Anatomic pathology selected abstracts

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Pseudocarcinomatous squamous hyperplasia involving bone

August 2021—Pseudocarcinomatous squamous hyperplasia within the bone is uncommon and closely mimics well-differentiated squamous cell carcinoma. It arises from cutaneous or mucosal surfaces and grows directly into the bone. The authors conducted a study in which they analyzed a series of 31 pseudocarcinomatous squamous hyperplasia (PSH) cases and discussed the clinicopathologic features that distinguished PSH from squamous cell carcinoma (SCC). The 31 cases were composed of 21 males, nine females, and one person of unknown gender, all of whom were between the ages of 20 and 87 years (average, 59 years). Involved anatomical sites included the mandible (17), maxilla (five), toes (four), and finger, femur, tibia, ischium, and unknown (one case each). Fourteen patients had a history of SCC of the oral cavity with extension into the mandible. Thirteen of these were treated with resection and chemoradiation, while one was treated with only resection. Four patients had medication-related osteonecrosis of the jaw, while three had peripheral vascular disease and diabetes mellitus, three had previous trauma, three had osteomyelitis, three had unknown medical histories, and one had hematologic malignancy. All cases exhibited severe osteomyelitis and nests of reactive keratinizing squamous epithelium that matured toward the bone surface and lacked significant atypia or mitotic activity but permeated the medullary cavity. Patients with previous SCC developed PSH after two months to eight years (average, four years). Nineteen of 30 patients had follow-up of two to 48 months (average, 17 months). Six patients experienced repeated debridements over two months to one year, and no patient developed SCC. The authors concluded that PSH involving bone is infrequent, complicates severe osteomyelitis, and is often therapy related. The clinical findings usually are not concerning for malignancy. However, the histologic findings are an important diagnostic pitfall because they mimic SCC.

Spasić S, Kryvenko ON, Kerr DA, et al. Pseudocarcinomatous squamous hyperplasia involving bone: A diagnostic pitfall mimicking squamous cell carcinoma. *Am J Surg Pathol*. 2021;45(2):263–269.

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Intraoperative frozen consultation for GI signet ring cell carcinoma

Signet ring cell carcinoma is difficult to recognize on intraoperative frozen sectioning and has high false-negative rates. The authors conducted a study to investigate common factors that contribute to discrepancies between intraoperative frozen diagnoses and those made on review of permanent sections. They summarized their experiences and lessons learned regarding minimizing errors on intraoperative frozen diagnoses of gastrointestinal signet ring cell carcinoma (SRCC). The authors retrospectively examined their pathology database from May 25, 2000 to Jan. 1, 2018 and re-reviewed intraoperative frozen sections and permanent hematoxylin-and-eosin (H&E) slides for specimens with confirmed SRCC on permanent sections. The study included 83 specimens from 50 patients and found an accuracy rate of 85.5 percent when comparing initial intraoperative frozen interpretations with the subsequent permanent section diagnoses for all SRCC cases. Among the most common factors causing discrepancies in diagnosing SRCC between intraoperative frozen procedures and permanent sections were the resemblance of clusters of SRCC cells to a myxoid background; SRCC cells frequently presenting as normal or reactive cells (histiocytes, macrophages, large reactive lymphocytes, plasma cells, or adipocytes) due to their relatively clear or depleted cytoplasmic mucin; and histological sampling errors leading to misses of small foci of SRCC on frozen section slides. An accurate diagnosis of SRCC during intraoperative frozen consultations remains challenging. Based on the authors' experiences and lessons, the most important strategies to reduce diagnostic

errors are understanding the unusual histomorphological features of SRCC cells on frozen sections, including, but not limited to, intracellular mucin depletion, absence of desmoplasia, and lack of adjacent precancerous changes. Another strategy to reduce diagnostic errors involves paying close attention to the abrupt pattern transition from normal architecture (for example, glandular or submucosal loose connective tissue) to a myxoid or inflammatory-like appearance, or both, as SRCC cells with rich intracellular mucin may present a myxoid appearance after frozen processing.

Chen F, Jiang K, Han B. Diagnostic challenges of intra-operative frozen consultation for gastrointestinal signet ring cell carcinoma. *Histopathology*. 2021;78:300–309.

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IHC analysis of gastrointestinal and Müllerian phenotypes of ovarian mucinous cystadenomas

Mucinous cystadenoma is one of the most common benign ovarian neoplasms. However, the immunophenotypes and histogenetic relationships of mucinous cystadenomas with a Müllerian-type epithelium have not been explored fully. The authors conducted a study in which they elucidated the direction of differentiation of the mucinous epithelium that constitutes mucinous cystadenomas. They paid special attention to the gastrointestinal (GI)-type mucinous epithelium and its association with background Müllerian-type epithelium. IHC was performed in 139 cases of mucinous cystadenoma to evaluate the expression of Claudin-18 (CLDN18), a novel marker of gastric differentiation; CDX2, a marker of intestinal differentiation; and estrogen receptor (ER), a marker of Müllerian differentiation. GI differentiation characterized by CLDN18 or CDX2 positivity, or both, was observed in the mucinous epithelium of most mucinous cystadenomas (129 of 139 cases; 93 percent). In a subset of these cases, the tumor was composed of mucinous epithelium exhibiting an intermediate GI and Müllerian phenotype (CLDN18+/CDX2±/ER+). Of note, a transition from background Müllerian-type epithelium to mucinous epithelium with GI differentiation was identified in 12 cases. A minor subset (six percent) of mucinous cystadenomas was considered a pure Müllerian type because the epithelium exhibited a CLDN18–/CDX2–/ER+ immunophenotype. The authors concluded that mucinous cystadenomas consist of three major subtypes: GI, Müllerian, and intermediate. Most mucinous cystadenomas are GI type and should be considered a precursor of GI-type mucinous borderline tumors. The presence of intermediate-type mucinous cystadenomas and areas of transition from Müllerian-type to GI-type epithelium suggest that GI-type mucinous epithelium can arise from Müllerian duct derivatives or surface epithelium exhibiting Müllerian metaplasia in the ovary.

Halimi SA, Maeda D, Ushiku-Shinozaki A, et al. Comprehensive immunohistochemical analysis of the gastrointestinal and Müllerian phenotypes of 139 ovarian mucinous cystadenomas. *Hum Pathol*. 2021;109:21–30.

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Spectrum of serrated colorectal lesions: new entities and unanswered questions

Hyperplastic polyps of the colon and rectum historically were not associated with an increased risk of developing colorectal cancer. Recognition of variants of serrated colorectal lesions that possess relatively subtle but significant morphological differences to those of hyperplastic polyps and that could be associated with epithelial dysplasia and colorectal cancer led to the characterization of sessile serrated lesions (SSLs) and traditional serrated adenomas (TSAs). These links were supported by the identification of genetic alterations—for example, *BRAF* and *KRAS* mutations—that are commonly found in hyperplastic polyps, SSLs, TSAs, and colorectal cancer. The “serrated pathway” to colorectal cancer may progress faster than the traditional adenoma-carcinoma sequence, emphasizing the importance of identifying these lesions. The diagnostic histological criteria for SSLs have been more clearly defined in parallel with efforts to increase recognition of these lesions at endoscopy. Lesions showing morphological and molecular features overlapping those of hyperplastic polyps, SSLs, and TSAs have been described. These include the mucin-rich TSA, serrated tubulovillous adenoma, and those showing mixed

histological features—for example, comprising differing combinations of hyperplastic polyps, SSLs, and TSAs. Morphological and molecular study of this range of lesions is providing insights into the relationship of serrated colorectal lesions to each other and with colorectal cancer.

Bateman AC. The spectrum of serrated colorectal lesions—new entities and unanswered questions. *Histopathology*. 2021;78:780–790.

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Use of MUC4 and GATA3 to distinguish pleural sarcomatoid mesothelioma from pulmonary sarcomatoid carcinoma

Distinguishing pulmonary sarcomatoid carcinoma from pleural sarcomatoid mesothelioma is challenging because of overlapping histology, immunophenotype, and clinical features. Reliable IHC markers to aid in this distinction would be valuable. Recent studies have proposed that MUC4 expression is common in sarcomatoid carcinoma but not in sarcomatoid mesothelioma, with the converse pattern reported for GATA3. The authors conducted a study to further explore the utility of MUC4 and GATA3 in distinguishing pulmonary sarcomatoid carcinoma from sarcomatoid mesothelioma. The study focused on well-characterized cases of sarcomatoid carcinoma (n=32) and sarcomatoid mesothelioma (n=64). Diagnoses were confirmed by two thoracic pathologists based on morphology, immunophenotype, and clinical and radiographic features. Whole tissue sections were stained for GATA3 and MUC4. Patients with sarcomatoid carcinoma and sarcomatoid mesothelioma had similar median ages and age ranges and were predominantly male. GATA3 was positive in 63 of 64 sarcomatoid mesotheliomas (98 percent; 42 diffuse, 16 patchy, five focal) and 15 of 32 sarcomatoid carcinomas (47 percent; three diffuse, eight patchy, four focal). MUC4 was positive in two of 64 sarcomatoid mesotheliomas (three percent; one patchy, one focal) and 12 of 32 sarcomatoid carcinomas (38 percent; five diffuse, six patchy, one focal). The authors concluded that diffuse GATA3 expression favors sarcomatoid mesothelioma over sarcomatoid carcinoma, with the latter rarely showing diffuse expression (sensitivity and specificity of GATA3 for sarcomatoid mesothelioma over sarcomatoid carcinoma, 66 and 94 percent, respectively). They found that focal and patchy GATA3 expression is observed in both tumor types, so it is not helpful in distinguishing between them. The sensitivity of MUC4 for sarcomatoid carcinoma was low in the authors' cohort, but it was quite specific.

Terra SBSP, Roden AC, Aubry MC, et al. Utility of immunohistochemistry for MUC4 and GATA3 to aid in the distinction of pleural sarcomatoid mesothelioma from pulmonary sarcomatoid carcinoma. *Arch Pathol Lab Med*. 2021;145:208–213.

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Incidence and significance of GATA3 positivity in gallbladder adenocarcinoma

GATA3 immunostaining is a sensitive marker for mammary and urothelial carcinomas. It is used routinely in surgical pathology during workup of carcinomas of unknown origin. To the best of the authors' knowledge, this is the first focused study of GATA3 expression in gallbladder adenocarcinomas. In this study, the authors evaluated GATA3 expression in 38 gallbladder adenocarcinomas. Eight of 38 (21 percent) gallbladder adenocarcinomas were positive for GATA3, and the GATA3 expression tended to be moderate to strong. In four of those cases, it was patchy (less than 50 percent positivity) and characterized by discrete clusters or groups of malignant cells with areas of intervening negative tumor cells. In the other four cases, it was diffuse (more than 50 percent positivity). GATA3 expression did not show any significant correlation with clinicopathologic features, such as gender, histologic grade, perineural invasion, vascular invasion, pathologic stage, or distant metastasis. The results of this study show that a subset (21 percent) of gallbladder adenocarcinomas can be GATA3 positive. Awareness of this phenomenon is important while working up GATA3-positive carcinomas immunohistochemically.

Guo W, Lee W, Lu Y, et al. Incidence and significance of GATA3 positivity in gallbladder adenocarcinoma. *Hum*

Pathol. 2020;106:39–44.

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Evaluation of micronodular PEComas of the appendix

Perivascular epithelioid cell tumors of the appendix have rarely been reported. The authors conducted a study in which they described three cases of a distinctive micronodular proliferation in the appendix consistent with a variant of PEComa. The lesion corresponds with what was previously known as granular degeneration of appendiceal smooth muscle. However, the authors propose that the lesion represents an indolent form of PEComa. The authors' study involved two patients who were female (ages 33 and 41 years) and one who was male (aged 41 years). None had a history of tuberous sclerosis. Each case demonstrated a multifocal nodular proliferation toward the distal tip of the appendix composed of epithelioid cells with abundant granular eosinophilic to clear cytoplasm. The lesional cells in each case were determined through immunohistochemistry to be positive for muscle markers (smooth muscle actin [SMA] and desmin), melanocytic markers (HMB-45 and melan A), cathepsin K, and the lysosomal marker NKI-C3. MITF was positive in two of three cases. None of the cases expressed S100 protein. Electron microscopy in one case revealed striated electron-dense structures consistent with pre-melanosomes. Follow-up, available in one case, showed no recurrence at five years. The authors proposed the term micronodular PEComa for this appendiceal lesion to more accurately reflect its histological and immunohistochemical characteristics, which include consistent positivity for muscle and melanocytic markers. Micronodular PEComa seems to follow an indolent course, consistent with its uniformly low-grade histologic features, and appears to be unassociated with tuberous sclerosis.

Anderson WJ, Kojc N, Fletcher CDM, et al. Micronodular PEComas of the appendix. *Histopathology*. 2021. doi:10.1111/his.14341

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