Anatomic Pathology Selected Abstracts, 4/15

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Uterine smooth muscle tumors with features suggesting *fumarate hydratase* aberration

Rare, sporadic uterine leiomyomas arise in the setting of severe metabolic aberration due to a somatic *fumarate hydratase* mutation. Germline mutations account for hereditary leiomyomatosis and renal cell cancer syndrome, which predisposes for cutaneous and uterine leiomyomas and aggressive renal cell carcinomas. Altered *fumarate hydratase* leads to fumarate accumulation in affected cells with formation of S-(2-succino)-cysteine (2SC), which can be detected with the polyclonal antibody. High levels of these modified cysteine residues are characteristically found in *fumarate hydratase*-deficient cells but not in normal tissues or tumors unassociated with hereditary leiomyomatosis and renal cell cancer syndrome. The authors hypothesized that 2SC-positive leiomyomas, indicating *fumarate hydratase* aberration, have morphologic features that differ from those without 2SC positivity. They conducted a study in which H&E-stained slides of uterine smooth muscle tumors were prospectively analyzed for features suggesting hereditary leiomyomatosis and renal cell cancer syndrome, such as prominent eosinophilic macronucleoli with perinucleolar halos, yielding nine cases. Germline genetic testing for *fumarate hydratase* mutations was performed in three cases. A detailed morphological analysis was undertaken, and 2SC immunohistochemical analysis was performed with controls from a tissue microarray (leiomyomas [19], leiomyosarcomas [29], and endometrial stromal tumors [15]). Of the nine study cases, four had multiple uterine smooth muscle tumors. All cases had increased cellularity, staghorn vasculature, and fibrillary cytoplasm with pink globules. All cases had inclusion-like nucleoli with perinuclear halos (seven diffuse and one focal). All showed diffuse granular cytoplasmic labeling with the 2SC antibody. Two of three patients tested had germline *fumarate hydratase* mutations. Only one leiomyoma from the tissue microarray controls was immunohistochemically positive, and it showed features similar to other immunohistochemically positive cases. Smooth muscle tumors with *fumarate hydratase* aberration demonstrated morphological reproducibility across cases and 2SC immunopositivity. Although the features described are not specific for the germline fumarate hydratase mutation or the hereditary leiomyomatosis and renal cell cancer syndrome, their presence should suggest *fumarate hydratase* aberration. Identifying these cases is an important step in the diagnostic workup of patients with possible hereditary leiomyomatosis and renal cell cancer.

Reyes C, Karamurzin Y, Frizzell N, et al. Uterine smooth muscle tumors with features suggesting *fumarate hydratase* aberration: detailed morphologic analysis and correlation with S-(2-succino)-cysteine immunohistochemistry. *Mod Pathol.* 2014;27:1020–1027.

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Histologic and immunohistochemical assessment of penile carcinomas in a North American population

Penile squamous cell carcinoma is sometimes an aggressive disease that has a variable worldwide incidence, in part due to differing rates of inflammatory and infectious risk factors. In the developed world, penile squamous cell carcinoma (SCC) is a rare malignancy, so most studies originate in less developed countries. The authors undertook a study to examine the morphologic and immunohistochemical features of penile SCC from a region with low disease incidence. They reviewed 62 complete or partial penectomy specimens from 59 patients. Twenty-six patients had metastasis; three had recurrent disease; and seven were deceased due to tumor. Most patients were uncircumcised (72 percent). Twenty-two percent of carcinomas were associated with lichen sclerosis. Perineural invasion was significantly associated with metastasis (P=0.007). Most SCCs (65 percent) had the usual keratinizing morphology, and these tumors were significantly associated with the differentiated form of intraepithelial lesion (P<0.0001), p53 positivity (P=0.002), cyclin D1 positivity (P=0.007), and EGFR overexpression (P=0.003). Human papilloma virus (HPV)-associated tumors accounted for 27 percent and were basaloid (eight percent), warty (10 percent), mixed (six percent), or lymphoepithelioma-like carcinoma (four percent) variants. These were significantly associated with p16 expression (P<0.0001) and the undifferentiated form of intraepithelial lesion (P<0.001). Among all SCCs, there was no difference in the immunohistochemical or in situ hybridization profile between primary tumors and metastases. Although penile SCC is rare in the United States, the tumor variants, immunohistochemical profiles, and proportion of HPV-associated tumors are similar to those in less developed countries. Two distinct pathways appear to lead to carcinogenesis. One is related to underlying chronic inflammatory states, involves p53 mutation and cyclin D1 overexpression, and culminates in classic keratinizing SCC. The other pathway involves high-risk HPV infection, demonstrates strong p16 expression, and results in SCC with varied but distinctive morphologies.

Mentrikoski MJ, Stelow EB, Culp S, et al. Histologic and immunohistochemical assessment of penile carcinomas in a North American population. *Am J Surg Pathol.* 2014;38:1340–1348

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Predictive value of IASLC/ATS/ERS classification of lung adenocarcinoma in tumor recurrence and patient survival

This study investigated the pattern of recurrence of lung adenocarcinoma and the predictive value of histologic classification in resected lung adenocarcinoma using the new International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification system. Histologic classification of 573 patients undergoing resection for lung adenocarcinoma was determined according to the IASLC/ATS/ERS classification system, and the percentage of each histologic component—lepidic, acinar, papillary, micropapillary, and solid—was recorded. The pattern of recurrence of those components and their predictive value were investigated. The study investigators found that the predominant histologic pattern was significantly associated with gender (P<0.01), invasive tumor size (P<0.01), T status (P<0.01), N status (P<0.01), tumor-node-metastasis stage (P<0.01), and visceral pleural invasion (P<0.01). The percentage of recurrence was significantly higher in micropapillary predominant and solid-predominant adenocarcinomas (P<0.01). Micropapillary predominant and solid-predominant adenocarcinomas had a significantly higher possibility of developing initial extrathoracic-only recurrence than other types (P<0.01). The predominant pattern group (micropapillary or solid versus lepidic, acinar, or papillary) was a significant prognostic factor in overall survival (P<0.01), probability of freedom from recurrence (P<0.01), and disease-specific survival (P<0.01) in multivariate analysis. For patients receiving adjuvant chemotherapy, solid-predominant adenocarcinoma was a significant predictor for poor overall survival (P=0.04). The authors concluded that in lung adenocarcinoma, the

IASLC/ATS/ERS classification system has significant prognostic and predictive value regarding death and recurrence. Solid-predominant adenocarcinoma was also a significant predictor in patients undergoing adjuvant chemotherapy. Prognostic and predictive information is important in stratifying patients for aggressive adjuvant chemoradiotherapy.

Hung JJ, Yeh YC, Jeng WJ, et al. Predictive value of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in tumor recurrence and patient survival. *J Clin Oncol.* 2014;32(22):2357–2364.

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Histomorphology of Lynch syndrome-associated ovarian carcinomas with regard to a screening strategy

Women with Lynch syndrome are at increased risk of developing epithelial ovarian cancer. Analogous to previous studies on BRCA1/2 mutation carriers, there is evidence to suggest a histotype-specific association in Lynch syndrome-associated ovarian cancers (LS-OCs). Whereas the diagnosis of high-grade serous carcinoma is an indication for BRCA1/2 germline testing, there are no screening guidelines for triaging ovarian cancer patients for Lynch syndrome testing based on histotype. The authors performed a centralized pathology review of tumor subtype on 20 germline mutation-confirmed LS-OCs on the basis of morphologic assessment of H&E-stained slides, with confirmation by immunohistochemistry when necessary. Results from mismatch-repair immunohistochemistry (MMR-IHC) and microsatellite instability phenotype status were documented, and detailed pedigrees were analyzed to determine whether previously proposed clinical criteria would have selected these patients for genetic testing. A review of pathology revealed all LS-OCs to be pure endometrioid carcinoma (14 cases), mixed carcinoma with an endometrioid component (four cases), or clear cell carcinoma (two cases). No high-grade or low-grade serous carcinomas or mucinous carcinomas of intestinal type were identified. Tumor-infiltrating lymphocytes were prominent (40 or more per 10 high-powered fields) in only two cases. With the exception of one case, all tumors tested for MMR-IHC or microsatellite instability had an MMR-deficient phenotype. Within this cohort, 50 percent, 55 percent, 65 percent, and 85 percent of patients would have been selected for genetic workup using Amsterdam II criteria, revised Bethesda guidelines, Society of Gynecologic Oncologists (SGO) 10 percent to 25 percent criteria, and SGO five percent to 10 percent criteria, respectively, with fewer than 60 percent of index or sentinel cases detected by any of these schemas. To further support a subtype-driven screening strategy, MMR-IHC reflex testing was performed on all consecutive nonserous ovarian cancers diagnosed at one academic hospital during a two-year period. MMR deficiency was identified in 10 of 48 (21 percent) cases, all with endometrioid or clear cell histology. The authors concluded that a strong association exists between endometrioid and clear cell ovarian carcinomas and hereditary predisposition due to MMR gene mutation. These findings have implications for the role of tumor subtype in screening patients with ovarian cancer for further genetic testing and support reflex MMR-IHC or microsatellite instability testing, or both, for newly diagnosed cases of endometrioid or clear cell ovarian carcinoma.

Chui MH, Ryan P, Radigan J, et al. The histomorphology of Lynch syndrome-associated ovarian carcinomas: toward a subtype-specific screening strategy. *Am J Surg Pathol.* 2014;38:1173–1181.

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