Anatomic pathology selected abstracts

Editors: Rouzan Karabakhtsian, MD, PhD, professor of pathology and director of the Women's Health Pathology Fellowship, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY; Rachel Stewart, DO, PhD, assistant professor, Department of Pathology and Laboratory Medicine, University of Kentucky, Lexington; Nicole Panarelli, MD, associate professor of pathology, Albert Einstein College of Medicine, Montefiore Medical Center; and Shaomin Hu, MD, PhD, pathology resident, Albert Einstein College of Medicine, Montefiore Medical Center.

Frequent *GNAQ* and *GNA14* mutations in hepatic small vessel neoplasm

April 2019—Hepatic small vessel neoplasm is a recently described infiltrative vascular neoplasm of the liver composed of small vessels. Although its infiltrative nature can mimic angiosarcoma, hepatic small vessel neoplasms (HSVNs) are thought to be benign or low-grade neoplasms because they lack cytologic atypia and increased proliferation. To characterize the molecular pathogenesis of HSVN, the authors performed targeted panel sequencing and exome sequencing on 18 benign or low-grade vascular neoplasms of the liver, including eight HSVNs, six classic cavernous hemangiomas, and four variant lesions with overlapping features between HSVN and cavernous hemangioma. All 18 lesions had simple genomes without copy number alterations. Seventy-five percent (six of eight) of the HSVNs demonstrated known activating hotspot mutations in *GNAQ* (two of eight, p.Q209H) or *GNA14* (four of eight, p.Q205L), and the remaining two had the same missense mutation in *GNAQ*, p.G48L, which has not been previously described. Twenty-five percent (one of four) of variant lesions had a hotspot *GNAQ* p.Q209H mutation and another variant lesion had a *GNAQ* p.G48L mutation. Known pathogenic mutations were not identified in any of the six cavernous hemangiomas. These data suggest that HSVNs share a similar molecular biology to several other vascular lesions—congenital hemangioma, tufted angioma, anastomosing hemangioma, lobular capillary hemangioma, and kaposiform hemangioendothelioma—recently reported to have *GNAQ, GNA11*, or *GNA14* mutations.

Joseph NM, Brunt EM, Marginean C, et al. Frequent *GNAQ* and *GNA14* mutations in hepatic small vessel neoplasm. *Am J Surg Pathol.* 2018;42(9):1201–1207.

Correspondence: Dr. Nancy M. Joseph at nancy.joseph@ucsf.edu

Relevance of tumor grade among MMR-deficient colorectal carcinomas

Intestinal-type colorectal adenocarcinomas are graded based on extent of glandular differentiation, although mucinous, signet-ring cell, and solid cancers are, by convention, classified as high grade. Mismatch repair (MMR)-deficient tumors frequently show high-grade histologic features, yet the World Health Organization classifies them as low grade to reflect their favorable prognosis compared with MMR-proficient cancers. Although some MMR-deficient colorectal cancers behave aggressively, few authors have identified features that predict their behavior. The authors of this study sought to determine which histologic features, if any, predict outcome among MMR-deficient colorectal carcinomas. They identified 116 MMR-deficient colorectal carcinomas, including 77 localized (stage I to II) and 39 advanced (stage III to IV) tumors, and evaluated them for extent of gland formation, extracellular mucin, signet-ring cell differentiation, solid growth, nuclear grade, tumor-infiltrating lymphocytes, and tumor budding. The authors assessed relationships between these features, pathologic stage, and disease-free survival. They found that high-grade MMR-deficient tumors were more often of advanced stage than low-grade tumors (46 percent versus 23 percent; $P = .01$). Disease-free survival was inversely associated with a dominant high-grade component and tumor budding ($P = .01$ and 0.04, respectively). Predominantly solid tumors, in particular, were significantly associated with decreased disease-free survival compared with low-grade tumors ($P = .001$). Nuclear grade and tumor-infiltrating lymphocytes were not associated with pathologic stage or outcome. The authors concluded that low-grade MMR-deficient carcinomas present at an earlier stage and pursue a more favorable course than those primarily composed of high-grade elements. These findings suggest that MMR status should not supplant histologic grade in the assessment of colorectal carcinomas.

Johncilla M, Chen Z, Sweeney J, et al. Tumor grade is prognostically relevant among mismatch repair deficient

colorectal carcinomas. *Am J Surg Pathol.* 2018;42(12):1686–1692.

Correspondence: Dr. Melanie Johncilla at mej9041@med.cornell.edu

Histopathologic findings in breast tissue from female-to-male gender reassignment surgery

Breast-reduction surgery or mastectomy following administration of androgen therapy is part of the female-to-male gender reassignment process. Details regarding the histopathologic findings in breast tissue from patients undergoing female-to-male gender reassignment surgery are limited. The authors reviewed hematoxylin-and-eosin–stained sections of breast tissue from 148 patients who underwent breast-reduction surgery or mastectomy as part of the female-to-male gender reassignment process at their institution between January 2014 and May 2017. The spectrum of histologic features in each case was cataloged. The median patient age was 27 years (range, 18–60 years). Lobular atrophy was seen to some degree in 73 percent of cases and was prominent in 42 percent. A predominantly fibrotic stroma was seen in 45 percent of cases, and areas resembling the fibrous stage of gynecomastia were seen in 41 percent. Other features included variably ectatic ducts in 96 percent of cases, cysts in 42 percent, apocrine metaplasia in 32 percent, fibroadenomatous change in 27 percent, usual ductal hyperplasia in 26 percent, and pseudoangiomatous stromal hyperplasia in 19 percent. Five cases (three percent) demonstrated atypical hyperplasia—atypical ductal hyperplasia in two, atypical lobular hyperplasia in two, and both atypical ductal hyperplasia and atypical lobular hyperplasia in one. One case demon-strated high-grade ductal carcinoma in situ. No invasive carcinomas were identified. The authors concluded that the majority of breast specimens from patients undergoing female-to-male gender reassignment demonstrate at least some degree of lobular atrophy as well as ectatic ducts, fibrous stroma, and areas resembling the fibrous stage of gynecomastia. Cases rarely showed atypical lesions, for which clinical significance is uncertain.

Torous VF, Schnitt SJ. Histopathologic findings in breast surgical specimens from patients undergoing female-to-male gender reassignment surgery. *Mod Pathol.* 2018. doi: 10.1038/s41379-018-0117-4. Published October 11, 2018.

Correspondence: Dr. Stuart J. Schnitt at sschnitt@bwh.harvard.edu

Gastric crystal-storing histiocytosis: a clue to hematolymphoid malignancies

Crystal-storing histiocytosis is an under-recognized entity that has a striking association with lymphoproliferative disorders. To study the typical morphologic features of gastric crystal-storing histiocytosis (CSH), the authors retrieved all lymphomas diagnosed using in-house gastric specimens at the Ohio State University between Jan. 1, 2008 and Jan. 1, 2017. This search yielded 66 specimens from 51 unique patients. All cases were reviewed, and CSH was identified in seven stomach biopsies from four patients (two men and two women; average age, 69 years; range, 56–82 years). The patients' endoscopic findings were abnormal—diffuse nodularity and white discoloration (n = 1), patchy nodularity (n = 1), and malignant-appearing fundic mass with lymphadenopathy (n = 2). The typical gastric CSH lesion displays full-thickness expansion of the lamina propria by a lymphohistiocytic infiltrate that distorts the usual gastric glandular architecture. On high power, all cases were defined by the presence of macrophages with abundant eosinophilic cytoplasm containing nonrefractile, nonpolarizable fibrillary cytoplasmic inclusions. Three of the four patients had a kappa-restricted lymphoma; the one patient with a lambda-restricted lymphoma had the fewest macrophages. Follow-up data were available up to 228 weeks. All four patients had persistent/recurrent lymphoma, and two patients died of lymphoma-related complications. None of the CSH cases were prospectively recognized as CSH, and one case was initially misdiagnosed as a xanthoma. Because CSH can be so florid as to obscure the concomitant lymphoma, awareness is crucial for accurate diagnosis.

Arnold CA, Frankel WL, Guo L, et al. Crystal-storing histiocytosis in the stomach: A clue to subtle hematolymphoid malignancies. *Am J Surg Pathol.* 2018;42(10):1317–1324.

Correspondence: Dr. Christina A. Arnold at christina.arnold@osumc.edu

Landscape of immune microenvironment in hepatocellular carcinoma

Immune cells constitute an important element of tumor tissue. Accumulating evidence indicates their clinicopathological significance in predicting prognosis and therapeutic efficacy. Nonetheless, the combinations of immune cells forming the immune microenvironment and their association with histological findings remain largely unknown. Moreover, it is unclear which immune cells or immune microenvironments are the most prognostically significant. The authors conducted a study in which they comprehensively analyzed the immune microenvironment and its intratumor heterogeneity in 919 regions of 158 hepatocellular carcinomas (HCCs) and compared the results with corresponding histological and prognostic data. They classified the immune microenvironment of HCC into three distinct immunosubtypes: immune high, immune mid, and immune low. The immune-high subtype was characterized by increased B-/plasma-cell and T-cell infiltration, and the immune-high subtype and B-cell infiltration were identified as independent positive prognostic factors. Varying degrees of intratumor heterogeneity of the immune microenvironment were observed, some of which reflected the multistep nature of HCC carcinogenesis. However, the predominant pattern of immunosubtype and immune cell infiltration of each tumor was prognostically important. Of note, the immune-high subtype was associated with poorly differentiated HCC, cytokeratin 19+ (CK19+), Sal-like protein 4+ (SALL4+) high-grade HCC, and Hoshida's S1/Boyault's G2 subclasses. Patients with high-grade HCC of the predominant immune-high subtype had significantly better prognosis. These results provide a rationale for evaluating the immune microenvironment in addition to the usual histological and molecular classification of HCC.

Kurebayashi Y, Ojima H, Tsujikawa H, et al. Landscape of immune microenvironment in hepatocellular carcinoma and its additional impact on histological and molecular classification. *Hepatology.* 2018;68(3):1025–1041.

Correspondence: Dr. M. Sakamoto at msakamot@z5.keio.jp