Anatomic pathology selected abstracts

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HER2 overexpression and amplification in uterine carcinosarcomas with serous morphology

October 2022—Uterine carcinosarcoma is an aggressive malignancy with few treatment options. A recent clinical trial has shown an increase in progression-free survival in patients with human epidermal growth factor receptor 2 (HER2)-positive serous endometrial carcinomas treated with anti-HER2–targeted therapies. However, few studies have evaluated HER2 expression and amplification in uterine carcinosarcoma. Like serous endometrial carcinoma, the majority of uterine carcinosarcomas have *TP53* mutations and a serous epithelial component, suggesting that the diseases may show similar rates of HER2 positivity and therapeutic response. Therefore, the authors evaluated the rates of HER2 overexpression and amplification in a cohort of uterine carcinosarcomas and determined whether a correlation exists between HER2 positivity and programmed cell death-ligand-1 (PD-L1) expression and mismatch repair (MMR) status. They assessed HER2 expression and amplification in a cohort of uterine carcinosarcomas over a five-year period. The authors performed HER2 IHC and chromogenic in situ hybridization on tissue microarray and whole tissue sections and scored them according to the most recent clinical trial recommendations. Three of 48 (six percent) uterine carcinosarcomas had strong (3+) HER2 IHC expression, and three (six percent) cases were equivocal (2+). Seven (15 percent) cases had HER2 amplification by chromogenic in situ hybridization, including the three with overexpression and two that were equivocal by IHC. MMR protein, p53, and PD-L1 expression status were obtained from prior whole section analyses. All HER2-positive cases had a serous morphology and aberrant p53 expression. Only minimal PD-L1 expression was seen in the HER2-positive cases, and none had MMR loss. A subset of uterine carcinosarcomas with serous morphology have overexpression or amplification of HER2, or both, which may predict response to HER2-targeted therapies. HER2-positive uterine carcinosarcomas may be less susceptible to immune checkpoint inhibition as it is uncommon for them to show MMR deficiency or strong PD-L1 expression, or both. Therefore, HER2-targeted therapies could be of clinical utility in a subset of uterine carcinosarcomas that do not have other adjuvant treatment options.

Jenkins TM, Cantrell LA, Stoler MH, et al. HER2 overexpression and amplification in uterine carcinosarcomas with serous morphology. *Am J Surg Pathol*. 2022;46(4):435–442.

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Interobserver agreement in the diagnosis of anal dysplasia

As institutions move toward subspecialty sign-out, they must decide whether to assign anal biopsies to the gastrointestinal (GI) or gynecological pathology service. Because this decision is complex and multifactorial, the authors conducted a study in which they identified 200 archival tissue biopsies of anal mucosa and circulated them among three GI and three gynecological pathologists. Each pathologist scored each biopsy as normal, atypical, low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL). The GI and gynecological pathologists then convened (as separate groups) to generate an in-person consensus diagnosis on cases with discordant individual interpretations. Six months later, each pathologist again reviewed the biopsies, blinded to their original diagnoses, to assess the impact of the consensus conferences. The GI pathologists agreed on 97 (49 percent) cases prior to the consensus conference, and the gynecological pathologists agreed on 33 (17 percent). For the three GI pathologists, the sensitivities in detecting HSIL were 47, 100, and 21 percent. For the three gynecological pathologists, the sensitivities were 74, 89, and 84 percent. The sensitivities of the GI and gynecological consensus diagnoses were 74 percent. For the GI pathologists, the specificities in detecting HSIL

were 99, 90, and 100 percent. For the gynecological pathologists, the specificities were 99, 92, and 91 percent. The specificities of the GI and gynecological consensus diagnoses were 100 percent. The authors concluded that a mild to moderate degree of interobserver variability exists in pathologists' diagnosis of anal dysplasia but that their study cannot indicate sufficiently whether GI or gynecological pathologists should sign out anal biopsies. The study supports the utility of consensus conferences, as overall agreement among the GI and gynecological pathologists improved following such conferences.

Abu-Farsakh S, Drage MG, Huber AR, et al. Interobserver agreement in the diagnosis of anal dysplasia: comparison between gastrointestinal and gynaecological pathologists and utility of consensus conferences. *Histopathology*. 2022;80:648–655.

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Assessment of GI stromal tumors arising in uncommon locations

Risk stratification of gastrointestinal stromal tumors is based on experience with tumors of the stomach, small bowel, and rectum, which are far more common than gastrointestinal stromal tumors (GISTs) of other sites. The authors conducted a study involving 47 institutions, in which they analyzed GISTs of the esophagus (n=102), colon (n=136), and appendix (n=27) for their size, mitotic rate, morphology, and outcome to determine which criteria predict their behavior. Esophageal GISTs were small (median, 2.5 cm) with spindle cell morphology and a low mitotic rate (mean, 3.6/5 mm^2). Twelve of those tumors progressed, including 11 with a mitotic rate greater than 5/5 mm^2 and one large (6.8 cm) GIST with a mitotic rate of 2/5 mm^2. Colonic GISTs were smaller (median, 1.4 cm) and presented with abdominal pain or bleeding in 29 percent of cases. Most (92 percent) were composed of spindle cells with a mean mitotic rate of 4.6/5 mm^2. Sixteen of those tumors progressed: 14 had mitotic rates greater than 5/5 mm^2, and two were greater than 5 cm and had a mitotic rate of less than 5/5 mm^2. All but one appendiceal GIST measured less than 2 cm. These tumors were composed of spindle cells with low mitotic rates (less than 5/5 mm^2), and none progressed. The results suggest that progression risk among esophageal and colonic GISTs is associated with increased mitotic activity (greater than 5/5 mm^2) and size greater than 5 cm. These findings support the use of size and mitotic rate for prognostication of GISTs in these locations, similar to the prognostication of tumors of the stomach, small bowel, and rectum.

Hu S, Alpert L, Cates JMM, et al. Rare GIST risk stratification group. Gastrointestinal stromal tumors (GISTs) arising in uncommon locations: clinicopathologic features and risk assessment of esophageal, colonic, and appendiceal GISTs. *Mod Pathol*. 2022;35(4):554–563.

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Analysis of false-negative Pap tests with invasive endocervical adenocarcinoma and AIS

The authors conducted a study to identify factors that contribute to false-negative Papanicolaou tests in patients with endocervical adenocarcinoma (EA) or adenocarcinoma in situ (AIS) and to analyze the impact of educational instruction on interobserver agreement in these cases. A consensus group and six cytopathologists and six cytotechnologists reviewed false-negative Pap tests from patients with EA/AIS in two rounds, with an educational session on glandular neoplasia in Pap tests conducted between the rounds. Of 79 Pap tests from patients with EA/AIS, 57 (72.2 percent) were diagnosed as abnormal and 22 (27.8 percent) as negative. Of the 22 false-negative cases, 10 remained negative on consensus review, with false-negative diagnoses attributed to sampling variance. The other 12 cases were upgraded to epithelial abnormalities, of which eight were upgraded to glandular lesions. Two of the latter 12 false-negative diagnoses were attributed to screening variance and 10 to interpretive variance. On individual review, abnormal cells were misinterpreted as reactive glandular cells or endometrial cells in 88 percent (seven of eight) and 63 percent (five of eight) of cases upgraded to glandular abnormalities,

respectively. With education, the proportion of reviewers demonstrating at least moderate agreement with the consensus diagnosis (Cohen's kappa >0.4) increased from 33 percent (4 of 12) to 75 percent (9 of 12). Sampling and interpretive variance each accounted for nearly half of the false-negative Pap tests, with the main source of interpretive variance being underclassification of neoplastic glandular cells as reactive glandular or endometrial cells. Educational instruction significantly decreased the interpretive variance and interobserver variability in diagnosing glandular abnormalities.

Lin M, Narkcham S, Jones A, et al. False-negative Papanicolaou tests in women with biopsy-proven invasive endocervical adenocarcinoma/adenocarcinoma in situ: a retrospective analysis with assessment of interobserver agreement. *J Am Soc Cytopathol*. 2022;11(1):3–12.

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Differentiating between interval appendicitis and acute appendicitis based on histological findings

While many patients presenting with clinical signs and symptoms of acute appendicitis undergo surgical intervention shortly after presentation, some are initially managed without surgical intervention and undergo appendectomy later. The histology of such interval appendicitis has only been described in small series. Furthermore, the authors noticed a recent increase in interval appendicitis specimens at their institution. The authors identified appendectomy specimens at their institution during 2018 via H&E slides and electronic medical records and evaluated the cases based on multiple histological findings. Their cohort included 165 patients (125 acute appendicitis and 40 interval appendicitis). Patients were placed in the acute appendicitis group if they presented to the hospital within one week of symptom onset and underwent appendectomy within 48 hours. They were placed in the interval appendicitis group if appendectomy was delayed at least one week. Findings significantly more common in the acute appendicitis group included mucosal acute inflammation, mural acute inflammation, and acute serositis. Findings significantly more common in the interval appendicitis group included Crohn-like mural inflammation, mural chronic inflammation, mural fibrosis, goblet cell hyperplasia, granulomas, hemosiderin-laden macrophages, granulation tissue, chronic serositis, and serosal adhesions. Xanthogranulomatous inflammation was specific to interval appendicitis. The authors concluded that these histological patterns can guide sign-out and prevent diagnostic errors, particularly when clinical information is not available.

Malvar G, Peric M, Gonzalez RS. Interval appendicitis shows histological differences from acute appendicitis and may mimic Crohn disease and other forms of granulomatous appendicitis. *Histopathology*. 2022;80:965–973.

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