Anatomic pathology selected abstracts

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Quantitative pathologic analysis of digitized images of colorectal carcinoma

June 2023—The authors conducted a study to examine whether quantitative digital pathology can derive valuable information from readily available and inexpensive H&E slides and thereby augment routine pathologic reporting of colorectal carcinoma. They applied a quantitative segmentation algorithm (QuantCRC) to 6,468 digitized H&E slides of colorectal carcinoma (CRC). Fifteen parameters from each image were recorded and tested for associations with clinicopathologic features and molecular alterations. A prognostic model was developed to predict recurrence-free survival using data from the internal cohort (n=1,928) and validated on an internal test (n=483) and external cohort (n=938). There were significant differences in QuantCRC according to stage, histologic subtype, grade, venous/lymphatic/perineural invasion, tumor budding, CD8 IHC, mismatch repair status, *KRAS* mutation, *BRAF* mutation, and CpG methylation. A prognostic model incorporating stage, mismatch repair, and QuantCRC resulted in a Harrell's concordance index (c-index) of 0.714 (95 percent confidence interval [CI], 0.702–0.724) for the internal test and 0.744 (95 percent CI, 0.741–0.754) for the external cohort. Removing QuantCRC from the model reduced the c-index to 0.679 (95 percent CI, 0.673–0.694) for the external cohort. Prognostic risk groups were identified and provided a hazard ratio of 2.24 (95 percent CI, 1.33–3.87; *P*=.004) for low- versus high-risk stage III CRCs and 2.36 (95 percent CI, 1.07–5.20; *P*=.03) for low- versus high-risk stage II CRCs in the external cohort after adjusting for established risk factors. The predicted median 36-month recurrence rate for high-risk stage III CRCs was 32.7 percent versus 13.4 percent for low-risk stage III, and it was 15.8 percent for high-risk stage II CRCs versus 5.4 percent for low-risk stage II. The authors concluded that QuantCRC provides a powerful adjunct to routine pathologic reporting of CRC. A prognostic model using QuantCRC improves prediction of recurrence-free survival.

Pai RK, Banerjee I, Shivji S, et al. Quantitative pathologic analysis of digitized images of colorectal carcinoma improves prediction of recurrence-free survival. *Gastroenterology*. 2022;163(6):1531–1546.e8.

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A clinicopathologic study of localized malignant peritoneal mesothelioma in women

Localized malignant peritoneal mesothelioma is a rare tumor for which there is limited information in the literature. The authors conducted a study in which they presented their experience with 18 cases seen in their hospital during a 43-year period (1978–2021). Patients were a median age of 55 years (range, 33–79 years) and most were Caucasian. They presented with abdominal pain (11), ascites and right leg swelling (one), abdominal mass (one), and as incidental finding (one). Thirty percent of patients reported asbestos exposure, and all patients who had information available had a family history of tumors. A third person had a personal history of tumors. Seventy-seven percent of patients had some form of abdominopelvic surgery or inflammatory process, or both. Most cases exhibited microscopic features typically seen in malignant mesothelioma. However, some had confounding features, such as signet-ring cells, spindle cells, clear cell changes, and adenomatoid tumor-like appearance. BAP-1 by IHC was lost in one-third of cases. Only one patient underwent genetic testing, and that patient had an *MSH2* germline mutation. Homozygous deletion of *CDKN2A* by FISH was not found in one tested case, although next-generation sequencing identified a *CDKN2A* pathogenic mutation. Eighty-eight percent (16 of 18) of patients had surgical treatment, and some also received adjuvant chemotherapy. Patients' mean overall survival was 80.4

months (95 percent confidence interval, 54.3–106.52). The three-year overall survival was 79 percent, and the five-year overall survival was 52.6 percent. Fifty-three percent of patients had recurrences, and 20 percent had tumor progression. Although the limited sample precluded definitive conclusions, a small tumor size, low-grade cytology, and low mitotic index appeared to be associated with indolent behavior.

Malpica A, Euscher ED, Marques-Piubelli ML, et al. Localized malignant peritoneal mesothelioma (LMPeM) in women: A clinicopathologic study of 18 cases. *Am J Surg Pathol*. 2022;46(10):1352–1363.

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Histological and serological features of acute liver injury after SARS-CoV-2 vaccination

Liver injury with autoimmune features after SARS-CoV-2 vaccination is increasingly being reported. The authors conducted a study in which they investigated a large international cohort of people who had acute hepatitis arising after SARS-CoV-2 vaccination, focusing on histological and serological features. The study included people who did not have a history of pre-existing liver disease but had transaminase levels of five times or more the upper limit of normal within three months of a SARS-CoV-2 vaccine, liver biopsy available for central review, and clinical follow-up of at least three months or until liver transplantation or death, after diagnosis of acute liver injury. Fifty-nine patients were recruited for the study, 35 of whom were female (median age, 54 years). The patients were given mRNA, vectorial, inactivated, and protein-based vaccines in various combinations. Liver histology showed predominantly lobular hepatitis in 45 (76 percent) cases, predominantly portal hepatitis in 10 (17 percent), and other patterns in four (seven percent). Seven cases had fibrosis Ishak stage 3 or higher, which is associated with more severe interface hepatitis. Autoimmune serology for 31 cases, conducted in a central location, showed antinuclear antibody in 23 (74 percent), anti-smooth muscle antibody in 19 (61 percent), anti-gastric parietal cells in eight (26 percent), anti-liver kidney microsomal antibody in four (13 percent), and anti-mitochondrial antibody in four (13 percent). Ninety-two percent of patients were treated with steroids, with or without azathioprine. Serum transaminase levels improved in all patients and were normal in 24 of 58 (41 percent) after three months and in 30 of 46 (65 percent) after six months. One patient required liver transplantation. Three of 15 (20 percent) patients re-vaccinated for SARS-CoV-2 relapsed. The authors concluded that acute liver injury arising after SARS-CoV-2 vaccination is frequently associated with lobular hepatitis and positive autoantibodies. Whether a causal relationship exists between liver damage and SARS-CoV-2 vaccination remains to be established. Close follow-up is warranted to assess the long-term outcomes of this condition.

Codoni G, Kirchner T, Engel B, et al. Histological and serological features of acute liver injury after SARS-CoV-2 vaccination. *JHEP Rep*. 2022. https://doi.org/10.1016/j.jhepr.2022.100605

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Histological and molecular analysis of cellular leiomyoma with sclerosis linked to HMGA2 overexpression

HMGA2 overexpression is found in 10 to 15 percent of leiomyomas. It is common in variants of hydropic leiomyoma, intravenous leiomyomatosis, and lipoleiomyoma. Cellular or highly cellular leiomyoma (CLM) is a leiomyoma variant of a less well-defined molecular nature. The authors conducted a study in which they identified and examined 52 hypercellular leiomyomas with sclerotic collagen, herein referred to as cellular leiomyoma with sclerosis (CLM-S). The CLM-S showed large tumor size (average, 12.2 cm) and characteristic histology of tumor cells, arranged in cellular fascicles, sheets, and trabeculae with abundant dense, pink sclerotic extracellular matrix in bands and nodules, and increased vascularity. The tumor cells were uniform and had small round–oval nuclei and scant pale–eosinophilic to vacuolated cytoplasm reminiscent of pericytes. The differential diagnosis of CLM-S includes conventional CLM, endometrial stromal tumors, and perivascular epithelioid cell tumor. IHC profile (HMGA2, fumarate hydratase, smooth muscle markers, Melan A, and HMB-45) and molecular alterations (by HMGA2 mRNA reverse transcription–polymerase chain reaction [RT–PCR], *HMGA2* FISH, and *MED12* sequencing)

were analyzed in comparison to matched myometrium and CLM controls. Ninety-six percent (50 of 52) of CLM-S demonstrated diffuse positive immunoreactivity for HMGA2 and up to an 80-fold increase in HMGA2 mRNA, determined by RT–PCR. FISH analysis with break-apart probes at intron three and the 5' UTR detected *HMGA2* rearrangements in 47 percent (18 of 38) of CLM-S. All CLM-S retained expression of fumarate hydratase. *MED12* mutations were not found in CLM-S. The findings show that CLM-S has a unique and characteristic histomorphology, probably driven by HMGA2 overexpression.

Griffin BB, Feng Y, Saini P, et al. Histological and molecular analysis of cellular leiomyoma with sclerosis: linked to HMGA2 overexpression. *Histopathology*. 2022;81(5):587–599.

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Relationship between ductal and lobular components of mixed ductal-lobular carcinomas

The relationship between the ductal and lobular components of invasive ductolobular carcinomas has not been fully elucidated. The authors conducted a study in which the molecular alterations of both components were analyzed in a series of 20 invasive ductolobular carcinomas (IDLC) that were selected based on morphologic criteria and loss of E-cadherin expression in the lobular component. The authors found that 80 percent of tumors shared alterations of driver genes in both components, with *PIK3CA* being the most common alteration. In addition, 45 percent of IDLC carried *CDH1* mutations in their lobular components that were absent in the ductal components. FISH analysis of the *CDH1* gene excluded homozygous *CDH1* loss as a frequent cause of E-cadherin loss in tumors that did not have *CDH1* mutations. No pathogenic mutations in catenin genes were detected in this series of tumors. In 25 percent of tumors, actionable mutations in *PIK3CA, AKT1*, and *ERBB2* were found in only one component. The results of the study confirm that most IDLC derive from invasive carcinoma of no special type, in which a population of cells lose E-cadherin and acquire a lobular phenotype. The frequency of *CDH1* mutations in IDLC appears to be lower than in conventional invasive lobular carcinomas, suggesting alternative mechanisms of E-cadherin loss. Moreover, molecular heterogeneity between ductal and lobular areas suggests the need for molecular characterization of both components to guide targeted therapies.

Pérez-Mies B, Caniego-Casas T, Carretero-Barrio I, et al. The clonal relationship between the ductal and lobular components of mixed ductal-lobular carcinomas suggested a ductal origin in most tumors. *Am J Surg Pathol*. 2022;46(11):1545–1553.

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