqCC) was seen in part. The former was positive for AR, GCDFP-15 and EGFR. Case 1 consisted of SDC and SqCC. Case 2 was a 70-year-old Japanese female. SqCC was seen, whereas large cell neuroendocrine carcinoma (LCNEC), which were positive for NCAM and synaptophysin, was observed in the central area of this tumour. Case 2 consisted of SqCC and LCNEC.
Conclusion: HC is an extremely rare entity. Although the combination of SDC and adenoid cystic carcinoma or epithelial-myoepithelial carcinoma has been reported, only three cases of combination between SDC and SqCC has been reported. Moreover, case 2, which was composed of SqCC and LCNEC, is the first case. In the diagnosis of HC, carcinoma with high-grade transformation should be ruled out.

E-PS-11-002
Necrotising sialometaplasia of the larynx: a case report and review of the literature
M. Garcia Martos[1], C. Perna Monroy[2], R. Carrillo GIjon[3], C. Prada Puentes[3]
[1] 11312, Spain, [2] Univ. Hosp. Ramon y Cajal, Spain, [3] Univ Hosp Torrejon, Spain

Background & Objectives: Necrotizing sialometaplasia (NS) is a benign condition that usually involves major and minor salivary glands of the oral cavity and the upper aerodigestive tract. Only four cases of NS of the larynx has been reported. The importance of NS lies in its potential for clinical and pathologic confusion with either squamous cell carcinoma or mucoepidermoid carcinoma. The pathogenesis is unknown but may occur in response to a variety insults include previous biopsy, ischemia, surgery or radiotherapy
Methods: A 59-year-old male with dysphonia, without dyspnea and throat pain. On the fiberoptic exploration, he presented an arytenoepiglottic fold thickening with a light impairment of the motility of the right hemilarynx. CT scan revealed a mass in this region. Multiple biopsies did not revealed malignancy.
Results: The surface of the mucosa was partially ulcerated and covered by an irregular acanthotic epithelium. The general architecture of the glands was preserved within pronounced and extensive squamous metaplasia of the salivary gland ducts and acini. In some instances, there was a pseudo infiltrative pattern and light surrounding inflammation. Some ducts were dilated within mucous or necrotic debris. Immunohistochemistry pointed flattened basal cells at the periphery of epithelial islands. P53 was negative.
Conclusion: NS is a benign condition that usually involves salivary glands of the oral cavity and upper aerodigestive tract. NS can mimic malignancy, being confused with squamous cell carcinoma or mucoepidermoid carcinoma. Well-characterised morphological features and IHC expression of basal cell markers are helpful in differential diagnostic, mainly when material is limited.

E-PS-11-004
An exceptional case of clear cell oncocytoma of palatine minor salivary gland
S. Tzorakoleftheraki[1], M. Givannakis[2], S. Triaridis[2], G. Tsiropoulos[3], T. Koletsa[4]
[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece, [2] A' Otorhinolaryngology Department AUTH, AHEPA Hospital, Greece, [3] Medical Department, AUTH, Greece, [4] Pathology Department, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background & Objectives: Clear cell oncocytoma (CCO) constitutes a rare subtype of oncocytoma, characterised clinically by major salivary gland involvement and histologically by replacement of oncocytes with clear cells. Cases of CCOs located at minor salivary glands have not been reported. Herein we present an exceptional case of CCO arising in palatine minor salivary gland.
Methods: A 44-year-old female proceeded to the hospital due to a left-sided, painless palatine swelling. After clinical examination, imaging and Fine Needle Aspiration Biopsy, which showed findings consistent with benign mixed tumour, she underwent surgical excision of the tumour. The surgical specimen regarded a nodular, grayish-white, solid tumour, measuring 1,9 cm.
Results: Histologic examination showed a circumscribed, encapsulated neoplasm, consisted of oncocytes and clear cells, which were arranged into nests and surrounded by basal cells. Occasionally, characteristic transition from oncocytes to clear cells was evident. Phosphotungstic Acid-Hematoxylin revealed oncocytic granular positivity. Both oncocytes and clear cells were immunoreactive to CK8/18, CEA and alpha-1-antichymotrypsin antibodies and negative to CD10, GFAP, S100, p63. The latter immunostain highlighted the basal cells. The specimen included fragments of minor salivary gland. The diagnosis of CCO was set.
Conclusion: The majority of head and neck neoplasms may potentially show clear cell change, causing diagnostic issues. CCO can affect minor salivary glands and total excision of the lesion is the mainstay of therapy. Since most mimickers of CCO are malignant neoplasms with adverse prognosis, thorough morphologic, histochemical and immunohistochemical examination are crucial for making a safe diagnosis.

E-PS-11-005
Primitive pure signet-ring cell intestinal type adenocarcinoma of the sino-nasal tract: an extremely rare entity
R. Cepurnaite[1], E. Guadagno[1], M. Fuggi[1], S. Pigniatiello[1], L. Insabato[1]
[1] Department of Advanced Biomedical Science of the University of "Federico II" in Naples, Italy

Background & Objectives: Sino-nasal adenocarcinomas (SNACs) are rare and clinically aggressive tumours. They are broadly categorized into the intestinal- and non-intestinal type.

A pure signet-ring cell carcinoma is an extremely rare subtype of the intestinal-type adenocarcinomas. To our knowledge only 5 cases have been reported in the literature. Our aim is to present a case of primitive pure signet-ring cell intestinal type-adenocarcinoma of the sino-nasal tract with immunohistochemical profile and compare it with other cases reported in the literature.
Methods: A 75-year old male, ex-carpenter, with a history of nasal obstruction and diplopia for 3 months had his biopsy taken at our hospital in 2019. It showed an inflammatory polyp with some atypical reactive cells. Due to a high suspicion of malignancy, the patient underwent MRI following a total excision of the lesion. The tumour measured 8x3,5 cm. Microscopically, it was purely composed of signet-ring cells floating in pools of extracellular mucin. Foci of bone infiltration were observed.
Results: The immunohistochemical study revealed a strong expression of CK7, CK20, CDX2 and MUC2. An increased proliferative activity (Ki67 expression) using MIB-1 antibody was observed. Total body CT scan did not reveal any other lesion. All these results led to the diagnosis of primary pure signet-ring cell of intestinal type adenocarcinoma. The immunohistochemical evaluation of mismatch repair proteins revealed a microsatellite stability state (MSS). ALK protein and chromogranin were negative.
Conclusion: Pure signet-ring cell SNACs are rare and aggressive tumours. Their intestinal differentiation can be displayed by immunohistochemistry (positive staining for CK20 and CDX-2). To exclude the possibility of these lesions being metastatic, careful digestive endoscopical examination is recommended.
These tumours show specific clinical, macroscopical and histological features and they must always be considered in the differential diagnosis of sino-nasal neoplasms.

E-PS-11-006
Spindle cell carcinoma:a unique and rare neoplasm
I. Kourtesis[1], K. Koulia[1], A. Tsavari[1], K. Manoloudaki[1], G. Sotiropoulou[2], T. Vasilakaki[1]
[1] Tzaneio General Hospital of Piraeus, Greece, [2] General Hospital of Korinthos Greece

Background & Objectives: Spindle cell carcinoma (SPCC) is an uncommon subtype of squamous cell carcinoma. It is a biphasic tumour consisting of a combination of squamous cell carcinoma (in situ or invasive) and a malignant spindle cell component with a mesenchymal appearance but of epithelial origin.
SPPC is observed mainly in the larynx especially in the glottic region. Its rarity and histopathological pattern poses a diagnostic challenge.
Methods: A 66-year-old man presented with a ten-month history of hoarseness of the voice and dyspnea. Laryngoscopic examination revealed a polypoid mass 1,8cm. in dimension on the right vocal cord. Lymph nodes were not palpable. The mass was removed endoscopically.
Results: Histological examination revealed a tumour showing foci of well differentiated squamous cell carcinoma and a malignant spindle cell component which formed the bulk of the tumour.
In the immunohistochemical study the lesional cells (both squamous cells and spindle cells) were positive for CK5/6,P63,pankeratin and vimentin and negative for CD34,desmin,actin and S100p. The diagnosis was spindle cell carcinoma.
Conclusion: Spindle cell carcinoma is a rare tumour.
Surgical excision combined with adjuvant radiotherapy has a better survival outcome.

E-PS-11-007
Inflammatory myofibroblastic tumour of the parotid gland: report of a rare case
I. Kourtesis[1], K. Koulia[1], A. Tsavari[1], G. Sotiropoulou[2], T. Vasilakaki[1], K. Manoloudaki[1]
[1] Tzaneio General Hospital of Piraeus, Greece, [2] General Hospital of Korinthos Greece

Background & Objectives: Inflammatory myofibroblastic tumour is a term that refers to a bening neoplastic disorder of unknown etiology that can appear in various locations, mainly affecting the lung. It affects individuals of both sexes and of a wide range of ages. It can sometimes mimick other malignant entities under the clinic and pathologic viewpoint. Our aim is to report one case of inflammatory myofibroblastic tumour located in the parotid gland.
Methods: A 73-year-old male presented with a palpable right parotid mass. Computed tomography revealed a tumour-like lesion measuring 4,5 cm. in diameter. The lesion was surgically removed. Gross examination revealed a firm, yellowish tumour.
Results: Microscopic examination revealed a benign neoplastic proliferation of spindle cells with histological characteristics of myofibroblasts, in a highly vascular stroma comprising mainly of chronic inflammatory cells, such as plasma cells, lymphocytes and histiocytes. No nuclear atypia or mitotic figures were present. In peripheral and a few central sites, residual parotid parenchyma and a microscopic growth of Warthin tumour were detected. Immunohistochemical analysis was positive for SMA, vimentin, HHF35 and desmin and negative for pankeratin, EMA,S100,ALK,CD34,CD23,CD21 and LCA.
Conclusion: Parotid gland inflammatory myofibroblastic tumour is a very rare lesion which along with its nonspecific clinical appearance may pose diagnostic difficulties. The differential diagnosis includes sialadenitis and various benign and malignant neoplasms, such as myoepithelioma, proliferative and nodular fasciitis, solitary fibrous tumour, spindle cell sarcoma, fibrosarcoma etc. Therefore, a comprehensive histopathological assessment is necessary.

E-PS-11-008
Odontogenic developmental cysts: reclassification according to the 2017 World Health Organisation Classification
I. Msakni[1], F. Gargouri[1], R. Hedhli[2], N. Mansouri[1], A. Saidi[1], A. Bouziani[1], B. Laabidi[1,2]
[1] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia, [2] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: Odontogenic developmental cysts is a heterogeneous group that has undergone many changes in the new World Health Organisation (WHO) published in 2017. Odontogenic keratocysts and Calcifying odontogenic cysts considered a neoplasia in the 2005 WHO classification are now considered developmental lesions. Orthokeratinized odontogenic cysts were considered a variant of the odontogenic keratocysts. In the new 2017 WHO classification, it has been considered as a separate entity. Our aim was to reclassify these cysts according to the new 2017 WHO classification.
Methods: It was a retrospective study of odontogenic developmental cysts collected in our department over a period of 5 years (2012-2017).
Results: We collected 12 odontogenic developmental cysts. Dentigerous cyst was observed in 6 cases. The median age was 34 years (sex ratio=1).Odontogenic keratocyst was observed in 5 cases.The median age was 44 years (sex ratio=4). Orthokeratinized odontogenic cyst was observed in a single 25-year-old male patient.
Three dentigerous cyst were reclassified to 2 radicular cysts and one inflammatory collateral cysts. Three odontogenic keratocyst were reclassified to one dentigerous cyst, one orthokeratinized odontogenic cyst and onefibro-dentinoma.
Conclusion: In our study, histological diagnosis after revision of the slides and anatomoclinical confrontation did not agree with the initial

diagnosis in 50% of cases (n = 6).This is due, to the lack of clinical and radiological data for the pathologist, but also to the absence odontogenic cysts classification up to the year 2017.

E-PS-11-010

Adenoid cystic carcinoma with cervical spine metastasis: case report

A. Kilitci[1], Z. Asan[2], E. Tugcugil[3], î Aykanat[2], A. Yüceer[2], F. Durna[4]
[1] Ahi Evran University Medical Faculty, Dept of Pathology, Turkey, [2] Ahi Evran University Medical Faculty, Dept of Neurosurgery, Turkey, [3] Karadeniz Technical University Medical Faculty, Dept of Anesthesiology, Turkey, [4] Ahi Evran University Training and Research Hospital, Dept of Neurosurgery, Turkey

Background & Objectives: Adenoid cystic carcinoma (ACC)s are malignant tumours that typically originate from glandular structures and demonstrate metastasis by local invasion and via the hematogenous route at advanced stages. Involvement of neighboring organs is also common. The literature does not include any cases of ACC with vertebral metastasis.
Methods: 45-year-old male patient was evaluated for findings of sudden neck pain and nearly total loss of strength in the right arm.His medical history revealed that he had been under follow-up for five years due to a diagnosis of ACC with a parotid gland origin.Cervical CT and MRI examinations determined compression fracture in the corpus of C5 and spinal cord compression.The case,who did not report a history of trauma,was urgently operated considering that the vertebral fracture could be a pathological fracture.
Results: Vertebral resection was made. Histopathological examination of the specimen revealed a tumour with solid and cribriform pattern that was composed of atypical epithelial and myoepithelial cells. The case, whose motor deficit showed partial improvement following corpectomy, underwent rehabilitation in the postoperative period. The case who had been followed-up for metastases in the neck area and in intracerebral structures and who had undergo combined radiotherapy and chemotherapy died two years later due to multi-organ metastasis.
Conclusion: No information could be found in the literature regarding the vertebral metastasis of ACC. In these cases, localized tumourous formations are treated with radiotherapy, while chemotherapy is administered for multi-organ involvement. Vertebral metastasis can lead to pathological fractures.

E-PS-11-011

Synovial sarcoma of the palatine tonsil: a case report

J. Rajc[1], K. Marjanović[1,2], V. Zubčić[3,2], B. Dumenčić[1,2], S. Nekić[1,2], D. Dumić[1,2]
[1] Clinical Department of Pathology and Forensic Medicine, Osijek University Hospital, Croatia, [2] Faculty of Medicine, University of Osijek, Croatia, [3] Clinical Department of Maxillofacial Surgery, Osijek University Hospital, Croatia

Background & Objectives: Most synovial sarcomas arise in the extremities (80%), with only 3-5% located in the head and neck region. We report a case of synovial sarcoma based in the palatine tonsil, as an extremely rare primary site of involvement.
Methods: A 51-year-old man presented with sore throat and dysphagia. On the physical examination, a palpable pedunculated right tonsillar mass, with no cervical lymphadenopathy was noted. An MRI showed a well-demarcated solid mass confined to the tonsil, measuring 3.6 cm in greatest dimension with no involvement of the other surrounding structures. The patient underwent a tonsillectomy.
Results: Intra-operative frozen section showed a malignant mesenchymal tumour along with the remnant of normal tonsillar tissue. Histological and immunohistochemical investigation showed a biphasic synovial sarcoma with gland-like structures, lined by cuboidal/columnar cells. The neoplastic epithelial cells were positive for Cytokeratin and EMA, while the sarcomatous component was positive for Vimentin, bcl2 and CD99. Additional molecular analysis revealed t (X;18) translocation of the SYT gene with the detection of the SYT-SSX1 fusion type. Surgical margin was free of tumour.
Conclusion: Synovial sarcoma is a rare malignant tumour, which can occur in the head and neck region. Tonsillar synovial sarcoma should be considered in the differential diagnosis when working up a tonsillar mass. In such rare cases, preoperative incisional biopsy could be considered to aim with optimal surgical strategy.

E-PS-11-012

Components of the peritumoral zone of laryngeal carcinoma as additional morphological criteria of tumour aggressiveness

A. Semenova[1], A. Shamanova[1], E. Kazachkov[2], A. Gyz[1], T. Shamaeva[2], E. Glazirina[2]
[1] Chelyabinsk Oncology Clinic, Russia, [2] South-Ural State Medical University, Russia

Background & Objectives: To characterise the morphological features of the components of peritumoral zone in laryngeal carcinomas depending on the degree of differentiation, the presence metastases.
Methods: The object of the study was the surgical material of 94 patients with laryngeal squamous cell carcinoma, which was formed depending on the degrees of tumour differentiation (G1=32, G2=32, G3=30). Further, the material was grouped according to the presence (n = 33) or the absence of metastases in the lymph nodes of the neck (n = 86). Immunophenotyping of microenvironment components was carried out.
Results: When the degree of differentiation from G1 to G3 changes, were increases of cells which positive to CD7, CD8, CD56, CD79a, CD20, CD68, CD15 antibody ($p<0.001$). High cell level (210.0 cells positive to CD8 antibody, 587.0 (CD79a), 345.0 (CD20), 428.0 (CD15) is a significant additional marker of metastases in the cervical lymph nodes. In the presence of metastases in the lymph nodes, the volume density of collagen and reticular fibers of microenvironment significantly increases. The volume density of the blood and lymphatic vessels is not significantly different.
Conclusion: Components of microenvironment of laryngeal carcinoma have morphological features characteristic of different degrees of tumour differentiation and depend on the presence of metastases in the cervical lymph nodes.

E-PS-11-013

Lymph node metastasis of the epithelial component with squamous differentiation of biphasic synovial sarcoma in the head and neck region

L. Lozneanu[1], B.M. Cobzeanu[2], M.D. Cobzeanu[2], G. Bandol[3], I.D. Florea[4]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] Department of Otorhinolaryngology, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania, [3] Department of Surgery, Institute of Regional Oncology, Iasi, Romania, [4] Department of Morphofunctional Sciences II-Immunology, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania

Background & Objectives: Synovial sarcoma (SS) is rarely diagnosed in the head and neck region. SS has predilection for middle aged adults. We report a rare case of biphasic SS in the soft tissues of the neck with lymph node metastasis of epithelial component with squamous differentiation, of the biphasic SS.
A 46 years old female patient was hospitalized for metastatic laterocervical adenopathy with unknown primary site.

Methods: The patient underwent imagistic analysis and surgical excision, followed by histopathological examination through routine staining and immunohistochemistry.
Results: The magnetic resonance imaging of the cervical region indicated a tumoral mass associated with laterocervical adenopathy. The patient was treated surgically with wide local excision. The histopathological examination of the cervical tumoral mass revealed a biphasic proliferation with high mitotic rate consisting predominantly of spindle cells. The lymph node presents metastasis comprising sheets of keratinized squamous cells. Immunohistochemistry for cervical tumour and lymph node showed diffuse positivity for TLE1, weak positivity for CD99 and positivity for cytokeratin AE1/AE3 and p63 markers in epithelioid component of the cervical tumour and in the lymph node metastasis.
Conclusion: Taking into account the above mentioned results, a metastatic lesion of SS with squamous differentiation was considered. At the same time, we cannot exclude a lymph node metastasis of a squamous carcinoma with unknown primary site. SS metastasis could be overdiagnosed and this can lead to wrong therapeutic management. Additional exams are mandatory to exclude a primary squamous tumour in the case of biphasic SS with squamous differentiation.

E-PS-11-014
Lymphoma of mandible: a case report
P. Tziakou[1], E. Delliou[2], V. Papamichail[3], A. Zizi-Sermpetzoglou[1]
[1] Department of Pathology of Tzaneio General Hospital of Piraeus, Greece, [2] Laboratory of Pathology - Xanthi, Greece, [3] Laboratory of Pathology "ISTODOMI" - Piraeus, Greece

Background & Objectives: Non-Hodgkin's lymphomas are a group of neoplasms that originate from the cells of the lymphoreticular system. Forty percent of non-Hodgkin's lymphomas arise from extra nodal sites. Non-Hodgkin's lymphomas detected primarily in the bone are quite rare, but among jaw lesions, they are more frequently present in the maxilla than in the mandible. In the reported cases, 0.6% are found in the mandible.
Methods: We report a case of a 53-year-old male who presented with painless swelling of the jaw. Radiographic examination and incisional biopsy were performed.
Results: The histopathological exam showed a diffuse proliferation of atypical medium-sized lymphoid cells. Immunohistochemical analysis revealed that tumour cells expressed immunopositivity for CD20, CD79a, PAX5, bcl2, bcl6 and Ki67 and negative expression for CD3 and EMA. A diagnosis of diffuse, high-grade, large B-cell NHL was confirmed.
Conclusion: Lymphomas of the oral cavity typically present as intraosseous lesions, most commonly DLBCL. Viral infections and immunological elements have been proposed as major contributing factors. Most common chromosomal abnormality associated with NHL is (14; 18) (q32; q21). The most common manifestations are pain, discomfort and swelling in the jawbone. They may imitate a dental infection or any odontogenic process. Hence, the diagnosis of lymphoma is often delayed. Though lymphoma of mandible is rare, it must be considered in differential diagnosis of swellings arising in that region. Prognosis is excellent in localized disease, whereas in disseminated disease, it is less favourable. They may be effectively managed by chemotherapy alone.

E-PS-11-015
Epitheloid hemangioendothelioma of external ear and periauricular area: one case report of a rare tumour
M. Genadieva-Yordanova[1], A. Vlahova[2], P. Stanimirov[2], D. Dikov[3]
[1] Aleksandrovska University Hospital, Bulgaria, [2] Aleksandrovska University Hospital, Bulgaria, [3] Centre Hospitalier de Marne-la-Vallee, France

Background & Objectives: Epitheloid hemangioendothelioma is a rare low-grade vascular tumour with unpredictive cours, first classified by Weiss and Enzinger in 1982 as having "not completely benign clinical behavior" . Since then more than 200 cases and a lot of data had been gathered about the clinical presentation and metastatic potential of these tumours. We report on a 53-year-old female patient with a multifocal ulcerative tumour nodules in the external ear and retroauriclar space.
Methods: Routine biopsy examination was performed with additional immunohistochemistry.
Results: Histology revealed epitheloid cells, some with intracytoplasmic lumens, forming abortive vascular structures and small cell groups embedded in myxoid stroma. IHC for conformation of the vascular origin was performed. In some of the regional lymph nodes there was extensive vascular transformation, raising the suspicion of metastatic disease. Immunohistochemically the tumour cells were positive for vascular markers, such as CD34, ERG and negative for CK AE1-AE3.
Conclusion: Although rare, we should increase our awareness of epitheloid hemangioendothelioma, which must be differentiated from other more aggressive tumours such as metastatic carcinoma and angiosarcoma. Applying the accepted histologic criteria and with the adjunct of IHC this distinction appears relevant due to the different survival rate and evolving therapeutic options.

E-PS-11-016
EGFR and Bcl-2 expression as a prognostic marker in head and neck squamous cell carcinoma (HNSCC) - a tissue microarray (TMA) based study in a resource-poor setting
S. Phaniraj[1], J. Krishnamurthy[1]
[1] JSS Medical College, JSS University, Mysore, India

Background & Objectives: Epidermal growth factor receptor (EGFR) and B-cell lymphoma-2 (Bcl-2) are critical mediators of signal transduction pathways in HNSCC. This study was undertaken to assess the expression of EGFR and Bcl-2 in HNSCC cases according to the new scoring system, and to evaluate their association with various clinicopathological prognostic factors and patient survival.
Methods: A total of 60 surgically resected cases of HNSCC were studied for expression of EGFR and Bcl-2 by immunohistochemistry on manual tissue microarray (TMA). EGFR expression was scored by proportion score (PS), intensity score (IS) and total score (TS) while Bcl-2 cytoplasmic staining was scored as either positive or negative. These were then correlated with known prognostic factors and patient survival.
Results: High EGFR TS was recorded in 88.3% cases and Bcl-2 positivity in 80% cases. A significant correlation was observed between EGFR TS and perineural invasion (PNI) [p=0.017], whereas a trend toward significance was observed with tumour size and lymphovascular invasion (LVI). Bcl-2 positivity correlated with nodal stage [p=0.023]. Survival analysis showed better outcome in patients with lower EGFR PS and Bcl-2 negativity as also in patients with inherently better prognostic factors (non-smokers, females, carcinoma of tongue, well differentiated tumours, cases without PNI, stages T1 & T2 and stages N0 & N1).
Conclusion: Our data demonstrate that EGFR and Bcl-2 overexpression are markers of what is considered to be more advanced disease. This suggests that EGFR and Bcl-2 can be used as prognostic markers and possibly as predictive markers for targeted therapy in patients with locally advanced HNSCC.

E-PS-11-017
Association of tumour budding and number of metastasized lymph nodes in laryngeal carcinomas
A.P. Rodrigues[1], E. Muhongo[1], E. Amaral[1], J. Pardal[1]
[1] Hospital de Braga, Portugal

Background & Objectives: Tumour budding, described as the presence of single cells or small clusters of up to five tumour cells at the invasive margin, is an established adverse prognostic factor for a few carcinomas. Its unquestionable prognostic value in colorectal carcinomas raises the question whether such prognostic value can also be present in other types of carcinoma. In the current study, we addressed laryngeal carcinomas and aimed to determine if there is a relation between tumour budding and the number of metastasized lymph nodes, an already established prognostic factor for this pathology.
Methods: The surgical specimens of thirty-nine patients with primary larynx carcinomas were included. The presence of tumour budding was determined through assessment of all tumour-containing H&E slides using the "hot spot" approach. The cases were grouped as having mild budding when up to 4 tumour buds were identified; moderate, for 5 to 9 tumour buds and marked for 10 or more tumour buds. The number of lymph nodes involved by metastasis per case was also recorded.
Results: Mild, moderate, and marked budding was observed in 12 (30,8%), 20 (51,3%), and 7 (17,9%) cases, respectively. Cases with marked and moderate budding were associated with higher number of metastasized lymph nodes comparatively to cases with mild tumour budding (p=0,044).
Conclusion: Our results demonstrate that higher tumour budding is associated with increased number of metastasized lymph nodes, hinting that it could be a valuable prognostic factor for laryngeal carcinomas. We are currently extending our cohort to address if tumour budding is an independent prognostic factor.

E-PS-11-018
Biphenotypic sinonasal sarcoma – a new and rare entity

C. Quadros[1], I. Alves[1]
[1] CHULN - Hospital de Santa Maria, Portugal

Background & Objectives: Biphenotypic sinonasal sarcoma (BSNS) is a rare sinonasal tumour recently added to the WHO classification with only few cases described so far. Herein, we present a case of BSNS from our routine practice.
Methods: A 55-year-old woman that presents with progressive obstruction of the left nasal cavity, without other symptoms. A CT-scan revealed a soft-tissue mass that was removed endoscopically.
Results: A polypoid mass with 4,5 cm in greatest dimension, grey with cystic areas filled with white gelatinous material was received. Histologically, a spindle-cell proliferation arranged in intersecting fascicles with a monotonous appearance was observed. No mitosis or necrosis were noted. The neoplastic cells showed diffuse immunoexpression to TLE-1, partially to S100 and focally to SMA and myogenin, without cytokeratin expression. Due to the morphology, immunohistochemistry results and location, the critical differential diagnosis comprised BSNS and monophasic synovial sarcoma. The molecular studies directed to SYT and MAML3 genes demonstrated MAML3 gene rearrangement, corroborating the diagnosis of BSNS.
Conclusion: BSNS is a low-grade sinonasal sarcoma with neural and myogenic features, which has a slowly progressive growth that may recur locally and has no metastatic or death-related outcomes associated.

E-PS-11-019
A case report of non-paediatric ganglioneuroma of parapharyngeal space: an important pitfall in differential diagnosis

M. Chraszczewska[1], O. Kuczkiewicz-Siemion[1], M. Durzyńska[1]
[1] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland

Background & Objectives: Ganglioneuroma is a rare benign tumour arising from the neural crest cells and generally occurs in children and young adults. It is commonly localized in the posterior mediastinum, the retroperitoneum or the adrenal gland. Ganglioneuroma of the head and neck region, including parapharyngeal space, is extremely rare diagnosis, especially in adult patients (six reported cases). Most ganglioneuromas usually present as a slowly enlarging, asymptomatic mass found incidentally. The aim of this report was to present a rare ganglioneuroma case in parapharyngeal location.
Methods: A 70-year-old female presented with a 7 cm-sized tumour on the left side of the neck and difficulty in swelling. Clinically the tumour of the left parotid gland was suspected. Ultrasonography revealed a lesion measuring 3.2 × 2.9 x 1.9 cm with inhomogeneous echogenicity. Computed tomography demonstrated a well-circumscribed, smooth-contoured, solid tumour located in the left parapharyngeal space without connection to the parotid gland. Deformation of oropharynx with lateral displacement of cervical vessels were present. There was no features of invasion of surrounding structures.
Results: An open biopsy of the lesion was performed. Histopathological examination revealed tumour comprising of spindle cells similar to neurofibroma crossing each other in an irregular fashion with mature ganglion cells lying singly and in clusters. On immunohistochemical analysis, the tumour cells stained positive for synaptophysin, S100 and neuron specific enolase, which confirmed ganglioneuroma diagnosis.
Conclusion: Reported case increase awareness of ganglioneuroma occurence in the adult patient population. It is important to remember about this rare entity, especially evaluating biopsy specimens.

E-PS-11-020
Cribriform adenocarcinoma of minor salivary gland with cervical lymph nodes metastases: a case report highlighting the significance of cytology

O. Kuczkiewicz-Siemion[1], M. Chraszczewska[1], O. Stanowska[1], M. Durzynska[1]
[1] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland

Background & Objectives: Cribriform adenocarcinoma of minor salivary gland (CAMSG) is a rare low-grade malignancy of salivary glands presenting cytologic features resembling papillary thyroid carcinoma (PTC) without expression of TTF-1 and thyroglobulin. Commonly the first manifestation of disease are cervical metastases. Although fine-needle aspiration biopsy (FNAB) is a method of choice in peripheral lymphadenopathy diagnosis, there are only three publications evaluating CAMSG cytology. The aim of this report was to present a CAMSG case in the light of cytological features, thus enriching the spectrum of FNAB differential diagnosis.
Methods: We report a case of 76 year-old female with submucosal tumour of the pharynx. The patient presented two solid lesions diagnosed accidentally by cervical ultrasonography. In physical examination slightly enlarged submandibular lymph node was detected. Computed tomography revealed a lesion (22x18x24mm) situated in the masticator and the parapharyngeal space.
Results: FNAB of submandibular lymph node showed cribriform, dense clusters of monomorphic round-oval tumour cells with scant cytoplasm, which was inconclusive. Subsequently, an open biopsy was conducted. Histologically, the tumour was composed of oval, overlapping cells with bright nuclear chromatin and nuclear grooves. Cells formed cribriform, papillary and solid structures. Immunohistochemistry panel revealed: TTF-1 (-), thyroglobulin (-), S100 (+), p63 (+), Gal-3 (+), CK19 (+) focally. Status of EBV and HPV by hybridization in situ was negative.
Conclusion: CAMSG could be misdiagnosed as PTC or other tumour presenting similar cytological and morphological features. In view of frequent node metastases observed in this tumour, appropriate evaluation of cytological smear seems to be crucial for patient management and allows establishing final diagnosis and treatment.

E-PS-11-021
Clear cell carcinoma of the nasopharynx: report of two new cases

J. Filipe[1], M. Rito[1,2], I. Fonseca[1,2]

[1] Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [2] Instituto de Anatomia Patológica, Faculdade de Medicina, Universidade de Lisboa, Portugal

Background & Objectives: Clear cell carcinoma (CCC) is a rare low-grade salivary gland neoplasm, accounting for <1% of all salivary tumours. Most cases occur in the minor salivary glands of the oral cavity, mainly at the palate and tongue. Its morphological diagnosis is challenging since it is often confused with other clear cell-rich neoplasms. *EWSR1-ATF1* gene fusion supports the diagnosis. Nasopharyngeal involvement is uncommon, with few cases described. Due to its rarity and diagnostic difficulty, we present two cases of primary nasopharyngeal CCC.
Methods: Two cases of nasopharyngeal CCC are described, along with a review of the literature.
Results: A 77-year-old female (1) and a 67-year-old-male (2) clinically presented with a history of hearing loss and epistaxis. Imaging studies revealed an expansive lesion in the lateral wall of the nasopharynx (1) and an infiltrative lesion in the posterior wall surrounding the internal carotid artery (2). Microscopically the tumours were similar, with a nested and trabecular pattern in a hyalinized stroma, composed by cells with distinct borders, round to oval nuclei, pale eosinophilic and clear cytoplasm. A diastase-sensitive positive PAS reaction revealed the presence of intracytoplasmic glycogen, and tumour cells were positive for AE1/AE3 and p63. Rearrangements of the *EWSR1* gene were found by FISH, confirming the diagnosis.
Conclusion: Although rare, nasopharyngeal CCC should be considered in the differential diagnosis of nasopharyngeal neoplasms and represent a diagnostic challenge. An accurate diagnosis is relevant as these patients have indication for radiotherapy alone but not for chemoradiotherapy as do for the common nasopharyngeal carcinoma.

E-PS-11-025
Adenoid cystic carcinoma of salivary glands. A study of 40 cases with clinicopathologic correlation
I. Dimitriadis[1], G. Venetis[2], D. Anestakis[3], N. Pastelli[1], S. Papaemmanouil[1]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Oral and Maxilofacial Surgery, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [3] Department of Autopsy Histopathology, Aristotle University of Thessaloniki, Greece

Background & Objectives: Adenoid cystic carcinoma occurred more commonly in the minor salivary glands. This study was to analyse the clinicopathological characteristics of this neoplasm.
Methods: All the cases recorded in our hospital from 1996-2017 were assessed. Age, gender, anatomical location, and histology of all the specimens were evaluated. Between 1985-2000, (40) patients with ACC of salivary glands were treated in the Clinic of Oral/Maxillofacial Surgery. The age range was 22-87 years. The distribution of the primary sites was buccal mucosa (19), floor of the mouth (5), hard /soft palate (6), parotid (4), and tongue (6). All the patients were treated radically with surgery.
Results: Univariate analysis revealed that the factors impacting the prognosis were age, presence (14 patients) or absence (26 patients) of nerve invasion, histological subtypes, (37: Gr2, 3:Gr3) ,clinical stage, positive (13) or negative (27) surgical margin. Patients aged >50, presence of nerve invasion, solid/tubular subtype, advanced clinical stage (stages III-IV), and positive surgical margin had poorer prognosis than those aged <50, absence of nerve invasion, cribriform subtype, early clinical stage (stages I-II), and negative surgical margin. Multivariate analysis showed that the presence of nerve invasion, solid histological subtype, advanced clinical stage (stages III and IV), and positive surgical margin were independently associated to poor prognosis.
Conclusion: Presence or absence of nerve invasion, histological subtype, clinical stage, and positive or negative surgical margin are the independent factors affecting the prognosis of patients with adenoid cystic carcinoma of salivary glands.

E-PS-11-026
Mucoepidermoid carcinoma of salivary glands: a clinical study of 22 cases and review of the literature
I. Dimitriadis[1], K. Vaxtsevanos[2], A. Cheva[3], A. Baliaka[1], S. Papaemmanouil[1]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Oral and Maxilofacial Surgery, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [3] Department of Pathology, Aristotle University of Thessaloniki, Greece

Background & Objectives: Mucoepidermoid carcinoma (MEC) is a malignant tumour with a widely diverse biological behavior. The purpose of this study was to analyse the clinicopathological characteristics of this neoplasm.
Methods: Between 1997-2017, (22) patients with MEC were treated in the Clinic of Oral/Maxillofacial Surgery. The age range was 26-84 years. The distribution of the primary sites was: hard/soft palate (8), parotid (6), buccal mucosa (5), and tongue (3). All patients were treated radically with surgery. The expression of the Ki-67 was evaluated on a subset of all cases.
Results: Lymph node metastases occurred in one patient. The Pearson chi-square statistical analysis was used for comparing the Ki-67 values in correlation with histological grade of the tumours. The Ki-67 expression was 2-3% in low-grade, in intermediate-grade it was estimated (4-8%) and the high-grade tumours had increased expression (70%) of tumour cells.(50%) of tumours were classified as low grade, (18,18%) as intermediate and (31,81%) as high-grade MECs. Positive surgical margins were documented in (8)cases (36,3%). The 5-year overall disease specific survival rate was 85%. Statistical analysis demonstrated that the factor that significantly correlated with overall survival was the histological grade of tumours (p=0.013). Poorer survival was observed in patients aged >50 years.
Conclusion: Complete surgical excision is the treatment of choice for MECs. Multivariate analysis demonstrated that the factor that significantly correlated with overall survival was the histological grade of tumours. The immunohistochemical study of Ki-67 expression may provide additional prognostic information for this tumour.

E-PS-11-027
Clear cell ameloblastic carcinoma of the maxilla - an extremely rare odontogenic tumour
L. Manojlovic[1], K. Krstanac[1], P. Senjug[2], S. Manojlovic[1,3]
[1] Department of Pathology and Cytology, University Hospital Dubrava, Zagreb, Croatia, [2] Unit of Nephropathology and Electron Microscopy, Department of Pathology and Cytology, Dubrava University Hospital, Zagreb, Croatia, [3] University of Zagreb, School of Medicine, Croatia

Background & Objectives: Maxillary clear cell variant of ameloblastic carcinoma (AMEC) is exceedingly rare and diagnostically challenging. Treatment modalities are still debated.
Methods: We present a case of a 56-year-old male with swelling around the second right maxillary molar. Orthopantomography revealed a well delineated radiolucent lesion. A biopsy revelead alveolar nests of large atypical epithelial cells with vesicular nuclei and clear cytoplasm, high mitotic activity, central necrotic foci and peripheral palisading, suggesting ameloblastic differentiation. Immunohistochemical analysis excluded the possibility of metastasis or clear cell salivary gland carcinoma. The tumour expanded rapidly, therefore the patient underwent primary radiotherapy resulting in tumour regression. Surgical treatment followed. Three years follow-up revealed no evidence of recurrent or metastatic disease.

Results: Malignant intraosseous epithelial tumours are most frequently metastases, therefore the diagnosis of primary intraosseous carcinoma must be made by exclusion. At present, there is no single definitive microscopic criterion for AMEC. The lack of specific histologic, immunohistochemical, and ultrastructural markers to confirm the odontogenic origin of these lesions, makes diagnosing it very difficult. The presence of palisading and many clear cells strongly suggests an ameloblastic carcinoma. Early and complete removal of the tumour offers the best chance of survival. In our case, due to aggressive growth of the tumour, primary radiotherapy was performed achieving an excellent result.
Conclusion: AMEC is a very rare odontogenic neoplasm. Differential diagnostics are demanding, and treatment modalities are still disputed. According to our experience and a review of literature, preoperative radiotherapy of such aggressive tumour greatly increases the chances of a positive outcome.

E-PS-11-028

Chondromyxoid fibroma of craniofacial bones - report of three cases

K. Krstanac[1], L. Manojlovic[1], P. Senjug[2], S. Manojlovic[1,3]
[1] Department of Pathology and Cytology, University Hospital Dubrava, Zagreb, Croatia, [2] Unit of Nephropathology and Electron Microscopy, Department of Pathology and Cytology, Dubrava University Hospital, Zagreb, Croatia, [3] University of Zagreb, School of Medicine, Croatia

Background & Objectives: Chondromyxoid fibroma (CMF) is unusual in craniofacial localization, frequently showing bone erosion or destruction, which could be misdiagnosed as malignancy.
Methods: We present three cases of CMF diagnosed over the last 18 years in our Institution. The first case was a 24-year-old man with swelling of the mandible, the second was a 53-year-old man with a tumour of the temporal bone and the third was a 36-year-old woman with swelling of the temporomandibular area. CT analyses revealed radiopaque-radiolucent well-circumscribed multilocular areas with fine trabeculation. The lesion of the temporal bone eroded the bone surface. Biopsies revealed abundant myxoid matrix with scattered chondroid and spindled cells. The temporal bone tumour was misdiagnosed as chondrosarcoma. Histopathological analysis of surgical specimens revealed, lobulated, encapsulated nodules composed of chondroid tissue with bland chondrocytes and scattered multinuclear osteoclasts, surrounded by spindled cells in a myxoid stroma. The final diagnosis in all three cases was CMF. Follow-up revealed no signs of recurrent disease.
Results: CMF is a rare benign bone tumour, most commonly occuring in the metaphyseal region of long bones in young adults. It is a locally destructive lesion with a high recurrence rate (>25%), but does not undergo malignant transformation. Small biopsies or curettings may often lead to misdiagnosis. Although head and neck involvement is extremely rare, CMF should be included in the differential diagnosis.
Conclusion: CMF of craniofacial bones is exceedingly rare. Because of its similarity to various malignant bone tumours, such as chondrosarcoma, diagnosing this tumour can be challenging, and requires clinical, pathological and radiological correlation.

E-PS-11-029

Human Papillomavirus-related oropharyngeal high-grade large cell neuroendocrine carcinoma: a case report

O. Casiraghi[1], C. Ngo[2], N. Labaied[2], A. Benlakhdar[2]
[1] Gustave Roussy, France, [2] Gustave Roussy, Paris-Saclay University, Biopathology Dèpartment, Villejuif, France

Background & Objectives: In the 2017 WHO classification, two subtypes of poor differentiated neuroendocrine carcinoma (NEC) are described, in the supraglottic larynx especially: large cell NEC (LCNEC) and small cell NEC (SmCC). In the oropharynx, only the HPV-related SmCC is mentioned, as an uncommon and aggressive variant of HPV-related oropharyngeal carcinoma (OPC). A very few cases of oropharyngeal HPV-LCNEC have been described. We report a new case of this very rare entity.
Methods: a 51-year-old woman, without history of cancer, smoking or alcohol habits, presented a large necrotic polypoid tumour of the base of the tongue, vallecula and epiglottis, with bilateral cervical lymphadenopathies. Pet Scan and TDM highlighted disseminated bilateral pulmonary metastases and mediastinal lymphadenopathies.
Results: On biopsies, the aspect was that of a highly necrotic and mitotic (> 100 mitoses/2mm²) large cell undifferentiated carcinoma. Tumour cells were positive for some epithelial (CK AE1/AE3, EMA) and neuroendocrine markers (Chromogranin B, Synaptophysin, CD56 and INSM1). Chromogranin A, CK5-6, p63, p40, PS100, TTF1 and NUT were negative. Proliferative Index (Ki67) was 90%. p16 was overexpressed and high-risk HPV was evidenced by Chromogenic In Situ Hybridization (CISH). The diagnosis of HPV-LCNEC was established. The patient was treated by chemotherapy.
Conclusion: In oropharynx, HPV-LCNEC is an uncommon variant of HPV-related OPC, even rarer than HPV-related SmCC. It's crucial to identify by immunohistochemistry the neuroendocrine differentiation of these oropharyngeal carcinomas, because HPV-related NEC are very aggressive, their treatment and prognosis being very different from that of the classical HPV-related non keratinizing OPC, which prognosis is good.

E-PS-11-030

Lengarhans cell hystiocytosis of cranial bones - diagnostic challenge

J. Sopta[1], L. Simic[1], G. Djuricic[2], M. Petrovic[3]
[1] Institute of Pathology, Medical Faculty, University of Belgrade, Serbia, [2] Institute for Oncology and Radiology, Belgrade, Serbia, [3] Clinic for maxilofacial surgery, Belgrade, Serbia

Background & Objectives: Langerhans cell hystiocytosis (LCH) is a lesion characterised by the presence of cells with characteristics similar to bone marrow. Frequent localizations of LCH are cranial bones.
Methods: All cases of LCH (25) diagnosed in the cranial bones during 20 years at the Institute of Pathology, Medical Faculty, University of Belgrade are included in study. Biopsies were stained by: HE, Vimentin, S-100, CD1a, CD68, CD163, Langerin, LCA and Ki 67. Expression of CD1a and Langerin were analysed.
Results: The majority of patients were male (57,2%), with average age 2.14 ± 24.84 years (range 1–28 years). Frontal bone was the most frequent localization (82%), followed by temporal bone. Tumour size ≥5cm, was observed in 3 (12%) of patients. The most common subtype was eosynophilic granuloma 23 cases, Hand–Schüller–Christian and Letterer–Siwe disease were diagnosed at one patient .
All systemic and polyostotic forms of LCH were positive for both (CD1a and Langerin) primary antibodies. Single bone disease presentations (19 cases) had different immunoprofiles. The majority of cases 16/19 had coexpression of antibodies. CD1a was positive in 8 cases were Langerin was negative. Sprucely, one biopsy showed Langerin expression without CD1a positivity. In that case electron microscopy was done, and Birbeck granules were confirmed into LCH cells.
Conclusion: Histological appearance and immunophenotype of LCH are in correlation with clinical presentation. CD1a antibody is more sensitive than Langerin, but Langerin is more specific for LCH. In LCH diagnostic procedure application of electron microscopy could be useful.

E-PS-11-031

Laryngeal pleomorphic rhabdomyosarcoma: a case report

X. Ara-Mancebo[1], C. Alborch[1], E. Fuentes-Camps[1], C. Romagosa Pèrez-Portabella[1], I. Ramos-Oliver[1], S. Ramón y Cajal[1], J. Temprana-Salvador[1]
[1] Vall d'Hebron University Hospital, Spain

Background & Objectives: Rhabdomyosarcomas are rare soft tissue tumours in adults. They usually arise in lower extremities, in their alveolar variant –the other subtypes (embryonal, pleomorphic and spindle cell/sclerosing) being less frequent. Thus, the diagnosis of a pleomorphic rhabdomyosarcoma in an uncommon location, like the larynx (with only 22 cases reported in the literature), poses a true challenge.
Methods: We report the case of a 66-year-old man, ex-smoker without other remarkable history, who sought medical consultation for a three-month history of catarrh, dysphony, odynophagia, left otalgia and dysphagia. Endoscopy showed a submucosal lesion in the left arytenoid, occupying the piriform sinus. A TC confirmed a 43x33x22mm infiltrative lesion, without lymphatic node enlargement. A diagnostic incisional biopsy was performed.
Results: The histologic examination showed an intact epithelium along with a cellular proliferation with a mesenchymal pattern, composed of epithelioid cells with a striking pleomorphism, and abundant eosinophilic cytoplasm with polygonal outlines. Nuclei were irregular, with prominent hyperchromatic nucleoli.
A broad immunohistochemical panel was performed: negative cytokeratins (AE1/AE3, CAM5.2), p40 and EMA ruled out an epithelial origin; negative HMB45, MelanA and S100, a melanocytic origin; negative synaptophysin and CD56, a neuroendocrine origin; and negative CD45, a lymphoid origin.
The rhabdoid morphology suggested a muscular origin, and desmin, myogenin and MyoD1 were positive. The diagnosis of pleomorphic rhabdomyosarcoma was established.
Conclusion: In head and neck, one must rule out epithelial/squamous neoplasms and, secondly, undifferentiated tumours. Morphology is fundamental when considering a diagnosis, as identifying a rhabdoid pattern was crucial in this case.

E-PS-11-032
A rare case of villonodular synovitis with synovial chondromatosis of the temporomandibular joint
F. Kaya[1], M.F. Acikalin[1], A. Incesulu[2]
[1] Eskisehir Osmangazi University, Department of Pathology, Turkey, [2] Eskisehir Osmangazi University, Faculty of Medicine, Department of Otolaryngology-Head and Neck Surgery, Turkey

Background & Objectives: Pigmented villonodular synovitis (PVNS) most commonly occurs within the large joints of the extremities. The temporomandibular joint is the rare site of occurrence of the disease. Here we present a case of simultaneous occurrence of pigmented villonodular synovitis and synovial chondromatosis (SC) in the temporomandibular joint (TMJ).
Methods: A 37-year-old female presented with a complaint of a enlarging mass at her right TMJ and hearing loss for 1.5 years. Computed tomographic imaging demonstrated a soft tissue mass around the right TMJ. The lesion was removed and sent to our laboratory.
Results: Microscopically, the slices of gray-brown tissue were composed of nodules of synovium-like monocytes, small histiocytoid cells and multinucleated giant cells. There were hemosiderin deposits and aggregates of foam cells. Immunohistochemically, histiocytoid cells were positive for D2-40, CD163 and CD68. They were negative for S100 protein, HMB-45, keratin and desmin. Multinucleated giant cells were positive for CD68. The slices of gray-white tissue are composed of loose bodies of SC.
Conclusion: A review of the English language literature revealed 3 cases of simultaneous PVNS and SC involving the temporomandibular joint. Although rare in this location, PVNS should be considered in the differential diagnosis of aggressive preauricular swellings.

E-PS-11-033
Mucinous Cystadenoma of parotid gland: a case report
D. Chiba[1], S. Chaieb[2], S. Yacoub[2], N. Beizig[3], B. Sriha[2]
[1] Department of Pathology Farhat Hached Hospital, Tunisia, [2] Farhat Hached Hospital, Tunisia, [3] Pathologic Laboratory, Tunisia

Background & Objectives: Salivary gland cystadenoma especially in the parotid gland is rare benign tumour that was clearly defined, in the second World Health Organization's Histological Classification of Salivary Gland Tumours published in 1991, as a distinct histopathological entity. It's characterised by predominantly multicystic growth in which the epithelium demonstrates adenomatous proliferation. The epithelial lining is frequently papillary and rarely mucinous.
This work highlights the clinical and histopathological features of mucinous cystadenoma of the gland parotid and its differential diagnosis.
Methods: We describe a 33-year-old woman without clinical history, who had a slowly painless enlarging tumour, 35mm in diameter, in the superficial lobe of the right parotid gland. The tumour was surgically excised with wide margins under general anesthesia. The specimen was referred to the laboratory of pathological anatomy. Grossly, the parotidectomy weighed 10gr and measured 3.5×2.5×2 cm which contained a well circumscribed encapsulated tumour with myxoid appearance, soft consistency and whitish color on cut section.
Results: Histologically, the tumour was surrounded by a fibrous capsule and composed of multiple cystic spaces which were lined by tall columnar mucus-producing cells. There was no cellular atypia or invasive growth. The surrounded parotid parenchyma was without abnormalities. In view the complexity and histomorphological diversity of salivary gland tumours, the pathological differential diagnosis included a large spectrum of benign and malign tumour like Papillary Cystadenoma, Cyst Adenocarcinoma … The final histological diagnosis was Mucinous cystadenoma, without signs of malignancy.
Conclusion: To the best of our knowledge, from analysis of the cases in the literature (1990-2018) we report the third case of mucinous cystadenoma of parotid gland. Despite its benignity, follow up of the patient is necessary since recurrences, and a case of malignant transformation to invasive micropapillary adenocarcinoma in mucinous cystadenoma of parotid gland have been reported.

E-PS-11-034
The role of molecular pathology in the diagnosis of salivary gland tumours: new advances and "pitfalls"
J. Costa[1], S. Petronilho[2], J. Vieira[3], S. Lisboa[3], M. Teixeira[3], R. Henrique[2], M. Jácome[2]
[1] Department of Pathology IPOP, Portugal, [2] Department of Pathology, IPO-Porto, Portugal, [3] Department of Genetics, IPO-Porto, Portugal

Background & Objectives: Recent advances in the molecular characterization of salivary gland tumours (SGT) have uncovered new diagnostic markers and promising therapeutic targets. However, the rapid advances in this field are often hard to integrate and interpret in routine practice.
Methods: We reviewed the current literature and report two cases that illustrate the strength and pitfalls of molecular testing of SGT during routine practice. In case 1, an 11-year-old female disclosed a parotid swelling with 6 months of evolution, whose scant biopsy material prevented a conclusive diagnosis. In case 2, a 61-year-old female with a cervical mass with 8 months of evolution was biopsed.
Results: Case 1: The biopsy revealed a solid and cystic tumour, with cuboidal and mucous cells (CK7+/P63+) and histiocytes (CD68+), suggestive of mucoepidermoid carcinoma(MEC). Detection of a MECT1-MAML2 rearrangement confirmed the diagnosis of MEC. Case 2: The biopsy revealed a neoplasm with hyalinized stroma and clear cells (PAS+,CK7+,p63+). Identification of an EWSR1 rearrangement raised suspicion of a clear cell carcinoma(CCC). The examination of the

surgical specimen, however, revealed a high-grade SGT mainly composed of clear cells (CKAE1/AE3+,CK14+,p63+,HHF35+,CD10+ ,calponin+,vimentin+), consistent with myoepithelial carcinoma(MC).
Conclusion: Recent data has associated MECT1-MAML2 rearrangements with lower local aggressiveness and histologic grade. In SGT, EWSR1 rearrangements have been reported in CCC, MC and rare cases of MEC. Reporting both fusion partners in the fusion gene is of the utmost importance. Molecular findings in SGT should be integrated alongside clinical, morphological and immunohistochemical features in a holistic diagnostic approach.

E-PS-11-035
Perioperative finding of metastatic papillary cystic thyroid carcinoma presenting as lateral neck cyst
E. Molnarova[1], K. Kajo[2], P. Veres1 and A. Stanikova[1]
[1] Medicyt s.r.o, Slovakia, [2] SZU Ustav patologie a Onkologicky ustav sv. Alzbety, Slovakia

Background & Objectives: Here we present a case of perioperative finding of metastatic papillary thyroid carcinoma in the lateral cervical lymph node cyst.
Results: Microscopy demonstrated foci of lymphoid tissue with a large cystic structure containing papillary projections and accessory glandular elements resembling thyroid tissue. The cyst lumen was filled with hemosiderin laden macrophages. The epithelial lining of the large cyst and accessory glandular structures consisted of a single layer of cuboidal cells crowded nuclei and identified pseudonuclear inclusions. The epithelial lining showed focal apical cytoplasmic positivity for thyroglobulin, in addition to positivity for CK19, TTF, CKAE1/3. The Ki67 proliferation index was 1%. The Diagnosis of cystic metastatic papillary thyroid carcinoma a lateral cervical neck lymph node was made. Clinical, radiological and genetic examination for occult papillary thyroid carcinoma was advised.
Conclusion: Metastatic papillary thyroid carcinoma should be considered in the differential diagnosis of clinically benign appearing cystic neck mass. Perioperative biopsy of these lesions should be indicated and handled with care. Bearing in mind that clinical, biochemical and imaging parameters are lacking for determining the definite diagnosis.

E-PS-11-036
Clinico-pathological features of ameloblastoma in the center of Tunisia
E. Ben Hadj Khalifa[1], N. Abdessayed[2], D. Chiba[2], H. Salifou[1], S. Ben Khalifa[1], S. Jacoub[1], B. Sriha[1]
[1] Cytology and Pathology Department CHU Farhat Hached, Sousse-Tunisia, [2] Department of Pathology Farhat Hached Hospital, Tunisia

Background & Objectives: Ameloblastoma is a rare odontogenic tumour which is known by its benignity despite a local expansive character. This tumour is the most common odontogenic neoplasm after odontoma.The nonspecific clinical and radiological presentations are responsible of pre-surgical misdiagnosis and an inadequate excision. The aim of this study was to compare the clinical, radiologic and histopathological results, surgical management, and evolution of patients with ameloblastoma with data reported in the literature.
Methods: The study included all cases of ameloblastoma diagnosed in the central region of Tunisia between 2005 and 2018. The data were extracted from the clinical records of the cancer registry of the central region.
Results: 15 cases of histologically confirmed ameloblastoma were found over a period of 14 years. They are divided into 8 men and 7 women. The average age is 43.7 years. 78.6% of cases are developed in the mandible. The most reported radiological aspects are an osteolytic image in 50% of cases and a unicystic image in 30% of cases. Macroscopically, the tumour measures 5.6 cm in average. It has a mixed solid-cystic appearance in 77.8% of cases. Microscopically, the follicular type represents 46.7% of cases while the unicystic type accounts for 20% of cases. Wide surgical exegesis was performed in 66.7% of cases. The exeresis' margins were infiltrated by the tumour in 33.3% of cases. Transformation into ameloblastic carcinoma was identified in only one case.
Conclusion: Ameloblastoma is a locally aggressive tumour which can be associated with a significant local morbidity. This study confirms that a wide surgical resection in the treatment of ameloblastoma appears to be a very important predictor of tumour clearance.

E-PS-11-037
Lymphoepithelial carcinoma of the parotid gland: a rare entity
B. Laabidi[1,2], R. Hedhli[3], R. Yaich[1,2], F. Gargouri[4], N. Mansouri[1,2], A. Saidi[5], A. Bouziani[4], I. Msakni[4]
[1] Tunis El Manar University, Medicine School of Tunis, Tunisia, [2] Military Hospital of Tunis, Department of Pathology, Tunisia, [3] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia, [4] Pathology Department, Military Hospital for Instruction of Tunis, Tunisia, [5] Pathology Department; Military Hospital for Instruction of Tunis, Tunisia

Background & Objectives: Lymphoepithelioma-like carcinoma (LELC) of the salivary gland is a rare tumour accounting for 0.4% of all malignant salivary gland tumours. We present a rare case of LELC of the parotid gland.
Methods: A 61-year-old man was diagnosed with a mass in the left parotid gland with no other symptoms or past medical history. Ultrasound revealed hypoechoic, inhomogeneous mass of the parotid gland. Patient underwent surgical removal of the mass by a superficial parotidectomy.
Results: Initial frozen sections analysis rendered a diagnosis of malignancy. A complete neck dissection was performed. Histopathologic examination of the specimens revealed a parotid gland with solid carcinomatous sheets, trabeculae and isolated small groups of malignant epithelial cells intermingled with lymphoid stroma. The satellite lymph node showed no infiltration. Immunohistochemical analysis showed neoplastic cells with positive staining for pancytokeratin and epithelial membrane antigen and focal expression of LMP1. Lymphoid cells were positive for both CD20 and CD3 markers. On the basis of these findings, a diagnosis of stage II, undifferentiated LELC of the parotid gland was made.
Conclusion: LELC of the salivary gland is a rare entity with a better prognosis than other poorly differentiated tumours; surgical excision with post-operative radiotherapy is the treatment of choice.

E-PS-11-038
Human papilloma virus (HPV)- related multiphenotypic sinonasal carcinoma: report of two cases
I. Dumitru[1], M. Wassef[2,3], A.C. Baglin[2,3], P. Hèlène[4,3], A. Coste[1], P. Bedbeder[1], A. Boyez[1]
[1] CHI Créteil, France, [2] Lariboisière Hospital, France, [3] Paris, France, [4] Hôpital Europèen Georges-Pompidou

Background & Objectives: HPV-related carcinoma with adenoid cystic carcinoma-like features defines a rare HPV-related sinonasal neoplasm, a provisional entity in the 2017World Health Organization Classification (WHO) of Head and Necktumor. Dr Justin Bishop, who initially described this tumour in 2013, recently emphasized the fact that this tumour showeda morphologicalspectrum,broader than initially thought, and proposed a new name: "HPV-related multiphenotypicsinonasal carcinoma" (HMSC). We reporttwo cases ofthis neoplasm, which multiple samples show this histologic spectrum.
Methods: Eight sinonasal samples were available from two patients (one female, one male, both 39 years old at initialdiagnosis). Each patient had two initial tumour samples and two recurrence samples. Immunohistochemistry with p16, CD117, S100, p40, p63, CK5/6 antibodies and HPV detection and genotyping (using theINNO-LiPA HPV Genotyping Extra II kit) were performed.

Results: All samples showed highly cellular and mitotic proliferation of basophilic cells.
Initial tumour samples from the male patient showed cribriform architectural foci, whereas these foci were not present in recurrence samples but highly atypical cells had appeared. Female patient samples showed cribriform but also ribbon-like pattern and foci of squamous differentiation within the invasive tumour.
Conclusion: Conclusion: HMSC has abroad histologic spectrum, not always reminiscent of adenoid cystic carcinoma, a fact pathologist should be aware in order to propose the appropriate diagnosis.

E-PS-11-039
An unusual nasal mass
A. Keogh[1], S. Momdouh[2], O. James Paul[3], S. McWilliams[3], M. Redmond[4], H. Barrett[4]
[1] Department of Histopathology, Beaumont Hospital, Ireland, [2] Department Otolaryngology, Head & Neck Surgery, Beaumont Hospital/ RCSI, Ireland, [3] Department of Radiology, Beaumont Hospital, Ireland, [4] Department of Histopathology, Beaumont Hospital, Ireland

Background & Objectives: We present the case of a 52-year-old female who presented with a two month history of nasal congestion, loose teeth and right maxillary pain.
Methods: Multiple imaging studies, biopsies and molecular testing were completed for investigation into this nasal mass.
Results: Radiology studies showed a 6.4 X 5.9 X 4.1 cm bone lesion appearing to arise from the right side of the hard palate involving the maxillary alveolus, maxillary sinus, and inferior nasal cavity. There was evidence of chronic remodelling of the left middle and inferior turbinates suggesting a long-standing process. The differential diagnosis based on radiology included primary bone lesions such as fibrous dysplasia and a low-grade cartilaginous neoplasm. Biopsy of this tumour showed a predominantly clear cell tumour infiltrating bone. Immunohistochemical studies showed positivity for AE1/3, CK7, CK5/6, and negativity for smooth muscle actin, S100, HMB45, PAX8, DOG-1, RCC, and CD10. Subsequent genetic analysis showed a rearrangement in MAML2 (11q21) gene while EWSR1 (22q12) gene was not rearranged. Given the histological, immunohistochemical and molecular findings, a diagnosis of clear cell mucoepidermoid carcinoma was made.
She was treated surgically with maxillectomy and palatectomy. The resected specimen showed low grade clear cell MEC, stage pT4b.
Conclusion: Mucoepidermoid carcinomas can have variable morphologies causing a diagnostic challenge, particularly in small biopsy specimens. The clear cell variant is, as seen in this case, very rare and genetic analysis is beneficial in these challenging cases.

E-PS-11-040
Epithelial-myoepithelial carcinoma - a diagnosis at the breaking point
C. Dahlstedt-Ferreira[1], J. Oliveira[1]
[1] Hospital Garcia de Orta, EPE, Portugal

Background & Objectives: Epithelial-myoepithelial carcinoma is a rare (< 5% of salivar gland tumours), low-grade, biphasic tumour, associated to frequent local recurrence. We report a case of an extremely rare salivar gland tumour, which has a very bland histology.
Methods: A 94-year-old female presented with a painless mass on the left mandible angle, in 2016, which had grown for a year. She underwent an ultrasound and computerized tomography (CT), which revealed a neoplastic lesion on her left parotid. The study was proceeded with an aspiration cytology, which showed a benign salivar gland neoplastic lesion with myoepithelial differentiation. In 2018 she went to the emergency department because of sudden mass enlargement and inflammatory signals. She was submitted to a new CT, which confirmed the rapid mass enlargement. She agreed to be submitted to a subtotal parotidectomy with facial nerve preservation.
Results: Clinically, it is predominant in women, with mean age of 60 years, more commonly in the parotid gland. It has potential to metastasize. Grossly, it has 6 cm in length and has an expansive growth axis. Histologically, it is characterised by a low grade, multinodular, intraglandular neoplastic lesion, noncapsulated, with epithelial and myoepithelial components - an outer rim of myoepithelial cells and inner ductal cells with eosinophilic cytoplasm and round, insipid nuclei. Perineural invasion was identified.
Conclusion: This entity is a rare and its histological diagnosis is of great significance, since it generally is a treatable low-grade tumour, but can have high grade transformation, hence the importance of correct diagnosis and ressection.

E-PS-11-041
Carcinomas ex-pleomorphic adenomas: morphologic and immunophenotypic criteria
M. Tourne[1], M. Wassef[1], O. Casiraghi[2], C. Badoual[3], M. Lefevre[4], S. Albert[1], A. Couvelard[1], M. Hourseau[1]
[1] Bichat Hospital, APHP, France, [2] Gustave Roussy, France, [3] HEGP, APHP, France, [4] Montsouris Institute, France

Background & Objectives: The etiological factors associated with carcinomas ex-pleomorphic adenomas (CXPA) are poorly defined, as are the diagnostic criteria for asserting malignant transformation of a pleomorphic adenoma (PA).
The aim was to determine whether proliferation and expression of cell cycle molecules (p53, p16, Rb and Cyclin D1) can support the diagnosis of CXPA.
Methods: We performed a multicenter retrospective study including 82 tumours, subdivided into : cell-rich PA (crPA; n=25), multinodular recurrent PA (mrPA; n=20), encapsulated CXPA (eCXPA; n=20) and widely invasive CXPA (wiCXPA; n=17). We analysed the mitotic index/2mm² and the proliferation index Ki-67 using an artificial intelligence software (Machine Learning). These proliferation data were correlated with an immunohistochemical study on Tissue Microarrays of p53, Rb, p16 and Cyclin D1, calculating a H score [0-300].
Results: The median Ki-67 in crPA, mrPA, eCXPA, wiCXPA was respectively of 2.2% [0,8-6,3], 2.3% [0,35-3,9], 8.1% [2,2-30,3] and 18.4% [3,6-41,6] ($p<0.05$).The median mitotic index in crPA, mrPA, eCXPA and wiCXPA was respectively 0, 1, 2 and 8 ($p<0.05$). p53 staining was considered of wild type (WT) in all PA, in 64,3% (9/14) of eCXPA, and in 30% (3/10) of wiCXPA. The median p16 score in crPAs, mrPAs, eCXPAs, wiCXPAs was respectively of 30, 35, 70 and 165. The median Cyclin D1 score in crPAs, mrPAs, eCXPAs, wiCXPAs was respectively of 20, 15, 25 and 40. Rb was WT in all tumours.
Conclusion: The mitotic and proliferation index in association with expression of p16, cyclin D1 and p53 could be efficient diagnostic markers for differentiating Ca ex-AP from AP in litigious cases.

E-PS-11-042
A unique case of giant peripheral ossifying fibroma with a focus of Langerhans cell histiocytosis
D. Beypinar[1], H. Kacar[1], M.F. Acikalin[1], D. Arik[1], M.î Pinarbasli[2], U. Toprak[3]
[1] Eskisehir Osmangazi University, Department of Pathology, Turkey, [2] Eskisehir Osmangazi University, Department of Ear, Nose and Throat, Turkey, [3] Eskisehir Osmangazi University, Department of Radiology, Turkey

Background & Objectives: Peripheral ossifying fibroma (POF) is a reactive, non-neoplastic tumour-like growth of the gingiva. POF usually measure less than 2 cm in diameter, but larger lesions have been rarely reported. Langerhans cell histiocytosis (LCH) is an uncommon disease involving clonal proliferation of Langerhans cells. Here we report an unusual example

of POF reaching a large size. More interestingly and importantly, within the lesion, there was a focus of LCH measuring 0.4 cm in diameter.
Methods: A 46-year-old female presented with a five-year history of a painless, slow-growing mass in the mouth. She has no significant clinical history. Physical examination showed well circumscribed, approximately 7 cm, vegetative mass on the gingiva.
Results: A mucosal biopsy was performed, and histopathological findings were consistent with peripheral ossifying fibroma. Radical surgery of the tumour was performed. Totally 18 slices were sampled from the tumour. The microscopic evaluation showed a peripheral ossifying fibroma with a 0.4 cm focus of Langerhans cell histiocytosis.
Conclusion: To the best of our knowledge, this case represents the first case of LCH occurring within the POF. This case showed the importance of extensive sampling in large sized masses to identify concurrent lesions.

E-PS-11-043
PD-L1 expression in head and neck cancer patients from a center in Colombia

M. Ramos[1], A. Baldion[1], D. Suarez[1], S. Perdomo[1], M. Palau[1], A. Avello[1], A. Hakim[1], A. Escallon[1], V. Ospina[1], P. Bernal[1], G. Ucros[1], A. Muñoz[1], O. Torres[1], P. Rodriguez[1]
[1] Hospital Universitario Fundacion Santa Fe de Bogota, Colombia

Background & Objectives: Immunotherapy with PD-L1 inhibitors have shown promise improving survival in some solid tumours, their role in Head and Neck Cancer (HNC) is being studied but is not clear. Our objective is to determine PD-L1 expression in a cohort of HNC patients.
Methods: PD-L1 expression was evaluated with immunohistochemistry of tissue microarrays (TMA) from 38 HNC patients of the Hospital Universitario Fundacion Santa Fe de Bogotá from the InterCHANGE study. Ventana SP263 and Dako 22C3 antibody assays were used. Positivity for PD-L1 expression was calculated using the Combine Proportion Score (CPS), scores of ≥1 were considered positive.
Results:

PD-L1 POSITIVITY	VENTANA SP263		DAKO 22C3		REPORTED IN LITERATURE
	n	%	n	%	%
ORAL CAVITY (n=20)	19	95	18	90	51-71
OROPHARYNX HPV + (n=13)	12	92,3	10	76,9	49-87
OROPHARYNX HPV - (n=1)	1	100	1	100	29-61
LARYNX (n=4)	4	100	3	75	64-66

Conclusion: PD-L1 expression varied according to the antibody used. Our data showed a high rate of PD-L1 expression in all locations of HNC irrespectively of HPV status. Further studies should be done to standardize the measurement of PD-L1 expression, type of clone and clinical significance for HNC.

E-PS-11-044
Salivary gland lipoma: a rare entity

A. Faur[1], S. Bolintineanu[1], A. Sisu[1], L. Grigorita[1]
[1] V. Babes University of Medicine and Pharmacy, Romania

Background & Objectives: Lipomas of the salivary glands comprise between 0.5% -1.2% of neoplasms of the parotid gland. We present a case report of a lipoma of the parotid gland to further characterise its gross and microscopic appearance.
Methods: A 59-year-old man presented to the Oro-Maxillo-facial Surgery Department, City Hospital of Timisoara, with a left parotid painless mass. A resection of the mass with tumour-free margins was performed.
Results: Macroscopicaly the tumour was a well-circumscribed 4.8/3/2.3 cm, yellow mass with smooth texture and about 0.1 cm thick capsule . Microscopic examination revealed a tumour composed of mature adipose tissue, a thin fibrous capsule but with some peripheral areas with foci of glandular parenchyma.
Conclusion: Salivary gland lipomas are rare tumours that can sometimes present with some elements of glandular tissue. The differential diagnosis has to be made with the adipose replacement of glandular parenchyma that manifests in old age or inflammatory conditions associated with diabetes mellitus and alcoholism. In this cases there are foci of residual residual parotid parenchyma scattered throughout the adipose tissue. In our case the parotid acinar tissue was evident only along the periphery without any of the clinical signs mentioned previously.

E-PS-11-045
Salivary acinic cell adenocarcinoma: an epidemiologic study with rare histopathological aspects

A. Faur[1], M. Cornianu[1], C. Gurban[1], S. Bolintineanu[1]
[1] V. Babes University of Medicine and Pharmacy, Romania

Background & Objectives: Acinic cell adenocarcinoma (ACC) represent a malignant salivary neoplasm in which tumour cells demonstrate serous acinar differentiation. ACC accounts for about 11-17% of the primary epithelial malignancies of the salivary glands. In this study were reviewed in retrospect all the ACC diagnosed at City Hospital of Timisoara over a period of 10 years.
Methods: The cases were selected from the Pathology Department. We identified 279 cases of salivary gland tumours. The clinicopathological data were retrieived from the records. The slides were reevaluated, classified and discussed.
Results: We found 11 ACC. There was a male predominance (n=6) with the majority of ACC occuring in the parotid gland (n=9) and in patients between 61-80 years-old (n=8). The tumours had cytoplasmic positive granules for periodic acid-Schiff and alcian-blue stains. The ACC showed a variable growth pattern: sheets of solid tumour cells, microcystic growth pattern, papillary-cystic growth patterns and areas with undifferentiated carcinoma. One case showed a unique aspect and had brown pigment granuls in the cytoplasm that were positive for Fontana-Masson silver impregnation stain and HMB-45 antibody.
Conclusion: ACC represented in our study only a small number of patients (n=11) with salivary gland neoplasms. HMB-45 positive granules were previously described in in periductal and periacinar fibrous salivary tissue in small groups. Until now in salivary gland tumours studies in with such granules were described they were found in 2 adenoid cystic carcinomas, and melanocytes were found in 4 mucoepidermoid carcinoma and one pleomorphic adenoma but in none of the salivary ACC.

E-PS-11-046
Primary adenocarcinoma of the nasal cavity and paranasal sinuses: a retrospective study of 6 cases

S. Ben Khalifa[1], R. Hadhri[1], M. Njima[1], A. Bellalah[1], N. Ben Abdeljelil[1], A. Zakhama[1], L. Njim[1]
[1] Pathology Department of Fattouma Bourguiba Hospital, Monastir, Tunisia

Background & Objectives: Malignant sinonasal tract tumours comprise <1% of all neoplasms and about 3% of those of the upper aerodigestive tract. Primary sinonasal adenocarcinomas (SNA) represent 15% of these malignancies.
Methods: We retrospectively analysed the clinical and pathologic data of 6 patients, diagnosed with SNA in the department of pathology of Fattouma Bourguiba hospital from 2008 to 2018.The size, location and histological type of the tumours were analysed.

Results: There were 5 men and 1 woman with a mean age of 45 years (22-60years). Unilateral nasal obstruction, epistaxis and rhinorrhea were the most common symptoms. The average tumour size was 2,6 cm (1 to 5 cm). The tumour was located at the nasal cavity in three cases, at the ethmoidal sinus in two cases and at maxillary sinus in one case. SNAs were of non-intestinal type in 66,6% of cases(n=4) and of intestinal type in 33,3% of cases(n=2).
Conclusion: Among primitive SNA the 2017 WHO classification distinguishes two main categories: intestinal type adenocarcinoma (ITAC) and non-intestinal adenocarcinoma (NITAC), entities with different clinical and epidemiological characteristics. ITACs may occur sporadically or as an occupational-related disease, especially in cases of wood dust exposure. This tumour histologically resembles intestinal adenoma or adenocarcinoma with an intestinal type profile (CK20+/CK7-/CDX2+/villin+). It is locally aggressive with ~50% local recurrence. Locoregional / distant metastasis occurs in 10 - 20% cases and 5-year cumulative survival rate is ~40%. NITACs are morphologically heterogeneous tumours, mostly with glandular or papillary patterns showing a respiratory type phenotype (CK20-/CK7+/CDX2-/villin-). Approximately 25% of NITACs recur and only 6% of patients die of their tumours.

E-PS-11-048
Respiratory epithelial adenomatoid hamartoma: a retrospective study of 3 cases
S. Ben Khalifa[1], R. Hadhri[1], N. Ben Abdeljelil[1], M. Njima[1], A. Bellalah[1], A. Zakhama[1], L. Njim[1]
[1] Pathology Department of Fattouma Bourguiba Hospital, Monastir, Tunisia

Background & Objectives: Respiratory epithelial adenomatoid hamartoma (REAH) is an uncommon lesion of the upper aerodigestive tract first described by Wenig and Heffner in 1995 as prominent glandular proliferations lined by ciliated respiratory epithelium originating from the surface epithelium.
Methods: We report 3 cases of REAH diagnosed in the department of pathology of Fattouma Bourguiba hospital from 2008 to 2018.
Results: There were three male patients aged 50, 55 and 60 years old. The main symptom was nasal obstruction associated in one case with reccurent rhinorrhea. Endoscopic nasal evaluation showed bilateral polypoid lesions in all cases. Radiologic assessment revealed polypoid lesions in middle meatus, in nasal septum and in the upper nasal cavity. CT scan revealed bilateral opacification of ethmoid sinuses in one case. All patients underwent polypectomy and the tissue was sent for histopathological examination with a clinical diagnosis of inflammatory polyposis. Microscopic findings revealed bilateral REAH in one patient and sinonasal REAH associated with inflammatory nasal polyposis in two patients.
Conclusion: REAH is seen most often in male adults. Clinically the lesion presents as a polypoid mass, often in one or both nasal cavities. While REAH is benign, awareness and recognition of the lesion is important because it can be easily confused clinically with more threatening tumours such as inverted papilloma and sinonasal carcinoma.

E-PS-11-049
Similarities and differences of Cyclin D1 expression in tooth germ development
I.D. Caruntu[1], S.D. Savinescu[2], L. Lozneanu[1], R. Balan[1], C. Amalinei[1], S. Giusca[1]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania, [2] County Service of Forensic Medicine Vaslui, Romania

Background & Objectives: Cyclin D1, a nuclear protein directly involved in cell growth and differentiation, is scantily explored in tooth development. Consequently, our work aimed to analyse the Cyclin D1 during the tooth germ formation.
Methods: The study group included teeth germs from 15 aborted fetuses (10 weeks' gestation – 3 cases, 14 weeks' gestation – 3 cases, 18 weeks' gestation – 2 cases, 22 weeks' gestation – 3 cases, 24 weeks' gestation – 3 cases). Fragments from cephalic extremities and/or mandibles were processed for light microscopy and immunohistochemistry, by using anti-Cyclin D1. Cyclin D1 expression was semi-quantitatively assessed, based on the intensity of staining and percentage of positive cells.
Results: Cyclin D1 revealed a different expression in epithelial and mesenchymal components of the tooth germs, without differences between the germs corresponding to incisors, canine, and molars. In early and late cap stage, we noted a strong nuclear Cyclin D1 expression in all epithelial structures of the enamel organ, and a moderate one in the mesenchymal/ectomesenchymal cells of dental papilla. The early bell stage was characterised by a similar pattern of expression, with the highest intensity of immunoreaction in the ameloblasts nuclei. In late bell stage, the ameloblasts presented only a cytoplasmic positivity, the reticular, intermediate and extern epithelium of the enamel organ being Cyclin D1 negative, whereas odontoblasts showed a strong nuclear positivity.
Conclusion: Cyclin D1 is a valuable marker for cell cycle progression; its expression indicates the different functional status of ameloblasts and odontoblasts during odontogenesis, with results in the completion of amelogenesis, while dentinogenesis is still progressing.

E-PS-11-050
Sclerosing variant of mucoepidermoid carcinoma: an indication for molecular testing
A. Ali[1], D. Kamel[1]
[1] Broomfield Hospital, United Kingdom

Background & Objectives: Sclerosing variant of mucoepidermoid carcinoma can be easily misdiagnosed as a benign condition of the salivary gland such as chronic sclerosing sialadenitis, sclerosing polycystic adenosis or polycystic dysgenetic disease. With less than 30 reported cases in the literature, it is important to emphasise on the use of genetic testing in this rare tumour as an essential diagnostic tool.
Methods: Herein we are presenting a case of this rare variant in a middle-aged male patient arising in the parotid gland. Patient underwent a superficial parotidectomy after inconclusive fine needle aspiration cytology result. Grossly, the tumour was firm, white, with slightly irregular outlines and no areas of haemorrhage or necrosis. Histologically, the parotid tissue was replaced by neoplasm composed of variable sized cystically dilated ducts and some smaller normal looking ducts. These were associated intervening markedly sclerotic stroma. No perineurial invasion were seen. Background tissue showed dense inflammatory cell infiltrate admired with atrophic salivary gland tissue. Alcian blue special stain identified rare goblet cells in the duct epithelial lining.
Results: A provisional descriptive report was issued concluding a low-grade salivary gland neoplasm with unusual morphology and differential diagnosis between sclerosing polycystic adenosis and mucoepidermoid carcinoma. The case was sent for expert opinion where the diagnostic difficulty was confirmed and molecular testing was thought, and showed evidence of t(11;19)(q21;p13) resulting in gene fusion of CREB-regulated transcription coactivator 1 with Mastermind-like gene family (MAML2) confirming the diagnosis of sclerosing variant of mucoepidermoid carcinoma.
Conclusion: This particular variant comprises a diagnostic challenge for many pathologists due to the deceptively benign-looking epithelial component of this tumour and lack of convincing infiltrative pattern of growth. A high index of suspicion may be required in view of finding of cystically dilated ducts despite the absence of other classic components of mucoepidermoid carcinoma. Some Tumours may only show rare or no goblet cells as was shown in our case. Molecular testing for specific translocation linked to mucoepidermoid carcinoma such as genetic testing for t(11;19)(q21;p13) which fuses CREB-regulated transcription coactivator 1 with MAML2 or t(11;15)(q21;q26) translocation resulting in CRTC3/MAML2 Gene fusion is considered mandatory to confirm the diagnosis.

E-PS-11-051

Duct papilloma of minor salivary glands: a benign tumour with many malignant mimics

A. Ali[1], C. Waites[1]
[1] Broomfield Hospital, United Kingdom

Background & Objectives: Sialadenoma Papilliferum (SP) is a rare benign exophytic tumour of minor salivary glands. The incidence of SP is approximately 1% of all minor salivary gland tumours. SP is one of the three known ductal papillomas described by World Health Organisation (WHO) along with Inverted ductal papilloma and Intraductal Papilloma. Most common site of occurrence is the palate (greater than 80%), particularly at junction of the hard and soft palates. Other minor salivary glands sites of involvement include buccal mucosa, retromolar region, tonsillar pillar, lip, and nasopharynx.
Methods: This report focuses on a 72-year-old gentleman who was referred urgently to our hospital with multiple painless slow-growing verrucous lumps on the inside of his lower lip of 6 months duration which he constantly traumatised during mastication. On examination, he had no obvious cervical lymphadenopathy. Surgical excision was performed.
Results: Grossly, the cut section of the tumour revealed a well-defined, exophytic lesion with papillary structures in the centre. Histologically, it comprised of a squamo-proliferative lesion with surface papillomatosis and ductal proliferations of the minor salivary glands consistent with Sialadenoma Papilliferum.
Conclusion: The clinicopathological and morphological characteristics of this rare tumour are discussed and our approach to narrowing the differential diagnoses which include mucoepidermoid carcinoma, papillary cystadenoma and verrucous carcinoma is detailed.

E-PS-11-052

Giant cell tumour of the larynx - a rare entity

T. Oğuzsoy[1], I.s. ısgor[2], l. cinel[2]
[1] Marmara University Training and Researching Hospital, Turkey, [2] Marmara University Faculty of Medicine, Turkey

Background & Objectives: Giant cell tumours (GCT) are typically found at the ends (epiphysis) of long bones. GCT of the larynx is a rare entity. Most of GCT of larynx located at thyroid cartilage.
Methods: A 35-year-old male was admitted to hospital with progressive hoarseness and a growing neck mass for the past 2 months. He had no abnormalities in blood tests (including serum calcium). CT imagining showed a 4 cm diameter destructive mass in right ala of the thyroid cartilage. The patient referred to FNA.
Results: Cytopathologic analysis showed abundant multinucleated osteoclast-like giant cells and oval shaped scattered cells on the background. The patient underwent a supra-cricoid laryngectomy.
Grossly, the lesion was expansive, white to tan colored, un-encapsulated, 4.5 cm diameter, located to the thyroid cartilage. Histologically the tumour showed an expansive - infiltrative growth pattern. Histopathologic findings revealed numerous multinucleated osteoclast- like giant cells within a cellular, oval shaped, mononuclear stromal cells. The nuclei of giant cells were similar to stromal cells. The mitotic activity of the mononuclear cells was 1/10 HPF, but there was no atypical mitosis.
Conclusion: GCT of the head and neck are usually benign but they can be transformed into malignant GCT or can be primary de novo malignant GCT. GCT of the larynx is a rare entity and Giant cell granuloma, Brown Tumour, Osteoblastoma and Chondroblastoma should be considered in differential diagnosis.

E-PS-11-054

Low-grade sinonasal sarcoma with neural and myogenic features: a case report

S. Yonat[1], O. Erdem[1], A. Ozdemir[1]
[1] Gazi University Medical Faculty Pathology Department, Turkey

Background & Objectives: Dendritic cells (DCs) are antigen presenting cells which also detect tumoral antigens. Their significance in tumour progression is on debate. Our aim was to investigate the CD1a positive DC count in ovarian serous tumours.
Methods: A total of 96 consecutive ovarian serous tumours were collected from the archival files of our department between the years of 2007-2013. CD1a-immunohistochemical staining was performed. CD1a positive DC count was calculated as the average score of three hotspots counted at high power field (X40).
Results: The study population was composed of benign serous tumours (BST, n=36/96, 40,6%), borderline serous tumours (BRST, n=18/96 18,8%) and malign serous tumours (MST, n=39/96, 40.6%). The number of CD1a positive DC was between 0 to 47,6 with a mean of score of 6. CD1a positive DC was classified as low if the score was <6 (n=67/96,70%) and high if the score was >6 (n=29/96, 30%). Tumours with low CD1a scores were significantly more common in BST (94.9%, n=37/39) than BRST (33%, n=6/18) and MST (61,5%, n=24/39) (p=0.000). The number of MST with high CD1a score (38,5%, n=15/39) was less than BRST with high score (66,7%, n=12/18).
Conclusion: The proportion of tumours with high CD1a score significantly increased from BST to BRST but showed a considerable decline from BRST to MST. The preliminary findings of our study suggest that CD1a positive DCs are destroyed by malignant tumour cells and further studies can shed a light on whether DC vaccines could be used as an additional treatment in MST.

E-PS-11-055

Metastasis of renal cell carcinoma to the thyroid gland: a case report and review of the literature

A. Dhaoui[1], Z. Nfikha[1], K. Hamza[1], D. Ben Ghachem[1], K. Bellil[1]
[1] Forces de Securite Interieure, Tunisia

Background & Objectives: Renal Cell Carcinoma (RCC) is the most frequent malignant neoplasm of the kidney. It is well-known for its propensity to metastasize to unusual sites, and late metastasis, even after several years, is common. Metastases to the thyroid gland are rare. In a clinical series, up to 1-3% of the oncologic thyroidectomies were due to thyroid metastases and the most frequent metastasizing tumour was RCC, followed by lung and breast cancer.
Methods: A fifty-seven-year-old female patient presented with a single and palpable EU-TIRADS5 left thyroid nodule. She has a past medical history of right clear cell RCC diagnosed in 2014 and treated with left radical nephrectomy in our Institution.
Results: Final histological examination showed a clear cell neoplasm positive for PAX8, CD10 and CK7. TTF1 stain was negative excluding a parathyroid parenchym. Thyroglobulin was negative exluding primitive carcinoma of thyroid gland and calcitonin was negative excluding medullary carcinoma.
Conclusion: A thyroid nodule in a patient with a history of renal malignancy should be considered as potentially metastatic. Clinical manifestation and radiographic findings are nonspecific. Histological examination and immunochimestry may be able to distinguish between primary and secondary thyroid neoplasms. Despite being a sign of poor prognosis, diagnosis and surgical intervention are crucial and may increase the survival.

E-PS-11-056

Evaluation of p16 immunohistochemistry expression in squamous cell carcinoma of the upper aerodigestive tract

J. Kini[1], S. Nazareth[1], S. Krishnaraj[1], S. Sreeram[1], H. Kini[1], P. Suresh[1]
[1] Department Of Pathology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India

Background & Objectives: Immunohistochemistry serves as a tool to detect overexpression of p16 and can be used as a surrogate marker for the detection of HPV 16. Though oral squamous cell carcinoma is common in

older individuals, non-keratinizing basaloid oropharynx squamous cell carcinoma caused by HPV was most commonly found in younger age group of patients. Most of head and neck squamous cell carcinoma have been caused by high risk HPV in 5%-75% of the population studied. Recent studies have shown that oropharyngeal carcinomas (88%) caused by HPV were more common than non-oropharyngeal carcinomas and their incidence rates have been increasing in both genders though there is a males predominance.p16 immunohistochemistry is used to detect oral and oropharyngeal carcinomas instead of HPV PCR as it is simple and feasible to perform. p16 IHC is cost-effective and hence should be included in histopathology reports. p16 immunohistochemistry can be used as strong survival predictor and as an aid for early detection of HPV positive oral and oropharyngeal squamous cell carcinoma which can help in better treatment of the patient.

Methods: A retrospective and prospective cross-sectional study was done. The study was conducted in Pathology department of Kasturba Medical College, Mangalore. All histologically confirmed cases of squamous cell carcinoma and its variants of the upper aero digestive tract were included in the study. Histopathological records of Department of Pathology, KMC Mangalore were reviewed. A total of 198 consecutive histopathology samples received over a period of 18 months were evaluated. The relevant clinical details were noted from the patient files. Based on the data collected, the study population data was analysed with respect to age, gender, risk factors, type, grade and stage. Immunohistochemistry findings and intensity of p16 staining were correlated with respect to grade, stage and site of the lesion.

Results: In this study, 73 cases of oral, 65 of oro/hypopharngeal, 40 of laryngeal and 20 cases of nasopharyngeal squamous cell carcinomas were analysed. The age of the patients ranged from 27 to 80 years. The mean age at presentation was found to be 57.26 years. Majority of the cases (n =53, 72.6%) were seen in the age group of above 50 years. There was a marked male preponderance in our study with a male female ratio of 2.7:1.

It was observed that 49 cases of oral squamous cell carcinoma were positive for p16 immunohistochemistry. Out of the positive cases, 24 cases showed score 1 positivity, 19 showed score 2 positivity. Six cases showed score 3 positivity. On analysing the results of p16 staining of oro and hypopharyngeal tumours it was found that p16 was positive in 59 cases. Among those found positive,12 had low score, 41 had score 2, and the rest six had score 3. Of the 24 laryngeal cases scored as p16-positive, three were strongly positive, 13 moderately positive and eight demonstrated only weak positivity. Nine cases of nasopharyngeal were scored as p16-positive, out of which, three were strongly positive and two demonstrated only faint positivity. Only those with score 2 and 3 were considered as positive.

Conclusion: Oropharyngeal and hypopharyngeal squamous cell carcinomas caused by high risk HPV should be distinguished from non HPV squamous cell carcinomas because it is clinically relevant. As p16 is up-regulated in oropharyngeal and hypopharyngeal squamous cell carcinomas, p16 immunohistochemistry could be used as surrogate marker. P16 immunohistochemistry is cheap, simple and easy to perform alternative to HPV-PCR and fluorescent in situ hybridization testing which is relatively expensive. atient files. Based on the data collected, the study population data was analysed with respect to age, gender, risk factors, type, grade and stage. Immunohistochemistry findings and intensity of p16 staining were correlated with respect to grade, stage and site of the lesion.

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E-PS-11-057

Primary myxofibrosarcoma of parotid gland

S.Y. Ercetin[1], B. Keskin[1], H.K. Turkoz[1]
[1] Marmara University, Turkey

Background & Objectives: Myxofibrosarcoma commonly arises in the limbs of. Head and neck location is quite rare and primary parotid disease has been reported only twice previously.

Methods: We present a 64 year old male patient who had a painless swelling in preauricular region. Patient recieved partial parotidectomy elsewhere with the diagnosis of malignant mesencyhmal tumour, NOS. Patient applied to our center with recurrent swelling in the same location and underwent total parotidectomy with left sided neck dissection.

Results: Pathologic examination revealed a nodular, hypocellular tumour with myxoid background and infiltrative margins within parotid gland. The tumour cells were spindle shaped with scanty eosinophilic cytoplasm and had hyperchromatic, mildly pleomorphic nuclei. There were apparent curvilineer vessels, where the spindle cells clustered around . 18 mitoses per 10 high power field were detected. Necrosis (%5 of tumour) and extensive perineural invasion was seen. Deep parotid surgical margins were positive. Tumour cells were negative with CD34, smooth muscle actine, desmin, S100 protein and MUC4 immune stainings. No staining was detected with AE1/AE3 antibody.

Conclusion: Head and neck region is a very rare site for myxofibrosarcoma. When facing a spindle cell lesion of parotid gland, mesenchymal tumours other than more common primary salivary gland tumours originating from epithelial/myoepithelial cells should be suspected for a correct diagnosis and appropriate treatment.

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E-PS-12 | History of Pathology

E-PS-12-001

Professor Leonid Iosifovich Aruin - famous Russian scientist, pathologist-gastroenterologist (29.05.1924-24.01.2018)

A. Zubritsky[1]
[1] Moscow, Russia

Background & Objectives: This work has the aim to collect and systematize the biographical information according to the questionnaire prepared by me. Born in Moscow in the family of doctor. Married. Children: Michael. Graduated from the Higher Naval School of Naval Medical Academy (1947); PhD thesis on "Changes in adrenal cortex in rheumatism (clinical, morphological and histochemical study)" (1965), Doctoral – on "Pathomorphology of stomach and small intestine in postresection syndromes" (1971).

Methods: Doctor, Pacific and Baltic Fleet, anti-aircraft regiment, Sakhalin Island; Chief, Pathological Department, Naval Hospital, Liepaja; demobilized in rank of Lieutenant-Colonel in connection with the reduction of army; Head, Pathology Laboratory, Research Institute of Gastroenterology.

1/80 words

Results: Retirement and moving to permanent residence in Israel to their children and grandchildren (1995). For the first time intratissue regulators of regeneration of gastric mucosa were detected – the keylons, and differences in their activity in gastric ulcer were established; he developed methods of differential diagnosis of chronic liver diseases and described their morphological features; initiator of creation of Russian group for study of Helicobacter pylori.Laureate of many nominal awards.Research interests: Clinical and functional morphology of digestive system.

Conclusion: Author of over 200 scientific works, including many monographs.Distinctive feature: Kindness, responsiveness, tireless researcher, gift of diagnostic heuristics, ability to easily and clearly talk about fundamental problems of medicine. Hobby: Internet, liked to communicate with colleagues on Skype. He died at age of 93 from lung edema and was buried in cemetery of Beit Shemesh, located 23 km from Jerusalem.

E-PS-12-002

George Vladimirovich Shor - Russian pathologist, scientist and educator (23.04.1872-18.07.1948)

A. Zubritsky[1]
[1] Moscow, Russia

Background & Objectives: This work has the purpose to collect and systematize the biographical data for Professor G.V.Shor in accordance with the questionnaire I have developed. Born in St. Petersburg in family of postal official. Married. Spouse: Bogen-Shor (Petkovich) Olga Konstantinovna . Graduated from the gymnasium and the St. Petersburg Military Medical Academy with honors (1895); doctoral thesis on "Primary cancer of bronchi, lungs and pleura in relation to pathology" (1903).
Methods: Pathologist in different hospitals of St. Petersburg; Head, Department of Pathology, 1st Leningrad Medical Institute; one of the founders of thanatology; Honored worker of science of the USSR (1933); Chairman of the officer of the Court of honor during naval service.
Results: Founded the first experimental laboratory for research on cancer; one of founders of Leningrad Society of Pathologists; proposed in autopsy method of full evisceration of internal organs and a comprehensive study without the disturbance of anatomical relations, the method for preservation of anatomical preparations, which consists in preconditioning liquid of Shor followed by putting them in hermetically sealed vessels simultaneously with creation of archive macropreparations ("Museum of Shor"), method of carrying out clinical-anatomic mapping and introduced residency for future pathologists.
Conclusion: Research interests: Problems of thanatology, oncology, pathology equipment, etc. Author of over 70 scientific works, including main work "On human death, introduction to thanatology". Distinctive trait: Man of crystal purity and honesty.Died in Leningrad on the 77th year of life from cardiovascular insufficiency due to obesity heart. Buried in Leningrad.

E-PS-12-003
Questionnaire portrait of the well-known Russian forensic medical expert and pathologist Professor Mikhail Ivanovich Avdeev (16.11.1901-15.03.1978)
A. Zubritsky[1]
[1] Moscow, Russia

Background & Objectives: This work has the goal to collect and systematize the biographical information according to questionnaire prepared by me. Born in Vyazma, Smolensk Province in the family of an employee. Graduated from the medical faculty of Moscow State University and full-time postgraduate study at the Department of Forensic Medicine; defense of doctoral thesis on the topic "Pathological anatomy and pathogenesis of myocardial fragmentation".
Methods: Military service: regimental physician, participated in battles for the elimination of basmachism in Turkestan;Head, Department of Forensic Medicine, 1st MMI named after I.M.Sechenov;Senior Researcher, Institute of State and Law, USSR, etc. Organized a system of forensic institutions and developed instructions to determine the severity of injuries.
Results: During the Great Patriotic War took part in the work of the State Commission to investigate the atrocities of Nazi invaders in the USSR; various rewards. Research interests: Anatomical pathology of sudden death, questions of the degree of severity of bodily injuries, forensic medical examination in cases of self-mutilation, forensic traumatology, organization of forensic medical service, etc. Author of more than 100 scientific works, including many textbooks, manuals, practical guides and monographs.
Conclusion: Chairman of the Board of Moscow and Deputy Chairman of the All-Union Scientific Society of forensic doctors, etc. Distinctive feature: Inherent high sense of humor, did not like negligent and dishonest people. Hobbies: Loved theater and even took part in various amateur performances; had a beautiful voice, sang well. Died in Moscow on the 77th year of his life.

E-PS-12-004
Vladimir Petrovich Shishkov - outstanding Russian veterinary pathologist, scientist and educator (24.05.1927-07.01.2001)
A. Zubritsky[1]
[1] Moscow, Russia

Background & Objectives: To collect and systematize the biographical data according to the questionnaire prepared by me. Born in village Ivitsy of Odoevsky district of Tula region. Graduated from Moscow Veterinary Academy named after K.I. Skryabin with distinction, All-Union Legal Correspondence Institute (1954) and postgraduate studies at Moscow Veterinary Academy.
Methods: Defense of thesis on theme “Pathomorphological changes of cardiovascular system in high-yielding cows under metabolic disorders”, doctoral – on “Pathomorphology and some issues of pathogenesis of gastrointestinal diseases in newborn calves”. Professor, Pathology Department with course of forensic veterinary medicine, Moscow Veterinary Academy named after K.I.Skryabin, etc. Academician-Secretary, Department of Veterinary Medicine. For the first time in our country the systems of veterinary-prophylactic measures of reception for lambs-gnotobiotes are developed and on this model experimental colibacteriosis is studied.
Results: Development of complex and fundamental research on study of etiology and pathogenesis in development of diagnostic methods and measures to control leukemia of cattle; much has been done for development of gnotobiology, the use of its methods in solving problems of veterinary medicine. Awarded the Gold Medal named K.I.Skryabin for successful work on problem of pathology of farm animals (1985), etc.
Conclusion: Author of more than 300 scientific works, including 23 books and brochures, 15 copyright certificates and patents for inventions. Member of Board of All-Union Scientific Society of Haematology and Oncology, of Committee of World VeterinaryAssociation for Cattle Diseases (1974). Distinctive feature: Diligence, organizational skills. Died on January 7, 2001 in Moscow on 74th year of life.

E-PS-12-005
The role of the federal state autonomous educational institution of higher education ”Belgorod State University” in the history of the development of paediatric pathomorphology
T. Pavlova[1], V. Kulikovskiy[1], L. Pavlova[1], A. Nesterov[1]
[1] Belgorod State University, Russia

Background & Objectives: The exploration of historical aspects of pathological anatomy of diseases of children, fetus and newborn allows to establish ways of its further development.
Methods: Work with archive materials, monographs and textbooks
Results: The first book of pathological anatomy was issued in 1826. The first chair of pathological anatomy in Russian Empire was founded in 1845, the independent chair in Moscow was founded in 1859. The actual questions of obstetric, inflectional and somatic pathology are considered (V. Zinserling (St. Petersburg), A. Milovanov (Moscow). The children’s prosectorium in Belgorod was founded in 1989. It became one of the educational bases for students of medical institute (T.Pavlova, the head of the chair) .
Conclusion: The research of pathological anatomy of diseases of children, fetus and newborn promotes to formation of scientific knowledge as well as to correct diagnosis for preservation of health and vital activity of human.

E-PS-12-006
170 years at the head of Russian Anatomic Pathology (devoted to the 170 years anniversary of Anatomic Pathology Department named after academician A.I. Strukov First Moscow State Medical University named after I.M. Sechenov)
E. Kogan[1], V. Paukov[1], T. Demura[1], D. Protsenko[1]
[1] First Moscow State Medical University (Sechenov University), Russia

Background & Objectives: To show 170 years history of anatomic pathology department in First Moscow State Medical University named after IM Sechenov in Russia.
Methods: Analyses of literature and historical data.

Results: The first departments of were opened in Russia simultaneously in 1845 in Kiev (University of St. Vladimir) and in 1849 in Moscow (Moscow State University). In 1848 Alexey Ivanovich Polunin - 29-year-old educated doctor who graduated in Europe and knew 5 languages - became the chair of the department of anatomic and physiologic pathology. A.I. Polunin appreciated the importance of the views of R. Virchow and his microscopic method for studying pathological processes. He created a museum of grosses, that was initiated by the collection of bones, brought to Russia by Kh.I.Loder. The scientific school of the Anatomical Pathology Department in Sechenov University has history of 170 years. Department was headed by famous Russian pathologists: A.I. Polunin (1849-1869) , I.F. Klein (1869-1898), I.M.Nikiforov (1898-1916), V.I. Kedrovsky (1916-1918), A.I.Abrikosov (1918-1953), A.I.Strukov (1953-1972), V.V.Serov (1972-1990), Paltsev M.A. (1990–2009), VS Paukov (2009-2016) and Kogan EA (2016 - present). In 2015 the department was named in the honor of academician A.I.Strukov.
Conclusion: The level of scientific methods and technologies advancement on the Department resulted in anatomic pathology scientific school development in Russia, which is based on the following postulate: clinical anatomy, functional morphology, immunomorphology, molecular pathology, digital pathology, pathology of stem cells and their niches.

E-PS-12-007
A brief history of the atomic level studies on human pathologies and personal perspectives based on the summary of results of the first pan-cancer 'in vivo' interdisciplinary clinical-scale analysis
K. Taran[1]
[1] Medical University of Lodz, Poland

Background & Objectives: Mass spectrometry (MS) is awarded the four Nobel Prizes analytical method. Isotope Ratio Mass Spectrometry (IRMS) is the most precisely and currently highly developing MS type which alights an previously unknown atomic level of pathological tissue biology. Although IRMS studies for medical purposes are considerably scars they open a new window on human pathology. Recently IRMS was showed to be applicable to the direct cancer tissue evaluation and its use has allowed to discover a new area of biomarkers and potential targeted therapies
Methods: Interdisciplinary analysis of an isotope effect referred to isotopic fractionation in highly selected human 'in vivo' pan-cancers tissues with the use of IRMS incorporating a search for the relation to the established histological prognostic parameters.
Results: Isotopic profile of cancer tissues with the significant breakthroughs at a key moment of cancer cell spread was revealed. Nitrogen enrichment was identified as a new isotopic hallmark of cancer and the relation of isotopic fractionation to the established prognostic parameter, especially of the light microscope type was confirmed as an universal rule.
Conclusion: IRMS opens a new age of an atomic level research on human pathologies. This extremely modern method does not compete with microscopic or molecular assessment, contrary it may act as their valuable complement especially dedicated to personalised medicine and targeted therapies for cancer patients. Complete understanding of fractionation processes in cancer tissue and available benefits of IRMS use requires integration of data by overcoming interdisciplinary barriers.

E-PS-12-008
Is fluid biopsy a biopsy: vocabulary and usage
S. Mozgovoi[1], E. Abrosimova[2], A. Kononov[1]
[1] Omsk State Medical University, Russia, [2] Omsk State Agrarian University, Russia
Background & Objectives: The term, on the one hand, has gnoseological and heuristic functions, because it makes it possible to discover and name new concepts, and on the other hand, it forms and systematizes knowledge, ensuring their continuity from generation to generation. Consider from this point of view a relatively new medical term - liquid biopsy.
Methods: Diagnostic methods are constantly being improved, and the scope of the concept of biopsy is expanding, which leads to the appearance of clarifying definitions in the term. Thus, different types of biopsy are distinguished according to such semantic characteristics as the volume of material, method toolkit for obtaining material, type of accuracy control, organ from which biopsy is taken. All of the listed compound terms contain systemic semes of the term biopsy and are included in the notion of biopsy on the principle of hyponyms - a hyperonym.
Results: Diagnostic methods are constantly being improved, and the scope of the concept of biopsy is expanding, which leads to the appearance of clarifying definitions in the term. Thus, different types of biopsy are distinguished according to such semantic characteristics as the volume of material, method, toolkit for obtaining materia, type of accuracy control. Moreover, all of the listed compound terms contain systemic semes of the term biopsy and are included in the notion of biopsy on the principle of hyponyms - a hyperonym.
Conclusion: The meaning of the word biopsy is significantly modified in the terminological combination liquid biopsy. At the same time, the actual use of the term in modern media actualizes the semantic components of the term liquid biopsy, which are common with the concept of traditional biopsy, which can be explained by advertising purposes.

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E-PS-13 | Infectious Diseases Pathology

E-PS-13-003
A case of human cutaneous protothecosis: another addition to the literature from United Kingdom
M. Elgoweini[1], A. Bal[1], S. Allen[1], M. Strick[2], A. Waters[1]
[1] University Hospital Crosshouse, NHS Ayrshire & Arran, United Kingdom, [2] Glasgow Royal Infirmary, NHS Greater Glasgow & Clyde, United Kingdom

Background & Objectives: Protothecosis is a rare algae infection which primarily affects immunocompromised patients. We present a case of cutaneous protothecosis in an immunocompetent individual with diagnostic and treatment challenges.
Methods: A 67year old diabetic female, who regularly visited Mexico, presented with a lump on her upper back initially thought to be a sebaceous cyst. Shortly after excision, a 1 cm papulopustular eruption appeared in the region. Skin biopsy showed central ulceration and extensive inflammation with prominent eosinophils and histiocytes. Spherical periodic acid-schiff positive organisms, up to 15 μm in diameter, with occasional morula-like appearance characteristic of prototheca species were identified. *Prototheca wickerhamii* was confirmed on tissue culture and by PCR.
Results: The patient was commenced on oral itraconazole and fluconazole without success. The lesion increased in size with development of discrete papules within an area of approximately 7 x 4cm in spite of azole therapies. The patient was then commenced on (IV) Amphotericin B. However, the treatment had to be aborted due to underlying renal impairment. The lesion was surgically excised with a 1cm margin. She is currently under regular follow up with no early recurrence.
Conclusion: Cutaneous protothecosis is a rare infection with no specific clinical features. The diagnosis relies on recognition of characteristic histopathological features in conjunction with microbiological confirmation. Management is highly challenging and requires a multidisciplinary approach.

E-PS-13-004
Isolated pulmonary cryptococcosis confused with lung tumour
C. Fumagalli[1], E. Chenu[1], C. Berengua Pereira[1], F. Sánchez-Reus[1], R. Orellana[1], L. López-Villaró[1]
[1] Hospital de la Santa Creu i Sant Pau, Spain

Background & Objectives: Cryptococcosis is an opportunistic infection in immunosuppressed patients that usually presents as meningoencefalitis, while pulmonary disease is less frequently reported. Transplanted patients are a risk group due to the immunosuppressive therapy used to maintain the function of the transplanted allografts. Moreover, in this group, the incidence of malignancy increases due to the immunosuppression, so that it's occasionally difficult to distinguish between an infection and a malignancy when facing with a mass.
Methods: Herein we report a case of isolated pulmonary cryptococcosis 3 years after kidney transplantation that was clinically misdiagnosed as a lung tumour. A 35yo male received a kidney transplant for end-stage kidney disease when he was 32yo. During a routine control, a hypermetabolic mass was found in the middle lobe of the right lung. Due to radiologic findings, immunosuppressive therapy and the fact that the patient was a smoker, the mass was highly suspicious for malignancy and a lobectomy was performed.
Results: Macroscopically, a 1,7cm lesion with central necrosis was found. The microscopic study showed multiples granulomas with histiocytes and spherical fungi positive for periodic-acid-Schiff, Grocott-Gomor and mucicarmine staining. A part of the specimen was cultured in our microbiologic service, confirming the presence of *Cryptococcus neoformans*. Thus, the diagnosis of isolated pulmonary cryptococcosis was made.
Conclusion: In transplanted patients, the presence of a lung mass raises the differential diagnosis of an infection or a tumour, leading possibly to misdiagnosis and overtreatment, as occurred in this case, so a careful clinical analysis should be performed.

E-PS-13-005
Rhinosporidiosis: report of a case presenting as urethral polyp
G. Morgantetti[1], G.A. Medeiros[1], J.G.d.N. Barros[2], M.L. Balancin[1]
[1] University of Sao Paulo, Brazil, [2] Laboratório Laborocha Filho, Brazil

Background & Objectives: Rhinosporidiosis is a chronic granulomatous disease caused by *Rhinosporidum seeberi* infection, a protistan parasite previously regarded to be a fungus, transmitted through traumatized epithelium, most commonly in upper airways, genitals and rectum. Endemic in Asia, Africa and South America, the infection is acquired through bathing or working in stagnant water, and is not transmitted between individuals. Treatment is surgical, with complete removal of the lesion being sufficient in most cases.
Methods: A 69-year-old patient presented to the urology outpatient clinic with a 0,8 cm polypoid lesion protruding from the urethral meatus, with clinical suspicion of HPV infection. The patient had no relevant background data.
Results: The patient underwent excisional biopsy and histopathological examination revealed multiple thick-walled sporangia in various stages of maturation, surrounded by mild inflammation (Figures 1 and 2). Gomori-Methanamine Silver (GMS) stain demonstrated pathogen argirophilia (Figure 3). The histopathological analysis alone was enough to confirm the diagnosis of urethral rhinosporidiosis. No relapse was detected after one-year follow-up.
Conclusion: Although rare, rhinosporidiosis should be considered as a differential diagnosis of mucosal polypoid lesions, especially in patients coming from endemic regions and with history of exposure to contaminated water. Due to the disease´s unique morphological features, histopathological examination is sufficient for the diagnosis and no special stain or ancillary test is necessary.

E-PS-13-006
Pathology of rotavirus-driven multi-organ failure in infants
G. Tarris[1], G. Belliot[2,3], P. Cailler[4], L. Martin[5,6,7], A. de Rougemont[2,8]
[1] Department of Pathology - University Hospital of Dijon, France, [2] National Reference Centre for Gastroenteritis Viruses, Laboratory of Virology, University Hospital of Dijon, France, [3] UMR PAM A 02.102 Procèdès Alimentaires et Microbiologiques, Universitè de Bourgogne Franche-Comtè/AgroSup Dijon, France, [4] INSERM LNC UMR 1231, Equipe GAD, Universitè de Bourgogne Franche-Comtè, Dijon, France, [5] Service de Pathologie, CHU Dijon, France, [6] Plateforme de Gènètique des Cancers solides et des Hèmopathies malignes, CHU Dijon, France, [7] Unitè d'innovation en Gènètique et Epigènètique des cancers, CHU Dijon, France, [8] UMR PAM A 02.102 Procèdès Alimentaires et Microbiologiques, Universitè de Bourgogne Franche-Comtè/AgroSup Dijon, France

Background & Objectives: Child death from rotavirus infection remains exceptional in developed countries. Although diarrhea, dehydration and delayed care are the main causes of decease, other physiopathologic mechanisms consecutive to viremia in relation to human blood group antigens (HBGA) may play a role in some fatal outcomes. Our objective was to assess the replication and binding sites in the case of a 16 month-old boy which suffered from severe G1P[8] rotavirus acute gastro-enteritis with a fatal outcome.
Methods: Multiple organ sections from a fatal case of septic shock and organ failure linked to rotavirus acute gastro-enteritis in a 16-mo boy, with previous low-birth weight and intra-uterine growth retardation, were investigated using molecular biology, immunohistochemistry and immunofluorescence targeting VP2 and VP6 structural and NSP2, NSP4 and NSP5 non-structural rotavirus proteins, and the H and Lewis antigens.
Results: Histpathology revealed signs of early acute kidney injury and pulmonary diffuse alveolar damage. Immunodetection showed non-structural and structural rotavirus proteins colocalization within viroplasms and evidence of rotavirus binding to HBGAs in kidney and lung tissues.
Conclusion: *In vitro* studies have shown the ability of rotavirus to secrete IL-6 and IL-8 via its main toxin, the non-structural protein NSP4. This study brings new insights into mechanisms underlying extraintestinal rotavirus infection and highlights the relation between rotavirus replication and its abilities to bind to HBGAs in kidney. Further studies will be required in order to clearly determine the relationship of the rotavirus replication in multi-organ failure (i.e. acute kidney injury and diffuse alveolar damage). Rotavirus infections remain a major public health issue in France, as vaccinations are still not included in the National immunization schedule. Recent hospital-based studies have shown the impact of rotavirus vaccination in terms of delayed care, burden of disease and morbidity.

E-PS-13-007
What's in the guts?
I. Dumitru[1], B. Mohamed Amine[1], X. Sastre Garau[1], A. Boyez[1], N. Talhi[1]
[1] CHI Créteil, France

Background & Objectives: Nontuberculous mycobacterial infections can present as a rare and distinct entity called mycobacterial pseudotumors. M. pseudotumors affect immunosuppressed patients with or without AIDS. Pseudotumor of abdomen is a rare and distinct clinical entity that needs to be diagnosed before any surgery. We report a young female who was referred to our institution with a primary diagnosis of malignancy.
Methods: We report the case of a 38-year-old woman, HIV positive, who presented with chronic anaemia. The endoscopic findings described a suspicious obstruction of the duodenum and biopsies were obtained from the region. The pathological examination showed extensive infiltration of the lamina propria with foamy granular or striated histiocytes (pseudo-Gaucher cells) disposed singly, in clusters, or diffusely and packed with 'globi' of acid-fastbacilli. Special stains were negative for periodic acid-Schiff reagent and positive for acid-fast staining (Ziehl-Neelsen stain).
Results: Althow we don't have a culture to certify the diagnosis, the appearance of Whipple-like and the positivity for acid-fast staining (Ziehl-Neelsen stain) we retain the diagnosis of atypical mycobacteria infection.
Conclusion: The pitfall of the case was represented by the lack of clinical information that are critical to the diagnosis and the Whipple-like infiltration of the lamina propria with foamy granular histiocytes and of course the right

interpretation of the special stains. Clinicians and pathologists should be aware of this unusual manifestation of non-tuberculous mycobacteria which affects immunosuppressed patients in order to avoid unnecessary surgery.

E-PS-13-008

Rare organ involvements in echinococcal disease

H. Göbel[1], A.M. Lentzsch[2], K. Richter[3], J. Fries[1]
[1] Institute for Pathology, University Hospital Cologne, Germany, [2] Department of Ophthalmology, University of Cologne, Cologne, Germany, [3] Department of Urology, University of Cologne, Cologne, Germany

Background & Objectives: About 50-60 new cases of Echinococcosis are reported annually in Germany making it a rare entity with more cases in the southern part of Germany than in the north. Echinococcus granulosus is more prevalent worldwide whereas Echinococcus multilocularis is found within Europe and the southern part of Germany. Echinococcosis presents as a cystic disease most often involving lungs and liver, but it can be found occasionally also in other organs. Rarely it is found solely in other localizations without liver and/or lung involvement. We present two cases of cystic lesions in the left kidney and the eye respectively with no other organ involvement.
Methods: Case 1: The 23-year-old man presented with increased flank pain and fever up to 40°C which dropped after antibiotic treatment. The cystic disease was known at that time for 1 year. Due to the symptoms the decision to perform a complete nephrectomy was made. Standard histology was applied. Case 2: The 5-year-old girl presented with proptosis and downward displacement of her left eye for 2 years. The cystic structure could be evaluated by magnetic resonance imaging. The lesion was surgically removed and also examined by standard histology.
Results: Microbiological examinations could not find vital organisms in the fluid harvested at the time of the kidney operation. In both cases the specimens showed a cystic disease involving the kidney and the eye respectively. Histologically the typical cuticula were found as well as scolices.
Conclusion: Renal or ocular involvement are rare occurrences in echinococcal disease, which is even more extraordinary, when a solitary involvement without the typical lung and/or liver disease is present.
We present here two cases of renal and ocular echinococcosis in young people who neither showed other locations of echinococcal cysts. To our knowledge the patients had no recurrent echinococcal involvement. Both patients came from countries outside of Germany which may indicate one should have this differential diagnosis in mind if confronted with cystic diseases in unusual areas.

E-PS-13-009

Trichuris Trichiura: the importance of histopathology in the diagnosis

F. Galante Pereira[1], C.A. Padrão[1], A.M.G. Pereira[1], R.S.S. Oliveira[1], J.P. Garcia[1]
[1] Hospital Prof. Doutor Fernando Fonseca, EPE, Portugal

Background & Objectives: *Trichuris trichiura*, commonly referred to as a human whipworm, is endemic in tropical and subtropical countries, but a few sporadic cases have occurred in nonendemic areas. Most infections are light and tend to be asymptomatic. The diagnosis is made by identifying *Trichuris trichiura* eggs in stool specimens; few reports have described detection of the parasite in a biopsy specimen. The purpose of this case report is to increase awareness of this uncommon, but treatable parasite.
Methods: A 54-year-old man, African descendent, with history of multifactorial anemia, asymptomatic, was submitted to a cecum biopsy on colonoscopy for iron deficiency anemia after a negative fecal occult blood test. Hematoxylin-eosin stain was performed.
Results: Histologically it was identified an adult female whipworm, *Trichuris trichiura* in an intestinal mucosa sample. It was composed by two distinct body regions: a slender, thread-like anterior segment, and a thick posterior segment, rounded and uncoiled, with the intestine and egg-filled uterus. The ellipsoid eggs had bipolar plugs. In the posterior region, there was a thick cuticle with prominent annulations, thin hypodermis and a layer of somatic muscle cells.
Conclusion: There should be a high degree of suspicion in patients coming from endemic areas presenting with typical symptoms, as this is a treatable disease when properly detected. The diagnosis of this case was made at the biopsy. This case report pretends to illustrate the essential role of pathology in the diagnosis of intestinal parasites besides the traditional stool specimens.

E-PS-13-010

Mycetoma in Portugal

F. Ramalhosa[1], R.C. Oliveira[1], G. Fernandes[1], J. Fraga[1], H. Moreira[1], M.A. Cipriano[1], M.J. Martins[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal

Background & Objectives: Mycetoma is a chronic tropical inflammatory disease, caused by inoculation of either fungi or filamentous bacteria. Infection slowly spreads to involve skin, bone and subcutaneous tissue. Is mostly predominant in poor tropical countries, associated with outdoor work-related activities, rarely found in Europe. Mycetoma diagnosis is based on clinical presentation: a subcutaneous mass, draining sinuses and grain discharge. Further study can be done, as bacteria PCR and culture.
Methods: A 57 years old man, born in Portugal, without travel records, referred to our Hospital with a clinical history of painful growing tumefaction on his right foot since 2000, despite several courses of antibiotics and surgical cleaning treatment. Ultrasound revealed nodular and cystic formations and X-ray and MRI showed chronic osteomyelitis with the destruction of deep structures and bone.
Results: Specimens obtained through needle aspiration, from the subcutaneous tissue, were sent to the pathology department, which histologically revealed suppurative granulomas surrounding grains. Periodic-acid-Schiff and Grocott-Gomori silver staining confirmed the fungi aetiology. Particularly, in this case, both PCR and culture were negative.
Conclusion: Despite the typical clinical presentation, the diagnosis and management were delayed because Mycetoma is rare in Portugal. The treatment depends on the causative organisms: a combination of antibiotics and antifungal agents. In the advanced state of the infectious process, amputation may be the only available treatment. In our case, the patient has foot deformity and loss of function, therefore an above-knee amputation was proposed.

E-PS-13-011

Rhino-orbital Mucormycosis in renal transplant recipient: a case report

A. Ok Atilgan[1], E. Yilmaz Akcay[1]
[1] Baskent University Faculty of Medicine Pathology Departmant, Turkey

Background & Objectives: Mucormycosis is an invasive fungal infection which is primarily caused by filamentous fungi belonging to the *Mucoraceae* family and is frequently seen in diabetic and immunocompromised patients. Mucormycosis is categorized as rhinocerebral, pulmonary, cutaneous, gastrointestinal or disseminated, depending on organ involvement; the most common form is rhinocerebral (39%).1 This form may be divided into subtypes based on which tissues are affected: rhinonasal, rhinoorbital or rhinoorbitocerebral.
Methods: We report a case of 28-year-old female who had renal transplantation from a cadaveric donor with vesicoureteral reflux etiology 4 years ago. Her immunosuppressive regimen was tacrolimus, mycophenolate mofetil.
Results: She presented with complaints of swelling of the right eye. On ophthalmologic examination proptosis, ptosis and lateral gaze limitation were observed in the right eye. Orbital magnetic resonance imaging (MRI) without contrast revealed widespread inflammatory changes in right optic nerve, medial rectus, retroorbital area and extending to right

paranasal sinuses. Biopsy taken from right sinonasal mucosa and histopathological diagnosis was mucormycosis than exenteration was performed on the right eye. Histopathological examination revealed Mucor organisms invading orbital connective, neural tissue, bone and mucosal tissue adjacent to areas of necrosis. Typical hyphae forms are broad with irregular, thin, nonparallel cell walls lacking septae. She was treated with systemic liposomal amphotericin B and local irrigation and followed without disease for 25 months.
Conclusion: Mucormycosis should be suspected in all immunosuppressed patients who present with persistent upper respiratory, ocular symptoms and not explained by other causes.

E-PS-13-012
A case of lethal angioinvasive fungal infection of the kidney in a critically ill patient
C. Masaoutis[1], S. Pantelakos[1], D. Sampaziotis[1], A. Sykaras[1], F. Dolkiras[1], C. Vourlakou[1]
[1] Department of Pathology, Evangelismos General Hospital, Athens, Greece

Background & Objectives: Fungal infections of the kidney are rare and encountered primarily in immunocompromised patients. Candida, Aspergillus and Mucor are the most common causative microorganisms. We present a case of a 74-year old male burn victim of the 2018 Attica wildfires, hospitalized in our ICU for sepsis, who developed acute renal injury with imaging findings consistent with kidney infarction. Left nephrectomy was performed.
Methods: We received a 152gr kidney measuring 12x8x5.2cm, diffusely pale, with an indistinct corticomedullary junction and numerous parietal thrombi in branches of the renal artery. Multiple sections were examined by light microscopy and histochemistry.
Results: Microscopy revealed extensive coagulative necrosis of the kidney consistent with infarction with areas of intraparenchymal haemorrhage. Many blood vessels were thrombosed. After meticulous examination of the necrotic tissue in H&E sections, branching and somewhat variable in width hyaline fungal hyphae were noted within the wall or the lumina of arterial branches. The hyphae were highlighted with the use of histochemical stains PAS and Grocott. The fungus, isolated from an intraoperatively obtained thrombus of the renal artery, was identified as Fusarium in culture.
Conclusion: These findings are consistent with an angioinvasive hyalohyphomycosis of the kidney. Fusarium spp. represent an uncommon cause of such infections. Despite antifungal treatment, the patient's condition continued to deteriorate and he died on the 30th day after nephrectomy.
This case points out the possibility of a fungal infection in renal infarcts of immunocompromised / critically ill patients. These infections, unless treated early, progress rapidly and have a high mortality rate.

E-PS-13-013
Visceral leishmania - a rare event
R. Caetano Oliveira[1], P. Carreira[2], H. Garcia[2]
[1] Pathology Department, CHUC, Coimbra, Portugal, [2] CEDAP, Portugal

Background & Objectives: Leishmaniasis is a disease cause by a parasite – Leishmania, endemic in some parts of the World, namely in Mediterranean countries. The most common form in visceral leishmaniasis, especially with liver and bone marrow involvement, more frequent in patients with immunodeficiency. Colon involvement is rare, with scarce case reports in the literature.
We describe a rare case of colonic leishmaniasis.
Methods: Male patient, HIV positive, with 60 years old and complains of diarrhea. Colonoscopy showed no mucosal alterations. Biopsies were taken.
Results: Biopsies showed diffuse histiocytic population, between the colon glands, with multiple small and oval organisms with bar shaped paranuclear kinetoplast, positive for Giemsa and negative for silver stainings.
Conclusion: Visceral leishmaniasis with colon involvement is an infrequent event. The possibility should be raised in patients with immunocompromised status, providing an early diagnosis with correct treatment.

E-PS-13-014
Mucormycosis of the maxillary sinus complicated by osteitis: a case report
E. Ben Hadj Khalifa[1], S. Chaieb[1], A. Bdioui[1], A. Baccouche[1], S. Ben Khlifa[1], M. Mokni[2]
[1] Cytology and Pathology Department CHU Farhat Hached, Sousse-Tunisia, [2] Department Of Pathology, University Farhat Hached Hospital, Tunisia

Background & Objectives: Mucormycosis is a rare opportunistic mycosis infection. The responsible agent is a filamentous fungus in the order of the Mucorales, which are ubiquitous, saprophytes of the soil and many plants. It may be responsible of different clinical pictures. The rhino-orbito-cerebral form is the most common clinical form in the literature. We present a case of mucormycosis of the maxillary sinus complicated by osteitis. In this observation we will illustrate the clinical, radiological and pathological aspects of this infection.
Methods: We report the case of a 49-year-old woman who consulted for purulent rhinorrhea and a pain of the right maxillary sinus evolving for 21 days.
Results: A 49-year-old woman without any pathological history admitted for right maxillary sinusitis evolving for 3 weeks. The radiologic exams showed a right maxillary sinusitis complicated by diffuse maxillary osteitis. A sinus biopsy was performed bringing back 3 fragments of inflammatory and suppurative necrotic material containing spores and branched, septate mycotic filaments positive for PAS and Grocott staining. Then, the diagnosis of mucormycosis was made. The evolution was favourable after surgical cleaning and the use of high-dose amphotericin B
Conclusion: The fungi and spores of Mucorales show minimal pathogenicity toward normal persons, they can initiate aggressive infections under clinical conditions responsible for decreased immunity.

E-PS-13-015
Hydatid disease: two soft tissue cases and 20-year review in our center
M. Trujillo Coronado[1], B. Tristan Martin[1], M. Arguelles Pintos[1], L. Lopez Brasal[1], P. Ramos Ponton[1], F.J. Pinedo Moraleda[1]
[1] Hospital Universitario Fundacion Alcorcon, Spain

Background & Objectives: Hydatid disease (HD) is a helminthic zoonosis caused by tapeworm *Echinococcus granulosus* larvae. It presents a worldwide distribution, being endemic to the Mediterranean area, Australia and South America.
After ingesting contaminated food, oncospheres are released in the human small bowel, passing through the mucosa and entering the portal system, with hepatic involvement (75%), or reaching the systemic circulation, hypothetically through lymphatic/venous bypasses, with lung (15%) or splenic (8%) involvement. Primary soft tissue HD is very rare.
Methods: Two primary soft tissue HD cases have been diagnosed in our hospital: 59-year-old male, with a 2 cm-gluteal lesion with progressive growth for years; 69 year-old male, with a 20 cm-thigh mass in the vastus lateralis muscle.
Results: In the first case, the subcutaneous lesion was excised, revealing a 2 cm-cyst, formed by a fibrous pericyst, laminated layer and proligerous membranes, and protoscolicex.
In the second case, radiology ruled out hepatic or pulmonary involvement, and positive serologies for *E. granulosus* were obtained. After 6 months of treatment with albendazole, with serological negativization but lesion stability, percutaneous drainage was performed, sending 15 ml of pasty and yellowish fluid, where laminated membrane debris and degenerate (probably parasitary) fragments were identified.

We reviewed our database from 1997 to 2019 for HD, finding 20 cases, with 14 hepatic lesions, 4 soft-tissue lesions, 1 lesion in sputum, and 1 orally expelled nodule.
Conclusion: Soft tissue HD should be considered in the differential diagnosis, even without hepatic or pulmonary involvement. In suspicious cases, it could be crucial for patient management.

E-PS-13-016
Atypical localisation of cryptococcosis as the reason for exitus letalis
Y. Korneva[1], R. Ukrainets[2]
[1] Smolensk Regional Institute of Pathology, Russia, [2] Smolensk State Medical University, Russia

Background & Objectives: GIT may be affected by opportunistic infections, but very rarely. Most often Oesophagus and colon are affected, but stomach involvement is uncommon and usually found as post-mortem finding in cases of dissemination. Cases of cryptococcal affection of stomach are very rarely described in literature, and only few of them became the reason to seek medical help.
Methods: 50-year-old patient without an improved immune status died in 40 minutes after admission to the Emergency Hospital due to intensive bleeding form gastrointestinal tract. During autopsy on the lesser curvature a perforating defect of stomach wall, penetrating to omentum minor with erosion of vessels and manifestations of profuse bleeding was detected. The case was considered as K25.6 (ICD-10). But histological examination revealed in the margins of ulcer as well as stomach wall revealed clusters of round and oval cells with optically empty cytoplasm, which have clearly defined contours, these formations turn purple on Mouri stain, surrounded by non-specific inflammatory infiltrate. Additionally fungi *Candida* and *Aspergillus* in the superficial layers of defect margins were detected, while *Cryptococci* involved full thickness of stomach wall. Cryptococcal dissemination also was seen in heart, lungs, liver, kidneys.
Results: Mycotic etiology of stomach ulcers, as one of the manifestations of generalized cryptococcosis, was not diagnosed in a patient during his lifetime and became unexpected findings in a postmortem histological examination of the patient's tissues. The formation of mycotic granulomas in the stomach with further destruction led to acute ulcer formation, complicated by penetration to the omentum minor and involvement of its arteries - is an extremely rare clinical observation. Subsequent gastric bleeding and hemorrhagic shock were the immediate cause of the patient's death.
Conclusion: It is necessary to remember about the possibility of gastrointestinal tract affection by opportunistic infections and their specific morphological picture, especially in patients with immunodeficiency. It is very important for investigation of biopsy specimens from alive patients, since the verification of mycotic lesion requires additional histological stains and layering of inflammatory infiltrate blacks out *Cryptococci,* but verification of this etiological agent is essential for correction of treatment regimen.

E-PS-13-017
IL-10 modulating immunosuppression in disseminated cutaneous leishmaniasis
L.P. Sousa dos Santos[1], A. de Queiroz Sousa[1], P.D. Torres Sindeaux Filho[1], D.I. Magno Cavalcante[1], K. Miranda Sá[1], M.M. de Lima Pompeu[1]
[1] Federal University of Ceará, Brazil

Background & Objectives: Disseminated cutaneous leishmaniasis (DCL) is a rare and emerging disease, mainly caused by *Leishmania (V.) braziliensis*. It starts usually as a single ulcerated lesion followed by hematogenous parasite spread, leading to the appearance of multiple lesions compromising at least two body parts. The lesions are pleomorphic, ulcerated, papular, nodular and acneiform. The mechanism of parasite spread are not yet well understood and transitory Th1 cells immunosuppression is supposed to be the cause. We evaluated IFN-γ and IL-10 production in cutaneous lesion of patient with DCL and localized cutaneous leishmaniasis (LCL).
Methods: A case-control study was carried out with 12 patients with LCL and 8 with DCL, matched by age. IFN-γ and IL-10 were labelled by immunohistochemistry in skin lesions biopsies. Cytokines quantifications were performed manually using ImageJ software in 10 captured microsections (400X) per lesion. Relative frequency of the cytokine producing cells was calculated.
Results: Seven (87.5%) patients with DCL were males and 1 (12.5%) female and all with LCL were males. There was no significant difference between the two groups regarding IFN-γ production by the inflammatory cells infiltrating the lesions, the median of IFN-γ labelled cells was 2.0% in LCL and 4.6% in DCL ($p = 0.18$). IL-10 production occurred in 1.6% of inflammatory cells of DCL patients skin biopsies and in 0.4% of the ones with LCL ($p = 0.04$).
Conclusion: Higher IL-10 production observed in the lesions of patients with DCL suggests a possible mechanism for the modulation of immunosuppression favoring parasite dissemination.

E-PS-13-018
Morphometric evaluation of paracoccidiomycosis cutaneous depth of infection
D. Nunes Oliveira[1], V. Holanda Ferreira[2], G. Bitu dos Santos Ponte[2], P.V. Pereira Motoyama[2], S. Capelo Barroso Garcia[2], S. Andrè de Souza Júnior[2], J. Carneiro Melo[1], M. Luiz Balancin[3]
[1] Department of Pathology, Postgraduate Program in Public Health, Faculty of Medicine, University of Fortaleza, Brazil, [2] Faculty of Medicine, University of Fortaleza, Brazil, [3] Pathology Division, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil

Background & Objectives: Paracoccidioidomycosis (PCM) is an infection caused by a dimorphic fungus with severe consequences if not diagnosed and treated properly, having the highest mortality rate among systemic mycosis. The disease has a slow progression, with peak between 10 and 20 years old, however clinic manifestations usually occurs between 30 and 50 years old. The infection is primarily pulmonary, with the skin being involved secondarily, but it may also involve other organs. The objective of this study was to analyse the paracoccidioidomycosis' skin slides to determine the depth of the lesions.
Methods: Observational, analytical, cross-sectional study, in which students of the University of Fortaleza's Pathology League analysed 53 skin slides. To this matter, CaseViewer, a digital microscope software, was utilized to analyse the slides.
Results: After the analysis of the slides, we classified them in four groups according to the depth of the lesion. Group 1 included lesions of depth up to 1mm, group 2 those between 1mm and up to 2mm depth, group 3 between 2mm up to 4mm and group 4, lesions with depths greater than 4mm. There were 12 lesions (22,64%) classified into group 1, 22 (41,5%) into group 2, 19 (35,8%) into group 3 and no lesions were classified into group 4. The arithmetic average was 1,70mm and the median was 1,63mm.
Conclusion: We concluded that paracoccidioidomycosis cutaneous lesions are located preferentially within the epidermis and the dermis. As it is an infection that can affect almost every organ, further studies are needed to determine the extension of the lesions in other organs and tissues.

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E-PS-14 | IT in Pathology

E-PS-14-001
Digital microscopy - is there a need for standardisation?
S. Schöniger[1], G. Bänfer[1], R. Diezko[1], B. Jasani[1]
[1] Targos Molecular Pathology GmbH, Germany

Background & Objectives: Digital and light microscopy are often used interchangeable for evaluation of tissue specimens. The aim of this study was to compare both methods and to highlight major influencing factors.
Methods: Comparisons were performed between the 20x magnification of Aperio ImageScope on a 3K computer with a screen size of 31 cm (resolutions: 1920 x 1080, 2560 x 1600, 2048 x 1152, 2736 x 1824; screen scaling factors: 200%, 150%, 100%), a Zeiss Axio Scope A1 and a Labomed CxL microscope, respectively.
Results: The respective field of view is influenced by the resolution and screen scaling factor as well as the microscope and type of 20x objective. In digital microscopy, a larger field of view corresponds to a lower resolution and a higher screen scaling factor. This impacts in particular on the cell count of highly cellular tumours containing small cells. In urothelial cancers up to 50% differences in cell numbers per 20x visual field were obtained (100%; 1920 x 1080 or 2736 x 1824). In comparison to the rectangular computer screen, the microscope has circular field of view. This disparity influences the evaluation of lateral aspects of identical tissue areas.
Conclusion: This study emphasizes the need for standardization for light and digital microscopy. Variations in size and shape of the field of view can have an impact on the cell count and tissue evaluation and therefore can cause interobserver differences.

E-PS-14-002
Microorganisms in gastrointestinal lesions: educational and collaborative software
F. Mundim[1], J.B. Assis[1], A. Mendonca[1], J. Neto[1]
[1] UNIVAS, Brazil

Background & Objectives: The introduction of technological applications or collaborative software has become an important alternative in the search for knowledge optimization, offering high-resolution images through mobile devices with unlimited accessibility, but for diagnosis of gastrointestinal lesions, there is a technical difficulty to find image Bank. Objective: To construct, validate and register collaborative and educational software with images and texts referring to microorganisms of gastrointestinal lesions and that will be adapted for mobile devices.
Methods: Retrospective, observational, transversal, analytical, individual and uncontrolled study. For the construction of collaborative software, after eligibility criteria, 11 images from gastrointestinal biopsies reports of patients, provided by the Laboratory of Pathology of the Clinical Hospital Samuel Libânio, Pouso Alegre, Minas Gerais from 2007 to 2016 were used. Twenty (20) medical pathologists participated in the study, which evaluated as partially adequate, adequate and totally adequate.
Results: It was considered as partially adequate, adequate and totally adequate in the first validation. In the second validation, through the use of the Delphi technique, it was considered as appropriate and fully adequate. The questions used in the validation of the collaborative software contributed favorably to the internal consistency of the instrument and its validated content since the respective Cronbach alpha (α) was 0.8692 and the Global Content Validity Index (IVCg) was 0, 93 in the first validation and 0.94 in the second validation.
Conclusion: The collaborative software showed reliability and consistency for professionals in the Surgical Pathology practice, which made possible the construction of the MICROP application in the approach of microorganisms in gastrointestinal lesions.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-15 | Molecular Pathology

E-PS-15-001
Mycosis fungoides during imatinib mesylate treatment - true lymphoma or cutaneous drug reaction?
M. Jovanovic[1], M. Milinković Srećković[2], D. Milčić[2], S. Ćirović[3], M. Denčić Fekete[3], M. Nikolić[2], M. Bosić[1]
[1] Institute of Pathology, School of Medicine, University of Belgrade, Serbia, [2] Clinic for Dermatology and Venerology, Clinical Center of Serbia, [3] Laboratory for Molecular Pathology, Institute of Pathology, School of Medicine, University of Belgrade, Serbia

Background & Objectives: Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma characterised by clonal proliferation of lymphocytes with cytogenetic alterations (e.g. *TP53* or *CDKN2A* deletion and *c-MYC* translocation). Imatinib mesylate (IM) is a tyrosine kinase inhibitor used for the treatment of leukemia and gastrointestinal stromal tumour (GIST). Secondary solid or hematopoietic neoplasms have been described during or several years after IM treatment. IM treatment induced antinuclear antibodies and MF-like skin reactions were previously described but true MF has not been reported yet.
Methods: Histological, immunohistochemical, and genetic characteristics assessed by fluorescent in situ hybridization (FISH) were analysed in skin lesions.
Results: We present a case of a 51-year-old woman treated with IM due to GIST. Three months after the IM initiation non-pruritic erythematous scaly plaques appeared on face and trunk. Dominant histopathologic finding was epidermotropic infiltrate of atypical T-lymphocytes, mostly of CD4+ phenotype with partial loss of CD5, diffuse loss of CD7 and PD-1, Ki67 positivity in 10% of dermal T-lymphocytes. Deletion of *CDKN2A* was confirmed by FISH without concomitant *c-MYC* or *TP53* rearrangement. Altogether these findings suggested an MF development.
Conclusion: IM causes clonal proliferation of lymphocytes and secondary non-Hodgkin lymphomas. Loss of T-cell markers and aberrant molecular findings by FISH can be useful diagnostic tools differentiating true MF from drug-induced skin reactions after IM treatment.

E-PS-15-002
Dietary methyl donors can influence proliferation of human cell lines in vitro
E. Kiss[1], Z. Nemeth[1], M. Dank[1]
[1] Cancer Centre, Semmelweis University, Budapest, Hungary

Background & Objectives: DNA methylation has role in gene expression, cell proliferation or maintenance of DNA integrity. Nutrition is an important factor, which considerably influences the development and progression of cancer. Dietary methyl donors are food components, which provide methyl groups for the one-carbon metabolism supporting methylation processes. Our aim was to examine the effect of dietary methyl donors on cell proliferation on different human cancer cell lines to investigate whether could be used as a potential complementary therapy in cancer treatment.
Methods: Panc-1 and MCF7 cell lines were grown in 96 well plates and treated with different concentrations (1x, 10x, 20x) of methyl donors. Basal concentration (1x) was: 17 mg/L L-methionine, 9 mg/L choline chloride, 3 mg/L folic acid and 2 mg/L vitamin B12. Cell proliferation was measured by absorbance at 490nm after 24, 48 and 72 hours using MTS cell proliferation assay. Two-way Anova and Bonferroni posthoc test was used to compare the absorbance of the treatment groups to the controls.
Results: Methyl donor treatments caused reduction in the absorbances in both observed cell lines. Basal and twenty times higher concentrations caused significant, dose-dependent decrease in the proliferation of Panc-1 cells ($p \leq 0.05$ and $p \leq 0.01$, respectively) at 48 hours treatment, compared to the control. In case of MCF7 cells, treatments caused dose-dependent decrease in the proliferation after 48 and 72 hours ($p \leq 0.01$ and $p < 0.001$, respectively).
Conclusion: Our results indicate that methyl donor supplementation induces significant decrease in cell proliferation of Panc-1 and MCF7

tumour cells as well. Our results suggest that an appropriate dietary guidance might be an effective complementary treatment for cancer patients but need further, and more detailed investigation.

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E-PS-15-003

A case of large B-cell lymphoma with IRF4 rearrangement in inguinal lymph nodes

C. Masaoutis[1], P. Lampropoulou[2], D. Rontogianni[3]
[1] Evaggelismos General Hospital of Athens, Greece, [2] Metaxa Hospital, Greece, [3] Department of Pathology, Evaggelismos Hospital, Athens, Greece

Background & Objectives: A 21-year-old male presented with isolated bulky left inguinal and iliac lymphadenopathy and massive ipsilateral leg oedema, gradually established over the course of 7 months, without B-symptoms, lymphocytosis or organomegaly. Incisional lymph node biopsy was performed.
Methods: Light microscopy, immunohistochemistry and fluorescent in situ hybridization (FISH).
Results: The biopsy revealed a diffuse, monotonous, medium-sized cell population with a small to moderate amount of cytoplasm and homogeneous chromatin with only occasional, inconspicuous nucleoli. No starry sky pattern was appreciated. The immunophenotype was: CD20[+], CD10[-], BCL6[+], MUM1/IRF4[+] uniformly, c-MYC[+] ~50%, BCL2[-] <25%, CD5[-], CD23[-], cyclin-D1[-], CD30[-] with a Ki67 index >95%. FISH with break-apart probes revealed a translocation involving the DUSP22/IRF4 locus and was negative for c-MYC, BCL2 or BCL6 rearrangements. The patient responded favourably to treatment with CHOP.
Conclusion: The large B-cell lymphoma with IRF4 rearrangement is an uncommon lymphoma, typically affecting the head and neck lymph nodes, the Waldeyer ring or the intestine of children and young adults. The unusual location, as in this case, reported only once until now, should not deter from testing for IRF4 rearrangements, especially in young patients with suggestive morphological and immunophenotypical findings.

E-PS-15-005

Case presentation: sarcomatoid renal cell carcinoma with MDM2 amplification

T. Čugura[1], J. Jeruc[1]
[1] Institute of Pathology, Ljubljana, Slovenia

Background & Objectives: A 66-yeard old male underwent abdominal surgery due to a large retroperitoneal tumour causing accute ileus. An intraoperative frozen section of the tumour infiltrating intestinal wall showed pleomorphic spindle and epithelioid cells with high mitotic rates and areas of necrosis. The preliminary diagnosis of a malignant tumour, suspicious of a high-grade sarcoma, was made. The resected specimen revealed a tumour measuring 23 x 18 cm, infiltrating the descending colon, spleen, pancreas and extending into the hilum of the left kidney.
Methods: Considering location, clinical setting and morphology, analysis of MDM2 amplification by DNA fluorescence in situ hybridization (FISH) was performed. Immunohistochemical staining for cytokeratin AE1/AE3 (CKAE1/AE3), racemase, CD10 was performed.
Results: The specimen was extensively sampled: most of the sections showed similar morphology as the frozen section with tumour cells focally positive for CKAE1/AE3, racemase and CD10. A minor part of the tumour adjecent to the hilar kidney area showed papillary architecture morphologically and immunohistochemically consistent with papillary renal cell carcinoma (RCC). FISH analysis showed MDM2 gene amplification. A final diagnosis of sarcomatoid papillary RCC with sarcomatoid component showing MDM2 amplification was made.
Conclusion: RCC with sarcomatoid dedifferentiation is a relatively rare but agressive form of RCC, occuring in 5% of all RCC cases.The sarcomatous areas in RCC may, in addition to a non-specific spindle cell morphology, show more specialized lines of differentiation such as osteosarcomatous or leiomyomatous.

E-PS-15-008

Molecular classification of bladder tumours: about 40 cases and literature review

A. Douida[1]
[1] Department of Pathology, Hassan II University Hospital, Fez, Morocco

Background & Objectives: Molecular heterogeneity is a characteristic feature of all human cancers. In this study, we established the molecular subtype of urothelial bladder cancers and we correlated these molecular subtypes with WHO grade, TNM classification and the clinical evolution.
Methods: We retrospectively reviewed the data of 40 patients who were diagnosed with bladder cancer in the departments of urology and pathology at the Hassan II university hospital center, over a period of 6 years (2013-2018). We recorded patients' age and sexe, the type of sample, the degree of atypia, grade and TNM stage at diagnosis. An immunohistochemical study was carried out by the antibodies against CK5/6, CD44, CK20 and P53.
Results: The mean age was 60 years (42-82).The sex ratio=5.6. Transurethral resections of the bladder were performed in 85% of cases. The diagnosis was made on an operative specimen in 15% of cases. Atypia was minimal in 25% of cases, moderate in 22.5% and severe in 52.5% of cases. A molecular classification was performed for the 40 cases. 52.5% were classified as basal, 32.5% as luminal and 15% were not classified (10% triple negatives and 5% triple positives). Basal tumours were more common in women, and were clinically aggressive, characterised by advanced stage (42.8% were classified in T2 at the time of diagnosis) and metastatic disease at presentation (62,5% of cases).
Conclusion: The bladder cancer molecular subtypes were associated with different prognoses and targeted therapies. If validated in prospective studies, molecular subtyping will be integrated into bladder cancer clinical management.

E-PS-15-009

"Fishing" ALK in urinary bladder: report of two cases of inflammatory myofibroblastic tumour

I. Filipovic[1], J. Filipovic[1], M. Zivotic[1], S. Radojevic-Skodric[1], S. Cirovic[1], M. Bosic[1], J. Markovic-Lipkovski[1]
[1] Institute of Pathology, Faculty of Medicine, University of Belgrade, Serbia

Background & Objectives: Inflammatory myofibroblastic tumour (IMT) is an intermediate, rarely metastasizing neoplasm of urinary bladder, consisting predominantly of myofibroblastic spindle cells and inflammatory cells. Anaplastic lymphoma kinase (ALK) 1 immunopositivity is required for the differentiation of IMT from other aggressive spindle cell tumours. In addition, fluorescence in situ hybridization (FISH) is usually used as a confirmation of the diagnosis.
Methods: We evaluated morphology, immunohistochemical (IHC) profile and FISH of urinary bladder tumour samples, obtained from two male patients. The following antibodies were used: vimentin, CK (AE1/AE3), ALK-1, p16, p53, KI67, HHF35, alfa-SMA, HMWCK, p63, CD34, GATA3, desmin, myogenin, and S100. Additionally, ALK gene rearrangement was determined by FISH analysis.
Results: In both cases, the histopathological examination revealed similar morphology. Lamina propria and the muscle were infiltrated by spindle and polygonal cells arranged in fascicles, accompanied by an inflammatory infiltrate consisted of plasma cells, lymphocytes, neutrophils, and eosinophils, with prominent blood

vessels in the edematous stroma. IHC showed positive staining to vimentin, CK (AE1/AE3), ALK-1, p16, p53, KI67, HHF35, and alpha-SMA, while HMW-CK, p63, CD34, GATA3, desmin, myogenin, and S100 were negative in both cases. However, the FISH analysis revealed 20% of cells with ALK gene rearrangement in one case, while the other showed an absence of this mutation.
Conclusion: FISH analysis of ALK gene rearrangement in IMTs of the urinary bladder may be variable. Performing FISH alone might fail to provide reliable diagnosis. Therefore, when ALK-1 immunostain is positive, but FISH fails to confirm ALK gene rearrangement, the diagnosis of IMT may still be made by an exclusion of other spindle cell neoplasms.

E-PS-15-010
Microsatellite instability evaluation in colorectal cancer cases
Z. Mikola[1], Z. Szollosi[1], N. Konyhas[1]
[1] BAZ County Hospital, Hungary

Background & Objectives: Current clinical reference methods for evaluating microsatellite instability are immunohistochemical staining of mismatch repair proteins and/or PCR analysis of frequently mutated repetitive regions of DNA. The fully automated Idylla MSI Assay performs the detection of microsatellite instability directly from FFPE human cancer tissue sections utilizing a PCR reaction followed by high-resolution melting curve analysis. The main objective of the study was to compare the reliability of these two methods.
Methods: To assess the suitability of the novel marker set to detect MSI status in colorectal cancer cases, we retrospectively evaluated MSI status in 20 colorectal cancer FFPE samples This sample set included a 50/50 ratio of MSI versus MSS samples evaluated by immunohistochemical markers for mismatch repair genes MLH2, MSH2, MSH6, PMS2.
Results: Testing the 10 microsatellite stable cases on the Idylla MSI Assay, it detected no mutation in the 7 novel biomarkers, confirming the MSS status. On the contrary, the 10 samples which displayed mismatch repair gene loss by immunohistochemical markers, the Idylla MSI Assay detected microsatellite instability (MSI-H) in five cases.
Conclusion: The IdyllaMSI Assay provides a much more reliable method than the immunohistochemical markers for mismatch repair genes in order to evaluate MSI-H vs MSS status, the latter demonstrating 100% sensitivity but only 75% specificity.
This study on a diverse set of colorectal samples successfully demonstrated the validity of the novel MSI biomarkers to discriminate between MSI-H and MSS status.

E-PS-15-011
InflammAging: SASP as molecular landscape of cell senescence
V. Rodichkina[1], I. Kvetnoy[1], V. Polyakova[1]
[1] Otts Institute of Obstetrics, Russia

Background & Objectives: Aging at the cellular and organ levels negatively affects reproductive function. It is proved that immune cells play a crucial role in the physiology of the reproductive system. Inflamaging - associated with aging, chronic and systemic inflammatory condition caused by cells acquired SASP phenotype (senescence associated secretory phenotype). In current study we reviewed biomolecules characterizing the SASP phenotype (Lamin B1, CDKN1A) and supposed new related markers (SIRT-1, SIRT-6, p53 and ki-67). Endometrial material in patients without endometrial pathology (n = 15) was obtained by carrying out a pipe biopsy to create cell cultures. All patients were of reproductive age (23-45 years) and had normal menstrual cycles. The patients did not receive hormone therapy (neither GnRH analogues nor danazol or COCP).
Methods: Endometrial cells were fixed and examined at 3 and 14 passages. Primary monoclonal antibodies to Lamin B1, CDKN1A, β-galactosidase, ki-67, p53, SIRT-1, SIRT-6 were used for ICC reaction. Alexa Fluor 488 and Alexa Fluor 647 (1:1000, Abcam, UK) were taken as secondary antibodies. Scanning of samples was performed on a microscope FluoView1000 (Olympus, Japan).
Results: All investigated markers were detected in endometrial culture in all age groups. The lowest level of the relative expression area of p53 (5,9%) was registered in the cells of 25-30 age group at 3 passage, while the value of relative expression area of ki-67 was the highest (15.89%). Statistically significant increase in the relative area of immunopositive staining depending on the age, was observed in the analysis of the relative expression area of SIRT-1 ($r=0.92$, $p<0.01$) and SIRT-6 ($r=0.99$, $p<0.01$). The minimum level of the expression of SIRT-1 (5.25%) and SIRT-6 (6.33%) was observed at 14 passage of group 35-45 years, the maximum - at 3 passage in all studied groups.
Conclusion: The data on the change in the expression of the molecules characterizing the SASP phenotype were confirmed with increasing age of the patients, and a number of molecules were also identified that item showed a change in expression in the SASP type cells. We propose the use of new biomarkers that are capable of assessing biological versus chronological age and status of female reproductive system.

E-PS-15-012
Small nuclear RNA (RNU6-1) is a novel susceptibility gene for diffuse large B cell lymphoma in Arab descent population: a case-control study
S. Al-Khatib[1], N. Abdo[1], L. Al-Eitan[1], D. Zahran[1]
[1] Jordan University of Science and Technology (JUST), Jordan

Background & Objectives: In addition to messenger RNAs, transfer RNAs, and ribosomal RNAs, a group of regulatory RNAs are identified. Those regulatory RNAs are non-coding and form the vast majority of the human genome. Regulatory RNAs sequence is highly preserved found in both bacteria where they termed as small RNA and in eukaryotic cells where they known as non-coding (nc) RNAs which includes small nuclear ribonucleic acid (snRNA) and small nucleolar RNA (snoRNA). The (nc) RNAs or microRNAs found within the splicing regions. They encode no proteins and their primary function is in the processing of pre-messenger RNA in the nucleus by serving as a catalytic center within the splicesome. The length of an average snRNA is approximately 150 nucleotides. They are transcribed by either RNA polymerase II or RNA polymerase III. ncRNAs form complexes with one of the ribonucleoproteins (snRNP) associated proteins. Among the most common snRNA in those complexes are U1, U2, U4, U5, and U6 splicesomal RNAs. Named according to their Uridine content. The U6 snRNA or RNU6-1 is nuclear based belongs to Lsm-class of snRNA that transcribed by RNA polymerase III and forms the non-coding small nuclear RNA (snRNA) component of U6 snRNP. U6 snRNA through its combination with snRNP and U4snRNA forms a large RNA-protein molecular complex or splicesome, responsible for post-transcriptional modification of pre-mRNA. A step took place in the nucleus by excision of the introns from pre-mRNA. The importance U6 snRNA is emphasized by the presence of many back-up copies of the gene and the highly conserved sequence of U6 snRNA across species. The aim of this study is to analyse the relationship between RNU6-1 single nucleotide polymorphism (SNP) rs 6457327 and the overall risk and prognosis of DLBCL cases in Jordanian Arab population.
Methods: The study population composed of 125 patients whom diagnosed with DLBCL at KAUH from the period of 2013 to 2018 and 235 healthy cancer-free control subjects with similar geographic and ethnic background to patients. All cases of DLBCL has been diagnosed independently by a hematopathologist according to the 2008 WHO classification of tumours of haematopoietic and lymphoid tissues.

DNA extraction: Genomic DNA was extracted for the DLBCL patients from formalin-fixed and paraffin-embedded (FFPE) tissue using commercially available kit, DNeasy Blood & Tissue Kit (Qiagen Ltd., West Sussex, UK), using the manufacturer's protocols. Genomic DNA from control-subjects blood samples was extracted using the QIAamp® or Promega DNA Mini Kit according to the manufacture's instruction. The quality of extracted DNA was examined by agarose gel electrophoresis and ethidium bromide staining. The concentration and purity of extracted DNA was assessed by using NanoDrop 1000® spectrophotometer. The selected polymorphisms were analysed within candidate genes using Sequencing technique (Sequenom® iPLEX assay). RNA extraction and real-time quantitative PCR: Total RNA was isolated with TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. The reverse transcription was performed using Transcriptor First Strand cDNA Synthesis Kit (Roche, Indianapolis, IN). Real-time PCR was performed with SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA) on a Bio-Rad CFX96 real-time PCR system. The RT-PCR conditions were as follows: sufficient denaturing at 95°C for 50 seconds, denaturing at 94°C for 50 seconds, annealing at 55°C for 50 seconds, elongation at 72°C for 50 seconds (30 cycles) and a final cycle at 72°C for 10 minutes. β-actin served as the internal positive control. The RT-PCR products were examined by gel electrophoresis. Statistical analysis: All Overall survival (OS) was calculated from the date of diagnosis to the date of death or last visit for those who were alive at the time of final data collection and analysis. All statistical analyses were performed using IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). The clinical characteristics and response rate of the patients were compared using Chi square tests. Hardy–Weinberg equilibrium Test was estimated by a goodness-of-fit $\chi 2$ test. The Kaplan–Meier method was used to construct survival curves, and results were compared using a log-rank test. The association between polymorphism and the risk for DLBCL was calculated by unconditional logistic regression. The survival curves were displayed using GraphPad Prism 6 software. All significant variables (

Results: In this study, 125 DLBCL patients and 238 ethnically and geographically matched healthy controls were enrolled. Of the patients, 52.8% were males and 47.2% were females with mean age of 53.7 years (17 – 89). The mean age for the controls was 43.2 years (6-89) and 38.7% were males. Our study showed that the frequency of C and A alleles of the RNU6-1 SNP 6457327 among patients were 84% and 16%, respectively. additionally, an increased risk of DLBCL associated with RNU6-1 rs6457327 C>A in the co-dominant, dominant, and recessive models [odds ratio 2.04, 1.62, and 2.11, respectively; 95% confidence interval (CI) 1.14-3.64, 0.96-2.73, and 1.18-3.74, respectively; p value=0.021, 0.067; and 0.0088, respectively]. Kaplan-Meier survival analyses showed no statistically significant results.

Conclusion: This study is the first to reveal the relationship between RNU6-1 rs6457327 gene polymorphism and DLBCL patients, indicating that RNU6-1 may serve as a novel susceptibility gene for DLBCL patients in Jordanian Arab descent population.

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E-PS-15-013

Erdheim-Chester BRAF mutation in liquid biopsy - two case reports

L. Carvalho[1], A. Alarcão[1,2,3], A.F. Ladeirinha[1,2], M. Reis Silva[1,2,3], T. Ferreira[1,2], A.I. Rodrigues[1], E. Gaspar[4], A. Aparício Martins[4], V. Sousa[1]
[1] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, [2] CIMAGO - Research Center for Environment, Genetics and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [3] Centre of Pulmonology, Faculty of Medicine of the University of Coimbra, Portugal, [4] Internal Medicine, University Hospital Coimbra, Portugal

Background & Objectives: Erdheim-Chester disease (ECD), a rare inflammatory disorder with broad non-specific clinical spectrum, is characterised by infiltration of organs by CD68+ and S100– cells. Commonly affects bones, kidneys, retroperitoneal space, skin and brain. If untreated, progresses rapidly being causing fatal. Although a rare disease, the number of new cases is increasing and 53 years is median age at diagnosis without gender influence.
BRAF (V600E) mutation has become a parameter concurrent for the diagnosis.
Methods: Case report 1: bone biopsy of 68-years-old female with PET positive images scattered over large bones, Planar xanthomas were reported in clinical registry. Bone biopsy revealed CD68+ and S100– cells.Case report 2: pericardial surgical biopsy of a 70-years-old female with PET positive revealing multisystemic images understood as inflammatory process with pancreatic, vascular and renal involvement. Positive CD68 and negative S100 cells were identified supporting the diagnosis.
Results: In both cases due to non-solving clinical status with common treatment, liquid biopsies were performed on *Idylla™ ctBRAF Mutation Assay* for *BRAF* codon 600 mutations. *BRAF* codon 600 mutation was observed and allowed vemurafenib prescription.
Conclusion: Molecular analysis of ECD samples has demonstrated the prevalence of *BRAF* (V600E) mutation in more than 50% the cases, and opened a new area for treatment options with promising results.
Two more cases of liquid biopsies of two female of ECD cases, with CD68+, S100– cells, allowed identification of *BRAF* codon 600 mutations, enlarging the therapeutic possibility, beyond the concurrence for the diagnosis.

E-PS-15-014

EGFR mutation analysis in lung adenocarcinoma in cerebrospinal fluid and peripheral blood: a case presentation

O. Hurdogan[1], M. Sari[2], D. Yilmazbayhan[1], Y. Ozluk[1]
[1] Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Turkey, [2] Istanbul University, Oncology Institute, Division of Medical Oncology, Turkey

Background & Objectives: This case has been accepted for presentation at Molecular Pathology and Trainees SS session. We present a demonstrative case representing the use of molecular pathology in precision medicine.
Methods: EGFR mutation testing was performed with Cobas® EGFR Mutation Test v2.
Results: A 57-year-old female presented with a metastatic lung tumour. Transthoracic needle biopsy showed adenocarcinoma. Mutation analyses for EGFR were reported to be wild-type. After six-cycle course of chemotherapy her metastases regressed. Two months later masses in the lung and brain progressed. Liver metastases reoccurred after four months and a liver biopsy was performed to repeat EGFR mutation analysis. EGFR p.L858R mutation was detected and patient received EGFR tyrosine kinase inhibitor (TKI) therapy. After one year of uneventful follow-up, newly-developed brain metastases were detected. Cerebrospinal fluid (CSF) cytology revealed metastatic carcinoma. Synchronous plasma was also obtained for a paired EGFR mutation analysis. EGFR p.L858R mutation was detected in CSF puncture, whereas cfDNA from the plasma was positive for p.T790M mutation. The treatment was switched to a third generation EGFR TKI. The brain metastases showed complete response and CSF puncture proved to become negative at 5 months.
Conclusion: We think, this case poses a good example for the feasibility of small amounts of cytological samples in mutation analyses and guidance of treatment. This case also shows how EGFR mutation status may differ in synchronous plasma and CSF samples and emphasizes the complementarity of both techniques.

E-PS-15-016

Cell stress and apoptosis associated biomarker expression correlates with triple-negative breast cancer prognosis

Á. Nagy[1], T. Krenacs[1]
[1] 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Hungary

Background & Objectives: Breast cancer, including its triple negative subtype (TNBC) is heterogeneous. TNBC shows the worse outcome despite novel treatment options. Here, we studied the prognostic relevance of cell stress and apoptosis related biomarker expression for revealing clinically relevant subgroups within TNBC.
Methods: 59 primary cases of CK5 positive (basal-like) TNBC were immunostained for cell stress (hsp70, calreticulin, HMGB1) and apoptosis (p53, AIF1, bcl-2, cytochrome C, cleaved-caspase-3 and caspase-8) related biomarkers in tissue microarrays and marker expression was correlated with disease outcome. Survival analysis was also performed *in silico* based on Affimetrix mRNA expression databases mined with the KM-potter (http://kmplot.com) software.
Results: In TNBC, *in silico* mRNA data allowed to correlate biomarker levels with recurrence-free survival (RFS), while *in situ* protein data could be linked to OS (overall survival) and PFS (progression-free survival). Cleaved-caspase-3 and caspase-8, and AIF1 levels showed positive correlation with RFS, OS and PFS at mRNA and protein level. Calreticulin, bcl2 and HMGB1 mRNA expression significantly correlated with OS, but did not reach significance at protein level, while hsp70 protein (but not mRNA) production was inversely associated with OS and PFS. Spearman-rank analysis showed significant positive correlations of cleaved/activated caspase-3 expression with those of cleaved-caspase-8, cytochrome C, AIF1 and calreticulin.
Conclusion: Our results suggest that potential activation of the endoplasmic reticulum stress, as well as the extrinsic and intrinsic caspase-dependent apoptosis, and the AIF1 mediated caspase-independent cell death pathways may reflect a better disease outcome in TNBC.

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E-PS-15-017

Next generation sequencing in TRK/ROS1/ALK and other rare genes fusions detection - a single institution experience from clinical trail

A. Tysarowski[1], K. Seliga[2], M. Wagrodzki[3], A. Szumera-Cieckiewicz[1], A. Gos[2], R. Zub[2], M. Kotarska-Puerto[4], M. Krzakowski[5], J.A. Siedlecki[2], M. Prochorec-Sobieszek[3]
[1] Department of Pathology and Laboratory Medicine, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Warsaw, Poland, [2] Molecular And Translational Oncology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [3] Department of Pathology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [4] Ignyta, Inc., San Diego, CA, USA, Poland, [5] 3Department of Lung Cancer and Chest Tumour, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Background & Objectives: Patients with solid tumours harboring *TRK/ROS1/ALK* or other rare gene fusions account for <3% of cancer population; however, those fusions have been seen in over 40 different tumour types, including gastrointestinal, lung, head & neck, and sarcoma. Phase 1 studies of entrectinib reported a 79% Overall Rate of Response across multiple histology types in patients with gene fusions who were naive to inhibitors of these targets, received an efficacious dose, and had extracranial disease. A potentially registration-enabling Phase 2 global basket trial (The STARTRK-2:Studies of Tumor Alterations Responsive to Targeting Receptor Kinases) of the investigational tyrosine kinase inhibitor compound entrectinib in patients with solid tumours harboring *TRK/ROS1/ALK* gene fusions was initiated. The aim of the study was to identify the *TRK, ROS1, ALK* other rare gene fusions in patients treated in single institution.
Methods: FFPE and cytological specimens from 1121 patients were enrolled to the study. For FFPE samples 2-step diagnostic test was performed: (I) the IHC screening using a pan-receptor tyrosine kinase cocktail of antibodies targeting *TRK/ROS1/ALK* proteins, (II) an RNA-based anchored multiplex-PCR next generation sequencing (NGS) assay in IHC positive specimens. In case of cytological specimens and FFPE samples with limited tissue, IHC was omitted and NGS was performed directly.
Results: The 480/1121 specimens were positive after IHC. In 34 (3%) samples gene fusions were detected and characterised.
Conclusion: The two-step IHC/NGS testing approach is an effective strategy to identify patient populations with gene fusions, enabling discrimination of active fusions and identification of novel ones.

E-PS-15-018

Expression analysis of HH network in histological subtypes of germ cell tumours in children

E. Iżycka-Świeszewska[1], D. Kuleszo[1], B. Lipska-Zietkiewicz[1], K. Czarnota[1], W. Grajkowska[2], G. Drabik[3], J. Stefanowicz[1], E. Drozynska[1]
[1] Medical University of Gdansk, Poland, [2] Institute Memorial Childs Health Center Warsaw, Poland, [3] Iagiellonian University Krakow, CM, Poland

Background & Objectives: Germ cell tumours (GCTs) are a group of neoplasms with different levels and directions of differentiation. Several signaling pathways participate in migration and specification of germ cell line in embryogenesis, including Sonic Hedgehog (SHH) pathway. The abnormal function of this signaling is observed in many type of cancer- gastric, lung, breast, pancreatic, prostate, and medulloblastoma. The role of SHH signaling in GCTs has not been analysed in detail.
Methods: 30 cases of tumours of different histological categories of paediatric GCTs (*mature teratoma, immature teratoma, mixed GCT, yolk sac tumour, dysgerminoma/seminoma, embryonal carcinoma)* and control tissues were studied for expression of SHH pathway related genes. Paraffin-embedded tissue sections underwent DNA and RNA isolation. Expression analysis was performed with 3 repeats qPCR in each case with Quiagen kits (Hedgehog Signaling Pathway RT^2 Profiler PCR Array) including 84 genes engaged in SHH signal transduction. The next step was analysis with dedicated software Geneglobe (Qiagen).
Results: The significant differences in expression between control and tumour samples were observed concerning some key genes: *SMO, GLI1, HHIP, GLI3.* In addition, *PTCHD1, ERBB4, FGFR3, WNT3, FGF9*, *ZIC1, ZIC2, LRP2,* and *WIF1* were overexpressed in different tumours. Some significant differences in expression between various GCTs histological categories were also found.
Conclusion: Performed analysis showed that some SHH pathway- related proteins are involved in GCTs biology in context of level and direction of differentiation. Expression of some related genes is lowered than in normal tissue.
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E-PS-15-019

A rapid and customisable NGS library preparation for down to 0.1% allele frequency mutation detection

F. Hernandez-Guzman[1], X. Peng[1], G. Luo[1], K. Park[1], A. Kraltcheva[1], B. Ding[1], A. Hatch[1], Y. Fu[1], V. Mozhayskiy[1], C. Van Loy[1], J. Kilzer[1], M. Andersen[1]
[1] Thermo Fisher Scientific, USA

Background & Objectives: Multiple research applications require high sensitivity for mutation detection which is beyond the error rate of commonly available Next Generation Sequencing (NGS) platforms. For example, "liquid biopsy", which scans blood samples for low frequency tumour derived DNA, has been described as a promising early cancer detection tool with the potential for improved survival rates for various cancers such as colon, breast and skin.
Methods: Our recently launched Ion AmpliSeq™ HD technology enables down to 0.1% Limit of Detection (LOD) from cell free DNA (cfDNA). In combination with Ion AmpliSeq™ HD Library Kit, custom Ion AmpliSeq™ HD panels and Ion GeneStudio™ S5 sequencing system, Ion AmpliSeq HD technology enables detection of low level variants from various sample types. The libraries can be prepared in as little as 3 hours. Control DNA and RNA samples were used for evaluation with 20 ng input.
Results: An Ion AmpliSeq Oncology Panel and the equivalent Ion AmpliSeq HD panel were evaluated using control DNA with known variants present at 5%, 1%, 0.5% and 0.1% frequencies. Both Ion AmpliSeq and Ion AmpliSeq HD panels performed well with the higher (5%) variant frequency samples. Only Ion AmpliSeq HD retained the high sensitivity and specificity for low frequency variant calls. Additionally, we have successfully detected copy number variation and fusions.
Conclusion: Ion AmpliSeq™ HD technology combined with analysis with Ion GeneStudio™ S5 system enables fast detection of low-level variants from liquid biopsy and other samples with 0.1% limit of detection.

E-PS-15-020
Development of an NGS solution for targeted and immune checkpoint therapies
V. Mittal[1], S. El-Difrawy[1], D. Cyanam[1], P. Williams[1], N. Khazanov[1], E. Wong-Ho[1], C. Van Loy[1], S. Sadis[1]
[1] Thermo Fisher Scientific, USA

Background & Objectives: Next-generation sequencing (NGS) is used to support routine clinical research in oncology. However, the advent of cancer immunotherapies requires that clinical research solutions must also address biomarkers for immune checkpoint inhibitors including tumour mutational burden (TMB) and microsatellite instability (MSI). Therefore, we developed an NGS solution appropriate for FFPE tissues that addresses biomarkers for targeted and immune checkpoint therapies.
Methods: Gene content was selected based on prioritization of actionability and variant prevalence of biomarkers in solid tumours. The assay uses Ion AmpliSeq™ technology with manual or automated library preparation, automated templating on the Ion Chef™, and sequencing on the Ion Torrent GeneStudio™ S5 sequencing platform. An automated variant calling workflow is provided within Ion Reporter. Streamlined access to clinical decision support software is enabled by Oncomine Reporter.
Results: Over 400 genes with known DNA based alterations and over 50 RNA fusion drivers are included. A coding sequence footprint to support TMB was generated and microsatellite regions are included to support MSI. In preliminary development studies, the assay displayed good uniformity and consistent read depth to support robust variant calling. In-silico assessment of TMB using publicly available whole-exome cancer sequencing data resulted in high correlation ($R^2 > 0.90$, 0-40 mut/mb). MSI detection was concordant with results from on-market MSI assays.
Conclusion: A comprehensive NGS assay was developed to support routine clinical research in oncology that includes endpoints for TMB and MSI. More detailed information on the assay and an update on performance will be presented.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-16 | Nephropathology

E-PS-16-001
IgA nephropathy with Human-Deficiency-Virus (HIV) infection: case reports with immunohistological study
M. Otani[1], T. Tsuji[2], K. Ono[3], N. Uesugi[4], N. Kato[5], T. Inoue[5], E. Ashikaga[5], S. Iwasaki[5]
[1] Division of Diagnostic Pathology, Yokohama City University Medical Center, Japan, [2] Department of Pathology, Sapporo City Hospital, Japan, [3] Department of Pathology, Yokohama Municipal Citizen's Hospital, Japan, [4] Department of Pathology, Fukuoka University Faculty of Medicine, Japan, [5] Department of Nephrology, Yokohama Municipal Citizen's Hospital, Japan

Background & Objectives: Renal diseases associated with HIV infection include acute renal failure, chronic kidney disease, and renal side effects of therapy. IgA nephropathy occurs as one of the HIV-associated immune-mediated glomerulopathies. We encountered two cases of IgA nephropathy in patients with HIV infection, and examined their renal biopsy specimens for the presence of HIV and property of IgA in the immune-complexes (ICs).
Methods: The first case is a 51-year-old man with HIV infection who had been under anti-HIV therapy for 20 years. Proteinuria was first noted 10 years after the initial HIV infection. Gradually, the urinary protein excretion increased up to 3+, with occult urinary blood. The second case is a 25-year-old man, who was detected to have urinary protein and blood at the diagnosis of HIV infection. The serum level of IgA was increased.
Results: Renal biopsy was done in both cases. The first case revealed mesangial cell hypercellularity and prominent infiltration of lymphocytes in glomeruli. IgA, IgG and C3 were positive. Paramesangial and subendothelial electron-dense deposits (EDD) were noted. The second case showed mild mesangial hypercellularity. IgA, IgG, IgM was positve, and paramesanbial EDDs were identified. Immunohistologically, the staining for galactose-deficient (Gd)- IgA1 was positive, but, HIV protein antibodies were not detected in both cases.
Conclusion: In Japan, IgA nephropathy is most common in patients with HIV infection. It has been reported that the ICs contain HIV-specific IgA antibody and HIV protein antigen. However, we could not find HIV protein antibodies in both cases. They were almost the same as common IgA nephropathy, even if the disease was caused by HIV infection.

E-PS-16-002
Lyme-associated membranous nephropathy. A case report and review of literature
M. Wagrowska-Danilewicz[1], Z. Zbrog[2], M. Bonczysta[3], O. Stasikowska-Kanicka[1], M. Danilewicz[3]
[1] Nephropathology Department, Medical University of Lodz, Poland, [2] Mikolaj Copernik Hospital in Lodz, Poland, [3] Pathology Department, Medical University of Lodz, Poland

Background & Objectives: In approximately 20% of cases in adults, membranous nephropathy is secondary to various disorders, including infection, systemic disease, drugs, and malignancy. Lyme disease is a chronic, multi-systemic, inflammatory disorder of humans and animals associated with infection by the tick-borne spirochaete, *Borrelia burgdorferi.* Kidneys are not typically involved in the disease. The literature is scant regarding renal involvement of Lyme disease in humans.
Methods: We present a 40 years-old-male with a past medical history of arthritis developing after a tick bite. He did not get early treatment. On the basis of clinical manifestation and serological tests a late stage of Lyme disease was diagnosed. Since January 2018 the patient received doxycycline, rovamycine and tynidazole. Since September 2018 he observed a crural oedema. Finally,

patient was admitted to Nephrology Department with massive crural oedema and nephrotic syndrome without renal insufficiency. Kidney biopsy was preformed
Results: Light microscopy, immunofluorescence study and electron microscopy examination revealed membranous glomerulonephritis.
Conclusion: In conclusion, this case indicates that secondary causes of membranous glomerulonephritis include infection of Borrelia burgdorferi. This association presumably results from immune complex injury to the glomeruli caused by bacterial antigens.

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E-PS-16-003
Primer Hyperoxaluria in a 4 month boy: a case report
S. Aydin Mungan[1], E.B. Ozdogan[2], A. Ahmetoglu[3], E. Cakir[1], T. Bulduk[4]
[1] Karadeniz Technical University, School of Medicine Pathology Department, Turkey, [2] Karadeniz Technical University, School of Medicine, Department of Paediatric Nephrology, Turkey, [3] Karadeniz Technical University, School of Medicine, Radiology Department, Turkey, [4] Karadeniz Technical University, School of Medicine, Pediatry Department, Turkey

Background & Objectives: Primary hyperoxcaluria (PH) is caused by a deficiency of the liver peroxisomal enzyme alanine: glyoxylate-aminotransferase (AGT), which catalyzes glyoxylate to glycine. When AGT activity is absent, glyoxylate is converted to oxalate that accumulate in the kidney and other organs. People with PH are at risk for recurrent nephrolithiasis, nephrocalcinosis, end stage renal disease. We report a 4 month old boy with hyperoxaluria who was brought to the pediatry clinic with diarrhea. He also had high levels of creatinin (2,5 mg/dl).
Methods: Renal biopsy was performed bacause of high levels of creatinin and suspicious radiological findings. Rutin sections were evaluated by H&E, histochemical reactions and polarised light microscopy.
Results: Renal biopsy had 12 glomeruli, and their morphological findings were consonant with the patient's age. In the interstisium almost all tubulary lumens were filled with a light-grayish material. This material had birefrigence under polarised light microscope but could not be seen with light microscope. These materials called oxalate crystals. Radiological and clinical findings also supported the diagnosis of renal oxalosis or hyperoxaluria.
Conclusion: Oxalate occurs as end product of metabolism and is easily eliminated in the stool or urine. However, under specific circumstances, excessive buildup of crystal deposits in the kidneys causes loss of renal function. It is important to consider hyperoxaluria in patient who presents with unexplained material deposition in the tubular lumens, because oxalate crystals might be missed under light microscope.

E-PS-16-004
A case report of collagenofibrotic glomerulopathy with a "full house" pattern of immunohistochemistry staining.
Z. Abdawn[1], O. Cain[2], E. Curtis[1]
[1] University Hospitals Birmingham NHS Foundation Trust, United Kingdom, [2] University Hospitals of Birmingham NHS Foundation Trust, Cellular Pathology, Queen Elizabeth Hospital, United Kingdom

Background & Objectives: Collagenofibrotic glomerulopathy is a rare renal disease which is characterised by accumulation of type III collagen in the glomerular mesangial and subendothelial areas. Stains for immunoglobulins and compliments are usually negative. Here, we report a case of collagenofibrotic glomerulopathy with a "full-house" pattern of immunohistochemistry.
Methods: Clinical case review and review of the topic in published clinical literature.
Results: We Present a case of a 42-year-old female who presented with nephrotic-range proteinuria and preserved renal function. Immunology screen was negative. Renal biopsy showed evidence of a membranoproliferative glomerulonephritis with mesangial matrix expansion and double contours formation. Immunohistochemistry for IgG, IgA, C3d and C1q was positive. Electron microscopy showed masses of atypical collagen fibrils within the mesangial and the subendothelial areas of the glomeruli. Based on these findings a diagnosis of collagenofibrotic glomerulopathy was made.
Conclusion: Collangiofibrotic glomerulopathy is a rare diagnosis in which immunoglobulins and complements are not usually detected. This is however the second such case with a "full-house" pattern of staining, possibly reflecting entrapment of proteins within the accumulated collagen fibrils. This highlights the importance of performing routine electron microscopy in native renal biopsies to avoid misdiagnosing such cases as lupus nephritis.

E-PS-16-005
Interstitial nephritis and membranoproliferative glomerulonephritis in primary Sjögren syndrome: a report of 2 cases
V. Almeida[1], C. Faria[2], R. Nogueira[2], C. Pardinhas[2], N. Oliveira[2], A. Belmira[2], R. Alves[2,3], V. Sousa[1]
[1] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, [2] Centro Hospitalar e Universitário de Coimbra, Portugal, [3] Faculdade de Medicina da Universidade de Coimbra, Portugal

Background & Objectives: Sjögren syndrome is a rare progressive autoimmune exocrinopathy, affecting primarily the lacrimal and salivary glands. Renal involvement is frequent, being interstitial nephritis the most common histopathologic diagnosis. Glomerulonephritis, an unusual manifestation, is generally associated with mixed cryoglobulinemia. The following cases illustrate the complexity and diversity of findings on Sjögren syndrome.
Methods: A 59-years-old man (Case 1) and an a 50-years-old woman (Case 2) with primary Sjögren syndrome were referred to the Nephrology department due to nephrotic range proteinuria. Both patients had low C3 levels. HBV and HCV antibodies and HIV were negative. Cryoglobulinemia was negative. Serum protein electrophoresis showed no spike. Renal biopsy was decided.
Results: Both cases had a few glomeruli with global sclerosis, while the majority were lobulated with diffuse thickening of the GBM, and some had cellular crescents. Mesangial proliferation was revealed by PAS staining, while GBM spike formation and double-countorned membrane were recognized on silver staining. Immunofluorescence on case 1 revealed granular deposits of IgA (2+/3+), C3 (1+/2+), IgG (faint staining) and IgM (faint staining) along the GBM; case 2 had deposits of IgA (2+), C3 (1+) and C1q (2+). Both cases showed mononuclear cell infiltration of the interstitium.
Conclusion: These two cases with simultaneous tubulo-interstitial and membranoproliferative glomerulonephritis, the latter not associated with cryoglobulinemia, expose the broad spectrum of renal involvement in Sjögren syndrome. Renal biopsy is essential to obtain an accurate diagnosis because glomerular commitment may affect the clinical management. Both patients are currently receiving prednisolone and mycophenolate mofetyl, which is being well-tolerated and has resulted in renal function stabilization.

E-PS-16-006
Lupus-like membranous glomerulopathy in a patient under pembrolizumab: report of a rare case
H. Gakiopoulou[1], P. Korkolopoulou[1], S. Havaki[2], A. Stofas[1], A. Gkivalou[3], E. Athanasiadis[4], I. Giatras[5], A. Gerakis[5]

[1] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [2] Department of Histology and Embryology, School of Medicine, National and Kapodistrian University of Athens, Greece, [3] Department of Biology, The National & Kapodistrian University of Athens Greece, [4] Department of Medical Oncology, Mitera Hospital, Athens, Greece, [5] Department of Nephrology, Hygeia Hospital, Athens, Greece

Background & Objectives: Immune checkpoint inhibitors (ICPIs) have revolutionized the treatment of malignancies. Among them, monoclonal antibodies directed against programmed death 1 (PD-1), like pembrolizumab, prevent the engagement of PD-1 with its ligands, leading to T-cell stimulation. The potent activity of ICPIs results in inflammatory manifestations characterised as immune-related adverse events (irAEs). Two different forms of ICPI-induced renal damage have been identified: acute tubulointerstitial nephritis (TIN) and immune complex glomerulonephritis (ICG). To the best of our knowledge, until now, pembrolizumab has been associated with TIN but not with ICG. We present a rare case of a patient under pembrolizumab developing nephrotic syndrome due to a lupus-like membranous glomerulopathy.
Methods: A 69- year-old woman with lung cancer metastatic to brain underwent immunotherapy with pembrolizumab. Eight months later, she developed heavy nephrotic syndrome. Pembrolizumab therapy was stopped and a renal biopsy was performed.
Results: Renal biopsy demonstrated a podocytopathy with a membranous pattern and a tubulointerstial nephritis. Immunohistochemistry [IgG4(-), PLA2R(-)] and immunofluorescence (full-house pattern) suggested a secondary, lupus like membranous glomerulopathy. Immunihistochemistry for PD-L1 revealed staining in the glomerular capillary walls, some peritubular capillaries and rare epithelial tubular cells.
Conclusion: Although cases with TIN secondary to pembrolizumab therapy have been reported, this is the first case of an immune complex lupus-like membranous glomerulopathy related to pembrolizumab therapy. This is also the first time that PD-L1 expression is demonstrated in the glomeruli of a patient under pembrolizumab suggesting a possible association between the glomerular damage and the irAEs of the check point inhibitors, probably through disturbance of the tolerance against self-antigens.

E-PS-16-007
Congophilic fibrillary glomerulonephritis

H. Tennekoon[1], T. Cook[2,1], A. Palmer[1], C. Roufosse[2,1]
[1] Imperial College Healthcare NHS Trust, United Kingdom, [2] Imperial College London, United Kingdom

Background & Objectives: Fibrillary glomerulonephritis is charactorised by IgG-positive, amyloid-like fibrils which are Congo red negative. The recent description of Congophilic fibrillary glomerulonephritis (CFGN) changes this paradigm.
Methods: N/A
Results: A 65-year-old female with hypertension, hypercholesterolaemia and fatty liver disease was referred to nephrology for investigation of haemoproteinuria. Her urine protein to creatinine ratio was 398mg/mmol, serum albumin 37g/L and serum creatinine 104Umol/L. A renal biopsy showed 20 glomeruli with increased mesangium and segmental capillary wall thickening. These areas were weakly PAS-positive and silver-negative. Congo red showed green-birefringence under polarized light in glomeruli with no staining in the vessels or interstitium. Four glomeruli were obsolete and 3 had segmental sclerosis, with moderate tubulointerstitial scarring. Immunofluorescence staining showed mesangial and capillary wall IgG and C3. IgA, C1q and IgM were negative. There was equal intensity staining for kappa and lambda light chains. Electron microscopy showed non-branching fibrils (9.6 - 13.8 nm) in the mesangium and within glomerular basement membranes. Immunoperoxidase staining for Amyloid A was negative and DNAJB9 was positive. Mass spectrometry confirmed DNAJB9 without any amyloid signature. The findings were interpreted as CFGN.
Conclusion: Congo red positivity in CFGN makes distinction from amyloidosis challenging. The underlying cause, treatment and the prognosis for these entities are different. Amyloidosis generally warrants aggressive treatment and has poorer overall prognosis. Mass spectrometry and immunostaining for DNAJB9 can make this distinction; with the latter being applicable in the routine diagnostic pathology lab. Pathologists and clinicians need to be aware of this entity and the pitfalls it presents to ensure accurate diagnosis.

E-PS-16-010
Anticoagulation related nephropathy in a post renal transplant patient

H. Tennekoon[1], A. Kousios[1], R. Gardiner[1], L. Moran[1], D. Goodall[1], D. Taube[2,1], J. Galliford[1], C. Roufosse[2,1]
[1] Imperial College Healthcare NHS Trust, United Kingdom, [2] Imperial College London, United Kingdom

Background & Objectives: Anticoagulation-related nephropathy (ARN) presents as acute kidney injury (ATI) during periods of over-anticoagulation. ARN has only been described once in a transplant.
Methods: N/A
Results: A 61-year-old-man 8-years post-transplant, on long term anticoagulation with warfarin following mitral valve replacement presented to hospital with urosepsis. Serum creatinine was 224umol/L and INR 2.5. During treatment with antibiotics, serum creatinine and INR rose to 570umol/l and 3.5 respectively. Anticoagulation was bridged from warfarin to heparin and a renal biopsy was performed.
The biopsy contained eight glomeruli. There was severe ATI with widespread red blood cell casts occluding the tubules. Moderate interstitial oedema and inflammation with foci of severe lymphocytic tubulitis was seen. Occasional tubules contained neutrophil casts. There was no microvascular inflammation. Moderate tubulointerstitial scarring was present. C4d and SV40 immunostains were negative. Immunofluorescence was negative for IgG, IgA, IgM, C3, C1q or kappa and lambda light chains. Electron microscopy showed dysmorphic RBC within tubules.
The biopsy was concluded as ARN with evidence of resolving urinary tract infection and features of concomitant T-cell mediated rejection (Banff 1b). Antibiotics were continued; however immunosuppression was not augmented in view of concomitant infection and frailty. He was started on acenocoumarol aiming for INR 2-3. His renal function and inflammatory markers were back to baseline at discharge and at four month follow-up.
Conclusion: Given the limited management options, poor renal and overall prognosis of ARN, transplant patients on anticoagulation should be monitored with the aim of early detection and prevention of ARN.

E-PS-16-012
Secondary paraneoplastic membranous glomerulopathy (MG) mimicking serologically and histologically autoimmune lupus like MG

H. Gakiopoulou[1], H. Theodoropoulou[2], S. Havaki[3], A.C. Lazaris[1]
[1] 1st Department of Pathology, School of Medicine, The National and Kapodistrian University of Athens, Greece, [2] Renal Unit, General Hospital "Alexandra", Athens, Greece, [3] Department of Histology and Embryology, School of Medicine, National and Kapodistrian University of Athens, Greece

Background & Objectives: Paraneoplastic glomerulopathies are well documented and are related to altered immune responses in the presence of malignancy.

Methods: A 70-year-old male underwent a right radical nephrectomy in 2017, for a long standing renal mass thought to be an angiomyolipoma. Pathologic diagnosis reported a clear-cell renal cell carcinoma with perinephric fat invasion, without renal sinus invasion, with clear surgical margins (pT3aN0). One year post-nephrectomy the patient presented with proteinuria (3 g/day), mild decline of his renal function, ANA (+), anti-Ro(+) and anti-ds-DNA(+), albeit asymptomatic for lupus. The patient underwent a percutaneous biopsy to its sole left kidney.
Results: Light microscopy showed a glomerulopathy with a membranous morphologic pattern without morphological signs of secondary membranous glomerulopathy (MG). However, immunohistochemistry suggested a secondary MG (IgG4-, PLA2R-, TSH7DA -) and immunofluorescence showed a full-house pattern with IgG+IgA+IgM+C3+C1q strong positivity, reminiscent of lupus MG. Electron microscopy showed subepithelial and some mesangial electron dense deposits. The histological diagnosis was that of a secondary lupus-like MG. To determine the starting point of the MG, immunohistochemistry (C4d, IgG) was performed in the renal tissue adjacent to the clear-cell carcinoma of the nephrectomy specimen. Immunohistochemical markers of MG were negative suggesting that the MG started after tumour resection. The clinical dilemma was if we had to deal with a paraneoplastic secondary MG due to possible tumour recurrence or with an additional autoimmune disease, like lupus. Patient's investigation revealed metastatic thoracic lymph nodes rendering more possible the scenario of altered immunity triggered by the release of tumour antigens.
Conclusion: MG may precede not only the diagnosis of a primary neoplasm but also the discovery of its relapse. In this context, paraneoplastic MG may rarely mimic, serologically and histologically, an autoimmune lupus-like disease.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
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E-PS-17-001
Epithelioid glioblastoma: case report of a rare histological variant of glioblastoma in a 17 year-old boy

F.F. Cheo[1], K. Merchant[2], J.G.C. Teo[2], K.T.E. Chang[2]
[1] Department of Anatomical Pathology, Singapore General Hospital, Singapore, [2] Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore

Background & Objectives: Epithelioid glioblastoma is a rare variant of IDH-wild type glioblastoma (WHO IV) which occurs predominantly in young adults and children. We report a case of epithelioid glioblastoma diagnosed locally in KK Women's and Children's Hospital, Singapore.
Methods: The patient presents with worsening headache and vomiting for a week. Magnetic Resonance Imaging (MRI) shows a 3.5 cm right temporal solid mass with perilesional oedema and midline shift. Microscopically, the tumour demonstrates sheets of tightly packed pleomorphic epithelioid and rhabdoid cells, with abundant multinucleated giant cells seen. Numerous mitoses with atypical mitotic figures are identified. Necrosis is present.
Results: On immunohistochemistry (IHC), the tumour is positive for GFAP, S100, vimentin and patchily positive for neurofilament and EMA. Few tumour cells are highlighted by synaptophysin. The tumour is negative for pancytokeratin AE1/3. Wild type staining pattern is noted on P53. Cell proliferation index Ki67 (MIB-1) is approximately 30 to 40% in the tumour. INI-1 (SMARCB1) and SMARCA4 are both retained in the tumour cells. In addition, BRAF V600E mutation is detected in this case using IHC method. IDH-1 mutation is negative(wild-type).
Conclusion: The overall immunomorphological features are in keeping with an epithelioid glioblastoma, WHO grade IV. This is further supported by the positive BRAF V600E mutation. In both adult and paediatric patients, epithelioid glioblastoma has a particularly poor prognosis compared to the run-of-the-mill glioblastomas, with a median survival of 6.3 months in adults and 5.6 months in children despite various therapies.

E-PS-17-002
Epithelioid glioblastoma: a report of 2 cases, including an extra-axial epithelioid glioblastoma initially misdiagnosed as rhabdoid meningioma

H.Y. Lee[1], C.S.L. Ding[1], M.M. Bundele[1], K.L. Chuah[1]
[1] Tan Tock Seng Hospital, Singapore

Background & Objectives: Epithelioid glioblastoma, which was recently codified in the 2016 World Health Organisation classification of central nervous system tumours, is rare. We describe 2 cases and discuss the diagnostic challenges. Case 1: An 18-year-old male presented with a left frontal lobe brain tumour. Case 2: An 18-year-old female presented with a left fronto-temporal intracranial extra-axial tumour.
Methods: Case 1: The tumour showed epithelioid and rhabdoid cells. There was mitotic activity and abundant necrosis, but no microvascular proliferation. Glial fibrillary acid protein (GFAP) and OLIG2 stained rare cells, and INI1 was intact. Positive immunohistochemical staining for BRAF V600E supported the diagnosis of epithelioid glioblastoma. Case 2: The tumour showed rhabdoid cells. There was mitotic activity and necrosis, but no microvascular proliferation. Epithelial membrane antigen was positive, while GFAP was sparse. The tumour was diagnosed as a rhabdoid meningioma.
Results: The first patient died of disease 4 months post-surgery. In Case 2, following a multidisciplinary discussion where there was controversy about whether the tumour could have an intra-axial component, the case was reviewed at an external institution. There a diagnosis of epithelioid glioblastoma was rendered based on focal staining for GFAP and OLIG2, and no staining for somatostatin receptor 2. BRAF V600E mutation was negative. This patient showed no disease recurrence 24 months post-surgery.
Conclusion: Epithelioid glioblastoma is rare, and the differential diagnoses include metastases, atypical teratoid/rhabdoid tumour and rhabdoid meningioma. Possible sparse staining for GFAP, absence of microvascular proliferation, an often compact pattern of growth, and a superficial or extra-axial location add to the diagnostic challenges. OLIG2 staining and BRAF V600E mutation, if present, may be helpful.

E-PS-17-003
Tumour-to-tumour metastasis: breast carcinoma metastasis to meningioma

S. Mata[1], M. Mafra[2]
[1] Pathology Department, Instituto Português de Oncologia de Lisboa, Francisco Gentil, EPE, Portugal, [2] Serviço de Anatomia Patológica, Centro Hospitalar Universitário de Lisboa Central, EPE, Lisboa, Portugal

Background & Objectives: The diagnosis of a dural based nodule in patients with history of malignancy is challenging and includes meningioma, dural metastasis, and much less likely tumour-to-tumour metastasis. In a breast cancer patient, discernment of meningioma from metastasis is important because complete surgical resection may be curative for the former, while radiotherapy would be typically employed for the latter. Imaging alone is often unspecific and histological examination remains the only reliable diagnostic method whenever an accurate diagnosis is critical for clinical management.
Methods: We describe an unusual case of a dural based nodule in a breast cancer patient proved to be a metastasis within an intracranial meningioma.

Results: A 51-year-old woman with breast cancer metastatic to lymph nodes and bone, presented with a dural based nodule measuring 18x19x19mm, suspicious for meningioma or dural metastasis on MRI. Pathologic assessment of the surgical specimen revealed 2 different morphologies: a meningothelial proliferation with syncytial and whorling patterns (EMA+) without mitosis or anaplasia; and an epithelial glandular component (mammaglobin+). The diagnosis was transitional meningioma (Grade I, WHO) infiltrated by an adenocarcinoma compatible with breast origin. Months later, parenchymal brain lesions were identified.
Conclusion: Clinicians and pathologists should be familiar with the possibility of intrameningioma metastases of carcinomas, a well-recognized although rare phenomenon with 34 recorded cases in the literature. Given the challenges in differentiating a meningioma from breast cancer metastasis in imaging alone, surgical resection should be considered in patients with history of breast cancer presenting with a dural based nodule.

E-PS-17-004
Dysplastic cerebellar gangliocytoma (Lhermitee-Duclos disease) with frequent recurrences
C. Yoo[1]
[1] St Vincent Hospital, The Catholic University of Korea, Republic of Korea

Background & Objectives: Dysplastic cerebellar gangliocytoma (DCG, Lhermitte-Duclos disease) is a rare benign cerebellar tumour. DCG forms an important part of multiple hamartoma-neoplasia complexes (Cowden's syndrome). Because of the possibilities of a concurrence of other organ diseases, continuous follow-up is recommended for DCG. Clinically, DCG is known to show benign behavior and recurrence is rare, but no extensive prognostic studies have been done. The aim of this case report is to present a DCG case which showed an unusual clinical course.
Methods: 70-year male visited St Vincent Hospital because of severe dizziness. 18 years ago, he had undergone subtotal tumour removal for the mass lesion in the left cerebellum. Two years later, he felt severe dizziness and MRI showed slightly increased mass size. Partial tumour removal was done. He hasn't had any special symptoms since then. Recently, he felt severe dizziness again, and MRI showed an ill-defined mass in the same place. tumour was removed and the patient is now under observation.
Results: Pathologically, the cortical layer of the cerebellum was thickened and normal cortical layers were effaced duo to the proliferation of dysplastic ganglion cells. But the cerebellar gyrate architecture was preserved. Purkinje cells were hardly observed and a few granule neurons were scattered between ganglion cells. Calcifications were found in the white matter. Pathologic findings were consistent with dysplastic cerebellar gangliocytoma.
Conclusion: Patient had experienced two relapses, first two years after surgery and second after a long period of disease-free interval. It is uncertain whether subtotal tumour removal was associated with recurrence. Until today, evidence of concurrence of Cowden syndrome-associated other organ diseases was not found. We report this case to promote the understanding of the clinical course of this rare disease.

E-PS-17-005
Heavily lipidised variant of glioblastoma with gliomatosis cerebri growth pattern
N.J.H. Tan[1], Y.L.J. Wong[2], M.E. Nga[1], C.L. Tan[1]
[1] Department of Pathology, National University Health System, Singapore, [2] Department of Diagnostic Imaging, National University Health System, Singapore

Background & Objectives: Malignant gliomas with heavily lipidized tumour cells are extremely rare, with only limited case reports in the literature that were mostly published in the "pre-molecular" era. Recognition of this variant is important as it can masquerade as a lower grade localized glioma, such as a pleomorphic xanthoastrocytoma.
Methods: We report a case of a heavily lipidized variant of glioblastoma with gliomatosis cerebri growth pattern in a 50-year-old man, describe its clinicopathologic features and perform a literature review on this entity.
Results: The tumour was composed of pleomorphic lipidized cells with abundant vacuolated cytoplasm. Focally, there were spindled cells with fibrillary cytoplasm reminiscent of a conventional gliomatous component. Microvascular proliferation and necrosis were noted. Both lipidized and spindled cells were positive for GFAP and ATRX. Olig2 was positive only in the spindled cells. IDH1R132H was negative. Most patients documented in the literature were first diagnosed at an average age of 50 and their median survival was a year or less.
Conclusion: Distinguishing the heavily lipidized variant of glioblastoma from other tumours with abundant clear/vacuolated cytoplasm is critical as it confers serious prognostic and treatment implications. The rapidly fatal course of this tumour in most patients, an average presenting age of 50, negative IDH1R132H and retained ATRX suggest an IDH wild-type glioblastoma with no lower grade precursor.

E-PS-17-006
Gliomas with abscesses: a report of two cases of astrocytic tumours with intra-tumoral neutrophilic abscess and literature review
K.A. Yeo[1,2], M. Lee[2]
[1] Division of Forensic Medicine, Health Sciences Authority, Singapore, [2] Department of Anatomical Pathology, Singapore General Hospital, Singapore

Background & Objectives: Abscesses within brain tumours are uncommon; most are reported in sellar and parasellar tumours after direct extension from infected paranasal sinuses or from the anatomical "danger area" of the face. Cerebral gliomas with neutrophilic abscess formation are extremely rare, with few cases being reported.
Methods: We report two cases of astrocytic tumours with neutrophilic abscesses found on histological evaluation, and review the literature of gliomas associated with abscesses reported from 1986 to 2018.
Results: Two cases presenting with similar symptoms of headaches and altered mental status are reported. Neuroimaging identified a left thalamic intraparenchymal mass in the first case, and a cystic lesion in the right frontal lobe in the second case. The lesions were biopsied and showed malignant-appearing glial cells with intra-tumoral necrotic material and neutrophils. Our literature review showed 18 reported cases of gliomas with abscess formation. Challenges to diagnosing gliomas with abscesses clinically, radiologically and histopathologically are also discussed.
Conclusion: While gliomas with abscesses are rare, they are an important differential for intra-cranial space-occupying lesions. Both the neoplastic and infectious components of the lesion are important to recognize and diagnosis should be made in correlation with clinical, intraoperative, radiological and histopathological findings.

E-PS-17-007
Rare observation of recurrent papillary pineal tumour
S. Petrov[1], T. Akhmetov[1,2], N. Gizatullina[1,3]

[1] Kazan State Medical University, Russia, [2] Kazan Cancer Centre, Russia, [3] Interregional Clinical and Diagnostic Center, Kazan, Russia

Background & Objectives: Papillary tumour of pineal region is a new entity in neurooncology added to WHO classification in 2003 (ICD-0 Code 9395/3). By 2016 only 182 cases were reported.
A 33-year-old female was admitted with headaches, right sided hypesthesia, diplopia, left sided hearing loss, nausea and vomiting in January 2019. Enhanced MRI revealed a 36*32*31 mm mass in the free edge of cerebellar tentorium (suspected meningioma or recurrent pineal tumour).
Methods: First symptoms noticed in 2013, same year patient underwent resection of pineal neoplasm with ventriculoperitoneal shunting (diagnosis papillary tumour of pineal region). Symptoms appeared again in 2018, second operation (resection of tentorial lesion) performed in February 2019. On operation soft friable lesion extended to the right side from tentorial incisure, measured 34*32*30 mm.
Results: Tumour histologically was represented by small eosinophilic cells with hyperchromic polygonal nuclei and detectable nucleoli, arranged in solid and macropappilary structures. Fibrovascular stroma contained areas of hyalinization, pseudoangiomatosis and perivascular pseudorosettes. Necrotic areas were absent, only scarce mitotic figures recognized. Immunohistochemistry: positivity for GFAP, S100, vimentin, neuron-specific enolase, EMA, cytokeratins AE1/3, nuclear staining for p53, Ki67 4-5%, negative reaction for synaptophysin.
Diagnosis: Relapse of papillary pineal tumour (WHO grade II). Postoperative period with improvement of neurological state.
Conclusion: Due to papillary histological pattern, proximity to the cerebral aqueduct and symptoms related to hydrocephaly the newly added entity of Papillary tumour of pineal region should be considered in differential diagnosis with papillary ependimoma.

E-PS-17-008
Congenital high-grade gliomas with features of maldevelopment of brain: review of 2 cases with molecular studies

T. Mikhaleuskaya[1], N. Konoplya[1], A. Valochnik[1], A. Punko[1]
[1] Belorussian Research Center for Paediatric Oncology, Haematology and Immunology, Belarus

Background & Objectives: We report two cases of congenital high-grade brain tumours, in which areas of low-grade tumours of dysmorphogenetic origin – gangliocytoma and angiocentric glioma were identified. Usually these tumours do not undergo malignancy. In both cases large tumours of the right hemisphere were diagnosed prenatally. After birth they were subtotally removed and both of them relapsed a few month later.
Methods: In the first case, histologically, the diffuse growing tumour consisted of bundles of low-differentiated spindle cells with a network of small branching vessels. Mitotic activity was high. At the periphery of the tumour astrocytic differentiation could be mentioned, cells formed perivascular rosettes resembling angiocentric glioma. Immunohistochemistry revealed positivity for GFAP, D2-40, EMA.
In the second, the morphology of the primary biopsy corresponded to the gangliocytoma. Histological examination of a recurrent tumour showed areas of gangliocytoma and solid sheets of undifferentiated cells with high mitotic activity, Homer-Wright rosettes formation and focal ganglionic differentiation. IHC revealed positivity for neural markers, olig2, p53.
Results: In the first case molecular study didn't reveal mutations in p53, H3K27, H3G34,IDHR132H, BRAF V600E. The only cytological finding was loss of chromosome 6. The tumour was considered anaplastic astrocytoma with features of angiocentric glioma. In the second case by NGS mutations in FLT3 and p53 were found. Cytogenetic study detected deletion of CDKN2a. Diagnose of anaplastic astrocytoma with neural differentiation was made.
Conclusion: Some morphological features of low-grade neoplasms, seen in high-grade astrocytomas, could provide a hint towards mechanism of pathogenesis of paediatric brain tumours.

E-PS-17-009
Huntington disease in a female with 28-repeat CAG allele

S. Jevtic[1], J. Provias[2]
[1] McMaster University, Michael G. DeGroote School of Medicine, Canada, [2] Department of Pathology and Molecular Medicine, Hamilton Health Sciences, Canada

Background & Objectives: Huntington Disease (HD) is an autosomal-dominant inherited disorder that presents with chorea, psychiatric involvement, and dementia. The causative mutation is a CAG trinucleotide expansion in the huntingtin gene located on chromosome 4, where >36 repeats is disease-confirmatory. However, an intermediate range from 27-35 repeats has been reported to lead to disease in rare cases. We report here an 81-year-old female with clinical and autopsy-confirmed diagnosis of HD (CAG repeat = 28), which represents the lowest confirmed CAG repeat to date.
Methods: Gross examination of the brain was completed after which sections were formalin fixed and paraffin embedded for microscopic examination. Immunohistochemical staining was done for: glial fibrillary acidic protein, amyloid-beta, and tau. Immunofluorescence staining involved p62 primary antibody with AlexaFluor 488 secondary antibody.
Results: Brain autopsy revealed classic pathologic findings including severe neuronal loss in the caudate and putamen, with accompanying gliosis. p62 immunofluorescence showed rare intraneuronal inclusions suggesting minimal presence of huntingtin aggregates. Interestingly, there was significant and diffuse concomitant amyloid-beta plaque deposition with focal tau pathology, despite no signs of clinical dementia.
Conclusion: This case highlights several interesting points, including: (1) the role of genetic testing in predicting risk of HD and family testing, (2) the role of protein aggregates in disease pathology, and (3) co-occurrence of neurodegenerative diseases with overlapping symptoms.

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E-PS-17-010
Cervical meningioma presented with Brown-Sequard syndrome: a case presentation

Z. Asan[1], A. Kilitci[2], A. Yüceer[1], î Aykanat[1], E. Tugcugil[3], F. Durna[1], Z. Kaya[2]
[1] Ahi Evran University Medical Faculty, Dept of Neurosurgery, Turkey, [2] Ahi Evran University Medical Faculty, Dept of Pathology, Turkey, [3] Karadeniz Tecnical University Medical Faculty, Dept of Anesthesiology, Turkey

Background & Objectives: The clinical picture that emerges from a loss of function in one half of the medulla spinalis in the vertical plane is named as Brown-Sequard syndrome(BSS). This clinical picture usually appears after trauma and its appearance due to a spinal cord tumour is quite rare. Spinal meningiomas are the most prevalent extra-axial spinal cord tumours encountered after metastases. Clinical findings are concerned with the tracts where the spinal cord is impacted and radicular findings are rarely seen.

Methods: 57-year-old female patient was evaluated due to complaints of right hemiparesis, left hemihypesthesia, and ataxic gait. The cervical MRI examination of the case revealed a mass lesion with a lateral localization at levels C4-C5 that demonstrated homogenous contrast enhancement, caused spinal cord compression, and was consistent with meningioma.
Results: Histopathological and immunohistochemical examination of the light-brown material with a volume of approximately 3cc and a soft-consistency was consistent with grade 1 meningioma (meningothelial type). After the operation, improvement was observed in motor strength, ataxia, and sensory deficits in the presented order. No additional neurological deficits were encountered during the 4-year long-term follow-up period and tumour recurrence was not determined in radiological follow-up.
Conclusion: In the BSS, all tracts in one half of the spinal cord are expected to experience a loss of function. However, clinical findings are associated with the dominant corticospinal tract, spinothalamic tract, and dorsal column tracts. In this picture, which typically follows cord hemisection, partial/total recovery of neuronal function can be observed if there had not been a total loss of function due to compression. Treatment is total resection.

E-PS-17-011
Next generation sequencing-identified IDH-1, ATRX, TP53 mutation and MYCN amplification in glioblastoma with primitive neuroectodermal tumour-like feature and extensive subarachnoid spread: a case report
H. Hwang[1], K.S. Lee[1], H.S. Lee[1], G. Choe[1,2]
[1] Department of Pathology, Seoul National University Bundang Hospital, Republic of Korea, [2] Department of Pathology, Seoul National University College of Medicine, Republic of Korea

Background & Objectives: In recent years, there have been numerous molecular studies of glioblastoma. With regard to glioblastoma showing extensive subarachnoid spreading, however, the pathogenesis remains to be determined due to its low incidence. Present report describes a rare case of glioblastoma with primitive neuroectodermal tumour (PNET)-like feature, which spread extensively in subarachnoid space, as well as the result of its molecular analysis using next generation sequencing (NGS).
Methods: A 37-year-old male presented with a new onset, severe headache. Magnetic resonance imaging revealed a diffuse infiltrative mass in the right frontal lobe, spreading broadly in subarachnoid space. The patient underwent craniotomy and tumorectomy. Microscopically, glioblastoma showed PNET-like feature. On immunohistochemical analysis, tumour cells focally expressed GFAP and synaptophysin. *IDH-1* (p.Arg132His) mutation was found in the subsequent NGS test. Additionally, two frame shift genetic alterations were found: *ATRX* (p.Tyr2208fs) and *TP53* (p.Pro301fs).
Results: Interestingly, *MYCN* amplification was also present, identified by both NGS and fluorescence in situ hybridization (FISH) test. Despite post-operative therapies including temozolomide and radiotherapy, the tumour progressed aggressively and the patient expired nine months after the first symptom onset.
Conclusion: Although there have been previous reports of *MYCN* amplification in glioblastoma with PNET-like feature, this is the first case report of *IDH*-mutant type glioblastoma with such features. *IDH-1* mutation and younger age are usually associated with a better prognosis in glioblastoma. However, this case suggests that when *MYCN* amplification coexists in *IDH*-mutant type, the tumour behavior could be contrarily aggressive.

E-PS-17-012
A case report of a rare variant of meningioma
I. Msakni[1], N. Mansouri[1], R. Hedhli[1], F. Gargouri[1], A. Saidi[1], A. Bouzaini[1], B. Laabidi[1]
[1] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: Meningioma is the most common intracranial extracerebral tumours. The 2016 World Health Organization (WHO) classification recognises many subtypes of meningioma. Secretory meningioma is a rare meningioma variant which is a low grade tumour (Grade I). It accounts for 1% to 3% of all meningiomas with a predominance in female patients in the fifth decade. It is different from other subtypes, not only because of its pathological features but also because of its clinical features as well. Our aim is to discuss clinical and pathological features of this rare variant of meningiomas.
Methods: We report a case of a 57-year-old woman who presented with seizures. MRI showed an extracerebral temporal process that was enhanced after gadolinium injection. Total exision of the lesion was performed. We recieved a firm, white and lobulated nodule that measured 25 mm in diameter.
Results: Microscopic examination revealed a diffuse, lobulated proliferation composed of menigothelial cells with "whorls" formation. Tumour cells were medium-sized, with abundant eosinophilic cytoplasm and monomorphic nuclei arranged in a syncitial pattern. Intracellular lumina containing periodic-acid-Schiff (PAS) - positive eosinophilic secretions called pseudopsammoma bodies were observed. Mitoses were not seen. The tumour has infiltrated the dura. The edge between the tumour and the cerebral parenchyma could'nt be evaluated. Pseudopsammoma bodies showed immunoreactivity for carcinoembryonicantigen (ACE) and the surrounding tumour cells were positive for both ACE and Cytokeratin AE1/AE3. We concluded a seretory meningioma grade I (WHO 2016).
Conclusion: The diagnosis of secretory meningioma may be challenging in some cases. Clinical and imaging features are similar to other meningioma subtypes. However, pathological features may lead to differential diagnosis as psammomatous, chordoid, microcystic subtypes of meningioma or metastatic carcinoma. Immunohistochemistry is an essential tool to make the diagnosis and to rule out other diagnosis.

E-PS-17-013
A case of central neurocytoma: an uncommon neoplasm, examined in frozen and FFPE sections
A. Baliaka[1], M. Kilmpasani[1], N. Pastelli[1], S. Kottas[2], I. Karafoulidou[1], I. Matzarakis[1], S. Papaemmanouil[1]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Neurosurgery, General Hospital of Thessaloniki "G. Papanikolaou", Greece

Background & Objectives: Central neurocytomas account for 0.1-0.5% of all brain tumours. According to WHO classification, it is a neoplasm with uncertain biological behaviour. We present the case of a 21-year-old man, suffering from headaches, with an enhancing intraventricular tumour on imaging.
Methods: The tumour protruded into the right lateral ventricle and was accessed via minimally invasive approach. Intraoperatively, tissue material was sent for frozen sections. Subsequently, a gross total resection was undertaken. The obtained material was examined with hematoxylin-eosin and immunohistochemical stains.
Results: The frozen sections, as well as the formalin-fixed paraffin-embedded tissue sections, demonstrated a neoplasm, consisting of monomorphic, round cells, carrying uniform, round-to-oval nuclei, with finely dispersed chromatin. Mitoses were rare. Numerous, thin-walled, capillary vessels were evident between the cells. Necrosis or calcifications were absent.

The neoplastic cells were positive for CD56, synaptophysin, NSE, S-100, and negative for CAM5.2, chromogranin, and GFAP, among others. The proliferation index Ki67 was expressed in 1-2% of the neoplastic cells. In correlation with the patient age and the location of the tumour, the diagnosis was central neurocytoma. Postoperatively and in the follow-up, the patient recovered very well with no neurological deficits.
Conclusion: Central neurocytomas are rare neuroepithelial tumours, with neuronal immunophenotype and usually low proliferation index. They are predominantly found in young adults, attached to septum pellucidum, causing symptoms of increased intracranial pressure. They are surgically well-manageable, with a 5-year survival estimated at 90%, more favourable for intraverticular tumours and those who achieve complete resection. Patient age, high Ki67 expression and comorbidity are considered adverse prognostic factors.

E-PS-17-014
A case of intraparenchymal atypical meningioma in a 3-year old boy
S. Lypiridou[1], N. Foroglou[2], G. Karayannopoulou[1], E. Antoniadis[2], A. Cheva[1]
[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece, [2] 1st Department of Neurosurgery, AHEPA Hospital, University of Thessaloniki, Greece

Background & Objectives: Meningiomas are the most common benign tumours of the central nervous system. The vast majority of them correspond histologically to WHO grade I. They rarely appear in childhood, representing only 2.8% of all paediatric primary brain tumours. Intraparenchymal localization is even more uncommon. We present the case of a 3-year-old boy with an emerging, contrast-enchancing, highly vascularized parenchymal mass, located in the frontal and temporal lobes.
Methods: We received multiple, white-tan, soft, tissue fragments, measuring 8x7.8x0.9 cm. Tissue sections were examined with hematoxylin-eosin and immunohistochemical stains. Microscopically, the tumour mainly consisted of uniform, spindle cells, arranged in whorls, fascicles and rare small groups. Occasionally, cells with atypical features were encountered. Psammoma bodies were infrequent. The mitotic activity was low (1/ 10 HPF). Invasion of the brain parenchyma was evident, in the form of irregular, tongue-like protrusions of tumour cells.
Results: The neoplastic cells were immunoreactive for vimentin and EMA and negative for GFAP, S100, CD56, NSE, CD99, MelanA, Desmin, SMA, h-caldesmon, CK8/18 and CD34. Ki-67 staining index was approximately 7-10%. The final diagnosis was atypical intraparenchymal meningioma. The patient died a few months after the diagnosis.
Conclusion: Intraparenchymal meningiomas should be considered when other common lesions are excluded. Atypical meningioma is an intermediate grade tumour and corresponds histologically to WHO grade II. The case of an intraparenchymal atypical meningioma in childhood is rarely encountered. The presence of brain invasion is associated with higher mortality and recurrence rate. A detailed histological approach is mandatory for therapy-planning and prognosis assessment.

E-PS-17-015
A secondary gliosarcoma in the setting of a previously diagnosed primary glioblastoma
S. Lypiridou[1], A. Spiliotopoulos[2], K. Papadopoulou[2], A. Cheva[1]
[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece, [2] Neurosurgical Department of Aristotle University of Thessaloniki, AHEPA Hospital, Greece

Background & Objectives: Gliosarcomas comprise 2% of all glioblastomas, with similar clinical manifestation and equally poor survival rate. They affect middle-aged adults with a male predominance. We present the case of a 50-year-old male, with a recurring tumour in the right temporal lobe. He had reportedly received surgical treatment for a glioblastoma at the same site 3 months ago.
Methods: The patient underwent surgical excision for tumour-mass-reduction therapy before radiotherapy. We received multiple, white-tan, tissue fragments, measuring 4x3.2x0.6 cm. Tissue sections were examined with hematoxylin-eosin and immunohistochemical stains. We observed a biphasic tumour with alternating areas, displaying glial and sarcomatous differentiation. The gliomatous component consisted of pleomorphic and anaplastic astrocytes, with the presence of necrotic areas and prominent endothelial proliferation. The predominant sarcomatous component consisted of spindle cells, arranged in anastomosing fascicles, and single, atypical giant-cells with pleomorphic, vesicular nuclei. Mitotic activity was increased, with several atypical mitoses.
Results: The immunohistochemical expression of GFAP was evident in the gliomatous component and almost absent in the sarcomatous component, with scattered positive atypical giant-cells. P53 was expressed in both components, while S100, IDH-1 and CK8/18 were completely negative. Ki-67 staining index was 20-40%.
The final diagnosis was secondary gliosarcoma.
Conclusion: Gliosarcomas are a rare variant of glioblastoma, which correspond histologically to WHO grade IV. They contain distinct gliomatous and sarcomatous components, which seem to have a common cytogenetic background, as indicated by molecular studies. Secondary gliosarcomas are exceedingly rare. The literature on secondary gliosarcoma illustrates a more favorable survival than for primary gliosarcoma, although it still remains limited.

E-PS-17-016
Impact of IDH1 mutation on long-term survival in patients with diffuse brain glioma
E. Ochirjav[1], G. Choe[2], T. Baldandorj[1], B. Enkhbat[1]
[1] Mongolian National University of Medical Sciences, Mongolia, [2] Seoul National University Bundang Hospital, Republic of Korea

Background & Objectives: Diffuse brain gliomas are common primary brain tumour associated with a poor prognosis. In this study, we aimed to determine the impact of IDH1 mutation status on long-term survival.
Methods: Patients who underwent surgery for diffuse brain glioma were selected. Based on IDH1 mutation status, patients were separated into IDH1 mutant and IDH1 wildtype groups.
Results: A total of 124 patients with diffuse brain tumour were included (mean age 39±17, 48.4% male). The frequency of IDH1 mutant and IDH1 wildtype were 56.5% (n=70) and 43.5% (n=54), respectively. During follow-up, 76 patients (61.3%) died and the median follow-up was 8 months (IQR 4; 16). Patients with IDH1 mutant more likely younger (36±16 vs. 43±17, p<.05) and had low grade (grade II) tumour (64.3% vs. 20.4%, p<.001). After adjustment of possible predictors, such age, gender, tumour location and surgical type, IDH1 mutant was an independent predictor of all-cause mortality (HR=0.43, 95% CI 0.26-0.71, p<.001). Kaplan-Meier estimation showed IDH1 mutant is associated with longer survival compared with IDH1 wildtype in low grade tumour (log rank p<.001).
Conclusion: Mutated IDH1 is an independent predictor of all-cause mortality in patients with diffuse brain glioma and resulted in longer survival compared with IDH1 wildtype.

E-PS-17-017
Adult gliofibroma: report and discussion of a rare case
M.G. Lisievici[1], D. Pasov[1], L.C. Cocosila[1], F. Pop[2], A.C. Lisievici[3], F.M. Brehar[1], G. Petrescu[1]

[1] Bagdasar-Arseni Clinical Emergency Hospital, Romania, [2] Dr. Carol Davila Clinical Hospital, Romania, [3] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Background & Objectives: The term of gliofibroma was first proposed in 1978 describing a biphasic tumour of glial and mesenchimal morphology. While the glial component may be of varying grade, the mesenchimal one is always benign. Most of the cases described to date seem to affect the younger population, rarely exceeding the age of 20. Only a few adult patients have been reported.
Methods: Our patient, a 64 years old man, was referred to our hospital for headaches, nausea, dizziness and tinnitus. Initial neuroimaging described a large, temporal, apparently extraneuraxial mass with cystic/necrotic areas. Later examination also showed an infiltrating nature of the tumour.
During surgery, the neurosurgen could not asess the exact origin and described the mass as very adhesive to both meninges and brain tissue.
A small fragment was sent for intraoperative examination. Frozen sections as well as the squash technique revealed a mesenchimal, apparently fibrous lesion which was interpreted as fibrous meningioma.
A subtotal resection was performed.
Results: Macroscopically, the tumour fragments, totalizing 8/7,5/3 cm, were grayish-white, firm and slightly rubbery. Light microscopy revealed a large fibrous, hypocellular, collagenized component embedding small areas of a high grade infiltrating glioma.
While not dominant, the glial component showed both mitotic activity as well as necrosis and hints of vascular proliferation.
Our final diagnosis was of anaplastic gliofibroma, which was later supported by immunohistochemestry. The patient was referred to an oncologist.
Conclusion: Tumours of a biphasic mesenchimal-glial nature are not extremely uncommon, usually consisting of gliosarcomas in adults and desmoplastic infantile astrocytoma/gangliogliomas in children. Gliofibroma however, appears to be a distinct entity which makes prognosis and treatment options difficult to assess. Documenting the existing cases should help further understanding of these tumours.

E-PS-17-018

A rare case of glial tumour with metastasis

D. Lange[1], A. Stanek-Widera[1], M. Biskup-Fruzynska[1], R. Lach[1], B. Nikiel[1]
[1] Tumour Pathology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Background & Objectives: Extraneural metastases of glial tumours are rare, with approximately 2% incidence. The authors present a case of a 68-year old woman who was diagnosed with a right temporal lobe tumour measuring 2,5 cm in 2010. The patient did not agree to the suggested treatment, but was operated on after 4 years due to progression (the tumour increased in size to 5,5 cm).
Methods: The diagnosis of anaplastic oligodendroglioma G3 was established on the basis of histological images in H&E stain and immunohistochemical assays. 3 years later the patient presented with right cervical lymphadenopathy, which resulted in lymphadenectomy. After performing a wide panel of immunohistochemical stains and confirming 1p19q loss of heterozygosity in both primary tumour and the nodal metastasis.
Results: The patient was diagnosed with an extraneural (nodal) metastasis of oligodendroglioma.
Conclusion: The patient survived six months after the confirmation of the metastatic disease, with no signs of progression.

E-PS-17-019

A case series of diffuse midline gliomas harboring H3 K27M mutation

L. Barona García[1], B. Ferri Ñíguez[2], M.A. Torroba Carón[1], D. López Motos[2], T. Ribalta Farres[3], A. Salazar Nicolás[1], M.I. Oviedo Ramírez[1], M.I. Ortuño Moreno[1], A. Caballero Illanes[1], E. Martínez Barba[1]
[1] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [2] Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [3] Hospital Sant Joan de Dèu Barcelona, Spain

Background & Objectives: Brainstem gliomas are very uncommon tumours. They mainly occur in children and sometimes in young adults. "Diffuse midline gliomas with histone H3-K27M mutation" is a newly recognized entity in the revised 2016 World Health Organization classification. Classied as grade IV, even when mitotic figures, microvascular proliferation, and necrosis are not observed, these tumours are aggressive and predict a poor prognosis for the patient.
Methods: Retrospective review to determine the prevalence, morphologic features and outcome of "Diffuse midline gliomas with histone H3-K27M mutation" diagnosis in our center since 2016.
Results: 3 patients with brainstem gliomas were identified. 1 was female and 2 were male. Age at diagnoses was 1, 8 and 9 and magnetic resonance (MR) images showed that their tumours were located in the third ventricle, cerebellopontine anlge and thalamus. Pathology demonstrated a primitive neuroectodermal tumour arising within low grade astrocytoma in one case, diffuse astrocytoma in the second and high grade astrocytoma in the third. All 3 samples were negative for the IDH1 R132H mutation by immunohistochemistry and positive for the H3 K27M mutation. First patient died 4 years after diagnosis, the other two continue in treatment with 7 and 16 months of survival.
Conclusion: This newly defined entity represents a critical diagnostic challenge for practicing surgical pathologists. These cases underline the importance of molecular evaluation to correctly subtype gliomas due to its prognostic and clinical significance.

E-PS-17-020

Glioblastoma with carcinomatous differentiation or tumour-to-tumour metastasis?

A. Fioravanzo[1], M. Simbolo[1], D. Giampiccolo[2], R. Damante[2], G. Pinna[2], A. Scarpa[3], V. Barresi[1]
[1] Department of Diagnostics and Public Health, Section of Anatomical Pathology, University and Hospital Trust of Verona, Italy, [2] Department of Neurosciences, Unit of Neurosurgery, Hospital Trust of Verona, Italy, [3] Department of Diagnostics and Public Health, Section of Anatomical Pathology and ARC-Net Research Center, University and Hospital Trust of Verona, Italy

Background & Objectives: Glioblastomas can be heterogeneous neoplasms with carcinomatous components of challenging interpretation. Herein we describe a glioblastoma with carcinomatous features and clues for differential diagnosis between aberrant differentiation and tumour-to-tumour metastasis.
Methods: A 70-year-old man presented with a month history of motor and speech difficulties and mood deflection. Magnetic resonance imaging revealed an inhomogeneous frontal mass with ring enhancement. Total-body computed tomography identified a solid lesion in the left lung with mediastinal multi-nodal involvement. The patient underwent surgical removal of the brain mass and biopsy of the lung tumour. Histopathological, immunohistochemical and molecular analyses were carried out on both tumours.
Results: The brain tumour showed two intermingled components: one with glioblastomatous morphology; one with carcinomatous morphology. The former was positive for GFAP and OLIG-2, while the latter was

positive for cytokeratin AE1/AE3, CK7 and NapsinA and negative for TTF-1. Molecular analysis revealed *KRAS Gly12Asp* and *AKT1* mutation in the carcinomatous, but not in the glioblastomatous component; none of the components had *IDH1/IDH2* or *ATRX* mutations. The pulmonary lesion was a primary adenocarcinoma (CK7, TTF-1 and NapsinA positive) with *KRAS Gly12Asp* mutation.
Conclusion: Molecular features indicated that the brain tumour was an *IDH* wild-type glioblastoma containing a metastasis from lung adenocarcinoma, with loss of TTF-1 expression and *AKT1* mutation acquisition during metastatization. Metastases to glioblastomas are exceedingly rare and this is the first report supported by molecular analysis.

E-PS-17-021
Intracranial hemangiopericytoma: a case presentation
A. Baliaka[1], M. Kilmpasani[1], N. Pastelli[1], I. Dimitriadis[1], I. Matzarakis[1], I. Karafoulidou[1], S. Papaemmanouil[1]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece

Background & Objectives: Central nervous system hemangiopericytoma (HPC) is a rare, dural-based neoplasm, accounting for <1% of all intracranial tumours. It arises from the Zimmerman pericytes and postcapillary venules and usually affects adults in the 4th-6th decade of life.
Methods: A 70-year-old woman presented to our Hospital suffering from tinnitus and headaches. Radiological evaluation revealed a hyperdense, highly vascular, dural-based lesion in the left temporal region. Intraoperatively, tissue material was sent for frozen sections. Subsequently, a gross total resection was undertaken.
Results: The histological examination revealed a neoplasm characterised by high cellularity with closely apposed ovoid or spindle cells with mild to moderate atypia, arranged in a haphazard pattern, surrounding numerous, thin-walled, branching vessels (SMA+, CD31+, CD34+). A rich network of reticulin fibers (Gomori+) typically invested individual tumour cells. Focal necrosis and 4-5 mitoses per 10 HPF were also observed. Immunohistochemically, the neoplastic cells were strongly positive for CD34 and focally for BCL-2 and SMA and negative for CAM5.2, EMA, Vimentin, S-100, CD57, CD31 and desmin. The proliferation index Ki67 was expressed in 5% of the neoplastic cells. The morphological and immunohistochemical features favored the diagnosis of a grade II HPC.
Conclusion: Intracranial hemangiopericytoma (HPC) is a rare neoplasm that remarkably mimics a meningioma clinically and radiologically; thus, the detailed histopathological review is the only means of its accurate diagnosis. Total surgical resection, when feasible, is the first choice of treatment in all the cases of HPC. In case of malignant HPC, postoperative radiotherapy is strongly recommended even after an apparently complete tumour resection.

E-PS-17-022
Chondroma in the lumbar spine: case report
F. Mundim[1], M. Engelman[1], R. Grande[1], S. Vasconcelos[1], A. Fontes[1], B. Godoy[1], G. Assis[1], R. Gusmao[1], T. Guimaraes[1], P. Mundim[2]
[1] UNIVAS, Brazil, [2] UNIFENAS, Brazil

Background & Objectives: Chondromas are benign tumours that rarely present within the lumbar spine. Although chondromas are generally asymptomatic, they can cause many neurological symptoms of slow development. Careful preoperative diagnosis and complete removal of the tumour are important due to transformation into malignant neoplasia.
Methods: Analyzing medical records with patient's permission and respecting confidentiality.
Results: A 75-year-old man presented to the neurology department of Samuel Libânio Hospital (Pouso Alegre, MG, Brazil) with a complaint of paresthesia in the lower limbs. Magnetic nuclear resonance was performed, demonstrating an intracanal, extradural, lobulated solid lesion located in the left posterolateral epidural region of L3-L4, compressing and deforming the dural sac and the cauda equina roots. In the histopathological analysis, it showed fragments of fibroadiposal connective tissue and hyaline cartilage, histologically benign, well differentiated, mature, suggestive of a Chondroma without evidence of anaplasia. This diagnosis was confirmed by immunohistochemical examination revealing that the chondroid nodulation observed corresponds to a small chondroma of soft parts with positivity for S-100 protein.
Conclusion: Based on our experience, we propose that chondromas should be considered as a differential diagnosis in the assessment of spinal tumours.

E-PS-17-023
Papillary Glioneuronal Tumour (PGNT) in a 12 years old girl: a case report of a rare CNS neoplasm
L.L. Sousa Veras[1], A. Costa Rendeiro[1], N. Soares de Menezes[2,1], R. Manuel Reis[1], M. de Medeiros Matsushita[1]
[1] Barretos Cancer Hospital, Brazil, [2] European Society of Pathology, Brazil

Background & Objectives: A 12 years old girl with generalized tonic-clonic seizure in the last 3 weeks, in use of anticonvulsant therapy and normal neurological examination. MRI showed an expansile solid-cystic lesion in the left temporal lobe, with ill-defined limits, measuring 3.5 x 2.6 x 3.1 cm. The imaging studies suggest a low-grade glial lesion or a tumour of neuronal lineage and the lesion was totally resected. This case report intends to present an exceedingly rare CNS neoplasm.
Methods: Microscopically, it is a biphasic tumour, with cells arranged in a perivascular fashion forming pseudopapillary structures. A layer of cuboidal to fusiform glial cells is seen lining the hyalinized vessels which are strongly positive for GFAP. A neuronal cell population is seen variably admixed with glial cells exhibiting immunoexpression for synaptophysin. Mitoses, microvascular proliferation and necrosis are absent. Ki-67 is positive in less than 1% of tumour cells and EMA was negative.
Results: The morphological findings and the immunohistochemical profile corroborate the diagnosis of PGNT, WHO grade I. PGNT is a rare, low-grade biphasic neoplasm (glioneuronal) with pseudopapillary architecture, representing less than 0.02% of intracranial tumours. It affects young adults (mean age 27 years). The most common location is supratentorial mainly in the temporal lobe. The translocation t (9; 17) (q31; q24), resulting in a fusion oncogene SLC44A1-PRKCA, is present in a high proportion of cases.
Conclusion: Most PGNTs have an indolent behavior but a minority of the cases present atypical morphological features or late biological progression. There have been reports of extraneural metastases involving the pleura bilaterally and the left breast, 4.5 years after the initial resection.

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E-PS-17-024
Intratumoral heterogeneity in a paediatric posterior fossa group-A ependymoma: a case report
A. Araki[1], M. Kool[2,3], J. Gojo[4], I. Slavc[4], T. Czech[5], C. Haberler[1]
[1] Institute of Neurology, Medical University of Vienna, Austria
[2] Hopp Children's Cancer Center at the NCT Heidelberg, Heidelberg, Germany, [3] Division of Paediatric Neurooncology of the German Cancer Research Center, Heidelberg, Germany, [4] Department of Paediatrics, Medical University of Vienna, Austria, [5] Department of Neurosurgery, Medical University of Vienna, Austria

Background & Objectives: Ependymomas represent the third most common brain tumours in children. DNA methylation patterns unraveled considerable heterogeneity classifying into nine molecular subgroups including posterior fossa group-A (PFA) and B tumours. PFA-ependymomas are most frequent in children and associated with a less favorable prognosis than PFB ependymomas. Within PFA-ependymomas chromosome 1q gain proved as poor prognosis marker. PFA ependymomas could be further classified into nine subtypes with PFA-1c enriched for 1q gain. To date, intratumoral heterogeneity has not been described in ependymomas. We report a PFA-1c tumour showing two distinct tumour parts with different histopathological and genomic alterations.
Methods: A 2.5-year-old female presented with a brain tumour in the fourth ventricle. Despite total resection, postoperative RTX and CTX she died 4 years after diagnosis. Histopathological analysis, FISH, and DNA methylation profiling was performed using formalin-fixed paraffin-embedded (FFPE) tumour tissue.
Results: Histological examination revealed two morphologically different parts: part-I had characteristic features of an anaplastic ependymoma with chromosome 1q gain, part-II demonstrated an unusual morphology with small gemistocytic astrocytes reminiscent of astrocytoma with balanced chromosome 1. DNA methylation profiling classified both tumours as PFA-1c, yet copy umber profiles were different with 1q gain and 10q loss in part-I, and a balanced chromosome 1 and chromosome 2, 9, 11 and 17 gains in part-II.
Conclusion: This case illustrates that different molecular subclones may be present in EPN and emphasizes the importance to control the morphology of tumour tissue used for molecular analyses.

E-PS-17-025
Multiple Sclerosis and bronchoalveolar carcinoma: a double case study report

I. Dimitriadis[1], N.D. Savvidou[2], D. Kamplioni[2], P. Konstantinidou[2], F. Louka[2], D. Anestakis[2]
[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Autopsy Histopathology, Aristotle University of Thessaloniki, Greece

Background & Objectives: Multiple sclerosis (MS) is a chronic autoimmune disorder of the CNS that induces the formula of plaques-areas characterised by demyelination, axon loss and oligodendrocyte death. MS is accompanied by disturbances of sensory-motor and autonomic functions.Bronchoalveolar carcinoma (BAC) is defined as a lung adenocarcinoma which presents a non-invasive lepidic growth and is predominantly asymptomatic.Thefollowing case is of considerable interest due to the rare combination of both diseases.
Methods: We received histological sections of brain, lung, kidney, liver and heart tissue samples. The samples were studied immunohistochemically with appropriate antibodies.
Results: Histological section of brain tissue presents edematous areas, reactive astrocytes, as well as cell autolysis/degeneration, perivascular lymphocyte accumulation, hemorrhagic infiltrations and capillary congestion in several locations.Examination of lung tissue shows edema, signs of pneumonia/ pulmonary fibrosis.Characteristics of neoplasia are also detected, including adenoid formations and disseminated squamous cells with relatively abnormal nuclei and granular chromatin. Myocardium presents ischemic areas.
Conclusion: MS is a multifaceted disease related to *HLA-DRB1* gene in the MHC class II region and environmentally to Epstein-Barr virus infection, vitamin D deficiency and cigarette smoking.Prognosis centers on the quality of life and prospects for disability.Nowadays, there aren't curative FDA-approved therapies for MS, though immunomodulator agents are used for symptomatic relief. Future treatment may involve hematopoietic and mesenchymal stem cells.Genetic pathogenesis of BAC includes stepwise genetic hits, mostly K-ras, EGFR and HER2 mutations. Significant prognostic factors are tumour size and mitotic rate. Treatment includes surgical resection or targeted chemotherapy and EGFR tyrosine kinase inhibitors.

E-PS-17-026
Intracerebral schwannoma in a 20-year-old girl: a case report

B. Laabidi[1,2], R. Hedhli[1,2], R. Yaich[1,2], N. Mansouri[2], F. Gargouri[2], A. Saidi[1,2], A. Bouziani[2], I. Msakni[2]
[1] Tunis El Manar University, Medicine School of Tunis, Tunisia, [2] Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: Intracerebral schwannoma is an extremely rare brain tumour accounting for about 6 to 8% of all primary intracranial tumours. It is typically occurring at middle age.
We report our experience with the diagnostic management of this entity through a case report describing its clinical, radiological and pathological features.
Methods: The present report is of a 20-year-old female who presented a cystic and solid parietal mass. The patient presented seizures and elevated intracranial pressure. Neuroradiologic features showed a right parietal lesion with cystic and tissular components, intensely enhanced after injecting intravenous gadolinium. The tumour was removed through a right parietal craniotomy.
Results: Histological and immunohistochemical findings confirmed the diagnosis of intracerebral schwannoma. The patient is alive without progressive local disease or metastasis.
Conclusion: Intracerebral schwannoma is an extremely rare benign tumour. It is important to recognize it, particularly in younger patients, given its benign nature, radiological resemblance to other tumours and favorable response to surgical removal without toxic treatment.

E-PS-17-027
Review of ependymal tumours in La Paz University Hospital

R.S. Melean Jauregui[1], O. Cerezo Aranda[1], N. Ibarra Soraluce[1], A. Pezzella Risueño[1], R. Regojo[1], I. Esteban-Rodriguez[1]
[1] Hospital Universitario La Paz, Spain

Background & Objectives: To review the clinical records of all ependymal tumours diagnosed in La Paz Hospital between 2000 and 2018.
Methods: We searched our database for all subependymomas, myxopapillary ependymomas and ependymomas and collected clinical data about age, location, histomorphology, treatment and outcome. Grade was reviewed and given in accordance to WHO 2017 criteria.
Results: Among 45 ependymal tumours, the most common were ependymomas (36 cases) followed by myxopapillary ependymomas (7) and subependymomas (2). Ependymomas were frequently located in the posterior fossa whereas myxopapillary ependymomas and subependymomas were spinal. Of the 13 cases diagnosed in children (mean age 5) most of them were located in the posterior fossa (69%) and half of them recurred even when complete resection was achieved. In adults (mean age 44): 2 subependymomas, 7 myxopapillary ependymomas and 23 ependymomas were diagnosed. The most frequent location was the spine and the majority were grade II. Posterior fossa tumours recurred the most and were mainly partially resected. Ependymomas were the only tumours with a fatal outcome (8 cases), most of them were grade II and were equally located in the supra and infratentorial space.
Conclusion: Ependymal tumours have a highly variable clinical behaviour. Our results match the literature highlighting that in children they are frequently located in the posterior fossa, and in this location complete resection is not always possible, leading to a higher chance of recurrence. Also, a lower grade does not warrant a better outcome, hence molecular sub-classification is expected to significantly support treatment decisions and help predict biological behaviour.

E-PS-17-028

Diffuse leptomeningeal glioneuronal tumour presenting with long standing intractable seizure

L. Pal[1], S. Katiyar[2], A. Mehrotra[3]
[1] Sanjay Gandhi Postgraduate Institute of Medical Sciences, India,
[2] Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, India, [3] Department of Neurosurgery, Sanjay Gandhi Postgraduate Instute of Medical Sciences, India

Background & Objectives: Diffuse leptomeningeal glioneuronal tumours (DL-GNT) are uncommon neoplasms with recent acquisition in WHO 2016 classification of central nervous system tumours and less than 100 cases have been reported till date. DL-GNT is characterised by predominant and widespread involvement of the leptomeninges, oligodendroglial like cytology with evidence of neuronal differentiation. The vast majority of DL-GNTs present as low-grade tumours, however, WHO grade has yet not been assigned due to less number of reported cases and inadequate clinical follow up. DL-GNT are commonly encounterd in children and mostly located in posterior fossa and spinal cord. However, we present two cases of this newly added entity located supratentorially in adults.
Methods: The cases were retrieved from the institutional data base. After routine histopathology, immunohistochemistry was performed on 3.5-micron thick paraffin embedded sections using polymer based avidin-biotin peroxidase method. The primary antibodies used were GFAP, Vimentin, Neurofilament, NeuN, Synaptophysin, Ki-67, IDH-1, ATRX and p53. Diaminobenzidine /H2O2 was used as substrate chromogen.
Results: Case 1: A 24-year-old male presented with left sided focal seizures for 5 years. Imaging revealed a large ill-defined mass in right frontotemporal lobe of approximately 10x6 cm which was T1 hypointense and T2 hyperintense. Right fronto-temporal craniotomy and gross total excision of the tumour was performed. On histopathology, the tumour was seen diffusely infiltrating the leptomeninges with presence of intraparenchymal nodules. Multiple cystic spaces of varying sizes filled with mucinous material were noted. These cystic spaces were surrounded by small oligodendroglial like cells. Mitosis / endothelial proliferation /necrosis were not observed. Areas of astrocytic morphology could also be appreciated. On immunohistochemistry, the tumour cells were variably positive for synaptophysin, vimentin, GFAP and NeuN. IDH1 was negative. There was no ATRX mutation. Ki67 index was ~2%. Case 2: A 50-year-old gentleman presented with multiple episodes of seizures for 16 years. MRI revealed well defined lesion in medial part of left temporal lobe. Histopathology showed multiple foci of leptomeningeal tumour composed of bland oligodendroglioma like cells that were positive for GFAP, synaptophysin and vimentin. Ki67 index was < 1%. IDH1 and ATRX were negative. Foci of calcification were also observed. Underlying brain parenchyma was involved focally.
Conclusion: Diffuse leptomeningeal glioneuronal tumour was first described by Yamamoto et al as multifocal neurocytoma/gangliocytoma with extensive leptomeningeal dissemination in 1996. These tumours are commonly encountered in children and less frequently in adults. Both of our cases presented in adults, located supratentorially. Clinical behavior in reported series is not uniform and anaplastic changes has also been reported. As both our patients presented with long standing seizure with glioneuronal features immunohistochemically, probably indicates the diverse spectrum of this entity.

E-PS-17-029

Rosette-forming glioneuronal tumour: a case report

R.I. Bermudez Cameo[1], H.P. Almanzar Comas[1], A. Arellano Alvarez[1], J.I. Franco[1], M.J. Viso Soriano[1], S. Bakali Badesa[1], A. Sobrino Prados[1], N. Estrada Mallarino[1], J. Alfaro Torres[1], I. Marquina Ibañez[1], B. Roche Latasa[1], M.F. Aznar Uson[1], L. Hombria Laviña[1], A. Valero Torres[1]
[1] Hospital Universitario Miguel Servet Zaragoza, Spain

Background & Objectives: Rosette-forming glioneuronal tumour (RGNT) is an unusual central nervous system (CNS) tumour more frequently in young adults, with barely 150 cases reported. Nowadays, RGNT is considered as a rare slow growing mixed glioneuronal tumour, and it has been classified as a new CNS tumour in the 2007 WHO classification. Before it has belonged to the group "rosette-forming glioneuronal tumours from IV ventricle". In 2016 those tumours have been renamed as "rosette-forming glioneuronal tumours" because other locations have been reported (brainstem, pineal gland, thalamus).
Methods: A 13-year-old boy with frontal headache and fever for months. No other neurological symptoms were described. The magnetic resonance image (MRI) revealed a pineal tumour with triventricular hydrocephalus. Surgical resection of the tumour was performed in May 2018. After the surgery, we received several irregular fragments that measures 2,1 x 2,3 cm.
Results: Histological examination showed areas composed by rounded cells with clear cytoplasm with round and monotonous nuclei located around capillaries, arranged as rosettes with fibrilar content. Other areas showed fibrillar neuropilo with rounded cells that resembles oligodendrocites with loose mucoid areas. Rosettes and some tumour areas expressed Synaptophysin. Also stained positivity for glial fibrillary acidic protein (GFAP). IDH1 and p53 were both negatives. Ki67 index was< 1%.
Conclusion: RGNT is a biphasic tumour. The first component consists of neurocites forming perivascular rosettes and/or pseudo rosettes. These component is made up by astrocytes, resembling a pilocytic astrocytoma. Clinical, radiological and immunohystochemial features of RGNT are not well-defined, and current treatments and prognosis are hard to establish, that indicate the need of further investigations. Despite the benign histological grade, knowledge of the truly biology of this tumour remains unclear. Some papers have described aggressive behavior of RGNT as recurrence and metastasis.

E-PS-17-030

A parasagittal fibrous meningioma in a Sturge-Weber Syndrome patient

M. Alorjani[1], S. Al Bashir[1], S. Daoud[1]
[1] King Abdullah University Hospital, Jordan University of Science and Technology, Jordan

Background & Objectives: Sturge–Weber syndrome (SWS) is a rare sporadic neurocutaneous disease, usually characterised by features including facial angiomas in the form of port-wine stain with ipsilateral leptomeningeal angiomatosis and choroidal angioma. Brain angiomas are thought to arise from a mutation in the guanine nucleotide-binding protein G(q) subunit alpha (GNAQ), resulting in dysregulation of endothelin, a G-protein coupled receptor, resulting in the vascular malformations found in SWS. Meningiomas in SWS patients have been described in only two case reports in the literature, both of intraventricular location; one of them was of psammomatous type and the second was angiomatous. We report a parasagittal fibrous meningioma arising in a 30-year-old male with SWS.
Methods: A 30-year-old, man known to have SWS, with history of epilepsy for the last 6 years. His seizure attacks worsened recently; a reason for which he was investigated. CT scan in February, 2019 showed gyriform pattern of calcification in the left cerebral hemisphere with relatively reduced parenchymal volume (findings in keeping with the patient history of SWS), with a large hypoattenuating area seen in the left frontoparietal lobe. On MRI scan, there was a well-defined dural-based soft tissue mass in the left parasagittal parietal region, measuring 2.7 * 2.5 cm, in keeping with meningioma. The tumour was excised and sent to the laboratory for pathological examination.
Results: Diagnosis: Fibrous meningioma, WHO grade I. The included portion of leptomeninges appeared thickened showing prominent dilated and thin vascular spaces along with increased cortical vascularity, features supporting the imaging findings of SWS.

Our case is diagnosed in a 30-year-old male with SWS, different from the two previously reported cases in location and type. Both of the other two cases were of intraventricular location; one was of psammomatous type in a 30-year-old female, while the other was angiomatous in a 3-year-old boy.
Conclusion: Meningioma has been rarely reported in association with SWS. It would be wise to investigate such rare cases of meningioma arising in SWS patients for the GNAQ gene mutation (known in SWS angiomas) to see if there is a shared mutation that may suggest a common pathway.

E-PS-17-031
Molecular imaging for automated tissue differentiation in high heterogeneous tumours
V. Sergeeva[1], A. Sorokin[2], D. Ivanov[2], V. Shurkhay[3], P. Nikitin[3], V. Eliferov[2], S. Pekov[4], K. Bocharov[4], I. Popov[2]
[1] Emanuel Institute for Biochemical Physics, Russian Academy of Sciences, Russia, [2] Moscow Institute of Physics and Technology, Moscow, Russia, [3] N.N. Burdenko National Scientific and Practical Center for Neurosurgery, Ministry of Healthcare of the Russia, [4] V.L. Talrose Institute for Energy Problems of Chemical Physics, Russian Academy of Sciences, Russia

Background & Objectives: Implementation of mass spectrometry for molecular profiling allows automated malignant and intact tissue differentiation in surgical samples. However, it requires the application of multi-criteria classifiers and regressors to overcome high natural biological variability between samples. In this study, we apply MALDI-imaging mass spectrometry (MALDI-MSI) to high-heterogeneous glial tumours in order to determine the spatial distribution of lipids through the histological sample for improvement of tissue differentitation algorithms.
Methods: Stereotactic biopsy samples of glial tumours were cryosectioned and covered with 2,5-dihydroxybenzoic acid by sublimation. MALDI-images were obtained using Bruker ultrafleXtreme mass spectrometer in positive ion mode. Then, the MALDI matrix was washed out, and slides were stained with H&E.
Results: Major zones on each mass spectrometry image were determined using nonlinear dimension reduction algorithm (t-SNE) application followed by k-means clustering. Each zone was classified accordingly to the histological annotation of the sample, and characteristic mass spectra of each type of tissue were determined. Based on these spectra the multi-criteria classifiers and regressors for tissue differentiation were constructed.
Conclusion: Combination of MALDI-MSI and tissue staining is the only way to reliably determine the characteristic molecular profiles for high-heterogeneous tumours as it became possible to match each mass spectra to exact tissue type. This information allows creating algorithms for tissue differentiation based on distinctive features combinations extracted from characteristic spectra. Therefore it reveals the possibility for automated pathological tissue differentiation in biopsy samples of glial tumours with high accuracy.

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E-PS-17-032
On an integrative psychoneuro-pathology: examples for neurological education and research
E. Neu[1], M. Michailov[1], M. Bornhausen[1], V. Foltin[2], B. Rattel[3], C. Lütge[4], G. Weber[5], D.G. Weiss[6]
[1] Inst. Umweltmedizin c/o ICSD/IAS e.V. Muenchen, Germany, [2] St. Elisabeth Univ., Bratislava, Slovakia, [3] Amgen Res. Munich (Exec. Dir.) & IUM c/o ICSD/IAS e.V., Germany, [4] Techn. Univ. Muenchen, Inst. Ethics (Dir.), Germany, [5] Univ. Lxbg. and Vienna, Fac. Psychology (Dean), Austria, [6] Univ. Rostock, Inst. Physiology (Dir.a.D.), Germany

Background & Objectives: Neurology is essential clinical discipline for all health-sciences (medicine-psychology,etc.). An example for practical *holistic& multidimensional psychoneuro-pathology* is given.
Methods: Psychological items/electrical & motor-activities. Ref.: Neu, Michailov et-al. 1-Pathology: ESP-2018-Bilbao, Eur.J.Pathol. 473/Suppl.1:S180; ESP-2017-Amsterdam, Eur.J.Pathol. 471/Suppl.1:S245/S284/S307;Int.Acad.Pathol./ESP-2016-Köln, Eur.J.Pathol. 469/Suppl.1:S245. 2-WFN-2016-Santiago-de-Chile, J.Neurol.Sci.357/S1, no.183,187,199,234). EAN-2015-Berlin Eur.J.Neurol.22/S1, p.281,487-490,832. 3-WPA-2018-Mexico-City (psychiatry), Abs.-Book WCP18-0584/-0625/0643/0654. EPA-2019-Warschau (Eur.Psychiatry 56/S1, S689); 2018-Nice, Eur.Psychiatry 48/S1, S623&567&662. 4-[a]-IUPsyS-2012-Cape-Town, Int.J.Psychol 47:407; 2008-Berlin, 43/3-4:154,248,615,799. [b]-EFPA-2009 Oslo (psychology), 55-56. [c]-IUPS-2017-Rio-de-Janeiro (physiology), AB:No. 997,999,1001,1003; 1977-Paris Proc13/1497-9; 1974-New-Delhi, Proc.11/273&378&1133. 5-SIU-2016-Buenos-Aires, WorldJ.Urol. 34/S1,126&223. 2007-Paris 70/S3A:232-3/2004-Honolulu Br.J.Urol. 94:24-5/258-9/305.
Results: A-PSYCHONEURO-PHYSIOLOGY. *Probands-Patients* (n=30, p<0.05-0.01): Physical education from Indian medicine incl. Yoga (asanas & pranayamas): Voluntary apnoea/duration increase/10-25%, respiratory rate/10-30% & heart rate decrease/5-10%. Effects augmentation after 2 months/voluntary apnoea>100%, vital capacity>10%. Respiratory therapy/pranayama led to positive changes in psychic items: relaxed-45%/tranquil-50%/clear-10%. Also Music therapy had positive item influence, relaxed-20%/tranqui1-5%/passive-25%/open-25%. Effects are stronger before surgical intervention (oncological patients) then after this. B-Angio-Cardiological Psychoneuro-Pathology. (*Patients-animals/*n=20+25, p<0.05-0.01): Observations on patients about pathophysiological reactions of bronchodilators & tocolytic therapy (*ß-sympathomimetics)* are conform with experiments: After buphenin/fenoterol adrenalin-contraction of rat aorta decreased, cardiac&respiratory frequency in cats increased, blood pressure decreased. It appear EEG-patterns synchronization in cats (stereotaxically implanted electrodes: hippocampus/hypothalamus posterior/nucleus tractus solitarii). C-GENITO-UROLOGICAL PSYCHONEURO-PATHOLOGY. Neurological-gynaecological-urological patients (cystotonometry/n=150, p<0.05-0.01): After radiochemotherapy (radiocystitis: Gamma- & X-irradiation-70Gy) vesical-tone increased, micturition-pressure & urothelial-electropotentials decreased. Psychophysiological training (see A) counteracted functional disturbances, acc.to B&C.
Conclusion: Observations from A-C demonstrate example for an *integrative psychoneuro-pathology,* i.e. application of practices from clinical&experimental research in neurological education of students (graduate&post-graduate) in context of UNO-Agenda21 for better health-education,etc. Interdisciplinary neurological observations are reflected in ref.

E-PS-17-033
Neuropathology in context of anthropology and psychosomatics
M. Michailov[1], E. Neu[1], P. Birkenbihl[1], T. Plattner[1], B. Rattel[2], T. Senn[1], J. Foltinova[3], C. Lütge[4], M. Schratz[5], G. Weber[6]
[1] Inst. Umweltmedizin c/o ICSD/IAS e.V. München, [2] Amgen Res. Munich & IUM c/o ICSD/IAS e.V., [3] Univ. Bratislava, Med. Fac., [4] Techn. Univ. Muenchen, Inst. Ethics, [5] Univ. Innsbruck, School Educ., [6] Univ. Lxbg. and Vienna, Fac. Psychology

Background & Objectives: Neurology is fundamental discipline for anthropological sciences – medicine, psychology upto biophysics/-

chemistry. Future needs creation of an integrative neurology considering holistic&multidimensional the human. Psychosomatics is essential for neurological therapy and prophylaxis.
During Opening-Ceremony of 18th-World-Congress-Psychosomatic-Medicine (ICPM-2005-Kobe) were present their majesties Emperor and Empress of Japan, Prime&Ministers for Science-Education-others&prominent-scientists. Emperor AKIHITO honoured congress by strategical ideas, "total symptoms of mind&body, seeking ways of holistic care… it is extremely important for patients … my hope contributes … the progress of medical science and people's happiness in the entire world".
Methods: Dedication for moral-scientific support of project: Austria: K.Lorenz*, E.Busek, France: J.Dausset*, J.-M.Lehn*, Germany-GB: M.Eigen*, E.Neher*, H.Michel*, B.Vogel, W.Scheel, J.&Th.v.Uexküll, GB: A.Hewish*, B.Josephson*, N.Tinbergen*, India-USA: D.Hubel*, H.G.Khorana*, L.Pauling*, K.Singh, Japan-USA: K.Fukui*, Y.Ikemi, S.Tonegawa*, Norway: D.Föllesdal, L.-R.Langslet, Russia: N.Basov*, A.Prokhorov*, A.Sacharow*, Sweden: S.Bergström*, B.Samuelson*, South-Africa: Bishop D.Tutu* (*Nobel Laureate).
Results: Conception Model for an integrative neurology related to integral-anthropology based on physiological and pragmatic anthropology from Immanuel KANT considers different "human-areas" of human ("Integrationsebenen"), related to psychosomatic (Thure von UEXKÜLL) and somatopsychic theories (Yujiro IKEMI) is necessary. Somatic/psychical/mental/philosophical-spiritual, also human interaction with nature&society (ref. see Neu et al. this congress).
Conclusion: Foundation of International Academy for Neurology by network of clinics from selected trans-European countries (America/Asia/others), similar to European-Acad-Neurology/EAN-2015-Berlin, but enlarged scientific-organizatory principles such as common personnel (similar to UNO-employees), honorary-permanent directors, professors (meritocratic principle), possibility for whole life working, scientist-participation from different disciplines (inter-disciplinarity) could help for creation of integrative neurology supporting UNO-Agenda21 for better health-education-ecology-economy on global level.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-18 | Ophthalmic Pathology

E-PS-18-001
Ciliary body melanoma with optic nerve invasion and peculiar growth pattern

A. Dumitru[1], M. Costache[1,2], M. Sajin[3,4,5], T. Georgescu[1]
[1] Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [2] Department of Pathology, Emergency University Hospital Bucharest, Romania, [3] SUUB, Romania, [4] UMF Carol Davila, Romania, [5] European Society of Pathology, Romania

Background & Objectives: The most common primary malignancy of the eye in adults is the uveal melanoma. Frequently, uveal melanoma arises from choroid or iris. Ciliary body melanoma is a rare if not exceptional subtype of uveal melanoma being reported in 1 of 10 cases of all intraocular melanomas. In this paper we will expose a case report about a multinodular growth pattern of a ciliary body melanoma with optic nerv invasion and an unusual anterior extraocular extension.
Methods: The patient, age 80, presented with permanent atrial fibrillation and a large tumoral protrusion outside the left eye globe. After clinical and imagistic re-evaluation, the patient was diagnosed with multiple hepatic and lung metastases. The patient was firstly diagnosed with a small ciliary melanoma 10 years ago but at that time, she refused surgical treatment. After surgical excision, the specimen was sent for histopathological examination to the Department of Pathology of the Emergency University Hospital in Bucharest
Results: Specimen samples were fixed with 10% buffered formalin and were processed by conventional histopathological methods using paraffin embedding, sectioning and Hematoxylin–Eosin staining. We have also performed immunohistochemical tests. Light microscopy examination revealed a large-sized ciliary body melanoma consisting of heavily pigment spindle and epithelioid type cells (mixed cell type according to the modified Calendar classification). The posterior chamber of the eye was not affected but we observed multiple scattered malignant cells within the optic nerve, a very unusual feature.
Conclusion: A comprehensive insight of the genetic, molecular and histopathological alterations in ocular melanoma can lead to an effective treatment. More information about drivers of uveal melanoma proliferation and metastasis should be gathered from multiple trials. Ciliary body melanoma has a poor prognosis due to early metastases but in our case, we emphasize the long-lasting evolution and peculiar anterior growth pattern.

E-PS-18-002
Intravascular Kaposi's sarcoma of the bulbar conjunctiva in an immunocompetent patient

T.A. Georgescu[1], A.C. Lisievici[2], A. Dumitru[2], L.M. Voinea[3,4], M. Sajin[2,5,6], M. Costache[1,2]
[1] Department of Pathology, Bucharest Emergency University Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Ophthalmology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [4] Department of Ophthalmology, Emergency University Hospital Bucharest, Romania, [5] SUUB, Romania, [6] European Society of Pathology, Romania

Background & Objectives: Kaposi's sarcoma (KS) is an uncommon spindle cell tumour of vascular origin, closely related to human herpes virus 8 infection. It usually appears in patients with acquired immunodeficiency syndrome (AIDS), immunosuppression or organ transplantation. Most cases involve the skin, but mucosa, lymph nodes and visceral organs can be affected as well. Conjunctival KS is extremely rare and encountered mostly in patients with AIDS. It tends to be indolent, but, as the tumour grows, it can alter ocular adnexal structures.
Methods: We report the case of a 60-year-old heterosexual male with unremarkable clinical history, presenting to the Department of Ophthalmology of the Emergency University Hospital in Bucharest, Romania with a recently emerged mass in the bulbar conjunctiva of the right eye. Biomicroscopy revealed a dark red nodular lesion of 6/3 mm, in the lower nasal bulbar conjunctiva. The left eye revealed no abnormalities. The patient was HIV negative, with no past or present lymphadenopathies or skin vascular lesions.
Results: After surgical excision, histopathological examination of the nodule revealed a variably whorled proliferation of monomorphic spindle cells, featuring 4 mitoses per 5HPF, with slit-like vascular spaces and extravasated erythrocytes, typical for KS. The nodule was completely surrounded by a thin vascular-like muscular wall, which was positive for SMA and desmin. Immunostaining for HHV8, CD34 and D2-40 revealed diffuse positivity across all tumour cells. The final diagnosis of intravascular KS of the bulbar conjunctiva was established.
Conclusion: Although conjunctival KS is rare in immunocompetent patients, the peculiarity of this case lies in its histopathological presentation as an intravascular tumour. To our knowledge, literature data on intravascular KS is limited to a series of six cases, including both immunocompetent and immunocompromised patients. We believe that our finding may represent an extremely rare morphological variant of KS.

E-PS-18-004

Eye and adnexa melanoma: experience of tertiary center

R. Almeida[1,2], B. Pimentão[1], H. Moreira[1], J. Fraga[1], A. Lai[1], C. Faria[1], V. Almeida[3], F. Ramalhosa[1], R.C. Oliveira[1], M.J. Julião[1], M.A. Cipriano[1]
[1] Centro Hospitalar e Universitário de Coimbra - Pathology department, Portugal, [2] Faculty of Medicine in Coimbra, Portugal, [3] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Portugal

Background & Objectives: Ocular melanoma is very uncommon, accounting for 5% of all melanomas, more common in white populations, rare in young people. It can develop de novo or from previous naevi, and in some cases is not be possible to determine the precise primary anatomical location, particularly in advanced lesions. Generally, the diagnosis is above 60y, there is no gender predilection, and a considerable proportion of patients have no clinical manifestations. Those with symptoms can experience photopsia, loss of vision, redness or pain.
Methods: We performed a retrospective research at Coimbra Hospital and Universitary Centre, over a period of 10y (2009-2019), and 18 cases of ocular melanoma were found. Then, we performed a basic statistical analysis with clinicopathological correlation.
Results: Our sample included 18 patients, ages between 34y and 84y, 11 males and 7 females. Anatomical location: conjunctiva (4 cases), choroid (7 cases), ciliary body (3 cases) and orbit (2 cases); eleven cases were diagnosed through biopsy and nine in surgical specimens; the median size of the tumours (among those 9 diagnosed in surgical specimen) was 19,3mm, dimensions between 12 and 30mm. Morphologically, 11% were fusocelular (2 cases), 50% were epithelioid (9 cases) and 39% had mixed pattern (6 cases). Of the 9 patients submitted to surgical excision, only 1 relapsed in the orbit, a case of a choroid melanoma, with extraocular extension of more than 5mm.
Conclusion: Ocular melanoma is associated with several characteristic chromosomal anomalies and mutations in several genes: GNAQ, GNA11, BAP1, SF3B1, and EIF1AX. In the following, we intend to perform some complementary studies, like BAP1 immunostaining, associated with high risk of metastasis. This work pretends to add some knowledge about this uncommon malignancy in a more uncommon location.

E-PS-18-005

Orbital Langerhans cell histiocytosis: a challenging diagnosis

G. Sahraoui[1], L. Bouzidi[1], R. Doghri[1], L. Charfi[1], K. Mrad[1], M. Driss[1]
[1] Institut Salah Azaiez, Tunisia

Background & Objectives: Langerhans cell histiocytosis (LCH) is a rare disorder of mononuclear phagocytic system. It is often diagnosed in the childhood. It primarily affects the skeletal system. Here we report a case of a solitary orbital LCH to highlight its pathological features and remind its differential diagnosis.
Methods: A previously healthy 2-year -old boy presented with a 2-month history of diffuse left periorbital swelling.
Results: MRI of the orbit showed left orbital rim lesion with bony destruction. Several diagnosis were discussed such as rhabdomyosarcoma, leukemia, lymphoma and neuroblastoma. Biopsy was performed. Microscopic examination showed a diffuse proliferation of mildly atypical cells resembling Langerhans cells, exhibiting vesicular and angulated nuclei, visible nucleoli with abundant cytoplasm, associated with eosinophil, lymphocyte, and macrophage. Immunohistochemistry was positive for protein S-100 and CD1a and negative for CD20, CD3, CD 30, Chromogranin, Synaptophysin, myogenin, desmin and CD68. Hence, a diagnosis of LCH was made.
Conclusion: Despite its rarity, any case of a child that presents an orbital involvement with osteolytic consequences may raise the suspicion of a Langerhans histiocytosis. The correlation between the particular histological features and S100 protein/CD1a positivity of Langerhans cells, the clinical findings and the radiological images confirming the bone erosion are considered adequate criteria for the diagnosis of the disease.

E-PS-18-006

Orbital lymphoma

G. Sahraoui[1], N. Redissi[1], R. Sellami[1], L. Charfi[1], R. Charfi[1], K. Mrad[1], M. Driss[1]
[1] Institut Salah Azaiez, Tunisia

Background & Objectives: Orbital lymphomas (OL) are rare, comprising only 1% of all non-Hodgkin's lymphoma. However, lymphomas are the most common primary orbital tumour in adults 60 years of age and older. Our study aimed to study the epidemiological and anatomopathological characteristics of OL.
Methods: We identified cases of OL diagnosed between January 2010 and December 2018.
Results: Our series included 9 cases of OL. The sex ratio was 1.2. The average age was 51 years (3-71 years). Diagnosis was made on biopsies in 5 cases and on tumour exicion in 4 cases. Tumour was on the right side in 3 cases, left in 2 cases and bilateral in 1 case. The side was not specified in the rest of the cases. All these lymphomas were phenotype B. The cells were small in 5 cases, medium in 1 case and large in 3 cases. Immunohistochemical study allowed to make the diagnosis of marginal zone lymphoma (MALT) in 5 cases, follicular lymphoma in 2 cases, large B-cell lymphoma developed on follicular lymphoma in 1 case and Burkitt lymphoma in 1 case.
Conclusion: MALT lymphomas constitute the majority of orbital non-Hodgkin'slymphomas. Clinical signs are unspecific. Surgical biopsy is essential for diagnosis.

E-PS-18-007

Massive retinal gliosis in a young woman with congenital toxoplasmosis

F. Pedica[1], M. Callea[1], N. Ahmed[2], F. Sanvito[1], C. Doglioni[1,2]
[1] Pathology Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy, [2] Vita-Salute San Raffaele University, Milan, Italy

Background & Objectives: Massive retinal gliosis in a rare benign condition characterised by a proliferation of non-atypical glial cells, called Müller cells, that affects the eye and has been described in association with several conditions, such as congenital malformations. We described a very rare case of a young woman with a history of congenital toxoplasmosis.
Methods: A young 25-year old woman underwent enuclation of the eye for a painful microphtalmia, caused by congenital toxoplasmosis. The eye was tough and shrunken with a maximum diameter of cm 1,8 and a short segment of optic nerve of cm 0,2. On cut section the bulb was substituted by a calcified nodule of cm 1,2 in diameter. The whole tissue was examined.
Results: The eye architecture was completely subverted by the presence of a diffuse nodular proliferation of spindle-shaped cells organized in whorls, with mycrocystic areas, involving 80% of the bulb and replaced the retina. These cells were immunoreactive for glial fibrillary acidic protein (GFAP) and neuron specific enolase (NSE), partially for S100 and negative for melanin marker Melan-A. These cells were intermingled with thick vessels with hyaline wall and there was extensive bone marrow metaplasia. No mitosis were identified and the optic nerve was preserved.
Conclusion: We concluded that this was a very rare case of massive retinal gliosis developed in collapsed shrunken eye because of a congenital toxoplasmosis. To our knowledge this is a very rare case and, since this is a mass-forming lesion growing inside the eye, histology is necessary for diagnosis.

E-PS-18-008

Mixed choroidal melanoma of the left eye - a case report and review of the literature

N.J. Lamas[1], M. Oliveira[1], L. Ferreira[1], C. Fleming[1], R. Amorim[2], J.R. Brandão[2], B. Fernandes[2], J.R. Alves[1], J.R. Vizcaíno[1]
[1] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Porto, Portugal, [2] Centro Hospitalar do Porto, Portugal

Background & Objectives: Melanoma of the uvea is the most frequent intraocular malignant tumour in adults with an estimated incidence of nearly 5 cases per million per year. Almost 90% of the tumours are located in the choroid. The long-term survival for patients with uveal melanoma is conditioned by the risk of metastasis, especially to the liver.
Methods: We report the case of a 77-year-old male with complaints of unspecific visual changes lasting for 4 months. The left eye examination revealed a bulky pigmented lesion associated with retinal detachment. The right eye was unremarkable. The patient had a diagnosis of skin melanoma 10 years before, without further recurrence; and a previous history of multiple skin basal cell carcinomas. Enucleation of the left eye was performed.
Results: An eye specimen weighing 10g was received, comprising a 3x2,8x2,8cm ocular globe, with a 1,9x1,2cm cornea and a 0,3cm optic nerve segment. Upon section, in the posterior area of the posterior chamber, we observed a neoplasia measuring 2,5cm (thickness) x 2cm (largest basal diameter), with well-defined limits, elastic consistency and heavily pigmented (dark brown). The morphological study revealed a solid neoplasia composed by both fusiform and epithelioid cells, with nuclear pleomorphism and frequent mitosis. Intense cytoplasmic brown pigment was observed focally. The neoplasia was permeated by a sparse lymphocytic inflammatory infiltrate. The estimated proliferative index (%Ki-67) was nearly 40%. The neoplasia did not involve the ciliar body, retina, optic nerve, vitreum, iris, lens, Schlemm channel, sclera and cornea. The diagnosis of mixed melanoma of the choroid was made. Additional positron emission tomography (PET) scan studies did not reveal metastasis.
Conclusion: This case illustrates the main features of these rare lesions, which might display aggressive behaviour. The metastasis risk significantly increases for lesions having largest basal diameters above 0,3mm. Thus, a long-term follow-up of the patients is mandatory.

E-PS-18-009

Primitive conjunctival sarcoma: clinical and histological features of three consecutive cases

N. Boujelbene[1], A. Rouatbi[2], L. Charfi[1], R. Doghri[1], I. Abbes[1], N. Ben Hamida[1], K. Mrad[1], M. Driss[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia, [2] National Eye Institute of Tunis, Tunisia

Background & Objectives: Primitive conjunctival sarcoma are rare malignancies. There has been a significant recent rise in the reporting of ocular and ocular adnexal sarcomas in association with acquired immunodeficiency syndrome, and irradiation of the orbits of children with hereditary retinoblastoma. We describe clinical, histological and immunohistochemical features of three cases of conjunctival growth with sarcomatous histological appearance.
Methods: Three consecutive cases were described. Conjunctival growth was present in all cases. Orbital imaging and excisional biopsy were performed in all cases. Immunohistochemical stains including Vimentin, CD68, PS100, CD34, Desmin and Cytokeratin was performed.
Results: Two men and a woman aged respectively of 38, 56 and 76 years old consulted for an expansive conjunctival process of a mean of one month duration. Clinical course was rapid in two cases with orbital extension in one case. An excisional biopsy was performed in all cases. Histological examination revealed undifferentiated sarcoma in two cases and histiocytic sarcoma in one case with pleomorphic lesional cells with abundant granular eosinophilic cytoplasm, large oval or round nuclei with prominent nucleoli, and occasional infolding of nuclei. Imunohistochemistry reveal vimentin positivity in all cases and CD68 positivity in histiocytic sarcoma. All the other antibodies were negative. Tumour recurrence occurred in two cases. A complement of external radiotherapy was performed in one case and surgical exenteration in another case.
Conclusion: Conjunctival sarcoma are very rare malignancies that we must consider in front of any conjunctival mass. Poor prognosis is often related to the diagnosis delay and insufficient initial surgical excision.

E-PS-18-010

Orbital location of Langerhans cell histiocytosis: clinical aspect and histological features

N. Boujelbene[1], A. Rouatbi[2], I. Abbes[1], L. Charfi[1], R. Doghri[1], N. Ben Hamida[1], H. Guizani[1], K. Mrad[1], M. Driss[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia, [2] National Eye Institute of Tunis, Tunisia

Background & Objectives: Orbital location of langerhans cell histiocytosis (LCH) is a rare entity usually affecting the child or young adult. The diagnosis is often difficult based on the lesional biopsy. Here we present four cases of orbital LCH with emphasize clinical presentation and histological features.
Methods: A comprehensive ophthalmological and general exam were performed in all cases. Orbital imaging (computed tomography or magnetic resonance imaging) and orbital biopsy were performed in all cases.
Results: Two men and two women were followed. Respectively aged 6, 20, 23 and 46 years old. All four patient presented with acute exophthalmos. Rapid growth was noted in two cases. Blurred vision was noted in 3 cases. Orbital imaging showed diffuse orbital tumour in all cases with orbital osteolysis in one case. Orbital incisional biopsy was performed in 3 cases and excisional biopsy in one case. Histologic features included numerous histiocytes with varying degrees of giant cell (GC) formation and scattered eosinophilic granulocytes (EG). Langerhans cells was confirmed by CD1a and S100 immunostaining. The diffuse character of the orbital invasion enabled excisional resection in 3 cases. We there for performed systemic chemotherapy in 3 cases with systemic corticosteroids in one case. Complete regression of the orbital lesion was achieved in all cases with no recurrence after a mean follow up of 18 months.
Conclusion: GC and EG should alert the pathologist to perform adequate immunohistochemistry. The clinical course of LCH is variable and the therapeutic response generally favorable.

E-PS-18-011

Pathological prognostic factors in retinoblastoma: a study of 85 cases in Tunisian children

N. Boujelbene[1], I. Abbes[1], R. Doghri[1], L. Charfi[1], R. Ben Ghorbel[1], D. Kacem[1], K. Mrad[1], M. Driss[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Retinoblastoma is the most common primary intraocular malignancy of childhood representing 3% of all childhood cancers. The main therapeutic priority for retinoblastoma is to first save the child's life through early tumour detection and prevention of metastatic spread. We aimed to assess histopathological factors in a series of children and to determine the most significant histopronostic factors in terms of risk recurrence, metastasis and death.

Methods: We retrospectively analysed the data of consecutive children diagnosed in our hospital between 1993 and 2009 as having retinoblastoma. For bilateral cases, only the most affected eyeball was included in the study. After pathological confirmation of the diagnosis, histological risk factors were noted. Survival curves were performed by the Kaplan-Meier and Cox regression methods.
Results: A total of 76 cases of retinoblastoma were included. Retinoblastoma has a good prognosis (overall survival rate at 2 years = 91.4%). In multivariate analysis, bilaterality and infiltration of the sectional section of the optic nerve were independent predictors of death. In univariate analysis, large size, massive choroid invasion, extra-scleral invasion, and invasion of the optic nerve section were significantly associated with high rates of death and metastasis. Invasion of the anterior chamber, extensive necrosis, invasion of the subarachnoidal space, and laminar and pre-laminar invasion of the optic nerve were not associated with a poor prognosis.
Conclusion: For optimal therapeutic management, it is necessary to insist on the collaboration between the pathologist and the clinician for a better precision and taking into consideration the histopronostic factors.

E-PS-18-012
Conjunctival melanoma
R. Narjess[1], N. Boujelbene[2], M. Driss[2], R. Doghri[2], I. Abbess[2], H. Arbi[2], K. Mrad[2], L. Charfi[2]
[1] Institut of Carcinology Salah Azaiz Tunis, Tunisia, [2] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives: Invasive melanoma of the conjunctiva accounts for 2%–5% of ocular malignancies. It is potentially deadly tumour despite progress and therapeutic advances in the management. The aim of this study was to undertake a retrospective analysis of the prognostic factors for conjunctival melanoma.
Methods: Demographic and clinicopathologic features including: location, tumour thickness, ulceration, mitotic rate, histology, lymphovascular invasion and association of primary acquired melanosis were reviewed.
Results: Our study identified 13 cases including 9 men and 4 women. The average age was 63 years old. The samples consist of excision specimens in 7 cases, 4 of which were incomplete, biopsies in 6 cases and one case of complete exenteration. The tumour was localized on the bulbar conjunctiva in 8 cases and in non-bulbar conjunctiva in 5 cases. The average thickness of the tumour was 3.8 (range from 1 to 13 mm). In 3 cases we noted the presence of a primary acquired melanosis. The average number of mitoses was 4 (1 to 15 mitotic figures per ten high-power fields). None of the specimens had a vascular embolus, ulceration or necrosis. The extension assessment was negative in all cases and 3 of the patients presented a local recurrence of which one presented 3 recurrences.
Conclusion: Conjunctival melanoma is a very rare malignancy. The tumour typically presents with a rapidly progressive, well defined mass that is, in some cases, amenable to macroscopically intact excision. The precision of the various histological prognostic factors is important to guide the therapeutic management.

E-PS-18-013
Patterns of biomolecular markers expression in patients with corneal endothelial dystrophies before and after injections of hyaluronic acid
V. Zakharava[1], G. Semak[1], I. Zherka[1], T. Liatkouskaya[1,2], S. Kletski[1]
[1] Belarusian State Medical University, Belarus, [2] ESP, Belarus

Background & Objectives: Corneal endothelial dystrophy (CED) is associated with primary non-inflammatory damage of endothelium with progressive edema and dystrophic changes in the cornea. The aim was to evaluate the changes of CD44, MMP9 and TGFβ1 expression in corneas with CED after HA injections.
Methods: The study was performed on the surgical material of 14 corneas explants: healthy corneas, secondary CED, Fuchs' corneal endothelial dystrophy (FECD), lattice corneal dystrophy, type I (LCED). Expression of CD44, MMP9 and TGFβ1 was assessed by morphometric analysis (Aperio ImageScope and WCIF ImageJ).
Results: Expression level of CD44 was significantly higher in CED group then in normal tissues (p=0,03) and in secondary CED group then in hereditary CED, (p<0,001). CD44 expression was significantly higher in LCED then in FECD. Expression of MMP9 in corneal epithelium and keratocites was lower in CED group (p=0,03 and p<0,001 respectively) then in normal tissues. In hereditary CED group level of MMP9 expression was significantly lower then in control and secondary CED groups. Expression level of TGFβ1was higher in LCED group then in secondary CED, FECD (p=0,033) and control groups (p<0,001). After HA subconjuctival administration: 1) CD44 expression decreased in FECD group; 2) MMP9 epithelial and stromal expression levels decreased in secondary CED and FECD group; 3) TGFβ1 expression level decreased in epithelium in LCED and keratocites in secondary CED groups.
Conclusion: Injections of hyaluronic acid allow to achieve clinical effect in CED treatment, accelerates CD44 associated regeneration, decrease propoptotic effect TGFβ1 in corneal epithelium, MMP and TGFβ1 mediated remodeling of corneal stroma.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-19 | Other Topics

E-PS-19-001
Pure de-novo 4.5 Mb duplication at Xp11.22-Xp11.23 in an 18-month-old boy: phenotypic and molecular characterisation
D. Jovanovic[1], N. Breland[1]
[1] Trinity School of Medicine, USA

Background & Objectives: In males pure duplications of the short arm of chromosome X are rare, in most cases are inherited from a heterozygote mother. We report here phenotypic and molecular characterization of a de-novo 4.5 Mb duplication at Xp11-22-p11.23 in an 18-month-old boy with hypotonia and developmental delay.
Methods: Single nucleotide polymorphism was performed using the Affymetrics Cytoscan HD platform applying the probes having median spacing of 0.88 kb. With NspI digested patient's genomic DNA was ligated to NspI adaptors and amplified using Titanium Tag with a GeneAmp PCR system 9700. Purified fragmented biotin labeled DNA was hybridized to the HD gene chip. Data was analysed using Chromosome Analysis Suite. Maternal FISH analysis was used to determine inheritance pattern.
Results: The patient is unable to utilize the large muscle systems in his body to move from place to place, assume a stable posture when moving, and to raise self to a standing position. He is not yet saying words. Chromosome microarray test found Xp11.23-p11.22 (48,237,630-52, 737, 268) x2 including numerous OMIM genes (start: SSX4 to end: SSX7) and SHROOM4. Maternal FISH analysis did not detect duplication of Xp11.23.
Conclusion: The patient has a large duplication containing multiple genes many of which are important for normal development. Many children have speech delay, cognitive deficits, sleep disorders and epilepsy. Since Mom does not have the duplication she can not pass it on to other children. This is de novo change for our patient not caused by anything that occurred during pregnancy.

E-PS-19-002

Primary gestational fallopian tube choriocarcinoma arising in dizygous twin pregnancy

J. Wright[1], W. Hamarneh[1]
[1] Northwick Park and St. Mark's Hospital, United Kingdom

Background & Objectives: Choriocarcinoma is an incredibly rare and malignant subtype of gestational trophoblastic disease that may coincide with normal, molar or ectopic pregnancies. Choriocarcinoma associated with ectopic pregnancy has an incidence of 1.5/million. Fallopian tube choriocarcinoma is most frequently gestational, and is associated with serious morbidity, as by the time of diagnosis, metastasis is highly likely due to rupture of the tubal wall into the pelvic cavity.
Methods: We report a case of primary gestational tubal ectopic choriocarcinoma that ruptured and metastasised to the lungs, arising in a dizygous twin pregnancy, where the intrauterine foetus was successfully delivered.
Results: A 37-year-old pregnant female, who was fit, developed intermittent abdominal pain at 19/40. At 34/40 weeks she presented acutely to our regional centre. Pelvic ultrasound suggested an ovarian torsion. Histology revealed choriocarcinoma within fallopian tube. Normal placenta, omental deciduosis and benign peritoneal fluid cytology.
CT Pulmonary Angiogram demonstrated bilateral lung nodules confirmed histologically as metastatic choriocarcinoma. Post-operatively, the patient recovered well and commenced chemotherapy at a specialist trophoblastic unit. The metastatic deposits disappeared, and the patient is still alive.
Conclusion: Primary gestational fallopian tube choriocarcinoma is extremely rare, and should always be considered whilst examining ectopic pregnancy specimens. To our knowledge, this is the first report of such case occurring as part of a dizygous twin pregnancy.

E-PS-19-003

Clinicopathologic features of rheumatoid nodule: a study of 57 cases

B. Seong Sik[1], S. Su-Jin[1], J. Kiseok[1], P. Seung Sam[1], K. Yeseul[1]
[1] Department of Pathology, College of Medicine, Hanyang University, Republic of Korea

Background & Objectives: The clinical and histopathologic features of 57 cases that have been diagnosed with rheumatoid nodules were investigated.
Methods: This study included 57 cases of rheumatoid nodule confirmed by histologic assessment between 2005 and 2018 at Hanyang University Hospital. According to the *American College of Rheumatology* (ACR) criteria, only patients with a total score of 6 or more were included, patients of lack of evidence of rheumatoid arthritis were excluded. The clinical data of all patients were obtained from electronic medical records. Clinical impression and imaging assessment before histologic diagnosis were also collected.
Results: The median age of the patients at the time of diagnosis was 57 years. Most of them showed high-positive rheumatoid factor (RF) or high-positive anti-citrullinated protein antibodies (ACPA), a few patients showed low-positive RA or low-positive ACPA. The most common anatomical location was the foot. In all cases, the central necrobiosis was present, and the necrobiosis contained neutrophils and nuclear debris. The palisading of histiocytes, perivascular lymphocytic infiltration, stromal fibrosis, cleft or cystic degeneration were observed in many cases.
Conclusion: In this study, we reviewed the clinical, imaging, and histologic features of 57 patients diagnosed with the rheumatoid nodule. The clinicopathological review of cases diagnosed with rheumatoid nodule histologically was performed to confirm the characteristics that can help to understand the pathophysiology and make an accurate diagnosis of the rheumatoid nodule.

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E-PS-19-004

Nuclear structure alteration after anti-cancer drugs incubation by acoustic microscopy

K. Miura[1], K. Yamashita[1], Y. Egawa[2], T. Moriki[2]
[1] Basic Nursing, Health Science, Hamamatsu Univ School Med, Japan, [2] Department of Diagnostic Pathology, Shizuoka City Hospital, Japan

Background & Objectives: Acoustic parameters of speed-of-sound and attenuation-of-sound correspond to tissue stiffness and viscosity. If special materials bind to nucleus, conformational change may occur to effect on acoustic properties. We tried to investigate anti-cancer drugs such as cisplatin and arsenic solution to alter nuclear images of histology sections after incubation.
Methods: Acoustic images of cytology and tissue slides were observed to be compared before and after incubation by scanning acoustic microscope. For anticancer drugs, cisplatin and arsenic solution were used. Acoustic images were compared with the corresponding light microscopic (LM) images.
Results: AOS and SOS values of nuclei increased after incubation with cisplatin. Fresh tissues showed more conspicuous changes compared with FFPE sections. On the contrary, arsenic solution revealed no remarkable changes. The corresponding LM images displayed no apparent changes before after incubation.
Conclusion: Acoustic microscope can detect cisplatin distribution on the nuclei to induce conformational changes.These changes were not detected by LM.

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E-PS-19-005

Modulated electro-hyperthermia enhances doxorubicin efficacy in colorectal adenocarcinoma in vitro

T. Vancsik[1], E. Kiss[1], G. Forika[1], A. Balogh[2], T. Krenacs[1]
[1] Department of Pathology and Experimental Cancer Research, Semmelweis University, Hungary, [2] Institute of Clinical Experimental Research, Semmelweis University, Hungary

Background & Objectives: Modulated electro-hyperthermia (mEHT) is a non-invasive complementary treatment to radio- or chemotherapy which can induce selective cell stress and heat shock at ~42°C in tumour tissue. Here we studied the molecular background of mEHT mediated tumour damage and its combination with the topoisomerase inhibitor and DNA-intercalating doxorubicin treatment *in vitro*.
Methods: Coverslip cultures of C26 mouse colorectal adenocarcinoma cell line were treated with mEHT at 42°C (2x60 min with 120 min breaks) alone or in combination with 1 μM doxorubicin (mEHT+Dox). Stress response, cell death, apoptosis and proliferation related markers were detected using immunocytochemistry and qPCR; complemented with resazurin viability assay, flow-cytometry for cell death response and clonogenic assay for counting cancer progenitor cells.
Results: MEHT induced significant hsp70 and calreticulin protein release (24h) and reduced the tumour stem-cell colonies (10-days). Significant decrease of anti-apoptotic XIAP, BCL-2, BCL-XL, and elevation of pro-apoptotic BAX, PUMA mRNA levels were detected, besides increased P21 rates. Between 24-48h mEHT progressively reduced of tumour cell-viability by apoptosis what was increased after mEHT+Dox combination, while Dox dominantly induced necrosis. Nuclear phospho-p53(Ser15) protein levels were significantly increased in all treated groups, while phospho-Akt(Ser473) levels were reduced but only after mEHT and mEHT+Dox.
Conclusion: MEHT can induce apoptotic cell-death and inhibition of tumour-cell proliferation in colorectal adenocarcinoma, possibly linked to p53 activated $p21^{waf1}$ upregulation and the concomitant reduction of active Akt protein, which could normally inhibit p53 functions. This mEHT induced mechanism could potentiate the cytotoxic effect doxorubicin.

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E-PS-19-006

Human identification using molecular techniques based on genetically variant peptides

D. Anestakis[1], M. Psallida[1], E. Chatzifotiou[1], F. Louka[1], P. Pavlidis[2], N. Raikos[1]

[1] Department of Autopsy Histopathology, Lab. of Forensic Medicine and Toxicology, Aristotle University of Thessaloniki, Greece, [2] Lab. of Forensic Medicine, Medical School, Democritus University of Thrace, Greece

Background & Objectives: While time goes by, human body tissues and cells change, decay and are led to death. The way of death plays an important role in human identification, because of the difficulties in samples' microscopic examination. If the body is found either in very advanced sepsis or burned, even if the only remain is a skeleton or a bone, without tissue, analyzing the samples may be troubling.

Methods: In many cases such as these, there is no way to extract DNA, or even if it is, there may be many contaminations and alterations during the processing. To overcome these dangers, there is an analyzing method using peptides, which are extracted in different ways comparing with DNA. During bone identification, there can be Genetically Variant Peptides (GVPs) extracted from it.

Results: In the first step, Single Amino acid Polymorphisms and Single Nucleotide Polymorphism alleles are extracted, so they can be analysed with Mass Spectrometer and compared with polymorphism databases . These Genetic Variant Peptides will be put in likelihood ratios and according to them they will be matched in the first place with population groups and in the second place with a single person in this group.

Conclusion: This is a high deficiency method, which has many advantages comparing with others due to the contamination restriction. It uses polymorphisms and databases, so there is a limitation-prohibition of the false-positive results. This method can be also used in other tissues as well as in combination with other techniques it can cover a large field in forensics.

E-PS-19-008

Validation of histology tissue processing

P. Locatelli[1], S. Caboni[1], F. De Angelis[1], F. Pellegrino[2], C. Lupo[3]

[1] LaboPath Diapath S.p.A, Italy, [2] SAMAR Medical Center, Rome, Italy, [3] Innovation Department, Diapath Headquarter, Italy

Background & Objectives: The increasing incidence of disease, especially cancer, has been the major driver of tissue processing quality into the diagnostics workflow. A proper processing confers quality to the tissue and preserves morphological and molecular information, very important for diagnostic purposes. Losing information during processing prevents a correct diagnosis, so the possibility of associating the correct oncologic target therapy, even leading to therapeutic failures. To prepare samples for diagnosis, with automatic tissue processors, the common machines in the market use up to 12 different tanks of chemicals (formalin, alcohol, xylene and paraffin) and 4-5 litres each are used: this poses a huge problem in the disposal of the waste chemicals, significant costs for the operator and the environment and the risk for samples due to possible failures in each step during the tissue processing. Another key issue in this process is about the formalin, the first chemical used during the process, that guarantees the preservation of cellular morphology. The purpose of this work is to validate a next generation tissue processor (Donatello Series 2) with aims to: 1) integration of the tissue processor into workflow process, 2) evaluate specimen quality.

Methods: We assessed technical quality of block processing, and slide cutting by histotechnologists and quality of H+E staining, special and immunohistochemical stains by pathologists with a standard input form. 2500 specimens were dissected and split by 2 PAs. 3 parts scheme with free text comments used for histology assessment (High, Average, Low Quality) and pathologist' microscopic evaluation (Acceptable, Inferior, Unacceptable for diagnosis).

Results: The study validates the technical, H&E and immunohistochemical stain quality obtained with a the generation tissueprocessor Donatello Serie 2. The experienced benefits tested, in comparison with standard tissueprocessors, in terms of processing quality, are enhanced by the addition of various technical improvements, as the selfcheck technology, that dramatically reduce the the incidence of adverse events and overnight tissueprocessor errors and the reagent replacement system, that allows to easily and safely replace reagent and paraffin, avoiding mistakes and spillages.

Conclusion: After five months and more than 2000 samples processed, morphology evaluation on both standard HE and IHC, the results confirms that Donatello 2 can be used as standard tissue processor in any pathology lab, with all the benefits previously listed.

E-PS-19-009

A 5-year retrospective study of extracutaneous melanomas

B.R. Nataras[1], A. Dema[2], C.D. Lazureanu[1,3], D. Herman[2], S. Taban[1,3], M. Cornianu[1,3], D. Szilagyi[1], A. Muresan[1,4], S. Costi[1], I. Uglai[1], S.C. Suciu[1,3], D. Anderco[1], M. Iacob[5]

[1] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania, [2] Department of Pathology, Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania, [3] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Pathology, Romania, [4] "Victor Babes" University of Medicine and Pharmacy'' Timisoara, Department of Pathology, Romania, [5] Department of Pathology, Emergency County Hospital Timişoara, Romania

Background & Objectives: Diffuse chorionic haemosiderosis (DCH) is an abnormality of the placental membranes, characterised by the deposition of iron pigment. It is usually secondary to recurrent venous bleeding from early pregnancy. In many papers, it is associated with pre-term delivery. Fetal vascular malperfusion (FVM) is an abnormality of the fetoplacental circulation that may be seen at any gestational age, but often in the third trimester. No link has been identified in the placental literature, but we have noted the two conditions co-existing. This study examined the association of these two entities.

Methods: Laboratory records were searched for singleton cases diagnosed as DCH on H&E stain over a 5-year period. These were classified as showing high-grade FVM (HGFVM), low-grade FVM (LGFVM) or no FVM. Controls were gestational-matched cases without DCH. Cord length, coiling, insertion, or other abnormalities were noted. Membranes were classified as normal or circumvallate. Results were analysed using Graphpad.

Results: There were 66 cases of DCH between 16 and 41 weeks gestation and 130 controls. 14/66 (21%) cases of DCH showed HGFVM and 2/66 (3%) showed LGFVM. 16/130 (12%) controls showed HGFVM and 20/130 (15%) had LGFVM. Where FVM is present, high-grade FVM is significantly associated with DCH versus controls ($P<0.0031$ Fischer's Test).

Conclusion: HGFVM occurs significantly more often in placentas with DCH. Histologic correlates of FVM have been under-explored to date. We have previously shown that FVM occurs four times more commonly in placentas with maternal vascular malperfusion (MVM) (Cooley et al JOG 2011). Both FVM and DCH are among 9 lesions significantly increased in placentas from infants with neurologic injury, and both are independently related to neurologic injury (Redline & ORiordan Arch

Pathol Lab Med 2000). Whether iron in high quantities causes or contributes to vascular damage in the developing placenta requires further study.

E-PS-19-010

Oncomine comprehensive cancer panel analysis of metastatic melanoma for two year experience

H. Kim[1], K. Jang[1], J. Lee[2]
[1] Department of Pathology and Translational Genomics, Samsung Medical Center, Republic of Korea, [2] Division of Haematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background & Objectives: Next-generation sequencing (NGS)-based cancer panel test can be applied in precision oncologic medicine for refractory metastatic melanoma. Here, we summarized our two-year experience of Oncomine comprehensive cancer panel test for melanoma.
Methods: From January 2017 to December 2018, 85 cases of metastatic melanoma were sequenced. After histological assessment, macrodissection of tumour areas in formalin-fixed paraffin-embedded sections was performed followed by DNA extraction, NGS, and analysis using an Oncomine knowledgebase reporter.
Results: The average mapped reads were 8,826,878 and that of tumour purity, mean depth, ontarget and uniformity were 65.28%, 3624.5, 97.75% and 89.43%, respectively. In quality score, 81 out of 85 cases revealed good or very good. In Tier I class of SNV/Indel, 16(18.82%) BRAF and 10(11.76%) NRAS were noted with no CNV and any fusion. In Tier II class, SNV/Indel of 7 genes were noted overlapped. In Tier II of CNV, 13 genes were noted overlapped.
Conclusion: NGS-based cancer panel test using FFPE can be applied in precision oncologic treatment. Although detected genetic alteration of Tier I and II class was relatively small, we suspect NGS-based genetic analysis will provide more actionable targets in melanoma treatment.

E-PS-19-011

In situ and humoral sensitivity to native type V collagen in early synovial fibrosis of a rat model of arthritis

L.K. Ramos da Silveira[1,2], A.P. Pereira Velosa[3], S. Catanozi[1,4], A. Santos Filho[3,2], S. Fernezlian[1,5], E. Eher[1,5], J. Tomaz de Miranda[1,2], V.L. Capelozzi[1,6], W. Rosolia Teodoro[1,2]
[1] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [2] Rheumatology Division, Brazil, [3] Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [4] Department of Endocrinology, Brazil, [5] Department of Pathology, Brazil, [6] Department of Rheumatology, Brazil

Background & Objectives: The immune reactivity to type V collagen (ColV) in patients with rheumatoid arthritis have suggested a role for autoimmunity to ColV as a major disease mechanism. The occurrence of in situ and humoral antibodies (AB) against collagen types during a histologically well-defined synovitis have been lacking. We evaluate the synovial extracellular matrix and the autoantibodies in arthritis model.
Methods: Sprague-Dawley rats (n=9) were subcutaneously immunized with mBSA/PBS (500μg/200μl) in Freund's adjuvant. Arthritis was induced on day 21, by intraarticular injection of mBSA/PBS (10μg/15μl) in the right knee. The animals were divided into three groups: 24 hours (AI-24h), 21 days (AI-21d) and 30 days (AI-30d) after induction of the arthritis. ELISA assays were employed to detect anti-collagen I-V AB in sera. Synovial tissue was evaluated by H&E, immunohistochemistry and immunofluorescence.
Results: Significant levels of circulating AB against collagen I, III and IV could not be detected in any group. The greatest elevation of AB directed against type II collagen was found in AI-24h. Most strikingly, AB against ColV were markedly elevated in AI-24h. The occurrence of high levels of AB against ColV was associated with the early stage of disease characterised by histologically documented inflammation and coincided with significant increase of ColV and decrease of Collagen I largely in the pericellular matrix of synovia.
Conclusion: The results suggest that AB to ColV occur as a consequence of tissue destruction and an evidence for a pathogenetic role of this immunogenic collagen in rat arthritis thus emerging as a promise biomarker of early detection of fibrosis.

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E-PS-19-012

Aberrant isotopic composition of tumour environment in growing 'in vivo' cancers in developmental age

K. Taran[1], P. Paneth[2]
[1] Medical University of Lodz, Poland, [2] Lodz University of Technology, Poland

Background & Objectives: Current efforts in understanding of cancer biology have focus on the evolving interplay between the tumour cells and their environment. It was proved that connective tissue surrounding tumours brings substrates for further anabolism. Although a passive role of fatty tissue is mostly recognized it may also act as the key organ of homeostasis able to evoke systemic effects. The highest credibility of Isotope ratio Mass Spectrometry proved in forensic, makes the method a perfectly precise tool ffor as deep and effective histoanalysis, which seems to be especially desirable in complex and hardly known tumour environment.
Methods: We took an advanced Continuous Flow IRMS coupled with elemental analyser to create 48 isotopic profiles of morphologically unchanged cancer environment (connective and fatty tissue) as well as of the same tissues from healthy individuals obtained in post-mortem examinations to search for potential differences.
Results: Isotopic signatures of nitrogen and carbon appeared different in tissues from healthy individuals and cancer patients, appropriately. Unexpectedly, both tissues from tumour environment - fatty tissue the same as connective tissue showed isotopic profiles on average nitrogen enriched and carbon depleted.
Conclusion: Our findings highlight connective tissue as the most universal source of heavy nitrogen giving natural support to arising and growing cancer cells. Furthermore, they may indicate an important role of fatty tissue in metabolic and homeostatic support during according to changing demands of the tumour cells during cancer expansion.

E-PS-19-013

Immune reactivity to collagen V-150kD fragment: biomarker of interstitial lung disease in systemic sclerosis

L. Brito[1,2], A. Santos Filho[3,2], J. Tomaz de Miranda[1,2], V.L. Capelozzi[1,4], W. Rosolia Teodoro[1,2], A.P. Pereira Velosa[3]
[1] Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [2] Rheumatology Division, Brazil, [3] Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil, [4] Department of Pathology, Brazil

Background & Objectives: Type V collagen (ColV) has antigenic properties and the potential to become an autoantigen in interstitial lung diseases, the most serious complication associated with Systemic sclerosis (SSc). Previously, we demonstrated that ColV-induced tolerance decreased inflammation and pulmonary fibrosis in the SSc model. Our objective was to evaluate the autoimmunity for ColV fragments in the model of SSc before and after tolerance induced by ColV for future diagnostic biomarker.
Methods: SSc model was induced in health rabbits (IM, n=12), by ColV immunization and in the 150 day six IM rabbits were submitted to ColV-induced nasal tolerance during 30 days (IM-TOL). All animals were

maintained until 210 days and sera samples were collected on 0, 150 and 210 days. The ColV was biochemically fractioned in aspartic acid-proline linkages and enzymatically by pepsin and tripsin. The antibodies frequency to ColV-fractionated portions in sera of the SSc model was evaluated by immunoblotting and image analysis.
Results: The ColV biochemically fractionated resulted in about 6 fragments to aspartic acid-proline linkages; 6 and 5 fragments, respectively to pepsin and tripsin enzymatic treatments. All 150 and 210 days sera samples reacted with the ColV fragments resulting of the enzymatic and biochemical treatments. However, only the 150kD-ColV fragment was immunologically identify with less intensity in IM-TOL compared to IM in the pepsin treatment (60.77±10.04 vs 288.7±155.9, p<0,001) and aspartic acid-proline linkages (-80.72±5.979 vs 82.22±17.7, p<0,001).
Conclusion: Decreased reactivity to a 150kD-ColV fragment after ColV-induced tolerance indicates that antigenic determinants important in autoimmunity to ColV in SSc model interstitial lung disease could be inserted in these protein fractions. It suggests that this fragment may be a possible biomarker of immune reactivity in SSc interstitial lung disease.

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E-PS-19-014
Epidemiological and histopathological profile of metastatic melanoma
V. Nica[1], C. Socoliuc[1,2], R. Andrei[1], C. Constantinescu[1], C. Luca[1], G. Tudor[1], O. Stefan[1], R. Tanasă[1], G. Grigore[1], S.A. Zurac[1,2]
[1] Colentina Clinical Hospital, Romania, [2] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: The main cause of death in melanoma is widespread metastases. Metastases can develop in lymph nodes or in distant organs. Our objective was to analyse metastatic melanoma from epidemiological and histopathological standpoints.
Methods: We performed a retrospective study on all cases of metastatic melanoma diagnosed in our pathology department between 2015 and 2019. Data collected included, age, sex, location and morphology.
Results: The study group comprised 88 patients with 14 cases without a known primary site based on available clinical information. The most frequent metastatic site was cutaneous (27 cases - 30,68%) followed by nodal (25), cerebral (22), pleuro-pulmonary (5), gastrointestinal (4), skeletal (3), ocular (1) and genitourinary (1) locations. Mean age at diagnosis was 60,07 in the group of cutaneous metastases, 59,08 in cases with lymph nodes metastases and 55,5 years in the group of cerebral metastases. The morphology of tumour proliferation was diverse, with various cell types encountered: epithelioid, spindle, mixed epithelioid and spindle, clear cells, lymphoid and rhabdoid cells. The epithelioid and mixed variants needed immunohistochemical confirmation in 47 (60,25%) cases and the more unusual variants (spindle, clear cell, lymphoid and rhabdoid) in 7 (70%) cases.
Conclusion: Metastatic melanoma can have diverse anatomical locations and various morphological aspects mimicking other malignancies (carcinoma, lymphoma, sarcoma). Considering the significant number of cases without a known primary in our study, in the absence of melanin pigment in tumour cells, the diagnosis can be difficult, requiring immunohistochemical confirmation.

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E-PS-19-015
Mesenteric lymph nodes cavitation as the presenting feature of coeliac disease - the role of pathologist
A. Fattori[1], N. Weingertner[1], X. Argemi[2], A. Nicolae[1], M. Chenard[3]
[1] Department of Pathology, University of Strasbourg, Strasbourg, France, [2] Department of Infectious and Tropical Diseases, University of Strasbourg, Strasbourg, France, [3] CHU de Strasbourg, Dèpartement de Pathologie, Strasbourg, France

Background & Objectives: Cavitation of mesenteric lymph nodes is a rare complication of celiac disease of unclear pathogenesis, frequently associated with hyposplenism. The diagnosis is usually made by radiologists in a clinical setting of known celiac disease.
Methods: A 63 years-old male complained of chronic abdominal pain and weight loss. Biologically, he showed thrombocytosis and anemia. A PET/CT scan revealed non-hypermetabolic conglomerate of necrotic mesenteric lymph nodes, measuring 13 cm. Clinicaly, the differential diagnosis included lymphoma, mycobacteriosis and Whipple disease. By laparoscopy, an excisional lymph node biopsy was performed.
Results: Histologically, central acidophilic lipid-containing, partly calcified necrosis, surrounded by dense fibrosis and non-atypical lymphoid tissue was seen. No granulomatous reaction was observed. Ziehl and Grocott stains, mycobacterial culture and PCR for Tropheryma Whipplei were negative. We proposed the diagnosis of mesenteric lymph node cavitation and recommended to explore a possible association with celiac disease. Small bowel biopsies were subsequently performed, showing atrophic villi with intra-epithelial lymphocytosis. A gluten-free diet was initiated with remarkable improvement of gastrointestinal symptoms. An atrophic spleen was detected after re-reviewing the abdominal imaging, which might account for the patients' thrombocytosis. Unfortunately, the patient died few months later of myocardial infarction, confirmed by autopsy.
Conclusion: Cavitation of mesenteric lymph nodes is a rare complication of celiac disease, with fewer than 40 cases reported to date. Although under recognized, its histological aspect is characteristic. Therefore, a correct identification becomes of paramount importance mainly when imagistic findings are non-specific and celiac disease is unknown.

E-PS-19-016
The importance of Major Histocompatibility Complex class I (MHC I) and clinicopathological correlations in the diagnosis of Idiopathic Inflammatory Myopathies (IIM)
R.-Z. Bulf[1], A. Vrancianu[2], M. Dincă[1], V. Mageriu[3], E. Manole[4], A. Bastian[2,5]
[1] Clinical Hospital Colentina, Romania, [2] Pathology Department, Colentina University Clinical Hospital, Bucharest, Romania, [3] MedLife Clinic, Bucharest, Romania, [4] Colentina Clinical Hospital; "Victor Babes" National Institute of Pathology, Molecular Biology Laboratory, Romania, [5] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: The main purpose of this study is to evaluate muscle biopsies in IIM - dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), autoimmune necrotizing myopathy (AINM) - taken from patients who received or not an anti-inflammatory treatment before tissue prelevation.
Methods: 141 patients (adult and juvenile cases) with clinical suspicion of IIM were divided in two groups: group I: 72 cases without prior steroid therapy; group II: 69 cases with prior steroid therapy initiated due to severe symptoms or non-responsiveness to therapy. Other cases with inflammation, but without IIM were microscopic polyangiitis, Pompe disease, trichinelosis. We performed histological stainings, histoenzymology, histochemistry and immunohistochemistry (MHC I) on cryosections/paraffin embedded tissue; the fragment of skeletal muscle was obtained by open surgical biopsy.
Results: 43 cases had pathological confirmation of IIM: 32 in Group I - 17 cases DM, 11 cases PM, 2 cases AINM, 2 cases IBM; only 11 in Group II: 5 cases DM, 2 cases PM, 3 cases AINM, 1 case IBM. 40 (56%) cases in Group I and 58 (84%) cases in Group II had non-specific changes. MHC I was positive in all IIM cases in both groups.
Conclusion: Using MHC I marker is mandatory in diagnosing myositis even in corticotreated patients, when morphological aspects are non-conclusive. Corticotherapy increases the number of cases with non-specific

diagnosis by up to 30%. It is strongly recommended to perform a biopsy before initiating anti-inflammatory therapy and clinical and pathological correlations are crucial.

E-PS-19-017

Secondary malignancy: concept of development, etiopathogenetic features, clinical and morphological comparison

D. Kushch[1], M. Mnichovich[1], M. Nikita[1]
[1] Research Institute of Human Morphology, Russia

Background & Objectives: A secondary malignansy is a new tumour that occurs several years after the treatment of the first cancer and has a structure and degree of malignancy different from the primary neoplasia. In connection with the increase in life expectancy in cancer patients, the number of patients with this pathology increases. The main problem is the early removal of the patient from the register in oncological institutions, and, as a result, the decline in quality control of people at risk.
To study the etiology, the creation of a classification of secondary tumours.
Methods: Statistic - 85 cases of sectional observations and medical histories of patients with primary multiple and secondary tumours with detailed histological, immunohistochemical studies of tumour material were studied.
Results: A tumour is considered secondary if there is a fact of using high doses of carcinogenic drugs in the treatment of primary cancer. It should also be more malignant compared with the first neoplasia. Secondary malignant tumours should be classified according to the type of therapy of the primary disease. 1. Secondary tumours resulting from chemotherapy. 2. Secondary tumours resulting from the use of hormone therapy. 3. Secondary tumours resulting from targeted therapy. 4. Secondary tumours arising after radiation therapy.
Conclusion: We need to create a specialized cancer registers, isolating secondary malignant tumours with a separate diagnosis, preventing their development, especially in risk groups, as well as choosing effective and at the same time sparing methods of antitumor therapy to reduce its long-term effects, is becoming increasingly obvious.

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E-PS-20 | Paediatric and Perinatal Pathology

E-PS-20-001

Comparative post-mortem CT characteristics of air/gas accumulations in the bodies of stillborn and dead newborns

U. Tumanova[1], V. Lyapin[1], V. Bychenko[1], A. Shchegolev[1], G. Sukhikh[1]
[1] NMRCOGP, Russia

Background & Objectives: The use of postmortem CT allows for an objective non-invasive assessment of the localization of gases, which helps to clarify the severity of postmortem changes and links of tanatogenesis.
To study the features of localization of gas accumulations in organs and tissues of stillborn and dead newborns by postmortem CT.
Methods: 18 bodies of stillborn at 25-39 gestation weeks (Group-I) and 42 deceased newborns (Group-II) were studied. CT scan was performed after 4-15 hours from the death before the autopsy. Localization of gas accumulations in vessels and body cavities was determined on tomograms. The flotation tests were performed during autopsy. In Group-I gas was detected in 50% of observations, in Group-II - in 90.5%.
Results: In Group-I, gas was visualized in the heart cavities, heart and liver vessels (38.9%), in brain vessels (33.3%), in abdominal vessels (27.8%), in aorta (22.2%).
In Group-II, air accumulations were observed in the lungs (59.5%), in the intestines (57.1%), in the stomach (38.1%), in the liver vessels (19.0%), in the abdominal vessels (16.7%), in the heart cavities (16.7%), in the heart (11.9%) and in brain vessels (9.5%). Air accumulations in the vessels were not detected in 66.7% of deceased newborns.
Conclusion: The presence of gas in the lungs, stomach and intestines in the group of newborns indicates respiratory processes. Most often gas detected in the heart cavities, heart and liver vessels at stillborn, and in the liver vessels at dead newborns.

E-PS-20-002

Childhood gastric carcinoma: a report of a case simulating langheransian histiocytosis

A. Bdioui Thabet[1], H. Busby[2], N. Mhamdi[2], A. Max[2], C. Pierre[2]
[1] Georges Pompido Hospital Paris, France, [2] Brabois Hospital, Nancy, France

Background & Objectives: Tumours of the stomach usually affect patients after the fifth decade of life. It has been estimated that patients younger than 40 years of age represent between 2% and 8% of all patients with gastric carcinoma. Symptoms are non-specific and deceiving, so diagnosis is usally belated.
Our objective is to report an extremely rare case of metastatic childhood gastric carcinoma clinically simulating an histiocytosis.
Methods: An 8-year-old boy, with no medical history, in particulary there was no familiar history of young age gastric carcinoma, admitted in paediatric departement for sous clavicular thrombosis. Radiologic examination shows many laterotarchial an cervical lymph nodes enlargment asociated with thoracic compression vertebra and lung interstitial syndroma; this clinical presentation suggested a langheransian histiocytosis.
A cervical lymph node and a bone vertebra were biopsed and sent for microscopic examination.
Results: On histology, the lymph node was massivly infiltrated by large tumour cells with abondant cytoplasme and atypical repressed nuclei, having the morphology of signet ring cells.The bone biopsy was also infiltrated by the same cells.
On immunohistochemestry, histiocytic markers was negatives, although cytokeratin AE1/AE3 and cytokeratine 7 was strongly postive.
Conclusion: Gastric carcinoma in children is extremely rare. However, any persistent symptoms in children should be carefully examined. We should consider and investigate the possibility of malignancy even in young patients, and the diagnosis should be made at earlier stages, to provide better chances for these patients to undergo curative treatment.

E-PS-20-003

Postmortem MRI and CT at autopsy of newborn with EPIGNATUS: a case report

U. Tumanova[1], V. Lyapin[1], V. Bychenko[1], A. Kozlova[1], A. Shchegolev[1]
[1] NMRCOGP, Russia

Background & Objectives: Objective: to evaluate the effectiveness of postmortem MRI and CT for the newborn with epignatus.
We present the case of a newborn girl, born at gestational age of 30 weeks and died in the first minutes after birth. Tumour-like formations from the mouth and nose were on external examination. CT and 3TMRI were performed 8 hours after death before the autopsy. The analysis of tomograms and 3D-reconstructions were performed. Virtopsy data were compared with the autopsy results.
Methods: When complex Virtopsy, a teratoma of the soft tissues of the face - epignatus (volume 200 cm^3) was revealed. It originated from the nasal cavity (os ethmoidale) spreading to the oral cavity and to the front of the neck. Obstruction of the upper respiratory tract, deformation and underdevelopment of the upper jaw bones and face soft tissues, displacement of the organs of the neck by tumour, gas in the vessels of the neck were detected.
Results: At postmortem MRI and CT, the structure of the formation revealed a soft tissue component with the fat inclusions and bone fragments, multiple cysts with liquid up to 5 cm in diameter.
At microscopic examination was a picture of mature teratoma with the presence of elements of dense and loose fibrous connective tissue,

adipose and muscle tissue, salivary glands, cartilage, neuroglia, choroid plexuses, cysts lined with multi-row, ciliated or intestinal epithelium.
Conclusion: Postmortem CT and MRI allowed to identify the growth source and structural features of the tumour at our research case. Virtopsy increases the efficiency of pathological study, which demonstrates the feasibility of postmortem CT and MRI in the cases of congenital malformations.

E-PS-20-004
Placental myofibroblastic units remodeling in pregnancies of women with congenital heart disease
L. Rudiuk[1,2], O. Reshetnikova[1]
[1] Immanuel Kant Baltic Federal University, Kaliningrad, Russia, [2] Regional Clinical Hospital of the Kaliningrad region, Kaliningrad, Russia

Background & Objectives: A pregnancy with congenital heart disease (CHD) carries a high-risk of complications during pregnancy and delivery both for mother and a fetus. Surgical interventions are not curative; therefore pregnant women with CHD may face hemodynamic impairments. A range of pregnancy complications for the mother and baby are rooted in placental dysfunction. The favorable outcome of pregnancy and delivery is provided when placental function is adequate to fetal-maternal system demands. The aim of present study is the research of myofibroblastic units remodeling of placental villous chorion in cases when pregnancy is complicated with CHD.
Methods: 35 term placentas, including 20 cases of CHD and 15 cases of physiological pregnancy (controls) were studied morphologically. Histological slides, stained with hematoxylin and eosin, were studied microscopically, then they were analysed by point count method and using the computer morphometry. Histopathologic findings were correlated with medical history data and immunohistochemical studies. The immunohistochemical staining protocol with monoclonal mouse antibodies to SMA (Dako, 1:500), Collagen IV (Neomarkers, 1:25) for placental tissue samples had been developed. Differences between groups' data were elucidated by non-parametric Mann-Whitney. Reliability established at $p<0.05$.
Results: The research showed the increased volume fraction (VF) of the terminal villi both in central and peripheral areas of placental disk in cases of CHD. Intervillous spaces were smaller mainly due to fibrinoid accumulations. SMA expressions were higher and diffuse than in controls. VF of a cell surface with SMA positive reaction revealed in 14.0(5) % in the central area and 24,0(5)% in peripheral zone of placentas with CHD (respectively -11,0(5)% and 20,5(9,25)%, $p<0,05$ in controls).
VF of a cell surface with Collagen IV positive reaction also was higher in CHD group with more intense reaction at placental periphery than in a central areas (26,0(9)% and 19,0(6)% compared with18,5(7)% and 11,5(7,75)% , $p<0,05$ in controls).
Conclusion: Placental myofibroblastic units remodeling considered in the aspect of placental adaptation to circulatory hypoxia due to hemodynamic impairments in women with CHD.

E-PS-20-007
Congenital pulmonary airway malformation type 2: a rare cause of perinatal death
M. Riekstina[1,2], I. Franckevica[1,2], R.M. Verdijk[3], I. Strumfa[2,4]
[1] Children's Clinical University Hospital, Latvia, [2] Riga Stradins University, Latvia, [3] Erasmus MC University Medical Center Rotterdam, The Netherlands, [4] Department of Pathology, Latvia

Background & Objectives: Congenital pulmonary airway malformation (CPAM) is lower respiratory tract developmental abnormality comprising up to 25% of all congenital lung lesions, with favourable perinatal survival. Poor outcome mostly is associated with large, progressive lesions and hydrops fetalis. Up to 70% of type 2 CPAM has related malformations. Here we demonstrate two cases of CPAM.
Methods: Retrospective case analysis.
Results: Case 1: A 32-week-old female neonate died of respiratory insufficiency 37min after birth. At 30 week-appointment CPAM of right lung was diagnosed, followed by intrauterine left pleuro-amniotic shunting. During autopsy facial and genital dysmorphias, anal atresia and generalised edema is noticed, as well as pleural and peritoneal effusions. Right lung is enlarged (36g), multicystic, compressing on mediastinum and left lung (6g). Case 2: A 23-week-old female fetus after an elective pregnancy termination due to prenatally diagnosed, rapidly progressive CPAM, involving whole right lung, therefore expected to lead to perinatal death. External examination does not reveal any dysmorphic features. Internally *in situ* organ localisation with enlarged right lung and shifting mediastinum, compressing on heart and left lung. Microscopically lung masses from both, fetus and neonate, were similar: dilated bronchiole-like cystic spaces dispersed among gestation propriate lung tissue, lined by columnar, ciliated epithelium, surrounded by fibromuscular layer, without mucin-producing cells, cartilage structures, consistent with type 2 CPAM.
Conclusion: CPAM is rare cause for neonatal death, therefore early diagnosis, purposeful screening for associated malformations and dynamic evaluation is crucial, as it can affect perinatal outcome and help in consulting and decision-making process for parents.

E-PS-20-008
Wilms tumour arising in a metanephric adenoma of kidney
P. Khneisser[1], S. Asmandar[1], R. Ramirez[1], P. Cervera[2], s. boudjemaa[1], R. Braum[3], C. Pasqualini[4], E. Colomba[5], A. Verschuur[6], A. Coulomb[7]
[1] Sorbonne Universitè- APHP6, Hôpital Armand Trousseau, Service d'Anatomie et Cytologie Pathologiques, Paris, France., France, [2] APHP Sorbonne Universitè, France, [3] Centre mèdico-chirurgical Ambroise Parè/Pierre Cherest, Clinique Hartmann, Paris, France, [4] Dèpartement de Cancèrologie de l'Enfant et de l'Adolescent Gustave Roussy, Villejuif, France, [5] Institut Gustave-Roussy, service d'oncologie, Villejuif, France, [6] Paediatric oncology and haematology department, La Timone Hospital, Marseille, France, [7] Sorbonne University, APHP6, Pathology department, Armand Trousseau Hospital, Paris, France

Background & Objectives: Wilms tumour (WT), the most common paediatric renal malignant tumour, may occur in adults. Metanephric adenoma (MA), a benign epithelial tumour of the kidney, occurs predominantly in adults and children. Because of morphological similarities between these two entities, MA may represent maturing WT or nephrogenic rests. Coexistence of two or more renal tumours is extremely rare as described in case reports. MA may notably be associated with WT and renal cell carcinoma.
Methods: We reviewed clinical, pathological and genetic data of these renal tumours to establish the links between WT and MA.
Results: A 39-year-old man presented a 19 cm kidney tumour diagnosed as WT on biopsy. The patient was treated by preoperative chemotherapy according to localized WT International Society of paediatric Oncology (SIOP) protocols followed by right total nephrectomy. The nephrectomy specimen showed a multinodular, solid/cystic, 20 X 9 X 8.5cm tumour developed on the convexity of the kidney. Microscopically, Chemotherapy induced changes (CIC) were evaluated at 40% and viable tumour showed immature epithelial component (60%) with stromal (39%) and blastemal (1%) components. At the periphery of the tumour, a rim of benign looking epithelial cells suggestive of an underlying MA was present. A diagnosis of WT arising in MA was made and confirmed by BRAF expression on immunohistochemistry and BRAF (V600E) mutation using NGS in the MA component.
Conclusion: WT may develop in a MA in adult. Despite morphological similarities, these two entities have different pathogenesis and molecular alterations, notably BRAF mutation in MA.

E-PS-20-009

Diagnostic challenges in hydatidiform mole

R. Balan[1], I.D. Caruntu[1], S. Giusca[1], L. Lozneanu[1], T.A. Balan[1], A. Grigoras[1], C. Amalinei[1]
[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Background & Objectives: Hydatidiform moles (HMs) are subdivided into complete and partial, according to genetic, morphologic, and clinicopathologic differences. Although typical forms are diagnosed on routine histopathology, the ultrasound diagnostic of pregnancy reveals incipient morphological features of HM, difficult to recognize and differentiate. We aimed to assess the histopathology of complete and partial HM, creating a diagnostic algorithm, based on routine and immunohistochemical examination.
Methods: Our retrospective study included 48 gestational products represented by 34 partial moles and 14 complete moles. The routinely stained slides were histopathologicaly reevaluated and the expressions of p57 and Ki-67 were immunohistochemical assessed on archival tissues.
Results: Partial moles presented scalloped enlarged edematous and small fibrotic villi, with less central cisterns, and mild trophoblastic hyperplasia. Complete moles showed round enlarged edematous villi, with central cisterns, circumferential trophoblastic proliferation, with cytologic atypia. p57 expression was diffuse in the villous stroma and the cytotrophoblast of partial moles and absent or low in the intermediate trophoblast of the complete moles. Ki-67 presented a stronger immunoexpression in complete moles.
Conclusion: The most important aspect of histopathological diagnosis of HM is to distinguish complete from partial moles, due to the higher risk of the former to develop persistent gestational trophoblastic disease. When microscopical features are very subtle, the immunohistochemical evaluation of p57 and Ki-67 can be helpful, as complete mole does not express p57 but has a high Ki-67 index. However, because HMs share distinct molecular genetic features, the difficult cases can be assessed by genotyping the products of conception.

E-PS-20-010

Double Meckel's diverticulum described in a foetus with trisomy 18

T. Domsa[1], T. Kovacs[2,3], D. Crisan[1], F. Stamatian[2], A. Staicu[3], C. Albu[2,1]
[1] Iuliu Hatieganu University of Medicine and Pharmacy, Department of Pathology, Cluj-Napoca, Romania, [2] IMOGEN- Centre of Advanced Research Studies, Cluj-Napoca, Romania, [3] Iuliu Hatieganu University of Medicine and Pharmacy, 1st Department of Obstetrics and Gynaecology, Cluj-Napoca, Romania

Background & Objectives: Meckel's diverticulum is the most common congenital anomaly of the digestive tract, resulting from the incomplete obliteration of the omphalomesenteric duct. The presence of a double Meckel's diverticulum is a very rare finding. We describe such a case, discovered at the post-mortem examination of a fetus with trisomy 18.
Methods: A 22 weeks of gestation fetus, resulted from a spontaneous pregnancy, was diagnosed at routine ultrasound with a polymalformative syndrome. Following quantitative flourescent PCR that revealed trisomy 18, after proper counseling, the patient opted for therapeutic termination of pregnancy. Upon arrival in the pathology service, the fetus was analysed by conventional autopsy. The internal organs were immersed in 10% formalin and subsequently a microscopic examination was performed.
Results: Postmortem examination revealed a 500g female fetus with low-set, malformed ears, bilateral undeveloped thumbs and radial agenesis. At internal examination, ventriculomegaly, right-sided bronchial isomerism and double Meckel's diverticulum were identified. The rest of the organs were developed according to gestational age. At the microscopic examination, two true diverticuli were confirmed, layered by small intestinal-type mucosa. At the tip, one of them also contained heterotopic colonic mucosa.
Conclusion: We present, to our knowledge, the first case of double Meckel's diverticulum described in a fetus.

E-PS-20-011

How to find a pin in a haystack? An autopsy case of rare genetic mutation causing immunodeficiency

K. Ristmägi[1]
[1] East-Tallinn Central Hospital, Estonia

Background & Objectives: Life was like a box of chocolates. You never know what you're gonna get. You can easily adjust this saying to pathology. You can have a new finding just by doing your everyday work.
Methods: In Estonia guidelines for pregnancy monitoring and delivery exist for decades. Still sometimes infant does not survive and then it`s obligatory to perform an autopsy. In 2017 the infant mortality rate was 2,3 per 1000 livebirths. This number has been quite stable.
Results: A case presentation is about a boy who was born from the normal pregnancy at term. The family had one sibling before. The child become ill on the second week of life, was admitted to the hospital with the symptoms of acute respiratory disease. On a regular examination nothing significant was found. After a week of supportive treatment he was dismissed at home. The second episode of similar illness was two weeks later. The child had a fever, respiratory distress and signs of shock. With the progressive worsening of a status he died 2 days later. The autopsy and gene analyses were requested. At autopsy the signs of acute shock were found, on histological slides the unusual picture of pulmonary candidiasis was presented and the results of gene test – a rare mutation – concluded and explained the course of this odd case.
Conclusion: The case presentation illustrates the good collaboration between different institutions. Autopsy like a method of investigation loses it's significance day by day, but what about the role of pathologist?

E-PS-20-012

Pathological factors in nephroblastoma: a study of 100 cases in Tunisian children

N. Boujelbene[1], I. Abbes[1], R. Doghri[1], L. Charfi[1], R. Ben Ghorbel[1], D. Kacem[1], K. Mrad[1], M. Driss[1]
[1] Department of Pathology, Salah Azaiez Institute, Tunisia

Background & Objectives:
Nephroblastoma is the most frequent malignant renal tumour in children. Microscopic examination evaluate the tumour stage often after chemotherapy. We aimed to assess histopathological factors in a series of children treated for nephroblastoma.
Methods: We retrospectively analysed the data of consecutive children diagnosed in our hospital between 2001 and 2017 as having nephroblastoma. All tumours were identified and categorized according to the International Society of Paediatric Oncology (SIOP) 2001. Staging system and the histology risk grouping were also determined according to SIOP 2001.
Results: A total of 100 cases of nephroblastoma diagnosed in 48 boys and 52 girls were included. The median age was 38 months (range from 2 to 156 months). Bilateral tumour was observed in 7 cases. Surgery was performed after chemotherapy in 95 of 100 patients.Ninety-one patients (91%) presented with localized disease, whereas 9 patients had metastases at diagnosis (lung only). Wilms tumours were unilateral in 93 children and bilateral in 7 children.Histopathologically, 79% were classified as "intermediate-risk" tumours, 17% were classified as "high-risk" tumours and 4% as "low-risk" tumours.The final local stage (ie, the stage on which post-operative treatment was based) was stage I in 39.5%, stage II in 25%, stage III in 19%, stage IV in 9.5% and stage V in 7%. All patients who had ruptures were staged pathologically as stage III.
Conclusion: It is important to perform a standardised macroscopic and microscopic examination in the management of nephroblastoma (SIOP 2001 protocol) for optimal therapeutic management.

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E-PS-21 | Pathology in Favour of Developing Countries

E-PS-21-001
Ensuring cancer patient safety in gross room; analysis of 175 near-miss events and errors in tumour specimens at a university affiliated hospital in Lahore, Pakistan
F. Rehman[1], S. Mahmood[1], S. Hameed[1], N. Khalil[1], S. Ahmed[1], M.Z. Sarwar[1]
[1] King Edward Medical University, Lahore, Pakistan

Background & Objectives: All the tumour specimens submitted at pathology receptions are subjected to gross examination in the gross room. Negligence at any step during gross examination may result in misinterpretation of the lesion thus significantly affecting patient treatment & prognosis. Aim was to document errors generated in handling of surgical specimens from patients with malignancies.
Methods: A total of 175 tumour specimens including biopsies and resection specimens were included in the study. Following parameters were assessed during gross examination. Pre-analytical errors like; crushed, fragmented biopsies not receiving all components of specimen, putting specimen from different sites in same jar, margins unlabeled, mislabeled specimen, autolysed specimen, inappropriate fixative, inappropriate lymph nodes sampling/location whereas some of the analytical errors include inappropriate recording of specimen dimensions, insufficient tumour sampling, inadequate decalcification and margin selection.
Results: Most of the errors observed during pre-analytical phase significantly affected the interpretation of gross examination findings. Errors during analytical phase mainly resulted from negligence, inappropriate training, and supervision of the designated staff handling the gross specimens.
Conclusion: Standard operating procedures for grossing the tumour specimens must be followed in true spirit. Individuals involved in the specimen grossing have to be fully trained and vigilant in performing their assigned task so as to avoid potential harm to the cancer patient as a result of any mischievous act and negligence during grossing of tumour specimen.

E-PS-21-002
Critical alerts in surgical pathology; physician's perception, practice and expectations from pathologist
F. Rehman[1], S. Mahmood[1], K. Naz[1], S. Ahmed[1], M.Z. Sarwar[1]
[1] King Edward Medical University, Lahore, Pakistan

Background & Objectives: To avoid any delay in the management of patient, critical alerts have to be identified and notified timely to the physicians. However, in developing countries, the concept of Critical Alerts is not yet fully addressed. The main purpose of this study was to analyse the current practices in identifying and reporting critical alerts, to evaluate perception of physicians and to apprehend their expectations regarding Critical Alerts in histopathology department of King Edward Medical University/Mayo Hospital, Lahore.
Methods: A total of 188 physicians participated in the study with a 100% response rate. Participants were selected by non-probability, convenient sampling. A questionnaire covering different aspects of perceptions, practices and expectations of physicians regarding critical alerts in surgical pathology was distributed among practicing physicians from affiliated hospitals of King Edward Medical University, Lahore. Ethical approval was taken from institutional review board.
Results: Only few of the Physicians (22.87%) were aware of the concept of Critical Alerts in surgical pathology whereas only 26.9% of them agreed that they receive notification of Critical values in surgical pathology reports. Respondents (62.4%) were mainly concerned regarding delayed turnaround time of the reports having critical alerts. Majority of physicians (93.5%) were of view that Information (Date, time, responsible individual and person notified) must be documented during critical alerts notification on the report.
Conclusion: In developing countries like Pakistan, there's dire need to improve the approach of the pathologists towards identifying, reporting and timely communicating the critical alerts so that physicians can initiate rapid & effective management of the patient.

E-PS-21-003
Use of electronic & social media in the education and training of pathology resident; an experience from Lahore, Pakistan
F. Rehman[1], S. Mahmood[2], A. Hassan[3], H.T. Khan[3], S. Ahmad[3], M.Z. Sarwar[3], A. Momina[4]
[1] King Edward Medical University, Lahore, Pakistan, [2] King Edward Medical University, Lahore, Pakistan, [3] King Edward Medical University, Lahore, Pakistan, [4] King Edward Medical University, Lahore, Pakistan

Background & Objectives: Social media is defined as a web or mobile-based technology that helps in the production and colloquy of user-generated content. There are various means of training and education in the field of medicine such as worldwide web, YouTube, Facebook, WhatsApp, Twitter, Messenger etc.
The aim of this study is to determine the role of electronic and social media in the education and training of pathology residents working in different medical institutions of Lahore, Pakistan.
Methods: A cross sectional descriptive survey was conducted involving 125 postgraduate residents working in four sub-specialties of the pathology including haematology, histopathology, chemical pathology and microbiology. The respondents were evaluated by means of a self-designed questionnaire prepared after extensive literature search. It covered various aspects of demographic profiles of pathology residents and their awareness and patterns of using different social networking sites relevant to the field of pathology. Data was entered and analysed using SPSS version 21.
Results: All postgraduate residents filled the questionnaire with a 100% response rate. Most of the respondents (78.81%) had access to internet with 100 % of them having mobile-based technology for using social networking sites. Most frequently used social networking site was WhatsApp (83.05%), followed by Facebook (62.71%), YouTube (44.91%), messenger (33.05%) and twitter (30.50%). Awareness & patterns of use of social media by pathology residents is depicted in table 1 and figure 1 & 2.
Conclusion: Since the evolution of 21st century electronic media, use of social networking sites has significantly affected our lives and attitudes. It has also opened new horizons in the field of pathology education by providing a platform for sharing of pathology lectures, posting of routine & problematic cases in pathology, live streaming of slide seminars and participation in various discussion forums.

E-PS-21-004
Female genital tuberculosis clinically masquerading as a neoplastic process
B. Simona[1], A.C. Lisievici[2], T.A. Georgescu[3], F. Pop[4]
[1] Spitalul Universitar de Urgenta Bucuresti (SUUB), Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Pathology, Bucharest Emergency University Hospital, Romania, [4] "Dr. Carol Davila" University Hospital of Nephrology, Romania

Background & Objectives: Genital tuberculosis is a rare form of secondary tuberculosis, comprising approximately 9% of all extrapulmonary forms. Patients with Mycobacterium Tuberculosis infection affecting the female genital tract usually present with infertility, dyspareunia and chronic inflammatory pelvic disease, but, rarely, they can also have tumour-like symptoms.

Methods: We report the case of a 66-year-old female from a rural region in Romania, with no history of pulmonary tuberculosis, who presented to our clinic with weight loss, abnormal vaginal discharge and pelvic pain. Computerized tomography revealed thickened endometrium and a diffuse parenchymal process in the uterine corpus, extending bilaterally to the fallopian tubes and ovaries, with ascites buildup. Findings were suggestive for serous carcinoma. After multidisciplinary evaluation, the patient underwent total hysterectomy with bilateral oophorectomy and peritoneal washing.

Results: Histopathological examination of the surgically resected specimen revealed massive tissue destruction with disseminated caseous granulomas, composed of lymphocytes, epithelioid cells and giant multinucleated Langhans cells involving the uterus, endocervix and fallopian tube. Ziehl-Neelsen staining revealed red acid fast bacilli, consistent with the diagnosis of tuberculosis. No neoplastic process was identified. Clinical management involved major ethical issues, because the patient refused treatment, but after developing pleurisy, she eventually accepted bacteriostatic treatment.

Conclusion: Although rather frequent in Romania and other developing countries, genital tuberculosis may not have specific symptoms and may even mimic a neoplastic process. It is associated with increased morbidity and adequate treatment should be rapidly administered, in order to prevent an otherwise curable disease from having an unfortunate course of evolution.

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E-PS-22 | Pulmonary Pathology

E-PS-22-001
Broncho-pulmonary cancers, about a series of 180 cases
Z. Merad[1]
[1] CHU Sidi Bel Abbes, Algeria

Background & Objectives: Brocho-pulmonary cancer is the most common cancer in the world. It is the leading cause of cancer mortality. The prognosis is bleak with a 5-years survival estimated at less than 10% due to late diagnosis. The objective of the work is to carry out a descriptive epidemiological and histopathological study to highlight the extent of morbidity of bronchopulmonary cancers

Methods: This is a series study of 180 cases of primary bronchopulmonary cancers collected in the Department of Anatomy and Cytology Pathologies at the Sidi Bel Abbes Hospital University from January 1996 until December 2014

Results: Diagnosis was made on biopsies in 117 cases, pleural fluid in 61 cases and surgical specimens in 02 cases There is a clear male predominance, 73% for the male and 27% for the female The distribution by age shows a peak frequency between 68-77 years with extremes ranging from 24 years to 82 years. Histopathologically non-small cell lung cancer (98%) predominates largely in small cell lung cancer (02%). Squamous cell carcinomas (79%) and adenocarcinomas (17%) are the most frequent.

Conclusion: This study gives an overview of the distribution of lung cancers in the Department of Pathology at the Sidi Bel Abbés Hospital-University, which declares late, hence the importance of developing a screening program and appropriate management for those with advanced cancer.

E-PS-22-002
Cytogenetic damage in buccal epithelium in lung cancer patients
M. Byakhova[1], K. Anoshkin[2], V. Byakhova[3]
[1] M.F. Vladimirskiy Moscow Region Research Clinical Institute, Moscow, Russia, [2] Research Center for medical genetics, Moscow, Russia, [3] Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Background & Objectives: Genomic damage is probably the most important fundamental cause of developmental and degenerative oncological diseases. It is essential to have reliable and relevant minimally invasive biomarkers to improve the implementation of biomonitoring, diagnostics, and treatment of diseases caused by, or associated with, genetic damage. The micronucleus (MN) assay in buccal cells is potentially can be such a biomarker. The aim of our study was to determine the cytogenetic status of buccal epithelium in patients with lung cancer (LC).

Methods: This study was based on a group of patients (38 patients), median age 63,7 years old, with the diagnosis of LC. The control group included 30 apparently healthy people, who didn't have either acute or chronic diseases at the time of this study.

Results: There was a trend for a significant increase ($p < 0.01$) of cells with cytogenetic abnormalities in patients with LC in buccal epithelium: cells with micronuclei (1,76 (1,01÷2,5)‰) was 2,8 times higher than healthy ones (0,6 (0,19÷1,05)‰). The ratio of cells with protrusions (1,5 (1,0÷2,0)‰) is 2 times higher than healthy ones (0,75÷1,49)‰). Total indicators of the share of cells with micronuclei and protrusions (3,2 (2,2÷4,3‰) are 2,5 times higher compared with the same indicators in healthy ones (1,3 (0,3÷2,37)‰).

Conclusion: Thus, the increase in cytogenetic damage in the cells of buccal epithelium indicates the systemic nature of the changes in LC cancer.

E-PS-22-003
A rare case of lung adenofibroma
N. Balint[1], M. Charton-Bain[1], P. Riera[1]
[1] Centre Hospitalier du Pays d'Aix, France

Background & Objectives: Lung adenofibroma is not a defined entity in books but rare numbers of cases have been described in the literature.

It was first described by Scarff and Gowar in 1944 whom implied that its origin might be identical to lung cartilaginous hamartoma. We present a case of pulmonary adenofibroma located in the inferior lobe of the left lung in a 71-year old patient with a history of hemangiopericytoma. The lesion was discovered by scanner examination because of a persistent cough.

Methods: Macroscopically the lesion measured 2.2 x 2.4 cm and had a lobulated appearance, being well delimited by surrounding tissue with a white homogenous surface, a firm consistency. The microscopical examination showed a biphasic tumour with an epithelial glandular component forming ramified spaces surrounded by a spindle-cell lax stroma. The glandular spaces were compressed and coated by a cuboidal or flattened epithelium without atypia. An immunohistochemical panel containing CK7, CD34 and Ki67 was used.

Results: The histological aspect, combined with the immunohistochemical panel which showed positivity for CK7 in the epithelial component, focally for CD34 on the stromal component and the Ki67 index of about 2%, led us to the conclusion that this was indeed an adenofibroma.

The diagnostic is easily made because of the fibroepithelial aspect which resembles a breast fibroadenoma, but it imposes a differential diagnosis with other benign tumours of the lung: hamartomas or solitary fibrous tumour.

Conclusion: It is important to note that such lesions are benign entities, easily recognizable by their histological appearance with an extremely rare localisation in the lung for which the surgical excision is the curative gesture.

E-PS-22-004

Anaplastic lymphoma kinase (ALK) expression in lung adenocarcinoma - clinicopathologic and morphologic features

D. Jasar[1], K. Kubelka-Sabit[1], V. Filipovski[1,2]
[1] Clinical Hospital Acibadem Sistina, Department of Histopathology and Cytology, Republic of North Macedonia, [2] Medical Faculty, University Goce Delchev, Republic of North Macedonia

Background & Objectives: The aim of this study is to explore the status of ALK in lung adenocarcinomas and to evaluate the relationship between ALK expression and clinicopathological and morphological features of the primary tumour.
Methods: In total, 86 cytological and biopsy specimens were tested for ALK status using automated immunostainer with Ventana anti-ALK (D5F3) antibody. The expression of ALK was correlated with patient's age, sex and histological features of the primary tumour.
Results: ALK positive expression was detected in 15 (17,4%) cases, in significantly younger age group than ALK negative patients ($p<0.05$). Mucinous type of lung adenocarcinomas were predominantly ALK positive (43,7%), followed by papillary type (25%), acinic type (13%) and solid type (3%). There was strong correlation between the ALK expression in surgical biopsy and cytological specimens ($p<0.05$).
Conclusion: These results represent that immunohistochemical expression of ALK gene rearrangement is valid detection technique revealing distinctive clinicopathological and morphological features of the tumour especially in scant biopsies and cytological specimens.

E-PS-22-005

Genetic analysis of multiple synchronous lung cancer in a single lobe showing three different histological types

S. Aida[1], M. Kato[1], N. Sakaniwa[2], T. Okunaka[2]
[1] Department of Pathology, Mita Hospital, International University of Health and Welfare, Japan, [2] Department of Respiratory Surgery, Sanno Hospital, Japan

Background & Objectives: We experienced a case of multiple synchronous lung cancer in a single lobe showing three different histological types. The results of genetic analysis of the tumours showed interesting findings to suggest a developmental mechanism of collision cancer.
Methods: Case presentation: A 73-year-old Japanese woman with a history of smoking for 20 years (50 cigarettes daily). She had undergone a partial colectomy due to colon cancer 7years before. The follow up CT revealed tumour shadows in S6 and S10 of the right lower lobe of lung. Partial lung resection of right S6 and S10 was performed on the suspicion of colon cancer metastasis. The resected tumours were histopathologically, immunohistochemically and genetically examined.
Results: S6; A 10mm sized solid adenocarcinoma was seen. The tumour cells were immunohistochemically positive for TTF1. P53 mutation Ex6 S215G was detected, S10: Two distinct adjacent tumours were seen. One was 20mm sized large cell neuroendocrine carcinoma which was immunohistochemically positive for TTF1, synaptophysin and CD56. P53 mutation Ex7 P250L was detected. Another was 12mm sized lepidic adenocarcinoma, immunohistochemically positive for TTF1. P53 mutation Ex7 P250L was detected. The two tumours were connected each other in a small area.
Conclusion: The two tumours in S10 are morphologically consistent with collision cancer but the genetic analysis of p53 mutation suggests that they are derived from a common multipotential cell. The tumour in S6 has different p53 mutation from S10 tumours and is proved to be not a metastasis but a primary cancer.

E-PS-22-006

Correlation predominant type of adenocarcinoma of the lung with characteristics of primary tumour

M. Miladinovic[1], M. Golubović[1], L. Vučković[1], F. Vukmirović[1], T. Lakic[2,3]
[1] Medical Faculty, University of Montenegro, Clinical center of Monetenego, Montenegro, [2] University of Novi Sad, Faculty of Medicine, Serbia, [3] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia

Background & Objectives: In 2015, the World Health Organization (WHO) adopted a new classification of adenocarcinoma of the lungs (AD), which almost completely accepted the recommendations of the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) 2011. The prognostic importance of the new classification of AD is still not clear. We analysed the correlation of predominant histologic subtypes of AD with the characteristics of the primary tumour (size, infiltration of pleura and surrounding structures).
Methods: 148 operatived patients with invasive AD were analysed. We defined the predominant type using the IASLC / ATC / ERS criteria (solid, acinar, papillary, micropapillary and lepidic). We compared the correlation of prevalent types with tumour characteristics.
Results: The most prevalent types of AD were solid (35.1%), acinar (31.1%) and papillary (16.9%). The smallest average tumour size was found in papillary (39.6 mm), solid (49.9 mm), acinar (47.8 mm), while the highest was in the lepidic (52,4 mm) and micropapillary (55.8 mm). The most prevalent type with pleural infiltration was solid (6.8%), acinar (6.1%) micropapillary (6.1%), with statistically significant association (Fisher's non-parametric test, $p = 0.011$). Infiltration of surrounding structures was found in acinar (2%) and solid (2%).
Conclusion: In this paper, we point the importance of an accurate assessment of the subtype of AD highlighting certain aspects of its clinical relevance and potential impact on future new research in this direction.

E-PS-22-007

A case report of exon 20 resistant insertion

S. Boukansa[1], S. El Bardai[2], Z. Benbrahim[3], N. Mellas[3], H. El Fatemi[4,5]
[1] Medical Centre of Biomedical and Translational Research, Faculty of Medicine and Pharmacy Fez, Morocco, [2] Anatomy and Cytopathologycal department, CHU HASSAN II Fez, University Sidi Mohamed Ben Abdellah, Morocco, [3] Department of Oncology, CHU HASSAN II Fez, University Sidi Mohamed Ben Abdellah, Morocco, [4] Department of Pathology, Hassan II University Hospital, Fez, Morocco, [5] Faculty of Medecine and Pharmacy of Fez, Morocco

Background & Objectives: Most patients whose tumours harbor exon19 deletions or L858R mutations have substantial clinical and radiographic responses to EGFR TKIs. In contrast to the classic activating EGFR mutations, insertions in exon 20 are not often associated with clinical benefit and radiographic responses with EGFR TKIs, they have been linked to insentivity and resistance to reversible and irreversible EGFR TKIs. These include the exon 20 insertion mutants D770(ins G)N 771T, D770ins(SVQ), D770_N771(inS NPG) that account for about 4% of all EGFR mutations.
Methods: We report a case of 36 year-old-male, occasional smoker for 5 years, presented with a two month history of bone pain. Chest radiograph revealed a large opacity overlying the right upper lobe. Magnetic resonance imaging (MRI) showed lung, bone and liver metastases. A bronchial biopsie was performed for pathological diagnosis, which revealed an acinair adenocarcinoma with intensively positive TTF-1 and CK7 in differentiated glandular structure. For genetic testing, the extraction of DNA was performed with invitrogen DNA FFPE Tissue Kit from

obtained histological sample. EGFR mutations was detrminated by PCR amplification followed by automatic direct sequencing.
Results: Molecular analysis revealed an EGFR exon 20 insertion (D770_N771insG), wich associated with resistance to targeted EGFR TKIs and correlated with a poor patient prognosis. As treatment, the patient received radiotherapy with 20 cycles, followed by 6 cycles with palliative chemotherapy. 5 month later, the patient had progressive disease. Then, a new strategy of treatement will be discussed with oncologists.
Conclusion: A few studies have focused on exon 20 insertion, wich D770_N771insG is a rare mutation, that may reflect the fact that the clinical and pathological characteristics associated with this subset are not well established. The present report highlits the clinicopathological characteristics of a young patient with exon 20 resistant insertion.

E-PS-22-008
Unusual case report: intimal sarcoma of pulmonary artery for a young male
A. Ruminaite[1], L. Poskiene[1], V. Sarauskas[1]
[1] Member of Lithuanian Society of Pathologists, Lithuania

Background & Objectives: To present extraordinary uncommon case-based scientific research of intimal sarcoma of pulmonary artery (PAS) in a 33-year-old male patient. PAS are very rare tumour with only a few hundred cases reported. The incidence is estimated between 0.001 and 0.003% but is likely underestimated because of frequent misdiagnosed as pulmonary embolism and may remain unrecognized if not examined histologically.
Methods: In 2018, a 33-year-old male presented with a complaint of fatigue, progressive dyspnoea and fever that last for a few months. Heart magnetic resonance imaging and computed tomography revealed tumour in a proximal segment of pulmonary artery with secondary thrombosis and ischemic changes in a right lung. A biopsy of pulmonary artery mass was performed confirming a diagnosis of high grade mezenchymal tumour with more evidence for intimal sarcoma. Tumour cells were positive for vimentin, CD31, around 30% of cells were positive for smooth muscle actin and F VIII factor. Ki67 proliferation index reached nearly 70%.
Results: Later on, pathologists received surgical specimen of the right lung and segment of pulmonary artery with tumour masses. Additional immunohistochemistry reactions were done. The final diagnosis – pulmonary artery intimal sarcoma, G3, with pulmonary artery obstruction and infiltration into the lung tissue. One day after the surgery patient died.
Conclusion: PAS most commonly occur in right or left pulmonary artery or pulmonary valve. These malignancies primarily metastasize to lung and mediastinum (50%). Currently, there is no recognized staging and specific grading system. Overall prognosis is dismal with median survival below 18 months.

E-PS-22-009
A case of primary pulmonary Hodgkin lymphoma presenting as lung abcsess
K. Zarampouka[1], E. Margariti[2], K. Tziomalos[2], S. Tsagkaropoulos[3], C. Foroulis[3], T. Koletsa[1]
[1] Pathology Department, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2] First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece, [3] Department of Cardiothoracic Surgery, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

Background & Objectives: Primary Hodgkin lymphoma (HL) of the lung is very rare. We present a case of primary pulmonary HL with clinical and radiological presentation of abscess in order to raise awareness of this lymphoma manifestation.
Methods: A 26-year-old female patient complained for fever for the last two weeks, persistent after antibiotics administration. Chest X-ray showed an area of consolidation occupying the right lower lobe of the lung, while computed tomography (CT) suggested lung abscess. A thoracotomy was followed. A lung tissue specimen measured 11x1,5x1,3cm was sent for intraoperative consultation.
Results: Frozen sections showed fibrosis, necrosis and suppuration. At the periphery of the specimen there were scarce large cells. For permanent sections, a lung specimen measured 7X6X4cm was sent. Paraffin sections from both specimens revealed central area of necrosis and suppuration, at the periphery of which, a lymphogranulomatous tissue containing a few Hodgkin and Reed-Sternberg cells was identified. Immunohistochemically, these neoplastic cells were positive to CD30 and CD15 antibodies and negative to CD45. Thus, the diagnosis of classical HL was made.
Conclusion: When HL infiltrates lung without mediastinal involvement or hilar lymphadenopathy, the term primary pulmonary HL (PPHL) is used. PPHL may present necrosis and suppuration imitating clinically and radiologically lung abscess. Although PPHL is rare, it should be included in the differential diagnosis of lung abscess and a high index of suspicion from pathologists is recommended for the accurate diagnosis.

E-PS-22-010
Immunohistochemical profile of small-cell neuroendocrine carcinoma of lung: review of 110 cases
M.I. Oviedo Ramírez[1], G. Ruiz García[2], A. Salazar Nicolás[2], L. Barona García[2], M.I. Ortuño Moreno[2], M. Capelini[3], J.O. López Ojeda[4], A. Caballero Illanes[2], E. Gómez Plata[5], E. Martínez Barba[2]
[1] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [2] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [3] Urgencias atencion primaria Cartagena, Spain, [4] Hospital General Universitario los Arcos del Mar Menor, Spain, [5] Centro Oncológico Estatal ISSEMYM, Spain

Background & Objectives: Small-cell neuroendocrine carcinoma of lung is one of the most frequent types within endobronchial biopsies. Although it shows characteristic histopathological finding, immunohistochemistry is necessary in many cases due to the variety of possible differential diagnoses. The expression of the different markers usually employed as CKAE-1AE3, TTF-1 and neuroendocrine markers varies according to the literature. In particular, it is very important to know that these neoplasms can show negative immunostain for epithelial markers and even for TTF-1.
Methods: The archive were reviewed between the years 2009-2014, obtaining 110 cases. There were 97 mens and 13 women.The median age was 72 (range betwen 41 to 90 year old). We studied 78 biopsies and we also included 32 cases of lung FNA.
Results: From 110 cases we found 7.27% that were negative for TTF1 immunostain and 1.8% with negative immunostain for CKAE1-AE3. The rest of neuroendocrine markers were chromogranin, synaptophysin and CD56, which were negative in 11.92%, 22% and 2.75% respectively with varying degrees of immunostaining.The immunochemistry of TTF-1 was intense and difusse in 34 cases. Two cases showed TTF-1 immunostain multifocal and the rest of cases were of low intensity. We exclude 33 cases in which the immunostaining was not performed.
Conclusion: There are few bibliographical references to the percentage of negativity for TTF1 and CKAE1-AE3 in this tumour. The negativity for CKAE1-AE3 and TTF-1 is considered extremely rare. This study contributes important information, since it characterises immunoprofile of small-cell carcinoma. This information is useful in cases that show a usual morphology of small cell neuroendocrine carcinoma but with unusual immunohistochemical expression.

E-PS-22-011

Intraoperative frozen sections of an undiagnosed pulmonary artery intimal sarcoma. A case report

M. Kilmpasani[1], A. Baliaka[1], A. Madesis[2], E. Serasli[3], T. Karaiskos[2], G. Drossos[2], S. Papaemmanouil[1]

[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Cardiothoracic Surgery, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [3] Pulmonary Department, General Hospital of Thessaloniki "G. Papanikolaou", Greece

Background & Objectives: Intimal sarcoma is an extremely rare, aggressive malignant neoplasm. A few hundred cases are described in the literature, mostly located in the pulmonary artery, and often diagnosed postmortem. We present the case of a 69-year-old woman, admitted with symptoms of massive pulmonary embolism.

Methods: Intraoperatively, material from the right pulmonary artery was obtained and examined in frozen sections. Subsequently, a right pneumonectomy was undertaken. We observed a mass protruding in the lumen of the pulmonary artery and filling its branches in a mold-like manner. We performed hematoxylin-eosin and immunohistochemical stains.

Results: The frozen sections demonstrated a malignant neoplasm with sarcomatous features. It consisted of highly pleomorphic cells with evident mitotic activity, in an oedematous or slightly myxoid background. The cells were either spindle-shaped with enlarged, elongated nuclei, or round to oval-shaped with vesicular nuclei. There were also scattered multi-nucleated cells with lobular nuclei.

The interpretation of the frozen sections as sarcoma was confirmed in the paraffin sections. Moreover, the tumour seemed to originate from the intima of the pulmonary artery. The neoplastic cells stained positive for smooth muscle actin and negative for CD34 and desmin. The diagnosis of a pulmonary artery intimal sarcoma was given.

Conclusion: The true incidence of pulmonary artery intimal sarcoma is unknown, because it is most often misdiagnosed. The initial symptoms of pulmonary embolism, as well as the radiologically demonstrated intravasal growth of the tumour, may be misleading, regarding the immediate need for surgical therapy. In these cases, histologic examination is the most reliable tool for the correct diagnosis.

E-PS-22-012

A case of congenital pulmonary airway malformation in adulthood, presenting as hemoptysis

M. Kilmpasani[1], N. Pastelli[1], A. Baliaka[1], I. Dimitriadis[1], T. Karaiskos[2], K. Bismpa[3], S. Papaemmanouil[2]

[1] Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [2] Department of Cardiothoracic Surgery, General Hospital of Thessaloniki "G. Papanikolaou", Greece, [3] CT and MR Department, General Hospital of Thessaloniki "G. Papanikolaou", Greece

Background & Objectives: Congenital pulmonary airway malformation (CPAM), previously known as congenital cystic adenomatoid malformation (CCAM), is a rare lung parenchyma hamartomatous lesion, diagnosed mainly in the prenatal period, infancy or early childhood. We present the case of a 38-year-old man, admitted with hemoptysis, due to a hitherto undiagnosed CPAM.

Methods: A segmentectomy of the upper lobe of the right lung was performed. The material was examined with hematoxylin-eosin and immunohistochemical stains.

Results: The lung tissue demonstrated multiple, variably sized cystic formations, measuring 0.2-3.5cm in diameter, causing effacement of the lung architecture. These were covered by cuboidal or columnar respiratory epithelium, as well as mucinous epithelium, with well-differentiated goblet cells, forming scattered groups or tufts. The cysts were separated by fibrous septa, with only rare presence of cartilaginous tissue. These formations were mingled with dilated alveoli, filled with numerous foamy macrophages and mucin.

In correlation with the radiologic findings and the patient's history, the diagnosis was congenital pulmonary airway malformation, type 1.

Conclusion: The incidence of CPAM is approximately 1 case per 10,000-35,000 pregnancies, and is constantly increasing, due to the improvement of prenatal ultrasound diagnostics. About 80% of the cases are diagnosed in the first 2 years of age. Its clinical manifestation varies from asymptomatic to as severe as perinatal death. CPAM is rarely diagnosed in adulthood, and the most common symptom is cough. It is associated with a risk of recurrent pulmonary infections, as well as malignant transformation. Therefore, resection and histological examination of the affected tissue is advised, even in the asymptomatic cases.

E-PS-22-013

Calcified pachypleuritis, a major sign of exposure to asbestos: eliminate a malignant mesothelioma first!

F. Chadi[1], N. Bourhroum[2], N. Mahassini[2]

[1] Pathology Department of Mohamed V Military Teaching Hospital, Rabat, Morocco, [2] Pathology Department of Ibn Sina Universitary Hospital, Rabat, Morocco

Background & Objectives: If cancers are the main concern of the health consequences of exposure to asbestos, it is the non-malignant diseases, largely dominated by pleural plaques, which are by far the most frequent affections due to exposures to this mineral.

Methods: We report the case of a 70-year-old woman who worked at the Moorish bath for 45 years, admitted for the management of acute chest pain with acute coronary syndrome.

The discovery of basal-thoracic pleural thickening with a syndrome of fluid effusion having motivated the realization of a CT scan which showed the presence of a non-parenchymal calcified pleural plaque.

Results: After inconclusive pleural biopsies, a parietectomy decision with pathological examination in favour of a calcified pachypleuritis without sign of malignancy.

Conclusion: This observation also confirms the diagnostic difficulties raised by minor pleural or pulmonary images, frequently identified during routine CT screening, and the need for precise diagnostic criteria, given the compensatory consequences attached to them.

E-PS-22-014

Emperipolesis-type giant cell carcinoma of the lung: relevance of PDL1

A. Handra-Luca[1], I. Onorati[1], P. Guiraudet[1]

[1] APHP University Paris Nord, France

Background & Objectives: The emperipolesis-type (null-type) of lung giant cell carcinoma (GCC) was recently identified as specific tumour group (Weissferdt and Moran 2016) as different from the syncytial-type. We aimed to report the morphological and immunohistochemical features of a series of 7 cases of emperipolesis-type GCC of the lung.

Methods: The 7 tumours, detected on surgical resection specimens, were analysed for morphological and immunohistochemical features.

Results: The gender ratio was 1:6 (female:male), the age ranged 41-79 years. Excessive smoking was known in 5/7 cases, neoadjuvant chemotherapy in 1/7, radiochemotherapy in 1/7 (12 years previously for breast cancer). The tumour size ranged 1.5-6.5 cm. All tumours showed necrosis, mild in 3. All 7 tumours were TTF1-positive and contained adenocarcinoma-type zones (mucus-secreting, 4). Squamous cell differentiation (CK5/6 and/or p63 positivity) was detected in 4 tumours. PDL1 was expressed in 6/6 tested tumours. PDL1 expression by giant tumour cells was heterogenous within a same tumour.

Emperopoletic PDL1-positive tumour cells contained PDL1-positive or PDL1-negative emperipolesied tumour or inflammatory cells. There was no relationship to PD1-positive inflammatory cells.
Conclusion: Emperipolesis-type GCC of the lung may show TTF1 expression and may occur in association to adenocarcinoma or squamous cell differentiation. PDL1 expression in emperipoletic tumour cells suggest a possible interference with the acquisition of phagocytic capacities, being known that macrophages also express PDL1.

E-PS-22-015
Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) accompanied by a pulmonary adenocarcinoma: case report
K. Revelos[1], Z. Almpanis[1], K. Siafakas[2], M.T. Revelou[1], C. Spiliadi[3]
[1] Pathology Department, 251 Hellenic Air Force General Hospital, Greece, [2] Thoracic Surgery Department, 251 Hellenic Air Force General Hospital, Greece, [3] Pathology Department, Athens Medical Center, Greece

Background & Objectives: DIPNECH is an exceedingly rare disorder which is being recognized with increasing frequency. It is usually presented in combination with carcinoid tumorlets, obliterative bronchiolitis and fibrotic lung diseases. Reports of DIPNECH in association with an adenocarcinoma are extremely limited in the literature.
Methods: A 78 - year old female patient referred to our hospital because computed tomography and PET-CT scans revealed a tumour-like lesion measuring 3,5 cm, in its widest dimension, in the upper lobe of the left lung. The patient had a long history of chronic obstructive complaints such as cough, shortness of breath and wheezing and was under treatment for chronic obstructive pulmonary disease (COPD). She had no smoking history. In previous CT scans, over a 10 year's period, the lesion of the upper left lobe and small nodular lesions in both lungs were identified, but there were considered as fibrotic processes. The main lesion became larger in size and with a central compact component.
Results: A left upper lobectomy was performed and a well differentiated adenocarcinoma of mixed subtype, with lepidic and papillary pattern, was diagnosed. Within the tumour but also in distant sites of the lobe DIPNECH foci were identified in association with terminal airways and measured less than 5mm in greatest diameter. The diagnosis was confirmed by immunohistochemistry.
Conclusion: DIPNECH in association with an adenocarcinoma is a rare condition and a causal relationship was previously suggested. Increased awareness for the diagnosis and better understanding of the disorder and its associated pathologies is needed.

E-PS-22-018
Ancient schwannoma of the pleura
I. Vamvakaris[1], E. Psychogiou[1], D. Riga[1], P. Megas[1], A. Papadopoulou[1], A. Tsonou[1]
[1] General Hospital of Thoracic Diseases of Athens "Sotiria", Greece

Background & Objectives: Schwannomas are rare benign tumours originating from Schwann cells. Ancient schwannoma is a variant of schwannoma which presents as an encapsulated tumour usually located retroperitoneally. Ancient pleural schwannomas are rare, with less than twenty cases reported in the literature.
Methods: We report the case of a 57-year-old female who presented with sudden onset breathlessness and cough. HRCT revealed an enhancing mass in the right thoracic cavity. The patient underwent thoracotomy and excision of a well circumscribed encapsulated pleural mass measuring 5,8 x 5,1 x 4,8 cm.
Results: The specimen we received was tan-white to yellow, with cystic change and haemorrhage. Microscopy revealed a hypercellular mesenchymal neoplasm consisting of spindle/elongated cells (S-100+), cytologically bland with wavy nuclei, granular chromatin, arranged in a palisading or organoid fashion /Verocay bodies (Type A areas) intermingled with hypocellular areas with abundant edema (Type B areas). Some cells exhibited atypia and hyperchromatic nuclei. Mitotic activity was low (Ki67<5%). Calcification and infiltration by lymphomononuclear cells and histiocytes as well as hyalinized vessels were observed. Our diagnosis was pleural ancient schwannoma.
Conclusion: Ancient schwannoma of the pleura is a rare entity. Patients become symptomatic when tumours attain large size. Complete surgical excision is curative with excellent prognosis. Malignant transformation is rare. It is important to keep this rare tumour in mind for the differential diagnosis of intrathoracic lesions.

E-PS-22-019
Pulmonary Langerhans Cell Histiocytosis (PLCH)
I. Vamvakaris[1], E. Psychogiou[1], D. Riga[1], A. Mandilara[1], P. Megas[1], A. Papadopoulou[1]
[1] General Hospital of Thoracic Diseases of Athens "Sotiria", Greece

Background & Objectives: Langerhans cell histiocytosis (LCH) is a pathological entity characterised by proliferation of Langerhans cells. It can present either as a localized or as a systematic disease. PLCH is uncommon and presents either as a diffuse process or as a solitary nodule. The majority of patients are current or former smokers, aging approximately 40 years, with no significant sex predilection. In 38-57% of cases V600E/BRAF mutations are found.
Methods: A 38-year-old female patient, current smoker, presented to our hospital with chest pain and dyspnea. Chest X-ray revealed interstitial-like lung lesions in the lingular parenchyma. After thorough clinical/laboratory examination, the patient underwent open lung biopsy.
Results: The specimen from the lingula included a solitary nodule 0,4 cm in greater diameter, white-tan, solid and elastic in consistency. Microscopically we observed interstitial infiltration by many eosinophils, variable numbers o mononuclear inflammatory cells and numerous large sized cells with morphological and immunohistochemical (CD1a+, S-100+) features consistent with Langerhans cells. The neighbouring parenchyma was characterised by BOOP-like lesions. We concluded to the diagnosis of PLCH.
Conclusion: The localized and solitary form of PLCH is a rare entity affecting young smokers. It may be totally asymptomatic or present with acute pulmonary and/or systemic symptoms and may be a clinical mimicker of malignancy. Its correlation with V600E mutations of BRAF oncogene plays significant role in targeted therapies.

E-PS-22-020
Primary Pulmonary Malignant Melanoma (PPMM)
I. Vamvakaris[1], D. Riga[1], E. Psychogiou[1], G. Chamalakis[1], P. Megas[1], A. Mandilara[1], A. Papadopoulou[1]
[1] General Hospital of Thoracic Diseases of Athens "Sotiria", Greece

Background & Objectives: Malignant melanoma (MM) is one of the most aggressive and treatment-resistant skin cancers. Primary pulmonary malignant melanoma (PPMM) is extremely rare, accounting and with a rather poor prognosis. To assure the diagnosis, extrapumonary origin must be ruled out by thorough evaluation.
Methods: A 56-year-old male patient was referred to our hospital with progressive dyspnoea and cough. Medical history included high arterial pressure and smoking. Physical examination was normal. Chest X-ray and HRTC revealed an enhancing mass in the left upper lobe extending to the splachnic pleura. Thoracotomy revealed a black-pigmented mass measuring 4 cm in greatest diameter and wedge biopsy was performed.
Results: The specimen we received included a lobular black-pigmented lesion, solid in consistency, infiltrating the resected pleura. Microscopically, the tumour displayed histological and immunohistochemical features compatible with MM (HMB45+, S100+). Mesothelial

and epithelial markers were negative (Calretinin, BerEp4, KLMW). We asked the clinicians for a detailed search of possible sites of primary MM (skin, mucous membranes, scalp, palms, plants, eyes, nasopharyngeal/oral mucosa, genitals) which was negative. We concluded to the diagnosis of PPMM. The patient underwent 12 months chemotherapy and immunotherapy and is still on strict follow-up program.

Conclusion: Although extremely rare, PPMM should be considered in the differential diagnosis of primary pulmonary tumours. It can masquerade as histologic types of tumours such that the pathologist must "think melanoma". During the investigation of a suspected PPMM, one must always bear in mind that MM of the skin may spontaneously regress despite having metastasized, posing a diagnostic challenge.

E-PS-22-021

Combined SCLC recognised by immunohistochemistry will not exclude patients from molecular treatment

R. Almeida[1,2], A. Alarcão[3,4,5], A.F. Ladeirinha[3,4], M.R. Silva[6,7], T. Ferreira[3,4], A.I. Rodrigues[3], V. Sousa[3], L. Carvalho[3]

[1] Centro Hospitalar e Universitário de Coimbra - Pathology department, Portugal,

[2] Faculty of Medicine in Coimbra, Portugal,

[3] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal, [4] CIMAGO - Research Center for Environment, Genetics and Oncobiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [5] Centre of Pulmonology, Faculty of Medicine of the University of Coimbra, Portugal, [6] Institute of Anatomical and Molecular Pathology, Faculty of Medicine, University of Coimbra, Portugal, [7] CIMAGO - Research Center for Environment, Genetics and Oncobiology, Faculty of Medicine, University of Coimbra, Portugal

Background & Objectives: Combined small cell lung carcinoma (C-SCLC), correspond to 5%–28%, most commonly associated with adenocarcinoma (ADC) and with squamous cell carcinoma (SCC); EGFR mutations occur in less than 5% of pure SCLC, reaching 15%–20% in C-SCLC.

Methods: Four cases of C-SCLC were selected, where two were combined with ADC (one male and one female, between 70-73y), and the other two cases, combined with SCC (males, aged between 72-77y); staged from IA2 to IVA (AJCC). Global survival was between 4-61months, being between 6-8months in C-SCLC/ADC, and 4-61months in C-SCLC/SSC.

All cases were submitted to Ion AmpliSeqTM Colon and Lung Cancer Research Panel v2. (22 genes), after manual independent microdissection.

Results:

	Histopathology	Immunohistochemistry	NGS
Case 1	SCLC	CK7+, TTF1+, CD56+, Ki67 100%	***PIK3CA*****:** .1633G>A;p(Glu545Lys) ***BRAF*****:** c.1397G>A;p(Gly466Glu) ***TP53*****:** c.586C>T;p(Arg196Ter) ***TP53*****:** c.305C>T;p(Thr102Ile) ***STK11*****:** c.109C>T;p(Gln37Ter)
	ADC	CK7+, TTF1+, CD56-, Ki67 50%	Non amplified
Case 2	SCLC	CK7+, TTF1+, CD56+, Ki67 100%	***EGFR*****:** c.2582T>A;p.(Leu861Gln) ***TP53*****:** c.376T>G;p(Tyr126Asp)
	ADC	CK7+, TTF1+, CD56-, Ki67 40%	***EGFR*****:** c.2582T>A;p.(Leu861Gln) ***TP53*****:** c.376T>G;p(Tyr126Asp)
Case 3	SCLC	CD56+, Chromogranin+, CK5.6+, Ki67 100%	***TP53*****:** c.814G>A;p(Val272Met)
	SCC	CD56-, Chromogranin-, CK5.6+, Ki67 50%	Non amplified
Case 4	SCLC	CK5.6-, Chromogranin-, CD56+, Ki67 95%	*Wild-type*
	SCC	CD56-, Chromogranin-CK5.6+, Ki67 40%	*Wild-type*

Conclusion: p53 pathway persisted as the common mutation, raising similar progression as verified in germinative tumours. In this series we cannot follow any particular molecular trace, while the applied immunohistochemical panel showed homogenous expression in both patterns of the combined tumours, allowing the diagnosis in biopsies. Treatment demanding molecular studies will gather further knowledge to not exclude patients.

E-PS-22-022

Bronchial fibroepithelial polyp - case report of a histologically benign lesion with potentially severe clinical implications

B. Simona[1], A.C. Lisievici[2], T.A. Georgescu[3], F. Pop[4]

[1] Spitalul Universitar de Urgenta Bucuresti (SUUB), Romania, [2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3] Department of Pathology, Bucharest Emergency University Hospital, Romania, [4] "Dr. Carol Davila" University Hospital of Nephrology, Romania

Background & Objectives: Endobronchial fibroepithelial polyp is a rare and benign tumour first described by Patterson in 1930. Benign tracheobronchial tumours account for 1.9 % of all pulmonary tumours and there are only about 30 case reports of airway fibroepithelial polyps in the scientific literature. The average age at diagnosis is 61 years and men are most frequently affected. These lesions feature an increased risk of complications, including life threatening conditions.

Methods: We report the case of a 65-year-old male presenting with dry cough, right latero-thoracic pain and recurrent pneumonia. The patient underwent bronchoscopy which revealed a mobile branching polypoid lesion, partially obstructing the right lower lobe bronchus. A biopsy was performed and histopathological examination revealed a polypoid fibrovascular stroma with lymphocytic infiltrate, covered by normal respiratory epithelium. The findings were suggestive for an endobronchial fibroepithelial polyp and the patient underwent lower lobectomy due to consolidation and recurrent episodes of pneumonia.

Results: Upon gross examination, the specimen revealed diffuse fibrosis and changes of chronic congestion. The right lower lobe bronchus

presented a 1.3/1.1/1.0 cm endobronchial polypoid mass with lobulating contour, glistering surface and no signs of bronchial wall invasion. Histopathological examination revealed multiple papillary projections branching from a central fibrovascular core, covered on multiple sides by columnar pseudostratified cells with cilia and focal squamous metaplasia. Although a straight-forward histological diagnosis, bronchial fibroepithelial polyp may sometimes raise clinical suspicion of malignity.
Conclusion: Airway fibroepithelial polyps are uncommon benign lesions of unknown etiology that are usually diagnosed due to symptopms related to the bronchial obstruction, such as recurrent pulmonary infections or atelectasia. Clinically, they can sometimes mimic a malignant neoplasm, but the characteristic lobulated contour might be helpful in the differential diagnosis of various other endobronchial neoplasms.

E-PS-22-023

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. A case report and review of literature

A. Sanz Zorrilla[1], M.T. Gonzalez Serrano[2], F. Granados Pacheco[3], A. Martínez Lopez[2], H. Fuentes Vaamonde[1]
[1] Hospital Universitario Reina Sofía, Córdoba, Spain, [2] Pathology Department Hospital Universitario Reina Sofía, Córdoba, Spain, [3] Agencia sanitaria Hospital Costa del Sol, Marbella, Spain

Background & Objectives: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare idiopathic disease with only about 100 cases reported in the literature to date. WHO Classification 2015 has considered it as a precancerous lesion of a lung neuroendocrine tumour. It is characterised by diffuse clustered, linear or nodular neuroendocrine cell hyperplasia without basement membrane breakthrough within bronchial mucosal epithelium. If localized infiltrative growth and nodule formation are shown with basement membrane breakthrough, nodule diameter ≤5 mm is called a carcinoid tumourlet and nodule diameter >5 mm is called a carcinoid. Here we report a case of this infrequent disease.
Methods: A 67-years-old woman presented had no smoking history. The patient had ERGE and long evolution cough syndrome. A routine chest radiography and chest Computed Tomography (CT) revealed multiple small nodules scattered in all pulmonary areas. A double pulmonary wedge resection was performed.
Results: Histologically, the pulmonary architecture was preserved, and there was a proliferation of pulmonary neuroendocrine cells within and around bronchiole. Also, there was partially broke through bronchial wall and displayed nodular infiltrative growth; nodules were all <5 mm in diameter; cell size and morphology were relatively consistent; chromatin was fine granule-like. Immunohistochemical staining of the cells all showed AE1/AE3 (+), synaptophysin (Syn) (+), chromogranin A (CgA) (+), and Ki-67 hyperplasia index 2%.
Conclusion: DIPNECH is a rare and preinvasive disease that could be difficult to diagnose. The minimum criteria needed for this diagnosis are the presence of several group PNE cells in small airways combined with carcinoid tumourlets. It should be included in the differential diagnosis of micronodular formations, especially in middle-aged women without history of smoking. The accurate diagnosis of DIPNECH allows for the implementation of appropriate treatment and channels further management of the patient into the right direction.

E-PS-22-024

PD-L1 expression study in 130 non-small cell lung cancer (NSCLC) surgical specimens and correlation with clinic, histology and survival

S. Hernandez Bonilla[1], L. Blasco Santana[2], L. Gutierrez Sainz[3], C. Rodriguez-Antolin[4], R. Rosas[5], P. Cruz Castellanos[3], E. Ruiz-Bravo[6], I. Esteban Rodriguez[1,5]
[1] Pathology department, La Paz University Hospital, Madrid, Spain, [2] Pathology Department, La Paz University Hospital, Madrid, Spain, [3] Medical Oncology Service, La Paz University Hospital, Madrid, Spain, [4] Cancer Epigenetics Laboratory, INGEMM, La Paz University Hospital, Madrid, Spain, [5] Biomarkers and Experimental Therapeutics in Cancer, IdiPAZ, Madrid, Spain, [6] Hospital Universitario La Paz, Spain

Background & Objectives: PD-L1 nowadays is the most important biomarker in order to select patients with NSCLC who will receive immunotherapy. We have studied the relation between PD-L1 expression, clinic-histologic factors and survival.
Methods: PD-L1 was analysed in 130 lung surgical specimens from our department between 2017 and 2018 by immunohistochemistry with 22C3 Dako Clon and EnVision Flex visualization system in immunostaining autostainer Link 48. We collected histologic and clinical factors (histologic subtype and grade, lymphovascular invasion (LVI), perineural invasion, stage, age, sex and smoking status). Grading Adenocarcinoma (AD) is obtained by the addition of the percentages of the subtypes with same grade and choosing the highest result. Survival analysis has been studied using IBM SPSS statistics 22 program and a descriptive analysis was carried out, followed by a survival analysis using the Kaplan-Meier estimator. To correlate PD-L1 expression and the histological and clinical factors, we performed Kruskal-Wallis, Wilcoxon and Spearman tests.
Results: We retrieved 46 women and 84 men cases. The average age is 68 years old. 41 were smokers, 68 ex-smokers, 19 non-smokers and 2 unknown. 92 were AD, 35 squamous cell carcinoma (SCC), 2 Adenosquamous carcinoma and 1 NDCLC. PD-L1 expression related with histologic subtype SCC (p=0,003), grade 3 (P= 0,0001), LVI (p=0,003), solid (p=0,028) AD pattern (p= 0,046) and no driver mutations (p= 0,01). The median overall survival (OS) was greater in patients without mediastinal lymph node involvement than in patients with mediastinal lymph node involvement (p=0.006, HR= 0,2 95% ic (0,05-0,71)).
Conclusion: Our results are consistent with the literature, although we haven´t found reported LVI and as a histologic factor related with PD-L1 expression, so this is our main contribution. In survival study we haven´t found statistically significant differences in most factors probably because of the short follow-up. We propose to enlarge the follow-up and further studies.

E-PS-22-025

Pulmonary adenocarcinoma with micropapillary component metastasizing to the breast

Z. Mijovic[1], D. Mihailovic[1]
[1] Institute of Pathology, Medical Faculty, University of Nis, Serbia

Background & Objectives: Although lung cancer is the most common cancer worldwide, the incidence of pulmonary carcinoma, particularly with micropapillary component, metastasizing to the breast is very rare. We present a case of breast metastasis from pulmonary adenocarcinoma, which was initially interpreted as a primary breast cancer.
Methods: A 67-year-old female patient presented with dyspnea and chest pain. On chest radiograph pleural effusion was found. After physical examination poorly defined mass was noted in the upper outer quadrant of the right breast. The patient underwent excisional breast biopsy and thoracoscopy.
Results: On histological analysis the breast biopsy specimen demonstrated multiple foci of adenocarcinoma with micropapillary component, desmoplastic reaction and lymphovascular invasion, which was morphologically similar to that seen in the pleural biopsy. The surrounding breast parenchyma demonstrated fibrocystic dysplasia without evidence of in situ carcinoma. The immunohistochemical staining markers for breast including estrogen receptor (ER), progesterone receptor (PR), mammaglobin and gross cystic disease fluid protein-15 (GCDF-15) were negative. Lung cancer markers of thyroid transcription factor-1 (TTF-1) and Napsin A were strongly positive which further supported the diagnosis of primary lung adenocarcinoma with micropapillary pattern with metastasis to the breast and pleura.

Conclusion: The distinction between metastasis from lung adenocarcinoma, particularly with micropapillary pattern which is recently recognized as an important prognostic factor, and primary breast adenocarcinoma may cause a significant diagnostic dilemma. The contribution of immunohistochemistry to the correct diagnosis is very important.

E-PS-22-026

Morphological and microscopic features of the oral cavity in patients with pulmonary tuberculosis

B. Aitbay[1]
[1] Karaganda Medical University, Kazakhstan

Background & Objectives: Today tuberculosis (TB) referred as one of the widespread diseases. Kazakhstan is among the countrieswith the highest burden of the tuberculosis in terms number of TB cases during the year. However, for the last 10 years the morbidity rate of the tuberculosis in Kazahkstan reduced in 2.4 times (from 125.5 in 2008 till 52.2 in 2017 for 100 thousand people). Despite the numerous studies and greatest achievements, the relationship of the disease and dentistry is not completely explored. Aim of the study is investigate the changes in the hard tissue of the teeth and oral fluid of patients with pulmonary tuberculosis for the detection of Mycobacterium tuberculosis.
Methods: The dental status of 250 patients (58.7% males and 41.2% females) with diverse destructive forms had been investigated. Morpho-histological object: 10 biopsies of dentin with hematoxylin and eosin staining (Van Gieson's and Weigert's stain). Bacterioscopic study: saliva of 15 patients stained with Fuxin by Gram's and Ziehl-Nielson/
Results: Morpho-histological studies of microscopies of hard tissues of teeth demonstrated that polymorphism of cell-tissue disorders, including distrophy of dentin and enamel structures of odontoblasts, where between the layers of dystrophic epithelium and layers of inflammatory tissue should be noted to traced dystrophy of enamel structures and dentin layers. In the smears-prints taken from the dorsal surface of the tongue, mycobacteria tuberculosis was not detected, however, squamous epithelial cells were found, as well as single layers of epithelial desquamated cells, among which inflammatory cell elements were revealed. Microscopic bacterioscopy in smears prepared from the saliva of patients with destructive forms of tuberculosis abundant accumulation of mycobacterium of dark pink color, merged in the form of lumps were detected.
Conclusion:

1. The presence of mycobacteria in saliva obliges dentists to adhere to caution and strict observance of all protection measures during the examination of the oral cavity.
2. The results showed the importance of comprehensive studies of patients with pulmonary tuberculosis to assess the differential diagnosic values in the dental aspect.

E-PS-22-028

Morphological features of the pulmonary sequestration

M. Rybakova[1], I. Kuznetsova[1], E. Markusevich[1]
[1] Pavlov First Saint Petersburg State Medical University, Russia

Background & Objectives: This study aimed to analyse clinico-morphological features of pulmonary sequestration (PS).
Methods: We analysed clinical data and examined surgical specimens from 3 patients with the diagnosis of intralobar PS (in 2 cases aberrant vessels were revealed during surgery, in 1 case – on CT with angiography).H&E, Ziehl–Neelsen and Van Gieson's stains were used for histopathological examination.
Results: Patients' meanage was 40±3years. Patients suffered from repeated pneumonias, dry cough and episodic chest pains and hemoptysis. Macroscopically, lung specimens showed multiple variably sized cysts separated by grossly normal lung parenchyma. Microscopic changes included areas of necrosis, microcalcification, granulomatous inflammation with macrophages, incl. multiple giant cells, lymphocytes and plasma cells. A large number of cysts contained mucus admixed with inflammatory debris and macrophages. In two cases cysts werelined with cylindrical to cuboidal epithelium and in one case the lining epithelium was focally attenuated and flattened. Perivascular areas showed various degrees of lymphocytic infiltration. Bronchial walls demonstrated chaotic distribution of smooth muscle fibers. The transverse sections of bronchi were lined with ciliated pseudocolumnar epithelium with goblet cells. In blood vessels, smooth muscle cell proliferation was found.
Conclusion: Use of computerized diagnostic imaging techniques is required to prove anomalous systemic arterial supply of the sequestrated lobe which is essential to the diagnosis. The microscopic changes per se are non-specific and manifest with hypoplasia/cyctic lesions and inflammatory reactions of variable type and intensity, which sometimes hide the underlying disease.

E-PS-22-029

Pleural epithelioid malignant mesothelioma with psammoma bodies in a young female: a diagnostic challenge

î Ilyès[1], O. Iurcsuk[1], K. Straub[1], B. Nagy[1], T. Kálmán[1], A. Burszán-Barabás[2], M. Szántó[3], A.C. Dobrică[4]
[1] Emergency County Hospital, Pathology Department, Romania, [2] Emergency County Hospital, Radiology Department, Romania, [3] Emergency County Hospital, Pneumology Department, Romania, [4] Emergency County Hospital, Thoracic Surgery Department, Romania

Background & Objectives: Malignant mesothelioma is an invasive and fatal neoplasm that arises from mesothelium, in general after decades of asbestos exposure. It is considered a disease of the elderly, but rarely is diagnosed in patients under 40 years. These patients may have an increased genetic predisposition to developing mesothelioma or may have environmental exposures to carcinogenic mineral fibers from an early age.
Methods: We present a case of a 31 years old, healthcare worker female, who was admitted to the Pneumology Department with dry cough, shortness of breath, night sweats, chills and severe asthenia. Her medical history was no significat, excepting that 10 month earlier she gave birth to a child, since than she had intermittent brownish vaginal secretion.
Results: On the CT scan multiple pleuro-pulmonary, mediastinal and paravertebral lesions was described with 75x48x40 mm in greatest dimension, without any abnormality at the abdominal or pelvic organs. A lymphoproliferative or a metastatic disease with unknown primary was suspected. The gynaecological examination and the serum HCG level was normal. A pleuro-pulmonary biopsy was performed and the histopathological examination revealed a partially necrotic tumour with solid architecture, composed of small to medium sized epithelioid cells, with eosinophilic and clear cytoplasm, mild to moderately pleomorphic round nuclei, some of them hyperchromatic, some with vesicular chromatin and prominent eosinophilic nucleoli. A few cells presented intranuclear inclusions. In the stroma a PAS positive material was present, as well as numerous psammoma bodies. After the conventional histologic examination a series of differential diagnoses were listed and the pathological examination was completed with immunohistochemical study. After the interpretation of the immunohistochemical reactions a final diagnosis of epithelioid malignant mesothelioma was confirmed.
Conclusion: Malignant mesothelioma is a very rare, aggressive malignancy, commonly associated with asbestos exposure. Our patient could not prove any occupational origin for the asbestos exposition, but she confirmed that in every year at the winter time the heating of the house she lived in her child- and early adulthood was provided by an asbestos-based radiator. If the exposure to the asbestos mineral fiber can not be confirmed, the presence of the germline BAP-1 mutation should be investigated. The psammoma bodies are much more frequently reported in peritoneal mesothelioma, their presence in the pleura are quite uncommon.

E-PS-22-031

Primary pulmonary synovial sarcoma: a report of three cases confirmed by fluorescence in situ hybridisation

I. Savic[1], L. Simic[2], M. Ninkovic[2], G. Djuricic[2], D. Ristic[2], J. Sopta[1]
[1] Institute of Pathology, Medical Faculty, University of Belgrade, Serbia,
[2] Institute for Oncology and Radiology, Belgrade, Serbia

Background & Objectives: Primary pulmonary synovial sarcoma is extremely rare and aggressive neoplasm, comprising 0.3-1.3% of all lung malignancies.
Methods: Here, we present three cases of primary pulmonary synovial sarcoma diagnosed at the tertiary institution.
Results: Our patients were two males and one female age 20y/o, 67y/o and 56y/o respectively. They all presented with cough and chest pain. After imaging methods, tumour masses were found in their lungs. Tumour dimensions on CT scans were >10cm in diameter. They were all initialy diagnosed as a primary epithelial tumours in the lungs. Pathology specimens were sent for revision in our institution. Microscopically, all tumours consisted of monomorphic, elongated spindle cells aranged in fascicular and hemangiopericytoma-like pattern with hyperchomatic nuclei. Area of necrosis, hemorrhage and moderate/intensive neoangiogenesis was noted. Differential diagnoses included other lung mesenchymal tumours: SFT, MPNST, ES, as well as metastases outside the lung. Immunohistochemically, spindle cells were positive for: TLE-1, vimentin and bcl2. EMA, CD99 and cytokeratin were positive in 2 of 3 cases. FISH was performed in all cases which showed positive results in SS18 gene rearrangment. After complete staging, all cases were diagnosed as primary pulmonary synovial sarcoma. In follow-up one patient developed systemic metastases. Two other patients were metastases free. They are all alive.
Conclusion: Primary pulmonary synovial sarcoma should be considered in differential diagnosis of spindle and round blue cell tumours. In that case, FISH could be very significant diagnostic tool.

E-PS-22-032

Tissue preservation in non-small cell lung cancer (NSCLC) - a major quality parameter

T. Neuman[1], T. Graziani[2], G. Vainer[1]
[1] The Hebrew University - Hadassah Medical Center, Jerusalem, Israel,
[2] The Technion Medical School, Haifa, Israel

Background & Objectives: Tissue handling in NSCLC is challenging as the samples are tiny and the required information beside the diagnosis is wide (i.e. immunoprofiling, PD-L1 status, genetic analyses). The ability to maximize information gained from limited samples is a major quality parameter for pathology departments; however, data on what are the optimised utilization parameters is absent.
Methods: We developed a specific protocol for tissue handling in lung biopsies. PD-L1 immunostains were performed in our institution between July 2016 and March 2019 for previously diagnosed NSCLC. Part of the cases were in-house while others were referrals. In-house cases come from two different hospitals. We analysed the utilization parameters of the different groups and compared them also to the utilization results in the Israeli early access program(2015-2016).
Results: Overall, 92/1176(7.82%) of the cases could not be determined for PD-L1 due to lack of material. For in-house case 131(3.09%) could not be determined compared to 795(10.46%) for the outside cases($p<0.0001$, Fisher's exact test). 35 specimens taken outside but diagnosed in our hospital showed none who could not be determined. In the Israeli early access program(all of them were referral cases) the rate was 11.55%.
Conclusion: Outside cases show ~X4 more undeterminable cases compared to the in-house cases. This is more likely due to the pathology lab performance as executing the entire processing yields similar cases even tissues which are obtained in another hospital. Priority should be given to laboratories that can do both the diagnosis and the additional assays. A rate of 3% for undeterminable cases is achievable.

E-PS-22-034

Clinico-pathological features of primary pulmonary hepatoid adenocarcinoma (PPHAC): an under-recognised and aggressive lung neoplasm with distinct immunophenotype (CK7-pos/HepPar1-pos/TTF1-neg)

K. Varshney[1], R. Kaushal[1], N. Mittal[1], T. Pai[1], A. Janu[1], A. Joshi[1], J. Agarwal[1], K. Prabhash[1], C. Pramesh[1]
[1] Tata Memorial Centre, India

Background & Objectives: Primary pulmonary hepatoid adenocarcinoma (PPHAC) is a rare, aggressive neoplasm. Till date, it has failed to establish a distinct place in WHO classification for lung tumours. We hereby, present the clinico-pathological spectrum of PPHAC.
Methods: PPHAC diagnosed between 2012-18 were retrieved from pathology archives. Cases with known extra-thoracic primary were excluded. Clinico-radiological details were recorded and histopathological features were reviewed.
Results: A total of 45 cases of PPHAC were recognized. Exclusive predominance for males (43/45) and smokers (39/40) with median age of 55 years (range 43–78 years) was noted. Tumour was predominantly located in upper lobe [(N=32/45(71%)] and ranged from 3cm – 11cm in size. Mediastinal lymph nodes were enlarged in 78% (35/45). AFP levels were raised in 1/3 cases. Histopathological examination, revealed predominantly solid (n=20) and trabecular pattern (n=12). Tumour cells were large polygonal with abundant eosinophilic to clear cytoplasm in 89%(40/45) cases. IHC showed a consistent and distinctive immunoprofile i.e. $CK7^{+}$/HepPar-1^{+}/$TTF1^{-}$in all 45 cases. Molecular evaluation (n=25) revealed consistent negativity for EGFR mutations, EML4-ALK, ROS1 gene rearrangements and MET amplification in all except two cases (one with EGFR exon19 mutation and other with MET Amplification). Chemo-radiotherapy (n=25) was the main treatment modality. Surgical resection was possible in only 4 cases. Median follow up was 12 months (range: 2 months – 5 years) and 8 patients (24%) succumbed within six months of diagnosis. Almost half of the patients (22/45) had metastatic disease at presentation (16 -skeletal and 8-both visceral and skeletal metastases).
Conclusion: PPHAC is emerging as a distinctive, highly aggressive, under-recognised entity which occurs exclusively in smoker males. In view of consistent Hep-Par1 positivity and TTF1 negativity, it may represent a potential diagnostic pitfall.

E-PS-22-035

PDL-1 in EBUS-TBNA material: a retrospective study of results in 127 patients and review of the literature

A. Sobrino Prados[1], R.I. Bermudez Cameo[1], R. Álvarez Alegret[1], L. Ferrando Lamana[1], P. Gambó Grasa[1], A. Valero Torres[1], M. García García[1], J.J. Vengoechea Aragoncillo[1], E. Mincholè Lapuente[1], J.I. Franco Rubio[1], M.J. Viso Soriano[1]
[1] Hospital Universitario Miguel Servet, Zaragoza, Spain

Background & Objectives: Because lung cancer treatments are increasing so much in the last years, we need to improve our knowledgment of diagnosis methods and its possibilities. Programmed death-ligand 1 (PD-L1) is one of the last discoveries and its expresion in lung cancer has become crucial for the patients outcome. On the other hand, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technic to diagnose and stadify lung cancer, on which we can perform PDL-1 in order to have the information of its expression before the surgical excision.
Methods: Using 127 EBUS-TBNA samples from a single institution (Universitary Hospital 'Miguel Servet' of Zaragoza) between 2018 and 2019, we have analysed the incidence of the different types of lung cancer, age of diagnosis, gender and PDL-1 expression (PDL-1 IHC 22C3).
Results: Out of 127 patients, 97 were males. 57 out of 127 patients expressed PDL-1 in their EBUS-TBNA material. From our sample, the

predominant histologic type was adenocarcinoma (44,88%) and the second and third one, the squamous cell and microcitic lung cancer (28,34% and 7,87% respectevely). PDL-1 was equivalently expressed in adenocarcinoma and squamous carcinoma, whithout relevant differencies between both groups. 34 out of 127 patients died, 38, 2% of them suffering from an adenocarcinoma.

Conclusion: In our sample, a clear male predominance existed but there were no significative differencies between PDL-1 expression neither in the different histological lung cancers nor in gender predilection. Anyway, further research about PDL-1 and its expression is needed for offering the best diagnosis and treatment options for patients.

E-PS-22-036

Lower BRMS1 expression is associated with high grade histologic subtypes in lung adenocarcinomas

P. Bulutay[1], P. Firat[2], H. Zeren[3], S. Erus[4], S. Tanju[4], Ů Dilege[4]

[1] Koç University School of Medicine, Pathology department, Turkey, [2] Koç University School of Medicine, Pathology department, Turkey, [3] Acibadem University School of Medicine, Pathology department, Turkey, [4] Koç University School of Medicine, Thoracic surgery department, Turkey

Background & Objectives: Breast cancer metastasis suppressor1 (BRMS-1) shows a decreased expression in some tumour types which is related with poor prognosis. The aim of this study is to investigate the relationship between BRMS1 expression and histopathologic prognostic parameters in lung adenocarcinomas.

Methods: Tissue microarrays prepared from 147 lung adenocarcinoma resections were studied. Histologic subtypes were given by consensus of three pathologists, intratumoral BRMS-1 immunostaining was scored due to intensity (0-3). For statistical analysis 0-1 and 2-3 were grouped together as low and high expression, respectively. The results were compared with histopathologic subtypes (lepidic, acinar, papillary, mucinous patterns were grouped as low/intermediate grade; micropapillary, solid, cribriform patterns were grouped as high grade), T/N stages, lymphovascular and pleural invasion

Results: 273 microarray cores from 147 patients were analysed. Histologic subtypes were composed of 2 lepidic, 77 acinar, 35 papillary, 39 micropapillary, 96 solid, 16 cribriform and 8 mucinous. BRMS1 expression was high in 84%, and low in 16% of cores. 19,1% of high grade and 5,7% low grade histologic subtypes showed low BRMS1 expression and this difference was statistically significant(p:0,00). No significant relation was detected between BRMS1 expression and other histopathologic parameters evaluated in this study.

Conclusion: Loss of BRMS-1 expression was more frequent in micropapillary, solid and cribriform comparing to lepidic, acinar, papillary and mucinous adenocarcinomas. The relation between low BRMS-1 expression and poor prognostic subtypes was significant. However, this study didn't show any relation with other prognostic parameters, most importantly with lymph node metastases. Further studies on larger series including also survival analysis are needed.

E-PS-22-037

Correlation between EGFR, ALK and ROS1 and 22C3-PD-L1 expression in lung adenocarcinoma

T. Neuman[1], G. Vainer[1]

[1] The Hebrew University - Hadassah Medical Center, Jerusalem, Israel

Background & Objectives: Modern treatment of lung adenocarcinoma requires the analysis of programmed death ligand 1 (PD-L1), EGFR, ALK and ROS1.

This facilitate the selection of biological, first-line therapies in advanced lung cancer. However, the frequency of overlap of these biomarkers in routine clinical practice is not well reported.

Methods: Between July 2016 and March 2019, 820 lung adenocarcinoma patients were analysed at the Hadassah Medical Center.

We measured PD-L1 expression (Tumour proportion score; 22C3 based LDT), EGFR mutations (COBAS or Oncomine 22 gene panel), ALK and ROS1 were screened by IHC, and confirmatory FISH was done if needed.

Results: We recorded a PD-L1 TPS of ≥50% in 30.27% (244/806 cases), EGFR activating mutations in 20.03% (122/609 cases; del Ex19 57.6%, L858R 29.6%, Others 12.8%), ALK positivity in 4.38% (21/484 cases), and ROS1 positivity in 2.13% (9/421 cases).

No occurrence of EGFR mutation, ALK or ROS1 found.

TPS of ≥50% shows correlation to del Ex19 (70%) while TPS of < 1% shows correlation to L858R (38.29%).

Overall, this common drive mutations express PD-L1 TPS of ≥50% in 24.59% (30/122) for EGFR, 33.33% (7/21) for ALK and 55.55% for ROS1 (5/9).

Conclusion: A TPS of ≥50% shows less overall prevalence with EGFR alterations but with specific affinity to different exons. However, ALK and ROS1 shows higher prevalence for TPS ≥50%.

E-PS-22-039

A 1-year study of pathological aspects and incidence rate of pulmonary carcinomas

F. Neacsu[1], M. Sajin[1], G. Simion[1]

[1] Carol Davila University of Medicine and Pharmacy of Bucharest, Romania

Background & Objectives: Malignant lung tumours have the highest rate of deaths caused by cancer worldwide. Most of the pulmonary malignant tumours are carcinomas.

The histologic types are: adenocarcinoma, squamous cell carcinoma, small cell carcinoma and large cell carcinoma. Between 1977-1981, the most common histologic type was squamous carcinoma(30%) followed by adenocarcinoma(<30%).

Methods: This study aims to determine the incidence rate of primary lung carcinoma among patients diagnosed between May 2017 - May 2018 at the University Emergency Hospital from Bucharest, Romania.

The diagnoses were established based on gross, microscopic and immunohistochemical examination.

Results: Among the 43 patients diagnosed with lung cancer, 15 were females and 28 males, aged 41-81 years.

The most common histologic types were: adenocarcinoma(72,1%), squamous cell carcinoma(23,25%), small cell carcinoma(2,3%) and lung neuroendocrine tumour(2,3%).

30,23% of patients presented with lymph nodes invasion with patterns of adenocarcinoma(76,9%), squamous cell carcinoma (15,38%) and small cell carcinoma(7,7%).

Pleural invasion was found in 9 patients(20,9%): 8 with adenocarcinomas, 1 with squamous cell carcinoma.

The tumour invasion in the mediastinum was found in 7 patients.

Conclusion: This study focuses on the pathological aspects and the incidence rate of pulmonary carcinomas. Even though the study is done on a short period of time, it can be seen that adenocarcinomas incidence rate is increasing.

E-PS-22-040

Pulmonary sclerosing epithelioid fibrosarcoma: a case report and review of literature

J. Martin Lopez[1], J.L. Rodriguez Carrillo[1], M. Colomès[1], E. Verdu Martin[1], H. Tavarez Alvarez[1], C. Salas Anton[1]

[1] Department of Pathology. Hospital Universitario Puerta de Hierro, Spain

Background & Objectives: Sclerosing Epithelioid Fibrosarcoma (SEF) is a rare neoplasm that usually affects deep soft tissues in lower extremities and less frequently head and neck region. The primary visceral origin is rare with similar morphology: diffuse areas of collagen sclerosis with epithelioid cells arranged in cords or nests.

Commonly, the immunohistochemical techniques are positive for vimentin and MUC4 and in some cases has been associated with FUS gene alterations.
Methods: We report a case of pulmonary SEF with mediastinal lymph node involvement and discuss it in the context of the current literature.
Results: A 55-year-old male admitted to the coronary care unit with a diagnosis of acute coronary syndrome showed in radiological studies a 26 mm lung lesion in the right lower lobe. After his clinical recovery, an intraoperative wedge resection was performed.
Histopathological examination showed epithelioid cells arranged in cords and nests within diffuse areas of sclerosis. The cytological detail showed small to medium-sized epithelioid cells with clear to eosinophilic cytoplasm and small nucleoli identifying frequent mitosis. The immunohistochemical study was diffusely positive for vimentin, BCL2, CD99 and MUC4; with isolated positivity for EMA. CK AE1-AE3, S100, HMB45, CD34, actin, desmin were negative. The Ki67 proliferative index was 8%. FUS testing was negative. In regional lymphadenectomy, one lymph node was involvement.
After the diagnosis, a detailed clinical examination and a PET-CT scan were performed to exclude a soft tissue origin.
Conclusion: Sclerosing epithelioid fibrosarcoma is rare arising from the lung. Visceral presentation is usually due to a metastasis from a soft tissue origin. Immunohistochemical staining with MUC4 is specific and in a percentage of cases it is associated with alterations on FUS gene.

E-PS-22-041
Transfusion-related acute lung injury: clinical, role of HLA class I antibodies and histopathological features of a case report
J. Martin Lopez[1], L. Nuñez Martín Buitrago[2], S. Garrido Paniagua[2], J.L. Rodriguez Carrillo[1], M. Colomes Iess[1], E. Verdu Martín[1], H. Tavares Alvarez[1], A. Beneitez Fernandez[2], I. Krsnik[2], J.L. Bueno Cabrera[2], R. Cabrera Marin[2], C. Salas Anton[1]
[1] Department of Pathology, Hospital Universitario Puerta de Hierro, Spain, [2] Department of Haematology, Hospital Universitario Puerta de Hierro, Spain

Background & Objectives: Transfusion-related acute lung injury (TRALI) is an uncommon clinical outcome characterised by the rapid onset of respiratory distress early after transfusion. Its diagnosis is based on clinical and radiographic changes that are indistinguishable from acute lung injury/acute respiratory distress syndrome (ALI/ARDS). TRALI is presumed to be a form of ALI/ARDS; however, it differs in its triggering events and associated mortality.
Methods: We describe a case report of TRALI with all the clinical and histopathological details.
Results: A 59-year-old woman with personal history of cirrhosis and hepatic encephalopathy went to the emergency room due to clinical worsening with sudden vaginal bleeding. Because thrombocytopenia a pool of platelets and a plasma unit were transfused. Two hours after presented with severe hypoxemia and chest CT scan reveals a diffuse pulmonary infiltrates. After respiratory failure biopsies were taken by fibrobronchoscopy. The histopathological study showed an acute phase of ALI with pulmonary edema and hyaline membranes lining the alveolar spaces with granulocyte aggregation within the pulmonary microvasculature. After histological diagnosis of ALI excluding other morphologic etiologies, clinical worsening and positive results of anti-HLA Class IA and IB IgG Antibodies, treatment with methylprednisolone was initiated. Despite this, patient dies.
Conclusion: TRALI is an uncommon adverse side effect related with transfusion. TRALI case reports describe a classical morphology of acute phase of ALI, or pulmonary edema with neutrophil accumulation within alveolar capillaries or even just neutrophils within alveolar spaces. In our case, consisting in edema with hyaline membranes lining the alveolar spaces. In addition to the clinical and immunological findings we established a diagnosis of TRALI.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-23 | Soft Tissue and Bone Pathology

E-PS-23-001
Tenosynovial giant cell tumour, localised type with extensive chondroid metaplasia: a case report with immunohistochemical and molecular genetic analysis
R. Maruyama[1], M. Nagase[1], A. Araki[2], N. Ishikawa[1], N. Nagano[1], N. Yamagami[1], S. Yamamoto[1]
[1] Shimane University School of Medicine, Japan, [2] Institute of Neurology, Medical University of Vienna, Austria,

Background & Objectives: Tenosynovial giant cell tumour (TSGCT) is divided into localized and diffuse types. In contrast to diffuse type, it is easy for experienced pathologists to render a diagnosis of TSGCTs of localized type. However, when it shows extensive chondroid metaplasia which has been reported almost only in diffuse type, it may be extremely difficult to differentiate from chondroid tumours. We have experienced such a case and histological, immunohistochemical and molecular genetic findings of the tumour are presented.
Methods: A 72-year-old man presented with a well circumscribed subcutaneous tumour on his left hand. He first noticed the lesion 7 years prior to admission with a gradual increase in size since its onset. Clinical and radiological findings indicated TSGCT of localized type and the tumour was excised. We performed gross and microscopic examinations, immunohistochemistry including clusterin, CD68, CD163, CD45, S-100 and podoplanin, and fluorescent in situ hybridization (FISH) on formalin-fixed paraffin embedded sections using custom-made probes.
Results: Grossly, the excised specimen consisted of a well circumscribed tumour, which was about 2.5cm in maximum diameter. Microscopically, the tumour showed a vaguely lobular pattern of growth with extensive chondroid appearance with low power view. With high power examination, the lobules with chondroid stroma were surrounded by large mononuclear cells, osteoclastic multinucleated giant cells and smaller histiocytoid cells. Immunohistochemically, the large mononuclear cells were positive with clusterin, and FISH demonstrated a *CSF1-COL6A3* fusion gene.
Conclusion: It is necessary to be aware that not only diffuse type but the localized type of TSGCT can exhibit extensive chondroid features. IHC and/or FISH analysis should be recommended to differentiate it from cartilaginous tumours. We suspect there is a possibility that at least some soft tissue chondromas of the hands are reclassified as TSGCT with extensive chondroid metaplasia.

E-PS-23-002
Analysis of molecular alterations in undifferentiated pleomorphic sarcomas
G. Raskin[1], E. Preobrazhenskaya[2], O. Gorustovich[2], V. Heinshtein[3], K. Shelekhova[3], E. Suspitsin[4]
[1] Academic A.M. Granov Scientific Center for Radiology and Surgical Technology, Russia, [2] N.N. Petrov Institute of Oncology, Russia, [3] City Cancer Center, Russia, [4] St.-Petersburg Paediatric Medical University, Russia

Background & Objectives: Undifferentiated pleomorphic sarcoma (UPS) is an aggressive type of tumour; it is thought to arise from primitive mesenchymal stem cells yet there is no consensus about its origin. Many researchers believe that it cannot be considered a separate nosology but

rather unites a group of mesenchymal tumours comprised of cells which progenitors cannot be clearly established. The objective of the study was to investigate the spectrum of molecular alterations in UPS.
Methods: Tumour cDNA samples of 41 patients with UPS have been collected. Copy number of CDK4, MYCN, MDM2, HER2, KIT, and PDGFRA genes was analysed using digital droplet PCR. Presence of 12 variants of fusion transcripts involving EWS (EWS ex7/FLI ex6, EWS ex7/FLI ex5, EWS ex10/FLI ex6, EWS ex9/FLI ex4, EWS ex10/FLI ex5, EWS ex8/FLI ex6, EWS ex10/FLI ex8, EWS ex7/FLI ex8, EWS ex7/ERG ex10, EWS ex7/ETV1 ex12, EWS ex7/ETV4 ex9, EWS ex7/FEV ex2) was assessed using quantitative real-time PCR.
Results: Amplification of CDK4 was observed in 18 (44%), MYCN – in nine (22%), and MDM2 – in one (2%) patient, respectively. Seven UPS samples (17%) demonstrated simultaneous amplification of CDK4 and MYCN, and one sample – of CDK4 and MDM2. No increase in HER2, KIT, or PDGFRA copy number was detected. 3 samples (7%) had EWS ex7/ETV1 ex12 translocation.
Conclusion: CDK4 and MYCN amplifications are commonly observed in undifferentiated pleomorphic sarcomas. Sarcoma-specific translocations may also be found in a small fraction of UPS patients.

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E-PS-23-003
Intraosseous schwannoma of the rib with cortical breakdown; resembling chondrosarcoma radiologically
K.B. Lee[1], K.S. Kwack[2], S.J. Haam[3]
[1] Pathology, Ajou University Hospital, Republic of Korea, [2] Radiology, Ajou University Hospital, Republic of Korea, [3] Thoracic & Cardiovascular Surgery, Ajou University Hospital, Republic of Korea

Background & Objectives: Intraosseous schwannomas of rib are extremely rare, and only four cases have been reported. We experienced a case of intraosseous schwannoma arising in the rib, which suggested chondrosarcoma radiologically by its aggressive behavior. We present this case by its rarity and radiological differential diagnosis.
Methods: A 58-year-old male was admitted due to a rib mass. He had a history of trauma three years ago at this area. He complained of pain. Plain X-ray showed an expansile osteolytic lesion at the anterior arc of right seventh rib. Computed tomography of the chest revealed a 3.6cm sized mass with curved calcification peripherally. Cortical breakdown was noted, resulting in soft tissue mass formation. Radiologic impression was low grade chondrosarcoma. There was no lung invasion. Wide excision was done.
Results: Grossly, the tumour showed an expanding growth into the surrounding soft tissue with cortical breakdown. Margin of the mass was solid, but most central area revealed multilocular hemorrhagic cysts. Microscopically, the tumour was composed of spindle cells with Antoni A and B areas.Verocay bodies were evident. Tumour cells infiltrated into the cortical bone. Immunohistochemical staining for S-100 protein was positive. Pathological diagnosis was intraosseous schwannoma with aneurysmal bone cystic change.
Conclusion: Schwannoma is a benign tumour, but when occurs in the rib, it infiltrates into the cortical bone and results in cortical breakdown and soft tissue extension. This behavior makes a suggestion of chondrosarcoma and other malignant tumours radiologically.
The study was supported by the Russian Science Foundation grant 18-15-00256.

E-PS-23-004
Cellular neurothekeoma with anaplastic features: report of two cases
T. Hirose[1,2], T. Takai[3]
[1] Department of Diagnostic Pathology, Hyogo Cancer Center, Japan, [2] Pathology for Regional Communication, Kobe University School of Medicine, Japan, [3] Department of Dermatology, Hyogo Cancer Center, Japan

Background & Objectives: Cellular neurothekeoma (CN) is a rare, cutaneous mesenchymal tumour of unknown histogenesis. Despite occasional worrisome features, this tumour follows a benign clinical course. We herein report two cases of CN with anaplastic features, one of which behaved aggressively.
Methods: Case 1. A 73-year-old female complained of a subcutaneous mass of 55 mm in diameter in the left upper arm, which was widely resected. During the follow-up period of four years, the tumour recurred two times. Case 2. A 70-year-old female noticed a subcutaneous mass, 70 mm in size, located in the left subscapular region and underwent a wide excision of the tumour.
Results: Both tumours were located in dermis and subcutis and composed of epithelioid to short-spindle tumour cells arranged in clusters, nests, and fascicles. Nuclear pleomorphism was noted in some areas and mitotic figures, including atypical ones, were frequent: 10 (Case 1) and 20 (Case 2) per 10 HPF. Immunohistochemically, tumour cells in both cases were diffusely positive for NKI-C3, MITF and CD10, but negative for S-100 protein, SOX10, and HMB45. Ki-67 labeling indices were 22% (case 1) and 45% (case 2).
Conclusion: The pathologic and immunohistochemical features of the present two cases were basically consistent with those of CN. Cellular anaplasia, increased proliferative activity and repeated recurrences in case 1, however, may suggest the presence of malignant counterpart of CN.

E-PS-23-005
Denosumab has limited therapeutic effect on giant cell tumour of bone: a study of 7 recurrent cases
I. Kato[1], M. Furuya[1], Y. Kawabata[2], M. Takeyama[2], K. Hayashida[2], R. Tanaka[3], K. Ohashi[1]
[1] Yokohama City University, Japan, [2] Orthopaedic Surgery, Yokohama City University Hospital, Japan, [3] Medical Mycology Research Center, Chiba University, Japan,

Background & Objectives: Denosumab, a human monoclonal antibody against RANKL, has been introduced into the therapy of giant cell tumour of bone (GCTB). We have recently reported that the H3.3G34W(mutation specific marker)-positive osteoblastic tumour cells survive denosumab therapy in contrast to the dramatic histological alterations including disappearance of giant cells and formation of woven bone (Histopathology. 2018;72:914-22). The histology of recurrent case has not been reported so far.
Methods: We studied 7 patients with recurrent GCTB. All patients underwent curettage with neo-adjuvant (5 to 11 times) and adjuvant (4 to 8 times) denosumab therapy. The typical histology (mixture of fibrohistiocytic lesion and reticular woven bone) was confirmed. All patients underwent re-curettage after additional or no denosumab therapy. Histological and immunohistochemical findings were investigated.
Results: Seven patients experienced local recurrence in 11-43 months after initial curettage. The histological appearances of re-curettage were mixture of conventional GCTB and typical denosumab-treated GCTB with variable proportion. The proportion of two components seemed to correlate with the duration of the latest denosumab therapy (0 to 4 times) just before re-curettage. An extraosseous mass was observed in one case, which was composed of reticular woven bone with focal conventional GCTB histology. Constantly, H3.3G34W immunohistochemistry was diffusely positive in all cases.
Conclusion: Denosumab led to dramatic histological alterations not only in initial GCTBs but also in recurrent and extraosseous lesions; however, actual therapeutic effect appeared to be limited. Pathologists should carefully evaluate anti-tumour effects of denosumab in the treated specimens.

E-PS-23-006

Cutaneous giant cell tumour of the scalp

S. Sotiriou[1], A. Fragoudi[2], P. Hytiroglou[1]
[1] Pathology Department, Faculty of Medicine, Aristotle University of Thessaloniki, Greece, [2] Anatomic Pathology Laboratory, Drama, Greece

Background & Objectives: Giant cell tumours of soft tissue (GCT-ST) are rare neoplasms; few have been described in the head and neck. Morphologically, they are identical with the more common giant cell tumour of bone (GCT-B). In contrast to the majority of GCT-Bs, which are characterised by point mutations of the H3F3A gene, GCT-STs do not bear this molecular aberration. The aim of this case report is to raise awareness regarding this entity and to point out the importance of the differential diagnosis.
Methods: An 87-year-old woman has undergone resection of a nodule of the scalp, which caused ulceration of the overlying skin. Tissue sections were stained with H&E and immunohistochemical stains for vimentin, CD68, and smooth muscle actin (SMA).
Results: Microscopically, the nodule represented a well-circumscribed tumour of the dermis and the subcutaneous tissue, characterised by a dense biphenotypic cellular population composed of a mixture of round to oval mononuclear cells and regularly distributed osteoclast-like giant cells embedded in a highly vascularized stroma. Atypia was absent. On immunohistochemical stains, the osteoclast-like giant cells showed immunoreactivity for vimentin, and CD68 and the mononuclear cells for vimentin, and SMA.
Conclusion: Based on the histological findings, and the absence of any bone lesion or the history of GCT-B, our final diagnosis was that of a GCT-ST. GCT-STs should be differentiated from metastatic GCT-B, but also from other cutaneous giant cell-rich neoplasms, such as plexiform fibrohistiocytic tumour, and atypical fibroxanthoma . Clinicopathological correlation and immunohistochemical/molecular assays are crucial in the differential diagnosis.

E-PS-23-008

β-catenin nuclear localisation and Wntless expression in synovial sarcoma

V.K. Lee[1], S.S.S. Hue[1]
[1] National University Hospital, Singapore

Background & Objectives: Wnt pathway is an extensively featured signalling pathway that is known for its role in embryonic development, tissue homeostasis and oncogenesis. Recent studies have implicated the role of constitutively active Wnt/β-catenin signalling in synovial sarcoma (SS) tumourigenesis. Although the activation of canonical Wnt/β-catenin pathway has been investigated in SS, the role of Wntless (WLS), a protein found upstream of Wnt pathway affecting both canonical and non-canonical Wnt ligands, has not been well explored. In this study, we evaluated the protein expression of WLS in SS by immunohistochemistry (IHC) on a tissue microarray (TMA) block consisting of SS patient samples.
Methods: A total of 72 SS cases from 2000 - 2016 were identified from the database record of the Department of Pathology, National University Hospital (NUH). Suitable cases with sufficient tissue material were subsequently included for TMA construction (n=22 per TMA set). Two sets of TMAs were immunohistochemically stained with YJ5 (Wntless / WLS antibody) and β-catenin. Using a three-tiered scoring system, staining expressions of these antibodies were quantitatively and qualitatively reviewed and scored by two histopathologists.
Results: 1) WLS expression was present in all samples (n=22), with 4 cases (18.2%) exhibiting weak WLS staining, 8 cases (36.4%) exhibiting moderate staining and 10 cases (45.5%) exhibiting strong staining. Thus, overall our results showed that the majority of SS cases (81.8%) demonstrated significant expression (moderate to strong) of WLS protein.
2) β-catenin nuclear expression was seen in 20 of 22 cases (91%).
3) Correlation between β-catenin nuclear expression and WLS expression is identified in most SS cases. All 4 cases of weak WLS expression are accompanied by β-catenin nuclear expression; however, 2 of 18 SS cases with moderate to strong WLS expression lack aberrant β-catenin nuclear expression.
Conclusion: This is a novel study characterising both WLS expression and β-catenin nuclear localisation in SS patients. Our results show that the majority of SS tumours overexpressed WLS with visible β-catenin nuclear localisation, suggesting a possible correlation of WLS overexpression and β-catenin nuclear localisation. Specific SS cases where WLS is overexpressed with no β-catenin nuclear localisation observed could be attributed to the activation of the non-canonical Wnt pathway. Hence inhibition of WLS is hypothesised to have a leverage in SS treatment over suppression of downstream canonical pathway. Our findings pave an avenue for this possibility of novel SS treatment strategy. Much further work is warranted to reveal possible mechanistic insights to validate our results.

E-PS-23-009

Cancer stem cell markers expression in soft tissue sarcoma and their clinicopathologic siginificance

U. Jo[1], K. Cho[2], J.S. Song[1]
[1] Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Republic of Korea, [2] Department of Pathology, Asan Medical Center, Republic of Korea

Background & Objectives: Soft tissue sarcomas (STSs) are rare heterogeneous mesenchymal malignant tumours and recent studies have shown an association of cancer stem cells (CSCs) with STSs pathogenesis. However, the clinicopathologic role of CSCs in the STSs is still poorly characterised. Herein, we investigate the expression of CSCs markers including SOX2, OCT4 and Nanog in the STSs and examine the prognostic impact of these proteins.
Methods: Immunohistochemistry was performed on tissue microarray using 262 cases of STSs and the results were analysed with clinicopathologic parameters.
Results: 72.1% (230/262), 26.6% (85/262) and 29.2% (93/262) of STSs showed immunopositivity for SOX2, OCT4 and Nanog, respectively. Most frequent SOX2-expression tumour was Ewing sarcoma (80%), followed by malignant peripheral nerve sheath tumour (MPNST, 71.4%) and pleomorphic liposarcoma (57.1%). Most frequent Nanog-expression tumour was undifferentiated pleomorphic sarcoma (83.3%), followed by osteosarcoma (66.7%) and MPNST (57.1%). SOX2 and Nanog were correlated with the higher FNCLCC grade ($p = 0.024$ *and* $p < 0.001$, respectively), but OCT4 wasn't ($p = 0.239$). Three of these proteins were not correlated with each other (SOX2 *vs* Nanog, $p=0.217$; SOX2 *vs* OCT4, $p=0.750$; Nanog *vs* OCT4, $p=0.767$). Overall survival (OS) according to SOX2, OCT4 and Nanog showed also no statistical significance ($p = 0.759$, $p = 0.053$, and $p = 0.427$, log-rank, respectively) although OCT4-expressed group had a tendency to poor OS.
Conclusion: CSCs markers were expressed differently according to tumour types. These findings potentiate the targeting of these CSCs for novel therapeutic interventions in STSs.

E-PS-23-010

Clear cell chondrosarcoma of the Rib: a rare tumour in an uncommon location

D.F. Martins[1,2], E. Rios[3,4,5]
[1] Department of Pathology of Centro Hospitalar Universitário São João, Portugal, [2] Faculty of Medicine of the University of Porto, Portugal, [3] Department of Pathology, Centro Hospitalar de São João, Porto, Portugal, [4] Department of Pathology, Faculty of Medicine of the

University of Porto (FMUP), Porto, Portugal, [5] Institute of Molecular Pathology and Immunology at the University of Porto (Ipatimup), Instituto de Investigação e Inovação em Saúde (i3S), Porto, Portugal

Background & Objectives: Clear cell chondrosarcoma (CC-CSA) is a rare, low-grade variant of chondrosarcoma, accounting for 2% of all chondrosarcomas. It typically involves long bones, especially proximal femur and humerus. Rib involvement is exceedingly rare, with less than 20 cases reported. We herein report an incidental finding of CC-CSA in the rib.
Methods: A 57-year-old male was found to have on chest X-ray a 3-cm nodular lesion in the third left rib, during preoperative evaluation for inguinal hernia repair. Both thoracic computed tomography scan and T2-weighted magnetic resonance revealed an expansile heterogeneous rib lesion with indistinct margins. Wide resection of the lesion was performed.
Results: Grossly an expansile, firm, tan-white to gray and glistening lesion extending through the cortex and contained by the periosteum, was seen. Histology showed sheets of large cells with clear-pink, vacuolated cytoplasm and scattered osteoclasts surrounded by a prominent osteoid-rich matrix. The tumour cells exhibited infiltrative growth pattern, encasing preexisting bone, and were diffusely positive for S100 protein and focally for CK8/18. Final Diagnosis was CC-CSA. At one-year follow-up the patient has no evidence of recurrent or metastatic disease.
Conclusion: Despite its rarity, CC-CSA can arise in the ribs becoming a diagnostic challenge due to its morphologic features that often mimics other entities, like chondroblastoma, osteosarcoma and metastatic carcinoma. CC-CSA behaves as low-grade tumour and an accurate diagnosis is essential to ensure the most effective and appropriate treatment, to minimize local recurrence (<20%). Yet, long term follow-up is required because even rare, metastases may occur up to 20 years following initial diagnosis.

E-PS-23-011

Prognosis impact of surgical margins quality in soft tissue leiomyosarcoma: a retrospective study of 40 cases

D. Chiba[1], S. Mestiri[1], S. Chaieb[1], T. Zahmoul[2], S. Ben Khalifa[1], S. Yacoub[1], N. Abdessayed[1], B. Sriha[1], M. Mokni[1]
[1] Department of Pathology, Farhat Hached Hospital, Tunisia, [2] Cancer Registry of the Tunisian Center, Tunisia

Background & Objectives: Soft tissue leiomyosarcomas (LMS) are aggressive tumours and are difficult to treat. The prognosis is poor, with survival rates among the lowest of all soft tissue sarcomas.
Treatment is based on adequate surgical resection.
Our aim was to conduct a retrospective study of 40 cases of soft tissue LMS retrieved at the Central Tunisia Cancer Registry to determine the prognostic impact of surgical margins quality on local recurrence, distant metastasis and 5-year overall survival in soft tissue LMS.
Methods: We have reported retrospectively during a period of 25 years (1996- 2012) the patients with LMS that were diagnosed at the pathology department of F. Hached hospital in Sousse, Tunisia.
We have classified the margins according to the recent dataset from the royal college of pathologists that takes into account whether there is tumour at the cut edge (R1) or not(R0).
The end-points of this study were 5-year overall survival, local recurrence and distant metastasis.
Results: 5 patients who had initially metastasis at presentation did not undergo surgical treatment, surgical margins were intra-lesional in 15 patients (R1), and 20 patients had negative surgical margins (R0).
Recurrence rate was of 80 % in positive margin cases and 25 % in negative margin cases. The difference was statistically significant (p=0,0039).
Metastasis occurrence was seen in 5 patients with positive margin and in 6 patients with negative margins, the difference was statistically not significant (p= 0,83).
Conclusion: 5-year overall survival was of 16 % in positive margin and 83% in negative margin cases. The difference was statistically significant (p=0,0028). In our study, positive surgical margins have a strong adverse prognosis effect on local recurrence and 5-year overall survival. These findings justify a policy of surgical adequacy in soft tissue LMS.

E-PS-23-012

Frequency of GNAS mutation in intramuscular myxoma

R. Erber[1], R. Stöhr[1], F. Haller[1], A. Hartmann[1], A. Agaimy[1]
[1] Institute of Pathology, University Clinics Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany

Background & Objectives: Intramuscular myxoma (IMM) is a rare benign lesion of the soft tissue that can arise sporadically or in patients suffering from fibrous dysplasia (Mazabraud's syndrome). Mutation rates of the GNAS gene (20q13) described in literature range between 20 and 83 % of IMM depending on method used.
Methods: We searched our archive for cases with the diagnosis of IMM. Clinical and pathological parameters including results of diagnostic GNAS gene mutation analysis were retrieved from our original reports. All cases were reviewed to verify diagnosis.
Results: 71.7 % of included IMM, mostly occurring in the thigh (55.6 %), were females (33/46). Mean age at diagnosis was 53.4 years, mean diameter 6.1 cm. IMM showed hypocellular myxoid matrix with embedded spindle cells, scarceness of vessels, positivity of vimentin, variable CD34 positivity and negativity of MUC4. Checkerboard like edema of surrounding muscle was a constant feature. Of 17 cases with successful GNAS mutation testing (performed at initial diagnostic workup), 3 harboured a GNAS mutation (17.6 %).
Conclusion: In our study, the frequency of GNAS mutations lies within the lowest range of GNAS mutation frequency reported in literature. It has to be discussed whether GNAS mutations vary according to different subsets (e.g. cellular) in the spectrum of intramuscular myxomas or whether there is need for more sensitive mutation detection methods in these predominantly paucicellular lesions.

E-PS-23-013

Lipoma arborescens of the knee, a rare tumour

S.Y. Celik[1], O. Ilhan Celik[1], U. Canbek[2], Y. Dere[1]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Orthopaedics, Turkey

Background & Objectives: Synovium is an unusual site for primary tumours most of which are benign. Lipoma Arborescens(LA) is one of these rare benign tumours of the synovium. It's a chronic, slowly progressive, intra-articular lesion characterised by villous, lipomatous proliferation of the synovium.
Methods: A 72-year-old male suffering from furtive onset of painless swelling of his left knee persisting for many years and followed by progressive pain with motion limitation was admitted to orthopaedics clinic. In physical examination diffuse suprapatellar swelling and tenderness were present without any calor and rubor. All laboratory tests were within the normal range. Left knee magnetic resonance revealed hiperintense synovial thickening and

presence of fatty mass in the joint cavity and especially in the suprapatellar bursae.
Results: Surgical synovectomy was performed and the material excised was 7x5x3cm in size, yelow, white in color. In the histopathological examination diffuse, mature, uniform lipocytic proliferation without atypia was present in most of the material covered by papillary sinovial projections accompanying mononuclear inflamatory cells; so the lesion was diagnosed as LA.
Conclusion: LA (diffuse articular lipomatosis) can be seen in patients aged between 9 and 68 years. It has 2 aetiological types depending on the age of onset and underlying precipitating conditions. Primary type is less common, idiopathic and seen in younger ages in second/third decades. Secondary type is more common, generally seen in older-patients, associated with an underlying chronic irritation, like degenerative disease, synovitis, trauma and meniscal injury. Synovectomy is the treatment. Recurrence is unusual and malign transformation is not seen.

E-PS-23-014
Malign Ossifying Fibromyxoid tumour of axilla; a rare case
S.Y. Celik[1], O. Ilhan Celik[1], Y. Dere[1], O. Dere[2]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Surgery, Turkey

Background & Objectives: Ossifying fibromyxoid tumour(OFMT) is rare soft tissue tumour of uncertain origin. It generally occurs skeletal muscle of the extremities or subcutaneous tissues and less commonly in head, neck, trunk, mediastinum or retroperitoneal region. Although majority of them behave like a benign tumour, very rare cases including cellular atypia, elevated mitotic activity and infiltrative behaviour proceed very aggressive and are called Atypical or Malign OFMT.
Methods: A 20-year-old male was admitted to surgery clinic because of a soft, fixed, rapidly growing mass in his right axillary region. The ultrasound revealed an infitrative, solid-heterogeneous, 6cm mass containing cystic and calcified areas.
Results: Total excision of the mass was performed and in the histopathological examination the hypercellular lesion was composed of ovoid/round, pleomorphic, mitotic active(4/10HPF) cells composing nodular, trabecular, cord-like areas in a fibromyxoid matrix rich in vessels. Also dense collagenous and ossifying areas were present in the lesion. The tumour cells, expressing Vimentin and s100 were infiltrating the surrounding adipous tissues. As a result the lesion was diagnosed as Malign OFMT.
Conclusion: OFMT was firstly described as a benign tumour with low risk of recurrence; however later it was seen that as this tumour contained more mitosis, cellularity and atypia the recurrence rates elevated, even metastasis were seen in the most atypical cases. So it was classified as typical, atypical and malignant OFMT. Cases showing high nuclear grade, high cellulrity and mitotic activity>2/50HPF were named as malign OFMT like our case.

E-PS-23-015
Giant cell reparative granuloma as clinical presentations of a secondary hyperparathyroidism: awareness is necessary
F. Ramalhosa[1], C. Faria[1], R.C. Oliveira[1], M.J. Martins[1], M.A. Cipriano[1]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal

Background & Objectives: Giant Cell Reparative Granuloma (GCRG) is a reactive intraosseous proliferation, characterised as a well-defined lytic lesion that may involve any portion of the bone. However, GCRG shares histologic features with conventional Giant Cell Tumour (GCT). GCT has a benign behaviour with high local aggressiveness, rarely multifocal. Multifocal lytic lesions are strongly suggestive of GCRG. Nowadays it is an unusual clinical presentation since it is a lesion related to the terminal stage of the bone remodelling process in prolonged hyperparathyroidism.
Methods: A fifty-year-old white woman reported to the Orthopedic Department of our hospital with a pathological elbow fracture. Past medical history includes hypertension and chronic renal failure (CRF), requiring haemodialysis since 2010. Computed Axial Tomography (CAT) revealed osteolytic lesions involving the distal humerus and proximal femur.
Results: Surgical biopsy of the humerus lesion revealed brown spongy material, histologically characterised by large numbers of multinucleated giant and spindle cells in a dense collagenous background. These findings were histologically consistent with a diagnosis of GCT, however a serological evaluation revealed high levels of parathyroid hormone (PTH). Ultrasound confirmed bilateral parathyroid adenoma.
Conclusion: Osteolytic lesions of hyperparathyroidism are rare and histologically indistinguishable from GCT, which can be misdiagnosed. The gold standard for definitive diagnosis is multidisciplinary: radiographic, clinical presentation and biochemical testing. Treatment of GCRG consists mostly of parathyroidectomy.

E-PS-23-016
Sporadic giant diffuse neurofibroma in a 40-year-old patient. Case report and literature review
O.C. Voinea[1], A. Dumitru[2,3,4], C. Savlovschi[2,3], T.A. Georgescu[2,3], C. Secara[1], M. Sajin[2,3,4]
[1] CCSMM, Romania, [2] SUUB, Romania, [3] UMF Carol Davila, Bucharest, Romania, [4] European Society of Pathology, Romania

Background & Objectives: Gigantic neurofibroma is an extremely rare tumour, with a challenging surgery management and pathologic differential diagnostic, more often seen in neurofibromatosis syndromes, exceptionally rare in a sporadic form.
Methods: A 40-year-old male with no significant medical history presented in the surgery department with a gigantic tumour localized on the forearm for a wide local excision. His only complains were aesthetic and functional because of the difficulties in getting his armed dressed. After imagistic evaluation, surgical excision was performed, and the resected specimen was entirely submitted for pathological examination in the Department of Pathology of the University Emergency Hospital of Bucharest.
Results: The gross examination revealed a 14/10/8 cm nodular tumour. The histopathological examination revealed a monomorphic proliferation of small to medium-size spindle cells, with wavy hyper-chromatic nuclei organized in poorly formed fascicles. No capsule was identified, and the profound margins extended to the deep hypodermic layer, in the vicinity of a muscular fascia. The proliferation entrapped eccrine glands and pilosebaceous units. No mitotic figures, necrosis or hemorrhage were observed. The diagnosis of giant diffuse neurofibroma was confirmed by additional ancillary tests: the cells were 100% positive for S100, negative for CD34 and SMA and only about 3% were positive for Ki67.
Conclusion: The particularity of this case is underlined not only by the rarity of this tumour type and the multidisciplinary management required, but also by the differential diagnostic with MPNST, fibrosarcoma or other malignant tumours, considering the localization and also the apparently invasive behaviour.

E-PS-23-017
Biphasic synovial sarcoma mimicking Morton neuroma- a case report

L. Tomescu[1], V. Enache[2], I. Salem[3], F. Andrei[3], C. Girbea[3], A. Curte[3]
[1] University Emergency Hospital, Bucharest, Romania, [2] Victor Babes National Institute of Pathology, Romania, [3] Elias University Emergency Hospital, Romania

Background & Objectives: Synovial sarcoma (SS) is a rare malignant mesenchymal neoplasm, associated with chromosomal translocations involving genes like SS18 and SSX1, SSX2 or SSX4 and it accounts for 5-10% of all soft tissue sarcomas. SS affects young adults with a median age of 35, predominantly males and involves mainly the extremities (68,7%). Morphology includes monophasic, biphasic and poorly differentiated patterns.
Methods: This report describes a case of a 51-year-old female who presented for painful subcutaneous tumour located in the third interdigital space of the right lower limb having MRI characteristics suggestive of Morton neuroma. After surgery, the specimen was processed and examined by standard H&E technique, PAS, Giemsa, and immunohistochemistry.
Results: Gross examination identified a well circumscribed, partially encapsulated, firm, subcutaneous mass, measuring 1.5 cm in maximum diameter. Microscopically, the tumour showed a biphasic proliferation consisting of spindle cells with mild to moderate nuclear pleomorphism and gland-like epithelial structures containing mucus and abundant intermixed mast cells, which were positive on Giemsa stain. The tumoral stroma showed hemangiopericytomatous vessels with focal thrombosis and microhemorrhagic areas, hemosiderin deposition, and frequent calcifications. The histological aspects were suggestive of synovial sarcoma. The diagnosis was confirmed by immunohistochemistry: the spindle cell component was positive for S100, CD99 and CD56 and negative for desmin and CD34, and the gland-like structures were positive for CK7. The tumour was incompletely excised.
Conclusion: The particularity of this case is the misleading clinical presentation resembling Morton neuroma, the small dimension, and abundant mast cells and microcalcifications.

E-PS-23-018
Neoplastic stromal cell persistence in a case of giant cell tumour of bone successfully treated with Denosumab before surgery - immunohistochemical analysis
D. Costache[1], D.M. Pop[2]
[1] Pathology Department, Colentina University Clinical Hospital, Bucharest, Romania, [2] "Foişor" Clinical Orthopaedics and Traumatology Hospital, Bucharest, Romania
Background & Objectives: Giant cell tumour of bone (GCTB) is a benign, locally aggressive, primary bone tumour composed of mononuclear neoplastic stromal cells which express receptor activator for NF-κβ ligand(RANKL), admixed with mononuclear macrophage-like osteoclast precursors and osteoclast-type giant cells, which both express RANK. Denosumab is a monoclonal antibody that binds to RANKL, thus preventing osteoclastic activation. The purpose of this study is to evaluate the impact of Denosumab in GCTB and to provide histopathological and immunohistochemical proof of the benefits of this treatment.
Methods: We present a case of GCTB, of distal ulna, in a 65-year-old, female, diagnosed in "Foişor" Clinical Hospital, in 2018. Clinical and imaging assessment was performed. Histopathologic diagnosis of GCTB was established by tumour biopsy. Due to the size and soft tissue extension of the tumour the patient received Denosumab therapy before surgery for resection of the distal ulna and reconstruction. H&E and p63, CD56, CD34, SMA, Ki67 immunohistochemical markers were performed for both the biopsy and the resection specimen.
Results: After Denosumab the tumour had better-defined margins, decreased in size and showed increased reactive bone formation with numerous CD56+ osteoblasts. Few osteoclast-type cells remained and they were smaller and had fewer nuclei. Neoplastic stromal cells persisted only in small areas of the tumour, fact confirmed by the decreased positivity of p63 on the resection specimen compared to the biopsy and the decrease of the proliferation index Ki67 from 15%, to <2% after therapy. CD34+ in vessels and SMA+ in stroma.
Conclusion: Neoadjuvant therapy with Denosumab considerably reduced the number of mononuclear neoplastic cells, osteoclast-type cells, the proliferation index Ki67 and tumour size, producing reactive ossification which altogether favoured complete and safe resection of the tumour.

E-PS-23-019
A case series of 3 primitive myxoid mesenchimal tumour of infancy, including one case with brain metastasis; histopathologic, immunohistochemical and molecular investigation
î Kutlu[1], H.K. Türköz[2], T. Celkan[3], S. Çınar özel[3], N. Çomunoğlu[1]
[1] Istanbul University Cerrahpasa-Cerrahpasa Medical Faculty Department of Pathology, Turkey, [2] Marmara University, Turkey, [3] Istanbul University Cerrahpaşa Medical Faculty Paediatric Oncology Department, Turkey

Background & Objectives: Primitive myxoid mesenchymal tumour of infancy (PMMTI) is a distinct, relatively rare soft tissue tumour characterised by proliferation of immature mesenchymal cells, diffuse myxoid background with delicate vascularity on histopathology. To this date, 31 cases had been reported in literature in total. It is known to have a relatively good clinical course with mainly local recurrences, although one case with differentiation to undifferentiated sarcoma and one case with brain metastasis was reported. In this study we present 3 PMMTI cases, one with brain metastasis
Methods: 3 PMMTI cases detected in Istanbul University, Cerrahpaşa-Cerrahpaşa Medical Faculty between 2015 and 2018 were presented. The histopathologic properties of the cases were compared as they were seen in light microscopy. An immunohistochemical work up panel made up of desmin, CD99,myo-D1, S100,Bcl6,CyclinD1 were used. ESWR-1 rearrengement, N-myc rearrengement, DDIT-3 translocation and ETV6–NTRK3 gene fusion was investigated with FISH.
Results: Ages of the babies when they presented with tumour were 18 weeks, 5 months and 7 months respectively. Female/male ratio was 1/2.Histopathologic investigation showed a tumour made up of primitive small tumour cells with myxoid background. Immunhistochemical work up stained positive for Bcl-6 and cyclin D1 in all cases. ESWR-1 rearrengement, N-myc rearrengement,DDIT3 translocation ETV6–NTRK3 gene fusion were negative with FISH. One case presented with brain metastasis during follow up and died 18 months after diagnosis.
Conclusion: PMMTI is a rare infanil tumour, often with local aggressive behaviour. Metastasis is not a common finding. In recent years BCOR tandem duplication was defined to be positive in PMMTI cases, a property shared with some of the soft tissue undifferentiated round cell sarcomas, suggesting a possible grey zone between those two entities. In this study we share our experience with 3 PMMTI cases, 1 with brain metastasis and aggressive behaviour.

E-PS-23-020
Giant myelolipoma of adrenal gland - presentation of two cases with review of the literature
A. Szumera-Cieckiewicz[1], O. Kuczkiewicz-Siemion[2], P. Rutkowski[3], T. Goryn[3], M. Zdzienicki[3], M. Prochorec-Sobieszek[2]
[1] Institute of Haematology and Transfusion Medicine, Diagnostic Haematology Department, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland, [3] Maria Sklodowska-Curie Institute - Oncology Center,

Department of Soft Tissue/Bone Sarcoma and Melanoma, Poland

Background & Objectives: Adrenal myelolipoma (AML) classified according to the latest update of the World Health Organization on endocrine tumours as a benign mesenchymal and stromal neoplasm which is composed of mature fat and trilinear myeloid tissue. AML after adrenocortical adenoma is the second most common primary adrenal incidentaloma. Tumours exceeding 10 cm in diameter are called giant myelolipomas. Although it has benign behaviour the clinical and radiological diagnosis might be difficult or confusing since AML might mimic the malignant neoplasm.
Methods: We present two cases of males a 78 and a 64-year old who were admitted to Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland with suspicious adrenal gland tumours. Both patients after radiological evaluation underwent surgical excision of tumours.
Results: Macroscopically, the first was encapsulated with dimensions 19x13x12 cm; the second one was characterised by lack of capsule and dimensions 14x13x5.5 cm. Microscopically, tumours were a mixture of a dense adipose tissue with hematopoietic tissue including abundant mature erythroid and granulocytic elements as well as megakaryocytes. The immunohistochemical panel confirmed trilinear hematopoietic differentiation. Furthermore, the extramedullary hematopoiesis caused by chronic hematopoietic disorders and endocrine disorders were excluded.
Conclusion: The variable proportion of fat and hematopoietic elements and, the absence of the tumour capsule may direct the differential diagnosis of AML to adrenocortical cancer. Detailed imaging including computed tomography and magnetic resonance imaging might be helpful. The giant AML even asymptomatic usually requires surgical intervention which typically resolves associated endocrine disorders; the histopathological examination is the ultimate method in AML recognition.

E-PS-23-021
Metal-related histiocytosis of lymph node and dendritic pseudotumour of iliac bone - a spectrum of the same entity - two cases of metallosis after arthroplasties
A. Szumera-Cieckiewicz[1], K. Sokol[1,2], M. Wagrodzki[2], T. Goryn[3], B. Szostakowski[2], A. Pienkowski[2], M. Prochorec-Sobieszek[2]
[1] Institute of Haematology and Transfusion Medicine, Diagnostic Haematology Department, Poland, [2] Maria Sklodowska-Curie Institute - Oncology Center, Department of Pathology and Laboratory Medicine, Poland

Background & Objectives: Metallosis is an arthroplasty complication consisting of periprosthetic soft tissue and bone infiltration by metallic particles and may be associated with significant osteolysis around the implant. It has been described after total hip, knee, and shoulder arthroplasties with prostheses containing titanium, cobalt, and chromium. The most frequent localized adverse reactions to metal debris include aseptic lymphocytic vasculitis, diffuse chronic synovitis, and well-defined granulomas; the lymph node involvement is exceptionally reported.
Methods: The first case was a 43-year-old man with a left inguinal mass, which in ultrasound examination showed were described as metastatically suspected enlarged lymph nodes. The patient underwent removal of the distal femur with prosthetic replacement due to high-grade osteosarcoma twenty years ago with soft tissue relapse after four years.
The second case was 72-yeard old female administered with a pelvic tumour. The patient underwent right hip replacement eight years earlier because of arthropathy. Computed tomography showed an osteolytic tumour in iliac bone with damage of bone and soft tissue. Radiologically the metastases were considered.
Results: The microscopic image of lymph nodes and iliac tumour showed solid fields of macrophages and histiocytes with focal necrosis accompanied by the giant multinucleated cells with asteroid bodies and birefringent foreign particles (polyethylene). The metastases were excluded and the final diagnosis of metal-related sinus histiocytosis and dendritic pseudotumor were identified respectively.
Conclusion: Lymphadenopathy or tumour mass after joint replacement rarely is a reactive reaction to implant material. In the histopathological assessment, immunohistochemical panel both with polarizing light evaluation is useful in establishing the diagnosis

E-PS-23-023
A case of cutaneous Ewing sarcoma in a young female with a history of acute myeloid leukaemia
C. Masaoutis[1], I. Themeli[2], F. Dolkiras[1], V. Pantelaion[1], E. Dimitriadis[3], D. Rontogianni[1]
[1] Evaggelismos General Hospital of Athens, Greece, [2] Hygeia Hospital, Greece, [3] Aghios Savvas General Oncology Hospital, Greece

Background & Objectives: A 17-year old girl with a history of acute myeloid leukaemia 3 years ago presented with a 1.2cm cutaneous nodule of the interdigital space of the left foot. No osseous lesion is appreciated. Excisional biopsy was performed.
Methods: Light microscopy, immunohistochemistry, reverse transcription polymerase chain reaction (RT-PCR) and fluorescent in situ hybridization (FISH).
Results: The dermis is involved by a uniform medium-sized cell population with scant cytoplasm, stippled chromatin, brisk mitotic activity and a lobular pattern with occasional cystic spaces.
Immunohistochemistral findings: Expression of vimentin, CD99, and, focally, FLI1 and desmin, without immunoreaction for haematolymphoid or neuroendocrine markers, cytokeratin or neurofilaments. Retained expression of INI1. RT-PCR revealed EWS/FLI chimeric transcripts due to a t(11:22)(q24:q12) translocation. FISH with break-apart probes revealed rearrangement of the EWSR1 gene.
Conclusion: These findings are diagnostic of Ewing sarcoma (ES). Development of leukaemia has been reported following treatment of cutaneous ES, but not preceding it. Its distinction from haematolymphoid malignancies (myeloid sarcoma or lymphoblastic lymphoma) is crucial due to morphological overlap and CD99 or FLI1 expression. Cutaneous presentation of ES is very unusual (<3% of soft tissue ES), has a wide anatomical distribution, female preponderance, a predilection for children, adolescents and young adults, and a rather favourable prognosis (10-year survival rate >90%).

E-PS-23-024
Retroperitoneal myelolipoma: a case report
E. Ben Hadj Khalifa[1], A. Baccouche[1], S. Ben Khlifa[1], D. Chiba[1], O. belKacem[3], H. Salifou[1], B. Sriha[1]
[1] Pathology Department, Farhat Hached Hospital, Sousse, Tunisia

Background & Objectives: Myelolipomas are rare, benign tumours which occur usually in the adrenal glands and are composed of mature adipose tissue and benign hematopoietic cells. Extra-adrenal myelolipomas are rarer. This entity should be recognized as it can reach a significant size and be responsible of pressure symptoms and it is often mistaken for malignant tumours. We present a myelolipoma case in the retroperitoneal region. In this observation we will illustrate the clinical, radiological and pathological aspects of myelolipoma.
Methods: We report the case of a 63-year-old woman presenting for low back pain that has been evolving for few months. The clinical and

complementary examinations concluded to a tumoral process of the retroperitoneal region suggestive of liposarcoma.
Results: The patient had a complete resection of the tumour and biopsy samples of the adrenal gland. The macroscopic examination concerned a well-circumscribed and encapsulated mass, measuring 10 * 9 * 4 cm and weighing 260 g. It has a gray color and show numerous foci of hemorrhagic reshuffle and yellow foci of adipose appearance.
The microscopic examination revealed that this mass is done by two contingents: a mature adipose tissue and a hematopoietic tissue rich in myeloid, erythroid, and megakaryocytic elements. The tumour is largely remodeled by hemorrhage and fibrinoid necrosis. It includes a 3mm ossification focus.
The adrenal biopsy showed a normal adrenal cortex without any tumour.
Conclusion: Myelolipoma is an invariably benign tumour. Its diagnosis must be raised if the tumour has a slow-growing and a mixed radiologic nature. Small and asymptomatic myelolipomas need clinical and radiologic monitoring, while large and symptomatic myelolipomas should incur resection.

E-PS-23-025
Adrenal lipomatous ganglioneuroma: a case report
M. Oliveira[1], L. Brochado Ferreira[2], C. Estima Fleming[2], R. Amorim[3], B. Fernandes[2], N. Jorge Lamas[1], J.R. Brandao[2], J.R. Vizcaino[1]
[1] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Porto, Portugal, [2] Centro Hospitalar e Universitario do Porto, Portugal

Background & Objectives: Ganglioneuroma is a rare, benign tumour that arise from neural crest cells of sympathetic ganglia or adrenal medulla. Lipomatous ganglioneuroma is an uncommon variant, characterised by a conventional ganglioneuroma admixed with a mature adipocytic component. The present case documents an adrenal ganglioneuroma with an adipocytic component.
Methods: An incidental adrenal mass was identified in an asymptomatic 46-year-old male. Radiological examination suggested that the mass had unspecific characteristics. His physical examination was unremarkable. Routine laboratory test results were within normal limits. He underwent right adrenalectomy, the specimen was routinely processed, sections were stained with hematoxylin-eosin and immunostains were performed.
Results: Grossly, the tumour was well circumscribed but not encapsulated, it had a whitish cut surface and rubbery consistency. It was adhered to the right adrenal gland, causing an expansive effect. Microscopically, the tumour was predominantly composed of mature ganglion cells scattered in a background of Schwann cells arranged in small intersecting fascicles. Intermixed clusters of non-atypical mature adipocytes were found. Cellular atypia, mitoses and necrosis were absent. The tumour had clear association with adrenal cortex. By immunohistochemistry, both ganglion cells and Schwann cells were positive for S100 protein, neurofilament protein and synaptophysin, whereas ganglion cells were also positive for chromogranin.
Conclusion: To the best of our knowledge, this is the second report of a lipomatous ganglioneuroma in adrenal gland. Ganglioneuroma with adipocytic component should be considered in the differential diagnosis of fat-containing adrenal and retroperitoneal masses, and more cases of this entity should be studied in order to understand this phenomenon.

E-PS-23-026
TFE3-rearranged PEComa in a Lynch syndrome patient, with literature review
A.B. Larquè[1], G. Frigola[1], S. Díaz-Mercedes[1], N. Castrejón[1], A.M. Lacy[2], A. Castells[2], M. Cuatrecasas[1]
[1] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic of Barcelona, Spain, [2] Gastrointestinal Surgery Department, Clinic Institute of Digestive and Metabolic Diseases (ICMDiM), Hospital Clinic of Barcelona, Spain,

Background & Objectives: Lynch syndrome (LS) patients have a high risk of developing various tumours specially colorectal and endometrial cancers. We report the first case of TFE3-rearrangement-associated PEComa described in a LS patient.
Methods: A 2,5 cm pelvic nodule was detected on a follow-up MRI of a 38-year-old male with LS and previous history of mucinous adenocarcinoma of the rectum. Surgical exeresis with clinical suspicion of metastatic adenopathy was performed.
Results: Histologically, the lesion was constituted of nests of neoplastic epithelioid cells with abundant clear cytoplasm and round or oval nuclei with small nucleoli separated by delicate fibrovascular septa, with presence of hemosiderin and melanin pigments. Occasional nuclear pleomorphism without necrosis or mitotic activity was noted. Neoplastic cells were positive for HMB-45 and TFE3. Scattered cells were positive for MelanA and actin, whereas cytokeratins, S-100, desmin, PAX-8, and RCC were negative. Nuclear expression of MLH1, MSH2, MSH6 and PMS2 proteins was preserved. TFE3 gene rearrangement was confirmed by FISH. Pathological diagnosis was PEComa with TFE3 rearrangement. Only 41 TFE3-rearranged PEComas have been reported in the literature; 8 (19%) had an aggressive behavior. Our patient has no tumour recurrence 10 months after surgery.
Conclusion: To our knowledge neither classic PEComas nor TFE3-rearranged PEComas have been described before in LS patients. Based on this fact and on its mismatch repair proteins proficiency, we consider it as a rare sporadic LS-unrelated tumour.

E-PS-23-027
Sporadic epithelioid sarcoma, proximal type, in a woman with Muir-Torre Syndrome type one
A. Abuomar[1]
[1] Hospital General Universitario de Elda, Alicante, Spain

Background & Objectives: Muir–Torre syndrome (MTS) is a rare hereditary autosomal dominant syndrome, a variant of Lynch syndrome, characterised by sebaceous neoplasia or keratoacanthomas associated with visceral malignancies. Sarcomas are rarely associated with MTS. Up to our knowledge this the first case in the literature with epithelioid sarcoma associated with Muir -Torre syndrome.
Methods: 80 years old woman with medical history of MTS type one: endometrial adenocarcinoma, colorectal adenocarcinoma, multiple sebaceous and squamous cell carcinoma of the skin with a loss of expression of MLH1 and PMS2. During the last follow-up CT scan evaluation a diffuse enlargement of left iliacus muscle was seen, suggesting hematoma. Core needle biopsy of the lesion was performed.
Results: The tumour was composed of sheets of atypical large round or polygonal epithelioid cells mixed with spindled cells. Neoplastic cells showed an abundant ill-defined eosinophilic cytoplasm, pleomorphic hyperchromatic nuclei with open chromatin, irregular nuclear membrane and prominent nucleoli. Frequent mitosis were seen. Immunohistochemical (IHQ) stains showed:CK7+,Vimentin +,S M Actin+, Caldesmon+,MLH1+,PMS2+ ,MSH2+,MSH6+,CKAE 1-3-,CK20-,CDX2-,TTF1-.Desmin-, CD34-,CD31-,CD117-,P63,EMA-, HMB45- S100-,Uroplakin3-, Sinaptoficina-,Calretinin-. KI67>80%. Morphology and IHC findings were consistent with a mixed type proximal type Epithelioid sarcoma
Conclusion: Epithelioid sarcoma is a rare, high-grade, malignant soft tissue tumour with unknown histogenesis, characterised by epithelioid and/or spindled cells morphology. It accounts for less than 1% of all soft tissue sarcomas. It´s association with Lynch Syndrome is extremely rare, if existed. Diagnosis is based on clinical, morphological, IHC and

molecular study. The differential diagnosis should be made mainly with granulomatous inflammatory process, undifferentiated carcinoma, amelanotic melanoma, rhabdomyosarcoma and synovial sarcoma.

E-PS-23-028

An extra-osseous Ewing sarcoma after successful treatment of primary osteosarcoma: an unexpected pathological finding

M. Mellouli[1], O. Boudawara[1], C. Chaari[1], A. Sallemi[2], R. Kallel[1], T. Sallemi Boudawara[1], H. Mnif[1]
[1] Department of Pathology, Habib Bourguiba Hospital, Sfax, Tunisia, [2] Department of Radiology, Habib Bourguiba Hospital, Sfax, Tunisia

Background & Objectives: Since the introduction of chemotherapy as a therapeutic standard in osteosarcomas, the risk of secondary-malignant-neoplasms (SMN) has increased. Soft-tissues sarcomas have been rarely reported as SMN in survivors. This report tries to illustrate secondary Ewing sarcomas'characteristics.
Methods: We present the case of a boy who developed an extra-osseous Ewing sarcoma in his right thigh 5 years after treatment of a primary osteosarcoma.
Results: A 13-year-old-boy was diagnosed with a non-metastatic osteosarcoma of the left femur. He had a history of a myxoidchondrosarcoma of the scapula in his grandfather. The patient received preoperative chemotherapy (methotrexate, etoposide, ifosfamide) followed by a tumour resection. Pathological examination of the resection specimen concluded to a poor response to chemotherapy (amount of induced-tumour-necrosis didn't outreach 82%). Thus, the patient underwent an intensified post-operative chemotherapy (adriamycin, cisplatinum). Five years after, he developed a 2cm-right-thigh-swelling. Soft-tissues-ultrasound-imaging revealed a 2cm-hyper-vascular mass suggesting a subcutaneous metastasis of his osteosarcoma. Surprisingly, pathological findings of the resection specimen evidenced sheets of monomorphic-small-round-cells with some pseudo-rosettes. Immuno-histochemical staining showed CD99-strong-cytoplasmic-membrane positivity. NSE was weakly positive while chromogranin, synaptophysin, PS100, LCA and pan-cytokeratin were negative. A secondary extra-osseous-Ewing-sarcoma was then diagnosed.
Conclusion: We report the first case in literature of secondary extra-osseous-Ewing-sarcoma after successful treatment of osteosarcoma.

E-PS-23-029

Disseminated form of epidemic HIV/AIDS-associated Kaposi Sarcoma in a young male - a case report

L. Tomescu[1], A. Tita[2], L. Luca[2], M. Bosa[2], D. Enea[1], M. Ceausu[2]
[1] University Emergency Hospital, Bucharest, Romania, [2] "Mina Minovici" National Institute of Legal Medicine, Bucharest, Romania

Background & Objectives: Kaposi Sarcoma (KS) is an angioproliferative malignant tumour caused by human herpesvirus 8 infection. The epidemiological classification of KS includes four subtypes, such as: classic KS in elder men of Mediterranean origin, endemic KS in younger African men, iatrogenic KS due to immunosuppressive therapies and epidemic HIV/AIDS- associated KS. Today, KS is the most common neoplasm of people with HIV/AIDS.
Methods: We present the case of a 26-year-old deceased man known as intravenous drug-addict, with a medical history of HIV/AIDS, Kaposi Sarcoma, HCV hepatitis and bronhopneumonia. Unfortunately, he died due to systemic complications caused by multiorgan failure. Specimen samples taken from lung, liver, kidney, oesophagus, spleen and skin were processed and examined with standard H&E technique, Van Gieson and Gomori stains and immunohistochemistry.
Results: The forensic autopsy revealed multiple reddish tumours localized on the skin, oesophagus and spleen. Microscopically, the integumentary tumour showed a diffuse fascicular spindle cell proliferation infiltrating dermis and numerous blood filled spaces between the spindle cell component. Moreover, spindle endothelial cells aggregates and dilated vascular channels containing erithocytes were noticed on spleen parenchyma and oesophageal mucosa and submucosa. The tumour stroma showed intermixed abundant plasma cells, associated with microhemorrhagies and hemosiderin deposition. The histological aspects were suggestive of disseminated KS. The vessels stained positive focally to CD34, isolated to vimentin and negative to SMA. Gomori stain showed a liniar continuous network of capillaries with a nodular pattern.
Conclusion: The particularity of this case is the disseminated form of KS at an intravenous drug-addict patient with HIV/AIDS.

E-PS-23-030

Langerhans cell histiocytosis of bone with BRAF V600E mutation: a case report and the review of published work

N. Kaya Terzi[1], I. Yilmaz[2]
[1] University of Health Sciences, Sultan Abdulhamid Han Training Hospital, Istanbul, Turkey, [2] Ministry of Health, Provincial Health Directorate Istanbul, Sultan Abdulhamid Han Sample Training and Research Hospital, Department of Pathology, Turkey

Background & Objectives: Histiocytoses, including Langerhans cell histiocytosis (LCH) are rare disorders characterised by the proliferation of cells derived from monocyte/macrophage lineages. The etiology of these diseases remains unclear. However, oncogenic $BRAF^{V\ 600E}$ mutations have been identified in LCH.
Methods: Here, we report the case of a 26-year-old man with a 3-month history of left acetabulum posterior mass. No abnormality was detected in his other organs, and incisional curettage of the mass was performed. Routine pathological examination was performed. After immunohistochemical examination Sanger sequencing PCR was used to detect BRAF-V600E mutation in paraffin-embedded tissue samples.
Results: In pathological examination; among the bone trabeculae, Langerhans cells with a diameter of 12 - 15 microns were observed with irregular and long-core, fine chromatin and indeterminate nucleoles, with abundant, pale eosinophilic cytoplasm, prominent nuclear grooves and folds. Eosinophils were observed in groups between these cells. Histopathological examination revealed the coexistence of LCH. Immunohistochemistry showed that most of the large histiocytes were positive for CD68, S100, and CD1a, supporting the diagnosis of LCH. In addition, these cells were positive for $BRAF^{V\ 600E}$ mutation. BRAF inhibitors were given for medical therapy.
Conclusion: Children with LCH tend to have a high OS rate and a high incidence rate of BRAF-V600E mutation. The positive rate of BRAF-V600E gene mutation is not associated with age, sex, affected organ, clinical classification, early treatment response, recurrence, and 2-year OS of the children with LCH, but it is associated with clinical grouping of LCH. On the otherside some of the researches show that ,in children with LCH, BRAF(V600E) mutation was associated with high-risk features, permanent injury, and poor short-term response to chemotherapy. So we should follow up this patient carefully.

E-PS-23-031

Cell composition in the bone giant cell tumour

V. Zakharava[1], M.T. Mohammadi[1,2], L. Pashkevich[2], I. Shpileuski[2]
[1] Belarusian State Medical University, Belarus, [2] Belarus Republic Scientific and Practical Center for Traumatology and Orthopaedics, Belarus

Background & Objectives: Giant cell tumour (GCT) of bone consists of 3 different cellular types: stromal fibroblast-like cells, mononucleated-macrophage cells and multinucleated giant cells. Only stromal fibroblast-like cells are truly tumour cells in the heterogeneous cell mass of GCT.

Methods: We used immunohistochemistry (IHC) for differential diagnosis of various forms of giant cell tumour (GCT) and identification of cell specificity in GCT.
Results: Given the GCT morphogenesis, consisting of 3 cell elements, we used various antibodies that detect common mesenchymal, osteoblastic, endothelial, B- and T-cells, and monocytic-macrophage cells. Vemintin showed an immunopositive reaction in almost all tumour cells. CD68 shows immunopositive coloration with macrophages and giant cells. In this case, uneven jagged cytoplasmic membranes of giant multinucleated cells are noted, which indicates similarity with osteoclasts. Proliferative activity of stromal tumour cells with Ki-67 showed more intense nuclear staining in malignant cases of GCT as compared to benign GCT. In the tumour, foci with increased proliferative activity of tumour cells are determined - "hotspots". We also observed that in the GCT with infiltrating growth in the "invasive fronts" of the tumour, i.e. in areas of the tumour with an extra-bone extension into the periosteum or the surrounding soft tissue, tumour cells have more pronounced pro-liferative activity. IHC studies with CD5, CD20 and CD79a, CD45 and CD138 showed a weak immune response. The distribution of lymphocyte cells in the tumour is uneven.
Conclusion: GCT has high osteoblastic and osteoclastic activity. The processes of osteogenesis and osteolysis synchronously and permanently occur in the GCT. The quantification of osteoblasts with osteonectin, together with proliferative activity index with Ki-67, can provide useful information in the differential diagnosis between benign and malignant forms of GCT.

E-PS-23-032
A dedifferentiated lipoarcoma of the buttock with unusual presentation
G. Agrogiannis[1], A. Terra[2], S. Kykalos[2], A. Lazaris[1], G. Tsourouflis[2]
[1] 1st Department of Pathology, School of Medicine, National and Kapodistrian University of Athens, Greece, [2] 2nd Department of Propedeutic Surgery, School of Medicine, National and Kapodistrian University of Athens, Greece

Background & Objectives: A 52-year-old female patient presented to our clinic with a soft tissue growth on her right buttock which had been present for the past 5 years. The mass had been slowly growing with a more prominent growth in size over the last 2 years. At the time of presentation, the patient complained of atypical symptoms such as tenderness when seated and right-sided lower back pain. Physical examination revealed a soft, nontender palpable right buttock mass, 4-5cm in diameter. After the initial clinical evaluation, a soft tissue ultrasound and MRI of the pelvis was obtained, and these demonstrated a heterogeneous subcutaneous mass (64x23x46 mm) with no evidence of infiltration of the gluteus maximus. One month after presentation, a complete surgical excisional biopsy with clear margins was performed under local anesthesia.
Methods: Grossly, the surgical specimen was measuring 7.5x3.4x5 cm fully covered by adipose tissue. Upon sectioning, a circumscribed mass was revealed, about 6,5 cm in its largest diameter, with extensive cystic appearance. Histological examination revealed a cytologically malignant neoplasm with multifocally prominent giant cells. The cells had round and spindle morphology and the stroma was extensively hyalinized. In areas, the tumour cells were lining pseudovascular spaces, partly filled with erythrocytes. Mitotic figures were very rare and there wereno necrotic areas. The tumour was well demarcated having a fibrous pseudocapsule and the surrounding fatty tissue appeared normal. Immonohistochemistry initially showed a focal positivity for S100, while AE1/AE3, CK19, EMA, CD30, SMA, desmin, SOX10, CD34, CD31, ERG, TLE-1, were negative. Ki67 index was positive in 1-2% of the neoplastic cells. A secondary immunohistochemical staining was performed for MDM2 and CDK4 and these markers were positive in most of the neoplastic cells. The *MDM2/CDK4* genes amplification was confirmed by fluorescence in situ hybridization. Finally, the tumour was diagnosed as a dedifferentated liposarcoma,
Results: There are some basic points in this case that, at least initially, could mislead the diagnosis. The basic diagnostic problem was the total absence of an atypical lipomatous tumour component. This is probably due to an extensive dedifferentiation. Moreover, the dedifferentiated component, generally represents a high grade sarcoma. In the remaining cases in which that component is of low grade, it usually resembles "fibromatosis" or it shows a whorling "meningothelial" pattern. The subcutaneous location is also extremely rare. And finally, from the clinical aspect, the tumour was very slowly growing which is not usually compatible with a sarcoma.
Conclusion: Dedifferentiated liposarcoma is a tumour that shows a significant histological heterogeneity, with multiple patterns of differentiation. Thorough sampling is needed to detect the atypical lipomatous component which is very helpful to the final diagnosis.

E-PS-23-033
Pleomorphic lipomas: case series
S. Demir[1], A. Avci[1]
[1] Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Pathology, Turkey

Background & Objectives: Pleomorphic lipomas are very rare, benign neoplasms resembles the usual type of lipoma, except for gray-white gelatinous foci, representing the areas of increased cellularity. They constitute in the subcutaneous tissue of the posterior neck, shoulder, and back. Most of them between 3 and 5 cm and usually well circumscribed. We aimed to review these cases we encounter in our daily practice.
Methods: All the patients with pleomorphic lipomas who were operated in our hospital between October 2006 and February 2019 were evaluated retrospectively. Demographic characteristics, size, location and other associated lesions were recorded.
Results: A total of 6 pleomorphic lipoma cases were detected.Three (% 50) of the cases were male and 3 (50%) were female. The mean age was 49 years (32-59). Two (%33) of the cases were localized right hand and the other locations were right leg (%16), left heel (%16), neck (%16) and right-left conjunctiva (%16). The mean diameter of the lesions was 3 cm (0.8-6). Macroscopically, most of the lesions circumscribed,solitary and centered in the subcutaneous tissue. Histopathologically, lesions were predominantly composed of mature adipose tissue with scattered spindle cell or pleomorphic elements in the majority of cases.
Conclusion: Pleomorphic lipomas are very rare lesions, often slowly growing, painless, arising mainly in men. Excision is basic treatment. These lesions are a rare entity requiring differential diagnosis with many subcutaneous tumours.

E-PS-23-034
Gastrointestinal stromal tumour with dedifferentiation to leiomyosarcoma
S. Bagbudar[1], A.F.K. Gok[2], K. Gunay[2], I. Yilmaz[3], M. Buyuk[1], B. Bilgic[1], G. Unverengil[1]
[1] Istanbul Faculty of Medicine, Department of Pathology, Turkey, [2] Istanbul Faculty of Medicine, Department of General Surgery, Turkey, [3] Ministry of Health Istanbul, Provincial Health Directorate Istanbul, Sultan Abdulhamid Han Sample Training and Research Hospital, Department of Pathology, Turkey

Background & Objectives: Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal gastrointestinal tumours. Unlike other sarcomas, dedifferentiation is unusual for GISTs. Dedifferentiated GIST without previous imatinib therapy is even rarer, with few cases published to date. We describe an unusual case of GIST with dedifferentiation to leiomyosarcoma without history of previous therapy.

Methods: We report a case of 50-year-old male with an abdominal mass on greater gastric curvature, pathologic lymph nodes and colon implants for three months.
Results: Gross examination revealed a tan-white, focally-necrotic and hemorrhagic 25 cm-mass of 2850 gr. Microscopic examination demonstrated two demarcated areas: a well-differentiated spindle cell component and a pleomorphic component. Well-differentiated tumour composed of rather uniform, fusiform cells, with eosinophilic cytoplasm, arranged in intersecting fascicles or a short storiform pattern. Pleomorphic tumour was composed of eosinophilic polygonal cells with bizarre nuclei, abundant cytoplasm, and increased mitotic activity with abundant tumour necrosis. On immunohistochemical studies, the well-differentiated component was positive for CD34, CD117 and DOG-1. Ki-67 proliferation index was 1%. Pleomorphic component stained positivite for smooth muscle actin and kaldesmon. Ki-67 labelling index was 70%. Both were negative for S-100 and desmin. No loss of succinate dehydrogenase B expression was determined. A diagnosis of dedifferentiated GIST with leiomyosarcomatous differentiation was rendered. Molecular studies did not show any activating mutations for KIT, platelet derived growth factor alpha and BRAF gene.
Conclusion: Dedifferentiated GIST should be considered in the differential diagnosis of abdominal masses and adequate gross sampling should be performed to reveal conventional and dedifferentiated components.

E-PS-23-035
Primary Rosai-Dorfman disease of bone; a case report
A.N. Yildirim[1], R.B. Girgin[1], T. Zenginkinet[1], B. Simsek[1], K. Ozkan[2]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, Department of Orthopedics and Traumatology, Turkey

Background & Objectives: Rosai-dorfman disease (RDD) is a rare, benign condition that causes proliferation of histiocytes, a type of white blood cells, within the lymph nodes and other organs of the body such as the skin, bone, breast, respiratory airways, and central nervous system. Osseous involvement without lymphadenopathy (primary disease of bone) is stil rare and has been reported in only a small number of patients. We present a case of primary osseous RDD which is a 2-year-old boy presenting with a solitary osseous mass lesion in the talus.
Methods: We present the case of a 2-year-old boy who presented with a pathological fracture. Computed tomography revealed a soft tissue mass which was observed in the 17x10 mm size that affected all part of the talus, leading to loss of continuity in the cortex.
Results: Histopathological evaluation of biopsy specimen showed consisted of a background of a variably cellular mixed inflammatory infiltrate composed of plasma cells, lymphocytes, neutrophils, foamy macrophages, eosinophils, and numerous large histiocytes. Characteristically, the large histiocytes contained abundant eosinophilic cytoplasm and demonstrated conspicuous emperipolesis with intracytoplasmic lymphocytes, plasma cells, or neutrophils. Immunohistochemical stains showed that the large histiocytes were strongly positive for s-100 and CD68, negative for CD1a.
Conclusion: RDD is a rare, nonmalignant histiocytic disorder with unknown etiology. RDD infrequently affects bone as a primary or secondary form of the disease. The differential diagnosis often includes osteomyelitis and hematopoietic neoplasms. Diagnosis rests on the identification of the characteristic large s-100 positive histiocytes that demonstrate prominent emperipolesis.

E-PS-23-036
Clear cell myomelanocytic tumour (CCMT) of the falciform ligamentum of teres: a case report
T. Oğuzsoy[1], H. Sahin Ozkan[1], H.K. Turkoz[1]
[1] Marmara University Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: Perivascular epitheloid cell tumour (PEComa) is a rare mesenchymal tumour family composed of angiomyolipoma, clear cell 'sugar' tumour of the lung, lymphangiomyomatosis and a group of histologically and immunohistochemically similar tumours arising in various soft tissue and visceral organs. Clear cell myomelanocytic tumours of falciform ligamentum of teres is an extremely rare variant of PEComas.
Methods: A 27- year –old woman presented with a 70x35x20 mm diameter mass lesion between duodenum and liver. It was found incidentally during her pregnancy. She had idiopathic thrombocytopenic purpura disease and no other remarkable symptoms. A tumour arising from falciform ligamentum of teres was found and resected during surgery.
Results: Grossly; size of the resection specimen was 12.5x9x4 cm . On the cut surface, a 8x4x3 cm tumour was detected. It was solid, yellow in color, had foci of hemorrhage and a thin fibrous capsule. Histological examination revealed epithelioid or spindle shaped tumour cells that had clear to eosinophilic cytoplasm, and organized in a fascicular pattern. Tumour cells arranged around hyalinized arterioles and capillaries. Immunohistochemical analysis showed that tumour cells were positive for SMA, HMB45 and negative for Desmin, CK, EMA, CD34 and CD117. We reported the case as PEComa with uncertain malignant potential, according to proposed classification of PEComas because of its size.
Conclusion: Clear cell myomelanocytic tumours of falciform ligamentum of teres are very rare and usually benign tumours. They must be distinguished from gastrointestinal stromal tumours, melanomas, and clear cell sarcomas. Our patient was treated with a resection without any adjuvant therapy and no recurrence has been detected in follow up.

E-PS-23-037
Cellular cannibalism in giant cell rich lesions: is it worth scanning?
G. Gul[1], O. Oz[2], M. Sezak[3], I. Tamsel[4], D. Sabah[5], B. Doganavsargil[6]
[1] Tepecik Training and Research Hospital, Department of Pathology, Izmir, Turkey, [2] Bergama Hospital, Department of Pathology, Turkey, [3] Ege University Faculty of Medicine Department of Pathology, Turkey, [4] Ege University Faculty of Medicine Department of Radiodiagnostics, Turkey, [5] Ege University Faculty of Medicine Department of Orthopedics, Turkey, [6] Ege University Faculty of Medicine, Department of Pathology, Izmir, Turkey

Background & Objectives: Cellular cannibalism, a phenomenon in which a larger cell engulf a smaller one (lymphocyte, erythrocytes), has been previously defined in several malignancies and in Giant cell tumour of bone (GCT) as well.
Methods: We designed a pilot study to search for the presence of cannibalistic giant cells (CGC) in giant cell rich lesions (13 consecutive chondroblastoma (CB), 13 Giant cell tumour (GCT), 13 Tenosynovial giant cell tumour (TSGCT) cases). Number of giant cells (GC) and CGC per 10 high power field (hpf) (x40 magnification; 0.54 mm radius; Olympus BX50 microscope) were recorded and correlated with nonparametric tests.
Results: CGC were observed in 100% of GCT, 84.6% of CB and 53.8% of TSGCT (p=0.012, chi-square). Median number of CGCs/10hpf were higher in GCT than in CB, and in TSGCT; 6±6.9 (range:1-23), 2±1.7 (range: 0-5), 1±2.2 (range: 0-7), respectively (p=0,004; Kruskal-Wallis). Overall GC density was highest in GCT, followed by CB and TSCGT (p=0.000, Anova). Recurrence rate was 53.8% for GCT, 30.8% for TSGCT and 15.4% for CB. Among recurrent cases 7 GCT (100%), 1 CB, 2 TSGCTs had CGCs.
Conclusion: Canniballistic cells were more frequently observed in GCT in keeping with literature while TSGCT presented with the

lowest number of GCs and CGSs. Despite lower number of cases in the present study, the correlation of CGCs with recurrence appears to be a promising area of interest for further research.

E-PS-23-038

Symptomatic spinal epidural angiolipoma in a 32 year-old pregnant patient: a case report

A. Saidi[1], B. Laabidi[1], R. Hedhli[2], F. Gargouri[1], N. Mansouri[1], A. Bouziani[1], I. Msakni[1]
[1] Pathology Department, Military Hospital for Instruction of Tunis, Tunisia, [2] Tunis El Manar University, Medicine School of Tunis Military Hospital of Tunis, Department of Pathology, Tunisia

Background & Objectives: Spinal angiolipomas are uncommon benign tumours composed of mature fat cells and prominent abnormal capillary-type vascularity. They predominantly arise in the mid-thoracic posterior epidural space. Pregnancy and weight gain are suggested to be predisposing factors. Angiolipomas are traditionally classified into non-infiltrating and infiltrating subtypes. The latter infiltrates the adjacent tissues, most commonly bone. However, both subtypes have an excellent prognosis with a low recurrence risk after surgical treatment and no malignant transformation potential. Clinical symptoms include back pain, leg weakness and lower limb numbness or parasthaesia. These signs usually have a progressive course and are related to spinal cord and/or nerve root compression, or infiltration of surrounding tissue. The treatment consists of surgical removal of the tumour.
We report a case of a symptomatic spinal epidural angiolipoma discovered during pregnancy in a 32-year-old patient.
Methods: In a case of a spinal epidural angiolipoma in a pregnant young patient, the clinical and pathological parameters are studied and discussed.
Results: We report the case of a 32-year-old female presenting with a progressively worsening paraparesis. Symptoms have appeared during pregnancy. MRI performed in the postpartum period revealed a well circumscribed spindle shaped epidural mass extending from T4 to T6. Signs of spinal cord compression were notable. On gross examination, the removed lesion measured 4x2x0,5 and presented as an elongated smooth mass with an homogenous brown cut surface. On histological examination, the tumour consists of a double proliferation of mature adipocytes admixed with abnormal vascular elements composed of irregularly thickened walls and flat regular endothelial cells. The patient had an indolent, recurrence free outcome in a one-year follow-up assessment.
Conclusion: Spinal epidural angiolipomas are rare, but well recognized causes of spinal cord compression. The infiltrative form can be radiologically mistaken for a malignancy or aggressive vertebral haemangiomas. Histologic diagnosis is usually evident, and the surgical treatment is curative with excellent outcome.

E-PS-23-039

GNAS mutations in differential diagnosis of fibrous dysplasia and myxomas

A. Tysarowski[1], M. Wagrodzki[2], K. Seliga[1], T. Goryn[4], R. Zub[3], J.A. Siedlecki[3], P. Rutkowski[5], M. Prochorec-Sobieszek[2]
[1] Department of Pathology and Laboratory Medicine, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Poland, [2] Department of Pathology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Poland, [3] Molecular And Translational Oncology, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Poland, [4] Department of Soft Tissue/Bone Sarcoma and Melanoma, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Poland, [5] Maria Sklodowska-Curie Institute - Oncology Center, Department of Soft Tissue/Bone Sarcoma and Melanoma, Poland

Background & Objectives: Fibrous dysplasia (FD) is a benign fibro-osseous bone tumour accounting for 5%-10% of benign bone tumours that includes monostotic fibrous dysplasia (70%-80%), polyostotic fibrous dysplasia (20%-30%), McCune-Albright (2%- 3%) and Mazabraud's syndromes. In 40-90% of FD somatic mutations in *GNAS* gene (encoding α subunit of stimulatory G-protein-coupled receptor (Gsα)), mostly missenses at codons 201 or 227 are detected. The same *GNAS* mutations are also identified in majority (up to 60%) of intramuscular myxomas, rare benign soft tissue musculoskeletal tumours. Thus, determination of GNAS mutations status may allow reliable differentiation of FD and myxoma from their close histologic mimics-low-grade osteosarcoma and myxofibrosarcoma respectively. The aim was to identify somatic *GNAS* mutations in selected fibro-osseous/musculoskeletal tumours and to assess the utility of *GNAS* molecular analysis in FD and myxomas differential diagnosis.
Methods: DNA was isolated form 64 FFPE sections of : 23 newly diagnosed FD, 10 longer lasting FD lesions, 5 low grade osteosarcoma, 4 intramuscular myxomas, 7 myxofibrosarcoma, 14 myxoma and 1 undifferentiated myxoma/myxofibrosarcoma. Mutations p.Arg201 and p.Gln227 in *GNAS* gene were verified by Sanger sequencing.
Results: Mutations p.Arg201His/Cys were found in 15/23 (65%) of newly diagnosed FD and 7/18 (39%) myxomas. No mutation was detected in other fibro-osseous lesions of bones and low-grade myxofibrosarcomas.
Conclusion: Molecular verification of *GNAS* mutation in DNA isolated from FFPE enables differential diagnosis in significant number of fibrous dysplasia and myxomas from their close histologic mimics and, hence, can be incorporated as an additional test for routine diagnostic procedure.

E-PS-23-040

Giant cell tumour of the soft tissue presented as an unusual breast lesion

M. Ninkovic[1], J. Septa[2], N. Lujic[3], G. Đuricic[4], S. Rajkovic[3]
[1] Institute of Pathology, University of Belgrade, Serbia, [2] Institute of Pathology, Medical Faculty, University of Belgrade, Serbia, [3] Institute for Surgical and Orthopedic Diseases "Banjica", Serbia, [4] Institute for Oncology and Radiology, Belgrade, Serbia

Background & Objectives: Giant cell tumour of the soft tissue is a rare entity showing similar gross and histological features of giant cell tumour of the bone. It most frequently occurs in the superficial and deep soft tissue of the thigh, trunk, and upper extremities.
We report a case of 69-year-old female patient with 3 month long history of a rapidly growing, 6,4 cm nodule in the right breast region. The lesion was fixed, nontender and adherent to the skin. The skin surface was focally ulcerated. Ultrasound and mammography confirmed aggressive lesion in the right breast. The clinical diagnosis was breast carcinoma. Clinically there was no regional lymphadenopathy. Biopsy was indicated.
Methods: In "frozen section" analysis malignant breast tumour with giant cell component was diagnosed. On definitive pathological slides primary diagnosis was corrected. Tumour was a well-circumscribed multinodular lesion involving the dermis and consisting of fibroblasts, histiocytes and osteoclast-type giant cells. The nuclei of the giant cells were very similar to those of the mononuclear cells. A distinct fascicular pattern with focal storiform arrangement of spindle neoplastic cells was noted in the lesion. Nuclear pleomorphism of mononuclear cells and rare mitotic figures were presented. Immunohystochemical analysis was indicated.
Results: Immunohystochemistry studies revealed mononuclear and multinuclear cells strong positivity for CD68 and vimentin and negative for cytokeratin, EMA, S-100 protein,SMA markers and

CD 31. Ki 67 as proliferative factor was positive in less than 5% of cells.
Conclusion: According to the histological and immunohystochemical appearance final diagnosis was giant cell tumour of the soft tissue.
Now, 7 years later, the patient has no symptoms or signs of disease.

E-PS-23-041
Giant cell tumour of the tendon sheath: a clinicopathologic study of 31 cases
A. Kilitci[1], îF. Elmas[2]
[1] Ahi Evran University Medical Faculty, Dept of Pathology, Turkey, [2] Ahi Evran University Medical Faculty Dept of Dermatology, Turkey

Background & Objectives: Giant cell tumour of the tendon sheath (GCTTS) is the second most common benign tumour of the hand after ganglion cysts. Feet, knees and others, can also be involved. It is a slowly growing, usually painless lesion of soft tissues. The most widely accepted etiologic theories include trauma, infection, inflammation, osteoclastic proliferation, metabolic disease, and neoplasia. We describe here a series of 31 cases of GCTTS to try to define the epidemiological and clinicopathologic findings of the disease.
Methods: The case records of all patients diagnosed to have GCTTS by our pathology department from 2009 to 2018 were analysed. We introduced 31 cases of GCTTS in this study. Four cases of fibroma of the tendon sheath were excluded from the study. The age of patients, gender, site of occurrence, size of the lesion, presenting symptoms, treatment modality, histopathological reports, and recurrence were investigated, and noted.
Results: Ages of patients ranged from 14 to 74 years with most cases occurring in their thirties. There was a female predominance of 11 males to 20 females. The majority of patients had a painless subcutaneous palpable mass which gradually increased in size. The most frequent site of the tumour was the finger in 61.3 % (n=19). The other lesions were detected over the hand in 32.3% of the patients(n=10), foot in 3.2% (n=1), over the right knee (large joint) in 3.2% of patients (n=1). Among the small digit tumours the frequent affected site was the thumb. Single nodules (n=21) were more common than multiple (n=10). One male had maximum lesions on his left little finger with 18 GCTTS. The most common preoperative clinical diagnoses were GCTTS, fibroma, lipoma, schwannoma and epidermal cyst. Complete excision was the treatment in all of the cases. The tumours were firm/elastic, usually encapsulated, regular in shape, with smooth contour varying in size from 0.4 to 2.5 cm (average size 1.25 cm). Cut section of the tumour was grayish white mottled with yellow. Histologic appearance of the tumours consisted of multinucleated giant cells, polygonal histiocytes, foamy histiocytes and hemosiderin laden macrophages. Immunohistochemically, CD68 and ki-67 were applied in some of the patients to support the diagnosis. Local recurrence was not seen.
Conclusion: We must distinguish GCTTS from other similar pathological processes. A different histopathologic variation can be noticed between GCTTS involving the digits and large joints. The location and the strict adherence of the tumour to the tendon or neurovascular bundles may cause difficulties. Early diagnosis and treatment with wide excision prevent local recurrence.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-24 | Thymic And Mediastinal Pathology

E-PS-24-001
Metastatic melanoma presenting as an anterior mediastinal mass
O.P. Balisan[1], G.N. Valloso[1], L. Cale-Subia[1]
[1] Philippine Heart Center, Philippines

Background & Objectives: Metastatic melanoma to the anterior mediastinum is a rare event. Intrathoracic metastases usually occur as pulmonary nodules, solitary nodules, mediastinal and hilar lymphadenopathy, and pleural effusions. We hereby report a rare case of metastatic melanoma presenting as an anterior mediastinal mass.
Methods: Tissue sections submitted after surgery were fixed in 10% neutral buffered formalin and embedded in paraffin. Some 5-micrometer sections were stained with hematoxylin-eosin, and immunohistochemical stains for morphologic and immunohistochemical evaluation.
Results: The patient was a 24-year old male who presented with dyspnea when recumbent. Physical examination revealed a non-ulcerated, pigmented, skin lesion on the anterior chest, measuring 2.2 x 1.4 cm. CT scan showed an anterior mediastinal mass measuring 20 x 14 x 10 cm. Excision biopsy of the skin lesion and tumour debulking of the mediastinal mass were performed. Immunohistochemical studies of both specimens show S100+, HMB45+, and Melan-A+. Ki-67 showed 60% proliferation. These findings are consistent with metastatic melanoma.
Conclusion: This is a rare case of metastatic melanoma presenting as an anterior mediastinal mass. The usual disease course of metastatic melanoma to the thorax shows mediastinal and hilar lymph node involvement, which is not observed in our patient. This patient underwent tumour debulking surgery to relieve compression symptoms but died a month after due to tumour recurrence.

E-PS-24-002
Posterior mediastinal chondrosarcoma with unusual presentation as a cystic tumour mass: a case report
D. Udovicic-Gagula[1], J. Redzepagic[1], N. Bilalovic[1]
[1] Department of Pathology, Clinical Center University of Sarajevo, Bosnia and Herzegovina

Background & Objectives: Chondrosarcoma is a malignant cartilage-forming tumour of bone, usually arises within long bones or ribs. Although chondrosarcoma is the most common malignant tumour of the chest wall, it is still a rare entity. It is unexpected to find it in the posterior mediastinum, where neurogenic tumours are considered the commonest.
Methods: We report a case of a 46-year-old woman whom presented with a complaint of intermittent pain in the right side of chest over three months period. Chest X-ray and subsequent CT scan reveald wellcircumscribed, mainly cystic mass located in the upper right part of the posterior mediastinum, without infiltration of lung parenchyma and only discreetly remodeling the ninth vertebrae and posterior part of rib.
Results: Histopathological examination of surgical resection specimen was consistent with a grade I chondrosarcoma with undoubtedly invasion of bone.
Conclusion: Because of possibility of local recurrence patient is recommended close clinical and radiological follow up.

E-PS-24-003
Diagnosis of a thymic carcinoma in mediastinal biopsy
C. Faria[1], J. Fraga[1], V. Almeida[2], F. Ramalhosa[1], A. Lai[1], M.B. Pimentão[1], R. Almeida[1], H. Moreira[1], R.C. Oliveira[1], V. Sousa[1], L. Carvalho[2]
[1] Centro Hospitalar e Universitário de Coimbra, Portugal, [2] Institute of Anatomical and Molecular Pathology, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal

Background & Objectives: Mediastinal tumours are among the most difficult lesions examined by the Pathologist because many different types of lesions occur at this location. Thymic carcinoma

is a rare, invasive mediastinal neoplasm with tendency to metastasize. It represents 1% of the anterior mediastinal tumours and occurs in all ages but more frequently between 30 and 60 years, with a slightly male predominance. Diagnosis may be threattened by mediastinal methodology of sampling.
Methods: Case report: 76-years-old woman presented chest pain, dyspnoea, cough, astenia and anorexia during seven months. PET scan revealed a malignant mass in the superior and anterior mediastinum with well delineated borders and without evidence of disease at other levels. Mediastinoscopy was performed for diagnosis.
Results: Histopathological study of small fragments accounting for 4mm^2 revealed a neoplasia composed of smooth-countered islands of large polygonal cells with hyperchromatic nuclei and eosinophilic cytoplasm in a fusocellular stroma infiltrated by scattered chronic inflammatory cells. In immunohistochemistry, tumoral cells had expression of CK5.6, CK8.18, p63 and there were also positivity for CD20 (B lymphocytes) and CD3 (T lymphocytes). CD5, CD117 and CD10 were not expressed. The diagnosis of thymic carcinoma was reported.
Conclusion: Thymic carcinoma even with negativity for CD117 was favoured as thymoma was excluded due to the organoid pattern described. Clinically, thymic carcinoma is usually not associated with paraneoplastic syndromes. This patient did not present other lesions in the mediastinum and the lungs, supporting the diagnosis.

E-PS-24-004
Ectopic ACTH-producing thymic typical carcinoid tumour: a case report
J. Filipe[1], T. Ferro[2], C. Costa[3], V. Leite[3], F. Cunha[1,2]
[1] Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, [2] Faculdade de Ciências Mèdicas da Universidade Nova de Lisboa, Lisbon, Portugal, [3] Serviço de Endocrinologia, Instituto Português de Oncologia do Porto Francisco Gentil, Porto, Portugal

Background & Objectives: Thymic carcinoid is a rare entity, may be associated with endocrine manifestations and part of the spectrum of multiple endocrine neoplasia syndrome type I (in 25%). There are few data regarding the prognosis of this entity, but propensity for recurrence, lymph node and distant metastasis have been described.
Methods: We describe the clinical-pathologic features of an unusual case of thymic typical carcinoid tumour, with ectopic ACTH secretion.
Results: A 27-year old man, without familial history of MEN1, presented with facial enlargement, asthenia, insomnia, and muscle atrophy. Laboratory data revealed a 24-hour urinary free cortisol measurement of 891μg/24h (NR 10-80μg/24h), plasma ACTH of 110pg/mL (NR <46pg/mL) and serum potassium of 2,8mEq/L (NR 3.5 to 5.5mEq/L), featuring a Cushing's syndrome. Complete Imaging evaluation found a mediastinal mass. A 3cm infiltrative white-brown firm tumour with pericardium invasion was excised. Microscopically it had an organoid pattern, with trabeculae and nests surrounded by a delicate vasculature, without cell atypia, mitotic activity nor necrosis. Neoplastic cells were immunoreactive for AE1/AE3, CAM 5.2, Synaptophysin, Chromogranin A, CD56, and ACTH. Final diagnosis was thymic typical carcinoid tumour with ACTH secretion. The patient underwent radiotherapy after surgery and several lymphadenectomies due to metastatic disease. He died 6 years after the initial diagnosis of disease progression.
Conclusion: Ectopic ACTH-producing thymic typical carcinoid tumours should be considered in the context of an anterior mediastinal tumour associated with endocrine manifestations even with low-grade histological features.

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-25 | Uropathology

E-PS-25-001
EBV positive squamous cell carcinoma of the urinary bladder: a case report
G. Richter[1], C. Schmitt[2], M. Baumann[3]
[1] Institute of Pathology, Hameln, Germany, [2] GenOPath, Bonn, Germany, [3] Sana Klinikum Hameln-Pyrmont, Germany

Background & Objectives: Tobacco smoking is an important risk factor for squamous cell carcinoma of the bladder. Moreover, it is relatively common in the tropics and is associated with Schistosoma haematobium infection. Until now Epstein-Barr virus (EBV) genomic material was not identified in a case of squamous cell carcinoma using polymerase chain reaction (PCR) or hybridisation. We report a case of squamous cell carcinoma in the bladder with positive detection of EBV specific DNA by using real-time
Methods: We present a case of a 84 years old caucasian female with a solid tumour of the bladder. Following histological examination of transurethral resection of the urinary bladder after routinely H&E-staining shows undifferentiated cells. Immunhistochemistry and molecularpathologic investigations using PCR with following sequencing were performed. DNA was isolated from the histological sample with the QIAsymphony DSP DNA Mini Kit (QIAGEN). EBV was detected by real-time PCR using the artus® EBV RG PCR Kit (QIAGEN, Hilden) according to the manufacturers protocol.
Results: Routinely H&E-staining poorly defined islands of undifferentiated cells were detected. The tumour cells have uniform, vesicular nuclei with prominent nucleoli. In immuohistochemistry using the Roche benchmark XT we identify cytokeratin 5/6 and p63 and a negative reaction using anti-GATA3 and anti-CK 20-antibodies. This seems to be the morphologic correlation of a poorly differentiated non-keratinizing squamous cell carcinoma.The PCR analysis revealed positivity for EBV.
Conclusion: This is the first case of squamous cell carcinoma of the bladder with positive detection of Epstein-Barr Virus (EBV). The predictive value of this detection is now unclear, and more studies are needed to investigate the potential role of EBV squamous cell carcinoma carcinoma of the bladder.

E-PS-25-002
Urinary bladder cancer in Gwagwalada, Abuja, North-Central, Nigeria
O. Oluwole[1]
[1] University of Abuja, Nigeria

Background & Objectives: Bladder cancer is the 7th most common cancer worldwide, accounting for 3.2% of all cancers.It is considerably more common in males than in females, with an estimated 260,000 new cases occurring each year in men and 76,000 in women worldwide.
To determine the histopathological pattern of bladder cancer in our environment and to compare with similar research work elsewhere.
Methods: This is a 5-year retrospective histopathological study of bladder cancer seen between 2005-2009 in the Department of Histopathology, University of Abuja Teaching Hospital, North-Central Nigeria. All the Haematoxylin &Eosin stained slides and paraffin embedded blocks were retrieved and studied. The relevant clinical data such as the age, sex, site of lesion and clinical summary were extracted from the histology request forms.
Results: A total of 13 patients (10 males and 3 females) with bladder cancer were seen during the period of study. The male to female ratio is 3.3:1. The mean age was 65 years. The most common histological type of

bladder cancer in our environment is urothelial carcinoma no other histological types was seen in this review.
Conclusion: Although, Gwagwalada is in the schistosomiasis endemic belt, the histological type of bladder cancer (urothelial carcinoma) seen in this review do not seem to reflect this as reported in similar studies. Therefore, there is need to further study the role of Schistosoma infestation and squamous cell carcinoma of the bladder in our environment.

E-PS-25-003
Sampling of radical prostatectomy specimens: complete vs partial sampling methods
A.R. Paz[1], A. Billis[2], L. Freitas[1], L. Costa[1], I. Barreto[1]
[1] Dep. Anatomic Pathology, School of Medical Sciences, State University of Campinas (Unicamp), Brazil, [2] State University of Campinas - Unicamp, Brazil

Background & Objectives: Complete prostate sampling most accurately provides prognostic parameters. However, it demands labor, time and financial expense due to a high number of paraffin blocks which is particularly important in some countries. In a retrospective study, we compared several partial methods to a series of 113 step sectioned and completely processed prostates aiming to find the one with lower number of paraffin blocks but higher prognostic parameters.
Methods: 1: only posterolateral quadrants (PLQs); 2: only anterolateral quadrants (ALQs); 3: all quadrants (Qs) of transverse section (TS) but skipping one TS; 4: alternating only PLQs and only ALQs; 5: all Qs of predominant side in needle biopsy (NB) plus contralateral PLQ skipping one TS; 6: all PLQs plus ALQ of predominant side in NB skipping one TS; 7: all PLQs and the ALQ skipping one TS of predominant side in NB plus contralateral PLQ skipping one TS.
Results: Methods 4 and 7 showed the best results. In both methods, there was a 50% reduction of paraffin blocks with a detection of positive margins and extraprostatic extension of 81.6% and 77.2% in Method 4, and 89.8% and 82.5% in Method 7, respectively. Invasion of the middle and distal portion of the seminal vesicle (SV) was always associated with invasion of the proximal portion, and vas deferens invasion occurred only when the proximal portion of the SV was invaded.
Conclusion: It was consensus in a 2009 ISUP meeting that sampling of radical prostatectomy specimens may be complete or partial. In methods 4 and 7 we obtained a 50% reduction in number of paraffin blocks and the highest percentage of prognostic parameters. Sampling of SV may be restricted to the proximal portion, and sampling of the vas deferens is not necessary.

E-PS-25-004
A curious case of mixed adenocarcinoma of the prostate: a case report and literature review
V. Caamaño[1], R. Ruiz[1], E. Camacho[1], A. Viguri[1], N. Barriobero[1], L. Lorente[1], A. Perez[1], I. Gorostiaga[1], A. Martinez[1]
[1] Araba University Hospital, Spain

Background & Objectives: Prostate cancer is the second most common malignancy. Acinar adenocarcinoma is one of the most common variants. However, few cases combined acinar adenocarcinoma with and ductal adenocarcinoma. Is important to make differential diagnoses with prostatic intraepithelial neoplasia because it has a better prognosis corresponding to Gleason score 6 (3+3).
Methods: 69 years old man with a history of urinary tract symptoms and haematuria over the last two months. Physical exam showed an abnormal digital rectal examination. Serum PSA level was 20ng/ml. MRI-guided biopsy was performed and showed: Acinar adenocarcinoma of the prostate, Gleason score 8 (4+4).
Results: The patient underwent surgery: Radical prostatectomy. Pathology report showed: Cribriform glands, sheets of individual cells, cords, solid nest cells and comedonecrosis, Gleason score 9 (4+5) combined with glans lined by tall columnar pseudostratified epithelium, elongated nuclei with severe atypia, prominent nucleoli and mitotic figures. For all this reasons the final diagnoses was: Mixed adenocarcinoma of the prostate: Acinar adenocarcinoma Gleason score 9 (4+5) associated to Ductal adenocarcinoma.
Conclusion: Mixed adenocarcinoma of the prostate accounts for approximately 2.6 - 3% of all prostate cancers. Most cases combined acinar adenocarcinoma Gleason score 9- 10 and ductal adenocarcinoma. This kind of mixed pattern a is more aggressive than the usual adenocarcinoma with higher risk of recurrence after radical prostatectomy. The ductal component often elicits desmoplastic reaction with hemorrhage, edema and inflammation.

E-PS-25-005
Acantholytic penile intraepithelial neoplasia
C. Beggan[1]
[1] St George's Hospital London, United Kingdom

Background & Objectives: Penile Intraepithelial Neoplasia (PeIN) is a recognised dysplastic precursor to penile squamous cell carcinoma. PeIN is subcategorised into differentiated and undifferentiated forms that vary in morphology and relationship to high risk HPV infection. Undifferentiated PeIN (uPeIN) is characterised by full thickness squamous atypia with loss of polarity, basaloid morphology and frequent atypical mitoses. UPeIN is related to high risk HPV infection and as such shows diffuse strong positive staining with p16 immunohistochemistry.
Methods: This case describes a patient with both classic uPeIN and a separate but adjacent acantholytic precancerous abnormality, designated Acantholytic PeIN.
Results: This 72year old man presented with redness around the urethral meatus. He underwent perimeatal glans excision which showed multifocal areas of classic uPeIN on the glans surface and extending into urethra. Also present on the glans surface were foci of acantholysis. The intraepithelial bullae were lined by large cytologically malignant keratinocytes with similar morphology to those seen in the area of uPeIN. p16 was positive in both areas of classic uPeIN and in the cells lining the acantholytic bullae.
Conclusion: Acantholytic precancerous squamous lesion have previously been described in skin and oral cavities. This is the first described case of PeIN showing acantholytic morphology, which may represent a variant of uPeIN. Acantholytic (pseudoglandular) sqaumous cell carcinoma of the penis is a recognised subtype and this acantholytic PeIN may represent a precursor to this rare cancer.

E-PS-25-006
Coexistence of prostatic adenocarcinoma and mantle cell lymphoma
T. Lakic[1,2], J. Ilic Sabo[1,2], A. Ilic[1,2], Z. Vrekic[2], M. Panjkovic[1], D. Cuk[2]
[1] University of Novi Sad, Faculty of Medicine, Serbia,
[2] Clinical Center of Vojvodina, Novi Sad, Center for Pathology and Histology, Serbia

Background & Objectives: Adenocarcinoma is the most common prostatic malignancy for which clinical management Gleason score and recent updates in prostate cancer staging (ISUP/WHO) plays critical role. Mantle cell lymphoma (MCL) results from malignant transformation of a B lymphocyte in the outer edge of lymph node follicle with overexpression of cyclin D1, tipically. Our objective was to present a case of patient with coexistenced tumours.
Methods: We report the case in which hematoxylin and eosin (HE) as well as immunohistochemical stainings (IHC) showed coexisting tumours- prostatic adenocarcinoma and MCL. A 68-year-old man without remarkable medical history was admitted to our hospital for elective radical

prostatectomy because adenocarcinoma shown earlier due to prostate core biopsy. Computer tomography detected enlarged retroperitoneal lymph nodes. As a routine part of this surgical procedure, lymph nodes were removed.

Results: Having performed thorough histological examination, HE sections confirmed the diagnosis of prostatic adenocarcinoma, Gleason score3+4=7, ISUP/WHO grade group2, measuring about 30% of prostatic parenchima. Lymph nodes microscopic analyses showed unexpected pattern consisted of small lymphoid cells, some with irregular nuclear contours centrocyte-like, with wide mantle zone and hyalinized blood vessels. IHC showed positivity for CD20,bcl2,CD5,CyclinD1 and CD43 staining, while CD3,CD10 and bcl6 were negative. Ki67 expressed in~20% cells. According to morphological pattern and IHC staining diagnose of MCL was set.

Conclusion: A prostate adenocarcinoma can extremely rarely be in coexistence with undiagnosed lymphoproliferative disease, as in our case with non-Hodgkin mantle cell lymphoma.

E-PS-25-007

Plasmacytoid and nested variant invasive urothelial carcinoma: case report

T.C. Savli[1], O. Okcu[2], T. Bolme Savli[3], B. Yeni[4], K. Behzatoglu[5]
[1] Istanbul Training and Research Hospital, Turkey, [2] Recep Tayyip Erdogan University Education and Research Hospital, Turkey, [3] Bagcilar Training and Research Hospital, Turkey, [4] University of Health Sciences, Department of Pathology, Turkey, [5] Acibadem Healtcare Group, Turkey

Background & Objectives: Bladder cancer cases are originated mostly from epithelium. Urothelial carcinomas accounts for 85-90% of epithelium originated cancers. Different morphological variants are observed about 10-25% of cases. Due to the different prognostic significance and treatment modalities, these variants should be recognized and reported in pathology reports.

Methods: A 72-year-old male patient was admitted to the urology polyclinic with the complaint of bleeding from the urine. In microscopic examination, tumoral cells with eosinophilic cytoplasm, small hyperchromatic, centrally or eccentrically located nucleus was observed in a loose or myxoid stroma. Small nests forming tumoral cells with a benign appearance was observed near these areas. Pancytokeratin and CD138 was positive in the cells which invaded the muscle layer. Our case was reported as invasive urothelial carcinoma with plasmacytoid and nested features.

Results: The high metaplastic capacity of the bladder urothelial epithelium and its origin from different embryological layers may lead to very different differentiations in invasive urothelial carcinomas. The plasmacytoid variant can accompany %50 of high-grade urothelial carcinoma cases. The nested variant is composed of cytologically bland tumour cells with a nesting growth pattern. Therefore, the differential diagnosis is nephrogenic adenoma and Von Brunn islands. As in our case, multiple variants can be seen together in rare cases.

Conclusion: Most frequently squamous, glandular and micropapillary variants are reported in the literature, while plasmacytoid and nested variants are rarely detected. Plasmacytoid and nested variant urothelial carcinomas are aggressive tumours due to their early invasion, lymph node and distant organ metastasis capacities, and are often advanced at the of diagnosis.

E-PS-25-008

Utility of Vimentin in immunohistochemical differential diagnosis of renal tumours with eosinophilic appearance

L. Zakhartseva[1], A. Romanenko[2,3], V. Baranovska[1], L. Nekrasova[1]
[1] National Medical Bohomolets University, Ukraine, [2] Institute of Urology, Ukraine, [3] National Academy of Medical Sciences of Ukraine, Ukraine

Background & Objectives: Absence of strict morphological criteria and variable immunoreactivity of renal tumours with eosinophilic cytoplasm make its differential diagnostics difficult. Differentiation of oncocytoma and chromophobe cell carcinoma requires application of such markers as Vimentin, C-kit (CD117), CK7, CD10. We report statistics of tumour immunoreactivity in clinical cases which were observed in our institution.

Methods: Operative material from 19 patients (26-69 years old), with clinically diagnosed renal mass and eosinophilic tumour histopathology was investigated. Hematoxylin and eosin staining and immunohistochemical markers Vimentin (Vim3B4), CD117(CD7272), CD10(56C6) were used for verification of diagnosis.

Results: 21% of cases (n=4) demonstrated typical features of a chromophobe renal cell carcinoma with Vimentin positive in 25% cases, CD117 positive in 67% cases, CD10 positive in 66% cases. In 21% of cases (n=4) histopathology of a renal oncocytoma has been observed with Vimentin negative staining, CD117 positive reaction in 67% and CD10 negative staining. 6 tumours (32%) had appearance of papillary cell renal cell carcinoma (eosinophilic variant), and 5 tumours (26%) had appearance of clear cell renal cell carcinoma.

Conclusion: In our study, tumours with eosinophilic morphology show overlapping immunoreactivity. The usefulness of Vimentin for differential diagnostics of tumours with eosiniphilic appearance remains controversial. Panel for differential diagnostics of eosinophilic renal cell tumours should be improved by some additional markers.

E-PS-25-009

Histologically confirmed distant metastatic urothelial carcinomas from the urinary bladder: a retrospective review of one institution's 16-year experience

J. Lee[1], Y. Yoo[1], E. Choi[1], H.S. Park[1], S. Park[1], M. Cho[1], S.H. Sung[2]
[1] Department of Pathology, Ewha Womans University College of Medicine, Seoul, Republic of Korea, [2] Department Pathology Ewha Womans University Mokdong Hospital, Republic of Korea

Background & Objectives: Bladder cancer is the seventh most common cancer. 90% cases are urothelial carcinoma. Tumour size, stage, grade, the presence of lymphovascular invasion (LVI) or perineural invasion (PNI) have a significant impact on prognosis, risk of recurrence, and metastasis. Distant metastasis of urothelial carcinoma after radical cystectomy is common, but histologic confirmation for metastatic lesions has not been performed routinely. In this study, we present clinicopathologic characteristics of 15 cases of histologically confirmed metastatic urothelial carcinomas of the urinary bladder.

Methods: Retrospective review of 744 patients who underwent radical cystectomy for primary urothelial carcinomas of the urinary bladder during 16-year period (2002 to 2018) was conducted. Fifteen patients were selected who had histologically confirmed distant metastases. Every HE slides were reviewed and the stage, grade and histologic variants were reclassified according to the Cancer Staging Manual of the AJCC, 8th edition and 2016 WHO/ISUP system, respectively. Clinical data were obtained from medical records.

Results: Fifteen patients (M:F=12:3) were identified. The mean age was 62.1 years. The average interval between the first diagnoses and distant metastases was 36.6 months (range 0-123 months). Average follow-up was 55.9 months (range 5–151 months). The metastases occurred in the lung (n=5), lymph node (n=4), liver (n=2), bone (n=2) colon (n=1), and adrenal gland (n=1), respectively. Histologic variants include discohesive (n=3), squamous (n=2), micropapillary (n=1), sarcomatoid (n=1), and

alphafetoprotein-producing (n=1) features (8/15, 53%). Ten showed LVI or PNI (10/15, 67%).
Conclusion: The frequency of histologic confirmation for distant metastatic lesions is very rare. In this retrospective slide review, histologic variants showing aggressive clinical behaviour and LVI or PNI are frequently observed in the primary urothelial carcinomas of the urinary bladder. Thorough histologic evaluation of the primary urothelial carcinoma of the urinary bladder is needed for predicting clinical outcome.

E-PS-25-010
Sarcomatoid renal cell carcinoma (carcinosarcoma) of the left kidney with extension to the spleen: a case report
E. Koniaris[1], I. Nikolopoulos[1], K. Tsiardis[1], E. Moula[1], G. Kafiri[1]
[1] "Hippokratio" General Hospital of Athens, Greece
Background & Objectives: We report a rare case of high grade sarcomatoid renal cell carcinoma (carcinosarcoma, CS) of the left kidney. To our knowledge, only a limited number of such cases have been described so far. CSs are highly malignant tumours, composed of both mesenchymal and epithelial components. Our case was characterised by its focal extension to the spleen. CSs were dived into three groups: a) collision (coincidentally arise), b) combination (from a pluripotential cell) and c) composition tumours (from the same tissue).
Methods: Our patient admitted to the hospital with hematuria and left flank pain, underwent abdominal CT, which revealed a solid mass on the upper pole of the left kidney measuring 7cm. Decision of a radical resection of the left kidney was taken and we received a surgical specimen measuring 10,5X6,5X6,7 cm and of weight 1640gr, the left adrenal gland m.d. 3cm, and the spleen measuring 10,2X8X3,2cm. On dissection, a whitish/brownish in hue tumour was recognized, measuring 7X5X5cm.
Results: Two elements were recognized, the first a renal cell carcinoma with a papillary/follicular growth pattern and the other sarcomatoid with either spindle or pleomorphic cell growth pattern, with bizarre morphology and neoplastic giant cells , severe pleomorphism and multilobulated nuclei, with abundant cytoplasm. The lesion showed many mitosis, lot of them atypical, and areas of necrosis. The neoplasm was highly invasive affecting the perirenal fat and the spleen. The adrenal gland or the vessels of the hilum were not affected.
Conclusion: CSs have been described in many anatomical sites, but very few have been reported in the kidney. CSs are known to be rapidly progressive tumours, with relapses, with poor outcome and their survival is yet to be determined.

E-PS-25-011
Prostate cancer leads to a change in the composition of tissue carbohydrates
A. Romaniuk[1], A. Piddubnyi[1], M. Lyndin[1], V. Sikora[1], N. Gyryavenko[1], R. Moskalenko[1]
[1]Sumy State University, Medical Institute, Pathology Department, Ukraine

Background & Objectives: The objective of the investigation is following - to study the changes in the composition of the carbohydrate components of prostate cancer tissue (PCa).
Methods: 60 PCa samples (30 samples of PCa with intraluminal inclusions (prostatic calculi and corpora amylacea) and 30 without them) were used for study. 20 samples of benign prostatic hyperplasia tissue were used as control. All samples were examined by hematoxylin-eosin staining and by histochemistry (PAS reaction, alcian blue staining at pH 2.5).
Results: Positive PAS staining was found both in the tissue of the prostate gland and in the secret. Strongest intensity of the signal was found in glands filled by secret. Corpora amylacea and the secret of the PCa glands were PAS-negative. BPH tissue had a weak alcian blue staining intensity. The secret of PCa glands was very positive for alcian blue staining. We indicate the presence of higher amount of acid mucopolysaccharides in the connective tissue component of PCa.
Conclusion: Changes in the carbohydrate composition of the prostate tissue during carcinogenesis were found. It manifests in reduced amount of glycosaminoglycans and increased amount of acid mucopolysaccharides in both the secret of the glands and the tumour tissue.

E-PS-25-012
Primary malignant melanoma of the urinary bladder: a case report
S. Aydin Mungan[1], G. Teoman[2], I. Saygin[2]
[1] Karadeniz Technical University School of Medicine Pathology Department, Turkey, [2] ESP, Turkey

Background & Objectives: A primary malignant melanoma of the genitourinary tract is a rare lesion that accounts for only 0.2% of all melanomas. Rather than being a primary lesion, malignant melanomas of the bladder are more commonly metastatic lesions, which originate from a distant primary site. We report a case of amelanotic malignant melanoma of the bladder, which mimics high grade urothelial carcinoma.
Methods: The surgical specimens were formalin-fixed and paraffin embedded. The sections were stained with routinary H&E. Immunohistochemistry was performed.
Results: A 59-year-old woman was admitted to the department of general surgery for inguinal hernia. İncidentally, 13x12 mm mass in the anteroinferior wall of the bladder was demonstrated in tomography. Transurethral resection of the bladder was performed. The spesmen was collectively 1.5 cm in diameter. In microscopic evaluation, the tumour was predominantly composed of spindle cell infiltration. Immunohistochemical study showed that tumour cells were positive for S-100 and Melanoma triple marker, and negative for GATA 3, desmin and CD 117.
Conclusion: Malignant melanoma in the bladder is very rarely seen. It must be kept in mind that we may witness malignant melanoma, particularly the amelanotic type, in the urinary bladder. Therefore, a careful review of histological features and performing necessary immunohistochemical staining procedures for S-100 and HMB-45 are very important in achieving a correct diagnosis.

E-PS-25-013
Intrarenal adrenal cyst presenting as a renal mass: a case report
S. Aydin Mungan[1], G. Teoman[2], E. Cakir[2]
[1] Karadeniz Technical University School of Medicine Pathology Department, Turkey, [2] ESP, Turkey

Background & Objectives: Ectopic intrarenal adrenal tissue can be found in 6% of general population. The site of its apperance is closely related to the migration of primordial adrenal cells in the course of organogenesis. Occasionally, diagnosis of adrenal rest is difficult. If detected, they often need to be differentiated from neoplastic lesions. We present a patient diagnosed as intrarenal adrenal cyst presenting as a renal mass.
Methods: The surgical specimens were formalin-fixed and paraffin embedded. The sections were stained with routinary H&E. Immunohistochemistry was performed.
Results: A 31-year-old woman suffering from recurrent urinary tract infection.94x85 mm well-defined hyperdense mass in the right kidney was demonstrated in tomography.Laparoscopic cystectomi was performed. Macroscopically; collectively 5 cm diameter tissue samples in

the view of the cyst wall were admitted to our pathology department. Microscopically, the tissues compatible with the cyst wall were normal adrenal cortical tissue. Adrenal cortical cells were positive with inhibin A, Melan A and focal synaptophsin and negative for EMA, Pax 8, CD 10 and RCC.
Conclusion: The present report describes a rare case of adrenal cyst in a background of ectopic intrarenal adrenal tissue, which clinically and radiographically mimicked a renal mass such as clear cell carcinoma and clear cell malignant melanoma.

E-PS-25-014
Paratesticular high grade myxoid liposarcoma: a case report
S. Aydin Mungan[1], A. Cicek Malat[2], I. Saygin[2], G. Ay Haldiz[2]
[1] Karadeniz Technical University School of Medicine Pathology Department, Turkey,
[2] ESP, Turkey

Background & Objectives: Paratesticular sarcomas are rare and account for about 2% of all soft tissue sarcomas. Paratesticular myxoid liposarcomas are considered very rare, accounting for approximately 3.3% of liposarcomas in this anatomic location and is seen in the fourth-fifth decade. We report a rare case of high grade myxoid liposarcoma in a young adult's paratesticular tissue.
Methods: The surgical specimens were formalin-fixed and paraffin embedded. The sections were stained with routinary H&E. Immunohistochemistry was performed.
Results: A 31-year-old man was admitted to the hospital with pain in his chest and hand mass in this area. In the examination, it was learned that he had a mass in the testicular region for 2 years. Orchiectomy and mass excision were performed. Macroscopically mass was necrotic, solid and gelatinous. In microscopic evaluation,the tumour consisted of round cell populations and plexiform vascular structures in myxoid stroma. Immunohistochemical studies showed that tumour cells were positive for Vimentin,CDK4,S-100(focal), and they were negative for MDM2, SMA,Desmin,CD34 and p16.
Conclusion: Myxoid liposarcoms are very rare malignant tumours in paratesticular area. As in our patient, this tumour can be considered benign because it has been present for a long time. In conclusion, if the patient would have been diagnosed earlier, he would have chance to be cured by mass excision. As a result, this rare entity should be kept in mind, which is very rare in young people.

E-PS-25-015
Prostatic adenocarcinoma and lymphoma- common malignancies, but uncommon coexistence
S. Masic[1], M. Ulamec[1,2], T. Regovic Dzombeta[1,2], B. Kruslin[3,4]
[1] Clinical Department of Pathology and Cytology "Ljudevit Jurak", University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia, [2] Department of Pathology, School of Medicine, University of Zagreb, Zagreb, Croatia, [3] Department of Pathology and Cytology, Sestre Milosrdnice University Hospital Center, Croatia, [4] School of Medicine, University of Zagreb, Croatia

Background & Objectives: Prostatic carcinoma is the second most common malignancy in male population. Also, Non- Hodgkin lymphoma is well- known and common clonal lymphoproliferative malignancy. However, association of prostatic adenocarcinoma with incidental finding of lymphoma is rare and occurs from 0.2- 1.2 % of all cases of radical prostatectomy with regional lymphadenectomy. We present 2 cases of this uncommon association.
Methods: Case 1: After being diagnosed with prostatic adenocarcinoma, a 61- year- old male patient underwent radical prostatectomy with regional lymphadenectomy and was confirmed having adenocarcinoma (Gleason score 3+4, pT2N0). In 8 isolated lymph nodes no metastatic spread of adenocarcinoma was found, however, architecture was disfigured.
Case 2: In a 65- year- old male patient, localized prostatic adenocarcinoma (Gleason score 3+4, pT2N0) was diagnosed. In combination with radical prostatectomy, 2 enlarged regional lymph nodes with possible tumoral infiltration were removed.
Results: Case1: H&E stains of the lymph nodes revealed large follicles containing atypical centrocytes with large, irregular nuclei and rare centroblasts. Histological and immunohistochemical analysis concluded follicular lymphoma B cell- immunophenotype, low grade, as additional malignancy. Case 2: On H&E stains of the lymph nodes, no metastases from prostatic carcinoma were observed, but instead, diffuse infiltration of the nodes with small lymphatic cells was found. Histological and immunohistochemical analysis confirmed the diagnosis of small lymphocytic lymphoma B cell- immunophenotype (B-SLL).
Conclusion: Despite the fact that regional lymph nodes in cases of prostatic adenocarcinoma are removed in order to estimate metastatic spread of the tumour, it is important for the pathologist to be alert of other malignancies arising in the lymph nodes to ensure patient's benefit.

E-PS-25-017
Bone metastasis revealing renal carcinoma related to Xp11.2 translocation in an elderly patient
F. Chadi[1], N. Bourhroum[2], N. Mahassini[2]
[1] Pathology Department of Mohamed V Military Teaching Hospital, Rabat, Morocco, [2] Pathology Department of Ibn Sina Universitary Hospital, Rabat, Morocco

Background & Objectives: Renal carcinoma related to the Xp11.2 translocation has long been known in childhood kidney cancer and young adult cancers. It is exceptional in the elderly subject. The aim of this work is to focus on this rare entity.
Methods: We report the case of an 80-year-old patient with psychosis. Who consulted for bone, lumbar and iliac pain. CT shows osteolytic lesions of metastatic appearance, the radiological assessment shows the presence of a renal mass.
Results: Histological and immunohistochemical study performed on the bone biopsy results in bone metastasis of renal carcinoma with Xp11.2 translocation. It was the immunohistochemical study that showed the involvement of a translocation of the locus of the TFE3 gene located in Xp11.2.
Conclusion: Renal carcinoma with translocation Xp11 was uncommon in adults after 50 years, but probably often unknown because of little research. It seemed associated with a poor prognosis. Larger studies must be carried out to optimise its specific management.

E-PS-25-018
New approaches in pathomorphological diagnosis in oncourology
T. Pavlova[1], V. Kulikovskiy[1], I. Pavlov[1]
[1] Belgorod State University

Background & Objectives: The cancer diseases of kidney, bladder and prostate are extremely common, and they demonstrate steady dynamics of growth all over the world.
Methods: Tissues of patients with cancer (55 patients with kidney cancer, 35 patients with bladder cancer, 75 patients with prostate cancer) were researched with additional usage of scanning microscope (SEM) "FE1 Quanta 200 3D" with console for elemental analysis.
Results: The characteristic of depth of tumour's spreading within tissues, quantity of cells, their sizes, contacts between them, and stages of formation of tumour embolus were given. The most representative elements at verification of cancer were oxygen, sodium, magnesium, phosphorus. The content of oxygen was in direct

relation from the number of cells in clone. Initially, it exceeded the amount in tissues without tumour cells, and then it decreased. The content of potassium increased in 1.5-2 times.
Conclusion: Scanning Electron Microscopy makes possible the conduction of express diagnosis for determination of stages of tumour growth, as well it makes premises for further study of pathogenesis of tumour's growth, methods of pathomorphological diagnosis and treatment.

E-PS-25-020
Primary squamous cell carcinoma of renal pelvis without nephrolithiasis history
Z.C. Olgun[1], G. Kir[1], A. Yildirim[2]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, Department of Urology, Turkey

Background & Objectives: Primary squamous cell carcinoma (SCC) of renal pelvis constitues less than 1% of renal neoplasms. There is high association between nephrolithiasis and primary SCC of renal pelvis.
Methods: 71-year-old male patient presented with macrohematuria for last 3 years. The patient had 30 years history of analgesic use and 50 years/pack smoking history. A CT scan revealed a solid mass which was compatible with renal cell carcinoma in upper pole of left kidney. Renal pelvic biopsy was diagnosed as high-grade carcinoma with extensive squamous differentiation. He underwent left radical nefroureterectomy.
Results: On macroscopic examination, there were gray-white solid tumour with ill-defined borders, 14cm in dimension and involving the upper and middle pole of kidney and proximal ureter. Tumour invaded beyond gerota's fascia macroscopically. There were contiguous extention into the ipsilateral adrenal gland microscopically. In spite of extensive sampling (sample per cm) there were no clue of invasive and in-situ urothelial carcinoma. The tumour was composed of SCC purely. Clinically PET-CT scan was unremarkable except left kidney, and the tumour was immunhistochemically negative for CK7, CK20 and GATA-3. For this patient there were no nephrolithiasis history. Tumour reported as moderately differentiated primary SCC of renal pelvis (pT4 N0 Mx L1 V1 Rx).
Conclusion: Primary renal SCC has challenging differential diagnosis, including high grade urothelial carcinoma with extensive squamous differentiation and metastatic SCC. Extensive tumour sampling, immunhistochemistry and clinical evaluation have significance in terms of differential diagnosis.

E-PS-25-021
A rare case of an adult cystic nephroma
I.A. Ungureanu[1], A. Iliesiu[1,2], L.A. Ursache[1], D.I. Enea[1]
[1] University Emergency Hospital Bucharest, Romania, [2] Carol Davila University of Medicine and Pharmacy, Romania

Background & Objectives: Cystic nephroma is a rare benign tumour characterised by multiple cystic lesions of the kidney. It is usually seen in paediatric population under different names and most of the cases are discovered incidentally. We report a case of an adult cystic nephroma with further discussion on microscopic findings, differential diagnosis and prognosis.
Methods: A 41-year-old female was hospitalized for left lumbar pain with no family history of any kidney tumour. Laparoscopic total nephrectomy was performed and the specimen was sent for gross examination. The microscopic analysis was performed on paraffin embedded tissue samples stained with hematoxylin-eosin. Immunohistochemistry was completed for the following markers: ki-67, Vimentin, Desmin, CD10, AE1/AE3, CK20, PAX8, CEA, EMA, TTF-1.
Results: Gross examination revealed an encapsulated multicystic mass in the left kidney. Microscopy showed cystic non-communicating cavities lined by a single layer of flattened cells and Hobnail cells. Degenerative changes were also present. Immunohistochemistry showed positivity for AE1/AE3 in the cystic epithelium and for desmin and vimentin in stromal cells. PAX8, TTF-1, CEA and CK20 were negative. The proliferation rate was 1-2%. Therefore, a renal cell carcinoma was excluded, and the final diagnosis was adult cystic nephroma.
Conclusion: Differential diagnosis between multicystic adult nephroma and renal cell carcinoma is extremely important. Prognosis and treatment differ as multicystic adult nephroma is a benign unharmful condition with an excellent prognosis, whereas renal cell carcinoma has a poor prognosis.

E-PS-25-022
Stromal Tumours of Uncertain Malignant Potential (STUMP)
S. Stifter[1], R. Barbazza[2], A. Cescato[3], G. Dordevic[1], S. Gasparic[4]
[1] Department of Pathology, Clinical Hospital Centre Rijeka, Croatia, [2] University of Trieste, Italy, [3] Laboratori Riuniti Trieste, Italy, [4] County Hospital Pozega, Croatia

Background & Objectives: Prostatic Stromal Tumours of Uncertain Malignant Potential (STUMP) are non-epithelial mesenchymal spindle-cell origin prostate tumours classified as a specialized stromal tumour of the prostate. They represent rare neoplastic proliferative lesions that according to WHO classification together with prostatic stromal sarcoma (SS) comprise up to 0.2% of all malignant prostate tumours.
Methods: We present a case of patient clinically presented with symptoms of acute urinary retention (AUR). Digital rectal examination (DRE) showed the presence of a pronounced prostatic hyperplasia and a transurethral prostatic adenomectomy (TURPA) was performed. The primary pathological evaluation was performed at Laboratorii Uniti, Italy and second opinion at the Department of Pathology, Clinical Hospital Centre Rijeka, Croatia upon an incidental and unexpected diagnosis of prostatic STUMP. It was morphologically discriminated based on following criteria: stromal cellularity, presence of occasional mitotic figures, necrosis, and stromal overgrowth. Thorough immunohistochemistry evaluation and tumour immunophenotyping was performed.
Results: Presented tumour was immunohistochemically positive for CD34, Vimentin, progesterone and cytokeratin negative. It diffusely infiltrated the prostate gland and extend into adjacent tissues. Mitotic count was low, while focally marked cellular atypia was observed throughout the lesion. The capacity of recurrence placed it into the group considered to have frank neoplastic capacity. Therefore the clinical and further therapeutic management should be made keeping in mind the probability of progression into sarcoma.
Conclusion: Currently, due to a small number of cases and consequent follow up the recommended treatment algorithm does not exist. According to some authors and literature data, radical prostatectomy seem to be the treatment of choice, especially in young patient or for extensive recurrent lesion. The presented case stresses out the need for extensive sampling in order to fully appreciate tumour heterogeneity, because STUMP remains diagnosis by exclusion.

E-PS-25-023
LELC of the ureter: a rare finding
M. Bercea[1], A. Dema[1], A. Stetco[1], D. Herman[1]
[1] Emergency Clinical County Hospital "Pius Brinzeu" Timisoara, Romania

Background & Objectives: Lymphoepithelioma is a malignant epithelial tumour of the nasopharynx. Tumours with similar morphological characteristics which are found in other sites of the body are known as lymphoepitelioma-like carcinomas (LELC). Ureteral LELC is an extremely rare tumour, with only 10 cases previously reported.

Methods: A 72-year-old male was admitted in our Urology department with left hydronephrosis due to a periureteral nodular mass, adjacent to the left renal hilum; the clinical suspicion was of lymph node metastasis. Excision of the mass was performed, followed up by nephroureterectomy 2 months later.
Results: The initial mass measured 46/30/27 mm and was greyish-white on the cut surface. Histological sections revealed a nodular, relatively well circumscribed tumour, with focally infiltrative margins in the surrounding fatty tissue, consisting of solid syncytial sheets of neoplastic epithelial cells, accompanied by an abundant lymphoid cell population, suggestive of LELC. The immune profile (positive for cytokeratin 7, cytokeratin 20, GATA 3 and p63) is supportive for the urothelial origin of the tumour.
Conclusion: Considering that ureteral LELC is such a rare entity, recognising this type of tumour is extremely important in order to avoid misdiagnosis with lymph node metastases, lymphomas or inflammatory lesions, due to the completely different therapeutic management required for each of them.

E-PS-25-024
A rare tumour in genitourinary system: presentation 2 cases diagnosed with large cell neuroendocrine carcinoma
Y. Cakir[1], M. Ozsen[1], C. Uzun[1], A.E. Bilici[1]
[1] Erzurum Regional Training and Research Hospital, Turkey

Background & Objectives: Primary neuroendocrine tumours in the genitourinary system (GUS) account for 1-2% of genitourinary malignancies. They have been separated to four groups as small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma (LCNEC), well-differentiated neuroendocrine tumour, paraganglioma in WHO 2016 classification. LCNEC is the most of rare among them.
Methods: Case 1: An 68-year-old man presented with a history of gross hematuria. CT revealed a 4x4 cm mass in the left posterolateral wall of the bladder. PET-CT showed multiple metastatic lesions on lung, liver, bones. Transurethral resection was performed.
Case 2: An 65-year-old man presented with a history of gross hematuria. MR revealed that tumoral lesion that covering at left prostate lobe. Transurethral resection was performed.
Results: The histological examination of the both of tumour were similar. Tumours were composed of large, polygonal cells, with a low nuclear/cytoplasmatic ratio. Coarse chromatin and frequent nucleoli, brisk mitotic activity, necrosis was also present. Tumour cells were positive with synaptophysin, chromogranin, CK 7, focal positive with CK 20 and GATA-3. HMWCK, PSA, TTF-1 were negative.
Conclusion: The differential diagnosis includes metastatic LCNEC from pulmonary or gastrointestinal primary sites, primary large cell lymphomas, high-grade prostatic carcinoma and undifferentiated urothelial carcinomas. LCNEC in the GUS is a very rare, but its diagnosis is important, due to its poor prognosis. As long as it is kept in mind, it is easy to diagnose with the help of immunhistochemistry.

E-PS-25-025
Xp11 translocation renal cell carcinoma with TFE3 gene fusion: two case reports to expand the clinical and morphologic spectrum
L. Barona García[1], B. Ferri Ñíguez[1], D. López Motos[1], M. Biscuola[1], Î Girón Vallejo[1], A. Salazar Nicolas[1], M.I. Oviedo Ramírez[1], M.I. Ortuño Moreno[1], A. Caballero Illanes[1], E. Martínez Barba[1]
[1] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca

Background & Objectives: The Xp11 translocation renal cell carcinoma (Xp11 tRCC) is a recently reconognized subset of renal cell carcinoma (RCC) that belongs to the MiT family translocation RCC. Xp11 tRCC is an infrequent neoplasm that tends to appear at younger ages than other subtypes of RCC. The prognosis of Xp11 tRCC in children is good, unlike when it occurs in adults. We report a case in a child with unusually aggressive behavior and a case in an adult with more indolent course.
Methods: We report two cases of RCC Xp11: a 12-year-old girl with a 14-cm renal mass found incidentally, with lymph node involvement at the time of diagnosis, and a 45-year-old woman with an 8-cm renal mass without extrarenal extension. Histologically, in both cases there were large epithelioid cells with eosinophilic/granular appearance and focal vacuolation arranged in alveolar/nested growth pattern, predominantly. No psammoma bodies were found.
Results: In both cases, the diagnosis was confirmed by diffuse and strong nuclear labeling for TFE3 by immunohistochemistry. A break-apart of the TFE3 genes was identified by fluorescence in situ hybridization analysis in 62% and 72% of the evaluated cells, respectively.
Conclusion: The diagnosis Xp11 tRCC is not possible with the clinical and morphological findings exclusively, being essential to demonstrate the genetic alteration that characterises it: a translocation that takes place in the X chromosome and that produces a rearrangement in the TFE3 gene.

E-PS-25-026
Small Cell Carcinoma (SCC) of urinary bladder: a case report
P. Tziakou[1], G. Galanopoulos[1], M. Nifora[1], A. Zizi-Sermpetzoglou[1]
[1] Department of Pathology, Tzaneio General Hospital of Piraeus, Greece

Background & Objectives: SCC of the urinary bladder is a rare but highly aggressive malignancy. The mean age at the time of diagnosis is 66 years, with a male predominance and a history of smoking.
Methods: We report a case of 65-year-old female who presented with hematuria and pelvic pain. Cystoscopy revealed a 5 cm polypoid mass at the lateral wall and trans urethral removal of bladder tumour (TUR-BT) was performed.
Results: The histopathological exam showed development of a carcinoma, consisting of sheets of small-sized cells, invading the muscularis propria. Coexisting areas of urothelial carcinoma and in situ urothelial carcinoma were also observed.
Immunohistochemical analysis showed that tumour cells express immunopositivity to chromogranin, CD56, CK20(dot-like), CK7 and TTF-1. Chest CT scan was normal, so the diagnosis of a Small Cell Carcinoma was made.
Conclusion: SCC is a rare malignant neuroendocrine neoplasm of the urothelium that accounts for less than 1% of urinary bladder cancers. A significant proportion of patients also present initially with metastatic cancer. It exhibits both epithelial and neuroendocrine differentiation. Jones et al. showed that approximately 40% of patients with SCC of the urinary bladder had positive TTF-1 staining. Therefore, TTF-1 immunostaining cannot reliably distinguish between a lung or urinary bladder primary tumour and the distinction can be made only by knowledge of the clinical setting. The overall prognosis is poor. Cytotoxic chemotherapy plays a major therapeutic role in the treatment of limited-stage and advanced-stage SCC of the urinary bladder, while neoadjuvant therapy appears to improve survival.

E-PS-25-027
Foamy cell angiosarcoma localised to the pelvis: a rare case report
R. Akpinar[1], N. Comunoglu[1], C. Demirdag[2], I. Gurses[1]
[1] Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Pathology, Turkey, [2] Istanbul University-Cerrahpasa, Cerrahpasa Medical Facult, Department of Urology, Turkey

Background & Objectives: Angiosarcoma is a malignant vascular tumour, often seen in the head&neck of the elderly men. There are uncommon variants such as epithelioid, clear cell, granular cell, verrucous, pseudolymphomatous and signet-ring cell types. In addition, a rare form

of angiosarcoma is the so-called foamy cell variant that has been described a few cases localized in the skin.
Methods: A 58-year-old female patient referred with hematuria occasionally. She had received radiotherapy 48 years ago with the diagnosis of dysgerminoma. Transurethral resection (TUR) of the bladder has been reported as angiosarcoma. After that, she has been undergoing total abdominal hysterectomy, unilateral salphingo-oophorectomy and total cystectomy.
Results: TUR specimen was included only mucosa of the bladder that had irregular vascular spaces lined with atypical endothelial cells. All organs of resection specimen were firm and infiltrated by tumour. Microscopically, there were two growth patterns within tumour. Well-formed vessels were just seen in the submucosa of the bladder and solid islands were comprised foamy cells that had large, pale vacuolated cytoplasm and hyperchromatic nucleus. Solid islands were seen all layers of the organs and soft tissue around them. Tumour cells were positive for ERG, CD31 and c-myc while HMB45, MelanA, PanCK, TFE-3, SMA were negative. C-myc was negative with FISH.
Conclusion: Foamy cell angiosarcoma is a very rare entity and described only cutaneous tissue with %10-20 overall survive in five years. This variant has also not been described before in deep soft tissue or any organs in the literature.

E-PS-25-028
Adult-type granulosa cell tumour of the testis: a case report
O. Semerci[1], M.S. Ayazoğlu[1], R. Bedir[1], H. Uzun[2]
[1] Department of Pathology, Recep Tayyip Erdogan University, Medical Faculty, Turkey, [2] Department of Urology, Recep Tayyip Erdogan University, Medical Faculty, Turkey

Background & Objectives: One of the most common causes of infertility in young males are testicular neoplasms. Sex cord-stromal tumours which include granulosa cell tumours are uncommon testicular tumours. Granulosa cell tumours divided into juvenile and adult type. Adult-type granulosa cell tumours are extremely rare and to the best of our knowledge, few than 50 cases have been reported to the date. Here, we present a case of a 30-year old male with testicular mass.
Methods: A 30-year-old male patient presented with complaint of infertility. Physical examination revealed a painless, palpable right testicular mass. Serum AFP and HCG levels were within normal ranges. Azoospermia detected on spermiogram. Scrotal ultrasound revealed a 4.2x3.5 cm heterogeneous solid mass lesion with a marked increase of central and peripheral vascularity in the testicular parenchyma. Both physical examination and radiological findings were consistent with a testicular tumour. A radical orchiectomy performed.
Results: Macroscopically there was an intratesticular solid firm yellow-white tumour measured 3.8x2.6 cm. Histological examination demonstrated nests and cord composed of small cells with scant cytoplasm and coffee bean-like angulated and grooved pale ovoid nuclei which is typical morphology of the of granulosa cells. There is few mitotic figures. There was no pleomorphism and necrose. Immunohistochemically, tumour cells were strongly positive for inhibin and vimentin and showed focal positivity for CAM5.2 while they were negative for PLAP, CD117, CD45, CD138 and S-100. The Ki-67 proliferation index of tumour was low (%1-2). The case was diagnosed as adult-type granulosa cell tumour.
Conclusion: The diagnosis of granulosa cell tumour is mostly based on histopathological features. Our report emphasizes on this uncommon entity which is quite challenging in terms of diagnosis. Although adult-type granular cell tumour is a very uncommon entity in testis compared to ovary, it should be kept in mind when making a differential diagnosis on testicular tumours.

E-PS-25-029
Prostatic schistosomiasis by schistosoma mansoni in a patient with prostatic adenocarcinoma: case report
R. Brandao[1], A.C. Andrade[2], G. Santos[3], R. Souza[2], C. Dias[1], D. Alvarenga[1]
[1] Laboratorio Alvarenga, Governador Valadares, Brazil, [2] Federal University of Juiz de Fora - GV, Governador Valadares, Brazil, [3] Vale do Rio Doce University, Governador Valadares, Brazil

Background & Objectives: Schistosomiasis is an infectious disease endemic in Brazil and of broader global relevance. Despite high rates of schistosomiasis, rates of genitourinary involvement by *Schistosoma mansoni* (*S. mansoni*) are low. We report a case of prostatic schistosomiasis mansoni identified incidentally in a prostatic adenocarcinoma patient's biopsy. Current studies indicate a possible association of schistosomiasis with the development of adenocarcinoma, however, there are few cases present in current literature.
Methods: Patient, 54 years old, Brazilian, was referred for a prostate biopsy, given clinical suspicion of adenocarcinoma. Histopathological analysis confirmed the diagnosis of usual acinar prostatic adenocarcinoma, Gleason 6 (3 + 3) present in two of the six samples. A chronic granulomatous inflammatory process containing giant cells encompassing calcified eggs compatible with *S. mansoni* was additionally observed.
Results: The findings of *S. mansoni* are common in liver and spleen, however, ectopic forms are of special importance in endemic areas, such as Brazil. Studies suggest schistosome egg antigens are capable of inducing oxidative stress and oncogenic phenotypes through inactivation of the p27, a tumour suppressor gene, and genetic hyperactivation of B-CL2, an apoptosis inhibitory protein. Therefore, the interaction of these factors is associated with the development of malignant neoplasm.
Conclusion: The finding of prostatic schistosomiasis by *S. mansoni* concomitant with adenocarcinoma is uncommon, being predominantly incidental in biopsies. More studies are needed to better evidence causal factors that explain the association between prostatic schistosomiasis and adenocarcinoma, with the objective of early diagnosis and better prognosis of patients.

E-PS-25-030
Primary synovial sarcoma of the testis
A. Vlahova[1], M. Genadieva-Yordanova[1]
[1] Aleksandrovska University Hospital, Bulgaria

Background & Objectives: Synovial sarcoma occurs at any age, with peak incidence between 10 and 40 years of age and slight male predominance. Usually arises in the lower limbs but many other primary sites are reported.
Methods: 68 years old man with testicular enlargement. CT found no remarkable changes in the other organs. Surgical excision /orchiectomy / followed by routine biopsy processing was performed with additional immunohistochemistry.
Results: Tumour replaced the normal structures of the testis with no residual tissue left. The mass was 7 cm in diameter with fleshy appearance and small areas of necrosis and hemorrhages. Microscopy revealed proliferation of poorly differentiated round cells with vesicular nuclei and predominantly nested growth pattern, separated by delicate to abundant collagen; one area with hyaline change and vascular invasion. Immunohistochemically tumour cells were negative for Smooth muscle actin, Desmin, Cytokeratin AE1-AE3, MPO, CD34 and positive for CD 99 (perinuclear dot-like reaction), CD 56, bcl-2 and TLE-1, focal positive reaction for Calretinin. No genetic molecular analyses was performed /not available for soft tissue tumours in the country/.
Conclusion: These findings were consistent with poorly differentiated synovial sarcoma of the testis - unusual primary site for this tumour, unfrequently reported in the patient's age group.

E-PS-25-031

Squamous cell carcinoma of the prostate following treatment with an LHRH-agonist: a rare case of transformation of adenocarcinoma of the prostate

R. Ayadi[1], F. Gargouri[1], N. Mansouri[2], B. Laabidi[2], A. Bouziani[1], I. Msakni[1]
[1] Pathology Department, Military Hospital, Tunis, Tunisia. University of Tunis El Manar, Faculty of Medicine of Tunis, Tunisia

Background & Objectives: Squamous cell carcinoma (SCC) of the prostate accounts for less than 1% of all cases of prostate cancers. Squamous differentiation may arise subsequent to endocrine or radiation treatment, but it is very rare. To date, a few cases have been reported in the literature. The aim of this study is to describe a case of SCC of the prostate developing in a patient with adenocarcinoma of the prostate following hormonal therapy.
Methods: We report, a case of a patient who was diagnosed with recurrence adenocarcinoma (ADK) of the prostate at the bladder, treated with an LHRH–agonist and subsequently found to have SCC.
Results: A 71-year–old male presented with lower urinary tract symptoms and a PSA level of 2.7ng/ml. A diagnosis of Gleason 6 adenocarcinoma of the prostate was made on biopsies. Treatment consisted on radical prostatectomy and radiotherapy. 11 years later, he achieved a PSA nadir of 0.59ng/ml with hematuria. The cystoscopy with resection confirmed recurrence tumour at the bladder. The patient began hormonotherapy (Triptoréline+Cyprotérone). 6 months later, he presented again a hematuria. The histopathologic findings identified a SCC with no ADK.
Conclusion: SCC of the prostate is an infrequent and aggressive malignancy. It is associated with a high incidence of recurrence and carries a poor prognosis.

E-PS-25-033

Synchronous seminoma of the right testis and mixed germ cell tumour of the left testis without history of cryptorchidism

G. Kir[1], T. Soylemez[1], A. Yildirim[2]
[1] Istanbul Medeniyet University, Department of Pathology, Turkey, [2] Istanbul Medeniyet University, Department of Urology, Turkey

Background & Objectives: Bilateral testicular germ cell tumours(TGCTs) are uncommon. The incidence of bilateral TGCTs is %1-5 among all TGCTs.
Methods: A 23-year-old male patient, without a history of cryptorchidism, presented with bilateral testicular swelling for a week. The patient underwent bilateral testis-sparing orchiectomy.
Results: On microscopic examination of the right testis, the tumour was arranged in a diffuse, sheet-like pattern interrupted by fibrous septa containing lymphocytes. Tumour cells had uniform, hyperchromatic nuclei and large, clear cytoplasm. The immunoprofile of this tumour showed diffuse positive staining for CD117, PLAP and OCT4. These findings were consistent with seminoma. Intratubular germ cell neoplasia was detected. On microscopic examination of the left testis, the tumour included two different components. The first and the relatively more common component (%90) was composed of cohesive, anaplastic epithelial cells in glandular patterns. The immunoprofile of this component showed diffuse staining for CD30 and OCT4. The other component (%10) comprised generally solid and occasionally duct-like formations. Tumour cells had vesicular nuclei and scanty cytoplasm. This component showed positive staining for glypican3 and AFP, negative staining for OCT4. These findings were consistent with mixed TGCT (%90 embryonal carcinoma and %10 yolk sac tumour).
Conclusion: Bilateral TGCTs can be metachronous or synchronous. Most bilateral TGCTs are seen as metachronously and they are generally seminomas. Risk factors include cryptorchism, family history of TGCT, and most important risk factor is presence of TGCT diagnosis in patient's history.

E-PS-25-034

Metanephric adenoma - case report in a 58-year-old woman

O. Neagu[1], G. Berdan[2], C. Paranici[1], A. Petrescu[2], D. Diaconescu[2], F. Vasilescu[3]
[1] University Emergency Hospital Bucharest, Romania, [2] "Prof. Dr. Th. Burghele" Clinical Hospital, Bucharest, Romania, [3] "Victor Babes" National Institute of Pathology, Bucharest, Romania

Background & Objectives: Metanephric adenomas are rare benign epithelial renal tumours that mainly affect middle-aged women. Less than 200 cases have been reported in the English literature. We report a case of a 58-year-old woman who was admitted with an echographic diagnosis of a right renal tumour.
Methods: We examined the right nephrectomy specimen that presented a well circumscribed but not encapsulated, yellowish-grey, solid tumour of 3/2/1 cm involving the upper pole of the kidney, right beneath the renal capsule.
Results: Histopathological examination revealed tightly packed tubular and glomeruloid-like structures or solid areas composed of round cells with scant cytoplasm and hyperchromatic, overlapping nuclei with inconspicuous nucleoli and mitoses. No capsule or pseudocapsule, lymphovascular emboli or infiltration into the perinephric adipose tissue or renal sinus fat was seen. Immunohistochemistry: WT1 and CD57 showed diffuse positivity in tumour cells, AMACR, CK7, Chromogranin, Synaptophysin, AE1/AE3 and CD10 were negative in tumour cells with a Ki67 of 1-2%.
Conclusion: Clinical and imaging findings are relatively limited so MA is often misdiagnosed as renal cell carcinomas, renal cysts, and other kidney diseases. It is very important to make a histopathological differentiation between MA and other entities that share similar morphological features such as the solid variant of papillary renal cell carcinomas (PRCC) or epithelial-predominant nephroblastoma. Immunohistochemistry is very helpful in distinguishing these entities. Clinical outcome is very good for patients with MA although presence of regional lymph node metastases in a 7-year-old child was reported.

E-PS-25-035

A rare lesion of the kidney: epidermoid cyst

S.Y. Celik[1], O. Ilhan Celik[1], M. Cetinkaya[2], Y. Dere[1], H. Sahin[2]
[1] Mugla Sitki Kocman University, Faculty of Medicine, Department of Pathology, Turkey, [2] Mugla Sitki Kocman University, Faculty of Medicine, Department of Urology, Turkey

Background & Objectives: Epidermoid Cyst of renal pelvis (ECRP) is a rare benign entity. The possible histogenetic mechanisms of ECRP are debated to be the epidermal remnants of Wolffian duct, squamous metaplasia after chronic irritation with urinary stone and traumatic implantation of epithelium during external manipulation.The symptoms depend upon the associated disease or size of the cyst.
Methods: A 55-year-old man was referred to Urology clinic because of severe pain in his right waist and hematuria. The ultrasound examination showed partial enlargement of right kidney, dilatation of pelvicaliceal system, hydronephrosis and staghorn type calculus in pelvicaliceal region affecting upper pole of the kidney. Also, there was a simple cortical cyst with a diameter of 5cm.
Results: Partial nefrectomy preserving the lower pole was performed and the histopathologic diagnoses were chronic pyelonephritis, lipomatosis,

lithiasis and a cystic lesion which had a wall comprising of mature squamous epithelium with granular layer and the lumen full of compact lamellated keratinous material. All of the material was microscopically examined, and no atypia, dysplasia or carcinoma was identified. The cyst was diagnosed as Epidermoid cyst.
Conclusion: Epidermoid cyst is a very common lesion of the skin; however, ECRP is extremely rare. The treatment of it is surgical excision. No recurrence, lymph-node and distant metastasis were considered. The importance of this lesion is that it may mimic malignancy on radiologic examination and thus may lead to unnecessary nephrectomy. Better clinical awareness of the entity and a preoperative biopsy may preserve the kidney.

E-PS-25-036
Sporadic renal hemangioblastoma: report of a case and review of the literature
R. Amorim[1], C. Fleming[2], M. Oliveira[2], L. Brochado Ferreira[1], N. Lamas[1], B. Fernandes[1], J.R. Brandão[1], A. Coelho[2], J.R. Vizcaíno[2]
[1] Centro Hospitalar e Universitario do Porto, Portugal, [2] Anatomical Pathology Service, Department of Pathology, Hospital and University Center of Porto, Porto, Portugal

Background & Objectives: Hemangioblastoma is a rare benign tumour which is known to occur in association with von Hippel-Lindau disease (VHL) in approximately 25% of cases. Occurrence outside the central nervous system (CNS) is exceptionally rare. We describe a case of sporadic renal hemangioblastoma with a review of the literature in order to determine the typical immunological and morphological profile of hemangioblastomas arising outside the CNS.
Methods: A 62-year-old man presented with abdominal pain and an abdominal ultrasound scan revealed a lower pole renal tumour. CT confirmed the tumour and the appearances were highly suspicious for renal cell carcinoma. A partial nephrectomy was performed, and a subcutaneous nodular lesion suspected of metastasis was also resected.
Results: Histologically, the renal tumour was composed of rounded or polygonal cells with pale cytoplasm and small bland central nuclei. Many of these cells have microvacuolated cytoplasm. There are numerous small capillary-sized stromal blood vessels. Immunohistochemically, renal tumour cells showed diffuse expression for inhibin-alpha, S-100 protein, vimentin and only the vascular endothelial cells expressed CD34. A renal hemangioblastoma was diagnosed. The separately excised soft tissue lesion showed characteristic cytoarchitectural features of a spindle cell lipoma, *fat-free* variant.
Conclusion: To the best of our knowledge, 31 cases of primary hemangioblastoma of the kidney have been reported, and little is known about their clinicopathologic features. The differential diagnosis of hemangioblastomas includes several benign and malignant entities. Careful morphological examination and immunohistochemical evaluation are crucial for correct categorization of these neoplasms. Regarding the concomitant subcutaneous lesion, there is no relationship between these tumour types.

E-PS-25-037
Urotelial carcinoma of the bladder with signet ring cells: a case report
A. Ok Atilgan[1], E. Yilmaz Akcay[1]
[1] Baskent University Faculty of Medicine Pathology Departmant, Turkey

Background & Objectives: The presence of numerous signet ring cell without any type of adenocarcinoma cells originating in papillary urothelial carcinoma is very rare.
Methods: We report a case of 58-year-old male with invasive papillary urothelial carcinoma of the urinary bladder with signet ring cell differentiation, without glandular differentiation
Results: The patient presented with intermittent gross hematuria. Cystoscopy revealed a polypoid solid mass. Transurethral resection was performed and subsequent local chemotherapy by Mitomycin followed. The patient underwent cystoscopic resection twice in a year. Histopathological examination revealed classic papillary urothelial carcinoma morphology with lamina propria invasion. Additionally, numerous signet-ring cells were present in some parts. Mucinous or glandular differentiation was not seen any part of the tumour.
Conclusion: Urothelial carcinoma has several variant morphologies. Approximately 20% of urothelial carcinomas contain areas of squamous or glandular differentiation, occasionally signet ring cells may be present. Determining of these variants is very important in the staging, treatment, prognosis.

E-PS-25-038
Primary Seminal Vesicle Adenocarcinoma (PSVA): the critical role of morphology in a rare neoplasm
L.L. Sousa Veras[1], S.R. Morini da Silva[1], N. Soares de Menezes[2,1]
[1] Barretos Cancer Hospital, Brazil, [2] European Society of Pathology, Brazil

Background & Objectives: A 77-year-old male with rectal pain, hematuria and weight loss in the last five years. Biochemical tests: PSA 2.73 ng/ml and CEA 1.59 ng/ml. MRI showed an expansile, lobulated, solid-cystic and haemorrhagic mass (13.8 X 5.7 X 3.2cm), located superiorly to the prostate. The lesion had an intimate contact with the ejaculatory duct. Bladder, rectum and prostate were normal. The mass was resected with lymphadenectomy. This case report intends to present an exceedingly rare neoplasm of the GU tract.
Methods: Grossly, the lesion was regular, lobulated, with smooth surface measuring 10.0 x 8.5 x 3.0cm. The sections demonstrated cystic areas filled with a central and dense brownish or blackened material, with a polypoid appearance and thick white walls. Microscopically, it was an epithelial neoplasm, with a predominant papillary architeture and scattered glandular structures. The cells had round, large, clear nuclei, prominent nucleoli and sparse eosinophilic cytoplasm. Extensive areas of necrosis and desmoplasia were observed and two lymph nodes were positive.
Results: Morphological findings associated with the immunohistochemical profile (positivity for CK7, CA-125 and negativity for CK20, PSA, GATA 3, RCC, Thyroglobulin, Prostein, p53, WT1 and SALL4), clinical and radiological history and exclusion of neoplasms in other sites such as bladder, prostate and rectum confirm the diagnosis of PSVA. PSVA is a rare tumour, with about 60 cases reported to date. The etiology may be related to testosterone stimulation. The main differential diagnosis is secondary infiltration of the seminal vesicle.
Conclusion: According to Dalgaard e Giertson (1956) the required criteria for the diagnosis of PSVA are: the tumour must be a carcinoma located exclusively or mainly in the seminal vesicle; the exclusion of another primary carcinoma is mandatory and the tumour must be preferentially a papillary adenocarcinoma. The prognosis is poor with survival usually less than 3 years.
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E-PS-25-039
Histochemical techniques applied in freezing cuts during intraoperative biopsies in a renal transplantation
A. Salazar Nicolas[1], M.I. Ortuño Moreno[1], L. Barona Garcia[1], A. Caballero Illanes[1], N. Villa Lorente[2], M.A. Menárguez Arnaldos[3], M.D. Perez Caparros[4], G. Ruiz Garcia[1], M.I. Oviedo Ramirez[5], E. Martinez Barba[1]

[1] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [2] Servicio de Anestesia y Reanimación, Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [3] Servicio de Urgencias. Hospital Clínico Universitario Virgen de la Arrixaca, Spain, [4] Servicio de Ginecología y Obstetricia, Hospital de Mèrida, Spain, [5] Servicio de Anatomía Patológica, Hospital Clínico Universitario Virgen de la Arrixaca, Spain

Background & Objectives: The introduction of more extended clinical criteria when considering the suitability of a donor has led to an increase in the number of transplants, especially kidney transplants, and this implies a rise in intraoperative biopsies performed in the pathology department. Given this growth in transplants from "not ideal donors" makes the histological study should be more precise, optimal and objective.
Methods: 18 cases about intraoperative renal transplant biopsy between the months of December and January of 2018-2019 were studied. The samples were stained with Hematoxylin-Eosin and Chromotrope Aniline Blue was applied to enhance fibrosis. The results obtained in techniques were compared each other.
Results: In the study about glomerular fibrosis comparing Hematoxylin-Eosin and Chromotrope Aniline Blue stainings, 5 cases showed a greater lesion in their study with Aniline (27.7%), 3 cases with a diagnosis of lesion of lesser degree (22.3%) and 11 showed similar lesions between HE and Aniline (50%). Regarding the study about interstitial fibrosis, 5 cases presented a greater lesion with the Sudan technique (27.8%), 2 cases with lesion of lesser degree (11.1%) and 11 showed a similar lesion (61.1). %).
Conclusion: The introduction of Chromotrope Aniline Blue techniques in the intraoperative study of liver transplantation allows a more objective and sensitive study to detect possible organic alterations. These specific techniques enhance the fibrous lesions that we must study and their application does not significantly increase the time of histological study. In case of diagnostic doubt these techniques can offer a more reliable diagnosis.

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E-PS-25-040
Biphasic Squamoid Papillary Renal Cell Carcinoma with metastatic involvement - case report of a rare entity and literature review
S. Lopes Petronilho[1], M. Cantante[1], J. Vieira[2], R. Vieira[1], A. Rodrigues[1]
[1] Pathology Department, IPO-Porto, Portugal, [2] Genetics Department, IPO-Porto, Portugal

Background & Objectives: Biphasic Squamoid Papillary Renal Cell Carcinoma (BSPRCC), is a recently described entity, thought to represent a rare variant of Papillary Renal Cell Carcinoma(PRCC). BSPRCC is morphologically characterised by 2 populations arranged in organoid structures, containing small, low-grade cells lining alveolar-like structures, and central compact nests of larger squamoid-cells with vesicular nuclei and ample cytoplasm. Since the 1st report (2013) only ~100 cases were described. We report a BSPRCC case with classical PRCC areas and metastatic spread.
Methods: 62-year-old female, with incidentally found 5cm solid/expansile nodule associated with hilum adenomegalies, who underwent radical nephrectomy and lymphadenectomy. Macroscopically, we found an intraparenchymal expansile, pseudocapsulated, solid nodule(size:4,5x4,2x3,5cm), with heterogeneous, firm/whitish-yellow and tan/friable cut surface and extensive hemorrhage and necrosis. A tumour nodule was identified in the lymphadenectomy specimen.
Results: The tumour nodule comprised two distinct areas. The predominant (90%) was characteristic of classical-PRCC, composed of papillae covered by cells with pale cytoplasm and predominantly low-grade nuclei, extensive hemorrhage and necrotic foci. The remaining (10%) had typical dual BSPRCC morphology, with prominent cytophagocytosis/emperipolesis. We observed diffuse positivity for Cam5.2/CK7/CK903/Vimentin/Racemase, focal positivity for CD15/CD10 and negativity for CK20/CD117/HMB45/Melan-A. Cyclin-D1 was positive exclusively in squamoid areas. Gains of chromosomes 7/17 were detected. The hilar metastasis exhibited solid/papillary growth pattern.
Conclusion: Recognizing BSPRCC as a distinct variant of PRCC is important, as published data suggest it may present aggressive behaviour and metastatic potential. However, given the low number of reported cases, the prognosis is still hard to predict. In our case, 11-months after surgery the patient is alive with no evidence of disease.

E-PS-25-041
Lymphoepithelioma-like carcinoma of the bladder: a case report
O. Semerci[1], O. Okcu[1], M.Y. Akar[1]
[1] Recep Tayyip Erdogan University, Department of Pathology, Turkey

Background & Objectives: Lymphoepithelioma-like variant of the bladder carcinoma is an infrequent variant of urothelial carcinoma that microscopically mimics lymphoepithelioma of the nasopharynx. It has been recently described entity and it is recognized in the WHO classification as a variant of urothelial carcinoma. Most patients are elderly male. We aimed to present this rare case with microscopic and immunohistochemical features
Methods: We report a case of a 72-year old male who presented to our hospital with hematuria. The clinical impression was consistent with a bladder tumour. Transurethral-resection of the bladder tumour was performed.
Results: In microscopic examination tumoral infiltration composed of cords and sheets of undifferentiated appearing cells with large nuclei and prominent nucleoli observed in the lamina propria. Cytoplasmic borders were indistinct giving the tumour syncytial appearance. A prominent and dense mix type inflammatory cell was present at the background. There was an accompanying focal non-invasive urothelial carcinom at neighboring epithelium. The invasive component of the tumour was showing purely lymphoepithelioma-like morphology. Immunohistochemically the tumour cells were strongly positive for panCK, CK7 and weakly positive for GATA3 and negative for p63. Inflammatory cells in the background were positive for CD3, CD20 and CD68. Based on the morphological examination and immunohistochemical features the diagnosis of lymphoepithelioma-like urothelial carcinoma was made. The patient received intravesical BCG treatment. After a 1 month follow up a re-transurethral resection performed and no residual tumour was detected in the specimen.
Conclusion: Lymphoepithelioma-like variant of the urothelial carcinoma is a rare tumour. A proper morphological and immunohistochemical evaluation is needed to avoid diagnostic pitfalls because histological features may mimic other tumours such as poorly differentiated urothelial carcinoma, poorly differentiated squamous cell carcinoma or lymphoma. Some reports confirmed favorable prognosis when it is pure. Our case is also responded well to chemotherapy treatment. We believe this responsiveness is related to lymphoepithelioma-like morphology of the invasive tumour. It is crucial to report whether these cases are pure or have concurrent other carcinomas. The patient does well and has no recurrence after 5 months of initial diagnosis.

E-PS-25-042
Succinate-dehydrogenase deficient renal cell carcinoma: a case study
D. Koumoundourou[1], V. Tzelepi[1], D. Mpantouna[1], P. Ravazoula[1], M. Melachrinou[1]
[1] University Hospital of Patras, Greece

Background & Objectives: Succinate-dehydrogonase is an enzyme of the mitochondrial complex whose germ line mutations are related with familial pheochromocytomas/paragangliomas, GISTs,

and less frequently, renal cell carcinomas with distinct histological and immunohistochemical features. We present a case of a renal cell carcinoma correlating with succinate-dehydrogonase deficiency.
Methods: A 49 years-old woman referred to our hospital because of urine bleeding and left vague flank pain. CT revealed a left kidney mass measuring 17cm in greatest diameter. Macroscopically the kidney was totally replaced by a well circumscribed mass 16 cm in greatest diameter, with pushing margins, a tan brown surface and soft consistency. The mass was confined to the kidney with no macroscopic invasion of the renal fat or sinuses. Microscopically the neoplasm was composed of tubules lined by low cuboidal cells with smooth nuclear contours and abundant eosinophilic cytoplasm with eosinophilic vacuoles. Another distinctive feature was the presence of entrapped benign tubules as well as small numbers of endotumoral mast cells.
Results: Immunohistochemically the tumour cells expressed EMA, P504S and PAX-8 with loss of Immunohistochemical staining for SDH in tumour cells, and positive expression in the adjacent renal parenchyma. Based on the microscopy and the immunohistochemical findings the diagnosis was that of a succinate-dehydrogonase-deficient renal cell carcinoma
Conclusion: Succinate-dehydrogonase-deficient renal cell carcinomas are rare neoplasms with indolent biologic behavior. Their molecular abnormality is double hit inactivation of one of the SDH genes. Genetic testing and long term follow up for early detection of other succinate-dehydrogonase-related noplasms are always necessary (even in patients with absence of germ-line mutations).

E-PS-25-044
Thyroid-like follicular carcinoma of the kidney: a case report
F. Kaya[1], H. Kacar[1], M.F. Acikalin[1], B. Baseskioglu[2]
[1] Eskisehir Osmangazi University, Department of Pathology, Turkey, [2] Eskisehir Osmangazi University, Faculty of Medicine, Department of Urology, Turkey

Background & Objectives: Thyroid-like follicular carcinoma of the kidney is a rare variant of renal cell carcinoma with a morphology that closely resembles well-differentiated thyroid follicular neoplasms. It is a newly emerging histological variant of renal cell carcinoma, but it is not included in the 2016 World Health Organization classification of renal tumours. Only 42 cases reported in the literature to date.
Methods: A 26 year-old-woman presented with a complaint of pain on right side, under back ribs. Physical examination was normal. The computed tomography (CT) scan showed a 38x37 mm, well-circumscribed lesion in the mid portion of her right kidney. A partial nephrectomy was performed.
Results: Macroscopically, the partial nephrectomy specimen demonstrated a 39x38x34 mm, well-circumscribed, gray-yellow, gray-brown lesion. Microscopically, the tumour was characterised by a notable follicular architecture composed of macrofollicles and microfollicles filled with colloid-like material. The follicles were lined by cuboidal cells with round to ovoid nuclei. Staining for thyroid transcription factor (TTF-1) and thyroglobulin were both negative.
Conclusion: Because this tumour shows similar histology to thyroid follicular carcinoma, it is very important to exclude metastatic carcinoma from the thyroid. A correct histopathologic diagnosis is crucial for appropriate treatment.

E-PS-25-045
Granulomatous inflammation after intravesical BCG immunotherapy for bladder cancer
A. Chikha[1], N. Ibisevic[1], F. Skenderi[1], S. Bajramovic[2]
[1] University Clinical Center of Sarajevo, Pathology Department, Bosnia and Herzegovina, [2] University Clinical Center of Sarajevo, Urology Clinic, Bosnia and Herzegovina

Background & Objectives: Bladder cancer is common cancer worldwide, with three to four times higher incidence in males than females. Intravesical administration of bacillus Calmette-Guérin (BCG) immunotherapy, after transurethral tumour resection, is considered the gold standard in treatment for superficial high-grade non–muscle-invasive bladder cancer
Methods: We report two cases of post –treatment BCG complications that presented as granulomatous orchi-epidydimitis, and granulomatous nephritis.
Results: A 69-years old male previously treated with intravesical BCG for superficial high grade bladder cancer presented with disuria, scrotal edema and pain in groins. Ultrasound revealed a hypoechoic, solid mass. Patient underwent left orchidectomy. Microscopic examination revealed a necrotizing granulomatous inflammation. An 79 years old man treated with BCG for high grade bladder cancer presented asymptomatic for regular follow up after completion of BCG treatment. Ultrasound and CT revealed moth-bite like changes in the right kidney, not seen on previous imaging evaluations. Patient was subjected to core needle biopsy and, at the same time, urin sample was obtained for mycobacterial culture on Löwenstein-Jensen medium, which resulted negative. Histopathological analysis showed necrotizing granulomatous inflammation.
Conclusion: The etiology of granulomatous inflammation is broad and expands over many etiologies including infectious, autoimmune, toxic, allergic, and neoplastic. Despite its weakened state, BCG has the potential to cause local and systemic complications in treated patients. Knowledge of prior BCG therapy and awareness of the potential related complications are essential for making the correct diagnosis prospectively and guiding appropriate treatment without delay.

E-PS-25-046
Granulomatous vasculitis in testis associated with seminoma
D. Pouloudi[1], A.C. Lazaris[1], G. Liapis[1]
[1] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background & Objectives: Granulomatous reaction in testicular seminoma is a rather common finding encountered in up to 50% of the cases. In contrast, granulomatous vasculitis as accompanying paraneoplastic lesion is exceptionally rare. Herein, we report a case of granulomatous testicular vasculitis in association with seminoma.
Methods: A 43-year-old man was admitted to the Hospital due to a palpable painless mass in the right scrotum. Imaging examination confirmed the presence of a testicular tumour and a radical right orchiectomy was performed.
Results: Cross sections revealed a whitish tumour measuring 4.5 cm in largest diameter. Histologically, the tumour was a classic seminoma accompanied by very dense lymphoid infiltrates, as well as by granuloma formations. In addition, a limited number of small and medium sized veins and lymph vessels, particularly in the hilum of testis, showed granulomas within the wall, partially protruding into the lumens, while a larger number of veins showed focal or diffuse lymphocytic venulitis. No ANCAs were detected in the serum, nor other systemic manifestations of vasculitis were observed.
Conclusion: We report a rare case of granulomatous vasculitis of the test is associated with seminoma. The absence of underlying immunological disorder suggestive of systemic or organ-limited vasculitis favours tumour antigens-related granulomatous reaction in vessel walls. Our findings expand the spectrum of granulomatous vasculitis.

E-PS-25-047
Clear cell renal cell carcinoma with a distinct hemangioblastoma-like component: case report and review of literature

N. Castrejon[1], A. Nadal[2], I. Archilla[3], L. Izquierdo[4], A. Sierra[4], L. Buñesch[5], M. Sole[6], S. Diaz-Mercedes[1]
[1] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic of Barcelona, Spain, [2] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic de Barcelona, IDIBAPS, Barcelona Spain, [3] Pathology Department, Hospital Clinic. University of Barcelona, Spain, [4] Clinical Institute of Nephrology and Urology (ICNU), Hospital Clinic de Barcelona, Spain, [5] Radiology Department (CDI), Hospital Clinic de Barcelona, Spain, [6] Pathology Department, Biomedical Diagnostic Center (CDB), Hospital Clinic de Barcelona, Spain

Background & Objectives: Diagnosis of renal cell carcinoma is challenging in cases with uncharacteristic histology. Recently it has been described clear cell renal cell carcinomas (CcRCC) with an hemangioblastoma-like morphology. Few cases have been reported showing an unusual immunoprofile and an unknown prognostic. Our aim is to describe a case of a metastatic CcRCC with hemangioblastoma-like features.
Methods: 73 years-old man with a solitary kidney, transplanted due to chronic renal insufficiency. After 22 years he developed a tumour in the transplanted kidney. Biopsy was performed with the diagnosis of CcRCC, low nuclear grade. Two years follow-up revealed a second tumour in the native kidney. He underwent nephrectomy and transplantectomy. Tumours were analysed histologically and immunohistochemically. Genotyping Polymerase Chain Reaction (PCR) was performed.
Results: Microscopically, tumours were constituted by sheets, trabeculae and dilated tubules of low nuclear grade clear cells combined with areas of cells with scarce cytoplasm in a rich capillary network. The CcRCC cells were positive for CKAE1/AE3, CD10, PAX-8 and Vimentin, whereas the hemangioblastoma-like component expressed □-inhibin, NSE and S-100. CD34 underscored the rich vascular structures. Genotype of both tumours showed the presence of donor alleles in native kidney tumour, demonstrating that the neoplastic cells corresponded to the donor. Last control showed no recurrence.
Conclusion: CcRCC with hemangioblastoma-like features is a difficult diagnosis for the heterogeneous morphology and immunophenotype. Clinical relevance and prognostic implications are unknown. We present a case with an aggressive behavior and metastasis to the native kidney. Further studies will be necessary to understand its biology.

E-PS-25-048
Multilocular cystic renal cell neoplasm of low malignant potential: a study of four cases
M. Mellouli[1], M. Zghal[1], I. Bahri[1], M. Walha[1], T. Sallemi Boudawara[1], L. Ayadi[1], N. Gouiaa[1]
[1] Department of Pathology, Habib Bourguiba Hospital, Sfax, Tunisia

Background & Objectives: Multilocular cystic renal cell carcinoma (MCRCC) is a distinct subtype of clear cell renal cell carcinoma (RCC). It represents a rare variant of RCC (1 à 4 %). The aim of this work is to analyse the clinicopathological, therapeutic and prognostic aspects of this rare histological variant through 4 observations.
Methods: Four cases were identified as MCRCC at our institution from 2008 to 2017. Their clinical characteristics, treatment, pathological features and outcomes were retrospectively reviewed. All cases met the WHO criteria defining MCRCC.
Results: The patients included 2 women and 2 men. The ages ranged from 45 to 65 years (median age was 54). All tumours were solitary and unilateral. Macroscopically, tumour size ranged from 3 to 5 cm. It consisted of non-communicating cysts separated by thin septa. Solid areas or substantially discernible mural nodules were absent in all cases. Histologically, single layer of cubical and flattened epithelial tumour cells were lined in the cysts; the nuclei were small and grade nuclear was low (grade1 in 3 cases). Necrosis and mitosis were absent. Fibrous septa contained clusters of clear cells similar to those of the border. Immunohistochemically, the tumour cells were positive for keratin and negative for CD 68 in 2 cases. The treatment was surgical in all cases. No tumour recurrence or metastasis was found in a mean follow up period of 18 months.
Conclusion: The MCRCC is a rare variant of RCC. It is a tumour with low malignancy potential and excellent prognosis.

E-PS-25-049
Pagetoid spread of urothelial carcinoma to the glans penis. A case report
A. Simoulis[1], A. Almorched[1]
[1] Pathology department, Skåne University Hospital, Malmö, Sweden

Background & Objectives: We report the case of the pagetoid spread of urothelial carcinoma to the glans penis, eleven years after the initial presentation of the urothelial cancer and five years after the cystectomy. A few cases of the same entity, usually under the term extramammary Paget's disease secondary to urothelial cancer, is being described in the literature.
Methods: A 58 years old gentleman presented with an erythematous lesion around the urinary meatus. A biopsy performed. Microscopically a pagetoid distribution of atypical cells in the squamous epithelium was seen. A minimal panel of stains was applied. The tumour cells were positive for CK5D3 and CK7 and negative for Melan A, S100, p16, and CEA. The diagnosis of Extramammary Paget's disease proposed.
Results: The case discussed at the national conference for Penile Cancer. The possibility of a pagetoid spread of urothelial carcinoma emerged. Supplementary immunostains used. The tumour cells were positive to CK20, GATA3 and Uroplakin II. This phenotype supports the urothelial origin of this cancer. Therefore, the diagnosis revised to Extramammary Paget's disease secondary to urothelial cancer. New biopsies confirmed the presence of urothelial CIS in the urethra.
Conclusion: Pathologists must be aware of the possibility of this entity in penile material, especially when there is a history of urothelial malignancy in the background. A panel of immunostains, which include GATA3 and Uroplakin II, can help to make the differential diagnosis between a true Extramammary Paget's disease and a pagetoid spread of urothelial carcinoma.

E-PS-25-050
Glomerulations, perineural invasion and muscinous fibroplasia. How common are they as diagnostic criteria in prostatic adenocarcinoma? A morphologic study of 30 cases on prostatic core biopsies
K. Adoke[1], S. Ahmed[2], Y. Iliyasu[2], F. Mohammed[2]
[1] Federal Medical Centre Birnin Kebbi, Nigeria, [2] Ahmadu Bello University Zaria Nigeria, Nigeria

Background & Objectives: Diagnosis of prostate cancer is based on microscopic criteria. It relies on the combination of architectural and cytological features. Cytomorphological features like lack of basal cells, prominent nucleoli and infiltrative growth pattern are useful criteria for diagnosis of prostatic adenocarcinoma. Pathognomonic features of prostatic cancer are glomerulations, perineural invasion and mucinous fibroplasia. We review these three later features in 30 prostatic needle biopsies.
Methods: Thirty cases of prostatic cancer were diagnosed over a three year period (2015-2017).Information were extracted from the patients case notes. Paraffin embedded tissue blocks were retrieved from the departmental archives. Fresh H&E slides were prepared. Cytomorphological features were viewed under the microscope using low(x40) and high(x100) magnifications. Data was analysed using SPSS version 20.

Results: A total of 30 patients were seen during the study period. The mean age was 67±11.7 years. There PSA ranges from 24-115ng/dl. On cytomorphology, 18(60%) cases had perineural invasion, 6(20%) had glomerulation while, 1(3.3%) had mucinous fibroplasias. Five (16.7%) had none of these features, although absent of basal cells, necrosis and infiltrative growth pattern were demonstrated.
Conclusion: Glomerulation and mucinous fibroplasias are infrequent diagnostic findings on needle biopsies.

E-PS-25-051
Renal cell carcinoma with papillary architecture. Analysis of 8 cases
E. Fuentes Vaamonde[1], A. Sanz Zorrilla[1], M.T. González Serrano[1], F. Leiva-Cepas[1], M.d.M. Moreno Rodríguez[1]
[1] University Hospital "Reina Sofía", Spain

Background & Objectives: The second most common type of renal carcinoma is papillary carcinoma (it is the tumour that is most frequently composed of papillae). However, the papillary architecture can be shown in many other entities. So a wide differential diagnosis should be made, since the biological behavior and its treatment can differ from one another.
Methods: Eight renal cell carcinomas with papillary architecture were selected. Tumours were evaluated morphologically, immuno histochemically and the differential diagnosis problems were studied. Although they did not compose all the types of neoplasms that can show papillary pattern, they were the most frequently found in the histopathological study.
Results: One case of clear cell carcinoma, 3 of type 2 papillary carcinomas, one clear cell papillary renal cell carcinoma, two type 1 papillary carcinomas, one mixed clear cell carcinoma and papillary type 1 carcinoma and one carcinoid tumour are presented. Diagnostic problems were solved with adequate sampling, immunohistochemistry and, in one case, with FISH.
Conclusion: Not all tumours with a papillary pattern correspond to a renal papillary carcinoma. A thorough evaluation of all the cytological and architectural characteristics of these tumours is required, not only papillary pattern and of other associated patterns, but also the stromal component. Up to about thirty neoplasms with papillary features are described, differentiated by their behavior and morphology. Complementary tests, such as immunohistochemistry, FISH and others, are necessary for its classification.

E-PS-25-052
Pure prostatic ductal adenocarcinoma mimicking a papillary urothelial carcinoma. A case report
A. Simoulis[1]
[1] Pathology department, Skåne University Hospital, Malmö, Sweden

Background & Objectives: Ductal adenocarcinoma can be a mimicker of the papillary urothelial carcinoma, both for urologists and pathologists. The right diagnosis is critical as the two types of cancer have a different therapeutic approach.
Methods: We discuss all the cases of invasive urothelial cancer of the Skåne region at the interdisciplinary cancer conference of our hospital. Therefore, we reviewed the glasses from the transurethral resection specimens of an 85-year-old gentleman. The initial diagnosis was benign prostatic tissue and papillary urothelial cancer of the prostatic urethra with invasion in lamina propria, pT1.
Results: We reviewed eleven HE slides from the transurethral resection material. Microscopically we saw cancer with the formation of papillary fronds with pseudostratified epithelium. The tumour cells were tall and columnar, with prominent nucleoli and many mitotic figures. We revised the initial diagnosis to prostatic ductal adenocarcinoma (papillary form). The immunohistochemical stains confirmed our diagnosis. Tumour cells were positive to NKX3.1 and AMACR and negative to GATA3, p63, CK 34 beta E12. We did not find acinar prostate adenocarcinoma at all.
Conclusion: Pure prostatic ductal adenocarcinoma is an uncommon form of prostatic carcinoma (0,2 – 0,4 % of prostate cancers). Pathologists and urologists must be aware of this rare type of malignancy when they are dealing with papillary neoplasms of the prostatic urethra.
Immunostains can help to support the diagnosis.

E-PS-25-053
Testicular neuroendocrine tumour: case report
H. Ozkayalar[1], F. Dirilenoğlu[1], A.U. Onder[1], G. Mocan[1]
[1] Near East University Faculty of Medicine, Cyprus

Background & Objectives: Neuroendocrine tumours (NETs) consist of a spectrum of malignancies that can arise from neuroendocrine cells throughout the body. Among these tumours, 85% occur in the gastrointestinal tract, mostly in the ileum and appendix. Testicular neuroendocrine tumours (TNET) account for less than 1% of all testicular neoplasms. TNET appears to be a young man's cancer and they are associated with an excellent prognosis
Methods: A 42-year-old man had an asymptomatic, enlarged scrotum on the right side. Ultrasonography revealed a solid tumour, measuring 2,7x2,1x2,2cm in the right testis. Beta-human chorionic gonadotropin and alpha-feto protein lactate dehydrogenase levels were normal. Right radical orchidectomy was performed
Results: Grossly, the orchiectomy specimen showed a 2,7 cm well circumscribed, yellow-tan solid mass. Histologically, the tumour cells which were arranged in insular, and trabecular patterns in a background of fibrous stroma; had abundant granular, eosinophilic cytoplasm and round to oval nuclei with a “salt and pepper” chromatin pattern. Immunostains for neuroendocrine markers (synaptophysin, and CD56) were strongly positive. Teratomatous elements or other germ cell components were not identified. A diagnosis of TNET was confirmed.
Conclusion: Primary TNETs are rare. They represent less than 1% of all testicular neoplasms. TNET appears to be a young age patients but may occur in children as in the elderly. Most cases primary testicular neuroendocrine tumours have an excellent prognosis following orchiectomy

E-PS-25-054
Collision tumour of squamous cell carcinoma and primary malignant melanoma of the glans penis: a case report
A. Simoulis[1]
[1] Pathology department, Skåne University Hospital, Malmö, Sweden

Background & Objectives: The most common penile malignancy is squamous cell cancer while the primary penile melanoma is a rare tumour. About 220 cases of penile melanoma are described in the literature.
We present an unusual case of a collision tumour of primary melanoma of glans penis and penile squamous cell carcinoma.
Methods: A 53-year-old gentleman appeared at the local hospital emergency department because of very painful back pain. The clinical examination revealed a suspect penile cancer. Computed tomography showed numerous metastases. The patient was remitted to our hospital and our urologists performed a partial penectomy. On gross examination, we observed that almost the whole glans penis was darkly pigmented. We were able to recognize a few whitish areas and some areas of ulceration.
Results: During the histological examination, we saw an extensive invasion of malign melanoma and an area of a well-differentiated invasive squamous cell cancer. The malign melanoma destroyed areas of squamous cell cancer. In addition, we observed a lentiginous proliferation of atypical melanocytes within the basal layer of squamous cell cancer and at the remaining intact mucosa. The melanocytic component showed a

varying degree of pigmentation, with polygonal epithelial-like cells and spindle-shaped cells, growing in nests or densely packed aggregates.
Conclusion: Primary penile melanoma is a rare type of penile malignancy. We present a collision of malign melanoma with squamous cell cancer. The unusual characteristics of this case are that the malign melanoma actively destroyed the squamous cell cancer and that we recognized a lentiginous proliferation of moderately atypical melanocytes in the squamous cell cancer nests and the remaining squamous mucosa.

E-PS-25-055
Extramedullary plasmacytoma of the bladder: a case report
A. Simoulis[1], M. Ehinger[2]
[1] Pathology department, Skåne University Hospital, Malmö, Sweden, [2] Department of Clinical Sciences, Pathology, Skane University Hospital, Lund University, Lund, Sweden

Background & Objectives: A few cases of extramedullary plasmacytoma with involvement of the urinary bladder have been described in the literature. We present a case of this rare entity. A 52 years old man was under medical investigation due to a feeling of pain and pressure in the bladder area. Urologists performed a cystoscopy and they found two areas of abnormal but not papillary urothelium, 4 cm and 0,7 cm in diameter. The initial clinical diagnosis was cystitis. Biopsies were taken from these areas.
Methods: Microscopically examination revealed a reactive but benign urothelium. The lamina propria was rich in immune cells in a lichenoid–like pattern. Almost all of this population consisted of plasma cells that were CD138. The cytoplasmic kappa/lambda ratio of CD138-positive plasma cells showed kappa monoclonality.
Results: Monoclonal gene rearrangements of IGH and IGK were also detected with PCR Hematological work-up and bone marrow examination showed no signs of plasma cell neoplasia. The final diagnosis was extramedullary plasmacytoma with involvement of the urinary bladder. The patient follows the appropriate therapy.
Conclusion: We report a case of a rare entity. The role of the pathologist is crucial for the diagnosis because an extramedullary plasmacytoma in the bladder can be clinically interpreted as cystitis.

E-PS-25-056
Primary renal pelvis mucinous adenocarcinoma
T. Muzashvili[1], G. Burkadze[1]
[1] Tbilisi State Medical University, Georgia

Background & Objectives: Oral Squamous Cell Carcinoma (OSCC) showed a significant risk to develop local recurrences or second primary tumours during follow-up. Recently, we developed a non-invasive assay based on oral brushing and DNA methylation analysis to early detect OSCC. In the present study using this assay, we investigated the adjacent area of surgical resection in a series of OSCC during follow-up for prognostic purposes.
Methods: 42 consecutive OSCC patients were sampled during routine follow-up after 6 months from surgical treatment, brushing the regenerative mucosa covering the region that underwent the surgical OSCC excision. DNA methylation level of *ZAP70, GP1BB, KIF1A, ITGA4, LINC00599, MIR193, MIR296, TERT, LRRTM1, NTM, EPHX3, FLI1* and *PARP15* was evaluated by quantitative Bisulfite-NGS. After calculating a score by Linear-Discriminant-Analysis, the samples were dichotomized using a predefined threshold previously developed for early diagnosis. One-Way-ANOVA and Kaplan-Meier curves served to evaluate any significant difference between patients who experienced a second neoplastic manifestation and the group who did not.
Results: 6/42 (14,3%) patients developed a second neoplastic manifestation during follow-up period (mean follow-up: 14.3 months), of which 5 showed a positive methylation score. Additional 11 patients exceeded the threshold but up to date they have not experienced any second manifestation. Among the remaining 26 negatives, only one developed a recurrence. A positive score correlated with a worse locoregional control of disease ($p<0.05$).
Conclusion: The DNA methylation analysis of 13 genes can be a useful non-invasive method to identify surgically treated OSCC patients at risk of developing a second neoplasia.

E-PS-25-057
Low-grade oncocytic kidney tumour with papillary features
N.E. Alkanat[1], K. Kosemehmetoglu[1]
[1] Hacettepe University Faculty of Medicine, Department of Pathology, Turkey

Background & Objectives: "Oncocytic renal tumour" definition embraces various entities such as renal oncocytoma, chromophobe renal cell carcinoma (RCC), type 2 papillary RCC (including oncocytic papillary RCC), and eosinophilic variant of clear cell RCC. In a recent study, Trpkov et al. defined a new tumour referred to as "low-grade oncocytic tumour of kidney", characterised by a solid/nested morphology with remarkable low grade features, as well as CK7 positivity and CD117 negativity. Papillary architecture is not a feature described in this new entity. Here, we report a low grade oncocytic kidney tumour with papillary features.
Methods: A 1,4 cm renal tumour was identified incidentally in a 57-year-old woman in an abdominal computed tomography. The patient underwent partial nephrectomy and specimen was sent to pathology department. Formalin-fixed, paraffin-embedded tissue was prepared from the tumour. 4 μm slides were obtained from paraffin blocks and stained for hematoxylin eosin for routine microscopic examination. 4 μm sections were also stained for CK7, CD10, AMACR, vimentin, CD117 and CA IX immunohistochemistry using Leica Bond-Max Autostainer.
Results: Partial nephrectomy revealed a well-circumscribed, solid, tan-brown coloured tumour with small cyst like areas. Microscopically, tumour was composed of both solid and true papillary areas with delicate fibrovascular cores. Tumour cells had low-grade (grade 1-2) morphology with oval-round nuclei, small nucleoli and granular oncocytic cytoplasm. There was no foamy histiocytes within the papillary cores. Immunhistochemically tumour was diffusely positive for CK7 and focally positive for CD10, while AMACR, vimentin, CD117 and CA IX were all negative.
Conclusion: This is the first report of low grade oncocytic kidney tumour showing prominent papillary features. Differential diagnosis clearly included type 2 papillary RCC; however, absence of foamy histiocytes and AMACR, Vimentin, CD10 negative immunophenotype were not consistent with this diagnosis. Although well-formed papillae are not a morphological feature of oncocytoma and chromophobe RCC, the diagnosis of our case was most consistent with "low-grade oncocytic tumour of kidney" and delicate papillary formations could be a rare finding and expand the spectrum of morphological presentations in this recently described entity.

E-PS-25-058
Can the total PSA value predict the Gleason score before prostate biopsy?
M. Asmae[1], A. Douida[2], H. El Fatemi[2,3], J.E. El Ammari[4]
[1] University Hospital Center Hassan II of Fez, Morocco, [2] Department of Pathology, Hassan II University Hospital, Fez, Morocco, [3] Faculty of Medicine and Pharmacy of Fez, Morocco, [4] Department of Urology, Hassan II University Hospital, Fez, Morocco

Background & Objectives: Prostate cancer is the most common malignancy in men. Our objective is to determine if there is a correlation between Gleason score and total prostate specific antigen (PSAt) in patients newly diagnosed with prostate carcinoma.

Methods: We retrospectively reviewed the data of 73 men who were diagnosed with prostate cancer between 2012 and 2017, within the departments of urology and pathology at the Hassan II university hospital center. We recorded Patients' age, prostate-specific antigen levels at diagnosis, prostate biopsy and radical prostatectomy specimen Gleason scores.
Results: The mean age of our patients was 69.60 years (52-98), the mean prostate specific antigen level was 258.27 ng/mL (5 - 3330 ng/mL). The mean Gleason score was 7.1, 38.35% of patients were graded group 1; 12.33% group 2; 8.22% group 3; 15.07% group 4 and 26.03% were graded group 5. Adenocarcinoma was the histological type in 100% of our cases. Prostatectomy was performed in 38.4% patients. In our study, the PSA level and the biopsy Gleason score were higher in patients with bone metastases. However, there was no statistical significant correlation between PSA level and the Gleason score (correlation coefficient = 0,30).
Conclusion: Gleason score is the most important parameter in prostate cancer. According to our study, there is no relationship between Gleason score and PSAt level. The obtained results are not similar to those cited in the literature. This is probably due to the restricted number of our cases.

E-PS-25-059
Low-grade oncocytic renal tumour (CD117-negative, cytokeratin 7-positive): a new entity? Report of four new cases

M. Muñoz Martín[1], C. Gómez-de María[2], M. Pèrez-Expósito[2], A. Serantes[1], R. Morellón[1], P. San Miguel[1], J. Ortiz-Rey[1]
[1] Hospital Álvaro Cunqueiro, Spain, [2] Povisa, Spain

Background & Objectives: Low-grade Oncocytic Renal Tumour (LORT) CD117-negative and Cytokeratin 7-positive, has been recently proposed as an emerging/provisional entity different from oncocytoma, eosinophilic chromophobe renal cell carcinoma (ChRCC) and hybrid oncocytic tumour.
Methods: We have reviewed 64 surgical specimens diagnosed as ChRCC, searching for features of LORT.
Results: Five LORTs (7,8% of the ChRCCs) were identified. One previously reported is excluded from this communication. The other four affected 3 women and 1 man, aged 69-83 years. Two were in the right and two in the left kidney. Tumour size was 6, 2, 6,5 and 3,5 cm. Histologically, they were well delimitated unencapsulated tumours, with a compact nested, focally tubular, architecture. The cells had oncocytic cytoplasm and round to oval nuclei. Nucleolar grade would be 2. Only focal perinuclear clearing was seen. One case showed focal necrosis. Immunohistochemistry: Positive for CK7, cadherin E, EMA and SDHB; and negative for CD117, CD10, vimentin, CA9 and CK20. AMACR was negative in 2 cases and focal/faint positive in the other two. After a follow-up of 8 months - 7 years the patients are alive and without relapse or metastases.
Conclusion: A subset of oncocytic tumours with the features described as LORT could be recognised among our ChRCCs. Our cases have had a favourable evolution although follow-up has been short in three of them. We report the first case of LORT with necrosis, whose impact on prognosis remains to be established. Further studies of new cases are needed to validate LORT as a new entity.

E-PS-25-060
Gleason score correlation between prostate biopsy and radical prostatectomy specimens

M. Asmae[1], A. Douida[2], H. El Fatemi[2,3], J.E. Elammari[4]
[1] University Hospital Center Hassan II of Fez, Morocco, [2] Department of Pathology, Hassan II University Hospital, Fez, Morocco, [3] Faculty of Medecine and Pharmacy of Fez, Morocco, [4] Department of Uroology, Hassan II University Hospital, Fez, Morocco

Background & Objectives: Prostate cancer is the most common malignancy in men. In this study, we evaluated the correlation between biopsy Gleason scores and radical prostatectomy specimen scores.
Methods: We retrospectively reviewed the data of 73 men who were diagnosed with prostate cancer between 2012 and 2017, within the departments of urology and pathology at the Hassan II university hospital center. We recorded Patients' age, prostate-specific antigen levels at diagnosis, and prostate biopsy and radical prostatectomy specimen Gleason scores.
Results: The mean age of our patients was 69.60 years (52-98), the mean prostate specific antigen level was 258.27 ng/mL (5 - 3330 ng/mL). Adenocarcinoma was the histological type in 100% of our cases. The mean Gleason score was 7.1, 38.35% of patients were graded group 1; 12.33% group 2; 8.22% group 3; 15.07% group 4 and 26.03% were graded group 5. Prostatectomy was performed in 38.4% patients. The biopsy Gleason score and the prostatectomy Gleason score were correlated in 48%, upgraded in 48%, and downgraded in 4% of cases with a correlation coefficient of 0.69.
Conclusion: Gleason score is the most important parameter in prostate cancer. This study has permitted to obtain results that are closely similar to the result cited in the literature.

E-PS-25-061
Paratesticular angiolipoma: an unusual entity involving in the paratesticular region

R. Ayadi[1], F. Gargouri[1], N. Mansouri[1], I. Msakni[1], A. Bouziani[1], B. Laabidi[1]
[1] Pathology Department, Military Hospital, University of Tunis El Manar, Faculty of Medicine of Tunis, Tunisia.

Background & Objectives: Angiolipomas (AGLs) are not uncommon tumours of the soft tissue, but are rarely found in other parts of the body such as the breast, gastrointestinal tract, thyroid, bone and oral cavity. Intrascrotal angiolipomas (AGLPs) are an uncommon paratesticular tumour that has seldom been reported in the literature.
We aimed to report a new case of AGLP and to describe its histopathological features
Methods: A 21-year old man presented a large scrotal mass of approximately 2-years duration. He was managed conservatively untill he reported a testicular hypotrophy. The patient had no history of pelvic surgery or testicular trauma. Clinical examination revealed an approximately 21 mm scrotal mass. Ultra-sonography showed a solid mass with microcalcification. An orchidectomy was performed.
Results: On gross examination, mean size, of the specimen, was 3,5cm. Cut section showed a well-circumscribed reddich-brown paratesticular mass measuring 15mm with focal areas of hemorrhage.The histological examination showed a tumour composed of mature adipocytes surrounded by thin-walled capillaries and fibrin microthrombi found in blood vessel lumens. Based on these histologic findings, the final diagnosis of AGLP was considered.
Conclusion: This case has unique features regarding its location and diagnosis. AGLP are rare introscrotal masses but can grow slowly necessitating surgical incision. It has to be distinguished from aggressive angiomyxoma and liposarcoma.

E-PS-25-062
Plasmocytoid urothelial carcinoma: an unusual and aggressive variant of urothelial carcinoma

A. Dhaoui[1], K. Hamza[1], D. Ben Ghachem[1], K. Bellil[1]
[1] Forces de securite interieure, Tunisia

Background & Objectives: Plasmacytoid urothelial carcinoma (PUC) is a variant of infiltrating urothelial carcinoma that is characterised by tumour cells that have striking morphologic resemblance to and immunohistochemical overlap with plasma cells. It is an uncommon aggressive urothelial carcinoma accounting for 1-5% of invasive urothelial carcinoma.
Methods: We reported a case of bladder PUC in a 62 years-old man who presented a recurrence of macroscopic hematuria after BCG intravesical instillation.
Results: Transurethral resection of the bladder showed a high-grade tumour arranged in discohesive cords and plasmocytoid features without

penetrating the muscle and presented an urothelial papillary differentiation in surface. Plasmocytoid morphology is a source of diagnostic dilemmas and amongst the differential diagnosis commun ones are cystits with plasma cell infiltration, melanoma, plasmocytoma and rhabdomyosarcoma. The urothelial differentiation and positivity expression of plasmocytoid cell for CD138 confirmed the diagnosis.
Conclusion: Compared with conventional urothelial carcinoma, PUCs have greater chance for higher-stage disease, surgical margin positivity, and metastasis at presentation that translate into its poorer outcome. Because of its unfavorable behavior, a more aggressive management approach is being recommended including the consideration for cystectomy in pT1 disease. That's why it must be distinguished from the other carcinoma variants.

E-PS-25-066
On electropathophysiology and ultrastructure of pyeloureter
M. Michailov[1], E. Neu[1], B. Rattel[2], U. Welscher[3], M. Wirth[3], U. Härlin[3], D. Martin[3], H. Dahlheim[4], J. Foltinova[5], U. Matis[6], G. Werner[7], D.G. Weiss[8]
[1] Inst. Umweltmedizin c/o ICSD/IAS e.V. Muenchen, Germany, [2] Amgen Res. Munich (Exec. Dir.) & IUM c/o ICSD/IAS e.V., Germany, [3] Inst. Umweltmedizin c/o ICSD/IAS e.V. Muenchen, Germany, [4] Univ. Muenchen, Inst. Physiol., Germany, [5] Univ. Bratislava, Med. Fac., Slovakia, [6] Univ.Muenchen, Fac. Vet. Med., Chir. Clinic (Dir.a.D.), Germany, [7] Klinikum Darmstadt, Med. Clinic (Dir.), Germany, [8] Univ. Rostock, Inst. Physiology (Dir.a.D.), Germany

Background & Objectives: Despite enormous information about normal and pathological electrical&motor physiology of pyeloureter (P&U), also reports about ultrastructure are essential open questions which are to be discussed, supporting better therapy in genitourology.
Method: Recording of electrical activity (intracellular) of P&U; ultrastructure.
Results: Systematic observations about action potentials in guinea-pig demonstrate presence of very different electrical patterns – spikes/S, burst/B, burst-plateaus/BP, etc. (n=63). They are dependent on ratio KCl:Ca Cl_2 (5.6mmol/l:2.16mmol/l = 1:1), e.g. after 8:2 S are transformed into BP, similar to addition of $BaCl_2$. $MgCl_2$ has only negative chronotropic effect. Recording of myocytes from human P&U is very difficult – action potentials are present (n=120). Ultra-structural observations by electron microscopy demonstrate essential differences between Guinea-pig/GP&human/H U, e.g. cell-distance GP:40nm, H:200nm (magnification 10.000x,n=20). Open questions: a. Correlation of various electrical patterns with motor ones. What are normal&pathological patterns? b. Importance of renin-angiotensin system and mechanosensitive ion channels for normal&pathological electrical&motor activities of P&U. c. Interaction between spontaneous phasic (SPC:1-5/min) and tonic contractions (STC:0.1-0.2/min) after $BaCl_2$ in relation to various electrical patterns (cystotonometry in vitro). d. Importance of differences in ultrastructure for a-c.
Conclusion: Clarification of these questions could be of essential importance for uro-pathology, incl. also for angiocardiac and neurohormonal pathology supporting UNO Agenda 21 for better health, medical education,ecology, economy,etc. on global level.

Ref (see also Neu et al. this congress): [1]-IUPS-2017-Rio-de-Janeiro, AB:No. 997/999/1001/1003; 2009-Kyoto, J.Physiol.Sci., 59/S1:168&214&447-8. FEPS-2018-London-Europhysiol AB:p334P-337P; 2014-Budapest, Acta Physiol. 211/s697:p62-64; 1999-Prague, PhysiolRes48/S5:138. DPG-2002-Tübingen, EurJPhysiol443/S1:S334. [2]-FISP-2018-Beijing (Philos.) No.1348-50/1374-5; 2013-Athens AB:464-5&503-4&766. IAB-2018-India (Bioethics) AB:392&393; 2016-Edinburgh Proc93-95; 2008-Istria 290&307.

E-PS-25-067
On an integrative pathology of pyeloureter
E. Neu[1], M. Michailov[1], B. Rattel[2], V. Foltin[3], U. Welscher[4], H.W. Bauer[5], A. Hofstetter[6], E.R. Weissenbacher[7], M. Schratz[8], G. Weber[9], D.G. Weiss[10]
[1] Inst. Umweltmedizin c/o ICSD/IAS e.V. Muenchen, Germany, [2] Amgen Res. Munich (Exec. Dir.) & IUM c/o ICSD/IAS e.V., Germany, [3] St. Elisabeth Univ., Bratislava, Slovakia, [4] Inst. Umweltmedizin c/o ICSD/IAS e.V. Muenchen, Germany, [5] Univ. Muenchen and Free Univ. Berlin, Med. Fak., Germany, [6] Univ.Muenchen, Klinikum Grosshadern (Dir.a.D.), Germany, [7] Univ. Muenchen Med. Fak., Premium Med. Clinic (Dir.), Germany, [8] Univ. Innsbruck, School Educ. (Dean), Austria, [9] Univ. Lxbg. and Vienna, Fac. Psychology (Dean), Austria, [10] Univ. Rostock, Inst. Physiology (Dir.a.D.), Germany

Background & Objectives: Angiocardiac and neuro-pathology depends on nephrology. Reports on integrative genitourology&physiology are given. Pathophysiology is underrepresented in pathology. Presently is considered pyeloureter in context of an integrative pathology.
Method: Motor activity (isotonic rec.), neurogenic contractions to electrostimulation (nCES 10+100Hz,0.3ms,3s,5-30V) [3]. Electronmicroscopy.
Results: A. Spontaneous phasic contractions (SPC): More than 10 SPC-patterns (1-2/min) were observed in isolated pyelon/P & ureter/U of guinea-pig/GP & human/H (n=242): Irr-®ular (frequency), non-&uniform (amplitudes), burst-like, others were evident. B. Motor reactions after nCES: nCES induced only single contr. of U, but a temporary (1-3min) strong increase of SPC of P from GP&H. TTX (1μg/ml) & hypothermia (25,15°C) antagonized this (neurogenic excitation). C. Pharmacological analysis: Adrenergic & cholinergic blocking agents inhibited P&U. D. Essential differences in motor patterns of GP&H pyeloureter exist, e.g. burst-like contractions in H-preparations. E. Ultra-structure demonstrates essential differences between GP-H-ureter, e.g. cell distance GP:40nm, H:200nm (magnification 10.000x, n=20). OPEN QUESTIONS: Role of various motor patterns for normal & pathological P&U function. Participation of excitatory & inhibitory non-cholinergic & non-adrenergic (co-)transmitters. Role of ultrastructure for pathological motor patterns.
Conclusion: It is evident necessity of holistic & multidimensional research in context of integrative pathology conc. pathophysiology and pathomorphology of pyeloureter leading to better diagnosis and therapy of renal diseases, supporting UNO-Agenda21 for better health, medical education, developing help, etc. on global level. *Ref.:* [1]-Pathology: ESP-2018-Bilbao, Eur.J.Pathol. 473/Suppl.1:S180; ESP-2017-Amsterdam, Eur.J.Pathol. 471/Suppl.1:S245/S284/S307; Int.Acad.Pathol./ESP-2016-Köln, Eur.J.Pathol. 469/Suppl.1:S245. [2]-SIU-2016-B-Aires (IntSocUrol) Abstr-Book/AB:136&223; 2011-Berlin-CongrUrol 78/S3A:S188/S385; 2007-Paris 70/S3A:232-3; 2004-Honolulu-BrJUrol 94:24-5/258-9/305. Physiology and Philosophy (*see Michailov et al.* this congress)

E-PS-25-068
Prognostic role of pre-operative neutrophil - lymphocyte ratio (NLR) in urothelial carcinoma: experience of tertiary center
K. Sahu[1], M. R[2], P. KS[3], J. Kini[1], F. Lobo[2]
[1] Department of Pathology, Kasturba Medical College, Mangalore, India, [2] MAHE, India, [3] MAHE

Background & Objectives: Neutrophil-Lymphocyte ratio (NLR) as an indicator of heightened systemic inflammatory response, predicts increased disease burden and poor oncological outcomes in urothelial carcinoma (UC). The study was undertaken with an aim to evaluate the association of NLR with clinicopathological variables and survival outcomes.
Methods: A total of 80 patients of UC were enrolled in the current retrospective study. Pre-operative NLR (within 1 month prior to the procedure), patient age, sex, tumour grade, pathological stage, recurrence free survival (RFS), progression free survival (PFS) and cancer specific survival (CSS) were recorded. We chose a cut-off value 2.7 for NLR and patients were divided into two groups (NLR<2.7 and ≥2.7).

Results: NLR ≥2.7 was significantly associated with advanced tumour stage (p=0.001) but not with tumour grade (p=0.116). Progression (p=0.032) and death rates (p=0.026) were high in patients with NLR ≥2.7. Mean RFS (p=0.03), PFS (p=0.04) and CSS (p=0.04) were reduced in patients with NLR ≥2.7. On univariate analysis, NLR ≥2.7 predicted worse RFS (HR= 2.928, P=0.007), PFS (HR=3.180, P=0.006) and CSS (HR=3.109, p=0.016). However, it was not an independent predictor of outcomes on multivariate analysis.
Conclusion: Only tumour stage and grade are independent predictors of RFS, PFS and CSS. High NLR at a cut-off value ≥ 2.7 is associated with advanced pathological stage, but does not have an independent predictive value for RFS, PFS and CSS.

E-PS-25-069
Paratesticular adenomatoid tumour: case report
A. Kilitci[1], E. Erşekerci[2]
[1] Ahi Evran University Medical Faculty, Dept of Pathology, Turkey, [2] Ahi Evran University Medical Faculty Dept of Urology, Turkey

Background & Objectives: Adenomatoid tumour (AT) is a kind of specific and uncommon benign tumour of female and male genital tracts. It is thought to arise from mesothelial cells. AT represents a diagnostic challenge due to their clinicopathological signs similar to those of other testicular neoplasms.
Methods: A 45-year-old male presented with palpable, painless mass in the right scrotum. There was no history of trauma or sudden enlargement of swelling. Plasma levels of β-hCG, AFP and LDH were also within normal ranges. Testicular ultrasonography demonstrated a heterogeneous, hipoechoic, well-demarcated mass between the right medial testis and the head of the epididymis. The tumour was hard in consistency with no evidence of invasion in the testis. Intraoperative frozen section was done with neoplastic mass suspicion.
Results: Grossly the mass was 1.4 cm in diameter. Benign tumoral proliferation was considered in the frozen section. Testis reserved tumorectomy was preferred. Microscopically, the lesion was unencapsulated. There was a proliferation of cells which form cords and tubules with focal cytoplasmic vacuoles in the fibrocollagenous stroma. Immunohistochemically, HBME-1, Cytokeratin 7, D-2-40 and WT-1 showed positive reaction. Final pathological diagnosis was made as AT.
Conclusion: Normal levels of preoperative plasma tumour markers combined with intraoperative frozen section, when indicated, can avoid unnecessary orchiectomy, thereby preserving endogenous testicular function and fertility potential.

E-Posters One-Day CPS

Sunday, 8 September 2019 – Wednesday, 11 September 2019
E-PS-CP-01 | 1-Day Computational Pathology Symposium

E-PS-CP-01-001
Up-converting nanoparticles as a tool for histopathological tissue evaluation with multiplexing and machine learning potential
K. Krawczyk[1], S. Andersson-Engels[2], A. Sjögren[1]
[1] Lumito AB, Sweden, [2] Biophotonics@Tyndall, Tyndall National Institute, Cork, Ireland

Background & Objectives: In the field of histopathology, a risk for misdiagnosis is a serious issue. A standard way to visualise cell morphology is through H&E staining often combined with DAB chromogenic stain. However, this method suffers from narrow dynamic range, problems with quantitation and difficulties with multiplexing and co-localisation. Fluorescent IHC techniques generate a more quantitative readout but suffer from photobleaching. Here we present that the use of up-converting nanoparticles (UCNPs) allows to overcome problems associated with commonly used imaging techniques.
Methods: Novel luminescent UCNPs were used together with a prototype instrument to image selected markers, e.g. Her2, in the human tissue. Formalin-fixed paraffin-embedded human colon and breast cancer tissues were sectioned and stained using autostainer. UCNP fluorescence imaging of the human tissue sections was compared with a standard DAB based IHC. Pulsed excitation and gated detection were explored to improve the scanning speed. UCNP and H&E co-staining and co-imaging were also investigated.
Results: Images obtained with our novel device clearly show that developed by us antibody-UCNP conjugates can be used to successfully stain the human tissues. Brightfield images show that UCNPs are not visible in white light and hence do not interfere with standard tissue evaluation by a pathologist. Additionally, brightfield and luminescent images can be merged to provide better understanding of tissue morphology.
Conclusion: Emerging field of UCNPs opens up new possibilities. Staining solutions and a novel device developed by us give hope for more accurate diagnosis by keeping the advantage of H&E staining and combining it, in one image, with luminescent data, ideal for generating ground truth for machine learning algorithms.

E-PS-CP-01-003
Nuclei segmentation of immunohistochemically stained slides using transfer learning from classical histopathological domain
A. Ion Margineanu[1], A. Serag[1], H. Qureshi[1], R. McMillan[1], M. Saint Martin[1], A. Kennedy[1], J. Diamond[1], M. Salto-Tellez[2], P. Maxwell[2], P. O'Reilly[1], P. Hamilton[1]
[1] Philips Digital & Computational Pathology, United Kingdom, [2] Queen's University Belfast, United Kingdom

Background & Objectives: The objective of this study was to create a generic segmentation algorithm for immunohistochemically (IHC) stained pathology slides, regardless of the IHC antibodies used for staining. Because of the large amount of annotations already available for classical histopathological slides stained with hematoxylin and eosin (HE), this study focused on transferring knowledge from one domain to another.
Methods: A deep learning model was trained on 1000 HE images acquired from different tissues, which were manually annotated for cell nuclei by a senior pathologist. This model was tested on multiple cases: 4000 unseen HE images, 9000 counterstained IHC images, 1000 nuclei stained IHC images, and 500 membrane/cytoplasm stained IHC images. DICE scores for the segmented nuclei were computed as a performance measure.
Results: The average DICE score for the test HE images was 72%, while for the rest of the IHC images the average DICE scores were around 50%.
Conclusion: A deep learning model for nuclei segmentation trained only on images from the HE domain constitutes a good starting point for transfer learning towards the IHC domain.