Anatomic pathology selected abstracts

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Histologic variants of Kaposi sarcoma in the gastrointestinal tract

April 2023—Kaposi sarcoma can pose diagnostic challenges in biopsy specimens. Multiple histologic variants of cutaneous Kaposi sarcoma (KS) have been described. However, the histomorphologic spectrum of gastrointestinal KS has not been systematically studied. The authors presented a large multi-institutional case series that comprehensively evaluated 46 cases of KS involving the GI tract and identified seven histomorphologic variants, some of which had not previously been described. Five of the variants—lymphangioma/lymphangiectatic like (n=17), mucosal hemorrhage/telangiectatic like (n=17), mucosal inflammation like (n=15), granulation tissue like (n=13), and mucosal prolapse like (n=4)—were inconspicuous but had unique morphologic patterns. These variants easily can be misdiagnosed or misinterpreted on routine examination if KS is not considered and if the IHC stain for human herpesvirus-8 is not utilized. The other two morphologic variants presented as spindle-cell proliferations (GI stromal tumor like [n=8] and inflammatory myofibroblastic tumor like [n=2]). These variants may raise a broad differential diagnosis of spindle-cell tumors of the GI tract and could pose diagnostic challenges. In summary, GI KS lesions exhibit variable and often unconventional histomorphologic patterns. Kaposi sarcoma should be included in the differential diagnosis even if features of conventional KS are not seen, particularly in limited biopsies of immunocompromised patients, such as those with HIV infection. Although the clinical significance of these morphologic variants is yet to be determined, they are important from a diagnostic standpoint. Misdiagnosis and delay in managing the disease can be avoided by recognizing the morphologic diversity of GI KS and using the human herpesvirus-8 IHC stain appropriately.

Zheng W, Obeng RC, Graham RP, et al. Histologic variants of Kaposi sarcoma in the gastrointestinal tract: a contemporary multi-institutional clinicopathologic analysis of 46 cases. *Am J Surg Pathol*. 2022;46(11):1500–1506.

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Development and validation of ultra-rapid periodic acid-Schiff stain for fungus on frozen section

No standardized process exists for using periodic acid-Schiff during intraoperative frozen sections to identify fungal organisms. Therefore, the authors conducted a study to develop an ultra-rapid periodic acid-Schiff stain and determine the fastest turnaround time for identifying fungal organisms on frozen section. They also sought to develop a quality control tissue block that would be stained simultaneously with the submitted tissue to provide a validated and reproducible method for intraoperative diagnosis of fungal organisms on frozen section. For the study, lean muscle tissue was inoculated with two species of fungi (*Aspergillus fumigatus* and *Paecilomyces* spp) and grown at three temperatures for 72 hours. Inoculated tissue was embedded in optimal cutting-temperature compound, cut, and stained using a modified periodic acid-Schiff stain. The optimal control was designated for future use as the standard control. Multiple control slides were cut and stained, using successively shorter time intervals for each step. The staining process that provided accurate results in the shortest amount of time was deemed ultra-rapid periodic acid-Schiff. This method was validated by carryover studies and clinical specimens. *Paecilomyces* spp incubated at 30°C for 72 hours was the optimal positive control and had an even mixture of yeast and hyphal forms. The fastest staining process involved two minutes of periodic acid and Schiff reagent and 10 dips of light-green solution. Tap water was as effective as distilled water as a component of the process. Validation was achieved. All clinical cases stained identically to formalin-fixed paraffin-embedded tissue stained with H&E and periodic acid-Schiff. The authors concluded that ultra-rapid periodic acid-Schiff quickly and reliably

identifies fungal organisms on fresh tissue. Development of a concurrent positive control allows for quality control and validation.

Broadwater D, Messersmith LM, Bishop BN, et al. Development and validation of ultra-rapid periodic acid–Schiff stain for use in identifying fungus on frozen section. *Arch Pathol Lab Med*. 2022;146(10):1268–1272.

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Solid variant of papillary thyroid carcinoma: a multi-institutional retrospective study

The definition of papillary thyroid carcinoma, solid variant varies from more than 50 percent to 100 percent of solid/trabecular/insular growth (STI). The authors conducted a multi-institutional study to identify prognostic factors and establish an appropriate STI cutoff for papillary thyroid carcinoma, solid variant (PTC-SV). The study involved 156 PTCs with STI. Nodal metastases were seen in 18 percent and associated with a higher percentage of papillary and STI entities. When substratified by infiltration or encapsulation status, the STI percentage did not impact the risk of nodal metastasis. PN1 stage was seen in 51 percent of infiltrative tumors and one percent of encapsulated lesions. Overall, PTC with STI had an excellent prognosis. The 10-year disease-free survival rate was 87 percent for the entire cohort, 94 percent for those with encapsulated lesions, and 76 percent for those with infiltrative tumors. The STI percentage did not impact the disease-free survival rate. Fifty-four patients had noninvasive encapsulated lesions with two to 100 percent STI. None developed recurrence. Encapsulated lesions were enriched with *RAS* mutations (54 percent), whereas infiltrative lesions lacked such mutations (four percent). The *BRAF* V600E mutation was an infrequent event, noted in 11 percent of the entire cohort. The authors concluded that in PTC with STI, the determining factor for nodal metastasis and disease-free survival is encapsulation and infiltration status rather than STI percentage. Encapsulated noninvasive tumors with STI follow an indolent course with a very low risk of nodal metastasis and recurrence. Overall, PTC with STI has an excellent prognosis, with a 10-year disease-specific survival and a disease-free survival rate of 96 and 87 percent, respectively. Therefore, the classification of PTC-SV as an aggressive papillary thyroid carcinoma subtype should be reconsidered.

Xu B, Viswanathan K, Zhang L, et al. The solid variant of papillary thyroid carcinoma: a multi-institutional retrospective study. *Histopathology*. 2022;81(2):171–182.

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Use of training and validation radical prostatectomy cohorts to define ‘large’ cribriform prostatic adenocarcinoma

Cribriform growth pattern is well established as an adverse pathologic feature in prostate cancer. The literature suggests that “large” cribriform glands are associated with aggressive behavior. However, published studies vary in their definitions of large. The authors of this study aimed to identify an outcome-based quantitative cutoff for large versus small cribriform glands. They conducted an initial training phase using the tissue microarray-based Canary retrospective radical prostatectomy cohort. Cribriform growth was observed in 307 (24 percent) of 1,287 patients analyzed. Using Kaplan–Meier estimates of recurrence-free survival curves that were stratified by cribriform gland size, the authors identified 0.25 mm as the optimal cutoff for identifying more aggressive disease. In univariable and multivariable Cox proportional hazards analyses, size of more than 0.25 mm was a significant predictor of worse recurrence-free survival than cribriform glands of 0.25 mm or less, independent of preoperative prostate-specific antigen, grade, stage, and margin status ($P<.001$). Furthermore, two different subset analyses of low-intermediate risk cases (cases with a Gleason score of $\leq 3+4=7$ and cases with a Gleason score of $3+4=7/4+3=7$) likewise demonstrated that patients who had the largest cribriform diameter (greater than 0.25 mm) had a significantly lower recurrence-free survival rate than patients who had cribriform glands of 0.25 mm or less (each subset, $P=.004$). No significant difference in outcomes was noted between patients who had cribriform glands of 0.25 mm or less and patients who did not have cribriform glands. The 0.25-mm or greater cutoff was validated as statistically significant in a separate 419-patient completely embedded whole-section radical

prostatectomy cohort by biochemical recurrence, metastasis-free survival, and disease-specific death, even when cases with admixed Gleason pattern 5 carcinoma were excluded. The authors concluded that these findings support the reporting of cribriform gland size and identify 0.25 mm as an optimal outcome-based quantitative measure for defining large cribriform glands. Moreover, cribriform glands greater than 0.25 mm are associated with a potential for metastatic disease independent of Gleason pattern 5 adenocarcinoma.

Chan E, McKenney JK, Hawley S, et al. Analysis of separate training and validation radical prostatectomy cohorts identifies 0.25 mm diameter as an optimal definition for “large” cribriform prostatic adenocarcinoma. *Mod Pathol*. 2022;35(8):1092–1100.

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Use of GRM1 IHC to distinguish chondromyxoid fibroma from histologic mimics

Chondromyxoid fibroma is a rare benign bone neoplasm that manifests histologically as a lobular proliferation of stellate to spindle-shaped cells in a myxoid background. It exhibits morphologic overlap with other cartilaginous and myxoid tumors of bone. Chondromyxoid fibroma (CMF) is characterized by recurrent genetic rearrangements that place the glutamate receptor gene *GRM1* under the regulatory control of a constitutively active promoter, leading to increased gene expression. The authors conducted a study in which they explored the diagnostic utility of GRM1 IHC as a surrogate marker for *GRM1* rearrangement using a commercially available monoclonal antibody. The study involved 230 tumors, including 30 CMF cases represented by 35 specimens. GRM1 was positive by IHC in 97 percent (34 of 35) of CMF specimens and exhibited moderate to strong staining in more than 50 percent of neoplastic cells. Staining was diffuse (more than 95 percent of cells) in 25 (71 percent) specimens. Among the nine CMF specimens that had documented exposure to acid decalcification, four (44 percent) exhibited diffuse immunoreactivity (more than 95 percent) for GRM1. All 15 CMF specimens that were not exposed to decalcification reagents were diffusely immunoreactive (P=.003). High *GRM1* expression at the RNA level was previously observed by quantitative reverse transcription polymerase chain reaction in nine CMF cases that were also positive by IHC. Low *GRM1* expression was observed by quantitative reverse transcription polymerase chain reaction in the single case of CMF that was negative by IHC. GRM1 IHC was negative (less than five percent) in histologic mimics of CMF, including conventional chondrosarcoma, enchondroma, chondroblastoma, clear cell chondrosarcoma, giant cell tumor of the bone, fibrous dysplasia, chondroblastic osteosarcoma, myoepithelial tumor, primary aneurysmal bone cyst, brown tumor, phosphaturic mesenchymal tumor, CMF-like osteosarcoma, and extraskeletal myxoid chondrosarcoma. These results indicate that GRM1 IHC may have utility in distinguishing CMF from its histologic mimics.

Toland AMS, Lam SW, Varma S, et al. GRM1 immunohistochemistry distinguishes chondromyxoid fibroma from its histologic mimics. *Am J Surg Pathol*. 2022;46(10):1407–1414.

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Impact of liver biopsy size on histopathologic evaluation of liver allograft rejection

Allograft liver biopsy is the gold standard for assessing transplant recipients for graft dysfunction. The impact of biopsy sample size on the diagnosis of acute cellular rejection (ACR) has not been studied, according to the authors, who assessed the relationship between biopsy sample length and diagnosis and determined optimal biopsy sample size in the transplant setting. They retrospectively reviewed core biopsies from 68 patients who had a history of liver transplant. Each biopsy sample was read on five occasions using differing lengths to assess for ACR per Banff criteria. Categorical agreement was calculated using rejection severity. The length of biopsy samples strongly correlated with the number of portal tracts. ACR rates increased from 73.5 to 79.4 percent with an increase in length from 1 cm to 2 cm, and moderate rejection increased from 27.9 to 33.82 percent. No cases of severe rejection were detected at 1 cm and 1.5 cm; one case was detected at 2 cm; and two cases were detected

at 3 cm. The major error rate was reduced to less than 10 percent with a length of 2 cm, at which length the average number of complete and partial portal triads was 10 and 13, respectively. The likelihood of diagnosing ACR and rejection grade rose substantially with an increase in biopsy sample length. This study suggests that a minimum length of 2 cm and 10 complete portal triads or 13 partial/complete portal triads should be obtained to confidently exclude or grade ACR.

Agarwal AN, Nania J, Qiu L, et al. Impact of liver biopsy size on histopathologic evaluation of liver allograft rejection. *Arch Pathol Lab Med*. 2022;146(12):1530–1534.

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