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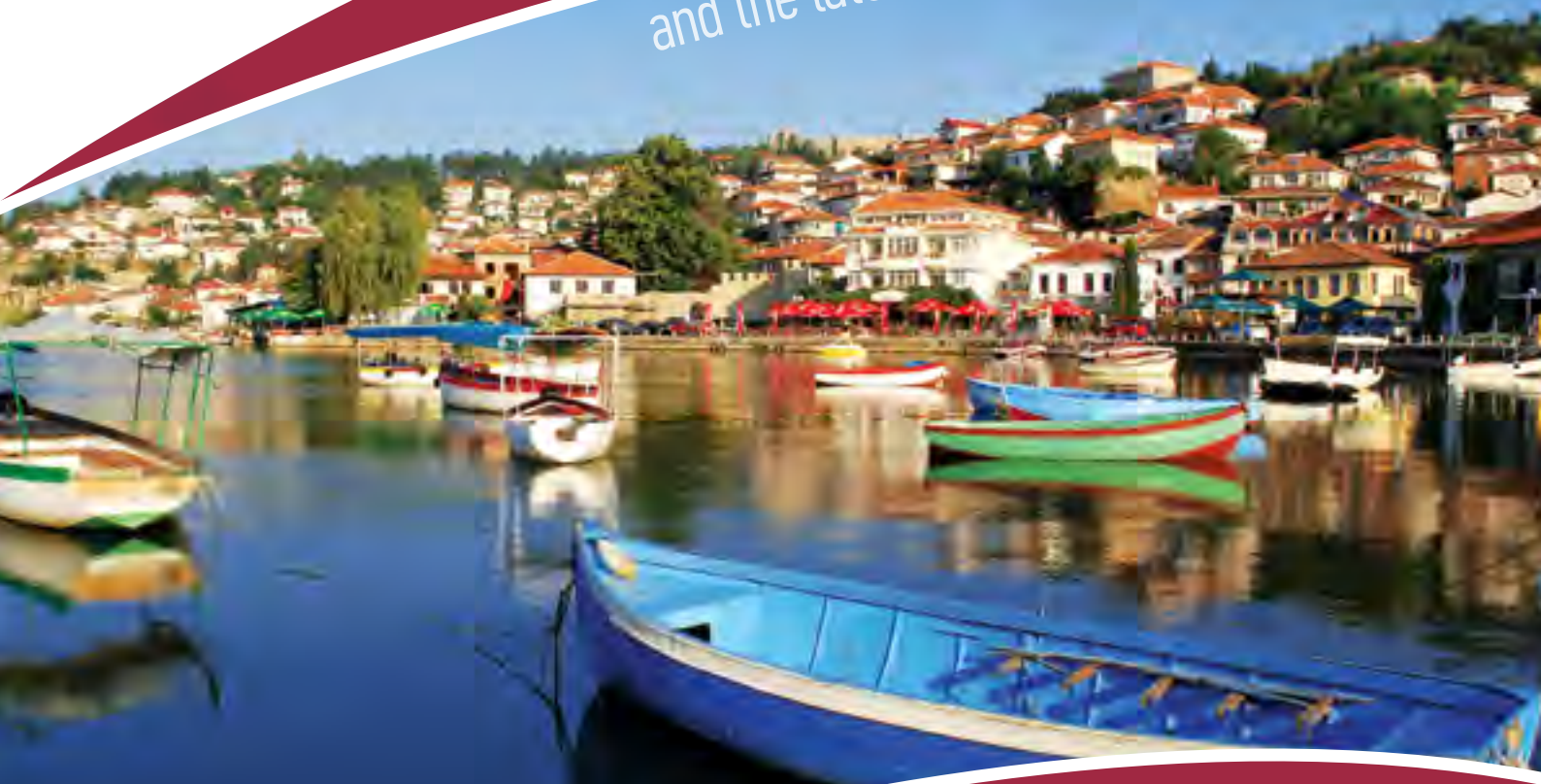

2nd Macedonian Congress of Pathology

WITH INTERNATIONAL PARTICIPATION

European School of Pathology Workshop
Breast pathology in 21st century

September 1-4, 2016, Hotel Metropol, Ohrid, Republic of Macedonia

PROCEEDINGS & ABSTRACTS

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KEYNOTE LECTURES

KN01

Molecular pathology of colorectal cancer

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Until recently, adenomas were considered as precursor lesions of almost all sporadic colorectal carcinomas (CRC). Nowadays, it has been demonstrated that a distinct group of colorectal lesions, called serrated lesions, are precursor diseases for a subset of CRC.

The adenoma-carcinoma sequence describes the stepwise progression from normal to dysplastic epithelium to carcinoma associated with the accumulation of multiple genetic/epigenetic events. Features that are considered as risk factors for the malignant evolution of adenomas are their size, growth pattern and grade of dysplasia. Mutations in the APC gene represent a crucial event in colorectal carcinogenesis. APC mutations have been found in 20-82% of adenomas and 52-60% of CRC, suggesting that these mutations occur early in colorectal cancer development. KRAS mutations occur in 35-42% of CRC, 50% of large adenomas (>1cm) and only in 9% of small adenomas (<1cm). Our experience in tissue sections from colorectal tumors showed that KRAS expression was higher in adenomas than in carcinomas and in adenomas was increased according to the degree of dysplasia. Loss of 18q, where DCC gene is located, has been observed in 10-30% of early adenomas and 50-60% of late adenomas. The tumor suppressor genes in 18q region, such as SMAD2 and SMAD4, have been mutated in 25-30% of CRC. Alterations of p53 gene have been reported in 4-25% of adenomas, 50% of invasive foci within adenomas and 50-75% of CRC.

The serrated neoplasia pathway consists of serrated polyps and its end point is the serrated adenocarcinoma. The earliest genetic alterations are BRAF and KRAS gene mutations. BRAF mutations were found to be more common in sessile serrated adenomas (75-80%) and mixed polyps (40-90%) compared to hyperplastic polyps (19-36%) and serrated adenomas (20-33%). BRAF mutations have been reported in 43-76% of sporadic CRC. KRAS mutations were found in approximately 80% of serrated adenomas and less frequently in sessile serrated adenomas (7%) and hyperplastic polyps (4-37%). Microsatellite instability (MSI) was first described in association with hereditary non-polyposis CRC (HNPCC), where germ-line mutations of mismatch repair genes (MMR) result in high frequency MSI (MSI-H) in >90% of the cases. Sporadic CRC with MSI-H are developed as result of MMR gene MLH1 transcriptional inactivation through acquired promoter methylation. MLH1 methylation has been detected in 30% of hyperplastic polyps, 70% of sessile serrated adenomas and 86% of sporadic MSI-H CRC. Low levels of MSI (MSI-L) are associated with MMR gene O-6-Methylguanine DNA Metrhyltransferase (MGMT). MGMT methylation has been found in 22% of hyperplastic polyps, 25% of sessile serrated adenomas, 16-22% of serrated adenomas and 50% of serrated adenocarcinomas.

In conclusion, triggered by morphologic observations, molecular studies now provide evidence that, except the long held paradigm of the traditional adenoma-carcinoma sequence, the serrated neoplasia pathway is responsible for colorectal carcinogenesis. Serrated precursor lesions of CRC are not so homogeneous lesions and pathologists do not have relatively uniform criteria for their recognition. Further morphological and molecular determination of features is needed in order to obtain the best therapeutic strategies.

KN02

The dynamic evolution of pathology

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The historical development of pathology as a separate academic discipline in the 19th century followed very different ways in different European countries: whereas surgical pathology as a clinical discipline was a main focus in some places, others, particularly in Germany and some countries of the K-u-K monarchy, in the tradition of R. Virchow pathology was structured as the scientific heart of medicine in general. From there the knowledge on the biologic basis of human diseases evolved from organs to tissues, from tissues to cells and molecular pathways.

In the main field of pathology today, namely cancer diagnostics, the focus evolved from the histogenetic classification to prospective risk profiles of tumor classes and molecular genetic targets allowing individualized treatment approaches. In this evolutionary process the profile of pathology has made fundamental changes in the past. Risks and challenges of today will have also a great impact on the structure of our discipline of tomorrow. A definition of its specific scientific and academic tasks may be a basis for its role and logistic requirements in the great clinical orchestra.

KN03

Evolving classification of human tumors: a WHO perspective

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Adequate disease classifications are universal: every medical professional should be able to use them in daily patient care, in communicating with peers and patients and in medical research. Credible classifications have to be clinically relevant, based upon understanding of the biology of the disease and rooted in consensus.

Clinically meaningful implies assisting clinicians in making diagnoses, in deciding on the most promising therapy for each individual patient and providing information on disease course. 'Entities' should have sufficiently defined criteria for making the diagnosis along with a set of matching clinical signs and symptoms. Sub-classifications without clinical consequences should be avoided: pathologists need to lump when they can, and split only when they have to.

Biologically valid implies that the practice of diagnostic pathology is rooted in understanding disease or, as the Royal College of Physicians puts it 'the science behind the cure. A classification not based upon understanding the pathophysiology of the condition is prone to create confusion and fruitless debate.

Consensus implies that all pathologists use the same terminology. We should also realize that diagnostic terms do not only translate into treatment decisions or convey prognostic information but in addition form the basis for the coding systems used by epidemiologists. **Consensus** implies exchange between specialists to reach conclusions supported by large majorities and usable in daily diagnostic practice. A narrow majority vote to reach a consensus will not stand the test of time.

Disease classifications developed along with growing understanding of the biology of disease and mostly based upon notions of etiology and pathogenesis, paralleled by characteristic clinical signs and symptoms. They were initiated already in the 19th century but became mainstream when the World Health Organization was created and assumed responsibility for global survey of disease patterns, which required universally applicable classification schemes. This resulted in the International Classification of Disease (ICD) of which we all now use the 10th edition (ICD10). Tumor classification is part of ICD but evolved into a separate field, notably with the evolution of the WHO classification of human tumors and the ICD-O (for oncology) codes. WHO was not the only player in this field: the Armed Forces Institutes of Pathology (better known under its acronym AFIP) initiated the Fascicle series, which are continued by the American Registry of Pathology. Important difference between the Fascicles and the WHO classification of human tumor series (better known as 'Blue Books' due to the consistently used blue color of the covers) is the consensus notion: each volume of the 'Blue Book' series has more than 100 authors and its publication is preceded by a consensus meeting in which the main specialists in the field participate. The breakthrough for the Blue Books came when the Director of the International Agency for Research on Cancer (IARC) published the 3rd edition of the Blue Books in a format and with a content extremely useful in daily diagnostic working environment of pathologists. This has been consolidated in the 4th edition and the WHO classification of human tumors now constitutes a solid basis for truly universal tumor classification.

With the advent of molecular genetic approaches toward disease (sub)classification it has become obvious that revision of classifications needs to be more efficient than what can be attained in a 10 year revision cycle (the time it took to complete the 4th edition). It is therefore likely that the 5th edition will have an 'electronic' format, allowing revision of chapters according to need rathabstraer than of complete volumes in their order of initial appearance. Classifications will remain firmly rooted in a morphological basis but they will evolve into greater complexity, with subgroups increasingly based upon characteristic and targetable molecular abnormalities. New molecular subtypes will have to provide key information for a more precise choice of therapy, befitting the individual patient.

GENITOURINARY PATHOLOGY

Symposium

L01

Intratumour heterogeneity in clear cell renal cell carcinoma

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Intratumor heterogeneity (ITH) is an inherent process in cancer development which follows for most of the cases a branched pattern of evolution, with different cell clones evolving independently in space and time across different areas of the same tumor. The determination of ITH is nowadays critical to enhance patient's treatment and prognosis.

Clear cell renal cell carcinoma (CCRCC) provides a good example of ITH. Sometimes the tumor is too big to be totally analyzed for ITH detection and pathologists decide which parts must be sampled for the analysis. For such a purpose, pathologists follow internationally accepted protocols. On the light of the last findings, however, current sampling protocols seem to be insufficient for detecting ITH with significant reliability.

The arrival of new targeted therapies, some of them providing promising alternatives to improve patient's survival, pushes forward the pathologist to obtain a truly representative sampling of tumor diversity in routine practice. How large this sampling must be and how must be performed are unanswered questions so far.

L02

Primary carcinomas of the urethra

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Background: Primary urethral carcinomas (PUC) account for <1% of urinary tract malignancies. Due to rarity of these tumors, the morphologic, immunohistochemical and clinical features are not well elucidated. Herein, we report 119 cases of PUC.

Design: We identified 119 cases of PUC from 1986-2014. PUCs were defined as tumors arising primarily in the urethra. Cases with secondary involvement of the urethra by urinary bladder carcinoma or from the glans penis were excluded. All cases were re-reviewed to confirm the diagnosis. Immunohistochemical stains were performed on 82 tumors with the following antibodies: CK 7, CK 20, CK 5/6, CK903, p63, CDX2 and thrombomodulin. P16 and GATA-3 were performed on a subset (n=18). Four urothelial carcinomas (UC) secondarily involving the urethra were also stained as controls. Follow-up information was obtained from medical records and/or provided by referring physicians.

Results: The mean age at diagnosis was 61 years (range: 29-85 years). The male: female ratio was 3:2. Most patients presented with dysuria, decreased urinary stream or urinary retention. Median tumor size was 4 cm (range: 0.5-6.5cm). Histologically, most tumors (n=98) showed overlapping morphologic features of UC and squamous cell carcinoma (SCC), which we propose calling Urethral Carcinoma (UCa). Of the remainder, 17 were adenocarcinoma, 2 sarcomatoid carcinoma, 1 lymphoepithelioma-like carcinoma and 1 adenoid cystic carcinoma. Immunohistochemical profile for the UCa was CK7, CK5/6, CK 903, p63, Thrombomodulin positive; and CK20, CDX2 negative. P16 was positive in 66.7% (12/18) of UCa; GATA-3 was negative in 77.8% (14/18) of UCa. The 4 control cases of UC were all positive for GATA-3 and two were positive for p16. Adenocarcinomas (8) have a distinctly different immunohistochemical profile: CK7 positive in all 8 cases; CK20 in 6; CDX2 in 5 and thrombomodulin in 2 cases. CK5/6 and p63 stains were negative in all 8 cases.

All patients were treated by surgical excision. 22 patients had lymph node metastases (17 cases of UCa and 5 cases of adenocarcinoma) with left inguinal lymph nodes as the most common site. 15 patients had distant metastases (12 cases of UCa and 3 cases of adenocarcinoma), with the lung as the most common site. In addition to surgery, 22 patients had chemotherapy, 8 had radiation and 12 had chemoradiation. Clinical outcome data were available on 114 patients, with a follow-up interval of 0.03 to 236.8 months (median: 19.7 months). 24 patients were alive with no disease (median: 17 months); 35 patients were alive with disease (median: 20 months). 28 patients died of disease (median survival: 11 months); 2 patients died of other causes; while 25 patients died of unknown causes.

Conclusion: Primary urethra carcinomas are rare, with the majority having overlapping morphological features and immunohistochemical profile of UC and SCC. We propose these should be called Urethral Carcinoma, rather than UC or SCC. PUC may behave aggressively with lymph nodes metastasis, distant metastases and a short median survival time.

L03

Intra-surgical total and re-constructible pathological prostate examination for safer margins and nerve preservation: Istanbul preserve

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Introduction: Performing frozen section (FS) analysis during radical prostatectomy improves nerve-sparing without compromising cancer control. Techniques described focus on FS of tissue adjacent to the neurovascular bundle (NB) and result in significant tissue loss not allowing for perfect reconstruction for final whole-mount evaluation. We describe a novel FS technique in which the entire prostate is examined for margins and perfect reconstruction is conceivable.

Methods: 54 patients underwent Pathological Prostate Examination for Safer Margins and Nerve Preservation during nerve-sparing robot-assisted radical prostatectomy between 10/2014 and 6/2015. Prostate was removed via extending the lateral 12-mm. assistant port and incision re-tightened with suturing. Hemostasis, lymphadenectomy (LND) and anastomosis were performed during FS. A genitourinary pathologist and 2 technicians were involved. Prostate tissue adjacent to NVB was inked with 3 different colors depicting apex, mid and base. The right and left lobes were also inked separately. Prostate was entirely sectioned at 3–4mm intervals from apex to bladder neck. The margins of the prostate were excised in two halves (R & L) at a width of 4–5mm. Tissue was frozen and 5–7 micron cryosections were cut from each half border, H-E stained, and reviewed. If margin was positive (R1) extensively, further resection was performed from the corresponding NB area until negative margins were reached. If R1 was a small focus, excised tissue from corresponding area was sent for permanent analysis. In large prostates, anterior zone was not always examined.

Results: The risk categories were low, medium and high in 8, 31, and 16 patients, respectively. LND was performed in 52 (96%). Median time for pathologic analysis was 55 (35–95) minutes; overall operative time was 34 mins longer in cases with FS and LND. Twenty-four patients (44%) had R1 at surgery and further tissue was resected; 25%, 41% and 60% with increasing risk category. Malignant tissue was found in 8% of resected bundle tissue. Two patients had R1 at permanent pathology. False negative rate of R1 at FS was zero. All prostates were reconstructed with negligible tissue loss for final whole mount examination.

Conclusion: "ISTANBUL Preserve" allows for intrasurgical complete pathological examination of the prostate for margin status and for perfect re-construction for whole mount permanent examination. It guarantees safer margins together with increased rate of nerve sparing.

Acknowledgements: *Mourmouris P, Saglican Y, Argun B, Obek C, Tufek I, Tuna M, Keskin S, Kural AR.* Departments of Urology and Pathology, Acibadem University Medical School

L04

Update on testicular germ cell tumours

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Abstract

An updated review of etiopathogenesis, morphology and classification of testicular germ cell tumors, supplemented by discussion on macroscopy, differential diagnosis and immunohistochemical characteristics of different tumor types, includes new WHO classification as well as ISUP recommendations on immunohistochemistry and prognostic factors.

Introduction

Testicular tumors are the most frequent cause of a clinically detectable intra-scrotal mass. Only rarely the testicle size remains unchanged or even reduced. More than 90% of testicular tumors belong to the Type II group of germ cell tumors (GCTT2), derived from germ cell neoplasia in situ (GCIS). Other tumors are far less common and include Types I and III of germ cell tumors (GCTT1, GCTT3), primary tumors of sex cord/gonadal stroma, primary testicular lymphoma, tumors of other anatomic locations within the scrotum, and metastases. An updated review on testicular germ cell tumors (GCTs), with emphasis on novelties included in the new WHO classification (WHO 2016) is given.

Epidemiology, histogenesis

Incidence

Although accounting for only 1% of male cancers worldwide, the incidence of GCTs shows a remarkable race dependent geographical variation. On one hand, the racial variation is supporting the importance of genetic susceptibility, and on the other, the causative role of environmental factors in industrialized lifestyles.

The overall worldwide incidence is approximately 1.5/100.000 persons, being highest in white men living in Norway and Switzerland (>12/100.000) and lowest in black men from Africa and Asia (0.5/100.000). In Slovenia, testicular tumors account for 1.6 % of cancers diagnosed in men (being on the 14th place), with the crude incidence of 10.1/100.000 in years 2006-2010, and 10.3 in year 2012. The incidence in Europe and worldwide is rising steadily and has almost doubled in the last 30 years. This increasing trend, which appears to have stabilized in the countries with highest incidence, is acknowledged as at least partly being a consequence of a birth cohort phenomenon.

Etiology

“Genetic susceptibility” is important in the development of GCTs, as are “environmental and other” risk factors/associated conditions. Here, our understanding that tumor initiation occurs during embryonal development is also based on birth cohort studies. The four most important among etiologic factors for GTS are: cryptorchidism, prior testicular (contralateral) GCT, family history of testicular GTC and certain disorders of sex development. Among those, gonadal dysgenesis and androgen insensitivity syndrome are most frequent, with proven 3.5 – 15x or even 50x increased estimated risk for testicular GCTT2.

Age at presentation

Most GCTs have a peak incidence in young adults, in late twenties and thirties. Mean age of seminoma patients is approximately 10 years higher than that of patients with non-seminomatous GCT (NSGCT). There is an intermediate peak for cases of seminoma mixed with non-seminoma.

Exceptions in epidemiology are a distinct peak in incidence in infants, usually representing Type I group of GCT (GCTT1) prepubertal type-yolk sac tumor (PTYST) and prepubertal type-teratoma (PTT) and Type III GCT (GCTT3), namely the spermatocytic tumor (ST), generally occuring in old men.

Cell of origin

The cells of origin in GCTT2 are transformed gonocytes and neoplastic caricatures of early embryonic development represented by Germ cell neoplasia in situ (GCNIS). This new term (WHO 2016) refers to neoplastic, embryonic type germ cells confined to the spermatogonial stem cell niche, and is unifying the previous designations »Carcinoma in situ« and »Intratubular germ cell neoplasia, unclassified«.

GCNIS, found adjacent to invasive tumors in most cases, shows similar patterns of aneuploidia as other GCTs diagnosed in young/middle aged adults. Therefore, GCNIS as a common precursor lesion of GCTT2, is also a unifying factor of the most frequent invasive tumor types occurring in pure forms and as mixed GCTs, namely: seminoma, embryonal carcinoma (EC), post-pubertal yolk-sac tumor (YST), choriocarcinoma (CC) and post-pubertal teratoma (teratoma, T) .

GCTT1 and GCTT3 are not related to GCNIS. No precursor lesion was identified for GCTT1. For GCTT3, intratubular ST is the likely precursor.

Histogenesis and progression

In the revised model of testicular germ cell tumor histogenesis and progression, seminoma plays a pivotal role as a precursor of most (adult type) forms of testicular GCT (GCTT2). The exceptions in the model, that also lack adjacent GCNIS, are PTYST, PTT, and ST.

In the model, GCNIS shows default progression via intra-tubular seminoma into invasive seminoma. Invasion is, among others, associated with amplification of isochromosome p12. Amplified i(12p), with deregulation of the G1/S cell cycle checkpoint, is believed to permit survival of invasive tumor cells outside of the microenvironment of the seminiferous tubules by inhibiting apoptosis.

NSGCT develops, when a seminoma or GCNIS undergo reprogramming to an EC cell, expressing pluripotency factors and contributing to higher aggressiveness comparing to seminoma, as confirmed by allelotyping studies. EC cells are the main component of tumor emboli in vessels in NSGCT (lymphovascular invasion, LVI). Additionally, they are capable of producing the extraembryonic components in situ (testis) and in the metastatic sites, transforming into YST, trophoblastic giant cells and/or CC, into various somatic tissue lineages as well as the germ lineage.

The embryonal phenotype is lost upon (somatic) differentiation into teratoma, of which the adult tissue stem cells can survive DNA damage by prolonged G1 and G2 arrest and proficient repair. This change also explains the phenomenon of residual teratoma after chemotheraphy, often associated with primary tumors having a T component.

Progression of T into a teratoma with somatic type malignancy (TSTM) is occurring in 3-6% of primary testicular non-seminomas, 8% of post chemotherapy retroperitoneal specimens and >20% of late recurrences. Those tumors, in addition of 12p anomalies, may have the characteristics of their somatic counterparts.

Morphology, immunohistochemistry

Usual types

The most frequent invasive testicular GCTs belong to GTT2. GTT2 are of a single histological type (pure forms) or composed of more than one histologic type (mixed tumors). Pathologists should specify individual components of mixed GCT in the biopsy report. The amount (percentage) of each component has to be estimated, as well.

Morphologically, GCTT2 are classified as seminomas and a group of NSGCT, including EC, YST, T (without need to distinguish between mature and/or immature) and CC. Classical morphology of these tumor types, familiar to most pathologists, doesn't need further description or use of immunohistochemistry (IHC). Although focal and weak positivity for individual markers can occur in different tumor types, use of IHC can't be avoided in all cases.

Immunohistochemistry

The most useful traditional IHC markers remain placental-like alkaline phosphatase (PLAP) and CD117 for seminoma (also positive in GCNIS), CD30 for EC, alpha-fetoprotein (AFP) for YST and beta-chorionic gonadotropin (beta-HCG) for CC, additionally labelling syncytiotrophoblastic cells in seminoma and EC.

The most relevant among increasingly used new markers is OCT3/4, which is labelling seminoma, EC and GCNIS. NANOG, another among new markers with nuclear reaction, has similar distribution. The other relevant marker is Glypican-3, which is reportedly more specific and sensitive than AFP in the diagnosis of YST (with SALL4 being an equally good alternative). For the accurate subtyping of primary testicular tumors, International Society of Urological Pathology (ISUP) has published a paper summarizing the consensus diagnostic guidelines in the form of diagnostic algorithms confronting differential diagnostic questions concerning testicular neoplasms.

Rare types

Recently, unusual variants of GTCs were described, showing features that may be confused with other tumor types, therefore warranting special attention. Uncommon seminoma variants include seminoma with microcystic, tubular or signet ring appearance. Fortunately, immunophenotyping as well as nuclear morphology are in keeping with that of classical seminoma.

Spermatocytic tumor (previously named Spermatocytic seminoma) deserves special consideration. ST is rare, with higher age at presentation, unique histogenesis and distinct morphology, as it is composed of three different tumor cell types (giant, medium, small). It is important not to confuse ST with the more aggressive classical seminoma, EC or lymphoma. ST follows an indolent course and the treatment of choice is orchidectomy alone. Unless there is a tumor dedifferentiation to form a sarcoma-an event with a 50% metastatic rate, ST is only rarely metastasizing.

In NSGCT, it is important to recognize the rare somatic (non-germ cell) malignancy in teratoma (TSTM). TSTM characteristically fails to respond to conventional teratoma chemotherapy and carries poor prognosis. Somatic malignancy in a teratoma is rare, usually occuring as a post-chemotherapy phenomenon. Sarcomatous differentiation predominates over carcinomatous. Rhabdomyosarcoma, leiomyosarcoma, chondrosarcoma, glioblastoma multiforme, epithelioid hemangioendothelioma, and malignant peripheral nerve sheath tumor are the most common types of somatic malignancy, which may transform into a primitive neuroectodermal tumor (PNET). In order to make a diagnosis of TSTM, the somatic type malignancy has to occupy an area of at least one low-power field in a light microscope (x4 objective, 5mm in diameter).

Another important but benign tumor entity is the dermoid cyst, which has to be distinguished from “mature” differentiated teratoma, capable of metastasis. The absence of adjacent GCNIS is one of the diagnostic clues in dermoid cyst, usually surrounded by testicular parenchyma with intact spermatogenesis. Those tumors, which only exceptionally occur in adults, have been included in the separate, GCTT3 group of tumors in WHO 2016. This group consistists of Teratoma – prepubertal type (Dermoid cyst and Epidermoid cyst-with excellent prognosis; Well differentiated neuroendocrine tumor-monodermal teratoma), Mixed teratoma and Yolk sac tumor-prepubertal type and Yolk sac tumor-prepubertal type.

GCT of unknown type-regressed GCT

Tumors that have undergone either partial or complete regression, leaving behind a generally well-delineated nodular focus of scar/fibrosis in the testis, are defined as regressed GCT (burnt-out GCTs). Often these tumors first present as retroperitoneal metastasis and in order to get diagnosed, require a high degree of clinical suspicion.

Spontaneous regression can occur in any tumor type, paralleling the normal distribution of GCT subtypes.

Non-neoplastic scarring is the most important differential diagnosis. Features within regressed areas that support a regressed GCT are lymphoplasmacytic infiltration, hyalinized tubular ghosts, increased vascularity, siderophages and coarse dystrophic calcifications, accompanied by GCNIS and atrophy/sclerosis of adjacent testicular parenchyma.

Staging and prognostic markers

Most testicular cancers are localized at presentation and qualify as clinical stage I. This is further refined by the postorchiectomy levels of serum markers (LDH, beta HCG, AFP). However, in localized tumors, clinicians are confronted with the most diffficult therapeutical choices and pathologists need to identify tumors without need for further therapy and those with a high risk of relapse.

Seminoma

In recent literature, although not yet included in the current (2010) TNM classification, dissimilar value of individual prognostic factors for localized testicular GCTs of different histologic types has been suggested.

In pT1 seminoma, the most important factors guiding clinicians should be the tumor diameter (>4 cm) and invasion of the rete testis, which have to be included in a biopsy report. Stromal invasion has to be distinguished from pagetoid invasion of rete testis, which is probably of no significance. Identification of lymphovascular invasion (LVI), currently important for pT staging of tumors limited to testis and epididymis (pT1 vs pT2), is problematic, since seminoma cells easily smear across tissue or embedded block. Although identification of LVI, even in expert hands, remains uncertain in lot of cases, it was not abandoned and remains included in the staging criteria for seminoma. Another adverse prognostic factor identified in seminoma patients is age ≥ 40 years.

NSGCT

LVI Identification is in NSGCT usually not problematic. Tumor thrombi are most frequently identified in the vicinity of tunica albuginea and attached to the vessel wall, sometimes distant to the tumor mass. Accordingly, the most powerful unfavorable prognostic factors for stage I disease in NSGCT are represented by the presence of LVA, the amount of EC and rete testis invasion.

Hilar soft tissue invasion (HSTI), a predominant pathway of the extratesticular extension for GCTs, is a problematic issue. Recent papers have suggested HSTI being a poor prognostic factor. Nevertheless, there is great variability in reporting HSTI, varying between T1 to T3, and no agreement even between experts. However, according to WHO 2016, in the absence of LVI, the testicular tumor limited to the testis and showing HSTI should be staged as pT1.

Conclusion

Testicular tumors are relatively rare, but complex. Surgical procedure is simple and every pathologist can become confronted with a challenge to diagnose a testicular cancer. In order to avoid diagnostic errors, which lead to inappropriate treatment, awareness of the relevant areas in testicular tumor pathology is necessary.

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Slide Seminar

Case 1 - 5

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Case 1

Clinical History

A 53-year-old man presented with testicular pain, underwent orchiectomy due to suspection of chronic inflamation.

Diagnosis: ***Adenocarcinoma of the rete testis v.s. Metastatic carcinoma***

Case 2

Clinical History

A 3-year-old boy, who presented with right painfull scrotal mass and underwent orchiectomy due to suspection of teratoma.

Diagnosis: ***Embryonal rhabdomyosarcoma***

Case 3

Clinical History

A 30-year-old male presented with hematuria underwent trans-urethral resection of a small nodular mass in the urinary bladder neck.

Diagnosis: ***Nephrogenic adenoma***

Case 4

Clinical History

A 69-year-old male presented with low abdominal pain and hematuria undervent trans-urethral resection of a bulky tumor mass in the urinary bladder, confirmed by ultrasonography and CT.

Diagnosis: ***Infiltrative high grade urothelial carcinoma - sarcomatoid variant***

Case 5

Clinical History

A 34-year-old male, who underwent orciectomy 11 months ago due to diagnosed embrionic carcinoma of the testis. Following up of the patient revealed two paraaortral nodes which were surgically removed.

Diagnosis: ***Para-aorthal metastases of testicular mixed germ cell tumor mimicing enteric duplication with malignancy.***

Acknowledgements: *Vanja Filipovski*, MD, Clinical Hospital Acibadem-Sistina, Skopje, Republic of Macedonia

Case 6 - 10

José Ignacio López, MD, Professor, Head

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Case 6

Clinical History

A 55-year-old man presented with a cystic mass in his left kidney.

Diagnosis: ***Tubulo-cystic renal cell carcinoma***

Case 7

Clinical History

A 47-year-old woman showed an incidental right renal mass on a routine exploration.

Diagnosis: ***Primary renal carcinoid tumor***

Case 8

Clinical History

A 75-year-old man consulted loin pain during the last 6 months. A left renal mass was discovered.

Diagnosis: ***Epithelioid angiomyolipoma***

Case 9

Clinical History

A 47-year-old woman showed an incidental right renal mass on a routine exploration.

Diagnosis: ***Clear cell papillary renal cell carcinoma***

Case 10

Clinical History

A 57-year-old kidney donor woman with tuberous sclerosis presented a left small renal tumour attached to the renal capsule.

Diagnosis: ***Sclerosing pecoma***

GASTROINTESTINAL PATHOLOGY

Symposium

L05

The pathology of inflammatory bowel disease: diagnostic criteria and differential diagnosis

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Chronic inflammatory bowel disease includes, strictly spoken, two diseases, that is, ulcerative colitis and Crohn's disease. Both represent a steadily growing burden for the European health care system. The pathologist's role in the management of the disease includes assistance in initial diagnosis, assessment of activity, differential diagnosis and diagnosis of dysplasia and/or cancer.

Analysis of multiple biopsies allows a correct diagnosis of inflammatory bowel disease in 66-75% of newly diagnosed patients. Providing additional endoscopic and clinical data to the pathologist increases the diagnostic accuracy, allowing a final diagnosis in more than 90% of cases, respectively.

The histological features useful for a diagnosis of inflammatory bowel disease may be grouped into four categories:

- Mucosal (crypt) architecture
- Lamina propria cellularity
- Infiltration by neutrophils
- Epithelial changes

Abnormalities in mucosal (crypt) architecture include crypt distortion, branching, atrophy (shortening), reduced crypt density and surface epithelium irregularities (pseudovillous change). These changes are particularly pronounced in ulcerative colitis (57-100% of cases), but may also occur in Crohn's disease (27-71% of cases). Within the stroma, there is a transmucosal increase of inflammatory cells with basal plasmacytosis. Neutrophils (cryptitis / crypt abscess formation) are markers of disease activity. Epithelial changes include epithelial damage and mucin depletion (at active sites), metaplastic changes (markers of chronicity).

The key histological features of ulcerative colitis are the following:

- Diffuse (continuous) mucosal disease that begins in the rectum and spreads variably to the proximal colon (it is usually worse distally)
- Severe diffuse mucosal architectural abnormalities (crypt shortening and distortion, decreased crypt density)
- Severe diffuse transmucosal increase of (predominantly mononuclear) inflammatory cells with basal plasmacytosis
- Epithelial abnormalities, such as surface epithelial damage and mucin depletion as well as Paneth cell metaplasia (in biopsies obtained distal to the hepatic flexure)
- Tissue fragments both within the same biopsy and within separately submitted specimens tend to show the same degree of inflammation

The key histological features of Crohn's disease are the following:

- Segmental (discontinuous) transmural disease ("skip lesions" with fissures, fistulae) with variable rectal involvement and variable disease severity (usually worse proximally)
- Focal (discontinuous) crypt architectural abnormalities (focal crypt atrophy and distortion)
- Focal (discontinuous) inflammation (focal mononuclear expansion of the lamina propria, focal cryptitis). Focal or patchy inflammation may be observed in biopsies submitted from different parts of the bowel or may be present within tissue fragments of the same biopsy, not rarely within a single biopsy specimen
- Aphthous erosions/ulcers and deep fissures, any location
- Epithelioid cell granulomas (not crypt related) in approximately 20% of mucosal biopsies (up to 50% in resections) – they need to be differentiated from so-called cryptolytic granulomas (unspecific foreign body reaction to ruptured crypts, may occur in several types of colitis)

While ulcerative colitis is usually restricted to the large bowel (apart from so-called backwash ileitis and rare upper tract involvement in children and adolescents), Crohn's disease may affect the whole gastrointestinal tract: Crohn's disease affecting both small and large bowel is seen in about 40-50% of cases, isolated small bowel or isolated large bowel disease in 30-35% and 15-25% of cases respectively. Upper tract involvement is common in Crohn's disease and may be detected in 50-75% of cases, usually in the form of focally enhanced gastritis (with and without granulomatous reaction).

The **differential diagnosis between ulcerative colitis and Crohn's disease** may be difficult, since overlapping morphological features are seen in 10-15% of cases. In unclear cases diagnosis of indeterminate colitis (for resection specimens) or IBD unclassified, IBDU (for biopsies) should be made. It has to be acknowledged that there is no single pathognomonic histological feature, and the diagnosis typically rests on a combination of clinical, laboratory, endoscopic, and histological observations, with ulcerative colitis showing more severe architectural and inflammatory abnormalities than Crohn's disease.

Please note: Differential diagnosis may be particularly challenging under therapy, since mucosal healing in ulcerative colitis may cause discontinuous inflammation (and "rectal sparing").

	Infectious colitis	**UC active phase**	**UC in remission**	**Crohn`s disease**
Crypt architectural abnormalities	- / (+)	+++	+/++	(+)
Metaplastic Paneth cells / mucin depletion	-	++	++ / (+)	(+)
Mononuclear cells ↑	(+)	+++	-	(+)
Neutrophils	+++	+++	-	++
Granulomas / giant cells	(+)	(+)	-	++
Continous morphologic changes	(+)	+++	++ / (+)	-
Discontinous morphologic changes	+	-	- / (+)	++

The pathologist's report should include information on the grade of disease activity. This mainly holds true for ulcerative colitis (and is less important for Crohn's disease due to its discontinuous nature). Different scoring systems have been developed. Please note: Endoscopic mucosal healing does automatically mean histology healing. The latter, however, is important for prediction of the disease course, that is, patient management.

Ulcerative colitis and Crohn's disease need to be differentiated from **other types of colitis**, such as infectious colitis (mainly active inflammation, no basal plasmacytosis, preserved crypt architecture), different types of drug-induced colitis (NSAIDs, antibiotics, chemotherapy, mycophenolate mofetil or MMF, biologicals), segmental colitis associated with diverticulosis (SCAD, syn. diverticular colitis) and also the so-called microscopic colitides. The latter include lymphocytic and collagenous colitis. Both show an increased transmucosal inflammatory infiltrate and preserved crypt architecture. The hallmark of lymphocytic colitis is increased intraepithelial lymphocytosis (>20 intraepithelial lymphocytes per 100 epithelial cells), the hallmark of collagenous colitis a thickened collagen band underneath the surface epithelium (>10µ).

Finally, patients with inflammatory bowel disease are at increased risk for cancer. Long disease duration, extensive bowel involvement, young age at onset and severity of microscopic inflammation have been identified as the main risk factors. On the histological level, dysplasia (intraepithelial neoplasia) represents the best and most reliable marker of malignancy risk. It develops only in areas with chronic inflammation and can be divided into four diagnostic categories: negative (regenerating epithelium), indefinite and positive for low-grade and high-grade dysplasia.

	Colitis-associated dysplasia	**Regenerating epithelium**
Crypt architecture	Altered (budding, branching, cribriforming, crowding or back-to-back growth)	Preserved
Cytologic atypia	Moderate (to marked)	Mild (to moderate)
N/C ratio	Increased	Normal
Nuclei	Hyperchromatic, stratification	No stratification
Nucleoli	Prominent, enlarged (or multiple)	May be prominent, usually not enlarged
Mitoses	Frequent, pathological mitoses	Frequent, normal looking
Surface maturation	No	Yes
Increased lamina propria inflammation	Variable	Usually present

Immunohistochemistry using antibody preparations directed against p53 may be of help in selected cases. Pathological staining patterns include p53 overexpression (due to impaired protein degradation) or total lack of staining (due to protein truncation; internal positive control of active non-mutated p53 necessary). According to international guidelines, confirmation of dysplasia by an independent expert gastrointestinal pathologist is recommended.

Patients may also develop dysplasia independent from the disease, that is, sporadic adenomas. The distinction is easy, when the neoplastic lesion is removed from uninvolved mucosa. However, if the neoplastic polyp originates from inflamed mucosa, the pathologist should at least try to differentiate colitis-dependent (raised) dysplasia (syn. dysplasia associated lesion or mass, DALM) from colitis-independent dysplasia (sporadic adenoma, syn. adenoma-like mass, ALM). The following table may help to guide the differential diagnosis.

	Colitis-associated elevated (raised) non-adenoma-like lesion	**Adenoma-like lesion (sporadic adenoma)**
Age	< 50 years	> 60 years
Extent of disease	Usually total	Usually subtotal
Activity of disease	Usually active	Usually inactive
Disease duration	Long (>10 years)	Short (<10 years)
Macroscopy	Large, velvety patches or irregular (asymmetric) plaques	Small, well circumscribed, regular (symmetric) polypoid lesions
Associated flat dysplasia	Common (no sharp delineation)	Absent (sharp delineation)
Histology of lesion	Irregular neoplastic glands (varying configuration, size and diameter) with varying amounts of stroma	Regular neoplastic glands (similar configuration, size and diameter) with low amounts of stroma
Increased (mononuclear) lamina propria nflammation	Usually present	Usually absent
Mixture of benign/ dysplastic crypts at surface	Usually present	Usually absent

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L06

Role of pathologist in the diagnosis of colorectal polyps

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Colorectal carcinoma (CRC) develops as a result of progressive accumulation of genetic and epigenetic alterations that lead to neoplastic transformation of colorectal epithelium. Three possibly overlapping molecular pathways of tumour progression are described in colorectal carcinogenesis: the chromosomal instability pathway, the microsatellite instability (MSI) pathway, and the CpG island methylator phenotype (CIMP) pathway. Most CRCs follow the chromosomal instability pathway which has a morphologic continuum known as the adenoma-carcinoma sequence. Most of these CRCs have mutation of the adenomatous polyposis coli (APC) gene on chromosome 5q and altered total DNA content (aneuploidy) with numerous allelic losses and gains. Germline mutations in APC lead to the hereditary syndrome of familial adenomatous polyposis (FAP).

A second carcinogenesis pathway characterized by high levels of MSI (MSI-H) is evident in more than 90% of CRCs in patients with hereditary non-polyposis colorectal cancer syndrome (HNPCC) and in about 15% of sporadic CRCs. MSI-H is caused by inactivation of both alleles of a nucleotide mismatch repair gene, usually hMSH2 or hMLH1. CRCs in the MSI-H pathway are characterized at the molecular level by numerous nucleotide substitutions and insertion/deletion mutations in repeated nucleotide sequences (microsatellites). Germline mutation of a mismatch repair gene causes HNPCC syndrome, while most sporadic MSI-H CRCs are due to transcriptional silencing of hMLH1 by promoter methylation.

A third molecular pathway of carcinogenesis in CRCs is CpG island methylation. CpG islands are 0.5- to 2-kb regions rich in cytosine-guanosine dinucleotide repeats present at the 5' region of approximately half of all human genes. Methylation of cytosine residues within CpG islands of promoter regions and proximal exons is associated with loss of gene expression by repression of transcription. In CRCs, transcriptional inactivation by methylation occurs in numerous genes, including the p16 cell-cycle regulator, p14 (ARF) gene on chromosome 9p, O^6-methylguanine DNA methyltransferase (MGMT) DNA repair gene, and the hMLH1 mismatch repair gene in tumour cells, but rarely in colorectal mucosa. Methylation is often concordant among numerous genes, and concordant methylation defines the CIMP. CRCs with hMLH1 methylation usually lose expression of hMLH gene product, as can be detected by immunohistochemistry, acquire defective mismatch repair, and progress via the MSI-H pathway. Other CRCs with methylation that does not involve hMLH1 have chromosomal instability but not MSI-H.

In this paper, the role of pathologist in the diagnosis of colorectal polyps with special emphasis to “advanced adenomas” and serrated polyps will be reviewed.

Colorectal polyps have two large groups of lesions characterized by the epithelium they possess: adenomatous polyps or adenomas and serrated polyps. Adenomas are further subclassified into tubular, tubulovillous and villous adenomas depending on their architectural features whereas serrated polyps comprise of hyperplastic polyp, sessile serrated adenoma/polyp and traditional serrated adenomas.

Intraepithelial Neoplasia/Dysplasia in colorectal adenomas

Intraepithelial neoplasia (IEN)/dysplasia comprises a continuum extending from low to high grade dysplasia to intramucosal carcinoma. In the context of IEN, some terms carry different meanings in different countries. Among the problems is the failure in the West to recognise "flat" or depressed adenoma and non-invasive carcinoma in the gastrointestinal tract, while in Japanese practice the term "dysplasia" is not used other than for borderline squamous lesions of the oesophagus. Furthermore, the Japanese concept of "mucosal carcinoma" in the colorectum—that is, neoplasia *without* submucosal invasion—is avoided by many Western pathologists since these cases do not have the potential to metastasize due to the lack of lymphatics in colorectal mucosa. Although it can be argued that submucosal invasion has to originate from an initial carcinoma confined to the mucosa (either in situ or invasion limited to the lamina propria of the mucosa), in the colorectum such "carcinomas" do not behave as biological malignancies—that is, they do not exhibit metastases. Therefore, such lesions can be adequately treated by local removal. In order to avoid labelling a patient as having a colorectal *cancer*, many Western pathologists include the same appearances within high grade dysplasia**.**

The grading of dysplasia is dependent upon cytologic and architectural features in a colorectal polyp. While, cytologically, nuclear crowding, stratification, high n/c ratio, prominent nucleolus, increased number of mitoses can be the differential criteria, irregular crypts, lack of lamina propria between the crypts, glandular budding and crowding are the criteria of architectural dysplasia. The presence of high grade dysplasia, in a villous adenoma, in particular, warrants a diagnosis of advanced adenoma which needs careful follow up with colonoscopy.

Carcinoma in colorectal polyps

A "malignant polyp" or an "advanced adenoma" is defined as an adenoma with foci of cancer invading the submucosa which carries a risk of lymph node metastasis. When there is invasive carcinoma into submucosa the risk factors are:

- Level of invasion (Haggitt' levels)
- Poor tumour differentiation (grade)
- Lymphovascular invasion
- Presence of tumour budding (groups of>5 cancer cells in a x20hpf)
- Kikuchi's Sm3 and possibly Sm2
- Positive resection margin
- Poor demarcation and differentiation at invasive front, cribriform pattern, absence of lymphoid infiltration are considered as relative factors for aggressive behaviour.

The incidence of malignant colorectal adenoma has been reported as 2.6-9.7% of all removed colonic polyps with an average of 4.7%. Treatment of malignant adenomas is highly dependent upon their pathologic assessment. Once the diagnosis is made the following points should be considered:

- A high or low risk malignant adenoma
- Polypectomy or surgery

Polypectomy is the treatement of choice in low risk malignant polyps while in patients with high risk malignant adenomas the adverse effect of malignancy against the morbidity and mortality of colonic resection should be weighed before making a decision for best treatment.

Serrated Polyps

The term "serrated polyp" is used for polyps demonstrating saw tooth-like infolding of the surface and crypt epithelium, likely as a consequence of an increase in the cellular proliferation zone, extending from lower to mid or upper crypts, as well as an inhibition of programmed cellular exfoliation (apoptosis/anoikis) of the surface mucosa. Putative precursor lesions for all serrated polyps are the hyperplastic subtype of aberrant crypt foci (ACF). However, it should be noted that epithelial serration is not restricted to "serrated polyps" but can also be observed in traditional adenomas with villous configuration, in particular, and in hamartomatous polyps.

The spectrum of serrated mucosal lesions of the colorectum comprises biologically distinct hyperplastic polyps (HPs), sessile serrated adenomas (SSAs), and traditional serrated adenomas (TSAs). Dysplasia can be observed in serrated polyps in two different forms: adenomatous or serrated dysplasia.

Hyperplastic polyps: Hyperplastic polyps (HPs) have traditionally been regarded as non-neoplastic lesions which are typically small (<5 mm) in diameter and are benign sessile or slightly raised mucosal lesions that appear to be more frequent in the distal colon and rectum. They tend to show spatial clustering with adenomas and colorectal carcinomas. Over the years, however, colorectal cancer has been linked to hyperplastic polyps that are large (>1cm) and/or multiple and/or located in the proximal colon. This view has been confirmed in cases of hyperplastic polyposis where multiple HPs occur throughout the colon with a 50% risk of colorectal carcinoma.

HPs have a prevalence of 10-12.5% in asymptomatic patients in large cohort studies. They comprise 80-90% of all serrated polyps. There are four histological characteristics of HPs including epithelial serration, simple elongated crypt architecture similar to normal mucosa, maturation of crypt epithelium towards the surface, and proliferative activity confined to basal third of the crypts, also similar to normal mucosa. Epithelial serration invariably involves the upper portion of the crypt and, in some, may extend into the mid-crypt zone. Elongated, enlarged crypts of the HPs are separated

by lamina propria and infrequently show basal bifurcation or branching. In HPs there is a thickened basement membrane beneath the surface epithelium which is never found in SSAs. HPs do not show nuclear atypia apart from vesicular nuclei which is limited to the basal crypt epithelium. HPs showing excess proliferation or slight architectural disorganisation, not fulfilling the criteria of SSA have been observed (personal observation as well as others) but their biological behaviour is unknown.

Sessile serrated adenomas/polyps: Sessile serrated adenoma (SSA) is the most recently described serrated polyp. The morphologic features of SSA were originally described by Torlakovic & Snover in the context of hyperplastic polyposis. The concept of SSA was reintroduced in 2003 when morphologic features of polyps resembling HPs, but with abnormal proliferation and metachronous colorectal carcinomas. Although the figures vary, SSAs seem to represent 8-20% of serrated polyps. SSA is considered as a larger variant of hyperplastic polyp, or possibly as an intermediary between hyperplastic polyps and serrated adenomas. SSAs have a predilection for proximal colon, but are distributed throughout the colon and rectum.

Histopathological diagnosis can be very difficult since it bears close resembles to HP. The diagnosis is mainly based on architectural features rather than cytological ones as abnormal proliferation and/or decreased apoptosis. These architectural features include branching of crypts, dilatation of the base of the crypts, horizontally oriented crypts, exaggerated serration throughout the polyp including the basal crypts, and inverted crypts. Mitoses in the upper half of crypts, vesicular nuclei with prominent nucleoli in the upper half of crypts, increased production of intracellular and/or luminal mucin, and irregularity in the distribution of goblet cells/presence of immature goblet cells are the cytological features that may be observed in most SSAs. Some of these features have been found in proximal HPs, suggesting a relationship with SSAs. Although separation of SSA from HP is critical to the understanding of these lesions, distinction from traditional serrated adenoma is potentially important and often difficult.

Traditional serrated adenomas: Traditional serrated adenoma (TSA) was originally described by Longacre and Fenoglio-Preiser as a subtype of adenomatous polyps. Although originally their prevalence was reported as 0.6%, it has been higher (2-3.5%) in recent reports. TSAs have a predilection for distal colon and rectum and they show a pedunculated or road-based polypoid growth. The significance of TSAs lies in their role as putative successors of HPs, and immediate precursors of colorectal carcinoma. They are lesions that simultaneously demonstrate the serrated architecture typical of HPs and the epithelial dysplasia of adenomas. TSAs differ from classic hyperplastic polyps in showing unequivocal epithelial dysplasia, increased architectural complexity, pronounced cytoplasmic eosinophilia, absence of thickening of the basement membrane underlying the surface epithelium, and a relative lack of endocrine cells.

TSAs may be sessile and flat with a tubular architecture; these closely mimic hyperplastic polyps. TSAs may also be protuberant with a tubulovillous or villous architecture; these may be confused with traditional tubulovillous or villous adenomas. Minor admixtures of hyperplastic and/or traditional adenomatous elements may be included within otherwise typical serrated adenomas. Some TSAs arise within pre-existing HPs or SSAs whereas others may represent serrated transformation within a pre-existing adenoma. Others, or may be the majority, arise *de novo*. The differential diagnosis of TSA from SSA may be difficult in some cases and the difference between these two types of polyps as on the uniform population of abnormal epithelial cells in TSA compared to SSA. The epithelial cell seen in TSAs is a columnar cell with eosinophilic cytoplasm and a central elongated nucleus that is hyperchromatic with mild pseudostratification, usually to a lesser degree than the traditional adenomas.

Dysplasia in Serrated Polyps

In serrated polyps two types of dysplasia have been described: conventional adenomatous and serrated dysplasia. Serrated dysplasia is defined as cytological abnormalities including round nuclei with vesicular chromatin pattern, increased n/c ratio, prominent nucleoli, loss of polarity and some degree of nuclear crowding without pseudostratification as seen in adenomatous dysplasia. Architectural dysplasia may not be as prominent as the cytological atypia that could be observed in these lesions. Conventional adenomatous dyplasia may result in a mixture of serrated and adenomatous epithelium in these polyps that may lead to a diagnosis of mixed polyps. However, reporting such polyps as mixed polyps bears the risk of underdiagnosing adenomatous dysplasia that is present within the polyp.

Consensus is necessary not only to clarify the histopathological identification of each lesion, but also to allow for prospective analyses in an effort to determine the clinical significance and thus the need for appropriate endoscopic follow-up. Currently, colonoscopic surveillance for the detection of metachronous hyperplastic polyps or adenomatous polyps following the identification of hyperplastic polyps is not recommended, although, special types of hyperplastic polyp, such as those greater than 1 cm, a multiplicity of more than 20 hyperplastic polyps (especially in a proximal

location) or polyps with associated dysplasia may require closer surveillance. On the other hand, it is still not clear how or if other serrated lesions should alter the management of patients. Nevertheless, as pathologists, we should, in our reports, emphasize that serrated mucosal lesions are also potential precursors of a smaller subset of colorectal carcinomas. The current view can be summarized as, "any lesion reported as a traditional serrated adenoma, or sessile serrated adenoma should be completely excised if possible, and the patient followed to ensure that there is no recurrence and that other similar lesions do not develop. The interval for follow-up is completely unknown but likely every 2–5 years should suffice once the large bowel is 'clean'. The development of any degree of dysplasia implies that the lesion is now an adenoma and follow-up should be according to guidelines for adenomas."

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L07

Molecular diagnostics of Lynch syndrome: A central role for the pathology laboratory

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Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome (LS) is a familial autosomal dominant cancer predisposition syndrome that accounts for 2-5% of colorectal cancers (CRC) usually proximally located. The renaming of the HNPCC syndrome to LS is in part due to the recognition of the risk of extra-colonic cancers.

LS is linked to germline mutations in one of the DNA mismatch repair (MMR) genes, tipically MLH1, MSH2, MSH6, or PMS2, which leads to microsatellite instability (MSI). However, there is recent evidence to suggest a role for alternative genetic pathways unrelated to mismatch repair, and so-called modifier or accessory genes that might predispose to the development of LS. The two main tests for the detection of MMR deficiency are MSI by PCR and immunohistochemistry (IHC) for MMR proteins. Most molecular tests of MSI use a panel of mononucleotide repeats, as these are probably the most sensitive and specific markers for MMR deficiency. IHC for the MMR proteins MLH1, MSH2, MSH6, and PMS2 is also a fairly sensitive and specific indicator of MMR deficiency.

There are several approaches to determine which tumors should be tested for the presence of MMR deficiency. One is the application of Revised Bethesda Guidelines which takes into account numerous factors, including the age of the individual, the histology of the tumor, and personal and family history of LS associated tumors. Another approach is universal screening, i.e. every CRC with or without endometrial cancer should be tested for MRR deficiency, usually by IHC.

Cancer genetics services should include pathologists and be organized on multidisciplinary team lines. In modern pathology practice pathplogists play a critical role in identifying such tumors but also in screening cases for LS by using modern molecular techniques. Correctly recognizing LS is essential for the application of appropriate screening and surveillance measures.

L08

Current views on pathology and etiopathogenesis of squamous cell carcinoma of the anus

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Despite being uncommon, anal carcinoma exhibits a variety of tumor types reflecting the complexity of anal histology. The vast majority are squamous cell carcinomas (SCC), representing approximately 80% of all anal tumors. Anal SCC is etiologically strongly associated with infection with human papillomaviruses (HPV), particularly HPV 16, which can be detected in up to 90% of cases. Risk factors include anoreceptive sexual intercourse, history of HPV-related genital tract disease, immune deficiency (e.g., in HIV infection or after transplantation), smoking and inflammatory bowel diseases.

Morphologically, HPV-positive anal SCC shows various patterns, from well differentiated, keratinizing tumors to poorly differentiated tumors that may require immunohistochemistry to confirm the diagnosis and exclude other tumors, such as lymphoma, adenocarcinoma, neuroendocrine carcinoma and melanoma. Though SCC with basaloid morphology, also referred to as cloacogenic carcinoma, is more likely to be HPV-positive, morphology alone is not helpful in determining the relation of carcinoma to HPV infection and does not predict prognosis.

Another variant of anal SCC is verrucous carcinoma, usually regarded as synonymous to giant condyloma (Buschke-Löwenstein tumor) (BLT). Our studies, using modern, highly specific and sensitive techniques for HPV detection, suggest that anal verrucous carcinoma is not related to HPV infection, similarly to verrucous carcinoma at other sites, for example in the head and neck. These new insights into etiology of verrucous carcinoma suggest that BLT and verrucous carcinoma are probably two entities: verrucous carcinoma is a well differentiated SCC, not related to HPV infection. It can cause extensive destruction, but does not metastasize. BLT is a condyloma, usually caused by HPV 6 or 11. It can grow over a large area, responds poorly to topical treatment and can recur, but does not cause deep tissue destruction.

Similarly to cervical cancer, anal SCC is associated with intraepithelial neoplasia (AIN), also called squamous intraepithelial lesion (SIL) and dysplasia, a precursor lesion to anal SCC. Two-tiered grading is now recommended. AIN can be diagnosed either by cytology or histology.

Immunohistochemistry for p16 and various methods for HPV detection is nowadays regarded as a helpful adjunct, but morphologic features remain the most important criterion for diagnosing anal carcinoma and AIN. An important new technique is *in situ* hybridization for E6/E7 mRNA, enabling to detect integrated, transcriptionally active virus, thus providing proof that the presence of HPV is causally related to the lesion and is not merely the result of viral colonization.

Slide Seminar

Case 1 & 2

Pitfalls in diagnosis of gastrointestinal tumors

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Case 1

Clinical History

16-year-old young adult with large exophytic gastric tumor mass that infiltrated gastric wall as well as liver tissue was surgically treated. Other clinical and laboratory analyses were not available.

Pathological Findings

Histologically the tumor was consisted from e lymphoid cells with blastic features growing in moderate cohesive arrange and areas with ``starry sky`` phenomena. The cells were CD20+, CD10+, bcl2-, bcl6+ with high proliferative index of 80%.

Diagnosis: ***B cell lymphoma, unclassifiable with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma.***

Case 2

Clinical History

70-year-old female with clinical suspicion for sarcomatous infiltration of the transversal colon has been surgically treated.

Pathological Findings

Histological and immunohistochemical analysis revealed polymorphic cellular infiltration consisted mostly from T cells, few B cells, histiocytes. Rare cells with round to oval nuclei were negative for lymphoid markers, epithelial markers as well markers for GIS but positive for MSH2, MSH6, CDX2, PMS2, MLH2 and MSH6.

Diagnosis: ***Medullary colonic carcinoma***

Discussion

Two cases surgically treated for primary gastric tumor and primary colonic tumor with morphology of round tumor cells are presented. In the first case however when classical morphology of BL is present, a diagnosis of classical BL should be done. Further studies that would shed new insights on the epigenetic and cytogenetic characteristics of DLBCL/BL are needed. In the second case although the morphology and dominant immunophenotype of CD3 positive T cells suggest PTCL, one should be careful and have in mind to do wider spectrum of immunohistochemical analyses due to the differential diagnosis of medullary colonic carcinoma. Close collaboration between smaller regional centers and large consultation centers for application of more sensitive techniques is important in order of the correct diagnosis to be done.

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Case 3 & 4

Signet ring cell change of the epithelium in the digestive tract

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Signet ring cells are characterized by distinctive morphological appearance i.e. by rounding up of cells with crescent-shaped nuclei displaced to the cell periphery secondary to intracytoplasmatic accumulation of mucin, vacuoles or inclusions. Their presence are generally considered a diagnostic indicator of aggressive signet ring cell adenocarcinoma, typically found in the stomach and the breast. However, rare reports of findings of these cells in clearly non-neoplastic conditions led to the designation of signet ring cell change (SRCC).[1] In that way, presentation of two very specific cases among several we experienced is very illustrative.

Case 3

Clinical History

A 43-year-old woman with a previous history of persistent indigestion and moderate weight loss presented to an outside hospital with an episode of abdominal pain, nausea, vomiting and melena. Subsequent gastroduodenoscopy revealed mucosal infiltration and ulcerative defects on inflammed and swollen background in the antral and angular regions of the stomach. Histopathological report of gastroscopic biopsies was inconclusive but suggestive of chronic gastritis with suspicious lymphoid infiltration. After repeated biopsy, the outside pathology report rendered a diagnosis of poorly differentiated adenocarcinoma with signet ring cell features. Based on these results, slides from both biopsies were reviewed in our department and the patient underwent third endoscopy in order to plan a gastric resection.

Pathological Findings

The sections of the first previous biopsy confirmed suspicious lymphoid proliferation with hyperplastic foveolar epithelium containing foci of dystrophic goblet cells and very few revealed SRCC in surrounding lamina propria. Biopsy examination of repeated previous endoscopy showed scarse lymphoid infiltration but multiple intramucosal epithelial clusters of SRCC, suggesting a diagnosis of gastric SRC carcinoma. However, on the third biopsy at our hospital, there was intense lymphoid infiltration morphologically and immunohistochemically consistent of low-grade B-cell lymphoma of MALT type associated with *H. pylori* positive chronic gastritis, but no epithelial clusters seen in the previous biopsies. At this stage the diagnosis of gastric MALT lymphoma with suspicious SRCC infiltration was formulated, but it was not possible to exclude synchronous occurrence of early gastric carcinoma. Although the patient received anti-*H.pylori* resulting in successful eradication of *H.pylori*, she had undergone partial gastrectomy. The resection specimen examination confirmed MALT lymphoma with microfoci of SRCC clusters, exclusively found in the area of lymphomatous infiltration. The patient received additional chemotherapy and so far she is well and free of disease (63 months). Follow-up biopsies of gastric remnant were negative.

Diagnosis: ***Gastric low-grade marginal zone lymphoma of MALT type with epithelial SRCC clusters.***

Case 4

Clinical History

A 76-year-old male patient presented to the emergency department of our hospital with acute abdominal pain and after clinical and radiological examination underwent laparotomy. Intraoperative findings showed chronic perforated pyloric ulcer and suggested biliary fistula due to prominent surrounding peritonitis that led to cholecystectomy.

Pathological Findings

Histology verified perforated chronic pyloroduodenal ulcer and chronic pericholecystitis. However, prominent histologic findings was extensive mucosal alteration, showing almost completely epithelial change with plethora of SRCCs accompanied by papillary hyperplasia and often multilayered proliferation. Collections of SRCCs were mostly found in the upper parts of papillary projections or admixed with necrotic material on the mucosal surface, but many sections revealed SRCCs confined by intact basement membranes. There were also SRCCs seen in the lumina of mucosal glands including Aschoff-Rockitansky sinuses. The vast majority of SRCCs lacked atypia and mitotic activity. However, we found some foci with atypical epithelium showing nuclear enlargement, hyperchromasia and mitotic figures consistent

with focal low grade dysplasia. Therefore, gallbladder was entirely submitted for histologic examination, but no erosions or ulcerations were found, nor invasion into the lamina propria or stromal invasion identified. All SRCCs were immunoreactive for pancytokeratin AE1/AE3 and negative for CD68, including intraluminal, desquamated and degenerated cells, confirming their epithelial nature. Almost all epithelial cells expressed strong membranous immunopositivity for E cadherin but focal lack was found in some group of cells with significant epithelial atypia (dysplastic cells). In addition, those cells associated with atypical SRCC morphology expressed high Ki-67 protein and p53 index. The patient is alive and well nearly two years later, without any evidence of morbidity or malignancy.

Diagnosis: ***Prominent signet ring cell change of the gallbladder mucosa with papillary hyperplasia and focal epithelial dysplasia.***

Discussion

The precise mechanism for production of epithelial SRCC in the digestive tract is still unclear, but seems to be related to ischemia, necrosis, ulceration or on occasion provoked by inflammatory process. It is proposed that mucosal ischemia and inflammation in non-neoplastic conditions may result in detachment and sloughing of columnar epithelial as well as goblet cells, leading to rounding up and compression of nuclei to the cell periphery assuming characteristic morphology of SRCC.[2] In other conditions reported to be associated with SRCCs with intracellular mucin pathogenesis was thought to result directly from fulminant inflammation and/or necrosis (pseudomembranous colitis, ischemic ileitis and acute erosive gastropathy).[3-5] In addition, similar SRCC is reported in the subserosa of ischemic small intestine, but is assumed to be originated by adipose tissue degeneration.[6]

Histomorphological features of SRCCs in gastrointestinal and biliary tracts involves mostly surface epithelium, but in some cases, often in eroded or ulcerated areas they could be situated in basal crypts and glands. Contrary to signet ring cell carcinoma, where dyshesive single cells or small clusters infiltrate in the lamina propria, SRCCs show linear distribution, often confined within the basement membrane and are mostly found in the upper portions of mucosa. Frequent associated histologic changes such as erosion or ulceration may detach SRCCs from the basement membrane and float or intermix with fibrinous or inflammatory exudates, mucus or desquamated epithelial cells and other cells in the propria, giving rise to pseudoinfiltrative growth pattern. However, there is no desmoplasia, lymphovascular or perineural invasion and other evidence of malignancy. Bland cytologic features are characterized by pale-pink cytoplasm and peripherally compressed nuclei show no nuclear enlargement, atypia, hyperchromasia, nucleoli and mitotic figures, but uniformity and evenly distributed nuclear chromatin.[7]

Although intracellular mucin can be demonstrated in SRCCs by mucicarmine, periodic acid-Schiff staining with digestion and reticulin stain can help in determination of growth pattern as the intact basement membrane is highlighted in this way. Combination of histochemistry and pancytokeratin immunohistochemistry may be very useful for the assessment of the epithelial architecture, as well as distribution and type of growth pattern of SRCCs, which are not invading beyond the basement membrane in the lamina propria or surrounding stroma. Ancillary immunohistochemical markers for E-cadherin, p53 and Ki-67 protein have been used to differentiate benign SRCCs from their malignant counterparts. Contrary to signet ring cell carcinoma, most SRCCs show normal membranous immunoexpression for E-cadherin, but are negative for p53. While Ki-67 protein labeling index in carcinoma typically is more than 40%, in SRCCs is less than 5%. In our case with SRCCs in the gallbladder, histomorphology and immunohistochemistry were consistent with most of findings in other reports.[8,9] We found immunohistochemistry to be very helpful both to remove doubt of primary signet ring cell carcinoma and to ascertain the finding of dysplastic epithelial changes in the gallbladder mucosa.[1,2,10]

Differential diagnosis of SRCCs in non-neoplastic conditions, besides invasive carcinoma includes so-called “signet ring cell carcinoma in situ” in patients with hereditary gastric cancer due to CDH1 gene mutation, characterized by partial replacement of the glandular lining by signet ring cells, their pagetoid spread in foveolar epithelium and are found on the normal, but not ulcerated or ischemic gastric mucosa background.[11]Similar cases can also be the matter of misdiagnosing preneoplastic lesions such as so-called “tubule neck dysplasia” or other reported as gastric globoid dysplasia.[12] However, SRCCs have to be differentiated from muciphages and other histiocytic infiltration by their immunopositivity for CD68 and CD163 antigens and morphologically by centrally located small round nuclei with foamy cytoplasm.[13,14] The differential diagnosis includes even Russell bodies gastritis, lymphoplasmacytic lymphoma or plasmacytoma, where the mucin-laden vacuoles of lymphoid (non)neoplastic cells may suggest Russell bodies.[15,16] Finally, SRCCs may be seen as a result of endoscopic artefacts and are important in recognition of potential mimics of adenocarcinoma, especially in surveillance biopsies of residual gastric cancer.[17]

In neoplastic conditions other than signet ring cell carcinoma, etiopathogenesis of SRCCs depends on the associated tumor type. In the digestive tract, most cases of SRCCs are reported in association with gastric lymphoma of MALT type (37%) or other lymphoid proliferations and might represent "foveolar type of lymphoepithelial lesions", i.e. dissagregated foveolar epithelial cells in lymphoepithelial lesions, although a proportion of these cells are lymphoid in origin.[18] Zamboni et al. stated SRCC are restricted: to MALT-type lymphoma, to upper foveolar level, just above classic lymphoepithelial lesions that are found in the neck region ("zoning phenomenon") and to areas of lymphomatous infiltration even in relapsed lymphomas, but are not spread in the deeper mucosa or other tissues. However, similar findings in endoscopic biopsies of gastric lymphoma were interpreted to be artifactual.[19] So-called "true" signet ring cell lymphoma appearance could develop as a consequence of intracellular accumulation of immunoglobulins.[20] In GIST, accumulation of glycogen is thought to be responsible for SRCC morphology of some neoplastic mesenchymal cells and in neuroendocrine tumors it is caused by neuroendocrine granules and myelin figures.[21] Several reports showed that SRCCs can also be found in gastrointestinal polyps, such as ulcerated tubular adenomas.[8] Long time ago, this pseudoneoplastic phenomenon was recognized in Peutz-Jeghers' hamartomatous polyp and focal mucosal ischemia was suggested to be mechanically induced by the stretching or torsion of the polyp itself.[22] In addition, similar SRCCs were reported in non-neoplastic and neoplastic conditions in a large number of other epithelium-lined organs, notably in the skin, genito-urinary, endocrine and central nervous systems, including "signet-ring" sinus histiocytosis of lymph nodes mimicking metastatic adenocarcinoma.[2,23]

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Case 5

Sessile serrated adenoma of the appendix

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Clinical History

50-year-old female patient was admitted to the University Clinic of Abdominal Surgery complaining of abdominal pain, vomiting and fever. Appendectomy was performed and a clinical diagnosis of acute gangrenous appendicitis was made.

Pathological Findings

Acute gangrenous appendicitis with perforation was confirmed associated with another distinct lesion. The diagnosis was based on architectural features as crypt branching and lateral growth along muscularis mucosae, dilatation and exaggerated serration down to crypt base, creating L- or inverted T-shape crypts. The growth pattern was accompanied by the presence of mature cells at the base of the crypt, asymmetrically extension of mitoses to upper crypts and absence of thickened subepithelial collagen layer. Cytologic dysplasia was not seen.

Diagnosis: ***Sessile serrated adenoma associated with acute appendicitis.***

Discussion

Intestinal mucosa can develop hyperplastic changes in association with inflammation and can mimic sessile serrated adenoma. It is recognized that not all serrated lesions can be easily classified, often because of sampling or poor orientation of specimen. In such cases the term “serrated polyp, unclassified” may be used. SSA/P is thought to be the precursor to sporadic carcinomas with microsatellite instability and is probably the precursor for CpG island-methylated microsatellite-stable carcinomas.

Appendiceal serrated polyps may have some special features despite similarities with their colorectal counterparts, so further studies are needed involving comparative evaluation on both morphologic and molecular grounds.

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Case 6

Cystic desmoid tumor of the pancreas

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Clinical History

We report a case of pancreatic cystic desmoid tumor (CDT) in a 47-year-old male presenting with recurrent epigastric pain and obstructive jaundice. Abnormal laboratory findings included elevated LDH 605 U/L, total.bilirubin 133 umol/L, dir.bilirubin 119 umol/L and alkaline phosphatase 608 U/L.The serum tumor markers were within normal limits for CEA 2.4 ng/mL and increased for Ca 19-9, 198.0 U/ml. Imaging studies revealed a homogeneous 4cm tumor in the pancreatic head, well-delimited, not encapsulated, mainly solid, with a cystic component. Due to the clinical suspicion for cystadenocarcinoma pancreatectomy was performed.

Pathological Findings

The removed portion of the pancreas measured 10x4,5x3,5 sm. and contained a 3,5x2x1,8 sm. well-circumscribed, not encapsulated white tumor mass with smooth cut surface and cystic component. Histological analysis showed that tumor had infiltrated the surrounding pancreatic parenchyma and consists of spindle cells with eosinophilic cytoplasm and hyperchromatic nucleus with minimal cytologic atypia, arranged in a fascicular pattern and with branched hemangiopericytoma-like vessels. No necrosis was found and mitotic figures were very rare, 1-2 mitosis per 10 high-powered fields. Hyalinization and myxoid degeneration areas were seen in parts, which were hypocellular. The cystic component was related to retentional cysts and duct dilatation. Immunohistochemical analysis showed that tumor cells were positive for beta-catenin, CD34, Vimentin, CD99, Actin, bcl-2 and negative for S-100, EMA, p53, Caldesmon, Desmin, S100 and Cytokeratins. Proliferative index on Ki-67 staining was below 1%.

Diagnosis: ***Benign cystic desmoid tumor of the pancreas***

Discussion

Cystic desmoid tumors (CDTs) is quite rare tumor, account for 0.03% of all neoplasms and 3% of soft tissue tumors, occurring very rarely in extrapleural localization. There is limited data regarding biological behavior of CDTs with extra-pleural localization, because they are quite rare tumors. Diagnosis of malignancy is based on nuclear atypia, cellularity, necrosis, high Ki-67, expression on p53, 4 mitoses in 10 HPFs and tumor larger than 10 cm.

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Case 7

Solid pseudopapillary tumor of pancreas

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Clinical History

A 60-year-old female with a history of postprandial discomfort, nausea and epigastric pain was admitted to hospital for further investigation. Blood tumor markers were normal. Abdominal ultrasound and CT scan was performed showing a 4 cm. hypoechoic mass in the mid-body of the pancreas. MRI was subsequently performed showing a 4x3x2 cm well-delimited, encapsulated solid tumor with foci of hemorrhage. Neoplasm have not been associated with a functional endocrine syndrome. The diagnosis of adenocarcinoma was suspected and partial pancreatectomy was performed.

Pathological Findings

The removed portion of the pancreas measured 6x6x2.8 cm. and contained a 4x3.3x2.5cm well-demarcated, encapsulated tumor. The cut section revealed very soft, lobulated, light brown to yellow solid areas and zones of hemorrhage. Histologically tumor was composed of sheets of relatively uniform, loosely cohesive cells with eosinophilic granular cytoplasm and uniform nuclei with nuclear groves. There was delicate background vasculatures and cells were loosely adherent to the blood vessels, forming characteristic pseudopapillae. Foam cells and red blood cells were scattered among the neoplastic cells. Some of the neoplastic cells had clear, vacuolated cytoplasm or intracytoplasmic eosinophilic PAS-positive globules. Infiltration of the surrounding pancreatic tissue, angioinvasion or perineural invasion were not detected. Immunohistochemical analysis on the resected tumor revealed that the tumor cells express diffusely positive for vimentin and CD56, focally positive for NSE, chromogranin and cyclin D1 and were negative for CK20, CK7 and CK19.

Diagnosis: ***Solid pseudopapillary neoplasm***

Discussion

The precise cellular derivation of this tumor remains elusive, so routine immunohistochemical staining is no consistent in determining its phenotype. A variety of stain expressions have been described, representing neural, epithelial and acinar elements. The histogenesis is unknown but an attractive hypothesis has been developed that these tumors originate from a primordial cells and lack definite endocrine and exocrine differentiation.

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GYNAECOLOGICAL PATHOLOGY

Symposium

L09

Recent developments in the pathogenesis and classification of epithelial tumours of the lower genital tract and their precursors

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The predominant cause of epithelial neoplasia of the lower female genital tract, whether arising in squamous or in glandular epithelium, is infection with high-risk human papillomaviruses (HPVs). Virtually all squamous lesions of the cervix and vagina are associated with HPV infection, as are the commonest glandular lesions, namely adenocarcinoma in situ and usual type adenocarcinoma. However, some intraepithelial and invasive lesions of the lower female genital tract are not HPV-associated. In particular non-HPV-associated vulval squamous neoplasia and non-HPV-associated cervical adenocarcinomas are well recognized and are included in the WHO 2014 classification of tumours of female reproductive organs.

HPV infection of the lower female genital tract is extremely common, particularly in young women. Over 200 HPV genotypes are recognized but lower genital tract neoplasia is associated with only a small subset of types, termed 'high-risk' HPVs. The prototypical high-risk HPV types are HPV16 and HPV 18, which account for around 70% of invasive cervical carcinomas, whether squamous cell or adenocarcinomas. Most anogenital HPV infections regress but persistent infection with high-risk HPV types is associated with an elevated risk of the development of intraepithelial lesions and their progression to invasive carcinoma.

The non-HPV-dependent development of invasive squamous cell carcinoma of the vulva, and its precursor lesion differentiated type VIN, is much less well understood. Indeed, little is known of the mechanisms, other than the lack of involvement of HPV infection. The association with vulval lichen sclerosis may provide clues to the pathogenesis but no clear mechanisms have been demonstrated. The investigation of this pathway is complicated by the subjectivity of diagnosis of the putative precursor lesion i.e. differentiated type VIN, which is problematic and overlaps with hyperplastic and reactive lesions. There is a pressing need for careful molecular analysis of both differentiated type VIN and non-HPV-associated vulval squamous cell carcinomas as these tumours are now recognized to be more aggressive clinically than those associated with HPV infection.

Non-HPV-associated adenocarcinomas of the cervix are being increasingly recognized. In particular, gastric-type adenocarcinoma, which includes adenoma malignum/minimal deviation adenocarcinoma, has been better characterized in recent years. These tumours have been shown to be more aggressive than HPV-associated adenocarcinomas and this diagnosis is therefore clinically important.

This discussion suggests that tumours of the lower female genital tract might be better classified primarily on the basis of their association with HPV infection. The 2014 WHO classification does not do this but it is likely that separation of tumours in this way will be incorporated into future classifications, particularly in view of their differences in clinical behaviour.

L10

Endometrial carcinoma and its precursors

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Endometrial carcinoma is classified into various histological types of which the most frequent is endometrioid carcinoma. The usual low grade endometrioid carcinoma consists predominantly of well-formed glands which typically resemble proliferative phase endometrium. High grade endometrioid carcinoma shows a predominantly solid pattern.

Variants of endometrioid carcinoma are characterized by various types of cellular differentiation such as squamous differentiation, secretory and ciliated cell changes or a predominantly villoglandular pattern. Mucinous differentiation may occur as pure mucinous carcinoma or within usual endometrioid carcinoma. Most non-endometrioid type carcinomas of the endometrium of which serous, clear cell and undifferentiated carcinomas are best known are high grade and resemble their ovarian counterparts. Undifferentiated carcinoma is separated into two categories, monomorphic and the dedifferentiated subtype.

Whereas the monomorphic type consists only of undifferentiated tumor the dedifferentiated type contains also a component of low grade endometrioid carcinoma.

Poorly differentiated neuroendocrine carcinomas are very rare and resemble their pulmonary and gastrointestinal counterparts. Mixed carcinomas need to contain a clear cell or serous carcinoma component.

A dualistic model for endometrial tumorigenesis

The pathogenesis of endometrial carcinoma distinguishes between two major pathways:

Type I and type II. Type I carcinomas develop usually along an adenoma-carcinoma sequence, particularly from atypical endometrial hyperplasia. They are associated with hyperestrogenism which is reflected by endometrial hyperplasia, hyperplastic myometrium, elevated serum estrogen and high body mass index. The tumors occur at younger age and usually are low grade and are diagnosed at low stage; the prognosis is favorable.

Histologically, type I carcinomas are of endometrioid type including variants or mucinous type, which express high numbers of estrogen receptors. Atypical endometrial hyperplasia is considered the precursor of type I carcinomas. In contrast, type II carcinomas are not associated with hyperestrogenism. They develop in an atrophic uterus in the background of atrophic endometrium and the serum estrogen is usually not elevated. They occur at older age, usually one decade later than type I carcinomas, are diagnosed at high stage and are associated with unfavorable prognosis. Histologically, type II encounters serous and clear cell carcinomas. Serous endometrial intraepithelial carcinoma, which may also be associated with clear cell carcinoma is considered the putative precursor lesion of serous carcinoma.

This model has been developed based on clinicopathological features to better explain the complexity behind the development of endometrial carcinoma. Certainly, it contains exceptions and is not able to explain everything. Attempts have been made to embed the upcoming molecular findings into this model. Type I and type II carcinomas show significant differences on the molecular level. Type I carcinomas frequently harbor mutations in K-Ras, PTEN, ß-catenin and ARID1a as well as microsatellite instability predominantly caused by inactivation of MLH1 due to promoter methylation. On the other hand, more than 80% of serous carcinoma show TP53 mutations. More recently detected mutations in uterine serous carcinoma involve PIK3CA, FBXW7 and PPP2R1A in about 20% each. The genetic alterations of clear cell carcinoma are less well known compared to serous carcinoma and involve PTEN, and TP53 in about 30% each whereas K-RAS mutations and MSI are rare.

A novel molecular classification by the TCGA project

The TCGA project revealed a novel type of genomic alteration which is interestingly associated with extremely favorable prognosis: mutations in POLE. Tumors harboring POLE mutations may histologically mimic serous type and high grade endometrioid carcinomas and are characterized by an enormous number of mutations which are not associated with marked chromosomal alterations and high copy number changes. The TCGA data unraveled 2 further prognostic groups: an intermediate group of tumors with MSI ("hypermutated") together with endometrioid-type carcinomas showing low copy number changes and a prognostic unfavorable group of serous-type carcinomas. This molecular stratification of endometrial carcinoma might become part of the diagnostic procedure as soon as the assessment of POLE mutations can be facilitated. The analysis of MSI and TP53 can be easily performed by immunohistochemistry, whereas POLE analysis still needs sequencing.

Immunohistochemical typing of endometrial carcinoma

Immunohistochemistry can be helpful for the typing of endometrial carcinoma by using a panel of antibodies. Low grade endometrioid carcinoma usually shows strong immunoreactivity for ER and PR, frequent loss of PTEN, nuclear ß-catenin and a wild type pattern for TP53, whereas high grade endometrioid carcinoma shows reduced ER and PR immunoreactivity and may show a heterogeneous but partially strong TP53 immunoreactivity. A strong diffuse or completely absent immunoreactivity for TP53 (all or null pattern), weak or absent ER/PR, negativity for WT1 and high Ki-67 is typical for serous carcinoma. Clear cell carcinoma is usually negative for ER and PR, shows a heterogeneous TP53 pattern and stains for HNF1ß, napsin A and racemase (AMACR). However, it has to be taken into account that these immunoreactive patterns need to be correlated with histology and they may show variations.

Endometrial hyperplasia

Classification of endometrial hyperplasia has been recently changed into 2 categories: hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia (AEH/EIN). AEH/EIN typically shows a complex architectural pattern with reduced volume percentage stroma combined with cytological atypia characterized by loss of polarity. The nuclei of AEH/EIN are usually irregularly distributed, round to oval shaped nuclei and show coarse chromatin and a prominent nuclear membrane.

A helpful criterion for the diagnosis of AEH/EIN is the comparison between the lesion and surrounding or entrapped "normal" (inactive, proliferative or secretory) glands. Immunohistochemistry for PTEN and Pax-2 can be used to receive additional information on a lesion histologically qualified as AEH/EIN. Loss of PTEN and/ or Pax-2 immunoreactivity is found in up to 77% of the AEH/EIN lesions. The distinction between AEH/EIN and well differentiated endometrioid carcinoma is based on the absence/ presence of destructive infiltrative growth, which is characterized by a labyrinth-like or cribriform pattern, complex papillary (villoglandular) structures or an altered ("desmoplastic") stroma.

Addendum

Table 1: Histopathological classification of endometrial carcinoma

- Endometrioid adenocarcinoma, usual type
- Endometrioid adenocarcinom, variant types
  - With squamous differentiation
  - With secretory differentiation
  - Villoglandular
  - With mucinous differentiation
  - Ciliated cell type
- Mucinous carcinoma
- Serous endometrial intraepithelial carcinoma
- Serous adenocarcinoma
- Clear cell adenocarcinoma
- Neuroendocrine carcinoma
  - Low-grade neuroendocrine tumor / carcinoid tumor
  - High-grade neuroendocrine carcinoma
    - Small cell neuroendocrine carcinoma
    - Large cell neuroendocrine carcinoma
- Mixed carcinomas
- Undifferentiated carcinoma
- Dedifferentiated carcinoma

Table 2: FIGO grading of endometrioid carcinoma of the endometrium

	Amount of solid non-squamous, non-morular growth
FIGO Grade 1*	≤5%
FIGO Grade 2*	6-50%
FIGO Grade 3	>50%

*The presence of bizarre nuclear atypia raises the grade by 1

Table 3: 2009 FIGO/UICC classification of endometrial carcinoma

Stage		pTNM	Definition
I			Tumor confined to the uterine corpus
	IA	pT1a	No or less than half myometrial invasion
	IB	pT1b	Invasion equal or more than half of the myometrium
II		pT2	Tumor invades cervical stroma but does not extend beyond uterus
III			Local and/or regional spread of the tumor
	IIIA	pT3a	Tumor invades serosa of the uterus and/or adnexae
	IIIB	pT3b	Vaginal and/or parametrial involvement
	IIIC		Metastases to pelvic and/or para-aortic lymph nodes
	IIIC1	pN1	Positive pelvic nodes
	IIIC2	pN2	Positive para-aortic nodes with or without positive pelvic nodes
IV			Tumor invades bladder and/or bowel mucosa; distant metastases
	IVA	pT4	Tumor invasion bladder and/or bowel mucosa
	IVB	pM1	Distant metastases including intra-abdominal metastases and/or inguinal nodes

L11

Uterine smooth muscle tumours

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LEIOMYOMA

Variants of leiomyoma

Cellular leiomyoma: Increased cellularity is significantly increased when compared to the surrounding myometrium. Highly cellular variants mimic endometrial stromal tumors. On gross examination many of them are softer than conventional leiomyoma and tend to have yellow or yellowish-tan in color.

Mitotically active leiomyoma: Typical or cellular leiomyomas with increased mitotic activity (5 to 15 MFs/10 HPFs) have a benign course after myomectomy, provided that they are benign by other criteria (lacking cytological atypia and tumor cell necrosis). These tumors are usually seen in the reproductive age group, are often submucosal, sometimes associated with progestin therapy. They are usually small (2-3 cm) and almost always smaller than 8 cm.

Leiomyoma with bizzare nuclei: These tumors have been referred to as "symplastic", "atypical", or "bizarre" leiomyoma. They contain bizarre cells with atypical nuclei, which can be distributed throughout the tumor, or may form discrete foci with a uni- or multifocal distribution. Many of them are multinucleated. Degenerative nuclear features such as nuclear smudged chromatin, karyorrhexis and presence of nuclear pseudoinclusions are usually present. Mitotic activity is typically low (Robboy). Mitotic counts up to 7 MFs/10HPF are reported. Mitotic figures are only rarely atypical. These lesions are distinguished from leiomyosarcoma by the absence of tumor cell necrosis and mitotic counts of < 10MFs/10HP Fs.

Leiomyoma with apoplectic change: This variant is characterized by zones of haemorrhagic infarction surrounded by hypercellular areas often associated with increased mitoses and sometimes myxoid change (WHO). Edema and nuclear plepmorphism also accompany. These changes are typically induced by progestational therapy or seen in pregnant patients. These changes are thought to be the result of variable degrees of infarction, hemorrhage with subsequent hemolysis, and hyalinization within a leiomyoma. Because of the pregnancy-related changes and the rarity of leiomyosarcomas in the reproductive age group, a diagnosis of uterine leiomyosarcoma should be rendered with caution in a pregnant patient or one on hormonal medication. Marisa R. Nucci and Esther Oliva

Cotyledonoid dissecting leiomyoma: This variant is characterized by irregular dissection of columns of bland smooth muscle cells into the surrounding myometrium. There may be extension outside the uterus, sometimes with conspicuous hydropic change. Grossly, they are lobulated with irregular, inidstinct margins. They present as congested, exophytic masses extending from the uterus into the surrounding tissues.

Diffuse leiomyomatosis: This is a rare condition in which there are innumerable, small, ill-defined leiomyomatous nodules in a symmetrically enlarged uterus. Mitotic figures are rare and atypia is lacking.

Metastasizing leiomyoma: In this rare condition, histologically benign smooth muscle tumors are present at distant sites, particularly the lungs of women with a history of typical uterine leiomyomas. Sometimes this may occur in the setting of intravenous leiomyomatosis or leiomyoma with vascular invasion. Other sites of involvement are retroperitoneal and mediastinal lymph nodes, soft tissue and bone. The presence of a prior myomectomy, hysterectomy or D&C in a high proportion of women with metastasizing leiomyoma supports the role of surgery in the subsequent spread. The lesions are treated by surgical excision and hormonal treatment by progestins or LHRH analogues.

Intravenous leiomyomatosis: This lesion is characterized by the presence of benign smooth muscle within vascular spaces outside the confines of a leiomyoma. Extrauterine involvement occurs in about 30% of the cases and is usually confined to pelvis. The intravascular tumor often has an extensive hydropic change or hyalinization, and thick-walled vessels. The cells are usually bland and mitoses are rare.

LEIOMYOSARCOMA

Leiomyosarcoma is a malignant smooth muscle tumor, most commonly displaying spindle cell morphology but occasionally showing epithelioid or myxoid features.

Leiomyosarcoma (LMS) is the most common uterine sarcoma accounting for 45% of all uterine sarcomas and 1-2% of all uterine malignancies. The patients frequently present with abnormal vaginal bleeding, pelvic mass and pelvic pain. Leiomyosarcomas are typically large solitary masses with a mean diameter of 10 cm. About two thirds are intramural. Five percent of them arise in the cervix. They are generally less circumscribed than leiomyomas. The cut surface is soft, bulging and focally haemorrhagic and necrotic.

A leiomyosarcoma with obviously malignant features exhibit hypercellularity, diffuse moderate to marked atypia and a high mitotic rate.

The diagnosis is based on the assessment of three histologic features:

Mitotic activity,
Nuclear atypia,
Coagulative tumor cell necrosis

Mitotic activity:

A high mitotic index is acceptable in benign uterine SMTs, in contrast to other soft tissues and organ-based SMTs, where any mitotic activity raises high suspicion for malignancy. Mitotic count:

Can be up to 19 in a typical leiomyoma, and should be

less than 10 in cellular leiomyoma,
less than 10 in bizarre leiomyoma,
less than 5 in epithelioid leiomyoma,
less than 5 in myxoid leiomyoma.

Apoptotic cells, pyknotic nuclei, lymphocytes, mast cells, precipitated hematoxylin or cellular debris should not be be misinterpreted as mitotic figures.

Nuclear atypia:

Nuclear atypia must be recognized and taken into account at low-power magnification (×10), comparing it with the nuclear features of the adjacent myometrium when possible (Toledo).

Degree of cellular atypia is classified as:

None/mild vs moderate/marked, and
Focal vs diffuse

Coagulative tumor cell necrosis:

This is seen in only LMSs. There is an abrupt transition from necrotic to nonnecrotic area without interposed granulation tissue. Infarct type necrosis, secondary to ischemia is characterized by the presence of either granulation tissue or hyalinization between the necrotic and nonnecrotic areas. Recent hemorrhage is common. An early necrotic lesion may be very difficult to classify.

Spindle cell LMS: These are composed of spindle, elongated cells with eosinophilic, fibrillary cytoplasm, They form interlacing fascicles. The degree of atypia and mitotic acticity is variable, and necrosis is seen in one third of the cases.

The diagnosis of LMS is established when any 2 of the following 3 criteria are present:

Diffuse moderate to marked cytologic atypia.

Mitotic rate 10 or more mitoses per 10 HPFs.

Tumor cell necrosis.

Epithelioid LMS: These tumors are composed predominanntly or entirely of round or polygonal cells with eosinophilic or less commonly clear cytoplasm. They have a softer and tan cut section when compared to classical LMS. The tumor cells display a diffuse growth pattern but can also form clusters or anastomosing cords. Stroma have varying degree of hyalinization or edema. Mitotic indices may be higher than in usual leiomyoma but lower than in most LMSs. Sometimes myxoid or epithelioid change is the reason for diagnostic difficulty.

Criteria for malignancy in epithelioid LMS:

Any degree of cytologic atypia and 5 or more mitoses per 10 HPFs in the absence of tumor cell necrosis.

Five or more mitoses per 10 HPFs and tumor cell necrosis with any degree of cytologic atypia.

Myxoid LMS: These tumors have an abundunt myxoid matrix and are hypocellular with relatively bland cytological features and infrequent mitoses (WHO).

Helpful features to establish the diagnosis of LMS:

The finding of high-grade areas,

Conventional areas of LMS,

Irregular infiltration of the myometrium,

Venous invasion.

A diagnosis of myxoid LMS can be made in cases:

With severe cytologic atypia and/or tumor cell necrosis, with any mitotic index.

With the finding of 2 or more mitoses per 10 HPFs, in the absence of atypia or tumor cell necrosis,

Stage is the most powerful prognostic indicator in LMSs. In LMSs that are confined to corpus, tumors with a diameter < 5 cm. have a better prognosis.

Smooth muscle tumour of uncertain malignant potential (STUMP) -WHO definition: is a smooth muscle tumor with features that preclude an unequivocal diagnosis of LMS, or its variants, and raise concern that the neoplasm may behave in a malignant fashion. The rare uterine SMTs that cannot be reliably classified as benign or malignant on histologic examination are appropriately designated STUMPs

STUMP categories in spindle cell smooth muscle tumors (Bell et al):

Smooth Muscle Tumor of Low Malignant Potential

Uterine smooth muscle tumor with coagulative tumor cell necrosis

No or mild (insignificant) atypia

A mitotic index < 10 mitoses per 10 high power fields

Experience too limited to draw definitive conclusions. One of the 4 patients experienced recurrence.

Atypical Leiomyoma with Low Risk of Recurrence

Uterine smooth muscle tumor with diffuse moderate to severe (significant) atypia

No coagulative tumor cell necrosis

MI: < 10 mitoses per 10 HPFs

Only one of 46 such tumors was clinically malignant

Atypical leiomyoma but limited experience

Focal moderate to severe atypia

MI: < 20 mitoses per 10 HPFs

No coagulative tumor cell necrosis

There were 5 cases all of which were clinically benign

L12

Serous tumours and tumour-like changes of the ovary, fallopian tube and peritoneum

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Surface epithelial-stromal ovarian carcinomas are traditionally classified with regard to histological type and degree of differentiation, the four most common subtypes being serous, endometrioid, clear cell and mucinous. Fallopian tube serous carcinomas, diagnosed by relatively strict morphologic criteria were thought to be extremely rare. The same is true for primary peritoneal carcinomas (1).

Until relatively recently, it has also been proposed that ovarian carcinomas arise from the ovarian surface epithelium, which is viewed as a type of mesothelium similar to the one lining the peritoneal cavity. It was thought that, after the ovulation the surface epithelium of the ovary invaginates into the ovarian cortex leading to the development of ovarian cortical inclusion cysts, being the origin of ovarian carcinomas. The explanation for the morphologic characteristics of ovarian carcinomas that resemble the epithelia of the genital tract derived from Mullerian ducts, and not to the tissues of the ovary itself was, that that the changes in the microenvironment of the ovarian stroma induce metaplasia of the inclusion cyst's epithelium into the Mullerian type epithelium. Investigations of the *HOX* gene family confirmed the *HOX* genes expression in many subtypes of ovarian carcinoma, but not in ovarian surface epitelium, confirming thus the Müllerian epithelial differentiation (2). Others have proposed that ovarian epithelial tumors develop from Mullerian-type epithelium lining paraovarian and paratubal cysts (the so called „secondary mullerian system") (1).

Epidemiological observations that led to connection between ovarian carcinoma and Fallopian tube, emerged after the increased number of prophilactic salpingo-oophorectomies in women carrying *BRCA 1* or *BRCA 2* germline mutations in the late 1990s and early 2000s. Meticulous section of the Fallopian tube and ovaries revealed no ovarian lesions, but a number of dysplastic changes and occult noninvasive and invasive carcinomas in the fimbrial region of the Fallopian tubes. Many of the occult malignancies detected on thorough sectioning of Falllopian tubes in these cases were microscopic and restricted to the Fallopian tube. These findings prompted careful and thorough examination of the Fallopian tubes from cases of pelvic, ovarian or tubal serous carcinomas that revealed the aforementioned changes of the tubal epithelium in over 70% of the cases (3-5).

Until today, a number of morphological and immunohistochemical changes of the tubal epithelium has been observed. On the basis of morphology and immunohistochemical and proliferative characteristics, the changes were divided into three categories: the first category named „p53 signature" consisted of bland appearing cuboidal to pseudostratified cells with polarized p53 positive epithelial segments, variable nuclear enlargement and a MiB1 index of 0% to 30%; the second category named serous tubal intraepithelial carcinoma (STIC) contained most frequently multilayered, poorly polarized, uninterrupted neoplastic cell populations that completely displaced the normal mucosa, with MiB1 index between 45 nad 70% (usually even more). The third category consisted of p53 positive foci with features intermediate between the first and the second category (preserved epithelial polarity, pseudostratification, incomplete replacement of the adjacent normal ciliated cells, and a MiB1 index between 40% and 75%), and was named tubal intraepithelial lesions in transition (TILT) (4,6-8).

To describe the incidental findings of spectrum of epithelial changes ranging from normal appearing tubal epithelium, expressing p53 (p53 signature), to lesions with increasing degrees of cytologic atypia that fall short of STIC features, and to avoid the confusion, Crum and co. suggested the use of term "serous tubal intraepithelial lesions" (STILs) (9).

The STIC changes were also found in the study of primary peritoneal serous carcinoma. The majority of them were in the fimbriated end of the Fallopian tube, adjacent to the ovarian surface (10). The reason for the the fimbrial localization of these lesions is supposed to be due to increased surface area of this site, or potential differences in characteristics of the cells from this region as opposed to more proximal sections of the tube. These findings support a possible means of spread to the ovary by exfoliation or tubo-ovarian adhesions.

Given the limitations of current options for ovarian surveillance, bilateral prophylactic salpingo-oophorectomy after the completion of child-bearing is the current standard recommendation for women with *BRCA 1* and *BRCA 2* mutations (11).

This procedure reduces the risk of subsequent development of pelvic serous carcinoma by 80%–90%, but does not eliminate it entirely. The remaining risk is mainly attributed to primary peritoneal serous carcinoma, which is similar to high-grade ovarian serous carcinoma in presence and response to treatment and seems to originate from the same cell lineage (12). The tubal epithelium can be linked only to some high grade peritoneal serous carcinomas, and the possibility that remains is, that the nearby peritoneal or ovarian surface epithelium also contains progenitor cells capable of different differentiation and neoplastic transformation (13).

Protocols that extensively examine the fimbria (sectioning and extensively examining the fimbriated end of the fallopian tube - SEE-FIM) maximize the detection of early tubal epithelial carcinoma in patients at risk for ovarian cancer, but can also detect early malignant and serous tubal intraepithelial lesions in women without *BRCA* mutations. Additional studies in which fallopian tubes were carefully examined confirmed that STICs and small, early invasive tubal carcinomas occurred not only in women with a genetic predisposition for the development of ovarian cancer but also in 50-60% of women without known *BRCA* mutations (sporadic ovarian cancer) (14).

The low grade serous carcinomas are much less common than high grade serous carcinomas and are thought to evolve sequentially from benign serous cystadenoma/cystadenofibroma into atypical proliferative serous tumour (serous borderline tumour), non-invasive micropapillary serous carcinoma (micropapillary serous borderline tumour) and finally into invasive low-grade serous carcinoma in a relatively slow process. It is presumed that cystadenoma/adenofibroma arises from epithelial inclusion glands in the ovary, but recent evidence suggests that the epithelium lining the inclusion cysts also originates in the Fallopian tube (15-17).

The difference in clinical behaviour, morphology and prognosis, but also with regard to the molecular pathways involved in their carcinogenesis, has lead to dualistic model of ovarian serous carcinoma, included also in the WHO classification of ovarian carcinomas (18).

Type I tumors include low-grade serous carcinomas (LG-SC), low-grade endometrioid carcinomas, clear cell and mucinous carcinomas, and Brenner tumors. Type I tumors are not clinically aggressive, generally present at early stage, rarely harbor *TP53* mutations, but instead display mutations involving specific cell signaling pathways, including *KRAS*, *BRAF*, *ERBB2, PTEN, CTNNB1, PIK3CA, ARID1A,* and *PPP2R1A*. Their development involves the multistep process, so that they show a spectrum of morphologic epithelial changes, from benign and atypical proliferative (borderline) to frankly malignant (20-23).

Type II tumors, which include high-grade serous carcinomas (HG-SC), high-grade endometrioid carcinomas, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas, frequently display *TP53* mutations and are genetically unstable, while the mutations found in type I carcinomas including *KRAS* and *BRAF* mutations are rarely found. This dualistic model has clinical, pathologic and molecular evidentiary support. Type II tumors are responsible for 75% of ovarian carcinoma morbidity, are identified usually in FIGO stages Ill or IV, have poor prognosis and relapse early (18). Low grade and high grade serous carcinoma represent two distinct tumour types with a different underlying pathogenesis rather than low grade and high grade variants of the same neoplasm. High-grade serous carcinomas, whether classified as ovarian/tubal/peritoneal, seem to behave as one disease entity with no significant difference in survival outcomes, therefore supporting the proposition of a separate classification of "tubo-ovarian serous carcinoma" (20).

There are also some other serous epithelial lesions that can develop in the region of Fallopian tubes and peritoneum. They are thought to develop from so called „secondary mullerian system“, that is the pelvic and lower abdominal mesothelium and the surrounding mesenchyma (20,21). The ectopic presence of müllerian derived tissue is reffered to as mullerianosis and encompasses endosalpingiosis, endometriosis, and endocervicosis (22). Endosalpingiosis is the presence of benign glands lined by tubal type epithelium, ans is most frequently found on the pelvic peritoneum of the uterus, Fallopian tubes, ovaries and cul de sac. These glands can be simple or complex, sometimes with irregular contours and intraluminal simple stromal papillae. Endosalpingiotic glands can also show atypical epithelial features, or even features of borderline malignancy. Transformation into low grade serous peritoneal carcinoma is rare, and the appearence is similar to invasive implants of serous borderline tumors. However, most serous peritoneal carcinomas are high grade, and are thought today to be associated with the origin in the Fallopian tubes (20).

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Slide Seminar

Case 1

Uterine tumor with sex-cord like elements

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Clinical History

56-year-old women presented with abnormal vaginal bleeding. Ultrasound examination found well circumscribed submucosal mass, 4 cm in diameter. Hysterectomy with bilateral adnexectomy was done.

Pathological Findings

On gross examination, solid, round, well-circumscribed submucosal tumor 4 cm in diameter, with yellow and soft cut surfaces was found. The microscopic examination show a variety of epithelial and stromal patterns: anastomozing cords one to two cells in width, diffuse sheets of uniform cells reminiscent of a diffuse adult granulosa cell and sertoliform tubular structures with small cuboidal cells with scanty cytoplasm. Immunohistochemical findings: CK +, Actin +, CD 10 –, EMA –, Calretinin +, Inhibin +, CD99 +.

Diagnosis: ***Uterine tumor with sex-cord like elements (UTROSCT)***

Discussion

UTROSCT are heterogeneous group of uncommon neoplasms characterized by pure or prominent microscopic patterns that resemble those of ovarian sex-cord tumors. Patients with UTROSCTs are in the reproductive and postmenopausal age groups. On gross examination, UTROSCTs are generally solid, round, well-circumscribed myometrial masses that range from 0.7 cm to 20 cm in diameter. The cut surfaces are soft and fleshy without the whorled pattern of a leiomyoma, often yellow, which is characteristic, but not specific, feature of UTROSCT. The cardinal features on microscopic examination are a variety of epithelial and stromal patterns that create a resemblance to those of ovarian sex-cord tumors, especially granulosa cell and Sertoli cell tumors, alone or in combination. The differential diagnosis of UTROSCT is potentially wide and may include: an endometrial stromal and an epithelioid smooth muscle neoplasm, metastatic ovarian sex cord-stromal tumor, carcinosarcoma and primary and metastatic epithelial neoplasms, especially endometrioid adenocarcinoma with sex cord-like features and lobular breast carcinoma. A perivascular epithelioid cell tumor (PEComa) might also be considered.

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Case 2

Female adnexal tumor of probable Wollfian origin

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Clinical History

30-year-old female, admitted to Department of Gynaecology because of the asymptomatic left paraovarian mass discovered in routine gynecological examination. Pelvic examination revealed left paraovarian cyst. Left salpingoophorectomy was done. Operation disclosed unilateral, encapsulated cyst within leaves of the left broad ligament. Patient is alive, without evidence of disease, ten year after operation.

Pathological Findings

Tumor was cystic, encapsulated, with smooth external surface, measuring 8 cm in the greatest diameter. On sectioning, inner surface of the tumor had spongy appearance produced by small cysts. Microscopy shows a variety of appearances with epithelial cells arranged in tubule, as multiple dilated cysts or as a diffuse sheets. Cystic pattern predominates.

Tubular pattern is formed by tubules lined by columnar epithelia. In some slides groups of tubules protruded into cysts creating a glomeruloid appearance. In the part of the tumor tubules were tightly packed, so, on HE stained sections they look as a solid sheets. Immunohistochemistry: CK7 +, Inhibin +, Calretinin +, Vimentin +.

Diagnosis: ***Female adnexal tumor of probable Wollfian origin (FATWO)***

Discussion

About 50 cases of this tumor have been reported in females from the second to ninth decades of life. They occur mainly within the leaves of the broad ligament, but also in the mesosalpinx, ovarian hilus and the retroperitoneum. Differential diganosis include: endometrioid carcinoma, adenomatoid tumor, Sertoli and granulosa cell tumor.

Patients have been treated surgically usually with benign outcome. Malignant behavior is uncommon. It is difficult to predict which cases will exhibit malignant behavior, but cytological atypia and frequent mitotic figures are important predictor of malignant behavior. Some aggressive tumors have had no significant atypia or mitotic activity in either the primary or the metastatic lesion. Careful follow up of all women with Wolffian adnexal tumor is prudent.

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Case 3

Gastrointestinal stromal tumour (GIST) of the uterus

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Clinical History

Female, 42-year-of-age, nullipara, underwent hysterectomy due to large uterine myoma and prolonged uterine bleeding. Subsequent clinical investigations revealed multiple tumour nodes in the peritoneal cavity and possible metastatic deposits in the liver. The gastroscopy was inefficient due to necrotic and substenotic oesophagus. The patient was recommended chemotherapy and symptomatic therapy, but she died within a few months.

Pathological Findings

Uterus without adnexa, weighing 666 g, with dimensions 9 x 11.5 x 7 cm was obtained for histopathological analysis. The anterior wall of the uterus contained solitary intramural tumour mass with diameter of 11.4 cm, soft and fleshy consistency, infiltrative margins and zones of necrosis and haemorrhages.

The histopathological analysis revealed cellular tumour composed mainly of uniform small round cells with granular cytoplasm, ill-defined cell membranes and round to oval nuclei. The mitotic index was up to 8 mitoses per HPF. Lymphovascular invasion was found in vessels of the myometrium and endometrium. The differential diagnoses included endometrial stromal sarcoma, leiomyosarcoma, neuroendocrine tumour, lymphoid neoplasm, melanoma and metastases from ovarian stromal neoplasm, but on immunohistochemistry the tumour cells were negative for CD10, actin, desmin, caldesmon, myoglobin, CD34, NSE, synaptophysin, chromogranin, LCA, HMB45, Melan A, inhibin-alpha, cytokeratins, WT1, EMA, ER and PR. The tumour cells were positive for vimentin and CD117. Molecular analyses were not performed due to their unavailability at the Institute. A diagnosis of gastrointestinal stromal tumor (GIST) was made with recommendation for clinical evaluation of other possible primary sites of the tumour.

Diagnosis: ***Gastrointestinal stromal tumor (GIST) of the uterus***

Discussion

GISTs are the most common mesenchymal tumours of the gastrointestinal tract arising mainly in the stomach and small bowel, but recently GISTs arising in extragastrointestinal organs have been reported. The unawareness of their existence in gynaecological sites may lead to misdiagnosis and inappropriate therapy. However, other primary sites of the tumour should be excluded first in order to manage the patients properly.

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Case 4

Mesonephric adenocarcinoma of the uterine cervix

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Clinical History

A 67-year-old, gravid 4, para 2 woman was admitted to the Mother Teresa Special Hospital of Gynecology and Obstetrics in Skopje due to postmenopausal bleeding of seven days duration. Her previous gynecologic history was unremarkable, and there was no family history of gynecological cancer. The patient underwent radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy at another institution (Acibadem Sistina Hospital, Skopje) where cervical carcinoma was staged at pT2B because of minimal (1mm) parametrial invasion. Six year after surgery and adjuvant radiotherapy there was no evidence of recurrence or metastatic disease.

Pathological Findings

A fractional dilation and curettage was performed and histological examination revealed that both materials, from the cervix and from the uterine cavum, contain only fragments of neoplasm without any endometrial fragments, nor fragments of normal cervical mucosa. Cervical involvement with neoplasm was confirmed with another endocervical biopsy. The neoplasm partly consisted of sheets of small round tubules with densely eosinophilic secretions in some of the lumens, partly of more complex tubules, cribriform structures and irregular slit-like branching tubules with intraluminal papillae. The tubules and papillae are lined by one to many layers of columnar, cuboidal or flattened cells with scant eosinophiliic cytoplasm. Neoplastic cells display nuclear hyperchromasia and mild to moderate nuclear pleomorphism. Mitotic rate was 1 to 5 per HPF. There was no stromal reaction.

Immunohistochemical findings showed positive reactions in the tumor cells for pancytokeratin, cytokeratin 7 (CK7), epithelial membrane antigen (EMA), vimentin, protein p16 and CD10. CD10 exhibited luminal positivity. Expressions of carcinoembrionic antigen (CEA), cytokeratin 20 (CK20), inhibin, calretinin, Wilms tumor protein (WT1), estrogen receptor (ER) and progesterone receptor (PR) were completely negative. Positive cells rate of Ki-67 were 30%.

Diagnosis: ***Mesonephric adenocarcinoma of the uterine cervix***

Discussion

Mesonephric adenocarcinoma is one of the rarest subtypes of cervical adenocarcinoma derived from remnants of the mesonephric ducts. The mesonephric (Wolffian) duct is one of the paired embryogenic tubules (along with the Mullerian duct) that drain the primitive kidney (mesonephros). In males and females the mesonephric duct gives rise to the trigone of the bladder. In the presence of testosterone the mesonephric duct develops into the rete testis, efferent ducts, epididymes, seminal vesicles and vasa deferentia. In the absence of testosterone the mesonephric duct regresses. Remnants may persist as the epoopheron, Skenes glands, and Gartner's duct, and may subsequently give rise to cysts and neoplasms.[1] Embryonic remnants of mesonephric ducts are usually detected in the uterine cervix, vagina, broad ligament, mesosalpinx and in the uterine corpus. They are detected in 1-22% of cervices removed during hysterectomy.[2]

Several types of mesonephric tumors have been described: adenomas and cystadenofibromas of the rete ovarii, female adnexal tumors of Wolffian origin (FATWOs)[3] and mesonephric carcinomas. Approximately 50 cases of mesonephric carcinomas have been described in the cervix[4-7] and a few cases in the uterine corpus,[2,8] vagina[9] and ovary.[10]

The histologic patterns of mesonephric adenocarcinoma are quite variable, including ductal, retiform, papillary, solid, spindle cell and sex cord-like. These are often mixed within the same tumor. Usually the stromal reaction is absent.[11] It has been reported that mesonephric adenocarcinomas are often accompanied by sarcomatous components. Mesonephric adenocarcinoma is not related to HPV infection.[6]

Recent immunohistochemical studies done in mesonephric adenocarcinoma[5,9,12] report that epithelial markers, including pancytokeratin, CK7 and EMA were consistently present in the tumor cells. Vimentin was positive in 70% and calretinin in 88% of the cases. CK20, CEA, ER and PR were negative. Ubiquitous expression of CD10 was found in mesonephric remnants and mesonephric tumors and absent CD10 expression in neoplastic and non-neoplastic mullerian epithelia.[12] However, all authors accept the fact that the immunophenotypes of paramesonephric (Mullerian) and mesonephric

(Wolffian) structures and their tumors are not substantially different, and that there is no specific marker for mesonephric structure. CD10 expression may be an exception and CD10 may be a good marker of mesonephric remnants and neoplasms.[5,12,13] Diffuse p16 positivity has been described in cervical mesonephric glands, presumably because of non–HPV-related mechanisms. In the presented case tumor cells showed positivity for pacytokeratin, CK7, EMA, vimentin, CD10, and protein p16, and negativity for CEA, CK20, inhibin, calretinin, ER and PR.

A major problem in the pathologic diagnosis of mesonephric carcinoma of the female genital tract in general, and especially when presenting in limited (biopsy or curettage) material, is the fact that its true identity is often hidden behind other Mullerian-like differentiation. These tumors may be confused with serous, endometrioid or clear-cell type of adenocarcinoma. The presence of the spindled cell component in the neoplasm may result in its confusion with a carcinosarcoma (malignant mixed Mullerian tumor). Besides that, the distinction from florid mesonephric hyperplasia may be very difficult since mesonephric hyperplasia often coexists with mesonephric carcinoma.[2] Because of these differential diagnostic problems it is important to be aware of the immunophenotype of mesonephric adenocarcinomas, especially with regard to markers that are commonly positive in those adenocarcinomas that are in differential diagnosis. A correct diagnosis can be achieved with the aid of immunohistochemistry.

Mesonephric adenocarcinoma may be confused with serous and clear-cell carcinomas because of their histological similarities. Serous carcinoma can be distinguished from mesonephric adenocarcinoma with immunohistochemical staining for protein p53 and WT1.[5,6,7] Most serous carcinomas are immunoreactive with these two markers. In contrast, mesonephric carcinoma does not express p53 and, as in the presented case, WT1. Clear-cell carcinomas show varying degrees of cystic, papillary and solid patterns as well as clear cells and hobnail cells, which are not usually seen in mesonephric neoplasms. Clear-cell carcinomas may also exhibit prominent tubules filled with eosinophilic hyaline material, but there is no mesonephric hyperplasia.[2] In the presented case clear-cell carcinoma was ruled out due to absence of clear and hobnail cells, and CD10 positivity of the neoplastic cells.

The ductal pattern of mesonephric adenocarcinoma may be similar to endometrioid adenocarcinoma, which is composed of glandular or villoglandular structures lined by cytologically malignant stratified columnar epithelial cells. Endometrioid adenocarcinoma is usually positive for ER and PR immunohistochemical stains. In this case endometrioid adenocarcinoma was excluded based on microscopic morphology and immunohistochemical negativity for ER and PR and positivity for CD10.

Biphasic mesonephric adenocarcinomas with a sarcomatoid component can be confused with malignant Mullerian mixed tumor (MMMT). However, in the present case, the stroma was benign without a sarcomatoid component, and that rules out the possibility of MMMT.

It can be also difficult to differentiate between diffuse mesonephric hyperplasia and mesonephric adenocarcinoma. Helpful features supporting a diagnosis of adenocarcinoma include mixed histologic pattern (tubular and solid, ductal or retiform), lymph-vascular space invasion, nuclear atypia, mitotic activity exceeding one mitosis per 10 HPFs, and necrotic luminal debris. The Ki-67 proliferation index of adenocarcinomas averages 15%.[2] In this case mesonephric hyperplasia was excluded due to cytologyc atypia of tumor cells, presence of ductal and retiform patterns, presence of 1 to 5 mitosis per HPF and Ki-67 positivity in 30% of the cells.

The biologic behavior, prognosis, and treatment strategies of this unusual tumor remain uncertain with some mesonephric adenocarcinomas displaying an aggressive clinical course. As there are no definite recommendations of a particular course of therapy for this uncommon disease, it would be reasonable to manage patients with mesonephric adenocarcinoma of the cervix according to current guidelines for cervical adenocarcinoma of similar stage.[4]

In conclusion, the diagnosis of malignant mesonephric tumors is challenging, as the pathologists need to be aware of the various morphologic patterns seen in this group of tumors. A panel of immunohistochemical stains may be useful in the differential diagnosis.

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Case 5

Aberrant prostatic tissue in uterine cervix

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Clinical History

30-years old female, unipara-unigravida, admitted to the University Clinic for Gynaecology and Obstetrics (UCGO) for cervical cone biopsy. Six months earlier she has had a positive PAP-smear interpreted as CIN2, followed by cervical biopsy which revealed moderate dysplasia of the cervical squamous epithelium. HPV genotyping revealed HPV type 16. No other relevant conditions have been noted in her medical history. Subsequent PAP cytology at the UCGO showed CIN3 lesion. Cervical cone biopsy was performed.

Pathological Findings

Cervical cone biopsy with epithelial surface measuring 1.6 x 2.5 cm, 2.2 cm long, dissected and paraffin embedded in 16 blocks. Microscopic analysis showed high grade dysplasia of the squamous epithelium in the lower left quadrant, diffuse foci of low grade squamous lesion, as well as focus of low grade endocevical glandular dysplasia in the lower left quadrant. In the right quarter (7-10 o'clock) of the cone biopsy, tubulo-alveolar glands were incorporated into the deep endocervical stroma, lined by two-layered, benign-looking epithelium. Immunohistochemical analysis showed cytoplasmic PSA positivity in the superficial secretory cells, while the basal cells were CKHMW and partially SMA positive.

Diagnosis: ***High-grade dysplasia of the cervical squamous epithelium accompanied by LCGIN and presence of aberrant prostatic glands in the cervical stroma.***

Discussion

Several authors have previously published findings of ectopic or aberrant prostatic tissue in the uterine cervix in women from 21 up to 82 years of age. To the best of our knowledge not more than 45-60 cases (depending on the criteria applied) have been previously reported in the literature. Most of the cases involving the cervix, and several cases with prostatic tissue in the vagina, vulva, and in one case the prostatic tissue was incorporated in myofibroblastoma. The theories of possible histogenesis include a developmental anomaly, intrauterine exposure to androgens, metaplasia of pre-existing endocervical glands, and mesonephric remnants derivation.

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Case 6

Primary malignant peripheral nerve sheath tumor of the uterine cervix

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Clinical History

The repeated curettements in a 57-year-old woman with a history of prolonged vaginal bleeding, revealed polypoid fragments of a sarcomatous neoplasm. Subsequently, total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Postoperatively, the patient received six courses of chemotherapy. Twenty-three months later, a local vaginal and left parametrial recurrence occurred. During the next 24 months, the pelvic mass persisted**,** causing excessive vaginal bleedings and necessitating numerous procedures of radiotherapy and chemotherapy. Eventually, 48 months following surgery lung metastases were confirmed and the patient died of respiratory failure nine months after.

Pathological Findings

The cervix was enlarged, markedly distorted by 5.5 x 2.5 x 2.5 cm neoplasm involving predominantly the anterior wall of the cervical canal. Microscopically, the tumor had a variable sarcomatous appearance, predominantly composed of cellular fascicles of spindle cells with hyperchromatic nuclei and eosinophilic cytoplasm. There were also hypocellular areas frequently with prominent myxoid stroma. Cytological atypia varied within the tumor, whereas mitoses were readily identified. The neoplasm penetrated deeply into the fibromuscular wall of the uterine cervix, infiltrating proximally the lower uterine segment and the myometrium of the distal part of the anterior wall of the uterine corpus. Beneath the mucosa the malignant spindle cells tended to infiltrate but not destroy the native endocervical glands. Immunohistochemical examination demonstrated that many of the tumor cells showed diffuse strong positive staining for S100 and vimentin, as well as S100A4, Wilms tumor 1 protein, and p16, and only focal positivity for CD56 and NSE. Tumor cells were negative for cytokeratin, EMA, CD57, GFAP, NFP, alpha-SMA, desmin, caldesmon, CD10, CD34, CD117, CD99, HMB-45, Melan-A, as well as estrogen and progesterone hormone receptors, while the proliferative index determined by Ki-67 was 15-20%.

Diagnosis: ***Primary malignant peripheral nerve sheath tumor (MPNST) of the uterine cervix***

Discussion

Primary malignant nerve sheath tumor (MPNST) of the uterine cervix is an extremely rare neoplasm. An extensive review of the literature shows only fifteen cases of MPNST at this location occurring in patients ranging in age from 22 to 73 (mean, 46) years, usually presenting with irregular bleeding. The majority of the tumors typically formed mass lesions or cervical polyps measuring from 1.2 to 8 cm (mean, 4.3 cm). Although up to 50% of MPNSTs arise in patients with neurofibromatosis type 1 (NF-1), so far no patient with MPNST of the uterine cervix has been reported to have NF-1. Nevertheless, one patient with endocervical fibroblastic MPNST had a history of unilateral acoustic schwannoma, benign nerve sheath tumor of the leg and dermatofibrosarcoma protuberans of the lumbar spine region raising a possibility of a unique manifestation of neurofibromatosis or possibly a previously undescribed syndrome.

The tumors were composed of mitotically active spindle cells, arranged in herring-bone, nodular or storiform fascicles pattern, often with alternating hypercellular and hypocellular areas. Hypocellular areas may be myxoid, fibrous or edematous. Morphological variations that have been reported include epithelioid areas in at least 2 cases and melanin pigmentation in one case. Immunohistochemically, most of them (13/15) showed S100 expression. The recently described endocervical fibroblastic MPNST shows diffuse of S100 expression in addition to CD34 expression suggesting that this tumor may be related to an anatomically restricted CD34-positive progenitor cell population.

The histological differential diagnosis includes spindle cell neoplasms such as cellular schwannoma, primary leiomyosarcoma, endocervical stromal sarcoma, and less likely rhabdomyosarcoma, Müllerian adenosarcoma, spindle cell squamous cell carcinoma, spindle cell malignant melanoma, gastrointestinal stromal tumor and monophasic synovial sarcoma. A combination of gross and microscopic findings along with immunohistochemical studies is commonly used to diagnose a case of MNPST. In the present case, there was a strong and diffuse S100 protein reactivity which contrasts with most conventional MNPST, characterized by weak and focal S100 expression.

Although meaningful follow-up information is only present in 12 of the 16 cases, MPNSTs of the uterine cervix appear to behave better than soft-tissue MPNSTs. Thus, 6 patients were alive without disease at 1-10 years follow-up, one with advanced stage disease was alive with disease at 2 months follow-up, local recurrences were documented in 5 patients, while pulmonary metastases developed in two of them.

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Case 7

Atypical polypoid adenomyoma with coexistent well-differentiated endometroid adenocarcinoma

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Clinical History

A 28-year old nulliparous patient with a clinical diagnosis of prolonged abnormal uterine bleeding underwent dilatation and explorative curettage procedure. Subsequently, a month after the initial diagnosis there were no abnormal findings on ultrasonography, while in the endometrial biopsy material taken during hysteroscopy only a few fragments of disordered endometrium were found. Due to the patient`s age the fertility preservation and reproduction was an issue; therefore, a conservative treatment (6-month high-dose gestagen therapy) and a close follow-up with repeated ultrasound and hysteroscopic monitoring were recommended. In addition, a cone biopsy was done three months after the first dilatation and curettage (D&C) procedure and subsequent biopsy. For 11 years, the patient was carefully followed up with semi-annual ultrasonography and cytological examinations. She is well and disease-free, being treated for infertility in the last 8 years with one unsuccessful pregnancy three years ago.

Pathological Findings

The material obtained by explorative curettage was abundant. Microscopical examination revealed several larger fragments of tissue measuring 0.3-1.2 cm in largest diameter containing numerous groups of tightly packed atypical endometrial glands intersected by septa of myofibromatous stroma. The glands exhibited severe architectural complexity with focal cribriform pattern and squamous metaplasia with central necrosis. Glandular cells showed varying degrees of nuclear atypia (from mild to severe) and prominent nucleoli. Mitosis were easily found. The microscopic appearance resembled atypical (complex) hyperplasia and in one focus measuring 3 mm in diameter, well-differentiated endometroid adenocarcinoma. By immunohistochemistry, most of the stromal cells showed strong immunostaining for alpha-smooth muscle actin, and vimentin, while some cells were desmin or CD34 positive. The tumor was hormone responsive, whereas Ki-67 proliferative index was 20-25% in the foci of atypical hyperplasia with severe atypia and well-differentiated endometroid adenocarcinoma. The majority fragments of uninvolved endometrium showed a disordered proliferative pattern with small areas of non-atypical or more frequently atypical hyperplasia with mild, moderate to severe cytological atypia. In addition, two small fragments of squamous epithelium of the uterine cervix having a morphology of high-grade squamous intraepithelial lesion (CIN2) were identified.

Diagnosis: ***Atypical polypoid adenomyoma (APA) with coexistent well-differentiated endometroid adenocarcinoma***

Discussion

Atypical polypoid adenomyoma (APA) is a polypoid lesion belonging to the mixed epithelial and mesenchymal tumors of the uterus. This unusual biphasic Müllerian uterine tumor was initially reported by Mazur in 1981. Most of these tumors occur in women in reproductive age (mean, 40 years; range 23-73), yet occasional tumors may occur in postmenopausal women. It may be associated with obesity, infertility, and nulliparity. Rare cases are associated with long-term unopposed estrogen therapy. Thus, Clement et al. reported three cases of atypical polypoid adenomyoma associated with Turner syndrome who have been prescribed unopposed estrogens. Some recent studies report that these tumors may be associated with MLH-1 promoter hypermethylation (approximately 40%) and microsatellite instability, as seen in complex atypical hyperplasia and endometroid adenocarcinoma.

The patients typically present with abnormal vaginal bleeding. Pelvic examination is usually negative, and in some cases, a polypoid mass may protrude from the external os of the uterine cervix.

These tumors frequently involve the uterine corpus or the lower uterine segment, and may also arise in the cervix. In most cases, the lesion has an obvious polypoid gross appearance, in a form of either solitary or rarely multiple, well circumscribed, pedunculated or broad-based polyp, ranging in size from 0.1 to 6 cm, with a mean diameter of 2 cm in greatest dimension. The sectioned surfaces are yellow-tan to grey and white, solid and firm or rubbery.

Microscopically, on low power view, most lesions have vaguely lobulated growth pattern, while the margin between the APA and the surrounding myometrium is rounded and well delineated in most cases, although in some occasions may show extensions into the superficial myometrium. The epithelial component has endometrioid glands with varying degrees of architectural and cytological atypia separated by myofibromatous stroma. The glands may be closely packed or widely spaced. There is often prominent squamous metaplasia in a form of squamous morules, which may show areas of central necrosis. Rare findings include cribriform pattern and ciliated and mucinous metaplasia. Most APAs show mild to moderate cytological atypia of the glandular component. Rarely severe atypia, or even foci with complex glandular architecture and severe cytological atypia resembling well-differentiated adenocarcinoma, may be seen. Some APAs are contiguous to or appear to be the origin of a well-differentiated adenocarcinoma. The stromal component contains in most cases interlacing bundles of cellular smooth muscle, proliferating myofibroblasts, or both. The study of Longacre et al. has shown that some APAs may contain areas of sclerotic or cellular fibrous tissue, but no case contains pure smooth muscle or fibrous tissue only. The stromal cells exhibit mild to moderate atypicality in a minority of cases. Occasional mitotic figures are usually seen, but they do not exceed 2-3 per 10 high-power fields as an average count and no atypical mitosis are found. The stroma does not condensate around the glands. There may be stromal calcification, chronic inflammatory cells and foreign body giant cell reaction to keratin. According to Longacre et al. APAs are typically noninvasive, with a well-circumscribed border in hysterectomy specimens, although rarely some of these tumors associated with foci resembling well-differentiated adenocarcinoma superficially invaded the myometrium.

By immunohistochemistry, the mesenchymal cells typically stain for smooth muscle actin, and frequently for desmin and other smooth muscle markers. They also may show some degree of positivity for CD34. The epithelial component is positive for cytokeratin (AE1/AE3 and CAM5.2), as well as hormone (estrogen and progesterone) receptor positive. The cells in squamous morular areas show strongly positive membranous CD10 and also nuclear beta-catenin staining.

The histological differential diagnosis includes endometrial adenocarcinoma, typical adenomyoma of the endometroid type, Müllerian adenosarcoma, and carcinosarcoma. Distinction from endometrial adenocarcinoma may be particularly difficult on dilatation and curettage (D&C) material when the whole lesion is not available. Nevertheless, it is unusual for the endometrial adenocarcinoma invading in the myometrium to be demonstrated in the D&C material. Furthermore, the orderly pattern of the smooth muscle or myofibromatous component of APA contrasts with the finding of desmoplastic stroma characteristically associated with endometrial adenocarcinoma. In addition, the young age of most the patients and the typical lower uterine segment location of APA often suggest the correct diagnosis. A typical adenomyoma of the endometroid type is more frequently encountered in the uterine corpus. In contrast to the APA these tumors have a rim of endometrial stroma between the glands and the smooth muscle, the glandular component is less abundant and it does not show cytological atypia or architectural complexity. Mülerian adenosarcoma may show prominent smooth muscle metaplasia; however it is characterized by the phyllodes-type architecture and neoplastic endometrial-type stroma frequently cuffing the glands. Carcinosarcoma is usually diagnosed in postmenopausal women and is composed of high-grade malignant epithelial and mesenchymal component.

Most of these tumors have an excellent prognosis. The treatment may consist of curettage or excision, with follow-up, or simple hysterectomy. In the study of Longacre et al. there was a recurrence index of 45% in patients treated conservatively and those treated in this manner rarely may progress to adenocarcinoma. APAs with foci resembling well-differentiated adenocarcinomas have higher recurrence rate (60% versus 33%), and for that reason, they have been designated by Longacre et al. as "atypical polypoid adenomyoma of low malignant potential". Nevertheless, nowadays this term is not recommended, and these foci which are virtually indistinguishable from should be best regarded as well-differentiated endometroid adenocarcinoma. These lesions may have locally aggressive, but not malignant behavior. If the lesion has only been curetted, it is important to search for endometrial hyperplasia in areas not involved by APA, which is not infrequent finding. In addition, there is about 10% risk of endometrial adenocarcinoma in women with APA, which is considerably higher than the overall risk of less than 1% in women with endometrial polyps.

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CYTOPATHOLOGY

Symposium

L13

The application of biomarkers in the personalized management of cervical lesions

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Introduction

The traditional simple algorithms and management strategies for women with ASC-US+ abnormalities at cytology have been effective at reducing the incidence of cervical cancer, albeit based on clinical tests with limited sensitivity and specificity. Establishing that HPV is causally associated with cervical cancer has led to major advances in cervical cancer primary and secondary prevention but has also set new challenges for the future[1]. Previously established recommendations and management algorithms are likely to be less applicable in future screening settings, while new tests exploring the viral genome may allow a more efficient and personalised management of women with positive screening results.

Advances in technology and scientific techniques created new horizons for improved understanding of the diseases' processes at a molecular level. With the explosion of new biomarkers targeting the viral DNA detection, the expression of oncoproteins and other cellular processes that promote carcinogenesis in the host, questions on how to best use these in different clinical settings are becoming increasing difficult to answer. With a continuously evolving evidence-base, the development a clinical decision support scoring system is a current unmet need. This can assist clinicians to use these new technologies to promote prevention, personalise management and improve targeted management.

This prospective study aims to develop a clinical decision support scoring system (DSSS) exploiting artificial neural network (ANN) systems and novel molecular markers for the personalized management of women with abnormalities at cytology-based screening.

Material and methods

Study population – Inclusion and Exclusion criteria

This was a multicentric prospective study that recruited patients from three University Hospitals. Ethical approval was obtained from the local research regulatory bodies. All women gave informed consent.

We included women that presented for opportunistic cytology-based screening between 2006 and 2014 and agreed to participate. We only included only women that had cytology taken (even if this was inadequate). We included women with cytological abnormalities as well as normal controls. All women underwent a colposcopic evaluation with or without biopsy for histological diagnosis. We included all women irrespective of their age, ethnicity and menopausal status. Women who were HIV or hepatitis B/C positive or women with autoimmune disorders were excluded.

Sample collection and tests

We prospectively collected detailed patient characteristics and recorded the colposcopic findings. We obtained a liquid-based cytology sample (LBC)(ThinPrep®) at the first visit before proceeding to the colposcopic assessment. The cytology was assessed by two experienced cytopathologists. The results were reported according to the revised Bethesda classification system (TBS2001 system).[2,3]

The remaining material was used to test a series of test and HPV-related biomarkers. These included: a) HPV DNA typing using the CLART® HUMAN PAPILLOMAVIRUS 2 (GENOMICA) kit for the simultaneous detection of 35 different HPV genotypes by PCR amplification of a fragment within the highly conserved L1 region of the virus[4]; b) Nucleic Acids Sequence Based Amplification (NASBA) assays[5] (NucliSENSEasyQ® HPV v1.0) that was used for the identification of E6/E7 mRNA of the HPV types: 16, 18, 31, 33 and 45; c) the PermiFlow® (Invirion Diagnostics, LLC, Oak Brook, IL) kit for the identification of E6/E7 mRNA expression of high-risk HPV (subtypes: 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66 and 68) using FLOW cytometry[6] and d) the immunocytochemical expression

of p16INK4a using the CINtec® Cytology Double staining (p16/Ki67) Kit.[7] Some of the included women had only results for some of these markers but not all. This was the case if some of the laboratories tests yielded invalid results or in cases where the material was insufficient for the processing of the whole set of biomarkers.

We used histology as the gold standard for the assessment of the accuracy parameters of the tests. The histology was taken by colposcopically-directed punch biopsies or by conisation (usually large loop excision of the transformation zone – LLETZ) for women requiring treatment. If histology was available from both punch biopsies and treatment cones, the most severe lesion was documented. If histology was not available as not clinically indicated (i.e. normal cytology and colposcopy), these women were considered as 'clinically normal' (CN) cases. The histological samples were prepared and fixed according to standard histopathology protocols. The three-tiered Cervical Intraepithelial Neoplasia (CIN) grading system was used for reporting histological diagnosis.

Analysis and Decision Support Scoring System

We aimed to classify each subject into one of three groups: a) normal or clinically normal, b) CIN1 and c) CIN2 or worse. The latter included cases with CIN2, CIN3, squamous cell carcinoma (SCC), adenocarcinoma (Adeno-Ca) or other histological types of cancer (Ca).

In this study, the DSSS was based on an ANN implemented by a Multi Layer Perceptron (MLP).[8] To assess the DSSS performance, various statistical measures were extracted: specificity, sensitivity, positive and negative predictive value (PPV and NPV), false positive and false negative rates (FPR and NPR) and overall accuracy (OA). These were subsequently compared to accuracy parameters for cytology (at the clinical thresholds of ASCUS+, LSIL+, HSIL+) and/or HPV DNA test.

The specific implementation of the MLP is an attractive approach, because this operates as a 'black box'. The clinical user imports the data to the system and receives an estimation of the woman's individual probability for the following histological diagnosis (i.e. normal, CIN1 or CIN2+). The MLP also has the capability to handle data with missing values as in the case of this study, and quite often in the clinical practice. Additionally the MLP provides an estimation of the probabilities that the specific woman falls into the three categories and appears in the form of a triplet. For example, if the output demonstrates a result of [92%, 7%, 1%] that indicates that the probability of normal histology is 92%, while the chances of harboring CIN1 or CIN2+ 7% and 1%, respectively. These probabilities serve as a score (Scoring System) and provide an evidence of the strength of the MLP estimation.

We obtained data from 3565 visits of 2267 participating women. The data used to train the MLP classifier were composed of:

1. the cytological outcome formally expressed as: Normal, atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intra-epithelial lesion (LSIL), atypical squamous cells -cannot exclude high-grade squamous intraepithelial lesion (ASC-H), high-grade squamous intra-epithelial lesion (HSIL), squamous cell carcinoma (SCC), adenocarcinoma (Adeno-Ca), other types of cancer not otherwise specified (Ca NOS) and Inadequate if the cytological criteria for reporting were not fulfilled.
2. the HPV DNA typing result expressed as 1 if the specific subtype was identified, 0 if not and empty if results for DNA typing were not available. The DNA typing tested for subtypes 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85 and 89.The MLP was fed with generated values: Has16Or18 if subtype 16 or 18 was present; No_Subtypes that described the number of subtypes found whether these were high or low risk; No_HR and No_LR that indicated the number of high risk and low risk subtypes respectively and; hasHR and hasLR as binary variables to indicate the presence of high and low risk subtypes.
3. the HPV mRNA typing result expressed as 1 if the specific subtype was identified, 0 if not and empty if results for mRNA typing were not available. The mRNA typing with NASBA technique tested for subtypes 16, 18, 31, 33 and 45.
4. the FLOW FISH (Fluorescent In Situ Hybridisation) outcome expressed as 1 if it was positive, 0 if it was normal and empty if results for this were not available.
5. the p16/Ki67 outcome expressed as 1 if it was positive, 0 if it was normal and empty if results for this were not available.

We applied a batch training algorithm for the MLP ANN. Additionally the available data were separated into training and test sets; the first was used to adjust the MLP ANN weights and the second set was used for test purposes (approximately 50% of the data randomly selected were used for each one of these two groups). We used 3561 out of the 3565 visits of

the participating women. Four cases were excluded from the test set, given that there were no cases in the training set that had identical values in all parameters, (note that the algorithm used automatically excludes such cases); 1751 (49.2%) composed the training set and 1810 (50.8%) cases the test set.

The final MLP architecture had 170 input neurons. Some of the variables used were not numeric; one unit was assigned for each value (i.e. cytology required 7 input units to address all diagnoses). Similarly, the output layer had three neurons; one for each histological category: normal, CIN1 and CIN2+). Finally, there was used one hidden layer with 8 neuron implementing a Hyperbolic tangent non linear function [8].

Results

We included data from 3565 visits of 2267 participating women. Four were excluded; 3561 were analysed. Of these 2419 had normal and 1142 had abnormal cytology results. One hundred and three cases with normal cytology underwent punch biopsy for clinical indications during colposcopy; two of these had CIN1 and the remaining 101 were normal. The remaining 2314 cases with normal cytology but no histology were considered clinically normal as the colposcopy was also negative in all cases.

According to our results cytology often correlated with the histological diagnosis. However, on several occasions there was substantial discordance, particularly in the underestimation of the disease severity. Seventeen cases of invasive cancer had less significant or inadequate findings in the cytology (ASC-H: 2 (11.8%); HSIL: 13 (76.4%); Inadequate: 2 (11.8%)). Sixty-two had CIN2 or 3 in the presence of minor cytological findings (ASCUS: 4 (6.5%); ASC-H: 6 (9.7%); LSIL: 41 (66.1%); Inadequate: 11 (17.7%)). Conversely, some women with HSIL cytology had less significant findings in histology (11/276 (4.0%) had CIN2) and others with minor cytological abnormalities (ACSUS, ASC-H, LSIL) had normal histology (ASCUS: 3/192 (1.6%); ASC-H: 6/16 (37.5%); LSIL: 5/582 (0.9%)) giving a 1.8% overestimation rate. The overall ability of the neural network to accurately predict the histological diagnosis was high. More specifically, in the total set for example, 99.5% of the normal cases were correctly classified, 96.7% of the CIN1 cases and 93.0% of the CIN2 or worse cases. The rates were largely similar in the training and testing sets separately.

The use of cytology at a cut-off of ASCUS yielded, as expected, very high sensitivity (100%) in predicting CIN2+ at the loss of specificity (76.4%). Although the NPV was optimal (100%), there was a high false positive rate (23.6%) suggesting that almost one in four women will have unnecessary interventions. On the contrary the use of HSIL (including ASC-H) as a cut-off yielded optimal specificity (99.4%) in predicting CIN2+ with a loss in sensitivity (87.5%). This accounted to 12.5% false negative rate, suggesting that more than 1 in 10 women with CIN2+ will be missed. The use of LSIL as the cytological cut-off improved the specificity (92.7%) with a small reduction in sensitivity (98.8%).

We further compared the accuracy parameters of the DSSS to those of high risk HPV DNA test with or without cytology at different cytological thresholds (ASCUS+ or LSIL+). HPV DNA test alone had high sensitivity (91.8%) and NPV (98.2%) at the loss of specificity (55.6%). The combination of either positive HPV test or cytology (at ASCUS+ or LSIL+ thresholds) predicted with 100% negative predictive value women without the disease (CIN2+) and maximized sensitivity (100%) but substantially reduced specificity to 46.8% and 49.9%, respectively. The combination of cytology (at ASCUS+ or LSIL+) with HPV DNA test positivity reduced the sensitivity to 91.8% and 90.6%, respectively and improved the specificity (46.6% and 49.9%, respectively) but this was lower than the accuracy of the DSSS. The MLP ANN DSSS produced comparably better results than cytology, HPV tests or the combination of these and yielded an optimal balance of sensitivity (93.0%) and specificity (99.2%), high positive (93.3%) and negative predictive value (99.2%) with very low false positive (<1%) and acceptable false negative rate (7.0%).

The overall accuracy for MLP ANN was higher (98.6%) than that of cytology at a cut-off of ASCUS, LSIL+ or HSIL+ (78.8%, 94.3% and 98.2%, respectively). This was also reflected in the odd ratios indicating better performance for MLP ANN (1684.22) followed by HSIL+ (1159.79), and ultimately LSIL+ (1042.41)(for ASCUS+ the sensitivity was 100% and odds ratio could not be calculated). As a final performance metric, we used the AUC (Area Under Curve) and demonstrated high performance for MLP for all three groups: normal (99.9%), CIN1 (99.8%) and CIN2+ (99.7%).

A total of 192 cases had ASCUS in the original cytology. Of these the histology confirmed CIN1 in 185 cases, CIN2+ in 4, while 3 were histologically normal. The DSSS classified 182(98.4%) of the CIN1 lesions as such and 3 (1.6%) as CIN2+. It correctly identified all (4) CIN2 cases and gave a prediction of CIN1 in the 3 histologically normal cases. Of 16 cases with ASC-H cytology, 8 had CIN2+ and 2 had CIN1 on histology; all these were correctly classified by the MLP ANN. From the histologically normal cases, 3 were overcalled CIN1 and 1 CIN2+ by the system.

Similarly in the subgroup of women referred with LSIL cytology (580 cases), the histology confirmed CIN1 in 535 cases,

CIN2+ in 40, while 5 had normal histology. 525 out of the 535 (98.1%) were correctly assigned as CIN1. However, the DSSS incorrectly assigned 2 cases of CIN1 and CIN2+ as normal and upgraded 3 histologically normal cases to CIN1 (5 in cytology).Overall the MLP correctly classified the disease when compared to the gold standard with a high positive predictive value.

Discussion

With this rapidly increasing evidence base around new HPV biomarker technologies and the increased awareness of the public, the translational potential of these biomarkers is hard to comprehend.[9-12] Clinicians are often asked to make sense of this 'jungle of biomarkers' and balance these against the traditional cytologic and colposcopic findings. It is imperative that advanced modeling techniques are employed to develop user-friendly tools that could assist clinicians' decision making. This prospective multicentric study of a large patient cohort employed advanced neural networks and artificial intelligence techniques for the development of a clinical DSSS. The system developed had the ability to exploit all the biomarker information in order to accurately predict which women had clinically significant lesions with true oncogenic potential (CIN2 or worse) and give a quantified probability for different histological diagnoses. The results clearly and consistently demonstrated that this DSSS could achieve an optimal balance of increased sensitivity and specificity and minimize the rate of false negative and false positive results as compared to cytology with or without HPV DNA test.

Cytology systematically under-called a substantial number of invasive or high-grade cases with the risk of missing progressive disease or, conversely, overcalled minor abnormalities leading potentially to a number of interventions for women at low risk. The DSSS, on the contrary, demonstrated very low false positive and acceptable false negative rate and misclassified a low number of cases when compared to cytology with or without HPV test. These cases may be true misclassifications of the system or could be explained by an imperfect gold standard as punch biopsies may be less representative when compared to the excision of the whole transformation zone (TZ).[13]

Our study included a large patient cohort with more than 3500 visits. Large sample sizes are particularly important for ANNs as the accuracy of these systems in correctly identifying the disease improves with increasing number of cases through learning and pattern recognition. The size of the cohort increases the strength of the evidence and reproducibility of these in future studies.

The great advantage of the MLP approach is that this allows the analysis of patients with missing data on a 'best effort basis', which tries to maximize performance on the basis of available data. In our cohort, 1693 cases had the full set of biomarkers, while the remaining 1872 lacked one or more. In clinical practice, missing data for some of the evaluated tests is not uncommon and may be due to various reasons (ie. inadequate biological material or low cell count, high red blood cell content or other technical reasons). This technique is a powerful tool in this setting.

It is the case however that many of the included women only had punch biopsy rather than a full excision of the squamo-columnar junction, whilst those with no abnormalities were considered normal without histological confirmation. Although the accuracy of colposcopically-directed punch biopsies has been questioned[13], this is the most accurate gold standard that can be used in women where excision of the TZ is not clinically indicated. Similarly, due to ethical constrains, biopsies from women with normal cytology and colposcopy are not possible and the acceptance of these cases as normal is justified for pragmatic clinical studies.

The DSSS did not incorporate the colposcopic findings. However, in cases where histology was not available and the colposcopy was in agreement with cytology on normal results, this was used to define clinically normal cases. Analysis incorporating the information and disease prediction of the colposcopic assessment may be of value in the support system particularly when this will be assessed for specific clinical applications in the future.

The DSSS had overall higher accuracy that cytology at different thresholds with or without the HPV DNA test. However, the population of this study was heterogeneous and therefore a direct comparison with current triage strategies in different clinical groups (such as the use of high-risk HPV DNA test in the triage of ASCUS and LSIL) was not possible and was beyond the scope of this study. Future studies should include direct head-to-head comparisons of the DSSS to current clinical algorithms.

The most extensively explored HPV biomarkers in the literature were chosen and assessed as part of this ANN. Although some were exploring the same disease process (ie. mRNA by NASBA and flow cytometry), these provided complimentary information on mRNA positivity for 5 specific individual subtypes (NASBA) or overall for several more subtypes (flow cytometry). Future research should assess the most cost-effective models by exploring different combinations of the tests in specific clinical groups.

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L14

Fibroepithelial neoplasms of the female breast: Cytopathology perspectives

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The category of fibroepithelial neoplasms of the female breast encompasses a variety of lesions including but not necessarily limited to sclerosing lobular hyperplasias (fibroadenomatoid mastopathies), usual fibroadenomas and variants thereof with myxoid and complex features, juvenile fibroadenomas, tubular adenomas, lactating adenomas, and phyllodes tumors with benign, intermediate and high grade malignant potentials.

In this brief program, the cytomorphologic features helpful in categorization of the various classes of fibroepithelial proliferations of the female breast are defined and conceptually supported via appraisal of relevant peer-reviewed literature and practical cytologic-histologic correlation. When appropriate, clinical/ultrasonographic/mammographic relationships are emphasized.

At the end of this session, participants should be able to recognize salient light microscopic features of mammary fibroepithelial lesions. In addition, participants will be more comfortable with clinical and radiologic correlations of fibroadenoma and phyllodes tumor, providing increasing comfort with cytodiagnostic categorization of these commonly encountered conditions.

L15

Urine cytology, New perspectives "UR in zone"

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Background: Urine specimens have been used in the detection of urothelial neoplasms for a long time, however, until recently, no standardization of terminology and morphological correlates of individual diagnoses have not been established.

Methods: With the experience and previous successes of the "Bethesda Systems" for cervical, thyroid and pancreatic cytology a working group was established during the May 2013 IAC Congress in Paris to work on building an international consensus on terminology and morphological criteria for diagnoses of urinary specimens.

Results: The efforts have culminated in a comprehensive publication, similar to the previous Bethesda System documents, detailing the "Paris System" definitions, criteria and atlas of images in individual categories. Definitions of diagnostic groups, including the adequacy issues have been described in detail. A separate chapter is dedicated to ancillary studies in urinary cytology, including UroVision®.

Discussion: Primary aim of urinary cytology is focused on the identification of high-grade urothelial malignancies in the Paris System. This is quite well-received in cytology and urology communities as it has been known for a long time that low grade and high grade urothelial neoplasms are clinically and prognostically separate entities and utility of urinary cytology in identification and follow up of low grade neoplasms is mediocre at best. Clinical and cytologic data on urine specimens are expanding. The Paris System acknowledges the fact that some issues such as the adequacy parameters are still largely institutional and likely to be updated in future versions of this system. Details of urinary cytology and the Paris System are discussed.

L16

Atypia in thyroid FNA: Dark side of the moon

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Fine needle aspiration (FNA) of the thyroid nodules is the initial diagnostic test for detecting or ruling out the presence of malignacy. 60-70% of tyhroid FNA specimens are benign; 5-10% are malignant. The remaining 20-30% of the cases fall into an intermediate category in which the diagnosis is uncertain ('grey'). This area is called "indeterminate zone" in the FNA diagnostic classification. This category is, in fact, constitutes "*the darkside of the moon*". Historically various diagnostic terms were used for this category such as "*atypia, borderline, Thy3 and suspicious"* by different laboratories and institutions. Variety of the terms caused confusion among the pathologists and doctors in charge of the medical/surgical management of the nodules. Moreover, the data showed the ratio of malignancy is generally 20-25%, whereas the ratio of benignity is 25-30% in "indeterminate category" who went to surgery.

Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is introduced to standardize the terms and the cytologic criteria in each term to be used in thyroid FNA specimens in 2009. A specific category is reserved for borderline cases under the name of "atypia of undetermined significance" (AUS) and "follicular lesion of undeterminate significance" (FLUS). However, AUS/FLUS is reserved for aspirates containing cells (follicular/Hurtle) with architectural and nuclear atypia that is more pronounced than that observed in benign nodules yet sufficient to be classified for SFN/FN, suspicous for malignancy. Nevetheless AUS/FLUS is a heterogenous category. Diagnostic criteria demonstrate inter/intraobserver variability. It has the potential to be overused. Some pathologists use this category like a "waste basket". The term of "atypia" is taken as "suspicious for malignacy" by some doctors in many countries, especially by those who are unfamiliar with the Bethesda Reporting System.

AUS/FLUS is comprised of a problemic group of FNA specimens that are not clearly benign, suspicious for malignacy and malignant. Its use is warranted, but care must be exercised, overuse should be prevented. In short, this area still constitues to be "the dark side of the moon" in thyroid FNA.

Slide Seminar

Cases 1-5

Atypia in breast FNA

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Despite the declining use due to gaining popularity of the core biopsy, fine needle aspiration (FNA) is stil an easy, practical, time-saving and cost effective method to assess the breast lumps (palpable and/or ultrasonographically detected). The diagnostic outcome depends on two main factors: a) obtaining sufficient and representative material, b) experience in reading breast FNA specimens. Both experienced aspirator (clinician, radiologist, pathologist) and cyto/pathologist are necessary. When these two elements are present, breast FNA is a valuable and economical method in differentiating benign and malignant breast lesions, especially in a busy outpatient settings. Ideal breast FNA should be applied under ultrasonogram with a close cooperation (presence) between radiologist and cyto/pathologist in a outpatient clinical setting so called “breast FNA clinic”.

Traditionally the following diagnostic terminology has been used in reporting breast FNA specimens: a) benign, b) atypical, c) suspicious, and d) malignant.

Data showed that both atypical and suspicious category include benign and malignant lesions in histopathology. Therefore, in order to avoid patient anxiety and other negative consequences; I use and recommend the following approach for reporting breast FNA: a) benign, b) atypia, c) malignant. I report all equivocal cases as “aytpia” together with the following comment: *“Aypia may be seen in proliferative lesions of the breast or may be a sign of underlying malignancy. Appropriate surgical procedure for tissue diagnosis is recommended (core / needle wire localization/ surgical biopsies).”*

Benign breast lesions causing atypia in FNA: a) fibrocystic lesion with florid epithelia proliferation (incl ADH), b) sclerosing adenosis, c) fibroadenoma, d)phylloides tumor, d) mastitis. Malignant breast lesions which may give aytpical picture in breast FNA: a) DCIS, b) lobular/ tubular / papillary carcinomas. Since lobular carcinoma is located in fibrous tissue, it may give rise to erroneous negative results or to “atypical cells”.

In summary, there is a still a place for breast FNA at least for the triage of time consuming and costly diagnostic tissue procedures.

Cases 6-10

Thyroid cytology, Indeterminate category

Idris Tolgay Ocal, MD, Associate Professor

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Background. 2015 Update of ATA Management Guidelines for Adult patients with Thyroid Nodules and Differentiated Thyroid Cancer maintained the comment "Thyroid FNA is the most accurate and cost effective method for evaluating thyroid nodules" in this addition, as expected. However, indeterminate category in thyroid cytology is still an issue of debate among cytologists.

Methods. Cases in the indeterminate category are reviewed in detail with cytologic features and clinical correlates.

Results. Indeterminate category is a heterogeneous group of morphologic patterns and findings that are difficult to delineate with well-defined borders. Inter-observer variability is very high particularly in the atypia of undetermined significance-follicular lesion of undetermined significance (AUS/FLUS). It has also been established that AUS/FLUS category in itself is formed by a mixed group of multiple histologic and clinical correlates with different malignancy risks. Similarly, follicular neoplasm diagnosis also correlates with a mixture of histologic diagnoses and malignancy risks.

Discussion. Indeterminate category is a mixture of cytologic findings with significant morphologic overlap. While the AUS/FLUS category was created in an attempt to define an intermediate, but low-risk category, its clinical significance was not clear at the time of the publication of the Bethesda system. It was acknowledged that it corresponded to a spectrum of histologic findings, similar to the "follicular neoplasm" category in cytology, however, the diagnostic correlates are even less defined for this category. Consequently, the malignancy risk associated with AUS/FLUS group shows wide variations in different institutions. Definition of atypia will be reviewed on a case-based discussion.

Additionally, cytologic diagnoses of AUS/FLUS, follicular neoplasm, suspicious for malignancy will also be discussed in the light of most recent recommendation by the Endocrine Pathology Society terminology of Non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP).

OTHER TOPICS

Symposium

L17

Undergraduate and postgraduate training in pathology - where are we and where do we go?

Ales Ryska, MD, PhD, Professor

The Fingerland Department of Pathology, Charles University Medical Faculty Hospital, Hradec Kralove, Czech Republic

Nobody would probably deny that pathology as one of the basic medical sciences is an integral part of any undergraduate curriculum. The main aims of the undergraduate pathology training are to elucidate etiopathogenesis of diseases, to teach classification of diseases, to show current spectrum of methods used in pathology and to help understand what the role of pathology is in modern medicine. Medical students should understand what clinician can expect from pathologist and what does pathologist require from clinician and the importance of multidisciplinary cooperation should be stressed.

However, as we see in different medical schools throughout Europe, it is not always represented as a self-standing subject. Namely in problem oriented curricula, this subject is integrated with other disciplines (both preclinical and clinical). Despite the advantages (better understanding of pathological issues in the entire context of medicine), it frequently results in misunderstanding of medical students what does pathologists work consist in or what is the matter of current pathology practice. This may lead to difficulties in recruitment of best candidates for a carrier in our discipline.

As a result of dramatic changes of daily pathology practice, we should probably reshape our methods of tuition. There is not a unanimous agreement if besides lectures and interactive seminars also autopsy classes, surgical pathology classes should be included and what is the need of practical microscopy classes and what knowledge of microscopic features should be required. There are also other unanswered questions, such as the need for active participation of students at autopsies.

In the postgraduate training we face the shift of the paradigm of training. Due to rapid development of the discipline, the spectrum of information for the residents must significantly change (understanding of molecular basis of the diseases, adoption of new methods, etc.) while the "classical" skills of gross and microscopic diagnostics must be still kept. Thus, the demands placed on the residents are dramatically increasing.

L18

Pathology and Public - We are here!

Sanja Milenković, MD, PhD, Associate Professor

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The aim of this lecture is to explain a variety of ways, with different media which we can use for promotion pathology to local healthy audience. Pathologists, laboratory scientists, institutions and organizations around the world are included in generating greater awareness and dispelling the many myths around the specialty that saves lives. It was not possible to take a same model from all countries because the nations are mutually different and each is special in its own way. The concept of organizing pathology differs between countries. International Pathology Day is an opportunity to celebrate the vital work of pathologists and to demonstrate to the public the important role of pathology in their lives.

Pathology (histopathology in the most narrow sense), as a part of medicine, demands to be presented to the public and to become more visible and recognizable with all its distinctiveness, not just as a profession, but also as a part of medicine that requires close communication with patients, as well as, with healthy people of different target groups. In many countries, when we say pathology we think only about anatomical pathology without microbiology, biochemistry, transfusion, etc. This significantly reduces the modality of promotion in these countries. We consider that the development of awareness in the public, on one hand, and in the population of pathologists, on the other, about the importance and place of pathology represents a process that cannot be short-term, but has to be sustained and measurable. Nations are mutually different and each is special in its own way. The concept of organizing pathology differs between countries and methods of financing are important and represent a major problem in low budget countries.

Forming of special body at the national level for promotion of Pathology in the Public would give the possibility to create an active network between the countries, and they could use the experience and materials from other countries during the promotion in their countries. Framework Approach, national small actions and reactions of "people to people" would make the system operational only if there is an exchange of material.

The target groups that would be included in promotion (healthy people population, population of healthy but disabled individuals, school children population, medical students, pathology residents, pathologists, etc.) regardless of national distinctiveness are suitable for a same way of promotion. The existence of free accessible promotional material (in English) in different format (movies, musical clips, logos, etc.) would facilitate the job and every country would also be able to translate the material in the national language.

As an important issue that attention should be paid to, is the opening of collaboration possibilities with NGOs and non-profit societies on the national level (we already have that kind of experience) in different countries in the sense of common appearance in promotion. With such collaboration, target groups should be organized in as easier way and providing of sustainability of the program for a time-limitless period by creation of a “bank” of promotional material. The creation of sufficient amounts of promotional material with international character (to overpass language barriers) is really important. Potential risks that can happen during the realization are: insufficient motivation of pathologists is one of the most serious risks and we suggest naming of potential leaders in every member country and including the young, as well as, it is going to be difficult to adjust the same model of promotion to every country so we think that the project design in the frame of the ESP should be different in the sense of flexibility, ideas and material exchange compared with the Royal College initiative (we focus on histopathology, not biochemistry or microbiology). I also want to show Serbian experience that we had over the past two years.

L19

Benign melanocytic lesions and malignant melanoma - differential diagnosis, classification, immunohistochemistry, molecular pathology and personalized therapy

Stoyan Alexov, MD, Head

Histopathology Department, Specialized Hospital for Oncology Diseases, Sofia, Bulgaria

Contemporary concepts of benign melanocytic lesions and malignant melanoma reporting focusing on histological features, melanoma variants, differential diagnosis, classification, immunohistochemistry, molecular pathology and personalized therapy will be presented (https://www.rcpath.org/resource-library-homepage/publications/cancer-datasets.html).

Benign Melanocytic Lesion: Junctional Nevus, Compound Nevus, Dermal Nevus, Banal Nevus versus Nevoid Melanoma, Banal Nevus Variants, Atypical Acral Nevus versus Acral Lentiginous Melanoma, Banal Nevus versus Dysplastic Nevus.Banal Nevus verusu Nevoid Melanoma, Banal Nevus Varians, Atypical Acral Nevus verusu Acral Lentigenous Melanoma, Spitz and Reed Nevus, Compaund Spitz Navus, Criteria for Grading Cytological Atypia in Dysplastic Nevi, Differential Diagnosis- Banal Nevus versus Dysplastic Nevus,

Dataset for the histological reporting of primary cutaneous malignant melanoma and regional lymph nodes

(https://www.rcpath.org/resourceLibrary/dataset-for-the-histological-reporting-of-primary-cutaneous-malignant-melanoma-and-regional-lymph-nodes.html)

Macroscopic Discription, Histopathological malignant melanoma by location and histological subtype, Breslow thickness, Tumor Infiltrating Lymphocytes, Clarck level invasion,

TNM Classification for Malignant Melanoma, Anatomic stage/ prognostic groups,

Immunohistochemistry IHC, Minimal IHC Panel, Recommended IHC Panel

Molecular Pathology: BRAF V600E, Exon11/15, NRAS, KIT Exon 1,13,9,17,18,20, HLA-A

Malignant melanoma: Superficial Spreading Melanoma, Melanoma Genaral, Minimal Histology Data Requirement Histopathological subtype Malignant Melanoma,

Personalized Therapy based on histology, IHC and molecular investigation (Vemurafenib inhibits V600muted BRAF kinase), Melanocytic tumors; UV damage and BRAF mutations, Immune signature of human melanoma (good prognosis), Pattern of metastasis maintenance proteins of melanoma, Genetic factors behind chemoresistance of melanoma.

European Society of Pathology

European School of Pathology Workshop: Breast pathology in the 21st Century

- **Lectures**
- **Breast Pathology Slide Seminar**

EUROPEAN SCHOOL OF PATHOLOGY WORKSHOP:

BREAST PATHOLOGY IN 21ST CENTURY

Lectures

Breast pathology in 21st century

European Society of Pathology

General pathology of the breast lesions with focus on radiological – pathological correlation

Tibor Tot, MD, PhD, Associate Professor

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Breast carcinoma is a chronic disease in which the individual cases vary in clinical and radiological presentation, morphology, molecular phenotype, prognosis, and in response to the applied therapy. Certain clinical, radiological, morphological, and molecular characteristics of the tumors help the observers to judge the risk of dying of the disease and other events during the follow-up period.

These so-called prognostic parameters can be categorized into a radiological-surgical and oncological group.

The radiological-surgical prognostic parameters are related to the subgross morphology of the tumor: the number of the tumor foci within the breast (lesion distribution or ´focality´), the size of these foci (tumor size), the volume of the breast tissue they occupy (disease extent), and the variability of their structure (heterogeneity). Assessed with radiological methods, these parameters guide the surgeon to plan and perform the adequate surgical intervention(s). Assessment of these parameters with the methods of pathological work-up of the specimen after surgery confirms or modifies the results of the radiological assessment, indicates the need of complete surgical intervention, and provides information about the risk of local recurrence of the disease and its metastatic capacity. All of the mentioned subgross parameters are also related to overall survival of the patients.

The oncological parameters are related to the genetic construction of the tumor cells and its expression at the level of protein synthesis (hormone receptor status, expression of growth factors, proliferative activity of the tumor cells, and grade of tumor tissue differentiation). These parameters predict the tumor´s responsiveness to certain type of therapy and as such guide the oncologist to plan individual treatment. They are also related to survival.

Invasive or in situ: difficulties in delineating non-invasive and invasive breast lesions

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The spectrum of breast cancer has changed considerably in the last decades following the introduction of screening programs which have led to diagnose early lesions that were rare during the pre-mammographic era, and also following the introduction of immunohistochemistry and molecular pathology.

Morphology is still the best tool to establish the correct diagnosis and especially to diagnose an in situ or invasive carcinoma for the correct treatment. It is appearing that the more we know in terms of histology, the more cases of problematic definition are surfacing.

Aim of this paper is to give a brief summary of those light microscopic findings that are the most important variables in defining behavior and treatment of breast cancer.

IN SITU CARCINOMA IS THE MOST TRICK LESION TO BE DEFINED CORRECTLY AS SUCH

In situ carcinoma is defined as a neoplastic proliferation still confined inside the pre-existing breast lobules and ducts, with preservation of basal lamina and of myoepithelial layer and without invasion of the surrounding stroma.

Most breast carcinomas take origin from the terminal duct lobular unit,[1] and the distinction between ductal and lobular in situ carcinoma is actually referred to the type of cells and of growth pattern rather than to the level of the glandular tree involved.

DUCTAL CARCINOMA IN SITU

Ductal carcinoma in situ (intraductal carcinoma, DCIS) is frequently a non-palpable lesion, usually mammographically detected, as a consequence of the frequent association with microcalcifications.[2] Many DCIS are not promptly visible macroscopically. However, the gross appearance of poorly differentiated lesions is quite characteristic. These lesions appear as ill defined areas of firm to hard consistency showing on cut surface a microcystic appearance with many tiny holes containing yellowish creamy material. This appearance is reminiscent of that observed in duct ectasia. Traditionally,[3] the microscopic subtypes of DCIS have been subdivided taking in account their structural appearance. Therefore they have been classified in comedo, cribriform, solid, and micropapillary variants. Thus comedocarcinoma refers to a lesion in which neoplastic cells fill the TDLUs but show a central necrotic core. Cribriform DCIS is an intraductal cell proliferation that fills entirely the TDLU and in which the neoplastic cells are arranged to form secondary glandular lumina. The solid variant is constituted be cells tha fill the TDLUs without undergoing necrosis. Finally the micropapillary type is characterized by a proliferation of neoplastic cells that replaces the epithelium lining the ducts and that shows small micropapillary projections or small trabeculae which tend to coalesce, forming curvilineous structures, or “Roman bridges”.[4] Azzopardi also described the earliest carcinomatous changes that he named clinging carcinoma. In this type of DCIS there is a mural proliferation along the TDLU walls that appear thickened.

The traditional pattern-based systems were found to lack any prognostic value and reproducibility.[5] Therefore, several new classifications have been proposed in the last decade. Lagios et al.[6] and Holland et al.[7] were among the first groups to demonstrate the importance of nuclear grade in sub-classifying DCIS. Holland et al.[7] proposed a classification based on a combination of nuclear grade and “cell polarization”, defined as the cell orientation towards the duct lumen or in secondary gland spaces. Accordingly, well differentiated, low grade DCIS is composed of cells having nuclei of the same size and shape, without prominent nucleoli and the neoplastic cells show consistent polarization. On the contrary neoplastic cells in poorly differentiated DCIS are non-polarized and show irregularly shaped nuclei with prominent nucleoli and frequent mitoses.

The presence and type of necrosis were other parameters proposed by many authors in the classification of DCIS.[8,9,10] However, when necrosis was studied in term of consistency and reproducibility, this parameter was found to have the lowest kappa statistics value, because of the difficulty in distinguishing comedo-type necrosis from non-comedo necrosis and even from non-necrotic eosinophilic intraluminal secretion.[11]

Nuclear grade has been found to be a good parameter also in predicting the mean time of recurrence.[6, 12]

In conclusion, the problem of DCIS prognostic classification is not completely solved. Most studies have shown that nuclear features are the best histological predictor of outcome in patients diagnosed with DCIS. In 1997 a Consensus Conference was held in Philadelphia. It was recommended that the pathology report on breast DCIS should contain information regarding nuclear grade (high, intermediate, low), polarization, architectural pattern, necrosis, tumor size, status of surgical margins, presence of microcalcifications and correlation with radiological features.[13]

The problem of grading and sub-classifying DCIS is also partly related to the distinction between benign proliferative lesions and early malignant in situ carcinomas. Many definitions have been proposed for ductal hyperplasia (DH) and atypical ductal hyperplasia (ADH) and the various authors have focused on different features (cell differentiation, structure, extent of the lesion) to trace a line between DH and ADH or between ADH and well differentiated, early DCIS.[4,14,15,16,17,18,19,20] Recently, in an attempt to overcome the diagnostic problems in separating ADH from well-differentiated DCIS, it has been proposed to apply to breast proliferative lesions the same terminology already used for other organs, such as prostate and uterine cervix.[21] In this new system DH, ADH and DCIS are grouped together under the term “ductal intraepithelial neoplasia” (DIN). This is subdivided into three grades: grade1 is referred to DH, grade 3 to poorly differentiated DCIS (nuclear grade 3) and grade 2 DIN comprehends both ADH and well differentiated DCIS. This system appears to offer the advantage of grouping together lesions (ADH and early DCIS) which are really difficult, if not impossible, to separate in many instances and which, actually, do not require a different management of the patients.

MICROINVASION AND PSEUDOINVASION IN DCIS

In many cases of mammary DCIS it may be difficult to establish whether part of the lesion has invaded the surrounding stroma. This is particularly difficult in cases involving areas of sclerosing adenosis[22] or in cases of poorly differentiated DCIS showing prominent periductal fibrosis and inflammation, which can simulate an early reaction to stromal invasion.

In such cases, the myoepithelial cell layer is very thin and difficult to appreciate as a consequence of the distension of the involved ducts. On the other hand, invasive carcinoma may sometimes simulate DCIS.[23]

In addition, the use of pre-operative diagnostic procedures as fine needle aspiration or stereotactic biopsies cause trauma-related artifacts (displacement of tumor cells within the stroma or fat tissue) that can simulate stromal invasion.[24,25]

Basal lamina (BL) and myoepithelial cell layer (ML) seen in non neoplastic glands, invariably surround true in situ lesions. The value of immunohistochemistry in revealing ML and BL has been recently stressed, and a variety of antibodies are commercially available against BL and ML.[26,27] Damiani et al.[28] studied a series of 38 cases of poorly differentiated DCIS using a panel of two antibodies to BL (laminin and collagen IV) and two antibodies to ML (smooth muscle actin and calponin). The immunohistochemical study was found determinant in the final diagnosis in 9 out 11 cases initially diagnosed as “uncertain invasion” on hematoxylin-eosin. Similar results on the utility of immunohistochemistry in differentiating DCIS from microinvasive carcinoma have been obtained by Prasad et al.[29] Therefore, the use of immunohistochemical markers to highlight the presence of a continuous rim of BL and ML is recommended in any equivocal case and particularly in poorly differentiated DCIS to avoid inadequate management of the patient.[28]

There are several carcinomas difficult to tell if in situ or invasive.

The term ***intracystic papillary carcinoma (IPC)*** is employed to define a papillary carcinoma that appears entirely contained within a large encysted duct[30,31] Therefore, IPC is considered as a solitary, localized form of in situ papillary carcinoma.[32,33] Nevertheless, a definite demonstration of a continuous layer of myoepithelial cells and / or rim of basal lamina around the fibrous wall of IPC is not easy in most cases. The prognosis of IPC is excellent and the frequency of axillary metastases is extremely low. Only one of 35 patients from the series of Fisher et al.[34] died of disease. In an other series,[32] the only patient who died of disease had a IPC associated to areas of ordinary IDC NOS.

Neoplastic papillae have usually scanty stromal cores. However, broad bands of hyaline collagen may be present within the tumor. Glandular structures and small aggregates of neoplastic cells may be seen entrapped within the collagen bands, creating areas suspicious for stromal invasion. However, it is generally accepted that the diagnosis of stromal invasion in IPC should be restricted to cases showing foci of frankly invasive carcinoma outside the peripheral wall of the cyst.[3] When invasive carcinoma occurs in association with IPC, it is usually of non-papillary, IDC NOS type. In one series this occurred in up to 40 percent of cases of IPC.[32]

Low grade adenosquamous carcinoma (LGASC)

LGASC is the breast counterpart of syringomatous carcinoma of the salivary glands[35] and it share many features with some types of eccrine carcinomas of the skin.[36,37]

LGASC presents as a firm to hard nodule, yellow to tan in color that shows ill defined infiltrative borders.

Histologically, the tumour consists in cords and glandular structures with angulated shape growing immersed in a hypercellular stroma rich in fibroblasts with plump, irregular nuclei. A moderate to intense inflammatory lymphocytic infiltrate is often present, sometimes forming true follicles with germinal centers. Neoplastic glands and cords show variable degrees of squamous differentiation,[38] and are surrounded by a layer of myoepithelial cells;[39] this finding is disturbing if we dogmatically accept the idea that an in situ lesion is encircled by myoepithelial cells, while invasive carcinomas do not have myoepithelial elements.

LGASC recurs locally and one patient developed bilateral asynchronous tumors. Distant metastases and deaths have been reported only in occasional cases.[39]

Cases difficult to tell if in situ or invasive are the papillary solid variant of breast carcinoma[40] and the breast tumour resembling the tall cell variant of papillary thyroid like carcinomas.[41]

Additional critical cases will be shown.

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The complex issue of assessing breast cancer predictive parameters

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Pathological breast cancer diagnosis has to be completed with the report of predictive factors.

The factors, widely accepted and unchanged in the last decades, are the Estrogen and Progesterone Receptors (ER and PR) and HER2 that predict the response to hormone and trastuzumab therapy, respectively.

They are analyzed by immunohistochemistry (IHC) and may be affected by problems related to antigen preservations. The first, as well as the most crucial step of antigen preservation is the proper collection of tissues. The Higher Health Council of the Italian Minister of Health has produced Guidelines that describe general procedures for "Tracking, Collection, Transport, Preservation and Storage of cells and tissues for diagnostic investigations of PATHOLOGICAL ANATOMY" (http://www.salute.gov.it/imgs/C_17_pubblicazioni_2504_allegato.pdf). The ASCO/CAP guidelines focus on problems related to ER/PR and HER2 antigenic preservation and the need for specific and standard protocols for their assessment. For example, they report "Up to 20% of current IHC determinations of ER and PgR testing worldwide may be inaccurate (false negative or false positive)". These guidelines recommend a testing algorithm that relies on accurate, reproducible assay performance. In analogy, referring to HER2 guidelines [3] report "Despite attempts within the international pathology community to improve the status of HER2 testing in routine practice, testing inaccuracy remains a major issue with both IHC and FISH" and recommend that "Testing must be performed in a laboratory accredited by CAP or another accrediting entity".

Nowadays, it is mandatory to perform IHC by automated immunostainers. The selection of the antibodies is another crucial step for the reproducibility of the results. Finally an accurate and reproducible evaluation of the results has to be assured by specific education programs and possibly by the use of automated system of analysis.

Breast Pathology Slide Seminar

European Society of Pathology

Case 1

Complex sclero-hyaline lesion with distorsion of gland structures

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CLINICAL HISTORY

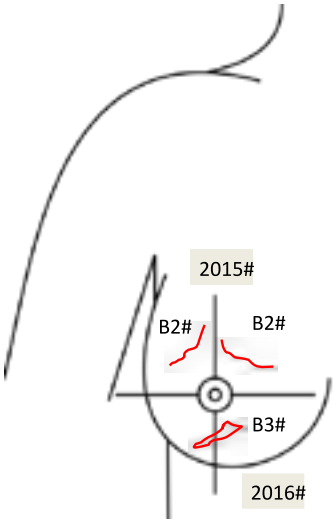
Age: 38 yrs.

Familiarity for breast cancer: YES

PARA: 0000

2015, March: right breast

- Self-palpation of mammary nodules.
- MX: two areas of architectural distortion with microcalcifications in Q2 right breast (radiological diameter 35 mm) and in Q1 right breast (radiological diameter: 20 mm) R3. Normal axillary lymph nodes at US examination.
- Core biopsy on both Q2 and Q1 right breast lesions; B2 [European guidelines for quality assurance in breast cancer screening and diagnosis, Fourth Edition]



2016, January: right breast

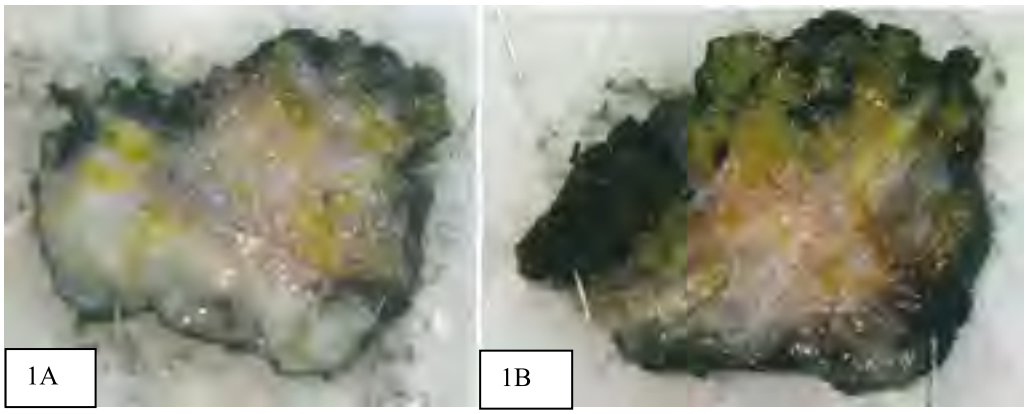
- breast pain and self-palpation of a mammary nodule in Q4.
- US: Q3-Q4 suspect area hypoecoic disomogenous.
- MRI lesion in Q1 right breast (25 mm). New lesion in Q3-Q4 right breast (35 mm). No pathological signs in Q1 and Q2. No lesions in the left breast.

2016, February: biopsy on Q3-Q4 lesion, right breast; B3 (sclero-elastotic lesion) European guidelines for quality assurance in breast cancer screening and diagnosis, Fourth Edition.

2016, March: Surgery in Q3-Q4 right breast.

PATHOLOGICAL FINDINGS

Gross examination. Linear scar (Fig. 1A) and on the deep margins that continues in a stellate lesion on the more superficial plan of 25 cm (Fig. 1B).



Microscopy

Deposit of sclero-hyaline and elastotic stroma around the ducts and the lobular structures that are distorted with a pseudoinfiltrative appearance (Fig 2A). Myoepithelial cells are scant and focally lacking. The epithelium of ducts is focally hyperplastic. TDLUs around the lesions show proliferative changes, involving the acini. Both columnar cell changes and usual epitheliosis are present.

Immunostaining

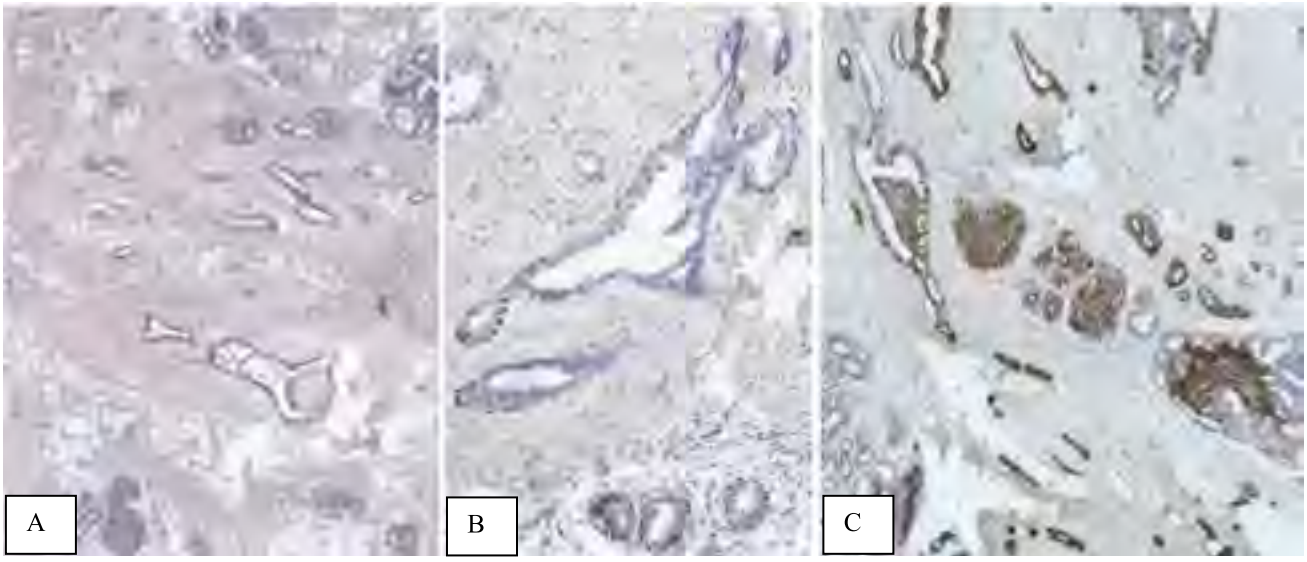
P40: positive in residual myoepithelial cells of ductal structures (Fig 2B)

CK5: positive in ductal structures distorted by sclerosis. Mosaic aspect in epithelial proliferation. (Fig 2C)

P40: positive in residual myoepithelial cells of ductal structures

ER: patchy expression

Diagnosis: ***Complex sclero-hyaline lesion with distorsion of gland structures. Usual ductal hyperplasia, cystic lobules with columnar epithelial hyperplasia.***



DISCUSSION

- **Imaging Findings**

Architectural distorsion is defined in the Breast Imaging Reporting and Data System (ie, BI-RADS) lexicon as “The normal architecture (of the breast) is distorted with no definite mass visible. This includes spiculations radiating from a point and focal retraction or distortion at the edge of the parenchyma. AD can also be an associated finding” [1]. Primary causes of architectural distortion include breast cancer, ductal carcinoma in situ, radial scar, complex sclerosing lesion, and fat necrosis. Secondary etiologies include previous breast surgery, trauma, and infection. Familiarity with imaging findings presenting as distortion on multimodality imaging will optimize detection and management of this subtle-yet-significant finding [2].

- **Core Biopsy B3: multidisciplinary management**

The European guidelines for quality assurance in breast cancer screening and diagnosis state that: “When dealing with radiological-pathological correlation in the multidisciplinary conference, B3 results other than atypical epithelial proliferations of ductal type are not always an indication for an excision biopsy. Reliable decisions on regular follow-up without further diagnostic intervention include: (a) findings of lobular neoplasia (except the pleomorphic type or those with necrosis, categorised as B5a) or (b) flat epithelial atypia, but only if they are associated with a benign histological lesion that correlates with the biopsy target (e.g. fibroadenoma, etc.), (c) papillary lesions without atypical findings that were completely removed by the diagnostic intervention and (d) radial scars detected as an additional microscopic finding to a benign lesion considered to be the biopsy target, provided no additional architectural distortion is present [3]”.

- **Complex sclerosing lesion/radial scar histology**

Under this heading are included sclerosing lesions with a pseudoinfiltrative growth pattern. Lesions greater than 10 mm are often suspicious radiologically due to their lack of circumscription and distortion of surrounding tissue. Histologically they are generally termed **complex sclerosing lesions**. They have all the features of radial scars and, in addition to their greater size, exhibit more disturbance of structure, often with nodular masses around the periphery. Some complex sclerosing lesions give the impression of being formed by coalescence of several adjacent sclerosing lesions. [3].

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Case 2

Invasive carcinoma of no special type (NST)

Anna Sapino, MD, Professor

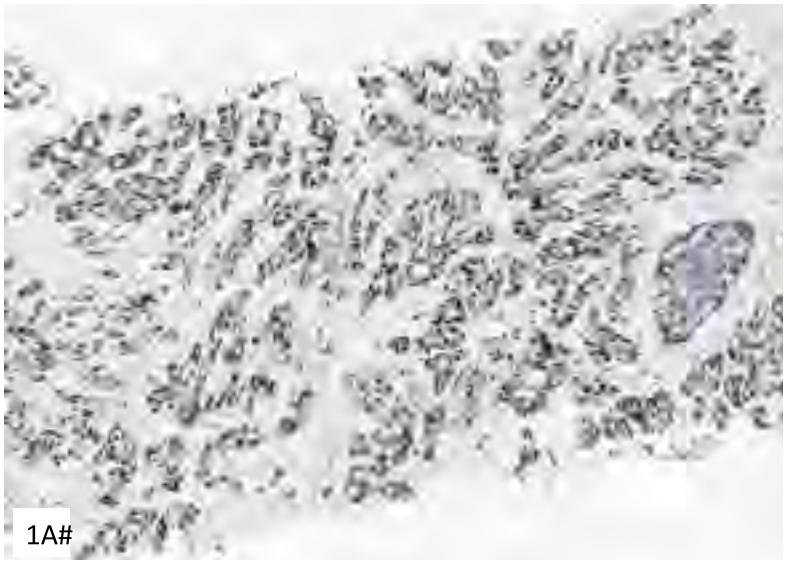
Department of Medical Science, University of Turin, Institute of Cancer Research IRCCs, Candiolo, Turin, Italy

CLINICAL HISTORY

Age: 42 yrs.

2015, January:

- MX: multiple nodular lesions in the right breast (R5); the largest located in Q1-Q2.
- MRI: lesions in Q1-Q2 (40 mm), in Q1-Q2-Q5 (diameter: 13 mm), in Q2 (8 mm), in Q2 (6 mm), in Q1-Q5 (10 mm) and in Q3-Q4 (8 mm).
- FNA on an axillary lymph node; C2 [European guidelines for quality assurance in breast cancer screening and diagnosis, Fourth Edition].
- Core biopsy on the largest lesion: invasive carcinoma, NST [WHO 2012], of intermediate nuclear grade, associated with cribriform DCIS with comedonecrosis; B5b [European guidelines for quality assurance in breast cancer screening and diagnosis, Fourth Edition].
- Immunophenotype:
  - ✓ ER expression: 98%
  - ✓ PgR expression: 98%
  - ✓ HER2 expression: negative (score 1+)
  - ✓ Ki67 expression: 32% (fig.1 A)



- FNA on an axillary lymph node; C2 (European guidelines for quality assurance in breast cancer screening and diagnosis, Fourth Edition).
- Multidisciplinary discussion: advanced breast cancer, not operable, neoadjuvant chemotherapy was proposed.

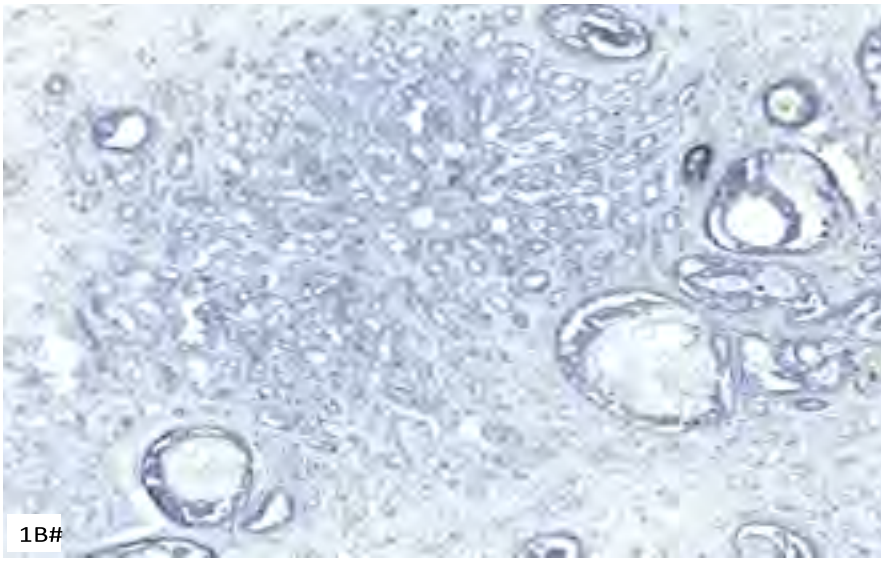
From January to April, 2016: neoadjuvant chemotherapy; FEC 100, 3 cicles - Docetaxel.

2016, May: RMI examination: stable disease; minimal decrease of the largest lesions (30 mm) at US examination; no suspect lymph nodes in the axilla.

PATHOLOGICAL FINDINGS

Multiple nodes of NST carcinomas, G1, associated with low-grade cribriform and micropapillary DCIS. No morphological signs of response, no necrosis, no apoptosis. Metastasis in one sentinel lymph node.

- Immunophenotype:
  - ✓ ER expression: 98%
  - ✓ PgR expression: 17%
  - ✓ HER2 expression: negative (score 1+)
  - ✓ Ki67 expression: 1% (fig.1 B)



DISCUSSION

Neoadjuvant chemotherapy is generally planned for patients with locally advanced carcinomas or with tumors primarily not suitable for breast-conserving surgery; thus, one of the aims of this therapeutic option is to downsize the disease burden (primary tumor + lymph node metastasis) [1]. However, the preoperative setting is also an effective way to study the activity of novel agents or therapeutic combinations in vivo [2]. Multiple core biopsies should be taken before neoadjuvant treatment to correctly assess the tumor heterogeneity [1]. In our routine experience, at least 4 core biopsies sampling of different tumor areas are performed. This should assure the exact definition of different tumor histotypes and the heterogeneity of the expression of hormone receptors, HER2, and Ki67 [1]. In the present case there was not a morphological response but the tumor proliferation was completely blocked, nodes of tubular carcinomas were not affected at all by chemotherapy. At multidisciplinary discussion after surgery only hormone therapy was suggested.

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Case 3

Extra abdominal fibromatosis

Vincenzo Eusebi, MD, FRCPath, Emeritus Professor

Service of Histopathology, Bellaria Hospital, University of Bologna, Bologna, Italy

Clinical History

Woman 63 yr old

In 1999, when she was 51, left upper outer quadrantectomy and axillary dissection (reactive nodes) followed by RT due to IDC (pN0).

In November 2009 mammography evidenced in the inner outer quadrant same breast a nodule showing circumscribed margins of 17 mm in size containing microcalcifications. The nodule was excised in January 2010.

Pathological Findings

Macroscopically the nodule was circumscribed and **histologically** was composed of spindle cells showing well evident cytoplasms. Mitoses were rare. Mature bone formation was well evident in the center of the lesion. Immunohistochemistry showed cells positive only for vimentin. Keratins and smooth muscle actin were distinctly negative.

A diagnosis of *ossifying fascitis* was rendered.

Follow up and Comments

In May 2011 ultrasound evidenced in the same quadrant a small nodule that was excised the following month

Histologically cells were very similar to the first biopsy. This latter was reviewed and showed some areas of invasion.

In view of the features of spindle cells running parallel, lack of mitoses, invasion along the borders and negativity for keratins, the original diagnosis was changed to ***extra abdominal fibromatosis***.

In the next case (case 2, same topic) all pertinent literature is included.

Case 4

Fibromatosis (fasciitis) like sarcomatoid carcinoma

Vincenzo Eusebi, MD, FRCPath, Emeritus Professor

Service of Histopathology, Bellaria Hospital, University of Bologna, Bologna, Italy

Clinical History

A 88-year-old female: in October 2011 mammographic evidence in the upper outer quadrant of left breast of a small area of 17 mm. A core biopsy was obtained of a spindle cell lesion that was interpreted as malignant (B5). In December a mastectomy was obtained together with a sentinel node which was reactive.

Pathological Findings

A circumscribed nodule was found of 2.5 cm of greatest axis.

The lesion consisted of atypical spindle cells running in different directions. Some pre existing entrapped glands were evident. No necrosis was visible and margins were mostly circumscribed, with minute areas of invasion. Mitoses were rare but present and Ki 67 stained about 3% of neoplastic cells. The mmunohistochemical results depicted a triple negative cellular proliferation. S100 protein, CD31 and actin were distinctly negative. Vimentin and all keratins tested were strongly positive.

The proposed diagnosis was ***fibromatosis (fasciitis) like sarcomatoid carcinoma***.[1]

Comment and differential diagnosis

Spindle cell neoplasms in breast include benign, low grade malignant lesions as well as malignant tumours.

Among benign lesions nodular fasciitis as well as benign stromal spindle cell tumours (BSSCT) are included.[2] The latter are constituted by a group of similar tumours of which the most frequent are myofibroblastoma,[3,4] solitary fibrous tumour/ haemangiopericytoma,[5] spindle cell lipoma.[6] The similarity resides on morphological criteria as well as immunohistochemistry and partly genetics. The correct diagnosis of these lesions is difficult being based on subtle criteria. Low grade malignant tumours can recur but rarely metastasize. These are represented by fibromatosis[7] that is also a clonal disease and fibromatosis (fasciitis) like sarcomatoid carcinomas.[1]

Malignant spindle cell tumours include sarcomatoid carcinomas[8] as well as spindle cell sarcomas of which fibrosarcoma amd myofibrosarcomas are the most frequent. All these lesions recur and metastasize.[2]

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Case 5

Diffuse invasive breast carcinoma

Tibor Tot, MD, PhD, Associate Professor

Department of Pathology and Clinical Cytology, Central Hospital Falun, Falun, Sweden

Clinical History

This 55-year-old woman felt a "thickening" in the medial portion of her breast. Her last mammograms was six years earlier. After that, she has declined attendance at three consecutive occasions. Clinical breast examination confirmed the presence of a 12x5 cm, hard diffuse lesion in the central and medial portion of the right breast, which was shrunk to a smaller size. Orange skin was observed overlying the lower portion of the right breast.

The actual mammography, ultrasound, and magnetic resonance imaging showed the presence of the large and diffuse lesion in her right breast. Core biopsy confirmed the lesion being invasive lobular carcinoma. The patient underwent mastectomy and axillary clearance.

Pathological Findings

A 85 x 38 mm diffuse invasive lobular carcinoma (Bloom-Richardson-Elston grade 2) associated with LCIS was seen growing like the spider's web in large-format histology sections. The tumor infiltrated the pectoral muscle. The tumor was ER and PR positive, HER2 negative (triploid for the HER2 gene) and the Ki67 proliferation index was 24%. Signs of lympho-vascular invasion were present and one of the eight examined axillary lymph nodes contained macro-metastasis

Diagnosis: ***Invasive lobular carcinoma of diffuse type***

Discussion

Diffuse invasive carcinomas comprise about 5% of all breast carcinomas 75% of them being of lobular histotype. They are usually extensive tumors growing like a spider's web and causing architectural distortion, rather than mass lesion, on the mammogram.[1] These tumors are characterized with an unfavorable prognosis compared to unifocal and multifocal breast carcinomas, especially if they are not lobular.[2] Although described for more than a century ago[3], they are rarely recognized as special entity[4] as their proper diagnosis requires use of large histological sections with detailed radiological correlation.

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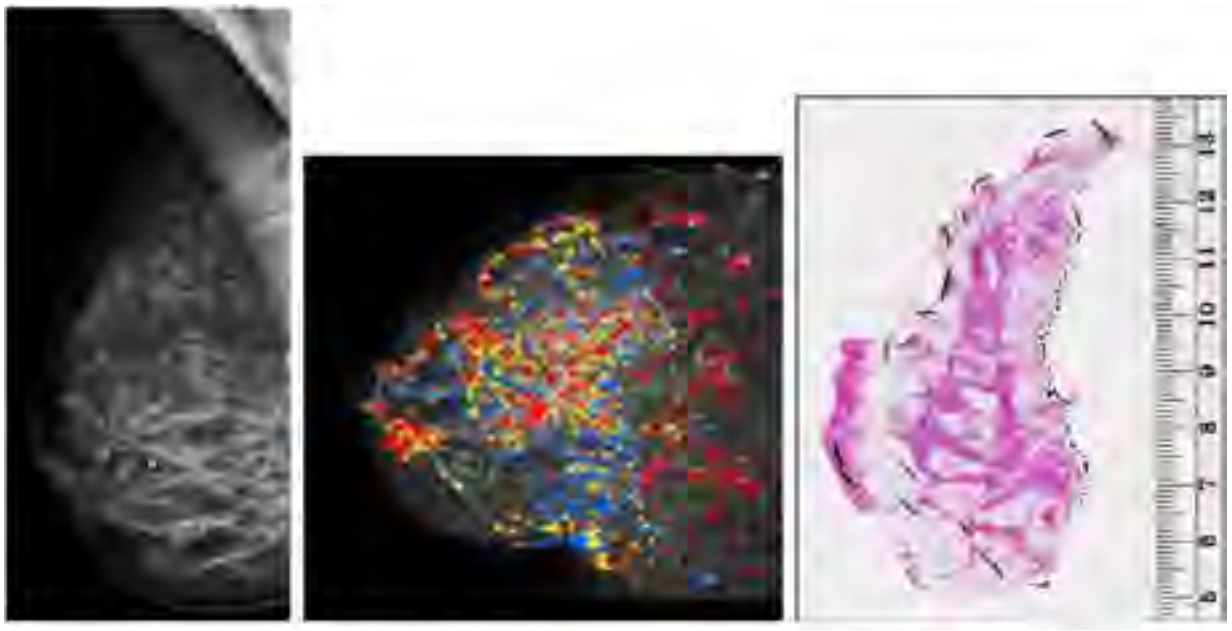
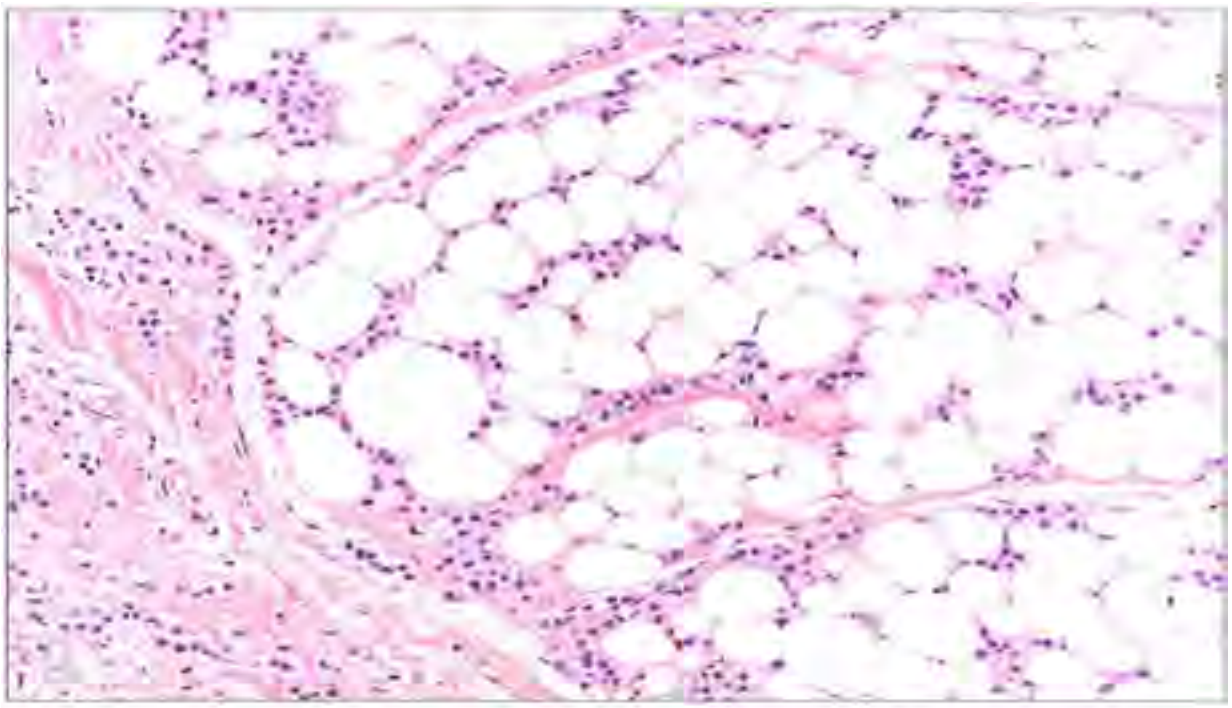


Case 5: Diffuse invasive carcinoma of the breast: mammography - MRI - large-format histopathology correlation



Case 5. Microscopic image of diffuse invasive cancer of the breast

Case 6

Micropapillary ductal carcinoma in situ of the breast

Tibor Tot, MD, PhD, Associate Professor

Department of Pathology and Clinical Cytology, Central Hospital Falun, Falun, Sweden

Clinical History

A 58-year-old woman, called back from mammography screening for assessment of the asymmetric density in the upper outer quadrant of her right breast. Mammographically, a small stellate lesion was detected and a very large non-specific asymmetric density associated with architectural distortion and rare microcalcifications. MRI detected a 10 x 9 x 8 mm solitary lesions suspicious of malignancy and also a lobe-like area showing low contrast enhancement indicating possible presence of an extensive in situ component. The stellate lesion was confirmed being invasive cancer on ultrasound-guided core-needle biopsy. Sectorial resection and sentinel lymph node biopsy was performed.

Pathological Findings

The large-format histopathology slides contained a 13 x 9 mm unifocal tubular carcinoma associated with a 65 x 58 mm area of micropapillary ductal carcinoma in situ. The invasive tumor was ER and PR positive, HER2 negative and showed a low Ki67 proliferation index. The in situ component was of grade 1 and was incompletely excised. A completing sector-resection was carried out and contained a 45 x 20 mm grade 1 micropapillary DCIS, still excised with dirty margin. The surgery ended up with mastectomy which still contained a 30x30 mm micropapillary DCIS.

Diagnosis: ***Invasive tubular carcinoma associated with extensive micropapillary ductal cancer in situ grade 1***

Discussion

Scott et al. were the first to propose to classify micropapillary in situ cancer as a 'special type', excluding it from the low, intermediate, and high grade categories of ductal carcinoma in situ because of its likelihood of extensive disease.[1] Micropapillary in situ carcinoma tends to involve the ducts extensively when present in pure form, regardless of the nuclear grade. This is a unique subset of in situ cancer that is frequently clinically occult but has a large mean size at diagnosis.[2] We carried out an interinstitutional study evidencing that micropapillary carcinoma gives more often local recurrences (Odds ratio 6.86) than the non-micropapillary ones.[3] Standard sampling may in effect underestimate the wide spreading of micropapillary in situ carcinomas and the involvement of surgical margins.

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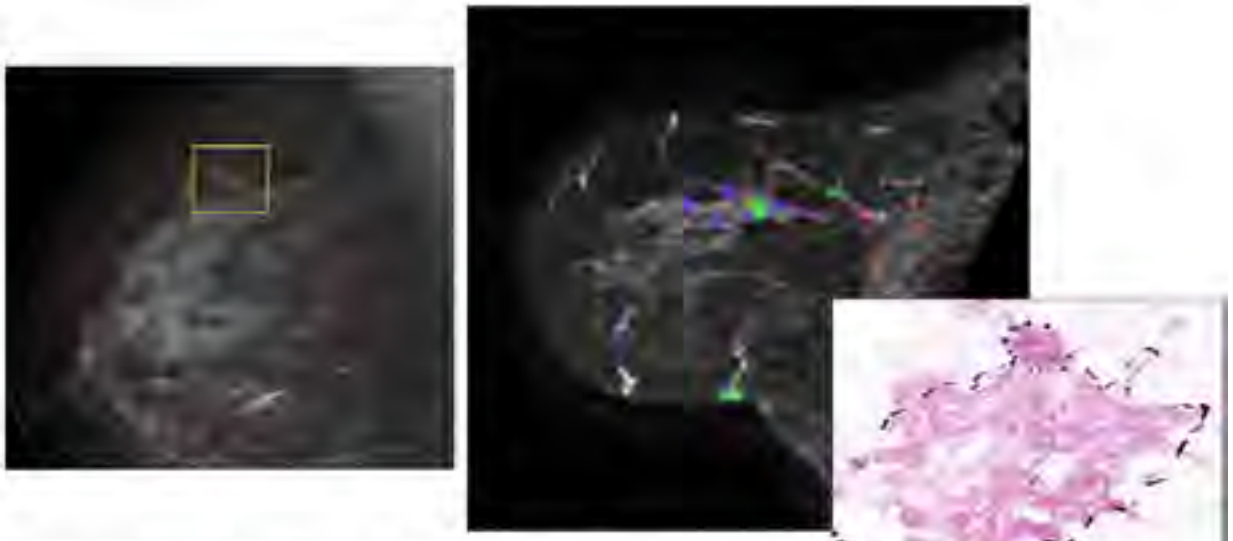
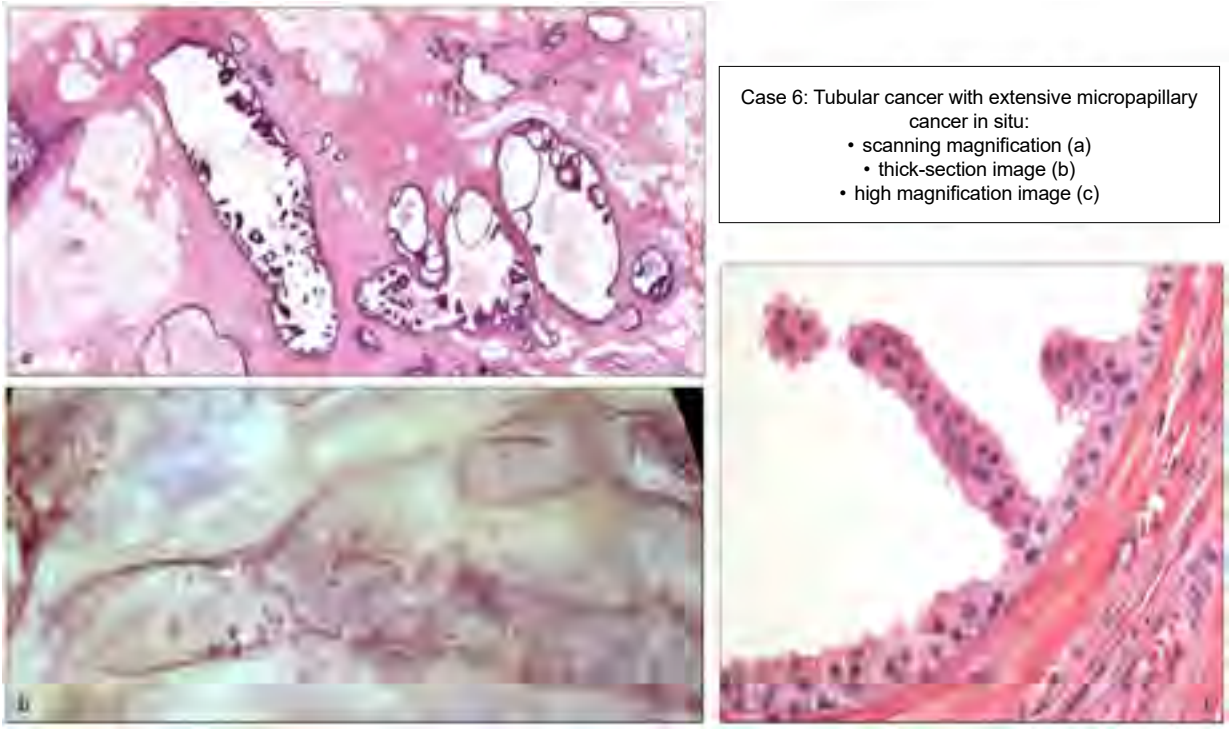


Case 6: Tubular cancer with extensive micropapillary cancer in situ.
Mammographic-MRI-large section histologic correlation. Total disease extent: 65x58 mm



Case 6: Tubular cancer with extensive micropapillary cancer in situ:
- scanning magnification (a)
- thick-section image (b)
- high magnification image (c)

Abstracts

- **Oral Presentations**
- **Slide Seminars - Selected Cases**
- **Poster Presentations**

ORAL PRESENTATIONS

OF01

Birmingham vasculitis activity score predicts relapse in ANCA associated vasculitides

Biljana Gerasimovska-Kitanovska[1], Svetlana Pavleska-Kuzmanovska[1], Slavica Kostadinova-Kunovska[2], Vesna Gerasimovska[1], Ladislava Grcevska[1]

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Objective: To predict treatment resistance and an early relapse in ANCA-associated vasculitides with the use of the Birmingham vasculitis activity score (BVAS, version 3).

Material and Methods: Five patients were admitted at the Department of Nephrology in the period 2015-2016 for rapid-progressive glomerulonephritis and signs of systemic involvement. All of them were biopsied and had crescentic glomerulonephritis on renal biopsy and were either c-ANCA or p-ANCA positive. All of them were treated with intravenous corticosteroids and cyclophosphamide, three of them had a need of hemodialysis treatment and one of them was treated with plasmapheresis according to the extent of pulmonary or renal involvement. One of them was discontinued from hemodialysis after treatment with immunosuppressive drugs. Birmingham vasculitis activity score (BVAS) version 3 was used in the beginning and the end of the hospitalization.

Results: Two of the patients had a BVAS score of 3 and 4, but three patients had BVAS of 9. 9 and 10. Patients with the high BVAS were re-admitted to the hospital with an early relapse and had a need of further treatment.

Conclusions: Birmingham vasculitis activity score may be used as a predictor of treatment resistance and an early relapse in ANCA-associated vasculitides.

OF02

Expression of protein arginine methyltransferase 1 in renal cell tumours

Jasmina Markovic-Lipkovski[1], Jelena Vjestica[1], Martina Bosic[1], Sanja Cirovic[1], Maja Zivotic[1], Dejan Djordjevic[2], Dusko Dundjerovic[1], Zoran Dzamic[2]

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Objective: Activity of protein arginine methyltransferase 1 (PRMT1) has been implicated in regulation of transcription, RNA metabolism, and DNA damage repair. However, dysregulation of PRMT1 has been observed in several malignancies.

Material and Methods: Quantitative real-time RT-PCR analysis of PRMT1 mRNA expression level in clear cell renal cell carcinomas (cRCC), papillary RCC (pRCC), chromophobe RCC (chRCC) and kidney tissue adjacent to the tumor was performed. In addition, 136 adult renal cell tumors, including 88 cRCC, 18 pRCC, 10 chRCC,7 multilocular cystic RCC (mlRCC), 4 collecting duct carcinomas (CDCs) and 9 oncocytomas, were immunohistochemicaly analyzed using tissue microarrays.

Results: PRMT1 mRNA expression levels revealed by qRT-PCR correlated to PRMT1 immunohistochemical findings. mRNA and immunohistochemical PRMT1 expressions were detected in all analyzed tumor types. Statistically, a significant decrease of PRMT1 mRNA expression level was noted in tumor, comparing to the adjacent kidney tissue ($p=0.001$), with tendency of decrease in tumors with higher nuclear grades. Immunohistochemical PRMT1 expression in mlRCC (6/6), CDCs (7/7) and in 67% oncocytomas (6/8), was significantly higher, comparing with other analyzed tumor types ($p=0.001$). Non-invasive cRCCs more frequently expressed PRMT1 ($p=0.041$).

Conclusions: Observed differences in PRMT1 mRNA expression level could suggest down-regulation during pathogenesis of RCCs. Differences in immunohistochemically obtained PRMT1 expression among different renal cell tumor types, different nuclear grades and invasiveness, could suggest its down-regulation in more malignant and advanced carcinomas.

OF03

New preoperative treatment decision algorithm in patients with prostate carcinoma

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Objective: Prostate carcinoma is a slowly progressive disease. Not all of the newly diagnosed cases should and have to be surgically treated. We tried to establish a new treatment decision algorithm using several existing biomarkers.

Material and Methods: The study group consists of 63 patients with prostate carcinoma and the control group consists of 63 patients with BPH. We analyzed the sensitivity and specificity of the number of core biopsies performed and the number of positive cores for prostate cancer. The level of expression of biomolecular markers Ki-67, p53, Her-2 and Bcl-2 with previously accepted protocols were also evaluated. The correlation was made with PSA, PSA density (PSAD), patient age and Gleason grade and score.

Results: The mean age of patients was 69.87±7.1. The higher Gleason score and grade were associated with higher PSAD and Ki-67 expression for $R=0.37$ ($p<0.05$) and $R=0.49$ ($p<0.05$) respectively. There was statistically significant correlation, between the expression of Ki-67 and PSA, for $R=0.3$ ($p<0.05$). Positive correlation was also seen when PSAD and Ki-67 expression was analyzed ($R=0.25$; $p<0.05$). Sixty percent of the patients in the study group showed moderate to high expression of p53, $p<0.01$ ($p=0.006$). There was a statistically significant positive expression of Her-2 in the study group $p<0.001$. Bcl-2 showed no expression in the study group and maximal expression in the control group. In the 12 core prostate biopsy more prostatic carcinomas were identified in comparison to the 10 core ones.

Conclusions: The 12 core prostate biopsy proved to be more accurate, especially revealing the latent, indolent prostate carcinomas. We found statistically relevant correlation between the expression of p53 and Ki-67 and with the patients` age, PSA, and PSAD. Bcl-2 showed expression in benign prostatic hyperplasia patients only. The above-mentioned parameters were used to establish a preoperative treatment algorithm that has still to be verified in everyday practice.

OF04

HER2/neu protein expression in gastric carcinoma and its association with tumor grading

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Objective: General objective: To evaluate the HER2 protein expression in gastric carcinoma and its association with histopathological grading. Specific objectives: 1. To carry out histopathological grading of diagnosed cases of gastric carcinoma. 2. To evaluate the frequency of HER2 positive gastric carcinoma by applying standard criteria.

Material and Methods: A total of 44 cases were consecutively included in the study as a sample. Histopathological types (Lauren classification - intestinal & diffuse) and grading were done according to Sobin et al (2009). Immunohistochemistry was done with a polymer-based detection system using a Herceptin kit to detect HER2 overexpression. Finally, the association between histological grading and HER2 status was assessed by chi-square test.

Results: More than two-thirds (68.2%) of the patients had the intestinal type of gastric adenocarcinoma and the rest (31.8%) diffuse type. In terms of grading, 31.8% were well-differentiated, 36.4% moderately differentiated and the rest 31.8% were poorly differentiated. Six (13.6%) patients were HER2 positive (overexpressed), 50% were negative and 36.4% were equivocal. Intestinal type of gastric adenocarcinoma were significantly prone to be HER2 overexpressed as compared to diffuse type (20% vs. 0%, p=0.035). HER2 overexpression was mainly associated with well and moderately differentiated carcinoma, but not with poorly differentiated carcinoma (21.4% vs. 18.8% vs. 0%, p=0.163).

Conclusions: One in every eight gastric carcinoma cases (13%) exhibits HER2 overexpression and it is well associated with the type and histological grading of the adenocarcinoma.

OF05

The influence of tumor associated lymphocytes to colorectal cancer progression

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Objective: The progression of colorectal cancer (CRC) is influenced by the interactions between the neoplasm and the host's tumor microenvironment. It is considered that immune cells present in the tumor associated stroma correlate with tumor progression and patient's outcome. High density of memory T cells and cytotoxic T cells correlate with longer patient's survival. Tertiary lymphoid structures (TLS) present in the tumor associated stroma are also considered to play role in the host's defense from tumor progression. In this study we correlated the quantity of tumor associated lymphocytes (TAL) to the tumor differentiation, local growth, nodal metastases (NM), lymphatic invasion (LI) and stage. We also defined the type of some of the infiltrating lymphocytes.

Material and Methods: The surgically removed material from 27 patients with CRC was standardly dissected and a standard procedure for histology and immunohistochemistry was done. The density of TAL in the tissue specimens from the tumor invasive front was semiquantitatively determined in three grades as scant, moderate and rich.

Results: CD4+, CD8+ CD20+ and CD68+ cells were found in all analyzed specimens. The density of TAL was higher in the tumors without NM and LI ($p<0.05$). The density was also higher in Stage I and Stage II disease but without statistical significance. TLS were present in 5 cases without NM and LI and were composed of T and B cell zones. We noticed depletion of macrophages in CRC with NM and LI.

Conclusions: TAL may be a good indicator for the progression of CRC.

OF06

Association of human papillomavirus in colorectal carcinoma in the Bangladeshi population

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Objective: Infection with the human papillomavirus (HPV) is associated with the development of several cancers, including oral, esophageal, skin, lung and cervical cancers. However, the association of HPV and colorectal cancers remains controversial. The aim of this study was to evaluate the association of HPV infection with colorectal carcinoma in the Bangladeshi population.

Material and Methods: Tumour tissues obtained from 60 patients with colorectal carcinoma were included in the study. Histopathological type and grading were done. HPV infection and genotypes (type 16 and 18) were examined from all samples by means of Real Time Polymerase Chain Reaction (PCR) using type specific primer (E7 protein).

Results: We found that HPVs were present in 25 (41.7%) cases. HPV type 16 was detected in 24 (96%) cases and both type 16 and 18 in only one (4%) case. Rectum was the commonest site of involvement (12/48%) followed by sigmoid colon (8/32%), caecum (3/12 %) and other sites (2/8%). Regarding histological type, out of 25 cases, 21 (84%) cases of adenocarcinoma, 3 (12%) cases of signet ring carcinoma and only 1 (1.6%) case of mucinous carcinoma were positive for HPV.

Conclusions: HPVs were present in colorectal carcinoma in the Bangladeshi population and HPV type 16 is a more frequent type.

OF07

The diagnostic and prognostic significance of p16, p53, bcl-2 expression and Ki67 proliferation index in benign and malignant uterine smooth muscle tumors

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Objective: This study aims to evaluate the diagnostic parameters such as mitotic count and tumor size in leiomyosarcomas (LMSs) and in uterine smooth muscle tumors (USMT) and to define the diagnostic value and prognostic significance of Ki-67, p16, p53 and bcl-2 expressions by immunohistochemical (IHC) methods.

Material and Methods: A total of 44 cases that were diagnosed as LMS, atypical leiomyoma, and cellular leiomyoma, in our pathology department from January 2010 through December 2015 were included in the study. IHC staining was performed for bcl-2, p16, p53, Ki-67 using standard techniques.

Results: Tumor size and mitotic index were significant prognostic factors (p=0.008, p=0.001, respectively). The rate of diffuse p16 expression was significantly higher in LMS group than in the other leiomyoma (LM) group (p=0.001). The rate of Ki-67 positivity more than 10% (increased proliferation) was significantly higher in LMS group than in the other LM group (p=0.0001). No statistically significant difference was found between LMS and LM groups for bcl-2 expression (p=0.892).

Conclusions: Mean tumor size in LMS is generally more than 10 cm and bigger than in LMs. The bcl-2 expression can not be used for LMS diagnosis and prediction of malignant USMT prognosis. In addition to histopathological findings, diffuse p16 expression and p53 overexpression can be used for distinguishing benign from malignant USMT. High mitotic index (>10/10 HPF) and high Ki-67 (more than 10%) can be used as useful indicators for LMS diagnosis, benign tumor distinction and prediction of aggressive clinical course.

OF08

The influence of clinicopathological factors, hormone receptor and Her2/neu status and Ki67 proliferative index on axillary lymph node involvement in breast cancer patients

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Objective: The aim of the study was to determine the influence of clinicopathological factors such as patient`s age, tumor status (pT), size, location, histological type, grade of differentiation and lymphovascular invasion, as well as steroid hormone receptor and Her2/neu status, and the proliferative index determined by Ki67 on the axillary lymph node (ALN) involvement in breast cancer patients.

Material and Methods: A total of 290 out of the 429 surgically treated breast cancer patients in 2014 year at the University Clinic of Thoracovascular Surgery with complete documentation for all examinations were included.

Results: Patients` age ranged between 18-90, mean of 57.6 years. The mean size of the primary tumor was 30.27+18.3 mm, while the mean number of the dissected ALNs was 13.81 (range, 8 to 39). ALN involvement was present in 59% of the patients. The mean number of positive ALNs was 3.14 (range 1-23). The univariant regression analysis showed that location, tumor size, grade of differentiation, tumor status (pT), proliferative index determined by Ki67 and presence of lymphovascular invasion significantly influenced the ALN involvement. Contrary there was no significant correlation between estrogen, progesterone receptor and HER2/neu status and ALN involvement. Using the multivariant model of logistic regression analysis tumor size and presence of lymphovascular invasion were determined as significant independent factors predicting the ALN status in breast cancer patients.

Conclusions: Our study showed that the potential influence of the proliferative index determined by Ki67 as an indicator of the biological aggressiveness of the tumor documented in the univariant analysis, was not confirmed in the multivariant analysis and it was not among the independent predictors of the ALN involvement in breast cancer patients.

OF09

Breast cancer susceptibility genes: beyond BRCA

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Objective: A number of susceptibility genes have been described that have different impact on the life-time risk for developing breast cancer (BC). BRCA1 and BRCA2 genes account for about 25% of familial cases. More than 20 other high to intermediate penetrance genes and >70 low penetrance alleles associated with BC risk have been identified, explaining additional 20% of familial cases. Still, more than 50% of the familial cases remain unexplained.

Material and Methods: We have performed BRCA1/2 mutation testing among 140 selected BC patients (with family history, young age, bilateral cancer, triple negative tumors and BRCA1ness profile) using Sanger, next generation sequencing (NGS) and multiplex ligation probe amplification (MLPA). A total of 38 patients were also screened with panel-based NGS of 94 cancer genes.

Results: Seven different BRCA1 and 11 BRCA2 mutations were detected in 13 and 16 unrelated families, respectively. Five mutations were recurrent, representing 55.2% of all detected mutations. Using panel-based NGS, pathogenic alleles were detected in 13 genes, including TP53, BLM, CHEK2, and NBN. Variants of uncertain significance (VUS) in more than 20 different genes were also detected. Subsequent association study among 180 familial BC patients and 180 controls showed higher frequency of 12 variants in AIP, ATM, BLM, BRIP, CHEK2, EXT2, FANCM and RECQL4 genes among BC patients. We have also shown that several known intermediate and low penetrance alleles are associated with BC risk among our patients.

Conclusions: In addition to BRCA1 and BRCA2, mutations in a number of other cancer genes contribute to the risk of developing BC among Macedonian women.

OF10

Utility of cell blocks and immunocytochemistry in routine fine needle aspiration and exofolliative cytology

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Objective: One of the constraints of the conventional FNA smear is the limited material available for additional diagnostic investigations such as immunocytochemistry (ICH).

Material and Methods: The cell block technique employs the retrieval of small tissue fragments from a FNA specimen which are processed to form a paraffin block. It is widely accepted that cell block technique increases the cellular yield and improves diagnostic accuracy. The ability to obtain numerous tissue sections allows multiple immunostains to be performed similar to paraffin sections produced in histopathology. ICH today is accepted as an indispensable adjunct to cytomorphology.

Results: The most striking contribution for improved diagnostic accuracy has been among lymphoproliferative disorders and metastatic cancers of unknown origin. Today it is possible to diagnose and subclassify most lymphomas using cytomorphology in conjunction with ICH. This should lead to an expanded use and acceptance of cytology in the work-up of patients with lymphoproliferative disorders. A similarly marked effect has been observed in patients with carcinomas of unknown origin. Today such patients can, in the majority of cases, have their primary tumour identified. The use of ICH for targeted therapies started with the analysis of estrogen and progesterone receptors in patients with inoperable or metastatic breast cancer over 25 years ago. Today new markers such as CD20, Her2, EGFR, and CD117 are being used for targeted therapy. It has led to a dramatic increase in diagnostic accuracy and also allowed the identification of markers both for prognosis and targeted therapies.

Conclusions: In our laboratory ICH has been used in over 3000 cases as an adjunct to cytology for the last 3 years. This review will to a large extent be based on our experience, while important results contributed by others will also be included.

OF11

A new animal model of neuronal migration disorder caused by prenatal vitamin C deprivation in guinea pigs

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Objective: The aim of the study was to investigate immunohistochemical characteristics of neurogenesis and gliogenesis of dysplastic cerebellar cortex in a new animal model of neuronal migration disorder caused by prenatal vitamin C deprivation in guinea pigs.

Material and Methods: The experiment included 40 fetuses of guiena pig sacrificed on the 50th day of intrauterine life. The first group of animals (N=20) was a control and the second was experimental, where mothers of fetuses were deprived for vitamin C from 10th to 50th day of gestation, when all animals were euthanised and brains of fetuses were removed and fixed. We analysed vermal region of cerebellum using neuronal (NeuN, calbindin, synaptophysin, and doublecortin) and glial immunohistochemical markers (PDGFR-O±, nestin, MBP, pTTT, olig2, and GFAP).

Results: In the analysis of dysplastic cerebellar cortex neuronal immunohistochemical markers show a morphological disturbance in Purkinje cell development (calbindin) and still persisting normal neuronal differentiation (doublecortin) and maturation (NeuN, synaptophysin) in ectopic granular cells. Using glial markers we show alteration of the direction and structure of Bergmann glial cells.

Conclusions: With prenatal vitamin C deprivation and the consequential disturbance in collagen synthesis we caused pial basal membrane rupture and subsequent development of dysplastic changes in the cerebellar cortex. The experiment showed that although the granular cells are located in ectopic medium, they properly differentiate and mature. Having in mind the fact that neither humans nor guinea pigs are able to synthesize vitamin C, this animal model creates a new view in understanding the pathogenesis of neuronal migration disorder similar to lissencephaly type II in humans.

OF12

European quality assurance scheme for breast cancer services

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Objective: The European Commission (EC) has initiated a project to develop a Quality Assurance (QA) scheme for breast cancer services. The scheme will be based on a revision of the European Quality Assurance Guidelines for Breast Cancer Screening and Diagnosis and is to be underpinned by accreditation in accordance with the provisions of EC Regulation No 765/2008. All aspects of breast cancer services including diagnosis, surgery, treatment, nursing care and palliative care will be covered by the QA scheme.

Material and Methods: The European QA scheme will need to cover all stages of care: Screening, Diagnosis, Treatment, Rehabilitation, Follow-up (including surveillance and, where necessary, management of recurrences), in addition to other aspects such as psychological support and palliative care, which are essential for a patient-centered concept of quality.

Results: An essential aspect of the scheme is the control of the various sources of risk inherent in diagnosis and treatment of breast cancer, via established and respected procedures based on evidence, best practices, and consensus, leading to an increase in quality of healthcare and a reduction of inequalities. European co-operation for Accreditation and National Accreditation Bodies will manage the scheme implementation.

Conclusions: Quality assurance scheme will provide a unique, evidence-based and publicly accessible scheme; there will be a legal procedure that will allow existing or new organisations to be accredited according to the QA Scheme and QA scheme requirements will be transparently agreed among a network of relevant stakeholders.

OF13

Surgical point of view in multidisciplinary treatment of osteosarcoma patients

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Objective: The main goal of this presentation is to show the process of multidisciplinary treatment of high-grade osteosarcoma patients from the surgical point of view. Also, we want to present the long-term follow-up results after treatment of pediatric and adolescent osteosarcoma patients in Macedonia.

Material and Methods: From the group of 22 patients with high-grade osteosarcoma, 4 patients were excluded, due to lung metastases at first presentation or pelvic localization. Another patient was excluded from the study due to indication for ablative surgery. The rest seventeen patients were planned for limb-sparing surgery. All 17 patients received neo-adjuvant chemotherapy protocol according to the Scandinavian Sarcoma Group XIV. After neo-adjuvant chemotherapy a clinical and radiological response of the tumor has been observed and analyzed.

Results: Response to neo-adjuvant chemotherapy was good in 9/17 patients (52.4%). Early local recurrence appeared in 7/17 patients (41,2%). From seventeen patients with limb-sparing surgery, additional 4/17 ended with amputation due to local recurrence (23.5%). Until now, 35.3% of the patients (6/17) are disease or event free with mean survival time of 55 months (range 27-108).

Conclusions: There was significant different overall survival time, in our study, between the groups of patients with good response to neo-adjuvant chemotherapy compared to the group of patients with bad response (p=0.0047). Furthermore, overall survival time in our group of patients was shorter than the time reported in the literature. We assume that the ”fund of lost time” prior the diagnosis was the main reason for that.

OF14

Important information from conventional radiography for pathologists who deal with bone tumors

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Objective: Proper analysis of conventional radiography (CR) should be done in an organized fashion in order to pay attention to specific radiographic features of bone tumors.

Material and Methods: Radiography gives information for bone tumor location in the skeleton (axial vs. appendicular or long vs. flat bones). Tumors may have predilection for sites of rapid bone growth (metaphyseal region), while other tumors tend to follow the distribution of red marrow. The location of the lesion within the bone may be assessed (central or eccentric, epiphyseal, metaphyseal or diaphyseal). Lesion may be lytic, sclerotic, or mixed. Focal lesion is the so called "geographic" lesion (type I). Infiltrative lesion has ill-defined margin and broad zone of transition and its pattern of bone destruction may be "moth-eaten" or "permeated". The pattern of tumor matrix mineralization may suggest histological diagnosis (chondral, osseous or fibrous tissue). Size and number of lesions may be a clue to diagnosis. Sharp margins and narrow transition zone at radiography are signs for benignity of the lesion, particularly when there is a sclerotic border.

Results: Periosteal reaction is an important radiographic feature that helps in characterizing a bone lesion. Solid or lamellar periosteal reaction suggests nonaggressive appearance; "onionskin" appearance suggests intermediate aggressiveness and interruption of periosteal reaction suggests aggressive process highly suspected for malignancy. Cortex may be affected by processes that originate in medullary canal, from periosteum or surrounding tissue. Displacement of adjacent fat lines suggests presence of soft tissue component.

Conclusions: Radiography gives important information about tumor location, size, and aggressiveness of the lesion. Sometimes tumor histology may be predicted.

OF15

Diagnostic work-out of acute myeloid leukemia (AML) patients in Republic of Macedonia

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Objective: Acute myeloid leukemia (AML) represents a heterogeneous complex of disorders resulting from diverse mechanisms of leukemogenesis. Correct diagnosis of AML subtypes plays a central role for individual clinical risk stratification and therapeutic decisions. Motivated to improve and simplify the diagnosis and management of AML in our Country, we conduct a prospective study at the University Clinic of Hematology. A total of 65 adult (>15 years) patients with acute leukemia who were consecutively admitted at the Clinic in a period of 12 months were enrolled in the study. Aim of our study was to establish and standardize diagnostic approach based on minimal screening tests which will facilitate risk adapted therapy for each single AML patient.

Material and Methods: The diagnosis of acute leukemia was made by standard criteria of the FAB Cooperative Study Group and confirmed by immunophenotyping bone marrow aspirates and/or peripheral blood samples following the criteria of the European Group for the Immunological Classification of Leukemia (EGIL) and the British Committee for Standards in Hematology (BCSH).

Results: Our results showed that morphology and cytochemistry established lineage in 58 (89.3%) of patients. Immunophenotyping furthermore revealed the exact lineage assignment of the blast cells in 11.7% patients and also change the lineage assignment in 3 patients and guided to implementation of specific molecular analyses for further definition of some AML cases. Using RQ-PCR assay we detected the presence of the fusion transcript PML/RAR alpha in 5 patients that were classified as acute promyelocytyc leukemia (APL). Those results were essential for more appropriate single patient therapeutic decisions.

Conclusions: Our multimodal diagnostic approach consisted of cytomorphology, cytochemistry, multiparameter flow-cytometry and molecular analyses improved the diagnosis and enabled initial individual clinical stratification in 27.7% of our AML patients.

SLIDE SEMINARS – SELECTED CASES

Genitourinary Pathology

Case 11

Mucinous tubular and spindle cell renal cell carcinoma - distinct type of renal cell carcinoma: a case report.

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Objective: Mucinous tubular and spindle cell renal cell carcinoma (MTSCRCC) of kidney is a rare, low-grade, polymorphic renal epithelial neoplasm. It occurs primarily in women, usually 32-79 years of age.

Material and Methods: 44-year-old woman presenting with a tumor in the upper pole of the kidney with dimensions 7.6x7x6.5 cm, was nephrectomized.

Results: Macroscopic findings: Soft, white-grayish cut surface with hemorrhagic areas. The tumor was confined to the renal parenchyma and surrounded by a pseudocapsule, compressing the renal pelvis, without invasion. Renal vein invasion and perinephric fat involvement were not identified. Histology: Tumor was delineated from the surrounding residual non-neoplastic kidney. Furthermore, the tumor had typical polymorphic features: cuboidal cells, with low-grade features, arranged in tightly packed, elongated tubules, somewhat resembling low-grade collecting duct carcinoma-Bellini, filled and/or separated by pale mucinous stroma, highlighted with Alcian blue stain. In some areas tubular structures revealed spindle cell configuration with bland characteristics, simulating leiomyoma or myofibroblastoma. Occasionally, areas of necrosis, chronic inflammation and papillary structures with foamy cell deposits, resembling papillary renal cell carcinomas were present. Immunohistochemical analysis: Positivity to low molecular weight keratins: CK8/18, CK19 and CK7, AMACR, EMA, vimentin, and E-cadherin, furthermore, CD10, CAIX, RCCM, P63, CK20, GATA3 and alfa-SMA negativity suggested a diagnosis of MTSCRCC.

Conclusions: MTSCRCC is a rare new entity with good prognosis, which needs to be separated from other renal tumors with more aggressive clinical course.

Fig. 1 Case 11

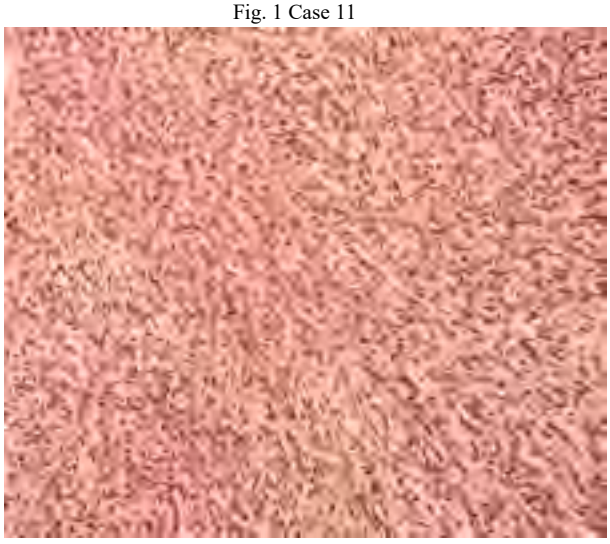

Fig. 2. Case 11

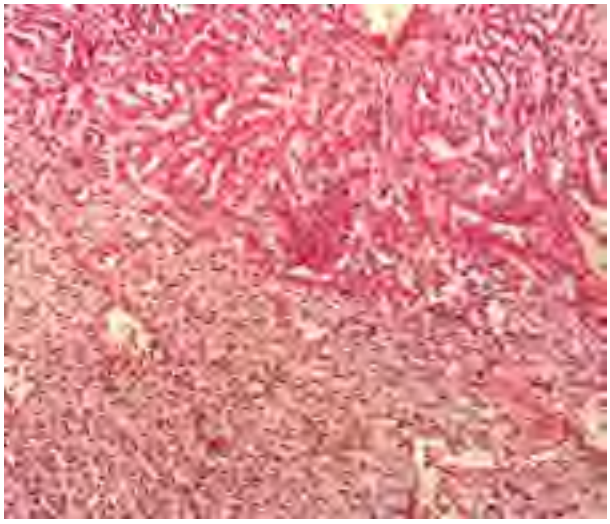

Fig. 3. Case 11

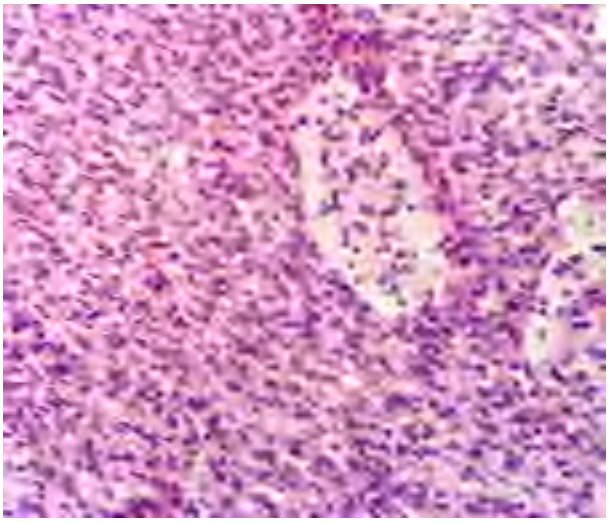

Fig. 4. Case 11

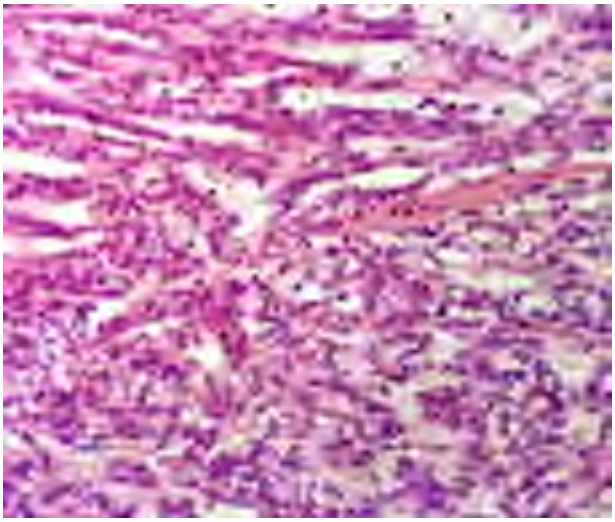

Fig. 5. Case 11

Case 12

A rare cause of hydronephrosis: polypoid renal pelvic mass

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Objective: The vast majority of upper urinary tract tumors are papillary urothelial lesions and they usually lead to hydronephrosis. Mesenchymal tumors located in renal pelvis are rare. Therewith, presentation of such tumors by hydronephrosis is extremely rare.

Material and Methods: Herein, a rare case of polypoid renal pelvic mass presented by hydronephrosis is reported.

Results: A 43-year-old female patient was admitted to the hospital with abdominal pain. Ultrasonography revealed the presence of a right renal mass in the interpolar region extending into the renal pelvis. Subsequent computed tomography showed a well-defined multiseptate cystic mass of 20 x 25 x 80 mm in the interpolar region of the right kidney. Dilation of renal pelvis was seen by both radiological methods. The patient underwent right radical nephrectomy with prediagnosis of renal pelvic mass. At the macroscopic examination of the specimen, polypoid mass in the dilated renal pelvis was observed. The mass was covered by hyperemic and smooth mucosa; cystic and solid areas were seen on the cut surface of the mass. Tumor tissue composed of spindle cells with uniform and elongated nucleuses and cystic dilated tubules covered by epithelium was observed in the microscopic examination. There weren't any mitotic activity and coagulation necrosis in the tumor tissue. The case was reported as "Mixed epithelial and stromal tumor".

Conclusions: Mixed epithelial and stromal tumor is a rare neoplasm of the kidney and extremely rarely can present as a polypoid mass in the renal pelvis. However, it should be on the mental list of the clinician in the differential diagnosis of cases with hydronephrosis.

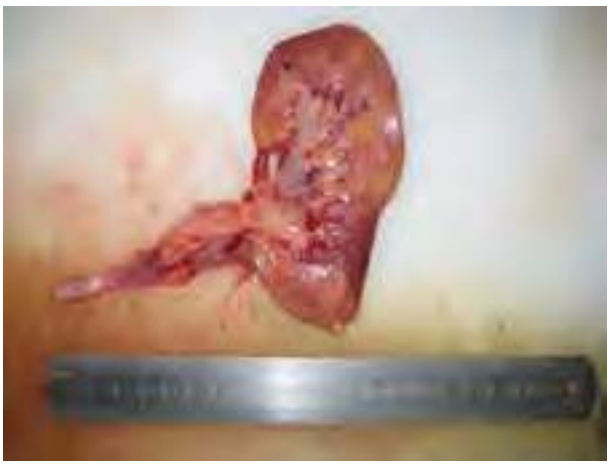

Fig. 1. Case 12

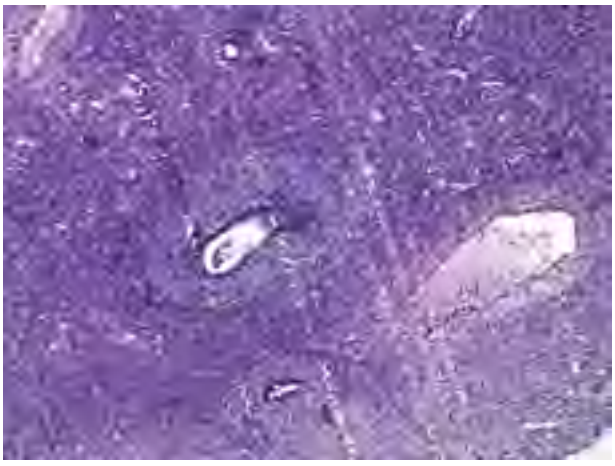

Fig. 2. Case 12

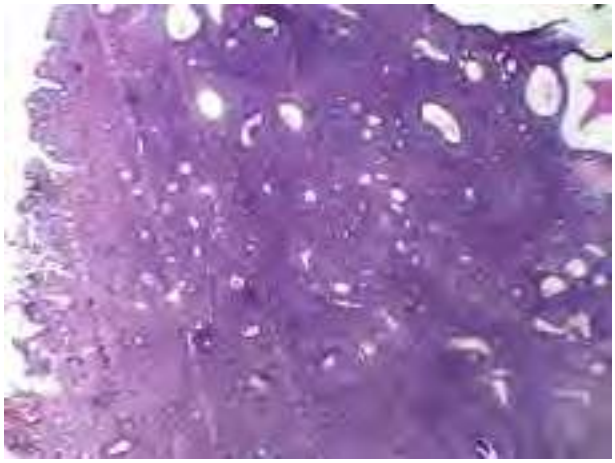

Fig. 3. Case 12

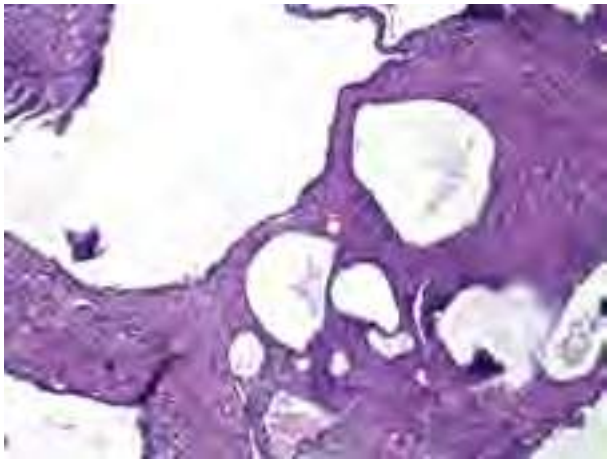

Fig. 4. Case 12

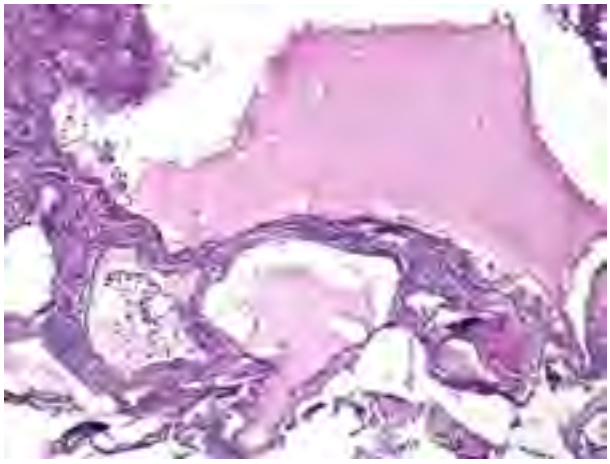

Fig. 5. Case 12

Case 13

Squamous cell carcinoma of the urinary tract: report of two cases

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Objective: Primary squamous cell carcinoma (SCC) of the renal pelvis and urinary bladder are extremely rare entities. Most of the patients are diagnosed at an advanced stage and are with poor outcome. Calculi and repeated chronic infections are predominant risk factors.

Material and Methods: We report two cases of primary squamous carcinoma of renal pelvis and urinary bladder respectively. The first case is a 49-year-old woman with longstanding history of nephrolithiasis. During the radiologic investigation, a renal mass and staghorn calculi were detected in the right kidney. The patient subsequently underwent right

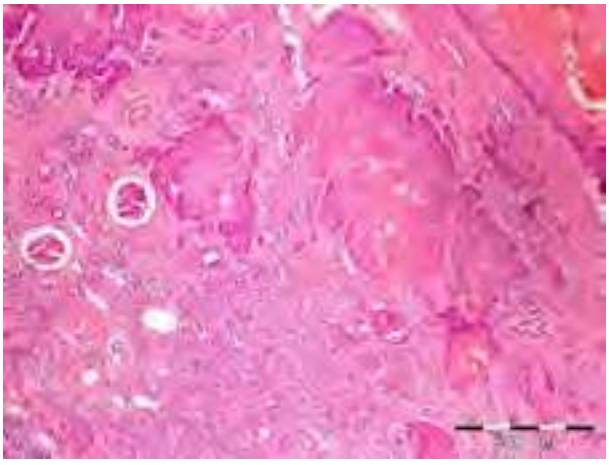


Fig. 1. Case 13

radical nephrectomy. The second case is a 61-year old man presenting with dysuria and haematuria. Cystoscopy revealed a bladder tumor which was resected transurethrally and diagnosed as squamous cell carcinoma. Cystoprostatectomy was performed two months later.

Results: Histopathology confirmed the diagnosis of squamous cell carcinoma in both cases after generous macroscopic sampling.

Conclusions: Squamous cell carcinoma of renal pelvis and urinary bladder is highly aggressive tumour and usually diagnosed at advanced stages. When complicated with calculi, SCCs are usually shaded by stones and underestimated clinically. Careful inspection of CT images and thorough histopathological examination remarkably help to diagnose and stage urinary tract SCCs. Although there are treatments for urinary SCCs, the overall prognosis is still poor.

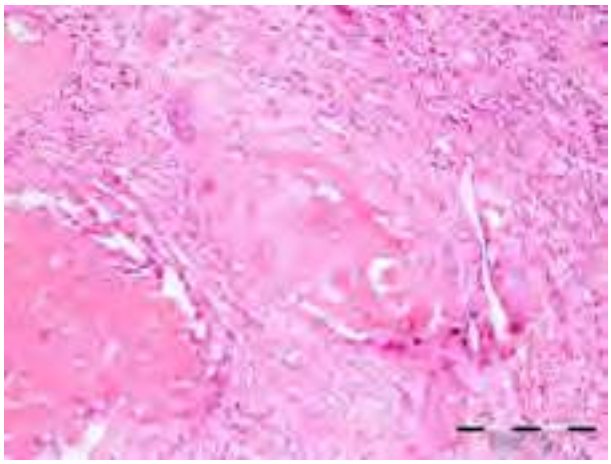


Fig. 2. Case 13

Case 14

A rare cause of ureteropelvic junction obstruction: ureteritis cystica

Khumar Ahmadova[1], Jamal Musayev[2], Rashad Sholan[3]

[1]Unification of Forensic Medical Expertise and Pathological Anatomy, Baku, Azerbaijan, [2]Department of Pathology, Azerbaijan Medical University, Baku, Azerbaijan, [3]Department of Urology, Central Hospital of Oil-Workers, Baku, Azerbaijan

Objective: Ureteropelvic junction obstruction (UPJO) is a common condition in children. Most of the cases are congenital. Acquired UPJO are rare and their causes may be different.

Material and Methods: Herein, an adult patient with acquired UPJO is reported. Clinical, radiological and histopathological examination results are analyzed.

Results: 41-year-old male patient was admitted to the hospital with left loin pain. Urine analysis showed microscopic haematuria. An ultrasonographic examination (US) of urinary tract showed mild left hydronephrosis. Computed tomography confirmed US findings. Serum creatinine level was within normal limits. Left UPJO was seen due to submucosal cyst formation by cystoureteroscopy. The patient underwent left ureteropelvic junction resection with plastic reconstruction. At the macroscopic examination of the specimen, ureteropelvic junction measuring 1x5 cm was observed. There were few cystically dilated von-Brunn nests and lymphocytes in the mucosa. Atypia and mitotic activity were not detected in the epithelial tissue. The case was reported as "ureteritis cystica".

Conclusions: Ureteritis cystica should be on the mental list of the urologists as a cause of hydronephrosis in adults.

Fig. 1. Case 14

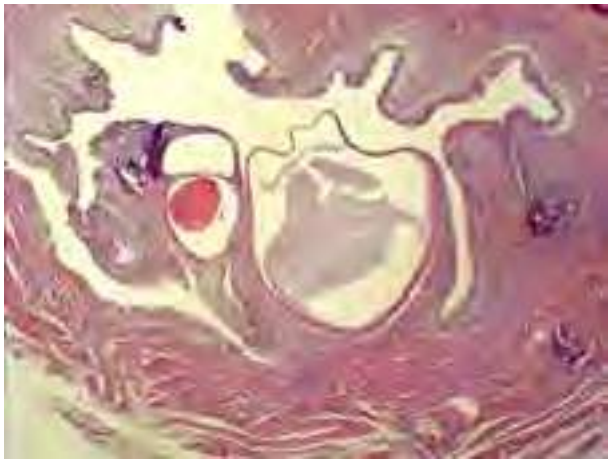


Fig. 2. Case 14

Fig. 3. Case 14

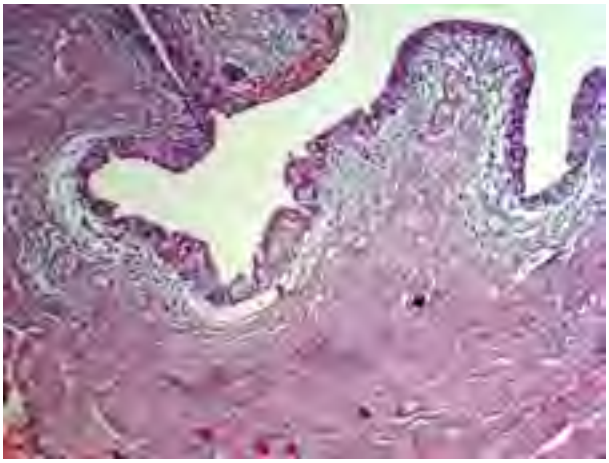


Fig. 4. Case 14

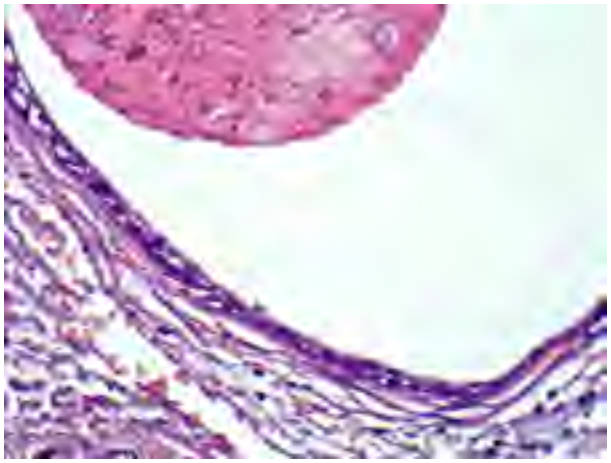


Fig. 5. Case 8

Case 15

Renal cell carcinoma, unclassified - a case report

Vanja Filipovski[1], Vesna Janevska[2], Katerina Kubelka-Sabit[1], Dzengis Jashar[1]

[1]Clinical Hospital Acibadem - Sistina, Skopje, Republic of Macedonia, [2]Institute of Pathology, Faculty of Medicine, University Ss. Cyril and Methodius, Skopje, Republc of Macedonia

Objective: We present an unusual case of highly aggressive undifferentiated renal cell carcinoma. The patient was 52-year-old and presented with large multifocal tumor mass in the left kidney that spread to the adrenal gland and renal hilus and several metastatic deposits were found in the lung. Radical nephrectomy was performed.

Material and Methods: Tumor samples were routinely fixed in buffered formalin and paraffin embedded. Sections were routinely stained with standard H&E stain. Additionally, extensive immunohistochemical analyses were performed using the following antibodies: Ki67, S-100, Vimentin, PAX-8, Desmin, SMA, CD117, RCC, E-cadherin, MelanA,

Fig. 1. Case 15

HMB45, CK7, TTF-1, CK34betaE12, EMA, CK18, Thrombomodulin, CK5/6, PAX-8, EMA, CEA, and CDX-2.

Results: Macroscopic analysis showed multinodular tumor mass throughout the whole kidney without finding of single dominant tumor nodule but the bulk of the tumor was arranged in the renal medulla in close relation to the renal pelvis. Histology showed highly pleomorphic tumor with focal rhabdoid, focal sarcomatoid and focal adenoid differentiation. Immunohistochemical analysis mirrored the histology finding. Differential diagnostic entities like sarcomatoid renal cell carcinoma, chromophobe carcinoma and collecting duct carcinoma were taken into account. Since the tumor was highly anaplastic and several lines of differentiation were noted with immunohistochemistry, a diagnosis of renal cell carcinoma, unclassified, was reached.

Conclusions: In the literature, highly aggressive renal cell carcinomas, with several lines of differentiation, were described originating from a distal nephron unit, using molecular studies, and in our case the bulk of the tumor was located in the renal medulla.

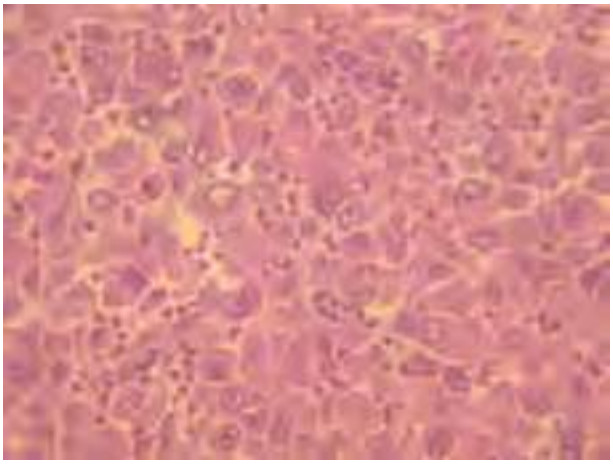


Fig. 2. Case 15, H&E

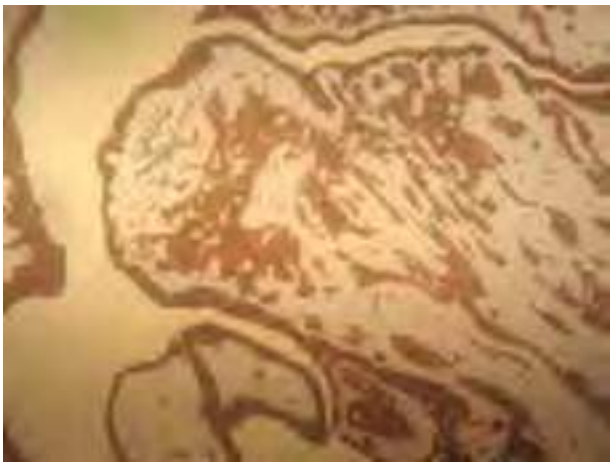


Fig. 3. Case 15, CK7

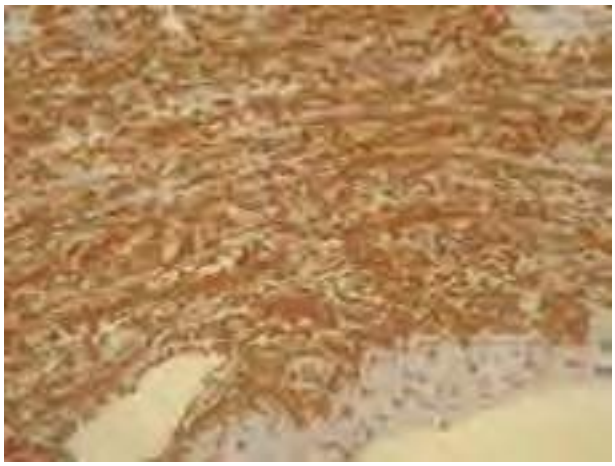


Fig. 4. Case 15, Vim

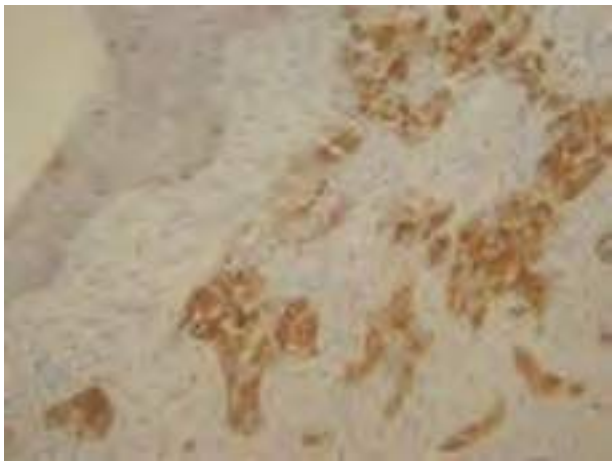


Fig. 5. Case 15, CD10

SLIDE SEMINARS – SELECTED CASES

Breast Pathology

Case 7

Pleomorphic lobular carcinoma of the breast, negative for ER, PR, Her2/neu - a case report

Tatjana Ivkovic-Kapicl[1], Dragana Djilas[1], Ferenc Vicko[1], Milana Panjkovic[2]

[1]Institute of Oncology of Vojvodina, Sremska Kamenica, Serbia, [2]Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia

Objective: Pleomorphic lobular carcinoma (PLC) is an uncommon variant of invasive lobular carcinoma, characterized by its poor prognosis and tendency to metastasize early.

Material and Methods: A 76-year-old woman with a breast mass underwent a lumpectomy and axillary lymph node dissection.

Results: Histopathologic examination of the mass showed an invasive tumor composed of very large cells with eosinophilic cytoplasm and pleomorphic nuclei. These coexisted with foci of classic and pleomorphic variant of lobular carcinoma in situ. Immunohistochemically, the invasive tumor was negative for E-cadherin, estrogen receptor, progesterone receptor, and Her2/neu, and positive for androgen receptor and gross cystic disease fluid protein-15 (GCDFP-15). Two of 11 lymph nodes were cancerous.

Conclusions: Unlike the usual form of a hormone positive, a pleomorphic variant of lobular carcinoma can be triple-negative, thereby adding to the challenge of planning the treatment strategy of this aggressive tumor. Pleomorphic lobular carcinoma should be also distinguished from apocrine carcinoma owing to their similar cytological features and expression of GCDFP-15 and androgen receptors.

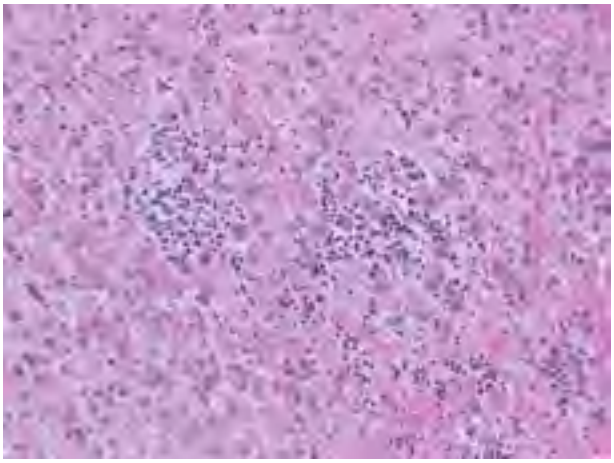


Fig. 1. Case 7, H&E

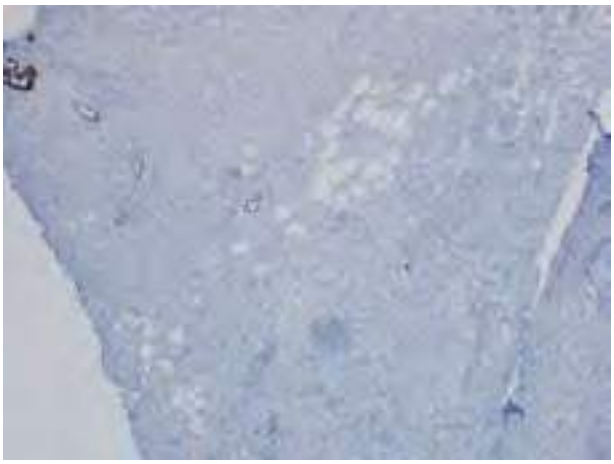


Fig. 2. Case 7, ER

Fig. 3. Case 7, AR

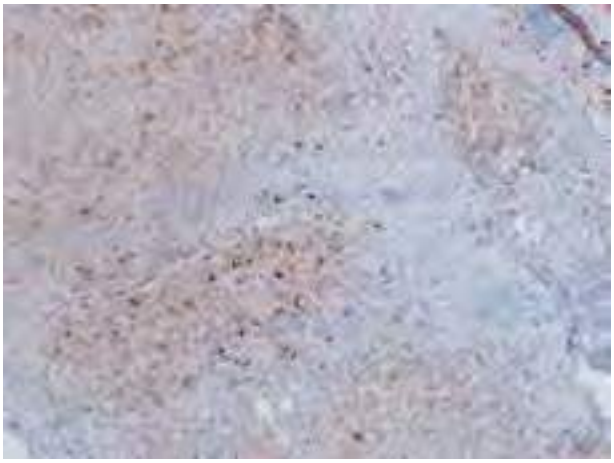


Fig. 4. Case 7, GDFP-15

Case 8

Carcinoma ex-pleomorphic adenoma of the breast

Zlatko Marusic

Clinical Hospital Center, Zagreb, Croatia

Objective: To describe a rare breast neoplasm in a 91-year-old female patient.

Material and Methods: A 91-year-old female underwent resection for a tumor of the left breast, together with axillar lymphadenectomy. Hematoxylin-eosin staining and immunohistochemistry for p63, estrogen receptors, progesterone receptors, Ki67 and HER2 were performed.

Results: The tumor measured 2 cm in the largest diameter and included two components. One component was pleomorphic adenoma, composed of chondro-myxoid stroma with tubular structures surrounded by myoepithelial cells positive for p63. The other component consisted of frankly invasive solid nests of carcinoma adjacent to the pleomorphic adenoma, stemming from in situ carcinoma within the pleomorphic adenoma. Carcinoma cells were positive for estrogen receptors (80%) and negative for progesteron receptors and HER2 (0). Proliferation index measured by Ki67 was 40%. In the axillar lymphadenectomy specimen, there was a 4 cm conglomerate of lymph nodes positive for carcinoma. Six months after the diagnosis, the patient died. Cause of death was listed as heart failure. Autopsy was not performed.

Conclusions: The case presents a rare example of carcinoma ex-pleomorphic adenoma of the breast. Whilst malignant transformation of salivary gland pleomorphic adenoma is a well-recognised, albeit uncommon event, only a handful of carcinoma ex-pleomorphic adenoma cases have been described in the breast.

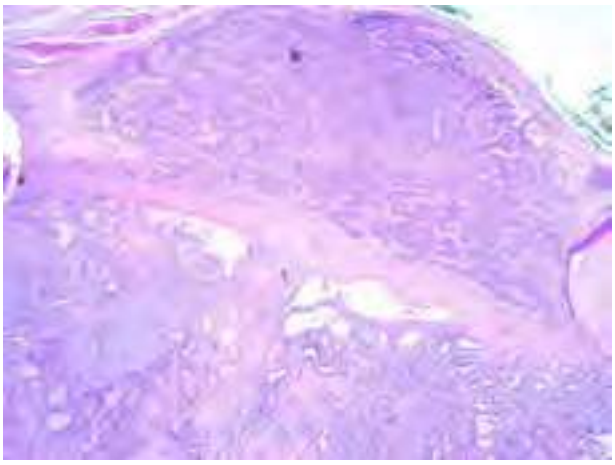


Fig. 1. Case 8

Fig. 2. Case 8

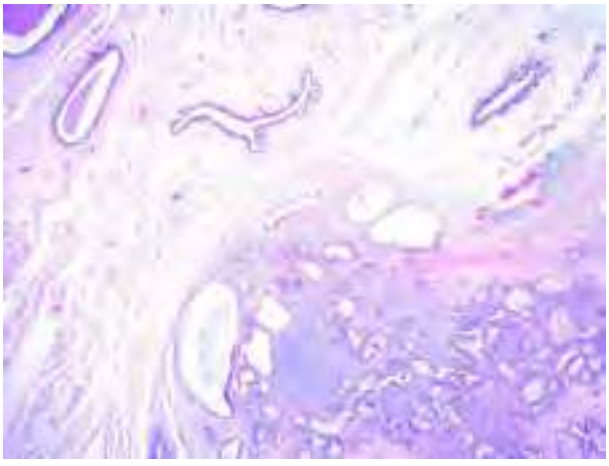


Fig. 3. Case 8

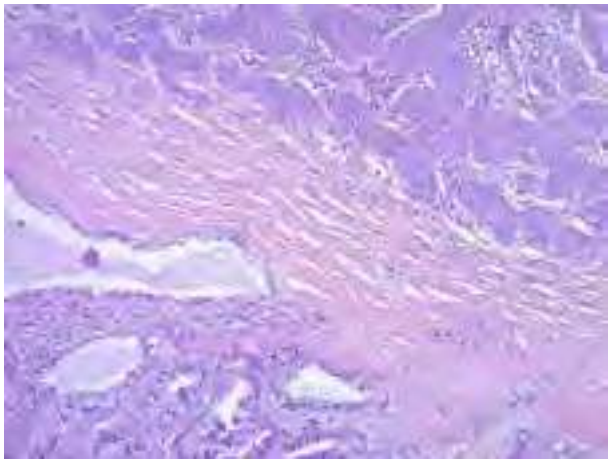


Fig. 4. Case 8

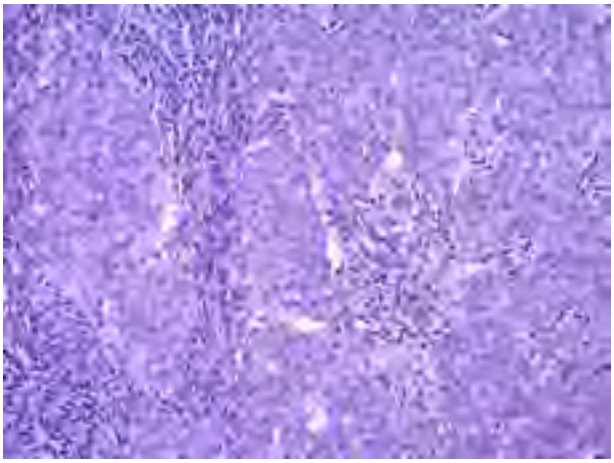


Fig. 5. Case 8

Case 9

Apocrine carcinoma in situ with microinvasion – a case report

Biljana Ognenoska-Jankovska, Adelina Qerimi, Elena Stojkoska, Neli Basheska

Department of Histopathology and Clinical Cytology, University Clinic of Radiotherapy and Oncology, Faculty of Medicine, University Ss. Cyril and Methodius, Skopje, Republic of Macedonia

Objective: Invasive apocrine carcinoma is a very rare type of breast malignancy, with an incidence of 0.5-4%, which presumably develops from apocrine precancerous lesions. We report a case of microinvasive apocrine carcinoma which was diagnosed by fine needle aspiration cytology (FNAC) and confirmed by histopathology.

Material and Methods: A 45-year-old woman following a routine mammography that showed irregular spiculated mass measuring approximately 2.5cm in the upper outer quadrant of the left breast was referred to our Department for FNAC. The patient subsequently underwent left-sided quadrantectomy and axillary lymph node dissection, followed by postoperative adjuvant chemotherapy and radiotherapy. After 3 years of follow-up, no local recurrence or metastases were found.

Results: FNAC yielded moderately cellular smears composed of loosely cohesive clusters of large, polygonal cells with abundant, basophilic and granular cytoplasm suggestive of malignant neoplasm with apocrine features. On gross examination of the quadrantectomy specimen, a grayish-white, solid growth with pushing borders measuring 2.5x1.7x1.5 cm was identified. Twenty-one lymph nodes measuring from 0.3 to 1.3 cm were dissected. Histologically atypical apocrine adenosis, low- and high-grade apocrine ductal carcinoma in situ (ADCIS) and 9 foci of microinvasive apocrine carcinoma (0.1-0.5mm) were found. Apocrine metaplasia was identified in the surrounding ducts. No nodal involvement was observed and the surgical margins were tumor free. Immunohistochemistry revealed that malignant cells (ADCIS and microinvasive carcinoma) were strongly positive for gross cystic disease fluid protein-15, Her2, and

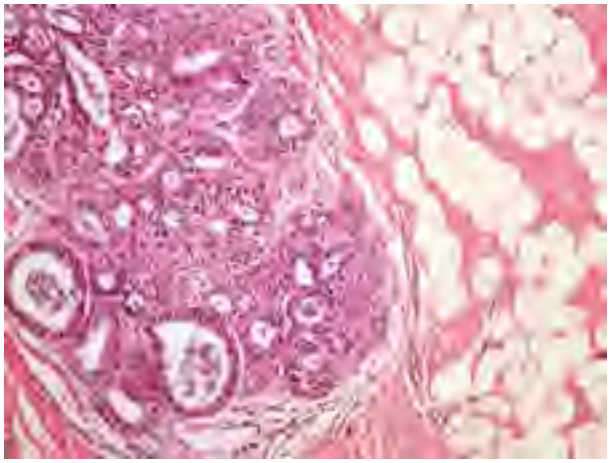


Fig. 1. Case 9

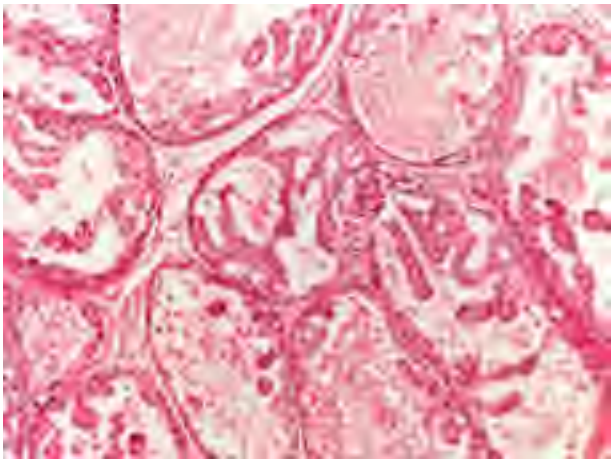


Fig. 2. Case 9

androgen receptor, and negative for estrogen and progesterone receptors. Ki67 proliferative index was approximately 15-20%, while 20-25% of the tumor cells were immunoreactive for p53.

Conclusions: Here we report a case in which all of the stages involved in apocrine carcinoma progression were identified, from benign metaplasia to hyperplasia, atypia, ADCIS, to microinvasive cancer.

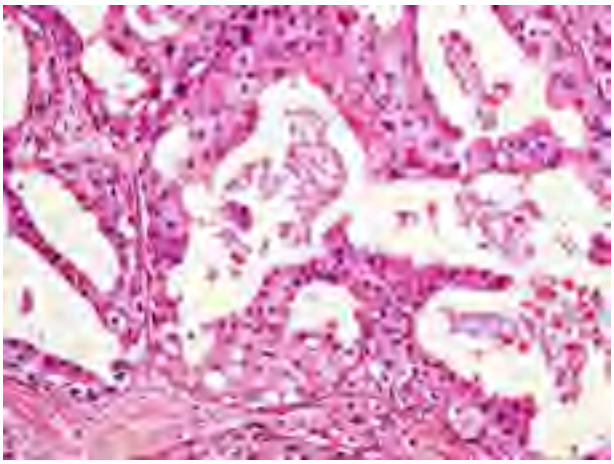


Fig. 3. Case 9

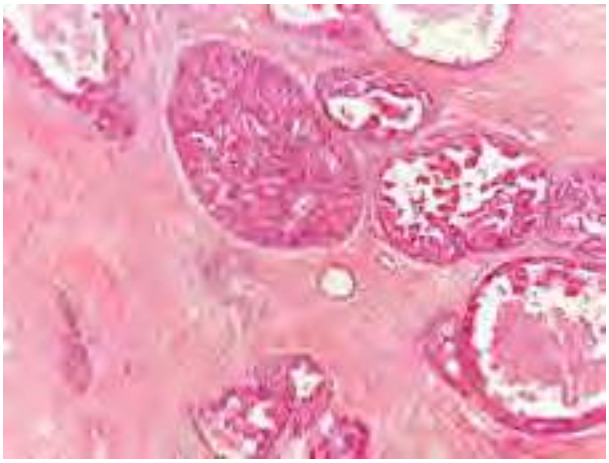


Fig. 4. Case 9

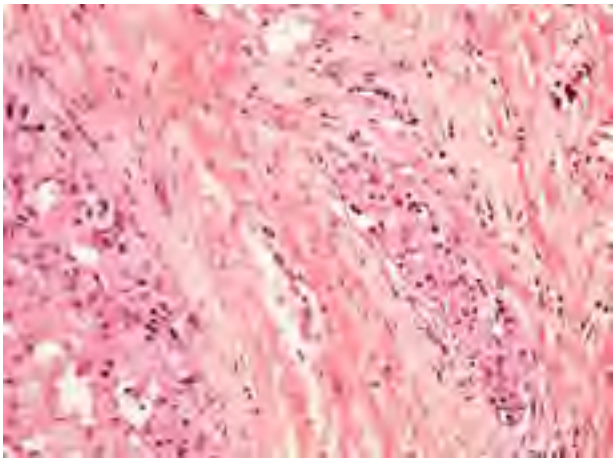


Fig. 5. Case 9

Case 10

Chemotherapy induced epithelial-mesenchymal transition in a high grade breast carcinoma: a case presentation

Burcin Pehlivanoglu[1], Serap Isler[1], Oguzhan Dincel[2], Bilge Aydin Turk[1], Ali Suner[3], Ibrahim Halil Erdogdu[4]

[1]Department of Pathology, Adiyaman University Training and Research Hospital, Adiyaman, Turkey, [2]Department of General Surgery, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey, [3]Department of Oncology, Adiyaman University Training and Research Hospital, Adiyaman, Turkey, [4]Department of Pathology, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey

Objective: Epithelial-mesenchymal transition (EMT) is a process in which cells lose epithelial features such as cell polarity and adhesion capability. Recent studies have shown that there may be a close link between EMT and chemoresistance and chemotherapy may induce EMT.

Material and Methods: A case of high-grade breast carcinoma with metaplastic features not responding to neoadjuvant chemotherapy (NCT) and showing a different phenotype after NCT is presented.

Results: Incisional biopsy of a 39-year-old female patient presented with ulcerating breast mass showed an ER/PR-positive HER2-negative high-grade invasive breast carcinoma with a high proliferation index. A 7.2 cm ulcerating, white-to tan tumor was seen in her post-NCT mastectomy specimen. There were large areas of necrosis in the center and tumor was composed of epithelial and spindle cells. Spindle cell component was not noted in the initial biopsy. Epithelial component was composed of bizarre, pleomorphic epithelial cells appearing much more aggressive than in the initial biopsy. Stromal hyalinization secondary to chemotherapy was present in limited areas. Atypical mitoses were plenty. No in situ component was found. Reticulin stain exhibited the difference between epithelial and mesenchymal components. However, all tumor cells were positive for pancytokeratin, cytokeratin 7 and vimentin and tumor was triple negative. E-cadherin was positive in the initial biopsy, and it was only focally positive in the epithelial component in mastectomy specimen. Other immunohistochemical markers showed variable staining. Twenty-six metastatic axillary lymph nodes with prominent surrounding soft tissue infiltration were detected.

Conclusions: The case will be discussed regarding chemotherapy-induced EMT in breast carcinoma and possible pathogenetic mechanisms.

Figure 1. Initial biopsy sample. A) General histopathological appearance HE, x20, B) Solid growth pattern, HE, x200, C) Atypical tumor cells with prominent nucleoli and several mitoses, HE, x400, D) High proliferation index, Ki67, x100

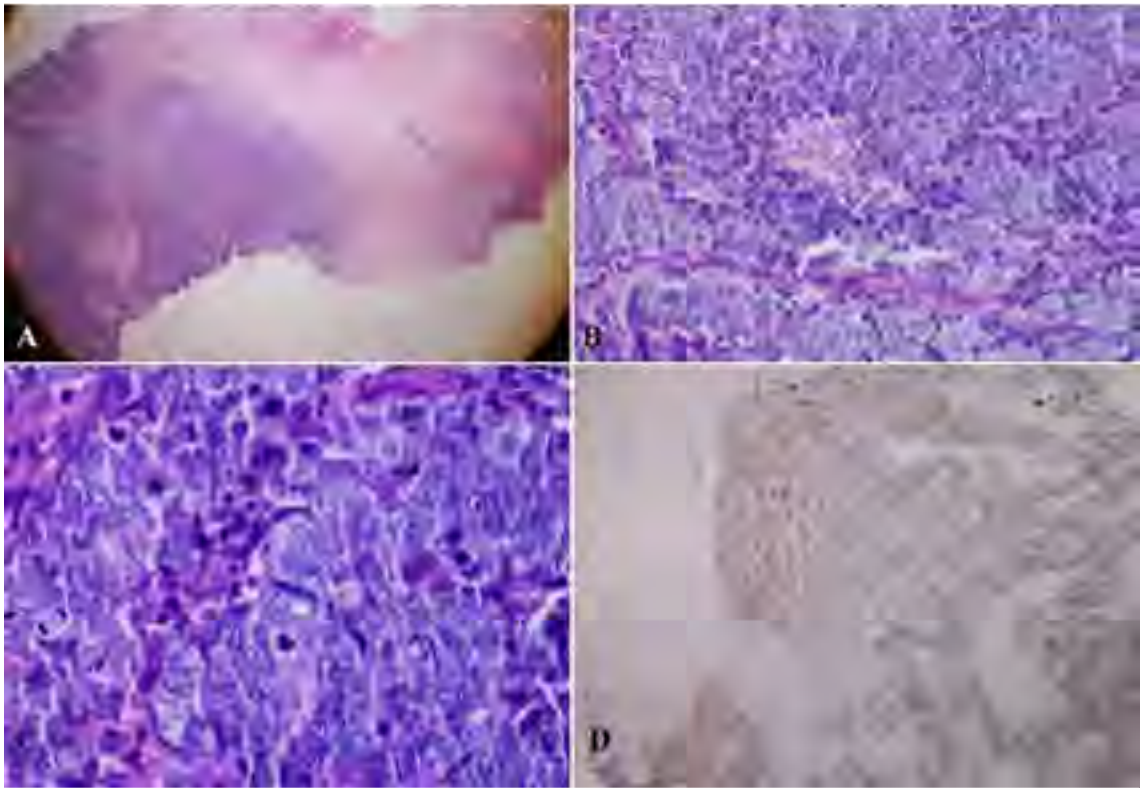
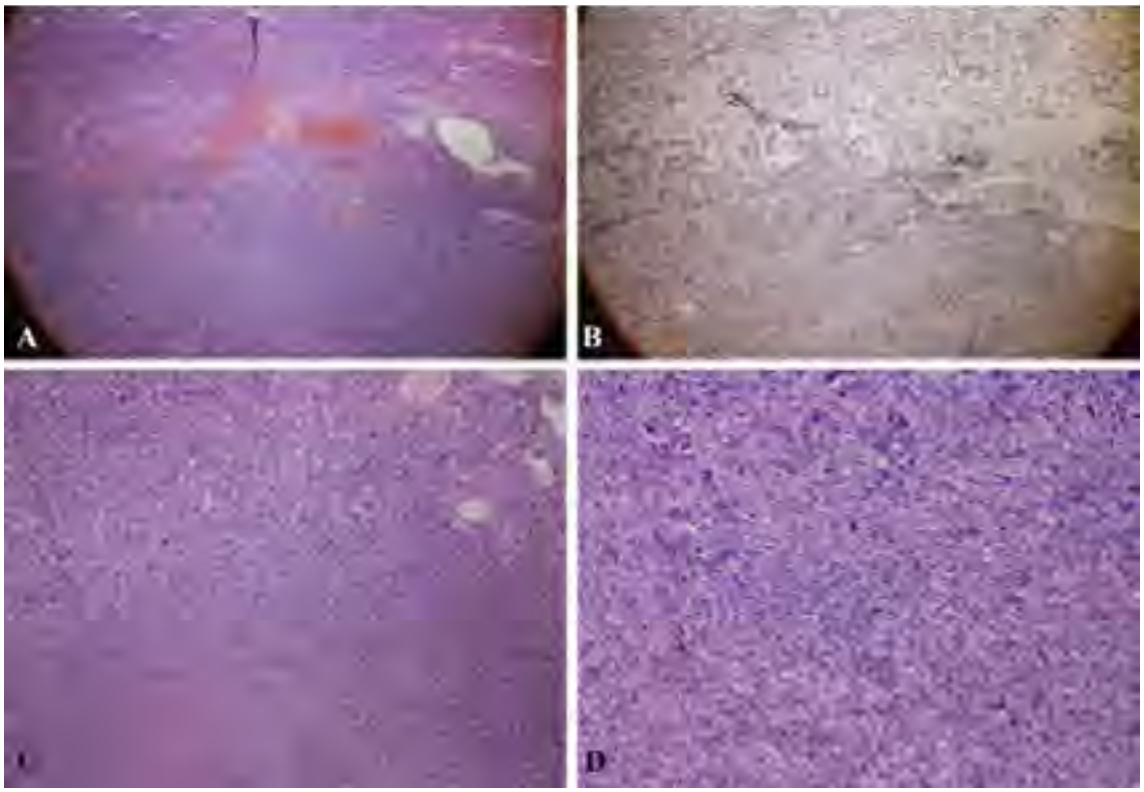


Figure 2. Mastectomy specimen. A) General histopathological appearance HE, x20, B) Reticulin stain, epithelial and mesenchymal staining patterns, x20, C-D) Transition between epithelial andspindle cell component, HE, x40 and x100.



Case 11

Rare breast lesion in a man

Iva Brcic[1], Martin Asslaber[1], Gregor Huber[2], Peter Regitnig[1]

[1]Institute of Pathology, Medical University of Graz, Graz, Austria, [2]Department of Surgery, Hospital Brothers of St. John of God, St. Veit/Glan, Austria

Objective: Phyllodes tumours constitute a complex group of fibroepithelial lesions of the breast. In females they account for up to 1% of primary breast tumours, only isolated cases have been reported in men. These tumours are classified into three categories: benign, borderline and malignant, depending on the histological features like mitoses, cytological atypia, tumour margins and stromal overgrowth and degree of stromal cellularity.

Material and Methods: A 55-year-old male patient presented with 3 cm large painless, movable perimamillary mass of the left breast. In 2000, he was diagnosed with prostate carcinoma and is to date under anti-hormonal therapy. Ultrasound examination and CT scan revealed a solid, lobulated lesion. Core biopsy showed gynecomastia. Subsequently, surgery was performed.

Results: Upon histology, a fibroepithelial tumour with pushing borders and characteristic leafy architecture was found, composed of double-layered epithelial component arranged in clefts surrounded by a hypercellular mesenchymal component with bizarre stromal cells; number of mitoses was 7/10 HPF rendering a diagnosis of borderline phyllodes tumour. Features of gynecomastia were appreciated in the surrounding tissue. The patient is currently with no sign of disease.

Conclusions: Phyllodes tumours are very rare in men. If the tumour does not show all histological features found in benign or malignant categories, it should be classified as borderline phyllodes tumour. We speculate that a link between the pathogenesis of this tumour and the anti-hormonal therapy might exist.

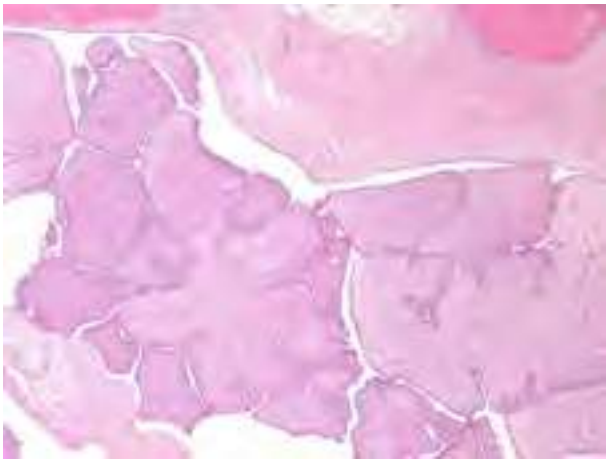


Fig. 1. Case 11

Fig. 2. Case 11

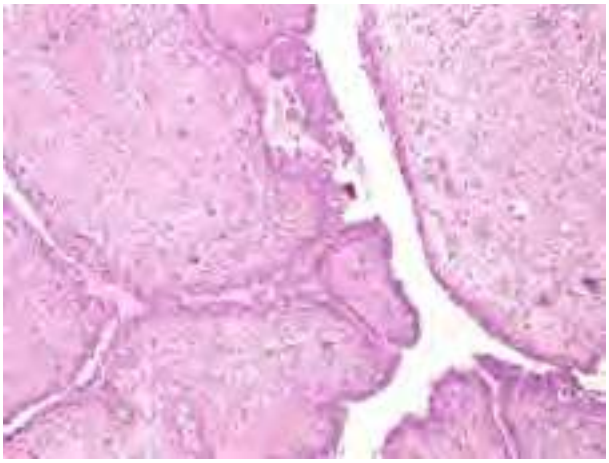


Fig. 3. Case 11

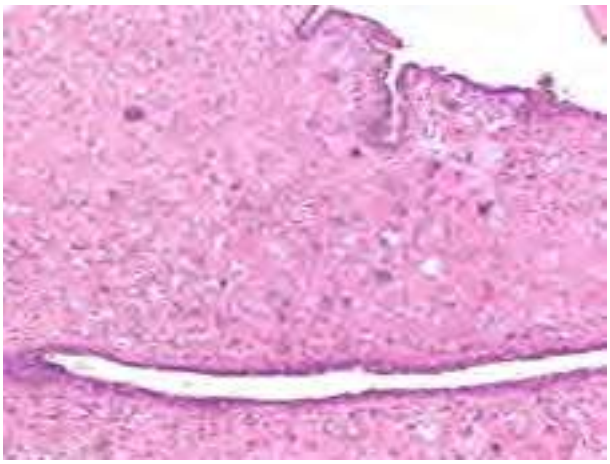


Fig. 4. Case 11

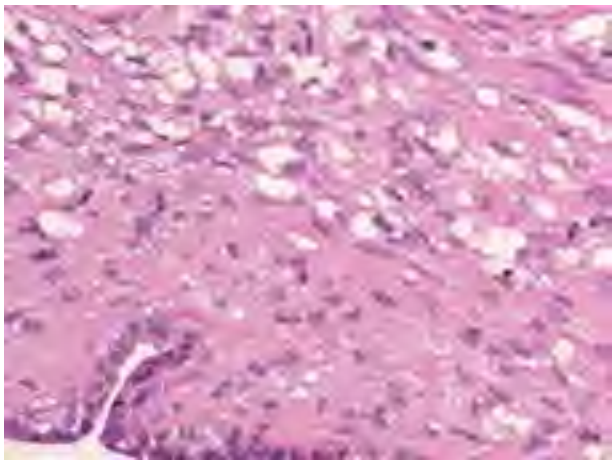


Fig. 5. Case 11

Case 12

Myxoid myofibroblastoma of the male breast

Katerina Kubelka-Sabit, Vanja Filipovski, Mitko Karagjozov, Dzengis Jashar

Clinical Hospital Acibadem - Sistina, Skopje, Republic of Macedonia

Objective: Myofibroblastoma is a benign stromal tumor of the breast. It consists of neoplastic cells showing a variable fibro-myofibroblastic differentiation at morphologic, immunohistochemical and ultrastructural levels. We present a case of mammary myxoid myofibroblastoma occuring in a young male patient and discuss the possible diagnostic pitfalls.

Material and Methods: A 25-year-old male patient presented at our clinic with a palpable lump on his left breast. The lump was surgically removed and submitted for histopathologic evaluation. The grayish-white lobulated tumor measured 5 cm in greatest diameter. The cut surface was homogenous or whorled, with myxoid appearance.

Results: The microscopic examination revealed a bland-looking spindle cell tumor, with extensive myxoid appearance. The spindle cells were arranged in parallel bundles or whorls, separated by a myxoid matrix in which thick collagen bundles were evident. Focal atypical cells were also present. The tumor cells showed expression of vimentin, desmin, and CD34, consistent with fibro-myofibroblastic differentiation.

Conclusions: This unusual benign tumor may represent a potential diagnostic pitfall, especially when interpreting fine-needle aspiration or needle core biopsy, or cases containing predominantly atypical cells with moderate to severe degrees of nuclear pleomorphism. Pathologists should be aware of the different subtypes in the morphologic spectrum of myofibroblastoma.

Fig. 1. Case 12, H&E

Fig. 2. Case 12, H&E

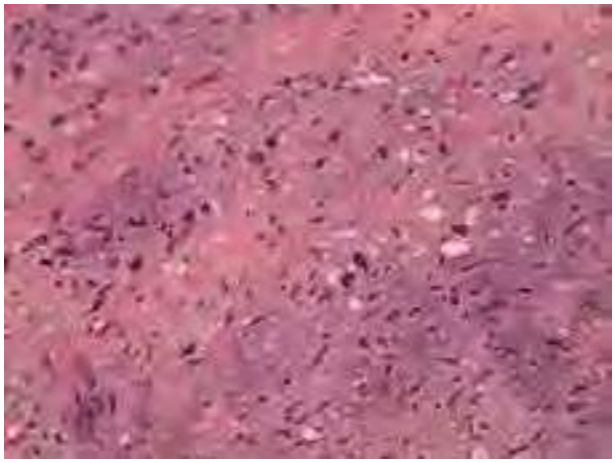


Fig. 3. Case 12, H&E

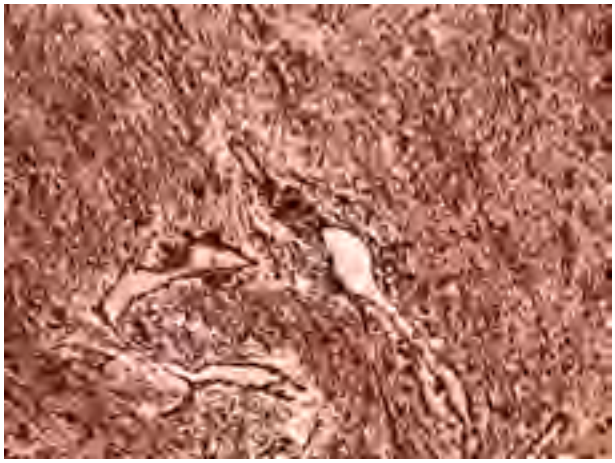


Fig. 4. Case 12, Vim.

Fig. 5. Case 12, SMA

POSTER PRESENTATIONS

PS-01 Genitourinary Pathology

PS-01-01

PAX8 transcription factor detection in acute and chronic kidney diseases

Jasmina Markovic-Lipkovski[1], Maja Zivotic[1], Sanja Cirovic[1], Jelena Vjestica[1], Nada Dimkovic[2], Radomir Naumovic[3]

[1]Institute of Pathology, Medical Faculty, University of Belgrade, Belgrade, Serbia, [2]Department of Nephrology, Clinical Hospital Center Zvezdara, Medical Faculty, University of Belgrade, Belgrade, Serbia, [3]Clinic of Nephrology, Clinical Center of Serbia, Medical Faculty, University of Belgrade, Belgrade, Serbia

Objective: Transcription factor PAX8 expressed during embryonic kidney development, has been previously detected in various kidney tumors. However, Pax8 has not been studied in the etiological different non-tumor kidney diseases.

Material and Methods: In order to investigate the expression of PAX8 transcription factor in acute and chronic kidney diseases, immunohistochemical analysis was performed. Presence, location, and extent of PAX8 expression were analyzed among 50 human kidney samples, including 25 autopsy cases of acute renal failure and 25 biopsy samples (20 patients suffering from various chronic kidney diseases and 5 patients exhibiting acute kidney injury).

Results: PAX8 nuclear expression was detected within distal tubules and collecting ducts in all biopsy samples, while expression by parietal cells of Bowman's capsule and loop of Henle was variable. In the proximal tubules, PAX8 nuclear expression was present only in those with signs of atrophy and in tubules surrounded by interstitial fibrosis. Dilatation of the proximal tubules, as a sign of acute renal failure, was not associated with PAX8 positivity. There was statistically significant correlation of PAX8 nuclear expression in the epithelial cells of the proximal tubules with tubular atrophy ($p<0.001$), and interstitial fibrosis ($p<0.001$). In the analyzed autopsy kidney tissues, PAX8 was not detected in any of the kidney tissue structures.

Conclusions: Various kidney diseases with chronic disease course that results in the formation of tubular atrophy and interstitial fibrosis, lead to PAX8 expression in the nuclei of proximal tubules. Acute renal parenchymal damages were not associated with reactivation of PAX8 in the proximal tubules.

PS-01-02

Carcinoma of the collecting ducts of Bellini - a case report

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Objective: Carcinoma of the collecting ducts of Bellini (CDC) is a rare variant of renal cell carcinoma (RCC) accounting for <1% of renal malignances, which originate from renal collecting duct epithelium. We present a case of a 65-year-old male with CDC complaining of abdominal pain and hematuria.

Material and Methods: An ultrasonogram and computerized tomography scan were performed and revealed a left kidney tumor located in the inferior pole with extension into perinephric fat, measuring 4.5x4.1x3cm. The patient underwent a left nephrectomy. The tissue specimens were fixed in 10% buffered formalin and embedded in paraffin. Immunostains with antibodies against CD10, CD15, CEA, CK7, CK8, CK19, CK AE1/AE3, CKHMW, EMA and RCC were done.

Results: On macroscopic examination the tumor showed a firm grey-white appearance. Microscopically, the tumor showed combined tubular and tubulopapillary growth pattern surrounded by a desmoblastic reaction with infiltrative borders. Cells were highly atypical with a basophilic or eosinophilic cytoplasm and polymorphic nuclei. The tumor cells were positive for CK7, CK8, CK AE1/AE3, EMA, RCC, CEA, CD15, focally positive for CK19 and CKHMW, and negative for CD10.

Conclusions: Identification of CDC has important diagnostic and prognostic ramifications and should not be misdiagnosed with other types of RCC because CDC pursues a more aggressive behavior and poor prognosis than other renal cell carcinomas with a high rate of local, lymphatic and haematogenous spread at the times of diagnosis and a poor long-term prognosis.

PS-01-03

Plasmacytoid urothelial carcinoma

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Objective: Plasmacytoid urothelial carcinoma (PUC) is a rare histological and aggressive variant of urothelial carcinoma that is often diagnosed at an advanced stage. We report a case of a 58-year-old male with hematuria and lower abdominal pain. After thorough clinical examination, he underwent a radical cystoprostatectomy.

Material and Methods: The cystoprostatectomy specimen showed gray-brown exophytic tumor measuring 10x8x5 cm on the front bladder wall. The tumor infiltrated the bladder wall, extended into the perivesical fat, and grossly infiltrated the prostate. Standard tissue samples were embedded in paraffin blocks and hematoxylin-eosin and immunohistochemical stainings were made.

Results: Histological analysis showed infiltrative high-grade invasive urothelial carcinoma, mainly composed of dyscohesive polygonal to round tumor cells, with hyperchromatic, eccentrically located nuclei with eosinophylic cytoplasm, with plasmacytoid appearance. The microscopic analyses confirmed the extension of the tumor into perivesical fat and the prostate, as well as into the mucous and submucous layer of the left ureter. Bilateral iliac and obturatory lymph nodes were free of tumor. Immunohistochemical staining showed positive signal for CK-7, CK-20, CK AE1/AE3, EMA, CD-138 and negative signal for LCA, S-100, kappa, lambda, CD79-a.

Conclusions: The diagnosis of this rare histological variant can be difficult because of its morphological resemblance with plasmacytoma, although the PUC cells are lacking prominent perinuclear clearing and there is no multinucleation. Our case did not have such a diagnostic dilemma, since alongside the PUC, there was a typical invasive urothelial carcinoma.

PS-01-04

Intestinal metaplasia of ureter and renal pelvis: a case report

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Objective: Transformation of the urothelium to the intestinal type of epithelium is rare in the pelvis with very few cases reported in the literature. The present study reports partial intestinal metaplasia of the renal pelvis with residual urothelium and subsequent focal stromal osseous metaplastic changes in a 61-year-old man with previous clinical suspicion of renal tumour.

Material and Methods: Left-sided nephrectomy was undertaken. The gross examination revealed papillomatous proliferation in the ureteropelvic junction measuring 1x0.8x0.3cm. On selected samples immunohistochemical analysis with Actin, CK7, CK20, CDX2 and Ki67 was made.

Results: The microscopic examination showed striking focal replacement of transitional epithelium of the ureteropelvic junction, with intestinal type of epithelium. The intestinal glands were lined by tall columnar epithelium with numerous goblet cells. Immunohistochemistry of the metaplastic epithelium revealed positive expression for CK7 with focal expression for CK20, CDX2 and low Ki67 index.

Conclusions: Although intestinal metaplasia is frequently encountered in the urinary bladder, it is very rare to find such metaplasia in upper urinary tract including renal pelvis and ureter. In this case metaplastic changes did not progress to adenocarcinoma which indicates that intestinal metaplasia is not always associated with malignancy.

PS-01-05

Histological characteristics of urinary bladder carcinoma

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Objective: Urothelial carcinomas are heterogeneous lesions with different histological features. The recognition of the morphological variants is important because of the diagnostic, prognostic, or therapeutic implications they have.

Material and Methods: We analyzed 840 cases of urinary bladder cancers received for histopathological analysis at the Institute of pathology in Skopje in the period of 01.01.2013 -30.03.2016 year as endoscopically or surgically obtained material. Transurethrally resected (TUR) material was completely embedded and standard dissection of operative material was performed. Immunostains with epithelial, mesenchymal, vascular and neuroendocrine markers were used in 43 cases with atypical morphology.

Results: There were 92 operative materials and 748 TURs. All operated patients underwent previous TUR. Seven hundred forty eight (748) cases (94.88%) were diagnosed as typical papillary urothelial carcinoma, 487 (57.98%) of low and 353 (42.02%) of high grade malignancy. There were 17 cases of high-grade urothelial carcinoma (HGUC) with squamous differentiation, 10 clear cell variant, 5 sarcomatoid variant, 3 cases of HGUC with glandular differentiation, 3 HGUC with neuroendocrine differentiation, 2 microcystic variant, 1 lymphoepithelioma-like, 1 HGUC with giant cells and 1 nested variant. The tumor was classified as pTa in 439 (52.26%) cases, pT1 in 166 (19.76%) cases, pT2 in 162 (19.28%) cases, pT3 in 39 (4.64%) and pT4 in 33 (3.92%).

Conclusions: Immunohistochemistry is a useful tool for diagnosing urothelial cancers and the recognition of types and subtypes of urothelial cancer has important prognostic and therapeutic implications.

PS-01-06

Sarcomatoid carcinoma of the urinary bladder with a large-cell neuroendocrine epithelial component: a case report

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Objective: Malignancies of the urinary bladder with a biphasic pattern are rare, especially carcinosarcomas with neuroendocrine differentiation, where the epithelial component exhibits large-cell neuroendocrine morphology, with only a few reported cases. We report a case of a 73-year-old male patient who presented with gross hematuria and was diagnosed with sarcomatoid carcinoma with large-cell neuroendocrine epithelial differentiation.

Material and Methods: Cystoscopy and MRI revealed tumor mass in the bladder. The patient underwent TUR followed with radical cystoprostatectomy. On gross examination the bladder`s lumen was filled by a 6.5x5x5cm polypoid tumor mass, originating from the posterior wall. Formalin-fixed, paraffin-embedded tissue samples were stained with H&E and immunohistochemically with CK, Vimentin, Actin, Desmin, NSE, CK7, CKAE1/AE3, Synaptophysin, CD57, S100, Chromogranin, and CD20.

Results: Microscopically the tumor consisted of malignant epithelial and mesenchymal component. The appearance of the first varied from high-grade papillary urothelial carcinoma, adenocarcinoma to focal squamous carcinoma, whereas the mesenchymal component consisted of round to spindle-shaped cells, with marked cellular atypia and frequent mitotic activity. The epithelial component was positive for CK, CK7, CKAE1/AE3, and neuroendocrine markers CD57 and NSE. The mesenchymal component was strongly positive for Vimentin and S100 protein. The patient died two months after diagnosis was established.

Conclusions: This rare tumor is a distinct variant and should be recognized as such in order to enrich the entity`s data and pay attention regarding the patients` follow-up.

PS-01-07

A case of intraductal carcinoma of the prostate gland - unexpected finding after limited prostate carcinoma on tru cut biopsy

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Objective: The intraductal prostate carcinoma is high grade tumor composed of intraductal neoplastic epithelial proliferation, usually associated with high grade and advanced stage prostate carcinoma.

Material and Methods: We report a case of a 70-year-old patient with limited prostate carcinoma on tru cut biopsy after detection of a high level of PSA – 10.26 ng/ml. The radical prostatectomy revealed intraductal prostate carcinoma. IHC for verification was performed.

Results: The radical prostatectomy specimen was with slightly enlarged organ and no visible tumor. The microscopy showed high grade neoplastic cells with predominantly solid growth isolated from the surrounding stroma by basal cells. IHC: p63+ and CKHMW+/-. The affected area was about 20% of the gland bilaterally. High grade PIN was also found. Although the whole specimen was examined, coexisting acinar adenocarcinoma of high grade was not found, the only infiltrating carcinoma was Gleason score 3+3=6 - grade group 1.

Conclusions: The diagnosis of intraductal carcinoma should be made carefully after rejection of urothelial neoplasia and confirmation of the basal cells.

PS-01-08

Androgen receptor expression in stromal and epithelial cells of prostatic cancer and benign prostatic hyperplasia

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Objective: The role of androgen receptor expression in the development of prostatic cancer, both in the epithelial and stromal compartment is not yet clarified. The aim of this study is to assess androgen expression in epithelial and stromal cells of prostatic cancer and benign prostatic hyperplasia in an effort to clarify, partly, the mechanism responsible of prostatic cancer progression.

Material and Methods: A retrospective analysis was performed using 70 samples of radical prostatectomy where prostatic cancer was diagnosed. Immunohistochemical analysis was then performed on these samples using the antibody Androgen Receptor. The average value of androgen receptor expression was estimated, in the nuclei of tumor cells, tumor stroma and the nuclei of surrounding benign epithelial and stromal cells, and the data was compared. Analysis of the data was made using a scoring system through grouping of the intensity of the signal and the percentage of positive cells.

Results: Immunoreactivity was greater in benign epithelial and stromal cells versus the malignant epithelial and stromal cells and the difference was greater between the benign and malignant stromal cells.

Conclusions: According to this data, changes exist in androgen receptor expression in both epithelial and stromal compartments in prostatic cancer.

PS-02 Gastrointestinal Pathology

PS-02-01

Biopsy-proven colorectal adenocarcinoma in UHC Rijeka patients in 2015

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Objective: To contribute to the collection of histopathological and clinical data of colorectal adenocarcinoma. Also to present carcinoma associated histopathological data (dimensions, localization, histologic grade, Dukes classification etc.)

Material and Methods: Our center provided pathohistological data of all UHC Rijeka colorectal biopsies in 2015.

Results: Altogether biopsies were performed in 211 patients and their mean age was 69.0±11.9. 132 (62.6%) patients were male and 79 (37.4%) were female. Most colorectal adenocarcinomas (61.6%) were localised in rectosigmoid part. Other localizations were: caecum ascendens (28.4%), transversum (1.9%) and descendens (8.1%). The mean dimension was 4.63±1.95 cm. 78.2% carcinomas were low grade tumors and 21.8% were high grade. 2.84% tumors were pT1, 8.06% pT2, 61.14% pT3 and 27.96% pT4. Every adenocarcinoma has its associated Dukes classification. 7.6% tumors were stage A, 42.2% stage B, 45% stage C and 5.2% stage D. 78.20% had lymphovascular invasion and 30.33% perineural invasion. 82% adenocarcinoma had infiltrative tumor border, 6.2% expansive border and 11.8% had mixed border.

Conclusions: This study confirmed that colorectal adenocarcinoma is a very common type of cancer, both in men and women. Most frequently it is localised in the rectosigmoid part. It is very important to discover colorectal adenocarcinoma in its early stage with colonoscopy and biopsy.

PS-02-02

Histopathological and immunohistochemical examination of the colon of rats with TNBS-induced colitis after administration of functional food containing microencapsulated synbiotic

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Objective: This work evaluates the effects of Lactic acid bacteria on the trinitrobenzene-sulphonic acid (TNBS) induced colitis in rats by histopathological and immunohistochemical analyses after oral administration of functional food product containing microencapsulated probiotic L. casei 01 and prebiotic oligofructose-enriched inulin (Synergy 1).

Material and Methods: Eighteen female Wistar rats were divided in three groups (180-250 g, 10-14 weeks old). The control group only recived drinking water and plain ayran. TNBS colitis was induced in the other two groups by rectal administration of 30 mg/kg TNBS. One group recived only plain ayran and the other recived ayran containing encapsulated synbiotic. Samples of the colon were fixed in 10% neutral buffered formalin, embedded in paraffin and cut with microtome on 3-4 μm thick sections. Slides for histopathology were stained with haematoxylin and eosin (H&E). CD3 and CD20 monoclonal antibodies with En Vision visualisation kit (DakoChemMate, Denmark) were used for immunostaining of the tissue sections.

Results: The histopathological examination showed better preserved mucosa of the colon tissue in rats treated with encapsulated synbiotic compared to the non-treated group which showed inflammation and ulceration of the mucosa and submucosa. The control group and the one treated with encapsulated synbiotic showed reduced concentration of CD3 and CD20 positive cells in the mucosa and submucosa compared to the non-treated group.

Conclusions: The histopathological and immunohistochemical examination of the colon revealed the anti-inflammatory effect of the ayran containing microencapsulated synbiotic.

PS-02-03

A rare tumor with variable prognosis: spectrum of goblet cell carcinoid tumors of appendix

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Objective: Goblet cell carcinoid (GCC) of appendix is a rare tumor exhibiting both neuroendocrine and adenocarcinoma characteristics.

Material and Methods: Herein, we present three cases of GCC showing variable histopathological features.

Results: Case No.1 was a 55-year-old male presenting with acute appendicitis. In appendectomy material an incidental solid, 1x1 cm tumor was found, composed of clustering goblet cells, showing chromogranin immunoreactivity. The tumor was mainly located in the submucosa, invading serosa and mesoappendix without an involvement of caecum and consistent with "typical GCC". Case No.2 was a 58-year-old male presenting with abdominal pain and 7 cm solid ileocecal mass. Right hemicolectomy showed a tumor originating from the appendix, but extending to caecum and composed of larger and more irregular goblet cell clusters, with large areas of extracellular mucin, signet-ring cells, perineural invasion, lymph node metastasis and peritoneal implants. The case was considered as "Adenocarcinoma ex GCC, with signet ring cells". Case No.3 was a 63-year-old male presenting with acute abdomen. He had a 7.5 cm ileocecal necrotic solid tumor that was composed of cribriform-comedo type adenocarcinoma with solid, less differentiated areas and cell clusters reminiscent of signet cells/goblet cells. The latter component showed focal neuroendocrine differentiation and was also seen in appendix samples. He was diagnosed as "Adenocarcinoma ex GCC, poorly differentiated carcinoma type". The patient had liver metastasis at the time of diagnosis and died two years after the surgery.

Conclusions: Our cases represent the clinicopathological spectrum of GCC, in consistence with the previously suggested classification by Tang et al. and will be discussed with their histopathological hints.

PS-02-04

Different types of gastric adenomas: interpretation of immunophenotypic features

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Objective: Gastric adenomas are sporadic polipoid lesions considered as precursor lesions of gastric adenocarcinoma. They are classified according to the epithelial cell type they contain: 'gastric type adenomas' consist of dysplastic foveolar epithelium whereas 'intestinal type adenomas' show intestinal differentiation and 'hybrid adenomas' may have both epithelial types. It has been shown that progression from high grade dysplasia to adenocarcinoma is more common in intestinal type adenomas. We hereby present a mini case series of gastric adenomas of different types.

Material and Methods: The mini case series was composed of 5 gastric adenomas taken from 4 male and one female patients during upper gastrointestinal endoscopy in the Department of Gastroenterology Ankara University School of Medicine. Endoscopic biopsies were routinely processed and stained with H&E. An immunohistochemical panel comprising CK7, CK20, CDX2, MUC2, MUC5AC, MUC 1, MUC6, CD10, p53 and Ki67 was performed using streptavidin-biotin peroxidase technique.

Results: The average age of the patients was 72.8 years with a range between 59 and 86 years. Of the 5 cases 3 were localized in gastric body while 2 were found in the antrum. Immunohistochemical analysis revealed two intestinal, one gastric type of adenomas and two hybrid adenomas. One of the intestinal adenomas and the gastric adenoma contained focal high grade dysplasia.

Conclusions: Gastric adenomas possess a significant risk of malignant transformation. Immunophenotypic features may provide additional information to the clinician to make the right decision for appropriate treatment and follow-up of the patient.

PS-02-05

Intra abdominal cysts

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Objective: Intra abdominal cysts in adults are rare lesions and their rarity fosters lack of information and difficulty in classification. We analyzed the clinical, radiological and histopathological findings in 9 patients with intra abdominal cysts in order to deepen the understanding of these lesions.

Material and Methods: The operative material consisted of 6 cysts and 2 resected cystic walls. Standard dissection procedure and paraffin embedded tissue sections were made, stained by HE, Von Kossa and immunohistochemicaly with CK7, CK20, CDX2, WT1, Podoplanin, CD68, CD 34 and Actin.

Results: The mean age of the patients was 41.7 years. The female to male ratio was 2:1. All the cysts were diagnosed as mesenteric cysts by imaging techniques. The most present symptom was abdominal pain. All the cysts were unilocular except one, which was multilocular with diameter from 10 to 27 cm. All the cysts had thin colagenous wall in which inflammatory infiltrate and small blood vessels were seen. The lining epithelium was missing except in small areas where it was flattened or cuboidal. Bundles of smooth muscle and calcifications were seen in 4 (2+2) of them. The lining epithelium was positive for CK7, WT1 and podoplanin in 6 cases, confirming the diagnosis of mesothelial inclusion cyst. One of the cysts was diagnosed as lymphatic and one as enteric cyst according to immunostains with CD31 and CK20 and CDX2, respectively.

Conclusions: All abdominal cysts we analyzed were diagnosed by imaging techniques and had nonspecific histological appearance, but immunohistochemistry is an useful tool in defining their type.

PS-02-06

A gastric hamartoma with unusual histological features

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Objective: Hamartoma is defined as a benign growth of cells normally found in that organ or area of the body, but abnormally arranged.

Gastric hamartomas, sometimes called adenomyoma of the stomach are rare lesions. We present a gastric hamartoma with unusual histological and immunohistochemical features.

Material and Methods: A 66-year-old female underwent upper and lower gastrointestinal (GI) endoscopy with a history of chronic diarrhea. Multiple polypoid lesions were detected in the gastric antrum and were removed. Histology showed a lipoma-like mature adipose tissue filling the submucosa where foci of cystically dilated glands surrounded by smooth muscle fibers were observed. Similar glands were also found in the mucosa-submucosa interface resembling heterotopic pancreatic ductular structures. In order to identify the origin of these epithelial structures, immunohistochemistry was performed for CK7, CK20, MUC-1, MUC2, MUC-5AC, MUC-6, CDX2 and CK19 antibodies using the streptavidin-biotin-peroxidase technique.

Results: The epithelium of the dilated glands stained positively with CK7, CK19, MUC-6 suggesting gastric antral origin while CK20, MUC-1, MUC2, MUC-5AC, CDX2 were negative.

Conclusions: GI hamartomatous lesions can be found incidentally during imaging for other reasons, stomach being the most common site where it can be a diagnostic challenge to differentiate these from gastric tumors and gastric polyps, lipomas, and heterotopic tissue. Our case resembled submucosal lipoma because of extensive adipose tissue and pancreatic heterotopia due to the presence of ductus-like glandular structures. Immunohistochemical analysis reveals the origin of the epithelium and helps to reach the correct diagnosis.

PS-02-07

Low-grade appendiceal mucinous neoplasm with low grade pseudomyxoma peritonei and bilateral ovarian metastases

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Objective: Low-grade appendiceal mucinous neoplasms (LAMNs) are rare conditions with a prevalence of less than 1% of all appendectomies, with also rare spreading to the peritoneum as pseudomyxoma peritonei. We present a case of LAMNs with low-grade pseudomyxoma peritonei and bilateral ovarian metastases in 66-year-old woman presenting with abdominal pain.

Material and Methods: Ultrasonography revealed left retrouterine cyst with honeycomb appearance filling almost whole abdominal cavity. The patient underwent hysterectomy with bilateral salpingo-oophorectomy, selective lymphadenectomy, appendectomy, omentectomy and pelvic et paracolic peritonectomy. Standard procedures for histology and immunohistochemical stains were done.

Results: The appendix was ruptured and covered with papillary proliferations and gelatinous-mucinous content, also present in its lumen. Large multilocular and small unolocular cyst, filled with mucinous content, was found in the right and left ovary respectively. The resected omentum and peritoneum showed multiple honeycomb like structures and pools of mucin. Microscopically LAMN with bilateral ovarian metastasis was diagnosed. LAMN was composed of papillae covered with mucinous epithelium showing benign cytology and only focal pseudostratification and atypia. The right ovarian cyst showed benign morphology and the left ovary, omentum and peritoneum showed low malignant histology. Immunohistochemistry revealed positivity for CK20, and negativity for CK7. No metastases were found in the lymph nodes. The patient is alive 8 months after the operation.

Conclusions: Although the ovary was thought as a common primary site for pseudomyxoma peritonei, immunohistochemistry has confirmed, that in most cases the appendix is the primary site, as it was in our case.

PS-02-08

Isolated retroperitoneal enteric duplication cyst: a very rare entity

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Objective: One of the developmental anomalies of the human digestive tract is enteric duplication cyst which occurs 1 in 4500 births. However, isolated retroperitoneal enteric duplication cysts (IREDC) are more interesting as they are much rarely reported in the literature hence creating a more challenging diagnosis. When a clinician faces a retroperitoneal cystic lesion, it is not likely to give the definite diagnosis without surgical excision. The aim of this case report is to underline this uncommon entity.

Material and Methods: With the urinary incontinence complaint, a 9-year-old female patient was taken to the pediatrics outpatient clinic. The urinary ultrasound was performed in order to search for any urological pathologies that can lead to incontinence.

Results: Indeed, a well demarcated, hypoechoic, 37x27 mm sized lesion was observed at the paravertebral region neighboring posteriorly to the pancreas tail. At first, the lesion was thought to be originating from the pancreas; however, the surgical operation revealed that it was completely isolated from the alimentary tract. After the surgical excision, macroscopically encapsulated cystic nodular lesion was evaluated and the histopathological assessment showed that this unilocular cystic lesion harbors columnar epithelia, where oxyntic mucosa is seen partly and the final diagnosis was made with radiological, clinical and histological findings.

Conclusions: IREDC's are an extraordinary phenomenon because of their unusual location. Although the aetiology and pathogenesis are unclear, this diagnosis should be kept in mind in the differential diagnosis of retroperitoneal cystic lesions.

PS-02-09

Encapsulating peritoneal sclerosis after long term peritoneal dialysis: report of two cases

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Objective: Encapsulating peritoneal sclerosis (EPS) or 'abdominal cacoon' is a rare but serious complication of long-term peritoneal dialysis (PD), with a mortality rate exceeding 30%. EPS can occur after kidney transplantation (KT) which is related to the concomitant use of profibrotic calcineurin inhibitors. EPS usually presents with partial or diffuse bowel obstruction due to marked sclerotic thickening of the peritoneal membrane. We, hereby, present two cases of EPS occurring after long-term PD.

Material and Methods: The first case was a 35-year-old female suffering from end-stage renal disease related to familial

Mediterranean fever. She was on PD for 12 years and had KT 3 years ago. She was using Tacrolimus, Azotiopurin, Prednisolone since transplantation. After recurrent subileus-ileus attacks, she underwent laparoscopic iridectomy. The second case was a 60-year-old female with end-stage renal disease who had received peritoneal dialysis for 8 years. She underwent surgical intervention because of lower gastrointestinal tract bleeding.

Results: Macroscopic evaluation of both cases showed thickened peritoneum and cacoon-like encapsulation of the entire wall of the resected bowel segments. Microscopically nonspecific inflammatory changes accompanied by extensive collagenous thickening and acellular fibrosis of the peritoneal surface were observed.

Conclusions: EPS is an infrequent but mortal complication of long term PD and KT. Patients on PD, especially those receiving this treatment for more than 8 years, should be carefully evaluated for risk factors associated with the development of EPS. Therefore, physicians and pathologists should be aware of intestinal obstruction symptoms and morphological features of EPS.

PS-02-10

Biphasic (mixed) subtype malignant peritoneal mesothelioma: a rare tumor

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Objective: Malignant peritoneal mesothelioma (MPM) is a rare tumor that usually arises from the serosal membranes of the abdominal cavity. Biphasic MPMs contain both epithelioid and sarcomatoid areas within the same tumor. Pure epithelioid and sarcomatous types can be seen in the peritoneum; however the incidence of biphasic (mixed) tumors is lower than in its pleural counterpart. Besides, biphasic subgroup has a significantly poorer prognosis and is unresponsive to treatment overall. We present a case of biphasic MPM, with its immunohistochemical features to emphasize on this rare subtype of peritoneal tumor.

Material and Methods: A 56-year-old man admitted to hospital with complaint of abdominal distention. Gastroscopy, colonoscopy and thorax CT revealed no abnormal findings. Abdominal CT showed diffuse thickening and enhancement of the peritoneum. His occupational and residential history showed no apparent exposure to asbestos. Peritoneal biopsy revealed a biphasic tumor composed of spindle and epithelioid tumor cells with atypical hyperchromatic nuclei and eosinophilic cytoplasm infiltrating the peritoneum. Immunohistochemistry was performed for pan-CK, calretinin, D2-40, Ki-67 and WT-1 antibodies using streptavidin biotin-peroxidase technique to investigate both epithelioid and spindle cell components.

Results: Both epithelioid and spindle cell components stained positively for pan-CK, while epithelioid cells were positive for calretinin and D2-40. WT-1 stained both epitheloid and spindle cells. Tumor showed high proliferative index with Ki-67.

Conclusions: Diffuse malignancies of the peritoneum include MPM, primary peritoneal carcinoma, and secondary peritoneal carcinomatosis. Peritoneal carcinomatosis can be of ovarian, gastric, pancreatic, colonic, and, more rarely, breast origin. Differential diagnosis requires clinical, imaging, and pathologic evaluation. Therefore, immunohistochemistry panels have to be adjusted accordingly to reach an accurate diagnosis.

PS-02-11

Rare case: primary colonic leiomyosarcoma

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Objective: Investigation of 55-year-old woman with complex gastrointestinal symptoms.

Material and Methods: 55-year-old woman presented in December 2015 with 2 week history of symptoms (constipation, loose stools, fresh bleeding per rectum, hypogastric pain. Urinary urgency, weight loss and rigors were also present. Initial colonoscopy showed polypoid mass in transverse colon. Clinician stated that this "does not have the feel of malignancy". Multiple biopsies were taken. On the basis of results from biopsies, EMR (Endoscopic Mucosal Resection) was scheduled, but lesion was seen to extend into submucosa, and this could not be carried out. Extended right hemicolectomy was performed. Staging CT did not show any lesions elsewhere.

Results: Biopsies: Pieces of severely necrotic tissue, discohesive highly pleomorphic cells, dispersed giant tumor cells, and numerous atypical mitoses were seen. Immunohistochemistry: Focal desmin positivity, scanty SMA positivity. Negative stains: S100, CD34 CD117, MNF116, CK7, CK20, HCG,LSA, ABPAD. Diagnosis: Pleomorphic malignant tumour with necrotic background. Results of hemicolectomy: Macroscopically, a large pedunculated polyp in transverse colon. Histology: Polyp contains tumour comprising plump spindle cells, in interlacing fascicles. Some were markedly hyperchromatic and pleomorphic, with prominent nucleoli. Multinucleate giant cells were also seen. Numerous mitoses were present - at least 50 in 10 high power fields. Coagulative necrosis was also present, but this was less than 50% of the tumour. Diagnosis: Grade 3 leiomyosarcoma.

Conclusions: A literature search shows that primary colonic leiomyosarcoma is rare. Details will be included in the presentation, plus information about typical histological features, management, prognosis. This case is currently being referred to Royal Marsden Hospital, London, specialist centre for sarcomas. Outcome of this referral will be included in the presentation.

PS-02-12

Adenosquamous carcinoma of the gallbladder - a case report

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Objective: Adenosquamous carcinoma of the gall bladder (ASC) is a rare neoplasm accounting 1.4-10.6% of all gallbladder cancers which is characterized by aggressive local growth and bulky tumor mass. We report a case of a 65-year-old female with ASC presenting with abdominal pain, who underwent cholecystectomy due to clinical diagnosis of chronic calculous cholecystitis.

Material and Methods: The surgical material was a gall bladder with thickened anterior wall in which a white-grayish neoplastic tissue measuring 4x1.3x1 cm was found. The mucosa over the tumor mass was rough and ulcerated. Formalin-fixed, paraffin-embedded tissue blocks were stained with H&E.

Results: Microscopically the neoplastic tissue was composed of regular and irregular in shape gland formations lined with atypical epithelium with large vesicular pleomorphic nuclei and sheets of

atypical squamous cells with pleomorphic and bizarre nuclei. Central keratinization was visible in many of the sheets. Numerous mitotic figures were present in the tumor tissue in which large areas of necrosis were also present. The peritumoral gall bladder tissue showed a marked desmoplastic reaction with lymphocytic infiltration. The neoplasm infiltrated the whole gall bladder wall but did not penetrate the serosa. The postoperative TNM was determined as pT2, pNx, pMx. The patient died 6 months later after the diagnose has been established.

Conclusions: The diagnosis of this rare histological variant of gall bladder cancer should be recognized because it pursues a more aggressive local growth. It broadens the spectrum of gall bladder neoplasms.

PS-02-13

Inflammatory fibroid polyp of the ileum - a case report

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Objective: Inflammatory fibroid polyp is an uncommon, benign submucosal lesion, first described by Vanek in 1949. Incidence is extremely low: from 0.1% to 2%. They are mostly found in gastric antrum (70%) or in the ileum (20%). Clinical presentation depends on the size and location of the lesion. The etiology is unknown, the inflammatory or neoplastic nature of this lesion is still a matter of debate. Here, we report the first case of inflammatory fibroid polyp in the Department of Pathology, General Hospital, Prilep.

Material and Methods: This is a case of a 46-year-old woman operated because of the clinically diagnosed obstruction. The operative material consisted of an 11 cm long segment of the small intestine. Macroscopic examination of the specimen revealed a polypoid white mass measuring 7.5 cm in greatest dimension. Its surface was covered with ulcerated mucosa and it was sharply demarcated from nearby normal mucosa.

Results: Microscopic, the lesion revealed spindle cells with bland nuclei intermingled with mixed inflammatory cell population. There were also numerous eosinophils and marked vascularity. The immunohistochemical analysis was made with the following antibodies: CD34-positive, vimentin-positive, CD68-positive, actin-positive, CD117-negative, bcl2-negative.

Conclusions: The morphological features of the lesion and the immunoprofile indicate an inflammatory fibroid polyp. In the current case, we reported a rare case of inflammatory fibroid polyp of the ileum that presented as obstruction.

PS-02-14

Gastric pyloric gland adenoma: report of two cases and a brief review

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Objective: Pyloric gland adenomas (PGA) are rare neoplasms that compose 2-3% of all gastric polyps. They arise in the setting of autoimmune atrophic gastritis and are mostly observed in gastric body mucosa. PGAs present as nodular, polypoid or dome-like lesions. They are composed of closely packed tubular glands lined by columnar or cuboidal cells that have clear or pale eosinophilic cytoplasm, oval to round-shaped nuclei with no apical mucin caps. Few reports have described development of adenocarcinomas in association with PGAs. We present two cases of pyloric gland adenoma together with a brief review of the literature.

Material and Methods: The first case was a 91-year-old male presented with symptoms of anemia, hematemesis and melena. Upper gastrointestinal endoscopic investigation revealed a polypoid lesion 3mm in greatest diameter. The second case was a 58-year-old female suffering from long-standing emesis. She also had a diagnosis of multiple hyperplastic polyps on previous examination and recently had multiple polyps in gastric body and antrum.

Results: On histological examination of both cases, closely packed tubular glands focally showing cystic dilation, lined by basophilic cuboidal epithelial cells with no cytological atypia were observed in gastric mucosa showing foveolar hyperplasia on the surface. The tubular glands resembled antral or antropyloric type glands of normal gastric mucosa. Immunohistochemistry showed expression of MUC6 which was diffusely positive in the tubular glands and MUC5AC which was expressed in the surface foveolar epithelium.

Conclusions: Gastric PGAs are rare benign lesions, but may have a potential for development of subsequent adenocarcinoma. They can easily be missed in routine histopathologic examination unless the pathologist is aware of this entity.

PS-02-15

The influence of helicobacter pylori pathogen proteins in human gastric pathology

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Objective: Helicobacter pylori bacterium is one of the most common infective pathogens in the World. It is associated with numerous gastric disorders such as peptic ulcer, autoimmune gastritis, gastric cancer etc. There are different diagnostic approaches but most promising one is immunoblotting. In our study, we tried to find an association between different bacterial pathogens (proteins) and different gastric diseases.

Material and Methods: We tested blood samples from 60 patients in which helicobacter pylori infection was previously confirmed with ELISA test, fecal antigen test, and gastroscopy. Complete blood count and Immunoblot test with bands for urease, CagA, VacA and four outer membrane proteins (Testline, Czech Republic) were performed.

Results: In 30 patients only helicobacter pylori infection was present and they had no gastric lesions. Twenty patients had chronic gastritis, 8 had gastric ulcer and 2 had gastric cancer. The immunoblot test was positive in all 60 patients. 16 patients the majority of which were with chronic gastritis had low MCV and hemoglobin levels which indicated iron deficiency anemia. These patients also had a positive band for 33 KdA outer membrane protein (OipA). Both patients with gastric cancer had two positive bands for CagA and VacA.

Conclusions: In conclusion, helicobacter pylori infection in this study was associated with iron losing, while positive bands for CagA and VacA were associated with gastric cancer. Thus, positive bands for CagA and VacA may represent gastric cancer markers and should be included in further studies of patients with helicobacter pylori infection.

PS-02-16

Malignant rhabdoid tumor of the stomach: a rare entity

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Objective: Malignant rhabdoid tumor (MRT) is an aggressive neoplasm that has been reported in several extrarenal sites, including gastrointestinal tract (GIT). There are a few reported cases in the stomach with an aggressive clinical course. We present a case of MRT of the stomach with its immunohistochemical features to emphasize on this rare subtype of gastric tumor.

Material and Methods: A 61-year-old female was admitted to an outside hospital because of severe gastric pain for three weeks. CT revealed a 10 cm mass located at the posterior gastric wall and invaded adjacent structures. The patient was referred to our hospital for surgery which comprised of total gastrectomy, partial colectomy, pancreatectomy, splenectomy and adrenalectomy.

Results: Macroscopically, a large ulcerated mass in the stomach infiltrating proximal colon, pancreas, left adrenal gland and perihilar splenic tissues was observed. Microscopically, the tumor was characterized by a diffuse infiltration of large, polygonal discohesive cells with eccentric vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasms. Immunohistochemically, tumor cells were strongly and diffusely positive for vimentin, cytokeratin, EMA and focally with myoglobin. The tumor was diagnosed as MRT. The patient died 11 days after surgery.

Conclusions: Identification of the rhabdoid phenotype in gastric tumors is very important because these tumors are associated with poor prognosis, distant organ metastasis and unresponsiveness to conventional therapy. Rhabdoid morphology and keratin positivity together with vimentin expression is crucial for diagnosis. GIST, sarcoma, malignant melanoma and lymphoma should be considered in the differential diagnosis of this rare tumor.

PS-02-17

Adenosquamous carcinoma of the gallbladder - a case report

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Objective: Squamous and adenosquamous carcinomas are rare subtypes of gallbladder cancer, traditionally considered more aggressive and with a poorer prognosis than adenocarcinoma. We report a patient with an advanced adenosquamous carcinoma of the gallbladder.

Material and Methods: A 72-year-old woman with abdominal pain underwent CAT scan evaluation which demonstrated cholelithiasis and gallbladder wall thickening. Cholecystectomy due to cholelithiasis was performed.

Results: The macroscopic analysis revealed 3.3 cm transmurally invasive, ulcerated malignant tumor in the neck of the gallbladder. The histological analyses showed mixture of malignant glandular and squamous components infiltrating the gallbladder wall, which led to the diagnosis of adenosquamous carcinoma.

Conclusions: Gallbladder carcinoma is an uncommon disease, with an incidence of 0.72 to 21 cases per 100,000 worldwide, a male-female ratio of 1:3 and an average age at the diagnosis of 72.2 years (median age is 73 years). Adenosquamous carcinoma constitutes 4% of all gallbladder carcinomas and is characterized by formation of a large tumor with local invasiveness of neighboring organs, but lacks metastasis in lymph nodes or viscera. There are no specific signs and symptoms until the tumor has grown substantially and the carcinoma is at advanced stages. It is important to differentiate between adenosquamous carcinoma from squamous or adenocarcinoma, since its prognosis is worse due to rapid growth and wide infiltration.

PS-03 Gynaecological Pathology

PS-03-01

Reactive changes in uterine morphology induced by high therapeutic dose of medroxyprogesterone acetate

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Objective: Medroxyprogesterone acetate (MPA) is a synthetic progestin that interferes with the function of the reproductive organs. The aim of the study was to determine the influence of high therapeutic dose of MPA on the uterine structural components.

Material and Methods: 24 female Wistar rats were divided into two equal groups. The experimental group was treated with MPA at a high therapeutic daily dose of 150 mg/kg body weight, whereas the control group was administered physiological solution. The substances were applied intramuscularly in a period of 7 days. Uterine paraffin sections were stained according to the methods: hematoxylin-eosin, Masson`s trichrome, and Azan.

Results: Histological analysis showed reduced thickness of the uterine wall which was due to the reduction of the thickness of endometrium and myometrium. Mitoses that were seen both in epithelium and supporting stroma in the control group of rats were lacking in the treated group. Atrophy of uterine glands was also observed. Reduction of the thickness of the myometrium was due to the reduction of the internal and external muscle layer thickness. Contrary, an increase of the connective tissue between the muscle layers as well as between the individual muscle bundles in the muscle layers was observed.

Conclusions: Our results indicate that application of a high therapeutic dose of MPA within 7 days provoked reactive changes of the structural components of the rats` uterus that lead to the uterine atrophy.

PS-03-02

Cervical cancer - knowledge, prevention and exposure to risk factors among students from various countries

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Objective: The aim of this study was to assess possible differences in knowledge of residents from countries with different mortality and morbidity rates of cervical cancer. Furthermore, we aimed to find out if there was any association between the level of awareness and preventive behavior.

Material and Methods: It was a cross-sectional study conducted by means of a questionnaire. The study group consisted of academic students aged 20-25 years old, both men and women. The survey included 4 parts with questions about demographic information, a short test of knowledge about human papillomavirus (HPV) and cervical cancer, questions about applied preventive methods and possible exposure to risk factors among respondents. The survey was conducted among students from 10 countries with a different incidence of cervical cancer. Answers from 5632 students were compared in accordance to the incidence of cervical cancer in these countries presented by World Health Organization - International Agency for Research on Cancer.

Results: Students from countries with age-world-standardized incidence rate lower than 10 had better knowledge concerning risk factors such as high number of sexual partners ($p<0.001$), smoking ($p<0.001$) or HPV infection ($p<0.001$). Use of preventive methods was more frequent in countries with lower cervical cancer incidence: Pap smears [$p<0.001$, RR=1.67 (1.53-1.82)], HPV tests [$p<0.001$, RR=3.77 (3.03-4.60)] and HPV vaccines [$p<0.001$, RR=2.43 (2.14-2.75)].

Conclusions: It seems that the best method for decreasing cervical cancer incidence in countries with high morbidity could be an improvement of knowledge levels concerning the disease, followed by facilitated access to preventive services.

PS-03-03

Extraovarian pelvic seromucinous tumour: a case report

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Objective: In 2002, Shappell et al. recommended the term "seromucinous" for ovarian tumours composed of a mixture of endocervical-type mucinous, serous, endometrioid, squamous and undifferentiated cells. The revised World Health Organization Classification of Tumours of the Female Reproductive Organs established that seromucinous neoplasms are a new category of ovarian epithelial tumours. Borderline seromucinous variants are considered rare but are generally well described, while seromucinous carcinomas could be finger enumerated. Pathogenetically, these tumours are supposed to be associated with endometriosis, usually express ER and PR, but are WT-1 negative.

Material and Methods: We were challenged to diagnose a pelvic seromucinous tumour in a 60-year-old female. Previous medical history was notable for adnexectomy and hysterectomy for ovarian cancer, at that time reported as serous carcinoma, grade non-identified. 20 years later, the patient was referred to our hospital and underwent surgery for pelvic tumor exceeding 150 mm, with a heterogenous structure on CT.

Results: On gross examination, tumour`s cut surface demonstrated variegated appearance with cystic spaces containing gelatinous material. Routine H&E slides reviewed a peculiar combination of low-grade serous papillary structures and admixed mucinous and endometrioid glands within the fibrotic stroma.

Conclusions: Borderline seromucinous extarovarian neoplasm was diagnosed, supported by immunohistochemistry. Review of available literature will be provided.

PS-03-04

Fibroadenoma of the vulva: a case report

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Objective: Herein a rare case of fibroadenoma of the vulva is presented. It is biphasic fibroepithelial neoplasm composed of an epithelial glandular and a stromal component, arising in the anogenital mammary-like glands (AGMLG).

Material and Methods: Light microscopic and immunohistochemical study.

Results: The patient was a 30-year-old female with the painless mass in the vulva. A history of hormonal therapy was not recorded. Removed tumor was 1.0 cm in size, with smooth margins, elastic and homogeneous. Microscopically, it was sharply demarcated neoplasm with pericanalicular and intracanalicular growth patterns, and with focal dilatation of duct lumens. The stroma was homogeneous with rare mitotic figures. Decapitation apocrine secretion was noted in some ducts. There was no pleomorphism either in the epithelial or stromal component. The glandular component reacted positively for cytokeratins (CK7, cytokeratin AE1-AE3), ER and PR. The stromal cells were positive for CD34 and negative for ER and PR. There was not any c-erbB-2 or p53 expression. Patient has not had a recurrence of disease for 7 years.

Conclusions: In conclusion, fibroadenoma arising in AGMLG is the same as its mammary counterpart. It may represent potential diagnostic pitfall due to an extraordinary location.

PS-03-05

Liquid-based cytology versus conventional cytology in women with squamous intraepithelial lesions of the uterine cervix

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Objective: The aim of the study was to compare the results of two cervical cytology techniques, liquid-based and conventional, using the cervical biopsy as the gold standard for diagnosis of squamous intraepithelial lesion (SIL) of the uterine cervix.

Material and Methods: This comparative prospective study was conducted in a series of 200 sexually active patients, aged from 19 to 49, who came to their annual gynecological exam at University Clinic of Gynecology and Obstetrics in Skopje between January and October 2015. In all patients, simultaneously, conventional Papanicolaou smear and Thin Prep liquid-based samples were taken. The performance of both techniques was compared with the gold standard of the biopsy results in a series of 118 patients with squamous cell abnormalities of the uterine cervix. In all these patients a colposcopically directed biopsy with endocervical curettage was taken.

Results: When comparing the cytological diagnoses the agreement between two cytology methods for all 200 cases was 76%. The diagnostic efficiency between the two methods was further evaluated by comparing the cytological diagnosis of each method with the histopathological diagnosis in the series of 118 patients. Histology confirmed a presence of a low-grade squamous intraepithelial lesion in 54 and a high-grade squamous intraepithelial lesion in 6 cases, while

the remaining 58 cases had negative diagnostic interpretation. The liquid-based cytology was in agreement with histology in 81% of the biopsies in comparison to the conventional cytology which was in agreement with histology in 61% of the biopsies.

Conclusions: In conclusion, the results of our study suggest that the liquid-based cytology is a more sensitive (80%) and specific (83%) technique than the conventional cytology (sensitivity=57%, specificity=65%) in comparison to histology as a gold standard.

PS-03-06

Correlation between cytopathology and histopathology in women with squamous cell abnormalities of the uterine cervix

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Objective: The objective of our study was to investigate the correlation between cytology and cervical biopsy findings in women with squamous cell abnormalities on cervical cytology.

Material and Methods: A comparative retrospective study was conducted in the period from September 2015 to March 2016 in a series of 184 sexually active women, aged from 20 to 60 years, with squamous cell abnormalities in the liquid-based cytology test. In all women, cervical biopsy with endocervical curettage was performed colposcopically for histopathological analysis.

Results: Cytologically, there were 118 (64.13%) atypical squamous cells of undetermined significance (ASC-US), 22 (11.96%) low-grade squamous intraepithelial lesions (LSIL), 38 (20.65%) high-grade squamous intraepithelial lesions (HSIL) and 6 (3.26%) invasive squamous cell carcinoma cases. According to the histopathological findings in the cervical biopsy and/or endocervical curettage material in 108 (58.70%) women only nonneoplastic lesions were diagnosed. Twenty-four (13.04%) women had histologically confirmed LSIL, 42 (22.83%) had HSIL and in 10 (5.43%) cases invasive SCC was confirmed. For all squamous cell abnormalities, the sensitivity of the liquid-based cytology test in LSIL and higher grade lesions was 58.70% (108/184) and false positivity was 41.30% (76/184). Excluding ASC-US lesions, the sensitivity of the liquid-based cytology test was 78.80% (52/66) and the false positivity was 21.21% (14/66). The positive predictive value was 100% (6/6) for invasive SCC, 68.42% (26/38) for HSIL and 31.82% (7/22) for LSIL.

Conclusions: The high sensitivity of the liquid-based cytology test for HSILs shows that it is an effective screening test for cervical cancer and its precursor lesions.

PS-03-07

Strumal carcinoid of the ovary - a case report

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Objective: Primary ovarian carcinoids comprise 0.1% of all ovarian malignancies and approximately 0.5-1.7% of all carcinoid tumors. Strumal carcinoid (SC) is a type of germ cell tumor characterised by an intimate mixture of thyroid tissue and carcinoid with other teratomatous elements.

Material and Methods: A 47-years-old woman was referred to gynecology department with complex bilateral adnexal masses for surgery. On gross examination, the right ovary was 11x10x7 cm, yellowish brown in color, with a polynodular surface, and the left ovary was 8x7.5x7 cm with a smooth surface. Cut sections revealed predominantly cystic multilocular masses, partially filled with greasy content with hair and smooth solid areas.

Results: On histopathologic examination the cystic spaces of the right ovary were lined by squamous epithelium with underlying adnexal structures, glandular epithelium and thyroid follicles containing colloid. All tissue components were mature. Among the thyroid follicles there was a population of monomorphic cells with moderate amount of eosinophilic cytoplasm, arranged in solid, trabecular and rosetoid patterns suggestive of a carcinoid. The suspicion has been confirmed by the immunoprofile of the tumor cells, which were diffusely immunopositive for CKAE1/AE3, synaptophysin, chromogranin, NSE and CD57, and the thyroid follicles including the central colloid were immunopositive for thyroglobulin, TTF-1 and thyroid peroxidase (TPO). The left ovarian cyst was a dermoid cyst.

Conclusions: The differential diagnosis of SC includes other entities, such as granulosa-cell tumor and Sertoli-Leydig-cell tumor. However, characteristic histological pattern, immunoprofile, and in some cases the clinical manifestations due to the neuroendocrine activity of the tumor, are usually conclusive for the diagnosis.

PS-03-08

Ovarian Leydig cell tumor (hilus cell tumor): a case report

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Objective: Leydig cell tumor is a rare ovarian tumor that belongs to the group of sex-cord stromal tumors. They produce testosterone leading to hyperandrogenism. As a subtype of steroid cell tumors of the ovary characterized by the presence of Reinke crystals, it comprises 19% and affects mainly young women.

Material and Methods: A 24-year old nulliparous patient clinically presented with hirsutism, oligomenorrhea, and infertility. Ultrasonography showed a left ovarian tumor mass with the greatest diameter of 4.3cm. The patient underwent a laparoscopic tumorectomy followed by gradual withdrawal of the symptoms at the first check-up after 6 months follow-up.

Results: The laparoscopically obtained material consisted of 15 yellow to orange-tanned, soft and solid fragments with a diameter ranging from 0.5 to 5.5cm. Microscopically, the tumor was solid, relatively well circumscribed, and composed of cellular areas with clustering of nuclei separated by eosinophilic anuclear zones. Some of the tumor cells had scant and others abundant eosinophilic or clear cytoplasm with lipid-rich, oil Red O-positive vacuoles and oval, hyperchromatic or bizarre nuclei. Mitotic figures were scarce, while Reinke crystals were found after a prolonged search. Immunohistochemically, tumor cells showed diffuse positivity for vimentin, focal for cytokeratin AE1/AE3, alfa-smooth muscle actin, S100, CD99, calretinin, inhibin-alpha, melan A, CD56 and were steroid hormone receptor negative.

Conclusions: Although idiopathic hirsutism and other benign androgen excess disorders like polycystic ovarian syndrome are common, the presence of an ovarian mass in younger patients should raise suspicion of Leydig cell tumor or other steroid cell tumors. This case confirms that Reinke crystal quest should always be tenacious.

PS-03-09

Benign multicystic peritoneal mesothelioma: report of two cases

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Objective: Benign multicystic peritoneal mesothelioma (BMPM) is a rare neoplasm which is considered as a clinically borderline variant between the benign adenomatoid tumor and malignant mesothelioma because of its potential for recurrence. We describe two cases of BMPM based on histology and immunoprofile.

Material and Methods: In both cases, patients were females (17 and 15 year-old) with a history of low abdominal pain. Surgery was performed based on ultrasonography findings of cysts in the abdominal cavity in the first case, and right paraovarian region in the second case. The operative material in one of the cases consisted of resected omental segment with translucent, multilocular cysts, containing serous, gelatinous fluid, and in other case, the operative material consisted of two multilocular cysts.

Results: Microscopic examination showed that the cysts' inner surfaces were lined with flattened or uniform cuboid cells, with oval or fusiform nuclei and scarce cytoplasm, lying on a layer of acellular collagen connective tissue. The immunohistochemical staining showed that the lining cells were positive for calretinin, pan-cytokeratin, vimentin and epithelial membrane antigen and negative for carcinoembryonic antigen and CD34. Two years after surgery recurrence of the disease was diagnosed in one of the patients.

Conclusions: Due to rarity of BMPM, similarity of patients' presentation and comparable features on imaging, diagnosis of this entity is difficult and is based on histological findings.

PS-03-10

Follicular variant of papillary thyroid carcinoma arising in struma ovarii: a case report

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Objective: Struma ovarii is a rare form of ovarian mature teratoma and is the most common type of monodermal teratoma (3% of all ovarian teratomas). 5-10% of such tumors are malignant with papillary carcinoma as the most common type (70%) while 26% of them are a follicular variant of papillary thyroid carcinoma (FVOPTC). We report a case of FVOPTC arising in struma ovarii focusing on the clinical, histopathological and immunohistochemical features.

Material and Methods: A 29-year old nulliparous female underwent laparoscopic surgery of a 7 cm a large right ovarian cyst, diagnosed by ultrasound. Clinically and biochemically she was euthyroid with normal serum TSH level, and without previous significant medical or gynecological history.

Results: Grossly, a laparoscopically obtained material consisted of 8x3 cm fragment of cyst wall measuring 0.2 to 0.6 cm in thickness with a focus of 5 mm large grayish-white tumor. Histology of the cyst wall showed thyroid tissue characteristic of cystic struma ovarii while the tumor showed typical nuclear features of papillary thyroid carcinoma with follicle formation and minimal presence of papillary structures typical for FVOPTC arising in thyroid tissue. Immunohistochemical staining showed positive expression for thyroglobulin, TTF-1, and cytokeratin-19 in the tumor cells.

Conclusions: FVOPTC arising in struma ovarii is difficult to assess because it is a rare tumor with about 60 published cases and lacking standard criteria for diagnosis. Thus, the morphological criteria for the diagnosis of this tumor are based on classical criteria for primary thyroid carcinoma. Prognostically, FVOPTCs measuring less than 2 cm arising in struma ovarii are considered as low-risk lesions with a low rate of recurrence and metastasis.

PS-03-11

Serous adenocarcinoma of the fallopian tube: a case report

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Objective: Primary serous adenocarcinoma of the fallopian tube (PSAFT) is a rare tumor which histologically and clinically resembles epithelial ovarian cancers. Although it has been postulated that both ovarian and tubal high-grade serous carcinomas actually share common histogenesis, PSAFT has a worse prognosis than ovarian cancer. We report a case of PSAFT that presented clinically as hydrosalpinx.

Material and Methods: A 62-year-old patient with complaints of a low abdominal pain and vaginal discharge was admitted at the gynecological department. During the diagnostic procedure, the ultrasound examination revealed uterine fibroid and a right-sided hydrosalpinx. The patient underwent hysterectomy with bilateral adnexectomy. Due to the clinical assessment of benign disease, no tumor markers were required preoperatively, nor biopsy from the omentum and parietal peritoneum, as well as peritoneal washing, were obtained intraoperatively. The operative material was routinely dissected and a standard procedure for histology and immunohistochemistry was performed.

Results: The right tube was tortuous, 17 cm in length, having 5 cm long dilatation in the proximal third. In the dilated part, few exophytic, neoplastic, white-grayish soft lesions were found. The histopathologic examination revealed areas of in situ as well as high-grade PSAFT with lamina propria involvement. The malignant cells were positive for CK7 and WT1. The tumor did not infiltrate the muscle layer, so it was defined as FIGO stage IA. The leiomyoma previously diagnosed by ultrasound was histologically confirmed, while the left adnexa and right ovary revealed regular morphology and were free of tumor. Two months after the operation the patient is in good health and disease-free.

Conclusions: PSAFT should be distinguished as a different clinical entity from primary ovarian epithelial neoplasms so that the patient could receive adequate therapy and follow-up.

PS-03-12

Adjuvant chemotherapy in patients with stage IIIA endometrial carcinoma with solitary adnexal involvement

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Objective: The optimal adjuvant therapy in endometrial cancer patients with solitary adnexal involvement is still controversial. The purpose of this study was to evaluate, retrospectively, the outcome and efficacy of adjuvant chemotherapy in these patients.

Material and Methods: The medical records of the patients with stage IIIA endometrial cancer with solitary adnexal involvement who were treated with surgical resection and adjuvant chemotherapy between 2005 and 2010, were retrospectively analyzed. A total of 40 patients treated with platinum-based adjuvant chemotherapy were included. Following surgery, all patients received 4 cycles of Carboplatin 300 mg/m2 and Paclitaxel 175 mg/m2 by intravenous injection every 3 weeks. The survival and recurrence rates were evaluated.

Results: The median follow-up period was 5 years (60 months). Recurrences occurred in 12.5 % (n=5) of the patients. One local recurrence (1/5, 20%) and 4 distant metastases (4/5, 80%) in liver (n=2, 40%), lung (n=1, 20%) and paraaortal lymph nodes (n=1, 20%) were observed. The 3-year disease-free survival (DFS) and overall survival (OS) rates were 87.5% and 92.3%, respectively.

Conclusions: In conclusion, platinum-based adjuvant chemotherapy may improve prognosis and survival in stage IIIA endometrial cancer patients with solitary adnexal involvement and could be considered as a potential adjuvant treatment. Although adjuvant chemotherapy has demonstrated improved both disease-fee and overall survival compared to radiotherapy (DFS 87.5% vs 69%; OS 92.3% vs 78%), further studies are needed to define the optimal treatment strategy.

PS-03-13

Multimodality treatment of brain metastases from ovarian cancer

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Objective: Brain metastases from ovarian cancer are uncommon and usually associated with mean survival less than 12 months. In some cases, multimodality treatment may achieve an improved outcome in these patients.

Material and Methods: Two cases of multiple brain metastases from ovarian cancer are presented. A combination of whole-brain-radiotherapy (WBRT) and chemotherapy (Topotecan) was used.

Results: Case 1: A 62-year-old patient was diagnosed and treated for primary ovarian cancer in 2012. She underwent optimal surgical resection and adjuvant platinum-based chemotherapy (Carboplatin/Paclitaxel, 6 cycles). Eleven months after the initial treatment the patient developed right hemiparesis. Brain CT documented multiple brain metastases in the left frontal and parietal lobe. She proceeded to WBRT and subsequent 4 cycles of Topotecan. At a follow-up of 24 months, there is no evidence of recurrent disease. Case 2: A 63-year-old patient was diagnosed with primary ovarian cancer in 2012. Initially, she received neoadjuvant chemotherapy (Carboplatin/Paclitaxel, 6 cycles and Doxorubicin/Carboplatin, 3 cycles) followed by surgical treatment. After 1-year follow-up, multiple brain metastases in the right temporoparietal and occipital lobe were detected by brain MRI. She underwent WBRT followed by 4 cycles of Topotecan. Better motor performance was achieved and the MRI scan evaluation showed volume reductions of brain metastases. Nine months later, CT scan revealed a progression of the metastatic disease and re-WBRT was performed. At a follow-up of 18 months, she is in good clinical condition.

Conclusions: In ovarian cancer patients with multiple brain metastases, multimodal therapeutic approach including radiotherapy followed by chemotherapy may lead to prolonged survival.

PS-03-14

Metastatic granulosa cell tumor - a case report

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Objective: Granulosa cell tumors (GCT) are rare ovarian tumors composed of granulosa cells, theca cells, and fibroblasts in varying degrees and combinations. GCTs account for approximately 2% of all ovarian tumors, and 20-30% of them show clinical and pathological features of malignancy.

Material and Methods: We present a case of metastatic GCT in a female patient who was 32-year-old at her first admission in the hospital for left ovarian tumor (FIGO stage IC), preoperatively treated with chemotherapy. In the next 9 years, she had multiple operations for recurrent and metastatic GCT, involving liver, peritoneum, omentum and mesenterium, consecutively.

Results: The histological analyses of all operative materials revealed solid neoplastic tissue with cystic areas, composed of uniform cells with coffee bean-like longitudinal nuclear groove and scant cytoplasm, with a low mitotic index of 4/10 high power fields. Micro-follicular structures (Call-Exner bodies) have also been found. The stroma was inconspicuous. Lymphovascular emboli were found. Despite the information for previous chemotherapy, the tumor was predominantly vital, with scant areas of necrosis. The tumor cells were diffusely immunopositive for vimentin and alpha-inhibin, and negative for CD99, CD34, CD31, actin, neuroendocrine and epithelial markers.

Conclusions: GCT is considered an unusual indolent neoplasm of low malignant potential, with the number of mitoses and dyskaryosis as histological indicators for malignancy. Still, this case emphasizes the need for close monitoring of all patients with GCT, regardless of the histological features, due to unpredictable behaviour of this tumor and its potential for recurrences.

PS-03-15

Neuroendocrine cells in the endometrial adenocarcinomas

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Objective: Sixty endometrial adenocarcinomas were examined immunohistochemically for the presence of amine-containing or neurohormonal peptide-containing cells particularly in relation to histological tumor grade.

Material and Methods: Operative material archived in paraffin blocks was used for research. Neuroendocrine cells were examined in well (n=20), moderately (n=20), and poorly differentiated adenocarcinomas (n=20). On 4μm sections, classical H&E method for determining the histological grade and immunohistochemical ABC method with chromogranin A, bombesin, insulin, gastrin, somatostatin, glucagon and serotonin antibodies were applied. After quantitative analysis of antibodies expression, software package SPSS (version 13.0) was used.

Results: Chromogranin A-containing cells were detected in 39 of the 60 adenocarcinomas. Besides chromogranin A-containing neuroendocrine cells, cells with brown, almost black deposits of insulin were found. Well-differentiated tumors contained small, round, isolated or multifocal insulin-immunoreactive cells. In poorly differentiated carcinomas these cells were numerous and formed solid structures. Strong perinuclear deposits of bombesin were always present in anaplastic epithelial cells. Conspicuous perimembranous gastrin deposits were found focally, in isolated cells, usually in poorly differentiated tumours. Serotonin-secreting cells with annulary distributed deposits were present mostly in poorly differentiated carcinomas. Scattered, polymorph, somatostanin-containing cells were present in well and moderately differentiated tumours. Glucagon activity was detected only in macrophages and mast cells of the tumour stroma.

Conclusions: Functional polymorphism of neuroendocrine cells is present in endometrial adenocarcinomas. The density of neuroendocrine cells correlates with histological tumor grade. Hyperplasia of neurohormonal peptide-containing and serotonin-containing cells is prominent in poorly differentiated and undifferentiated adenocarcinomas.

PS-04 Breast Pathology

PS-04-01

Squamous cell carcinoma presenting as a bleeding, ulcerating breast tumor: a case presentation

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Objective: Squamous cell carcinoma is a very common neoplasm generally seen in sun exposed skin areas. It is rarely seen in breast skin.

Material and Methods: Here, a case of a squamous cell carcinoma arising in breast skin is presented.

Results: An-83-year-old female patient presented with a large ulcerating and bleeding mass located on her left breast near axillary tail. Patient underwent a mastectomy with clinical diagnosis of breast cancer. An ulcerating tumor of 6.5 cm in diameter, which had white-to-tan cut surface, was observed in gross examination. Microscopic examination revealed a moderately differentiated squamous cell carcinoma showing p63, cytokeratin 5/6 and cytokeratin 19 positivity. No evidence of invasion of the breast parenchyma was found and there was no other in situ and/or invasive carcinoma component. There was a sharp transition between the tumor and intact epidermis. Squamous dysplasia was not noted either. Common lymphovascular and perineural invasion were notable. Metastatic deposits were detected in 16 out of 26 axillary lymph nodes.

Conclusions: The tumor was considered to be originating from skin given the fact that there was no relation with breast parenchyma and lack of a different morphological component or in situ ductal/lobular carcinoma indicating a metaplastic carcinoma or collision tumor. The case is presented because of its rarity and will be discussed in regard to differential diagnosis.

PS-04-02

Paget's disease of the male breast: a case report

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Objective: Paget's disease of the nipple is a rare form of breast cancer. Herein we present a case of an extremely rare Paget's disease of the male breast.

Material and Methods: Light microscopic and immunohistochemical study.

Results: A 71-year-old man with an itching, eczematous nipple of his right breast presented to the dermatology department. A bloody nipple discharge or palpable tumor was not identified in the breast at the first admission. The patient started with local steroid therapy. Due to unsuccessful 12 months treatment, he was admitted to the cancer center. Mammography showed no abnormalities. After punch biopsy, Paget's disease of his right nipple was diagnosed. A right mastectomy with level 1 axillary clearance was carried out. Microscopically, the nipple and areolar region showed widespread Paget's disease, however without the involvement of breast tissue and without signs of intraductal cancer. Isolated and small clusters of tumor cells within the squamous epithelium of the nipple were typified by abundant pale eosinophilic or amphophilic cytoplasm and hyperchromatic or vesicular nuclei. Neoplastic cells were strongly cytokeratin-7 positive, expressed estrogen receptor without progesterone receptor expression. All dissected lymph nodes were tumor-free. The patient denied taking medication and has been free of tumor for 28 months.

Conclusions: In conclusion, while Paget's disease is nearly always associated with an underlying carcinoma, it may be entirely intraepidermal. Paget's disease is important to keep in mind despite the rarity in the male breast.

PS-04-03

Pathohistological and immunohistochemical analysis of breast cancer in Montenegro

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Objective: Breast cancer is a heterogenic and multifactorial disease. It is also the most common malignant tumor and the leading cause of death from malignant diseases in women in many countries. According to data from the American Cancer Society, 1300000 new cases of breast cancer are diagnosed in the world every year and about 465000 women die from this disease annually. We have analyzed the traditional histological prognostic factors, as well as the distribution of

clinicopathological subtypes, in a group of patients suffering from breast cancer in Montenegro.

Material and Methods: We have analyzed 36 surgically treated breast cancer patients who had undergone histopathological analysis of tumor tissue, regional lymph nodes, and immunohistochemical analysis of steroid receptors, HER2 status, and Ki67 proliferative index.

Results: The average age of the patients was 60.7 years. 29 patients were in menopause. Invasive ductal carcinoma was diagnosed in 21 patients, lobular carcinoma in 6 and other histological types in 9 patients. Tumors with the largest diameter between 2-5cm (pT2, 61%), and those with positive lymph nodes (52.7%) were most common. The frequency distribution of clinicomolecular subtypes - luminal A like, luminal B like (HER2 negative), luminal B like (HER2 positive), HER2 positive (nonluminal) and triple negative was: 42%, 28%, 8%, 17%, and 5%, respectively.

Conclusions: According to our results, breast cancer is more common in older women, in postmenopause. The invasive ductal carcinoma is the most frequently diagnosed type. The disease is most frequently diagnosed in advanced stages, while the most common clinicopathological subtypes are luminal A like and luminal B like (HER2 negative).

PS-04-04

Association of breast cancer receptor status and copy number alterations in several chromosomal regions

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Objective: The identification of copy number variations (CNV) of numerous genes can reveal distinctive groups of breast cancer (BC) and identify the mechanism of cancerogenesis. This study was designed with an aim to detect amplifications, gains and losses of 23 genes on 7 chromosomes in breast cancer tissues and observe their correlation with receptor status.

Material and Methods: We analyzed 250 female BC tissues with multiplex ligation-dependent probe amplification (MLPA) kit P078 probemix (MRC-Holland). The analysis of MLPA data was performed with Coffalyser software. Statistical analysis was performed using SPSS software.

Results: Amplifications (cut off >1.75 DQ-Dosage Quotient score) and gains (interval 1.3-1.75 DQ) were more common than losses (cut off <0.65 DQ) of the genes. The frequencies of amplifications and gains of genes were highest on 8p11, 8q13, 8q22, 8q24, 17q12 and 11q13 regions. Amplifications and gains of genes in 17q12 chromosomal region were significantly correlated with positive HER2 status, especially MED1, ERBB2, CDC6 and TOP2A genes (p=1.96x10-15, p=7.1x10-30, p=2.8x10-6 and p=0.001, respectively). The majority of losses were identified in the 8p11 chromosomal region. Loss of the genes in this region (FGFR1 and ZNF703) was significantly correlated with estrogen negative breast tumors (p=0.005 and p=0.001, respectively).

Conclusions: In summary, the results of this study suggest that copy number alterations in several disposed chromosomal regions (8p11, 8q13, 8q22, 8q24, 17q12 and 11q13) are associated with receptor status in breast cancer tissues.

PS-04-05

Mammary gland after thyroidectomy. What happens next?

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Objective: To investigate histopathological changes in the mammary gland of rats after unilateral thyroidectomy.

Material and Methods: The study was performed on 56 female virgin albino Wistar rats, divided into three groups: 1) unilaterally thyroidectomized rats (n=32), 2) rats with sham thyroidectomy (n=12) and 3) control animals (n=12). After 35 days half of each group of the animals was sacrificed and their left fifth mammary glands extirpated. The surviving animals remained under the same conditions until the 70th day, when they were sacrificed and their left fifth mammary glands removed. Complete material underwent routine preparations and was embedded in paraffin blocks. The 4μm thick sections were prepared and the routine H&E, histochemical van-Gieson, Gommori, Toluidine-blue and immunohistochemical ABC method with alpha Lactalbumin (ALA) and Prolactin (PRL) antibodies were implemented.

Results: Histopathological examination of mammary glands of the thyroidectomized rats verified a spectrum of hyperplastic-dysplastic changes of ducts, ductules and terminal duct-lobular units (TDLU). Severe hyperplasia of smaller ducts and ductules was followed by nuclear hyperchromasia. Hyperplastic acini were presented as epitheliosis. In some animals, lobular and ductular hyperplasia were more prominent and giving the picture of microadenoma. Apart from epithelial aberrations most of the animals showed stromal collagenization, mononuclear infiltration and mast cell hyperplasia. Strong immunohistochemical expression of ALA was verified in TDLU, ductal and lobular epithelium. A strong activity of PRL was present in the ducts, ductules and lobules.

Conclusions: Unilateral thyroidectomy in rats induces preneoplastic changes of ducts, ductules and TDLU in mammary glands. The degree of dysplastic changes correlates with duration of the postoperative period.

PS-04-06

Expression of CD44 as cancer stem cell marker in breast carcinoma: correlation with clinicopathological parameters

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Objective: CD44 positive cells have been demonstrated to have tumor-initiating properties in breast cancer and stem cell characteristics, like self-renewal, proliferation, and differentiation. The aim of our study is to correlate the expression of CD44 with clinicopathological/prognostic parameters, such as tumor size, tumor grade, stage, axillary lymph node involvement, steroid hormone receptors (HR), HER2 status, Ki67 and p53 expression in breast cancer patients.

Material and Methods: Immunohistochemical analysis was used for quantification of expression of CD44, HER2, HR, Ki67 and p53 in 28 samples of patients with invasive ductal breast carcinoma. Information for other clinical characteristics was available for all the patients.

Results: CD44 expression was determined in 22 of 28 analyzed cases ranging in proportion from only a few to more than 70% of tumor cells. Ten of cases showed membrane staining in less than 10% of

cells and 12 of cases showed staining in more than 10% of the cells. High expression of CD44 was associated with large tumor size, high histological grade, and lymph node metastasis. CD44 positive cells showed a positive correlation with HR status, Ki67, and p53 expression. HER2 receptor was expressed in three CD44 positive and one CD44 negative case.

Conclusions: Our results showed a positive correlation between CD44 positive cells and some adverse prognostic factors in invasive ductal breast carcinomas. This marker can be used to determine the best treatment and can contribute to a development of new targeted therapies.

PS-04-07

Comparison of Her2 expression in primary breast cancer and metastases - Hemera: preliminary results

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Objective: HER2 is an important target in breast cancer – as a prognostic factor for patient's survival and predictive factor for an adjuvant treatment of primary and metastatic disease. Discordance in HER2 status in primary and recurrent breast cancer is well-known fact. Retrospective studies have shown discordance in HER2 status between primary and metastatic cancer in 7-26%. Primary objective is finding out the degree of discordance between HER2 status in primary breast cancer and metastases. Secondary objective is the characterization of clinical and histopathological characteristics of the primary and metastatic disease.

Material and Methods: Tumor tissue obtained from surgery and core needle biopsies was formalin-fixed and paraffin-embedded. Histological type, lymphovascular and perineural invasion, necroses, estrogen and progesterone receptor status, tumor site, and proliferative index were recorded. Assessment of HER2 status was determined according to new 2013 ASCO-CAP guidelines.

Results: Until April 1, 2016, we have tested 930 tumors from 860 patients (876 primary cancers and 54 metastases). Core needle biopsies and excisions were performed in 167 primary tumors. Pairs of primaries and metastases were present in 35 patients. The discordance among them was present in 6 patients (17.1%). There were 4 cases with a switch from HER2 positive status in primary cancers to negative one in metastases and 2 cases with a switch from negative in primaries to positive HER2 status in metastases.

Conclusions: Our preliminary result fits with the data from the literature.

PS-04-08

Sclerosing adenosis of the breast - mammographic presentation

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Objective: To evaluate radiologic presentation of sclerosing adenosis (SA).

Material and Methods: We retrospectively analyzed 12 patients who underwent wire localization and were histopathologically confirmed as sclerosing adenosis. On mammography, SA may consist of architectural distortion, microcalcifications or both, mass lesion and asymmetrical density. It can be difficult to distinguish mammographically from infiltrating carcinoma. We used digital mammography machine Mammomat Inspiration. All mammographic reports were BI-RADS 4 according to BI-RADS system.

Results: SA mostly presents as a nonpalpable lesion (10/12). The most common finding were microcalcifications (7/12) on mammograms. Mass lesions were found in 3 and architectural distortion and asymmetry in 2 cases. Sclerosing adenosis is a benign process and it is commonly an incidental finding. SA needs a biopsy because of various mammographic presentation.

Conclusions: The radiological features of SA may sometimes mimic malignancy, so histopathologic examination is a method of choice for definite diagnosis.

PS-04-09

Detection of the sentinel node in patients with early breast cancer

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Objective: The aim of the study was to present the initial results of the detection of the sentinel lymph node (SLN) in patients with early breast cancer at the University Clinic of Thoracovascular Surgery.

Material and Methods: A total of 32 patients in whom SLN biopsy was done were included in the study. The 99mTc-Saint-Scythian radioisotope was administered on the day of surgery. The static scans were done with two-headed SPECT gamma camera, at 2 and 4 hours after application. Thereafter the patients were transferred to the operating room. After the introduction to anesthesia, 20ml of 0.05% methylene blue solution was also administered. The localization of the sentinel node intraoperatively was performed by using the hand gamma camera.

Results: The SLN was successfully detected in all 32 patients by the static gamma camera. At the same time, the SLN in which there was an accumulation of the radioisotope and methylene blue was successfully detected in all 32 patients intraoperatively. The frozen section histological analysis was done on 36 SLNs, detecting atypical cells in 3 patients, which were confirmed in the paraffin sections in two of them (one macrometastasis that extended out from the node and one micrometastasis), while the paraffin sections were negative in one case (false positive). Axillary lymphadenectomy was performed in these 3 cases. In two patients all removed lymph nodes were negative for metastasis, while in the third patient with macrometastasis in the SLN, metastatic deposits were found in additional 3 lymph nodes.

Conclusions: In conclusion, our initial results confirm that SLN biopsy is a safe and minimally invasive method for determining of the axillary lymph node status in early breast cancer patients.

PS-04-10

Presence of the axillary skip metastasis in patients with primary breast carcinoma treated with axillary lymphadenectomy

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Objective: Axillary lymph node (ALN) status is an important prognostic factor for the breast carcinoma patients. The introduction of the sentinel lymph node biopsy enabled the determination of the ALN status by removing a single node. Yet, the possibility of presence of axillary discontinuous or "skip" metastasis could influence the correct prediction of the ALN status. The aim of this study was to determine the rate of axillary skip metastasis in surgically treated breast cancer patients.

Material and Methods: We retrospectively analyzed the histopathological reports of 144 breast cancer patients surgically treated by one surgeon at the University Clinic of Thoracovascular Surgery. The three axillary levels (level I, II and III) were marked intraoperatively, and the contents in each level were submitted and examined separately.

Results: The mean age of the patients was 57.3+12.8 years. The mean tumor size was 29.54+18.89 mm. The mean number of removed ALNs was 15.45, while the mean number of removed level III ALNs was 2.61. The mean number of ALNs positive for metastatic deposits was 3.76+6.25, and the mean number of positive level III ALNs was 0.37+1.26. Skip metastasis were detected in only two patients (1.38%), with metastatic deposits present in 1-2 level I nodes and positive level III nodes. On the other hand, there was no patient with positive level III ALN, without level I and II ALN involvement.

Conclusions: The low rate of skip axillary metastasis in our study suggests that sentinel node biopsy could be a highly effective and accurate alternative to standard level I and II axillary clearance in the vast majority of patients with early breast cancer.

PS-04-11

Distribution of molecular subtypes of breast cancer determined by immunohistochemistry in surgically treated patients

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Objective: The St. Gallen International Expert Consensus 2011 has proposed a new classification system for breast cancer. The purpose of this study was to analyze the distribution of the molecular subtypes of breast cancer in surgically treated patients at the University Clinic of Thoracovascular Surgery.

Material and Methods: A total of 290 out of 429 surgically treated breast cancer patients during 2014 year with complete documentation for all examinations were included in the study. The operative materials in all these cases were analyzed by standard histological analysis including macroscopic and microscopic analysis using routine H&E staining, while standard immunoperoxidase technique was used for determining the hormone receptor (ER, estrogen receptor; PR, progesterone receptor), Her2 status, and Ki67 immunostaining. According to the expert panel of the St. Gallen meeting proposals for classifying breast cancers using immunohistochemistry in "surrogate intrinsic subtypes", subtype definitions by biomarkers were as follows: luminal A (ER+ and/or PR+, HER2-, Ki-67<14%), luminal B, HER2 negative (ER+ and/or PR+, HER2-, Ki-67 ≥14%), luminal B, HER2-positive (ER+ and/or PR+, HER2+, any Ki-67), HER2-enriched (ER-, PR-, HER2+), and basal-like (triple negative) (ER-, PR-, HER2-, CK5/6+ and/or EGFR+).

Results: According to the immunohistochemistry staining results 39 (13.45%) cases were classified as luminal A, 129 (44.48%) as luminal B, Her2-negative, 58 (20.00%), as luminal B, Her2-positive, 32 (11.03%) as HER2-enriched and 32 (11.03%) patients basal-like (or triple negative) subtypes.

Conclusions: Knowledge of the breast cancer molecular subtype is important for the prognosis of the disease, but also for determining patients` treatment response and implementing an appropriate therapy. Thus, it is necessary to determine "surrogate intrinsic subtypes" of breast cancer using immunohistochemistry in a routine histopathological analysis.

PS-05 Cytopathology

PS-05-01

Ascitic cytology: cell blocks versus smears

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Objective: Malignant ascites is the end-stage manifestation in a variety of cancers and associated with a poor prognosis. Sometimes it can be the first presentation of the malignancy (an ascites of unknown origin). The sensitivity of ascitic cytology is known to be rather low (around 60%) but it can be raised by the combination of routine smears and method of cell block preparation using residual sediment. The aim of the study is to assess the utility of this method in increasing the sensitivity of cytodiagnosis of effusions and determining the primary origin of malignancy.

Material and Methods: A total of 351 peritoneal effusions were subjected to routine smear examination. Samples providing enough residual sediment were submitted to cell block preparation (115 cases, 32.76%). Each case was analyzed for cellularity, cellular arrangement, cytoplasmic and nuclear details.

Results: Out of 160 malignant cases, on routine smears 83 cases (51.87%) were positive. The combination of cell block and smear examination yielded additional 15 malignant effusions which made total of 98 (61.25%) and raised sensitivity for 9.38%. The remaining 62 cases were confirmed for malignancy only on subsequent histology. Better morphological assessment contributed to ascertain the primary origin in 85% of malignant effusions.

Conclusions: The cell block technique increases the sensitivity of cytodiagnosis and provides a better estimation of architectural pattern and morphological details. It also enables multiple section examination and immunohistochemical staining, hence providing a more precise diagnosis.

PS-05-02

The role of fine needle aspiration in the intraosseous jaw masses: review of 14 cases

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Objective: Fine needle aspiration (FNA) cytology is an important diagnostic tool in the initial investigation of palpable masses in various organs. However, it is used rarely in jaw masses. We aimed to evaluate the diagnostic accuracy of FNA in the diagnostic process of intraosseous jaw masses using cytological-histological correlation.

Material and Methods: We retrospectively evaluated all patients who underwent FNA of intraosseous jaw masses and subsequently had histological diagnoses. FNA and cytological examination were performed by (cyto)pathologist with rapid onsite adequacy assessment of aspiration samples.

Results: A total of 14 patients had both cytology and histopathological diagnoses. Thirteen cases (92.85%) were negative for malignancy by FNA. Just one case (7.15%) was positive. We detected 1 true positive, 12 true negative and 1 false negative results. There was no false positive case. The calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive value of FNA were 50%, 100%, 92.85%, 100% and 92.3%, respectively for intraosseous jaw masses. True negative results included 4 odontogenic cyst, 3 ameloblastoma, 2 central giant cell granuloma, 2 fibrous dysplasia and 1 odontogenic myxoma cases. Histologically, single false negative case was central low grade osteosarcoma, and single true positive case was destruction of maxillary bone caused by squamous cell carcinoma of the maxillary sinus.

Conclusions: FNA of intraosseous jaw masses is reliable with high diagnostic accuracy, specificity, positive and negative predictive values. We think that, in studies with large case series it can achieve higher sensitivity.

PS-06 Other Topics

PS-06-01

Microcysts in the thymus induced by dexamethasone and medroxyprogesterone

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Objective: Despite the dominant immunosuppressive effect dexamethasone and medroxyprogesterone acetate (MPA) provoke side morphological effects on thymic tissue. The aim of our study was to observe eventual structural side effects on the thymic tissue induced by therapeutic and maximal therapeutic doses of dexamethasone and MPA.

Material and Methods: The experiment was conducted with 60 female Wistar rats divided into 5 groups. The control group of rats received saline, while the other groups were treated with dexamethasone (0.6 and 3 mg/kg bw) and equivalent doses of medroxyprogesterone acetate (30 and 150 mg/kg bw). Drugs were applied intramuscularly, for 7 days. Paraffin sections of the thymuses were stained according to the methods: H&E, elastica Van-Gieson and PAS-method.

Results: In addition to the major finding of a reduction of thymic lymphoid tissue and increased amount of stroma, the occurrence of microcysts was observed in all groups of treated rats. Numerous microcysts scattered in the lymphoid tissue were the most common finding. Solitary microcysts were observed less frequently. Luminal surfaces were coated with a layer of epitheliocytes with large oval nuclei. Rarely epithelial cells were arranged in two layers or absent from the free surface. Microcysts` lumen was mostly filled with eosinophilic, PAS-positive colloid-like substance. Rare lymphocytes or residues of apoptotic cells were observed in some microcysts, too.

Conclusions: Our results showed that the occurrence of microcysts in the thymic tissue was the dominant structural side effect after application of both therapeutic and maximal therapeutic doses of dexamethasone and MPA.

PS-06-02

Cystic structured follicles of thyroid gland in young Wistar rats provoked by high doses of amiodarone and methimazole

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Objective: We performed histological morphometric analysis of thyroid gland of young Wistar rats treated with high doses of antiarrhythmic drug amiodarone and thyroid inhibitor drug methimazole.

Material and Methods: 30 young Wistar rats were divided into three groups. Control rats received drinking water; experimental rats were divided into a group drinking aqueous solution of amiodarone (0.1%) and a group drinking methimazole (0.05%) in one-month period. The thyroid gland was processed by usual light microscopic histological technique.

Results: Thyroid gland weight was significantly increased in both amiodarone and methimazole experimental groups. Some of the thyroid gland follicles were with increased dimensions and some of them sustained cystic enlargement. Cystic follicles were located in the peripheral gland area and were found in 37% of the experimental animals from amiodarone rats group and in 41% in the methimazole rat group, both treated with high doses of these drugs. Panoramic view of thyroid gland tissue revealed distinct cysts as the most outstanding histological finding. In most of the cases of cystic structures, it was characteristic that there were groups of cysts containing two, three or four cysts. Some solitary cysts were observed also. Dimensions of the cystic follicles ranged between 110 and 470 μm. The height of follicular epithelium was significantly decreased in the cystic follicles in comparison with the epithelium of the peripheral follicles. Damage of the septa between the follicles was observed, too.

Conclusions: Both drugs alter thyroid gland tissue in terms of provoking appearance of solitary cysts or groups of cysts in the peripheral area of the gland.

PS-06-03

Histological features of 5-day-old bruises

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Objective: In forensic medicine, there is often a need to determine the age of the bruises in order to establish the time of injury. The objective of this study was to determine histological features of 5-day-old bruises.

Material and Methods: Ten samples of normal, healthy human skin were used as a control group and 10 samples of 5-day-old bruised human skin, were used as an experimental group. Skin tissue was processed by a routine histological procedure using paraffin sections, stained with hematoxylin-eosin and Prussian blue method of dyeing, evaluated by light microscope enhanced with a digital camera.

Results: Histological analysis of bruised skin samples showed ruptured small blood vessels, extravasated erythrocytes and dilated fibrous septa in the connective tissue. In the area of bleeding, cell infiltration was noticed, presented with few neutrophils, which were not seen in the control group samples, and plenty of hemosiderin containing macrophages. Rare macrophages were seen in the skin samples from the control group, but they did not contain hemosiderin.

Conclusions: In 5-day-old bruises, cell infiltration of the bruised skin with hemosiderin containing macrophages is a main histological hallmark which offers data for establishing the time when injury happened.

PS-06-04

The depth of the stromal invasion of cutaneous squamous cell carcinoma in correlation with tumor size and tumor differentiation

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Objective: The aim of this study was to determine the correlations between stromal invasion and the grade of differentiation as well as tumor's size in squamous cell carcinoma of the skin (SCC).

Material and Methods: Surgically resected skin specimens from 30 patients with cutaneous SCC, were included in the study. The hematoxylin-eosin stained histological sections containing the tumor tissue and the surrounding normal skin prepared from routinely processed paraffin blocks were analyzed by light microscopy. In each analyzed SCC, the degree of histological differentiation (G) and the postoperative tumor status (pT) of the neoplasm according to TNM classification (AJCC) were determined. The depth of stromal invasion in each case was measured on low power field (x40) using morphometry software. The distance from the basement membrane of the epidermis to the deepest invasive neoplastic focus of the tumor and the obtained values are presented in absolute numbers expressed in micrometers.

Results: The SCC in 21 (70%) cases was classified as pT1 and in 9 (30%) cases as pT2 category tumor. Twelve tumors (40%) were classified as well (G1), 13 (43.3%) as moderately (G2), and 5 (16.7%) as poorly (G3) differentiated tumors. The depth of stromal invasion was ranging from 1561.2 μm to 13000.1 μm. A statistically significant difference was found between the depth of invasion in tumors belonging to different pT category (Mann-Whitney U test, p=0.003034 for pT1 and pT2), and different grade (Kruskal-Wallis test, p=0.00008 for G1, G2, G3).

Conclusions: The depth of stromal invasion was higher in larger SCCs with a maximal diameter greater than 2 cm (pT2) and in poorly differentiated (G3) tumors.

PS-06-05

Basal cell carcinoma in the facial region: easy pathohistological diagnosis, but reconstructive challenge

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Objective: Basal cell carcinoma (BCC) is the most common malignant skin tumor with 80% percent of it affecting the facial skin. Although this tumor rarely metastasizes, it can cause significant destruction and disfigurement by invading surrounding tissues. Even though the pathohistological diagnosis is not usually a problem, it's excision and reconstruction in the facial region can sometimes be challenging.

Material and Methods: All the patients were operated at the University Clinic of Plastic and Reconstructive Surgery in Skopje and had BCC in the facial region. They were treated by standard surgical excision using surgical blade or electrocautery. The postoperative defects were closed in a single stage procedure using local skin flaps (transpositional, rotational, advancement, island flaps) and skin grafts. The specimen were evaluated for the pathohistological diagnoses at the Institute of Pathology in Skopje.

Results: The postoperative complications rate was 2-3%. The follow-up period was 5 years. The recurrence rate in that period was less than 5%. Functional and cosmetic outcomes were satisfactory.

Conclusions: Considering the basal cell carcinoma in the facial region, the main effort falls on adequate tumor excision and subsequent reconstruction.

PS-06-06

Isolated endobronchial Langerhans cell histiocytosis in a child: surprising diagnosis for pediatric oncologists

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Objective: We aimed to present the first case to our knowledge of isolated endobronchial Langerhans cell histiocytosis (LCH) without parenchymal lesion in an 11 year-old child.

Material and Methods: A 11-year-old girl was admitted with acute hemoptysis. Computed tomography of thorax revealed a mass on distal trachea extending to the right main bronchus. Rigid bronchoscopy revealed an endobronchial lesion which originated in and obstructed right main bronchus and protruded to the trachea. Multiple punch biopsies were performed.

Results: On microscopic examination, there was cellular infiltrate composed of histiocytes, eosinophils, lymphocytes and plasma cells in a fibrotic background. Histiocytic cells showed strong reactivity for

CD1a antigen and S-100 protein, on immunohistochemistry. These findings strongly suggested for LCH. Laboratory findings, bone marrow biopsy, bone scan, PET scan, abdominal US did not show any abnormalities suggestive of systemic involvement. Flexible bronchoscopy was performed after first initial treatment course. Regression of the endobronchial lesion was observed. Computed tomography of thorax revealed a decreease in the mass' size.

Conclusions: Pulmonary LCH in children generally occurs in the context of multisystem LCH. Isolated pulmonary LCH in children is a rare entity and has been reported as case reports. When isolated pulmonary LCH occurs in childhood, there is consistently parenchymal lesion in the lung. However, endobronchial LCH without parenchymal lesion is an extremely rare entity. Here, to our knowledge, we present the first case of isolated endobronchial LCH without parenchymal lesion in childhood. Since there is no electron microscope in our center, we did not demonstrate the Birbeck granules. But we proved both CD1a and S-100 positivity by immunohistochemistry. The treatment response which was a confirmation of our diagnosis, was compatible with better category according to definition of the treatment response for first course of chemotherapy.

PS-06-07

The story of desiccation of a tree nearby the macroscopy room

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Objective: To bring up the detrimental effects of formaldehyde on human health and environment to the agenda based on the desiccated tree is indispensable for our pathology laboratory.

Material and Methods: There used to be a 15 meters high tree with 90 cm in diameter nearby our macroscopy room. Vent tubes of our macroscopy room were mounted directly towards the area where the tree was located. The tree desiccated in a couple of months.

Results: Formaldehyde (CH2O) is broadly utilised particularly in industrial and medical fields. It is derived in liquid state from methanol oxidation. It rapidly transforms into toxic gas in room temperature and mixes into the atmospheric air. Formaldehyde is a by-product of methane cycle in natural environment. Respiratory tract toxicity of formaldehyde turns out to be between 0.35-0.90 ppm even in low concentrations. Acute and chronic sensory irritation occurs among the general population in concentrations measured as 0.08 ppm (0.1 mg/m3). The limit value to prevent carcinogenic effect is 0.08 ppm. Development of nasal tumor when exposed to 6-15 ppm of formaldehyde was observed during the performed animal testing. Apart from nasopharyngeal carcinoma, lymphohematopoietic malignancy, brain cancer, gastrointestinal tract cancer cases are encountered due to exposition to formaldehyde toxicity. Formaldehyde which is normally available in the organisms may harm our bodies and wildlife if utilised in an insensible attitude.

Conclusions: The tree which lived in our macroscopy cabin room's exhaust air duct and eventually desiccated in a short period of time being exposed to formaldehyde is merely a small example demonstrating how do we destroy the nature. For this reason, we must take the other living organisms within our environmental areas into account during transforming the areas where formaldehyde is broadly utilised into areas where formaldehyde dose is reduced.

PS-06-08

Foetus acardius amorphous - report of two cases

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Objective: Foetus acardius amorphous is a rare congenital malformation with an incidence of 1:35000 births, which usually is a complication in multiple pregnancies. The main diagnostic dilemma is placental teratoma, a non-trophoblastic, extremely rare tumor, with only 27 cases reported in the literature. We present a case of a triplet pregnancy of a 35-year-old mother and a twin pregnancy of a 32-year-old mother.

Material and Methods: Case 1. Along with three live births, there was a teratogenic, skin-covered, oval tumor mass, weighing 1450 grams and 21x15x6 cm in size, with two epidermal buds with a diameter of 2-3 cm on the surface. On dissection, there were fatty tissue, muscle, cartilage, bone and large intestinal loops. Case 2. Along with a stillbirth, there was an oval, skin-covered structure weighing 67 grams and diameter of 9.5 cm, with visible elongated bud, resembling a limb, at one pole. The dissection showed autolytic organoid structures and cavities.

Results: There are a few criteria for differentiating acardiac fetus from placental teratoma: a presence of umbilical cord, skeletal structures, visible rudimentary extremities and partially developed visceral organs. On the other hand, a placental teratoma is predominantly composed of a disorganized collection of mature tissues. The gross and histological findings solved our diagnostic dilemma.

Conclusions: There is a great overlap between these two entities and the proposed criteria are useful only in clear cases. Some authors consider them as different levels of development and differentiation of a single pathological event. Nonetheless, the clinical information for multiple gestation pregnancies is very important and helpful for diagnosing foetus acardiacus.

PS-06-09

Persistent cloaca - “Human bird” malformation

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Objective: Persistent cloaca is a rare, early stage developmental malformation and one of the most complex developmental disorders of the female anorectal, vaginal and urogenital tract, with an incidence of 1:250,000 newborns. It is defined as a confluence of the rectum, vagina, and urethra into a single common channel. We present a case of persistent cloaca that was detected in a 24th gestational week of pregnancy.

Material and Methods: A 23-year-old pregnant patient underwent a routine ultrasound test that showed transient fetal ascites. The MRI confirmed umbilical cord with two blood vessels, distended duodenum, colon and bladder and mild hydronephrosis. The medical ethics committee approved termination of the pregnancy. After performing a feticide, induced abortion was done.

Results: Autopsy revealed ambiguous genitalia with absence of the labia folds and clitoris. There was a stenosis of the distal part of the duodenum and the terminal portion of sigmoid colon was opened into the uterine fundus. The uterus was dilated and anteriorly dislocated, situated on the left side of the urinary bladder. The neck of the bladder and the vagina were fused, creating a single common channel with a

single perineal opening. The urethra was absent. The histological examination confirmed two vessel umbilical cord and immaturity of the tissues.

Conclusions: Because of the complexity of this multisystemic, anatomic variation and presence of persistent cloaca, sometimes it is difficult to make a correct diagnosis. This rare developmental malformation should always be considered as one of the differential diagnosis of urinary tract malformations, dilated bowel loops or cystic pelvic masses.

PS-06-10

Different ultrastructural patterns of early-stage Wilson's disease

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Objective: Wilson's disease is an autosomal recessive genetic disorder of copper metabolism. Electron microscopy is a worthwhile and valuable diagnostic tool, especially in the early stages of this disease. We report two different ultrastructural patterns in patients that have similar clinical and histological features.

Material and Methods: Two seven-year old female patients were admitted at the Pediatric Clinic because of abdominal pain and mild jaundice. Laboratory results showed elevated aminotransferases, low serum ceruloplasmin levels and negative serology for hepatotropic viruses. Liver biopsy was done and the biopsy specimens were fixed in glutaraldehyde and embedded in Durcupan resin. Semi-thin sections dyed with Toluidine blue and ultra-thin sections treated with uranyl acetate and lead citrate were made.

Results: Light-microscopic analysis of the semi-thin sections of both cases showed early-stage cirrhosis presented by steatohepatitis and fibrosis with focal piece-meal necrosis. Electron-microscopic analysis of the ultra-thin sections in both cases showed hepatocytes` cytoplasm with a variable increase in the number of enlarged, pleomorphic mitochondria and peroxisomes, dilatation of smooth and rough endoplasmic reticulum and presence of neutral lipid vacuoles. We found two different patterns of cytoplasmic copper accumulation: electron densities with cribriform appearance and discrete, diffusely dispersed electron-dense material, especially in the perinuclear and paranuclear regions, as well as in some artificially degenerated mitochondria.

Conclusions: Although these two cases have relatively similar clinical, laboratory and histological findings, they present very different and distinctive ultrastructural features, which from a diagnostic point of view can be subtle and non-specific in the early stages of this disease.

PS-06-11

Amniotic band syndrome: a case report

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Objective: Amniotic band syndrome is a set of congenital malformations ranging from minor constriction rings and lymphoedema of the digits to complex, bizarre multiple congenital anomalies that are attributed to amniotic bands that stick, entangle and disrupt fetal parts. The present study reports amniotic sheets broadly attached to the fetal skull and face, associated with major anomalies of those structures.

Material and Methods: Artificial abortion in the 21st gestational week was performed due to ultrasonography findings of multiple malformations in the development of the fetus. Autopsy with careful examination of the fetal surface and viscera, placenta and placental membranes was performed on male fetus weighing 400g, with body length of 31cm.

Results: The finding of the autopsy showed a presence of ADAM complex - Amniotic Deformities, Adhesions and Mutilation, with multiple malformations in the development of the fetal skull, which was closely attached to broad sheets of amnion tethered near the umbilical cord. The amnion was contiguous with the ectoderm of the foetal face and skull, causing agenesis of parietal and frontal bones with exencephaly, meningocoele, agenesis of the left eye and cleft palate. Multiple amputations of portions from upper and lower extremities were also present, some of them visibly caused by amniotic band loops.

Conclusions: The incidence of amniotic bands is difficult to assess because there is no apparent hereditary component, increased risk of recurrence, nor association with amniocentesis or relation to trauma. The prenatal screening is essential for diagnosis and the management will depend largely on the type and extent of malformations.

PS-06-12

Morphological characteristics of the cerebellar arteries and clinical significance

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Objective: The superior, anterior inferior and posterior inferior cerebellar artery are the main vessels that provide blood supply to the cerebellum. Knowing the origin, course and area of supply of the cerebellar arteries is important in understanding the symptoms of stroke and preventing complications during surgical and endovascular procedures. The aim of this study was to describe the morphological characteristics of the cerebellar arteries in terms of origin and diameter and to emphasize their clinical significance.

Material and Methods: We examined radiographs of 103 patients who had CT angiography undertaken for a variety of clinical reasons, performed as part of their medical treatment at the University Clinic of Radiology in Skopje, R. Macedonia. The study population included 103 patients, 58 male and 45 females, age range from 25-82, mean age 58.4 years.

Results: The mean value of the outer diameter of the left superior, anterior inferior and posterior inferior cerebellar artery was 1.36 mm, 0.89 mm and 1.24 mm, respectively. The mean value of the outer diameter of the right superior, anterior inferior and posterior inferior cerebellar artery 1.32 mm, 0.88 mm and 1.18 mm, respectively. The most frequently found variations of the cerebellar arteries are duplication in the origin and variable origin of the cerebellar arteries.

Conclusions: Although anatomically interesting, the awareness of the anatomy and variations of the cerebellar arteries is clinically important

for radiologists and surgeons for safe performance of procedures, and forensic pathologists since variants may have forensic consequences.

PS-06-13

Anatomical features of the triangle of Koch

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Objective: The triangle of Koch occupies the atrial component of the muscular AV septum. The aim of this study was to present the anatomical features and clinical importance of the triangle of Koch.

Material and Methods: The study consists of two parts: basic and clinical. In the basic part, 100 human hearts fixed in formaldehyde were examined using common anatomical and histological methods. The numerical features of the triangle of Koch were measured in two different ways. In the clinical study, the analysis was made on 100 patients who were treated in the Electrophysiological laboratory of the Institute for Heart Diseases in Skopje. Using the data of patients weight and height, the numerical features of the triangle were calculated.

Results: In the basic part of the study, length of the triangle of Koch was: side a 26.1 mm, side b 20.8 mm and side c 24.5 mm. The value of the area of the triangle was 256.2 mm2. In the second type of measuring length of side a was 20.8 mm, side b 13.9 mm and side c 19.8 mm. The value of the area of the triangle was 139.47 mm2. In the clinical part of the study, value of the length of the side a was 28.5 mm, side b 12.9 mm and side c 21.1 mm. The value of the area of the triangle was 116.6 mm2.

Conclusions: Knowledge of the variations of numerical features of the triangle of Koch is fundamental for successful catheter placement in electrophysiological studies and radiofrequent catheter ablations.

PS-06-14

Role of ex tempore biopsy in the treatment of the brain tumors

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Objective: Intraoperative diagnosis of central nervous system lesions is of utmost importance for neurosurgeons to modify the approach at the time of surgery and to decide on the further plan of management. The aim of this study was to present a case with ex tempore biopsy of a brain tumor.

Material and Methods: Report of the case.

Results: A 68-year-old female patient was admitted to University Clinic of Neurosurgery in Skopje. Several months prior to admission she felt generally fatigued. Ten days before admission, the patient woke up with right-sided weakness. The neurological examination demonstrated a hemiparesis that involved the right arm and leg. The patient also had motor dysphasia. A head MRI scan with contrast was made after admission to hospital and revealed a large mass in the left parietal lobe, with associated edema and shift of the midline structures. Family history was negative for any type of malignancy. Several days after admission, a craniotomy was performed and the ex tempore biopsy specimen demonstrated the mass lesion to be a glioblastoma gr. IV. Complete surgical excision of the mass was preformed. Postoperatively the material was sent for histopathological examination and the diagnosis glioblastoma gr. IV was confirmed. Her postoperative course was without complications.

Conclusions: Ex tempore diagnosis is a sensitive, reliable diagnostic method for brain tumors. During surgery it is very helpful for the surgeon to make a decision on further management of the brain tumor in order to avoid major resection of vital anatomical structures.

PS-06-15

Glomus tumor of uncertain malignant potential

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Objective: To deepen our understanding of the malignant potential, histological and immunohistochemical characteristics of the glomus tumors.

Material and Methods: The operative material was a resected muscle tissue measuring 10x10x4 cm. On cut surface deep under the fascia, a white-yellow hemorrhagic poorly demarcated nodular neoplastic mass with dilated blood vessels filled with blood and blood clots was seen. Standard histological procedure and immunohistochemical stains were done.

Results: Microscopically the neoplasm was composed of vascular channels separated by fibrous stroma in which aggregates and nests of uniform round cells with pale to eosinophilic cytoplasm with round nucleus were found. The cells had perivascular arrangement in many areas. Immunohistochemistry showed diffuse expression of SMA and caldesmon, as well as collagen IV expression in groups of cells. Ki67 was approximately 10% in areas with the highest proliferative index (1 mitosis/50HPF at H&E). A diagnosis of glomus tumor of uncertain malignant potential was made due to histological features, tumor size, and subfascial localization.

Conclusions: Multiple glomus tumors are rare condition that can be misdiagnosed and should be considered in soft tissue pathology.

PS-06-16

Salivary duct carcinoma of the parotid gland: a case report with cyto-histologic characteristics

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Objective: Salivary duct carcinoma (SDC) is a rare, but aggressive neoplasm of the parotid gland which resembles high-grade breast ductal carcinoma.

Material and Methods: We present a case of a 68-year-old patient with a rapidly growing, asymptomatic mass in the left parotid gland. Computer tomography scan identified a neoplasm in the parotid gland, involving the surrounding soft tissue and regional lymph nodes. Based on the fine needle aspiration cytology which reported a malignant epithelial neoplasm of probable parotid gland origin, left radical neck dissection was performed.

Results: Histopathology, supported by immunohistochemical analysis showed features of salivary duct carcinoma of the parotid gland. Despite aggressive oncotherapy, the patient died 12 months after surgery.

Conclusions: SDC is one of the most aggressive salivary malignancies. Pathologists need to be familiar with diagnostic features of this entity to assist in the optimal surgical-oncologic therapeutic planning.

PS-06-17

Warthin-like papillary carcinoma of the thyroid: a case report

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Objective: Warthin-like variant of papillary carcinoma (WLPCT) is an uncommon variant, first described in 1995, with a clinical presentation and prognosis similar to the classic papillary thyroid carcinoma (PTC). We report a case of WLPCT focusing on the histopathological and immunohistochemical features.

Material and Methods: A 60-year old female, with no remarkable past medical history, underwent surgical treatment of an enlarged multinodal goiter with previous negative fine-needle aspiration biopsy findings. A left total and right subtotal thyroidectomy was performed. The patient is alive and well 4 months after the surgery.

Results: On gross examination, the right lobe of the thyroid gland measured 4.5x1.5x1 cm, and the left lobe with adjoined isthmic lobe measured 5x3.5x2 cm. In the right lobe an oval, firm, grey, 0.8 cm large nodule was found, while in the left lobe another well circumscribed, pale-brown, 2.5 cm large nodule was present. The left lobe nodule was diagnosed as an atypical follicular adenoma with no capsular or vascular invasion. Histology of the right lobe nodule showed an encapsulated tumor composed of papillary structures lined by oncocytic cells and rich lymphoid stroma, with germinal centers in the papillary stalks, typical for WLPCT. Immunohistochemically, tumor cells of WLPCT showed positive expression for cytokeratin 19, thyroid transcription factor-1 and thyroglobulin.

Conclusions: Warthin-like variant is one of the rarest variants of PTC (less than 100 reported cases in the literature) with as favorable prognosis as the classic PTC. Morphology and immunohistochemistry are of decisive significance in differentiating these neoplasms from benign lymphoepithelial lesions, Hurthle cell carcinoma and tall cell variant of PTC.

PS-06-18

Soft tissue reconstruction after excision of extensive skin carcinomas

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Objective: When considering extensive skin carcinomas both the radical excision and the subsequent soft tissue reconstruction are an equally challenging problem for the surgeon. Moreover, the postoperative surveillance is a very important issue that sometimes determines the reconstructive method.

Material and Methods: We are presenting patients with extensive skin carcinomas on different areas of the head and body. The patients were operated at the University Clinic of Plastic and Reconstructive Surgery in Skopje. The pathohistological diagnoses included both basal and squamous cell carcinomas and the diagnoses were established at the Institute of Pathology in Skopje. All the patients were treated by standard surgical excision using surgical blade or electrocauthery. The postoperative defects were generally closed in a single stage procedure. The reconstructive methods included skin grafting together with loco-regional flaps.

Results: In 5% of the patients with extensive carcinomas of the epicranium, there was bone involvement due to which bone resection was performed. In one patient due to carcinoma involvement, reconstruction of dura matter was also carried out. The recurrence depended on the pathohistological finding, as well as on the possibility for radical operation.

Conclusions: Considering the treatment of extensive carcinomas the main effort falls on adequate tumor excision and subsequent reconstruction at the same time taking into account the possibility for adequate surveillance as well as providing adequate function.

PS-06-19

Analysis of the postmortal diagnoses in 566 patients who died during ten years period

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Objective: Although clinical non-forensic autopsy is considered to be of high value, its rate has consistently declined during last decades. The aim of this study was to analyze autopsy cases according to the major type of the disease and the death cause.

Material and Methods: 566 autopsy cases of the Department of Pathology, Institute of Pulmonary Diseases of Vojvodina, during ten years period (2005-2014) were analyzed retrospectively. Major pathological diagnoses were grouped into seven disease groups according to the International Classification of Diseases, 10th edition.

Results: The majority of patients have had malignant (37.8%), cardiovascular (26.7%) and respiratory non-neoplastic diseases (24%), while digestive, infectious and parasitary, genitourinary and other diseases were found in 4.1%, 1.6%, 0.2% and 5.6% respectively. Bronchopneumonia (24.2%) and myocardial dilation (17.7%) were the most common causes of death. Pulmonary thromboembolism, pulmonary edema, respiratory insufficiency, myocardial infarction have caused death in 14.3%, 11.1%, 6.2% and 4.2% of patients respectively, while other death causes were found in 22.3% of autopsied cases. The majority of patients (42%) died within first 24 hours of hospitalization, 29.9% of patients died during first week and 13.3% of patients died during second week of the hospitalization.

Conclusions: Autopsies still have a high value and can identify patient profiles which may aid both pathologists and clinicians to

identify cases at increased risk for a discrepant diagnosis and possibly optimal treatment intra vitam in the future.

PS-06-20

Osteoma cutis - pathological features of 6 cases.

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Objective: Osteoma cutis is a rare lesion characterized by bone formation in the dermis and subcutaneous tissue. It may be primary, with no preceding lesions, secondary (metastatic), when associated with parathyroid metabolism abnormalities, or dystrophic, when ossification occurs at a site of an inflammatory process. We analyzed the clinical and morphological findings of 6 patients with osteoma cutis.

Material and Methods: The material consisted of 6 skin resection specimens from 6 patients. Standard dissection procedure and paraffin embedded tissue sections were made, stained with H&E.

Results: The mean age of the patients was 46 years. The female to male ratio was 2:1. The most present clinical symptom was chronic pain. Three of the lesions were localized in the fingers skin, two in the toes skin and one in the facial skin over the mandible. All resected skin specimens contained hard nodules measuring from 0.6 to 1.5 cm in the dermis and subcutaneous fat tissue. The nodules were composed of lamellar bone with osteocytes in small lacunae. The majority of them were lined by benign osteoblasts and some osteoclasts were present in the fibrous tissue between the bone trabeculae. Prominent cement lines and calcifications could be seen in some bone trabeculae. No ulcerations of the epidermis or transepidermal elimination were seen in any of the analyzed cases. The subsequent clinical and laboratory examinations in all patients did not reveal any other concomitant or preceding pathological condition.

Conclusions: Primary osteoma cutis should only be diagnosed by correlating clinical, laboratory and pathological findings, as it may be an indicator of another underlying pathological condition.

PS-06-21

Muscle histopathological features in patients with titin myopathy.

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Objective: The goal was to establish pathohistological finding in six Serbian patients with titin (TTN) myopathy which were genetically validated. Titin is the largest described protein, which plays key structural, developmental, mechanical and regulatory roles in cardiac and skeletal muscles. The highly variable expression and the multitude of known and unknown functions form the background for a large variation of phenotypes with defects in TTN. TTN mutations have been reported to contribute to four purely skeletal muscle disorders with no cardiac involvement: late-onset tibial muscular dystrophy, limb-girdle muscular dystrophy type 2J, hereditary myopathy with early respiratory failure and centronuclear myopathy.

Material and Methods: Diagnostic skeletal muscle biopsies were snapp-frozen on site and prepared for cryostat sectioning. Tissue slides were stained with Periodic acid-Schiff, Congo red and Gomory trichrome histochemical stains, NADH and SDH enzyme histochemistry, as well as immunohistochemically. After staining, tissue slides were examined histopathologically.

Results: The most common findings were muscle fiber size variation, internal nuclei, eosinophilic inclusions or deposits and rimmed vacuoles in all samples. The deposits were red or dark green in trichrome stained section and had absent NADH, SDH and Periodic acid-Schiff staining. Histochemical and immunohistochemical analysis excluded known dystrophinopathies, dysferlinopathies, myofibrillar myopathies and inclusion body myositis.

Conclusions: The genetic basis of many of the different forms of myopathy has been identified. The relationship between titin myopathy, defined on histological ground, and the genetic cause is complex, therefore systematic approach to clinical diagnosis is important and crucial.

PS-06-22

Kaposi sarcoma as initial presentation of HIV infection

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Objective: Kaposi's sarcoma (KS) is a common clinical manifestation of human immunodeficiency virus (HIV) infection and it is the most frequently diagnosed sarcoma in immunodeficiency. All forms of this neoplasm are etiologically linked to the human herpes virus 8 (HHV-8).

Material and Methods: We report a case of a 40-year-old male patient, who has undergone excisional biopsy of the cervical lymph node in the setting of generalized lymphadenopathy.

Results: Pathological analysis showed impaired lymph node structure due to the presence of tumor proliferation. Immunohistochemical staining has shown intense, diffuse expression of vimentin and vascular markers (CD31, CD34, ERG-1, FVIII, D2-40), and focal immunopositivity for HHF-35, alpha-SMA, bcl-2 and p53. Tumor cells were negative for CK AE1/AE3, CK7, CK20, EMA, CD99, Desmin, S-100, HMB-45, Melan-A, LCA, CD21, MPO, CD68, Napsin, and GLUT-1. The morphological and immunohistochemical characteristics of the tumor, associated with intense nuclear expression of HHV-8, indicated a diagnosis of KS, a malignant mesenchymal tumor of vascular origin. After the diagnosis of KS was set, we suggested additional clinical examinations to confirm/exclude the Acquired Immunodeficiency Syndrome. The patient was found to be HIV positive. He underwent an endoscopic examination of the gastrointestinal tract (GIT). Representative samples of GIT lesions confirmed the presence of Kaposi's sarcoma in GIT.

Conclusions: The gastrointestinal tract and lymph nodes are typical and most common sites for KS in HIV-positive patients. All vascular lesions found in these areas need to be examined for expression of HHV-8 in order to verify associated acquired immunodeficiency.

PS-06-23

Presence of anti-nuclear antibodies in a patient with chronic hepatitis C - a case report

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Objective: Hepatitis C infection may be associated with the development of chronic liver disease with high potential for evolution to cirrhosis, and that is why it represents a serious public health problem. In addition to the primary disease, serum autoantibodies such as antinuclear antibody (ANA) are frequently detected in patients with chronic hepatitis C virus (HCV) infection. ANAs are a specific class

of autoantibodies that have the capability of binding and destroying certain structures within the nucleus of the cells. ANA positivity seems to represent an immunological epiphenomenon in patients with hepatitis C infection, with still debatable relevance.

Material and Methods: We tested a serum sample from a 36-year-old male patient with confirmed hepatitis C infection with immunoblot test for 18 types of anti-nuclear antibodies.

Results: We found positive bands for PM-Scl and RNP-A types anti-nuclear antibodies, both autoantibodies with capability for degrading various types of RNA molecules.

Conclusions: Our case confirms the association of hepatitis C virus infection with the presence of ANAs, detected with immunoblot test. It suggests that a larger study on this issue is required in order to determine the relevance of this association.

PS-06-24

The role of immunohistochemistry in lymphoplasmacyte-rich meningioma

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Objective: Lymphoplasmacyte-rich meningioma is a very rare subtype of benign meningioma, which is characterized by prominent inflammatory cell infiltration with sparse meningothelial component. The incidence is less than 1% of all meningiomas. We present a case of 45-year-old male without any systemic hematologic abnormalities.

Material and Methods: The patient was admitted to the University Clinic of Neurosurgery with headache, confusion, disorientation, nausea and vomiting. Neurological examination and complete blood count were normal. The MRI revealed isodense, contrast-enhanced dural mass in the right frontal parasagital region. Total tumorectomy was done and gross examination showed oval, well-circumsribed tumor with diameter of 4 cm.

Results: Microscopic analysis showed neoplasm composed of rare nests of meningothelial cells surrounded by extensive lymphocytic and plasma cell infiltrate, separated by proliferated collagenous connective tissue bands. The meningothelial cells had round to oval nuclei without clear cytoplasmic borders. Immunohistochemistry showed positive signal for EMA, PR, CD3, CD4, CD20, LCA, CD79alfa, and Bcl2; focal positive signal for CD138, IgA, IgD, IgG, IgM, kappa, lambda and negative signal for CD34, CD10,CD23. The proliferative index for Ki-67 was low (4%).

Conclusions: Immunohistochemical analysis had a crucial diagnostic role in differentiating this rare tumor subtype from intracranial inflammatory process.

PS-06-25

Malignant transformation of nodular hidradenoma

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Objective: Malignant nodular hidradenoma (MHN) was first reported as clear cell eccrine carcinoma by Keasbey and Hadley in 1954. MNH is an infrequent, highly malignant, primary skin tumour derived from eccrine sweat glands. Most tumours occur in elderly individuals. They are usually malignant from their inception, but some develop from a benign counterpart. MNH also known as hidradenocarcinoma is very rare adnexal tumour with exceedingly low incidence of 0.001%. We present a case of 61-year-old male with left supraclavicular nodular swelling of the neck. He had small node for 2 years and within the last three months, the swelling progressed rapidly.

Material and Methods: The patient was admitted at the University Clinic of Surgical Diseases for local excision and gross examination showed dermal multi nodal tumor with dimension of 2.1x1.8x1.5 cm.

Results: Histopathology showed nodular tumour with irregular margins. Cells with clear cell changes and focal glandular formations (PAS+) were evident. Three histological distinct components were seen in this tumour: typical nodular hidradenoma; papillary structures and carcinoma with areas of transition. Atypical mitoses were frequent (5/HPF). Immunohistochemistry showed positive signal for EMA, CK AE1/AE3, and CK7; focal positive signal for CK5/6, p63, NSE and negative signal for CK20, CD34, Actin, Vimentin, S100-protein, Melan A, HMB45 and Synaptophysin. The proliferative index for Ki-67 was low (1%) in benign and high (45%) in malignant areas.

Conclusions: Histologically, this case was concluded as a hidradenocarcinoma arising from a long-standing nodular hidradenoma. The recognition is very important because eccrine carcinomas have potential of local destruction and distant metastasis.

PS-06-26

Glomus tumors - the pathological features of 4 cases

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Objective: Glomus tumors are uncommon, but due to improved radiologic imaging techniques their appearance seems to increase. Glomus tumors are usually benign, subcutaneus neoplasms of the perivasculature. They occur in wide age range, more frequent in children. They arise from modified smooth muscle cells of glomus body, a specialized arteriovenous anastomosis involved in thermoregulation. We analyzed the clinical findings of 4 patients with glomus tumor and the pathological features of the operative material.

Material and Methods: Standard dissection procedure of the operative material and paraffin embedded tissue sections were made, stained by HE and immunohistochemicaly with Actin, Caldesmon, S100, CKWS and CD34.

Results: The mean age of the patients was 40 years. The most present clinical symptom was chronic pain. The diameter of the nodules measured from 0.3 to 0.7 cm. Two of the lesions were located under fingernails, one in the leg and one in the forearm. All glomus tumors had branching vascular channels separated by stroma containing nests, aggregates and cohesive clusters of uniform round cells with scanty cytoplasm. Glomus cells were arranged around vessels. The cells had small, regular, round, indistinct nuclei with very low mitotic activity.

Conclusions: Glomus tumor is distinct entity and should be recognized in order to distinguish it from malignant variant.

PS-06-27

Multifocal Hurthle cell (oxyphilic) variant of papillary thyroid carcinoma associated with Hashimoto`s thyroiditis: a case report

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Objective: Oxyphilic (Hurthle cell) variant of papillary thyroid carcinoma (OVPTC) is a rare subtype accounting for 1-11% of all cases of papillary thyroid carcinomas (PTCs). The clinicopathological features and biological behavior of OVPTC have not yet been thoroughly characterized. We present a case of multifocal OVPTC with concurrent Hashimoto`s thyroiditis.

Material and Methods: A 51-year old female patient with multinodular goiter underwent a fine-needle aspiration biopsy which was reported as negative, followed by a subtotal thyroidectomy procedure.

Results: The surgically obtained material consisted of two oval fragments designated as right and left thyroid lobe with the largest diameter of 5 cm and 4.5 cm, respectively. Grossly, on the cut section of the left lobe two well-circumscribed, white to grey-tanned foci with the largest diameter of 1.3 cm and 0.6 cm, respectively, were found. Microscopically, in a background of Hashimoto`s thyroiditis, the two foci revealed a neoplasm with predominantly insular growth pattern and focally follicular or papillary structures composed of large polygonal cells with abundant eosinophilic granular cytoplasm and optically clear nuclei with the characteristic intranuclear pseudoinclusions and nuclear grooves. Psammoma bodies and areas of calcification were also present. Mitoses were rare and no vascular or capsular invasion was encountered. Immunohistochemically, tumor cells showed diffuse positivity for low-molecular-weight cytokeratin and cytokeratin 19 and focal positivity for thyroid transcription factor-1.

Conclusions: This case confirms that although OVPTC remains controversial, it usually displays the morphological and immunohistochemical features of the classical type of PTC, which can aid in avoiding the diagnostic pitfalls in distinguishing this subtype of PTC from other benign or malignant Hurthle cell lesions.

PS-06-28

Histological and cytological diagnosis of parathyroid tumors - a retrospective analysis for a period of 5 years

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Objective: The aim of our study was to review the histological and cytological diagnosis, if present in all patients with primary hyperparathyroidism, consecutively operated for a period of 5 years.

Material and Methods: A total of 142 patients with surgically removed parathyroid tumor were included. In 33 of them, FNB under ultrasound control of the suspicious parathyroid lesion (PTL) was done preoperatively.

Results: The histological diagnosis was parathyroid adenoma (PA) in 136 cases (96%, male-26, female-110 ratio-1:4; mean age 55.18±13.03 years) and PC in 6 cases (4%, male-2, female-4, mean age 52.6±11.7 years). The size of PA showed great variations (range, 0.4 to 4 cm; mean 1.61±0.93 cm) but was significantly smaller compared to that of PC (range, 2 to 6 cm, mean 3.17±1.44 cm; p=0.006). Histologically all PA were well-capsulated tumors, while almost all PC showed an infiltrative multinodular growth (2 invading the trachea) and desmoplastic reaction with fibrous septa. During the follow-up recurrence and lymph node metastasis was detected in 3 patients. Preoperative FNB cytology was performed in 30 cases with PA and in 3 cases with PC. It was classified as unsatisfactory in 6 cases, suspicious for PTL in 17 cases, and positive for PTL in 10 cases (including the cases with PC).

Conclusions: In our case series, parathyroid adenomas show typical histology and variation in size. The diagnosis of PC is based on the combination of atypical clinical and histological features. FNB cytology of suspicious PTL prior to surgery is helpful, although the smears are often with scant cellularity.

PS-06-29

Stratification of patients with chronic lymphocytic leukemia – single centre experience

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Objective: The clinical course of patients with chronic lymphocytic leukemia is extremely heterogeneous; some patients have indolent disease, never needing treatment, whereas others have an aggressive disease requiring early treatment. Wierda proposed to combine a set of clinical risk factors, to develop a prognostic index (PI) stratifying patients in three risk groups with different expected median survival, and a nomogram, estimating individual patient survivals. Herein, we report the initial results from a study designed to evaluate clinical and biological prognostic factors in patients risk stratification.

Material and Methods: Traditional laboratory, clinical prognostic, and biological prognostic factors were evaluated at first patient`s visit to University Clinic of Hematology, Skopje, R. Macedonia. We used Wierda`s prognostic index and a nomogram, to calculate 5- and 10-year survival probability and estimated median survival time.

Results: A total of 70 previously untreated patients who had traditional and biological prognostic factors evaluated, were included in the study group. According to prognostic index, a classification tree was built that identified three subsets of patients. Estimated median survival was 22.5 years for low-risk subset of patients, 10.8 years for intermediate-risk and 4 years for high-risk subset of patients. Projected 5-year and 10-year survival was 70%, 92.5%, 100%, and 100%, 99%, 60%, for low-, intermediate- and high-risk groups respectively.

Conclusions: We use this model to identify patients at high risk for progression to treatment. This prognostic model may help clinicians in clinical decision making as well as in clinical research and clinical trial design.

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CORRIGENDA

of the Proceedings and Abstracts of the 2nd Macedonian Congress of Pathology with International Participation

After all technical preparations of the Proceedings and Abstracts book of the 2nd Macedonian Congress of Pathology were completed a few minor changes to the Congress Programme were required for which the organisers sincerely apologise.

MOVED

(1) Abstract OF04 (page 91)

Due to some unforeseen circumstances the authors *Ahmed ASMM, et al.* decided to have a poster instead of the oral free presentation of their abstract entitled **HER2/neu protein expression in gastric carcinoma and its association with tumor grading.** Therefore, the Scientific Committee agreed that their abstract is moved from Oral Presentation section (OF04, page 91) to the Poster Presentation section of the Proceedings and Abstracts and will be presented as poster PS-02-15 (page 115) as a part of the poster presentation session of Gastrointestinal Pathology (PS-02) on September 2, 2016. The correct abstract is below:

PS-02-15

HER2/neu protein expression in gastric carcinoma and its association with tumor grading

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Objective: General objective: To evaluate the HER2 protein expression in gastric carcinoma and its association with histopathological grading. Specific objectives: 1. To carry out histopathological grading of diagnosed cases of gastric carcinoma. 2. To evaluate the frequency of HER2 positive gastric carcinoma by applying standard criteria.

Material and Methods: A total of 44 cases were consecutively included in the study as a sample. Histopathological types (Lauren classification - intestinal & diffuse) and grading were done according to Sobin et al. (2009). Immunohistochemistry was done with a polymer-based detection system using a Herceptin kit to detect HER2 overexpression. Finally, the association between histological grading and HER2 status was assessed by chi-square test.

Results: More than two-thirds (68.2%) of the patients had the intestinal type of gastric adenocarcinoma and the rest (31.8%) diffuse type. In terms of grading, 31.8% were well-differentiated, 36.4% moderately differentiated and the rest 31.8% were poorly differentiated. Six (13.6%) patients were HER2 positive (overexpressed), 50% were negative and 36.4% were equivocal. Intestinal type of gastric adenocarcinoma were significantly prone to be HER2 overexpressed as compared to diffuse type (20% vs. 0%, p=0.035). HER2 overexpression was mainly associated with well and moderately differentiated carcinoma, but not with poorly differentiated carcinoma (21.4% vs. 18.8% vs. 0%, p=0.163).

Conclusions: One in every eight gastric carcinoma cases (13%) exhibits HER2 overexpression and it is well associated with the type and histological grading of the adenocarcinoma.

(2) Abstract OF06 (page 91)

Due to some unforeseen circumstances the authors *Ahamad MSU, et al.* decided to have a poster instead of the oral free presentation of their abstract entitled **Association of human papillomavirus in colorectal carcinoma in the Bangladeshi population.** Therefore, the Scientific Committee agreed that their abstract is moved from Oral Presentation section (OF06, page 91) to the Poster Presentation section of the Proceedings and Abstracts and will be presented as poster number PS-02-02 (page 111-2) as a part of the poster presentation session of Gastrointestinal Pathology on September 2, 2016. The correct abstract is below:

PS-02-02

Association of human papillomavirus in colorectal carcinoma in the Bangladeshi population

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Objective: Infection with the human papillomavirus (HPV) is associated with the development of several cancers, including oral, esophageal, skin, lung and cervical cancers. However, the association of HPV and colorectal cancers remains controversial. The aim of this study was to evaluate the association of HPV infection with colorectal carcinoma in the Bangladeshi population.

Material and Methods: Tumour tissues obtained from 60 patients with colorectal carcinoma were included in the study. Histopathological type and grading were done. HPV infection and genotypes (type 16 and 18) were examined from all samples by means of Real Time Polymerase Chain Reaction (PCR) using type specific primer (E7 protein).

Results: We found that HPVs were present in 25 (41.7%) cases. HPV type 16 was detected in 24 (96%) cases and both type 16 and 18 in only one (4%) case. Rectum was the commonest site of involvement (12/48%) followed by sigmoid colon (8/32%), caecum (3/12 %) and other sites (2/8%). Regarding histological type, out of 25 cases, 21 (84%) cases of adenocarcinoma, 3 (12%) cases of signet ring carcinoma and only 1 (1.6%) case of mucinous carcinoma were positive for HPV.

Conclusions: HPVs were present in colorectal carcinoma in the Bangladeshi population and HPV type 16 is a more frequent type.

(3) Abstract PS-02-02 (page 111-2)

Due to the unforeseen circumstances that influenced the need minor changes to the programme of the 2nd Macedonian Congress of Pathology, the Scientific Committee decided that the abstract entitled **Histopathological and immunohistochemical examination of the colon of rats with TNBS-induced colitis after administration of functional food containing microencapsulated symbiotic** by *Gjurovski I, et al.* originally accepted for poster presentation (PS-02-02, page 111-2) will be presented as Oral Free Presentation (OF06, page 91) as a part of the oral free presentation session of Gastrointestinal Pathology scheduled for September 2, 2016. The correct abstract is below:

OF06

Histopathological and immunohistochemical examination of the colon of rats with TNBS-induced colitis after administration of functional food containing microencapsulated symbiotic

Ivica Gjurovski[1], Tanja Petreska-Ivanovska[2], Trpe Ristoski[1], Lidija Petrushevska-Tozi[2], Kristina Mladenovska[2], Slavica Kostadinova-Kunovska[3]

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Objective: This work evaluates the effects of Lactic acid bacteria on the trinitrobenzene-sulphonic acid (TNBS) induced colitis in rats by histopathological and immunohistochemical analyses after oral administration of functional food product containing microencapsulated probiotic L. casei 01 and prebiotic oligofructose-enriched inulin (Synergy 1).

Material and Methods: Eighteen female Wistar rats were divided in three groups (180-250 g, 10-14 weeks old). The control group only recived drinking water and plain ayran. TNBS colitis was induced in the other two groups by rectal administration of 30 mg/kg TNBS. One group recived only plain ayran and the other recived ayran containing encapsulated synbiotic. Samples of the colon were fixed in 10% neutral buffered formalin, embedded in paraffin and cut with microtome on 3-4 μm thick sections. Slides for histopathology were stained with haematoxylin and eosin (H&E). CD3 and CD20 monoclonal antibodies with En Vision visualisation kit (DakoChemMate, Denmark) were used for immunostaining of the tissue sections.

Results: The histopathological examination showed better preserved mucosa of the colon tissue in rats treated with encapsulated synbiotic compared to the non-treated group which showed inflammation and ulceration of the mucosa and submucosa. The control group and the one treated with encapsulated synbiotic showed reduced concentration of CD3 and CD20 positive cells in the mucosa and submucosa compared to the non-treated group.

Conclusions: The histopathological and immunohistochemical examination of the colon revealed the anti-inflammatory effect of the ayran containing microencapsulated synbiotic.

MOVED & CHANGE OF PRESENTING AUTHOR

(1) Abstract PS-02-15 (page 115)

Due to the unforeseen circumstances that influenced the need minor changes to the programme of the 2nd Macedonian Congress of Pathology, the Scientific Committee decided that the abstract entitled **The influence of helicobacter pylori pathogen proteins in human gastric pathology** by *Petrov J, et al.* originally accepted for poster presentation (PS-02-15, page 115) will be presented as Oral Free Presentation (OF04, page 91) as a part of the oral free presentation session of Gastrointestinal Pathology scheduled for September 2, 2016. In addition, **Snezana Stojkovska** will be the presenting author instead of Jordan Petrov. The correct abstract is below:

OF04

The influence of helicobacter pylori pathogen proteins in human gastric pathology

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Objective: Helicobacter pylori bacterium is one of the most common infective pathogens in the World. It is associated with numerous gastric disorders such as peptic ulcer, autoimmune gastritis, gastric cancer etc. There are different diagnostic approaches but most promising one is immunoblotting. In our study, we tried to find an association between different bacterial pathogens (proteins) and different gastric diseases.

Material and Methods: We tested blood samples from 60 patients in which helicobacter pylori infection was previously confirmed with ELISA test, fecal antigen test, and gastroscopy. Complete blood count and Immunoblot test with bands for urease, CagA, VacA and four outer membrane proteins (Testline, Czech Republic) were performed.

Results: In 30 patients only helicobacter pylori infection was present and they had no gastric lesions. Twenty patients had chronic gastritis, 8 had gastric ulcer and 2 had gastric cancer. The immunoblot test was positive in all 60 patients. 16 patients the majority of which were with chronic gastritis had low MCV and hemoglobin levels which indicated iron deficiency anemia. These patients also had a positive band for 33 KdA outer membrane protein (OipA). Both patients with gastric cancer had two positive bands for CagA and VacA.

Conclusions: In conclusion, helicobacter pylori infection in this study was associated with iron losing, while positive bands for CagA and VacA were associated with gastric cancer. Thus, positive bands for CagA and VacA may represent gastric cancer markers and should be included in further studies of patients with helicobacter pylori infection.

NOTE: All the above-mentioned corrections are included in the Final Programme of the 2nd Macedonian Congress of Pathology with International Participation.