Anatomic Pathology Selected Abstracts, 1/13

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Relationship between PAX2-null secretory cell outgrowths in the oviduct and pelvic serous cancer

With the exception of germ-line mutations in ovarian cancer susceptibility genes, genetic predictors for women destined for ovarian serous cancer cannot be identified in advance of malignancy. The authors recently showed that benign secretory cell outgrowths (SCOUTs) in the oviduct increase in frequency with concurrent serous cancer and typically lack PAX2 expression (PAX2-null). They conducted a study in which they examined the relationship of PAX2-null SCOUTs to high-grade serous cancers by comparing oviducts from women with benign gynecologic conditions and high-grade serous cancers. PAX2-null SCOUTs were identified by immunostaining and computed as a function of location, frequency (F) per number of cross-sections examined, and age. The authors examined 639 cross-sections from 35 serous cancers (364) and 35 controls (275). PAX2-null SCOUTs consisted of discrete linear stretches of altered epithelium ranging from cuboidal/columnar to pseudostratified, the latter including ciliated differentiation. They were evenly distributed among proximal and fimbrial tubal sections. A total of 114 (F=.31) and 45 (F=.16) PAX2-null SCOUTs were identified in cases and controls, respectively. Mean individual case-specific frequencies for cases and controls were .39 and .14, respectively. SCOUT frequency increased significantly with age in both groups (P=.01). However, when adjusted for age and the number of sections examined, the differences in frequency between cases and controls remained significant (P=.006). The authors concluded that this study supports a relationship between discrete PAX2 gene dysregulation in the oviduct and both increasing age and, more significantly, the presence of co-existing serous cancer. They propose a unique co-variable in benign oviductal epithelium—the PAX2-null SCOUT—that reflects underlying dysregulation in genes linked to serous neoplasia.

Quick CM, Ning G, Bijron J, et al. PAX2-null secretory cell outgrowths in the oviduct and their relationship to pelvic serous cancer. *Mod Pathol.* 2012;25:449–455.

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Broad range of adverse cutaneous eruptions in patients on tumor necrosis factor-alpha antagonists

Biologic therapies targeting tumor necrosis factor (TNF)-α have become a mainstay in managing a number of autoimmune diseases. The authors reported on a series of adverse skin eruptions in six patients (four female, two male; age, 21–58 years; mean, 39 years) receiving four months to 10 years (mean, 3.1 years) of anti-TNF-α therapies (infliximab, n=4; adalimumab, n=1; or etanercept, n=1). The following drug-associated diagnoses were made in eight skin biopsies performed at Massachusetts General Hospital between March 2007 and October 2010: pustular folliculitis, psoriasis, interface dermatitis, neutrophilic eccrine hidradenitis, Sweet's syndrome, lupus, vasculitis, and palmoplantar pustulosis. The descriptions of neutrophilic eccrine hidradenitis-like and Sweet's-like hypersensitivity eruptions induced by anti-TNF-α therapies are the first such cases described in the literature. Each cutaneous eruption improved or resolved by switching to a different TNF-α inhibitor, discontinuing the anti-TNF-α agent, and/or using topical or systemic steroids. There was a clear chronologic relationship with, and clinical remission upon, withdrawal or steroid suppression of the anti-TNF-α agents. The mechanism for such diverse cutaneous eruptions among this class of medications remains poorly understood. The authors concluded that the cutaneous adverse reaction profile of TNF-α inhibitors is broad and should be considered in the histopathologic

differential in this clinical setting.

Hawryluk EB, Linskey KR, Duncan LM, et al. Broad range of adverse cutaneous eruptions in patients on TNF-alpha antagonists. *J Cutan Pathol.* 2012;39:481–492.

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A practical approach to HER2 testing in gastric cancer

Trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is approved by the European Medicines Agency to treat patients with human epidermal growth factor receptor 2 (HER2)-positive (immunohistochemistry 3+ or immunohistochemistry 2+/fluorescence in situ hybridization-positive or immunohistochemistry 2+/silver in situ hybridization-positive) metastatic adenocarcinoma of the stomach or gastro-esophageal junction. Approvals are underway in other countries and were recently granted in the United States and Japan. Experience and data from trastuzumab use in breast cancer have highlighted the importance of quality HER2 testing and scoring to ensure accurate identification of patients eligible for treatment. HER2 testing in gastric cancer differs from testing in breast cancer due to inherent differences in tumor biology. Gastric cancer more frequently shows HER2 heterogeneity (focal staining) and incomplete membrane staining. Consequently, gastric cancer-specific HER2 testing protocols have been developed and standardized, and it is imperative that these recommendations be followed. Given the predictive value of HER2 protein levels with response in the Trastuzumab for Gastric Cancer (ToGA) study, immunohistochemistry should be the initial testing methodology, and fluorescence in situ hybridization or silver in situ hybridization should be used to retest immunohistochemistry 2+ samples. Bright-field methodologies should be used whenever possible as these are considered superior to fluorescent methodologies for identifying heterogeneous staining. Specific training is required before embarking on HER2 testing in gastric cancer, irrespective of experience with HER2 testing in breast cancer. The authors' paper provides up-to-date, practical guidance on HER2 testing and scoring in patients with gastric and gastro-esophageal junction cancer, as determined by a panel of expert pathologists with extensive experience in HER2 testing, particularly reflecting the European Medicines Agency-approved indication. It is anticipated that these recommendations will ensure accurate and consistent HER2 testing, which will allow appropriate selection of patients eligible for treatment with trastuzumab.

Rüschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol.* 2012;25:637–650.

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Clinical assessment of PTEN loss in endometrial carcinoma

PTEN (phosphatase and tensin homolog) is a tumor-suppressor gene that negatively regulates the PI3K-AKT signaling pathway, which is implicated in the pathogenesis of endometrial carcinoma. Sanger sequencing has been considered the gold standard for detecting PTEN sequence abnormalities. However, this approach fails to address the epigenetic mechanisms that contribute to functional PTEN protein loss. Using a study cohort of 154 endometrioid and non-endometrioid endometrial carcinomas, the authors performed full-length PTEN sequencing and PTEN immunohistochemistry on each tumor. PTEN sequence abnormalities were detected in a significantly lower proportion of cases (43 percent) than PTEN protein loss (64 percent; P=.0004). Endometrioid tumors had a significantly higher proportion of PTEN sequence abnormalities and PTEN protein loss than non-endometrioid tumors. Within the latter group, PTEN sequence abnormalities and PTEN protein loss were most frequent in undifferentiated carcinomas, followed by mixed carcinomas; they were least frequent in carcinosarcomas. Overall, at least one PTEN sequence abnormality was detected in each exon, and the greatest number of sequence abnormalities was detected in exon 8. Pure-endometrioid tumors had a significantly higher frequency of sequence abnormalities in exon 7 than did non-endometrioid tumors (P=.0199). Importantly, no mutational hotspots were identified. While PTEN protein loss by immunohistochemistry was identified in 89 percent of cases with a PTEN sequence abnormality, PTEN protein loss was detected by immunohistochemistry in 44 percent of cases classified

as PTEN wild type by sequencing. For the first time, it was demonstrated that PTEN immunohistochemistry can identify the majority of cases with functional PTEN protein loss. However, PTEN immunohistochemistry also detects additional cases with PTEN protein loss that would otherwise be undetected by gene sequencing. Therefore, for clinical purposes, immunohistochemistry appears to be a preferable technique for identifying endometrial tumors with loss of PTEN function.

Djordjevic B, Hennessy BT, Li J, et al. Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry outperforms gene sequencing. *Mod Pathol.* 2012;25:699–708.

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A clinicopathological and immunophenotypic study of secretory breast carcinoma

Secretory breast carcinoma is a rare breast cancer with indolent clinical behavior. Recent research has shown that secretory breast carcinoma belongs to the phenotypic spectrum of basal-like breast carcinomas. The authors conducted a clinicopathological and immunophenotypic analysis of secretory breast carcinomas from 15 Chinese patients. The patient group consisted of two males and 13 females, who ranged in age from 10 to 67 years (median, 36 years). All patients presented with a painless and firm mass. Tumor size ranged from 10 to 55 mm. Most tumors were located in the outer upper quadrant of the breast. Two of 13 patients (15 percent) displayed positive axillary lymph nodes. At the microscopic level, the presence of intracellular and extracellular secretory material was the most remarkable feature. Most cases showed mild dysplasia cytologically. All cases were negative for estrogen receptor, progesterone receptor, and HER2. The expression rate of the basal-like marker (CK5/6 or epidermal growth factor receptor) was 87 percent (13 of 15). The basal-like phenotype was identified in 13 cases (87 percent). Followup time ranged from 10 to 55 months (median, 19 months). None of the cases had evidence of recurrence and metastasis. This study revealed that secretory breast carcinoma is a distinct subset of invasive breast carcinoma, with expression of basal-like markers. Furthermore, secretory breast carcinoma is different from conventional basal-like breast carcinomas. Additional studies are required to further understand the prognostic significance of expression of basal-like markers in secretory breast carcinoma.

Li D, Xiao X, Yang W, et al. Secretory breast carcinoma: a clinicopathological and immunophenotypic study of 15 cases with a review of the literature. *Mod Pathol.* 2012;25:567–575.

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Twenty-year survival among a population diagnosed with thin melanoma

The 20-year survival rates are unknown for the majority of melanoma patients—those with thin melanomas. The authors determined the 20-year survival rates for patients diagnosed with thin melanomas (1.00 mm or less) in the general population of Queensland, Australia. They also determined the main prognostic factors. Available clinical and histological data from the Queensland Cancer Registry were obtained for all patients diagnosed with a single thin invasive melanoma from 1982 to 2006 and matched against national death registration data. Melanoma-specific survival estimates to Dec. 31, 2007 were assessed, and subgroup differences in prognosis were determined by fitting multivariate Cox proportional hazard models. Among 26,736 people in the state of Queensland diagnosed with thin melanomas, the 20-year survival rate was 96 percent. The most influential determinants of prognosis were tumor thickness of 0.75 mm or greater (adjusted hazard ratio [HR], 4.33; 95 percent confidence interval [CI], 2.8–6.8 compared with tumors of less than 0.25 mm) and patient age at diagnosis older than 65 years (HR, 2.8; 95 percent CI, 1.8–4.5) compared with age younger than 25 years. Acral lentiginous and nodal tumors, male gender, tumor site on the scalp or neck, or tumor invasion of the entire papillary dermis each independently increased the risk of dying from thin invasive melanoma. The authors concluded that the outlook for patients with thin invasive melanoma is positive, although continued clinical vigilance is warranted for patients with nodular melanoma and those with the thickest tumors.

Green AC, Baade P, Coory M, et al. Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. *J Clin Oncol.* 2012;30(13):1462–1467.

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Molecular basis of EPCAM expression loss in Lynch syndrome-associated tumors

Germline deletions affecting the epithelial cell adhesion molecule (EPCAM) gene lead to silencing of MSH2 and cause Lynch syndrome. The authors recently reported that lack of EPCAM expression occurs in many, but not all, tumors from Lynch syndrome patients with EPCAM germline deletions. The differences in EPCAM expression were not related to localization of EPCAM germline deletions. The authors, therefore, hypothesized that the type of the second somatic hit, which leads to MSH2 inactivation during tumor development, determines EPCAM expression in the tumor cells. To test this hypothesis and evaluate whether lack of EPCAM expression can already be detected in Lynch syndrome-associated adenomas, the authors analyzed four carcinomas and two adenomas from EPCAM germline deletion carriers for EPCAM protein expression and allelic deletion status of the EPCAM gene region by multiplex ligation-dependent probe amplification. In four of six tumors, the authors observed lack of EPCAM expression accompanied by biallelic deletions affecting the EPCAM gene. In contrast, monoallelic retention of the EPCAM gene was observed in the remaining two tumors with retained EPCAM protein expression. These results demonstrate that EPCAM expression in tumors from EPCAM deletion carriers depends on localization of the second somatic hit that inactivates MSH2. Moreover, the authors reported lack of EPCAM protein expression in a colorectal adenoma, suggesting that EPCAM immunohistochemistry may detect EPCAM germline deletions already at a precancerous stage.

Huth C, Kloor M, Voigt AY, et al. The molecular basis of EPCAM expression loss in Lynch syndrome-associated tumors. *Mod Pathol.* 2012;25:911–916.

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Image and statistical analysis of melanocytic histology

The authors applied digital image-analysis techniques to study selected types of melanocytic lesions. They used advanced digital image-analysis to compare melanocytic lesions as follows: melanoma to nevi, melanoma subtypes to nevi, severely dysplastic nevi to other nevi, and melanoma to severely dysplastic nevi. The authors were successful in differentiating melanoma from nevi (receiver operating characteristics [ROC] area, 0.95) using image-derived features, among which those related to nuclear size and shape and distance between nuclei were most important. By dividing melanoma into subtypes, even greater separation was obtained (ROC area, 0.98 for superficial spreading melanoma; 0.95 for lentigo maligna melanoma; 0.99 for unclassified). Severely dysplastic nevi were best differentiated from conventional and mildly dysplastic nevi by differences in cellular staining qualities (ROC area, 0.84). The authors found that melanomas were separated from severely dysplastic nevi by features related to shape and staining qualities (ROC area, 0.95). All comparisons were statistically significant ($P<.0001$). The authors concluded that they offered a unique perspective into the evaluation of melanocytic lesions and demonstrated a technological application that has potential use as an adjunct to traditional diagnosis in the future.

Miedema J, Marron JS, Niethammer M, et al. Image and statistical analysis of melanocytic histology. *Histopathology.* 2012;61:436–444.
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