Anatomic pathology selected abstracts

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High-grade appendiceal mucinous neoplasm: clinicopathologic findings

July 2023—High-grade appendiceal mucinous neoplasm is a relatively recent term that describes a rare epithelial neoplasm of the appendix that demonstrates pushing-type invasion but high-grade cytologic atypia. Because it has been understudied, the authors conducted a multi-institutional retrospective study to describe the clinicopathologic features of high-grade appendiceal mucinous neoplasm (HAMN). They reviewed the clinical and histologic features of 35 HAMNs and the molecular features of eight of the cases. Patients were an average of 57 years old and most commonly presented with abdominal or pelvic pain. Histologically, 57 percent of the tumors showed widespread high-grade features. Architectural patterns in high-grade areas included flat, undulating, or villous growth, and, occasionally, micropapillary, cribriform, or multilayered growth. Thirteen cases had intact serosa, and the remaining 22 had perforated serosa, including seven with peritoneal acellular mucin beyond the appendiceal serosa and 10 with grade 2 pseudomyxoma peritonei. Molecular abnormalities included *KRAS* mutations in seven cases and *TP53* mutations in four. No tumor confined to the appendix recurred. Two patients who did not have pseudomyxoma peritonei at initial presentation developed pseudomyxoma on follow-up. Among 11 patients who presented with pseudomyxoma peritonei, five died of disease and three were alive with disease at last follow-up. The authors concluded that HAMNs have a presentation similar to that of low-grade appendiceal mucinous neoplasm, as well as similar stage-based prognoses. Most HAMNs spread to the peritoneum as grade 2 pseudomyxoma peritonei, which may be associated with a worse prognosis than classic grade 1 pseudomyxoma peritonei.

Gonzalez RS, Carr NJ, Liao H, et al. High-grade appendiceal mucinous neoplasm: Clinicopathologic findings in 35 cases. *Arch Pathol Lab Med*. 2022;146(12):1471–1478.

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Assessment of pleomorphic liposarcoma cases with emphasis on morphologic variants

Pleomorphic liposarcoma is a highly aggressive sarcoma comprising variable numbers of pleomorphic lipoblasts mixed with undifferentiated pleomorphic sarcoma-like areas. Morphologic variants, such as myxofibrosarcoma-like or epithelioid, may cause diagnostic difficulties, especially on core biopsy. Yet data on the prognostic significance of these patterns are limited. The authors conducted a study in which 120 pleomorphic liposarcoma biopsies and resection specimens were reviewed and cataloged in 10 percent increments based on the presence of myxofibrosarcoma-like, undifferentiated pleomorphic sarcoma (UPS)-like, and epithelioid foci. The study included 75 males and 45 females ranging in age from eight to 98 years (median, 62.5 years). Cases arose in the extremities (n=72), trunk (n=32), head/neck (n=10), bone (n=4), mediastinum (n=1), or viscera (colon polyp, n=1). Of those pleomorphic liposarcomas with known depth (n=81), 40 were intramuscular, 34 were subcutaneous, and seven arose in the dermis. They ranged from 1 to 24.5 cm (median, 7 cm). Five of the 70 patients with one month or more of follow-up had recurrence and 15 had metastasis. The five-year overall survival and event-free survival rates were 66.2 percent and 63.1 percent, respectively. Patients with tumors of 5 cm or more had inferior overall survival compared with those who had tumors of less than 5 cm. The presence of epithelioid areas was also statistically significant in terms of poorer overall patient survival and event-free survival, and patients who had tumors with 50 percent or more undifferentiated pleomorphic-like areas had better overall survival. A trend towards poorer outcomes in patients who had tumors with necrosis (one percent or more) was

noted. Pleomorphic liposarcoma is an aggressive adipocytic malignancy that is most commonly found in the extremities of older adults. The morphologic features of these tumors are diverse, and they may be mistaken for UPS or myxofibrosarcoma, carcinoma, and melanoma, particularly on biopsies. Tumor size, necrosis, and epithelioid morphology are associated with adverse prognosis.

Gjeorgjievski GS, Thway K, Dermawan JK, et al. Pleomorphic liposarcoma: A series of 120 cases with emphasis on morphologic variants. *Am J Surg Pathol*. 2022;46(12):1700–1705.

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Protein expression and morphologic factors in lung carcinoid tumors

World Health Organization classification of thoracic tumors defines lung carcinoid tumors as well-differentiated neuroendocrine neoplasms that comprise low-grade typical (TC) and intermediate-grade atypical carcinoids (AC). Limited data are available regarding protein expression and morphologic factors for predicting disease aggressiveness. Ki-67 has proven to be a powerful diagnostic and prognostic factor for gastroenteropancreatic neuroendocrine neoplasms (NENs), but its role in lung NENs is still being debated. The authors conducted a study to evaluate the role of the Ki-67 proliferation index and examine its correlation with disease evolution and recently proposed IHC markers for patients with lung carcinoid tumors. A retrospective series of 370 lung carcinoid tumors from two oncology centers was centrally reviewed. Morphology and IHC markers, including Ki-67, TTF-1, CD44, OTP, SSTR-2A, Ascl1, and p53, were studied and correlated with overall survival, cancer-specific survival, and disease-free survival. Carcinoid histology was confirmed in 355 patients: 297 (83.7 percent) TC and 58 (16.3 percent) AC. A Ki-67 of three percent was the best value for predicting disease-free survival. A Ki-67 of three percent or more was significantly associated with AC histology; stage III–IV; smoking; vascular invasion; tumor spread through air spaces OTP negativity; and TTF-1, Ascl1, and p53 positivity. After adjusting for center and period of diagnosis, AC histology and high Ki-67 (three percent or more versus less than three percent) were the strongest predictors of cancer-specific survival, together with age (10-year increase), stage (III–IV versus I–II), and OTP (present versus absent). In terms of disease-free survival, AC histology and high Ki-67 were again the strongest prognostic factors, together with age (10-year increase), lymph node involvement (N1/2/3 versus zero), residual tumor (R1/2 versus R0), and OTP (present versus absent). The authors concluded that Ki-67 of three percent or more plays a potentially pivotal role in lung carcinoid tumor prognosis, irrespective of histological grade.

Centonze G, Maisonneuve P, Simbolo M, et al. Lung carcinoid tumours: histology and Ki-67, the eternal rivalry. *Histopathology*. 2023;82(2):324–339.

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Cytomorphologic and molecular features of intraductal papillary neoplasm of the bile duct

Intraductal papillary neoplasm of the bile duct is a rare premalignant neoplasm that can progress to invasive adenocarcinoma. The authors conducted a retrospective study in which they reviewed cases of intraductal papillary neoplasm of the bile duct (IPNB) to examine cytomorphologic and molecular features. IPNB cytology cases with histopathologic confirmation were retrieved from participating institutions' pathology archives. The authors analyzed such cytomorphologic features as cellularity, architecture, cell type, and cellular details. The study cohort included 13 cases (six brushings, six fine-needle aspirations [FNA], and one combined brushing and FNA). The lesions involved the common bile duct in nine (69 percent) cases and hepatic duct in four (31 percent) cases. Original cytological diagnoses included adenocarcinoma (five, 38 percent), suspicious for adenocarcinoma (one, eight percent), neoplasm (three, 23 percent), atypical (three, 23 percent), and reactive (one, eight percent). The cytomorphologic features included moderate/high cellularity (12, 92 percent); papillary or complex papillary architecture, or both (10, 77 percent); columnar cells (11, 85 percent); vacuolated cytoplasm (12, 92 percent); enlarged nuclei (13, 100 percent); and fine granular chromatin (12, 92 percent). Background mucin, necrosis, and acute inflammation were seen in four (31 percent), four (31 percent), and two (15 percent) cases, respectively.

KRAS mutation testing was performed in nine cases, with mutant *KRAS* found in five (56 percent). The study demonstrated that IPNB cytology specimens were relatively cellular, with a wide spectrum of cytomorphology. However, most cases harbored adenocarcinoma or high-grade dysplasia. The characteristic cytomorphologic features included papillary/complex papillary clusters of columnar cells with vacuolated cytoplasm, enlarged nuclei, and fine granular chromatin in relatively cellular specimens. The *KRAS* mutations identified may have potential diagnostic and therapeutic implications.

Stendahl K, Gilani SM, Basturk O, et al. Intraductal papillary neoplasm of the bile duct: Cytomorphologic and molecular features. *Cancer Cytopathol*. 2023;131:37–49.

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A longitudinal comparison of urine cytological classification systems

Urine cytology is used to screen for urothelial carcinoma in patients with hematuria or risk factors, such as smoking or industrial dye exposure, and is an essential clinical-triage and longitudinal-monitoring tool for patients with known bladder cancer. However, urine cytology is semi-subjective and, therefore, susceptible to such issues as inadequate specimen quality, interobserver variability, and hedging towards equivocal, or atypical, diagnoses. These factors limit the predictive value of urine cytology and increase reliance on invasive procedures, such as cystoscopy. The Paris System for Reporting Urinary Cytology (TPS) was created to provide more quantitative, reproducible endpoints with well-defined criteria for urothelial atypia. TPS is often compared to other assessment techniques to justify its adoption. It results in decreased use of the atypical category and better reproducibility. Previous reports comparing diagnoses pre- and post-TPS did not consider temporal differences between diagnoses made under earlier systems and TPS. By failing to adjust for modifications across time, these previous studies may have underestimated the magnitude of differences between assessment methods. The authors conducted a large-scale longitudinal reassessment of urine cytology using TPS criteria and specimens collected from 2008 to 2018, prior to the mid-2018 adoption of TPS at an academic medical center. Their findings indicated that differences in atypical assignment were greatest at the start of the collection period and progressively decreased towards insignificance right before implementing TPS. The authors concluded that cytopathologists had begun to use the quantitative TPS criteria prior to it being officially adopted, and this approach could more broadly inform adoption, communication, and understanding of evolving classification systems in cytology.

Levy JJ, Liu X, Marotti JD, et al. Large-scale longitudinal comparison of urine cytological classification systems reveals potential early adoption of The Paris System criteria. *J Am Soc Cytopath*. 2022;11:394–402.

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A proposed risk-stratification model for uterine inflammatory myofibroblastic tumors

Inflammatory myofibroblastic tumor of the uterus is a rare mesenchymal tumor with largely benign behavior. However, a small subset demonstrate aggressive behavior. Clinicopathologic features have been associated with aggressive behavior, but these reports are based on small series and these features are imperfect predictors of clinical behavior. Inflammatory myofibroblastic tumors (IMTs) are most commonly driven by *ALK* fusions, with additional pathogenic molecular alterations being reported only in rare examples of extrauterine IMTs. The authors conducted a study in which a series of 11 uterine IMTs, five of which demonstrated aggressive behavior, were evaluated for clinicopathologic variables and subjected to capture-based next-generation sequencing with or without whole transcriptome RNA sequencing. *ALK* fusions were the sole pathogenic alteration in the six IMTs without aggressive behavior. In contrast, all five aggressive IMTs harbored pathogenic molecular alterations and numerous copy number changes, in addition to *ALK* fusions, with the majority of the additional alterations present in the primary tumors. The authors combined their series with cases previously reported in the literature and performed statistical analyses to propose a novel clinicopathologic risk-stratification score. The score assigned one point each for age above 45 years, size of 5 cm or larger, four or more mitotic figures per 10 high-power fields, and

infiltrative borders. No tumors with zero points had an aggressive outcome, while 21 percent of tumors with one or two points and 100 percent of tumors with three or more points had aggressive outcomes. The authors proposed a two-step classification model that uses a clinicopathologic risk-stratification score combined with molecular data to predict clinical behavior in uterine IMTs.

Ladwig NR, Bean GR, Pekmezci M, et al. Uterine inflammatory myofibroblastic tumors: Proposed risk stratification model using integrated clinicopathologic and molecular analysis. *Am J Surg Pathol*. 2023;47(2):157–171.

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Injury patterns and diagnostic pitfalls linked to radiation and radiochemotherapy in the stomach and gastroesophageal junction

Chemoradiation-associated injury may cause marked epithelial and stromal changes in gastric specimens. The authors characterized these histologic features in a retrospective series of cases. Nineteen cases of radiochemotherapy-associated gastropathy were identified, including 16 in-house cases and three from consultation material. Patient charts and H&E-stained slides were reviewed. Most patients were male (79 percent), with a median age of 66 years. All patients had a documented history of radiation, and 15 patients had also received chemotherapy. The median time from treatment to biopsy or resection was 2.3 months. Gross and endoscopic findings included erythematous, hemorrhagic, or ulcerated mucosa. Mucosal eosinophilia was seen in 16 (84 percent) cases, and 10 (53 percent) cases had acute inflammation, including neutrophilic microabscesses. Epithelial changes included increased apoptosis (six cases, 32 percent) and marked epithelial atypia (10 cases, 53 percent), potentially mimicking malignancy in some cases. However, the atypical cells featured voluminous eosinophilic cytoplasm with low nuclear-to-cytoplasmic ratio, a clue to their benign nature. Neuroendocrine cell nests were seen in four (21 percent) cases and were loosely aggregated in one case, potentially mimicking a well-differentiated neuroendocrine tumor or enterochromaffin-like cell hyperplasia in autoimmune gastritis. Eleven (58 percent) cases had vascular changes that included vessel dilation, hobnailed endothelial cells, and fibrin thrombi. Stromal changes were seen in 11 (58 percent) cases and included lamina propria hyalinization, submucosal fibrosis, and myofibroblast atypia. Injury associated with radiochemotherapy is histologically varied and may affect epithelial, stromal, and vascular compartments.

Birkness-Gartman JE, Hutchings DA, Montgomery EA, at al. Injury patterns and potential diagnostic pitfalls associated with radiation and radio-chemotherapy in the stomach and gastroesophageal junction. *Hum Pathol*. 2023;131:17–25.

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