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News in the WHO 2022 classification of urothelial neoplasms

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Objective: While morphology remains fundamental for tumor taxonomy, emerging approaches integrating molecular insights into the classification of urothelial carcinomas and the management of neoplasms with novel therapeutic modalities like immunotherapy are gaining prominence. However, further research is warranted to translate these advances into routine pathology practice and patient care.
Introduction: The fifth edition of the World Health Organization (WHO) Classification of Tumors series for urinary and male genital tract tumors has been released after six years, coinciding with advancements in treatment strategies and the accumulation of new molecular data on urological cancers.
Material and Methods: The 2022 WHO Classification of Tumors of the Urinary System and Male Genital Organs introduces updates in the classification of urinary tract tumors, offering fresh perspectives on grading heterogeneous non-invasive urothelial neoplasms, defining inverted neoplasms, grading invasive urothelial carcinomas, delineating the diverse morphological appearances of urothelial carcinomas, characterizing precursor lesions, and elucidating tumor lineage differentiation.
Results: Aligned with these advancements, this study aims to assess grading heterogeneity in non-invasive papillary urothelial carcinomas, addressing interobserver variability and proposing standardized diagnostic criteria essential for therapeutic decisions and prognostic accuracy. Following WHO 2022 guidelines, the study evaluates grading consistency in papillary tumors, particularly regarding high-grade component presence. Analysis reveals significant grading heterogeneity, underscoring the necessity for standardized criteria adoption. The proposed categorization of tumors with ≥5% high-grade component as high-grade enhances reproducibility and clinical correlation, aligning with evolving diagnostic paradigms.
Conclusion: Standardizing grading criteria, especially for heterogeneous tumors, is crucial for enhancing interobserver reproducibility and prognostic accuracy, facilitating future diagnostic advancements supported by emerging technologies like machine learning and artificial intelligence.

Keywords: Urothelial neoplasms, grading, papillary tumors, interobserver reproducibility, diagnostic criteria.

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Bland faces of aggressive intestinal lymphomas – report of two cases

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Objective: Gastrointestinal tract (GIT) is the most frequent extranodal localization of non-Hodgkin lymphoma (NHL). However, lymphomas account for only 1-4% of all GIT malignancies. Intestinal lymphomas comprise heterogeneous group of tumors with variable histology, biological behavior, and clinical outcomes. Herein, we present two cases of intestinal lymphomas with quite different clinical and gross presentation, but similar bland, uniform morphology and clinically aggressive course.
Case report: The first case is a 61-year-old gentleman with a family history of colorectal cancer who complains of pain in the lower right abdominal quadrant, slight weight loss (4kg in 4 months), and occasional night sweats. Colonoscopy reveals numerous sessile polyps throughout the terminal ileum and right colon, as well as fungating masses

adjacent to the ileocecal valve and in ascending colon. A biopsy of ileocecal mass was performed and the pathologist subspecialized in GIT pathology delivered a diagnosis of chronic active polypoid colitis with low grade dysplasia. However, because of the compelling endoscopic finding, the gastroenterologist decided to repeat the colonoscopy with a biopsy from the same location. Pathological analysis showed polypoid fragments of colonic mucosa with diffuse monomorphic lymphoid infiltration, and with no lymphoepithelial lesions. Tumor cells were small to medium size, with only slight nuclear pleomorphism and angulation, and scant pale cytoplasm. Immunohistochemically, lymphoid cells expressed CD20, CD79a, CD5, Bcl-2, CyclinD1, and SOX11, while CD3 was negative. Proliferative Ki67 index was 35%. The patient was diagnosed with classic Mantle cell lymphoma (MCL) with a presentation in the form of multiple lymphomatous polyposis. Subsequent gastroscopy found multiple polypoid lesions in the stomach and duodenum, while computed tomography discovered multifocal nodular infiltrates in the lungs and liver, as well as mesenterial and retroperitoneal lymphadenopathy. Bone marrow was unremarkable. At the time of diagnosis, the patient was in clinical stage IV, MIPI 7, ECOG 1. He was treated with 3 cycles of CHOP followed by 3 cycles of DHAP and partial remission was achieved. The patient was not motivated for stem cell transplantation, thus Ibrutinib has been recently introduced.

The second case is a 58-year-old overweight gentleman with a medical history of arterial hypertension and diabetes who was admitted to the emergency hospital with vomiting, a 3-day absence of stool, and acute abdominal pain. The patient had no history of inflammatory bowel disease or celiac disease. Paralytic ileus was suspected, and the patient underwent surgery. Resection of a -long segment of the jejunum was performed. Intraoperatively, a small perforation of the jejunum was found surrounded by a swollen, thickened, rubbery wall. Pathology revealed diffuse monomorphic cellular lymphoid proliferation that expands lamina propria, including the villi cores, and shows transmural propagation. Neoplastic infiltration was composed of small to medium size monotonous ovoid cells, with round nuclei, inconspicuous nucleoli and dispersed chromatin, and pale cytoplasm. Epitheliotropism was also noted. Immunohistochemical stains resulted in diffuse expression of CD3, CD8, CD56, granzyme B, and Bcl-2, while B-cell markers were negative. Proliferative Ki67 index was 80%. In correlation with clinical and radiological findings, the diagnosis of Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) of the jejunum was rendered (clinical stage IV, a, IPI2, ECOG0). Bone marrow was not infiltrated with neoplastic lymphoid cells. Currently, the patient is being treated with the fourth cycle of induction chemotherapy according to CHOEP14 protocol, with a plan for consolidation of the first response with autologous stem cell transplant.

Conclusion: Due to the wide spectrum of clinical presentations, intestinal lymphomas are diagnosed on small endoscopic biopsies, as well as on surgical specimens. Different types of NHL may have similar morphologic appearance, and may imitate indolent lymphoproliferative disorders or inflammatory conditions. Diagnosis of intestinal lymphoma may be quite challenging, especially in cases with bland, uniform morphology that may be overlooked in small biopsies, and requires training and experience in hematopathology.

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Keywords: gastrointestinal tract, immunohistochemistry, intestine, lymphoma, morphology

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Lymphoproliferative pathology - pattern approach

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Objective: Lymphoproliferative neoplasms are heterogeneous group of diseases characterized by uncontrolled clonal lymphocyte proliferation with/without bone marrow (BM) infiltration. Low grade lymphoma patients even with BM infiltration can be followed without treatment, while aggressive lymphoma needs to be treated upon diagnosis.
Case report: A 68-year-old female came to a hematologist complaining of fatigue and early satiety. Splenomegalia, anemia, thrombocytopenia and elevated ESR were present. BM examination revealed hypercellularity, 80-90%, with all three lineages hematopoiesis elements presented. Centromedullary, nodular and partly paratrabecular lymphoid infiltrate was observed, consisted of small and medium lymphoid cells with scanty cytoplasm, round or easily cut nuclei, loose chromatin, small nuclei, making about 50% of the BM cell population. Immunohistochemically, tumor cells expressed CD20, PAX5, CD23, Bcl6, MUM1 and IgM and were negative for CD3, CD5, LEF1, BCL2, CyclinD1, HCL, AnexinA1, CD25, CD11c, IgG, IgD. CD10 was inconclusive. Moderate fibrosis was detected by reticulin staining method (MF2). Findings corresponded to BM infiltration by Non-Hodgkin B-cell lymphoma. Lymph node biopsy was recommended, but there was no significant lymphadenopathy. Differential was diffuse large B-cell lymphoma (DLBCL)/follicular lymphoma grade 3 leading to treatment with R-CHOP.
Conclusion: BM infiltration assessment is important for staging and predicting clinical course, but not optimal for establishing diagnosis of lymphoproliferative neoplasm. Since BM involvement in DLBCL is quite discordant and frequently characterized by small lymphoid cells infiltrate with cleaved nuclear contours admixed with only rare or no large lymphoid cells, so morphologically suggestive for a low-grade lymphoma, close cooperation between pathologist and hematologist is essential.

Keywords: lymphoma; bone marrow; DLBCL;

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Diagnosis-guided treatment of chronic lymphocytic leukemia

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Objective: To determine the profile and frequency of predictive molecular markers in a group of patients diagnosed with chronic lymphocytic leukemia using NGS methodology, with the aim of selecting target therapy.
Introduction: Chronic lymphocytic leukemia (CLL) is a malignancy of mature CD5+ B lymphocytes that is characterized by exceptional clinical and biological heterogeneity. The Rai and Binet staging systems, developed in the late 1970s to early 1980s, are used in clinical practice to stratify CLL patients into risk categories and to help guide clinical follow-up options: to treat or to watch and wait. However, in early-stage disease, these systems are unable to predict what patients will face the progression to a more aggressive disease. Over the years and along with the development of molecular methods, new markers have been recognized that significantly contributed to a better stratification of CII patients. For instance, next-generation sequencing (NGS) studies have led to the discovery of recurrently mutated genes in CLL, such as NOTCH1, SF3B1, BIRC3, XPO1, POT1, NFKBIE and EGR2, that are associated with poor clinical outcome. Nowdays, a number of molecular markers with prognostic and/or predictive impact exist and

their assessment is strongly recommended in all patients prior to treatment initiation.

Material and Methods: During the one-year period (March 2023. - March 2024.) and using NGS technology, 189 patients diagnosed with CII and before the first therapy, were analyzed. The Sophia Genetic panel for CLL, which includes 23 genes and allows identification of the single nucleotide variations (SNVs), Insertions and deletions (InDels) and copy number variations (CNVs), was used. NGS data were compared with fluorescence in situ hybridization (FISH) and cytogenetic results.

Results: Our group includes 189 patients, 47 women and 142 men. The results of NGS analysis showed the presence of variants in 95% of patients, of which 24% had one and 76% had two or more variants. Changes in the number of gene copies were detected in 66% of patients.

TP53 gene mutation was detected in 23.3% of patients, of which 58.6% had the presence of a mutation without previously detected deletion of 17p by the FISH method. When comparing the findings of NGS and FISH methods, a high concordance between single gene mutations and chromosomal aberrations was found. Moreover, Also, markers of poor prognosis (NOTCH1, NFKBIE, SF3B1, POT1, XPO1, BIRC3, EGR2, BTK and PLCG2) were detected with high frequency.

Conclusion: Each patient with CLL may have several clinical and molecular markers of prognostic significance simultaneously, making the precise prognostication challenging.

Today is of the greatest importance to apply ultrasensitive techniques to deterime molecular profile of the CII patients before the first therapy, to reveal relapse after therapy initiation and to detect minimal residual disease after patient achieve complete response.

Keywords: Chronic lymphocytic leukemia, molecular markers, next-generation technology, target therapy

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Adrenal gland pathology: revision of nomenclature and genetic basis

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Objective: The objective of this study is to provide a comprehensive overview of the latest WHO classifications pertaining to tumors originating from the adrenal medulla, extra-adrenal paraganglia, and adrenal cortical proliferations.

Introduction: The World Health Organization (WHO) has recently introduced updated classifications (2022) for various endocrine neoplasms, reflecting significant advancements in understanding and diagnosing these conditions. In this paper, we aim to elucidate the embryonic origins, genetic predispositions, histological characteristics, and diagnostic markers associated with these tumor classifications.

Material and Methods: We conducted a thorough review of the literature to compile information regarding the classifications of tumors of the adrenal medulla, extra-adrenal paraganglia, and adrenal cortical proliferations as outlined by the WHO. This included an analysis of embryonic derivation, genetic predispositions, histological features, and diagnostic biomarkers associated with these tumors.

Results: Our review revealed that paragangliomas, comprising sympathetic and parasympathetic variants, represent a distinct subset of neuroendocrine neoplasms characterized by catecholamine secretion and genetic susceptibility. Diagnostic methodologies outlined in the WHO classification include specific biomarkers such as GATA3 and enzymes involved in catecholamine synthesis. Additionally, the classification of adrenal cortical proliferations encompasses a spectrum of pathologies, with refined classifications of nodular diseases and subtyping of carcinomas based on morphological attributes. Diagnostic algorithms and biomarkers such as SF1 and paranuclear IGF2 expression aid in precise diagnosis and prognosis assessment.

Conclusion: The updated WHO classifications provide valuable insights into the diagnosis and management of tumors originating from the adrenal medulla, extra-adrenal paraganglia, and adrenal cortical proliferations. This classification facilitates a more precise approach to diagnosis and prognosis assessment. This synthesis serves as a practical

resource for multidisciplinary endocrine oncology teams, offering the latest methodologies consistent with the 2022 WHO classifications.

Keywords: Paraganglioma, Pheochromocytoma, Adrenal cortical adenoma , Adrenal cortical carcinoma, Adrenal cortical hyperplasia

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Diseases of the parathyroid glands /WHO 2022/ - understanding of the basic pathogenetic mechanism

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Objective: The 2022 updates to parathyroid disease classification reflect new insights into their genetics and pathology, aiding specialists in improving diagnosis, treatment, and research, thus enhancing patient care and understanding of these conditions.

Introduction: The World Health Organization's (WHO) latest classification acknowledges the genetic and molecular heterogeneity of parathyroid lesions, offering a more nuanced approach to their categorization.

Material and Methods: The updates distinguish between various types of parathyroid adenomas, hyperplasias, and carcinomas, emphasizing the importance of genetic profiling in the differentiation of these conditions.

Results: Parathyroid adenomas, the most common cause of primary hyperparathyroidism, are now classified based on their genetic mutations, such as those involving the MEN1, CDC73, and CASR genes. This genetic lens aids in understanding their behavior, recurrence risk, and familial patterns. Hyperplasia of the parathyroid glands, often linked to secondary or tertiary hyperparathyroidism, has been redefined with a focus on the underlying pathophysiological mechanisms, such as those related to chronic kidney disease. Parathyroid carcinoma, a rare but aggressive form, is now better defined, with criteria that distinguish it from atypical adenomas and hyperplasias. The pattern of growth/invasion and molecular markers, such as parafibromin, Ki-67, galectin-3, PGP9.5, and Rb protein, are crucial to differentiate benign from malignant parathyroid tumors.

Conclusion: These updates facilitate a more precise and personalized approach to diagnosing and treating parathyroid diseases, underscoring the shift towards molecular and genetic factors in medical taxonomy. This new classification is a testament to the evolving understanding of parathyroid pathology, promising improved patient outcomes through tailored therapeutic strategies.

Keywords: WHO 2022, parathyroid glands, adenoma, carcinoma, hyperplasia

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Do not throw away the placenta - the importance of its histopathological analysis

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Objective: "Placenta pathology provides an autopsy of the pregnancy." The true nature of this statement is obvious knowing that the placenta is a part of the foeto-placental unit during intrauterine development and that in most pregnancies with adverse outcome there is some form/degree of abnormal function and/or histomorphology of the placental tissue. Earlier studies have shown that the quality of placenta investigation and the clinical usefulness of the final report – as prerequisites of our understanding what went wrong during that particular pregnancy - are hugely variable, especially when the report is not produced by qualified experts (perinatal or paediatric pathologists). This presentation intends: 1) to analyse the number of factors (i.e., clinical, pathological and other) which have impact on the quality of the final placenta report (which is a teamwork!) and, 2) how to create an efficient pathway of placenta investigation in practice. Our recent, better understanding of the pathophysiology of placenta and function, and the identification of numerous 'patterns' of histological changes in the placental tissue often associated with some of the well-defined obstetric syndromes (like premature deliver, intrauterine growth restriction, preeclampsia, maternal diabetes, stillbirth) improved both our diagnostic skills and

the ability to put those findings into a clinical context, and to create a meaningful clinico-pathological correlation. With this end product the pathologist offers the users better understanding of the reason and mechanism by which certain pregnancies had problems or adverse outcome.

Case report: Factors contributing to the quality of the pathological investigation of placenta can be divided into two rough categories. One is the clinicians' ability: i) to select appropriate placentas for investigation (defined by maternal. foetal and placental criteria), ii) to supply relevant clinical information to the pathologist; iii) to send selected placentas to appropriate experts, in a timely manner. The other group of factors relate to the pathologists' activity and consists of their: i) full awareness of 'normal' histology in developing placenta during pregnancy; ii) insight into the basics of related clinical disciplines (i.e., obstetrics, perinatology, etc.,) iii) knowledge about both naked eye & microscopic changes in placenta; iv) awareness of the interaction, correlation and clinical significance of these lesions; v) ability to use the most recent, standardised nomenclature/terminology; vi) to produce a comprehensive report with description relevant lesions, diagnoses and putting those findings into a clinical context, creating a meaningful clinico-pathological correlation, securing high level of clinical usefulness of the report, which is the ultimate purpose of the placental investigation.

Conclusion: Attention will also be given to microscopic diagnostic features of selected placental lesions/entities of particular clinical significance, including: Ascending Infections (Maternal & Foetal Inflammatory Responses), Villitis of Unknown Etiology/VUE, Histiocytic Intervillositis, Maternal Floor Infarct/Massive Perivillous Fibrin Deposition/MPFD, Villous Maturation Disorders (both Accelerated & Delayed), Maternal & Foetal Vascular Malperfusions/MVM &FVM, etc.,

Suggestions will also be given for a design of an efficient pathway for high quality pathological investigation of placenta and clinical usefulness, with short turnaround time, supporting the users needs.

Keywords: Placenta investigation, perinatal pathology, clinico-pathological correlation

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Cytological analysis of follicular thyroid lesions - old and new bethesda classification

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Introduction: Fine needle aspiration (FNA) of thyroid nodules and cytomorphologic examination of obtained material is the essential tool in evaluation non-neoplastic and neoplastic proliferations and considered as fast, reliable and minimally risky procedure in the diagnosis and treatment of thyroid gland lesions.

The first two editions of the Bethesda system for the interpretation of cytopathological findings of changes in the thyroid gland (The Bethesda System for Reporting Thyroid Cytopathology -TBSRTC) , published in 2010 and 2017, has allowed cytopathologist to use standardized, category based reporting system for thyroid fine needle aspirations based on cytomorphological findings, provided a a guide for clinicians to treat patients and presented the risk of malignancy (ROM) for each category based on clinical follow-up and pathological findings of surgical materials that were published in papers.

The third edition of the Bethesda system, published in 2023, standardizes the new, clearly explained names for six diagnostic categories: (I) nondiagnostic; (II) benign; (III) atypia of undetermined significance, nuclear/architectural atypia; (IV) follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant. In relation to the previous edition, they were eliminated alternative designation in three categories: "unsatisfactory specimen" (belonged to Bethesda I), "follicular lesion of undetermined significance - FLUS (belonged to Bethesda III) and "suspicious of follicular neoplasm" (belonged to Bethesda IV). For each of the six diagnostic categories, the "risk of malignancy" (ROM) was revised based on data from published studies, which was derived from the surgical pathology follow-up reported after the second edition TBSRTC. The new edition presents ranges for the ROM for each diagnostic category with and without non-invasive follicular thyroid neoplasm with papillary-like nuclear fea-

tures (NIFTP), as the low-risk neoplasm is a surgical diagnosis and cannot be diagnosed based on cytomorphology. Using new TBSRTC terminology and recommendation that all thyroid FNAC reports begin with the name of a diagnostic category followed by the category number, cytopathologists can effectively, concisely, unambiguously guide clinicians in the management of a patient (clinical follow-up, repeat FNA, molecular testing, surgery).

Nomenclature has been updated to align with the 2022 World health Organization Classification Of Thyroid Neoplasms. Regarding the previous term "follicular neoplasm, Hurthle cell type" recommends "follicular neoplasm-oncocytic follicular neoplasm". The term "papillary thyroid carcinoma variants is now changed to "papillary thyroid carcinoma, subtypes". The previously recognized "cribriform morular variant of papillary thyroid carcinoma" is now designated as a separate tumor entity. The older nomenclature of "poorly differentiated thyroid carcinoma" has been replaced with new term "high-grade follicular-derived thyroid carcinoma".

The latest TBSRTC introducing new separate chapters addressing clinical perspectives related to radiologic findings and molecular diagnosis, and reporting of thyroid FNA in pediatric population with estimates for ROM and recommendation for clinical management.

Conclusions: This classification, like the previous two, by introducing standardized reporting formats for thyroid FNAC specimens and ROM monitoring will allow comparisons in practice between different institutions and create the basis for a multitude of research publications focused on thyroid nodules and contribute to consider another review of the TBSRTC.

Keywords: Fine needle aspiration cytology; Thyroid gland; Bethesda system; WHO classification

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A rare mesenchymal tumor of the lung

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A solitary fibrous tumour (SFT) is a rare, slow-growing, mesenchymal neoplasms initially described in the pleura but have since been discovered in nearly every anatomic location. Klemperer and Rabin reported 5 cases of primary pleural neoplasms in 1931 and proposed that SFT was of submesothelial origin. However, in the subsequent decades, on the basis of immunohistochemical analyses and ultrastructural features, it is now recognized that SFTs arise from primitive fibroblast-like cells in connective tissue. The development of intrapulmonary SFT may be attributed to the direct continuity between the subpleural mesenchyme and interlobular septa or the presence of lung fibroblasts in the submesothelial areas of normal pulmonary parenchyma. SFTs most often occur in the pleura, but over the past 90 years, these tumors have been identified in numerous extrapleural locations. SFTs are extremely rare in the lung. To date, about 50 cases of intrapulmonary SFT have been reported in the English language literature.

Intrapulmonary SFTs are usually found incidentally and may be associated with chest pain and cough. Sometimes, patients with SFTs present with refractory hypoglycaemia, which is a paraneoplastic syndrome that secretes a prohormone form of insulin-like growth factor-II (IGF-II). Due to their atypical clinical and radiographic appearance as a common lung tumour, the diagnosis of intrapulmonary SFTs presents unique challenges. Imaging examinations, including chest X-rays, CT and MRI showed that intrapulmonary SFTs are well-defined ovoid or round pulmonary nodules.

Histologically, spindle-shaped cells, patternless and hemangiopericytic growth with variably fibrosis and collagenous deposits are characteristic, but SFTs can show many

faces, including round cells, giant-cells, myxoid areas, pleomorphic pattern, fat-forming tumors and dedifferentiated forms. Aberrant epithelial, muscular or neuroendocrine marker expression has been described which may lead to confusion with other tumors that share a similar morphology. For that reason, the diagnosis of SFTs may not be confirmed without immunohistochemical staining. The most valuable immunohistochemical marker in the diagnosis of SFTs is STAT6. However, STAT6 expression has also been reported in dedifferentiated liposarcoma and GLI1-amplified tumors, hence, in cases with overlapping morphology and STAT6 immunoreactivity, additional molecular studies are needed to establish a definitive diagnosis. On a molecular level, SFTs have been shown to be pathogenetically linked to a gene fusion secondary to a paracentric inversion on chromosome 12q13 and involves NAB2 and STAT6, which are highly sensitive and specific markers for SFT.

According to the WHO classification, the prediction of metastatic risk in SFTs are follows: (1) patient age in years (≥ 55); (2) mitoses per 10 high-power fields; (3) tumor size in cm, and (4) tumor necrosis. Although multiple factors, such as age and tumor size, have been associated with survival, higher histologic grade has been considered to have the strongest correlation with prognosis.

Complete resection with free margins is considered the treatment for intrapulmonary SFT. Adequate wedge resection, anatomic segmentectomy, and lobectomy, depending on the location of the mass, are the common procedures for surgical resection of intrapulmonary tumors. Careful follow-up of the postoperative course is important, even in cases hisologically diagnosed as low metastatic risk.

Keywords: intrapulmonary solitary fibrous tumor; STAT6; risk stratification systems

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Diagnostics of differentiated high-grade thyroid carcinoma

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Background & Objective: In the 5th edition of the World Health Organization (WHO), the histologic classification of thyroid tumors originating from follicular cells divides them into benign, low-risk, and malignant neoplasms (1,2). Several changes were introduced regarding terminological issues that reflect the molecular basis of lesions. For example, the term "follicular nodular disease" is introduced to account for multifocal hyperplastic/neoplastic lesions, and morphologically different papillary thyroid carcinomas (PTC) were designed as „subtypes" irrespective of tumor size instead of „variants". The term variant is reserved to describe lesions with distinctive genetic alterations such as invasive encapsulated follicular variant PTC. These changes do not reflect modifications in the diagnostic criteria, and they are not expected to have clinical significance (1-3). The main changes introduced by the latest WHO edition are related to the introduction of a grading scheme for the characterization of differentiated carcinomas. Accordingly, the presence of tumor necrosis and high mitotic count in the PTCs, follicular thyroid carcinomas and oncocytic carcinomas defined them as differentiated high-grade thyroid carcinomas (DHGTC). DHGTC together with poorly differentiated thyroid carcinoma (PDTC) determined according to Turine consensus, comprises a group of follicular-derived carcinomas with high-grade features, aggressive biological behavior and intermediated risk between well-differentiated

thyroid carcinomas and anaplastic carcinoma (1-4). The work aims to present the main clinicopathological characteristics of DHGTC with a literary review, as well as to present a diagnostics approach and results from our Institute.

General Features: DHGTCs account for less than 5% of primary thyroid malignancies, reported together with PDTC in the range between <1% to 6%. They occur in older age, usually over age 50 with a slight female predominance. Tumors are often larger than 4 cm and develop as rapidly growing masses with widely invasive growth, angioinvasion, gross extrathyroid extension and early development of lymph node metastases (2,4). Five-year disease-specific survival and 5-year overall survival, of DHGTC are similar to PDTC and are approximately 66% and 60%, respectively (2,4-6). The treatment includes a total thyroidectomy with central and possible lateral neck dissection and additional radioactive iodine therapy (4).

Pathology: Grossly, DHGTCs disclose invasive borders, or rarely tumors are circumscribed, partially or completely encapsulated. On cross-sections, tumors are often firm, solid, and white-tan or pink-tan. Necrosis and hemorrhage could be seen. To confirm the invasiveness of circumscribed and/or encapsulated tumors, extensive or total tumor capsule sampling should be done. For grossly invasive lesions at least one section per 1 cm of tumor tissue is required. Necrosis, hemorrhage, or areas of unusual appearance must be processed. For accurate diagnosis in microscopically insufficient cases, additional sections may be required. Staging of disease sometimes warrants correlation with clinical/surgical findings (2,4).

Histologically, the diagnostic criteria of PDTC have not been modified. According to the Turin criteria, adopted also by the last two WHO classifications, PDTC has a solid, trabecular and/or insular growth pattern, absence of the conventional nuclear features of PTC, and at least one of the following characteristics: convoluted nuclei, ≥3 mitosis per 10 high-power fields/~2 mm2, and tumor necrosis (1, 7). In cases when the morphological dedifferentiation is absent and tumors retain an architectural and/or cytological pattern of PTC, follicular or oncocytic carcinoma with the presence of necrosis and/or ≥5 mitoses per 2 mm2, the tumor should be diagnosed as DHGTC (1-4). Tumor necrosis is coagulative or comedotype and contains identifiable nuclear debris. Individual cell necrosis scattered throughout the tumor is a feature of PDTC/ DHGTC (2,4). Pathologic high-grade features may also be identified in subcentimeter tumors as well as in non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). In addition, poorly differentiated areas can be present as a minor component of DHGTC. In all these instances, the proportion of these components needs to be reported. In the pathological report, all the tumor components and their pathological characteristics should be described (2,3). Progression of well-differentiated tumors to poorly differentiated/high-grade morphology may be found in local or distant metastasis. Both DHGTC and PDTC should not have more than moderate nuclear pleomorphism, a useful feature for distinguishing them from anaplastic thyroid carcinoma. In the differential diagnosis, DHGTC needs to be separated from PDTC, well-differentiated carcinomas of follicular cell-derivation, most commonly solid subtype of PTC or carcinomas with necrosis induced by fine needle aspiration biopsy. Differentiation from medullary thyroid carcinomas with mitotic activity and tumor necrosis could be the most difficult and additional immunostaining must be done (2-4,8). DHGTC are positive for TTF1, PAX8, cytokeratin 7, and thyroglobulin. Thyroglobulin tends to be weak and focal with a dot-like appearance. Neuroendocrine markers and calcitonin are negative. The Ki67 proliferation index is elevated, usually in the range of 10 to 30% (2,4). Regarding molecular basis, the vast majority of DHGTC are enriched with V600EBRAF mutations, most display the cytoarchitectural features of PTC and have a propensity for cervical lymph node metastases. In contrast, PDTC have a higher prevalence of RAS mutations and are more prone to spread distantly. Additionally, DHGTC and PDTC commonly carry secondary mutations related to their aggressiveness, most frequently mutation of the TERT promoter or mutation of PIK3CA and TP53 (2-4,8).

Conclusion: The 5th WHO edition defined DHGTC, as a new entity that includes any differentiated thyroid carcinoma showing ≥5 mitoses per 2mm2 and/or tumor necrosis. New classification required more accurate histological characterization of differentiated carcinoma, specifically regarding the presence of mitosis and microscopic foci of necrosis. This approach shows a need for more extensive tissue sampling. The true incidence and clinical impact of DHGTC are yet to be established.

Keywords: WHO classification, Thyroid cancer, High-grade differentiated, Nomenclature

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What is new in the "Blue Book" of Urinary and Male Genital Tumors

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The classifications of benign pathological conditions and tumors represent a unique language that facilitates communication, both among pathologists and with clinicians. The fifth, revised classification of tumors of the urogenital system of the World Health Organization was issued in 2022. The current classification has many more chapters, since next are separated as new: tumors of the seminal vesicles, testicular adnexa, neuroendocrine neoplasms, metastatic, hematological, soft tissue tumors, melanocytic lesions and genetic tumor syndromes. Introductory chapters have been added: topographical and morphological coding of tumors, as well as TNM staging of tumors, which in the previous edition were at the beginning of each organ chapter. Nomenclature changes are noticeable: instead of „variant", the name "subtypes" is used, and the tumor names have been renamed to the following: "clear cell renal cell carcinoma" to "clear cell renal cell tumor", "TCEB1-mutated renal cell carcinoma (RCC)" to "ELOC"-mutated RCC", hereditary leiomyomatosis and renal cell carcinoma" in "fumarate hydratase-deficient RCC", "RCC Unclassified" in "RCC-Not Other Specified". In the group of kidney tumors, the division into type 1 and 2 papillary RCC was eliminated, the entity oncocytoma/chromophobe RCC-like features was also added, and "Eosinophilic solid and cystic RCC" was highlighted as a separate entity. It is recommended that the WHO/ISUP grade be applied to all RCCs. The current classification emphasizes the important connection of molecular tests in the framework of the pathological diagnosis of kidney tumors, and the chapter "Molecularly defined renal carcinomas" is highlighted. In the group of urothelial tumors, each tumor type is presented chronologically from benign to malignant development. The possible application of a classification based on the molecular characteristics of tumors in the near future is suggested. Grading for non-invasive urothelial carcinoma is high grade if the high-grade component is present in ≥5%, the application of The Paris System for cytological diagnosis of urine is also recommended, and special attention is also paid to inverted tumors. In the chapter on prostate cancer, the nomenclature has been changed from "basal cell carcinoma of the prostate" to "adenoid-cystic (basal-cell) carcinoma of the prostate" and the need to note intraductal carcinoma of the prostate IDC-P is emphasized, and it is emphasized that Prostatic intraepithelial neoplasia (PIN)-like carcinoma is not the same as ductal carcinoma. Special attention is paid to the grading of acinar adenocarcinoma and the prognostic significance of cribriform cancer growth. In the group of testicular tumors, new entities stand out: Signet ring stromal tumor and Myoid gonadal stromal tumor, with a change in the nomenclature "Well-differentiated neuroendocrine tumor (monodermal teratoma)" to "Testicular neuroendocrine tumor, prepubertal type", as well as "carcinoid" to "neuroendocrine tumor". The criteria for the diagnosis of "Teratoma with somatic transformation" have been changed, while in the group of sex-cord stromal tumors, mitoses are counted per mm2, instead of the high-power field. For Well-differentiated papillary mesothelial tumor, it was pointed out that the prognosis is good. In the penile tumor group, the nomenclature was changed from "subtypes" to "patterns". When a second component is observed in addition to the Usual type of invasive squamous cell carcinoma, the tumor is marked as mixed, while the term hybrid is omitted, with a note that it is useful to state the % of individual components. For the first time, a separate classification of scrotal tumors is present-

ed. Each classification highlights new entities that enable more precise pathohistological diagnosis and, in the spirit of modern medicine, along with molecular tests, they often represent a prerequisite for personalized therapy, which is a step forward in the fight against disease.

Keywords: WHO tumor classification; kidney; urinary bladder; prostate; testicle; penis; molecular analyses;

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Renal carcinoma with unusual morphological characteristics

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Renal cell carcinoma (RCC) is the most common kidney tumor, which despite the development of new diagnostic procedures and new therapeutic modalities is still the most lethal urologic malignancy. RCC subtypes show different genetic abnormalities, phenotypic characteristics, different biological behavior, which has significant implications on prognosis and therapeutic approach. The main morphologic feature of the RCC may be the presence of clear cytoplasm, papillary architecture or eosinophilic cytoplasm, which may be helpful in routine practice during diagnostics RCC with unusual morphologic features. RCC with clear cytoplasm include clear cell RCC (ccRCC) which may have a poor prognosis, while multilocular cystic renal neoplasm of low malignant potential and clear cell papillary RCC are tumors with indolent clinical course. Translocational RCC may exhibit different molecular changes compared to ccRCC and therefore sometimes do not respond to conventional targeted therapy used in ccRCC. Papillary architecture in RCC is not only a characteristic of papillary RCC (pRCC), but this growth pattern is present in different entities with different morphology, molecular alterations and clinical outcome. Mucinous tubular and spindle cell carcinoma is a rare subtype of RCC, which can show significant morphologic and immunophenotypic overlap with type 1 pRCC, with a typically indolent clinical course. On the other hand, hereditary leiomyomatosis and RCC (HLRCC) has morphological and immunophenotypic overlap with pRCC type 2. Also RCC arising in kidneys with acquired cystic disease and end stage renal disease can show papillary architecture with eosinophilic/clear cells, and it has an indolent course. Collecting duct carcinoma is aggressive tumor, which in some cases shows papillary and micropapillary growth. Although RCC with eosinophilic cytoplasm is a characteristic of chromophobe RCC, it can also be seen in succinate dehydrogenase deficient RCC, tubulocystic RCC, thyroid-like follicular carcinoma of the kidney, and RCC associated with neuroblastoma. Several subtypes of RCC can show morphological overlaps and the key in the diagnostic procedure is the recognition of the conventional component in the tumor, the application of immunohistochemical staining and, if necessary, the analysis of the entire tumor tissue and/or clinicopathological correlation.

Keywords: Morphology, Renal carcinoma, Prognosis, Subtypes

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Morphological parameters of aggressiveness in prostate cancer

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Prostate cancer, the most common cancer in Western men, is an illness with a diverse clinlcal presentation, histopathological tumor growth patterns and survival. Recent statistics for 2023. year estimates prostate cancer as number one for new cases and second for mortality in USA. Most tumors do not cause significant clinical symptoms, but there is a certain number of patients where prostate cancer takes an aggressive course. So, individual assessment of a tumor's aggressiveness is critical for clinical decision-making in therapy of prostate cancer. In every day practice, age, elevated serum PSA levels, suspicious digital rectal examination or trans-rectal ultrasonography are reasons enough for performing a needle biopsy of a prostate. Precise histopathological report must include Gleason score, presence of Gleason grade 4 and 5, perineural invasion, specific variants of prostate cancer (intraductal carcinoma, ductal adenocarcinoma, signet cell-like carcinoma, pleomorphic giant cell carcinoma, sarcomatoid carcinoma) and tumor volume both on needle biopsy and radical prostatectomy. By reporting needle biopsy and radical prostatectomy specimen in this way we help clinicians to choose the best therapeutic approach for each patient.This lecture serves as a comprehensive review and reiteration of morphological indicators pertaining to the aggressiveness of prostate cancer, alongside an elucidation of actual protocol advancements. Implementation of novel histopathological markers is required for individual assement of a tumor's aggressive potential and by that helping to reduce prostate cancer specific mortality and avoiding overtreatment.

Keywords: Gleason grade system, Morphology, Prostate cancer, Perinural invasion

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Kidney tumors with granular-oncocytic cytoplasm

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Kidney tumors with granular-oncocytic, eosinophilic cytoplasmic cells include a wide range of kidney lesions with different and very specific morphological, immunohistochemical and molecular genetic characteristics.. Regardless of all the above, they can have morphological overlaps and represent a real diagnostic challenge in the daily work of pathologists, regardless of whether whether it is a pathohistological analysis of material after partial and total nephrectomy or/ and a kidney tumor biopsy. In its latest classification of tumors of the kidney and male genital organs from 2022, the WHO even singles out a special subgroup of epithelial renal tumors, the so-called oncocytic and chromophobe renal tumors, which includes already well-known neoplasms, such as renal oncocytoma, chromophobe kidney carcinoma and tumors associated with "Birt-Hogg-Dube" syndrome (hybrid oncocytic tumors/HOT), but also completely new entities, such as "eosinophilic vacuolated tumor (EVT)" and "low-grade oncocytic tumor" (LOT). Of course, depending on the histological picture of the kidney tumor, one should think about other neoplasms of granulated-oncocytic cytoplasm, which are not part of this subgroup of renal epithelial tumors: "oncocytic papillary renal neoplasm with reverse polarity, succinate dehydrogenase deficient renal cell carcinoma, translocation-associated renal cell carcinoma, eosinophilic solid and cystic renal cell carcinoma, high grade clear cell renal cell carcinoma, acquired cystic disease-associated renal cell carcinoma, epithelioid angiomyolipoma (E-AML)/ epithelioid PEComa of the kidney (E-PEComa)" etc. Precise pathohistological typing of these tumors is necessary considering the differences in biological behavior from benign to malignant with indolent but also very aggressive.

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Role of oncogene-induced cellular senescence in malignant transformation and progression of breast tumors

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Despite the importance of certain prognostic factors, their accuracy in assessing outcomes and determining treatment strategies for breast cancer patients is limited. Therefore, the definition of new molecular biomarkers could provide a more reliable approach for prediction of the prognosis of this disease.

The aim of this study was to examine the expression of markers p16, p53, p21, pRb and GLB1 in benign and malignant breast changes, as well as their participation in malignant transformation.

The research included the analysis of tissue material of benign and malignant changes in patients operated at the University Clinical Center Kragujevac. All macro and micromorphological prognostic factors (histological type and grade of tumor, size, nodal status, desmoplasia, necrosis, mononuclear reaction, etc.) were defined on H&E stained preparations. Immunohistochemically, using antibodies (p16, p53, p21, pRb, GLB1) tissue expression of markers were determined by a semiquantitative reading of a positive reaction. By defining cut-off values, cancers were classified into positive and negative groups for each analyzed marker. The expression of all markers increased with the progression of cytological changes in the epithelium. Their ex-

pression positively correlated with various changes in the breast, with the proliferative index and HER2+ tumors. The expression of p16, pRb, p21, GLB1 is the highest in HER2+ breast cancers, while the expression of p53 is the highest in TNBC. A significant correlation was found between the expression of p16 and p53, p21 and pRb, p21 and GLB1, as well as between pRb and GLB1 in invasive cancer.
The analyzed markers play an important role in proliferation, malignant transformation, as well as in the progression of breast cancer, which recommends them for further research and possible use for diagnostic, prognostic and predictive purposes.

Keywords: breast cancer; cellular senescence; cyclin-dependent kinase inhibitor p16; tumor suppressor protein p53; cyclin-dependent kinase inhibitor p21; retinoblastoma protein.

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Depression and anxiety association with neurokinin receptor expression in women with breast cancer

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Breast cancer (BC) remains a pressing global problem, both in terms of incidence and mortality. In recent years, efforts have been made to define new molecular and signaling pathways involved in the pathogenesis of BC, in order to obtain a more complete and clearer picture in terms of predicting the prognosis and the effectiveness of the applied therapy.The aim of this research is to examine the relationship between anxiety and depression with the expression of neurokinin receptors (NKR) in breast cancer, as well as their possible relationship with clinical, pathohistological, and immunophenotypic characteristics of the tumor.
The research involved filling out questionnaires for self-assessment of depression/anxiety of the affected women, as well as a complete pathohistological analysis of the patient's tissue material. All significant morphological parameters of BC were defined on the standard stained preparations. Immunohistochemically, tissue expression of relevant markers was determined using antibodies (NKR, VEGF, CD105, Ki67, and caspase-3). Two groups of women were defined, with and without a present depressive/anxiety disorder, as well as existing differences in terms of clinical and histopathological characteristics.
Among the examined women, a significant number of those with a certain degree of depression/anxiety were found. The expression of NKR was positively correlated with a significant degree of depression and with the expression of significant predictors of cancer behavior such as the proliferative index marker Ki67, tumor angiogenesis markers VEGF and CD105, as well as the apoptosis marker caspase-3.
It has been unequivocally shown that the comorbidity of BC and depression is significant from a clinical point of view, that there are interwoven molecular mechanisms, the more detailed understanding of which would help in the field of discovering new therapeutic procedures that would act in a targeted manner in preventing tumor growth and invasion.

Keywords: breast cancer; depression; anxiety; carcinogenesis; angiogenesis; metastasis; neurokinin receptor NKR.

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Molecular markers of prostate cancer aggressiveness

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Prostate adenocarcinoma is the most common malignancy of the prostate gland that originates from prostatic secretory epithelium. The pathological diagnosis of prostatic adenocarcinoma is primarily based on histological features. The fifth WHO edition classifies prostatic glandular neoplasms as prostatic cystadenoma, high-grade prostatic intraepithelial neoplasia, intraductal carcinoma of the prostate, acinar adenocarcinoma, ductal adenocarcinoma and treatment-related neuroendocrine prostatic carcinoma. Subtypes of prostate adenocarcinoma are acinar, ductal, atrophic, pseudohyperplastic, microcystic, foamy gland, mucinous, signet ring subtype, pleomorphic giant cell ad-

enocarcinoma and sarcomatoid adenocarcinoma. More important for assessing tumor aggressiveness is morphological pattern presented through Gleason score. Regardless the subtype and Gleason pattern, the vast majority of prostatic adenocarcinomas express prostate specific antigen (PSA). It should be emphasized that up to 15% cancers with high grade features are completely negative for PSA by immunohistochemistry (IHC).

Tissue-based molecular biomarkers for prostate cancer diagnosis include PTEN IHC for intraductal carcinoma of the prostate, PIN-4 cocktail and ERG IHC for atypical small acinar proliferation (ASAP), RB1 and cyclin D1 IHC for neuroendocrine prostate cancer. Tissue-based diagnostic biomarker (Confirm MDx) is a DNA methylation assay that is prostate tissue biopsy based, and evaluates the methylation status of several genes known to be frequently found in prostate cancer. These markers have been demonstrated to have a "field effect", meaning that the test should be performed for management of men with elevated PSA and a cancer-negative prostate biopsy. It is included in the European Association of Urology (EAU) and NCCN 2020 guidelines for repeat biopsy decision making, for PIRADS 4 and 5 lesions on MRI (1). Molecular biomarkers for aggressive prostate cancer–targeted therapy include AR-V7 transcripts (androgen receptor signaling), somatic mutations, PTEN alterations, and gene fusions (recurrent molecular alterations), DNA repair mutations (PARP1 inhibition), and PDL1 IHC (immunotherapy). Loss of PTEN function can be detected via FISH or IHC and is associated with Gleason score upgrading, locally advanced disease, decreased recurrence-free survival and poor clinical outcome (2). The latest data reveals that germline or somatic alterations in DNA repair genes are present in as many as 20% of aggressive primary and metastatic prostatic carcinomas. BRCA1/2 mutations increase risk by 5-fold, BRCA1/2 associated cancers occur at a lower age, have worse survival outcomes, and are likely to respond to PARP1 inhibition, whereas patients with DNA mismatch repair-deficient cancers are offered immune checkpoint inhibitors. The presence of intraductal carcinoma and/or cribriform architecture (Gleason pattern 4) has been shown by some to be associated with a higher incidence of inherited germline alterations in DNA repair genes. There is a recommendation to do germline genetic testing in all patients with Gleason pattern 4 (3). It remains to be seen whether such an expensive approach will enter clinical practice.

Molecular regulator proteins of cell cycle, such as p53, Bcl-2, Ki-67, EZH2, CXCL12/CXCR4, allow the assessment of tumor growth, local invasion, distant metastases, and provide additional knowledge of aggressivity compared to standard markers. HIF-1 overexpression correlates with tumor aggressiveness and chemoresistance. HIF-targeting agents in combination with androgen receptor targeting, synergistically inhibits castration-resistant prostate cancer cells (4). Hypoxia, via HIF signaling can activate angiogenesis, enhance invasiveness and metastatic potential, and induce cancer stem cells (CSC) features. Recent studies have indicated that CSC have a key role in cancer development and progression by stimulating proliferation of metastatic clones resistant to apoptosis. Already established, prostate CSC (CD117, CD133, CD44, NF-kB) play key role in tumor initiation and development, disease progression, recurrence and metastasis, can modify the effect of chemotherapy and are important markers in assessment of prostate cancer aggressivity (5). Hypoxia leads to membranous NOTCH3 expression, which in turn, sustains proliferation of cancer cells. NOTCH3 pathway represents a promising target for adjuvant therapy in patients with radio/chemo resistant prostate cancer (6).

Everything summarized in this short review is recently discovered and leads to molecular approach in prostate cancer treatment.

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Prenatally diagnosed congenital malformations and fetal autopsy – a series of case reports

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Objectiv: To emphasize the importance of adhering to the fetal autopsy protocol in the evaluation of prenatally diagnosed congenital malformations through the presentation of several autopsy analyses.
Introduction: In modern fetal and perinatal pathology, it is essential to adhere to the modern protocol of autopsy analysis of the fetal phenotype and to use molecular diagnostic analyses as often as possible in accordance with the capacities of the health care system in developing countries.
Methods: Presentation of several fetal autopsy analyses in cases of prenatally suspected congenital malformations.
Results: Three fetal autopsies that followed prenatally diagnosed suspected congenital malformations are presented: Pierre-Robin sequence, Otopalatodigital syndrome type I, Megacystis microcolon intestinal hypoperistalsis syndrome.
Conclusion: Even in the circumstances of limited financial possibilities of the health care system and limited opportunities for education in specific areas of medicine, it is possible to perform analyses based on principles close to the requirements of modern medicine. Adherence to the fetal autopsy protocol with the special importance of photo-documentation and the increasingly frequent use of modern genomic analysis is of great importance in family planning.

Keywords: fetal autopsy, molecular diagnosis, congenital malformation, prenatal diagnosis

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Fetal growth restriction in stillbirths devoid of structural or genetic abnormalities

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Objective: This study aims to provide practical guidelines for detecting and estimating fetal growth restriction (FGR), as well as identifying its underlying causes, during routine perinatal post-mortem examinations.
Introduction: FGR is a pregnancy complication that represents a substantial cause of stillbirth, neonatal morbidity, and mortality. It is the result of one or more maternal, placental and fetal disorders.
Material and Methods: A retrospective review was conducted on all perinatal autopsies performed at the University Clinical Centre of Serbia, spanning from January 1, 2020, to December 31, 2023. This study analyzed a total of 331 stillbirths and neonates whose deaths occurred after 20 completed weeks of gestation but before the first 7 completed days of life. Assessment of fetal growth restriction (FGR) was limited to singleton pregnancies.
Results: By utilizing birth weight for gestational age below the 10th percentile and a brain to liver weight ratio greater than 4, we identified 68 cases (20.5%) at or beyond 20 weeks of gestation as fetal growth restriction (FGR), while 43 cases (12.9%) at or beyond 24 weeks of gestation were classified as FGR. The cause of FGR remained unclear in 4 out of 68 cases (5.8%).
Conclusion: Fetal and neonatal autopsy provides invaluable insights into the cause of death and underlying disease processes, offering crucial guidance for subsequent pregnancies to physicians. Consequently, pathologists must meticulously investigate the causes of stillbirth and fetal growth restriction, taking into account factors related to the placenta, fetus/neonate, and maternal health.

Keywords: fetal growth restriction, stillbirth,

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Mucoepidermoid carcinoma of the hard palate in a 9-year-old boy: Case report

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Introduction: Tumors of the salivary glands in children are rare, and when they appear, there is a high probability that they are malignant. Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary glands diagnosed in children and young adults, with a peak incidence in the second decade of life. It is made up of solid and cystically arranged mucinous, intermediate (bright cells), and squamoid tumor cells, and the most common localization is on the palate.

Aim: We present the case of a nine-year-old boy diagnosed with primary MEC of the hard palate. We would like to highlight the importance of timely diagnosis of MEC in the pediatric population and the criteria for differentiation from other neoplastic and non-neoplastic changes.

Case report: In the case of a nine-year-old boy, the parents noticed a change in the palate a month before coming to the examination. The examination revealed a change located on the border between the hard and soft palate, shaped like a hemisphere, 2x1.6cm in size. The change was vaguely bounded from the surrounding tissue, fixed, painful on pressure and fluctuating. The mucous membrane above the change was smooth, and partly bluish. The change was surgically removed (excision).

Macroscopically, the change was 1.7x1.4x1.3cm in size. On cross-section, it was partly cystic, with a softer consistency. Cystic spaces were filled with liquid, dark content. Histologically, the change was made up predominantly of cystic, and to a lesser extent, solid areas. Mucinous, intermediate and epidermoid cells were seen in the change. Cystic spaces were lined with mucinous cells and filled with mucus mixed with blood. The cells have a uniform appearance, low mitotic activity (0 - 1/10HPF), no invasion of lymphatic, blood and nerve structures and no necrosis. Between the cystic structures, there are partitions (septa) that make up the stroma. An inflammatory infiltrate, composed of lymphocytes, plasma cells and histiocytes, was focally present in the stroma. Based on the morphological characteristics, the diagnosis of MUC - low grade - was established. The patient tolerated the treatment well and is currently disease-free during the follow-up period (3 months).

Discussion: Malignant epithelial tumors in children are rare and represent a diagnostic challenge. In the differentiation of MUC of low grade of malignancy, non-tumorous cystic lesions of salivary glands, and other benign and malignant tumors of low grade of malignancy come into consideration. Differential diagnosis includes abscess, necrotizing sialometaplasia, mucocele, sclerosing polycystic adenosis, sclerosing sialoadenitis, pleomorphic adenoma with squamous metaplasia, Warthino's tumor, schwannoma, and neurofibroma. Most often, low-grade MUC localized intraorally is clinically understood as a mucocele. Morphologically, it can be misinterpreted as a mucinous retention cyst. MUC is categorized into tumors of low-, intermediate-, and high-grade malignancy based on nuclear polymorphism, necrosis, cell type (mucinous, intermediate, and epidermoid), the grade of mitotic activity, and predominant mode of growth (solid or cystic). Tumors of a low grade of malignancy grow slowly, are generally treated only surgically by excision with negative resection margins, and have a good prognosis.

Conclusion: Low-grade MEC needs to be differentiated from other tumor and non-tumor lesions. Complete surgical resection is the primary treatment for low-grade MEC.

Keywords: Mucoepidermoid carcinoma; Hard palate; Child.