Anatomic Pathology Selected Abstracts, 12/13

Anatomic pathology abstracts editors: Michael Cibull, MD, professor and vice chair, Department of Pathology and Laboratory Medicine, University of Kentucky College of Medicine, Lexington; Rouzan Karabakhtsian, MD, attending pathologist, Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; and Thomas Cibull, MD, dermatopathologist, Evanston Hospital, NorthShore University HealthSystem, Evanston, Ill.

Human papillomavirus-related carcinomas of the sinonasal tract

High-risk human papillomavirus is an established cause of head and neck carcinomas arising in the oropharynx. Human papillomavirus (HPV) has also been reported in some carcinomas arising in the sinonasal tract, but little is known about the overall incidence or clinicopathologic profile of these carcinomas. The surgical pathology archives of The Johns Hopkins Hospital were searched for all carcinomas arising in the sinonasal tract from 1995 to 2011, and tissue microarrays were constructed. P16 immunohistochemical analysis and DNA in situ hybridization for high-risk types of HPV were performed. Demographic and clinical outcome data were extracted from patient medical records. Of 161 sinonasal carcinomas, 34 (21 percent) were positive for high-risk HPV DNA, including type 16 (82 percent), type 31/33 (12 percent), and type 18 (six percent). HPV-positive carcinomas consisted of 28 squamous cell carcinomas and variants (15 nonkeratinizing or partially keratinizing, four papillary, five adenosquamous, and four basaloid), one small cell carcinoma, one sinonasal undifferentiated carcinoma, and four carcinomas that were difficult to classify but exhibited adenoid cystic carcinoma-like features. Immunohistochemistry for p16 was positive in 59 of 161 (37 percent) cases, and p16 expression strongly correlated with presence of HPV DNA; 33 of 34 (97 percent) HPV-positive tumors exhibited high p16 expression, whereas only 26 of 127 (20 percent) HPV-negative tumors were p16 positive (P<.0001). The HPV-related carcinomas occurred in 19 men and 15 women who ranged in age from 33 to 87 years (mean, 54 years). A trend toward improved survival was observed in the HPV-positive group (hazard ratio, 0.58; 95 percent confidence interval, 0.26, 1.28). The presence of high-risk HPV in 21 percent of sinonasal carcinomas confirms HPV as an important oncologic agent of carcinomas arising in the sinonasal tract. Although nonkeratinizing squamous cell carcinoma is the most common histologic type, there is a wide morphologic spectrum of HPV-related disease that includes a variant that resembles adenoid cystic carcinoma. The distinctiveness of these HPV-related carcinomas of the sinonasal tract with respect to risk factors, clinical behavior, and response to therapy remains to be clarified.

Bishop JA, Guo TW, Smith DF, et al. Human papillomavirus-related carcinomas of the sinonasal tract. *Am J Surg Pathol.* 2013;37(2):185–192.

Correspondence: J. A. Bishop at jbishop@jhmi.edu

Localized and metastatic myxoid/round cell liposarcoma

Myxoid liposarcoma, a disease especially of young adults that has potential for local recurrence and metastasis, lacks solid prognostic factors and therapeutic targets. The authors evaluated the natural history of the disease and outcome of patients with myxoid liposarcoma (MLPS) and commonly deregulated protein biomarkers. They retrospectively reviewed the medical records for patients who presented to their institution with localized (n=207) or metastatic (n=61) MLPS from 1990 to 2010. A tissue microarray of MLPS patient specimens (n=169) was constructed for immunohistochemical analysis of molecular markers. The five- and 10-year disease-specific survival rates among patients with localized disease were 93 percent and 87 percent, respectively. Male gender, age greater than 45 years, and recurrent tumor predicted poor outcome. The local recurrence rate was 7.4 percent, and the risk of local recurrence was associated with recurrent tumors and nonextremity disease location. Male gender was the main risk factor for metastatic disease, which occurred in 13 percent of patients. Forty percent of patients who had localized disease received chemotherapy, primarily in the neoadjuvant setting. Immunohistochemical analysis revealed significantly higher expression of C-X-C chemokine receptor type 4 (CXCR4) and platelet-derived growth factor receptor beta (PDGFR-β) in metastatic lesions versus localized lesions.

Tumors with a round cell phenotype expressed increased levels of CXCR4, p53, adipophilin, PDGFR-α, PDGFR-β, and vascular endothelial growth factor relative to myxoid phenotype. Only the receptor tyrosine kinase encoded by the AXL gene was identified as a prognosticator of disease-specific survival in univariate analysis.

Hoffman A, Ghadimi MP, Demicco EG, et al. Localized and metastatic myxoid/round cell liposarcoma: clinical and molecular observations. *Cancer.* 2013;119(10):1868–1877.

Correspondence e-mail not available.

Urothelial carcinoma with prominent squamous differentiation in neurogenic bladder: role of HPV infection

Squamous cell carcinomas of the urinary bladder are rare in the Western world; the majority of cases are reported in countries where Schistosoma parasitic infections are prevalent. Unlike with squamous tumors of the uterine cervix or oropharynx, human papillomavirus (HPV) is not commonly associated with bladder squamous cell carcinomas. However, the authors reported on two cases of HPV-positive urothelial carcinomas of the urinary bladder with extensive squamous differentiation showing the typical basaloid, poorly differentiated morphology of HPV-associated tumors. These occurred in patients with neurogenic bladders who had long-standing histories of self-catheterization and tumors that tested positive for HPV by in situ hybridization. A retrospective review of the authors' institutional database revealed four additional patients with bladder tumors showing squamous differentiation arising in the neurogenic bladder. Assessment of these cases showed the more common well-differentiated keratinizing appearance of squamous cell carcinomas of the bladder. These tumors showed only patchy positivity for p16 immunohistochemical stain (not the diffuse strong staining seen in HPV-positive tumors), and the one tested case was negative for HPV by in situ hybridization. HPV infection and neurogenic bladder have been independently associated with increased risk of developing carcinoma in the urinary bladder. However, this is the first report of squamous tumors arising in the concurrent neurogenic bladder and HPV infection. The morphology of these tumors is similar to that of other high-risk HPV-associated squamous carcinomas, with a basaloid, poorly differentiated appearance and little to no keratin formation.

Blochin EB, Park KJ, Tickoo SK, et al. Urothelial carcinoma with prominent squamous differentiation in the setting of neurogenic bladder: role of human papillomavirus infection. *Mod Pathol.* 2012;25:1534–1542.

Correspondence: Dr. K. J. Park at gynbreast@mskcc.org

Atypical leiomyomas of the uterus: a clinicopathologic study of 51 cases

Atypical leiomyoma is a well-described smooth muscle neoplasm of the uterus. Only one study has addressed long-term clinical followup in a large series, and little is known about the adequacy of treatment by myomectomy. The authors searched the surgical pathology archives for consecutive cases of uterine atypical leiomyoma from 1992 to 2003. Glass slides were reviewed to confirm diagnoses, and patient age, treatment modality, and clinical followup data were recorded. Fifty-one atypical leiomyomas with available glass slides and clinical followup data were identified. Thirty tumors exhibited diffuse, moderately to severely atypical cells, whereas 21 showed atypical cells in a more focal or patchy distribution. Twelve had ischemic-type necrosis. By the highest count method, 37 cases were found to have no more than one mitotic figure per 10 high-power fields, 13 showed one to three mitotic figures per 10 high-power fields, and one was nearly entirely necrotic, precluding mitotic assessment. Among the 46 cases in which adjacent non-neoplastic tissue was well visualized, all were found to have pushing margins. The average tumor size was 6.8 cm (median, 6.5 cm; range, 0.7–14 cm). The average patient age was 42.5 years (median, 42 years; range, 21–72 years). In all cases, the initial diagnostic procedure was hysterectomy (34) or myomectomy (17). Average followup was 42 months (range, 0.3–121.8 months). Of those treated with hysterectomy, one had recurrent atypical leiomyoma in the retroperitoneum at 87.5 months, one died of other causes, and the remaining 32 were free of disease. Of the myomectomy group, 82 percent had no evidence of recurrent disease on followup: Two had residual atypical leiomyoma in a subsequent hysterectomy specimen and

one underwent second myomectomy for atypical leiomyoma and had two subsequent successful pregnancies. The authors concluded that atypical leiomyoma has a low rate of extrauterine, intra-abdominal recurrence (less than two percent) with a negligible risk for distant metastasis. Patients may undergo myomectomy alone and have successful pregnancy, but they should be monitored for local intrauterine residual or recurrent disease.

Ly A, Mills AM, McKenney JK, et al. Atypical leiomyomas of the uterus: a clinicopathologic study of 51 cases. *Am J Surg Pathol.* 2013;37:643–649.

Correspondence e-mail not provided.

Clinicopathological significance of HER2/neu genetic heterogeneity in various breast carcinomas

HER2/neu is a significant prognostic marker for breast carcinomas. Recently, new guidelines defining HER2 genetic heterogeneity (GH) were published by the College of American Pathologists. The authors conducted a study to ascertain the prevalence of HER2 GH, as defined in primary invasive breast carcinoma, to determine its relationship with prognostic variables and to investigate its influence on concurrent axillary metastasis. In the study, 235 consecutive infiltrating breast carcinomas were evaluated for GH (defined as presence of five percent to 50 percent of neoplastic cells with a HER2/CEP17 ratio greater than 2.2) using fluorescence in situ hybridization. Pathological features of carcinomas with GH were compared with those lacking GH. Genetic heterogeneity was also evaluated in a subset of 37 paired primary carcinomas and its concurrent axillary nodal metastases using dual in situ hybridization. HER2 GH was noted in 27 percent of HER2-negative breast carcinomas. These carcinomas demonstrated aggressive characteristics, including larger size, higher grade, and greater incidence of lymph node metastasis, in comparison with HER2-negative cases without GH. Higher levels of GH were associated with equivocal HER2 status. Genetic heterogeneity was maintained in the concurrent lymph node metastases with some variations. However, two cases with clusters of HER2-amplified cells in the primary carcinoma showed HER2 amplification in the nodal metastases. The authors concluded that HER2 GH is present in 27 percent of breast carcinomas, portends an aggressive phenotype, and contributes to equivocal HER2 status. It may be beneficial to evaluate HER2 status in nodal metastases of select primary carcinomas with GH before selecting a treatment.

Shafi H, Astvatsaturyan K, Chung F, et al. Clinicopathological significance of HER2/neu genetic heterogeneity in HER2/neu non-amplified invasive breast carcinomas and its concurrent axillary metastasis. *J Clin Pathol.* 2013;66(8):649–654.

Correspondence: Dr. Hedyeh Shafi at hedyeh.shafi@cshs.org

EIN with secretory differentiation: features and underlying mechanisms

Endometrial intraepithelial neoplasia with secretory differentiation and ordinary EIN occurring in a secretory context are rare findings. The authors determined how often secretory differentiation in EIN was associated with evidence of circulating progestins in the background endometrium and studied clinical characteristics and clinical outcomes of affected patients. They selected 41 patients with secretory differentiation in the EIN (n=31) or background endometrium (n=38), or both. Most (90 percent) secretory EINs were associated with circulating progestins. Rare exceptions were observed, suggesting that secretory EIN may occur as a hormone-independent phenomenon. However, circulating progestins are not sufficient to induce EIN secretory differentiation, as 26 percent of EINs within a secretory background were of the ordinary, or nonsecretory, type. EIN patients with secretory endometrium in the background are younger (average age, 45 years) than the aggregate of all patients with EIN (53 years in other published studies) and are often premenopausal with a cyclical source of endogenous progestins. Involution of EIN during followup was more frequent (81 percent) for those with a secretory background at initial EIN diagnosis compared with historical averages (25 percent). These results suggest a potential role for endogenous progesterone and therapeutic progestins in modulating EIN outcomes.

Parra-Herran CE, Monte NM, Mutter GL. Endometrial intraepithelial neoplasia with secretory differentiation:

diagnostic features and underlying mechanisms. *Mod Pathol.* 2013;26:868–873.

Correspondence: Dr. G. L. Mutter at gmutter@rics.bwh.harvard.edu

Glypican 3 and arginase in diagnosing scirrhous hepatocellular carcinoma

Scirrhous hepatocellular carcinoma is a rare, ill-defined morphological subtype of hepatocellular carcinoma characterized by marked stromal fibrosis. This variant can be difficult to distinguish from intrahepatic cholangiocarcinoma and metastatic adenocarcinoma, especially on needle biopsy. The authors performed immunohistochemistry for hepatocellular- and adenocarcinoma-associated markers on 20 scirrhous hepatocellular carcinoma cases and compared the results with classical hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Scirrhous hepatocellular carcinomas were significantly less likely to be HepPar-1 positive than classical hepatocellular carcinomas (26 and 74 percent, respectively) and were significantly more likely to express adenocarcinoma-associated markers such as epithelial cell adhesion molecule (63 versus 11 percent), cytokeratin 19 (26 versus two percent), and cytokeratin 7 (53 versus two percent). At least one of these adenocarcinoma-related markers was positive in 80 percent of scirrhous hepatocellular carcinoma cases. Glypican 3 and arginase were positive in 79 and 85 percent of cases of scirrhous hepatocellular carcinoma, respectively, and the combined use of these markers yielded 100 percent sensitivity for scirrhous hepatocellular carcinoma. The authors concluded that scirrhous morphology, absence of HepPar-1 staining, and frequent positivity with adenocarcinoma-related markers in scirrhous hepatocellular carcinoma can lead to erroneous adenocarcinoma diagnoses. Glypican 3 and arginase are the most reliable markers for identifying hepatocellular differentiation in this setting.

Krings G, Ramachandran R, Jain D, et al. Immunohistochemical pitfalls and the importance of glypican 3 and arginase in the diagnosis of scirrhous hepatocellular carcinoma. *Mod Pathol.* 2013;26:782–791.

Correspondence: Dr. Sanjay Kakar at sanjay.kakar@ucsf.edu□n