Anatomic pathology selected abstracts

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Relationship between cytomegalovirus hepatitis and acute cellular rejection

December 2023—Cytomegalovirus hepatitis in allograft livers is a significant infectious complication for which the histology historically has been described as overlapping that of acute cellular rejection, a diagnosis that compels a different treatment regimen. The authors conducted a study to update the clinicopathologic features of cytomegalovirus (CMV) hepatitis and explore its clinical and histologic relationship with acute cellular rejection (ACR). They performed a retrospective analysis of 26 patients, across four institutions, who were diagnosed with CMV hepatitis, assessing clinical, histologic, and IHC features. Patients were predominantly CMV donor positive/recipient negative (D+/R-; n=9 of 15) and received a diagnosis of CMV hepatitis at a mean age of 52 years (standard deviation [SD], 17 years) and at a mean interval of 184 days (SD, 165 days) from transplantation. Mean CMV viral load at diagnosis was 241,000 IU/mL (SD, 516 000 IU/mL), and liver biochemical enzymes were elevated (mean alanine aminotransferase, 212 U/L [SD, 180 U/L]; mean aspartate aminotransferase, 188 U/L [SD, 151 U/L]; and mean alkaline phosphatase, 222 U/L [SD, 153 U/L]). Ten cases did not show histologic features of acute cellular rejection, and 16 had such features as marked bile duct injury and endotheliitis. All patients had viral cytopathic change. They were treated with a combination of antiviral therapy and CMV intravenous immunoglobulin, and all patients with undetectable or nearly undetectable CMV viral titers showed near resolution of biochemical enzymes. The authors concluded that CMV hepatitis and acute cellular rejection are complex processes with interlinking mechanisms that should be distinguished from each other. A subset of transplant patients with CMV hepatitis showed histologic changes that mimic acute cellular rejection but were treated successfully with antiviral therapy alone.

Shih AR, Naini BV, Westerhoff M, et al. Cytomegalovirus hepatitis in allograft livers may show histologic features of acute cellular rejection. *Arch Pathol Lab Med*. 2023;147(6):655–664.

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Toker cell hyperplasia in the nipple-areolar complex of transmasculine people

In a previous study of breast histopathologic features, the authors observed a high frequency of intraepidermal glands formed by Toker cells in the nipple-areolar complex (NAC) of transmasculine chest-contouring surgical specimens. In the study reported herein, they analyzed Toker cell hyperplasia (TCH)—the presence of clusters of Toker cells consisting of at least three contiguous cells or glands, or both, with lumen formation—in the transmasculine population. Increased numbers of singly dispersed Toker cells were not considered TCH. Eighty-two (18.5 percent) of the 444 transmasculine subjects in the study cohort had a portion of their NAC excised and available for evaluation. The authors also reviewed the NACs from 55 cisgender women who were younger than 50 years old and had undergone full mastectomies. The proportion of TCH in transmasculine people (20 of 82; 24.4 percent) was 1.7-fold higher than in cisgender women (eight of 55; 14.5 percent) but did not achieve significance (P=.20). However, in those with TCH, the rate of gland formation was 2.4-fold higher in transmasculine people, achieving borderline significance (18 of 82 versus five of 55; P=.06). Among the transmasculine subjects, TCH was significantly more likely to be present in those with a higher body mass index (P=.03). An Akoya Biosciences assay was used to stain for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), androgen receptor (AR), cytokeratin 7, and Ki67 in a subset of five transmasculine and five cisgender

cases. All 10 cases were cytokeratin 7+ and Ki67-, and nine out of 10 cases were AR+. Toker cells in transmasculine people demonstrated variable expression of ER, PR, and HER2. For cisgender cases, Toker cells were consistently ER+, PR-, and HER2-. The authors concluded that there is a higher rate of TCH in those who are transmasculine than in those who are cisgender, particularly among transmasculine people who have a high body mass index and are taking testosterone. To the authors' knowledge, this is the first study to demonstrate that Toker cells are AR+. Toker cells display variable ER, PR, and HER2 immunoreactivity. The clinical significance of TCH in the transmasculine population remains to be elucidated.

Baker GM, Bret-Mounet VC, Xu J, et al. Toker cell hyperplasia in the nipple-areolar complex of transmasculine individuals. *Mod Pathol.* 2023;36(6). https://doi.org/10.1016/j.modpat.2023.100121

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Study of thyroid oncocytic nodules with longitudinal nuclear grooves

Thyroid nodules with longitudinal nuclear grooves have been widely considered synonymous with papillary thyroid carcinoma. The authors conducted a study in which they assessed 15 cases of thyroid nodules that exhibited oncocytic, or Hürthle cell, features and contained longitudinal nuclear grooves yet failed to display aggressive behavior or the full features of papillary thyroid carcinoma (PTC). Next-generation sequencing was performed to examine 161 genes for oncogenic driver alterations associated with thyroid neoplasia. The lesions occurred in 11 women and four men aged 27 to 80 years and measured 0.2 to 2.3 cm in diameter (mean, 1.1 cm). The tumors were well circumscribed and noninvasive and showed a proliferation of large cells with abundant granular cytoplasm and centrally placed nuclei displaying scattered longitudinal nuclear grooves. IHC stains were negative for HBME-1, galectin-3, and CK19 in all cases. *NRAS* pQ61R was detected in six cases, *KRAS* p.Q61E in one case, and *AKT2* p.E17K in one case. None of the genetic changes classically associated with conventional PTC or high-grade thyroid malignant neoplasms were identified. Clinical follow-up in nine patients showed no evidence of recurrence or metastases between two and 13 years (mean, 5.7 years). The authors concluded that longitudinal nuclear grooves occasionally can be encountered in oncocytic tumors and should not lead to a diagnosis of PTC in the absence of other features supporting that diagnosis.

Suster D, Mackinnon AC, Suster S. Thyroid oncocytic (Hürthle cell) nodules with longitudinal nuclear grooves: clinicopathologic, immunohistochemical, and molecular genetic study of 15 cases. *Arch Pathol Lab Med*. 2023;147:684–691.

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POU2F3: A marker for neuroendocrine-low/negative small cell lung cancer

POU2F3 (POU class 2 homeobox 3) is a novel transcription factor used to define the special molecular subtype of small cell lung cancer known as SCLC-P. However, the sensitivity and specificity of POU2F3 IHC staining has not been investigated fully. The authors conducted a study in which they explored the expression of POU2F3 by IHC in a large cohort of SCLC clinical samples (n=246), other common lung cancer types (n=2,207), and various other cancer types (n=194). The results showed that POU2F3 was strongly nuclear stained in 13.41 percent (33 of 246) of SCLC cases, with negative or minimal labeling for thyroid transcription factor-1 and neuroendocrine markers. Compared with POU2F3-negative SCLC, SCLC-P harbored fewer *TP53* and *RB1* mutations. POU2F3 was also expressed in 3.13 percent (eight of 256) of squamous cell carcinomas and 20 percent (two of 10) of large cell neuroendocrine carcinomas (LCNECs), whereas other lung cancer types were POU2F3 negative. Furthermore, POU2F3 was expressed in 22.2 percent (four of 18) of thymic tumors. All other tumors were POU2F3 negative, except for thymic carcinoma, although sparsely distributed weak nuclear staining was observed in lung adenocarcinoma, cervical squamous cell carcinoma, and colorectal carcinoma. The sensitivity and specificity of POU2F3 in neuroendocrine-low/negative SCLC were 82.1 percent and 99.4 percent, respectively. Notably, some rare unique patterns of POU2F3 expression were observed. One case of thymic squamous cell carcinoma was characterized by diffuse and uniform cytomembrane staining. One case of esophageal neuroendocrine tumor was

nuclear positive, while the normal proliferating squamous epithelium was strongly membrane stained. The authors concluded that this is the largest cohort of clinical samples to confirm that POU2F3 is a highly sensitive and specific diagnostic marker for neuroendocrine-low/negative SCLC.

Wang Y, Jin Y, Shen X, et al. POU2F3: A sensitive and specific diagnostic marker for neuroendocrine-low/negative small cell lung cancer. *Am J Surg Pathol.* 2023;47(9):1059–1066.

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Multi-society Delphi consensus statement on fatty liver disease nomenclature

The principal limitations of the terms nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are their reliance on exclusionary confounder terms and the use of potentially stigmatizing language. The authors conducted a study to determine if content experts and patient advocates were in favor of changing the nomenclature or definition, or both. Three large pan-national liver associations led a modified Delphi process. Consensus was defined a priori as a supermajority (67 percent) vote. An independent committee of experts external to the nomenclature process made the final recommendation on the names and diagnostic criteria. A total of 236 panelists from 56 countries participated in four online surveys and two hybrid meetings. Response rates across the four survey rounds were 87, 83, 83, and 78 percent, respectively. Seventy-four percent of respondents indicated that the current nomenclature was sufficiently flawed to consider a name change. The terms “non-alcoholic” and “fatty” were considered stigmatizing by 61 and 66 percent of respondents, respectively. Steatotic liver disease (SLD) was chosen as an overarching term to encompass the various etiologies of steatosis. The term steatohepatitis was thought to be an important pathophysiological concept that should be retained. Therefore, metabolic dysfunction-associated steatohepatitis (MASH) was selected to replace nonalcoholic steatohepatitis (NASH). Metabolic dysfunction-associated steatotic liver disease (MASLD) was chosen to replace nonalcoholic fatty liver disease (NAFLD). There was consensus to change the definition to include at least one of five cardiometabolic risk factors. Those cases with no metabolic parameters and no known cause were deemed cryptogenic SLD. A new category, termed MetALD, was created to describe those with MASLD who consume greater amounts of alcohol per week (140 to 350 g/week for females and 210 to 420 g/week for males). The authors concluded that the new nomenclature and diagnostic criteria are widely supported and non-stigmatizing and can increase disease awareness and accelerate the development of biomarkers for MASLD, MASH, and MetALD.

Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol.* 2023. doi: 10.1016/j.hep.2023.06.003

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