Anatomic Pathology Abstracts

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Analysis of the surveillance of women diagnosed with atypical ductal hyperplasia on core needle biopsy

August 2018—A needle core biopsy diagnosis of atypical ductal hyperplasia is an indication for open biopsy. The launch of randomized clinical trials of active surveillance for low-risk ductal carcinoma in situ leads to the paradoxical situation of women with low-grade ductal carcinoma in situ being observed and those with atypical ductal hyperplasia having surgery. If the malignancies diagnosed after surgery for atypical ductal hyperplasia are dominated by low-risk ductal carcinoma in situ, women with atypical ductal hyperplasia may also be considered for surveillance. The authors conducted a 10-year prospective observational study of women diagnosed with atypical ductal hyperplasia on core biopsy after screening mammography. They retrieved their clinical, imaging, and histologic data and carried out a blind review of core biopsy histology, subclassifying the atypical ductal hyperplasia along a spectrum from hyperplasia to ductal carcinoma in situ. Using the final surgical pathology data, they calculated the proportion and grades of ductal carcinoma in situ and invasive cancers diagnosed at open biopsy; histologic extent of the malignancy at surgery; and biomarker profile and nodal status of any invasive cancers. They ascertained any independent predictors of any malignancy and high-risk malignancy, defined in this study as invasive cancer, or high-grade ductal carcinoma in situ, or intermediate-grade ductal carcinoma in situ with any necrosis. The authors extrapolated the above to simulate active surveillance for women with screen-detected atypical ductal hyperplasia. Between January 2005 and December 2014, 114 women (mean age, 59 years; range, 40–79 years) were included in this evaluation. Surgical pathology, which was available in 110 (97 percent) women, confirmed malignancy in 46 (40 percent). All 46 malignant cases had ductal carcinoma in situ, which was accompanied by invasive carcinoma in nine (eight percent) women. Together, 21 (19 percent) women had either invasive cancer (nine percent), high-grade ductal carcinoma in situ (six percent), or necrotizing, intermediate-grade ductal carcinoma in situ (six percent). Only one of nine invasive breast cancers was grade 1; three were multifocal; and all were 8 mm or less, node negative, and estrogen receptor positive, but two were HER2 amplified. The mean extent of ductal carcinoma in situ in any one specimen was 19.8 mm (median, 13 mm; range, 2–110 mm). Overall, 32 women (29 percent of the whole cohort and 70 percent of those 46 with malignancy) required additional surgery, including mastectomy in 12 (11 percent). A multivariable model for predicting the likelihood of any malignancy showed a statistically significant association only with the post-review subtype of atypical ductal hyperplasia, adjusting for lesion size. Independent predictors of high-risk malignancy (invasive cancer or non-low–grade ductal carcinoma in situ) were not identified. The authors concluded that if active surveillance is adopted for screen-detected atypical ductal hyperplasia diagnosed on core biopsy, 60 percent of women will avoid unnecessary surgery and an additional 24 percent will meet eligibility criteria for ductal carcinoma in situ surveillance trials. However, 18 percent of women will have undiagnosed invasive breast cancer or non-low–risk ductal carcinoma in situ. These women with high-risk lesions are not reliably identified preoperatively.

Farshid G, Edwards S, Kollias J, et al. Active surveillance of women diagnosed with atypical ductal hyperplasia on core needle biopsy may spare many women potentially unnecessary surgery, but at the risk of undertreatment for a minority: 10-year surgical outcomes of 114 consecutive cases from a single center. *Mod Pathol.* 2018;31:395–405.

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Assessment of lymph node involvement in breast implant-associated ALCL

Breast implant-associated anaplastic large cell lymphoma is a rare T-cell lymphoma that arises around breast implants. Most patients manifest with periprosthetic effusion and a subset develop a tumor mass or lymph node involvement. The authors conducted a study to describe the pathologic features of lymph nodes from patients with breast implant-associated anaplastic large cell lymphoma (BI-ALCL) and to assess the prognostic impact of lymph node involvement. They analyzed the clinical findings and histopathologic features of lymph nodes in 70 patients with BI-ALCL. Fourteen (20 percent) of those patients had lymph node involvement. All of the lymph nodes involved were regional and the most frequent were axillary (93 percent). The pattern of involvement was sinusoidal in 13 (92.9 percent) cases, often associated with perifollicular, interfollicular, and diffuse patterns. Two cases had Hodgkin-like patterns. The five-year overall survival rate was 75 percent for patients with lymph node involvement and 97.9 percent for patients without lymph node involvement at presentation ($P = .003$). Six of 49 (12.2 percent) patients with tumor confined to the capsule had lymph node involvement, compared with eight of 21 (38 percent) patients with tumor beyond the capsule. Most patients with lymph node involvement achieved complete remission after various therapeutic approaches. Two of 14 (14.3 percent) patients with lymph node involvement died of disease compared with no patients without lymph node involvement. Twenty percent of patients with BI-ALCL had lymph node involvement by lymphoma, most often in a sinusoidal pattern. The authors concluded that BI-ALCL beyond the capsule is associated with a higher risk of lymph node involvement. Involvement of lymph nodes was associated with decreased overall survival rates. Misdiagnosis as Hodgkin lymphoma is a pitfall.

Ferrufino-Schmidt MC, Medeiros LJ, Liu H, et al. Clinicopathologic features and prognostic impact of lymph node involvement in patients with breast implant-associated anaplastic large cell lymphoma. *Am J Surg Pathol.* 2018;42(3):293–305.

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Syphilis of the aerodigestive tract

Syphilis, a sexually transmitted infection caused by the Gram-negative bacterium *Treponema pallidum*, is increasing in prevalence in the United States. The authors observed that primary and secondary syphilis of the aerodigestive tract can afflict a large age spectrum with varied clinical and histopathologic findings, which can lead to diagnostic problems and frequent misdiagnosis. In this study, they described the histopathologic patterns of syphilis of the aerodigestive tract to increase awareness of its varied appearance. The authors identified three patterns of inflammatory response to syphilis: plasma cell rich, lymphohistiocytic, and lymphoma like. They also reported the presence of immunoglobulin G4-predominant plasma cells in the inflammatory response as a potential mimicker of immunoglobulin G4-related disease. The authors found that the use of *T. pallidum* immunohistochemical stain is more reliable than Steiner silver stain for identifying spirochetes. The study highlights the finding that despite convention, plasma cells are not always abundant in syphilis. Surgical pathologists' awareness of the histopathologic range of syphilis in the aerodigestive tract can lead to the correct diagnosis and guide appropriate treatment.

Tse JY, Chan MP, Ferry JA, et al. Syphilis of the aerodigestive tract. *Am J Surg Pathol.* 2018;42(4):472–478.

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Gastric poorly cohesive carcinoma: a study of mutational patterns

Genome-wide next-generation sequencing has revealed several driver mutations in gastric cancer and allowed the establishment of a molecular taxonomy of such cancer. However, there are few detailed studies on the mutational spectrum of poorly cohesive gastric carcinoma. Therefore, the authors conducted a study to investigate the mutation profile of the disease based on clinicopathological characteristics. They analyzed the mutational pattern of 77 genes using targeted sequencing in a cohort of 91 patients with poorly cohesive carcinoma and evaluated

the clinicopathological significance of the various mutations based on histological pattern, either signet ring cell (SRC) or other types of poorly cohesive carcinoma not otherwise specified (PCC-NOS). Panels of seven *(PIK3CA, CDH1, PTEN, RHOA, HDCA9, KRAS,* and *ATM*), three (*PIK3CA, CTNNB1,* and *KRAS*), and two (*HDCA9* and *IGF1R*) genes were associated with a diffuse infiltrative growth pattern, lymphovascular invasion, and perineural invasion, respectively. Furthermore, *PDGFRB* mutations were associated with a favorable prognosis, whereas *MET* mutations were associated with a poor prognosis. The PCC-NOS–predominant type was associated with a greater depth of invasion, lymph node metastasis, and poorer prognosis than the SRC-predominant type. Mutations in *TP53, BRAF, PI3CA, SMAD4*, and *RHOA* were associated with PCC-NOS. Interestingly, *RHOA*-mutated gastric cancers showed a distinct morphology, as they were characterized by a superficial SRC or tubular component and a deep invasive PCC-NOS component with desmoplasia. The authors concluded that the study demonstrates that gastric poorly cohesive carcinomas show several mutational patterns associated with specific clinicopathological characteristics and, in particular, distinct morphological findings when associated with *RHOA* mutation.

Kwon CH, Kim YK, Lee S, et al. Gastric poorly cohesive carcinoma: a correlative study of mutational signatures and prognostic significance based on histopathological subtypes. *Histopathology.* 2018;72:556–568.

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Distinguishing clear cell carcinoma from p16-positive squamous cell carcinoma

Clear cell carcinoma is a low-grade malignancy that commonly arises in minor salivary glands of the oropharynx and other sites. EWSR1-ATF1 gene fusions seem to be specific for this salivary neoplasm. Testing for EWSR1-ATF1 has expanded the histologic spectrum of clear cell carcinoma (CCC). For example, many CCCs have a predominantly squamous phenotype with few clear cells, a finding that can lead to it being confused with squamous cell carcinoma (SqCC). P16 immunohistochemical staining to determine human papillomavirus (HPV) status has become standard practice for all oropharyngeal carcinomas showing squamous differentiation. The authors conducted a study to determine whether this practice could contribute to the difficulty in distinguishing CCC from p16-positive SqCC. They searched their surgical pathology archives for cases of CCC and evaluated those cases using p16 immunohistochemistry, high-risk HPV RNA in situ hybridization (ISH), and EWSR1 gene break-apart fluorescence ISH. They identified 16 CCCs, all of which harbored an EWSR1 rearrangement, in 11 women and five men. The study subjects ranged in age from 30 to 85 years (mean, 58 years). The CCCs arose in the oropharynx (tongue base or tonsil: n = 8; 50 percent), oral cavity (n = 4; 25 percent), and nasopharynx (n = 4; 25 percent). Each case demonstrated clear cells, but the proportion was highly variable (10 to 90 percent; mean, 48 percent), with seven of 16 cases having fewer than 50 percent clear cells. Submitted diagnoses included SqCC (n = 3) and mucoepidermoid carcinoma (n = 2). Of the three patients diagnosed with SqCC, one was scheduled to undergo chemoradiation and one had already completed chemoradiation. All 16 CCCs demonstrated p16 staining, with the percentage of p16-positive cells categorized as 70 percent or more (n = 2), 50 to 69 percent (n = 3), and 10 to 49 percent (n = 11). Staining was cytoplasmic and nuclear. All cases were negative for high-risk HPV by RNA ISH. CCCs regularly show squamous features, often lack prominent clear cell changes, frequently arise in the oropharynx, and invariably show p16 staining. These features may cause confusion with SqCC, particularly HPV-related oropharyngeal SqCC. P16 staining is not to be taken as unequivocal evidence of an HPV-related SqCC, even for carcinomas showing squamous differentiation and originating in the oropharynx. Failure to recognize this pitfall could result in overly aggressive treatment of a low-grade carcinoma.

Bishop JA, Rooper LM, Chiosea SI, et al. Clear cell carcinoma of salivary glands is frequently p16 positive: a pitfall in the interpretation of oropharyngeal biopsies. *Am J Surg Pathol.* 2018;42(3):367–371.

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Frequency of *KRAS* mutations and high tumor budding in cecal

adenocarcinoma

Recent literature indicates that adenocarcinomas of the cecum differ from noncecal proximal colon adenocarcinomas with respect to molecular alterations and that cecal tumor site may be a prognostically relevant variable. The authors compared molecular alterations, histopathologic features, and disease-specific survival in a series of 328 colonic adenocarcinomas identified during a two-year period and stratified by tumor location (cecum, right colon, and left colon). Overall, cecal adenocarcinomas demonstrated the highest frequency of molecular abnormalities, with 74 percent harboring a *KRAS* exon 2 or 3 mutation, *BRAF* mutation, or DNA mismatch repair protein deficiency. *KRAS* mutations were more frequently seen in the cecum than in all other tumor sites ($P = .03$). They were identified in 46 percent of cecal adenocarcinomas compared with only 25 percent of adenocarcinomas of the right colon ($P = .004$). Cecal adenocarcinomas more frequently displayed adverse histopathologic features—in particular, high tumor budding (31 percent)—compared with tumors of the right colon (18 percent; $P = .04$) and left colon (17 percent; $P = .02$). Overall stage was the most important independent predictor of disease-specific survival in the multivariable analysis. However, cecal tumor site and high tumor budding were also predictive of poor survival, particularly in patients with stage III or IV tumors. The authors concluded that cecal adenocarcinomas are characterized by a high frequency of *KRAS* mutations compared with noncecal right colon tumors, frequently display high tumor budding, and may be a prognostically relevant variable, particularly in patients with stage III or IV disease.

Landau MA, Zhu BS, Akwuole FN, et al. Site-specific differences in colonic adenocarcinoma: KRAS mutations and high tumor budding are more frequent in cecal adenocarcinoma. *Am J Surg Pathol.* 2018;42:351–358.

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