Anatomic pathology selected abstracts

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Prognostic value of complex glandular patterns in invasive pulmonary adenocarcinomas

March 2023—Prognostic stratification of patients with surgically resected invasive pulmonary adenocarcinoma must be improved. The authors conducted a study to evaluate the prognostic value of complex glandular patterns (CGPs) in patients with resected stage I through IV lung adenocarcinoma. The presence of CGPs as a minor to predominant component was tested for association with overall survival (n=676) and relapse-free survival (n=463) after surgery. CGPs were observed in 284 (42 percent) tumors. Cribriform and fused gland were the predominant patterns in 35 and 37 cases, respectively. The presence of a cribriform pattern was associated with worse relapse-free but not overall survival. The fused gland pattern alone or grouped into CGPs with the cribriform pattern was not associated with overall or relapse-free survival. As a predominant pattern, cribriform was associated with worse survival rates than the five recognized histologic patterns. Patients with fused gland-predominant tumors had five-year survival between that of papillary- and micropapillary-predominant tumors. The authors concluded that the cribriform-predominant but not the fused gland-predominant subtype has poor prognosis that is similar to that of the solid and micropapillary subtypes. In contrast, the presence of a minor component of fused gland or CGPs (cribriform plus fused gland) is not associated with survival. The cribriform pattern alone offers prognostic stratification improvement, but this effect is attenuated when combined into CGPs to define a subset of acinar-predominant tumors with poor prognosis. This makes a case against combining cribriform and fused gland into CGPs to summarize high-grade patterns.

Bossé Y, Gagné A, Althakfi W, et al. Prognostic value of complex glandular patterns in invasive pulmonary adenocarcinomas. *Hum Pathol*. 2022;128:56–68.

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Well-differentiated papillary mesothelial tumor: a new name and new problems

Well-differentiated papillary mesothelial tumor is a morphologically distinctive lesion composed of expansile papillae with a myxoid core covered by a single layer of generally bland mesothelial cells. Whether some well-differentiated papillary mesothelial tumors (WDPMT), formerly called well-differentiated papillary mesothelioma, are precursors of invasive mesothelioma is uncertain. Contributing to this uncertainty are shallow biopsies of ordinary diffuse mesotheliomas that have superficial areas resembling WDPMT and the misinterpretation of some cases of mesothelioma in situ. Genetic analyses of a very small number of published cases of peritoneal WDPMT have shown a variety of mutations or copy number losses that do not overlap those found recurrently in invasive mesotheliomas. The newly described entity of mesothelioma in situ usually appears as a single layer of mesothelial cells that has lost BAP1 by immunostaining but sometimes is papillary and produces a morphologic mimic of WDPMT. The authors proposed that, at least in the peritoneal cavity, where most WDPMT occur, there are two morphologically identical but functionally distinct lesions: true WDPMT, which is a process that is probably benign, and papillary mesothelioma in situ with the configuration of WDPMT. For that reason, immunostaining for BAP1 and, if necessary, MTAP or *CDKN2A* FISH should be performed on cases with the appearance of WDPMT. It is possible, but speculative, that the small number of reports in the literature that describe invasive mesothelioma arising from WDPMT are, in fact, describing invasive mesothelioma arising from mesothelioma in situ that resembles WDPMT.

Churg A, Galateau-Salle F. Well differentiated papillary mesothelial tumor: a new name and new problems. *Mod Pathol*. 2022;35(10):1327–1333.

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Cytology and LGBT+ health: establishing inclusive cancer screening programs

Substantial disparities have been found in cancer screening for sexual minorities and gender non-conforming patients. In addition to such patients experiencing trauma from negative experiences with health care systems, disparities may be heightened due to the heteronormative and cisnormative design of screening programs and electronic health record systems. Furthermore, there are morphologic challenges specific to certain specimen types from the LGBT+ (lesbian, gay, bisexual, transgender, plus) population, including anal cytology samples, cervical cytology from transgender men taking testosterone, and neovaginal cytology samples. Men who have sex with men have a greater risk of anal cancer than does the general population. While early detection of anal dysplasia decreases the risk of invasive carcinoma, screening programs are not widespread. Cervical cancer screening may be psychologically and physically challenging for transgender men and nonbinary people. Exogenous testosterone therapy causes atrophic changes in cervical cytology samples that mimic high-grade dysplasia. The rate of unsatisfactory samples is also higher in this population. Although human papillomavirus (HPV)-driven cancers have been reported in patients with neovaginas, no guidelines exist regarding appropriate screening for transgender women and intersex patients who have neovaginas. The authors concluded that cytopathologists can improve or support the health of LGBT+ patients in many ways, such as by advocating for inclusive screening guidelines, validating self-collection of HPV and cytology samples, updating requisition forms to better capture the spectrum of gender expression, and recognizing the morphologic changes in cytology samples due to exogenous hormone use.

Compton ML, Taylor SS, Weeks AG, et al. Cytology and LGBT+ health: establishing inclusive cancer screening programs. *J Am Soc Cytopathol*. 2022;11(5):241–252.

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Persistent cholestatic injury and secondary sclerosing cholangitis in COVID-19 patients

COVID-19 has been associated with liver injury, and a small subset of patients recovering from severe disease have shown persistent markedly elevated liver biochemistries for months after infection. The authors conducted a study to characterize persistent biliary injury after COVID-19. A search of the surgical pathology files at Massachusetts General Hospital identified seven post–COVID-19 patients who had persistent biliary injury. Their clinical, radiologic, and pathologic features were assessed. All patients in this cohort presented with respiratory symptoms and had a complicated clinical course, with acute elevation of liver biochemistries. Alkaline phosphatase (ALP) was markedly and persistently elevated after discharge (median peak ALP, 1,498 IU/L at a median of 84 days after diagnosis). Magnetic resonance cholangiopancreatography identified three patients with irregularity, stricturing, and dilatation of intrahepatic ducts. No radiographic abnormalities were identified in the remaining four patients. Liver biopsies showed mild portal changes, with features of cholestatic injury (bile duct injury and canalicular cholestasis) in four patients and marked biliary obstruction (profound cholestasis, ductular reaction, and bile infarcts) in two patients. SARS-CoV-2 RNA was not found via in situ hybridization. At follow-up, most patients showed markedly improved liver biochemistries but mild persistent ALP elevation. A subset of critically ill COVID-19 patients demonstrated marked and persistent cholestatic injury, with radiographic and histologic evidence of secondary sclerosing cholangitis. This suggested that cholestatic liver disease and secondary sclerosing cholangitis may be long-term sequelae of COVID-19 acute illness as a longstanding manifestation of critical illness.

Shih AR, Hatipoglu D, Wilechansky R, et al. Persistent cholestatic injury and secondary sclerosing cholangitis in

COVID-19 patients. *Arch Pathol Lab Med*. 2022;146(10):1184–1193.

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Thymic mucoepidermoid carcinoma: a clinicopathologic and molecular study

Thymic mucoepidermoid carcinoma is a rare tumor, and its clinicopathologic features and outcomes have not been clarified. The authors conducted a study in which they investigated 20 cases of thymic mucoepidermoid carcinoma (MEC) to systematically characterize its clinical, histopathologic, and molecular features. The patients—12 male and eight female—were a median age of 56 years (range, 19–80 years old). Forty-four percent of the patients were asymptomatic at diagnosis. The tumors were a median of 6.8 cm in diameter, and 55 percent were pT1 tumors and 50 percent were tumor-node-metastasis (TNM) stage I tumors. All tumor cases were histologically graded using four grading systems for salivary MEC—Armed Forces Institute of Pathology, Brandwein, modified Healey, and Memorial Sloan Kettering. When assessing the grading systems as a whole, low-grade, intermediate-grade, and high-grade tumors accounted for 35 to 70 percent, five to 25 percent, and 25 to 50 percent of the cases, respectively. Many histologic variants were noted, and 70 percent of the cases were classified as nonclassic variants. *MAML2* rearrangement was detected in 56 percent of cases, and *CRTC1* was the fusion partner in all cases. *CRTC1-MAML2* fusion was associated with lower pT classification and lower TNM stage. The overall survival rate for all patients was 69 percent at five years and 43 percent at 10 years. Worse overall survival was associated with higher pT stage, higher TNM stage, residual tumors, greater tumor size, high-grade tumor histology (Armed Forces Institute of Pathology and Memorial Sloan Kettering only), and the absence of *CRTC1-MAML2* fusion. None of the patients with *CRTC1-MAML2* fusion-positive tumors died during follow-up. The authors concluded that the clinicopathologic and molecular findings of thymic MEC from this study could be used to help manage this rare tumor.

Murase T, Nakano S, Sakane T, et al. Thymic mucoepidermoid carcinoma: a clinicopathologic and molecular study. *Am J Surg Pathol*. 2022;46(8):1160–1169.

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Accuracy of the Cobas assay for detecting high-risk HPV in head and neck FNA specimens

The authors evaluated the detection accuracy of the Cobas human papillomavirus assay for high-risk human papillomavirus (hrHPV) and HPV-16 in head and neck fine-needle aspiration (FNA) specimens from patients with squamous cell carcinoma. They retrospectively searched their institutional databases for head and neck FNA biopsy specimens from 2012 to 2020. Cobas (Roche Diagnostics) HPV testing was subsequently performed on 90 FNA specimens with valid Cervista (Hologic) HPV testing results. The authors compared the results of the Cobas HPV and Cervista HPV assays. A Linear Array (Roche Diagnostics) or SPF10-LiPA25 HPV genotyping assay (Labo Bio-Medical Products) was used to resolve cases with discrepant results. The kappa value and accuracy of Cobas HPV testing were calculated. The accuracy of the Cobas HPV assay was also determined in 42 FNA needle-rinse specimens. Cobas HPV was positive in 82 percent (74 of 90) of the FNA specimens. The concordance between Cobas HPV and Cervista HPV test results was 88.9 percent (80 of 90) with substantial agreement ($\kappa = 0.669$; 95 percent confidence interval, 0.481–0.856). With HPV genotyping confirmation in cases with discrepant results between the two HPV assays, Cobas HPV testing showed 100 percent sensitivity and specificity for hrHPV. HPV-16 was detected in 88 percent (65 of 74) of HPV-positive cases. HPV genotyping confirmed one false-negative HPV-16 result and one false-positive HPV-16 result. The overall accuracy of the Cobas HPV assay for HPV-16 was 97.8 percent. The accuracy of the Cobas HPV in FNA needle-rinse specimens was 100 percent. The authors concluded that the Cobas HPV assay is highly accurate for determining HPV status in head and neck FNA specimens. FNA needle rinse is valid for Cobas HPV testing in patients with squamous cell carcinoma.

Guo M, Khanna A, Tinnirello AA, et al. Detection accuracy of the Cobas HPV assay for high-risk HPV in head and

neck FNA biopsy specimens. *Cancer Cytopathol*. 2022;130:523–530.

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