Anatomic pathology selected abstracts

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ALK expression in angiomatoid fibrous histiocytoma: a potential diagnostic pitfall

March 2019—The authors recently encountered a case of primary pulmonary angiomatoid fibrous histiocytoma (AFH), which was initially misdiagnosed as inflammatory myofibroblastic tumor based in part on anaplastic lymphoma kinase expression by IHC. Prompted by this experience, they evaluated anaplastic lymphoma kinase (*ALK*) expression in 11 AFH, 15 inflammatory myofibroblastic tumors (IMT), and 11 follicular dendritic cell sarcomas using three antibody clones: D5F3, 5A4, and ALK1. ALK IHC-positive cases were analyzed with FISH using a dual-color ALK break-apart probe kit. The majority of AFH cases studied were positive for ALK IHC with at least one antibody—nine of 11 D5F3, six of nine 5A4, one of nine ALK1—and most demonstrated moderate to strong cytoplasmic staining. AFH with positive ALK IHC showed no *ALK* gene rearrangement by FISH with *ALK* copy number ranging from 1.6 to 2.1. Sixty-seven percent of IMT were ALK positive by IHC—10 of 15 D5F3, eight of 15 5A4, seven of 15 ALK1—and nine of 10 cases were positive for *ALK* gene rearrangement by FISH. All follicular dendritic cell sarcomas were negative for ALK by IHC (D5F3 and 5A4). The results indicate that *ALK* expression in AFH is common, particularly with the highly sensitive D5F3 and 5A4 antibodies and enhanced detection systems, and potentially may present diagnostic confusion with IMT. The underlying mechanism of *ALK* expression in AFH is unclear, although it does not appear to be from *ALK* rearrangement or amplification.

Cheah AL, Zou Y, Lanigan C, et al. ALK expression in angiomatoid fibrous histiocytoma: a potential diagnostic pitfall. *Am J Surg Pathol.* 2019;43(1):93–101.

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PD-1 and PD-L1 expression in primary HNSCC and related lymph node metastasis

The expression profiles and clinical impact of programmed cell death ligand 1 (PD-L1) and programmed cell death 1 (PD-1) expressing tumor-infiltrating lymphocytes in head and neck squamous cell carcinoma (HNSCC) are not elucidated fully. The authors conducted a study to evaluate expression patterns in primary HNSCC and related lymph node metastasis and the impact on patients' clinical outcome. They analyzed IHC staining patterns of PD-L1 and PD-1 in 129 specimens of primary HNSCC and 77 lymph node metastases. The results were correlated with patients' clinical data. PD-L1 expression was observed in 36 percent of primary carcinomas and 33 percent of lymph node metastases and correlated significantly with decreased overall survival ($P=.01$) and disease-free survival ($P=.001$) in oral cavity squamous cell carcinoma patients. PD-L1 expression was associated with lymph node metastasis ($P=.0223$). Infiltration of PD-1–expressing lymphocytes correlated significantly with favorable overall survival ($P=.001$) and disease-free survival ($P=.001$) in oropharyngeal cancer patients and hypopharyngeal cancer patients (overall survival, $P=.007$; disease-free survival, $P=.001$). The presence of PD-1 tumor-infiltrating lymphocytes also correlated significantly with better overall survival ($P=.005$) and disease-free survival ($P=0$) in the human papilloma virus-negative cohort. Cox regression multivariate analysis revealed PD-1 tumor-infiltrating lymphocyte expression as an independent prognostic marker for overall survival ($P=.004$) and disease-free survival ($P=.001$), and T stage was validated as a negative prognostic marker for overall survival ($P=.011$). PD-1–expressing lymphocytes ($P=.0412$) and PD-L1 expression ($P=.0022$) patterns correlated significantly in matched primary cancers and lymph node metastases. These results characterize the expression profiles of PD-1 axis proteins in HNSCC, which may serve as possible clinical prognostic markers.

Schneider S, Kadletz L, Wiebringhaus R, et al. PD-1 and PD-L1 expression in HNSCC primary cancer and related lymph node metastasis—impact on clinical outcome. *Histopathol.* 2018;73(4):573–584.

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Role of stroma in relationships between risk factor exposure and age-related epithelial involution in benign breast

Delayed age-related lobular involution has been associated with elevated breast cancer risk. However, intraindividual variability in epithelial involution status within a woman is undefined. The authors developed a novel measure of age-related epithelial involution—density of epithelial nuclei in epithelial areas using digital image analysis combined with stromal characteristics (percentage of section area comprising stroma). They evaluated approximately 1,800 hematoxylin-and-eosin–stained sections of benign breast tissue from 416 participants having breast surgery for cancer or benign conditions. They studied two to 16 slides per woman from different regions of the breast. Epithelial involution status varied within a woman and as a function of stromal area. Percentage stromal area varied between samples from the same woman. The median difference between highest and lowest stromal area within a woman was 7.5 percent, but it ranged from 0.01 to 86.7 percent. Restricting the assessment to women with at least 10 percent stromal area (n = 317), epithelial nuclear density decreased with age (−637.1 cells/mm^2 per decade of life after age 40; $P < .0001$), increased with mammographic density (457.8 cells/mm^2 per increasing Breast Imaging Reporting and Data System density category; $P = .002$), and increased nonsignificantly with recent parity, later age at first pregnancy, and longer and more recent oral contraceptive use. These associations were attenuated in women with samples categorized as mostly fat (fewer than 10 percent stroma [n = 99]). Thirty-one percent of women evaluated had both adequate stroma (10 percent or more) and regions of breast tissue that were mostly fat (less than 10 percent stroma). The probability of having both types increased with the number of breast tissue samplings. Several breast cancer risk factors are associated with elevated age-related epithelial content, but associations depend on stromal context. Stromal characteristics appear to modify relationships between risk factor exposures and breast epithelial involution.

Chollet-Hinton L, Puvanesarajah S, Sandhu R, et al. Stroma modifies relationships between risk factor exposure and age-related epithelial involution in benign breast. *Mod Pathol.* 2018;31:1085–1096.

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Link between treatment for perianal Paget disease and mimicry of recurrent disease

The histologic differential diagnosis of perianal Paget disease includes malignant melanoma, pagetoid spread of squamous cell carcinoma, and secondary involvement by colorectal carcinoma. While it is useful to consider these entities when establishing a diagnosis, such consideration does not apply when patients with Paget disease undergo surveillance for recurrent disease. Treatment of perianal Paget disease consists of a combination of surgical excision with skin grafts and topical chemotherapeutic agents that induce cytologic alterations in benign cells and simulate recurrent malignancy. To evaluate the therapy-related changes and possible diagnostic pitfalls for patients with Paget disease, the authors reviewed 412 post-treatment tissue samples from three women with primary perianal Paget disease who underwent wide excision, skin grafting, and topical 5-fluorouracil therapy. Biopsy samples from engrafted skin often displayed single and clustered cells with hyperchromatic nuclei dispersed in the deep epidermis. Similar cells were scattered throughout all levels of the epidermis in biopsy samples following topical chemotherapy. The abnormal cells were negative for cytokeratin 7 (CK7) and mucicarmine in both situations. Disease recurred in all patients. Some Paget cells showed classic features with eosinophilic or mucinous cytoplasm and eccentric nuclei, while others were smaller with less conspicuous atypia. All Paget cells showed strong, membranous CK7 staining. The authors concluded that treatment of perianal Paget disease can elicit cytologic abnormalities in benign epithelial cells that simulate the cytologic features of recurrent disease and can diminish the atypia of Paget cells. Immunohistochemical stains for CK7 can be helpful when

evaluating surveillance samples from these patients.

Pittman ME, Milsom J, Yantiss RK. Treatment effects can mimic recurrent extramammary Paget disease in perianal skin. *Am J Surg Pathol.* 2018;42(11):1472–1479.

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Utility of p53 and Smad4 immunolabeling in distinguishing COD and HG-PanIN

Invasive pancreatic ductal adenocarcinoma can infiltrate and spread along pre-existing pancreatic ducts and ductules in a process known as cancerization of ducts (COD). Histologically, COD can mimic high-grade pancreatic intraepithelial neoplasia (HG-PanIN). The authors reviewed pancreatic resections from 100 patients with invasive pancreatic ductal adenocarcinoma (PDAC) for the presence or absence of ducts with histologic features of COD. Features supporting COD included adjacent histologically similar invasive PDAC and an abrupt transition between markedly atypical intraductal epithelium and normal duct epithelium or circumferential involvement of a duct. Because the *TP53* and *SMAD4* genes are frequently targeted in invasive PDAC but not HG-PanIN, paired PDAC and histologically suspected COD lesions were immunolabeled with antibodies to the p53 and Smad4 proteins. Suspected COD was identified on hematoxylin-and-eosin–stained sections in 89 (89 percent) of the cases. Immunolabeling for p53 and Smad4 was performed in 68 (76 percent) of 89 cases. P53 was interpretable in 55 cases, and all of those cases showed concordant labeling between COD and invasive PDAC. There was matched aberrant p53 immunolabeling in 37 (67 percent) cases, including overexpression in 30 (55 percent) cases and lack of expression in seven (13 percent) cases. Smad4 immunolabeling was interpretable in 61 cases, and 59 (97 percent) of those cases showed concordant labeling between COD and invasive PDAC. Matched loss of Smad4 was seen in 28 (46 percent) cases. The immunolabeling of invasive PDAC and COD for p53 and Smad4 supports the high prevalence of COD observed using hematoxylin and eosin and highlights the utility of p53 and Smad4 immunolabeling in differentiating COD and HG-PanIN.

Hutchings D, Waters KM, Weiss MJ, et al. Cancerization of the pancreatic ducts: demonstration of a common and under-recognized process using immunolabeling of paired duct lesions and invasive pancreatic ductal adenocarcinoma for p53 and Smad4 expression. *Am J Surg Pathol.* 2018;42:1556–1561.

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Colonic graft-versus-host disease in transplant patients

Histologic characterization of graft-versus-host disease in autologous stem cell transplant patients has been limited. The authors conducted a study to characterize colonic graft-versus-host disease in autologous stem cell transplant patients and compare those patients with a control group of allogeneic stem cell transplant patients to determine whether the disease can be diagnosed less than 21 days post-transplantation in autologous stem cell transplant recipients. The study was also intended to quantify colonic T-cell populations in autologous stem cell transplant patients. Colonic biopsies obtained to evaluate for graft versus host disease in allogeneic and autologous stem cell transplant patients were reviewed for the maximum number of apoptotic bodies per 10 contiguous crypts. Immunohistochemical stains for CD4, CD8, and FoxP3 were performed. Clinical information was collected through chart review. The study group consisted of 122 colonic biopsies from 84 patients. Sixteen patients underwent autologous stem cell transplant, and 68 underwent allogeneic stem cell transplant. Autologous stem cell transplant patients underwent biopsy significantly earlier than allogeneic stem cell transplant patients (median, 20 versus 87 days; $P = .0002$), had significantly higher apoptotic counts compared with matched-related donor patients (7.5 versus 3.9; $P = .03$), and had higher FoxP3-positive lamina propria lymphocyte counts compared with allogeneic stem cell transplant patients (9.2 versus 5.3; $P = .03$). In patients undergoing biopsy less than 21 days post-transplantation, allogeneic stem cell transplant patients had fewer CD8-positive lamina propria lymphocytes and a trend of fewer FoxP3- and CD4-positive lamina propria lymphocytes compared with autologous stem cell transplant patients. Autologous stem cell transplant patients have more prominent crypt apoptosis

compared with allogeneic stem cell transplant patients and do not have numerically decreased FoxP3-positive lamina propria lymphocytes. The presence of robust T-cell populations in the early period following transplantation suggests that the 21-day cutoff for diagnosing graft versus host disease is not applicable to autologous stem cell transplant patients.

Hartley CP, Carrillo-Polanco LF, Rowan DJ, et al. Colonic graft-vs.-host disease in autologous versus allogeneic transplant patients: earlier onset, more apoptosis, and lack of regulatory T-cell attenuation. *Mod Pathol.* 2018;31:1619–1626.

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