Anatomic pathology selected abstracts

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ALK-rearranged tumors in the STUMP subcategory of uterine tumors

May 2019—Smooth muscle tumor of uncertain malignant potential is a rare diagnosis rendered when there is uncertainty concerning the biological potential of a smooth muscle tumor. The initial differential diagnosis is often broad, as tumors in this subgroup are morphologically heterogeneous. Recent data suggest that uterine inflammatory myofibroblastic tumors (IMTs) with anaplastic lymphoma kinase (ALK) rearrangement may be misclassified as smooth muscle tumor of uncertain malignant potential (STUMP), but the extent to which this occurs has not been examined. The authors identified 60 female patients with tumors previously diagnosed as STUMP (48 cases) or prospectively considered for the diagnosis of STUMP (12 cases). Each case underwent histologic review, ALK immunohistochemistry, and confirmatory break-apart FISH for ALK if immunoreactive. Six of the 43 (14 percent) uterine and cervical tumors were ALK IHC positive, whereas tumors at all other sites were ALK IHC negative. Myxoid features, although limited in some cases, were present in all six ALK IHC-positive tumors, representing 35 percent (six of 17) of tumors displaying myxoid features at uterine and cervical sites. All ALK-immunoreactive tumors were confirmed to have ALK rearrangements by FISH, with one tumor showing numerous (three to eight) 3′ ALK signals, an unusual FISH pattern not previously described in uterine inflammatory myofibroblastic tumors. Two patients developed recurrent disease and were treated with ALK-targeted therapy, with initial response. The data demonstrate that a significant proportion of uterine and cervical tumors considered to be STUMPs are ALK-positive by IHC and FISH. Future screening of all uterine and cervical mesenchymal tumors under consideration for the diagnosis of STUMP, particularly those with myxoid features, is recommended to identify ALK-rearranged inflammatory myofibroblastic tumors that could potentially be treated with targeted therapy using tyrosine kinase inhibitors.

Devereaux KA, Kunder CA, Longacre TA. ALK-rearranged tumors are highly enriched in the STUMP subcategory of uterine tumors. *Am J Surg Pathol.* 2019;43(1):64–74.

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Study of molecular changes preceding endometrial and ovarian cancer

Molecular alterations preceding endometrial and ovarian cancer and their sequence of events are unknown. The authors profiled specimens from patients with lifelong surveillance for Lynch syndrome, a prevalent cancer predisposition syndrome associated with hereditary defects in DNA mismatch repair, to define the molecular trajectories of endometrial and ovarian cancer and guide patient management. They identified DNA mismatch repair gene mutation carriers with endometrial or ovarian carcinoma or endometrial hyperplasia from a nationwide registry. The authors collected endometrial biopsy specimens taken from these women during 20 years of screening. They retrieved 213 endometrial and ovarian specimens from Lynch syndrome mutation carriers and 197 histology-matched (nonserous) samples from sporadic cases. The specimens were profiled for markers linked to endometrial and ovarian tumorigenesis, including ARID1A protein expression, mismatch repair status, and tumor suppressor gene promoter methylation. In Lynch syndrome-associated endometrial and ovarian carcinomas, ARID1A protein was lost in 61 to 100 percent and mismatch repair was deficient in 97 to 100 percent, compared with none to 17 percent and 14 to 44 percent, respectively, in sporadic carcinomas ($P = .000$). ARID1A loss appeared in complex hyperplasia and deficient mismatch repair and tumor suppressor gene promoter methylation in histologically normal endometrium. Despite quantitative differences between Lynch syndrome and sporadic cases, ARID1A expression, mismatch repair, and tumor suppressor gene promoter methylation divided endometrial

samples from both patient groups into three categories of increasing abnormality, comprising normal endometrium and simple hyperplasia, complex hyperplasia with or without atypia, and endometrial cancer. Complex hyperplasias without atypia and with atypia were molecularly indistinguishable. The authors concluded that surveillance specimens from Lynch syndrome identify mismatch repair deficiency, tumor suppressor gene promoter methylation, and ARID1A loss as early changes in tumor development. These findings are clinically relevant for classifying endometrial hyperplasias and have potential implications for cancer prevention in Lynch syndrome patients.

Niskakoski A, Pasanen A, Lassus H, et al. Molecular changes preceding endometrial and ovarian cancer: a study of consecutive endometrial specimens from Lynch syndrome surveillance. *Mod Pathol.* 2018;31:1291–1301.

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Prognostic significance of tumor-infiltrating lymphocytes in DCIS of breast

Tumor-infiltrating lymphocytes provide prognostic value in invasive breast cancer, and there are published guidelines for assessing them. The authors conducted a study to evaluate methods of tumor-infiltrating lymphocyte (TIL) assessment and the prognostic significance of TILs in breast ductal carcinoma in situ (DCIS). They assessed hematoxylin-and-eosin–stained sections from two clinically annotated DCIS cohorts—a training set (n = 150 pure DCIS) and a validation set (n = 666 comprising 534 pure DCIS and 132 cases wherein DCIS and invasive breast carcinoma coexisted). Seven scoring methods were applied to the training set to identify the optimal reproducible method associated with the strongest prognostic value. Among the methods, TILs touching the ducts' basement membrane or one lymphocyte cell thickness away from it provided the strongest significant association with outcome and highest concordance rate (inter-cluster correlation coefficient, 0.95). The assessment of periductal TILs at increasing distances from DCIS (0.2, 0.5, and 1 mm) and percentage of stromal TILs was challenging and showed lower concordance rates than for touching TILs. TIL hotspots and lymphoid follicles did not exhibit prognostic significance. Within the pure DCIS validation set, dense TILs were associated with younger age, symptomatic presentation, larger size, higher nuclear grade, comedo necrosis, estrogen receptor negativity, and shorter recurrence-free interval ($P = .002$). In multivariate survival analysis, dense TILs were independent predictors of shorter recurrence-free interval ($P = .002$) in patients treated with breast conservation. DCIS associated with invasive carcinoma showed denser TILs than pure DCIS ($P = 9.0 \times 10^{-13}$). Dense TILs are an independent prognostic variable in DCIS. Touching TILs provide a reproducible method for their assessment that potentially can be used to guide management.

Toss MS, Miligy I, Al-Kawaz A, et al. Prognostic significance of tumor-infiltrating lymphocytes in ductal carcinoma in situ of the breast. *Mod Pathol.* 2018;31:1226–1236.

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Differential expression patterns of GATA3 in vulvar intraepithelial neoplasia

The two main precursors of vulvar squamous cell carcinoma, usual and differentiated vulvar intraepithelial neoplasia, have a distinctive etiology, pathogenesis, and natural history. Usual-type vulvar intraepithelial neoplasia (VIN) is often associated with high-risk human papillomavirus (HPV), and differentiated VIN has de novo p53 genetic alterations that are unrelated to HPV infection. GATA-binding protein 3 (GATA3) is a tumor suppressor that shows increased expression in several types of human malignancies, including breast and bladder carcinomas. Little is known about the expression of GATA3 in vulvar squamous neoplasms. The authors have systematically examined the expression of GATA3 in 119 vulvar lesions and neoplasms, including 20 cases of lichen sclerosus, 12 cases of lichen simplex chronicus, 30 cases of usual-type VIN, 34 cases of differentiated VIN, and 23 cases of squamous cell carcinoma. Similar to adjacent non-neoplastic epidermis, moderate to strong GATA3 expression was retained in all cases of lichen sclerosus, lichen simplex chronicus, and usual-type VIN. However, in comparison, the

GATA3 immunostaining pattern in differentiated VIN was distinct. Partial or complete loss of GATA3 expression in the basal layer with or without loss in the parabasal layer was observed in 30 of 34 (88 percent) differentiated VIN cases. Significant loss of GATA3 expression was observed in all (seven) squamous cell carcinomas associated with usual-type VIN and in 13 of 16 (81 percent) of those associated with differentiated VIN. There was no significant correlation between loss of GATA3 expression and overexpression of p53 in differentiated VIN. The study shows that loss of GATA3 expression is seen in the vast majority (87 percent) of vulvar squamous cell carcinomas. Downregulation of GATA3 may be an early event during tumorigenesis in differentiated VIN but not in HPV-related usual-type VIN. These data suggest that application of GATA3 immunohistochemistry along with p53 may be a useful tool in diagnosing VIN.

Goyal A, Zhang G, Yang B. Differential expression patterns of GATA3 in usual and differentiated types of vulvar intraepithelial neoplasia: potential diagnostic implications. *Mod Pathol*. 2018;31:1131–1140.

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Risk of lymph node metastasis in early gastric cardiac carcinomas

Clinical decision-making about endoscopic versus surgical resection of early gastric cardiac carcinoma remains challenging because of uncertainty about risk of lymph node metastasis. The authors conducted a multicenter study to investigate risk factors for lymph node metastasis in early gastric cardiac carcinoma. Guided by World Health Organization diagnostic criteria, they studied 2,101 radical resections of early gastric carcinoma for risk factors associated with lymph node metastasis, including tumor location, gross pattern, size, histology type, differentiation, invasion depth, and lymphovascular and perineural invasion. The authors found that the risk of lymph node metastasis was significantly lower in early gastric cardiac carcinomas (6.7 percent; 33 of 495) compared with early gastric noncardiac carcinomas (17.1 percent; 275 of 1,606; $P < .0001$). In early gastric cardiac carcinoma, no lymph node metastasis was identified in intramucosal carcinoma and uncommon types of carcinomas, irrespective of gross pattern, size, histologic type, differentiation, and invasion depth. Ulceration, size greater than 3 cm, and submucosal invasion were not significant independent risk factors for lymph node metastasis. In 33 early gastric cardiac carcinomas with lymph node metastasis, either lymphovascular invasion or poor differentiation was present in 16 (48.5 percent) cases, and both were present in six cases. Using multivariate analysis, independent risk factors of lymph node metastasis in early gastric cardiac carcinoma included lymphovascular invasion (odds ratio [OR], 7.6; 95 percent confidence interval [CI], 2.8–20.2; $P < .0001$) and poor differentiation (OR, 6.0; 95 percent CI, 1.4–25.9; $P < .05$). The authors concluded that lymph node metastasis was not identified in early gastric cardiac intramucosal carcinoma and uncommon types of carcinoma. The risk of lymph node metastasis was also significantly lower in tumors with submucosal invasion, especially for cases without lymphovascular invasion or poor differentiation. These results lend support to the role of endoscopic therapy in treating patients with early gastric cardiac carcinoma.

Huang Q, Cheng Y, Chen L, et al. Low risk of lymph node metastasis in 495 early gastric cardiac carcinomas: a multicenter clinicopathologic study of 2101 radical gastrectomies for early gastric carcinoma. *Mod Pathol.* 2018;31:1599–1607.

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