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## SPECIJALNA SESIJA: SESIJA SPECIJALIZANATA
## SPECIAL SESSION: RESIDENTS SESSION

### Primena transkripcionih faktora u reklasifikaciji „null-cell“ neuroendokrinih tumora hipofize

*Milena Mihajlović[1], Sandra Pekić[2], Mirjana Doknić[2], Dragana Miljić[2], Marko Stojanović[2], Zvezdana Jemuović[2], Milan Petakov[2], Emilija Manojlović Gačić[3]*

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**Cilj:** Utvrđivanje značaja primene transkripcionih faktora adenohipofize u histopatološkoj dijagnostici neuroendokrinih tumora hipofize (engl. Pituitary neuroendocrine tumors - PitNET). **Uvod:** Klasifikacija PitNET se zasniva na detekciji linije diferencijacije ćelija od kojih vode poreklo. U SF1 liniju diferencijacije spadaju gonadotrofni tumori, u PIT1 liniju spadaju somatotrofni, laktotrofni i tirotrofni tumori, dok u TPIT liniju diferencijacije spadaju kortikotrofni tumori. PitNET kojima nije prepozata linija diferencijacije se nazivaju „null-cell“ tumori. **Materijal i metode:** Studijom su obuhvaćeni pacijenti kojima je postavljena dijagnoza „null-cell“ PitNET u periodu pre uvođenja antitela na transkripcione faktore adenohipofize u rutinsku dijagnostičku proceduru. Od 186 pacijenata operisanih na klinici za Neurohirurgiju Univerzitetskog kliničkog centra Srbije u periodu od 2016. godine do 2019. godine, dijagnoza „null-cell“ PitNET je postavljena kod 58 (31,2%) pacijenata aplikacijom antitela na hormone adenohipofize. Od tkiva tumora ovih pacijenata je napravljen tkivni mikroniz, koji je imunohistohemijski obojen transkripcionim faktorima SF1, TPIT i PIT1, nakon čega je izvršena reklasifikacija „null-cell“ tumora. **Rezultati:** Ekspresija SF1 je uočena kod 46/58 tumora (79.3%), ukazujući na rekasifikaciju u gonadotrofne tumore. TPIT ekspresija kod 3/58 tumora (5.2%) je ukazala da PitNET treba reklasifikovati u grupu kortikotrofnih tumora. Dva tumora sa PIT1 ekspresijom su reklasifikovana u somatotrofne tumore (3.4%). Ekspresija transktipcionih faktora je odsutna kod 7 (12.1%) tumora. **Zaključak:** Primena transkripcionih faktora u rutinskoj dijagnostičkoj proceduri PitNET uzrokovalo je precizniju klasifikaciju i smanjenje zastupljenosti „null-cell“ tumora hipofize.

**Ključne reči: PitNET, transkripcioni faktori, SF1, TPIT, Pit1**

### Transcription factors application in reclassification of null-cell pituitary neuroendocrine tumors

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**Objective:** Recognition of the significance of the application of anterior pituitary transcription factors in the histopathological diagnosis of pituitary neuroendocrine tumors (PitNET). **Introduction:** The classification of PitNETs is based on the detection of the lineage of differentiation. The SF1-lineage includes gonadotroph tumors, the PIT1-lineage comprises somatotroph, lactotroph and thyrotroph tumors, and the TPIT-lineage represents corticotroph tumors. PitNETs without expression of transcription factors are classified as “null-cell” tumors. **Material and Methods:** The study included patients diagnosed with null-cell PitNET in the period before the introduction of antibodies to transcriptional factors of the adenohypophysis in a routine diagnostic procedure. Out of 186 patients operated on at the Neurosurgery Clinic of the University Medical Center of Serbia in the period from 2016 to 2019,

the diagnosis of "null-cell" PitNET was made in 58 (31.2%) patients using antibodies to anterior pituitary hormones. Tissue microarray (TMA) was made of the tumor tissue of these patients. Slides from TMA were treated immunohistochemically with antibodies for the transcription factors SF1, TPIT and PIT1. Reclassification of the null-cell tumor was performed. **Results:** SF1 expression was observed in 46/58 tumors (79.3%), indicating reclassification into gonadotroph tumors. TPIT expression in 3/58 tumors (5.2%) indicated that PitNET should be reclassified to the group of corticotroph tumors. Two tumors with PIT1 expression were reclassified as somatotroph tumors (3.4%). Expression of transcription factor was absent in 7 (12.1%) tumors. **Conclusion:** The use of transcription factors in the routine diagnostic procedure PitNET has caused a more precise classification and reduced the incidence of "null-cell" pituitary tumors.

**Key words: PitNET, transkription factors, SF1, TPIT, Pit1**

## Prognostički značaj ekspresije GATA3 i KI-67 u urotelnom karcinomu mokraćne bešike

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**Cilj:** Cilj ove studije je definisanje prediktivnog značaja zajedničke ekspresije GATA3 i Ki-67 u urotelnom karcinomu. **Uvod:** Urotelni karcinom je najčešće dijagnostikovana maligna neoplazma mokraćne bešike u kliničkoj i patohistološkoj praksi, gde klinički i patohistološki prognostički faktori imaju značajnu ulogu. Jedan od najznačajnijih patohistoloških prognostičkih faktora je intenzitet imunohistohemijskog bojenja. Među različitim imunohistohemijskim markerima za koje je dokazano da imaju uticaj na progresiju bolesti i preživljavanje pacijenta, zajednička uloga Ki-67 i GATA3 u predikciji prognoze bolesti nije još u potpunosti razjašnjena. **Materijal i metode:** 80 pacijenata je učestvovalo u studiji, pri čemu su formirane 4 grupe na osnovu patološkog stadijuma urotelnog karcinoma. Nakon upotrebe navedenih antitela, intenzitet bojenja je analiziran semikvantitativno. **Rezultati:** Statistička značajnost je dokazana između histološkog tipa, patološkog stadijuma i invazivnosti i različitog stepena ekspresije GATA3, kao i statistička značajnost između histološkog tipa i patološkog stadijuma i različitog stepena ekspresije Ki-67. Regresioni model je pokazao nisu prediktivnu vrednost zajedničke ekspresije GATA3 i Ki-67. Takođe je dokazana statistička značajnost između patološkog stadijuma i invazivnosti tumora pri analizi preživljavanja. **Zaključak:** Predikcija vrednost zajedničke ekspresije GATA3 i Ki-67 je rezultovala kao niskom vrednošću, ali je, prema literaturi, ovo prva studija koja ispituje prediktivni značaj navedenih antitela u uzorcima biopsije i transuretralne resekcije.

**Ključne reči: urotelni karcinom, biopsija, transuretralna resekcija, GATA3, Ki-67**

## Predictive value of GATA3 and Ki-67 expression in urothelial carcinoma of urinary bladder

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**Objective:** The aim of this study was to determine the predictive value of GATA3 and Ki-67 mutual expression in urothelial carcinoma. **Introduction:** Urothelial carcinoma is the most commonly diagnosed malignancy of urinary bladder in clinical and pathohistological practice where clinical and pathohistological prognostic factors play significant role. One of the most important pathohistological prognostic factors is the intensity of immunohistochemical staining. Among various immunohistochemical markers that have been proven to influence disease progression and patient's survival, role of Ki-67 and GATA3 in prediction of disease prognosis has not been completely clarified yet. **Material and Methods:** 80 patients were included in this study, where 4 groups were formed based on the pathological stage of urothelial carcinoma. After using preferred antibodies, their staining intensity was analyzed semiquantitatively. **Results:** Results showed that there was statistically important significance between type of urothelial carcinoma, pathological stage and invasiveness and different grades of GATA3 expression, as well as statistically important significance between type of urothelial carcinoma and pathological stage and different grades of Ki-67 expression. The regression model showed low value of GATA3 and Ki-67 mutual expression. There was also a statistical significance considering pathological stage and invasiveness of the tumor in survival analysis. **Conclusion:** Predictive value of GATA3 and Ki-67 mutual expression resulted as low from this study, but to our knowledge it was the first one to examine their predictive capability on biopsy and transurethral resection specimens.

**Key words: urothelial carcinoma, biopsy, transurethral resection, GATA3, Ki-67**

## Senzitivnost i specifičnost IgG4 imunohistohemijskog bojenja za dijagnozu idiopatske membranske nefropatije

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**Cilj:** U ovoj studiji želeli smo da ispitamo učestalost, distribuciju i obrazac IgG4 imunohistohemijske pozitivnosti kod pacijenata sa idiopatskom i sekundarnom formom MN, kao i da odredimo senzitivnost i specifičnost pozitivnog IgG4 nalaza za dijagnozu idiopatske forme bolesti. **Uvod:** Membranska nefropatija (MN) predstavlja hroničnu formu glomerulonefritisa koja se patohistološki karakteriše subepitelnim taloženjem IgG depozita imunoglobulina u glomerulima, a može biti idiopatska ili sekundarna. Do sada nije identifikovan nijedan pouzdan biomarker koji bi se mogao koristiti u diferencijalnoj dijagnozi idiopatske i sekundarne forme bolesti. Brojne dosadašnje studije ukazale su da je IgG4 dominatna subklasa koja se detektuje kod idiopatske MN, a koja se uglavnom ne sreće u sekundarnim formama MN. **Materijal i metode:** U studiji je korišćeno 50 biopsija bubrega (18 idiopatskih i 32 sekundarne MN). Na isečcima tkiva iz parafinskih kalupa, urađeno je imunohistohemijsko bojenje korišćenjem IgG4 antitela (IGHG4/1345, Abcam, 1: 100). Sitnozrnasti depoziti IgG4 istaloženih duž glomarularne bazalne membrane, detektovani metodom imunohistohemije, označeni su kao pozitivan rezultat. **Rezultati:** IgG4 bio je eksprimiran u glomerulima kod 16/18 idiopatskih MN, kao i kod 7/32 sekundarnih MN. Pacijenti sa sekundarnim MN kod kojih je detektovan IgG4 imali su dijagnostikovanu neku od plazmaćelijskih diskrazija ili IgG4- related disease. Odsustvo ekspresije IgG4 bilo je udruženo sa drugim sekundarnim uzrocima, kao što su lupus nefritis ili maligna ne-hematološka oboljenja. Dva pacijenta imala su negativan IgG4 i u trenutku dijagnoze MN nisu imali identifikovan nijedan potencijalni sekundarni razlog za nastanak oboljenja. Ovi rezltati ukazuju da je senzitivnost IgG4 pozitivnog nalaza za dijagnozu idiopatske forme MN bila 88,9%, dok je specifičnost iznosila 78,1%. **Zaključak:** IgG4 sitnozrnasti depoziti duž glomerularne bazalne membrane prisutni su kod 89% pacijenata sa idiopatskom formom bolesti, ali i u određenoj populaciji pacijenata sa sekundarnim MN (22%).

**Ključne reči: idiopatska membranska nefropatija, sekundarna membranska nefropatija, IgG4**

## Sensitivity and specificity of IgG4 immunohistochemistry for diagnosis of idiopathic membranous nephropathy

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**Objective:** In this study, we wanted to examine the frequency, distribution and the pattern of IgG4 immunohistochemical positivity in patients with idiopathic and secondary MN, and thus to determine the sensitivity and specificity of this biomarker in diagnosis of idiopathic MN. **Introduction:** Membranous nephropathy (MN) is a chronic glomerulonephritis, pathologically characterized with the subepithetial IgG deposits within glomeruli, and can be idiopathic or secondary. No reliable biomarker has yet been identified that could be used in the differential diagnosis of idiopathic and secondary forms of the disease. Numerous studies have shown that IgG4 is the dominant IgG subclass in glomerular immune deposits in idiopathic MN, which is usually absent in secondary MN. **Material and methods:** 50 kidney biopsies (18 idiopathic and 32 secondary MN) were used in the study. Immunohistochemical staining of IgG4 was performed from on paraffin sections (IGHG4/1345, Abcam, 1: 100). A positive glomerular IgG4 immunohistochemical staining was noted in all cases where fine-granular antibody deposits were observed along the glomerular basement membrane. **Results:** The IgG4 marker was expressed in glomeruli in 16/18 idiopathic MN and in 7/32 secondary MN. Among secondary MN with positive IgG4, patients had known haematological/immunological disorders (plasma cell dyscrasias or IgG4- related disease). The absence of IgG4 was related to all other known secondary causes of

MN (systemic lupus erythematosus or malignant non-haematological diseases). Two negative IgG4 patients without any evidence of secondary cause at the time of diagnosis, should be carefully followed for possible upcoming malignant disease. Overall, the sensitivity of IgG4 for the diagnosis of idiopathic MN was 88.9%, while the specificity was 78.1%. **Conclusion:** IgG4 glomerular deposits are observed in the majority of idiopathic MN (89%), but also in the subset of secondary MN (22%).

**Key words: idiopathic membranous nephropathy, secondary membranous nephropathy, IgG4**

## Aristolohična kiselina I kao uzročnik toksične nefropatije na animalnom modelu

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**Cilj:** Utvrditi histomorfološke, imunohistohemijske i biohemijske karakteristike oštećenja bubrega kod miševa u modelu toksične nefropatije izazvane aristolohičnom kiselinom I. **Uvod:** Nefrotoksin aristolohična kiselina I je supstanca odgovorna za nefropatiju koja nastaje usled korišćenja herbalnih preparata za mršavljenje. Pored toga predstavlja jednog od glavnih potencijalnih ekotoksikoloških uzroka za nastanak balkanske endemske nefropatije. **Materijali i metode:** U eksperimentu je korišćeno 64 miševa soja NMRI koji su podeljeni u tri grupe: grupa koja je dobijala aristolohičnu kiselinu I rastvorenu u polietilen glikolu (PEG) u dozi od 10 mg/kg telesne mase (n=32), grupa koja je dobijala 2,5% PEG 400 (n=16) i kontrolna grupa koja je dobijala fiziološki rastovor (n=16). Sve životinje su tretirane intraperitonealno svakodnevno tokom sedam dana. U narednih 60 dana, određenim danima je sakupljan dvadesetčetvoročasovni urin i krv za biohemijske analize. Na tkivu bubrega su sprovedene histohemijske, imunohistohemijske i morfometrijske analize. Dobijeni rezultati su testirani adekvatnim statističkim metodama i prikazani su tabelarno i grafički. **Rezultati:** Nakon intraperitonealne aplikacije, aristolohična kiselina I izaziva značajno oštećenje bubrežnog parenhima - u ranoj fazi u vidu akutne tubulske nekroze proksimalnih tubula, a u kasnijoj fazi u vidu hroničnog intersticijalnog nefritisa sa obilnim mononuklearnim infiltratima uz postojanje blage intersticijalne fibroze. Pri aplikaciji 2,5% PEG 400 i fiziološkog rastvora ne dolazi do vidljivog oštećenja bubrežnog parenhima. Kod eksperimentalnih životinja je morfometrijskim metodama utvrđen veći stepen bubrežnog oštećenja tubulointersticijuma u odnosu na kontrolne grupe. Biohemijske analize kod eksperimentalnih životinja su pokazale veće koncentracije serumske uree nego kod kontrolnih grupa. **Zaključak:** Aristolohična kiselina I predstavlja izuzetno nefrotoksično jedinjenje koje izaziva izrazite promene tubulointersticijuma kao i početak hronične bubrežne insuficijencije kod miševa.

**Ključne reči: aristolohična kiselina I, nefrotoksičnost, miševi, imunohistohemija, biohemija**

## Aristolochic acid I as a causative agent in an animal model of toxic nephropathy

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**Objective:** To determine histomorphological, immunohistochemical and biochemical characteristics of kidney injury in mice model of toxic nephropathy caused by aristolochic acid I. **Introduction:** Nephrotoxin aristolochic acid I is a substance responsible for nephropathy caused by herbal weight loss products. In addition, it is one of the potential ecotoxicological causes of Balkan endemic nephropathy. **Material and Methods:** In this study, 64 mice of the NMRI strain were used and divided into three groups: the group that received aristolochic acid I dissolved in PEG at a dose of 10 mg/kg body weight (n = 32), the group that received 2.5% PEG 400 (n = 16) and a control group receiving saline (n = 16). All animals were treated intraperitoneally daily for seven days. In the next 60 days, within several different euthanasia time points, twenty-four hours urine and blood were collected for biochemical analysis. Histochemical, immunohistochemical and morphometric analyzes were performed on kidney tissue. The obtained results were tested by adequate statistical methods and are presented in tables and graphs. **Results:** After intraperitoneal application, aristolochic acid I causes significant damage to the renal parenchyma - in the early phase in the form of acute tubular necrosis of the proximal tubules, and the later phase in the form of chronic interstitial nephritis with abundant mononuclear infiltrates with mild interstitial fibrosis. With 2.5% PEG 400 and saline, there is no visible damage to the

renal parenchyma. In experimental animals, morphometric methods showed a higher degree of renal tubulointerstitial damage compared to control groups. Biochemical analyzes in experimental animals showed higher serum urea concentrations than in control groups. **Conclusion:** Aristolochic acid I is a highly nephrotoxic compound that causes marked changes in the tubulointerstitium and the onset of chronic renal failure in mice.

**Key words: aristolochic acid I, nephrotoxicity, mice, immunohistochemistry, biochemistry**

## Sarkomatoidna varijanta duktalnog karcinoma parotidne žlezde: prikaz slučaja sa pregledom literature

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**Cilj:** Ovde opisujemo jedan slučaj sarkomatoidne varijante duktalnog karcinoma parotidne žlezde i poredimo ga sa slučajevima opisanim u literaturi. Duktalni adenokarcinomi pljuvačnih žlezda su retki tumori, koji čine 1-3% karcinoma pljuvačnih žlezda. U varijanti označenoj kao sarkomatoidna se, pored karakterističnog kribriformog i/ili solidnog tumorskog tkiva koje podseća na duktalni karcinom visokog gradusa, nalazi i vretenastoćelijska komponenta. Zbog malog broja slučajeva opisanih u literaturi, o ovom tumoru se još uvek malo zna, zbog čega je važno prikazati svaki dijagnostikovani slučaj. **Prikaz slučaja:** Prikazujemo slučaj 78-ogodišnjeg muškarca sa bezbolnim potkožnim izraštajem desne parotidne regije. Mikroskopski, nalazi se tumor dualne morfologije, sačinjen iz epiteloidne i sarkomatoidne komponente. Epiteloidnu komponentu čine duktalne strukture u kribriformnom obrascu, dok se u sarkomatoidnoj komponenti nalaze atipične vretenaste ćelije sa povećanim brojem mitoza, brojni vaskularni ogranci i višejedarne tumorske džinovske ćelije. Imunohistohemijski, ćelije epiteloidne komponente su pozitivne na CK, CK7, Her2Neu i fokalno na p63, dok su vretenaste ćelije sarkomatoidne komponente pozitivne na vimentin i αSMA, fokalno i na S100 i p63. Ki-67 antitelo boji do 10% jedara ćelija epiteloidne komponente i do 20% jedara vretenastih ćelija. **Zaključak:** Histološke i imunohistohemijske karakteristike ovog slučaja sarkomatoidne varijante duktalnog karcinoma parotidne žlezde poklapaju se sa slučajevima opisanim u literaturi.

**Ključne reči: duktalni karcinom pljuvačne žlezde, sarkomatoidna varijanta, parotidna žlezda**

## Sarcomatoid variant of the parotid gland ductal carcinoma: a case report with literature review

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**Objective:** Here we describe one case of sarcomatoid variant of parotid gland ductal carcinoma and compare it with the cases found in the literature.Salivary gland ductal adenocarcinomas are rare tumors comprising 1-3% of salivary duct carcinomas. In one variant, designated as sarcomatoid, in addition to the characteristic cribriform and/or solid tumor growth pattern reminiscent of the high-grade ductal carcinoma there is also a malignant spindle-cell component. Due to a small number of cases described in the literature, there is still a lot unknown about this tumor, which is why it is important to present each diagnosed case. Case report: We present a case of a 78-year-old man presenting with a painless subcutaneous growth of the right parotid region. Microscopically, tumor is characterized by dual morphology, and is composed of epitheloid and sarcomatoid components. The epitheloid component consists of ductal structures in cribriform growth patter, while the sarcomatoid variant contains atypical spindle cells with increased number of mitoses, numerous vascular branches and multinucleated tumor giant cells. Immunohistochemically, cells of the epitheloid component show positivity for CK, CK7, Her2Neu and focally p63, while the spindle cells are positive for vimentin and aSMA and focally for both S100 and p63. The Ki67 antibody stains up to 10% of the nuclei of the cells of the epithelial component and up to 20% of the nuclei of the spindle cells. **Conclusion:** Histological and immunohistochemical characteristics of one case of sarcomatoid variant of parotid gland ductal carcinoma presented here coincide with those of the cases described in the literature.

**Key words: ductal salivary gland carcinoma, sarcomatoid variant, parotid gland**

## SPECIJALNA SESIJA - KATEDRA ZA PATOLOGIJU MEDICINSKOG FAKULTETA UNIVERZITETA U NIŠU
## SPECIAL SESSION - PATHOLOGY DEPARTMENT, FACULTY OF MEDICINE, UNIVERSITY OF NIŠ

### Transformišući faktor rasta beta 1 u urotelnom karcinomu mokraćne bešike

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**Cilj**: Cilj ovog istraživanja bila je analiza ekspresije TGF-β1 i ispitivanje njenog značaja u urotelnom karcinomu mokraćne bešike. **Uvod:** Karcinom mokraćne bešike je najčešća maligna neoplazma urinarnog trakta i deveti po učestalosti maligni tumor u svetu. Zbog potrebe za doživotnim praćenjem, cistoskopskim kontrolama i lečenjem rekurentne bolesti, karcinom bešike predstavlja značajno ekonomsko opterećenje za zdravstveni sistem. Urotelni karcinom čini preko 90% karcinoma mokraćne bešike. Obuhvata dva različita entiteta sa posebnim molekularnim svojstvima i kliničkim ponašanjem: ne-mišićno invazivni (superficijalni) i mišićno invazivni urotelni karcinom. Superficijalni tumori bešike, ograničeni na mukozu ili sa infiltracijom subepitelnog vezivnotkivnog sloja, odlikuju se čestom pojavom recidiva (50-70%), dok je progresija retka, a petogodošnje preživljavanje oko 90%. Mišićno invazivni urotelni karcinom se najčešće dijagnostikuje de novo i karakteriše se čestim razvojem metastatske bolesti, sa dužinom preživljavanja 12-15 meseci. Nedavnim studijama genomske ekspresije utvrđeno je da urotelni karcinom obuhvata brojne molekularne podtipove, stratifikovane na osnovu kompleksnog mutacionog pejzaža sa alteracijama u mnogobrojnim genima i signalnim putevima, koji prevazilaze tradicionalnu podelu na osnovu gradusa i stadijuma bolesti. Nova saznanja o molekularnim karakteristikama i heterogenosti urotelnog karcinoma otvaraju nove mogućnosti za prognozu, praćenje bolesti i personalizovanu terapiju. Transformišući faktor rasta beta (TGF-β) je multifunkcionalni citokin i plejotropni faktor rasta, sa brojnim ključnim ulogama u ćelijskoj proliferaciji, diferencijaciji, migraciji, adheziji, imunskom odgovoru i ćelijskoj smrti. U ranim fazama karcinogeneze TGF-β je moćni inhibitor tumorskog rasta. Međutim, tokom tumorske progresije, povećana ekspresija TGF-β u ćelijama tumora, kao i parakrino u stromalnim ćelijama, intenzivno je uključena u tumorsku invaziju i metastaziranje. Pored dobro opisane uloge u epitelno-mezenhimnoj tranziciji, TGF-β je jedan od najpotentnijih regulatora apoptoze. Klasična TGF-β signalizacija odvija se pomoću intracelularnih posrednika iz Smad familije, koji stvaraju komplekse sa zajedničkim medijatorom Smad4 i, translokacijom u jedro, regulišu ekspresiju gena. Novije studije ukazale su da dejstvo TGF-β uključuje i epigenetske mehanizame regulacije, a da su mutacije u hromatin remodelujućim genima mnogo češće u karcinomu bešike nego u drugim solidnim tumorima. **Materijal i metode:** U ovoj studiji je imunohistohemijski analizirana ekspresija TGF-β1 na parafinskim uzorcima 647 urotelnih karcinoma bešike dobijenih transuretralnom resekcijom i inkorporiranih u tkivne mikroareje, kompleksne parafinske blokove. Analizirana je i ekspresija Smad4, koji ima centralnu ulogu prenosioca signala u klasičnoj TGF-β kaskadi, kao i EZH2, epigenetskog regulatora uključenog u TGF-β1 signalizaciju. Ispitivana je asocijacija ekspresije markera sa kliničko-patološkim parametrima i preživljavanjem pacijenata, kod kojih je srednje vreme praćenja bilo 61 mesec. **Rezultati:** Visoka ekspresija TGF-β1 u urotelnom karcinomu zabeležena je kod 66.5% ispitivanih tumora i bila je značajno povezana sa visokim histološkim gradusom ($p<0.001$) i uznapredovalim patološkim stadijumom tumora ($p<0.001$). Visoka ekspresija TGF-β1 je značajno učestalija u urotelnom karcinomu mokraćne bešike nepušača ($p=0.014$), starijem uzrastu ($p=0.010$) i značajno je povezana sa visokim histološkim gradusom i mišićno invazivnom bolešću ($p<0.001$), dok je redukcija ekspresije TGF-β1 prisutna u tumorima obolelih sa područja endemske nefropatije u odnosu na ostale tumore (0.015). Redukcija/gubitak ekspresije Smad4, prenosioca signala u kanonskoj TGF-β1 signalizaciji, koja je nađena u 52.9% tumora, značajno je povezana sa visokim tumorskim gradusom ($p=0.002$) i patološkim stadijumom ($p<0.001$), skvamoznom diferencijacijom u tumoru ($p=0.015$),

prisustvom carcinoma in situ u okolini infiltrativnog urotelnog karcinoma (p=0.021), kao i sa prisustvom obilnog limfocitog infiltrata u tumorskoj stromi (p=0.008). Visoka ekspresija Smad4 značajno je udružena sa pojavom recidiva (p=0.021). Gubitak ekspresije TGF-β1 u tumoru snažan je prediktor radikalne cistektomije (p=0.008). Kancer-specifični mortalitet direktno je povezan sa visokom TGF-β1 i EZH2 ekspresijom (p<0.001), a značajno inverzno korelira sa ekspresijom Smad4 (p<0.001). Visoka ekspresija TGF-β1 povezana je sa kraćim ukupnim preživljavanjem pacijenata (p=0.005). Ova studija identifikovala je ekspresiju TGF-β1 i EZH2 kao nezavisne prognostičke faktore u urotelnom karcinomu mokraćne bešike, gde visoka ekspresija TGF-β1, kao i i EZH2 u tumoru ukazuje na kraće preživljavanje i lošiju prognozu. **Zaključak:** Produbljivanje saznanja o kompleksnim ulogama i značaju TGF-β1 i analiza ekspresije TGF-β1 u urotelnom karcinomu mokraćne bešike mogla bi da ima važan uticaj na prognostičku stratifikaciju pacijenata i odlučivanje o njihovom lečenju. Analiza i procena imunohistohemijskog statusa TGF-β1 u urotelnom karcinomu mogla bi imati važnu ulogu u identifikaciji pacijenata koji bi imali najviše koristi od personalizovane ciljane terapije usmerene na TGF-β signalnu kaskadu.

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## Kvantitativna imunohistohemijska analiza ekspresije estrogenskih receptora u lobularnom karcinomu dojke: novi pristup

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Jedna od najvažnijih karakteristika karcinoma dojke je pozitivnost na estrogenske receptore (ER), od čega uglavnom zavisi prognoza i odgovor na terapiju[1]. Trenutni imunohistohemijski pristup ima neka ograničenja koja uključuju semikvantitativnu imunohistohemiju i smanjenje punog kvantitativnog potencijala imunohistohemijskih analiza tkivnih uzoraka. Stoga, da bi se dobili adekvatni imunohistohemijski rezultati za kvantifikaciju ceo postupak bojenja treba da bude standardizovan[2].
Cilj je da se uspostavi procedura za fotometrijsku i morfometrijsku analizu imunohistohemijskih parametara karcinoma dojke, koja bi se eventualno mogla koristiti u dijagnostičke svrhe, kao i da se izvrši poređenje sa aktuelnim semikvantitativnim sistemom skorovanja. Semi-kvantitativna analiza ER obojenih preseka tkiva je izvršena u skladu sa smernicama Allred sistema skorovanja[3]. Kvantitativna analiza je izvršena na slikama u softveru ImageJ nakon dekonvolucije boje. Kvantitativna analiza 66 slučajeva invazivnog lobularnog karcinoma dojke uključivala je: procenat ER pozitivnih ćelija, prosečan intenzitet bojenja jedara i kvantitativni ER skor. Za potrebe nesubjektivnog selektovanja jedara ispitivanih karcinoma, korišćen je planimetrijski mrežni "OVERLAY" sistem, koji spomenuti "Image analysis" sistem koristi kao "PLUG IN". Rastojanje između tačaka na kojima se ukrštaju linije mrežnog sistema je ekvivalent izračunatog prosečnog dijametra kancerskih ćelija iz pilot merenja na manjem broju slučajeva (n=30). Ovako definisan mrežni sistem upotrebljen je na svim slikama svih ispitivanih slučajeva. Uz upotrebu svetlosnog pera ocrtana je kontura jedra svake kancerske ćelije koja je bila pogođena nekom od tačaka testnog sistema, makar i u predelu njene citoplazme. Kod svakog analiziranog slučaja je mereno najmanje po 100 jedara. Digitalizovane mikroskopske slike su zatim podvrgnute dekonvoluciji boja, a uz upotrebu dekonvolucionog Landini-evog algoritma koji je inkorporisan kao "PLUG IN" u novije verzije programa Image J[4]. Ovaj algoritam izdvaja iz hematoksilin-DAB (H-DAB) slike, kao jednu od matrica, matricu koja sadrži koloritet koji pripada isključivo DAB hromogenu i ima braon prebojenost. Spomenuta matrica se snima kao osmobitna "TIFF" slika i služi kao supstrat za dalju fotometrijsku analizu slika. Preko ovih slika se zatim učitavaju prethodno snimljeni "outlines", koji predstavljaju granice ranije mrežnim sistemom selektovanih jedara, unutar kojih će se za svako jedro ponaosob fotometrijskim funkcijama izračunati optička gustina ("optical density") (OD). Fotometrijska kalibracija sistema: za potrebe kalibracije optičke gustine u opciji programa "calibrate" korišćena je funkcija "uncalibrated OD" za raspon intenziteta prebojenosti piksela od 0 do 255 i sa eksponencijalnim karakterom. Nakon kalibracije određena je prosečna vrednost optičke gustine svih piksela koji pripadaju u okvirima "outline"-a svakog od selektovanih jedara ponaosob, gde svetliji pikseli teže ka vrednosti 0 (na binarnoj slici bela boja, a na područjima H-DAB slike nespecifično vezanog hematoksilina-plavo), dok tamniji delovi teže ka višim vrednostima, gde je u okviru nekalibrisanog sistema optičke gustine vrednost za crnu 255 maksimalno. Dobijene vrednosti optičke gustine na prethodno opisani način za sva ispitivana jedra svih ispitivanih slučajeva su zatim poslužile za nepristrasno (unbiaset) skorovanje imunohistohemijskog intenziteta prebojenosti jedara na ER receptore. U skladu sa Lambert-Beerovim zakonom količina prisutne boje određena je na osnovu specifične talasne dužine boje, gde je optička gustina (OD) proporcionalna koncentraciji boje. Tako je količina boje linearno zavisna od OD (absorbance). Konverzija u optičku gustinu se dobija kao negativni logaritam za osnovu 10 intenziteta svetlosti detektovane nakon prolaska kroz preparat. Optička gustina je bezdimenziona logaritamska jedinica, gde absorbanca 0 znači da svi fotoni prolaze kroz preparat, OD = 1.0 znači da je absorbovano 90% fotona, a OD = 2.0 da je 99% fotona absorbovano. Imunohistohemijska bojenja mogu pojedinačno da imaju optičku gustinu najviše 1 OD[5]. Skor koji se tiče procentualne zastupljenosti jedara imunohisohemijski "pozitivnih" ili "negativnih" unutar jednog patohistološkog slučaja određivan je tako što je ukupan broj kvantifikovanih jedara po slučaju smatran 100%, a zatim je granica između „pozitivnih" i „negativnih" jedara postavljena u odnosu na vrednost 0,1, što predstavlja 10%

ukupne skale hromogenog intenziteta (optičke gustine) za DAB[6]. Kvantitativni ER skor po svakom ispitivanom slučaju određivan je, slično ASCO preporukama za semikvantitativni skor, zbirom skora prosečnog intenziteta jedara prethodno pomnoženim sa 100 i skorom procentualne zastupljenosti, a zatim deljenjem zbira sa 2.
Korelaciona analiza je pokazala značajnu pozitivnu korelaciju (r=0,886, p<0,001) između subjektivnih semi-kvantitativnih i kvantitativnih ER skorova, sa velikim efektom veličine (d=3,8215). Korelacije između pojedinačnih parametara ukupnog ER skora, % ER pozitivnih jedara i intenziteta boje dobijene dve nezavisne metode pokazuju jaku statistički značajnu korelaciju[2].
Sama procedura se lako može standardizovati, međutim interpretacija rezultata se zasniva samo na vizuelnom subjektivnom sistemu bodovanja kao u Allred sistemu skorovanja[3]. Stoga, predložena metoda dekonvolucije može biti od koristi jer smanjuje intralaboratorijske varijacije i isključuje subjektivnost tokom analize ER. Takođe, primena metode dekonvolucije može biti korisna za razlikovanje graničnih slučajeva ER pozitivnosti, što se može odraziti na hormonsku terapiju.

**Ključne reči: lobularni karcinom dojke, Allredov skoring sistem, estrogenski receptori, kvantitativna analiza**

## Quantitative immunohistochemical analysis of estrogen receptor expression in lobular breast cancer: a new approach

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One of the most important features of breast cancer is estrogen receptor (ER) positivity, where patient's disease prognosis mainly depends on[1]. The current immunohistochemical approach has some limitations which include semiquantitative immunohistochemistry and decrease in full quantitative potential of immuno-probe on tissue samples. Thus, in order to obtain an adequate immunohistochemical results for quantification the entire staining procedure needs to be standardized[2].
We aimed to establish a procedure for photometric and morphometric analysis of BC immunohistochemical parameters that can possibly be used for diagnostic purposes, as well as for comparison with a current semiquantitative scoring system. Semi-quantitative analysis of ER stained tissue sections was performed following Allred scoring system guidelines[3]. The quantitative analysis was performed on pictures in ImageJ software after colour deconvolution. The quantitative analysis of 66 cases of invasive lobular BC included: percent of ER positive cells, average nuclear coloration intensity and quantitative ER score. For the purposes of non-subjective selection of nuclei of examined cancers, a planimetric network "OVERLAY" system was used, which uses the mentioned Image analysis system as "PLUG IN". The distance between the points where the lines of the network system intersect is equivalent to the calculated average diameter of cancer cells from pilot measurements in a small number of cases (n = 30). The network system defined in this way was used in all images of all examined cases. Using a light pen, the contour of the nucleus of each cancer cell that was affected by one of the points of the test system was outlined, even in the area of its cytoplasm. At least 100 nuclei were measured in each analyzed case. Digitized microscopic images were then subjected to color deconvolution, using a deconvolutionary Landini algorithm that was incorporated as "PLUG IN" into newer versions Image J[4]. This algorithm extracts from the hematoxylin-DAB (H-DAB) image, as one of the matrices, a matrix that contains a color that belongs exclusively to the DAB chromogen and has a brown coloration. The mentioned matrix is recorded as an eight-bit "TIFF" image and serves as a substrate for further photometric analysis of images. These images are then loaded with previously recorded "outlines", which represent the boundaries of the previously networked system of selected nuclei, within which the optical density ("OD") will be calculated for each sail by photometric functions. Photometric calibration of the system: for the purpose of optical density calibration, the "uncalibrated OD" function was used in the "calibrate" program option for the pixel color intensity range from 0 to 255 and with exponential character. After calibration, the average value of the optical density of all pixels belonging to the "outline" of each of the selected nuclei were determined individually, where the lighter pixels

tend to 0 (in the binary image white, and in the areas of the H-DAB image of non-specifically bound hematoxylin-blue), while the darker parts tend to higher values, where within the uncalibrated optical density system the value for black is 255 maximum. The obtained values of optical density in the previously described manner for all examined nuclei of all examined cases were then used for „unbiaset" reduction of immunohistochemical intensity of nucleus coloration at ER receptors. According to Lambert-Beer's law, the amount of color present is determined based on the specific wavelength of color, where the optical density (OD) is proportional to the color concentration. Thus, the amount of color is linearly dependent on OD (absorbance). The conversion to optical density was obtained as a negative logarithm based on 10 light intensities detected after passing through the microscopic slide. Optical density is a dimensionless logarithmic unit, where absorbance 0 means that all photons pass through the microscopic slide, OD = 1.0 means that 90% of the photons are absorbed, and OD = 2.0 that 99% of the photons are absorbed. Immunohistochemical stains can have an individual optical density of up to 1 OD[5]. The score on the percentage of immunohysochemically "positive" or "negative" nuclei within a pathohistological case was determined by considering the total number of quantified nuclei per case as 100% and then the limit between "positive" and "negative" nuclei was set in relation to a value of 0.1, which represents 10% of the total chromogenic intensity scale (optical density) for DAB[6]. The quantitative ER score for each examined case was determined, similarly to the ASCO recommendations for the semiquantitative score, by the sum of the average core intensity score multiplied by 100 and the percentage score, and then by dividing the sum by 2.

Correlation analysis revealed significant positive correlation ($r=0.886$, $p<0.001$) between subjective semi-quantitative and quantitative ER scores, with the large effect size ($d=3.8215$). The correlations between individual parameters of the total ER score, % of ER positive nuclei and colour intensity, obtained by two independent methods show strong statistically significant correlation[2].

The procedure itself can easily be standardized, however the results interpretation are based only on a visual subjective scoring system as in Allred scoring system[3]. Therefore, the proposed deconvolution method may be useful because it reduces intralaboratory variations and excludes subjectivity during analysis ER. Also, the application of the deconvolution method can be useful for distinguishing borderline cases of ER positivity, which can be reflected in hormone therapy.

**Key words: lobular breast cancer, Allred scoring system, estrogen receptors, quantitative analysis**

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## Primena morfometrije u diferencijalnoj dijagnozi benignih i malignih tumora pljuvačnih žlezda

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**Cilj:** Često se i u jednom tumoru mogu videti više ćelijskih tipova, tako da je neophodno primeniti dodatna histohemijska i imunohistohemijska bojenja, kao i morfometrijsku analizu tumorskih ćelija u cilju adekvatne dijagnoze. **Uvod.** Tumori pljuvačnih žlezda su relativno retke neoplazme, koje karakteriše visok stepen pleomorfizma i histološkog preklapanja. **Materijal i metode.** Istraživanje je obuhvatilo 60 benignih i 60 malignih tumora, i to pleomorfni adenom (20), Warthin tumor (20), adenom bazalnih ćelija (12), mioepiteliom (8), adenoidno cistični karcinom (12), mukoepidermoidni karcinom (16), karcinom pljuvačnih kanala (12), polimorfni karcinom (12) i mioepitelni karcinom (8). Analizirana je ekspresija Ki67, p53, HER-2, p63, CEA, EMA, S-100, CK14, WT-1, GFAP, αSMA i vimentina. Morfometrijska analiza vršena je u softverkom paketu „ImageJ". Analizirani su: površina, perimetar, Feretov dijametar, integrisana optička gustina, cirkularnost i zaobljenost jedara. **Rezultati.** Proliferativni indeks Ki67 je statistički značajno veći kod malignih tumora (p<0,001). Najveću vrednost je pokazao adenoidno cistični karcinom, a najmanju adenom bazalnih ćelija. Imunohistohemijski, plemorfni adenomi su pozitivni na S-100, GFAP, CK14, αSMA WT1 i EMA. Warthin tumor je pozitivan na CK14, CEA i p63; adenom bazalnih ćelija pokazuje pozitivnost na S-100, CEA i vimentin, dok su mioepitelni tumori pozitivni na vimentin, GFAP, S100, CK14, α-SMA. Adenoidno cistični karcinom pokazuje pozitivnost na CEA i S-100; mukoepidermoidni eksprimira CK14; karcinom pljuvačnih kanala pozitivan na EMA, CEA, p53 i HER-2, dok je polimorfni karcinom niskog gradusa pozitivan na CK14, p63, EMA, S100 i vimentin. Morfometrijska analiza je pokazala statistički značajno povećane vrednosti integrisane optičke gustine (p<0,001) i parametara veličine jedara (p<0,05) kod malignih tumora. Određivanje Ki67 proliferativnog indeksa i morfometrijska analiza integrisane optičke gustine i površine mogu sa velikom preciznošću razlikovati benigne od malignih tumora. Prikazane vrednosti sugerišu dobijene rezultate kao granične (Cut-off) vrednosti. **Zaključak.** Imunohistohemijskom analizom ustanovili smo histogenezu tumora u cilju diferencijacije. Ki67 proliferativni indeks je jako koristan u diferencijaciji benignih od malignih tumora. Morfometrijski parametri integrisane optičke gustine i veličine jedara pokazuju statistički veće vrednosti u grupi malignih tumora.

**Ključne reči: tumori pljuvačnih žlezda, benigni tumori, maligni tumori, morfometrija, imunohistohemija**

## Application of morphometry in differential diagnosis of benign and malignant salivary gland tumors

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**Objective:** Very often, one tumor may contain several cell types, therefore, it is necessary to include additional histochemical and immunohistochemical staining, as well as the morphometric analysis of tumor cells, in terms of an appropriate diagnosis. **Introduction:** Salivary gland tumors are rather rare neoplasms characterized by a high level of pleomorphism and histological overlapping. **Materials and methods:** The research encompassed 60 benign and 60 malignant tumors, including pleomorphic adenoma (20), Warthin's tumor (20), basal cell adenoma (12), myoepithelioma (8), adenoid cystic carcinoma (12), mucoepidermoid carcinoma (16), salivary duct carcinoma (12), polymorphous low-grade carcinoma (12), and myoepithelial carcinoma (8). The expression of Ki67, p53, HER-2, p63, CEA, EMA, S-100, CK14, WT-1, GFAP, αSMA, and vimentin was analyzed. The morphometric analysis was performed using the "ImageJ" software pack. The area, perimeter, Feret diameter, integrated optical density, nucleus circularity, and roundness were analyzed. **Results:** The Ki67 proliferative index was statistically significantly higher in malignant tumors (p<0.001). Adenoid cystic carcinoma exhibited the highest value, whereas the lowest value was exhibited by basal cell adenoma. Immunohistochemi-

cally, pleomorphic adenomas were positive to S-100, GFAP, CK14, αSMA, WT1, and EMA. Warthin's tumor was positive to CK14, CEA, and p63; basal cell adenoma showed positivity to S-100, CEA, and vimentin, whereas myoepithelial tumors were positive to vimentin, GFAP, S100, CK14, αSMA. Adenoid cystic carcinoma exhibited positivity to CEA and S-100, mucoepidermoid carcinoma to CK14, salivary duct carcinoma to EMA, CEA, p53, and HER-2, while polymorphous low-grade carcinoma exhibited positivity to CK14, p63, EMA, S100, and vimentin. The morphometric analysis showed statistically significantly increased values of integrated optical density ($p<0.001$) and nuclear size parameters ($p<0,05$) in malignant tumors. The determination of the Ki67 proliferative index and morphometric analysis of integrated optical density and area can distinguish benign from malignant tumors with great precision. The values shown suggest the obtained results as cut-off values. **Conclusion:** The immunohistochemical analysis was used to determine tumor histogenesis with the aim of differentiation. The Ki67 proliferative index is highly useful in the differentiation of benign from malignant tumors. The morphometric parameters of integrated optical density and nuclear size show statistically higher values in the malignant tumor group.

**Key words: salivary gland tumors, benign tumors, malignant tumors, morphometry, immunohistochemistry**

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## NOTCH3 expression in the clinical follow-up of the urothelial bladder cancer patients

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### Introduction

The NOTCH pathway plays an important role in tumor cells differentiation, further proliferation, and neovascularization[1,2]. This pathway controls tumor cells fate through interactions between neighboring cells, either leading the tumor cells in unstoppable proliferation or entirely opposite, leading them into apoptosis[3]. Disrupted NOTCH activity is a driving event in urothelial bladder cancer (UBC) and NOTCH pathway mutations are equally common in superficial and invasive tumors[4,5]. Recent data revealed that hypoxia mediated NOTCH3 activation participates in tumor cell proliferation, acquisition of the EMT phenotype, squamous and mesenchimal features[6,7]. The aim of this research was to evaluate the immunohistochemical (IHC) expression of NOTCH3 in UBC and to determine its predictive impact on the clinical outcome: UBC-specific, overall, and recurrence-free patients' survival.

### Material and methods

The current study included 614 samples from the primary lesion of UBC patients with pathologic stage pTa to pT4, who had undergone transurethral resection (TUR), partial resection, or radical cystectomy. All cases were diagnosed at the Center for Pathology, University Clinical Center Niš, Serbia, between March 2006 and December 2010. The study was approved by local ethical committee (12-15637-2/6). The patients were diagnosed in pTa (31.1%), pT1 (45.9%), pT2 (17.3%), pT3 (3.9%), and pT4 (1.8%) stage. The accrual period was 4 years, while the follow-up period was 2 years. During that period, patients were monitored for recurrence and mortality.

Samples from 614 paraffin-embedded tissue blocks were extracted by 2 mm needle and incorporated in tissue microarrays. For constructing the microarrays, we chose the parts of the tumor with maximum of the angiogenic activity, according to microvessel density (established with CD34-positive endothelial cells) and high levels of vascular endothelial growth factor (VEGF) and VEGF receptor 1, which we established earlier and published previously[8-11]. After preparation, the slides were processed in a semi-automatic IHC diagnostic system (Ventana Inc.) and the IHC staining was performed using a rabbit polyclonal antibody to NOTCH3 (ab23426, Abcam, Cambridge, UK) at a concentration of 5 μg/ml. Only membranous expression was considered. Intensity scoring was as follows: 0 – for no expression at all; 1 – weak intensity; 2 – moderate intensity; and 3 – strong intensity. The other criterion was the percentage of positive cells as follows: 0 – no positive cells, 1 – up to 20% of positive cells, 2 – >20-50% of positive cells, 3 – >50-80% of positive cells, and 4 – > 80% of positive cells. Considering both criteria, the final IHC score was as follows: 0-2 = negative (0); 3-4 = mild/weak (1); 5 = moderate (2); and 6-7 = strongly positive (3). The samples with negative (0) and weak (1) NOTCH3 IHC score were considered negative, while the samples that showed moderate (2) and strong (3) expression were considered positive.

All analyses were performed with the SPSS statistical package (SPSS v. 20.0, Chicago, USA). Cox regression modeling, univariate and multivariate, was performed to determine the predictive value of various independent variables for patients' survival. The significance of NOTCH3 expression in survival prediction was depicted with Kaplan–Meier curves, $p < 0.05$ was considered statistically significant.

### Results

IHC staining for NOTCH3 showed that the vast majority of the UBCs expressed NOTCH3 (91.5%), at certain degree. The intensity of the membranous expression was semi-quantified (0-3), and the mean degree was 1.81 ± 0.94.

### Overall and recurrence-free survival

The median follow-up in the study group was 45.0 (24.0-64.0) months. During this period, the mor-

tality rate was 42.5%, UBC specific in most of the cases (69.7%). Recurrences occurred in 230 (37.5%) patients, mostly 1 time (58.7%). The median recurrence-free period was 12.0 (0.0-44.0) months. Figure 1 presents the overall survival of UBC patients according to NOTCH3 expression (0-3).

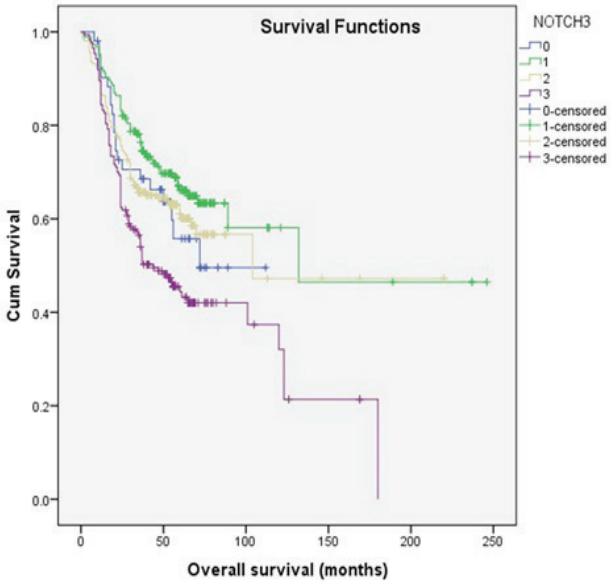


**Figure 1.** Kaplan–Meier survival curves showing overall survival of 614 UBC patients with negative (0=no staining; 1=weak and/or focal staining) and positive (2=diffuse, intermediate staining; 3=strong, diffuse staining) NOTCH3 expression.

Each higher degree of positivity is associated with 1.3 times higher risk of mortality ($p < 0.001$). Concerning UBC-specific survival, each higher degree of positivity was associated with 1.4 higher risk of UBC-specific mortality ($p < 0.001$) (Figure 2).

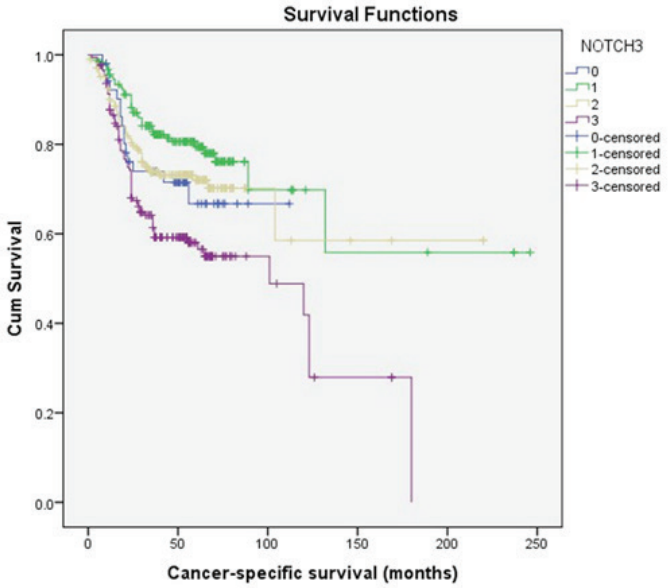


**Figure 2.** Kaplan–Meier survival curves showing UBC-specific survival of 614 UBC patients with negative (0=no staining; 1=weak and/or focal staining) and positive (2= intermediate, diffuse staining; 3=strong, diffuse staining) NOTCH3 expression.

Cox regression model identified NOTCH3 as an independent predictor of UBC-specific mortality ($p < 0.01$). The other independent predictors of UBC-specific survival were pathological tumor stage (HR = 2.520, $p < 0.001$), and the number of recurrences (HR = 0.515, $p < 0.001$). The same independent predictors were found for the overall mortality, as well. NOTCH3 expression was not a statistically significant predictor of recurrence-free survival ($p = 0.816$) (Figure 3).

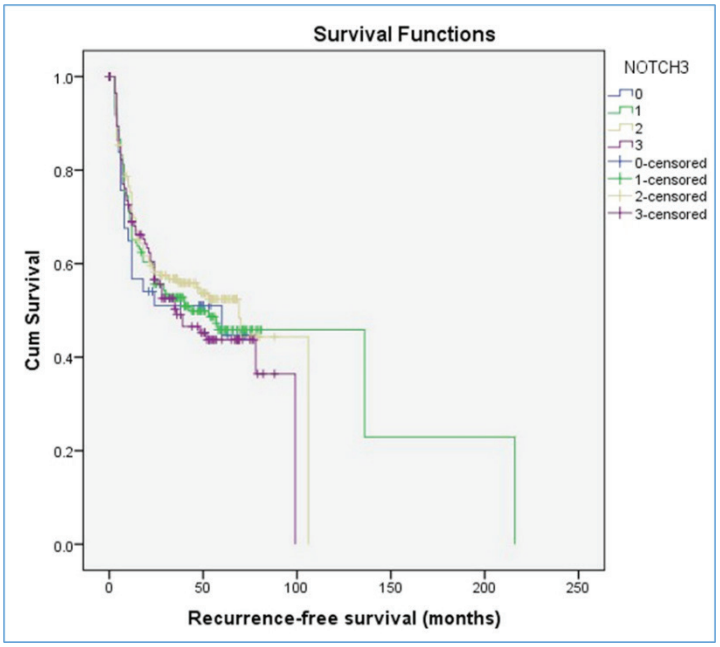


**Figure 3.** Kaplan–Meier survival curves showing recurrence-free survival of 614 UBC patients with negative (0=no staining; 1=weak and/or focal staining) and positive (2=intermediate, diffuse staining; 3=strong, diffuse staining) NOTCH3 expression.

## Discussion

The NOTCH pathway is an intercellular signaling mechanism that controls angiogenesis, cancer cell maintenance, and EMT in the oncological setting. After binding of ligands (DLL1, DLL3, DLL4, JAG1, and JAG2) to their receptors (NOTCH1-4), gamma-secretase cleaves the NOTCH intracellular domain of the transmembrane receptor, and activates NOTCH signaling[12]. Recent studies revealed the clinical significance and targetability of NOTCH signaling for the stage III and IV UBC specimens of patients that had undergone radical cystectomy, and tested for clinical associations including cancer-specific and overall survival. Combinatorial inhibition of NOTCH and MAPK signaling most strongly suppressed tumor growth. NOTCH and MAPK signaling can be repressed with the gamma-secretase inhibitor (GSI) dibenzazepine and the mitogen-activated ERK kinase (MEK)-inhibitor selumetinib[13,14]. The present study showed that NOTCH3 expression cor¬relates with UBC-specific mortality. Zhang et al. found that high NOTCH3 expression was associated with poor patient survival, which is in accordance with our results. The same authors suggested that decreased NOTCH3 expression sensitizes urothelial cancer cells to cisplatin[15]. Over 90% of our specimens showed a certain degree of NOTCH3 expression, suggesting that the NOTCH3 has relevant role in UBC. We evaluated the intensity of NOTCH3 expression in a semi-quantitative manner, which revealed that higher degree of NOTCH3 expression was observed in high-grade tumors and higher degree of positivity associated with higher risk of mortality. We identified NOTCH3 as an independent predictor of poor outcome. Our results indicate that NOTCH3 could be used as a marker of the UBC-specific mortality risk. NOTCH3 expression could be a prognostic IHC marker in select¬ing UBC patients who need to undergo control cystoscopy after a shorter time interval. More data is needed for potential utility in the novel therapy approach.

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## POČASNO PREDAVANJE „Dr. Đorđe Joannović"
## KEYNOTE LECTURE "Dr. Đorđe Joannović"

### Molecular Pathology Today and Tomorrow

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Laboratory tests performed by molecular methods are increasing in volume and complexity at an unprecedented rate. Molecular tests have a broad set of applications, and most recently have been advocated as the mechanism by which providers can further tailor treatments to the individual patient. Since molecular testing continues to increase, pathology practices may find themselves unprepared for the new wave of molecular medicine.

Molecular testing is a well-established yet rapidly developing field of pathology. Pertaining to the diagnostics of DNA, RNA and protein, it assists clinicians and pathologists alike in the diagnosis, prognosis, treatment and management of human diseases. The currently established role of molecular testing in medicine considers the testing of single mutations, single genes or small panels of genes. More extensive analysis of the genome (genomic analysis) is a developing field of pathology.

There are several reasons for change in pathology, such as increasing test repertoire and volume, budget constraints, ageing population with increasing prevalence of chronic diseases (DM, obesity, cancer), as well as new technologies development. Development of new technologies would be beneficial with regard to increasing accuracy of diagnosis, targeting personalized medical treatment, and improving patient outcome. All these facts should be performed by reducing the total Health Care costs and improving results accuracy and quality. A wide spectrum of new technologies could be implemented, such as automation and robotics, miniaturization (micro- and nano-technology), microfluidics, new analytical methods (genomics, proteomics), non-invasive methods (sensors, sweat, saliva, tears), mobile technology, tele-medicine, information technology (radio-frequency identification - RFID, networks, innovative software), and artificial intelligence.

Advances in understanding the molecular basis of rare and common disorders, as well as in the technology of DNA analysis, are rapidly changing the landscape of molecular genetics and genomic testing. High-resolution molecular cytogenetic analysis can now detect deletions or duplications of DNA of a few hundred thousand nucleotides, well below the resolution of the light microscope. Diagnostic testing for "single-gene" disorders can be done by targeted analysis for specific mutations, by sequencing a specific gene to scan for mutations, or by analyzing multiple genes in which mutation may lead to a similar phenotype. The advent of massively parallel next generation sequencing facilitates the analysis of multiple genes and now is being used to sequence the coding regions of the genome (the exome) for clinical testing. Exome sequencing requires bioinformatic analysis of thousands of variants that are identified to find one that is contributing to pathology; there is also a possibility of incidental identification of other medically significant variants, which may complicate genetic counseling. DNA testing can also be used to identify variants that influence drug metabolism or interaction of a drug with its cellular target, allowing customization of choice of drug and dosage. Exome and genome sequencing are being applied to identify specific gene changes in cancer cells to guide therapy, to identify inherited cancer risk, and to estimate prognosis.

Genomic testing may be used to identify risk factors for common disorders, although the clinical utility of such testing is unclear. Genetic and genomic tests may raise new ethical, legal, and social issues, some of which may be addressed by existing genetic nondiscrimination legislation, but which also must be addressed in the course of genetic counseling.

Nanotechnology offers novel materials with new possessions and functions for a variety of biomedical fields such as therapy, diagnostics, drug delivery, tissue engineering and, biosensors. In the nanotechnology field, big things are probable from really small things. The small size of nanomaterials helps

them to interact with biomolecules to enter in different areas of the body by passing through intracellular spaces. Identifying DNA changes associated with cancer using nanotechnology and nanomaterials has recently attained more attention from scientists. However, implementation in the diagnostic molecular pathology has not been widely accepted and would be still investigated, especially in the field of circulated cancer cells analysis, as a non-invasive procedure for patients.

Beside all currently available resources to identify specific molecular alterations underlying disease onset, progression or response to therapy, it seems that all these improvements would be able to completely change disease classification and nomenclature. Indeed, it would be only important to help to treat the underlying conditions based on the molecular alteration, thus disease would be probably named according to the carrying genomic change, rather than based on the organ involvement or on the morphological appearance.

Our future is not only defined by innovations and environment, because our response to all these factors is a key. Targeting education for pathologists about the transformation of pathology practice in the new molecular and digital age is warranted. On the other hand, it is important to assist physicians in recognizing where new approaches to genetic and genomic testing may be applied clinically and in being aware of the principles of interpretation of test results.

The infinity of macrocosmos should implicate the infinity of cellular microcosmos in an opposite direction. Thus, the predictions of our future could be simple, but getting it right is the hard part. It could be that artificial intelligence would help us soon to be more precise in each segment of our life.

## USMENE PREZENTACIJE
## ORAL PRESENTATIONS

### OP-1

### Multicentrični angiomiolipom i incidentalni onkocitom udruženi sa tuberoznom sklerozom: prikaz slučaja

*Nevena Poljašević, Goran Šarkanović, Ivana Čerkez, Zinaida Karasalihović, Elmir Čičkušić, Jasminka Mustedanagić-Mujanović, Mirna Alečković, Lejla Arnautalić*
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**Cilj:** Ovaj prikaz aktualizira diskusiju vezanu za biološki potencijal multicentričnih angiomiolipoma sa zahvatanjem limfnih čvorova. Dodatno, opisuje rijedak slučaj simultanog unilateralnog angiomiolipoma i onkocitoma bubrega. **Prikaz slučaja:** Angiomiolipom je rijedak mezenhimalni tumor sačinjen od masnog tkiva, glatkomišićnih ćelija i abnormalnih krvnih sudova. Iako je definisan kao uglavnom benigan tumor, opisani su rijetki slučajevi agresivnog ponašanja sa malignim potencijalom. Koegzistencija angiomiolipoma i onkocitoma, benignog tumora bubrega, vrlo je rijetka. Mi prikazujemo slučaj tridesetjednogodišnje pacijentice sa istorijom tuberozne skleroze i simultanim postojanjem angiomiolipoma i onkocitoma. Inicijalno je na MRI nalazu dijagnostikovan bilateralni angiomiolipom bubrega i tada je urađena desna nefrektomija zbog rupture tumora. Nakon sedam godina desila se ruptura angliomiolipoma na suprotnom bubregu, a uz njega je otkriven dodatni, agresivni angiomiolipom sa epiteloidnim histomorfološkim karakteristikama na širokom ligamentu, kao i incidentalni onkocitom. **Zaključak:** Pocjena biološkog potencijala agresivnih angiomiolipoma još uvijek nije u potpunosti shvaćena. Javljanje simultanih sinhronih i metahronih tumora sa zahvatanjem limfnih čvorova postavlja pitanje o njihovoj prirodi: multicentričnost ili potencijalne metastaze? Što se tiče koegzistencije sa onkocitomom, samo 17 slučajeva je opisano do sada, što čini ovaj slučaj ekstremno rijetkim.

**Ključne reči: angiomiolipom, onkocitom, biološki pocencijal, tuberozna skleroza**

### Tuberous sclerosis associated multicentric angiomyolipoma and incidental oncocytoma: A case report

*Nevena Poljasevic, Goran Sarkanovic, Ivana Cerkez, Zinaida Karasalihovic, Elmir Cickusic, Jasminka Mustedanagic-Mujanovic, Mirna Alecković, Lejla Arnautalic*
University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

**Objective:** This report actualizes discussion regarding biological potential of multicentric angiomyolipoma with lymph node involvement. Additionally, it describes rare occurrence of simultaneous unilateral kidney angiomyolipoma and oncocytoma. **Case report:** Angiomyolipoma is a rare mesenchymal tumor composed of adipose tissue, smooth muscle cells and abnormal blood vessels. Although defined as usually benign tumor, rare cases of aggressive behavior with malignant potential have been described. Coexistence of angiomyolipoma and oncocytoma, benign renal tumor, is extremely rare. Only 17 cases have been report so far. We report a case of a 31 year old female patient with history of tuberous sclerosis and simultaneous existence of angiomyolipoma and oncocytoma. Initially bilateral kidney angiomyoma had been diagnosed via MRI, and right nephrectomy was performed due to tumor rupture at that time. Seven years later rupture of contralateral kidney angiomyolipoma occurs and additional aggressive angiomyolipoma with epithelioid hystomorphological features of broad ligament with lymph node involvement as well as incidental oncocytoma is discovered. **Conclusion:** The assessment of biological potential of aggressive angiomyolipoma is still not fully understood. Occurrence of simultaneous synchronous and metachronous tumors with lymph node involvement prompts the question about its nature: multicentricity or potential metastasis? Concerning coexistence with oncocytoma, only 17 cases have been described so far, which makes this case extremely rare.

**Key words: Angiomyolipoma, oncocytoma, biological potential, tuberous sclerosis**

## OP-2

## Uticaj ekspresije leptin receptora (LEPR) na proliferaciju i neoangiogenezu u SCC kože

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**Uvod:** Leptin predstavlja snažan adiponektin koji svoje efekte ostvaruje preko transmembranskog receptora za leptin (LEPR). U mnogim malignim tumorima stimuliše rast, migratorni i invazivni potencijal malignih ćelija. Cilj našeg istraživanja je ispitivanje uticaja ekspresije receptora za leptin (LEPR) na indeks proliferacije i mikrovaskularne gustine u skvamocelularnom karcinomu kože (cSCC). **Materijal i metode:** Za istraživanje je korišćen operativni materijal cSCC, dostavljen službi za patohistološku dijagnostiku. Ispitivana grupa obuhvata 62 ekscizione biopsije skvamocelularnog karcinoma kože, dok kontrolna grupa obuhvata 62 biopsije ne tumorskog tkiva kože iz okoline tumora. Nakon rutinske obrade, kalupljenja u parafinske blokove, na presecima debljine 4 μm je primenjeno klasično histohemijsko HE bojenje i imunohistohemijsko ABC bojenje sa anti LEPR, anti Ki67 i anti CD34 antitelima. Nakon evaluacije ispitivanih biomarkera rezultati su obrađivani u statističkom programskom paketu SPSS za Windows 26.0. **Rezultati:** Intracitoplazmatska i intramembranozna ekspresija LEPR je nađena u 96,8% cSCC. Između uzoraka sa različitim brojem ćelija pozitivnih na leptin uočena je statistički značajna razlika ($p \leq 0,05$) u ekspresiji Ki67 i CD34. Najveća ekspresija Ki67 zapažena je kod uzoraka tumorskog tkiva sa izraženom ekspresijom LEPR. U uzorcima sa izraženom ekspresijom LEPR, u 70% slučajeva nađena je visoka ekspresija CD34, dok je kod uzoraka sa umerenom ekspresijom LEPR u 76,7% uzoraka ekspresija CD34 bila niska. Univarijantnom regresionom analizom pokazano je da je kod tumora sa izraženom ekspresijom LEPR 7 puta veća mikrovaskularna gustina i 4 puta veći proliferativni indeks. **Zaključak:** Naši rezultati ukazuju da je ekspresija LEPR prediktor malignog potencijala cSCC, i da se bazirano na ekspresiji LEPR može predvideti ekspresija LEPR; skvamocelularni karcinom kože; proliferativni indeks; neoangiogeneza.agresivan fenotip tumora.

**Ključne reči: ekspresija LEPR; skvamocelularni karcinom kože; proliferativni indeks; neoangiogeneza;**

## Significance of leptin receptor expression (LEPR) on proliferation and neoangiogenesis in cSCC

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**Introduction:** Leptin is a potent adiponectin that functions through its transmembrane receptors (LEPR). In many malignant tumors, it stimulates the growth, migratory and invasive potential of malignant cells. The aim of our work is to examine the significance of LEPR expression on the proliferation index and microvascular density in squamous cell carcinoma of the skin (cSCC). **Material and methods:** The cSCC operative material, delivered to the Pathohistology Department, was used for the research.The study group included 62 excisional biopsies of cSCC, while the control group included 62 biopsies of non-tumor skin tissue from the tumor environment. After routine processing and paraffin molding, classical histochemical HE-staining and immunohistochemical ABC-staining with anti-LEPR, anti-Ki67 and anti-CD34 antibodies were applied at 4 μm thick sections. After the evaluation of the examined biomarkers, results were processed in the statistical software package SPSS for Windows 26.0. **Results:** Intracytoplasmic and intramembrane expression of LEPR was found in 96.8% of cSCCs. A statistically significant difference ($p \leq 0.05$) in Ki67 and CD34 expression was observed between samples with different numbers of leptin-positive cells. Samples with pronounced LEPR expression

had high CD34-expression in 70% of cases, and 76.7% of samples with moderate LEPR expression had low CD34-expression. Univariate regression analysis showed that in tumors with pronounced LEPR expression, microvascular density was 7 times higher and proliferative index 4 times. **Conclusion:** Our results indicate that LEPR expression is a predictor of malignant cSCC potential, and that an aggressive tumor phenotype can be predicted based on it.

**Key words: LEPR expression, skin squamous cell carcinoma, proliferative index, neoangiogenesis**

**OP-3**

## Embolija amnionskom tečnošću kao uzrok smrti porodilje: autopsijski prikaz slučaja

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**Cilj:** Utvrđivanje dijagnoze embolije amnionskom tečnošću pri autopsijskom pregledu porodilje. **Prikaz slučaja:** Prikazujemo slučaj žene stare 32 godine, porođene u 39. gestacijskoj nedelji, kod koje je dva sata nakon porođaja, došlo do pojave bola u grudima, praćenog iznenadnim gubitkom svesti i srčanim zastojem. I pored reanimacije koja je trajala oko dva i po sata došlo je do smrtnog ishoda. Prilikom autopsijskog pregleda utvrđena je gojaznost, uz obostrane edeme ruku i potkolenica. Viđene su subendokradne hemoragije leve komore, dilatacija celog srca, hiperemija i edem pluća, bilateralni hidrotoraks (90 ml), uz subpleuralne hemoragije i znake šoka na bubrezima. Uterus je bio uvećan, sa suturiranim cerviksom. Histopatološkom analizom nađene su promene na više organa. U kardiomicitima leve komore i međukomornog septuma uočeno je intersticijalno krvarenje, uz znakove akutne ishemijske lezije i degenerativnih promena kardiomiocita, dominantno subendokardno. Viđena je izražena hipertrofija kardiomiocita, uz akumulaciju lipofuscina. U lumenu pojedinih arteriola i malih arterija pluća nađeni su mikrotrombi, mucin (alcian blue) i elementi koji imponuju kao keratinske skvame. Interalveolarne septe su bile proširene i infiltrisane mononuklearnim zapaljenskim infiltratom (dominantno CD3+ T-limfociti), sa kongestiranim kapilarima i leukostazom, uz fokuse fibroze i fibrina u organizaciji. U brojnim alveolama i bronhiolama uočene su grupe makrofaga sa smeđim lipopigmentom, uz multijedarne džinovske ćelije i fokuse fibrina sa znacima organizacije. U uterusu nisu nađene značajne promene. **Zaključak:** U prikazanom slučaju sumnja na emboliju amnionskom tečnošću je postavljena na osnovu kliničke slike i makroskopskog autopsijskog nalaza. Dijagnoza je potvrđena histohemijskim bojenjem na mucin kao komponenatu plodove vode u plućnoj cirkulaciji.

**Ključne reči: embolija amnionskom tečnošću, autopsija, imunohistohemija**

## Amniotic fluid embolism as cause of maternal death: A autopsy case report

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**Objective:** Confirming post-mortem diagnosis of amniotic fluid embolism. **Case report:** We report a case of 32-year-old female, in 39th gestational week. Two hours after delivery she experienced chest pain, sudden loss of consciousness and cardiac arrest. Death was pronounced after two and half hours of the reanimation. On gross autopsy decedent was obese, with bilateral arms and legs edema. Further findings included subendocardial hemorrhage of the left cardiac ventricle, dilatation of all four cardiac chambers, hyperemia and edema of lungs, bilateral hydrothorax (90ml), with subpleural hemorrhage

and shock kidneys. Uterus was enlarged with sutures on cervix. Microscopic examination of the left cardiac ventricle and the interventricular septum showed interstitial hemorrhage, with signs of acute ischemic lesion and degenerative changes dominantly subendocardialy. Cardiomyocites were hypertrophied, with lipofuscin accumulations. The lungs demonstrated microtrombi in arterioles and small arteries, mucin (alcian blue), squamous cells-like elements. Interalveolar septa were enlarged, with mononuclear inflammatory infiltrate (predominantly CD3+ T-lymphocytes), congested capillaries, leukostasis, and focuses of fibrosis and fibrin in organization. Macrophages with brown lipopigment, and multinucleated giant cells were detected in multiple alveoles and bronchioles. Significant pathological changes where not observed in uterus. **Conclusion:** In reported case, history and post-mortem examination were suggestive of amniotic fluid embolism. Diagnosis was confirmed by histochemical staining for mucin as a component of amniotic fluid elements in pulmonary circulation.

**Key words: amniotic fluid embolism, autopsy, immunohistochemical staining**

## OP-4

## Prognostički značaj ekspresije IGF-1R u karcinomu dojke kod žena sa diabetes mellitusom

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**Cilj:** Korelacija ekspresije receptora insulinu sličnog faktora rasta 1 (IGF-1R) sa osnovnim histološkim i imunohistohemijskim prognostičkim parameterima za karcinom dojke kod oboljelih od diabetes mellitusa (DM2) sa ekspresijom kod osoba bez metaboličkog poremećaja. **Uvod:** IGF-1R zajedno sa hormonskim receptorima regulise razvoj i diferencijaciju tkiva dojke. Visoka koncentracija insulina i receptora IGF-1 kod gojaznih osoba sa metaboličkim sindromom može biti povezana sa povećanim rizikom obolijevanja od karcinoma dojke i parametrima loše prognoze kod karcinoma dojke. **Materijali i metode:** Od ukupno 130 žena koje su liječene od karcinoma dojke (stadijum I – III), preoperativno dijagnostikovan DM2 je imalo 14 (10,8%) žena. Parafinski blokovi u formalinu fiksiranog tumorskog tkiva korišteni su za imunohistohemijsku vizualizaciju receptora: IGF-1R, estrogen receptora (ER), progesteron receptora (PR) i receptora humanog epidermalnog receptora (HER-2). Podaci su analizirani u statističkom programu SPSS verzija 17., uz primjenu uparenog t-testa. Preživljavanje do progresije bolesti (RFS) je ispitivan Kaplan-Meierovom krivom, a različitost između ispitivanih varijabli ispitivan je Log-Rank testom. **Rezultati:** Oboljeli od DM2 su imali veći stadijum tumorske bolesti (p=0.038), veći broj metastaski izmenjenih limfnih čvorova (p=0.019), dijametar tumora (p=0.039), ekspresiju ER (p=0.001), IGF-1R (p=0,039) i multiple tumore dojke (p=0.036). Log –Rank test je pokazao da su na vrijeme do progresije bolesti (RFS) uticali: DM2 (p=0.023), stadijum bolesti (p=0.039) i ekspresija HER-2 (p=0.033). **Zaključak:** Dijabetes mellitus tip 2 kod oboljelih od karcinoma dojke udružen je sa lošom prognozom bolesti zbog rane rekurencije i većeg lokalnog i limfonodalnog stadijuma bolesti. Kod osoba sa DM2 postoji povećana ekspresije receptora IGF- 1 i ER i češća pojava multiplih karcinoma dojke.

**Ključne reči: karcinom dojke, dijabetes melitus tip 2, receptor insulinu sličan faktor rasta 1 (IGF-1R)**

## Prognostic significance expression IGF-1R in diabetic women with breast cancer

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**Objective:** The aim of this study was correlation expression of IGF-1R with basic histopathological and immunohistochemical breast cancer parameters and the difference between diabetic (DM2) and non-diabetic women. **Introduction:** IGF-1R together with sex hormone receptors regulates the development of epithelium of the normal glandular breast tissue and results proliferation and differentiation of the cells. IGF-1R overexpression in breast tissue can be an important link between obesity, DM2 and unfavourable caracteristics of breast cancer. **Material and Methods:** A total of 130 women with invasive breast cancer (stage I-III), preoperative DM2 had 14 (10,8%) women. Formalin-fixed paraffin-embedded tumor samples we used for immunohistochemical staining for visualization: IGF-1R, estrogen receptor (ER), progesteron receptor (PR) and human epidermal growth factor receptor (HER-2). The data were analyzed by program SPSS version 17., using two-sample t-test. The relapse-free survival (RFS) was examined using Kaplan-Meier curves, and the difference between the examined variables was assessed by the Log-Rank test. **Results:** Women with DM2 had a high tumor stage (p=0.038), number of metastatic lymph node (p=0.019), diameter (p=0.039) of breast cancer, expression ER (p=0.001) and IGF-1R (p=0,039) and high rate multifocality/multicentricity (p=0.036) of breast cancer. DM2 (p=0.023), tumor stage (p=0.039) and HER-2 (p=0.033) were independent prognostic factors for RFS. **Conclusion:** Diabetes mellitus type 2 associated with adverse outcomes because of early recurrence of breast cancer and advanced tumor and lymph node stage. DM2 can induce the higher expression and increased the binding capacity of IGF- 1R and ER and occurrence preoperative multicentric or multifocal tumor growth.

**Key words: breast cancer, diabetes mellitus type 2 (DM2), Insulin-like growth factor receptor 1 (IGF-1R)**

## OP-5

## Potencijalni prognostički značaj ekspresije miR-101 i miR-125 u karcinomu kolona

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**Cilj:** Ispitati potencijalni prognostički značaj odabranih miRNK u karcinomu kolona. **Uvod:** Aberantna ekspresija miRNK, kroz uticaj na ekpresiju različitih onkogena i tumor supresorskih gena može imati ulogu u nastanku i progresiji malignih tumora. Pored poznatih kliničkih i molekularnih karakteristika tumora, miRNK bi u budućnosti mogle služiti kao biomarkeri u prognozi i terapiji maligniteta. **Materijali i metode:** U ovoj prospektivnoj studiji RT-qPCR metodom analizirani su nivoi ekspresije pet odabranih miRNK (miR-29a, miR-101, miR-125b, miR-146a i miR-155) u 22 tkivna uzorka pacijenata sa indikacijama za hirurški tretman karcinoma kolona. Patohistološkom analizom nađena su i tri adenoma kolona, koji su takođe analizirani. Nivoi ekpresije korelirani su sa kliničko-patološkim karakteristikama tumora. **Rezultati:** Povišena ekspresija miR-29a, miR-125b, miR-146a i miR-155 i niža ekspresija miR-101 nađene su u tumorskom u odnosu na okolno zdravo tkivo. Nije nađena statistički značajna razlika između nivoa ekspresije ispitivanih miRNK u odnosu na: veličinu tumora, lokalizaciju (lijevi ili desni kolon), histološki gradus, količinu i sastav upalnog infiltrata, karakteristike strome

i prisustvo limfo-nodalnih metastaza. Značajno niži nivoi ekspresije miR-146a nađeni su u uzorcima sa opsežnijom nekrozom, značajno viši nivoi ekspresije miR-155 u mukus-produkujućim tumorima, a značajno viša ekspresija miR-125b u uzorcima sa limfo-vaskularnom invazijom. Interesantno, značajno viša ekspresija miR-101 i niža ekspresija miR-125b nađene su u adenomima u odnosu na uzorke tumora. Analiza ROC krivih pokazala je 100% specifičnost i 89.5% senzitivnost (AUC=0.93) za miR-101 i 100% senzitivnost i specifičnost (AUC=1) za miR-125. **Zaključak:** Preliminarni rezultati ove studije ukazuju na potencijalni prognostički značaj miR-101 i miR-125b u karcinomu kolona, što je potrebno potvrditi na većem broju uzoraka.

**Ključne reči: karcinom kolona, miRNK, biomarkeri**

## Potential prognostic significance of miR-101 and miR-125 expression in colon cancer

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**Objective:** To examine the potential prognostic significance of selected miRNAs in colon cancer. **Introduction:** Aberrant miRNAs expression, through its influence on the expression of different oncogenes and tumor suppressors, may play a role in the development and progression of tumours. Apart from known clinical and molecular characteristics of tumours, in future miRNAs could serve as biomarkers in prognosis and treatment of malignancy. **Material and Methods:** Expression levels of five selected miRNAs (miR-29a, miR-101, miR-125b, miR-146a and miR-155) were analysed with RT-qPCR in 22 tissue samples of the patients with indications for surgical treatment of colon cancer. Three adenomas were found and also analysed. Expression levels were correlated with clinical-pathological characteristics of tumours. **Results:** Tumours showed increased miR-29a, miR-125b, miR-146a and miR-155 and reduced miR-101 expression levels in comparison with surrounding healthy tissue. No significant difference was found between the examined miRNAs expression levels and tumor size, localisation (left or right colon), histological grade, amount and composition of inflammatory infiltrate, stroma characteristics and the presence of lympho-nodal metastases. In cases with extensive necrosis, significantly reduced levels of miR-146a expression was found, while higher levels of expression of miR-155 was found in mucus-producing tumours and higher miR-125b expression in samples with lympho-vascular invasion. Interestingly, higher miR-101 and reduced miR-125b expression levels were found in adenomas in comparison to tumours. ROC curve analysis showed 100% specificity and 89.5% sensitivity (AUC=0.93) for miR-101 and 100% sensitivity and specificity (AUC=1) for miR-125. **Conclusion:** Preliminary results, which need to be confirmed, show the potential prognostic significance of miR-101 and miR-125b in colon cancer.

**Key words: colon cancer, miRNA, biomarkers**

## OP-6

## Mesonephric-like karcinom ženskog genitalnog trakta: prikaz slučaja i pregled literature

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**Cilj:** Predstaviti klinikopatološke odlike mesonephric-like karcinoma ženskog genitalnog trakta. **Prikaz slučaja:** Žena starosne dobi od 65 godina sa kliničkom istorijom karcinoma endometrijuma i pleuralnih nodula koji su prvobitno dijagnostikovani kao metastatski papilarni karcinom štitaste žlezde. Nakon ponovnog pregleda, i endometrijalni i pleuralni tumor karakteriše heterogena arhitektura, odsustvo skvamozne ili mucinozne diferencijacije, tubule sa luminalnim eozinofilnim sekretom i nuklearne karakteristike slične papilarnom karcinomu štitaste žlezde. Imunohistohemijski nalazi pokazuju da je tumor imunoreaktivan na PAX8, GATA3, TTF1 i luminalni CD10, i pokazuje odsustvo imunoreaktivnosti na ER i PR. p53 je normalne ekspresije. Molekularna analiza je pokazala KRAS mutaciju. Nalazi su u skladu sa mesonephric-like karcinomom endometrijuma. **Zaključak:** Mesonephric-like karcinomi su nedovoljno prepoznati tumori endometrijuma i jajnika koji se često pogrešno dijagnostikuju kao drugi podtipovi karcinoma (posebno endometrioidni). Oni pokazuju morfološke, imunohistohemijske i molekularne sličnosti sa mezonefričnim karcinomom. Ovi tumori se često javljaju u uznapredovalom stadijumu i imaju česte recidive, posebno u plućima. Ovi tumori mogu postojati u vezi sa drugim histološkim komponentama i deliti identične mutacije sa drugim histološkim komponentama kao što su endometrioidne, serozne, i mucinozne Mullerian komponente (između ostalih), podržavajući Mullerian poreklo ovih tumora. Nedavno su prijavljeni i mesonephric-like karcinosarkomi.

**Ključne reči: mesonephric-like karcinom, mesonephric, KRAS mutacija**

## Mesonephric-like cancer of the female genital tract: a case report and review of the literature

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**Objective:** To present clinicopathologic features of mesonephric-like carcinomas of female genital tract. Case report: 65 year old female with clinical history of endometrial cancer and pleural nodules originally diagnosed as metastatic papillary thyroid carcinoma. Upon re-review both endometrial and pleural tumor were characterized by heterogeneous architecture with admixture of patterns, absence of squamous or mucinous differentiation, tubules with luminal dense eosinophilic secretions, and nuclear features akin to papillary thyroid carcinoma. By immunohistochemistry, both tumors expressed PAX8, GATA3, TTF1, and luminal CD10, and exhibited absence of ER and PR, and wild type p53. Molecular analysis showed canonical KRAS activation and chromosome 1q gain. Findings are in keeping with mesonephric-like carcinoma of the endometrium. **Conclusion:** Mesonephric-like carcinomas are under-recognized tumors of endometrium and ovary which are often misdiagnosed as other carcinoma subtypes (particularly endometrioid). They exhibit morphologic, immunohistochemical, and molecular similarity to mesonephric carcinoma. The cumulative body of evidence shows that mesonephric-like carcinomas are aggressive neoplasms, which often present at advanced stage and have frequent distant recurrences, particularly to the lungs. These tumors may exist in association with, and share identical mutations with other histologic components such as endometrioid serous, and mucinous Mullerian components (among others), supporting a Müllerian origin of these tumors. Mesonephric-like carcinosarcomas have also recently been reported.

**Key words: Mesonephric-like carcinoma, Mesonephric carcinoma, KRAS**

## P0STER SESIJA II
## POSTER SESSION II

### PI-1

### Akcidentalna masna embolija nakon trostrukog bypass-a: prikaz autopsijskog slučaja

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**Cilj:** Prikazujemo autopsijski slučaj akcidentalne masne embolije kod pacijenta starog 81 godinu nakon hirurške revaskularizacije miokarda trostrukim bypass-om. **Prikaz slučaja:** Na Institutu za patologiju Medicinskog fakulteta Univerziteta u Beogradu urađena je autopsija pacijenta sa Instituta za kardio-vaskularne bolesti "Dedinje" pod uputnom kliničkom dijagnozom: Institio cordis non specificata. U otpusnoj listi je, kao značajna komplikacija, navedena pojava izrazite hipotenzije i hemoragičnog sadržaja u endotrahealnom tubusu nakon završene operacije trostrukog bypass-a. Zbog navedenih komplikacija indikovana je i učinjena atipična resekcija srednjeg režnja desnog plućnog krila, koji nije poslat na histopatološku analizu. Bez obzira na sprovedenu kardiopulmonalnu reanimaciju, trećeg postoperativnog dana dolazi do smrtnog ishoda, zbog čega je indukovana autopsija. Osnovni morfološki nalaz na obdukciji predstavljala su difuzna petehijalna krvarenja u beloj masi velikomoždanih hemisfera, mezencefalona i ponsa, praćena edemom mozga. Slična krvarenja su uočena i u parenhimu pluća bilateralno. Ostali morfološki nalaz je ukazivao na multiorgansko popuštanje. Tokom autopsije učinjena je ex tempore dijagnostika na reprezentativnim uzorcima iz mozga i pluća. Specijalnim histohemijskim bojenjem na oil red verifikovana je embolizacija masnim tkivom. **Zaključak:** Svi faktori rizika za nastanak masne embolije, koja se razvija u 24-72h nakon hirurške intervencije: pacijenti stariji od 65 godina, gojazni, pacijenti kod kojih su sprovedene neortopedske hirurške intervencije, posebno aorto-koronarni bypass, su bili prisutni i kod našeg pacijenta. Jedna od najređih komplikacija masne embolije pluća je intraparenhimsko krvarenje, koje je takođe verifikovano.

**Ključne reči: masna embolija, autopsija, histohemija**

### Accidental fat embolism following triple bypass: A autopsy case report

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**Objective:** We report accidental fat embolism autopsy case report of 81-year-old man after surgical triple bypass myocardial revascularization. **Case reports:** An Cardiovascular Diseases Institute "Dedinje" patient autopsy was performed at Pathology Institute "Prof. dr Đorđe Joannović", Faculty of Medicine, Belgrade University under clinical diagnosis: Institio cordis non specificata. Severe hypotension and hemorrhagic endotracheal airway content as marked complication was mentioned in hospital discharge list, after triple bypass surgery. Due to this kind of complications, atypical resection of the right lung wing middle lobe it was indicated and performed. Despite of cardio-pulmonary reanimation, the third day of recovery, lethal outcome occurred which indicated autopsy.
Diffuse petechial hemorrhage within cerebral, mesencephalon and white mass of pons followed by brain edema represented as main morphological autopsy finding. Similar hemorrhage was found bilateral in lung parenchyma. Other morphological finding is suggestive for multi-organ failure. During autopsy representative brain and lung samples were taken for ex tempore examination. Special histochemical oil red stain was used for fat embolism verification. **Conclusion:** Fat embolism risk factors, which are

developed within 24 to 72 hours after surgery, like: elderly patients over 65, obese, non-orthopedic surgery patients, especially aortic-coronary bypass, were also present at our patient. Parenchyma bleeding, as one of the less frequent fat embolism complication, was also verified.

**Keywords: fat embolism, autopsy, histochemistry**

## PI-2

### Sistemska amiloidoza sa post mortem dijagnozom multiplog mijeloma: prikaz autopsijskog slučaja

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**Cilj:** Prikazujemo bolesnika sa sistemskom amiloidozom, za koju se na autopsiji pokazalo da je udružena sa zaživotno nedijagnostikovanim multiplim mijelomom. **Prikaz slučaja:** Bolesnik starosti 54 godine je primljen u Urgentni centar Univerzitetskog kliničkog centra Srbije zbog gušenja koje traje poslednja tri meseca. Pacijentu je postavljena sumnja na amiloidozu srca, ali četiri dana nakon prijema umire, bez detaljnog ispitivanja. Na autopsiji je makroskopski uočen bilateralni hidrotoraks sa plućnim kolapsom. Srce je bilo uvećano, mase 680g, debljine zida leve komore 2,8cm, desne komore 1cm i obima trikuspidnog ušća 14cm. Miokard je na preseku bio svetlo-ružičaste boje, slaninastog izgleda. Jetra je bila uvećana, mase 2900g, zastojna. Slezina je na preseku bila crvene boje, čvrste konzistencije, težine 300g. Patohistološki, u srcu, bubrezima, slezini, nadbubrežnoj žlezdi i kostnoj srži uočeno je ekstracelularno deponovanje amorfnog sadržaja, eozinofilne boje, u intersticijumu, ali i u zidu krvnih sudova svih organa. Histohemijskim bojenjem na Congo Red i Tioflavin dokazano je prisustvo amiloida. Morfološki i imunohistohemijski u kostnoj srži je uočena difuzna infiltracija ćelijama plazmocitne loze (oko 80% CD138+ ćelija), koje su monoklonske (kappa+/lambda-), što odgovara multiplom mijelomu, gradus II, udruženom sa amiloidozom. **Zaključak:** Sistemska amiloidoza udružena sa multiplim mijelomom ima lošu prognozu sa prosečnim preživljavanjem kraćim od 6 meseci. Samo 10% pacijenata sa multiplim mijelomom razvije amiloidozu, a samo kod 5-10% pacijenata sa sistemskom amiloidozom na prezentaciji dijagnostikuje se kasnije multipli mijelom. Kod postojanja sumnje na sistemsku amiloidozu blagovremenom dijagnostikom i terapijom moguće je uticati na poboljšanje toka bolesti.

**Ključne reči: Sistemska amiloidoza, multipli mijelom, autopsija**

### Systemic amyloidosis with postmortem diagnosis of multiple myeloma: A autopsy case report

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**Objective:** We present a patient with systemic amyloidosis associated with undiagnosed multiple myeloma, discovered at autopsy. **Case report:** A 54-year-old patient was admitted at Emergency room of University Clinical center of Serbia due to suffocation that lasted for three months. It was suspected patient had cardiac amyloidosis, but four days after admission he died, without any thorough examination. During the autopsy, bilateral hydrothorax with pulmonary collapse was noticed. Hearth was enlarged, weighted 680g, left ventricular wall width 2,8cm, right ventricular wall width 1cm and circumference of tricuspidal valve was 14cm. On the section, myocard was bright-pink in color, bacon-looking. Liver was enlarged, weighted 2900g, congestive. Spleen was red, firm, weighted 300g. Pathohistologically, extracellular amorphous eosinophilic interstitial content was observed in the hearth, kidneys, spleen, adrenal gland, bone marrow, as well as in the walls of blood vessels of all organs.

Histochemical staining Congo Red and Tioflavin proved the presence of amyloid. Morphologically and immunohistochemically, diffuse infiltration of bone marrow with cells of plasma cell lineage (about 80% CD138+ cells), which were monoclonal (kappa+/ lambda-), was observed. These findings were consistent with diagnosis of multiple myeloma, grade II, associated with amyloidosis. **Conclusion:** Systemic amyloidosis associated with multiple myeloma has poor prognosis with average survival rate shorter than 6 months. Only 10% of patients with multiple myeloma develop amyloidosis, and only 5-10% of the patients with systemic amyloidosis at presentation are afterwards diagnosed as multiple myeloma. When there is a doubt of systemic amyloidosis, prompt diagnosis and therapy may improve the course of the disease.

**Key words: Systemic amyloidosis, multiple myeloma, autopsy**

## P1-3

## Invazivna diseminovana aspergiloza: prikaz autopsijskog slučaja

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**Cilj:** Prikaz slučaja invazivne diseminovane aspergiloze kod bolesnice sa dugogodišnjom neregulisanom hiperglikemijom. **Prikaz slučaja:** Pacijentkinja starosti 68 godina dovedena je na pregled u prijemnu ambulantu OB Subotica kada se konstatuje somnolentnost, nekontaktibilnost, generalizovane petehije kože, hiperglikemija, trombocitopenija i povišena vrednost CRP-a. Kompjuterizovanom tomografijom gudnog koša registrovana je obostrana atipična pneumonija. Nakon pet dana intezivnog hospitalnog lečenja sa veoma slabim terapijskim odgovorom, konstatovan je exitus letalis uz klinički nalog za autopsiju. Makroskopskim pregledom na autopsiji uočeni su morfološki znaci akutnog pankreatitisa, bilateralne bronhopneumije sa područjima nekroze, edem pluća, kao i promena u mozgu izgleda infarkta. Nakon uzorkovanja i standardne patohistološke obrade tkiva, mikroskopskim pregledom HE bojenih preparata u isečcima iz meningi, hipofize, miokarda, želuca i pluća uočena su nekrotična i gnojna inflamatorna područja sa prisustvom tankih septiranih hifa dihotomnog grananja koje invadiraju vaskularne prostore. Načinjena su i dodatna Grocott i PAS specijalna bojenja koja jasno vizuelizuju gljivičnu komponentu u navedenim organima, te potvrđuju sepsu kao uzrok smrti. **Zaključak:** Gljive roda Aspergillus su ubikvitarne gljive koje se nalaze u zemljištu, vazduhu, prašini i najčešće sporadično, inhalacijom spora izazivaju mikotoksikoze, mikoalergoze, lokalnu i mahom fatalnu sistemsku diseminovanu infekciju. Najčešći oblici aspergiloza su aspergilom, akutna invazivna pneumonija, hronična nekrotizirajuća aspergiloza, aspergiloza kože, mozga, miokarda i drugih organa. Visok rizik za nastanak invazivne generalizovane aspergiloze imaju osobe sa neutropenijom, bolesnici sa imunosupresivnom terapijom i hronični plućni bolesnici. Usled rezistencije na aktuelno dostupnu terapiju te nemogućnosti adektvatnog terapijskog pristupa, invazivna aspergiloza dovodi do smrti u velikom procentu.

**Ključne reči: Aspergilus, sepsa, invazivna diseminovana aspergiloza**

## Invasive disseminated aspergillosis: A autopsy case report

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**Objective:** To present a case of invasive disseminated aspergillosis in unregulated long-term hyperglycemic patient. **Case report:** A 68-year-old patient was reffered to Subotica's General hospital emergency where somnolence, non-contactability, generalized skin petechiae with hyperglycemia, thrombocytopenia and elevated CRP values were observed. Chest computed tomography registered bilateral atypical pneumonia. Five days after intensive hospital treatment with weak therapeutic response, exitus letalis was confirmed with a clinical autopsy request. The autopsy macroscopic examination showed acute pancreatitis morphological signs, bilateral bronchopneumonia with necrotic areas, pulmonary edema and brain infarction-like changes, as well. Having done standard pathohistological tissue samples processing, HE stained microscopic examinations of meninges, pituitary, myocardium, stomach and lungs, revealed necrotic and purulent inflammatory areas with the presence of thin septated hyphae of dichotomous branching with vascular invasion. Additional Grocott and PAS special staining were performed that clearly highlighte the fungal component in those organs, and confirmed sepsis as a death cause. **Conclusion:** Aspergillus genus fungi are ubiquitous finding in soil, air and dust. Usually due to spore inhalation sporadically it causes mycotoxicoses, mycoallergies, local infections and mostly fatal systemic disseminated infection. The most common aspergillosis forms are aspergillomas, acute invasive pneumonia, chronic necrotizing aspergillosis, aspergillosis of the skin, brain, myocardium and other organs. People with neutropenia, patients with immunosuppressive therapy and chronic respiratory disease have a higher risk of developing invasive generalized aspergillosis. A high death rate in invasive aspergillosis is likely due to the resistance to the currently available therapy and the impossibility of an adequate therapeutic approach.

**Key words: Aspergillus, sepsis, invasive disseminated aspergillosis**

## P1-4

## OEIS kompleks (omfalokela, ekstrofija, neperforirani anus, spinalni defekt): prikaz autopsijskog slučaja

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**Cilj:** Prezentujemo obdukcioni nalaz nakon planiranog feticida zbog ultrazvukom verifikovanih major malformacija ploda. OEIS kompleks (omfalokela, ekstrofija mokraćne bešike/kloake, neperforirani anus i spinalni defekt) je retka multisistemska kongenitalna malformacija koja nastaje u 1 na oko 300.000 trudnoća. **Prikaz slučaja:** Nakon odobrenja Etičke komisije, izvršen je feticid, te je plod poslat na obdukciju. Obdukovan je plod muškog pola gestacijske dobi 28 nedelja, dužine 38 cm, mase 1680 g. Infraumbilikalno prednji trbušni zid je nedostajao, a abdominalni organi su prominirali van trbušne duplje, prekriveni peritoneumom, koji je rubno srastao za kožu (omfalokela). Mokraćna bešika je takođe bila smeštena u peritonealnoj kesi, dok je ureterima bila povezana za normalne bubrege (ekstrofija mokraćne bešike). Na koži lumbalne regije nalazilo se lako ulegnuće dimenzija 1x1 cm (spina bifida okulta). Analni otvor je bio neperforiran. Pored gore navedenih glavnih anomalija OEIS kompleksa uočavala se i skolioza sa levostranim konveksitetom, dok su stopala bila u položaju unutrašnje rotacije (pes equinovarus). Spoljašnji genitalni organi nisu bili formirani i činili su ih samo rudimenti skrotuma. Testisi su bili formirani i smešteni u trbušnoj duplji. Levo plućno krilo nije bilo lobulirano.

**Zaključak:** Pravovremena i precizna prenatalna dijagnostika, kao i redovno praćenje trudnoće ima značajnu ulogu u savetovanju porodice radi donošenja odluke o daljem toku trudnoće, jer iako postoji mogućnost korektivne hirurgije pomoću organizovanog multidisciplinarnog lekarskog tima, treba uzeti u obzir dalji kvalitet života pacijenta.

**Ključne reči: OEIS kompleks, omfalokela, ekstrofija, atrezija anusa, spina bifida**

## OEIS complex (omphalocele, bladder exstrophy, imperforate anus, spinal defects): A autopsy case report

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**Objective:** We report autopsy findings after a planned feticide due to the ultrasonographic diagnosed major fetal malformations. OEIS complex (omphalocele, bladder exstrophy/cloaca, imperforate anus and spinal defects) is a rare multisystemic congenital malformation. It occurs in 1:300.000 pregnancies. **Case report:**The feticide was committed by decision of the Ethics Committee. The autopsy was performed on a male fetus, 28 weeks' gestational ages, 38 cm long, weighing 1680 grams. The infraumbilical anterior abdominal wall was absent, while the abdominal organs protruded outside the abdominal cavity, covered with peritoneum whose edges were coalesced to the skin (omphalocele). The bladder was also located in the peritoneal sac and connected with ureters to normal kidneys (bladder exstrophy). The lumbal skin region showed a discreet indentation 1x1 cm in size (spina bifida occulta). The anus was imperforate. In addition to the above-described major anomalies of the OEIS complex, scoliosis with left-sided convexity was also observed, whereby the feet were internally rotated (pes equinovarus). The external genitalia were underdeveloped and consisted solely of scrotal rudiments. The testicles were developed and positioned in the abdominal cavity. The left lung was not lobulated. **Conclusion:** Timely and accurate prenatal diagnosis, as well as, regular monitoring of pregnancy, plays a significant role in advising the family to decide upon the further course of pregnancy, since although an organized multidisciplinary medical team may perform corrective surgery, further quality of life should be taken into account.

**Key words: OEIS complex, omphalocele, exstrophy, anal atresia, spina bifida**

## P1-5
## Medijastinalni teratom kod fetusa udružen sa fetalnim hidropsom: autopsijski prikaz slučaja

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**Cilj:** Prikaz slučaja retkog medijastinalnog teratoma kod fetusa udruženog sa fetalnim hidropsom. **Prikaz slučaja:** Fetus u 30-oj nedelji gestacije je mrtvorođen nakon postavljene sumnje da ima tumor medijastinuma udružen sa neimunim fetalnim hidropsom (NIFH) i polihidramnionom, što je prikazano prenatalnim trodimenzionalnim ultrazvukom. Fetus je mrtvorođen i urađena je obdukcija. Makroskopskim pregledom, utvrđeno je da se radi o velikom multicističnom tumoru, prečnika 7,5x7x5,5

cm, sa cistama koje su ispunjene seroznom ili krvavom tečnošću i žućkastim želatinoznim materijalom. Mikroskopski, istaknuta komponenta tumora bilo je nezrelo neuroepitelno tkivo sastavljeno od nezrelih neuralnih tubula i rozeta obloženih tamnim hiperhromatičnim cilindričnim ćelijama, uz prisustvo neuroglijalnog tkiva. Ciste su bile obložene jednorednim do višerednim prizmatičnim i cilindričnim epitelom. Delom je bila prisutna svetloćelijska epitelna komponenta, kao i mukus produkujući cilindrični epitel nalik na gastrointestinalni epitel. Od ostalih komponenata u tumoru su bile prisutne hrskavica, glatko mišićno tkivo, hipocelularno mezenhimno tkivo, žlezde koje podsećaju na acinuse pankreasa, retina i brojne kalcifikacije. **Zaključak:** Važno je odlučiti se za ranu intervenciju ako se ultrazvučno u fetalnom životu otkrije medijastinalni teratom. Brzi rast u fetalnom životu može komprimovati pluća, srce i velike krvne sudove, što može dovesti do razvoja neimunog fetalnog hidropsa (NIFH). U slučajevima kada se NIFH razvije, ishod je uglavnom nepredvidiv jer se mogu razviti kratkoročne i dugoročne posledice kombinovanih efekata NIFH-a i pritiska teratoma na susedne organe kao što smo predstavili u našem slučaju.

**Ključne reči: medijastinalni teratom, hidrops, fetus**

## Mediastinal teratoma in a fetus associated with fetal hydrops: A autopsy case report

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**Objective:** To present a case report of a rare mediastinal teratoma in a fetus associated with fetal hydrops. **Case report:** A fetus at gestational week 30 was suspected of having a mediastinal tumor associated with non-immune fetal hydrops (NIFH) and polyhydramnion, as shown by prenatal three-dimensional ultrasonography. The fetus was stillborn and an autopsy was performed. On gross pathological examination, there was a large multicystic tumor, measuring 7,5x7x5,5 cm in diameter, containing cysts filled with serous or bloody fluid and yellowish gelatinous material. Microscopically, the prominent component of the tumor was immature neuroepithelial tissue composed of immature neural tubules and rosettes lined by dark hyperchromatic columnar cells with stratification. Also, there was neuroglial tissue. Cystic areas were partly lined by simple to stratified cuboidal and columnar epithelium. Clear cell epithelial component was partially present, as well as mucous columnar epithelium resembling gastrointestinal epithelium. Other components of the tumor included cartilage, smooth muscle, sparsely cellular mesenchymal tissue, exocrine glands resembling pancreatic acini, retinal tissue and numerous calcification. **Conclusion:** It is important to decide for early intervention if mediastinal teratoma is discovered with antenatal ultrasound in fetal life. Rapid growth in fetal life can compress lungs, heart and great vessels, which can lead to development of non-immune fetal hydrops (NIFH). In cases when NIFH develops the outcome is mainly unpredictable because short and long term sequelae of combined effects of NIFH and teratoma pressure on neighboring organs may develop as we presented with our case.

**Key words: Mediastinal teratoma, hydrops, fetus**

## P1-6

## Tuberkulozna sepsa: prikaz autopsijskog slučaja

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**Cilj:** Tuberkulozna sepsa je izuzetno retka komplikacija čak i kod imunokompromitovanih bolesnika. Prikazujemo autopsijski nalaz tuberkulozne sepse kod mlade bolesnice sa akutnom mijeloidnom leukemijom (AML), koja umire u fazi aplazije kostne srži posle indukcione hemioterapije. **Prikaz slučaja:** Bolesnica stara 21 godinu primljena je na Kliniku za hematologiju UKCS zbog glavobolja, malaksalosti i nalaza pancitopenije, kada joj je dijagnostikovana AML sa minimalnom diferencijacijom, ECOG1, citogenetskim nalazom 46,XX; FLT3-ITD negativnom. Hemioterapiju ara-C i daunorubicinom je započela 19 dana pre smrtnog ishoda. U fazi aplazije kostne srži nastale sedmog dana od započinjanja indukcione hemioterapije, pacijentkinja je imala intenzivne bolove u kostima, hematuriju, uz nalaz difuznih inspirijumskih pukota na plućima. Makroskopski autopsijski nalaz je sledeći: edem mozga, edem pluća sa suspektnom pneumonijom, dilatacija celog srca, obostrani hemoragični pleuralni izliv, ascites, struma, krvarenje u jajnicima, venski zastoj u svim organima. Mikroskopski, u plućima se uočava izražen venski zastoj sa leukostazom, u lumenu alveola obiman fibrinozni eksudat uz intraalveolarno krvarenje. U parenhimu jetre i mozga se uočava leukemijska infiltracija. U kostnoj srži je imunohistohemijski (CD34+) detektovano 80% blasta. Prisustvo hemoragičnog pleuralnog izliva, hemoragije jajnika, uz klinički podatak hematurije je zahtevala dodatna histohemijska bojenja u cilju ispitivanja udruženosti sa oportunističkom infekcijom, mada se hemoragijski sindrom očekuje kod AML. Bojenjem Ziehl-Neelsen detektujemo Kohov bacil u sledećim organima: pluća, bubrezi, jetra, slezina, kostna srž, štitasta i nadbubrežne žlezde, jajnici. Ni u jednom organu nije uočena kazeifikacija ni granulomatozno zapaljenje. **Zaključak:** Histohemijska analiza autopsijskih uzoraka je nužan preduslov postmortem dijagnostike tuberkuloze kod imunokompromitovanih bolesnika, čak i u odsustvu morfoloških obeležja patognomoničnih za tuberkulozu.

**Ključne reči: tuberkulozna sepsa, akutna mijeloidna leukemija, oportunističke infekcije**

## Tuberculosis Sepsis: A autopsy case report

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**Objective:** Tuberculosis sepsis is extremely rare complication even in immunocompromised patients. We present the autopsy finding of tuberculosis sepsis in young patient with acute myeloid leukemia (AML), who died after induction chemotherapy. **Case report:** The 21-year-old female was admitted to Clinic for Hematology due to headache, malaise and pancytopenia, when she was diagnosed with AML with minimal differentiation, ECOG1, cytogenetic findings 46,XX; FLT3-ITD negative. Chemotherapy with ara-C and daunorubicin was started 19 days before death. Seven days after beginning of induction therapy, during bone marrow (BM) aplasia, she had intense bone pain, headache, hematuria, with finding of diffuse inspiratory cracks in lungs. Macroscopic autopsy findings were as follows: brain edema, pulmonary edema with suspected pneumonia, dilatation of whole heart, bilateral hematothorax, ascites, goiter, bleeding in both ovaries, venous stasis in all organs. Microscopically, a pronounced venous stasis with leukostasis was detected in lung and extensive intraalveolar fibrinous exudate with bleeding. Leukemic infiltration was detected in liver and brain. Immunohistochemically (CD34+) was detected

80% blasts in BM. The presence of hematothorax, hemorrhage of ovaries, with clinical data of hematuria required additional histochemical staining in order to examine the association with opportunistic infection, although hemorrhagic syndrome was expected in AML. Ziehl-Neelsen staining detected Koch's bacillus in following organs: lungs, kidneys, liver, spleen, BM, thyroid and adrenal glands, ovaries. No caseification or granulomatous inflammation was found in any of organs. **Conclusion:** Histochemical analysis of autopsy specimens is necessary prerequisite for postmortem diagnosis of tuberculosis in immunocompromised patients, even in the absence of morphological features pathognomonic for tuberculosis.

**Key words: tuberculosis sepsis, acute myeloid leukemia, opportunistic infections**

## P1-7

## Angiomatoza medijastinuma kao uzrok iznenadne smrti: autopsijski prikaz slučaja

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**Cilj:** Prezentacija slučaja medijastinalne angiomatoze koja se klinički manifestovala u vidu respiratorne infekcije, a radiografski medijastinalnom masom koja je imitirala maligni tumor. **Prikaz slučaja:** Muškarac star 32 godine primljen je u Kliniku za pulmologiju zbog akutne simptomatologije koja se javila unazad 5 dana u vidu febrilnosti, gušobolje i kašlja .Pacijent navodi pojavu krvi u ispljuvku od oktobra 2018.godine. Klinička slika odgovarala je pneumoniji te je bolesnik hospitalizovan.Učinjen je multislajsni skener toraksa i abdomena kojim je opisana tumorska masa medijastinuma i nekoliko nodusa u plućima koje mogu odgovarati sekundarnim depozitima ili aspiraciji.Letalni ishod nastupio je drugog dana hospitalizacije. U Institutu za patologiju urađena je autopsija. Makroskopski je viđena nejasno ograničena tumorolika masa medijastinuma dimenzija 180x100x80 mm, od nivoa gornjeg otvora jednjaka, koja infiltriše larinks sa stenozom ulaza larinksa, zadnji zid orofarniksa, oba režnja štitaste šlezde, obe unutrašnje jugularne vene, oba parafaringealna prostora i stenozira jednjak celim obimom. Patohistološka analiza pokazala je da je ceo zid traheje neposredno subepitalno do peritrahealnog masnog tkiva infiltrisan brojnim dilatiranim vaskularnim prostorima prepunjenim eritrocitima uz fokalnu erozije sluznice sa pojavom akutne inflamacije i fibrina. Dilatirani krvni sudovi (imunohistohemijska analiza: CD 31+, D2.40 -, WT1-,alfaSMA boji perivaskularne ćelije), infiltrišu oba režnja štitaste žlezde,okolne skeletne mišiće i zid jednjaka. Na osnovu morfološkog i imunohistohemijskog nalaza postavljena je dijagnoza kavernozna (venozna) malformacija. **Zaključak:** Angiomatoze su benigne vaskularne lezije koje se zbog svoje proširenosti, infiltrativnog rasta i recidiviranja nakon ekscizije često pogrešno dijagnostikuju kao maligni tumori.

**Ključne reči: medijastinum, angiomatoza, hemoptizije**

## Mediastinal angiomatosis as a cause of sudden death: A autopsy case report

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**Objective:** Presentation a case of mediastinal angiomatosis that was clinically presented as a respiratory infection, and radiographically as a mediastinal mass that mimicked malignant tumor. **Case report:** A 32 year old man was admitted to the Pulmology Clinic due to acute symptoms that appeared 5 days earlier as fever, gout and cough.The patient reported bloody sputum from October 2018. The clinical picture corresponded to pneumonia and the patient was hospitalized. A multislice scan of the thorax and abdomen described mediastinal tumor and lung several nodules that may corresponded to secondary deposits or aspiration. The lethal outcome occurred on the second day of hospitalization. An autopsy was performed at the Institute of Pathology and discovered ill-defined mediastinal tumor measuring 180x100x80 mm from the level of the upper esophageal opening, which infiltrated the larynx with stenosis of its entrance, the posterior wall of the oropharynx, thyroid gland, both internal jugular veins, both parapharyngeal spaces and narrowed wall of the esophagus. Pathohistological review showed infiltration of tracheal wall subepithelial to the peritracheal adipose tissue by numerous vascular spaces filled with erythrocytes, focally with acutely inflamed mucosal erosion covered by fibrin. Dilated blood vessels (immunohistochemical analysis: CD 31+, D2.40 -, WT1-, alphaSMA staines perivascular cells), infiltrated both lobes of the thyroid gland, surrounding skeletal muscles and esophageal wall. Based on the morphological and immunohistochemical findings, the diagnosis of cavernous (venous) malformations was made. **Conclusion:** Angiomatosis is benign vascular lesion that is often misdiagnosed as malignant tumor due to its enlargement, infiltrative growth, and recurrence after excision.

**Key words: mediastinum, angiomatosis, hemoptysis**

## P1-8

## Iznenadna smrt mlade žene mesec dana posle infekcije COVID-19: autopsijski prikaz slučaja

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**Cilj:** Prikaz patohistoloških promena kod mlade osobe iznenada preminule nakon preležane COVID-19 infekcije. **Prikaz slučaja:** Žena, starosti 38 godina, preminula je u snu, nakon duge forsirane šetnje. Mesec dana ranije je bolnički lečena zbog lakšeg oblika COVID19 pneumonije. Nedelju dana nakon hospitalizacije je otpuštena na kućno lečenje sa negativnim PCR testom na SARS-CoV2, uz redovne kontrole. U bolnici i kod kuće je dobijala terapiju po protokolu za lečenje COVID-19 koja je obuhvatala antikoagulantnu terapiju. Heteroanamnestički se saznaje da je lečena od Hašimoto tireoiditisa i da je 3 godine pre letalnog ishoda imala parcijalnu tireoidektomiju. Urađena je sudsko-medicinska obdukcija prilikom koje su uzeti reprezentativni isečci za histopatološku analizu. Najznačajnije makroskopske promene su nađene na plućima i srcu. Pluća su bila voluminozna, kongestirana, edematozna, sa mrljastim subpleuralnim krvarenjiuma. U srcu su nađena mrljasta epikardna krvarenja, hipertrofija zida leve komore, dilatacija srca uz izraženu masnu infiltraciju desne komore i vrha leve komore. Histološki, u krvnim sudovima pluća srednjeg kalibra nađeni su okluzivni trombi različite starosti, kao i fokusi svežeg intraalveolarnog krvarenja uz izražen alveolarni edem. U alveolarnim septama je fokalno nađena lakostepena fibroza, uz hiperplaziju pneumocita II i perivaskularne limfocitne

infiltrate. Kardiomiociti su bili hipertrofični, sa perinuklearnim lipofuscinom. U predelu vrha srca postojala je izražena masna infiltracija, uz lakostepenu fibrozu intersticijuma i atenuaciju kardiomiocita. U miokardu su nađeni retki fokusi monunuklearnog inflamatornog infiltrata, dominantno sačinjenog od limfocita.U pojedinim intramiokardnim krvnim sudovima su nađeni parijetalni mikrotrombi u organizaciji. **Zaključak:** Obdukcije pacijenata nakon SARS-CoV2 infekcije su neophodne da bismo potpuno razumeli patogenetske mehanizme i kliničke posledice bolesti.

**Ključne reči: obdukcija, SARS-CoV2, COVID19**

## Sudden death of a young woman one month after COVID-19 infection: A autopsy case report

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**Objective:** Presentation of pathohistological changes in a young person who died suddenly after COVID-19 infection. **Case report:** A 38-year-old woman died during sleep after a long forced walk. One month before death she was hospitalized for a mild form of COVID19 pneumonia. She was released for home treatment, with a negative PCR test for SARS-CoV2, one week after hospitalization, with regular check-ups. She received therapy according to the COVID-19 treatment protocol, which includes anticoagulant therapy. She was treated for Hashimoto's thyroiditis and partial thyroidectomy 3 years before lethal outcome. A forensic autopsy was performed. The lungs were voluminous, congestive, edematous, with subpleural hemorrhages. Spotted epicardial hemorrhages, hypertrophy of the left ventricule, dilatation of heart chambers and pronounced fatty infiltration of the right ventricle and the top of the left ventricle were found. Histologically, occlusive organized and recent thrombi were found in the blood vessels of medium caliber of the lungs, as well as foci of recent intraalveolar bleeding and prominent intraalveolar edema. Focal mild fibrosis of the alveolar septa was found, with pneumocyte II hyperplasia and perivascular lymphocyte infiltrates. Cardiomyocytes were hypertrophic, with perinuclear lipofuscin. A severe fatty infiltration, with mild interstitial fibrosis and attenuation of cardiomyocytes was found in the region of heart apex. Rare foci of monocular inflammatory infiltrate, predominantly composed of lymphocytes, were found in the myocardium. Parietal organized microthrombi were found in some intramyocardial blood vessels. **Conclusion:** Autopsies of patients after SARS-CoV2 infection are necessary to fully understand the pathogenetic mechanisms and clinical consequences of the disease.

**Key words: autopsy, SARS-CoV2, COVID19**

## P1-9
## Klinički nedijagnostikovana sistemska amiloidoza: prikaz dva autopsijska slučaja

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**Cilj:** Prikaz dva slučaja klinički nedijagnostikovane amiloidoze dokazane na autopsijama. **Prikaz slučaja:** Prva bolesnica, starosti 65 godina je hospitalizovana zbog teško poremećenog stanja svesti. Nađeni su pancitopenija, hiperfibrinogenemija, hipoproteinemija, hipoalbuminemija i proteinurija. Bolesnica je dva meseca ranije hospitalizovana zbog dekompenzujuće kardiomiopatije, kada su utvrđeni hronična bubrežna insuficijencija, hipoglikemija i primarni hipotireoidizam. Dvadeset godina se lečila od reumatoidnog artritisa, a zbog karcinoma je imala resekciju želuca Billroth I. Neočekivan nalaz na obdukciji su bili slezina čvrste konzistencije, staklastog izgleda i ezofagitis sa sivkstim teško skidljivim naslagama. Patohistološkom analizom utvrđeno je prisustvo eozinofilne amorfne mase u interstici-

jumu brojnih visceralnih organa, kao i u krvnim sudovima svih visceralnih organa izuzev mozga, a Congo crvenim bojenjem dokazano je da se radi o amiloidu. Histopatološki je verifikovan Candida ezofagitis. Nađen je težak cistitis, a uzrok smrti je bila sepsa. Druga bolesnica, 46 godina, dugogodišnji dijabetičar, hospitalizovana zbog izraženog ascitesa nejasne etiologije. Na CT-u abdomena viđeni: edem zida kolona, suspektna tromboza vene mesentericae superior, hipodenzitet slezine. Na autopsiji su zapaženi uvećanje, čvršća konzistencija, voštani sjaj slezine, jetre i bubrega. Patohistološkom analizom na HE preparatima viđeni su eozinofilni, amorfni depoziti difuzno u intersticijumu slezine, duž sinusoida jetre, duž glomerularne bazalne membrane, u mezangijumu i krvnim sudovima bubrega i u kostnoj srži. Isključeno je postojanje mijeloma u uzorku kostne srži. Urađeni su: PAS (depoziti negativni), trihromno (depoziti svetlo sivo-plavi), Congo red (depoziti crveni) i Tioflavin T bojenje (fluorescentna pozitivnost depozita), čime je potvrđena amiloidoza. Uzrok smrti je kardiorespiratorna insuficijencija. **Zaključak:** Sistemska amiloidoza može biti klinički neprepoznata komplikacija hroničnih inflamatornih bolesti i dijabetesa.

**Ključne reči: sistemska amiloidoza, congo crveno bojenje, tioflavin T**

## Clinicaly unrecognised systemic amyloidosis: A two autopsy case reports

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**Objective:** Presentation of the two cases of clinically undiagnosed amyloidosis confirmed by autopsy. **Case reports:** Female, 65 year-old was admitted to the hospital due to coma. Pancitopenia, hyperfibrinogenemia, hypoproteinemia, hypoalbuminemia and proteinuria were found. About two months earlier she was hospitalised because of the decompensatory cardiomiopathia, chronic renal failure, hypoglicemia and primary hypothyreosis. She was being treated from rheumatoid arthritis for 20 years and had had the stomach resection because of the carcinoma (Billroth I). Unexpected findings on the autopsy were very solid, glassy spleen and esophagitis with hardly removable gray plaques. Pathohistologicaly, amorphic eosinophilic structure was seen in the interstitium of many visceral organs and blood vessels of all viceral organs except brain. Amyloid was confirmed by Congo red staining. Candida infection was found within the esophageal wall. Severe cystitis was found. The main cause of death was sepsis. The other patient, 46 year-old female, long-termed diabetic, was hospitalised due to severe ascites, unknown etiology. Edematous colon wall, suspectious thrombosis of the superior mesenteric vein and hypodensity of the spleen were noted by abdominal CT scan. Spleen, liver and kidney macroscopically showed enlargement, solid consistency and waxy appearance. Eosinophilic, amorphic deposits diffusely presented in spleen interstitium, liver sinusoids, glomerular basal membranes, mesangium, renal blood vessels and in bone marrow were noted during patohistologycal analysis. PAS staining (negative), trichrome staining (gray-blue deposits), Congo red (positive) and Thioflavin T (fluorescentic positivity) was performed, confirming amyloidosis. Cause of death was cardiorespiratory failure. **Conclusion:** Systemic amyloidosis could be clinicaly unrecognised complication of chronic inflammatory diseases and diabetes.

**Key words: systemic amyloidosis, Congo red, thioflavin T**

**P1-10**

## Mekel-Gruberov sindrom: prikaz autopsijskog slučaja

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**Cilj:** U ovom izveštaju predstavljamo slučaj Mekel-Gruberov sindrom (MGS) u kome je dijagnoza postavljena na obdukciji. MGS je trijada okcipitalne encefalocele, policističnih bubrega i postaksijalne polidaktilije. To je retko, smrtonosno autozomno recesivno stanje mapirano na 6 različnih lokusa u različnim hromozomima. MGS je stanje koje karakterišu ciliopatije uzorkovane disfunkcijom cilija i flagela. Širom sveta incidencija MGS procenjena je на 1 од 135.000 živorodenih. Mekel-Gruberov sindrom se nasleđuje u porodicama kao autozomno recesivna bolest sa 25% šanse da se ponovi u svakoj trudnoći. Glavni dijagnostički kriterijumi MGS-a uključuju najmanje 2 od 3 klasične manifestacije. **Prikaz slučaja:** U ovom izveštaju predstavljamo slučaj MGS u kome je dijagnoza postavljena na obdukciju muškog fetusa u 16 nedelji gestacije na osnovu tipične trijade bolesti. Makroskopski nalaz uključuje okcipitalnu encefalocelu, policistične bubrege i postaksijalnu heksadaktiliju. Ove karakteristike upučuju na dijagnozi Mekel-Gruberovog sindroma. Urađen je histopatološki pregled na presecima uzetih iz visceralnih organa pokazao je nezrelost koja odgovara gestacionoj starosti. Sekcije koje su proučavane iz oba bubrega pokazale su fetalne glomerule i cističnu dilataciju tubula koje odgovaraju cistama po gruboj morfologiji. **Zaključak**: Savetovanje je sastavni deo menadmenta, posebno o riziku ponovog pojavljanja narednih trudnoća. Naš cilj ovog pregleda je da unapredimo znanje i proširimo svest o ovoj retkoj i smrtonosnoj anomaliji.

**Ključne reči: Okcipitalna encefalocela, policistični bubreg, polidaktilija, Mekel -Gruberov sindrom**

## Meckel-Gruber syndrome: A case report

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**Objective:** In this report, we present the case of Mekel-Gruber syndrome (MGS) in which the diagnosis was made at autopsy. MGS is a triad of occipital encephalocele, polycystic kidneys, and postaxial polydactyly. It is a rare, lethal autosomal recessive condition mapped to 6 different loci in different chromosomes. Meckel-Gruber syndrome is a condition characterized by ciliopathies caused by dysfunction of cilia and flagella. The worldwide incidence of MKS has been estimated at 1 in 135,000 live births. Meckel-Gruber syndrome inherits in families as autosomal recessive disease with a 25% chance of recurrence in each pregnancy. The major diagnostic criteria of MGS include at least 2 of the 3 classic manifestations. **Case report:** In this report, we present a case of MGS in which the diagnosis was made on autopsy of male fetus at 16 weeks of gestation based on the typical triad of the disease. The macroscopic finding includes occipital encephalocele, polycystic kidneys and postaxial hexadactyly. These features were suggestive of the diagnosis of Meckel-Gruber Syndrome. Histopathological examination on sections taken from the visceral organs showed immaturity corresponding to gestational age. Sections studied from both the kidneys showed fetal glomeruli and cystic dilation of the tubules corresponding with the cysts on gross morphology. **Conclusion:** Counseling forms an integral part of management especially about the recurrence risk of subsequent pregnancies. Our aim of this review is to enhance the knowledge and spread awareness about this rare and lethal anomaly.

**Key words: occipital encephalocele, polysystic kidney, polydactyly, Meckel-Gruber Syndrome**

## P1-11

## Prevalenca i tipovi kongenitalnih anomalija gastrointestinalnog trakta u operativnom materijalu u petogodišnjem periodu (2016-2020.)

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**Cilj:** Analiza tipova i učestalosti kongenitalnih anomalija GIT-a u petogodišnjem periodu (2016-2020.) Instituta za patologiju "Prof. dr Đorđe Joannović" Medicinskog fakulteta u Beogradu**. Uvod:** Gastrointestinalni trakt (GIT) u toku intrauterinog razvoja prolazi kroz veliki broj kompleksnih i precizno regulisanih procesa, a poremećaji koji mogu nastati tokom različitog perioda razvoja dovode do nastanka čitavog spektra kongenitalnih anomalija. **Materijal i metode:** Retrospektivna analiza učestalosti različitih gastrointestinalnih anomalija operisanih u Univerzitetskoj dečijoj klinici Tiršova u Beogradu u petogodišnjem periodu (2016-2020). U istraživanje su uključeni pacijenti kod kojih je prisustvo kongenitalne anomalije GITa potvrđeno histopatološki i/ili imidžing tehnikama. **Rezultati:** U petogodišnjem periodu je registrovano 103 slučaja kongenitalnih anomalija GITa: 32 slučaja Hiršprungove bolesti (31,1%), 32 Mekelova divertikuluma (31,1%), 13 intestinalnih atrezija/stenoza (12,6%), 12 atrezija anusa (11,6%), 7 hipertrofičnih stenoza pilorusa (6,8%) i 3 cistične duplikature creva (2,9%). Retke anomalije, od kojih je svaka registrovana kod jednog pacijenta (9,7%) bile su: cistična duplikatura jednjaka, omfalomezenterična fistula, enterična cista gastrokoličnog ligamenta, anomalija građe mišićnog zida creva i segmentna dilatacija ileuma. Među pacijentima sa registrovanim kongenitalnim anomalijama 72 pacijenta su bila muškog a 31 ženskog pola. Medijana starosne dobi pacijenata u vreme hirurške intervencije bila je 13 meseci (3-110.75). **Zaključak:** Precizna dijagnoza kongenitalnih anomalija GITa je važna zbog prevencije mogućih komplikacija i udruženosti sa drugim anomalijama.

**Ključne reči: kongenitalne anomalije, gastrointestinalni trakt, Hiršprungova bolest, Mekelov divertikulum, atrezija**

## Prevalence and types of congenital anomalies of the gastrointestinal tract in the operative material

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**Objective:** Analysis of the types and frequency of congenital anomalies of the GIT in the five-year period (2016-2020) of the Institute of Pathology "Prof. Dr. Djordje Joannovic ", Faculty of Medicine, Belgrade. **Introduction:** The gastrointestinal tract (GIT) undergoes a large number of complex and precisely regulated processes during intrauterine development, and disorders that can occur during different periods of development lead to a whole spectrum of congenital anomalies. Aim: Analysis of the types and frequency of congenital anomalies of the GIT in the five-year period (2016-2020) of the Institute of Pathology "Prof. Dr. Djordje Joannovic ", Faculty of Medicine, Belgrade. **Material and Methods:** Retrospective analysis of the frequency of various gastrointestinal anomalies surgically treated at the University Children's Hospital Tirsova in Belgrade in a five-year period (2016-2020). The study included patients in whom the presence of a congenital GIT anomaly was confirmed histopathologically and/or by imaging techniques. **Results:** In the five-year period, 103 cases of congenital GIT anomalies were registered: 32 cases of Hirschsprung's disease (31.1%), 32 Meckel's diverticula (31.1%), 13 intestinal atresias/stenosis (12.6%), 12 anal atresias (11.6%), 7 hypertrophic pyloric stenosis (6.8%) and

3 cystic bowel duplications (2.9%). Rare anomalies, each of which was registered in one patient (9.7%) were: cystic duplication of the esophagus, omphalomesenteric fistula, enteric cyst of the gastrocolic ligament, anomaly of the muscular wall of the intestine and segmental dilatation of the ileum. Among patients with congenital anomalies, 72 were male and 31 female. The median age of patients at the time of surgery was 13 months (3-110.75). **Conclusion:** Accurate diagnosis of congenital anomalies of the GIT is important for the prevention of possible complications and association with other anomalies.

**Key words: congenital anomalies, gastrointestinal tract, Hirschsprung's disease, Meckel's diverticulum, atresia**

## P1-12

## Senescencija u meningiomima: imunohistohemijska studija

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**Cilj:** Cilj studije je bio ispitivanje uticaja procesa senescencije (ćelijskog starenje) na progresiju meningioma u viši gradus. **Uvod:** Meningiomi su tumori koji potiču od meningotelijalnih ćelija, gde većina njih pripada gradusu 1 prema klasifikaciji tumora Centralnog Nervnog Sistema Svetske Zdavstevene Organizacije (CNS WHO). Faktori koji utiču na progresiju u viši gradus (atipični meningiom – CNS WHO gradus 2 i anaplastični meningiom – CNS WHO gradus 3) još uvek nisu ispitani. Senescencija je predložena kao potencijalni mehanizam koji favorizuje malignu transformaciju ovih tumora. Lizozomalni enzim beta – galaktozidaza (β-gal) i inhibitori ciklin-zavisne kinaze p16 i p21 predloženi su kao pouzdani markeri procesa senescencije. **Materijal i metode:** U ovoj retrospetkivnoj studiji, analizirali smo 318 meningioma, od kojih je 178 bilo gradusa 1 prema CNS WHO klasifikaciji, 133 je bilo gradusa 2 i 7 je bilo gradusa 3 prema pomenutoj klasifikaciji. Tkivni mikronizovi (TMN) su formirani od tri cilindra svakog tumora. Tkivni mikronizovi su zatim bojeni imunohistohemijski, koristeći antitela za β-gal, p16 i p21, sa eksternom pozitivnom kontrolom za svaki marker i negativnom kontrolom za svaki slajd. **Rezultati:** Statistički značajna razlika između meningioma gradusa 1 i gradusa 2 prema CNS WHO klasifikaciji je uočena u vidu ekspresije markera p16 (p=0,006) i β-gal (p=0,004). Pozitivna povezanost gradusa tumora sa ekspresijom markera p16 (p=0,016) i β-gal (p=0,002) je takođe primećena. **Zaključak:** Povećana ekspresija u slučaju 2 od 3 markera senescencije kod atipčnih meningioma sugeriše aktivaciju procesa senescencije, a koji verovatno ne igra ulogu u progresiji gradusa mengioma.

**Ključne reči: senescencija, mengiom, atipični meningiom**

## Senescence in meningiomas: An immunohistochemical study

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**Objective:** Investigation of the influence of the senescence process on the progression to the higher grade of meningiomas. **Introduction:** Meningiomas are tumors originating from meningothelial cells, the majority of them belonging to the grade 1 according to the classification of the tumors of the Central Nervous System World Health Organization (CNS WHO). Factors contributing to the progression to the higher grade (atypical meningioma – CNS WHO grade 2 and anaplastic meningioma – CNS WHO grade 3) have not been elucidated yet. The senescence has been proposed as a potential mechanism constraining the malignant transformation of tumors. Lysosomal enzyme beta-galactosidase (β-gal) and inhibitors of cyclin-dependent kinases p16 and p21 have been suggested as reliable markers of the senescence process. **Material and Methods:** In this retrospective study, we analyzed 318 meningiomas, 178 being CNS WHO grade 1, 133 being CNS WHO grade 2 and 7 being CNS WHO grade 3. Tissue microarrays (TMA) were constructed with 3 cores of each tumor. TMA slides were stained immunohistochemically on the same run, using antibodies for β-gal, p16 and p21, with an external positive control for each marker and negative control for each slide. **Results:** Statistically significant difference between meningiomas CNS WHO grade 1 and grade 2 was observed in the expression of markers p16 (p=0.006) and β-gal (p=0.004). The positive correlation of the tumour grade with expression of markers p16 (p=0.016) and β-gal (p=0.002) was also noted. **Conclusion:** The increase in the expression of 2 out of 3 senescence markers in atypical meningiomas suggests the activation of the senescence process which likely does not play role in the progression of the grade in meningiomas.

**Key words: senescence, meningioma, atypical meningioma**

## P1-13

## Retke mutacije receptora epidermalnog faktora rasta u ćelijama uznapredovalog adenokarcinoma pluća

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**Cilj:** Cilj ovog istraživanja bio je da se utvrdi učestalost prisustva retkih EGFR mutacija kod pacijenata sa uznapredovalim adenokarcinomom pluća, te da se utvrdi pojedinačna zavisnost prisustva mutacije u tumorskim ćelijama sa određenim kliničko-patološkim karakteristikama. **Uvod:** Najčešće zastupljene EGFR mutacije su mutacije egzona 19 i 21, dok u retke tipove spadaju mutacije egzona 20 i 18. Retki tipovi EGFR mutacija su u vezi sa smanjenim odgovorom na terapiju inhibitorima tirozin kinaze, stoga tačna procena njihove zastupljenosti je ključna u efikasnom lečenju. **Materijal i metode:** Prospektivno-retrospektivna studija obuhvatila je 309 pacijenata sa uznapredovalim adenokarcinomom pluća u Institutu za plućne bolesti Vojvodine u Sremskoj Kamenici u periodu od 01. januara 2020. godine do 31. decembra 2021. godine. Mutacija je detektovana PCR metodom. Analizirane su kliničko-patološke karakteristike: pol, dob, pušačke navike, stadijum bolesti i histološki tip tumora. **Rezultati:** Od 309 ispitanih pacijenta EGFR mutacija je potvrđena kod 42 pacijenta (13,59%). Zabeležena je visoka učesta-

lost (30,95%) retke mutacije egzona 20 kod trinaest pacijenata, sedam žena i šest muškaraca, većinom pušača (83,33%) sa potvrđenim solidnim adenokarcinomom pluća u 50% slučajeva. Jedan pacijent, muškarac sa negativnim pušačkim statusom, imao je tačkastu mutaciju G719X egzona 18 (2,38%), mešanog patohistološkog tipa adenokarcinoma. Kod svih pacijenata sa retkom EGFR mutacijom dokazana je limitirana osetljivost na inhibitore tirozin kinaze. Od klasičnih EGFR mutacija najčešće je potvrđena mutacija egzona 21 (35,71%) i egzona 19 (28,57%). **Zaključak:** Rezultati naše studije ukazuju na visoku učestalost mutacije egzona 20 (30,95%) kod starijih pacijenata, pušača sa potvrđenim solidnim histološkim podtipom adenokarcinoma pluća i limitiranom osetljivošću na inhibitore tirozin kinaze.

**Ključne reči: adenokarcinom pluća, EGFR mutacija, PCR, ciljana terapija**

## Rare mutations of epidermal growth factor receptors in tumor cells of advanced lung adenocarcinoma

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**Objective:** To determine frequency of rare EGFR mutations in patients with advanced lung adenocarcinoma and individual dependence of the presence of mutations in tumor cells with certain clinical and pathological characteristics. **Introduction:** The most common EGFR mutations are exon 19 and 21 mutations, while rare types include exon 20 and 18. Rare types of EGFR mutations are associated with reduced response to tyrosine kinase inhibitor (TKI) therapy, so accurate assessment of their presence is crucial in effective treatment. **Material and Methods:** The prospective-retrospective study included 309 patients with advanced adenocarcinoma of the lung at the Institute for Lung Diseases of Vojvodina in two year period. The mutation was detected by PCR. Clinical and pathological characteristics were analyzed: sex, age, smoking habits, stage of the disease, and histological type of tumor. **Results:** Of the 309 patients, the EGFR mutation was confirmed in 42 patients (13.59%). A high incidence (30.95%) of rare exon 20 mutation was observed in thirteen patients, seven women and six men, mostly smokers (83.33%) with confirmed solid lung adenocarcinoma in 50% of cases. One patient, a man with negative smoking status, had point mutation in G719X exon 18 (2.38%) and mixed pathohistological type of adenocarcinoma. Limited susceptibility to TKI has been demonstrated in all patients with rare EGFR mutations. Of the classic EGFR mutations, the most commonly confirmed mutations were exon 21 (35.71%) and 19 (28.57%). **Conclusion:** The results of our study indicate high frequency of exon 20 mutation (30.95%) in smokers with confirmed solid histological subtype of lung adenocarcinoma, and limited susceptibility to TKI.

**Key words: lung adenocarcinoma, EGFR mutation, PCR, targeted therapy**

## P1-14

## Uticaj statina na ekspresiju bcl-2 u aorti

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**Cilj:** Cilj našeg istraživanja bio je ustanoviti prisustvo Bcl2+ makrofaga u zidu aorte pacijenata sa odnosno bez statinske terapije, i to u neizmenjenom zidu aorte, aorti sa promenama tipa ateroskleroze (blage i izražene), disekcije (D) i aortitisa (Ao). **Uvod:** Statini su lekovi koji inhibišu sintezu holesterola,

ali imaju i niz drugih efekata zbog čega su uključeni u terapiju različitih oboljenja Postoje indicije da utiču na preživljavanje tj. proces apoptoze makrofaga, što bi moglo uticati na tok oboljenja. **Materijal i metode:** Analizirano je 50 uzraka hiruirški odstranjene aorte pacijenta sa (Th-S grupa) tj. bez statina u terapiji (Th-nonS grupa). Tkivo je obrađeno standardnom histološkom tehnikom i obojen metodama hematoksilin-eozin (HE) i imunohistohemijskom metodom primenom anti-Bcl-2 antitela. Semikvantitativno je određeno uobičajeno, odnosno blago i izraženo pojačano prisustvo Bcl-2+ makrofaga. Graničnom vrednošću za pojačano prisustvo, smatrano je >5 Bcl-2+ makrofaga. Prikupljeni podaci su obrađeni u Microsoft Excell-u i IMB SPSS 23 Statistics-u. **Rezultati:** Primena statina povećala je prisustvo Bcl-2+ makrofaga u aortama bez i sa promenama u zidu (p<0,01). Izraženo pojačano prisustvo je značajno češće i u blagoj i izraženoj aterosklerozi Th-S (p<0,01). Izraženo pojačano prisustvo Bcl-2+ makrofaga u izraženoj aterosklerozi je značajno češće usled primene statina, u predelu intime i medije. I u disekciji i u aortitisu statini dovode do pojačanog prisustva Bcl-2+ makrofaga, bez razlike u prisustvu u određenom sloju zida. **Zaključak:** Statini dovode do pojačanog prisustva Bcl-2+ makrofaga, produžavaju njihov vek, kako u neizmenjenom tako i u obolelom tkivu aorte, kod svih posmatranih entiteta. Ovo ukazuje na potenciranje inflamacije i oštećenja zida aorte.
**Ključne reči: statini, Bcl-2, makrofagi, disekcija, aortitis**

## Efect of statins on bcl-2 expression in aorta

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**Objective:** We investigated the presence of Bcl2+ macrophages in the aorta of patients with or without statin therapy, in unaltered or aorta with pathohistological changes (atherosclerosis, dissection and aortitis). **Introduction:** Statins are cholesterol synthesis inhibitors, with other effects. There are indications that they affect macrophage apoptosis, which could affect the course of the disease. **Material and Methods**: Fifty aorta samples of a patients with (Th-S) or without statins in therapy (Th-nonS) were analyzed. After standard histological processing. tissue was stained by hematoxylin-eosin and immunohistochemical methods (anti-Bcl-2 antibodie). The usual, ie mild and pronounced increase of Bcl-2+ macrophages presence was determined semiquantitatively. The limit value for increased presence was >5 Bcl-2+ macrophages. The collected data were processed in Microsoft Excell and IMB SPSS 23 Statistics. **Results:** Statin administration increased the presence of Bcl-2+ macrophages in the aorta without and with pathohistological changes (p <0.01). Pronounced increase of Bcl-2+ macrophages is significantly more common in mild and severe atherosclerosis of Th-S samples (p <0.01). Statins lead to more frequent pronounced increase of Bcl-2+ macrophages in severe atherosclerosis, in the intima and media. In both dissection and aortitis, statins lead to increased presence of Bcl-2+ macrophages, with no differences to a particular wall layer. **Conclusion:** Statins lead to an increased presence of Bcl-2+ macrophages, prolonging their life, both in unaltered and in diseased aortic tissue, in all observed entities. This indicates an increase in inflammation and damage to the aortic wall.

**Key words: statins, BCL-2, macrophages, disection, aortitis**

**P1-15**

## Maligni mešoviti Milerov tumor (karcinosarkom) tela materice: iskustvo jedne institucije

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**Cilj:** Određivanje kliničkih i patohistoloških parametara koji karakterišu pojavu MMMT, procena faktora rizika i upotrebe imunohistohemije. **Uvod:** Maligni mešoviti Milerov tumor (MMMT) je redak, agresivni tumor materice koji se pretežno javlja u starijoj populaciji. Izgrađen je iz epitelne i mezenhimalne komponente i deli se na homologni i heterologni histološki tip. **Materijali i metode:** Studija je obuhvatila 30 pacijentkinja sa patohistološki verifikovanim MMMT u periodu od januara 2009. do decembra 2019. godine lečenih na Institutu za onkologiju Vojvodine. U studiji su procenjivani različiti kliničko-demografski parametri. **Rezultati:** Prosečna starost pacijentkinja iznosila je 65 godina. Faktori rizika bili su: menopauza, hipertenzija, gojaznost, dijabetes tip II, hereditet, nuliparitet, lečenje tamoksifenom i prethodno zračenje karlice. Najčešći simptom bilo je postmenopauzalno krvarenje. Patohistološka dijagnoza je u većini slučajeva postavljena nakon kiretaže. Kod svih pacijentkinja sprovedena je histerektomija sa obostranom adneksektomijom. Adjuvantnu terapiju je primilo 70% pacijentkinja, najčešće u vidu hemioterapije sa kompletnom radioterapijom. Hemioterapiju je primilo 57% pacijentkinja, najčešće kao polihemioterapiju kombinovanu sa drugim terapijskim modalitetima. Najčešći hemioterapijski protokol bio je Cisplatin-Ifosfamid (47,1% slučajeva). Većina pacijentkinja nalazila se u FIGO stadijumima I i II (80%). Kod 40% pacijentkinja primećeni su recidivi, prosečno nakon 16 meseci. Recidivi su se javljali kod pacijentkinja bez obzira na adjuvantu terapiju. Najznačajnija antitela u detekciji epitelne komponente bila su AE1/AE3 i CK-7, a u detekciji mezenhimalne Vimentin i Actin. **Zaključak:** MMMT je redak tumor koji se javlja kod starijih postmenopauzalnih žena koje se javljaju zbog postmenopauzalnog krvarenja. Bez obzira na primenjenu terapiju rano recidivira.

**Ključne reči: karcinosarkom, maligni mešoviti Milerov tumor, materica**

## Malignant mixed Miller tumor (Carcinosarcoma) of the uterus: experience of an institution

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**Objective:** Determination of clinical and pathohistological features of MMMT, assessment of risk factors and the use of immunohistochemistry. **Introduction:** Malignant Mixed Miller Tumor (MMMT) is a rare, aggressive uterine tumor that predominantly occurs in older women. It is consisted of epithelial and mesenchymal component and is divided into homologous and heterologous histological types. **Material and Methods:** Study included 30 patients with histopathological diagnosis of MMMT from January 2009 to December 2019 treated at the Oncology Institute of Vojvodina. The study evaluated different clinical and demographic parameters. **Results:** Average age of patients was 65 years. Risk factors included: menopause, hypertension , obesity, type II diabetes, heredity, nulliparity, tamoxifen treatment and pelvic radiation. Postmenopausal bleeding was the most common symptom. Pathohistological diagnosis was in most cases made after curettage. Hysterectomy with bilateral adnexectomy was performed in all patients. Adjuvant therapy was applied to 70% of patients, most often in the form of chemotherapy with complete radiotherapy. 57% of patients received chemotherapy, most often as polychemotherapy with other therapeutic modalities. Most common chemotherapy protocol was Cisplatin-Ifosfamide (47.1%). Majority of patients were in FIGO stages I and II (80%). In 40% of

patients, relapses were observed, on average after 16 months. Relapses occurred regardless of adjuvant therapy. Most significant antibodies in the detection of epithelial component were AE1 / AE3 and CK-7, and in the detection of mesenchymal component Vimentin and Actin. **Conclusion:** MMMT is a rare tumor that occurs in older postmenopausal women. Most common symptome is postmenopausal bleeding. Regardless of the therapy applied, it recurs early.

**Key words: carcinosarcoma, malignant mixed Mullerian tumor, uterus**

## P1-16

## Rezultati kliničko-patološke studije pacijenata sa Hodgkinovim limfomom u Kliničkom centru Crne Gore

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**Cilj:** U radu prikazujemo demografske karakteristike (pol i starosna dob) i patohistološke karakteristike Hodgkinovog limfoma kod pacijenata u Crnoj Gori u periodu od 2005. do 2015. godine. **Uvod:** Grupa Hodgkinovih limfoma je relativno rijetko oboljenje, govoreći globalno, sa incidencom od 2.7-2.8/100000. Značaj ovog obolejnja se ogleda u činjenici da je ovo jedan od najčešćih maligniteta u mlađoj životnoj dobi. **Materijal i metode:** U radu je korišćena baza podataka pacijenata liječenih od Hodgkinovog limfoma na Klinici za hematologiju Kliničkog centra Crne Gore. Prikupljeni su podaci o polu, starosti i histološkom tipu. **Rezultati:** Ukupno je bilo 130 registrovanih pacijenata u desetogodišnjem periodu. Većina registrovanih su bili muškarci, 83 slučaja ili 63,8%. Od svih ispitanika muškog pola 74,7% je bilo mlađe od 55 godina, a kod žena 61,7% je bilo mlađe od 55 godina. Najviše registrovanih je bilo sa nodularnom sklerozom, 45% ili 58 slučaja i sa mješovitom celularnošću, 42% ili 55 slučaja. Ostali pacijenti su bili sa nodularnom limfocitnom predominacijom, 7% ili 10 slučaja i klasičnim limfomom bogatim limfocitima, 6% ili 7 slučaja. **Zaključak:** Hodgkinov limfom je učestaliji kod muškaraca, bez statistički značajne razlike u distribuciji histološkog tipa i starosti prema polu. Pik je u uzrastu od 25 do 34 godine, na račun muškog pola, dok je kod žena broj ujednačen po dobnim grupama. Pacijenti sa nodularnom limfocitnom predominacijom i mješovitom celularnošću su značajno stariji, nego pacijenti sa klasičnim Hodgkinovim limfomom i nodularnom sklerozom. Trend kretanja je ujednačen i bez značajne razlike u brzini promjene između muškaraca i žena.

**Ključne reči: Hodgkinov limfom, histološki tip, baza podataka**

## Results clinical-pathological study of patients with Hodgkin's lymphoma, Clinical Center Montenegro

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**Objective:** Demographic characteristics (sex and age) and pathohistological characteristics of Hodgkin's lymphoma among patients in Montenegro from 2005 to 2015. **Introduction:** Group of Hodgkin's lymphomas is a relatively rare disease, an incidence of 2.7-2.8 / 100000. Significance of disease is reflected in fact that this is one of the most common malignancies at younger. **Material and Methods:** Database of patients treated from Hodgkin's lymphoma at Haematology Clinic at Clinical Center of Montenegro used in paper. Data on sex, age and histological type were collected. **Results:** Total number of registered patients for the last ten years is 130. The majority of those registered are male, 83 cases or 63.8%. Of all male respondents, 74.7% were under the age of 55, and 61.7% among women were under the age of 55. Most registered cases with nodular sclerosis are 45% or 58 cases and mixed cellula-

rity is 55 cases or 42%, with nodular lymphocyte predominant of 7% or 10 cases and classical lymphocyte-rich lymphoma 6% or 7 cases. **Conclusion:** Hodgkin's lymphoma is more common among males, no significant statistical difference in distribution of histological type and age by sex. Peak is between 25 to 34 age refers to male, for the women number is equal by age groups. Patients with nodular lymphocyte predominant and mixed cellularity are significantly older than patients with classical Hodgkin's lymphoma and nodular sclerosis. Trend movement is uniform and without a significant difference in the rate of change between men and women.

**Key words: Hodgkin's lymphoma, histological type, data base**

## P1-17

## Efikasnost citologije otiska i histologije smrznutih rezova u „ex tempore" analizi plućnih promena

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**Cilj:** Ova studija imala je za cilj da komparira pouzdanost citologije otiska i histologije smrznutih rezova u intraoperativnoj dijagnostici promena u plućima nerazjašnjene etiologije. **Uvod:** Histološka analiza smrznutih rezova je najčešće korišćen metod za intraoperativnu evaluaciju promena u plućima, međutim zahteva značajne kapacitete u smislu opreme, osoblja i vremena. Nasuprot tome, citologija otiska je brza, jeftina i pouzdana alternativa. **Materijal i metode:** Retrospektivna studija obuhvatila je 193 pacijenta koji su hospitalizovani na Institutu za plućne bolesti Vojvodine radi razjašnjenja etiologije i lečenja infiltrativne promene u plućima. U toku dijagnostičkog/terapijskog hiruškog zahvata dobijen je uzorak tkiva sa kojeg je prvo uzet otisak, a zatim je uzorak standardno obrađen za ex tempore histološku analizu. Senzitivnost, specifičnost, pozitivna i negativna prediktivna vrednost u određivanu malignosti lezije izračunati su u odnosu na konačni patohistološki nalaz. **Rezultati:** Citološkom analizom otiska nađeno je 65 benignih i 128 malignih oboljenja, dok je na histologiji smrznutih rezova nađeno 53 benignih i 140 malignih oboljenja. Na konačnim patohistološkim nalazima dokazano je 48 benignih, a 145 malignih bolesti. Senzitivnost, specifičnost, pozitivna i negativna prediktivna vrednost u citologiji otiska iznosili su, redom 88,03%, 100%, 100% i 67,92%, dok su isti parametri na histologiji smrznutih rezova iznosili, redom 96,53%, 100%, 100% i 90,57%. Nedostatak otiska je u mogućnosti dobijanja neadekvatnih uzoraka, međutim u našoj studiji adekvatnost je bila visoka, čak 97,30%. Lažno negativni nalazi citologije nađeni su u adenokarcinomima (n=8), skvamoznim karcinomima (n=2), sekundarnim tumorima pluća (n=5), karcinoidu (n=1) i solitarnom fibroznom tumoru (n=1). **Zaključak:** Citologija otiska pruža pouzdanu alternativu tradicionalnoj histološkoj dijagnostici u intraoperativnoj evaluaciji promena u plućima.

**Ključne reči: citologija otiska, „ex tempore", histologija smrznutih rezova, plućne promene**

## Efficacy of imprint cytology and frozen section histology in ex tempore analysis of lung lesions

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**Objective:** To examine the accuracy of imprint cytology (IC) and frozen section histology (FS) in the intraoperative diagnosis of lung masses with unexplained etiology. **Introduction:** FS is the most commonly used method for intraoperative evaluation of the lesions in the lungs, however it requires significant capacity in equipment, staff and time. In contrast, IC is a fast, cheap and reliable alternative. **Material and Methods:** The retrospective study included 193 patients who were hospitalized to clarify the etiology and treat the infiltrative lung lesion. During the diagnostic/therapeutic surgery, a tissue sample was obtained and imprint was taken. Then the samples were processed as standard procedure for ex tempore histological analysis. Sensitivity, specificity, positive and negative predictive value in determining the malignancy were calculated in a relation to final pathohistological diagnosis. **Results:** Analysis of IC revealed 65 benign and 128 malignant diseases, while 53 benign and 140 malignant diseases were diagnosed in the FS. At the final pathohistological findings, 48 benign and 145 malignant diseases were proven. Sensitivity, specificity, positive and negative predictive value for IC were, respectively, 88.03%, 100%, 100% and 67.92%, while the same parameters on FS were, respectively, 96.53%, 100%, 100% and 90.57%. Inadeqate samples were disadvantage of IC, however, in our study the adequacy was high (97.30%). False negative cytology findings were found in adenocarcinomas (n=8), squamous carcinomas (n=2), secondary lung tumors (n=5), carcinoid (n=1), and solitary fibrous tumor (n=1). **Conclusion:** IC provides a reliable alternative to the traditional histological diagnosis in the intraoperative evaluation of lung masses with unexplained etiology.

**Key words: imprint cytology, „ex tempore", frozen section histology, lung lesions**

## P1-18
## Nottingham prognostički indeks: iskustva jednog dijagnostičkog centra

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**Cilj:** Utvrđivanje distribucije NPI u ispitivanoj populaciji carcinoma dojke i poređenje pouzdanosti između NPI i NPI+ prognostičkih indeksa. **Uvod:** Nottingham prognostičkog indeksa (NPI) je jednostavan test koji se koristi za predviđanje progresije bolesti kod karcinoma dojke. **Materijal i metode:** Retrospektivnom i propsektivnom studijom je obuhvaćeno 130 operisanih žena zbog carcinoma dojke u period od 2008. do 2013. godine u Univerzitetskoj bolnici Foča. Nottingham prognostički indeks plus (NPI+) je izračunat po sledećoj formuli NPI + [HER2-PR]. Prognostičke grupe su formirane u sledećim intervalima: 2-2.4 (odlična prognoza); 2.4-3.4 (dobra prognoza); 3,5-5,4 (srednja prognoza); >5,4 (loša prognoza). **Rezultati:** Većina (80%) ispitivanih žena je pripadala grupi srednje i loše NPI prognoze. Pacijentkinje sa karcinom dojke koje su pripadale grupi odlične i dobre NPI prognoze nisu imale progresiju bolesti. Po šest osoba u grupi srednje i loše NPI prognoze razvila se progresija bolesti. Češće (8,7%) progresiju bolesti su imale osobe sa dobrom prognozom u odnosu nagrupu srednjeg (3,3 %) NPI rizika. U odnosu na poboljšani (NPI+) kod 12% osoba srednje grupe i kod 17,6% loše prognostičke grupe je došlo do progresije bolesti. Svih šest osoba sa progresijom bolesti kod lošeg NPI + prognostičkog indeksa su imale udaljene metastaze. U grupama odlične i dobre prognoze po NPI+ indeksu pacijentkinje nisu imale progresiju bolesti. **Zaključak:** Nepovoljan NPI indeks u našoj studiji

rezultat je malog broja carcinoma dojke koji su otkrivene skrining mamografskim pregledima. U našoj studiji NPI+ prognostički indeks je bolje korelirao sa progresijom bolesti i biološkim ponašanjem carcinoma dojke u odnosu na standardni NPI prognostički indeks koji se trenutno primjenjuje (p=0,0006, p<0,01).

**Ključne reči: Nottingham prognostički indeks, karcinom dojke, prognoza**

## Nottingham prognostic indexes: a single- centre experience

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**Objective:** Nottingham prognostic index (NPI) is a simple test use for predicting brest cancer recurrence. **Introduction:** Determining the distribution of NPI in the examined population with breast cancer and comparing the reliability between NPI and NPI +. **Material and Methods:** A retrospective and prospective study included 130 women with breast cancer operated from 2008 to 2013 in the University Hospital Foča. The Nottingham prognostic index plus (NPI +) was calculated according to the following NPI + [HER2-PR] formula. Prognostic groups were formed at the intervals: 2-2.4 (excellent prognosis); 2.4-3.4 (good prognosis); 3.5-5.4 (medium prognosis); > 5.4 (poor prognosis). **Results:** The majority (80%) of women who were examined belonged to the group of medium and poor NPI. In the good prognosis group 8,7% of women, and 3,3 % in the medium NPI group, developed disease progression. Progression was more common in women with a good prognosis compared to the group with medium NPI risk. In relation to the improved NPI (NPI +), 12% women in the medium NPI+ prognosis and 17.6% of the poor NPI+ prognostic group progressed. All six women with disease progression in the poor NPI +had distant metastases. In the excellent and good prognostics groups according NPI+, the patients did not have disease progression. **Conclusion:** The unfavorable NPI in our study is the result of the small number of breast cancers detected by screening mammograms. In our study the NPI+ prognostic index correlates better with the disease progression and biological behavior of breast cancer compared to the traditional NPI (p=0.0006, p<0.01).
**Key words: Brest cancer, Nottingham prognostic index, prognosis**

## P1-19

## Procena pupljenja tumora kao potencijalnog histopatološkog prognostičkog markera oralnog karcinoma

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**Cilj:** Korelisati broj tumorskih pupoljaka sa kliničko-patološkim karakteristikama oralnog planocelularnog karcinoma (OPK). **Uvod:** Pupljenje tumora (PT) je histopatološka karakteristika koja predstavlja raštrkani obrazac invazije koji se sastoji od izolovanih pojedinačnih tumorskih epitelnih ćelija ili tumorskih ćelija u malim klasterima koji se vide na invazivnom frontu dispergovanih unutar strome. Prethodne studije su otkrile da je prisustvo PT povezano sa metastazama u limfnim čvorovima, pojavom recidiva, udaljenim metastazama i smanjenim preživljavanjem kod brojnih karcinoma uključujući OPK. **Materijal i metode:** U studiju su uključeni uzorci 28 pacijenata sa OPK-om. Na osnovu preparata obojenih H&E, procenjen je broj tumorskih pupoljaka. PT je definisano kao malo tumorsko gnezdo sastavljeno od <5 tumorskih ćelija. Preparati tumora su najpre skenirani na 10× objektivu. Nakon toga, PT je prebrojano na području najveće invazije u 10 polja na ×200. Korelacija između klinič-

ko-patoloških podataka (pol, starost, recidiv, veličina tumora, lokacija, diferencijacija, dubina invazije, invazija u kost, status margine i TNM stadijum) i PT je sprovedena korišćenjem odgovarajućeg statističkog modela. **Rezultati:** Spirmanova korelacija je pokazala umerenu pozitivnu korelaciju (r=0,3) između PT i veličine tumora. Drugi kliničko-patološki podaci nisu pokazali međusobnu povezanost. Univarijantnim linearnim regresionim modelom nije nađena uzročno-posledična povezanost između PT kao zavisne varijable i ispitivanih paramtera. **Zaključak:** Suprotno drugim studijama, PT nije bilo u korelaciji sa drugim kliničko-patološkim karakteristikama pacijenata sa OSCC. Potrebna su buduća istraživanja, na većoj veličini uzorka, za procenu PT kao potencijalnog histopatološkog markera OPK.

**Ključne reči: oralni karcinom, pupljenje tumora, H&E bojenje**

## Assessing tumor budding as a potential histopathological prognostic marker of oral cancer

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**Objective:** To correlate the number of tumor buds with the clinico-pathological features of oral squamous cell carcinoma (OSCC). **Introduction:** Tumor budding (TB) is a histopathological feature that represents a scattered pattern of invasion consisting of isolated single tumor epithelial cells or tumor cells in small clusters seen at the invasive front dispersed within the stroma of variable distance. Previous studies revealed that the presence of TB has been linked with lymph node metastasis, recurrence, distant metastasis and reduced survival in numerous cancers including OSCC. **Material and Methods:** Archival clinical specimens of 28 OSCC patients were included in the study. On the basis of H&E-stained slides, number of tumor buds was evaluated. TB was defined as small tumor nests composed of <5 tumor cells. Tumor slides were scanned at 10× objective. Subsequently, TB was counted at the most invasion area in 10 fields at ×200. Correlation between clinico-pathological data (gender, age, recurrence, tumor size, location, differentiation, depth of invasion, bone invasion, margin status and TNM stage) and TB were carried out using appropriate statistical model. **Results:** Spearman correlation showed moderate positive correlation (r=0.3) between TB and tumor size. Other clinico-pathological data did not show any interconnection. The cause-and-effect relationship between TB as a dependent variable and the examined parameters was not found by the univariate linear regression model. **Conclusion:** On the contrary of other studies, tumor budding was not correlated with other clinico-pathological characteristics of OSCC patients. Future researches, on the greater sample size, are needed for evaluation of TB as potential histopathological marker of OSCC.

**Key words: oral cancer, tumor budding, H&E staining**

## P1-20
## Synchronous primary thyroid carcinomas: single-center series

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**Objective:** This study aims to present a series of cases of synchronous tumors in one or both thyroid lobes. **Intorduction:** Considering the relatively high prevalence of thyroid cancers, the synchronous occurrence of two histologically distinct thyroid carcinomas is uncommon. **Material and Methods:** We retrospectively researched our database for synchronous tumors of the thyroid gland. Out of the total 236 diagnosed thyroid malignancies on histology in a 10 years period, we have diagnosed five cases

of synchronous carcinomas, one of which is an extremely rare combination of synchronous occurrence of papillary carcinoma and intrathyroid thymic carcinoma. We present the microscopic and immunohistochemical analyses performed for diagnosing these cases, which represented serious diagnostic dilemmas. **Results:** Case1: Mixed medullary and follicular cell carcinoma in both thyroid lobes in a 19 years old girl. Case 2: Mixed medullary and papillary thyroid carcinoma in the same lobe in a 62-year-old woman. Case 3: Follicular and papillary carcinoma in the same lobe in a 46 years old woman. Case 4: Papillary carcinoma and a follicular tumor of uncertain malignant potential in the right lobe of a 35 years old woman. Case 5: Papillary carcinoma in the left thyroid lobe and an intrathyroid thymic carcinoma in the right lobe in a 45 years old woman. **Conclusion:** Synchronous occurrence of different histological types of primary malignant thyroid neoplasms is very rare, especially the extremely rare intrathyroid thymic carcinoma, even more intriguing due to its simultaneous occurrence with the papillary carcinoma.

**Key words: synchronous thyroid tumors, intrathyroid thymic carcinoma, papillary and follicular carcinoma, medullary and papillary carcinoma, medullary and follicular carcinoma, follicular tumor of uncertain malignant potential**

## P1-21

## Pouzdanost iglene biopsije u određivanju Glison skora karcinoma prostate

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**Cilj:** Utvrditi pouzdanost iglene biopsije (CNB) u određivanju GS karcinoma prostate uz analizu faktora koji utiču na promenu GS u CNB i operativnom materijalu. **Uvod:** Karcinom prostate je najučestaliji malignitet muškaraca. Glison skor (GS) ukazuje na histološki gradus tumora, te bolesnike smešta u jednu od pet kategorija (ISUP Grade Group) i među najznačajnijim je prediktorima prognoze. **Materijali i metode:** Retrospektivno, ispitivanje je sprovedeno u Centru za patologiju i histologiju Univerzitetskog kliničkog centra Vojvodine u Novom Sadu. Korišćeni su arhivski patohistološki nalazi bolesnika kojima je na osnovu vrednosti serumskog PSA i kliničkog pregleda prostate postavljena sumnja postojanja neoplastičnog procesa, te načinjena CNB. Studija je obuhvatila 56 muškaraca koji su u dvogodišnjem vremenskom periodu (2018-2019.) bili podvrgnuti obema procedurama (CNB i radikalnoj prostatektomiji) u našoj ustanovi. **Rezultati:** Prosečna starost obolelih bila je 66,75±4,24 godina, dok su vrednosti PSA varirale 1,18-31,31 ng/L. Najčešći tumor je bio GS 3+4 odnosno ISUP GG 2 (u 37,5%), stadijuma pT2 (60%). Perineuralna invazija je znatno češće registovana u odnosu na limfovaskularnu (59% vs. 20%). Kod polovine pacijenata na operativnom materijalu GS je „apgrejdovan", dok je svim bolesnicima sa CNB GS 3+3 zabeležen viši GS na operativnom materijalu. Kod 18 pacijenata (32%) skor je ostao nepromenjen, dok je 10 bolesnika (17,8%) imalo niži GS postoperativno. Metodama linearne regresije i analizom varijanse utvrđeno je da sa starošću pacijenata raste i GS (b=0,05, p=0,03) kao i broj bioptičkih uzoraka sa tumorom (b=0.025, p=0.005), za svaku narednu starosnu godinu. **Zaključak:** Iako je CNB pouzdana metoda određivanja GS/ISUP GG karcinoma prostate, procena istog na operativnom materijalu je svakako neophodna.

**Ključne reči: Glison skor, ISUP GG, karcinom prostate, iglena biopsija, prostatektomija**

## Reliability of needle biopsy in determining the Gleason score of prostate cancer

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**Objective:** To determine core needle biopsy (CNB) reliability in predicting final operative sample GS and to analyze factors influencing the change of GS in those two material types. **Introduction:** Prostate cancer is the most common male malignancy. The Gleason score (GS) represents the tumor histological grade, placing patients in one of five categories (ISUP Grade Group). GS is one of the most important prostate cancer prognosis predictors. **Material and Methods:** Retrospective study was conducted at the Center for Pathology and Histology of the University Clinical Center of Vojvodina. Using patients' histories, patients with suspected prostate cancer were identified (after physical examination and PSA values). The study included 56 men who underwent CNB and radical prostatectomy both at our institution in a two-year period (2018-2019). **Results:** Patients' average age was 66.75±4.24 years. PSA varied from 1.18 to 31.31 ng/L. The most common tumor was GS 3+4 (ISUP GG 2) - 37.5%, pT2 stage (60%). Perineural invasion was more frequently registered than lymphovascular invasion (59% vs. 20%). GS was upgraded on the surgical material in half of the total patients. All patients with CNB GS 3+3 had a higher GS on the surgical material. For 18 patients (32%) the score remained unchanged, while 10 patients (17.8%) had a lower GS postoperatively. Linear regression and analysis of variance showed that GS (b=0.05, p=0.03) and the number of positive biopsy samples (b=0.025, p=0.005) increase with the patients age for every year. **Conclusion:** Although CNB is a reliable method for GS/ISUP GG prostate cancer defining, surgical material assessment is necessary, too.

**Keywords: Gleason score, ISUP GG, prostate cancer, CNB, prostatectomy**

## P1-22

## Endobronhijalni lipom koji oponaša bronhopneumoniju i malignitet: prikaz slučaja

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**Cilj:** Prikazujemo slučaj endobronhijalnog lipoma, retkog, benignog tumora koji je pretežno lokalizovan u centralnim disajnim putevima, uglavnom u desnom plućnom krilu sa incidencom od 0.1% do 0.5% svih tumora pluća. Ukoliko postanu dovoljno veliki, ovi tumori mogu dovesti do endobronhijalne opstrukcije uzrokujući atelektazu i rekurentnu pneumoniju, često oponašajući maligni proces.**Prikaz slučaja:** Pacijentkinja starosti 62 godine javila se na klinici zbog upornog kašlja, kratkog daha, otežanog disanja, hemoptizija i bolova u grudima unazad mesec dana, sa istorijom rekurentne desnostrane pneumonije. Bila je strasni pušač i gojazna. Radiografija grudnog koša i kompjuterizovana tomografija (CT) pokazali su nepravilno proširenje desnog hilusa sa poljem konsolidacije u gornjem desnom režnju pluća. Endoskopski, endobronhijalna lezija je izgledala kao polipozna, žuta mekana masa glatke površine. Urađena je bronhoskopska resekcija i dostavljeno je više tkivnih uzoraka za mikroskopski pregled. Patohistološkom procenom bronhijalnih tkivnih uzoraka utvrđeno je zrelo masno tkivo sa fokalnim zapaljenskim promenama ispod epitela, bez mitotskih figura i ćelijske atipije. Normalan respiratoni epitel sa fokalno prisutnom skvamoznom metaplazijom pokrivao je lipom. Diferencijalna dijagnoza je uključivala hamartom, pleomorfni adenoma, metastatski liposarkom i angiomiolipom. Ki-67 indeks proliferacije je bio nizak što je potvrdilo benignu prirodu ove strukture i dijagnozu endobronhijalnog lipoma. Zaključak: Imajući u vidu mogućnost izazivanja upale pluća i simuliranja maligne neoplazme, ovaj prikaz slučaja ističe važnost razmatranja lipoma u diferencijalnoj dijagnostici.

**Ključne reči: lipom, endobronhijalne neoplazme, bronhopneumonija**

**An endobronchial lipoma mimiking the bronhopneumonia and malignancy: A case report**

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**Objective:** We present a case of endobronchial lipoma, a rare, benign tumor that is predominantly localized in the central airways, mainly in the right lung with an incidence of 0.1% to 0.5% of all lung tumors. If they become large enough, these tumors can lead to endobronchial obstruction, causing atelectasis and recurrent pneumonia, often mimicking the malignant process. **Case report:** A 62-year old female patient presented at clinic reporting with a persistent cough, shortness of breath, dyspnea, hemoptysia and chest pain for a month, with a history of the recurrent right pneumonia. She was a heavy smoker and obese. Chest radiography and computerized tomography scan (CT) showed irregular enlarging of the right hilus with consolidation area in the right upper lobe. Endoscopically, endobronchial lesion appeared as polypoid, yellow soft mass with smooth surface. Bronhoscopic resection was conducted and multiple tissue samples were delivered for the microscopic examination. Patohistological evaluation of the bronchial tissue specimens revealed mature adipose tissue with focal inflammatory changes underneath of the epithelium, without any mitotic figure and cell atypia. Normal respiratory epithelium with focally present squamous metaplasia covered the lipoma. Differential diagnose included hamartoma, pleomorphic adenoma, metastatic liposarcoma and angyomiolipoma. The Ki-67 proliferative index was low which confirmed the benign origin of this structure and diagnose of the endobronchial lipoma. **Conclusion:** Having in mind the possibility of causing a lung inflammation and simulating a malignant neoplasm, this case report highlights the importance of considering the lipoma in differential diagnose.

**Key words: lipoma, endobronchial neoplasms, bronchopneumonia**

**P1-23**

**Adenofibrom pluća: prikaz slučaja**

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**Cilj:** Tumori sa veoma niskom incidencijom predstavljaju potencijalni problem, jer nisu deo uobičajene prakse. Adenofibrom pluća pokazuje patohistološka preklapanja sa fibroadenomom dojke, hamartomom, ali i dobro diferentovanim adenokarcinomom pluća, te je za dalji tok lečenja veoma važno diferencirati prirodu promene. **Prikaz slučaja:** Pacijent muškog pola, starosti 67 godina, navodi tegobe u vidu svraba i nelagode. CT grudnog koša ukazuje na jasno ograničenu promenu dimenzija 35x25mm, periferne lokalizacije. Nakon parcijalne lobektomije i laboratorijske obrade, uradjena je detaljna patohistološka analiza. Načinjena su imunohistohemijska bojenja, kojima je potvrđeno da se radi o plućnom adenofibromu. Pacijent se nakon učinjene intervencije dobro oseća. **Zaključak:** Adenofibrom pluća, kao veoma retka bolest, predstavlja dijagnostički izazov, uzimajući u obzir nespecifične kliničke manifestacije i patohistolosku sliku koja pokazuje morfološka i imunohistohemijska preklapanja sa drugim promenama.

**Ključne reči: adenofibrom, pluća, imunohistohemija**

## Lung Adenofibroma: A case report

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**Objective:** Tumors with a very low incidence are a potential problem because they are not part of common practice. Pulmonary adenofibroma shows pathohistological overlaps with breast fibroadenoma, hamartoma, but also well-differentiated lung adenocarcinoma, so it is very important to differentiate the nature of the change for the further course of treatment. **Case report:** A 67-year-old male patient reported itching and discomfort. CT of the chest indicates a clearly limited change in the dimensions of 35x25mm, peripheral localization. After partial lobectomy and laboratory treatment, a detailed pathohistological analysis was performed. Immunohistochemical staining was performed, which confirmed that it was a pulmonary adenofibroma. The patient feels well after the intervention. **Conclusion:** Pulmonary adenofibroma, as a very rare disease, presents a diagnostic challenge, taking into account non-specific clinical manifestations and pathohistological picture showing morphological and immunohistochemical overlaps with other changes.

**Key words: adenofibroma, lung, immunohistochemistry**

## P1-24

## Pluća kao retka primarna lokalizacija tumora porekla perifernog nerva: prikaz tri slučaja

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**Cilj:** Plućni tumori porekla omotača perifernog nerva u literaturi se navode samo kroz prikaze slučajeva.Primarni mezenhimalni tumori pluća su retki. Sarkomi pluća, iako je njihova ukupna učestalost u primarnim tumorima pluća mala (<0,5%) dominiraju u odnosu na benigne lezije.
U periodu od jedne godine (2021-2022) na Institutu za patologiju Medicinskog fakulteta u Beogradu dijagnostikovana su tri primarna mezenhimalna tumora pluća neuralne diferencijacije. Dijagnoza je postavljena na osnovu morfološke i imunohistohemijske analize. **Prikaz slučaja:** U prvom slučaju se radi o ženi, staroj 45 godina sa Hornerovim sindromom izazvanim intrapulmonalnim, jasno ograničenim nodusom, najvećeg prečnika 3cm. Morfološke i imunohistohemijske karakteristike (Vimentin+, S100+, SOX10+, PRAME-) su ukazale na melanotični švanom. Relativno jasno ograničeni tumor u plućima, najvećeg prečnika 9 cm je opisan kod žene stare 56 godina sa dispnejom i kašljem. Histološki se verifikuje morfologija neuralnog tumora, uz povišen mitotski indeks, nuklearnu atipiju i imunofenotip; Vimentin+, S100+, CD10+, EMA+. Postavlja se dijagnoza niskogradusnog malignog tumora omotača perifernog nerva -MPNST gradus II. Najteže simptome izazvane brzorastućim tumorom u desnom plućnom krilu i kolapsom okolnog parenhima, ima dečak star 17 godina sa dijagnostikovanom Neurofibromatozom tip I. Punkciona biopsija pokazuje vretenastoćelijsku proliferaciju uz retke epiteloidne ćelije, izražene atipije i imonofenotipa; S100+, NF+, CD10+, CK AE1/AE3 -/+. Tumor odgovara visokogradusnom tumoru- MPNST gradus IV u sa fokalno epiteloidnom komponentom. **Zaključak:** Primarni tumori pluća porekla omotača perifernog nerva su do sada opisani kao sporadični slučajevi ili u sklopu neurofibromatoze kod mlađih pacijenata. S obzirom na učestalost metastatskih tumora u plućima, neophodno je isključiti primarne ekstratorakalne sarkome.

**Ključne reči: MPNST, melanotični švanom, sarkomi pluća, neurofibromatoza**

## Primary intrapulmonary nerve sheet tumor: A three cases presentation

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**Objective:** Primary pulmonary nerve sheet tumors are described in literature only as case reports. Primary mesenchimal tumors in lungs are rare. Lung sarcomas are more often than benign mesenchimal tumors, although they account less than 0,5% of all primary lung tumors. In one year (2021-2022) it has been identified three cases of lung primary nerve sheet tumors, in Institute of pathology in Belgrade. Diagnose is based on morphological and immunohistochemical findings. **Case reports:** We present, as a first case, women 45 years old with Horner syndrome, caused by pulmonary nodular tumor, 3 cm in size. Morphological and immunohistochemical characteristics (Vimentin+, S100+, SOX10+, PRAME-) proved melanotic schwannoma. Well circumscribed pulmonary tumor, 9cm in size was verified in woman 56 years old with dyspnea and cough. Microscopically and immunohistochemically (Vimentin+, S100+,CD10+, EMA+) tumor showed neural diferentiation, moderate nuclear atypia and increesed mitotic index. Diagnose of low grade malignant nerve sheet tumor (MPNST gradus II) was set. The most severe sympthoms caused by rapidly growing tumor in lung, had a 17 years old boy with Neurofibromatosis typ I. Biopsy revealed spindle cell tumor, highly atipycal with scatered epitheloid cells. According to histology and immunofenotype (S100+, NF+, CD10+, CKAE1/AE3-/+), we concluded this case as high grade MPNST gradus IV with epitheloid component. **Conclusion:** Primary lung nerve sheet tumor are found as sporadic cases or in patients with Neurofibromatosis type I. Metastases of extrathoracal sarcomas in lungs are much more frequent, so it is very important to distinguish them from primary lung sarcomas.

**Key words: MPNST, melanotic schwannoma, lung sarcoma, neurofibromatosis**

**P1-25**

## Bol u stomaku kao inicijalna klinička prezentacija mikrocelularnog karcinoma pluća: prikaz slučaja

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**Cilj:** Predstavljamo slučaj mikrocelularnog karcinoma pluća sa metastazom u transverzalnom kolonu. Mikrocelularni karcinom pluća predstavlja brzo rastući, visoko maligni tumor, sa visokom stopom proliferacije, agresivnim ponašanjem i ranim široko rasprostranjenim metastazama u vreme postavljanja dijagnoze. Najčešća mesta metastaza su mozak, jetra, nadbubrežne žlezde, kosti i koštana srž. Metastaze mikrocelularnog karcinoma pluća u gastrointestinalni sistem su retke, sa samo nekoliko objavljenih slučaja širom sveta. **Prikaz slučaja:** Pacijent je 61-godišnji muškarac, koji je primljen u bolnicu zbog bolova u stomaku. Pacijent nije imao respiratorne simptome, ali se mesecima žalio na gastrointestinalne tegobe. Urađena mu je hirurška resekcija debelog creva i patohistološkom analizom ustanovljen je invazivan tumor, neuroendokrinog izgleda, sastavljen od klastera sitnih tumorskih ćelija, oskudne citoplazme, pleomorfnih jedara, bez uočljivih jedaraca, koji je infiltrovao sve slojeve zida dostavljenog transverzalnog kolona. IHC analiza je pokazala da tumorske ćelije eksprimiraju TTF1, CD56, synaptophysin, chromogranin A i CK7. Ki67 je pokazao proliferativnu aktivnost u oko 70% jedara tumorskih ćelija. Mikromorfologija i IHC analize su ukazale na prisustvo visoko maligne neuroendokrine neoplazme, primarnog porekla iz pluća, što je CT snimanjem i potvrđeno. **Zaključak:** Iako su metastaze mikrocelularnog karcinoma pluća u debelom crevu veoma retke, trebalo bi obratiti više pažnje na gastrointestinalne simptome, obaviti kolonoskopiju i PET/CT snimanje na vreme, u

cilju preciznije dijagnostike neuobičajenih metastatskih mesta, kao što je gastrointestinalni trakt. Brža dijagnoza bi svakako obezbedila kraći vremenski interval od postavljanja dijagnoze do terapije.

**Ključne reči: mikrocelularni karcinom pluća, transverzalni kolon, metastaze, imunohistohemija**

**Abdominal pain as initial clinical presentation of small cell lung cancer: A case report**

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**Objective:** We present a case of the SCLC with the metastasis to transversal colon. Small cell lung cancer (SCLC) is fast growing, highly malignant tumor, with extremely high proliferative rate, aggressive behavior and early, widespread metastases at the time of diagnosis. The preferred metastatic sites are the brain, liver, adrenal glands, bone and bone marrow. However, metastasis in the gastrointestinal tract are rare, with only a few published cases worldwide. **Case report:** The patient was a 61-year old man admitted to the hospital due to abdominal pain. The patient had no respiratory symptoms, but he was complaining of gastrointestinal discomfort for months. The pathohistological examination of the resected transversal colon revealed an invasive tumor, with neuroendocrine appearance, composed of clusters of small tumor cells, with sparse cytoplasm, pleomorphic nuclei and no distinct nucleoli, which infiltrated all the layers of the transverse colon. IHC analysis showed that tumor cells expressed TTF1, CD56, synaptophysin, chromogranin A, and CK7. Ki67 showed proliferative activity in about 70% of tumor cell nuclei. Micromorphology and IHC analyzes indicated the presence of a highly malignant neuroendocrine neoplasm, of primary lung origin, which was confirmed by CT imaging. Conclusion: Although SCLC metastasis in the colon is very rare, we should pay more attention to gastrointestinal signs, performing colonoscopy and PET/CT scan on time that could provide valuable information for more precisely diagnosing of unusual SCLC metastatic sites, such as gastrointestinal tract. Faster diagnosis would certainly provide a shorter time interval from diagnosis to therapy.

**Key words: small cell lung cancer (SCLC), transversal colon, metastasis, immunohistochemistry**

**P1-26**

**Retki benigni tumori pluća pod kliničkom sumnjom maligniteta: prikaz tri slučaja**

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**Cilj:** Prikazujemo tri izuzetno retka benigna tumora pluća kod pacijenata kod kojih je klinički postavljena sumnja na malignitet.Benigni tumori pluća se najčešće dijagnostikuju rutinskom radiografijom ili ciljanom radiografijom kod pacijenata sa prethodno dijagnostikovanim malignim tumorom u okviru skrininga i praćenja pacijenata. **Prikazi slučajeva:** U našoj seriji slučajeva dva od tri bolesnika imala su prethodno dijagnostkovan maligni tumor druge lokalizacije. U prvom slučaju prikazujemo -69godišnju ženu kod koje je pre 9 godina dijagnostikovan svetloćelijski adenokarcinom bubrega. Ciljana radiografija pokazala je kružnu promjenu, veličine 12 mm u desnom plućnom krilu i postavila kliničku sumnju na metastatsku promjenu. Nakon patohistološke evaluacije dijagnostikovan je alveolarni adenom pluća. U drugom slučaju prikazujemo -60godišnju ženu kojoj je godinu dana ranije dijagnostikovan difuzni B krupnoćelijski Non-Hodgkin limfom želuca. Ciljana radiografija pluća pokazala je tumor veličine 50 mm u levom pluću pod kliničkom sumnjom na diseminaciju osnovne bolesti. Nakon patohistološke evaluacije postavljena je dijagnoza izuzetno retkog primarnog benignog tumora, meningeoma pluća. U trećem slučaju prikazujemo ženu od 46 godina kod koje su u plućima obostrano viđeni noduli veličine do 15 mm pod kliničkom sumnjom na metastatske promjene. Nakon patohistološke evaluacije postavljena je patohistološka dijagnoza lejomioma pluća u okviru benigne

metastazirajuće lejomiomatoze. **Zaključak:** Pluća su jedan od najčešćih ciljnih organa za metastaze malignih tumora. Postojanje metastaza u plućima može presudno uticati na izbor režima liječenja. Benigni tumori pluća mogu koegzistirati sa malignim tumorima, oponašajući radiološke nalaze metastatskih depozita. Hiruška ekstirpacija i patohistološka dijagnoza ostaju zlatni standard u dijagnozi.

**Ključne reči: benigni tumori, pluća, metastaze**

## Rare benign lung tumors mimicking malignancy: Review of three cases

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**Objective:** The aim of this study was to present three extremely rare benign lung tumors in patients with clinically suspected malignancy. Benign lung tumors are most often diagnosed by routine or targeted radiography in patients with previously diagnosed malignant tumor, as part of patient follow-up. **Case reports:** In our series of cases, two out three patients had a previously diagnosed malignant tumor of another localization. In the first case, we present a 69-year-old woman diagnosed with adenocarcinoma of the kidney 9 years earlier. Targeted radiography showed a circular change, 12mm in size in the right lung and a clinical suspicion of metastatic change. After pathohistological evaluation, alveolar lung adenoma was diagnosed. In the second case, we show a 60-year-old woman diagnosed with diffuse large B-cell Non-Hodgkin's gastric lymphoma a year earlier. A targeted radiograph of the lung showed a 50 mm large tumor in the left lobe under clinical suspicion of dissemination of the underlying disease. After pathohistological evaluation, the diagnosis of primary lung meningioma was made. In the third case, we present a 46-year-old woman in whom nodules, up to 15 mm in size, were visalised bilaterally in the lungs under clinical suspicion of metastatic changes. After pathohistological evaluation, pathohistological diagnosis of benign metastatic leiomyoma was made. **Conclusion:** The lungs are one of the most common target organs for metastases. The presence of lung metastases decisively influences the choice of treatment. Benign lung tumors can coexist with malignant, radiologically mimicking metastatic deposits. Surgical extirpation and pathohistological diagnosis remain the gold standard in diagnosis.

**Key words: benign tumors, lung, metastases**

**P1-27**

## Maligni melanocitni tumor omotača nerva medijastinuma sa pleuralnim metastazama: prikaz slučaja

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**Cilj:** Prikazujemo slučaj medijastinalnog agresivnog melanocitnog tumora omotača nerva sa pleuralnim metastazama U medijastinumu mogu nastati različiti benigni i maligni tumori poreklom perifernih nerava koji se označavaju kao medijastinlani neurogeni tumori (MNT). Neurogeni tumori medijastinuma su retki, a naročto prisustvo melanocitnih neurogenih tumora. **Prikaz slučaja:** Bolesnica, stara 34. godina javila se kod svog izabranog lekara sa 6-mesečnom istorijom povremenog kašlja i nejasnim bolovima u grudima. Kompjuterska tomografija (CT) je pokazala prisustvo velike apikalne mase u levom hemitoraksu i multinodularno zadebljanje pleure. Učinjena je leva torakotomija i parcijalna resekcija tumorske mase sa biopsijom pleure. Histološki, dokazano je prisustvo jako pigmentovane neoplazme vretenastih ćelija, raspoređenih u solidna polja i fascikuluse sa nekoliko jasno definisanih područja nekroze u medijastinalnoj masi i u pleuri. Imunohistohemijski je pokazano intenzivno di-

fuzno bojenje na S100, MelanA i HMB45, dok su pancitokeratin CK AE1/AE3, GFAP i PRAME bili negativni. Ki67 proliferativni indeks je iznosio oko 5% . Genetska analiza, metodom lančane reakcije polimeraze (PCR) pokazala je odsustvo mutacije (wild type) u BRAF V600E genu. Dalje genetske studije nisu preduzete. Postavljena je dijagnoza malignog melanocitnog tumora nervnog omotača sa pleuralnim metastazama i preporučen je dermatološki pregled kako bi se isključila mogućnost metastatskog melanoma. **Zaključak:** Melanocitni neurogeni tumor predstavlja dijagnostički izazov kod nalaza pigmentnih tumora grudne duplje koji zahteva pažljivu morfološku, imunohistohemijsku i genetsku analizu kako bi se postavila pravilna dijagnoza.

**Ključne reči: melanocitni tumor omotača nerva, tumori medijastinuma, metastaze pleure**

## Mediastinal malignant melanotic nerve sheath tumor with pleural metastasis: A case report

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**Objective:** We describe an unusual case of an mediastinal aggressive melanotic nerve sheath tumor with pleural metastasis. Various benign and malignant tumors of peripheral nerve origin can occur in the mediastinum, which are referred to as mediastinal neurogenic tumors (MNT). Neurogenic tumors of the mediastinum are rare, and especially the presence of melanocyte neurogenic tumors. **Case report:** We present a 34-year-old woman presented to her primary care provider with a 6-month history of intermittent cough and vague chest haeviness. Computer tomography (CT) revealed presence of a large apical mass in the left hemithorax and multipal nodular pleural thickening. Left thoracotomy and partial resection of the tumor mass with pleural biopsy were performed. Histology revealed a heavily pigmented spindle cell neoplasma, aranged in solid sheets and fascicles with several well-defined areas of necrosis, both in mediastinal mass and pleura. Immunohistochemistry showed strong staining for S100, MelanA and HMB45, while pancytokeratin CK AE1/AE3, GFAP and PRAME was negative. Ki67 was positive in 5% of the tumor cells. Genetic analysis by polymerase chain reaction (PCR) showed the absence of mutations (wild type) in the BRAF V600E gene. Further genetic studies were not undertaken. Diagnosis of malignant melanotic nerve sheat tumor with pleural metastasis was confirmed and dermatological review was recommended to rule out the possibility of metastatic melanoma. **Conclusion:** Melanocitic neurogenic tumor represent a diagnostic challenge for pigmented thoracic tumor and careful morphologycal, immunohistochemical and genetics analysis is required to lead to proper diagnosis.

**Key words: melanotic nerve sheath tumor, mediastinal mass, pleural metastasis**

## P1-28

## Tipični karcinoid i DIPNECH kod pacijentkinja obolelih od karcinoma dojke: prikaz dva slučaja

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**Cilj:** Prikaz dva slučaja DIPNECH-a (engl. diffuse idiopathic pulmonary neuroendocrine cell hyperplasia) koji je udružen sa karcinoidom i prethodno operisanim duktalnim karcinomom dojke. **Prikazi slučajeva:** Bolesnicama starosti 69 i 74 godina, sa istorijom operativno lečenog duktalnog karcinoma dojke i aktuelnim osećajem dispneje i nadražajnim kašljem, u sklopu redovnih onkoloških kontrola načinjena je kompjuterizovana tomografija pluća. Registrovane su višestruke nodularne promene koje

su bile suspektne na metastaze primarnog malignog oboljenja. Spirometrijskim pregledom verifikovan je lak opstruktivni poremećaj ventilacije. Nakon preoperativne pripreme urađena je hirurška intervencija (atipična resekcija gornjeg i srednjeg režnja desno kod prve i segmentektomija prvog segmenta levo kod druge pacijentkinje). Patohistološkom analizom nađene su linearne proliferacije uniformnih okruglastih ćelija fino dispergovanog jedarnog hromatina izgleda „so i biber" iznad bazalne membrane bronhiolarne sluznice, morfoloških karakteristika DIPNECH-a. Pored toga nađu se područja opisanih ćelija sa invazijom bazalne membrane koje odgovaraju tumorletu (veličina <5mm) i karcinoidu (veličina >5mm) stadijuma IA. Imunohistohemijskom analizom (CD56, sinaptofizin, hromogranin: pozitivni; estrogen, progesteron, TTF-1, napsin A i GATA- 3: negativni) u oba slučaja potvrđena je neuroendokrina diferencijacija opisanih ćelija. Registrovana je i bronhiolarna fibroza sa luminalnim suženjem. **Zaključak:** DIPNECH predstavlja retko oboljenje koje može biti asimptomatsko ili se može manifestovati simptomima konstriktivnog bronhiolitisa- nedostatkom vazduha i nadražajnim kašaljem što može biti pogrešno protumačeno kao astma. Suprotno tome, usled frekventnijeg radiološkog praćenja onkoloških bolesnika, češće se dijagnostikuje i kod asimptomatskih slučajeva, te je kod ovakvih pacijenata ekstenzivno uzorkovanje hirurškog materijala od velikog značaja, kako bi se izbeglo pogrešno dijagnostikovanje koje može uticati na dalji tok lečenja.

**Ključne reči: DIPNECH, karcinoid, tumorlet, neuroendokrine ćelije**

## Typical carcinoid and DIPNECH in patients with breast cancer: Review of two cases

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**Objective:** To present two cases of DIPNECH (diffuse idiopathic pulmonary neuroendocrine cell hyperplasia) associated with carcinoid and previously operated ductal breast cancer. **Case reports:** Case report: A 69-years-old and 74-years-old patients with surgically treated ductal breast cancer history and current dyspnea and irritable cough, underwent lung computed tomography as part of regular oncological follow-ups. Multiple nodulars were registered that were suspicious for primary malignancy metastases. Spirometric examination verified mild obstructive ventilation disorder. After preoperative preparation, surgery was done (right upper and middle lobes atypical resection in the first and left segmentectomy of the first segment in the second patient). Pathohistological analysis revealed linear uniform round cells proliferations with finely dispersed nuclear chromatin with "salt and pepper" appearance above the bronchial mucosa basement membrane, morphological characteristics of DIPNECH. In addition, areas of the described cells with basal membrane invasion corresponding to the tumorlet (size <5mm) and carcinoid (size >5mm) stage IA were found. Immunohistochemical analysis (CD56, synaptophysin, chromogranin: positive; estrogen, progesterone, TTF-1, napsinA and GATA-3: negative) in both cases confirmed the neuroendocrine differentiation of the described cells. Bronchiolar fibrosis with luminal narrowing was also registered. **Conclusion:** DIPNECH is a rare disease that may be asymptomatic or present with constrictive bronchiolitis symptoms- shortness of breath and irritating cough which can be misinterpreted as asthma. Conversely, due to more frequent radiological monitoring of oncology patients, it is more often diagnosed in asymptomatic cases, and in such patients extensive sampling of surgical material is of great importance, in order to avoid misdiagnosis that may affect the further treatment course.

**Key words: DIPNECH, carcinoid, tumorlet, neuroendocrine cells**

## P0STER SESIJA II
## POSTER SESSION II

### P2-1
### Leiomyosarcoma of the vagina: A case report

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**Objective:** Primary malignant tumors of the vagina represent only about 2% of all gynecological malignancies. Primary vaginal sarcomas account for about 2% of all malignant vaginal lesions, with leiomyosarcomas being the most common form of malignant vaginal mesenchymal tumors. **Case report:** We present a case of a 49-year-old woman who was admitted to the University Clinic of Obstetrics and Gynecology complaining of vaginal discharge, abdominal pain and vaginal bleeding within 8 months. Ultrasound and MR showed a solid tumor infiltrating the posterior wall of the vagina. Complete surgical excision of tumor was accomplished. The operative material was composed of two lobulated, solid tumor masses with a total weight of 192 g, with dimensions 11x7x2,5-4cm and 7x5x2cm. The cut surface of the tumor showed nonencapsulated, gray-white glistening mass with hemorrhagic and necrotic areas. The tissue specimens were fixed in 10% buffered formalin and embedded in paraffin. Immunostainings with antibodies against Vimentin, SMA, CD10, S100, Desmin, CD99, Caldesmon, Podoplanin, CKAE1/AE3 and CD31 were made. Histologically, this tumor was composed of spindle-shaped cells with blunt-ended nuclei, arranged in storiform pattern with marked pleomorphism and nuclear atypia. Many bizarre cells and multinucleated cells were also seen. There were large regions of coagulative necrosis and high mitotic rate (27 per 10 HPF). Immunohistochemically, the tumor cells were positive for Vimentin, SMA, CD10 and negative for S100, Desmin, CD99, Caldesmon, Podoplanin, CKAE1/AE3 and CD31. The Ki67 proliferative index was 40%. A final diagnosis of high grade leiomyosarcoma was made. Postoperatively, the patient received adjuvant chemotherapy with gemcitabine and docetaxel for eight cycles. The tumor showed a progressive growth with distant metastasis to liver and paraortal and retroperitoneal lymph nodes. The patient died of the disease 9 months after diagnosis. **Conclusion:** Vaginal leiomyosarcoma is an extremely rare disease with very poor prognosis in advanced stages and undetermined ideal treatment regimen. Reporting rare tumors contributes to collecting data for rare neoplasms in order for proper early diagnosis and adequate therapy to be established.

**Keywords: leiomyosarcoma, vagina, immunohistochemistry**

### P2-2
### Džinovski horangiom placente: prikaz slučaja

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**Cilj:** Horangiomi su netrofoblastni, benigni vaskularni tumori i sa prevalencom od 1% predstavljaju najučestalije tumore placente. Najčešće su malih dimenzija i asimptomatski, a njihov nalaz je slučajan. Džinovski horangiomi, veći od 5cm, izuzetno su retki, a kao uzrok nastanka mogući su povišen krvni pritisak i starost majke kao i višeplodne trudnoće. **Prikaz slučaja:** Pacijentkinja stara 27 godina dolazi na Kliniku za ginekologiju i akušerstvo u Novom Sadu u 31. gestacijskoj nedelji blizanačke trudnoće zbog ultrazvučno verifikovanog oligohidramniona, hidropsa i horangioma placente drugog ploda. Dan

nakon prijema, ultrazvučno je verifikovano odsustvo srčane radnje drugog ploda. Nakon deset dana izvršen je hitan carski rez sa živorođenim prvim i mrtvorođenim drugim gemelusom, a posteljice i tumor poslati su u Centar za patologiju i histologiju u Novom Sadu. Na makroskopskom pregledu tumor je lobulirane građe, glatke i zamućene površine, dimenzija 12x9x5,5 cm, dok je na preseku sivkasto-ružičaste boje, solidne građe i blago staklastog izgleda. Mikroskopskom analizom uzoraka, bojenih standardnom HE metodom, ustanovljeni su od okoline jasno ograničeni i umnoženi fetalni kapilarni krvni sudovi i njihova okolna placentalna stroma. Endotelne ćelije koje grade vaskularnu mrežu su bez znakova atipije, pleomorfizma i uočljivih mitoza, dok je stroma fokalno hijalinizovana sa prisutnim retkim hemosiderofagima. Endotelne ćelije su imunohistohemijski pozitivne na CD31, CD34, GLUT-1 i SMA, dok je proliferativni indeks Ki67 izuzetno nizak. Mikroskopska i imunohistohemijske analize potvrdile su klinički i radiološki postavljenu dijagnozu. **Zaključak:** Džinovski horangiomi placente su izuzetno retki tumori i povezani su sa prenatalnim komplikacijama i nepovoljnim ishodom trudnoće.

**Ključne reči: Džinovski horangiom placente, CD31, CD34, GLUT-1**

## Giant placental chorangioma: A case report

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**Objective:** Chorangiomas are nontrophoblastic benign vascular tumors which are the most common placental tumors with a prevalence of 1%. They are usually small and asymptomatic and their finding is incidental. Giant chorangiomas, greater than 5 cm, are rare. Maternal age, hypertension, as well as multiple gestation pregnancy may play a role in their development. **Case report:** A 27-year-old patient was admitted to the Gynaecology and Obstetrics Clinic in Novi Sad in the 31st gestational week of twin pregnancy due to ultrasound-verified oligohydramnios, hydrops and chorangioma of the second placenta. The following day, absence of cardiac activity of the second fetus was verified by ultrasound. After ten days, an emergency caesarean section was performed with a liveborn first and a stillborn second twin. Placentas and the tumor were sent to the Center for Pathology and Histology in Novi Sad. On gross examination, the tumor was lobulated, with smooth and blurred surface, measuring 12x9x5.5cm. On the cross-section the tumor was solid, grayish-pink and of a slightly glassy appearance. Microscopic analysis on standard HE staining, showed a well circumscribed mass of fetal capillary proliferation with surrounding placental stroma. The endothelial capillary cells were without signs of atypia, pleomorphism and noticeable mitoses, while the stroma was focally hyalinized with rare chemosiderophages being present. Endothelial cells were immunohistochemically positive for CD31, CD34, GLUT-1 and SMA, while the Ki67 proliferative index was extremely low. Microscopic and immunohistochemical analyses confirmed the clinical and radiological diagnosis. **Conclusion:** Giant placental chorangiomas are extremely rare tumors and are associated with prenatal complications and adverse pregnancy outcomes.

**Keywords: Giant placental chorangioma, CD31, CD34, GLUT-1**

**P2-3**

## Uznapredovali adenosarkom uterusa: prikaz slučaja

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**Cilj:** Prikazujemo slučaj adenosarkoma uterusa sa udaljenim metastazama. Adenosarkom uterusa je redak maligni tumor ženskog genitalnog trakta koji predstavlja oko 5% svih sarkoma uterusa. To je bifazni tumor, sagrađen od epitelne i mezenhimne komponente. Epitelnu komponentu karakteriše benigni žlezdani epitel, a mezenhimalna komponenta je maligna. **Prikaz slučaja:** Sedamdeset devetogodišnja žena je došla na pregled kod ginekologa zbog krvarenja iz vagine. Kliničkim pregledom utvrđeno je postojanje polipoidne tumorske promene u vagini koja prominira iz cerviksa. MR pregled male karlice pokazuje veliku heterogenu tumorsku masu koja nastaje iz tela uterusa, zauzima čitav kavum i cerviks i infiltriše vaginu, parametrijalno vezivno tkivo, adnexa i zadnji zid mokraćne bešike. Dodatno, CT grudnog koša i abdomena pokazuje prisustvo sekundarnih tumorskih depozita u plućima i jetri. Urađena je biopsija opisane tumorske promene. Histopatološki nalaz je pokazao prisustvo bifaznog tumor sa intraglandularnim „phylodes-like! projekcijama i periglandularnom kondenzovanom stromalnom atipičnom komponentom, mitotski aktivnom i fokalno nekrotičnom. Konačna histopatološka dijagnoza je bila adenosarkom. U daljem toku pacijentkinja je lečena simptomatskom i suportivnom terapijom zbog uznapredovale metastatske bolesti, lošeg performans statusa i kardiovaskularnih komorbiditeta. **Zaključak:** Kod žena svih starosnih grupa kod kojih je prisutna veća intrauterina polipoidna masa, neophodno, kao diferencijalnu dijagnozu, razmatrati i adenosarkom uterusa.

**Ključne reči: sarkom uterusa, adenosarkom, vaginalno krvarenje**

## A rare case of advanced adenosarcoma of the uterus

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**Objective:** We present a case report of uterine adenosarcoma with associated metastases. Uterine adenosarcoma is rare malignancy of the female genital tract, accounting for approximately 5% of uterine sarcomas. It is a biphasic tumor with both epithelial and mesenchymal component. The epithelial component is characterized by benign glandular epithelium and the mesenchymal component is malignant. **Case report:** A 79-year-old woman presented with a history of vaginal bleeding. Clinical vaginal examination revealed a fungating mass protruding through the cervical os. Magnetic resonance imaging (MRI) of the pelvis showed a large heterogenous mass that was arising from the uterine body, occupying the whole uterine cavity, extending beyond the uterus and involving parametrial connective tissue, adnexa, vaginal and urinary blader wall. Also CT scan of the thorax and abdomen showed secondary deposits in the lungs and liver. A biopsy of the described tumor mass was undertaken. Histopathological examination revealed biphasic tumor with phyllodes-like architecture and periglandular cuffing of atypical tumor cells, mitotic active, focally necrotic. Histopathological final diagnosis was adenosarcoma. The patient was simptomatic and suportive therapy treated because of the advanced stage of disease and cardiovascular comorbidity. **Conclusion:** In conclusion, in woman of all ages presenting with polypoid tumor mass, uterine adenosarcoma should be considered as a differential diagnosis.

**Keywords: uterine sarcoma, adenosarcoma, vaginal bleeding**

**P2-4**

## Folikularni limfom sa infiltracijom jajnika udružen sa karcinomom endometrijuma: prikaz slučaja

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**Cilj:** Prikazujemo slučaj folikularnog limfoma sa infiltracijom jajnika i desnih parametrija koji je verifikovan tokom operativnog lečenja karcinoma endometrijuma. **Prikaz slučaja:** Žena starosti 68 godina (P0, AB0) prikazana je Konziluijumu Instituta za Onkologiju Vojvodine nakon patohistološki verifikovanog karcinoma endometrijuma (Adenocarcinoma endometrioides cavi uteri, G1). MR abdomena i male karlice ukazao je na masivnu retroperitonealnu, mezenterijalnu i medijastinalnu limfadenomegaliju kao i masu uz lateralni rub tela materice desno. Indikovana je histerektomija sa obostranom adneksektomijom. Intraoperativno je uočena suspektna tumorska infiltracija desnih adneksa kao i konglomerat limfnih nodusa Ingvinalno desno i parailijakalno levo. Čvor ingivinalne regije se pošalje na ex tempore analizu (ne može isključiti limfoproliferativno oboljenje). Definitivni isečci pokazali su infiltraciju čvora atipičnim limfocitima koji su pozitini na CD20 (~100%), CD10, BCL-2 i negativni na CD23 i Cycilin-D, Ki-67 ~40%. Na osnovu morfološkog i imunohistohemijskog nalaza postavljena je dijagnoza: Lymphoma folliculare, "follicular pattern", G2. Definitini preparati operativnog matarijala pokazali su prisustvo seroznog "low grade" karcinoma endometrijuma koji je nastao u polipu endometrijuma (pT1aN0). Histološki se verifikuje infiltracija jajnika i paramterija prethodno opisanim limfomom dok se atipični limfociti verifikuju i u 6 od 12 limfnih nodusa ingvinalne regije desno. Postoperativno, indikuje se primena hemioterapije prema protoklu CHOP koja je uspešno sprovedena i pacijentkinja je nakon 6 meseci bez tegoba. **Zaključak:** U slučaju atipične limfadenopatije tokom operacije karicnoma endometrijuma., bez obzira na retkost ove pojave, treba isključiti prisustvo sinhronog folikularnog limfoma.

**Ključne reči: folikularni limfom, karcinom endometrijuma, sinhrono, limfadenomegalija**

## Follicular lymphoma with ovarian infiltration associated with endometrial cancer: A case report

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**Objective:** We report a case of follicular lymphoma with infiltration of the right ovary and parametrium, which was verified during the surgical treatment of endometrial cancer. **Case reports:** A 68-year-old woman (P0, AB0) was presented to the Consilium of the Institute of Oncology of Vojvodina after pathohistologically verified endometrial cancer (Adenocarcinoma endometrioides cavi uteri, G1). MRI of the abdomen and small pelvis showed massive retroperitoneal, mesenteric and mediastinal lymphadenomegaly, as well as mass along the lateral edge of uterine body. Hysterectomy with bilateral adnexectomy was indicated. Suspected tumor infiltration of the right adnexa as well as conglomerates of lymph nodes of right inguinal and left parailiac region was intraoperatively encountered. An inguinal lymph node was sent for ex tempore analysis (cannot rule out lymphoproliferative disease). Definitive sections showed node infiltration with atypical lymphocytes that are positive for CD20 (~ 100%), CD10, BCL-2 and negative for CD23 and Cycilin-D, Ki-67 ~ 40%. Based on morphological and immunohistochemical findings, the diagnosis was made: Lymphoma folliculare, 'follicular pattern', G2. Definite specimens of operative material showed the presence of serous "low grade" endometrial cancer that developed in a polyp (pT1aN0). The infiltration of the ovaries and parametrium by the previously described lymphoma was verified, while atypical lymphocytes was verified in 6 of the 12 lymph

nodes of the right inguinal region. Postoperatively, the chemotherapy according to the CHOP protocol is indicated, which was successfully performed and the patient is disease free 6 months after treatment. **Conclusion:** In the case of atypical lymphadenopathy during surgery of endomterial carcinoma, regardless of the rarity, the presence of synchronous follicular lymphoma should be ruled out.

**Keywords: follicular lymphoma, endometrial carcinoma, lymphadenopathy, synchronous**

## P2-5

## Sitnoćelijski neuroendokrini karcinom cerviksa: prikaz slučaja

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**Cilj:** Prkazujemo slučaj sitnoćelijskog neuroendokrinog karcinoma grlića materice. Sitnoćelijski neuroendokrini karcinom grlića materice je redak tumor koji čini 1 – 3% svih tumora grlića materice. Prvi put je opisan grliću materice 1957. i histopatološki i imunohistohemijski) podseća na sitnoćelijski karcinom pluća. **Prikaz slučaja:** Žena stara 54 godine u postmenopauzi, žalila se na krvarenje iz vagine u trajanju od tri meseca. U biopsijskom uzorku su nađeni slabo kohezivni agregati uniformnih sitnih ćelija sa nejasnim ćelijskim granicama, oskudne citoplazme, hiperhromatičnih jedara sa fino granuliranim hromatinom, nuklearnim uklapanjem, neprominentnih nukleolusa, mitotski aktivne sa ekstenzivnom nekrozom. Tumorske ćelije formiraju male aciinuse koji podsećaju na rozete i pokazuju pozitivno bojenje na neuroendocrine markere (CD56, sinaptofizin i hromogranin), TTF-1 i Ki67 i negativno bojenje na: HMB45, CD99, CD117, desmin, CD10, CD45 i vimentin. Magnetna rezonanca pokazuje da tumor zahvata donju trećinu vagine, bez ekstenzije u pelvični zid (TNM/FIGO; T3a N0M0/ IIIA). Ona je pdvrgnuta hemoradioterapiji. Tri meseca nakon tretmana, pacijentkinja je bez simptoma i bez lokalno-regionalnog recidiva bolesti. Zaključak: Multimodalni tretman je neophodan u lečenju bolesnika sa SCNCC.

**Ključne reči: Sitnoćelijski neuroendokrini karcinom, cerviks, imunohistohemija**

## Small cell neuroendocrine cervical carcinoma: A case report

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**Objective:** We report a rare case of the small cell neuroendocrine cervical carcinoma. Small cell neuroendocrine cervical carcinoma (SCNCC) is rare tumor that comprises 1- 3% of all cervical tumors, first described in the cervix 1957. and histopathologically and immunohistochemistry resembles small cell carcinoma of the lung. **Case report:** A 54-year-old, postmenopausal women presented with a complaint of bleeding of the vagina for three months duration. Cervical biopsy revealed loose aggregates of uniform small cells with indistinct cell borders, scant cytoplasm, hyperchromatic nuclei with fine granular chromatin, nuclear molding, indistinct nucleoli, mitotic activity with extensive necrosis. Tumor cells form small acini resembling rosettes and neuroendocrine positive stains (CD56, TTF1, synaptophysin, chromogranin and Ki67) and negative stains for: HMB45, CD99, CD117, desmin, CD10, CD45 and vimentin. A magnetic resonance image scan showed that tumor involves lower third of vagina, no extension to pelvic wall (TNM/FIGO; T3aN0M0/IIIA). She underwent chemoradiotherapy. Three months after treatment, the patient was asymptomatic without loco-regional recurrence disease. **Conclusion:** Multimodality treatment is necessary in treatment the patients with SCNCC.

**Keywords: Small cell neuroendocrine carcinoma, cervix, immunohistochemistry**

## P2-6

## Džinovski dezmoid tumor u trudnoći

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**Cilj:** Prikazujemo redak slučaj fibromatoze - dezmoid tip (miksoidni izgled) kod trudnice**. Prikaz slučaja:** Tridesetjednogodišnja trudnica se javila u Univerzitetski Klinički Centar Vojvodine u septembru 2019.godine. Nakon fizikalnog pregleda, ultrazvučnog pregleda i magnetne rezonance, urađena je laparatomija u 15. nedelji trudnoće. Dimenzije tumora su bile 110x180x180mm, a težina 2840g. Makroskopski, tumor je bio nepravilnog oblika, sivkasto-beličaste boje, prekriven prozirnom kapsulom, naglašenog vaskularnog crteža. Na serijskim rezovima tumor je bio žućkasto-beličaste boje, rubno mrke boje, homogene građe, sa prisustvom tačkastog krvarenja. Fokalno su bile prisutne manje cistične formacije. Histološki, tumor je bio niske do umerene celularnosti, sagrađen od proliferalisalih izduženih, vretenastih ćelija, sa ovalnim i izduženim jedrima, koje su bile aranžirane u duge, izukrštane snopove, smeštene u gustoj, kolagenoj stromi. U većim područjima, stroma je bila miksoidno izmenjena, a same ćelije uniformne, vretenaste, mestimično zvezdastog oblika, izduženog jedra. Delom je tumor bio prožet svežom krvlju, uz prisustvo brojnih krvnih sudova, dilatiranih vena i arterija sa zadebljalim mišićnim slojem, okruženih hijalinom i perivaskularnim edemom. Tumor je fokalno pokazao znake infilrativnog rasta u okolno masno tkivo. Mitoze nisu viđene mikroskopski. Imunohistohemijski, tumorske ćelije su bile S100-, CK AE1/AE3-, Inhibin α-, EMA-, β Catenin nuclear+, STAT6-, Desmin-, Calretinin-, CD34-, SMA-, CD117-, Bcl2-, DOG1-, Vimentin+, CD99-, MDM2-, dok je Ki67 proliferativni indeks bio nizak (4-5%). Pacijentkinja je rodila zdravo muško dete i do danas nije bilo znakova recidiva bolesti. **Zaključak:** Prikazali smo slučaj uspešno odstranjenog dezmoid tumora koji se nalazio u korenu mezenterijuma i koji se delimično prostirao u retroperitoneum kod trudne žene.

**Ključne reči: fibromatoza, dezmoid, trudnoća**

## A giant desmoid tumor in pregnancy

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**Objective:** We present a rare case of Desmoid-type Fibromatosis (myxoid pattern). **Case report:** A 31-year-old pregnant woman admitted to University Clinical Center of Vojvodina in September 2019. After physical examination, ultrasound and Magnetic resonance imaging, laparotomy was performed in patient<s fifteenth week of gestation. Tumor was about 110x180x180mm in size and weighted 2840g. Grossly, the tumor was irregular, oval, white-greyish, with translucent capsule and enhanced vascularity. The cut section revealed homogenous, glistening white-yellowish surface, with spotting and darker areas at the periphery. Focally, there were small cysts in the tumor. Histologically, the tumor was low to moderate in cellularity, composed of proliferating spindle-shaped cells, arranged in long fascicles with spindle nuclei and pale cytoplasm. The stroma was dense, rich in collagen. There were wide loose myxoid areas and stellate cells with spindle nuclei. Also, the areas with hemorrhage and numerous small blood vessels and arteries with thickened wall surrounded with hyalin and perivascular edema were present. The tumor showed infiltrative growth into surrounding adipose fat tissue. Mitosis were

not found in the tumor. Immunohistochemically the tumor cells were S100-, CK AE1/AE3-, Inhibin α-, EMA-, β Catenin nuclear+, STAT6-, Desmin-, Calretinin-, CD34-, SMA-, CD117-, Bcl2-, DOG1-, Vimentin+, CD99-, MDM2- and Ki67 proliferative index was low(4-5%). The patient gave birth to healthy boy and till today has no sign of tumor recurrence. **Conclusion:** We reported a case of successfully resected desmoid tumor that occurred at the root of the mesentery with partially extending into the retroperitoneum of pregnant woman.

**Keywords: fibromatosis, desmoid, pregnancy**

**P2-7**

## Strumalni karcinoid jajnika: prikaz dva slučaja

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**Cilj:** Prikazujemo dva slučaja strumalnog karcinoida jajnika. Strumalni karcinoid je redak tumor jajnika iz grupe monodermalnih teratoma koji čini svega 0,1% tumora jajnika. Može biti deo zrelog teratoma ili se javiti u čistoj formi. Tumor grade dve blisko pomešane komponente: tkivo štitaste žlezde i dobro-diferentovani neuroendokrini tumor-karcinoid. **Prikaz slučaja:**, klinički asimptomatskih pacijentkinja, uzrasta 61 i 40 godina kojima su na rutinskim ginekološkim pregledima otkriveni tumorski uvećani jajnici. Radiološki i klinički pregledi su ukazivali na unilateralne benigne tumore, te je indikovan operativni tretman prema protokolu za tumore jajnika. Na pregled smo dobili tumore prečnika 115mm i 70mm, oba intaktne, glatke kapsule, na preseku cistično-solidne građe. Mikroskopske i imunohistohemijske analize su pokazale tumor građen od tkiva štitaste žlezde po tipu proliferativne strume (TTF1, Thyreoglobulin, Cytokeratin7 pozitivnost), uz koji neposredno raste karcinoid građen od trabekula, acinusa i solidnih gnezda tumorskih ćelija, minimalne nuklearne atipije ( Synaptophysin i Chromogranin A pozitivnost). Nađena je niska proliferativna aktivnost u tumorima (Ki67 <2%). Na osnovu opisanih patoloških nalaza postavljena je dijagnoza strumalnog karcinoida jajnika. Diferencijalno-dijagnostički razmišljali smo i o sekundarnoj malignoj transformaciji koja može nastati na terenu ovarijalne strume**. Zaključak:** Strumalni karcinoid se javlja najčešće u IA stadijumu bolesti, što je i naš slučaj. Uprkos postojanju neuroendokrinog tumora-karcinoida, tumor ima odličnu prognozu i benigno kliničko ponašanje kada je ograničen na jajnik. Karcinoidni sindrom, recidivi ili postojanje metastaza su opisani izuzetno. Operativni tretman u skladu sa godinama pacijentkinje je terapijski dovoljan, nakon čega se savetuje samo praćenje. Danas, nakon tri, odnosno dve godine od postavljanja dijagnoze, obe pacijentkinje su bez znakova bolesti.

**Ključne reči: strumalni karcinoid, teratom jajnika, ovarijalna struma**

## Ovarian strumal carcinoid: Review of two cases

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**Objective:** We present two cases of ovarian strumal carcinoid. Strumal carcinoid is an uncommon ovarian tumor from group of monodermal teratomas which incidence is 0,1% of all ovarian tumors. It can be part of mature teratoma or it may occur in pure form. SC is composed from intimate mixture of thyroid tissue and well differentiated neuroendocrine tumor grade I (carcinoid). **Case reports:** We report two cases of clinically asymptomatic women, 61- and 40- years old, who were diagnosed with ovarian enlargment on routine gynecological examinations. Radiological and clinical analyses revealed unilateral, most likely benign ovarian tumors, so surgical treatment, in accordance with protocol for

ovarian tumors was indicated. On macroscopic examination, both tumors present with smooth surface and intact capsule, measured 115mm and 70mm, both with cystic-solid features. Histologically and immunohistohemically, tumors were composed of thyroid tissue in form of proliferative struma (TTF1, Thyreoglobulin and Cytokeratin 7 positive) and carcinoid tumor with trabecular, insular and solid growth patern (Synaptophysin and Chromogranin A positive). Low mitotic activity confirmed (Ki67 <2%). According to pathological findings, a diagnosis of ovarian strumal carcinoid was made. Differential diagnosis that we have considered were secondary malignancy that may arise in ovarian struma. **Conclusion:** SC is usually IA pathological stage, as in our cases. Despite the presence of NET, these tumors have excellent prognosis and benign biological behavior when they are limited to the ovary. Carcinoid syndrome, tumor relapses and metastases are exceptional. The treatment is primarily surgical with follow up recommendation. Today, our patients are disease free after three and two years respectively.

**Keywords: strumal carcinoid, ovarian teratoma, struma ovarii**

## P2-8
## Sklerozirajući lipogranulom penisa: prikaz slučaja

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**Cilj:** Prikazati slučaj sklerozirajućeg lipogranuloma penisa kod pacijenta nakon samostalnog ubrizgavanja supstanci u tkivo penisa. U vreme ekspanzije kozmetičkih zahvata, uvećanje obima penisa ubrizgavanjem različitih supstanci (parafin, silikon, mineralna ulja) ostaje kontroverzna procedura sa dugom istorijom. Ovu proceduru često izvode sami pacijenti ili druga lica bez licenciranog medicinskog obrazovanja. Ubrizgavanjem ovih supstanci nastaje lokalna zapaljenska reakcija praćena crvenilom, bolom, otokom, zadebljanjem kože penisa, sa posledičnim stvaranjem sklerozirajućeg lipogranuloma, a u ozbiljnijim slučajevima i ulceracijom, nekrozom i embolijom. Mogu nastati impotencija, bolna erekcija i dizurija. Metoda lečenja je ekscizija promene sa naknadnom rekonstrukcijom. **Prikaz slučaja:** Pacijent starosti 45 godina javlja se na pregled zbog promena na penisu. Inspekcijom, na ventralnoj strani penisa uočene su ožiljne promene sa ulkusima i početnim znacima inflamacije, te je pacijent upućen urologu. Ekscidiran je deo ožiljne promene sa znacima inflamacije, uzeta je biopsija, a zatim je načinjena rekonstrukcija. Patohistološkom analizom materijala dobijenog biopsijom uočeni su fragmenti kože i supkutanog vezivnog tkiva. Na delovima epidermisa prisutne su ulceracije sa prisutnim zapaljenskim infiltratom, područjima hiperkeratoze i parakeratoze. Inflamatorni infiltrat bogat epiteloidnim histiocitima ispunjenim lipidnim vakuolama prisutan je u supkutanom vezivnom tkivu, a pored se uočavaju manji fokusi nekroze i cistične promene u vidu "švajcarskog sira" Na osnovu patohistološkog nalaza i kliničkih podataka dijagnostikovan je sklerozirajući lipogranulom. **Zaključak:** Uvećanje obima penisa ubrizgavanjem različitih supstanci je opasna procedura koja u ekstremnim slučajevima može rezultovati smrtnim ishodom, a nikada neće pružiti rezultate koje pacijenti očekuju.

**Ključne reči: sklerozirajući lipogranulom, penis, parafinom, silikonom**

## Sclerosing lipogranuloma of penis: A case report

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**Objective:** We present a case of sclerosing lipogranuloma of penis in a patient after self-injection of substances into penile tissue. Increasing the volume of penis by injecting substances (paraffin, silicone, mineral oils) remains a controversial procedure. Procedure is performed by patients themselves or by others without a licensed medical education. Injecting these substances causes a local inflammatory reaction with redness, pain, swelling, thickening of penile skin, with the subsequent formation of sclerosing lipogranuloma, and sometimes, ulceration, necrosis and embolism. Impotence, painful erections and dysuria may occur. The treatment is excision with subsequent reconstruction. **Case reports:** A 45-year-old patient presents due to changes on penis. Inspection showed scarring with ulcers and signs of inflammation on ventral side of penis, and patient was referred to urologist. Part of the scar with inflammation was excised, biopsy was taken, and reconstruction was made. Pathohistological analysis revealed fragments of skin and subcutaneous connective tissue. Ulcerations with inflammatory infiltrate, hyperkeratosis and parakeratosis were present on parts of epidermis. Inflammatory infiltrate rich in epithelioid histiocytes with lipid vacuoles was present in subcutaneous connective tissue, and smaller foci of necrosis and cystic changes in the form of "Swiss cheese" were observed. Based on pathohistological findings and clinical data, he was diagnosed with sclerosing lipogranuloma. **Conclusion:** Increasing the volume of penis by injecting substances is dangerous, it can even result in death, and will never provide the expected results.

**Keywords: sclerosing lipogranuloma, penis, paraffinoma, siliconoma**

**P2-9**

## Abrikosov tumor vulve: prikaz slučaja

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**Cilj:** Prikazujemo slučaj Abrikosovog tumora na vulvi kod dvadesetogodišnje žene. Abrikosov ili „Granular cell" tumori obično su tumori kože regije glave i vrata, ali se retko mogu naći i u koži vulvarne regije. Kao promena kože genitalne regije, obično se vidja kod žena u 5toj deceniji života i tada su najčešće lokalizovani na malim stidnim usnama. **Prikaz slučaja:** Zbog prisustva vularvnog spororastućeg, bezbolnog čvora pacijentkinja stara 20 godina obratila se ginekologu. Nakon pregleda uradjena je ekscizija promene. Na histološku analizu priljen je isečak kože sa, u celosti uklonjenom, nodularnom, sivkastom promenom prečnika 1,5cm. Histološkom analizom vidjeno je tumorsko tkivo koje grade nejasno ograničene, poligonalne ćelije, sa obiljem granulirane eozinofilne citoplazme i sa sitnim, hiperhromatičnim centralno smeštenim jedrima. Tumorske ćelije su bile okružene vezivnim trakama. Perineuralna infiltracija nije uočena. Citoplazma tumorskih ćelija je bila PAS pozitivna i na imunohistohemijskim bojenjima S100 i NSE pozitivna i SMA i Ki67 negativna. Na osnovu histološkog izgleda i organizacije ćelija postavljena je dijagnoza Abrikosovog tumora. **Zaključak:** „Granular cell" tumor se retko može videti na koži vulve. Histološki izgled tumorskih ćelija je vrlo specifična i obično se dijagnoza postavlja na svetlosnoj mikroskopiji i imunohistohemijskom analizom.

**Ključne reči: vulva, granular cell tumor, koža**

## Abrikosov tumor of the vulva: A case report

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**Objective:** We present a case of granular cell tumor of the vulva in 20 years old women. Granular cell tumor or Abrikosov tumors primary tumor of skin in head and neck region, but rarelly they can develop into the skin of vulvar region. In the female genital scin they usually occurs in the 5th decade of life and located into the scin of labia minora. **Case report:** Due to the slow growing, painless change in the skin of the vulva, a 20-year-old patient wentto a gynecologist. After the gynecological examination perfomed excision of skin lesion. on histological analysis received a fragment of skin with grey nodule wich diameter was 1.5 cm, and which is taken as a whole. By histological analysis on the specimens was seen unclear demarcated tumor tissue into the dermis made from polygonal cells with abundant granular eosinophilic cytoplasm with small, centraly located hyperhromatic nuclei. Tumor cells were surrounded by fibrous bands. Perineual infiltration not found.Cytoplasm of tumor cells were PAS positive and immunohistochemically positive on S100 and NSE and negative on SMA, Ki67. The diaganosis of granular cell tumor (Abrikosov tumor) of the vulva was done considering the characteristic histological organisation and appearance of cells. **Conclusion:** Granular cell tumor is a rare form that can be seen in the skin of the vulva. Histological appearance of tumor is very specific and diagnosis is usually based on light microscopy and immunohistochemistry.

**Keywords: vulva, granular cell tumor, skin**

## P2-10
## CD10 negativni MEST

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**Cilj:** Prikazujemo slučaj CD10 negativnog mešovitog epitelnog i stromalnog tumora (MEST). MEST je veoma retka bubrežna neoplazma koja se najčešće dijagnostikuje kod perimenopauzalnih žena zbog čega se pretpostavlja da polni hormoni imaju značajnu ulogu u patogenezi. Imunohistohemijska potvrda se, između ostalog, zasniva na dokazivanju ER, PR i CD10 pozitivnih stromalnih ćelija, zbog čega je cilj prikaz CD10 negativnog slučaja MEST-a. **Prikaz slučaja:** Pacijentkinja stara 47 godina operisana je u KCS zbog tumorske promene bubrega. Na PH pregled dostavljen je solidno-cistični nodus čijom je mikroskopskom analizom utvrđeno postojanje dve komponente, epitelne i mezenhimalne. Epitelnu komponentu čine glandularne i cistične formacije različite veličine, obložene jednorednim epitelom sastavljenim od cilindričnih i klinastih ćelija, kao i epitelom prelaznog tipa, dok mezenhimalnu komponentu najvećim delom čine snopovi vretenastih ćelija, uz prisustvoređih hipocelularnih zona sa rastresitom stromom. Epitelne ćelije pokazale su imunoreaktivnost na CK, EMA i pax8, dok su stromalne ćelije bile pozitivne na desmin, SMA, calponin i H-caldesmon. Stromalne ćelije u neposrednoj okolini cisti pokazivale su ER i PR imunopozitivnost, uz izostanak CD10 imunoreaktivnosti. U stromi nisu uočene HMB-45 ni MelanA pozitivne ćelije, čime je isključen angiomiolipom sa epitelnim cistama. Morfološke karakteristike dopunjene IHH analizom odgovaraju MEST- u, bez obzira na negativnost CD10 markera. **Zaključak:** CD10 imunopozitivnost nije neophodan uslov za postavljanje dijagnoze MEST-a, već samo dokazuje prisustvo/odsustvo endometrijalne strome koja može, ali ne mora, biti deo stromalne tumorske komponente.

**Ključne reči: bubreg, MEST, CD10**

## CD10 negative MEST: A case report

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**Objective:** We present a case of CD10 negative mixed epithelial and stromal tumor (MEST). MEST is a very rare renal neoplasia that is most commonly diagnosed in perimenopausal women, which is why sex hormones are thought to play a significant role in pathogenesis. Immunohistochemical confirmation is, among other, based on the detection of ER, PR and CD10 positive stromal cells, which is why the aim is to present a CD10 negative case of MEST. **Case report:** A 47-year-old female patient underwent surgery at CCS due to a kidney mass. A solid cystic nodule was submitted for PH examination, and microscopic analysis revealed the existence of two components. The epithelial component consists of glandular and cystic formations of variable sizes, lined with simple epithelium composed of cylindrical and hobnail cells, as well as transitional epithelium, while the mesenchymal component is composed mostly of spindle cell bundles, with rare hypocellular areas. Epithelial cells showed immunoreactivity to CK, EMA and pax8, while stromal cells were positive for desmin, SMA, calponin and H-caldesmon. Stromal cells in the immediate vicinity of the cyst showed ER and PR immunopositivity, in the absence of CD10 immunoreactivity. No HMB-45 or MelanA positive cells were observed in the stroma, thus excluding angiomyolipoma with epithelial cysts. Morphology followed by IHC analysis confirm the diagnosis of MEST, regardless of the negativity of the CD10 marker. **Conclusion:** CD10 is not required for the diagnosis of MEST, since it only proves the presence / absence of endometrial stroma, which may or may not be part of the stromal component.

**Keywords: kidney, MEST, CD10**

## P2-11

## Cistični paramezonefrički embrionalni ostatak koji simulira malignu neoplazmu testisa: prikaz slučaja

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**Cilj:** Prikazujemo slučaja embrionalnog paramezonefričkog ostatka kao potencijalnog benignog imitatorima malignih neoplazmi testisa. **Prikaz slučaja:** Muškarac, starosti 27 godina, početkom 2020. godine pregledan je od strane urologa koji je tada postavio sumnju na tumor desnog testisa, nakon čega je MRI pregledom verifikovana retroperitonealna limfadenopatija. Anamnestički je dobijen podatak da je pacijent u detinjstvu operisao testis, ali nije znao da navede razlog. Serumskim analizama utvđen je porast LDH, dok su vrednosti AFP i B-HCG bile u referentnom opsegu. Nakon operacije u KCS, postavljena je dijagnoza seminoma testisa sa anaplazijom, delom u regresiji. Nakon 4 ciklusa hemioterapije, maja 2021. Verifikovana je regresija retropereritonealnih limfnih nodusa. Početkom 2022. godine otkrivena je ingvinalna i ilijačna limfadenopatija, a na spoljašnjem otvoru ingvinalnog kanala uočena je cistična promena interpretirana kao tumorski izmenjen levi nespušteni testis. Nakon odluke o operaciji, preparat „ektopičnog levog testisa" poslat je na PH analizu, gde je postavljena sumnja na teratom testisa, te su uzorci poslati na konsultativni pregled na Institut za patologiju. U analiziranom materijalu nije uočeno tkivo testisa, već policistična lezija obložena epitelom koji svojim morfološkim karakteristikama podseća na epitel Falopijeve tube, a unutar čijih lumena i strome je uočen gust neutrofilni infiltrat. IHH analizom potvrđeno je da se radi o strukturi porekla Milerovih kanala. **Zaključak:** Embrionalni restovi poput paramezonefričkih ostataka mogu simulirati maligne tumore što treba imati u vidu, čak i kada postoji klinička sumnja na malignitet.

**Ključne reči: paramezonefrički ostaci, testis, neoplazma**

## Cystic paramesonephric embryonic remnant simulating malignant testicular neoplasm: a case report

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**Objective:** We present cases of embryonic paramesonephric residue as a potential benign imitator of malignant testicular neoplasms. **Case report:** A 27-year-old man was examined by an urologist in the beginning of 2020, who then suspected a tumor of the right testicle, after which an MRI examination revealed retroperitoneal lymphadenopathy. Anamnestic data show that the patient had testicular surgery in childhood, but he did not know the reason. Serum analyzes revealed an increase in LDH, while AFP and B-HCG values were in the reference range. After the operation in CCS, the diagnosis of testicular seminoma with anaplasia, partly in regression, was made. After 4 cycles of chemotherapy, in May 2021, regression of retroperitoneal lymph nodes was documented. At the beginning of 2022, inguinal and iliac lymphadenopathy was discovered, and a cystic mass was observed on the outer opening of the inguinal canal, interpreted as a tumor-altered left undescended testis. After the decision on the operation, the preparation was sent for PH analysis, where testicular teratoma was suspected, and the samples were sent for a consultative examination to the Institute of Pathology. No testicular tissue was observed in the analyzed material, but a polycystic lesion lined with epithelium whose morphological characteristics resemble the epithelium of the Fallopian tube, and within whose lumens and stroma a dense neutrophilic infiltrate was observed. IHC analysis confirmed the structure of Mullerian duct origin. **Conclusion:** Embryonic rests such as paramesonephric remnants may simulate malignant tumors, which should be borne in mind, even when there is a clinical suspicion of malignancy.

**Key words: paramesonephric remnants, testis, neoplasia**

## P2-12

## Intratestikularni adenomatoid tumor: prikaz slučaja

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**Cilj:** Adenomatoid tumor je benigni tumor porekla mezotela, najčešće lokalizovan paratestikularno. Lokalizacija u parenhimu testisa je izuzetno retka i problematična, jer ovaj tumor u testisu može imitirati brojne malignitete. Neretko se dijagnoza adenomatoid tumora postavi nakon orhiektomije. **Prikaz slučaja:** Prezentujemo tridesetčetvorogodišnjeg pacijenta koji je primljen na kliniku za urologiju zbog operativnog lečenja tumora desnog testisa, koji se manifestuje lokalnim bolom. Pre 6 godina pacijent je preboleo desnostrani epididimitis kada mu je incidentalno ultrazvučno dijagnostikovan tumor na gornjem polu desnog testisa, koji se od onda kontinuirano prati. Pri ultrazvučnom pregledu opisan je kao ovalan, hiperehogen i jasno ograničen čvor promera 12 mm. U aktuelnoj hospitalizaciji, pri lokalnom pregledu konstatovano je postojanje na palpaciju bezbolne, čvrste i nepokretne tumorske mase. Laboratorijski nalazi su uredni. Nakon preoperativne pripreme učinjena je ekscizija tumora u opštoj anesteziji. Operativni materijal poslat je na ex tempore dijagnostiku na kojoj se definitivna dijagnoza odloži za trajne histološke preparate. Na trajnim patohistološkim preparatima postavljena je dijagnoza jasno ograničenog, nekapsulisanog adenomatoid tumora sagrađenog od nepravilnih pukotinastih prostora obloženih ovalnim ćelijama koje mestimično imaju izgled prstena pečatnjaka i lipoblasta, između kojih se prožima glatkomišićno tkivo. Ćelije koje oblažu pukotinaste prostore na imunohistohemijskim analizama su calretinin, WT1 i CKMNF 116 pozitivne, a EMA i CEA negativne. Opisano područje oivičeno je vezivnim tkivom sa dilatiranim krvnim sudovima, prožeto umereno obilnim limfocitnim

infiltratom. U okolini se uočavaju semeni kanalići testisa očuvane morfologije, obloženi pravilnim epitelom. Postoperativni tok protekao je uredno. **Zaključak:** Prikazani slučaj je primer pravilne dijagnostike i saradnje kliničara i patologa, kako bi se izbegla nesvrsishodna orhiektomija.

**Ključne reč: Adenomatoid tumor, testis, imunohistohemija**

## Intratesticular adenomatoid tumor: A case report

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**Objective:** Adenomatoid tumor is a benign tumor of mesothelial origin, most often localized paratesticularly. Localization in the testicular parenchyma is extremely rare and problematic, because this tumor in the testis can mimic numerous malignancies. Often the diagnosis of adenomatoid tumors is made after orchiectomy. **Case report:** We present a thirty-four-year-old patient who was admitted to the urology clinic for surgical treatment of a tumor of the right testicle, which is manifested by local pain. Six years ago, the patient overcame right-sided epididymitis when he was incidentally diagnosed with an ultrasound tumor on the upper half of the right testicle, which has been monitored continuously ever since. On ultrasound, it was described as an oval, hyperechoic, and clearly demarcated nodule 12 mm in diameter. In the current hospitalization, during the local examination, the existence of a painless, solid and immobile tumor mass on palpation was ascertained. Laboratory findings are in order. After preoperative preparation, tumor excision was performed under general anesthesia. The operative material was sent for ex tempore diagnostics where the definitive diagnosis is postponed for permanent histological specimens. On permanent pathohistological preparations, a diagnosis of a clearly limited, uncapsulated adenomatoid tumor composed of irregular fissure spaces lined with oval cells that in some places have the appearance of a seal ring and lipoblasts, between which smooth muscle tissue permeates, was diagnosed. Cells lining the fissure spaces on immunohistochemical analyzes were calretinin, WT1 and CKMNF 116 positive, and EMA and CEA negative. The described area is bordered by connective tissue with dilated blood vessels, permeated with moderately abundant lymphocyte infiltrate. Seed canals of the testis of preserved morphology, lined with regular epithelium, can be seen in the vicinity. The postoperative course went smoothly. **Conclusion:** The presented case is an example of proper diagnosis and cooperation of clinicians and pathologists, in order to avoid pointless orchiectomy.

**Key words: Adenomatoid tumor, testis, immunohistochemistry**

## P2-13

## Adultni cistični nefrom bubrega: prikaz slučaja

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**Cilj:** Prikazujemo slučaj adultnog cističnog nefroma bubrega. **Prikaz slučaja:** Prikazujemo slučaj 44-godišnje žene koja je primljena na Kliniku za urologiju Univerzitetskog kliničkog centra Vojvodine nakon slučajnog pronalaska lezije u levom bubregu. Na kompjuterizovanoj tomografiji uočena je unilokularna, jasno ograničena cista dimenzija 7x6x7 cm, lokalizovana u središnjem delu i gornjem polu levog bubrega. Makroskopskim pregledom opisana je jasno ograničena multicistična tumorska masa,

veličine 7 cm, sa žućkasto-beličastim pregradama i glatkim zidovima, ispunjena bistrom žućkastom tečnošću. Mikroskopski, tumor je bio izgrađen od cista različite veličine, obloženih uglavnom kubičnim epitelom, sa fokalnim hobnail izgledom bez atipije, mestimično aplatiranim. Septe su bile izgrađene od fibrozne strome sa hipercelularnim područjima i oblastima nalik stromi jajnika. Imunohistohemijskom analizom, epitelna komponenta je pokazala pozitivnost na Pax 8. Stroma je bila pozitivna na estrogenski receptor, progesteronski receptor, aktin, desmin, kalretinin, CD 10 i delimično pozitivna na inhibin α. **Zaključak:** CN je redak tumor na koji se mora misliti u slučaju multicističnih promena u bubregu i koji se u nedostatku svetlih ćelija često pogrešno dijagnostikuje kao prosta kortikalna cista bubrega. Iako u literaturi nema dokaza o lokalnom recidivu ili metastazama, preporučuje se dugoročno praćenje.

**Ključne reči: cistični nefrom, cista, bubreg**

## Adult cystic nephroma of the left kidney: A case report

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**Objective:** We present a case of adult cystic nephroma of the kidney. **Case report:** We report a case of a 44-year old female who was admitted to Urology Clinic of University Clinical Centre of Vojvodina after incidental finding of a mass in her left kidney. The Computed tomography scan showed a 7x6x7 cm, unilocular, well-circumscribed cyst, localized in the middle part and upper pole of the left kidney. Macroscopic examination revealed a well-circumscribed multicystic tumor mass, measuring 7cm. It contained tan-white septa and smooth walls and was filled with clear yellowish fluid. Microscopic examination showed variably sized cysts lined mostly by cuboidal epithelium, with a focal hobnail appearance without atypia, focally flattened. The septa consisted of fibrous stroma with hypercellular areas and areas of cellular con-densation ovarian stroma like. Immunohistochemical analyses showed that epithelial component was positive for Pax 8. The stroma was positive for estrogen receptor, progesterone receptor, actin, desmin, calretinin, CD 10 and partially positive for inhibin α. **Conclusion:** CN is a rare neoplasm that must be considered in the presence of multicystic changes in the kidney, and which in the absence of clear cells is often misdiagnosed as simple cortical cyst of the kidney. Although there has not been the evidence of local recurrence or metastatic in the literature, the long-term follow-up is recommended.

**Key words: cystic nephroma; cyst; kidney**

## P2-14

## Sklerozirajući lipogranulom koji oponaša tumor testisa: prikaz slučaja

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**Cilj:** Prikazujemo slučaj sklerozirajućeg lipogranuloma u testisu. **Prikaz slučaja:** Muškarac starosti 25 godina javio se u bolnicu zbog bezbolnog otoka testisa, koji je trajao unazad dva meseca. Pacijent je naveo prethodnu istoriju torzije levog testisa i brojne udarce loptom u predeo prepona, usled profesionalnih fudbalskih aktivnosti. Fizikalnim pregledom utvrđen je bolno neosetljiv, palpabilno tvrđi levi

testis u odnosu na desni. Ultrasonografskim pregledom detektovane su bilateralne mikrokalcifikacije parenhima testisa, izraženije u levom testisu uz prisustvo jednog ograničenog nodusa promera 1,8 cm. Nakon levostrane orhiektomije, patohistološkom analizom potvrđena je relativno jasno ograničena lezija sačinjena od masnog tkiva, sa cističnim i mikrocističnim područjima i brojnim masnim vakuolama različite veličine, koje su okružene fibroznom, hijalinizovanom stromom. Okolna stroma je bila prožeta pretežno mononuklearnim inflamatornim infiltratom sa fokalnim grupama hemosiderofaga uz izraženu hroničnu granulomatoznu reakciju tipa oko stranog tela sagrađenu od brojnih histiocita, epitelioidnih ćelija, penušavih makrofaga (ekspresija CD68) i višejedarnih džinovskih ćelija tipa oko stranog tela sa intracitoplazmatskim masnim vakuolama. Registrovana je nekroza masnog tkiva kao i brojne distrofijske kalcifikacije. Okolni parenhim testisa je bio narušene arhitektonike, sa brojnim atrofičnim i skleroziranim semenim kanalićima, dok su samo pojedinačni tubuli imali očuvan germinativni epitel i spermatogenezu. **Zaključak:** Sklerozirajući lipogranulom testisa je retko benigno stanje, koje imitira neoplastični proces testisa, te je detaljna anamneza neophodna za postavljanje kliničke diferencijalne dijagnoze. Najčešće se dijagnostikuje kod pacijenata mlađe životne dobi sa istorijom traume ili samoubrizgavanja egzogenog lipidnog materijala. Dobijanje precizne anamneze uz poznavanje specifičnih radioloških manifestacija doprinosi brzoj i konačnoj dijagnozi.

**Ključne reči: sklerozirajući lipogranulom, testis, granulomatozno zapaljenje**

## Sclerosing lipogranuloma mimicking testicular tumor: A case report

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**Objective:** Presentation a case of testicular sclerosing lipogranuloma. **Case report:** A 25-year-old man was admitted to our hospital due to 2-months lasting painless swelling of the testis. He reported previous history of left testicular torsion and numerous ball blows to the groin, as he is football player. Physical examination revealed painless, palpably harder left testis compared to the right. Ultrasonography showed bilateral microcalcifications of the testicular parenchyma, more pronounced in the left and the presence of a node with a diameter of 1,8 cm. After left orchiectomy, pathohistological analysis confirmed quite demarcated lesion composed of adipose tissue, cystic and microcystic areas and numerous different-sized fatty vacuoles, surrounded by fibrous, hyalinized stroma. The surrounding stroma showed mononuclear inflammation with focal groups of hemosiderophages and pronounced chronic granulomatous reaction of the foreign body type composed of numerous histiocytes, epithelioid cells, foamy macrophages (expressing CD68) and multinucleated giant cells of the foreign body type with intracytoplasmic fat vacuoles. Necrosis of adipose tissue as well as numerous dystrophic calcifications were seen. The surrounding testicular parenchyma was disturbed, with numerous atrophic and sclerosed seminal ducts, while only some tubules had preserved germinal epithelium and spermatogenesis. **Conclusion:** Testicular sclerosing lipogranuloma is rare benign condition, which mimics the testicular neoplastic process, so detailed anamnesis is necessary for clinical differential diagnosis. It mostly occurs in younger patients with a trauma or exogenous lipid material self-injection history. Precise anamnesis with knowledge of specific radiological manifestations contributes to a quick and final diagnosis.

**Key words: sclerosing lipogranuloma, testis, granulomatous inflammation**

## P2-15

## "Slabo kohezivni" karcinom žučne kese: prikaz slučaja

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**Cilj:** Prikazujemo slučaj slabo kohezivnog karcinoma, sa ili bez "signet ring" ćelija, kao ekstremno retkog histološkog tipa karcinoma žučne kese sa predominacijom kod žena. To je izuzetno agresivan karcinom, koji se dijagnostikuje u uznapredovaloj fazi sa prosečnim preživljavanjem kraćim od 4 meseca**. Prikaz slučaja:** Muškarac starosti 66 godina sa inicijalnom kliničkom dijagnozom akutnog holescistitisa imao je tipične simptome upale žučne kese. Ultrazvučni pregled je pokazao zadebljanje zida žučne kese i brojne kamenčiće u njenoj šupljini. Urađena je holecistektomija, a makroskopskim pregledom je utvrđeno zadebljanje zida žučne kese nalik linitis-plastika. Histološki pregled je pokazao difuznu infiltraciju zida žučne kese slabo diferentovanim tumorskim "signet ring" ćelijama. Slabo kohezivni karcinom karakteriše infiltrativni u obliku vrpce ili pojedinačni ćelijski rast. Infiltracija strome je upečatljiva i karakteristična. Manje od polovine slučajeva pokazuje fokalnu displaziju epitela visokog stepena. "Signet ring" morfologija nije uvek prisutna i mucini se mogu fokalno uočiti. Imunohistohemijska analiza tkivnih uzoraka je pokazala pozitivnost na CK AE1/AE3 i negativno bojenje na MUM1, ALK, CD5, CD20,BCL2, BCL6 i BSAP. Indeks proliferacije Ki67 bio je 70%. U prikazanom slučaju predstavljen je visoko invazivni slabo kohezivni karcinom sa invazijom "signet ring" ćelija u cistični duktus, limfovaskularnom, perineuralnom invazijom, metastazama u jetri, peritoneumu i regionalnim limfnim nodusima. **Zaključak:** Slabo kohezivni karcinom poreklom iz žučne kese je veoma redak, ali ga treba uzeti u obzir u diferencijalnoj dijagnozi diseminovanih slabo diferentovanih karcinoma u abdomenu.

**Ključne reči: slabo kohezivni karcinom, žučna kesa, "signet ring" ćelije**

## "Poorly cohesive" carcinoma of the gallbladder: A case report

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**Objective:** We present a case of poorly cohesive cancer, with or without signet ring cells, as an extremely rare histological type of gallbladder cancer with predominance in women. It is highly aggressive cancer, diagnosed at advanced stage with median survival less than 4 months. **Case report:** A 66-year old male with the initial clinical diagnosis of the acute cholecystitis presented with the typical gallbladder inflammation symptoms. The ultrasound showed gallbladder wall thickness and the multiple stones in the gallbladder cavity. Cholecystectomy was performed, and the gross inspection revealed linitis plastica-like thickening of the gallbladder wall. The histological examination showed diffuse infiltration of the gallbladder wall with the poorly differentiated signet ring tumor cells. Poorly cohesive carcinoma is characterized with cordlike or individual cell growth pattern. Infiltration into the stroma is characteristic. Only less than half of the cases show focal high-grade dysplasia of the overlying epithelium. Signet ring cell morphology is not always present, and mucin can be focally seen. The immunohistochemical analysis of the tissue specimens showed positivity for CK AE1/AE3 and negative staining of MUM1, ALK, CD5, CD10, CD20, BCL2, BCL6 and BSAP. The Ki-67 proliferative index was 70%. Presented case exhibited highly invasive poorly cohesive carcinoma with signet ring cells invasion of the cystic duct, lymphovascular, perineural invasion, metastases to the liver, peritoneum and regional lymph nodes. **Conclusion:** Poorly cohesive carcinoma originating in the gallbladder is very rare, however it should be consider in the differential diagnosis of disseminated poorly differentiated carcinomas in the abdomen.

**Key words: poorly cohesive carcinoma, gallbladder, signet ring cell**

**P2-16**

## Endometrioza apendiksa i jajovoda udružene sa niskogradusnom mucinoznom neoplazmom apendiksa: prikaz slučaja

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**Cilj:** Prikaz jedinstvenog slučaja endometrioze apendiksa i jajovoda udružene sa niskogradusnom mucinoznom neoplazmom apendiksa. **Prikaz slučaja:** Prikazujemo slučaj pacijentkinje starosti 42 godine, prezentovane sa bolom u donjem desnom kvadrantu abdomena, povećanim brojem leukocita i visokim C-reaktivnim proteinom. Radiološka dijagnostika (CT) je pokazala uvećan apendiks i tubo-ovarijalni apsces te je pacijentkinja hitno operisana. Učinjena je apendektomija i desna salpingektomija. Makroskopski, apendiks je bio dilatiran, ispunjen mukusom. Histološka analiza je pokazala epitelnu proliferaciju sa niskogradusnom displazijom i neinfiltrativnim, gurajućim načinom rasta. Neoplastični cilindrični epitel je pokazivao talasaste i vilozne proliferacije. Submukoza je bila fibrotična a lamina muskularis mukoze i submukozno limfoidno tkivo su bili odsutni. Fokalno je primećena mucinska disekcija zida apendiksa sa izlivanjem sadržaja lumena apendiksa na površinu seroze. Sve gorenavedene histološke karakteristike upućuju na niskogradusnu mucinoznu neoplazmu apendiksa (NMNA). U zidu apendiksa i jajovoda su bile prisutne i brojne dilatirane žlezde, obložene cilindričnim epitelom bez atipije. Pomenute žlezde su bile okružene bazofilnom stromom sačinjenom od vretenastih ćelija. Imunohistohemijska pozitivnost žlezda i strome na CD10, estrogen i progesteron sugeriše dijagnozu endometrioze. **Zaključak:** NMNA je veoma retka i čini 0,3% svih apendektomija. Iako izuzetno retko, NMNA i endometrioza apendiksa su nekoliko puta opisivani u literaturi, ali do sada ne postoji nijedan slučaj NMNA udružene sa endometriozom apendiksa i jajovoda.

**Ključne reči: endometrioza, niskogradusna mucinozna neoplazma apendiksa, LAMN, apendiks, jajovod**

## Endometriosis of the appendix and fallopian tubes associated with low-grade mucinous neoplasm of the appendix: A case report

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**Objective:** Presentation of unique case of appendiceal and fallopian tube endometriosis associated with low grade appendiceal mucinous neoplasm. **Case report:** We report a case of 42-year-old female patient presented with abdominal pain in right lower quadrant, elevated white blood cell count and increased C-reactive protein. CT scan showed enlarged appendix and tubo-ovarian abscess. The patient underwent appendectomy and right salpingectomy. Grossly, appendix was dilated, filled with mucus. Histological analysis showed low grade dysplastic epithelial proliferation with pushing border. Neoplastic columnar epithelium showed unduluations and villous proliferations. Submucosa was fibrotic, lamina muscularis mucosae and submucosal lymphoid tissue were absent. Mucin dissection of the appendiceal wall extending to peritoneal surface was focally noted. All aforementioned histological features indicated a diagnosis of low grade appendiceal mucinous neoplasm (LAMN). Numerous dilated glands lined with columnar epithelium without atypia were also noted in the wall of the appendix and fallopian tube. Aforementioned glands were surrounded with basophilic stroma made of spindle cells. Immunohistochemical positivity of glands and stroma for CD10, estrogen and progesteron suggested diagnosis of endometriosis. **Conclusion:** LAMN is very rare, comprising 0,3% of all appendectomies. Although extremely rare, LAMN and appendiceal endometriosis were reported several times in the literature, but there are no any reports of LAMN and appendiceal endometriosis associated with fallopian tube endometriosis.

**Key words: endometriosis, low grade appendiceal mucinous neoplasm, LAMN, appendix, fallopian tube**

## P2-17
## Kolizioni tumor adenokarcinoma i plazmablastnog limfoma debelog creva: prikaz slučaja

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**Cilj:** Prikazujemo kolizioni tumor sa dve komponente: adenokarcinomom i plazmablastnim limfomom, koji je izuzetno redak, naročito u debelom crevu. Neoplastična lezija koja se sastoji od različitih populacija ćelija u istom organu naziva se kolizioni tumor. **Prikaz slučaja:** Pacijentkinja stara 68 godina primljena je u Opštu bolnicu Užice zbog opstipacije i bolova u predelu abdomena, gde joj je dijagnostikovan maligni tumor debelog creva. Učinjena je kolektomija: dimenzije resekovanog segmenta su bile 35x10x7cm, sa tumorom prečnika 5cm. Mikroskopski nalaz je pokazao da tumor ima dve komponente, jednu do druge, relativno nezavisne, skoro bez ikakvog međusobnog prožimanja. Prvu komponentu je predstavljao tipični dobro diferentovani adenokarcinom koji je infiltrovao subserozni sloj i perikolično masno tkivo, sa limfovaskulnom invazijom. Nekroza je bila fokalna. Imunohistohemijsko bojenje je pokazalo pozitivnost na citokeratin, CDX2 i SATB2. Uz adenokarcinom uočeno je tumorsko tkivo difuznog tipa rasta, koje se sastojalo od ćelija plazmablastima slične morfologije, sa fokalnom plazmocitnom diferencijacijom. Ekstenzivna imunohistohemijska analiza ove komponente pokazala je pozitivnost samo na: vimentin, OCT2 (svi ostali markeri B-ćelija su bili negativni), CD38, CD138, kappa restrikciju lakog lanca, Ki67 indeks proliferacije 90%. FISH je pokazala rearanžman BCL-2 i BCL-6 gena, bez C-MYC rearanžmana, uz ALK poliploidiju (15/50). In situ hibridizacijom je pokazano odsustvo EBER. Navedeni nalazi odgovaraju plazmablastnom limfomu. Pacijentkinja je bila HIV negativna. Primila je dva ciklusa hemioterapije (CHOP), ali je preminula dva meseca nakon dijagnoze. **Zaključak:** Prilikom dijagnostikovanja kolizionih tumora značajno je ne prevideti agresivni limfom, koji morfološki može imponovati kao slabo diferentovani karcinom.

**Ključne reči: kolizioni tumor, adenokarcinom, plazmablastni limfom, debelo crevo**

## Collision tumor of adenocarcinoma and plasmablastic lymphoma of the colon: A case report

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**Objective:** We present a collision tumor with two components: adenocarcinoma and plasmablastic lymphoma, which is extremely rare, especially in the colon. A neoplastic lesion comprised of different cell populations in the same organ is known as collision tumor. **Case report:** A 68-year-old female was admitted to General Hospital Uzice due to constipation and abdominal pain, when she was diagnosed with colon cancer. Colectomy was performed: the length of portion was 35x10x7cm with tumor mass of 5cm in diameter. Microscopy showed the tumor had two components, adjacent to each other, but relatively independent, with almost no cross-growth. The first component was a typical well differentiated adenocarcinoma invading subserous layer and pericolic adipose tissue, with lymphovascular invasion. Necrosis was focal. Immunohistochemical staining showed positivity for Cytokeratin, CDX2 and SATB2. Along with adenocarcinoma, tumor tissue with diffuse type of growth was observed. It consisted of plasmablast-like cells with focal plasmacytic differentiation. An extensive immunohistochemical staining of this component showed positivity only for: vimentin, OCT2 (all other B-cell markers were negative), CD38, CD138, kappa light chain restriction, Ki67 proliferation index was 90%.

FISH detected rearrangement of BCL-2 and BCL-6 gene, no C-MYC rearrangement and ALK poliploidy (15/50). In situ hibridization showed EBER was negative. These findings were consistent with diagnosis of plasmablastic lymphoma. The patient was HIV negative. She had received two cycles of chemotherapy (CHOP), but passed away two months after diagnosis. **Conclusion:** In the diagnosis of collision tumors, the most important issue is to avoid a missed diagnosis when the high-grade lymphoma component may be morphologically missed as poorly differentiated carcinoma.

**Key words: collision tumor, adenocarcinoma, plasmablastic lymphoma, colon**

## P2-18

## Inflammatory myofibroblastic tumor of the appendix

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**Objective:** Inflammatory myofibroblastic tumor (IMT), also called inflammatory pseudotumor is a rare disease of mesenchymal origin, first described in 1937. Cases of IMT involving the appendix are exceptional, and they can mimic malignant appendicular tumors. **Case report:** A 25-year-old woman presented to the emergency department with pain in her right lower abdomen for three days. This was associated with increased body temperature and nausea. Other clinical findings included acute abdomen and laboratory analysis with mildly elevated inflammatory markers. No past history of serious illnesses or abdominal surgery. Because of the lack of specific clinical or imaging signs, IMT still offers a great deal of diagnostic challenge. The macroscopic examination of the appendix revealed a surgical specimen of 5.0x2 cm. The tip of the appendix was distended by mucinous material and had signs of acute appendicitis. Histological examination of the specimen stained with hematoxylin and eosin, revealed a mass showing fibroblastic proliferation accompanied by a dense inflammatory infiltrate in the mucosa and a clear widening of the submucosa. A few areas showed myxoid changes with spindle cells, alternating with polyclonal plasma cells and lymphocytes. Immunohistochemical analysis showed positivity for vimentin and partial positivity for CD68, SMA and desmin. **Conclusion:** Awareness of this type of tumor in the differential diagnosis of appendiceal masses, avoids overtreatment, and highlights the need of long-term follow-up regarding the tendency for local recurrence and small risk of distant metastasis.

**Key words: Inflammatory myofibroblastic tumor, inflammatory pseudotumor, appendicular tumor, appendectomy**

## P2-19

## Gastrointestinalna manifestacija Kapoši sarkoma: prikaz slučaja

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**Cilj:** Prikazujemo slučaj promena tipa Kapošijevog sarkoma na sluznici gastrointestinalnog trakta. Kapoši sarkom (KS) je redak, niskostepeni vaskularni tumor povezan sa infekcijom HHV-8. Jedna od četiri epidemiološke forme je Kapoši sarkom u sklopu AIDS-a i javlja se kod 20-tak % pacijenata inficiranih HIV-om. **Prikaz slučaja:** Pacijent starosti 37 godina se javlja zbog promena u vidu plikova na koži leve strane lica sa parezom levog facijalnog nerva. Postavljena je dijagnoza infekcije virusom Herpes zoster-a i postignut je dobar klinički odgovor primenom Aciklovira. Nakon godinu dana pacijent se ponovo javlja sa tegobama u vidu subfebrilnosti, gubitka na telesnoj težini i sa hemoroidima.

Fizikalnim pregledom se nalaze lividne promene u predelu gornjih desni i tvrdog nepca. Pacijent je testiran i dokazana je HIV infekcija. Laboratorisjki nalazi su pokazali vrednosti leukocita 4.47x109/l, CD4 T-limfociti 79 ćelija/mm3. Količina virusa je iznosila (PCR HIV) 1 914 766 kopija/mm3. S obzirom na perzistirajuće promene u usnoj duplji indikuje se kolonoskopija i gastroskopija. Kolonoskopijom i gastroskopijom su u području sluznice rektuma i u korpusnom delu na velikoj krivini želuca nađene plaže izgleda submukozne hemoragije koje su blago uzdignute u odnosu na okolnu površinu. Histološki, u uzorcima obojenim standardnom HE metodom bojenja, uočene su u lamini propriji vretenaste ćelije izduženih jedara koje su u vrtložastom rasporedu, kao i okruglasti i pukotinasti vaskularni prostori obloženi endotelom. Imunohistohemijski, ove ćelije su pokazale izraženu ekspresiju na HHV-8, potvrđujući postavljenu sumnju na KS sluznice želuca i rektuma. Zaključak: Rano indikovanje kolonoskopije i gastroskopije je veoma bitno za pravovremeno postavljanje dijagnoze. Upotreba imunohistohemijskih markera, posebno antitela na HHV-8, pruža izuzetnu dijagnostičku podršku.

**Ključne reči: Kaposi sarkom, HHV-8, AIDS/HIV, kolonoskopija, gastroskopija**

## Gastrointestinal manifestation of Kaposi sarcoma

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**Objective:** We present a case of Kaposi's sarcoma on the mucosa of the gastrointestinal tract. Kaposi sarcoma (KS) is a rare, low-grade vascular tumor associated with HHV-8 infection. One of the four epidemiological forms is KS as part of AIDS, it occurs in about 20% of HIV-infected patients. **Case report**: A 37-year-old patient presented with skin blisters on left side of the face with paresis of left facial nerve. Herpes zoster virus infection was diagnosed, and acyclovir is well-suited. After one year, the patient reappeared with fever (up to 37.5 <C), weight loss and hemorrhoids. Physical exam showed livid area of the upper gums and hard palate. The patient was tested, and HIV infection has confirmed. Laboratory findings show values of leukocytes 4.47x109/l, CD4 T-lymphocytes 79 cells/mm3. Viral load (VL) (PCR HIV) 1 914 766 copies/mm3. Due to persistent changes in the oral cavity, colonoscopy and gastroscopy is indicated. Colonoscopy and gastroscopy determined the submucosal hemorrhage areas of the rectal mucosa and in the corpus part of the stomach; slightly elevated from the surrounding surface. Histologically, in samples stained by standard HE staining method, in the lamina propria spindle cells of elongated nuclei in a vortex arrangement are observed, as well as round and cracked vascular spaces lined with endothelium. These cells showed immunohistochemical expression on HHV-8, confirming the suspicion of KS of the gastric and rectal mucosa. **Conclusion:** Early indication of colonoscopy and gastroscopy is very important for timely diagnosis. The use of immunohistochemical markers, especially antibodies to HHV-8, provides exceptional diagnostic support.

**Key words: Kaposi sarcoma, HHV-8, AIDS / HIV, colonoscopy, gastroscopy**

**P2-20**

## Kompletan odgovor na palijativnu hemioterapiju pacijenata sa karcinomom ushodnog dela debelog creva:prikaz slučaja

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**Cilj:** Prikazujemo pacijenta sa primarnim adenokarcinomom ushodnog dela debelog creva kod koga je postignunt kompletan patološki odgovor nakon hemioterapije po protokolu FOLFOX4.U svetu karcinom debelog creva je treći najčešći uzrok smrti koja je povezan sa rakom. Terapija u stadijumu IV karcinoma debelog creva je obično palijativna hemioterapija po protokolu FOLFOX4. **Prikaz slučaja:** Žena stara 57 godina primljena je u naš Institut radi odluke o daljem lečenju. Kolonoskopijom koja je urađena pre prijema otkriveno je postojanje infiltrativne stenoze ushodnog dela kolona. Patohistološkom analizom potvrđen je srednje diferentovan adenokarcinom, dok su na CT snumku uočena dva metastatska žarišta u jetri, zajedno sa brojnim uvećanim limfnim čvorovima i peritonealnom karcinozom. Primenjena je palijativna hemioterapija prema FOLFOX4 protokolu, koja je završena bez neželjenih efekata. Nakon toga je urađeno je PET/CT skeniranje, koje je pokazalo potpuni metabolički odgovor. Nakon ovog neočekivanog nalaza onkološka komisija je savetovala desnu hemikolektomiju. Urađena je operacija, a materijal je dostavljen na odeljenje patologije. Makroskopskim pregledom nije uočena tumorska promena, već samo ulegnuto područje na sluznici ushodnog dela kolona. Patohistološkom analizom iz opisane zone uočena je fibroza cele debljine zida creva bez prisustva vijabilnih tumorskih ćelija. U 12 pregledanih limfnih čvorova nije pronađen metastatski tumor. Na osnovu patohistološkog nalaza stadijum je ypT0N0, a šest godina nakon operacije pacijent je dobro i bez simptoma. **Zaključak:** Prikaz ovog slučaja pokazuje da upotreba palijativne hemioterapije prema FOLFOX4 protokolu za uznapredovali karcinom debelog creva može potencijalno dovesti do neočekivanog kompletnog terapijskog odgovora.

**Ključne reči: karcinom debelog creva, palijativna hemioterapija, kompletan terapijski odgovor**

## Complete pathologic response in a patient with right colon cancer following palliative chemotherapy: A case report

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**Objective:** We report a patient with primary adenocarcinoma of the ascending colon who has achieved a complete pathological response after FOLFOX4 chemotherapy.Colorectal cancer is the third most common cause of cancer related death worldwide. Treatment for stage IV colon cancer is usually palliative chemotherapy with FOLFOX4 regimen. **Case report:** A 57-year-old woman was admitted to our Institute for a decision on further treatment. Colonoscopy carried out prior to admission revealed infiltrative stenosis of the ascending colon. Histopathologic analysis confirmed moderately differentiated adenocarcinoma. CT scan imaging showed two metastatic foci in the liver along with numerous enlarged mesenteric lymph nodes and peritoneal carcinosis. A palliative FOLFOX4 chemotherapy had been prescribed and it was completed with no adverse effects. Subsequently a PET/CT scan was performed and it showed a complete metabolic response. Following this unexpected finding the tumor board

advised right hemicolectomy. Surgery had been performed and the specimen was submitted to the pathology department. Gross examination revealed no visible tumor but only a depressed area on the mucosa of the ascending colon. Histopathologic analysis confirmed fibrosis of the whole thickness of the wall with no viable tumor cells. No metastatic tumor was found in 12 examined lymph nodes. The pathologic stage assigned was ypT0N0. Six years after the surgery the patient is well and without symptoms. **Conclusion:** This study showed that the use of palliative FOLFOX4 chemotherapy for advanced colon cancer can potentially result in an unexpected complete therapeutic response.

**Key words: colon cancer, palliative chemotherapy, complete therapeutic response**

## P2-21

## Diferencijalno dijagnostički značaj inflamatornog fibroidnog polipa kao uzroka opstrukcije ileuma:prikaz slučaja

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**Cilj:** Cilj ovog prikaza je da se ukaže na retku benignu neoplazmu koja može da bude uzrok intestinalne opstrukcije i da se diferencijalno dijagnostički isključe drugi tumori mezenhimnog porekla. **Prikaz slučaja:** Žena starosti 64 godine se javila zbog intenzivnih bolova u trbuhu. Ultrazvučnim pregledom abdomena u jetri je verifikovana cistična promena promera 11 mm u S3 segmentu. Radiografija abdomena pokazala je prisustvo hidrogasnih nivoa ilijačno desno. MSCT abdomena je pokazao suspektnu invaginaciju ileuma u samom nivou Bauhinijeve valvule. Pacijentkinji je urađena desna hemikolektomija, sa termino-terminalnom anastomozom između ileuma i transverzalnog kolona. Makroskopskim pregledom u terminalnom ileumu, na 5 cm od Bauhinijeve valvule, uočen je pedunkularni polipoidni tumefakt najvećeg promera 4 cm koji je opstruirao lumen u potpunosti. Na preseku je bio svetlo sive boje, elastične konzistencije i homogene građe. Histološka analiza je pokazala da se radi o hipocelularnom tumoru građenom od vretenastih ćelija, bez atipičnih mitoza, u rastresitoj stromi bogatoj krvnim sudovima malog do srednjeg kalibra sa umereno obilnim mešovitim zapaljenjskim infiltratom, sačinjenim mestimično od eozinofila. Veći deo tumorske mase je zahvatao submukozu i samo površne delove mišićnog sloja, sa fokalnim ulceracijama mukoze. Diferencijalno dijagnostički razmatrani su slučajevi inflamatornog miofibroblastnog tumora, solitarnog fibroznog tumora, GIST-oma, švanoma, perineurioma i leiomioma. Primenom imunohistohemijskog bojenja uočena je jaka difuzna ekspresija vimentina, a samo fokalno vrtložni obrazac pozitivnosti na CD34 oko krvnih sudova, dok je imunohistohemijska reakcija na ALK, actin, CD117, DOG1 CKAE1/AE3, S100, desmin, EMA bila negativna, a Ki-67 proliferativni indeks je bio manji od 5%. **Zaključak**: Imunohistohemijska analiza, u odsustvu izraženijeg eozinofilnog infiltrata i preklapanja mikromorfologije sa drugim neoplazmama mezenhimnog porekla, je od pomoći u diferencijalnoj dijagnozi ove retke benigne neoplazme. Odsustvo atipičnih mitoza i nizak Ki-67 proliferativni indeks takođe ukazuju na benignu prirodu ove mezenhimne neoplazme koja može da izazove intestinalnu opstrukciju.

**Ključne reči: inflamatorni fibroidni polip, opstrukcija, ileum**

## Differential diagnostic significance of inflammatory fibroid polyp as a cause of ileal obstruction: A case report

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**Objective:** The aim of this case report is to point out a rare benign neoplasm that can be the cause of intestinal obstruction and to differentially exclude other tumors of mesenchymal origin. **Case report:** A 64-year-old woman reported intense abdominal pain. Ultrasound examination of the abdomen verified in the liver a cystic change in diameter of 11 mm in the S3 segment. Abdominal radiography showed the presence of hydrogas levels iliac right. Abdominal MSCT showed suspicious invagination of the ileum at the level of the ileocecal valve. The patient underwent right hemicolectomy, with a termino-terminal anastomosis between the ileum and the transverse colon. Macroscopic examination of the terminal ileum, 5 cm from the ileocecal valve, revealed a peduncular polypoid tumefact with a maximum diameter of 4 cm, which completely obstructed the lumen. The cross-section was light gray, elastic in consistency and homogeneous in structure. Histological analysis showed that it was a hypocellular tumor built of spindle cells, without atypical mitoses, in a oedematous stroma rich in small to medium-sized blood vessels with moderately abundant mixed inflammatory infiltrate, composed occasionally of eosinophils. Most of the tumor mass affected the submucosa and only the superficial parts of the muscle layer, with focal ulcerations of the mucosa. Cases of inflammatory myofibroblastic tumor, solitary fibrous tumor, GIST, schwannoma, perineurioma and leiomyoma were considered as differential diagnostics. Immunohistochemical staining showed strong diffuse expression of vimentin and only a focal whorled pattern of positivity for CD34 around blood vessels, while the immunohistochemical reaction to ALK, actin, CD117, DOG1, CKAE1/AE3, S100, desmin, EMA was negative and Ki-67 the proliferative index was less than 5%. **Conclusion:** Immunohistochemical analysis, in the absence of more pronounced eosinophilic infiltrate and overlapping micromorphology with other neoplasms of mesenchymal origin, is helpful in the differential diagnosis of this rare benign neoplasm. The absence of atypical mitoses and low Ki-67 proliferative index also indicate the benign nature of this mesenchymal neoplasm, which can cause intestinal obstruction.

**Key words: inflammatory fibroid polyp, obstruction, ileum**

## P2-22

## Medularni karcinom debelog creva: prikaz slučaja

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**Cilj:** Prikazujemo slučaj 55-godišnje žene sa medularnim karcinomom debelog creva. Medularni karcinom debelog creva je redak oblik kolorektalnih maligniteta sa karakterističnim patohistološkim, kliničkim i molekularnim karakteristikama. Ova forma neoplazme može biti povezana sa mikrosatelitskom nestabilnošću ili deficitom enzima popravke replikacionih grešaka DNK kao i sa naslednim nepolipoznim kolorektalnim karcinomom. Medularni karcinom ima generalno dobru prognozu u odnosu na druge forme kolorektalnih maligniteta, međutim mikrosatelitski nestabilni medularni karcinomi u odmaklom stadijumu tumorske bolesti imaju lošiju prognozu. **Prikaz slučaja:** Predstavljamo redak slučaj 55-godišnje žene sa rektalnim krvarenjem, bolom u stomaku i povremenom dijarejom. Porodična istorija kolorektalnih ili drugih maligniteta bila je negativna. Patohistološki pregled je pokazao karcinom sa negativnom ekspresijom homeoboks transkripcionog faktora, sinaptofizina, hromogranina A, citokeratina 20, citokeratina 7 i pozitivno bojenje na kalretinin. Ki67 proliferativni indeks bio je 49%. Karcinom kolona je bio slabo diferentovan i povezan sa deficitom enzima popravke replikacionih grešaka DNK (gubitak nuklearne ekspresije MLH1 (MutL Homologue 1) i PMS2 (Po-

stmeiotic Segregation increased 2) proteina) i sa stadijumom tumorske bolesti T3N2bMx (IIIC). Pomoću patohistološke i imunohistohemijske analize postavljena je definitivna dijagnoza medularnog karcinoma. **Zaključak:** Medularni karcinom sa mikrosatelitskom nestabilnošću ili deficitom enzima popravke replikacionih grešaka DNK potrebno je razlikovati od drugih nediferentovanih kolorektalnih karcinoma. Gubitak nuklearne ekspresije MLH1 i PMS2 proteina i snažna difuzna ekspresija kalretinina pomogli su da se potvrdi definitivna dijagnoza medularnog karcinoma.

**Ključne reči: medularni kolorektalni karcinom, imunohistohemijska analiza, mikrosatelitska nestabilnost**

## Medullary carcinoma of the large bowel: A case report

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**Objective:** We present the case of a 55-year-old woman with medullary colorectal cancer. Medullary carcinoma of the large bowel is a rare form of colorectal malignancies with caracteristic pathohistological, clinical and molecular features. This form of cancer can be associated with microsatelite instability or deficiency mismatch repair protein and hereditary non-polyposis colorectal cancer. Medullary carcinoma has a generally favorable prognosis compared to other forms of colorectal malignancies, however these carcinoma with microsatelite instability had a worse prognosis in advanced stage. **Case report:** We present a rare case of a 55-years-old woman with rectal bleeding, abdominal pain and intermittent diarrhea. Familly history of colorectal or other malignancies was negative. Pathohistological examination revealed a carcinoma with negative staining for homeobox transcription factor (CDX2), synaptophysin, chromogranin A, cytokeratin 20, cytokeratin 7 and positive staining for calretinin. Ki67 proliferative index was 49%. The cancer was poorly differentiated and associated with deficiency mismatch repair protein (loss of the nuclear protein expression mutL homologue 1 (MLH1) and postmeiotic segregation increased 2 (PMS2)) and stage T3N2bMx (IIIC) of the tumor disease. This pathohistological finding and immunohistochemical analysis provided the diagnosis of medullary carcinoma. **Conclusion:** Medullary carcinoma with microsatelite instability or deficiency mismatch repair protein should be distinguished from other undifferentiated colorectal cancers. The loss of the MLH1 and PMS2 nuclear protein expression and strong diffuse expression of calretinin helped us to confirm the final diagnosis of medullary carcinoma.

**Key words: medullary colorectal cancer, immunohistochemical analysis, microsatelite instability**

## P2-23
## Rijetki sinhroni tumori pankreatoduodenalne regije: prikaz slučaja

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**Cilj:** Prikazom rijetkog slučaja sinhronih tumora pankreatoduodenalne regije želimo dati doprinos postojećoj naučnoj literaturi. Ampularni karcinomi čine svega 0,2% maligniteta gastrointestinalnog trakta. Najčešće se ispoljavaju opstruktivnim ikterusom, bolom u abdomenu, povišenom tjelesnom temperaturom i gubitkom u tjelesnoj masi. Incidenca neuroendokrinih tumora (NET) pankreatoduodenalne regije varira od 0,8-10% usljed razlika u efikasnosti detekcije nefunkcionalnih i hormon-produkujućih tumora. Iako nefunkcionalni tumori zbog efekta mase mogu prouzrokovati simptomatologiju sličnu ampularnim karcinomima, najveći broj ovih tumora se dijagnostikuje slučajno. **Prikaz slučaja:** Pacijen-

tu muškog pola, starosti 65 godina, prilikom dijagnostičke obrade zbog opstruktivnog ikterusa, malaksalosti i povišene tjelesne temperature, postavljena je dijagnoza holecistoholangiolitijaze i akutnog purulentnog holangitisa. Tom prilikom je urađena holecistektomija i patohistološki je verifikovan hronični folikularni holecistitis. Zbog perzistiranja tegoba urađena je ERCP, a kako je biopsija uočene uvećane Vaterove papile otkrila postojanje srednje diferentovanog adenokarcinoma, uslijedila je duodenopankreatektomija. Makroskopskim pregledom hirurškog materijala, ispod sluznice Vaterove papile uočeno je bjeličasto tumorsko tkivo, najvećeg prečnika 1,1cm i uvećani pankreatoduodenalni i superiorni pankreatični limfni čvorovi. Histološkim pregledom je potvrđen pankreatobilijarni tip adenokarcinoma (CK7 i Ca19-19 pozitivan) sa infiltracijom duodenalne submukoze i sekundarnim depozitima u dva od 13 limfnih čvorova. U još dva limfna čvora nađene su metastaze G1-NET (hromogranin i sinaptofizin pozitivan, Ki67<3%), čije primarno ishodište nije otkriveno pregledom kompletnog dostavljenog materijala. Na osnovu lokalizacije metastatskih depozita i odsustva primarnog tumora u dostavljenom materijalu, najvjerovatnije ishodište primarnog NET je tijelo/rep pankreasa. **Zaključak:** Prilikom evaluacije opstruktivnog ikterusa treba misliti na tumore ampularne regije, a detaljnim patohistološkim pregledom operativnog materijala povećati vjerovatnoću detekcije potencijalno postojećih sinhronih, klinički nemanifestnih neoplazmi.

**Ključne reči: sinhroni tumori, ampularni adenokarcinom, neuroendokrini tumor**

## Rare synchronous tumors of pancreaticoduodenal region: A case report

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**Objective:** By reporting a rare case of synchronous tumors in pancreaticoduodenal region, we aim to contribute to the existing scientific literature.Ampullary carcinomas account for 0,2% of all gastrointestinal malignancies. Most commonly, they present with obstructive icterus, abdominal pain, fever and weight loss. The incidence of pancreaticoduodenal neuroendocrine tumors (NET) varies from 0,8-10% due to difference in detection rate of nonfunctional versus hormone-producing tumors. Although mass-effect may cause symptoms reminiscent of those seen in ampullary carcinomas, majority of NETs are diagnosed incidentally. **Case report:** During diagnostic work-up for obstructive icterus, malaise and fever, a 65-year-old male was diagnosed with cholecystocholangiolitiasis and acute purulent cholangitis. Upon cholecystectomy, chronic follicular cholecystitis was confirmed histologically. Due to persisting symptoms ERCP was performed, discovering a moderately differentiated adenocarcinoma of the Vater papilla. Pancreaticoduodenectomy was carried out and gross examination revealed presence of tumor measuring 1,1cm underneath the papillar mucosa, with enlarged pancreaticoduodenal and superior pancreatic lymph nodes. Histological analysis confirmed pancreaticobiliary type of adenocarcinoma (CK7 i Ca19-19 positive) infiltrating duodenal submucosa and metastasizing to 2 out of 13 lymph nodes. Two other lymph nodes contained metastases of G1-NET (chromogranin and synaptophysin positive, Ki67<3%), whose primary location remained unknown after complete examination of the specimen. Based on site of metastatic deposit and lack of primary tumor in resected organs, it is most likely that primary tumor was located within pancreatic body/tail. **Conclusion:** When investigating obstructive icterus, ampullary tumors should be kept in mind. Thorough histological examination of surgical specimens increases the likelihood of detecting a synchronous, clinically silent neoplasm.

**Key words: synchronous tumors, ampullary adenocarcinoma, neuroendocrine tumor**

## P2-24

## Primarni difuzni limfom B-ćelija u štitastoj žlijezdi: prikaz slučaja

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**Cilj:** Prezentujemo pacijentkinju sa primarnim difuznim krupnoćelijskim limfomom štitaste žlijezde B fenotipa. Primarni difuzni krupnoćelijski limfom štitaste žlijezde B fenotipa je rijedak i čini 1-5% svih maligniteta štitaste žlijezde i 2 % ekstranodalnih limfoma. Uglavnom nastaje kod žena u šestoj ili sedmoj deceniji života. **Prikaz slučaja:** Prezentujemo pacijentkinju starosti 80 godina koja je primljena u našu bolnicu radi operativnog liječenja uvećane štitaste žlijezde. Hormonalni status je bio u granicama referentnih vrijednosti. Nakon preoperativne pripreme urađena je totalna tireoidektomija i preparat je poslat na ex tempore dijagnostiku. Desni režanj štitaste žlijezde je veličine 7x5,5x3 cm, tumoroidno izmijenjen, čvrst, sivkasto-bjeličaste boje, sa područjima nekroze. Na brzim zaleđenim rezovima konstatuje se da je tumor malignih karakteristika. Na trajnim patohistološkim preparatima, dopunjenim sa imunohistohemijskom analizom, postavljena je dijagnoza krupnoćelijskog non-Hodgkin limfoma B-ćelijskog fenotipa. Tumorsko tkivo probija kapsulu štitaste žlijezde i infiltriše okolne mekotkivne strukture. Imunohistohemijski fenotip tumorskog tkiva je bio LCA i CD-20 pozitivan, Ki 67 pozitivan u 90% tumorskih ćelija, a BCL6 i Cyclin D1 negativan. Okolni parenhim štitaste žlijezde je bio kompromovan, bez elemenata Hashimoto thyreoiditisa. Kliničkim i radiološkim pretragama ustanovi se da je primarna lokalizacija u štitnoj žlijezdi. Dva mjeseca nakon operativnog zahvata pacijentkinji je započeta terapija po protokolu R-CHOP. U toku terapije pacijentkinja razvija simptome Sars-Cov2 infekcije, teški oblik bolesti. Letalni ishod nastupa usled respiratorne insuficijencije. **Zaključak:** Terapija lokalizovanog primarnog limfoma štitaste žlijezde podrazumijeva radioterapiju i/ili hiruršku terapiju kombinovanu sa hemioterapijom, kako bi se prevenirala diseminacija bolesti. Prognoza zavisi od histološke klasifikacije tumora i stadijuma bolesti.

**Ključne reči: limfom, štitasta žlijezda, dijagnoza**

## Primary diffuse B-cell thyroid lymphoma: A case report

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**Objective:** We present a patient with primary diffuse large cell lymphoma of the thyroid gland B phenotype. Primary diffuse large B-cell lymphoma in the thyroid gland is rare and accounts for 1-5% of all thyroid malignancies and 2% of extranodal lymphomas. It generally affects women in the 6th or 7th decade of life. **Case report:** We present an 80-year-old patient admitted to our hospital for surgical treatment of thyroid goiter. Her hormonal status was within the reference values. Total thyroidectomy was performed and the tissue sent for ex tempore diagnostics. The right lobe of the thyroid gland was 7x5.5x3 cm, firm, grayish-whitish, tumor-like appearance, with necrotic areas. Cryosections indicated that the tumor had malignant characteristics. After assessing the permanent pathohistological samples, supplemented with immunohistochemical analysis, a large B-cell non-Hodgkin's lymphoma was diagnosed. Tumor tissue penetrated the capsule of the thyroid gland and infiltrated the surrounding soft tissue structures. Immunohistochemical phenotype of tumor tissue was LCA and CD-20 positive,

Ki 67 positive in 90% of tumor cells, and BCL6 and Cyclin D1 negative. The surrounding thyroid parenchyma was compressed, with no elements of Hashimoto's thyroiditis. Clinical and radiological examinations showed that the primary localization is in the thyroid gland. Two months after the surgery, the patient was treated according to the R-CHOP protocol. During the therapy, the patient developed symptoms of Sars-Cov2 infection, a severe form of the disease. Fatal outcome occured due to respiratory failure. **Conclusion:** Treatment of primary thyroid lymphomas include the control of local disease with radiotherapy and/or surgery combined with chemotherapy to control disseminate disease. The prognosis depends on the histological classification of the tumor and the stage of the disease.

**Key words: lymphoma, thyroid gland, diagnosis**

## P2-25

## Superiornost protočne citometrije u dijagnostici neuroblastoma: prikaz tri slučaja

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**Cilj:** Cilj ovog rada je ispitivanje korisnosti metode protočne citometrije (PCM) u detekciji ćelija NB u uzorcima aspirata KS Kod pedijatrijskih pacijenata sa neuroblastomom (NB) u 4. stadijumu bolesti i metastatskim zahvatanjem koštane srži (KS), patohistološka analiza bioptata nije uvek dovoljno senzitivna za detekciju malignih ćelija. **Prikaz slučajeva:** Prikazujemo slučajeve 3 pedijatrijska pacijenta ženskog pola, uzrasta od 10 meseci do 2.2 godine. Kod 1. pacijenta je postojala klinička sumnja na akutnu limfoblastnu leukemiju, dok je kod 2. i 3. radiografski potvrđeno postojanje tumora abdomena, odnosno orbite. U sklopu hematološke obrade kod sva 3 pacijenta je učinjena analiza uzoraka aspirata KS metodom PCM i isključeno je postojanje hematoloških maligniteta. U sva 3 uzorka je detektovana populacija CD45-negativnih nehematopoeznih monojedarnih ćelija, imunofenotipskih karakteristika ćelija NB (CD56+/GD2+/CD81+). Citološka analiza aspirata KS sugerisala je infiltraciju ćelijama NB samo kod 1. pacijenta. Radiografski je naknadno i kod ovog pacijenta dijagnostikovan tumor retroperitoneuma. Indikovana je patohistološka analiza bioptata tumora kod sva 3 pacijenta i tako potvrđena dijagnoza NB. Kod 1. pacijenta je učinjena i biopsija KS u kojoj nije uočena infiltracija ćelijama NB. **Zaključak:** PCM je senzitivnija metoda za detekciju metastatskog NB u KS od citološke analize aspirata, odnosno patohistološke analize bioptata. PCM se može koristiti za preciznije otkrivanje pacijenata sa NB u 4. stadijumu bolesti i brzo postavljanje preliminarne dijagnoze, što ima značaj u ranom započinjanju adekvatne terapije kod životno ugroženih pacijenata.

**Ključne reči: neuroblastom, protočna citometrija, koštana srž**

## Superiority of flow cytometry in the diagnosis of neuroblastoma: Review of three cases

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**Objective:** The aim of this study was to investigate the usefulness of flow cytometry (FCM) in the detection of NB cells in BM aspirates.In pediatric patients with stage 4 neuroblastoma (NB) and bone marrow (BM) involvement, pathohistological analysis is not always sensitive enough to detect malignant cells. **Case reports:** We present cases of 3 pediatric female patients, aged from 10 months to 2.2

years. In the 1st patient there was a suspicion of acute lymphoblastic leukemia, while in the 2nd and 3rd patient the existence of an abdominal and orbital tumor was radiographically confirmed. FCM analysis of BM aspirates was performed in all 3 patients and the existence of hematological malignancies was excluded. In all 3 samples, a population of CD45-negative non-hematopoietic cells with immunophenotypic characteristics of NB cells was detected (CD56 +/GD2+/CD81+). Cytological analysis of BM aspirates suggested infiltration of NB cells only in the 1st patient. Retroperitoneal tumor was subsequently diagnosed radiographically in this patient as well. Pathohistological analysis of tumor biopsies in all patients was indicated and thus the diagnosis of NB was confirmed. A BM biopsy was performed in the 1st patient in which no infiltration with NB cells was observed. **Conclusion:** FCM is a more sensitive method for the detection of metastatic NB in BM than cytological analysis of aspirates, or pathohistological analysis of biopsies. FCM can be used to more accurately detect patients with stage 4 NB and to quickly make a preliminary diagnosis, which is important in the early initiation of adequate therapy in life-threatening patients.

**Key words: neuroblastoma, flow cytometry, bone marrow**

## P2-26

## Kastelmanova bolest: prikaz slučaja

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**Cilj:** Značaj adekvatnog dijagnostičkog pristupa kroz prikaz slučaja Kastlemanove bolesti. **Prikaz slučaja:** Pacijentkinji starosti 31 godina, bez pratećih komorbiditeta, tokom prvog trimestra trudnoće a nakon infekcije Kovid19, zbog perzistentnog kašlja načinjen je CT pregled grudnog koša. Registrovana je medijastinalna limfadenomegalija pozicija 2R-4R sa konglomeratima te načinjena biopsija usled sumnje na Hodgkin limfom. Prvobitno ex tempore, a zatim patohistološkim pregledom parafinskih rezova registrovan je fragmentisan limfni čvor delom folikularne građe CD10/Bcl-6 pozitivnih i Bcl-2 negativnih atretičnih germinativnih centara sa centralno penetrirajućim krvnim sudovima, tzv. "lollipop" formacije kao i okolnom hiperplastičnom mantle zonom "onion skin" karakteristika. Interfolikularno uočeni su umnoženi vaskularni prostori sa umerenom hijalinizacijom kao i grupe CD123 pozitivnih plazmocitoidnih dendritičnih ćelija i nešto poliklonalnih plazmocita (CD138/kappa/lambda+). Pojedinačni TDT pozitivni B-ćelijski prekursori u mantle zoni. CD23 naglašava folikularnu građu, a CyclinD1 je negativan. **Zaključak:** Kastlemanova bolest (KB) je retka bolest limfnog čvora nepoznate etiologije. Najčešće se javlja unicentrično i asimptomatski sa medijastinalnom limfadenopatijom ili retko multicentrično sa limfadenopatijom različitih grupa limfnih nodusa i organomegalije. Histološki se razlikuju hijalinovaskularna i plazmaćelijska varijanta. Unicentrični oblik etiološki se povezuje sa inflamatornom hiperprodukcijom IL-6, dok je multicentrični tip udružen sa HIV infekcijom, limfomima i autoimunim bolestima. Klinička manifestacija i radiološka slika Kastlemanove bolesti u velikoj meri imitiraju limfom, te prikaz slučaja naše pacijentkinje ukazuje na značaj patohistologije u dijagnostici limfadenopatija uz sugestiju da KB diferencijalno dijagnostički treba imati na umu.

**Ključne reči: Kastlemanova bolest, limfom, limfadenomegalija, medijastinum**

## Castleman's disease: A case report

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**Objective:** An adequate diagnostic approach based on the case report of Castleman's disease (CD). **Case report:** A 31-year-old female patient without comorbidities, after Covid19 infection during the first pregnancy trimester was chest-CT examinated due to persistent cough. Mediastinal lymphadenomegaly conglomerates of 2R-4R positions were found, suspected of Hodgkin's lymphoma, so a biopsy was performed. Initially ex tempore, followed by pathohistological examination of paraffin sections, a fragmented lymph node was registered partly with the follicular structures of CD10/Bcl-6 positive and Bcl-2 negative germinal centers in regression with centrally penetrating blood vessels, the so-called "Lollipop" formations and with surrounding hyperplastic mantle zone with "onion skin" characteristics and single TDT positive B-cell precursors inside. Interfollicularly, proliferated some hyalinizated blood vessels were seen, as well as groups of CD123 positive plasmacytoid dendritic cells, with some polyclonal plasma cells (CD138/kappa/lambda+). CD23 emphasized follicular structure, CyclinD1 was negative. **Conclusion:** CD is a rare lymph node disease of unknown etiology. Mostly, it is unicentric and asymptomatic with mediastinal lymphadenopathy or rarely multicentric with different lymph node groups lymphadenopathy and organomegaly. Two unicentric histological variants are described- hyalinovascular and plasmacellular and are associated with IL-6 inflammatory hyperproduction, while the multicentric goes with HIV infection, lymphomas and autoimmune diseases. As the clinical and radiological Castleman's disease presentation mimics lymphoma, this case report emphasizes the pathohistological importance in the diagnosis of lymphadenopathies and suggest that CB should be included as the differential.

**Key words: Castleman's disease, lymphoma, limphadenopathy, mediastinum**

## P2-27

## 2 u 1: prikaz slučaja

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**Cilj:** Prikaz retkog slučaja bolesnika sa dva neoplastična procesa u limfnom čvoru aksile. **Prikaz slučaja:** Bolesnik starosti 70 godina sa pet godina ranije patohistološki potvrđenim i lečenim B-sitnoćelijskim non-Hočkin limfomom, tj. leukemijom (SLL, tj. HLL) javio se na hematološki pregled nakon primećenog otoka u levoj aksili. Načinjena je kompjuterizovana tomografija (CT) kojom je verifikovana generalizovana limfadenomegalija sa progresijom u odnosu na prethodni pregled. Nakon standarne laboratorijske obrade uvećanog limfnog čvora, HE bojenjem je registrovano limfoidno tkivo zbrisane arhitektonike usled prisustva limfoidnog infiltrata sačinjenog od uniformnih sitnih zrelih limfocita B-ćelijskog imunofenotipa koji odgovara SLL (ekspresija markera Pax5, CD5, CD23 i Bcl2 uz delimičnu slabu ekspresiju CD20). Neočekivano, u centralnim delovima limfnog čvora uočeno je diskohezivno tumorsko tkivo izraženog ćelijskog i nuklearnog pleomorfizma sa brojnim patološkim mitozama a bez ekspresije gore navedenih markera. Paleta imunohistohemijskih markera u nekoliko navrata je dopunjavana, te je uz brojne primenjene markere bez ekspresije, dobijena imunopozitivnost na Vimentin, S100 i C-myc uz veoma visok proliferativni indeks Ki-67 (~90%). Širokom paletom primenjenih imunohistohemijskih antitela, isključeno je limfoproliferativno, epitelno i nervno poreklo metastatskog depozita te je diferencijalno dijagnostički na prvom mestu ukazano na slabo diferentovani maligni me-

zenhimalni tumor. Nakon konsultacije sa kliničkim lekarom dobijen je podatak o prethodnoj operaciji melanoma pre 4 godine, te je zaključeno da se radi o SLL sa metastazom melanoma u limfnom čvoru. **Zaključak:** U limfnom čvoru sa limproliferacijom, veoma retko nalazi se prisustvo druge tumorske proliferacije, kao što je u ovom slučaju metastaza melanoma. Patohistološki pregled limfnog čvora je neophodan i u slučajevima limfadenomegalije sa potrvđenim limfoproliferativnim oboljenjem.

**Ključne reči: non-Hogkin B-ćelijski limfom, SLL, melanom, limfni čvor, imunohistohemija**

## 2 in 1: a case report

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**Objective:** To present a rare case of two neoplasms presence in axillary lymph node. Case report: A 70-year-old patient with five years before pathohistologically confirmed and treated non-Hodgkin B-cell small cell lymphoma/leukemia (SLL/CLL) was reffered to hematologist after noticing left axillar swelling. Computed tomography (CT) verified generalized lymphadenomegaly with progression compared to the previous. Having performed standard laboratory tissue processing of enlarged lymph node, HE slides showed architecturally disturbed lymphoid tissue due to presence of dense infiltrate made of uniform small mature lymphocytes B-cell immunophenotype corresponding to SLL (expression of Pax5, CD5, CD23 and Bcl2, weak CD20). Unexpectedly, central lymph node parts revealed discohesive tumor tissue made of pleomorphic tumor cells, with numerous pathological mitoses and no expression of above applied markers. The immunohistochemical panel was expanded for several, and in long list of expressionless stains, immunopositivity for Vimentin, S100 and C-myc with high proliferative index Ki-67 (~90%) was obtained. According the wide range of applied immunostains, lymphomproliferative, epithelial and nerve origin of the metastatic deposit was excluded, so poorly differentiated malignant mesenchymal tumor was the first differential. After consulting the clinician, data on 4 years ago melanoma surgery were obtained, and it was concluded that it was SLL with melanoma metastasis in the lymph node. **Conclusion:** In the lymph node with lymphoproliferation, the presence of other neoplastic proliferation is very rare, such as in this case presence of melanoma metastasis. Pathohistological examination of the lymph node is also necessary in cases of lymphadenomegaly with previously confirmed lymphoproliferative disease.

**Key words: non-Hodgkin B-cell lymphoma, SLL, melanoma, lymph node, immunohistochemistry**

## P2-28

## Metastaza seminoma u koštanu srž kod pacijenta sa konkomitantnim folikularnim Non-Hočkin limfomom: prikaz slučaja

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**Cilj:** Prikazati slučaj metastaze seminoma u koštanu srž kod pacijenta sa konkomitantnim folikularnim non-Hočkin limfomom. Seminomi su najčešći tumori testisa. Primarnu terapiju predstavlja orhiektomija sa resekcijom lokalnih limfnih nodusa, nakon čega sledi adjuvantna radioterapija. Tumori testisa najčešće metastaziraju u retroperitonealne, medijastinalne limfne noduse, pluća, jetru, slezinu, gastrointestinalni trakt i nadbubrežne žlezde. Retki su slučajevi koštanih metastaza tumora testisa, dok metastaza seminoma u koštanu srž predstavlja kurioziet bez postojećih navoda u literaturi. **Prikaz slučaja:**

Pacijent starosti 66 godina, ranije lečen od folikularnog Non-Hodžkin limfoma, javlja se na pregled zbog tegoba u vidu malaksalosti, bolova u stomaku i leđima i hepatosplenomegalije. Nakon pregleda i radiološki verifikovanih uvećanih retroperitonealnih limfnih čvorova, pacijent je upućen hematologu. Na osnovu anamnestičkih podataka, postavljena je sumnja na relaps limfoma, nakon čega je načinjena biopsija koštane srži. U uzorku dobijenom biopsijom, bojenom hematoksilin-eozin metodom, uočena je difuzna ćelijska infiltracija krupnih ćelija, svetle citoplazme, poligonalnih jedara sa prominentnim jedarcima. Imunohistohemijskim bojenjem ćelije su pokazale pozitivnost na CD10, CD117, OCT3/4, PLAP, CK8/18 nakon čega je postavljena dijagnoza metastaze seminoma u koštatnoj srži. Ubrzo nakon postavljanja patohistološke dijagnoze, pacijent je preminuo. **Zaključak:** Seminom spada u prognostički povoljne tumore. Metastaze u koštanoj srži, zbog supresije hematopoeze, generalno dovode do lošije prognoze za pacijente. Ishod bolesti našeg pacijenta upravo ukazuje na lošiju prognozu, kao i na važnost pravovremene dijagnostike i terapije, čime bi šanse za preživljavanjem bile veće.

**Ključne reči: seminom, metastaza, koštana srž, testis**

## Bone marrow seminoma metastasis in a patient with concomitant follicular Non-Hodgkin's lymphoma: a case report

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**Objective:** To show a case of seminoma metastasis to bone marrow in a patient with concomitant follicular non-Hodgkin's lymphoma. Seminomas are most common testicular tumors. Therapy is orchiectomy with resection of local lymph nodes, followed by adjuvant radiotherapy. Testicular tumors most often metastasize to retroperitoneal, mediastinal lymph nodes, lungs, liver, spleen, gastrointestinal tract and adrenal glands. Bone metastases of testicular tumors are rare, while metastasis of seminoma to bone marrow is a curiosity. **Case report:** A 66-year-old patient, previously treated for follicular Non-Hodgkin's lymphoma, is examined due to malaise, abdominal and back pain and hepatosplenomegaly. After examination and radiologically verified enlarged retroperitoneal lymph nodes, the patient was referred to a hematologist. Lymphoma relapse was suspected, and bone marrow biopsy was performed. In the biopsy sample, stained with hematoxylin-eosin, diffuse cellular infiltration of large cells with bright cytoplasm, polygonal nuclei and prominent nucleoli was observed. The cells showed immunohistochemical positivity for CD10, CD117, OCT3/4, PLAP, CK8/18, after which the diagnosis of seminoma metastasis to bone marrow was made. Shortly after the pathohistological diagnosis was made, patient died. **Conclusion:** Seminoma is generally prognostically favorable tumor. Bone marrow metastases lead to a worse prognosis for patients. The outcome of our patients illness indicates the importance of timely diagnosis and therapy, which would increase his chances of survival.

**Key words: seminoma, metastasis, bone marrow, testis**

## P2-29

## „Giant cell rich“ tumor nosnog septuma: prikaz slučaja

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**Cilj:** Gigantocelularni tumor kosti, spada u grupu „giant cell rich“ lezija i čini 5% primarnih tumora kosti. Lokalizacija u kraniofacijalnim kostima je izuzetno retka. **Prikaz slučaja:** Prezentujemo pedesetjednogodišnjeg pacijenta koji je primljen u našu ustanovu zbog operativnog lečenja tumora nosnog septuma. Unatrag 3 godine pacijent se žalio na otežano disanje na nos koje se vremenom pogoršavalo. Na MSCT utvrđeno je postojanje ekspanzivne, inhomogene tumorske mase, promera 17x17 mm, koja je smeštena u prednjoj trećini nosnih hodnika i vrši njihovu subokluziju. Intraoperativno uočeno je da tumor potiče sa koštanog dela nosnog septuma i da u potpunosti razara njegov hrskavičavi deo. Na standardnim patohistološkim preparatima tumorsko tkivo sagrađeno je od brojnih multinuklearnih džinovskih ćelija izgleda osteoklasta između kojih se nalaze ovalne, okrugle i vretenaste monojedarne neoplastične ćelije eozinofilne citoplazme, umereno pleomorfnih jedara sa prominentnim sitnim jedarcima. Tumor je hipervaskularizovan, sa područjima svežeg krvarenja i obilnim depozitima hemosiderina. Mitoze su brojne, (15/HPFx200), ali nisu uočene patološke forme. U tumoru se nalazi i multifokalna produkcija osteoidnih i koštanih gredica. Osteoblasti se uočavaju uz same koštane gredice i zarobljeni u samim gredicama. Rub tumora prema kosti je infiltrativnog tipa. Na osnovu histomorfološke slike, kliničkih i radioloških podataka postavljena je dijagnoza koja odgovara ili gigantocelularnom tumoru kosti ili gigantocelularnom reparatornom granulomu. **Zaključak:** Precizna subtipizacija tumora iz grupe „giant cell rich“ je teška i zasnovana na sistematskoj integraciji histomorfoloških, radioloških i kliničkih podataka. U ovakvim dijagnostičkim dilemama jedina pouzdana metoda je testiranje za G34W mutaciju koja je prisutna kod gigantocelularnog tumora kosti i omogućava njegovo razlikovanje u odnosu na gigantocelularni reparatorni granulom.

**Ključne reči: gigantocelularni tumor kosti, gigantocelularni reparatorni granulom, G34W mutacija**

## Giant cell rich tumor of nasal septum: a case report

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**Objective:** Giant cell tumor of bone belongs to the giant cell rich group of lesions and accounts for 5% of primary bone tumors. Localization in craniofacial bones is extremely rare.
**Case report:** We present a fifty-one-year-old patient admitted to our hospital for surgical treatment of nasal septum tumor. In previous 3 years, the patient had complained of difficulties breathing through the nose, which had worsened over time. MSCT determined the existence of expansive, inhomogeneo-

us tumor mass, 17x17 mm in diameter, located in the anterior third of nasal cavities and suboccluding them. Intraoperatively was identified that tumor originated from the osseous nasal septum and completely devastated its cartilaginous portion. On standard pathohistological samples, tumor tissue composed of numerous osteoclasts-like multinucleated giant cells, between which oval, round, and spindle-shaped mononuclear neoplastic cells with eosinophilic cytoplasm, moderately pleomorphic nuclei and prominent small nucleoli are embedded. The tumor was hypervascularized, with hemorrhagic areas and abundant hemosiderin deposits. Mitoses were numerous (15/HPFx200), but no pathological forms were observed. Tumor contained multifocal production of osteoid and bone trabeculae. Osteoblasts were observed along the bone trabeculae and trapped in them. The tumor rim was infiltrative. Based on histomorphological, clinical and radiological data, a diagnosis either a giant cell bone tumor or a giant cell reparative granuloma was made. **Conclusion:** Precise subtyping of giant cell rich tumors is difficult and based on the systematic integration of histomorphological, radiological and clinical data. In diagnostic dilemmas, the only reliable method is testing for the G34W mutation that occurs in giant cell tumor of bone.

**Key words: Giant cell tumor of bone, giant cell reparative granuloma, G34W mutation**

## P2-30

## Mukoepidermoidni karcinom maksilarnog sinusa niskog gradusa: prikaz slučaja

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**Cilj:** Mukoepidermoidni karcinom (MEK) je najčešći maligni tumor pljuvačnih žlezda kod odraslih i kod dece. Međutim, MEK se ne javlja tako često u paranazalnim sinusima. Cilj ovog rada je da se opiše nesvakidašnji slučaj MEK-a maksilarnog sinusa, uz osvrt na njegove kliničke manifestacije i dijagnostički pristup. **Prikaz slučaja:** Sedamdeset devetogodišnja žena upućena je na pregled kod otorinolaringologa zbog dugotrajne glavobolje, otežanog disanja i povremene epistakse. Standardnim kliničkim pregledom utvrđeno je prisustvo tumorske promene glatke površine u srednjem nosnom hodniku nosne šupljine sa desne strane. Dodatno, kompjuterska tomografija otkrila je veliku heterogenu i hipervaskularizovanu masu u centru desnog maksilarnog sinusa, sa propagacijom u nosnu šupljinu i desne etmoidalne ćelije. Nakon hirurškog uklanjanja, tumor je poslat na patohistološku analizu. Tumor se sastojao iz mešovite populacije velikih mukoznih ćelija sa svetlom citoplazmom i periferno postavljenim jedrom, intermedijarnih ćelija sa bazaloidnim jedrom i epidermoidnih ćelija sa eozinofilnom citoplazmom, organizovanih u cistične strukture i solidna polja. Izražena atipija jedra, nekroza, neuralna invazija i mitoze nisu uočene. Bojenjem na mucikarmin dokazano je prisustvo mucina u citoplazmi tumorskih ćelija. Imunohistohemijska analiza pokazala je intenzivno bojenje na CK5/6, p63, fokalnu CK7 pozitivnost i negativno bojenje na S100, SMA i Kalponin. Na osnovu dobijenih rezultata, pacijentkinji je postavljena dijagnoza MEK-a niskog gradusa. **Zaključak:** U zaključku, u diferencijalnoj dijagnozi tumorske mase u paranazalnim šupljinama, tumori pljuvačnih žlezda ne bi trebalo da budu zanemareni pošto su odgovarajući pristup I rana dijagnoza odlučujući faktor u prognozi bolesti pacijenta.

**Ključne reči: mukoepidermoidni karcinom, paranazalna šupljina, tumori glave i vrata**

## Low-grade Mucoepidermoid-carcinoma of maxillary sinus: a case report

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**Objective:** Mucoepidermoid carcinoma (MEC) is the most common primary salivary gland malignancy in both children and adults. However, MEC has been rarely reported in the paranasal sinus. The present paper aimed to address an uncommon case of MEC arising in the maxillary sinus, by discussing its clinical manifestation and diagnosis. **Case report:** A 79 old woman was referred to an otolaryngologist-head and neck surgeon due to a history of headaches, difficulty breathing, and occasional epistaxis. Clinical examination revealed the presence of a smooth surfaced mass in the right nasal middle meatus. Additionally, computer tomography revealed a large heterogeneous and vascular mass at the center of the right maxillary sinus with extension to the nasal cavity and the right ethmoid air cell. After surgical removal, it was sent for histopathological analysis. The tumor was composed of varying proportions of large mucous cells with an empty cytoplasm and peripherally placed nucleus, intermediate cells with a basaloid nucleus, and epidermoid cells with eosinophilic cytoplasm arranged in the cystic structures and solid nest. Prominent nuclear atypia, necrosis, neural invasion, or mitosis were absent. Mucicarmin stain highlights cytoplasmic mucin in the tumor cell. Immunohistochemical examination revealed intense staining for CK5/6, p63, focal CK7 and negative for S100, SMA, and Calponin. Based on obtained findings we diagnosed the patient with a low-grade MEC. **Conclusion:** In conclusion, during the differential diagnosis of a tumor mass in paranasal cavity, salivary gland tumor tumor should not be ignored since early diagnosis and appropriate management are a determining factor in the prognosis of the patient.

**Key words: mucoepidermoid carcinoma, paranasal cavity, head and neck tumor**

**P2-31**

## Primarni peritonealni psamokarcinom sa karcinomom endometrijuma: prikaz slučaja

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**Cilj:** U ovom radu opisan je prvi slučaj primarnog peritonealnog psamokarcinoma (PPP) udruženog sa endometrijalnim endometrioidnim karcinomom (EEK). **Prikaz slučaja:** Pacijentkinja starosti 56 godina podvrgnuta je histeroskopiji usled perzistentne metroragije. Patohistološkom analizom je postavljena dijagnoza EEK visokog gradusa. Na magnetnoj rezonanci (MR) male karlice evidentirana je proliferacija endometrijuma sa invazijom miometrijuma i solidni tumor levog jajnika. Koncentracija serumskog karcinom antigena 125 (CA 125) je bila povišena (106.1 U/ml). Terapijski pristup je bio klasična abdominalna histerektomija sa bilateralnom adneksetomijom i parcijalnom omentektomijom. Makroskopski su nađene multiple priraslice na površini omentuma. Mikroskopskim pregledom, u omentumu su se videle žlezdane strukture obložene seroznim epitelom i centralno postavljenim psamoznim telima kao i brojna „gola" psamozna tela. Limfni nodusi omentuma su bili zahvaćeni psamokarcinomom. Citološki nalaz peritonealnog lavata je pokazao prisustvo psamoznih tela i retkih tumorskih ćelija. Definitivna dijagnoza bila je EEK visokog gradusa u the International Federation of Gynecology and Obstetrics (FIGO) stadijumu IIIA i PPP u FIGO stadijumu IIIA2. Po završetku 3 ciklusa hemioterapije paklitaksel i karboplatin otkrivena je promena iregularnih kontura u zadnjem bazalnom segmentu donjeg lobusa desnog plućnog krila. Onkološki konzilijum je doneo odluku o primeni 6 ciklusa hemioterapije doksorubicin i ciklofosfamid i transkutane radioterapije. Trenutno, pacijentkinja je 10 meseci bez recidiva bolesti. **Zaključak:** Moguće je postojanje vrlo retkih kombinacija sinhronih tumora u ginekološkoj patologiji. Terapijski pristup treba biti prilagođen agresivnijem tipu tumora.

**Ključne reči: psamokarcinom, peritoneum, endometrijalni karcinom, sinhroni tumori**

## Primary peritoneal psammocarcinoma with endometrial carcinoma: a case report

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**Objective:** We aimed to report the first primary peritoneal psammocarcinoma (PPP) case with synchronous endometrioid carcinoma of the endometrium (EEC). **Case report:** A 56-year-old premenopausal woman underwent hysteroscopy in response to persistent metrorrhagia. Pathohistological analysis confirmed the existence of high-grade EEC. The pelvis minor's magnetic resonance imaging (MRI) indicated endometrial proliferation with myometrial invasion and left ovarian solid tumor. Serum cancer antigen 125 concentration (CA 125) was elevated (106.1 U/ml). The treatment approach was a classical abdominal hysterectomy with bilateral adnexectomy and partial omentectomy. Grossly, multiple adhesions were found on the surface of the omentum. Microscopic examination revealed glandular formations lined by serous epithelium and centrally placed psammoma bodies, as well as numerous "naked" psammoma bodies in the omentum. Lymph nodes of the omentum were affected by psammocarcinoma. Cytological findings of peritoneal lavage were positive for psammoma bodies and rare tumor cells. The final diagnosis was a high-grade EEC the International Federation of Gynecology and Obstetrics (FIGO) stage IIIA and PPP FIGO stage IIIA2. After 3 cycles of chemotherapy with paclitaxel and carboplatin, a nodule with irregular contours was detected in the posterior basal segment of the lung's right lower lobe. The Oncology board suggested 6 cycles of chemotherapy with doxorubicin and cyclofosfamide and external beam radiotherapy. Currently, the patient is free of disease for 10 months. **Conclusion:** The existence of very rare combinations of synchronous tumors in gynecological pathology is possible. The therapeutic approach should be adjusted to a more aggressive tumor type.

**Key words: psammocarcinoma, peritoneum, endometrial carcinoma, synchronous tumors**

## P2-32

## Fibrozni kalcificirajući tumor u abdomenu: prikaz slučaja

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**Cilj:** Fibrozni kalcificirajući tumor (FKT) je retka benigna neoplazma porekla mekih tkiva. Tumor se češće javlja kod mladih odraslih osoba. U većini slučajeva se otkriva akcidentalno, jer pacijenti nemaju specifične simptome. **Prikaz slučaja:** Pacijentkinja 19 godina javlja se zbog osećaja tupog bola i pritiska u abdomenu. Na osnovu ultrazvuka i CT snimka abdomena otkrivena je tumorska formacija najvećeg prečnika 14 cm. Pacijentkinja je hospitalizovana na Kliniku za abdominalnu i endokrinu hirurgiju, KCV radi operativnog lečenja tumorske promene desnog hemiabdomena. Fizikalnim pregledom abdomen je u ravni grudnog koša i palpatorno mek. Tumor je u bliskom kontaktu sa duodenumom, glavom pankreasa i venom porte. Tumorska promena je odstranjena u celosti i nije infiltrovala okolne strukture. Makroskopski je tumor ovalnog oblika, inkapsulisan, tvrđe konzistencije, glatke i sjajne površine, dimenzija 11x9x7 cm. Na preseku tumor je vrtložast i bled, sa mrko prebojenim centralnim područjem. Histološki, isečci tumora, obojeni standardnom HE metodom, sastoje se od cirkumskriptnih snopova kolagenih vlakana delimično hijalinizovanih i sa oskudnim područjima inflamatornog infiltrata dominantno sagrađenog od limfocita i folikuloidnih agregata. U snopovima kolagenog veziva se nalaze retke vretenaste ćelije, oskudne citoplazme i izduženih jedara i žarišta distrofijskih kalcifikacija u vidu psamoznih telašaca. Imunohistohemijski profil je pokazao negativno bojenje na beta Katenin, STAT6, ALK, CD117, DOG1, dok su BCL2 i CD34 pokazali fokalno pozitivnu reakciju, a Ki67 je bio 1%. **Zaključak:** FKT je redak benigni tumor. Definitivna dijagnoza je postavljena na osnovu karakterističnog imunohistohemijskog profila za FKT.

**Ključne reči: fibrozni kalcificirajući tumor, CD34, ALK**

## Fibrous calcifying tumor in the abdomen: a case report

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**Objective:** Fibrous calcifying tumor (FCT) is a rare benign neoplasm of soft tissue origin. The tumor is more common in young adults. In most cases it is discovered by accident because patients don't have obvious symptoms. **Case report:** A 19-year-old woman presented with abdominal pain and pressure. Ultrasound and CT of abdomen discovered the tumor was 14 cm in maximum diameter. The patient is hospitalized in the Clinic for Abdominal and Endocrine Surgery, KCV for surgical treatment of a tumor in the right hemiabdomen. On physical examination, the abdomen is at chest level and palpably soft. The tumor is in contact with the duodenum, the head of the pancreas and the portal vein is observed surgically. The tumor was removed completely and didn`t infiltrate the surrounding structures. Macroscopically, the tumor was oval, encapsulated, harder in consistency, smooth and shiny surface, measuring 11x9x7 cm. At the cross-section, whirling, pale with a darkly colored central area. Histologically, in standard HE staining method, circumscribed bundles of collagen fibers partially hyalinized and with sparse areas of inflammatory infiltrate predominantly composed of lymphocytes and folliculoid aggregates are observed. The bundles of collagen contain rare spindle cells, sparse cytoplasm and elongated nuclei and foci of dystrophic calcifications form of psammosy bodies. Immunohistochemical profile: typical negative staining for beta Catenin, STAT6, ALK, CD117, DOG1, while BCL2 and CD34 showed a focally positive reaction, Ki67 was 1%. **Conclusion:** FCT is a rare benign tumor. Based on the characteristic immunohistochemical findings for FCT, a final diagnosis was rendered.

**Key words: fibrous calcifying tumor, CD34, ALK**

## P2-33

## Metastaza mikrocelularnog karcinoma pluća u transverzalnom kolonu: prikaz slučaja

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**Cilj:** Mikrocelularni karcinom pluća predstavlja brzo rastući, visoko maligni tumor, sa visokom stopom proliferacije, agresivnim ponašanjem i ranim široko rasprostranjenim metastazama u vreme postavljanja dijagnoze. Najčešća mesta metastaza su mozak, jetra, nadbubrežna žlezda, kosti I koštana srž. Međutim, metastaze u gastrointestinalnom sistemu su retke, sa samo nekoliko prijavljenih slučaja širom sveta. **Prikaz slučaja:** Predstavljamo slučaj asimptomatskog SCLC sa metastazom u transverzalnom kolonu. Pacijent je bio 61-godišnji muškarac, koji je primljen u bolnicu zbog bolova u stomaku. Pacijent nije imao respiratorne simtome, ali se mesecima žalio na gastrointestinalne tegobe. Urađena mu je resekcija debelog creva, i patološki pregled, pri čemu je imunohistohemijska analiza (IHC) tumorskog tkiva odgovarala SCLC. IHC analiza je pokazala da tumorske ćelije eksprimiraju TTF1, CD56, Synaptophysin, Chromogranin A I CK7. Ki67 je pokazao proliferativnu aktivnost u oko 70% jezgara tumorskih ćelija. IHC analiza je potvrdila metastatsko širenje SCLA u transverzalnom kolonu. **Zaključak:** Iako su metastaze SCLC u debelom crevu veoma retke, trebalo bi da obratimo više pažnje na gastrointestinalne simptome, obavljati kolonoskopiju I PET skener na vreme, koji bi mogli da pruža vredne informacije za preciznije dijagnostifikovanje neobičnih metastatskih mesta SCLC, kao što je gastrointestinalni trakt. Brža dijagnoza bi svakako obezbedila kraći vremenski interval od postavljanja dijagnoze do terapije.

**Ključne reči: mikrocelularni karcinom pluća, transverzalni kolon, metastaze, imunohistohemija**

## Metastasis of small cell lung cancer in the transversal colon: a case report

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**Objective:** Small cell lung cancer (SCLC) is fast growing, highly malignant tumor, with exceptionally high proliferative rate, aggressive behavior and early, widespread metastases at the time of diagnosis. The preferred metastatic sites are the brain, liver, adrenal glands, bone and bone marrow. However, metastasis in the gastrointestinal tract are rare, with only a few reported cases worldwide. **Case report:** We present a case of asymptomatic SCLC with metastasis to transversal colon. The patient was a 61-year old man admitted to hospital due to abdominal pain. The patient had no respiratory symptoms, but he was complaining of gastrointestinal discomfort for months. He underwent resection of the colon and the pathological examination, with the immunohistochemical (IHC) analysis of the tumor tissue corresponded to the diagnosis of SCLC. IHC analysis showed that tumor cells expressed TTF1, CD56, synaptophysin, chromogranin A, and CK7. Ki67 showed proliferative activity in about 70% of tumor cell nuclei. The IHC analysis confirmed the metastatic spread of SCLC in the transversal colon. **Conclusion:** Although SCLC metastasis in the colon is very rare, we should pay more attention to gastrointestinal signs, performing colonoscopy and PET scan on time that could provide valuable information for more precisely diagnosing of unusual SCLC metastatic sites, such as gastrointestinal tract. Faster diagnosis would certainly provide a shorter time interval from diagnosis to therapy.

**Key words: small cell lung cancer (SCLC), transversal colon, metastasis, immunohistochemistry**

**P2-34**

## Intraduktalni karcinom pljuvačnih žlezda: prikaz dva slučaja

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**Cilj:** Intraduktalni karcinomi pljuvačnih žlezda predstavljaju veoma retke neoplazme. Prvi put su opisani 1996. godine kao "low-grade salivary duct carcinomas", dok su u četvrtoj WHO klasifikaciji tumora glave i vrata od 2017. reklasifikovani pod ovim entitetom. Na osnovu imunohistohemijske analize data je podela na interkalatne, apokrine, mešovite i onkocitne, odnosno na low i high grade neoplazme. **Prikaz slučajeva:** Predstavljamo dva slučaja intraduktalnih karcinoma. Obe neoplazme su lokalizovane u parotidnoj žlezdi, kod muškaraca starosti 74 i 43 godine. U prvom slučaju reč je o neoplazmi veličine 21mm, u neposrednoj okolini pleomorfnog adenoma. Neoplazma se nalazi u gustom limfoidnom tkivu, dok je u drugom slučaju bila veličine 65mm, cistično degenerisana. Mikromorfološka prezentacija obe neoplazme je bila veoma slična. Ćelije su pokazivale visok stepen polimorfizma, formirajući kribriformne, papilarne i tubularne strukture sa opsežnim poljima nekroze. Invazija i proboj hijalinizovano izmenjenog kapsularnog tkiva nije uočena. Ćelije su ovalnog oblika, sa krupnim i vezikularnim jedrima, i prominentnim jedarcima. Citoplazma je svetlo eozinofilna i granulirana. Imunohistohemijska analiza neoplastičnih ćelija je pokazala pozitivnu ekspresiju HER2, AR, CK7, CK19, CKAE1/AE3, EMA, CEA, p53, kao i CK14, CK5/6 i p63 u mioepitelnim ćelijama. Proliferativni indeks Ki67 je bio visok, oko 27% u oba slučaja. Na osnovu mikromorfološke i imunohistohemijske analize postavljena je dijagnoza intraduktalnog karcinoma visokog gradusa, onkocitni histološki podtip. **Zaključak:** Histološki, intraduktalni karcinom može da oponaša sklerozirajuću adenozu, kribriformni karcinom, kao i neinvazivni karcinom iz pleomorfnog adenoma. Ćelijska atipija je bila prisutna, mitotske figure blago izražene, ali naglašena nekroze i visok proliferativni indeks. Imunohistohemijski je dokazano postojanje mioepitelnog ćelijskog sloja.

**Ključne reči: intraduktalni karcinom, tumori pljuvačnih žlezda, imunohistohemija**

## Intraductal salivary gland carcinoma: two cases report

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**Objective:** Intraductal salivary gland carcinomas belong to a group of extremely rare neoplasms. They were first described in 1996 as "low-grade salivary duct carcinomas", whereas in the fourth WHO classification of head and neck tumors from 2017 they were reclassified under this entity. Based on the immunohistochemical analysis, they are divided into intercalated, apocrine, mixed, and oncocytic, i.e., low- and high-grade neoplasms. **Case reports:** We presented two cases of intraductal carcinomas. Both neoplasms are localized in the parotid gland, in men aged 74 and 43 years, respectively. In the first case, it is a neoplasm of 21 mm in size, in the immediate vicinity of pleomorphic adenoma. The neoplasm is located in dense lymphoid tissue, whereas in the second case it is 65 mm in size, cystically degenerated. The micromorphological presentation of both neoplasms was rather similar. The cells showed a high degree of polymorphism, forming cribriform, papillary, and tubular structures with extensive fields of necrosis. The invasion and penetration of hyalinized altered capsular tissue were not observed. The cells were oval with large and vesicular nuclei and prominent nucleoli. The cytoplasm was light eosinophilic and granular. The immunohistochemical analysis of neoplastic cells showed a positive expression of HER2, AR, CK7, CK19, CKAE1/AE3, EMA, CEA, p53, as well as CK14, CK5/6, and p63 in myoepithelial cells. The proliferative index Ki67 was high, about 27% in both cases. Based on the micromorphological and immunohistochemical analysis, a high-grade intraductal carcinoma of the oncocytic histological subtype was diagnosed. **Conclusion:** Histologically, intraductal carcinoma may mimic sclerosing adenosis, cribriform carcinoma, as well as noninvasive carcinoma from pleomorphic adenoma. Cellular atypia was present, and mitotic figures were mild, but necrosis and a high proliferative index were pronounced. The existence of a myoepithelial cell layer was proven immunohistochemically.

**Key words: intraductal carcinoma, salivary gland tumors, immunohistochemistry**

## P2-35

## Angiosarkom srca:prikaz slučaja

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**Cilj:** Angiosarkomi su retki maligni tumori, čine 1-2% svih sarkoma. Najćešća lokalizacija je koža (oko 60% slučajeva), zatim visceralni organi, srce nije uobičajeno mesto. Zbog nespecifičnih simptoma dijagnoza je izazov i pored savremenih dijagnostičkih procedura. Histološki pregled je značajan za dijagnozu i potrebna je imunohistohemijska potvrda. **Prikaz slučaja:** Prikazali smo muškarca, 36 godina starosti, koji je od tegoba imao nedostatak vazduha, bol u grudima, osećaj napetosti u stomaku. U istoriji bolesti nije imao druga oboljena. Na ultrazvučnom pregledu viđen je perikardni izliv. Citološkom analizom su viđene maligne ćelije. Prilikom MDCT koronarografije opisana je masivna tumorska promena, koja zauzima najveći deo lateralnog zida desne pretkomore, promera 70x40x70mm. Urađena je resekcija tumora sa rekonstrukcijom desne pretkomore i gornje šuplje vene. Histološki tumor je građen od vazoformativnih i solidnih zona. Prisutni su brojni iregularni anastomozirajući vaskularni kanali obloženi atipičnim endotelnim ćelijama. Ćelije su ovalne, pleomorfne i mitotski aktivne. Tumor je izrazito infiltrativnog rasta. Prisutne su zone krvarenja i nekroze. Proliferativni indeks Ki67: 39,5%. Imunohistohemijsko bojenje: difuzno pozitivni u tumorskim ćelijama su: CD31, CD34, WT1, F8a, ERG,

FLI1, vimentin, a negativni su: CK AE1/AE3, EMA, CD45-LCA, SMA, bcl2, myogenin, desmin, D2 40, HMB45, Calretinin, Pax-8, HHV8. **Zaključak:** Primarni angiosarkomi srca su retki tumori sa lošom prognozom. Dijagnostikuju se kasno, kad su se već razvile metastaze. Nedostatak efikasnosti aktuelne terapije (hururška resekcija uz hemoterapiju i radioterapiju) ukazuje na potrebu targetirane terapije.

**Ključne reči: angiosarkom, srce, imunohistohemija**

## Angiosarcoma of the heart: a case report

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**Objective:** Angiosarcomas are rare malignant tumors, represents 1-2% of all sarcomas. The most common are cutaneus lesions (about 60% of cases), then visceral organs, but heart isn't common place. Despite use of modern diagnostic procedures diagnosis of angiosarcoma remains a challenge, due to it's non-speciticity of symptoms. Histological examination is important for diagnosis and immunohistochemical confirmation is required. **Case report:** We report case of a 36-year-old male who presented with shortness of breath, chest pain, feeling of tightness in abdomen. He didn't have past medical history. Ultrasound examination revealed pericardial effusion. Cytological findings showed malignant cells. MDCT coronary angiography showed massive tumor which occupies the largest part of the lateral wall of the right atrium, diameter: 70x40x70mm. Resection of the tumor was performed with reconstruction of the right atrium and vena cava superior. Histological tumor is formed of vasoformative and solid zones. Numerous irregular anastomotic vascular canals lined with atypical endothelial cells are present. The cells are oval, pleomorphic and mitotically active. The tumor is extremely infiltrative. Bleeding and necrosis zones are present. Ki67 proliferative index: 39.5%. Immunohistochemical staining: diffuse positive in tumor cells are: CD31, CD34, WT1, F8a, ERG, FLI1, vimentin, and negative: CK AE1 / AE3, EMA, CD45-LCA, SMA, bcl2, myogenin, desmin, D2 40, HMB45, Calretinin, Pax-8, HHV8. **Conclusion:** Primary angiosarcomas of the heart are rare tumors with a poor prognosis. The diagnosis is delayed, when metastases have already developed. Lack of efficacy of current therapy (surgical resection with chemotherapy and radiotherapy) indicates the need for targeted therapy.

**Key words: angiosarcoma, heart, immunohistochemistry**

## IZVODI IZ OSTALIH PREDAVANJA
IZVODI IZ OSTALIH PREDAVANJA

### Novine u klasifikaciji tumora pleure

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Peto izdanje Klasifikacije torakalnih tumora Svetske zdravstvene organizacije objavljeno je 2021. godine i donelo je značajne izmene u klasifikaciji pre svega mezotelnih tumora. Prefiks "maligni" je izbačen iz terminologije lokalizovanog i difuznog mezotelioma, s obzirom da se svi mezoteliomi smatraju malignim. Dobro diferentovan papilarni mezoteliom je preimenovan u dobro diferentovan papilarni mezotelni tumor (DDPMT) sugerišući njegovo indolentno kliničko ponašanje. DDPMT se odnosi na tumore sačinjene od papilarnih formacija prekrivenih jednim slojem mezotelnih ćelija bez atipije i bez invazije strome. Dijagnoza ovog retkog tumora zahteva histološki pregled cele lezije kako bi se isključila mogućnost uzorkovanja superficijalne komponente invazivnog difuznog mezotelioma. Makroskopski, ovaj tumor se prezentuje u vidu arborizovane mase ili manjih nodusa na površini visceralne ili parijetalne pleure, a klinički se kod pacijenata javlja dispnea zbog rekurentnih pleuralnih izliva. Nova saznanja u genomici mezotelioma dovela su do prepoznavanja novog entiteta mezotelioma in situ (MIS) kao prekursora invazivnog mezotelioma. Dijagnoza MIS zahteva multidisciplinarni pristup sa objedinjavanjem histoloških, imunohistohemijskih, molekularnih, kliničkih i radioloških nalaza. Definiše se kao jednoslojna proliferacija mezotelnih ćelija bez atipije (ponekad i sa formiranjem papilarnih struktura obloženih jednim slojem mezotelnih ćelija) sa imunohistohemijskim gubitkom BAP1 ili MTAP ili homozigotnom delecijom CDKN2A na FISH testiranju. Za dijagnozu MIS neophodno je isključiti postojanje komponente invazivnog mezotelioma. Iako se većina pacijenata sa MIS prezentuje sa rekurentnim pleuralnim izlivima nejasne etiologije, citologija pleuralnog izliva nije od koristi u diferencijaciji MIS od invazivnog mezotelioma. Po definiciji, da bi se postavila sumnja na dijagnozu MIS, ne sme biti vidljivih znakova tumora na imidžing metodama ili direktnoj vizuelnoj inspekciji pleure, a dijagnoza zahteva mutliple biopsije pleure. Lokalizovani mezoteliom je ostao izolovan entitet u odnosu na difuzni, s obzirom da lokalizovani mezoteliom ima bolju prognozu kada se kompletno resecira. Određene histološke karakteristike (arhitekturalni obrasci, ćelijske karakteristike i karakteristike strome) navedene su kao parametri od prognostičkog značaja kod pacijenata sa epitelioidnim difuznim mezoteliomom. Histološke karakteristike u epitelioidnom difuznom mezoteliomu koje su povezane sa boljom prognozom uključuju: tubulopapilarni, trabekularni i adenomatoidni arhitekturalni obrazac, limfohistiocitoidne ćelijske karakteristike ili prisustvo miksoidne strome (definiše se kao predominantno prisusutvo u više od 50% tumora sa manje od 50% solidne komponentne). Nepovoljne histološke karakteristike u epitelioidnom difuznom mezoteliomu uključuju: mikropapilarni i solidni arhitekturalni obrazac prisutan u više od 50% tumorskog tkiva, rabdoidne i pleomorfne ćelijske karakteristike ili prisustvo nekroze. U novoj klasifikaciji, mezoteliomi sa pleomorfnim karakteristikama mogu biti klasifikovani kao epitelioidni, bifazični ili sarkomatoidni na osnovu koegzistirajuće morfologije tumorskih ćelija.

Limfohistiocitoidne karakteristike se odnose na tumore sa naglašenom infiltracijom CD8 pozitivnih limfocita i poligonalnim malignim mezotelnim ćelijama histiocitoidne morfologije. U novoj klasifikaciji, mezoteliomi sa ovim karakteristikama mogu biti klasifikovani kao epitelioidni, bifazični ili sarkomatoidni na osnovu koegzistirajuće morfologije tumorskih ćelija. Mezoteliomi sa prelaznim ćelijskim karakteristikama se karakterišu izduženim do ovalnim kohezivnim ćelijama koje se po morfologiji nalaze između ćelija epitelioidnog i sarkomatoidnog mezotelioma. U novoj klasifikaciji, mezoteliomi sa prisustvom prelaznih ćelijskih karakteristika su klasifikovani kao sarkomatoidni uzimajuću u obzir njihovu lošiju prognozu. U slučaju da se prelazne ćelijske osobine nađu u inače epitelioidnom mezoteliomu, tumor se klasifikuje kao bifazični mezoteliom u zavisnosti od tipa uzorka

i procenta tumorskog tkiva sa ovim osobinama. Nova klasifikacija je donela i dvostepeni nuklearni sistem gradiranja epitelioidnih difuznih mezotelioma koji uključuje stepen nuklearne atipije (blaga, umerena, teška), broj mitoza i prisustvo ili odsustvo nekroze. Tumori nuklearnog gradusa 1 (sa ili bez nekroze) i nuklearnog gradusa 2 bez nekroze klasifikuju se kao low grade mezoteliomi, a tumori nuklearnog gradusa 2 sa nekrozom i nuklearnog gradusa 3 sa ili bez nekroze kao high grade mezoteliomi. Mezenhimalni tumori pleure prebačeni su u novo poglavlje „Mezenhimalni tumori toraksa", sa posebnim osvrtom na solitarni fibrozni tumor toraksa i uvođenjem 3- i 4-varijabilnog modela za predviđanje njegovog metastatskog rizika.

**Ključne reči: mesothelioma, World Health Organization classification, pleura, histopathology**

## Novelties in classification of pleural tumors

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The 2021 (fifth edition) WHO Classification of Thoracic Tumors has recently been published and brought significant changes in the new classification of mesothelial tumors. The prefix "malignant" has been omitted from localized and diffuse mesothelioma because all mesotheliomas are regarded as malignant. Well-differentiated papillary mesothelioma (WDPM) has been renamed as WDPM tumor (WDPMT), given its relatively indolent behavior. The definition of WDPMT is now restricted to tumors consisting of papillary formations covered by a single layer of bland mesothelial cells that lack stromal invasion. Accurate diagnosis of this rare tumor requires histologic examination of the entire lesion to exclude the possibility of superficial sampling from a component of an invasive diffuse mesothelioma. WDPMT typically appears as an arborescent mass or nodularity on the visceral or parietal pleura. Patients often present with dyspnea owing to recurrent pleural effusions. Recent advances in the understanding of genomics of mesothelioma have led to increased recognition of a new entity, mesothelioma in situ (MIS) which is regarded as a precursor to invasive mesothelioma. The diagnosis requires multidisciplinary correlation among histologic, immunohistochemical and/or molecular, clinical, and radiologic findings. MIS is defined as a single layer of relatively bland mesothelial cells growing along the pleural surface (sometimes the cells form simple papillary structures, but still with a single layer of covering cells) that have lost BAP1 or MTAP by IHC or homozygous deletion of CDKN2A by FISH. Invasive mesothelioma must be absent to make a diagnosis of MIS. Although, most patients with MIS present with recurrent pleural effusions of unknown cause, pleural fluid cytology specimens cannot separate MIS from invasive mesothelioma. By definition, there must be no evidence of tumor on imaging or by direct visual inspection of the pleura and the diagnosis requires multiple samples from different areas of the pleura. Localized mesothelioma remains distinct from diffuse mesothelioma because localized mesotheliomas have been found to be associated with better prognosis when completely resected. There has been increased recognition of histologic factors (architectural patterns, cytologic features, and stromal features) with prognostic significance that could improve risk stratification of patients with epithelioid diffuse pleural mesothelioma. Histologic features seen in epithelioid diffuse mesothelioma that are associated with better prognosis include tubulopapillary, trabecular, or adenomatoid architectural patterns, lymphohistiocytoid cytologic features, or the presence of myxoid stroma (when predominant, defined as present in more than or equal to 50% of a tumor with less than 50% solid pattern). Unfavorable histologic features in epithelioid diffuse mesothelioma include micropapillary pattern, solid pattern when present in more than or equal to 50% of a tumor, rhabdoid or pleomorphic cytologic features, or the presence of necrosis. In the 2021 WHO classification, mesotheliomas with pleomorphic features can be classified as epithelioid, biphasic, or sarcomatoid on the basis of coexistent tumor cell morpho-

logy. Lymphohistiocytoid features are characterized by marked lymphoid infiltrates composed of CD8-positive lymphocytes obscuring polygonal malignant mesothelial cells that have histiocytoid morphology. The 2021 WHO classification allows these tumors to be classified as epithelioid, biphasic, or sarcomatoid on the basis of tumor cell morphology. Mesotheliomas with transitional cytologic features are characterized by elongated yet plump and cohesive tumor cells that seem intermediate between epithelioid and sarcomatoid in morphology and have a sheet-like growth pattern. In the 2021 WHO classification, tumors with the presence of transitional pattern are now classified as sarcomatoid owing to recent studies revealing the presence of transitional features to be associated with worse prognosis. Therefore, if transitional features are seen in an otherwise epithelioid tumor, the tumor could be classified as biphasic mesothelioma depending on specimen type and percentage of transitional features seen. New classification brought a two-tier nuclear grading system for epithelioid diffuse mesothelioma that incorporates nuclear atypia (mild, moderate and severe), mitoses, and the presence or absence of necrosis. All nuclear grade 1 tumors (with or without necrosis) and nuclear grade 2 tumors without necrosis are classified as low grade, and nuclear grade 2 tumors with necrosis and any nuclear grade 3 tumors are classified as high grade. In the 2021 WHO classification, mesenchymal tumors of the pleura have been moved to a new chapter titled "Mesenchymal tumours of the thorax" with special reference to solitary fibrous tumor of the thorax and by introducing 3- and 4-variable model for predicting its metastatic risk.

**Key words: mesothelioma, World Health Organization classification, pleura, histopathology**

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## Autopsijska patologija u Srbiji – pogled u prošlost

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Autopsija (obdukcija ili nekropsija) predstavlja postmortalni pregled tela, uključujući i pregled unutrašnjih organa i struktura nakon disekcije, sa ciljem da se utvrdi uzrok smrti ili priroda patoloških promena. Zakon o zdravstvenoj zaštiti (2019) nalaže vršenje obdukcija kao posebne mere za utvrđivanje uzroka i porekla smrti umrlih lica, i navodi u kojim je okolnostima vršenje obdukcije obavezno. Značaj obdukcija se ogleda kroz više aspekata, kao što su kontrola rada bolničkih ustanova, naučno-istraživački i pedagoški rad, sudsko-medicinski i higijensko-epidemiološki aspekt. U narednim pasusima biće napravljen kratak osvrt na istorijat i razvoj autopsijske patologije u Srbiji.

Zakon koji se odnosio na formiranje narodne vojske, donet je 1861. godine na Preobraženskoj skupštini Kneževine Srbije. Iz tog Zakona i njegovih uredbi proisteklo je osnivanje Vojnog saniteta, a zatim je sagrađena prva Vojna bolnica u Beogradu u kojoj je postojala i Prosektura. Nova Vojna bolnica u Beogradu, koja je izgrađena 1904. godine je imala bolničku Prosekturu. Obdukcije su obavljali odeljenski lekari. Od osnivanja Srpskog lekarskog društva (SLD) 1872. godine, tema diskusija na redovnim sastancima su bili i bolesnici koji su umrli i obdukovani uz kliničko patološku korelaciju nalaza. Diskutovalo se i o potrebi za vršenjem kliničkih autopsija, o potrebi edukacije sa osposobljavanjem lekara za patološku anatomiju, i o potrebi stvaranja muzeja patoloških i teratoloških preparata u edukacione i naučne svrhe. U jednom od zapisnika sastanaka SLD-a iz 1889.godine, citira se predlog dr Đ. Jovanovića „... da je najbolji i najbrži put da se što pre dođe do teratološkog muzeja, da se od strane SLD umole kolege da obrate pažnju na retkosti, kako teratološke tako i patološke, i da sve šalju SLD, a ovo u muzej". Predlog biva usvojen, a doktori Subotić, Jovanović Batut, i Đoka Jovanović su izabrani da izrade projekt za patološku zbirku. U Zapisnicima SLD od 18.11.1889. i 2.12.1889 . godine, dr Subotić predlaže da „SLD umoli ministra unutrašnjih dela da se pošalje jedan ili đak pitomac, ili jedan od lekara da se stručno spremi za patološku anatomiju...jer bez jednog patološkog anatoma kod nas ne može biti napretka u medicini."
Prosektura u Opštoj državnoj bolnici u Beogradu (u današnjoj ulici Džorža Vašingtona), 1897. godine dobija specijalistu sudske medicine, patologije i bakteriologije, dr Eduarda Mihel-a koji se vratio iz inostranstva gde je bio upućen da specijalizira ove discipline. Prosektura se 1907. godine seli u novu Prosekturu u Opštoj državnoj bolnici na Vračaru. U ovoj prosekturi su se obavljale kliničke i sudsko medicinske obdukcije. Vetar u leđa razvoju patološke anatomije u Srbiji donosi osnivanje Medicinskog fakulteta u Beogradu 1920. godine. Dr Đorđe Joannović je od 1909. godine bio redovni profesor opšte i eksperimentalne patologije na bečkom Univerzitetu. Odazvavši se pozivu do dođe za redovnog profesora opšte patologije i patološke anatomije, on napušta Beč, i 1920. godine zauzima mesto u triumviratu osnivača Medicinskog fakulteta. Na inicijativu prvog vanrednog profesora sudske medicine novoosnovanog Medicinskog fakulteta u Beogradu, dr M. Milovanovića, Prosektura Opšte državne bolnice 1924. godine postaje Sudsko medicinski zavod Medicinskog fakulteta u Beogradu. U ovom Zavodu se i dalje obavljaju kliničke obdukcije, i nastavljen je naučni rad iz oblasti patološke anatomije. Do svečanog otvaranja Patološkog instituta 22.aprila 1926.godine, obdukciona nastava se izvodi u Prosekturama Opšte državne i Vojne bolnice. Doprinos dr Joannovića razvoju patologije u Srbiji daleko prevazilazi prostor predviđen ovim sažetkom, i u najvećem se ogleda u izgradnji prvih stručnih i naučnih kadrova za patološku anatomiju. Na dužnost upravnika Instituta za patologiju, nakon smrti dr Joannovića 1932. godine dolazi prof. Ksenofon Šahović, još jedno veliko ime srpske patologije. Pod vođstvom prof Šahovića, Institut od 1937-1940. izdaje prvi stručno-naučni specijalizovani časopis za patologiju u Jugoslaviji, „Acta Pathologica". Tokom bombardovanja u II svetskom ratu, Institut biva pogođen, a kao posledica razaranja uništen je i Muzej makroskopskih patološko-anatomskih preparata sa 1500 eksponata. Nakon smrti prof. Šahovića, veliki trag, na Institutu i šire,ostavio je prof. Živojin Ignjačev, koji je pored stručnog doprinosa učestvovao u razvoju patološke anatomije u Sarajevu, Novom Sadu i Prištini (bio je član matičnih komisija za osnivanje medicinskih fakulteta), u stvaranju Sekcije za patološku anatomiju SLD (1963.) i Udruženja patologa Jugoslavije (1967). Autor je brojnih radova i udžbenika od kojih bih istakao udžbenike: Obdukcijska tehnika i Patološko anatomski praktikum.
Prosektura Državne bolnice u Novom Sadu osnovana je 1921.godine. Prvo predavanje iz patološke anatomije na Medicinskom fakultetu u Novom sadu (osnovanom 1960.) održao je 1962 godine prof. Ž. Ignjačev. Patološko-anatomska prosektura u Nišu, u okviru Opšte bolnice, osnovana je 1941. godine. U Vojnoj bolnici u Nišu, 1944. godine, biva osnovana jos jedna patološko anatomska prosektura. Institut za patologiju Medicinskog fakulteta u Nišu je osnovan 1962. godine, uz pomoć profesora patologije iz Skoplja, Dragoslava Miletića i Epse Urumove. Prva klinička obdukcija u Prištini je obavljena 1958. godine. Medicinski fakultet u Prištini je osnovan 1969. godine, a patologija se odvaja

od sudske medicine 1972. godine. Patološka anatomija u Kragujevcu počinje sa radom 1966. godine. Institut za patologiju Medicinskog fakulteta u Kragujevcu je osnovan 1980 godine. Formiranjem Vojno medicinske akademije 1949. godine Prosektura Glavne vojne bolnice u Beogradu prerasta u Institut za patologiju i sudsku medicinu VMA.
Napredak patologije ne bi bio moguć bez saradnje i pomoći kliničara. Osetan pad broja obdukcija u poslednjim dekadama 20. veka i početkom 21. veka ukazuje na promene u trendovima u medicini, ali i ukazuje na manjak saradnje kliničara i patologa. Za kraj bih istakao, da nas je pandemija COVID-19 podsetila da je saradnja apsolutno neophodna, i u najboljem interesu pacijenata .

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## Zakonske odredbe u vezi sa vršenjem kliničke obdukcije

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Član 203. Zakona o zdravstvenoj zaštiti

Za svako umrlo lice utvrđuje se vreme i uzrok smrti, na osnovu neposrednog pregleda umrlog lica. Utvrđivanje vremena i uzroka smrti može vršiti samo doktor medicine.

Za lica umrla u zdravstvenoj ustanovi, vreme i uzrok smrti utvrđuje se u zdravstvenoj ustanovi i o tome obaveštava nadležni organ jedinice lokalne samouprave, u skladu sa zakonom.

Poreklo i uzrok smrti mogu biti utvrđeni i bez obdukcije, na osnovu primenjenjih dijagnostičkih metoda u toku bolničkog lečenja. U svim smrtnim slučajevima ne vrši se obdukcija – nije obavezna ako vršenje obdukcije u konkretnom slučaju nije propisano zakonskim odredbama.

Zakonske odredbe o vršenju obdukcije

- Zakon o zdravstvenoj zaštiti (ZZZ) – članovi 204 i 206
- Zakonik o krivičnom postupku (ZKP) - članovi 129 i 130

**Član 206. ZZZ** Kao posebna mera utvrđivanja uzroka i porekla smrti umrlih lica, vrši se obdukcija. Obdukcija se obavezno vrši:
1) na licu umrlom u zdravstvenoj ustanovi ukoliko nije utvrđen uzrok smrti;
2) ako smrt, čiji uzrok nije moguće jasno utvrditi iz postojeće medicinske dokumentacije, nastupi u roku od 24 sata od prijema lica u zdravstvenu ustanovu;
3) na mrtvorođenom detetu i novorođenčetu koje je umrlo u zdravstvenoj ustanovi odmah nakon rođenja ili tokom lečenja;
4) na zahtev doktora medicine koji je lečio umrlo lice;
5) na zahtev doktora medicine određenog za stručno utvrđivanje vremena i uzroka smrti od strane nadležnog organa opštine, odnosno grada;
6) kada je to od posebnog značaja za zaštitu zdravlja građana ili kada to nalažu epidemiološki ili sanitarni razlozi;
7) na zahtev nadležnog organa, u skladu sa zakonom;
8) na zahtev člana uže porodice umrlog lica;
9) ako smrt nastupi u toku dijagnostičkog ili terapijskog postupka, kao i nakon ovog postupka ukoliko postoji osnov sumnje da je smrt nastupila u vezi sa izvršenim postupkom;
10) u slučaju smrti lica umrlih u stacionarnoj zdravstvenoj ustanovi ili organizacionom delu stacionarne zdravstvene ustanove u kojoj se obavljaju specijalističko-konsultativni pregledi i bolničko lečenje lica sa mentalnim smetnjama, kao i u slučaju smrti pritvorenih i osuđenih lica;
11) u slučaju smrti lica koje je u vreme nastupanja smrtnog ishoda bilo uključeno u kliničko ispitivanje lekova ili drugo medicinsko istraživanje;
12) u slučaju smrti lica čiji se delovi tela mogu uzimati radi presađivanja u svrhu lečenja, u skladu sa zakonom.

Sudskomedicinska obdukcija je jedan od vidova veštačenja u sudskom postupku. Organ postupka je najčešće javni tužilac koji vrši procenu da li treba da se izvrši sudskomedicinska obdukcija u skladu sa članom 129 ZKP.

Veštačenje leša Član 129. ZKP
Ako postoji sumnja da je smrt određenog lica neposredna ili posredna posledica krivičnog dela ili je u trenutku smrti lice bilo lišeno slobode ili je nepoznat identitet leša, javni tužilac ili sud će odrediti da lekar specijalista za sudsku medicinu izvrši pregled i obdukciju leša.

Lekar ne zahteva SM obdukciju, već ima ulogu predlagača čiji zadatak je da obavesti nadležne organe (organe unutrašnjih poslova i preko njih javnog tužioca) da se radi o smrtnom slučaju u kojem bi trebalo izvršiti SM obdukciju

Član 204. Zakona o zdravstvenoj zaštiti
Doktor medicine koji vrši neposredan pregled umrlog lica radi utvrđivanja vremena i uzroka smrti, bilo da je smrt nastupila u zdravstvenoj ustanovi ili na nekom drugom mestu, dužan je da bez odlaganja o smrtnom slučaju obavesti nadležnu organizacionu jedinicu ministarstva nadležnog za unutrašnje poslove, ako:
1) nije u mogućnosti da utvrdi identitet umrlog lica;
2) pregledom umrlog lica utvrdi povrede ili na drugi način posumnja u nasilnu smrt;
3) na osnovu raspoloživih medicinskih činjenica nije moguće utvrditi uzrok smrti.

U navedenim slučajevima lekar mora bez odlaganja da o smrtnom slučaju obavesti policiju i predloži sudskomedicinsku obdukciju, a policija taj predlog prenosi nadležnom javnom tužiocu. Ako nadležni tu**žilac** ne zahteva sudskomedicinsku obdukciju, lekar ima zakonsku mogućnost da zahteva kliničku obdukciju (kao lečilac ili mrtvozorac – član 206 ZZZ stav 4 i 5).

Zablude o saglasnosti rodbine za vršenje obdukcije - Ranije se često (mada neosnovano) govorilo da rodbina umrlog ima pravo da zabrani vršenje kliničke, ali ne i sudskomedicinske obdukcije. Zakon ne predviđa (niti je ikada predviđao) potrebu pribavljanja saglasnosti članova porodice umrlog lica za vršenje bilo koje vrste obdukcije.
Nema zakonske odredbe kojom se rodbini daje pravo da zabrani vršenje bilo koje vrste obdukcije, tako da rodbina pokojnog ne može da zabrani vršenje ni patološkoanatomske ni sudskomedicinske obdukcije - odluku o storniranju obdukcije može da donese jedino organ koji je tu obdukciju i zahtevao.

**Član 206. ZZZ**
Zahtev za obdukciju može opozvati isključivo lice ili organ koji je obdukciju i zahtevao, ukoliko su prestali razlozi za vršenje obdukcije.

Zakonom o zdravstvenoj zaštiti predviđeno je obavezno vršenje obdukcije ukoliko to zahtevaju članovi uže porodice umrlog lica **Član 206. ZZZ, stav 8, s tim što tada r**odbina snosi troškove obdukcije.

## Kliničko-autopsijska korelacija

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Prve autopsije su rađene u Starom Egiptu oko 3000 godina p.n.e. Osnovni razlozi za izvođenje autopsije su utvrđivanje neposredanog uzroka smrti i sticanje saznanja o određenoj bolesti. Brojni autori ističu ulogu autopsija u proceni kvaliteta rada zdravstvene službe, posebno službe hitne medicinske pomoći i tercijarne zdravstvene službe[1,2,3]. Informacije koje lekari koji su lečili preminule bolesnike dobijaju nakon završene autopsije su dragocene jer omogućavaju procenu primenjenih dijagnostičkih procedura i uspešnost različitih terapijskih modaliteta čime se doprinosi proširivanju znanja o različitim bolestima[1,4].
Autopsije se mogu smatrati smatraju neizostavnim dijagnostičkim testom koji kao zlatni standard ima veoma visoku senzitivnost za utvrđivanje uzroka smrti. Međutim, poslednjih decenija je došlo do značajnog pada u broju kliničkih autopsija[5,6]. Uzroci pada broja kliničkih obdukcija su materijalni troškovi, strah lekara od otkrivanja propusta u lečenju i potencijalnih tužbi, kao i uverenje da su savremeni dijagnostički aparati superiornije dijagnostičko sredstvo od autopsija[7]. Jedan od parametara procene kvalteta zdravstvene zaštite se zasniva na poređenju kliničke i autopsijske dijagnoze. Kliničko-autopsijska korelacija je procenjivana na različite načine. Pojedini autori u radovima samo konstatuju postojnje diskrepance u vezi sa uzrokom smrti[8], bez kvantifikacije kliničko-autopsijskog neslaganja. Grupa istraživača iz Rumunije rezultate kliničko-patološke korelacije svrstava u tri grupe: grupu gde se klinička i autopsijska dijagnoza potpuno poklapaju, grupu gde je ovo preklapanje delimično i grupu gde se klinička i autopsijska dijanoza potpuno ne slažu[9]. Goldman i sar. su precizno definisali tri kategorije diskrepance, odnosno grešaka, a definisani kriterijumi nazivaju se Goldmanovim kriterijumima i često se koriste u radovima za analizu kliničko-autopsijske diskrepance. Velike greške u završnim dijagnozama povezanim sa uzrokom smrti označene su kao major diskrepance sa podkategorijama I i II. Postojanje neslaganja u kliničkim i autopsijskim dijagnozama koje nisu direktno povezane za uzrokom smrti je označeno kao minor diskrepanca, a one su podeljene u dve kategorije: III i IV. Potpuno slaganje kliničkih dijagnoza i autopsijskog nalaza predstavlja kategoriju V (T**abela 1**)[10].

| Tip diskrepance | Klasifikacija dijagnostičke greške | Definicija |
|---|---|---|
| Major | I | Direktno povezano sa smrću; da je prepoznato uticalo bi na terapiju ili preživljavanje |
| | II | Direktno povezano sa smrću; da je prepoznato ne bi bi uticalo na terapiju ili preživljavanje |
| Minor | III | Slučajan nalaz na obdukciji koji nije direktno povezan sa smrću, ali je povezan sa završnim tokom bolesti |
| | IV | Slučajan nalaz na obdukciji koji nije povezan sa uzrokom smrti ili slučajan nalaz na obdukciji koji je doprineo smrti kod pacijenata sa terminalnom bolešću |
| Nema diskrepance | V | Klinička i autopsijska dijagnoza se u potpunosti slažu |

**Tabela 1.** Klasifikacija dijagnostičkih grešaka po Goldmanu[10]

U poslednjih četrdesetak godina u pojedinim bolnicama zapažen je značajan pad incidencije greške klase I. Zastupljenost greške klase I u Univerzitetskoj bolnici u Ciruhu je na primer sa 16% smanjena na 1%. Ovo se može tumačiti boljim i dostupnijim dijagnostičkim i terapijskim procedurama, ali takođe i značajanim padom u broju izvršenih obdukcija u tom periodu[5]. Istraživanja sprovedena 80-ih godina prošlog veka u SAD grešku I klase nalaze u 12-13% slučajeva, dok je stopa obdukcija 30-40%. Deceniju kasnije u istraživanju u Belgiji, greška I klase na autopsijama internističkih pacijenata nađena je u nešto većem broju slučajeva – u 16%, ali je stopa autopsija bila preko 90%[5]. Procenjeno je da bi u slučaju 100% urađenih obdukcija u bolnicama procenat greške klase I bio sveden na najmanju moguću meru[7]. U istraživanju nemačkih autora potpuno slaganje kliničkih i autopsijskih dijagnoza na ukupno 1112 autopsija je postojalo u 73,8% slučajeva. Isti autori navode da su starost bolesnika, dužina lečenja u bolničkim uslovima i pridružene kardiovaskularne bolesti značajno povezani sa pojavom kliničko-autopsijske dikrepance[6]. Učestalost greške I klase je utvrđena u znatno većem procentu u zavisnosti od tipa bolnice gde su obavljene obdukcije. U pedijatrijskim bolnicama major diskrepanca se javlja u 10-14% obdukovanih bolesnika[11,12]. Greška I klase kod pacijenata koji su hospitalizovani na odeljenjima intenzivne internističke i hirurške nege može veoma da varira od 17,7%[3], 27%[13] do čak oko 61%[4]. U istraživanju domaćih autora na materijalu Instituta za patologiju „Prof. dr Đorđe Joannović“[14] major diskrepanca je ustanovljena kod oko 32% pacijenata koji su preminuli u periodu do 24 sata od hitne hospitalizacije. Ako se kliničko-autopsijska diskrepanca uzroka smrti analizira u posebno osetljivim grupma kao što su pshihijatrijski bolesnici, ukupna diskrepanca je čak oko 64%, pri čemu je neslaganje kliničke i autopsijske dijagnoze značajno češće kod bolesnika lečenih u specijalizovanim psihijatrijskim bolnicama.

Jedan od glavnih klinički neprepoznatih uzroka smrti je infekcija[11,14,15]. Drugi čest uzrok major diskrepance je trombna embolija pluća[16]. Na odeljenjima sa teško obolelim pacijentima često je neprepoznata invazivna aspergiloza[2,17], dok su česti uzroci major greške kod onkoloških bolesnika pored aspergiloze, neprepoznata trombna embolije pluća i recidiv malignog tumora[2]. Major diskrepanca je kod onkoloških bolesnika u istraživanju Khawaja i sar. konstatovana u čak 21% slučajeva[2].

Iako je medicinska tehnologija značajno napredovala autopsije i dalje imaju značajnu ulogu jer svaki napredak u medicini donosi nove izazove i nove nepoznanice[3]. Značaj kliničke obdukcije je ponovo dospeo u žižu interesovanja lekara pojavom COVID-19 epidemije kada su zahvaljujući autopsijskim istraživanjima otkivene brojne činjenice u vezi sa novom bolešću. To nas je ponovo podsetilo,da je autopsija neprevaziđena edukativna metoda[17,18,19].

## Clinical and autopsy correlation

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The first autopsies were performed in Ancient Egypt around 3000 BC. The main reasons for performing an autopsy are determining the cause of death and gaining knowledge about a certain disease. Numerous authors emphasize the role of autopsies in assessing the quality of work of the health service, especially the emergency medical service and the tertiary health service[1,2,3]. The informations that doctors who treated deceased patients receive after the autopsy are important because they enable the assessment of applied diagnostic procedures and the success of various therapeutic modalities, which contributes to expanding knowledge about various diseases[1,4].
Autopsies can be considered as an indispensable diagnostic test which, as the gold standard, has a very high sensitivity to determine the cause of death. However, in recent decades there has been a significant decline in the number of clinical autopsies[5,6]. The reasons for the decline in the number of clinical autopsies are material costs, the fear of doctors of discovering errors in treatment and potential lawsuits, as well as the belief that modern diagnostic devices are a superior diagnostic tool than autopsies[7]. One of the parameters of health care quality assessment is based on the comparison of clinical and autopsy diagnosis. Clinical and autopsy correlation was assessed in different ways. Some authors in the papers note only the existence discrepancies regarding the cause of death, without quantifying of the clinical-autopsy discrepancy[8]. A group of researchers from Romania classifies the results of clinical-pathological correlation into three groups: the group where clinical and autopsy diagnosis completely coincide, the group where this overlap is partial and the group where clinical and autopsy diagnosis completely disagree[9]. Goldman et al. have precisely defined three categories of discrepancies diagnostic errors, and defined criteria are well known as Goldman's criteria and often are used in works for the analysis of clinical-autopsy discrepancies. Important errors in the final diagnoses related to the cause of death are marked as major discrepancies with subcategories I and II. The existence of discrepancies in clinical and autopsy diagnoses that are not directly related to the cause of death is marked as a minor discrepancy, and they are divided into two categories: III and IV. Complete agreement of clinical diagnoses and autopsy findings is category V (Table 1)[10].

| Discrepancy | Diagnostic errors | Criteria |
|---|---|---|
| Major | I | Directly related to death; if recognized it would affect therapy or survival |
| | II | Directly related to death; if recognized it would not affect therapy or survival |
| Minor | III | Accidental autopsy finding not directly related to death, but related to the final course of the disease |
| | IV | Accidental autopsy finding not related to the cause of death or accidental autopsy finding that contributed to death in patients with terminal illness |
| No discrepancy | V | Clinical and autopsy diagnosis are in complete agreement |

**Table 1.** Goldman diagnostic error classification[10]

In the last forty years, a significant decrease in the incidence of class I error has been observed in some hospitals. The prevalence of class I error in the University Hospital in Zurich, for example, has been

reduced from 16% to 1%. This can be explained by better, efficiant and more accessible diagnostic and therapeutic procedures, but also by a significant decrease in the number of autopsies performed in that period[5]. Research conducted in the 1980s in the United States found class I error in 12-13% of cases, while the autopsy rate was 30-40%. A decade later, in the study in Belgium, class I error at autopsies of internal medicine patients was found in a slightly higher number of cases - in 16%, but the autopsy rate was over 90%[5]. It was estimated that in the case of 100% of autopsies performed in hospitals, the percentage of class I error would be reduced to a minimum[7].

In the research of German authors, complete agreement of clinical and autopsy diagnoses on a total of 1112 autopsies existed in 73.8% of cases. The same authors state that the age of patients, the length of treatment in hospital conditions and associated cardiovascular diseases are significantly associated with the occurrence of clinical autopsy discrepancy[6]. The frequency of class I error was determined in a significantly higher percentage depending on the type of hospital where the autopsies were performed. In pediatric hospitals, major discrepancies occur in 10-14% of autopsied patients (11,12). Class I errord in patients hospitalized in intensive care and surgical care can vary greatly from 17.7%[3], 27%[13] to as much as 61%[4]. In the research of Serbian authors on the material of the Institute of Pathology "Prof. Dr. Djordje Joannovic", major discrepancy was found in about 32% of patients who died within 24 hours of emergency hospitalization[14]. If the clinical-autopsy discrepancy of the cause of death is analyzed in particularly vulnerable groups such as psychiatric patients, the total discrepancy is as high as about 64%, with discrepancies between clinical and autopsy diagnosis being significantly more common in patients treated in specialized psychiatric hospitals.

Infection is one of the main clinically unrecognized causes of death[11,14,15]. Thrombotic pulmonary embolism is another common cause of major discrepancies[16]. Invasive aspergillosis is often unrecognized in departments with severely ill patients[2,17], while major causes of major errors in oncology patients beside aspergillosis are unrecognized thrombotic pulmonary embolism and recurrence of malignant tumors[2]. Major discrepancies in oncologyical patients are found in about 21% of cases[2].

Although medical technology has advanced significantly, autopsies still play a significant role because every advance in medicine brings new challenges and new questions[3]. The importance of clinical autopsy again came to the attention of doctors with the appearance of the COVID-19 epidemic, when, thanks to autopsy research, numerous facts related to the new disease were discovered. This reminded us again that autopsy is an superlative educational method[17,18,19].

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## Sistemska mastocitoza sa udruženom hematološkom neoplazmom – SMAHN:prikaz slučaja i pregled literature

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**Uvod:** Mastocitoza predstavlja klonalnu, neoplastičnu proliferaciju mastocita u jednom ili više organa. Karakteriše se infiltratima abnormalnih mastocita često u vidu multifokalnih kompaktnih klastera ili kohezivnih agregata, ali i kao difuzni intersticijalni infiltrati pojedinačnih mastocita bez agregata. Citomorfološki, mastociti mogu biti raznoliki, ali su uvek atipičnog izgleda- izduženi i hipogranulirani. Mnogobrojni bi/višejedarni mastociti ukazuju na agresivnu populaciju, mada čak i tada mitoze su retke. Fiziološki, metahromatske granule mastocita se lako registruju Giemsa ili toluidin-plavim bojenjem. Za identifikaciju nezrelih ili atipičnih mastocita najspecifičnija metoda je svakako imunohistohemijsko bojenje triptazom i CD117 (KIT) a za detekciju neoplastičnih mastocita to su CD25 i ređe

CD2. Kod mastocitoze najčešće je prisutna mutacija KIT D816. Aktuelna WHO klasifikacija razlikuje kutanu formu mastocitoze sa infiltratima atipičnih mastocita samo u koži, sistemsku formu (SM) sa infiltratima u najmanje jednom ekstrakutanom organu sa/bez zahvatanja i kože i veoma redak oblik mast ćelijskog sarkoma sa lokalizovanim destruktivnim rastom visoko atipičnih mastocita. Za patohistološku dijagnozu SM neophodno je zadovoljiti jedan glavni i minimalno dva od postojeća četiri sporedna kriterijuma. Po toku, SM može biti indolentna, tinjajuća, udružena sa drugom hematološkom neoplazmom (SMAHN), agresivna ili u formi leukemije mast ćelija. U SMAHN obliku, najčešće je to sa mijelodisplastično/mijeloproliferativnom neoplazmom (MDS/MPN) i to hroničnom mijelo-monocitnom leukemijom (HMML), ili udružena sa mijelodisplastičnim sindromom, mijeloproliferativnim neoplazmama ili akutnom mijeloidnom leukemijom. U zavisnosti od pridružene hematološke bolesti, uz KIT D816V mutaciju prisutne su i druge mutacije. Prava policitemija (PRV) je hronična mijeloproliferativa neoplazma (MPN) koju karakteriše povećana produkcija crvenih krvnih zrnaca nezavisno od regulatornih mehanizama eritropoeze. Postoje dve faze bolesti- policitemična faza sa povišenim vrednostima hemoglobina, hematokrita i eritrocita i spent-faza ili faza post-policitemične mijelofibroze praćena citopenijom podrazumevajući anemiju, neefektivnu hematopoezu, fibrozu koštane srži, ekstramedularnu hematopoezu i hipersplenizam. Za patohistološku dijagnozu PRV moraju biti ispunjena sva tri glavna kriterijuma (1. hemoglobin >16.5 g/dlL za muškarce, odnosno >16.0 g/dL za žene; hematokrit >49% za muškarce, odnosno >48% za žene; povišene vrednosti mase eritrocita, tj. >25% iznad predviđene srednje normalne vrednosti, 2. panmijeloza sa proliferacijom megakariocita različite veličine, 3. mutacija JAK2 V617F ili JAK2 egzon 12) ili da su ispunjena prva dva navedena glavna kriterijuma uz treći sporedni kriterijum (subnormalna vrednost serumskog eritropoetina). Obično je prisutna somatska mutacija JAK2 V617F. Vodeći morfološki nalaz kod PRV je panmijeloza, uz izraženu proliferaciju eritroidne loze i megakariocita hiperhromatičnih jedara različite veličine i oblika, često u labavim klasterima. Koštana srž je najčešće hipercelularna, naročito subkortikalno. U spent fazi prisutna je fibroza gradusa 3-2 (na skali do 3), uz mogućnost osteoskleroze kao i splenomegalije usled ekstramedularne hematopoeze. **Prikaz slučaja:** Pacijent starosti 68 godina sa izraženim generalizovanim dugotrajnim pa i bolnim svrabom dermatološki je bezuspešno lečen različitim medikamentima tokom 4 godine. Decembra 2020. godine pregledan je od strane interniste zbog od ranije poznate kalkuloze žučne kesice kada navodi i noćno preznojavanje, a u krvnoj slici prvi put je registrovana eritrocitoza (Hb 11 mmol/l; Hct 60%; Ery 6,91x1012/l) uz leukocitozu (Leu 17,6x109/l) i trombocitopeniju (139x1012/l). Postavljena je sumnja na MPN-PRV uz indikaciju za biopsiju koštane srži i prateće citomorfološke, molekularne i citogenetske analize. Januara 2021. godine ultrazvučnim pregledom isključena je splenomegalija. Biopsija koštane srži pokazala je hipercelularnu koštanu srž morfoloških karakteristika MPN, najpre PRV, bez fibroze. Citomorfološki registrovana je relativno normalna hematopoeza nešto poremećenog sazrevanja. Molekularnim analizama detektovana je JAK2 V617 mutacija, dok je citogenetski izolovan abnormalni aranžman sa trizomijom 8 i CNLOH 9p koje idu u prilog klinički suspektne PRV. Kao što su sve analize i upućivale, zaključeno je da se radi o PRV te je započeto lečenje hidroksikarbamidom. Zbog veoma slabog dejstva na svrab i pojave stomačnih tegoba, nakon oko tri nedelje korigovana je terapija, te je hidroksikarbamid zamenjen ruksolitinibom koji je redukovao svrab za 75% nakon nekoliko dana. Na redovnim kontrolama bolesnik je navodio dobar subjektivni osećaj, ali maja 2021. godine u apiratu periferne krvi registrovani su blasti (0,5% blasta) kao i povišene vrednosti serumskog LDH sa trendom porasta tokom narednih meseci (466...514 U/l), te je u avgustu 2021. godine hematolog indikovao novu biopsiju koštane srži uz citomorfologiju i protočnu citometriju. Septembra 2021. godine patohistološki pregled koštane srži ukazao je na nešto manje ali i dalje hipercelularnu srž sa slikom PRV, bez povišenog broja blasta ali uz blagu progresiju fibroze (MF1). Protočnom citometrijom nisu detektovane abnormalne ćelije u koštanoj srži, a citomorfološki registrovana je hematopoeza sa terapijskim efektima. Molekularnim analizama detektovane su dodatne KRAS i tri TET2 mutacije. Aspirat periferne krvi pokazao je blag porast blasta (1% blasta), dok je pregledom aspirata koštane srži procenjeno 3% blasta. Uz ruksolitinib, započeto je lečenje interferonom, sa planom daljeg praćenja i rebiopsiju kroz 4-5 meseci. Januara 2022. godine načinjena je biopsija koštane srži sa citomorfologijom i protočnom citometrijom. Citomorfološki registrovana je oskudna hematopoeza sa 1% blasta, što diferencijalno dijagnostički odgovara mijelofibrozi, dok molekularne analize nisu registrovale dodatne

mutacije. Protočnom citometrijom isključeno je postojanje akutne mijeloidne leukemije sa prisustvom 0,6% mijeloidnih prekursora očuvanog sazrevanja. Patohistološki verifikovana je hipercelularna koštana srž sa perzistetnom PRV ali uz dalju progresiju fibroze (MF2) i minimalnu ekstramedularnu hematopoezu, što u poređenju sa prethodnom biopsijom sada više odgovara post-PRV mijelofibrozi. Zbor porasta broja blasta u aspiratu, primenjena su imunohistohemijska bojenja. CD34 je bio negativan, ali primenom markera CD117 viđen je porast broja degranulisalih i izduženih mastocita u agregatima koji su eksprimirali i MCT i CD25, dok je CD2 bio negativan. Uz gore opisanu morfološku sliku MPN- tj. post-PRV-MF, nakon ispunjenog jednog glavnog uz dva sporedna kriterijuma, zaključeno je postojanje sistemske mastocitoze, iako KIT mutacija nije detektovana. Nakon nedelju dana registrovana je blago povišena vrednost serumske transaminaze (16,3 μg/l; ref<11,4). Retrospektivno je urađeno imunohistohemijsko bojenje triptazom na prve dve biopsije ali WHO kriterijumi za SM nisu bili ispunjeni. **Zaključak:** U čak 30% slučajeva sistemske mastocitoze, udružena hematološka bolest se dijagnostikuje pre, simultano sa ili posle potvrđene SM. Praktično svaka mijeloidna ili limfoidna neoplazma može da se javi udruženo sa SM, pri čemu su mijeloidne neoplazme češće i to najčešće hronična mijelo-monocitna leukemija i neklasifikovana mijelodisplastično/mijeloproliferativna neoplazma. Kod pacijenata sa potvrđenom hematološkom neoplazmom, a pre svega HMML i neklasifikovanom MDS/MPN, mora se razmotriti i eventualno postojanje SM koja usled deganulacije mastocita često ostane neprimećena pa i nelečena.

**Ključne reči: prava policitemija, sistemska mastocitoza, KIT mutacija, SMAHN**

## Systemic mastocytosis with an associated haematological neoplasm – SMAHN: case report and literature review

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**Introduction:** Mastocytosis is a clonal, neoplastic mast cell proliferation that accumulates in one or more organs characterized by abnormal mastocyte infiltrates often in multifocal compact clusters or cohesive aggregates, but also as diffuse interstitial infiltrates of single mastocytes without aggregates. Cytomorphologically, mastocytes can be different, but always atypical in appearance– spindle-shaped, elongated and hypogranulated. Finding of numerous bi/multilobated nuclei usually indicates aggressiveness, although even then mitoses are rare. Physiologically, Giemsa or toluidine-blue staining detect mastocyte metachromatic granules easily. The most specific method for immature or atypical mast cells identification is certainly immunohistochemistry with tryptase and CD117 (KIT) while CD25 and less often CD2 for neoplastic mast cells. In mastocytosis, mutation KIT D816 is usually present. The current WHO classification distinguishes cutaneous mastocytosis form where atypical mast cell infiltrates are found only in the skin, systemic form (SM) where the infiltrates affect at least one extracutaneous organ with/without skin involvement and a very rare mast cell sarcoma form with localized destructive growth of highly atypical mastocytes. For the pathohistological diagnosis of SM, one major and at least two of the existing four minor criteria must be met. SM can be indolent, smouldering, associated with another hematological neoplasm (SMAHN), aggressive or in mast cell leukemia form. If as SMAHN, it's most often with myelodysplastic/myeloproliferative neoplasm (MDS/MPN) and chronic myelo-monocyte leukemia (CMML), or associated with myelodysplastic syndrome, myeloproliferative neoplasms or acute myeloid leukemia (AML). Depending on the associated hematological neoplasm, other mutations may be present in addition to the KIT D816V mutation. Polycythemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) characterized by increased red blood cell production independent of the erythropoiesis regulatory mechanisms. There are two disease phases- polycythemic phase with elevated hemoglobin, hematocrit and erythrocytes and spent phase or phase of post-polycythemic myelofibrosis followed by cytopenia, including anemia, ineffective hematopoiesis, bone marrow fibrosis, extramedullary hematopoiesis and hypersplenism. All three major criteria must be met for the PV pathohistological diagnosis (1. Hb>16.5 g/dlL for men and >16.0 g/dL for women;

Hct >49% for men and >48% for women; elevated erythrocyte mass values, >25% above the predicted mean normal value, 2. panmyelosis, 3. JAK2 V617K or JAK2 exon 12 mutation) or that the first and the second major criteria are met with the minor criteria in addition (subnormal serum erythropoietin value). The somatic JAK2 V617F mutation is usually present. The leading morphological PV finding is panmyelosis with pronounced proliferation of erythropoiesis and megakaryocytes that are hyperchromatic, different in size and nuclei shape, often with loose clustering. The bone marrow is usually hypercellular, especially subcortically. In spent phase, fibrosis grade 2-3 is present (on scale of up to 3), with the possibility of osteosclerosis and splenomegaly due to extramedullary hematopoiesis. **Case presentation:** A 68-year-old patient with intesive generalized long-term and even painful itching was unsuccessfully dermatologically treated with various medications for almost 4 years. In December 2020, he was reffered to internal medicine doctor due to known gallstones when he also reported night sweats, and for the first time in the blood lab values erythrocytosis was registered (Hb 11 mmol/l; Hct 60%; Ery 6.91x1012/l) with leukocytosis (Leu 17.6x109/l) and thrombocytopenia (139x1012/l). The suspicion of PV was observed with the indication for spleen ultrasound examination and bone marrow biopsy with accompanying cytomorphological, molecular and cytogenetic analyzes. In January 2021, bone marrow showed hypercellular image consisted with PV, without fibrosis. No splenomegaly. Cytomorphologically was registered normal hematopoiesis with some dismaturation. Molecular analyzes detected JAK2 V617 mutation, while cytogenetics isolated trisomy 8 and CNLOH 9p in favor of PV. The overall conclusion was PV and hydroxycarbamide treatment started. Due to low itching effect and stomach problems, after about three weeks, the hydroxycarbamide was stopped and switched by ruxolitinib that reduced itching after a few days. At regular check-ups, the patient reported fine subjective feeling, but in May 2021, blasts (0.5% blasts) were registered in the peripheral blood aspirate and elevated serum LDH with an increasing trend during the following months (466...514 U/l). In August 2021. a hematologist indicated new bone marrow biopsy with following cytomorphology and flow cytometry. In September 2021, new marrow pathohistological finding showed slightly less but still hypercellularity with the persistent image of PV, no increased blast number but mild progression of fibrosis (MF1). The flow cytometry didn't detect abnormal marrow cell population and cytomorphology registered hematopoiesis with therapy effects. Molecular analysis detected additional KRAS and three TET2 mutations. Further slight increase in blast (1% blast) was registered in the peripheral blood aspirate, while the bone marrow aspirate estimated 3% of blasts. Interferon treatment started in addition to ruxolitinib, with rebiopsy plan in 4-5 months. In January 2022, the last bone marrow biopsy was done with cytomorphology and flow cytometry. Cytomorphology indicated poor hematopoiesis with 1% blasts that differentially fits myelofibrosis, molecular showed no additional mutations. Flow cytometry excluded AML with registered 0.6% of myeloid precursors with maturing. Histology verified hypercellular bone marrow with persistent PV but with further progression of fibrosis (MF2) and minimal extramedullary hematopoiesis, so in favor of post-PV myelofibrosis. Due to aspirate blast increase, immunohistochemical stains were applied. CD34 showed no blast increase, but CD117 showed increased number of degranulated and spindle shaped mastocytes in aggregates expressing both MCT and CD25, while CD2 was negative. In addition to the above described findings of post PV-MF, after fulfilling one major and two minor criteria, the presence of SM was concluded, although molecular didn't detect KIT mutation. After a week, slightly elevated serum transaminase was registered (16.3 μg/l; ref<11.4). Retrospectively, triptase stain was performed for previous two biopsies that were with no SM criteria met. **Conclusion:** In as many as 30% of systemic mastocytosis cases, an associated haematological neoplasm is diagnosed before, simultaneously or after SM. In general, any defined myeloid or lymphoid neoplasm can occur as an associated with SM, but myeloid neoplasms predominate, with CMML and unclassified MDS/MPN being most common. In patients with confirmed hematological neoplasm, CMML and unclassified MDS/MPN before all, possible systemic mastocytosis must be considered, that due to mast cell degranulation often goes unnoticed and untreated.

**Key words: polycythemia vera, systemic mastocytosis, KIT mutations, SMAHN**

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## Svijetla tumorska ćelija – dijagnostički nejasna, siva ćelija

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**Cilj:** Cilj ovog prikaza je da skrene pažnju na varijetete ispoljavanja i dileme koje se mogu javiti u dijagnostici svijetloćelijskih tumora. U dosadašnjoj patohistološkoj literaturi nije se dovoljno pridavala važnost svijetloćelijskim tumorima. Međutim, savremeni radovi i studije sve više ukazuju na dijagnostičke dileme kada je, ispostaviće se, ova heterogena grupa u pitanju. **Prikaz slučaja:** Pacijent je hospitalizovan u Centru za grudnu hirurgiju radi liječenja desnostranog pleuralnog izliva. Urađena je video asistirana torakoskopska hirurgija (Vats) desne pleuralne duplje i uzeta biopsija promjene. Evakuisana je serozna tečnost iz desnog pleuralnog prostora. Dobijen je bioptički materijal veličine do 0,6x0,3 cm. Na mikroskopskom planu tumorsko tkivo je građeno od krupnih, atipičnih ćelija, svijetle vakuolizovane citoplazme, povećanog nukleocitoplazmatskog odnosa, iregularnih hiperhromatičnih jedara sa prominentnim nukleolusima, aranžiranih u vidu trabekularnih i adenoidnih formacija. Stroma je vezivnovaskularna infiltrovana mješovitim inflamatornim infiltratima. Prema osnovnim početnim podacima radilo se o kardiološkom i hematološkom pacijentu, koji se liječi se od multiplog mijeloma verifikovanog 2007. godine. Zato se prvenstveno sumnjalo na depozit multiplog mijeloma. Na osnovu mikroskopskog izgleda biopsije, pojavila se sumnja da se možda radi o još nekom malignitetu i to pr-

venstveno svijetloćelijskom renocelularnom karcinomu. Nakon toga, došlo se i do podatka, da je pacijent 2017. godine imao operaciju karcinoma bubrega. Urađena imunohistohemijska analiza i tumorske ćelije su pokazale Renal Cell Carcinoma (Rcc), Cd10, Pax8 i Cytokeratin pozitivnost, Ki67=15%, a Leukocyte common antigen, Cd138, Cd79α, Mum1, Plasma cell, Cd68, Ttf1, Cd20, Calretinin, Cd5/6, Cytokeratin 7 i Cytokeratin 20 negativnost. Na osnovu svega prethodnog, bioptički materijal je odgovarao metastatskom depozitu svijetloćelijskog karcinoma bubrega. Za adekvatnu dijagnostiku svijetloćelijskih tumora veoma je važno poštovati dijagnostički red koraka. Citoplazmatsko rasvjetljenje ili svijetloćelijsku promjenu možemo vidjeti u različitim slučajevima na različitim lokacijama iz različitih razloga. Svaki put kada se uoče svijetle ćelije, potrebno je ići korak po korak. Za početak, potrebno je odlučiti da li je promjena uzrokovana artefaktom, usljed oponašanja tumora svijetlih ćelija ili se zaista radi o ovom tumoru. Kada se isključe oponašanje, artefakti i degenerativne promjene, mora se odlučiti da li je tumor prvenstveno svijetloćelijskog porijekla ili pokazuje sekundarnu promjenu. Nadalje, moramo provjeriti tumor u smislu epitelnog ili mezenhimalnog porijekla, kao i da li je benigni ili maligni. Razlika se može jednostavno napraviti, u zavisnosti o karakteristika kao što su arhitektonski obrazac, proces nekroze, pleomorfizam i mitotska aktivnost. Kada sumnjamo da je tumor maligne prirode, moramo isključiti metastatske tumore kao što su renocelularni karcinom, svijetloćelijski adenokarcinom jetre, prostate, pluća, gastrointestinalnog trakta, melanom, itd. Prije nego što se pokušamo usredsrijediti na konkretan tip tumora svijetlih ćelija, bilo da je benigni ili maligni, neophodno je biti dobro upućen u različite vrste karcinoma svijetlih ćelija drugih organa i njihove dijagnoze. Nakon patohistološke procjene, specijalna bojenja i imunohistohemija se mogu koristiti za postizanje konačne dijagnoze. U zavisnosti od vrste i lokacije tumora, potrebna su različita specijalna bojenja i imunohistohemijski markeri, a njihova upotreba može olakšati dijagnozu[1]. U literaturi su opisani povezani slučajevi multiplih mijeloma i karcinoma bubrežnih ćelija. Istovremena pojava multiplog mijeloma i renocelularnog karcinoma je izuzetno rijetka. Međutim, učestalost istovremene pojave ova dva maligniteta veća je od očekivane[2]. Da čitava situacija bude ekstremno zanimljiva, treba navesti da su opisani i slučajevi multiplog mijeloma sa svijetloćelijskim izgledom. Chen et al. su prvi opisali clear cell myeloma[3,4]. Dodatna zanimljivost je pojava pleuralnog izliva i metastatskog depozita svijetloćelijskog karcinoma bubrega. Pleuralni izliv zbog svijetloćelijskog karcinoma bubrega je rijetka pojava u kliničkom radu. Na osnovu kliničke prezentacije i snimanja, može se postaviti pogrešna dijagnoza. Veoma je komplikovano postaviti dijagnozu na osnovu citološke analize pleuralnog izliva. Zbog svega, za konačnu dijagnozu preporučuje se rana torakoskopija[5]. Od primarnih tumora, prije svega je važno isključiti mezoteliom. Što se tiče mezotelioma i karcinoma bubrežnih ćelija, oni mogu pokazati širok spektar citoloških i patohistoloških specifičnosti. Stoga se renocelularni karcinomi, koji su metastazirali u pleuru i pluća, mogu pomiješati sa mezoteliomom. Dostupni su različiti pozitivni kancerski markeri, uključujući markere vezane za bubrege[6]. Često se postavlja pitanje: "Kada su to stvarne metastaze renocelularnog svijetloćelijskog karcinoma, kada je to primarni tumor tog organa, odnosno metastatski depozit nekog drugog svijetloćelijskog tumora"? Njegove patohistološke osobine i imunohistohemijske karakteristike dodatno usložnjavaju čitavu priču. Zbog toga se mora uključiti šira paleta imunohistohemijskih markera. **Zaključak:** Važno je naglasiti, da svijetloćelijski tumori iako na prvi pogled često izgledaju vrlo slično, mogu imati veoma različito porijeklo, prognozu i predikciju. Dijagnostički i terapijski imperativi sve više nameću potrebu za širim multiopcionim posmatranjem maligniteta. Zbog toga i svih njihovih navedenih karakteristika, svijetloćelijski tumori će naročito dospijevati u centar interesovanja. Upravo zato će određivanje patomorfoloških, imunohistohemijskih, molekularnih, prognostičkih i prediktivnih parametara kod ovih tumora biti važnije i značajnije.

**Ključne riječi: svijetloćelijski tumori, patohistološki spektar, imunohistohemija**

## Clear cell carcinoma – diagnostically indeterminate grey cell

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**Objective:** This case aims at drawing attention to various forms of expression and dilemmas which may occur while diagnosing clear cell carcinoma. Previous histopathological literature has not paid too much attention to the significance of clear cell carcinoma. However, contemporary papers and studies are more and more vocal about diagnostic dilemmas in relation to this heterogeneous group of carcinomas. **Case report:** A patient was hospitalised in the Centre for thoracic surgery due to a pleural effusion on the right side. Video-assisted thoracoscopic surgery (VATS) of the right pleural cavity and biopsy were performed. The surgeons removed serum-like liquid from the right pleural cavity. The size of the biopsy-related material was up to 0.6 x 0.3cm. Microscopic analysis showed that the tumour tissue was composed of large, atypical cells with large, clear cytoplasmic vacuoles with an increased nuclear-cytoplasmic ratio, and irregular hyperchromatic nuclei with prominent nucleoli arranged in trabecular and adenoid patterns. Vascularised connective tissue stroma was infiltrated with mixed inflammatory infiltrates.According to the baseline data, this was a patient with cardiological and haematological health problems, treated against multiple myeloma, verified in 2007. This is why initially suspected the existence of multiple myeloma lesions.
Based on the microscopic analysis of the biopsy-related material, there was doubt whether this was another type of malignancy, or whether this was the case of clear cell renal cell carcinoma. Furthermore, we obtained data that this patient had surgery in 2017 to treat renal cell carcinoma.
Performed immunohistochemical analysis and tumour cells showed the existence of renal cell carcinoma (RCC), Cd10, Pax8 and Cytokeratin positivity, Ki67=15%, but Leukocyte common antigen, Cd138, Cd79α, Mum1, Plasma cell, Cd68, Ttf1, Cd20, Calretinin, Cd5/6, Cytokeratin 7 and Cytokeratin 20 negativity. Pursuant to the aforesaid, the analysis of the biopsy-related material pointed at metastatic deposits of clear cell renal cell carcinoma. For an appropriate diagnosis of clear cell carcinoma, it is of vital importance to respect the diagnostic procedure.
We can see cytoplasmic clearing or clear cell change in different cases of different locations because of different reasons. Every time clear cells are seen, it is necessary to go step by step. To begin with, it is necessary to make a decision whether the change was caused by an artefact, due to the imitation of a clear cell tumour, or whether it is really this tumour. When mimicry, artefact and degenerative changes are excluded, it must be decided whether the tumour is primarily of clear cell origin or shows a secondary change. Furthermore, we need to verify the tumour in terms of epithelial or mesenchymal source and whether it is benign or malignant. A distinction can be made easily, depending on features such as architectural shape, necrotic process, pleomorphism and mitotic activity. When we suspect the tumour is malignant in nature, we have to rule out, metastatic tumours such as renal cell carcinoma, clear cell adenocarcinoma of the liver, prostate, lung, gastrointestinal tract, melanoma, etc. Prior to trying to focus on a concrete type of clear cell tumour, whether benign or malignant, it is imperative to be well–versed in various clear cell cancers of other organs and their diagnoses. Following the histopathological assessment, special staining and immunohistochemistry may be used to arrive at a definitive diagnosis. Different special stains and immunohistochemical markers are necessary depending on the type and location of the tumour and their use can facilitate diagnosis[1]. The literature describes similar cases of multiple myelomas and renal cell carcinomas. The simultaneous occurrence of multiple myeloma and renal cell carcinoma is exceptionally infrequent. However, the frequency of simultaneous occurrence of these two malignancies is higher than expected[2]. To make the whole situation exceptionally more interesting, it should be noted that the cases of multiple myelomas with clear cell appearance have also been described. Chen et al. were the first to describe clear cell myeloma[3,4]. Additionally, it is interesting the simultaneous occurrence of pleural effusion and clear cell renal cell carcinoma. Pleural effusion due to renal clear cell carcinoma is a rare occurrence in clinical work. According to clinical presentation and imaging, one can make a wrong diagnosis. It is very complicated to make a diagnosis based on

cytological analysis of pleural effusion. Because of all, for the final diagnosis, an early thoracoscopy is recommended[5]. In terms of primary tumours, it is of vital importance to exclude the existence of mesothelioma. With regard to mesothelioma and renal cell carcinoma, they can show a broad spectrum of cytological and histopathological properties. Therefore, renal cell carcinomas, which have metastasized to the pleura and lungs, may be confused with mesothelioma. Different positive cancer markers are available, including markers related to the kidneys[6]. One question is very often asked: "When do we talk about real metastases of clear cell renal cell carcinoma, and when it is a primary tumour of that organ, i.e. when it is a metastatic deposit of some other clear cell carcinoma?"
Histopathological features and immunohistochemical characteristics of these carcinomas complicate the answer even further. Due to this, a wide spectrum of immunohistochemical markers must be included. **Conclusion:** It is very important to point out that clear cell carcinomas, although they look similar, can have very different origins and prognoses. From the standpoint of diagnosis and therapy, these malignancies must be interpreted from multiple viewpoints. Because of this and all of the abovementioned characteristics, clear cell carcinomas will remain in the spotlight. This is precisely the reason why the establishment of pathomorphological, immunohistochemical, molecular, prognostic and predictive parameters of these tumours will very important and significant.

**Key words: clear cell carcinoma, histopathological spectrum, immunohistochemistry**

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## Pseudosarkomatozni fibroepitelijalni polip sa atipijom na grliću materice: imitator sarkoma

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**Uvod.** Fibroepitelijalni stromalni polipi su lezije mezenhimskog porijekla koje se ne javljaju često u ženskom genitalnom sistemu, najčešće se javljaju u području vulve i vagine, a mogu nastati i području grlića materice[1]. Histološki ih karakteriše izražena celularnost, izražena ćelijska atipija sa prisustvom bizarnih džinovskih ćelija, vrlo često visok mitotski indeks i pojava atipičnih mitoza. Hipercelularnost, bizarna histologija i povećan mitotski indeks su razlozi zbog kojih ove promjene budu pogrešno proglašene malignim[1,2]. **Prikaz slučaja.** Prikazujemo slučaj žene stare 31 godinu kod koje je tokom rutinskog ginekološkog pregleda otkrivena velika polipoidna tvorevina koja se nalazila u vagini veličine 3x2,8 cm i koja je tankom peteljkom bila vezana za zid endocervikalnog kanala. Pacijentkinja ima dvoje djece,

jedno starosti 7 godina i drugo starosti 4 godine. Urađena je polipektomija i kiretaža endocervikalnog kanala. Površina polipolikog izraštaja je bila sivkastobjeličasta, dijelom sjajna dijelom zamućena. Na presjeku tkivo je bilo solidno, sivkasto, vlaknato i elastično. Histološki stromu polipolikog izraštaja su gradile dijelom vretenaste, uniformne, jednojedarne ćelije čija jedra su izdužena, hromatina su vezikularnog izgleda i posjeduju nukleoluse u većini ćelija. U leziji su bile prisutne i brojne, hiperhromatične, multijedarne, džinovske ćelije bizarnog izgleda. Mitotski indeks u tumorskim ćelijama je bio povećan ( 12- 14 mitoza/ 10 HPF) brojne mitoze su bile atipičnog izgleda. Površina polipolikog izraštaja je dijelom bila prekrivena uniformnim, skvamoznim epitelom bez orožavanja, a dijelom, jednorednim, pravilnim endocervikalnim epitelom. Zone nekroze i krvarenja nisu bile prisutne u tumoru. Imunohistohemijsko bojenje je pokazalo pozitivnost u stromalnim tumorskim ćelijama na vimentin, SMA, CD 68 u citoplazmi i estrogen i progesteron u jedrima i jedarnu i citoplazmatsku pozitivnost na p16. Stromalne ćelije su bile negativne na H- caldesmon, myogenin, myoglobin, GFAP, desmin, citokeratin AE1/AE3, citokeratin 5/6 i CD10. Imunohistohemijsko bojenje na myo D1 bilo tehnički neadekvatno za interpretaciju. Ki67 je urađen nakon postavljanja konačne dijagnoze i iznosio je oko 80%. Sugerisana je dijagnoza nediferentovanog stromalnog sarkoma i zahtijevano je drugo mišljenje. Drugo mišljenje je dobijeno u privatnoj ordinaciji u Beču. Imunohistohemijsko bojenje je pokazalo pozitivnu reakciju na p16 i negativne rezultate bojenja na desmin, citokeratin AE1/AE3, M-aktin, , S-100 i CD 34, a Ki67 je je iznosio 70%. Drugo mišljenje je glasilo da diferencijalno dijagnostički treba isključiti sarkom strome, a uzorak je poslan na treće mišljenje kod prof. Fletcher-a koji je postavio dijagnozu pseudosarkomatozni fibroepitelijalni stromalni polip sa atipijom kod kojeg je u slučaju nepotpune ekscizije moguć lokalni recidiv. U periodu dok su se čekali rezultati konsultativnih nalaza urađena je prosta histerektomija sa adneksektomijom. Tkivo grlića je pregledano kao konus i u analiziranom uzorku nije identifikovano tumorsko tkivo. Kod naše pacijentkinje nakon 55 mjeseci praćenja nisu zabilježeni znaci relapsa bolesti. **Diskusija.** Fibroepitelijalni stromalni polip je neuobičajena lezija koja se javlja u reproduktivnom periodu u distalnim dijelovima ženskog genitalnog trakta, najčešće u vagini, zatim na vulvi i najrjeđe na grliću materice. Patogeneza nastanka fibroepitelijalnog stromalnog polipa je još uvijek nejasna, smatra se da nastaju kao posljedica hormonske stimulacije i da su prije posljedica reaktivnog hiperplastičnog procesa nego rezultat prave neoplazije[1,2,3]. U jednom od pregleda literature u kojima su opisani slučajevi fibroepitelijalnih stromalnih polipa na različitim anatomskim lokalizacijama Nucci i autori su analizirali najveći broj slučajeva pseudosarkomatoznih, fibroepitelijalnih stromalnih polipa lokalizovanih na grliću materice. Od ukupno 33 analizirana slučaja sedam je bilo lokalizovano na grliću materice[1,4]. Lezije su najčešće pokazivale pozitivnost na vimentin, ER i PR, dok je bojenje na dezmin i SMA bilo varijabilno. Nivo ekspresije Ki67 se prema podacima iz literature kretao od približno 30% do 60% . Viša ekspresija Ki67 je zabilježena u celularnim dijelovima lezije. Celularne pseudosarkomatozne fibroepitelijalne polipe svakako treba razlikovati od sarkoma[1,4,5,6]. Lokalizacijana grliću materice celularnog, atipičnog, pseudosarkomatoznog, fibroepitelijalnog polipa prvenstveno uključuje diferencijaciju od lejomiosarkoma, rabdomiosarkoma, endometrijalnog stromalnog sarkoma niskog gradusa i malignog fibroznog histiocitoma. Prisustvo celularnosti, izražena ćelijska atipija i brojne atipične mitoze u celularnim pseudosarkomatoznim fibreopitelijalnim polipima mogu dovesti do postavljanja pogrešne dijagnoze sarkoma[2,4].

## Cellular pseudosarcomatous fibroepithelial stromal polyp with atypia of the cervix: sarcoma imitator

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**Introduction:** Fibroepithelial stromal polyps are rare mesenchymal lesions of female genital tract, the most frequent incidence is in vulva, than vaginal region but may occur in in the cervix[1]. Histological caracteristics of this lesions are hypercellularity, cells with marked atypia with giant multinucleated cells, frequent mitotic figures including atypical ones.Hypercellularity, bizarre hystomorphology, high mitotic index raises possibility of wrong diagnosis of malignant tumors[1,2]. **Case report.** A 31- year- old women on a routine gynaecological examination was founded polypoid mass measuring 3,2,8 cm in her vagina and its attachment with thin stalk with endocerical wall is identified. Patients has two children, 7 and 4 years old. Polypectomy and curettage of endocervical canal was performed. Surfice of the polyp was graywightish and partly glistened and partly blurred. Cross section was showed solid, homogenous, gray and elastic tissue. Histological examination revealed partly uniform, mononuclear, spindle- shaped cells with vesicular hromatine wit nucleoli in a many cells. Partly in lesion was identified numerous giant, multinucleated cells wit hyperchromatic and bizarre cytomorphology and frequent mitotic index (12-14 mitoses/HPF) and numerous atypical mitoses. The mass was covered with squamous epithelium without of keratinisation and endocervical, columnar epithelium. No area of necrosis or hemorrhage is seen within the tumor. On immunohistochemistry these stromal cells are showing strong positivity for vimentin, SMA, CD 68 in cytoplasm and ER and PR nuclear posityvity and cytoplasmic and nuclear positivity for p16. Stromal cells are showing negative staining for H- caldesmon, myogenin, myoglobin, GFAP, desmin, cytokeratin AE1/AE3, cytokeratin 5/6 and CD10. Staining for myo D1 was technicaly inadequat for interpretation. Ki67 labeling index was performed after final diagnosis and it was about 80%. Undifferentiated stromal sarcoma diagnosis was suggested and expert opinion was asked. Second opinion was made in private laboratory in Vienna and there was performed immunohistochemistry staining. Staining for p16 was possitive and for desmin, citokeratin AE1/AE3, M-aktin, , S-100 i CD 34 were negative, a Ki67 labeling index was about 70%. Second opinion diagnosis was " it is necesserily to exclude stromal sarcoma". Sample is sent from Vienna to Prof. Fletcher whos diagnosis was pseudosarcomatous stromal polyp with atypia with possible reccurene if excision is not complete. Simple hysterectomy with adnexectomy was performed in time waiting for expert opinion. Cervix was examined "in toto" as a cone sample, no tumor tissue was identified. Our patient did not show any evidence of recurrence on follow up 55months after the resection of lesion. **Discussion.** Fibroepithelial stromal polyp is unusual lesion that occur the lower female genital tract durring reproductive period, the most frequent incidence is in vulva, than vaginal region but may occur in in the cervix. The pathogenesis od fibroepithelial stromal polps is not well understood, however these lesions seem represent a reactive hyperplastic hormons stimulated rather than a true neoplasm[1,2,3]. In one review of literature describing fibroepithelial stromal polyps on a fifferent anatopic places Nucci at al. analised largest number of cervical pseudosarcomatous fibroepithelial stromal polyps Of these 33 patients 7 had cervical localisation[1,4]. Most frequently lesions showed expression for vimentin, ER i PR, variabil expression was reported for desmin and SMA bilo. Ki67 labeling index value in literature was between 30% and 60% . Hihger Ki67 expression was noted in celular parts of lesions. Cellular pseudosarcomatous fibroepithelial polyps should distinguish from sarcomas[1,4,5,6]. Cervical celular atypic pseudosarcomatous fibroepithelial polyp includes differentiations from leiomyosarcoma, rhabdomyosarcoma low grade endometrial stromal sarcoma and malignant fibrous hystiocytoma. Hypercellularity, cell atypia, high mitotic index including atypical mitoses in celular pseudosarcomatous fibroepithelial polyps can mislead to wrong diagnosis of sarcoma[2,4].

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## Eozinofil: od nevinog posmatrača do protagoniste

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Eozinofili su ćelije karakteristične citomorfologije, sa brojnim upadljivim eozinofilnim granulama u citoplazmi i segmentiranim, uglavnom bisagastim ili potkovičastim jedrom. Osnovna uloga eozinofila je u modulaciji reakcija neposredne hipersenzitivnosti i odgovoru na parazitarnu infestaciju i bazira se na strogo kontrolisanoj degranulaciji i oslobađanju sadržaja sekundarnih granula, koji obuhvata širok spektar interleukina, glavni bazični protein, eozinofilni katjonski protein, eozinofilni neurotoksin, TNF-α, TGF-β, i druge supstance. U uslovima homeostaze, većina eozinofila počiva u tkivima gastrointestinalnog trakta, izuzev u sluznici ezofagusa. Eozinofili se mogu naći i u timusu, uterusu i tkivu dojke. U patološkim stanjima eozinofili mogu biti regrutovani u različite anatomske lokalizacije, poput pluća, jednjaka, kože ili se značajno poveća njihov broj u sluznici želuca ili creva. Patolozi su sve češće u prilici da broje i prebrajaju eozinofile. Na primer, prisustvo više od 15 eozinofila po vidnom polju velikog uvećanja (40x) u sluznici ezofagusa je histološki kriterujem za dijagnozu eozinofilnog ezofagitisa. Međutim, na mnogim od anatomskih lokalizacija još uvek nije definisana pražna vrednost broja eozinofila koja se smatra patološkom. Pored toga, povećan broj eozinofila u skvamoznom epitelu sluznice jednjaka viđa se i kod gastroezofagealne refluksne bolesti, te je eozinofilni ezofagitis kliničkopatološka dijagnoza, koja zahteva pažljivu kliničkopatološku korelaciju i višestruke biopsije proksimalnog, srednjeg i distalnog dela jednjaka. Reaktivna eozinofilija je čest pratilac alergijskih i hipersenzitivnih reakcija, infekcija uzrokovanih parazitima i drugim agensima, solidnih tumora, autoimunih bolesti, stanja imunodeficijencije, a retko i kolonalnih proliferacija T- i B-ćelijskog porekla. U nekim patološkim stanjima eozinofili su prominentni elementi patohistološke slike i dominiraju mikromorfološkim pejzažem. Postoje grupe bolesti u kojima eozinofili predstavljaju osnovne histološke determinante i imaju ključnu ulogu u patogenezi. Bronhijalna astma je klasični primer oboljenja u kojoj aktivacija Th2 inflamatornog odgovora i oslobađanje velikih koncentracija Interleukina 5 (IL5), koji igra ključnu ulogu u diferencijaciji, preživljavanju, migraciji i aktivaciji eozinofila, rezultuje izdašnom eozinofilnom infiltracijom. Pored eozinofilije u bronhijalnom zidu česta je i alergijska polipoza nosne mukoze. IL5 je stoga važna terapijska meta u eozinofilnoj astmi, a razvija se sve veći broj monoklonalnih antitela na IL5 čijom primenom se postiže bolja kontrola bolesti, redukuje učestalost egzacerbacija i smanjuje potreba za glikokortikoidima, čime se sprečavaju ozbiljni, često ireverzibilni efekti steroidne terapije. Eozinofilna pneumonija predstavlja prisustvo eozinofila u intersticijumu i alveolarnim prostorima pluća, obično udruženo sa perifernom eozinofilijom, bez jasnog uzroka hipereozinofilnog sindroma.

Hronična eozinofilna pneumonija je intersticijani pneumonitis koji najčešće nastaje na terenu bronhopulmonarne aspergiloze, u sklopu sistemskih bolesti vezivnog tkiva ili reakcije na lekove. U plućima se javlja i veoma retka eozinofilna granulomatoza sa poliangitisom (Churg–Strauss), nekrotizujući vaskulitis koji može biti udružen i sa fokalnim glomerulonefritisom. U gastrointestinalnom traktu eozinofili su uključeni u patofiziologiju spektra bolesti koje se označavaju kao gastrointestinalna eozinofilna bolest. Pored eozinofilnog ezofagitisa, eozinofilnog gastroenteritisa i kolitisa, u digestivnom traktu eozinofili su udruženi sa brojnim neoplastičnim i inflamatornim stanjima, uključujući i inflamatornu bolest creva. S obzirom na to da eozinofili sluznice GIT predstavljaju plastičnu i heterogenu populaciju sa nekoliko funkcijski različitih fenotipova, u svim ovim okolnostima funkcionalni doprinos eozinofila je kompleksan i njihovo prisustvo u varijabilnoj meri doprinosi egzacerbaciji ili gašenju inflamacije u tkivu. U eozinofilnom cistitisu, koji najčešće pogađa žene i može da klinički i cistoskopski imitira neoplastični proces, jer se može prezentovati kao ulceracija ili polipoidna masa, prominentni eozinofilni infiltrat prisutan u zidu mokraćne bešike često je udružen sa edemom, nekrozom i kasnije fibrozom mišićnog sloja. Eozinofilne dermatoze obuhvataju spektar bolesti udruženih sa eozinofilnom ilnfiltracijom i/ili degranulacijom, koje mogu imati sličnu morfologiju, ali se veoma razlikuju u pogledu kliničke prezentacije i terapijskog pristupa. Pojava eozinofilije u krvi bez objašnjivog uzroka, poput alergije ili infekcije, može biti zloslutni znak okultne maligne neoplazme i uvek je signal da je detaljan klinički pregled pacijenta neophodan. Ponekad pažljivo i sveobuhvatano anamnestičko sagledavanje pacijenta, detaljan fizički pregled i laboratorijske analize ukažu na simptome poput groznice, gubitka telesne težine, limfadenopatije, splenomegalije ili otkriju citopeniju ili druge abnormalnosti hematoloških parametara, što usmerava dalje istraživanje uzroka eozinofilije. Upečatljivo prisustvo eozinofilnih leukocita na biopsiji limfnog nodusa mladića sa generalizovanom limfadenopatijom, mora nagnati patologa da pažljivo traga za Hodgkin Reed-Sternberg ćelijama. U histološkoj slici, eozinofili mogu biti prisutni u velikom broju u inflamatornom miljeu različitih hematoloških neoplazmi, uključujući folikularni limfom, anaplastični limfom velikih ćelija, adultnu T-ćelijsku leukemiju. Langerhansova ćelijska histiocitoza (LCH) je klonalni poremećaj mijeloidnih ćelija koje se diferentuju u pravcu Langerhansovih čelija i često se javlja kod dece, u vidu unifokalne bolesti sa dobrom prognozom ili u vidu multifokalne bolesti sa nepovoljnim kliničkim ishodom. LCH zahvata noduse ili ekstranodalne lokalizacije, najčešće skelet. Za mikromorfološku sliku karakteristična je infiltracija tkiva Langerhansovim ćelijama, obilne, bledeo-eozinofilne citoplazme i iregularnih, često reniformnih euhromatičnih jedara sa žlebom ili naborom, koje su najčešće izmešane sa velikim brojem eozinofila. Oblik LCH koji se prezentuje kao solitarna koštana lezija bogata eozinofilima čak se i naziva eozinofilni granulom. Mastocitoza je heterogena grupa poremećaja koja se karakteriše abnormalnom proliferacijom i akumulacijom mastocita u jednom ili više organa. Mastocitoza ima nekoliko oblika, među kojima je pored kutane forme najznačajnija sistemska mastocitoza, koja zahvata koštanu srž i može imati izrazito varijabilan klinički tok, od indolentnog, benignog i samoograničavajućeg do veoma agresivnog. U sistemskoj mastocitozi vide se gusti, kompakti granulomatoliki agregati atipičnih, vretenastih mastocita, koji su često izmešani sa upadljivim brojem eozinofila, plazma ćelija i limfocita i uronjeni u fibrohistiocitni matriks. Ponekad eozinofili dominiraju unutar granulomatolikih nakupina. Grupa mijeloidnih neoplazmi udruženih sa eozinofilijom periferne krvi obuhvata: 1) mijeloidne i limfoidne neoplazme udružene sa rearanžmanom PDGFRA, PDGFRB i FGFR1; 2) hroničnu eozinofilnu leukemiju (CEL, NOS) i 3) idiopatski hipereozinofilni sindrom (HES). Dok je primena imatinib mezilata i njegovih naslednika koji su inhibitori PDGFR iz korena promenila lečenje mijeloidnih neoplazmi udruženih sa eozinofilijom, novi agensi koji blokiraju IL5 se sve uspešnije primenjuju u lečenju HES. Tkivni eozinofili mogu biti neizostavni ili akcidentalni deo patohistološke slike u različitim alergijskim, inflamatornim i neoplastičnim stanjima, ali uvek opravdano izazivaju dužnu pozornost patologa, jer su neretko ključni deo odgovora koja je tačna dijagnoza.

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## Primena digitalne slike patohistoloških preparata u edukaciji studenata

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Tehnološka revolucija sa razvojem virutelne mikroskopije (VM) omogućili su nam kompletno novi pristup u edukaicji i učenju histologije i histopatologije. Ona je uzrokovala prelazak sa optičkih mikroskopa i upotrebe tradicinoalnih histoloških preparata na virtualnu mikroskopiju i virtuelne slajdove. Skeneri histoloških pločica su za vrlo kratak vremenski period od preparate na "staklu" omogućili dobijanje digitalizovanog sadržaja. Prednosti upotrebe VM zasnovane na petagogiji, efikasnosti i financijskom aspektu bi bile: nepostojanje konstantnog finansijskog utroška u održavanju brojnih studenskih mikroskopa i obezbeđivanju adekvatne kolekcije histoloških preparata; pružanju studentu mogućnost uvida u histološke karakteristike ispitivanih preparata kroz isti, često bolji kvalitet nego klasičnom mikroskopijom; pristum optimizovanim softverskim sistemima u okviru kojih student može da označi mesto od posebnog izbora uz veoma lako uveličanje ili smanjenje istog; takođe, analizom na velikom uveličanju, otvaranjem dodatnih dopunskih prozora u svakom trenutku može se identifikovati koja je regija preparata u fokusu; zahvaljujući velikom stepenu oštrine, optimizovanom konstrastu i stepenu osvetljenosti studentu je u svakom trenutku omogućen najveći kvalitet analiziranog preparata; upotreba navedenih softvera je izuzetno laka i za njenu upotrebu praktično i nije potrebna posebna obuka, sto nije slučaj kod mikroskopa; analiza preparata nije ograničena samo na jedan računar te se umrežavanjem više računara stvara mogućnost lake interakcija i grupne analize i interakcije između studenata i predavača; inicijalno ulaganje u skener, softver i održavanje servera su gotovo sva ulaganja u virtuelnu mikroskopiju u odnosu na tradicionalni pristup u okviru koga je potrebna neprekidna podrška histološke laboratorije i njegovog osoblja. Istovremeno sa unapređenjem aparata za skeniranje i pratećih softvera danas nam je omogućeno skladištenje velikih fajlova na internet mreži. Shodno tome formirane su specijalizovane platforme koje su kompatibilne sa većinom formata (tiff, jpg, ndpi i dr) i u ujedno poseduju prilagođeni program za online analizu istih. Ova mogućnost imala je veliki uticaj na organizaciju nastave u proteklim vremenima COVID 19 pandemije. Nedostatak dovoljnog broja mikroskopa kao i odgovarajućih kolekcija preparata bio je jedan od glavnih razloga zamene tradicionalnog za virtuelni pristup edukacije i učenja histologije i histopatologije na Medicinskom fakultetu,

Univerziteta u Novom Sadu. Tom prilikom formirana je virtuelna učionica sa 37 računara, projektorom i 6 televizora kojim je omogućeno da do 70 studenata istovremeno učestvuje u virtuelnoj analizi preparata. Proširenje pristupa preparatima na viruelne online platforme u velikoj meri doprinele su neometenom odvijanju nastave tokom COVID 19 pandemije. Danas, posle više od 5 godina iskustva u edukaciji upotrebom virtuelne mikroskopije možemo zaključiti da je kvalitet u velikoj meri unapređen.

## Practical use of virtual microscopy (VM) in education

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The technological revolution with developing virtual microscopy (VM) gives an entirely new approach to teaching and learning histology and histopathology. It causes a switch from optical microscopes and glass slides to virtual microscopy with virtual slides. The digital slide scanner machine can rapidly scan glass slides and convert them to digital data. The advantages of VM are numerous, based on pedagogy, efficacy and cost: constant financial drain due to maintenance of a large number of student microscopes and collections of glass slides; provides students with a viewing experience that is very comparable to standard histological glass slides; every student has equivalent access to the highest quality slide material; adequate software allows each student to select specific regions of interest on the slide, to zoom in and out and to move to other areas at their free choice; at high magnifications, it is easy for the student to maintain orientation concerning the entire section; image is always in focus, with optimized contrast and adjustable virtual illumination; use of labels enhances the learning process and many other; students and professors adapt very quickly to the use of the virtual microscope; single-use microscope laboratory can be converted into a multiuse computer laboratory; after an initial investment in the scanning stage, software and servers, the financial and administrative advantages allow enormous economic savings; in the long-term concerning equipment, technical staff and laboratory facilities. Following improvements in scanning machines and software, increasing web databases gives us today the opportunity to upload scanned slides on specialized platforms. They are usually compatible with most picture formats (tiff, jpg, ndpi, etc.), while software interfaces are usually user friendly. This possibility has the highest impact on organizing practical slide analysis in distance learning during COVID 19 pandemic. The lack of student microscopes and size-able collections of glass slides was one of the main reasons for switching the traditional approach to the Virtual microscopy concept of teaching and learning histology and histopathology in the Medical Faculty, University of Novi Sad was. With a specially equipped classroom which includes 37 computers, a projector screen, and six large 55-inch screens, around 70 students at the same time can follow virtual slide analysis. During COVID 19 pandemic, access to scanned slides was extended to an online platform which helps in distance learning. Today, after more than five years of virtual microscopy experience, we can conclude that teaching quality was noticeably improved.

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## Hirurgija raka dojke i aksile nakon neoadjuvantne terapije

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**Uvod:** Primarna sistemska (neoadjuvantna, preoperativna) terapija deluje tako što:

- Smanjuje veličinu tumora u dojci ili dovodi do cPR (complete patological regression), čak i do 80% u nekim slučajevima, a time omogućava veći procenat poštednih operacija[1]
- Smanjuje verovatnoću zahvaćenosti aksile čime proširuje mogućnost izbegavanja aksilarne disekcije tj omogućuje biopsiju limfnog čvora stražara (SLNB-sentinel lymph node biopsy)
- Omogućava procenu tumorskog odgovora in vivo na terapiju – informacije o prognozi
- Omogućava individualizaciju terapije procenom efekta terapije u toku lečenja kao i post-neoadjuvantnog tretmana
- Patohistološka kompletna regresija korelira sa boljom prognozom posebno u podgrupama (HER2-pozitivnih,TNBC, HR+/HER2neg/Grade3)

Očekivani ishod bolesti (DFS i OS) je sličan nakon neoadjuvantne i adjuvantne sistemske terapije kada se daju isti režimi i broj ciklusa[2]. NAST kod primarno operabilnog raka dojke dovodi do minimalnog ali povećanog broja lokalnih recidiva.Indikacija za NAST su rak dojke stadijuma IIA, IIB i T3N1M0, kada se ne može uraditi poštedna operacija zbog nepovoljnog odnosa veličine tumora/dojke i/ili kada pacijent odbija mastektomiju. Postoje dokazi za benefit NAST kod tumora II stadijuma pre svega za ER/PR, HER2-negativne (triple-negativni) i HER2-pozitivne tumore veličine preko 2cm i/ili pozitivnom aksilom,kao i za ER-pozitivne tumore kod postmenopauzalnih žena gde je procenat pCR, "down-staging / sizing" značajno viši[1]. Mladja životna dob, non-lobularni tip tumora i brz klinički odgovor su manje značajni pokazatelji za postizanje benefita nakon NAST. Monitoring za vreme NAST podrazumeva: palpaciju, UZ dojki, mamografiju, MRI dok je PET/CT od manjeg značaja.
Učinak NAST treba kontrolisati:

- Svake 6-8 nedelje
- Pri promeni režima terapije EC - T
- Na kraju NACT, a pre hirurgije
- Ako tumor brzo raste treba menjati režim kontrole
- Pokušati i tražiti istog radiodijagnostičara za istog pacijenta
- Neophodni kriterijumi za hirurgiju kod NAST-a su[3]:
- Nakon core biopsije obavezno je postavljanje klipsa u centar tumora
- Ukoliko marker nije postavljen za veme biopsije obavezno se mora postaviti pre započinjanja NAST/ alternativno ako nema tehničkih mogućnosti, lokalizaciju tumora iscrtati na koži dojke u poziciji kao na operacionom stolu i fotografisati (slikom vodjena ekscizija ležišta tumora).
- Obavezna FNAC / core biopsija limfnih čvorova klinički i/ili UZ sumnjivih na metastazu
- Klipsovanje metastatski izmenjenih/sumnjivih LČ se preporučuje kod limitirane zahvaćenosti aksile, kada se očekuje cN1– ycN0 (videti TAD)
- MR mamografija je poželjna za praćenje NAST i donošenje odluke o hirurškom planu, da se adekvatno proceni veličina i lokalizacija eventualne rezidualne bolesti.

Nakon NAST, odgovor na terapiju i volumen rezidualnog tumora predstavljaju važne prognostike faktore. Postignuti pCR (bez invazivnog ili in situ tumora u dojci i aksili) se mora jasno naznačiti[1]. Takodje, postojanje rezidualnog invazivnog i/ili in situ tumora se mora opisati kao i postojanje ili ne efekata hemioterapije kako u dojci tako i u limfnim čvorovima. Kvantifikacija rezidualne bolesti je poželjna metodom preostalog opterećenja tumorom (RCB - Residual Cancer Burden) mada postoje i druge metode[4].
Stažiranje nakon NAST je takodje poželjno koristeći TNM klasifikaciju[5].

**Hirurgija dojke**

- Indikacija za NAST, monitoring i preporuke za onkološko/hirurški tretman se trebaju doneti individualno za svakog pacijenta od strane multidisciplinarnog tima/onkološka komisija
- Tip hirurškog tretmana zavisi od efektivnosti NAST uzimajući u obzir odnos veličine rezidualnog tumora/veličine dojke,
- margine kao i kod primarnih operacija"no tumour cells on the inked margin",
- mogućnost postizanja dobrog kozmetskog efekta
- obavezno uraditi intraoperativnu specimen radiografiju /mamografiju.
- Ležište tumora obavezno klipsovati
- U izabranim slučajevima, poštedna operacija može da se izvede i u slučaju multifokalnih i/ili multicentričnih tumora ako se mogu postići histološki negativne margine (6).

Hirurgija aksile nakon NAST-a

- NACT dovodi do downstage-a aksile pCR i do 40% (prethodno pozitivni postali negativni)
- Dodavanjem anti Her-2 agensa postiže se dodatno poboljšanje kod HER2- pozitivnih tumora
- Idelano bi bilo da pacijenti sa pozitivnim nodalnim statusom postignu pCR, a negativna SLNB značila da nema potrebe za disekcijom aksile.

SLNB se može uraditi i pre i nakon sprovedene NAST[7]. Kada se uradi pre rezultat je sigurniji, procenat identifikacije čvora stražara je veći, disekcija se može uraditi odmah. Nedostatak je da pacijent ima dodatnu hirurgiju pre sistemske terapije, što je značajan ekonomski uticaj na zdravstveni sistem, ali glavni je da ne koristi eventualni benefit od kompletne histološke regresije izmenjenih limfnih čvorova aksile nakon terapije. Kada se SLNB radi nakon NAST, hirurgija dojke i aksile se uradi u jednom koraku, disekcija aksile se može izbeći u značajnom broju slučajeva (polovina pacijenata sa zahvaćenom aksilom imaju metastatski izmenjen samo jedan limfni čvor), tojest može uzeti u obzir postignutu regresiju bolesti u aksili. Nedostatak metode je manji procenat identifikacije SLN, kao i veći procenat lažno negativnih slučajeva, nešto veći procenat rekurentne bolesti u aksili i da kod pozitivne aksile ipak moramo uraditi disekciju iste[8]. Medjutim, nekoliko prospektivnih radomizovanih studija je pokazalo da uptrebom duplog markiranja SLN (boja+ radioizotop), uklanjanjem bar tri limfna nodusa stražara metoda može biti prihvatljiva kod ypN0 statusa nakon terapije[9]. ACOSOG Z1071 studija je dokazala da je lažno negativni nalaz aksilrnog statusa odredjenog sa SLNB manji od 10% kada se odstrane 3 ili više sentinel čvora, koji se odredjuju sa dualnim tracer-om, dok se najmanji FNR dobija kada se odstrani i biopsijom dokazan zahvaćeni limfonodus obeležen klipsom ili radioaktivnim semenom. Za sada nedostaju rezultati višegodišnjih praćenja[10].
Obzirom na ove dokaze preporuka je da je SLNB opravdana nakon NAST za procenu statusa aksile.
Klinički/UZ-no pozitivna aksila:

- AD je preoruka u slučaju kada su pre NAST FNAC/core biopsijom potvrdjene metastaze u LČ, a nakon NAST su ostale pozitivne klinički i/ili FNAC/core biopsijom dokazane.
- Ako je core biopsja / FNAC klinički sumnjivog LČ negativna, može se uraditi SLNB pre NAST, ako je SLN pozitivan, AD treba uraditi nakon NAST.
- Ako je core biopsja / FNAC klinički sumnjivog LČ negativna, a nije radjena SLNB pre NAST, ista može biti uradjena po završetku NAST obavezno sa duplim kontarstom ako je aksila i dalje negativna klinički i radiološki; pozitivan SLN znači obaveznu AD čak i u slučajevima kada su prisutne samo izolovane maligne ćelije ili mikrometastaza (videti novu St Gallen preporuku 2021 ypN0(i+) i ypN1(mi))[11].
- Ako je aksila klinički pozitivna (cN1) uz negativan core/FNAC, a nakon NAST postane klinički negativna, može se uraditi SLNB sa najmanje tri uklonjene SLN umesto AD. U slučaju da su sva tri bez metastaze dalja aksilarna hirurgija nije potrebna. Ako se odstrane samo dva ili jedan SLN, a isti su negativni histološki može se razmotriti ozračivanje aksile umesto disekcije.

- Ako su core/FNAC potvrdjene metastaze u LČ, a isti su markirani (klips ili drugo markiranje) pre NAST, a potom ekscidirani kao takvi(targeted axillary dissection-TAD), a histološki su bez metastaze zajedno sa još 1 ili 2 SLN, AD se može izostaviti[12,13,14].
- Pacijenti sa incijalnim cN2 treba da dobiju AD zajedno sa regionalnim ozračivanjem nakon NAST bez obzira na stepen regresije.
- Klinički/UZ-no negativna aksila:
- SLNB se može raditi i pre i posle NAST. Ako se radi nakon NAST obavezno sa duplim kontrastom i obaveznim uklanjanjem bar dva SLN.
- (ako se ukloni manje od dva SLN nakon NAST, a isti su histološki bez metastaza, razmotriti ozračivanje aksile zbog većeg procenta lažno negativnih nalaza.
- Ako se ne nalaze SLN u aksili nakon NAST na limfoscintigrafiji niti pomoću tehnika mapiranja SLN (izotop +boja) može se uraditi "sampling"aksile sa uklanjanjem najmanje 4 LČ ako su histološki negativni može se izostaviti AD.
- U situacijama koje su različite od gore opisanih onkolška komisija treba da odluči o tipu adjuvantnog tretmana na individualnoj bazi.

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## Slučaj kao noćna mora: rupa ili prazan prostor

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**Uvod:** Kod mišićnih biopsija veliku, krucijalnu, važnost ima preanalitička faza koja podrazumeva uzorkovanje mišićnog tkiva i transport do referentne laboratorije. Zbog grešaka koje se dešavaju u tom postupku, veoma je ugrožena analitička faza procesa, posebno postupak smrzavanja tkiva i enzimohistohemijska bojenja, a samim tim i interpretacija viđenog od strane patologa. Problem sa korišćenjem samog tečnog azota je u tome što on uzrokuje stvaranje azotne gasne barijere oko tkiva, koja deluje kao izolator i inhibira hlađenje tkiva. Da bi se izbegao ovaj efekat "parnog pokrivača" koristi se izopentan koji se hladi u tečnom azotu a koji je na sobnoj temperaturi izuzetno zapaljiv. Međutim, način primene lokalnog anestetika, neprimerena manipulacija mišićnim tkivom mogu uzrokovati pojavu „praznih" („core") prostora u inače finoj mrežastoj strukturi miofibrila. Tada prvo razmišljamo o sledeća tri momenta: artefaktu, patognomoničnim znacima za central cor[1] ili multimini cor miopatijama i targetoidnim vlaknima patognomoničnim za neurogena lezije. **Cilj:** Cilj prikaza ovih slučejeva je da ukaže na tehničke izazove prilikom obrade uzoraka mišićnog tkiva i na njihov uticaj pri analizi citoplazmatskih segmenata. **Prikazi slučajeva:** Pacijentkinja stara 37 godina upućena na biopsiju pod dijagnozom Sy Rejno i fibromialgija, pacijent star 14 godina i pacijent star 44 godine upućeni pod dijagnozom myopatija. Korišćeni su isti kontrolni uzorci zdravog mišićnog tkiva. Kod svih uzoraka su uočeni prazni prostori, koji su daljim analizama kod prvog pacijenta potvrdili postojanje neurogene lezije, kod drugog titinopatije[1], a kod trećeg pacijenta RYR 1 mutacije gena, tj. central cor kongenitalnu miopatiju[2]. Na uzorcima zdravog tkiva je bio jasan artefakt. **Diskusija i zaključak:** Tradicionalni pristup dijagnostike kongenitalnih miopatija kombinuje detaljnu kliničku i porodičnu anamnezu sa nalazima na biopsiji. Evaluacija mišićne biopsije je važna, međutim, treba imati na umu preklapanje brojnih drugih morfoloških abnormalnosti. Bitni klinički podaci su vrednosti serumske kreatin kinaze, elektromiografija (EMG) i studije nervne provodljivost (NCS), kao i distribucija mišićnog oštećenja koja se procenjuje magnetnom rezonancom (MR). Biopsija mišića i analiza histologije mišića, histohemija i imunohistohemija, i po potrebi elektronska mikroskopija (EM) su glavni oslonac postavljanja dijagnoze[3]. Sve to omogućava vođeno genetsko testiranje ili primenu nove generacije sekvenciranje (NGS) i proteomskih analiza[4].

**Ključne reči: mišićne biopsije, artefakti smrzavanja, targetoidna vlakna, RYR 1 gen**

## A nightmare case: A hole or void

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**Introduction:** In muscle biopsies, the pre-analytical phase is of great, crucial importance, which includes a sampling of muscle tissue and transport to the reference laboratory. Due to the errors that occur in that procedure, the analytical phase of the process is very endangered, especially the procedure of tissue freezing and enzymohistochemical staining, and thus the interpretation of what was seen by the pathologist. The problem with using liquid nitrogen itself is that it causes the creation of a nitrogen gas barrier around the tissue, which acts as an insulator and inhibits tissue cooling. To avoid this "vapour coating" effect, isopentane is used, which is cooled in liquid nitrogen which is extremely flammable at room temperature. However, the method of application of the local anaesthetic, inappropriate manipulation of muscle tissue can cause the appearance of "empty" ("core") spaces in the otherwise fine mesh structure of myofibrils. Then we first think about the following three points: artefact, pathognomonic signs for central cor[1] or multi mini cor myopathies, and targetoid fibres pathognomonic for neurogenic lesions. **Aim:** The aim of the presentation of these cases is to point out the technical challenges in the processing of muscle tissue samples and their impact on the analysis of cytoplasmic segments. Case reports: A 37-year-old patient was referred for a biopsy diagnosed with Sy Rejno and fibromyalgia, a 14-year-old patient and a 44-year-old patient were referred for a myopathy diagnosis. The same control samples of healthy muscle tissue were used. Empty spaces were observed in all samples, which confirmed the existence of a neurogenic lesion in the first patient, titinopathy[1] in the second patient, and gene mutations in the third patient RYR 1, ie. central cor congenital myopathy[2]. There was a clear artefact on the healthy tissue samples. Discussion and conclusion: The traditional approach to the diagnosis of congenital myopathies combines a detailed clinical and family history with biopsy findings. Evaluation of muscle biopsy is important, however, the overlap of a number of other morphological abnormalities should be borne in mind. Important clinical data are serum creatine kinase values, electromyography (EMG) and nerve conduction studies (NCS), as well as the distribution of muscle damage as assessed by magnetic resonance imaging (MR). Muscle biopsy and analysis of muscle histology, histochemistry and immunohistochemistry, and if necessary electron microscopy (EM) are the mainstay of diagnosis[3]. All this enables guided genetic testing or the application of new generation sequencing (NGS) and proteomic analysis[4].

**Key words: muscle biopsies, freezing artefacts, targetoid fibres, RYR 1 gene**

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## Slučaj kao noćna mora: PEComa-da ili ne?

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**Uvod:** U radu prikazujemo pacijentkinju starosti 48 godina primljenu zbog operativnog liječenja tumora ingvinalne regije. **Prikaz slučaja:** Tokom hirurške intervencije hirurg je poprečnim rezom kože i potkožnog masnog tkiva pristupio tumoru, koji je prominirao iz inginalnog kanala, pružajući se ka velikim usnama. Hirurg je lako odvojio tumor od okolnih struktura, uradio hirušku proceduru u cilju sprečavanja nastanka ingvinalne hernije kao komplikacije i rekonstruisao operativni rez po slojevima, dok je tumorski čvor poslao na patohistološku analizu. Kod pacijentkinje je nekoliko godina ranije urađena nefrektomija zbog angiomiolipoma. Takođe više godina se prati zbog tumorske promjene veličine 10cm na preostalom bubregu, radioloških karakteristika takođe angiomiolipoma. Na analizu je dostavljen tumorski čvor, glatke, sjajne površine, na serijskim rezovima bjeličaste boje, nodularnog izgleda, veličine 65x45x30mm, srednje čvrste konzistencije. Mikroskopske karakteristike tumorskog tkiva su ukazivale na solidne grupe i trabekularne aranžmane uniformnih okruglih i ovalnih ćelije, eozinofilne citoplazme, okruglih ili ovalnih jedara, prominentnih jedaraca. Stroma je bila obilna, slabo celularna. Nekroza nije nađena u tumorskom tkivu. Mitoze su uočene, veoma rijetke. Na kompletnoj površini tumorskog čvora se nalazila tanka vezivna kapsule. Rezultati imunohistohemijske analize tumorskog tkiva su bili sledeći: Vimentin+, Desmin+, SMA+, WT1+, HMB45+, Estrogen-, CD31-, CD32-, CD34-, FLI1-, D2-40-, S100-, SOX10-, AE1/AE3-, EMA-, MOC31-, p40-, miogen-, myoD1-, CD56-, caldesmon-, ALK-, CD68-, Melan A-, MiTF-. Na osnovu morfologije tumorskog tkiva, kao i imunohistohemijskog profila koji je ukazivao na ekspresiju mioidnih i melanocitnih markera postavili smo dijagnozu sklerozirajućeg perivaskularnog epiteloidnoćelijskog tumora - PEComa**.** **Zaključak:** PEComa je mezenhimalni tumor kojeg grade perivaskularne epiteloidne ćelije (Perivascular Epitheloid Cells) – karakteristične epiteloidne ćelije u perivaskularnom raporedu, a koje eksprimiraju markere melanocitne i glatkomišićne diferencijacije. Porijeklo tumorskih ćelija je nejasno, jer sličnu morfologiju i imunohistohemijsku ekpresiju nije moguće naći u humanoj histologiji. Ovi tumori su prvi put opisani 1963. godine (Liebow i Castleman), dok Bonatti i saradnici 1992. godine uvode termin PEComa. Svjetska zdravstvena organizacija (WHO) uvodi definiciju PEComa u klasifikaciju humanih tumora 2002. godine[1,2,3]. PEComi su rijetki tumori. Češće se dijagnostikuju kod žena (odnos muškarci:žene= 0.2:1). Mogu se javiti u svim životnim dobima, a najčešće u mlađem ili srednjem životnom dobu. Češće su javljaju sporadično, dok je manji procenat slučajeva povezan sa tuberoznom sklerozom. Familija PEComa uključuje renalni i ekstrarenalni angiomiolipom, zatim clear cell sugar tumor pluća, ekstrapulmonarni sugar tumor, limfangioleiomiomatozu, clear cell miomelanocitni tumor (ligamentum teres), primarni kutalni PEComa (kutalni clear cell miomelanocitni tumor) i PEComa NOS (not otherwise specified). Nabrojana grupa tumora sa različitim kliničkim i patološkim karakteristikama dijeli zajedničke molekularne promjene sa čestom mutacijom u TSC1 (Tuberous Sclerosis Complex 1) i TSC2 ( Tuberous Sclerosis Complex 2), što rezultira hiperaktivacijom mTOR signalnog puta. Najčešći i najviše opisani PEComa je renalni angiomiolipom (AML). Sporadične forme AML javljaju se kao male, dobro ograničene, asimptomatske lezije. AML udruženi sa tuberoznom sklerozom javljaju se kao multiple, velike lezije, koje progresivno dovode do renalne insuficijencije[4,5,6]. Najčešća lokalizacija PEComa su mezenterijum, ometnum, gastrointestinalni sistem, uterus i retroperitoneum. Meka tkiva i koža su rijeđe primarne lokalizacije. Makroskopski tumori su dobro ograničeni, solidni, srednje čvrste konzistencije, u prosjeku se dijagnostikuju kada dostignu veličinu od 5 do 8cm. Histološki, ove tumore najčešće karakterišu solidne grupe ćelija epiteloidnog izgleda, sa obilnom granuliranom, eozinofilnom ili svijetlom citoplazmom. Jedra su okrugla, jedarce se uočava. Grupe tumorskih ćelija su raspoređene oko tankozidnih kapilara. Mali broj slučajeva karakterišu vretenaste ćelije. Mitoze su ili veoma rijetke, ili se ne uočavaju. Opisani su slučajevi sa miksoidnim izgledom, zatim sa mikrocistama u stromi, zatim sa multijedarnim ćelijama. U oko 20% slučajeva , posebno kod žena, uočava se obilna, stromalna hijalinizacija (sklerozirajući PEComa)[6]. Opisani su i maligni PEComi, koje karakteriše visoka mitotska aktivnost, nekroza i pleomorfizam Takođe postoji povećan rizik za recidiv, ako je tumor veličine

veće od 5cm. U slučajevima malignih varijanti PEComa najčešće se metastaze javljaju u jetri, limfnim čvorovima, plućima i kostima (4). Imunohistohemijski PEComi pokazuje koekspresiju melanocitnih markera, kao što je HMB45, zatim Melan A ili MiTF. Takođe prisutna je ekspresija mišićnih markera kao što je SMA, aktin, mišićni miozin, kalponin i u pojedinim slučajevima h- kaldesmon. Desmin je rijeđe pozitivan, iako je zabilježena češća pozitivnost u kutanim lokalizacijama ili u slučajevima sklerozirajućih tipova PEComa. Pozitivnost na CK je zabilježena takođe. Trećina ovih tumora pokazuje pozitivnost i na S100 protein, obično fokalno. Opisana je pozitivnost i na CD1a. U dosadašnjoj literaturi kao najsenzitivniji marker melanocitne diferencijacije je opisan HMB45 (80% slučajeva) dok je pozitivnost na Melan A ili MiTF prisutna u nešto manjem procentu slučajeva. Epiteloidne varijenta ovih tumora značajnije eksprimiraju markere melanocitne diferencijacije, dok u slučajevima vretenastoćelijskih PEComa postoji izraženija ekspresija markera mišićne diferencijacije[1,2,3,6] . Diferencijalno dijagnostički kada je dijagnoza PEComa u pitanju dolaze u obzir tumori sa svjetloćelijskom morfologijom, zatim vretenastoćelijske i mezenhimalne neoplazme epitelioidne morfologije uključujući i gastrointestinalni stromalni tumor, zatim dolaze u obzir i tumori koji eksprimiraju melanocitne markere (melanom, clear cell sarkom, pojedini glatkomišićni tumori i karcinom kore nadbubrežne žlijezde) rabdomiosarkom, mioepitelni tumori, tumori masnog tkiva, kao i alveolar soft part sarkom. Epiteloidna varijanta PEComa može dijeliti morfologiju sa karcinomom bubrega ili karcinomima drugih lokalizacija. U diferencijalno dijagnostičkom algoritmu važno je uzeti u obzir kliničku prezentaciju, zatim morfologiju i imunohistohemijski profil tumorskog tkiva[2,3,5,6]. Sklerozirajući PEComi, slično kao i ostali tipovi PEComa češće se javljaju kod žena, srednje životne dobi. Ovaj tip PEComa najčešće se javlja u retroperitoneumu. Opisani su slučajevi gdje je prisustvo obilne, slabo celularne strome uočeno samo fokalno u tumoru. Dosadašnji objavljeni podaci ukazuju da sklerozitrajuće varijante PEComa karakteriše značajnija ekspresija markera mišićne diferencijacije (kao što su desmin ili kaldesmon). Takođe kao i kod drugih tipova PEComa najsenzitivniji marker melanocitne diferencijacije je HMB45. Iako su dosada objavljeni podaci limitirani malim brojem publikovanih slučajeva ovaj tip PEComa karakteriše indolentan klinički tok, ako morfologija tumorskog tkiva ne ukazuje da se radi o malignoj varijanti sklerozirajućeg PEComa[7,8,9,10].

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## Karcinom prostate:put do terapije uvek vodi preko patohistološke dijagnoze

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Klinički i patohistološki detektovan karcinom prostate, gledajući na svetskom nivo je drugi najučestaliji maligni tumor kod muškaraca iza karcinoma bronha, mada postoje razlike u distribuciji u različitim regionima i zemljama. U Evropi predstavlja najčešći karcinom kod muskaraca, sa oko 450.000 novodijagnostikovanih slučajeva godišnje i oko 100.000 umrlih. U Srbiji, rak prostate je po učestalosti odmah iza raka pluća i debelog creva, sa 2.300 do 3.000 obolelih muškaraca godišnje i preko 1000 umrlih. Najviša incidenca je i dalje u Severnoj Americi, Karibima, Brazilu, većini zapadnih zemalja Evrope, Australiji i Novom Zelandu. S druge strane su zemlje sa niskom incidencom, kao što je Azijski kontinent, neke zemlje Bliskog Istoka i Afrika. Ovakva distribucija incidence može se obrazložiti uticajem kako genetskih faktora, tako i faktora spoljne sredine, među kojima ne treba zanemariti ekonomsku razvijenost nabrojanih zemalja i stepen zdravstvene zaštite, što ima direktne reperkusije na „screening“ i dijagnostičke procedure. Što se tiče mortaliteta karcinom prostate se nalazi 5. mestu, takođe gledano na svetskom nivou. Stopa mortaliteta je izuzetno visoka u područjima sa muškarcima crne rase, kao što su sub-Saharska Afrika i Karibi, ali i kod Afro- Amerikanaca. Neočekivano visoka stopa mortaliteta je prisutna i kod muškaraca u Skandinaviji. Nizak mortalite je karakerističan za Aziju, Bliski Istok i zemlje Severne Afrike. Detektovana je i visoka prevalenca ovog tumora na autopsijama. U slučaju kompletno ukalupljenog tkiva prostate registrovan je kod 15-20% obdukovanih muškaraca Azije i kod čak 30-40% takođe obdukovanih muškaraca zapadnih zemalja. U zapadnim zemljama, kod muškaraca nakon cistoprostatektomije, kojima je potpuno kalupljeno tkivo žlezde nađen je karcinom prostate kod prosečno 50% slučajeva. Taj broj je značajno manji kod obdukovanih azijskih muškaraca i iznosi oko 10%. Ovaj tumor pogađa mahom muškarce starije životne dobi, > 60 godina života, a veoma se retko dijagnostikuje kod mlađih od 50 godina. Karakteristično je da mu učestalost raste sa godinama života. Nasuprot ovim tvrdnjama su rezultati studija na području SAD-a, koje su registrovale karcinom prostate kod 30% obdukovanih muškaraca starosti 30-50 godina. Stil života i navike u ishrani su već dugo dovode u vezu sa nastankom ove neoplazme. Karcinogeni, estrogeni i oksidansi iz hrane mogu biti okidač u nastanku karcinoma prostate. Brojni autori su u svojim radovima analizirali uticaj animalnih proteina, tj. upotrebu mesa i mlečnih proizvoda u ishrani i njihovu vezu sa nastankom tumora. Značajan je i broj studija koje su ispitivale dejstvo steroidnih hormona i hronične upale u etiopatogenezi ove neoplazme. Klinička sumnja na karcinom prostate se postavlja u koliko je povišen nivo PSA i nije uredan digitorektalni pregleda (DRE). DRE nije senzitivna i specifična metoda za dijagnostiku ovog tumora i u čak 25-50% slučajeva prisutnog tumora, ne registruje isti, pogodan je samo za dijagnostiku velikih i high grade tumora. Određivanje nivo PSA je u bronim zemljama skrining metoda, jer je nivo ovog antigena u serumu blisko povezan sa rizikom od karcinoma prostate. Vrednosti totalnog PSA 2-4 ng/ml predstavljaju tačku preseka, između normalnih i povišenih vrednosti. Određivanje serumskog nicvo PSA se koristi u dijagnostičke, terapijske i prognostičke svrhe. Većina adenokarcinoma prostate (85-90%) je multifokalnog tipa rasta, a lokalizovana su mahom u posteriornoj/posterolateralnoj perifernoj regiji žlezde, ali se beleži porast dominatno anteriorno lokalizovanih karcinoma. Centralna zona prostate je obično sekundarno zahvaćena ovim tumorom. Najčešći histološki tip karcinoma je acinarni adenokarcinom. Zlatni standard u dijagnostici karcinoma prostate je patohistološka analiza tkiva, koji je dobijen iglenom biopsijom prostate, pod kontrolom ultrazvuka. Patohistološka dijagnostika može biti inicijalna i definitivna, a vrši se na: bioptičkim uzorcima, materijalu nakon transuretralne resekcije prostete (TURP), zbog kompletne ili inkompletne retencije urina ili na operativnom materijalu nakon totalne ili radikalne prostatektomije. U cilju daljeg adekvatnog tretmana pacijenta i procene prognoze bolesti, svaki tumor, pa i karcinom prostate od strane patologa mora biti histološki tipizovan, gradiran i volumenski procenjen, a kada je u pitanju operativni materijal treba odrediti patološki stadijum bolesti, pTNM. U širokoj upotrebi je najnoviji Karcinoma protokol, Koledža američkih patologa iz novembra 2021. Godine, koji je u obaveznoj upotrebi za akreditovane laboratorije od marta 2022.

godine. U patohistološkom gradiranju i dalje je aktuelan revidiran „Gleason scoring system“ iz 2016. godine, uz upotrebu ISUP gradus grupa (International Society of Urological Pathology Grade Group), koje predstavljaju histološki gradus tumora i morfološki prognostički faktor biološkog ponašanja karcinoma prostate, naravno u kombinaciji sa drugim parametrima, kao što su nivo PSA, klinički i patološki stadijum bolesti. Sve navedeno omogućuje predviđanje toka bolesti i usmerava kliničke lekare, urologe i onkologe prema optimalnom terapijskom pristupu. I ako je acinarni adnokarcinom prostate najučestaliji histološki tip tumora, ne treba prenebregnuti i druge, manje zastupljene histološke tipove, kao što su intraduktalni, duktalni, skvamozni, urotelni karcinoma, karcinom bazalnih ćelija, neuroendokrine tumora, hematolimfoidne, mekotkivne neoplazme, te sekundarne tumore itd. Može se desiti da ne možemo na osnovu morfološke slike i imunohistohemijskih bojenja tipizovati tumor prostate u do sada poznate i prema klasifikaciji SZO (Svetske zdravstvene organizacije) tipizovane, onda treba u obzir uzeti radove, posebno eminetnih autora ove oblasti, koji prikazuju slučajeve ili studije sa novim, do sada neklasifikovanim histološkim tipovima karcinoma prostate, od kojih će neki sigurno, kao i mnogo puta do sada biti uvršteni u buduće klasifikacije tumora SZO.

**Ključne reči: Karcinom, prostata, terapija, patohistološka dijagnoza**

## Prostate cancer: the path to therapy always leads through pathohistological diagnosis

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Prostate cancer, detected clinically and pathohistologically, is the second most common malignant tumor in men after bronchial cancer worldwide, although there are differences in distribution in different regions and countries. It is the most common cancer in men in Europe, with about 450,000 newly diagnosed cases a year and about 100,000 deaths. In Serbia, prostate cancer is the most common cancer after lung and colon cancer, with 2,300 to 3,000 diagnoses a year and over 1,000 deaths. The highest incidence is still in North America, the Caribbean, Brazil, most Western European countries, Australia and New Zealand. On the other hand, there are countries with a low incidence, such as the Asian continent, some countries in the Middle East and Africa. This distribution of incidence can be explained by the influence of both genetic and environmental factors, among which the economic development of these countries and the level of health care should not be neglected, as they have direct repercussions on screening and diagnostic procedures. In terms of mortality, prostate cancer is on 5th place, also seen worldwide. The mortality rate is extremely high in black men areas, such as sub-Saharan Africa and the Caribbean, but also among African-Americans. High mortality rates are also unexpectedly present in men in Scandinavia. Low mortality is characteristic of Asia, the Middle East and North African countries. A high prevalence of this tumor at autopsies was also detected. In cases where prostatic tissue was completely analyzed, the tumor was registered in 15-20% of autopsied men in Asia and in 30-40% of autopsied men in Western countries. In Western countries, prostate cancer was found in men after cystoprostatectomy, in average of 50% of cases, where prostatic tissue was completely analyzed. This number is significantly lower in autopsied Asian men and is about 10%. This tumor mainly affects men older than 60 years, and is very rarely diagnosed in men under 50 years of age. It is characteristic that its frequency increases with age, but there are studies in the United States contrary to these claims, which registered prostate cancer in 30% of autopsied men aged 30-50 years. Lifestyle and eating habits have long been associated with the development of this neoplasm. Carcinogens, estrogens and food oxidants can be a trigger in the development of prostate cancer. Numerous authors have analyzed the influence of animal proteins in their works, such as use of meat and dairy products in the diet and their relationship to tumor formation. The number of studies examining the effect of steroid hormones and chronic inflammation in the etiopathogenesis of this neoplasm is also significant. Clinical suspicion of prostate cancer is raised by the level of elevated PSA levels and abnormal digital rectal examination (DRE). DRE

is not a sensitive and specific method for the diagnosis of this tumor and in as many as 25-50% of cases of the present tumor, it does not register the same, and it is suitable only for the diagnosis of large and high grade tumors. Determining the level of PSA is a screening method in many countries, because the level of this antigen in the serum is closely related to the risk of prostate cancer. Total PSA values of 2-4 ng/ml represent the point of intersection between normal and elevated values. Determination of serum PSA level is used for diagnostic, therapeutic and prognostic purposes. Most prostatic adenocarcinomas (85-90%) are of the multifocal growth type, and are localized mostly in the posterior/posterolateral peripheral region of the gland, but there is an increase in predominantly anteriorly localized cancers. The central zone of the prostate is usually secondarily affected by this tumor. The most common histological type of cancer is acinar adenocarcinoma. The gold standard in the diagnosis of prostate cancer is pathohistological analysis of tissue, which is obtained by needle biopsy of the prostate, under the control of ultrasound. Pathohistological diagnosis can be initial and definitive, and is performed on: biopsy specimens, material after transurethral prostate resection (TURP), due to complete or incomplete urinary retention, or on surgical material after total or radical prostatectomy. In order to further treat the patient and assess the prognosis adequately, each tumor, including prostate cancer, must be histologically typed, graded and volume assessed by a pathologist, and when it comes to surgical material the pathological stage of the disease, pTNM, should be determined. The latest Cancer Protocol from the College of American Pathologists from November 2021, is in wide use, and it has been in mandatory use for accredited laboratories since March 2022. The revised Gleason scoring system from 2016 is still relevant in pathohistological grading, using the ISUP grading group (International Society of Urological Pathology Grade Group), which represents the histological grade of the tumor and morphological prognostic factor of biological behavior of prostate cancer, of course in combination with other parameters, such as PSA level and clinical and pathological stage of the disease. All of the above enables the prediction of the course of the disease and directs clinicians, urologists and oncologists towards the optimal therapeutic approach. Although acinar adenocarcinoma of the prostate is the most common histological type of tumor, other, less common histological types should not be overlooked, such as intraductal, ductal, squamous, urothelial carcinoma, basal cell carcinoma, neuroendocrine, hematolymphoid, soft-tissue, and secondary neoplasms. It may happen that we cannot typify a prostate tumor in those known so far based on morphological picture and immunohistochemical staining, and according to the WHO (World Health Organization) classification, then we should take into account works, especially eminent authors in this field, which show cases or studies new, hitherto unclassified histological types of prostate cancer, some of which will certainly, as many times before, be included in future WHO tumor classifications.

**Key words: Cancer, prostate, therapy, pathohistological diagnosis**

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## Primary pulmonary Ewing's sarcoma: a case report

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**Introduction:** Ewing's (ES) sarcoma is a small round cells tumor, most often localized in the diaphysis or metaphysis of long bones in children, adolescents and young adults. It is less often primarily localized in soft tissues and in the elderly. The primary pulmonary location of this tumor is particularly rare. ES is genetically characterized by a translocation involving the EWSR1 gene. **Case report:** We present a 37-year-old patient in whom multiple focal lesions in the right lung were observed on computed tomography (CT) as part of the follow-up of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). The largest lesion was 10.5x9.2 cm in diameter, located in the upper lobe. Several smaller and one larger lesion in the middle lobe was also observed (6x5.7 cm). The right side pleural effusion was associated with compression atelectasis in all three lobes. An open lung biopsy of the upper lung lobe tumor area was done.
Results: Bioptic material consisted of several particles 0.6 cm to 2.5 cm in diameter. The lung parenchyma were occupied by tumor tissue made up of diffusely arranged round, small, blue cells with a high nucleo-cytoplasmic ratio, centrally located nuclei with abundant, granulated chromatin, and sparse, bright, diastase-PAS-positive cytoplasm. By immunohistochemistry, tumor cells showed positivity on vimentin, CD99 and were immunonegative on synaptophysin, chromogranin A, S-100, melan A, CD5, CD20, CD34, CD45, CD56, EMA, CK (AE1/AE3), Bcl2, TTF-1, CK7, CK18, CK19, HHF35, Calretinin, Desmin. Ki 67 positivity marked proliferative activity of around 60% of tumor cell nuclei. Based on the morphological and immunohistochemical characteristics, the diagnosis of Ewing sarcoma was determined. Molecular testing revealed the translocation involving the EWSR1 gene; t (21; 22) (q22; q12). Additional radiologic examinations did not show any bones or other visceral organs and soft tissues changes. The patient underwent surgery and six cycles of chemotherapy according to the appropriate SIOP protocol. **Discussion:** ES is small round cell sarcoma showing gene fusions involving one member of the FET genes family (usually EWSR1) and a member of the E26 transformation specific (ETS) family of transcription factors. In 90% to 95% of cases, they have a translocation of t(11; 22) (q24; q12) or t(21; 22) (q22; q12) on the EWSR1 gene. So far, 32 cases of ES primarily localized in the lungs have

been described in the available literature. The prognosis is poor and according to the cases shown, half patients died in the period from one to 54 months from the diagnosis. At the time of diagnosis, patients ranged from 4 years to 70 years (mean 31 years). According to the literature data, the prognosis is better in ES localized in the bronchus than in the lung parenchyma, as was the case with our patient. At the last control, the health condition of the patient was stable. The disease is in regression after the applied chemotherapy. This report aims to contribute to understanding the rare primary lung location of ES and its morphological and genetic characteristics. **Conclusion:** ES is a malignant tumor that is most often diagnosed in long bones in children and adolescents. Primary pulmonary location is extremely rare, and only 32 cases have been described in the available literature. In the differential diagnostic consideration of tumor lesions in the lung parenchyma in younger people, the rare possibility of extraosseous ES should be taken into account.

**Key words: Ewing sarcoma, extraosseous, primary lung tumor**

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Ako preterate sa referencama u Uvodu izgubićete „blago" za diskusiju i opteretićete spisak literature (većina časopisa dozvoljava, pa i mi najviše 25-30 referenci. Prilikom prikupljanja reference neophodno je citirato reference novijeg datuma, naravno da neka stara ("kapitalna") može naći svoje mesto. Redosled referenci koje citirate treba da sledi logičan raspored paragrafa uvoda. Prve reference su one koje se odnose na uopšteno znanje o problem i reference o istraživačkom problem. Zatim slede reference vezane za nova istraživanja - prethodna, aktuelna istraživanja i njihove limitacije

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**4. strana**

**Materijal i metode**

Opišite kako ste došli do rezultata (precizan dizajn studije, metoda koju ste koristili i kako ste analizirali podatke). Tačni podaci gde je studija sprovedena. Budite koncizni ( ne pišete turistički vodič). Ukoliko koristite standatdni metod citirajte referentnu literaturu. Sve mere koje saopštavate u poglavlju rezultati, u poglavlju metode moraju imati opisan način kao se do njih došlo. Prilikom čitanja ovog metoda, treba omogućiti čitaocima da imaju kritički uvid u vaš radi i da ponove vašu studiju baš na onaj način kako ste je vi uradili. Podnaslovi koji se koriste u poglavlju metoda kao što su: učesnici, dizajn studije, specifične metode, analiza podataka... klasično određuju njen sadržaj. Neophodno je da date detalje o odobrenju vaše studije, koje je dao etički komitet vaše institucije u kojoj je istraživanje sprovedeno. Zbog toga što su etnički principi fundamentalni za dobru istraživačku praksu, mnogi časopisi ne žele da publikuju članke koji ne uključuju detalje o etničkim odobrenjima (Materia Medica je prihvatila Principe dobre naučne prakse). Čitaoci žele da znaju na koji ste način uključili ljude u vašu studiju. Stoga, izbor učesnika mora biti jasno opisan i uključujući i isključujući detalji moraju biti opisani u sitnice. Prilikom opisivanja učesnika studije, njihova privatnost mora biti poštovana. Ne smete uključiti bilo kakve indentifikacione infomacije o njima, u tekstu, tabelama ili fotografijama. Ako se koristi fotografija, pismeni pristanak mora biti uzet od pacijenta ili ako su deca, od njihovih roditelja. Veličinu i karakteristike uzorka, ne stavljajte u poglavlje materijal i metode nego stavite na početak poglavlje rezultati. Mnoge istraživačke studije koriste upitnike pa u poglavlju metode morate dati precizne detalje o upitiniku, koje ste koristili, kako ste ga razvili, i testirali za ponovljivost. U eksperimentalnim studijama, detalji intervencija i kako su primenjeni moraju biti u potpunosti opisane.

**5. Strana**

**Rezultati**

Posle metoda, predstavlja najlakše poglavlje za pisanje. Možete koristiti interesantne kombinacije teksta, tabli i figura da odgovorite na pitanje studije u vidu jasne priče. Ovo poglavlje iz praktičnih razloga je poželjno pisati posle poglavlja metode, a pre pisanja uvoda i diskusije. Osnovno je da sopstvene rezultate učinite jasnim za čitaoca kako bi razumeli šta ste radili i dokle ste stigli. Ovo poglavlje mora voditi čitaova kroz proces istraživanja. Dužina ovog poglavlja je određena isključivo brojem rezultata koje želite da prikažete, a ne onim što vi želite da kažete o tome. Rezultate treba prikazivati postepeno.

Prvo se prikazuju elementi deskriptivne statistike koja opisuje karakteristike uzorka studije. To je prvi paragraf poglavlja rezultati i njegov cilj je da precizno i jasno prikaže detalje vašeg uzorka. To je veoma važno, jer epidemolozi žele da znaju kako ste definisali karakteristike vašeg uzorka, a kliničari žele da znaju koliko su učesnici u vašoj studiji slični sa njihovim pacijentima. Po završetku statističke analize podaci i rezultati se mogu prikazati na tri načina: tekstualno, tabelama i figurama.

**Tekst –** pojedine rezultate je bolje prikazati jednostavnim rečenicama sa podacima stavljenim u zagradu. *Primer: srednja vrednost proliferativnog potencijala za PCNA (2.20%) je veća nego srednja vrednost za Ki-67 P (1.64%) i Cyclin D1 (1.36%).*

**Tabele –** predstavljaju popis brojeva ili teksta u rubrikama pri čemu je svaka rubrika obeležena. Tabele pored prikazivanja podataka na pregledan način omogućavaju i ekonomično raspologanje prostorom u članku. Ne treba ih koristiti da bi se pokazao način kretanja nekih rezultata (trend) ili veza između pojedinih rezultata i to je bolje prikazati figurama (dijagramima). Na primer ukoliko želite da prikažete veličinu uzorka i odnos polova vaših ispitanika bolje je da koristite tabelu. Međutim, ukoliko želite da prikažete način na koji je pol povezan sa uzorkom populacije onda je bolje koristiti dijagrame. Legenda tabele se stavlja ispod tabele, levo orjentisana. U mnogim eksperimentalnim i opservacionim studijama je neophodno da prikažete osnovo upoređivanje studijskih grupa koje takođe definišu sposobnost generalizacije vaših rezultata. Nikada ne nazovite osnovnu karakteristiku vašeg uzorka „demografskim" jer shodno Oksfordskom rečniku, demografija je grana antropolologiju u kojoj se proučava statistika, rođenja, smrti i bolesti i stoga, to nije prikladno za ovaj kontekst. U bilo kojoj studiji, procenat, srednja vrednost i njena standardna devijacija ili medijana i njen rang su najprikladnije metode deskriptivne karakteristike i zavise od informacija koje opisuju.

**Figure –** prikazivanje rezultata figurama podrazumeva korišćenje dijagrama, fotografija, šema, mapa i crteža kako bi se na jasan i pregledan način prikazali rezultati dobijeni u istraživanju. Postoji više vrsta dijagrama (štapišasti dijagram *(engl. bar chart)*, histogrami učestalosti *(engl. histogram)* , pogačasti dijagrami *(engl. pie chart)* , linijski dijagrami *(engl. line graph)*, i grafikoni sa slikama *(engl. pictograph)* prilagođenih za opisivanje i prikazivanje različitih vrsta obeležja i rezultata.

Sledeći paragraf poglavlja rezultati se odnosi na opisivanje bivarijantnih analiza.

U trećem paragrafu se opisuju multivarijantne analize i to je mesto gde se završava cilj ili testiranje hipoteze, navedeno na kraju poglavlje uvod. Prilikom pisanja ovog paragrafa jedino je bitno da kažete čitaocu ono što on želi da zna. Nemojte dodavati ili uključivati bilo kakave podatke koji se udaljavalju od glavnog cilja. Podsećamo vas da rezultati i podaci nisu ista stvar, nije potrebno da ponavljate brojeve u tekstu koje ste prikazali u tabelama ili figurama. Čitaoci žele da prime poruku iz tabela ili figura i ne treba im dozvoliti da sami interpretiraju.

### 6. Strana

### Diskusija (1/3 vašeg teksta)

Diskusija je vrlo često najslabiji deo članka. Pojedine stvari u poglavlju diskusija praktično NE SMETE uraditi:

1. ne ponavljajte činjenice iz uvoda
2. izbegavajte ponavljanje rezultata
3. ne prikazujte rezultate koje niste prikazali u poglavlju rezultati
4. ne postoji ni jedan razlog da podvlačite koliko je „sjajan" vaš rezultat, dozvolite da čitaoci sami o tome prosude

Diskusija ne predstavlja jednostavno ponavljanje rezultata ili potvrde njihove tačnosti. Svaka diskusija iznosi ono izvan očiglednosti *(engl. beyond the evidence)*. Svaki članak sadrži zaključak koji se ne nalazi u poglavlju rezultati. Takođe svaki statistički značajan nalaz nema klinički značaj.

Diskusiju bi trebalo započeti, po mogućstvu jednom rečenicom - ponavljanjem glavnog nalaza. **1. paragraf** poglavlja diskusija se jednostavno može početi: „Naša studija pokazuje..." i izneti sažeto nalaz naše studije, po mogućstvu u jednoj rečenici.

**2. paragraf** - treba izneti jasno i precizno (praktično opširno) prednosti i nedostatke studije sa podjednakim naglaskom na oba elementa. Posebno treba imati na umu da će i urednici i čitaoci biti najzainteresovaniji baš za taj paragraf diskusije. Ukoliko urednik ili čitalac otkriju nedostatke u vašoj studiji, a vi ih niste opisali izgubiće poverenje u vašu studiju, jer praktično se postavlja pitanje: „Kolika je snaga vaše studije ako vi niste uočili nedostatak".

**3. paragraf** se odnosi na studiju koja je izvedena. Neophodno je izneti doprinos studije. Ne treba iznositi da li je i u kojoj meri bolja od prethodnih studija na osnovu kvaliteta ili nedostataka koje ste izneli u prethodnom paragrafu, nego treba prednosti i nedostatke sopstvene studije uporediti sa prednostima i nedostacimma drugih studija. Vrlo je važno da naglasite zašto ste vi dobili drugačije rezultate od ostalih ukoliko ste ih dobili. Pažnja! U ovom trenutku postoji opasnost da uđete u sferu špekulacija. Ukoliko ne znate zašto se vaši rezultati razlikuju od drugih iznesite to i ne pretendujte da su vaši ispravni, a tuđi pogrešni.