Anatomic pathology selected abstracts

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Association between a subset of GNETs and proton pump inhibitor use

September 2022—Hypergastrinemia states, such as achlorhydria from gastric mucosal atrophy or a gastrin-producing tumor, have been associated with the development of enterochromaffin-like cell hyperplasia and gastric neuroendocrine tumors. It has yet to be determined whether drugs that elevate serum gastrin levels, such as proton pump inhibitors, can produce the same tissue effect. No concrete evidence links the use of proton pump inhibitors to gastric neuroendocrine tumors (GNETs) outside of animal models and case reports. The authors conducted a study to explore and describe GNETs of presumed enterochromaffin-like (ECL) cell origin that cannot be reliably placed into any of the three categories recognized by the World Health Organization. The retrospective clinicopathologic study of GNETs focused on the body/fundus over 15 years (2005–2019). Of 87 cases, 57 (65.5 percent) were associated with atrophic gastritis and two (2.3 percent) with Zollinger-Ellison syndrome; 28 (32.2 percent) were unclassified. Of the latter, 11 were consistent with true sporadic/type 3 GNETs, while 17 had background mucosal changes of parietal-cell and ECL-cell hyperplasia but without underlying detectable gastrinoma. Fifteen of 17 (88.2 percent) ECL cases were linked to documented long-term use of proton pump inhibitors. This subtype of GNETs was more commonly multifocal and of higher grade (P=0.03) than true sporadic GNETs. The authors concluded that a subset of GNETs arises in the background of gastric mucosal changes suggestive of hypergastrinemia, but without underlying gastrinoma, and could be linked to long-term use of proton pump inhibitors.

Rais R, Trikalinos NA, Liu J, et al. Enterochromaffin-like cell hyperplasia-associated gastric neuroendocrine tumors may arise in the setting of proton pump inhibitor use: The need for a new clinicopathologic category. *Arch Pathol Lab Med*. 2022;146(3):366–371.

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Diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma lacking cytological atypia

Amplification of the *MDM2* gene, which is usually detected using FISH, is the key driving event for atypical lipomatous tumors/well-differentiated liposarcomas. The authors conducted a study in which they sought to determine concordance between histopathological findings and *MDM2* FISH in the diagnosis of atypical lipomatous tumors/well-differentiated liposarcomas (ALT/WDL) and identify the histological features of *MDM2*-amplified tumors lacking classic atypia. They performed a retrospective analysis of all mature lipomatous lesions subjected to *MDM2* FISH analysis at their institution. The analysis was performed on 439 mature lipomatous lesions: 364 (82.9 percent) were negative and 75 (17 percent) were positive. In 17 of 75 (22.6 percent) cases of ALT/WDL, cytological atypia was not identified on initial histological assessment, thereby favoring a diagnosis of lipoma. A review of the cases found that they shared common histological features. These consisted of a very low number of relatively small stromal cells within the tumor lobules, with mildly coarse chromatin and oval nuclei, admixed with unremarkable adipocytes in a tumor background devoid of fibroconnective septa, areas of fibrosis, or blood vessels. These cells matched the cells in which FISH showed *MDM2* amplification. In contrast, 13 (3.5 percent) cases regarded as suspicious for ALT/WDL on the basis of histology lacked *MDM2* amplification and were reclassified following the findings on FISH. The authors concluded that a subset of lipoma-like ALTs/WDLs are not associated with any of the features typically attributed to the neoplasm. They also concluded that tumors larger than 100 mm are more likely to be ALT/WDL. However, a history of recurrence and concerning clinical or radiological features were not

significantly associated with classification as ALT/WDL.

Vargas AC, Joy C, Cheah AL, et al. Lessons learnt from *MDM2* fluorescence *in-situ* hybridisation analysis of 439 mature lipomatous lesions with an emphasis on atypical lipomatous tumour/well-differentiated liposarcoma lacking cytological atypia. *Histopathology*. 2022;80(2):369–380.

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Nodular maturation of testis: a non-neoplastic pediatric lesion that may present as a mass

The authors assessed a lesion of the pediatric testis, termed nodular maturation, that clinically mimics a testicular neoplasm and presents as an abnormality on ultrasound that may lead to surgical excision. The lesion has been described in textbooks but, to the authors' knowledge, has not been reported in the literature. Therefore, the authors reported on eight cases, emphasizing clinical presentation, ultrasound findings, histologic features, and clinical follow-up, in an attempt to shed light on the lesion and prevent unnecessary orchiectomy in young boys. The patients ranged in age from five to 11 years (mean, 7.9 years). Precocious puberty was identified in one patient as isolated penile enlargement without other signs. Another patient had a history of McCune–Albright syndrome but did not have signs of precocious puberty. All patients had testicular abnormalities on ultrasound—six had a discrete lesion and two showed diffuse testicular enlargement. In the six cases for which data were available, the mean size of the lesion on ultrasound was 0.9 cm (range, 0.4–1.7 cm). In the three cases for which macroscopic descriptions were available, no gross abnormalities were noted in the testicular parenchyma, despite the ultrasound findings. Nodular maturation occurred as a zone of more mature testicular parenchyma having larger, lumen-bearing seminiferous tubules that contrasted with the smaller, immature cords of the remaining parenchyma. The mature tubules showed germ-cell maturation (to the level of late spermatids/spermatozoa in six cases), mature Sertoli cells, and, in four cases, admixed nodules of mature Leydig cells. Of the six patients with available follow-up information, none developed a testicular neoplasm. Because it can present as a lesion on ultrasound that leads to surgical intervention, it is important that pathologists, radiologists, and urologists be aware of nodular maturation.

Przybycin CG, Williamson SR, Kao CS, et al. Nodular maturation of the testis: a non-neoplastic lesion of boys that may present as a mass on clinical and ultrasound examination. *Am J Surg Pathol*. 2022;46(2):220–225.

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Comparison of SSLs to their right-sided colonic counterparts

Low-grade appendiceal mucinous neoplasms can occur concurrently with appendiceal sessile serrated lesions. To interrogate relatedness, the authors performed multigene and IHC characterizations of paired and unpaired sessile serrated lesions (SSLs) and low-grade appendiceal mucinous neoplasms (LAMNs). They evaluated 62 serrated lesions from 50 appendectomy specimens for hotspot mutations in *BRAF, KRAS*, and *GNAS* genes. The authors subdivided the cases into three groups: 20 unpaired SSLs, 18 unpaired LAMNs, and 12 cases with an SSL and concurrent LAMN. Beta-catenin and annexin A10 immunostaining were performed on the SSL and LAMN components in the 12 paired cases, and 14 colonic SSLs served as controls. There was no significant difference in *KRAS* hotspot mutation rates between appendiceal SSLs (17 of 26; 65.4 percent) and LAMNs (16 of 30; 53.3 percent) (p=0.42). *BRAF* V600E was identified in a single case (one of 50; two percent) of SSL and concurrent LAMN (p=1.0). Mutations in *GNAS* were more common in LAMNs (six of 30; 20 percent) than in SSLs (one of 31; 3.2 percent) (p=0.05). The molecular genotypes between paired SSLs and LAMNs were concordant in most cases (10 of 12; 83.3 percent). Annexin A10 immunostaining was significantly greater in colonic SSLs (14 of 14; 100 percent) than in appendiceal SSLs (one of 12; 8.3 percent) (p<0.0001). And β-catenin immunostaining was significantly greater in LAMNs (10 of 12; 83.3 percent) than in paired appendiceal SSLs (two of 12; 16.7 percent) (p=0.003). Overall, appendiceal SSLs are predominantly driven by *KRAS* mutations and are not characterized by annexin A10 immunostaining. The data suggest that at least a subset of LAMNs may arise from a precursor SSL in which *GNAS*

mutations or upregulation of the WNT signaling pathway, or both, are likely key events modulating the progression to LAMN.

Chezar K, Minoo P. Appendiceal sessile serrated lesions are distinct from their right-sided colonic counterparts and may be precursors for appendiceal mucinous neoplasms. *Hum Pathol*. 2022;122;40–49.

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Interobserver variability in measuring depth of submucosal invasion of esophageal adenocarcinoma

Emerging data indicate that submucosa-invasive (pT1b) esophageal adenocarcinomas can be cured via endoscopic resection provided that invasion measures 500 µm or less and the adenocarcinomas lack other histological features predictive of nodal metastasis and exhibit negative margins. Therefore, pathologists' measurements of the depth of submucosal invasion in endoscopic resections may dictate management—that is, endoscopic follow-up versus oesophagectomy. The authors assessed interobserver agreement in measuring the depth of submucosal invasion in oesophageal endoscopic resections. For their study, six subspecialized gastrointestinal pathologists from five academic centers independently measured the depth of submucosal invasion in micrometers from the deepest muscularis mucosa on 37 oesophageal endoscopic resection slides (round one scoring). They then participated in a meeting to discuss a consensus approach to measuring depth of invasion and assess potential pitfalls. Remeasuring (round two scoring) was conducted after the consensus meeting. Intraclass correlation coefficient (ICC) and Cohen's kappa statistics were used to assess interobserver agreement. A lack of agreement was seen among the six reviewers with poor ICC for rounds one (0.40; 95 percent confidence interval [CI], 0.26–0.56) and two (0.49; 95 percent CI, 0.34–0.63). When measurements were categorized as greater or less than 500 µm, overall agreement among the six reviewers was only fair for rounds one (κ=0.37, 95 percent CI, 0.22–0.53) and two (κ=0.29, 95 percent CI, 0.12–0.46). The authors concluded that this study shows a lack of agreement among gastrointestinal pathologists in measuring the depth of submucosal invasion in oesophageal endoscopic resections despite formulating a consensus approach for scoring. If important management decisions continue to be based on this parameter, more reproducible and concrete guidelines are needed.

Karamchandani DM, Gonzalez RS, Westerhoff M, et al. Measuring depth of invasion of submucosa–invasive adenocarcinoma in oesophageal endoscopic specimens: how good are we? *Histopathology*. 2022;80(2):420–429.

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Limited adenocarcinoma of the prostate on needle core biopsy

Grading small foci of prostate cancer on a needle biopsy is often difficult, and the clinical significance of accurate grading remains uncertain. The authors conducted a study to assess whether grading limited adenocarcinoma on prostate biopsy specimens is critical. They assessed 295 consecutive patients who had one-core involvement of adenocarcinoma and had undergone extended sextant biopsy followed by radical prostatectomy. The linear tumor lengths on the biopsy specimens were less than 1 mm (n=114), 1 mm to 2 mm (n=82), 2 mm to 3 mm (n=35), and 3 mm or more (n=64). Longer length was strongly associated with higher grade group on biopsy or prostatectomy specimens, higher risk of extraprostatic extension or seminal vesicle invasion and positive surgical margin, and larger estimated tumor volume. When cases were compared based on biopsy specimen grade group, higher grade was strongly associated with higher prostatectomy specimen grade group, higher incidence of pT3/pT3b disease, and larger tumor volume. Outcome analysis further showed significantly higher risks for biochemical recurrence after radical prostatectomy in patients with 1 mm or more, 2 mm or more, 3 mm or more, GG2-4, GG3-4, GG4, less than 1 mm/GG2-4, less than 1 mm/GG3-4, less than 2 mm/GG3-4, 3 mm or more/GG2-4, or 3 mm or more/GG3-4 tumor on biopsy specimens than in respective control subgroups. In particular, 3 mm or more, GG3, and GG4 on biopsy specimens showed significance as independent prognosticators by multivariate analysis. No significant differences were noted in the rate of upgrading or downgrading after radical prostatectomy among those subgrouped by biopsy specimen tumor length—that is, less than 1 mm (44.7 percent), 1 mm to 2 mm (41.5

percent), 2 mm to 3 mm (45.7 percent), and 3 mm or more (46.9 percent). These results indicate that pathologists should make every effort to grade relatively small prostate cancer on biopsy specimens.

Bell PD, Teramoto Y, Gurung PMS, et al. Limited adenocarcinoma of the prostate on needle core biopsy: Is grading critical? *Arch Pathol Lab Med*. 2022;146(4):469–477.

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Characterization of features of colonic injury in patients receiving tacrolimus

Tacrolimus is a common immunosuppressant used in solid organ transplant recipients. Although it has been reported that most patients develop symptoms of diarrhea, there are limited data regarding patterns of injury in patients taking the immunosuppressant. The authors performed a study to characterize tacrolimus-related features of colonic injury. They retrospectively identified colonic samples from 20 patients receiving tacrolimus monotherapy. Records were reviewed for symptoms, endoscopic findings, other medications, and infections. None of the patients had gastrointestinal infections or used other drugs known to cause colonic injury, and none had received mycophenolate within six months of presentation. Cases were evaluated for the nature and distribution of inflammation and crypt abnormalities, including distortion, destruction, and apoptosis. Eighteen of the 20 (90 percent) patients were solid organ transplant recipients, and 17 of the 20 (85 percent) had gastrointestinal symptoms, most often diarrhea (75 percent). Furthermore, more than 50 percent had endoscopic colitis and 15 percent had ulcers or erosions, or both. Most (90 percent) cases showed regenerative epithelial changes. Apoptotic crypt cells were present in 55 percent of cases and numerous in 10 percent. Neutrophilic cryptitis was present in 60 percent of cases, and 35 percent showed crypt destruction. Plasma cell-rich lamina propria inflammation and crypt distortion were observed in 40 percent and 25 percent of cases, respectively. There was no correlation between therapy duration and features of chronic injury. The authors concluded that tacrolimus can cause symptomatic colitis. Histologic abnormalities are often mild and include regenerative crypts and scattered apoptotic debris. However, 40 percent of symptomatic patients have chronic colitis, most likely reflecting drug-induced immune dysregulation. Pathologists should be aware of these associations because colitis often resolves with decreasing drug dosage rather than treatment directed toward inflammatory bowel disease.

Hissong E, Mostyka M, Yantiss RK. Histologic features of tacrolimus-induced colonic injury. *Am J Surg Pathol*. 2022;46(1):118–123.

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