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Rare tumors of the larynx – report of two cases of adenoid cystic carcinoma

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Objective: Although laryngeal tumors are the second most common malignancy in the head and neck region, adenoid cystic carcinoma is one of the rarest types, composing less than 1% of laryngeal tumors. We present two cases with a literature review.
Case reports: **Case 1**: 73-year-old man presented with cough and difficulty swallowing. CT verified right-sided subglottic tumor mass without regional lymphadenopathy. On biopsy, tumor was diagnosed as adenoid cystic carcinoma. Patient underwent total laryngectomy with bilateral neck dissection. Tumor penetrated the thyroid cartilage, showed lymphovascular but not perineural invasion and was present on resection borders. Lymph nodes showed reactive changes. Patient was staged as pT4aN0R1. Fourteen months post surgery, there is no sign of recurrence.
Case 2: 79-year-old man presented with hoarseness lasting several months. CT scan showed a hyperdense alteration adjacent to the glottis exerting pressure on right vallecula. Biopsy revealed adenoid cystic carcinoma. Patient underwent total laryngectomy with right sided neck dissection. Tumor penetrated the thyroid cartilage and showed both vascular and perineural invasion, while resection borders were clear. Lymph nodes showed reactive changes. Patient was staged as pT4aN0R0. Seven months post surgery, patient is still disease free.
Conclusion: Laryngeal adenoid cystic carcinoma is a rare malignancy, not associated with typical risk factors for laryngeal carcinoma, often diagnosed at advanced stage. It should be considered in cases of advanced laryngeal tumors in patients lacking usual risk factors, but final diagnosis needs to be pathohistological.

Keywords: adenoid cystic carcinoma, larynx, head and neck, surgery

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Malignant melanotic nerve sheath tumour of mediastinum - rare tumor on the rare localisation

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Objective: Malignant melanotic nerve sheath tumour (MMNST), formerly known as melanotic schwannoma, is a rare tumour of nerve crest derivation, typically characterised by PRKAR1A lost. Initially MMNST was classified as benign, it has been defined as a malignant tumour in the 2020 WHO classification due to its aggressive behaviour. We report a rare case of MMNST of the mediastinum.
Case report: A female patient, aged 72, was diagnosed with a mediastinal tumour close to the left atrium, ventricle, and left coronary artery. A surgical procedure involving a left-lateral thoracotomy, partial pericardiectomy and lymph node extirpation. The pathohistological analysis revealed the presence of a hypercellular tumour composed of spindle cells that had a generally consistent morphology, lacking defined boundaries. Tumour cells were organized into short fascicles with palisading arrangement around blood vessels, without signs of necrosis or bleeding. Certain cells exhibited a cytoplasmic pigment that varied from fine-grained brown to dark brown, which is proved to be a melanin pigment by Masson Fontana staining. The pericar-

dium had been infiltrated by the tumour, while there were no nodal metastases. The tumour expressed Vimentin, S-100, S0X-10, MiTF, H3K27ME, and p53, but not HMB-45, PRAME, CD10, or Melan A. The Ki-67 proliferation index was 5%, and the mitotic rate was < 2/mm2. Lost expression of the PRKAR1A was the basic diagnostic criterion for distinguishing from malignant melanoma.

Conclusion: MMNSTs are rare and diagnostically challenging tumours that may be associated with the Carney complex, especially when there is a loss in PRKAR1A expression.

Keywords: MMNST, PRKAR1A lost, rare tumour

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Hodgkin Lymphoma Associated with Peripheral T-cell Lymphoma, NOS: a Case Report

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Objective: In diagnostic setting, the co-occurrence of a classical Hodgkin lymphoma (cHL) and peripheral T-cell lymphoma (PTCL), NOS, each with appropriate morphology and immunophenotype, either in the same tissue or separate tissues, defines a composite lymphoma.

Case report: We present the case of 68-year-old patient who underwent an examination for cervical lymphadenopathy, which was associated with weight loss, night sweats, and chronic skin itching. A right cervical lymph node excisional biopsy was performed. Morphologic analysis revealed effacement of lymph node architecture by diffuse lymphoid infiltration. An atypical medium and large lymphoid cells were positive for LCA, CD2, CD3, CD4, CD5, CD7, CD30, CD43, LEF1, c-myc, MUM1, ICOS, and GATA3 and negative for TdT, PAX5, CD20, CD10, bcl-6, PD1, Granzyme B, perforin, TIA-1, CD8, TBX21, ALK-1, EBV-LMP, CD57, EMA, CD25. A Ki-67 proliferation index was 70%.
In the same tissue there were Hodgin-Reed-Strenberg cells negative for LCA and positive for PAX5, CD20, CD30, fascin, MUM1, EBV-LMP, EBER and focally positive for CD15.
Those morphologic and immunophenotypic features were consistent with diagnosis of composite synchronous lymphoma with co-occurrence of a cHL and a PTCL, NOS, GATA3 subtype.
The patient was scheduled for admission to the Hematology Department for staging procedure and further analyses to be reviewed by the hematology team for the therapeutic approach. However, the patient has still failed to appear six months after diagnosis.

Conclusion: Composite lymphomas are extremely rare. They pose a particular diagnostic challenge. In this case, morphologic and immunophenotypic features may simulate angioimmunoblastic T-cell lymphoma, cHL and ALK-anaplastic large cell lymphoma.

Keywords: Peripheral T-cell lymphoma, NOS, classic Hodgkin lymphoma, composite lymphomas.

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Aortic dissection in a young patient with clinically unrecognized sarcoidosis - an autopsy case

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Objective: Case report of undiagnosed sarcoidosis in a young man who died due to aortic dissection.

Case report: A 39-year-old man was urgently hospitalized due to suspected acute myocardial infarction. The patient had been treated for chronic obstructive pulmonary disease. The patient died shortly after admission to the hospital, prompting a clinical autopsy. Autopsy revealed dissection of thoracic aorta with propagation down the anterior descending branch of the left coronary artery and the abdominal aorta. The myocardium showed discoloration. The kidneys appeared in a state of shock. No specific substrate was found in other organs. Representative samples were

taken from all organs, and routinely processed. Sections were stained using various histochemical methods. The myocardium showed mild perivascular fibrosis, cytoplasmic vacuolization of subendocardial cardiomyocytes, and small foci of contraction band necrosis. Atherosclerotic lesions with luminal narrowing of approximately 50% were found in the initial part of the left coronary artery. Lung, liver, kidney, spleen, and mediastinal lymph nodes, showed well-defined, non-necrotizing epithelioid cell granulomas with multinucleated giant cells with rare asteroid and conchoid intracytoplasmic inclusions within. Histochemical staining excluded the presence of pathogenic microorganisms. This chronic granulomatous inflammation consistent with sarcoidosis. Granulomatous inflammation was not detected in sections from the aorta.

Conclusion: The significance of autopsies in sudden deaths cannot be overstated, even when clinical symptoms appear clear. It is crucial to systematically conduct autopsies in such cases. Histopathological analysis plays a crucial role, especially in cases that may initially seem clear, as it can provide valuable insights that may not be apparent macroscopically.

Keywords: aortic dissection, sarcoidosis, autopsy

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Epidermoid Cyst of the Kidney - Tumor Mimicry and Diagnostic Challenges

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Objective: This is a case report and discussion of benign lesion mimickers of malignant renal neoplasia.

Case report: Here we present a 76-year-old female admitted to the hospital due to pain in the lumbar area. An ultrasound revealed a kidney tumor, which was verified on computer tomography. Radical nephrectomy was performed, and the specimen was sent for pathological analysis. On gross examination of the kidney, a cystic nodule was observed on the upper pole, partially filled with a soft, compact material, with a maximal diameter of 50 mm. Underneath the cystic nodule, a calculus with a maximal diameter of 12 mm was detected. The ureter was also filled with the same material as seen in the nodule. Histologically, the tumor was composed of cysts lined with squamous epithelium, filled with abundant lamellar keratin. Immunohistochemical analysis including CK5/6,CKAE1/AE3, p40, showed diffuse positivity of the squamous epithelium as well as lamellar keratin. The preformed immunohistochemical analysis confirmed the diagnosis of an epidermoid cyst of the kidney. The material in the ureter was also keratin, verified by immunohistochemistry.

Conclusion: Renal epidermal cyst is a rare and benign lesion. The etiology of epidermoid cysts has not yet been explored, but the presence of the renal calculus can be an etiological factor due to mechanical irritation. Its preoperative diagnosis is a real challenge due to its rarity, low clinical, and especially radiological specificity, which can lead to mistaken diagnosis as a malignant tumor. The macroscopic appearance of the cyst can also mimic an echinococcal cys

Keywords: kidney, epidermoid cyst, immunohistochemistry

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Significance of histomorphological damage of saphenous vein grafts in coronary bypass surgery

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Objective: The aim of this study was to deterimine the degree of histomorphological damage on saphenous veins harvested by using three different surgical techniques and their significance in coronary artery bypass grafting (CABG).
Introduction: The great saphenous vein is mostly used conduit for coronary revascularisation. Early and late vein graft occlusion still represents insufficiently pathogenetically elucidated problem in patients with coronary artery disease (CAD).
Material and Methods: The study included 83 saphenous vein samples obtained from patients who underwent one of three different surgical techniques: conventional (CVH), endoscopic (EVH) and „no-touch“ (NT) vein harvesting on the Dedinje Cardiovascular Institute, Cardiac Surgery Department, Belgrade, Serbia between June 2019. and December 2020. Collected saphenous vein samples were stained by hematoxylin-eosin (H&E) and immunohistochemically analyzed by using CD31, factor VIII, Caveolin and eNOS antibodies.
Results: Histomorphological evaluation of H&E vein sections showed significantlly lower microstructural damage in NT harvested veins compared to CVH and EVH group of patients ($p<0.001$). Immunohistochemical examination revealed strong positive staining in the NT group compared to CVH and EVH group (CD31: $p=0.02$; FVIII: $p<0.001$; Caveolin: $p=0.001$; eNOS: $p=0.003$) which was confirmed a lower degree of structural damage and mostly intact wall integrity in NT group.
Conclusion: The preservation of structural integrity and vein patency represent essential factors for long-term functionality of saphenous vein grafts. NT vein harvesting showed the best morphological preservation of the vein wall, while leg wound complications were the least in EVH group of patients. Consequently, the development and implementation of the endoscopic no-touch technique would significantly advance coronary artery bypass grafting.

Keywords: coronary artery bypass grafting, conventional vein harvesting, endoscopic vein harvesting, no-touch vein harvesting, saphenous vein, vascular damage

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Pediatric ileal intussusception caused by myoepithelial hamartoma - a case report

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Objective: Myoepithelial hamartoma (MEH) is a benign tumor-like lesion composed of dilated glandular formations lined by single-layered columnar epithelium surrounded by bundles of smooth muscle cells. MEH is most commonly localized in the stomach and duodenum, while distal localization in the small intestine is very rare.
Case report: A male infant was urgently admitted to the University Children’s Hospital, Belgrade. Upon detailed examination, ileal intussusception was diagnosed. Fol-

lowing surgical intervention, a segment of the ileum with a tumor-like lesion was excised. Excised ileal segment revealed a submucosal tumor-like lesion, with multicystic appearance upon cross sectioning. Histopathological analysis revealed a well-demarcated lesion localized within the submucosa and muscularis propria, comprised of dilated tubular structures. These structures were lined by a single-layered columnar epithelium positive for CK7, as well as for CD10 (apical positivity). Focally, dilated structures were lined by stratified epithelium positive for CK 5/6 and p63 (basal cells). All epithelial cells demonstrate immunohistochemical positivity for PDX1, CDX2, CA19.9, MUC1, with some showing positivity for MUC5AC and focal positivity for MUC6. However, staining for SATB2, MUC2, CK20, and OCT4 is negative. Bundles of smooth muscle cells (□-SMA positive) were observed around each tubular structure.

Conclusion: Although the pathogenesis of this lesion remains incompletely understood, there are opinions suggesting that the lesion is an heterotopic pancreatic tissue. The positivity of certain immunohistochemical markers such as PDX1, CA19.9, CDX2 supports this theory. Despite its rarity, our case adds to the growing body of evidence in the literature, providing further insights into the diagnosis of this rare entity.

Keywords: myoepithelial hamartoma, intussusception, pediatric pathology

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Cytological and histological features of lung adenocarcinoma with positive predictive biomarkers

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Objective: Examination of differences in the frequency of morphological features between ALK, EGFR, PDL1, and TN group of patients with lung adenocarcinoma (LA).

Introduction: There is a limited data describing the cytomorphological features that could suggest mutation status or PD-L1 expression in LA.

Material and Methods: The retrospective study included 132 patients diagnosed with LA. Based on molecular findings, patients were categorized into four groups: PDL1 group, ALK group, EGFR group, and triple negative (TN) group. Examined morphological features encompassed: cell cluster size, arrangement of tumor cells, size of nuclei, nuclear atypia, visibility of nucleoli, presence of necrosis, intracytoplasmic vacuoles, signet ring cells, stromal characteristics, and inflammatory infiltrate presence.

Results: Solid arrangement, large nuclei, presence of intracytoplasmatic vacuoles, signet ring cells, and abundant stroma were statistically significantly more frequently present in PDL1 group compared to TN group ($p<0.05$). The predictive model composed of these features was statistically significant for high PD-L1 expression as criterion ($x^2=40.626;p<0.001$). Accuracy, sensitivity and specificity for this model were 83.61%, 86.67%, 80.65%. Statistically significant differences were observed in size of the nuclei, histological arrangement of cells, visibili-

ty of the nucleoli, and presence of intracytoplasmic vacuoles, and signet ring cells between ALK, EGFR, and TN group. The predictive model composed of these features was statistically significant for mutation status as criterion ($x^2=67.541;p<0.001$). The predictive model achieved classification success rate for ALK, EGFR, and |TN group of 72.4%, 69%, and 71%, respectively.

Conclusion: Our results confirm that certain cytological and histological features of LA are associated with the mutational status and PD-L1 expression in LA.

Keywords: Cytology; Histopathology; Lung Adenocarcinoma; Epidermal Growth Factor Receptor; Anaplastic Lymphoma Kinase; Programmed Cell Death Ligand 1

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Clinical-pathologycal characteristic of hormone-independent lobular breast carcinoma

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Objective: The eyelid can be the site of various tumors but primary non-epithelial tumors are rare. Solitary circumscribed neuroma is a benign neural tumour composed of Schwann cells, frequent on the head and neck, but it is rarely described on the eyelid. We aim to present a rare case of solitary circumscribed neuroma of the eyelid diagnosed at Clinic for Ophthalmology of University Clinical Centre of Serbia.

Case report: A 69-year-old female patient presented with solitary, slightly raised, painless nodule on the lower eyelid skin, 3.5 mm in the greatest diameter. Histopathological evaluation showed a well circumscribed, partially encapsulated intradermal nodular tumor. It was composed of elongated spindle cells arranged in irregular fascicles, with hyperchromatic nuclei without prominent atypia and no nuclear palisading. Mitoses were not noticed. The tumor cells expressed SOX10, S-100, and CD34 but not GFAP. Neurofilament was positive in entrapped small nerves. GLUT-1 was expressed in remnants of perineurium in the tumor periphery. There was no recurrence noted in this case.

Conclusion: Primary non-epithelial eyelid tumors are uncommon and may be a diagnostic challenge for ophthalmic pathologists. Other spindle cell tumors must be considered when encountered with solitary circumscribed neuroma, especially those that may be associated with systemic syndromes. Morphological features are usually enough for the diagnosis but immunohistochemical analysis can be helpful.

Keywords: solitary circumscribed neuroma, eyelid, peripheral nerve tumor

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Non-epithelial tumors of eyelid: a case of solitary circumscribed neuroma as an uncommon tumor

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Objective: The eyelid can be the site of various tumors but primary non-epithelial tumors are rare. Solitary circumscribed neuroma is a benign neural tumour composed of Schwann cells, frequent on the head and neck, but it is rarely described on the eyelid. We aim to present a rare case of solitary circumscribed neuroma of the eyelid diagnosed at Clinic for Ophthalmology of University Clinical Centre of Serbia.
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Conclusion: Primary non-epithelial eyelid tumors are uncommon and may be a diagnostic challenge for ophthalmic pathologists. Other spindle cell tumors must be considered when encountered with solitary circumscribed neuroma, especially those that may be associated with systemic syndromes. Morphological features are usually enough for the diagnosis but immunohistochemical analysis can be helpful.

Keywords: solitary circumscribed neuroma, eyelid, peripheral nerve tumor

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Primary intraosseous myxoid liposarcoma: a case report

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Objective: Liposarcoma is the most common type of sarcoma in adults which mostly arises in deep soft tissues of the extremities, especially the thigh. Primary intraosseous liposarcoma is an extremely rare tumor and accounts for less than 0.1% of all malignant bone tumors. Tumor is accompanied by non specific symptoms such as pain, swelling and decreased range of motion.
Case report: We present a 66 years old female patient with a one year history of pain and swelling in the left knee area. The X-ray showed a distal femoral osteolytic lesion. MRI revealed intramedullary lesion mass measuring in the greatest diameter 12.5 cm, destroying the cortex. Initially open biopsy revealed intraosseous malignant mesenchymal tumor - high grade myxoid liposarcoma, composed of uniform, small ovoid cells without significant atypia neither brisk mitotic activity embaded in abundant, lightly basophilic myxoid stroma with delicately arborizing capillary network. Approximately 15% of tumor contained hypercellular areas composed of small round cells which classified it in high grade neoplasm. Immunohistochemically, the tumor cells showed strong diffuse positivity for vimentin and focal positivity for p53 and desmin. Nuclear Ki67 positivity

was found in approximately 10% tumor cells. Diagnosis of myxoid liposarcoma confirmed by DDIT3 FISH analysis. Surgical procedure has been chosen as initially treatment modality followed by adjuvant chemotherapy.

Conclusion: Primary intraosseous myxoid liposarcoma has no specific symptoms neither radiography imaging, thus pathohistological finding is esencial in diagnosis. Considering myxoid liposarcoma could be mistaken with other tumors that have myxoid appereances, we emphasise importance of immunohistochemical and DDIT3 FISH analysis.

Keywords: bone, myxoid liposarcoma, primary tumor

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PD-L1 expression in metastatic colorectal carcinoma

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Objective: Programmed cell death ligand-1 (PD-L1) expression in colorectal cancer and its prognostic role in metastatic colorectal carcinoma (mCRC) is not well established. In our study we aim to evaluate the expression of PD-L1 in mCRC and its correlation with the clinicopathological characteristics in these patients.

Introduction: The treatment of metastatic colorectal carcinoma (mCRC) has been improved over the recent years mostly due to molecular classification and new technologies for personalized therapy. PD-L1 is the key inhibitor of the cytotoxic immune response and causes rapid tumor progression with poor prognosis.

Material and Methods: Diagnosed 75 cases of mCRC at Clinical Hospital Acibadem – Sistina were evaluated for PD-L1 expression using clone SP263 in tissue microarray. The expression was evaluated by different cut-offs of >1%, >10%, >50% of tumor cells.

Results: PD-L1 was evaluated positive in 17 cases of mCRC (26,6%). More than a half of positive cases (11) showed cut off >1%. Seventeen percent of positive cases showed cut off >10% and all of them were located in rectosigmoid colon with stage IIIB and IIIC. Three cases were evaluated with a cut off >50% all of them G3 mCRC, stage IIIC and IVA, of which 2 cases were in right colon associated with BRAF mutations.

Conclusion: Expression of PD-L1 was found in almost one third of the cases. A higher cut off was correlated with higher grade, high pathological stage and BRAF mutation. This suggests that mCRC with high PD-L1 expression may show a survival advantage with immune checkpoint inhibitors therapy.

Keywords: Colorectal carcinoma, PD-L1, immune checkpoint inhibitors

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Hepatic Echinococcosis – presentation of case reports

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Objective: To present the differences between cystic and alveolar echinococcosis with the first two cases of multilocular echinococcosis in Serbia.

Case report: The first case was a 67-year-old female from a small village in Srem municipality who was admitted to our hospital due to liver pain, which progressed over time. Differential diagnoses included haemangioma, cystic echi-

nococcosis and abscess formed in the cystic echinococcal lesion. Pathological examination clearly showed multilocular echinococcosis with numerous small and empty vesicle spaces with chitin membrane without protoscolices, surrounded by massive fibrosis and infiltrative type of growing into the liver parenchyma. The second case was a 57-year-old man who was admitted to our hospital due to 10-day lasting symptoms of jaundice, nausea, and stomach pain. Differential diagnoses included malignant tumor. The lesion of the liver underwent radical resection. It was confirmed as alveolar echinococcosis by pathological examination, which showed multiple multilocular cysts covered with chitinous membranes, accompanied by numerous foreign body granulomas and broad areas of necrosis. Perineural propagation of echinococcis and one hilar lymph node with wide necrotizing granulomas with chitinous membranes were also present. Both of the patients had no surgical complications after the operation and were discharged with an 800 mg daily dosage of Albendazole.

Conclusion: These are the two first recorded human cases of multilocular echinococcosis in Serbia. Infections with these parasites are considered extremely serious, contributing to significant morbidity and mortality. Therefore, we must improve prophylactic and diagnostic procedures and surgical techniques to cure this zoonotic disease.

Keywords: echinococcosis, cystic, multilocular, liver

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Metastatic synovial sarcoma of the uterus - Is it possible to diagnose it without FISH analysis?

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Objective: Synovial sarcoma is classified as a malignant mesenchymal tumor of unclear histogenesis, typical for the locomotor system. Its visceral localization has been rarely described. We present the significance of molecular FISH analysis in verifying a rare metastatic synovial sarcoma of the uterus with divergent smooth muscle and osteoblastic differentiation.

Case report: A lung tumor biopsy was performed on a 63-year-old patient. The scant biopsy sample showed tumor composed of pleomorphic epithelioid cells surrounded by an eosinophilic matrix. Immunophenotypically, the cells exhibited mesenchymal differentiation (positive Vimentin, CD99, SMA, SATB2, p16, TLE, WT1, Desmin). FISH analysis detected SS18 gene rearrangement in 40% of the nuclei typical for synovial sarcoma. Additionally, a heterozygous deletion of the CDKN1A gene was confirmed in 57% of the nuclei.

It was later discovered that the patient had undergone a hysterectomy three years prior, when the diagnosis of uterine leiomyoma was made. Reevaluation of the uterine biopsy demonstrated a tumor composed of pleomorphic spindle cells with mesenchymal differentiation (positive SMA, p16, Desmin, TLE, SATB2, negative for ER). FISH analysis

detected SS18 gene rearrangement in 28% of the nuclei, that led to a diagnosis of primary synovial sarcoma of the uterus.

Conclusion: A comparative analysis of both tumors showed immunohistochemical and FISH overlaps, indicating that both biopsies correspond to a rare form of malignant mesenchymal tumor- synovial sarcoma displaying divergent smooth muscle and osteoblastic differentiation. We concluded that the tumor in the uterus was the primary neoplasm, while the lung tumor should be considered a secondary deposit.

Keywords: Synovial sarcoma, SS18, smooth muscle and osteoblastic differentiation.

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Detection of EGFR mutations in cytology samples - liquid biopsy opens a new chapter in molecular diagnostics

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Objective: Activating mutations of the epidermal growth factor receptor (EGFR) are found in 10-15% of lung adenocarcinomas in the Caucasian population. The presence of these mutations is associated with sensitivity to EGFR tyrosine kinase inhibitors (TKIs). The secondary T790M mutation in exon 20 of the EGFR gene is the most common mechanism of acquired resistance to first- and second-generation TKIs, occurring in 50-60% of resistant cases with progressive disease. Although tissue is considered the gold standard for molecular biomarker testing, numerous studies and guidelines recommend the use of cytological specimens (smears and cell blocks) for EGFR testing, including detection of the EGFR T790M mutation. Considering tumor heterogeneity, a single sample is often insufficient to gain insight into the molecular profile of a malignancy. Liquid biopsies are promising minimally invasive procedures based primarily on the molecular analysis of circulating tumor cells or cell-free tumor DNA (ctDNA) isolated from blood and other body fluids. However, ctDNA is limited in the bloodstream and still represents a hurdle on the way to promising precision medicine. Therefore, pleural and pericardial effusions can be used as a source of biomarkers, such as ctDNA, in liquid biopsy to investigate tumor mutations.

Case report: In August 2022, a 69-year-old woman, a former smoker, came to the Institute for Pulmonary Diseases of Vojvodina in Sremska Kamenica due to dyspnea and weight loss. Computed tomography (CT) of the chest showed a tumorous lesion in the right upper lobe of the lung, with a diameter of 4 cm, mediastinal lymphadenomegaly, and a pericardial effusion. A pericardiocentesis was performed because of an impending cardiac tamponade. Numerous erythrocytes and individual reactive mesothelial cells were found in the cytological smear of the obtained pericardial effusion. A bronchoscopy was performed and the pathohistological examination confirmed lung adenocarcinoma at stage T3N3M0. EGFR testing was performed using the extracted genomic DNA from the cytological smear - brush from the right upper lobe. The real time PCR Cobas® EGFR Mutation Test V2 detected the presence of L858R mutation in exon 21. The patient received first-line therapy with afatinib (second-generation TKI), at a dose of 40 mg/day. The overall treatment with afatinib was carried out over a period of 15 months. A partial radiological response according to RECIST (Response Evaluation Criteria in Solid Tumours) v.1.1 was achieved. In December 2023, a CT scan of the chest showed a recurrence of the pericardial effusion. The patient underwent a pericardiocentesis. No malignant cells were found in the cytological smear of the pericardial effusion. A liquid biopsy was performed. The ctDNA was isolated from blood plasma and the molecular test was negative for EGFR mutations. The multidisciplinary tumor board decided to repeat a liquid biopsy from the supernatant isolated from the pericardial efussion. The Cobas® EGFR Mutation Test V2 revealed coexisting L858R mutation with T790M mutation in the ctDNA isolated from the pericardial effusion. In January 2024, the patient was administered second-line therapy with osimertinib (third-generation TKI) at a dose of 80 mg/day. The patient is currently on the proposed therapy without side effects. The first follow-up CT scan is expected shortly.

Conclusion: Malignant effusions can serve as alternative samples if no tumor tissue is available. The cell pellet obtained by centrifugation can be used for the preparation of smears or cell blocks and for genotyping if it contains a

sufficient number of tumor cells. The separated supernatant can be explored as an alternative source for liquid biopsy in lung cancer patients to diagnose early disease progression even if no malignant cells were seen in the effusion. Liquid biopsy using the supernatant of pleural/pericardial effusions could be more effective than blood plasma samples because the effusions are richer in tumor products released by the cancer cells. It is playing an increasing role as a complementary molecular testing strategy even when tissue tests are available so that more patients can receive targeted therapy.

Keywords: Cell-Free Nucleic Acids, Cytology, Lung Neoplasms

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