Anatomic pathology selected abstracts

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Controversy surrounding terminology for appendiceal mucinous neoplasms and pseudomyxoma peritonei

November 2022—Appendiceal mucinous neoplasms show a range of morphologic features and biological risk. At one end of the spectrum, high-grade adenocarcinomas are cytologically malignant and exhibit infiltrative invasion, lymph node metastases, and behavior similar to that of extra-appendiceal mucinous adenocarcinomas. At the other end, mucinous neoplasms confined to the mucosa are uniformly benign. Some of the cases in between these extremes may metastasize within the abdomen despite a lack of malignant histologic features. These patients have diverticulum-like pushing invasion of mostly low-grade epithelium through the appendix with or without concomitant organizing intra-abdominal mucin. The latter condition, widely termed pseudomyxoma peritonei, tends to exhibit a relentless course punctuated by multiple recurrences. Even with cytoreductive therapy, many patients die. The combination of bland histologic features and the protracted behavior of peritoneal disease has led some authors to question whether these metastatic tumors represent malignancies. The World Health Organization and its cadre of experts widely promote using low-grade appendiceal mucinous neoplasm as an umbrella term to encompass benign and malignant conditions and those that have uncertain biological potential. The authors conducted a literature review to determine a practical approach to diagnosing and classifying appendiceal mucinous neoplasms and their mimics. They found that while the term low-grade appendiceal mucinous neoplasm greatly simplifies tumor classification, it has caused confusion and consternation among pathologists, clinicians, and patients. It also increases the likelihood that at least some patients will undergo unnecessary surveillance and treatment for benign neoplasms and non-neoplastic conditions. The authors concluded that adopting nomenclature that conveys accurate information about biological risk could provide much needed clarity for pathologists and their patients and improve pathologists' communication with their clinical colleagues.

Hissong E, Yantiss RK. The frontiers of appendiceal controversies: Mucinous neoplasms and pseudomyxoma peritonei. *Am J Surg Pathol*.2022;46(1):e27–e42.

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Characteristics and neoplasia risk of colorectal inflammatory polyposis in inflammatory bowel disease

Inflammatory polyps in inflammatory bowel disease have been associated with increased neoplasia risk. Colonic mucosa in filiform polyposis and giant inflammatory polyposis may be difficult to visualize during endoscopic surveillance, perhaps contributing to early colectomy in these patients. The authors conducted a study in which they examined the clinicopathologic characteristics and significance of inflammatory polyps (IPs) and inflammatory polyposis in inflammatory bowel disease (IBD). They identified 336 resections from IBD patients (212 [63.1 percent] male; mean age, 40.3 years; 175 [52.1 percent] with ulcerative colitis), including 78 with fewer than 10 IPs, 141 with 10 or more IPs, and 117 with inflammatory polyposis, including 30 with filiform polyposis/giant inflammatory polyposis. The authors compared these IBD patients with 100 control subjects who did not have IPs using various parameters, including overall and occult (unexpected) dysplasia. They found that neoplasia was not increased in the resections with IPs when compared with resections from controls who were similar with regard to age, disease duration, degree of inflammation, extent of colitis, prevalence of primary sclerosing cholangitis, and tissue sampling. In multivariate analysis, increasing numbers of IPs and inflammatory polyposis were significantly associated with ulcerative and indeterminate colitis ($P = 0.003$) and shorter disease duration ($P = 0.01$) and

independently associated with lower rates of dysplasia overall, including all grades ($P = 0.001$) and advanced neoplasia ($P = 0.04$). No instances of occult dysplasia (any grade) were found among inflammatory polyposis cases. These findings support the conclusion that IPs, and inflammatory polyposis in particular, should not be considered an independent risk factor for the development of neoplasia in IBD patients but should be considered in the context of disease duration and inflammatory burden.

Ma YR, Polydorides AD. Clinicopathologic characteristics and neoplasia risk of colorectal inflammatory polyposis in inflammatory bowel disease. *Arch Pathol Lab Med*. 2022;146(2):172–181.

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Expanding the clinicopathologic spectrum of SDH-deficient renal cell carcinomas

Most succinate dehydrogenase-deficient renal cell carcinomas demonstrate stereotypical morphology characterized by bland eosinophilic cells with frequent intracytoplasmic inclusions. However, variant morphologic features have been increasingly recognized. Therefore, the authors investigated the incidence and characteristics of succinate dehydrogenase (SDH)-deficient renal cell carcinoma with variant morphologies. They studied a multi-institutional cohort of 62 new SDH-deficient renal cell carcinomas from 59 patients. The patients were a median age of 39 years (range, 19-80 years) at presentation and predominantly male (ratio, 1.6:1). A relevant family history was reported for nine (15 percent) patients. Multifocal or bilateral tumors were identified radiologically in five (eight percent) patients. Typical morphology was present at least focally in 59 (95 percent) tumors. Variant morphologies were seen in 13 (21 percent) and included high-grade nuclear features and various combinations of papillary, solid, and tubular architecture. Necrosis was also present in 13 tumors, seven of which showed variant morphology. All 62 tumors demonstrated loss of SDHB expression by IHC. None showed loss of SDHA expression. Germline *SDH* mutations were reported in the 18 patients for whom the results of testing were known. Among the patients for whom follow-up data were available, metastatic disease was reported in nine, eight of whom had necrosis or variant morphology in their primary tumor, or both. Three patients died of disease. The authors concluded that variant morphologies and high-grade nuclear features occur in a subset of SDH-deficient renal cell carcinomas and are associated with more aggressive behavior. Therefore, the authors recommend grading all SDH-deficient renal cell carcinomas and emphasize the need for a low threshold for performing SDHB IHC on any difficult-to-classify renal tumor, particularly if it occurs at a younger patient age.

Fuchs TL, Maclean F, Turchini J, et al. Expanding the clinicopathological spectrum of succinate dehydrogenase-deficient renal cell carcinoma with a focus on variant morphologies: a study of 62 new tumors in 59 patients. *Mod Pathol*. 2022;35(6):836–849.

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Accuracy of definitive ROSE cytopathology diagnoses as a quality assurance measure

Intraprocedural rapid onsite evaluation of cytology specimens enhances cytopathology practice. More recently, such diagnoses—for example, frozen section diagnoses—have guided immediate clinical decisions. The authors conducted a study in which they evaluated the diagnostic accuracy of definitive intraprocedural rapid onsite evaluation (ROSE) diagnoses in their institution's quality assurance system during a 52-month period. Cytopathology cases with ROSE from January 2017 to April 2021 were retrieved from the laboratory information system. After excluding cases that were deferred or considered nondiagnostic or unsatisfactory, each definitive ROSE diagnosis—that is, negative for malignant cells or positive for malignant cells—was categorized as agreeing or disagreeing with the final diagnosis. For comparison, concordance of frozen section diagnoses from the same time period were tabulated and compared with those of ROSE diagnoses using chi square testing, with $P < 0.05$ considered statistically significant. Of the 1,649 ROSE diagnoses, there were 15 disagreements (0.9 percent) and one final moderate interpretive disagreement (0.06 percent). By comparison, of the 17,469 frozen section

diagnoses, there were 141 disagreements (0.8 percent) and 49 final moderate or major interpretive disagreements (0.3 percent). The remaining disagreements were minor. No statistically significant differences in the rates of final moderate and major interpretive disagreements were noted. The final interpretive disagreement rates for definitive ROSE and frozen section diagnoses in this study were similar. Given the expanding role of ROSE and its use in immediate clinical decision-making in some cases, monitoring the accuracy of definitive diagnoses may serve as an initial quality assurance measure.

Geisler DL, Nestler RJ, Mosley BL, et al. Accuracy of definitive rapid onsite evaluation cytopathology diagnoses: Assessment of potentially critical diagnoses as a quality assurance measure. *J Am Soc Cytopathol*. 2022;11:133–141.

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Pathology and prognosis of colonic adenocarcinomas with intermediate primary tumor stage

Primary tumor stage is an important prognostic indicator in colonic adenocarcinomas. However, tumors lacking muscle fibers beyond the advancing tumor edge and that show no extension beyond the apparent outer border of the muscularis propria, termed $pT2_{int}$, have not been previously studied, according to the authors. The authors conducted a study to address the clinicopathologic characteristics and prognosis of $pT2_{int}$ tumors. They recharacterized 168 colon carcinomas and compared $pT2_{int}$ tumors with pT2 and pT3 tumors. In side-by-side analyses, 21 $pT2_{int}$ tumors diverged from 29 pT2 tumors only in terms of being larger ($P = 0.03$). However, when compared with 118 pT3 tumors, the $pT2_{int}$ tumors were less likely to show high grade ($P = 0.03$); lymphovascular ($P < 0.001$) and extramural venous invasion ($P = 0.04$); discontinuous tumor deposits ($P = 0.02$); lymph node involvement ($P = 0.001$); and advanced stage ($P = 0.001$). Combining $pT2_{int}$ with pT2 cases was a better independent predictor of negative lymph nodes in multivariate analysis ($P = 0.04$; odds ratio [OR], 3.96; confidence interval [CI], 1.09–14.42) and absent distant metastasis in univariate analysis ($P = 0.04$) compared with sorting $pT2_{int}$ and pT3 cases. Proportional hazards regression showed that pT2 and $pT2_{int}$ tumors together were associated with better disease-free survival than pT3 tumors ($P = 0.04$; OR, 3.65; 95 percent CI, 1.05–12.70). Kaplan-Meier analysis demonstrated that when $pT2_{int}$ and pT2 tumors were grouped together, those patients were significantly less likely to show disease progression than patients with pT3 tumors ($P = 0.002$; log-rank test) and showed a trend toward better disease-specific survival ($P = 0.06$) during a mean follow-up of 44.9 months. These data support the conclusion that $pT2_{int}$ carcinomas have distinct clinicopathologic characteristics and are associated with patient outcomes more closely aligned with pT2 versus pT3 tumors.

Paulsen JD, Polydorides AD. Pathology and prognosis of colonic adenocarcinomas with intermediate primary tumor stage between pT2 and pT3. *Arch Pathol Lab Med*. 2022;146(5):591–602.

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Kaposiform lymphangiomatosis: pathologic aspects in 43 patients

Kaposiform lymphangiomatosis is an uncommon generalized lymphatic anomaly with distinctive clinical, radiologic, histopathologic, and molecular findings. The authors documented the pathology in 43 patients evaluated by the Boston Children's Hospital Vascular Anomalies Center from 1999 to 2020. The most frequent presentations were respiratory difficulty, hemostatic abnormalities, and a soft tissue mass. Imaging commonly revealed involvement of some combination of the mediastinal, pulmonary, pleural, and pericardial compartments and most often included the spleen and skeleton. Histopathology was characterized by dilated, redundant, and abnormally configured lymphatic channels typically accompanied by dispersed clusters of variably canalized and often hemosiderotic spindled lymphatic endothelial cells that were immunopositive for D2-40, PROX1, and CD31. An activating lesional *NRAS* variant was documented in nine of 10 patients. The clinical course was typically aggressive and marked by hemorrhage, thrombocytopenia, diminished fibrinogen levels, and a mortality rate of 21 percent. The authors

concluded that it is critical to diagnose kaposiform lymphangiomatosis because it often has a progressive course. A diagnosis is best achieved via an interdisciplinary team. Biopsies or molecular studies should be undertaken if deemed necessary. Molecular alterations in kaposiform lymphangiomatosis validate the use of RAS-MAPK pathway inhibitors, which have shown promise in isolated cases.

Perez-Atayde AR, Debelenko L, Al-Ibraheemi A, et al. Kaposiform lymphangiomatosis: pathologic aspects in 43 patients. *Am J Surg Pathol.*2022;46(7):963–976.

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