Anatomic pathology selected abstracts

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Mucocele-like lesion of the breast diagnosed on core biopsy

August 2022—Mucocele-like lesion of the breast is an uncommon entity. Studies show low rates of upgrade from core needle biopsy to excision. The authors conducted a study to evaluate features associated with upgrade of cases of mucocele-like lesion of the breast (MLL) diagnosed on core needle biopsy. They reviewed 78 MLL diagnosed on core needle biopsy from November 1998 to March 2019 and subsequent excisions. The histologic parameters evaluated included presence of atypia, presence and morphology of calcifications, and morphologic variant (classic [C-MLL], duct ectasia like [DEL-MLL], or cystic mastopathy like [CML-MLL]). Forty-five MLL lacked atypia and 33 were associated with atypia (32 atypical ductal hyperplasia and one atypical lobular hyperplasia). Sixty-one were C-MLL, 14 were DEL-MLL, and three were CML-MLL. Half showed coarse and fine calcifications, with fewer showing only coarse or fine calcifications and some showing none. Subsequent excision or clinical follow-up was available for 25 MLL without atypia, of which two (eight percent) were upgraded to ductal carcinoma in situ (DCIS), and 23 with atypia, of which four (17.4 percent) were upgraded to DCIS. No cases were upgraded to invasive carcinoma. All upgraded cases showed coarse calcifications on core needle biopsy and were associated with residual calcifications on post-core needle biopsy imaging. Most MLL present as calcifications, and nearly half are associated with atypia. Upgrade to DCIS is twice as frequent in MLL with atypia as in those without atypia. The authors concluded that predominance of coarse calcifications and the presence of residual targeted calcifications following core needle biopsy may be associated with higher upgrade rates.

Towne WS, Michaels AY, Ginter PS. Mucocele-like lesion of the breast diagnosed on core biopsy. *Arch Pathol Lab Med*. 2022;146(2):213–219.

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Interobserver variability and overdiagnosis of dysplasia in fundic gland polyps

Fundic gland polyps arise sporadically and in combination with familial adenomatous polyposis. The criteria for distinguishing low-grade dysplasia (LGD) from regenerative atypia in familial adenomatous polyposis (FGPs) are not well established. The authors conducted a study to determine interobserver variability among pathologists in diagnosing LGD in FGPs and to determine whether diagnosis is influenced by knowledge of the clinical scenario. Five senior pathologists who were blinded to patients' clinical history reviewed 72 FAP-associated FGPs and 34 sporadic FGPs. Cases were classified as negative (score of zero) or positive (score of one) for LGD. Each case was assigned a combined dysplasia score ranging from zero (unanimous for no dysplasia) to five (unanimous for LGD). Fleiss' kappa showed only moderate interobserver agreement ($\kappa = 0.46$). Forty-one FGPs were classified as negative for dysplasia by consensus, including 10 (24 percent) originally diagnosed as LGD. In contrast, all 37 cases classified as LGD by consensus were originally diagnosed as LGD, indicating that overdiagnosis of dysplasia is more common than underdiagnosis ($P = 0.0012$). Cytological atypia in the surface epithelium and an abrupt transition between atypical and normal-appearing epithelia were the most sensitive (97 percent and 100 percent, respectively) and specific (100 percent and 98 percent, respectively) features of dysplasia ($P < 0.0001$ for both comparisons). Interobserver agreement was very good when a diagnosis of dysplasia was based on the presence of both features ($\kappa = 0.85$). The authors concluded that there is high interobserver variability and a tendency to overdiagnose LGD in FGPs. Strict criteria requiring cytologic atypia in the surface epithelium and abrupt transition for LGD in FGPs lead to low interobserver variability.

Orr CE, Beneck D, Jessurun J, et al. High interobserver variability and frequent overdiagnosis of dysplasia in fundic gland polyps can be improved by detecting atypia on the surface epithelium and an abrupt transition to non-neoplastic cells. *Histopathology*. 2022;80(2):314–321.

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Use of IHC and NGS as complementary tests to identify PTEN abnormality in endometrial carcinoma

The *PTEN* gene plays a central role in the pathogenesis of endometrial carcinoma. Previous studies have reported that PTEN IHC has good interobserver reproducibility. However, PTEN IHC is not used widely in laboratory practice, in part, because of its ill-defined interpretation criteria for staining. The authors conducted a study to re-evaluate the PTEN IHC pattern relative to next-generation sequencing for identifying PTEN abnormality. IHC and tagged-amplicon next-generation sequencing *PTEN* sequencing were performed on 182 endometrial carcinoma biopsy/curetting samples from five centers—in Canada, Netherlands, and the United Kingdom. Sensitivity, specificity, and accuracy of PTEN IHC to predict loss-of-function *PTEN* mutations were calculated. PTEN abnormalities associated with histotype and molecular subtype were assessed. Five PTEN IHC patterns were recorded—absent, subclonal loss, equivocal, reduced (relative to internal control), and retained. The sensitivity of absent PTEN IHC to predict a *PTEN* loss-of-function mutation was 75.4 percent (95 percent confidence interval [CI], 62.7–85.5 percent), while the specificity was 84.6 percent (95 percent CI, 76.2–90.9 percent), and the accuracy was 81.2 percent (95 percent CI, 74.4–86.9 percent). Abnormal PTEN, based on interpretation of the complementary assays, was present in 91.9 percent of endometrial endometrioid carcinoma, grade 1, and significantly higher in endometrial endometrioid carcinomas of all grades compared with endometrial serous carcinoma (80 versus 19.4 percent; $P < 0.0001$). PTEN abnormalities are common across all molecular subtypes of endometrioid carcinomas. The authors support using PTEN IHC in the diagnosis of endometrial neoplasms to provide PTEN status as ancillary information. However, they recommend complementary PTEN IHC and sequencing for clinical trials of therapies targeting loss of PTEN function.

Wang L, Piskorz A, Bosse T, et al. Immunohistochemistry and next-generation sequencing are complementary tests in identifying PTEN abnormality in endometrial carcinoma biopsies. *Int J Gynecol Pathol*. 2022;41(1):12–19.

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Pancreatic frozen section as a guide to operative management: likelihood of deferrals and errors

Surgery is the mainstay of treatment for pancreatic adenocarcinoma. Frozen section analysis is used to confirm the diagnosis and determine resectability and margin status. The authors conducted a study to evaluate the use and accuracy of frozen section and how the resulting diagnosis impacts surgical procedures. They reviewed the charts of patients who underwent planned pancreatic resections between January 2014 and March 2019 in which at least one frozen section was performed. The review included an assessment of frozen section results, preoperative cytology, final diagnoses, and synoptic reports. The frozen sections were categorized by margin, primary pancreatic diagnosis, metastasis, and vascular resectability, as defined by the surgeon. The deferral and error rates and surgeons' responses were noted. The authors identified 898 planned pancreatic resections and 221 frozen sections. The latter were performed for margin status (102), metastatic lesion evaluation (94), primary diagnosis (20), and to confirm vascular resectability (five). Frozen section diagnosis was deferred to permanent sections in 13 of 152 (8.6 percent) cases on 16 of 221 (7.2 percent) frozen sections: six for metastasis, eight for evaluation of margin status, and two for primary diagnosis. Discrepancies or errors were identified in four of 152 (2.6 percent) cases and four of 221 (1.8 percent) frozen sections. The surgeons' responses were different than expected in eight of 221 (3.6 percent) frozen sections, but those surgeons' actions were explained by other intraoperative findings for six of the eight. The authors concluded that frozen section remains an important diagnostic tool used primarily for evaluating margins and metastasis during pancreatectomy. In most cases, a definitive diagnosis is rendered, with occasional deferrals and few errors. Intraoperative findings explain most

cases in which surgeons act differently than expected based on frozen section diagnosis.

Chavez JA, Chen W, Freitag CE, et al. Pancreatic frozen section guides operative management with few deferrals and errors. *Arch Pathol Lab Med*. 2022;146(1):84–91.

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HPV-negative SCC of cervix with a focus on intraepithelial precursor lesions

The World Health Organization recently recognized human papilloma virus-independent invasive cervical squamous cell carcinoma without recognizing the existence of precursor lesions. The authors characterized three preinvasive lesions and six invasive squamous cell carcinomas (SCC) negative for HPV DNA (32 genotypes), HPV mRNA (14 genotypes), and genomic HPV sequencing. They evaluated histologic features; expression of $p16^{ink4a}$, p53, CK7, and CK17; aberrations in 50 cancer genes; and chromosomal copy number variations. HPV-negative preinvasive lesions were extensive basaloid or highly differentiated keratinizing intraepithelial proliferations three to 20 cell layers thick, partly with prominent cervical gland involvement. Two of three intraepithelial lesions and the in situ component of one of six SCC showed $p16^{ink4a}$ block staining, while one of six in situ components revealed heterogenous $p16^{ink4a}$ staining. All invasive components of keratinizing SCC were $p16^{ink4a}$ negative. Preinvasive and invasive SCC showed inconsistent CK7 and CK17 staining. Nuclear p53 overexpression was restricted to the *TP53* gene-mutated SCC. The highly vascularized peritumoral stroma showed a dense inflammatory infiltrate, including plasma cells and intratumoral and peritumoral eosinophilic granulocytes. Inconsistent somatic gene mutations (*PIK3CA, STK11, TP53, SMARC2B*, and *GNAS*) occurred predominantly in non-hotspot locations at low mutational frequencies in three of six SCC. Consistent aberrations included the pathogenic (angiogenic) germline polymorphism Q472H in the *KDR* gene (seven of nine patients) and chromosome 3q gains (four of nine patients). The authors concluded that HPV-negative intraepithelial cervical precancerous lesions exist as highly differentiated keratinized intraepithelial proliferations reminiscent of differentiated vulvar intraepithelial neoplasia or as undifferentiated basaloid intraepithelial lesions with occasional $p16^{ink4a}$ block staining resembling high-grade squamous intraepithelial lesion. Dense inflammatory infiltrates and the pathogenic germline variant Q472H in the *KDR* gene may contribute to tumor angiogenesis and progression of HPV-negative cervical carcinogenesis.

Regauer S, Reich O, Kashofer K. HPV-negative squamous cell carcinomas of the cervix with special focus on intraepithelial precursor lesions. *Am J Surg Pathol*. 2022;46(2):147–158.

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