Anatomic Pathology Selected Abstracts, 3/15

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Histopathologic spectrum of thecoma of the ovary: a report of 70 cases

The authors evaluated 70 cases of thecoma of the ovary to ascertain their histopathologic spectrum. The tumors occurred over a wide age range (average, 49.6 years). Presentation in the form of pelvic or abdominal pain was uncommon, but postmenopausal bleeding was relatively frequent. All the tumors were unilateral, ranging up to 22.5 cm (average, 4.9 cm) in greatest dimension. They were typically intact, uniformly solid, and yellow. Microscopic examination usually showed a predominant diffuse growth but was altered to varying degrees by hyaline plaques (37 cases), nodular growth (20 cases), calcification (20 cases), and keloid-like sclerosis (12 cases). Forty percent of the tumors had a minor component of fibroma. Reticulin stains typically showed an investment of single cells. The tumor cells characteristically had ill-defined cytoplasmic membranes and distinctive pale gray cytoplasm. Two tumors had degenerative so-called bizarre atypia, and 15 tumors had nuclear grooves, but they were rarely conspicuous. The differential diagnosis is primarily with other sex cord-stromal neoplasms, particularly sclerosing stromal tumor, microcystic stromal tumor, steroid cell tumor, and adult granulosa cell tumor. The nodules of sclerosing stromal tumors have a more heterogenous morphology than the uniform cell type of thecomas, and microcystic stromal tumors are distinguished because of microcysts and the differing character of the tumor cells. Steroid cell tumors also have contrasting cytoplasmic features. Granulosa cell tumor with a prominent thecomatous component is the most clinically important differential diagnosis and is largely solved by thorough sampling. The authors' experience indicates that thecomas have a relatively distinctive appearance, which contrasts with the lipid-rich character often emphasized in the literature. Awareness of this finding and a spectrum of other findings should enable the accurate interpretation of an almost invariably benign tumor.

Burandt E, Young RH. Thecoma of the ovary: a report of 70 cases emphasizing aspects of its histopathology different from those often portrayed and its differential diagnosis. *Am J Surg Pathol.* 2014;38:1023–1032.

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Diagnostic criteria for ductal adenocarcinoma of the prostate: interobserver variability

Ductal adenocarcinoma of the prostate is clinically important because its behavior may differ from that of acinar adenocarcinoma. The authors investigated the interobserver variability of this diagnosis among experts in uropathology and defined diagnostic criteria. For the study, photomicrographs of 21 carcinomas with ductal features were distributed among 20 genitourinary pathologists from eight countries. Ductal adenocarcinoma of the prostate (DAC) was diagnosed by 18 observers (mean, 13.2 cases; range, 6–19). In 11 (52 percent) cases, a two-thirds consensus was reached for a diagnosis of DAC, and in five (24 percent) there was consensus against such a diagnosis. In DAC, the respondents reported papillary architecture (86 percent), stratification of nuclei (82 percent), high-grade nuclear features (54 percent), tall columnar epithelium (53 percent), elongated nuclei (52 percent), cribriform architecture (40 percent), and necrosis (seven percent). The most important diagnostic feature reported for DAC was papillary architecture (59 percent), whereas nuclear and cellular features were considered to be most important in only two percent to 11 percent of cases. The most common differential diagnoses were intraductal prostate cancer (52 percent), high-grade prostatic intraepithelial neoplasia (37 percent), and acinar adenocarcinoma (17 percent). The most common reason for not diagnosing DAC was lack of typical architecture (33 percent). The authors concluded that papillary architecture was the most useful diagnostic feature of DAC, and nuclear and cellular features were considered to be less important.

Seipel AH, Delahunt B, Samaratunga H, et al. Diagnostic criteria for ductal adenocarcinoma of the prostate: interobserver variability among 20 expert uropathologists. *Histopathology.* 2014;65:216–227.

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Surgeon influence on use of needle biopsy in patients with breast cancer

Use of needle biopsy is a proposed quality measure in the diagnosis and treatment of breast cancer, yet literature documents underuse. From a national perspective, little is known about the contribution of a patient's surgeon to needle biopsy use, and knowledge regarding the downstream impact of needle biopsy on breast cancer care is incomplete. In a national Medicare study using 2003 to 2007 nationwide Medicare data from 89,712 patients with breast cancer and 12,405 surgeons, logistic regression was employed to evaluate the following outcomes: surgeon consultation before versus after biopsy, whether needle biopsy was used, and number of surgeries for cancer treatment. Multilevel analyses were adjusted for physician, patient, and structural covariates. The study found that needle biopsy was used in 68.4 percent (n=61,353) of all patients and only 53.7 percent (n=32,953/61,312) of patients seen by a surgeon before biopsy. Patient factors associated with surgeon consultation before biopsy included Medicaid coverage, rural residence, residence more than 8.1 miles from a radiologic facility performing needle biopsy, and no mammogram within 60 days before consultation. Among patients with surgeon consultation before biopsy, surgeon factors such as absence of board certification, training outside the United States, low case volume, earlier decade of medical school graduation, and lack of specialization in surgical oncology were negatively correlated with receipt of needle biopsy. Risk of multiple cancer surgeries was 33.7 percent for patients that underwent needle biopsy compared with 69.6 percent for those who did not (adjusted relative risk, 2.08; $P<0.001$). The authors concluded that needle biopsy is underused in the United States, resulting in a negative impact on breast cancer diagnosis and treatment. Surgeon-level interventions may improve needle biopsy rates and, accordingly, quality of care.

Eberth JM, Xu Y, Smith GL, et al. Surgeon influence on use of needle biopsy in patients with breast cancer: a national Medicare study. *J Clin Oncol.* 2014;32:2206–2216.

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Müllerian precursor lesions in serous ovarian cancer patients

Serous ovarian cancer is suggested to develop from epithelium embryologically derived from the Müllerian ducts. The authors conducted a study to thoroughly analyze the epithelium derived from those ducts (cervix, endometrium, and fallopian tubes) in serous ovarian cancer patients. Sixty women diagnosed with serous ovarian carcinoma were included in this multicenter, observational study. Tissues were embedded completely for histological assessment in accordance with the SEE-Fim (Sectioning and Extensively Examining the Fimbriated End) and SEE-End (Sectioning and Extensively Examining the Endometrium) protocols, and the prevalence of cervical, endometrial, and tubal pathology was analyzed. In 31 (52 percent) cases, a pathologic lesion was identified, and in 16 (27 percent) of these cases, coexistence of pathologic lesions was noted. Severe dysplasia was found in the cervix in one case. Endometrial intraepithelial carcinoma was found in nine (15 percent) cases; endometrial atypical hyperplasia in 19 (32 percent) cases; and serous tubal intraepithelial carcinoma in 23 (43 percent) cases. Serous tubal intraepithelial carcinoma was significantly more often concurrent with endometrial atypical hyperplasia or endometrial intraepithelial carcinoma than with benign endometrium (64 versus 28 percent; P=0.01). The authors concluded that histological assessment of epithelium derived from Müllerian ducts of serous ovarian cancer patients resulted in the identification of endometrial intraepithelial carcinoma, serous tubal intraepithelial carcinoma, or endometrial atypical hyperplasia in more than half of cases. Coexistence of these pathologic lesions was common and might represent an effect of field carcinogenesis or tumor implantation of migrating cells.

Mingels MJ, van Ham MA, de Kievit IM, et al. Müllerian precursor lesions in serous ovarian cancer patients: using the SEE-Fim and SEE-End protocol. *Mod Pathol.* 2014;27:1002–1013.

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Loss of 5-hydroxymethylcytosine and increasing morphologic dysplasia in melanocytic tumors

DNA methylation is the most well-studied epigenetic modification in cancer biology. The epigenetic mark 5-hydroxymethylcytosine can be converted from 5-methylcytosine by the ten-eleven translocation gene family. The authors recently reported the loss of 5-hydroxymethylcytosine in melanoma compared with benign nevi and suggested that loss of this epigenetic marker is correlated with tumor virulence based on its association with a worse prognosis. In this study, they further characterized the immunoreactivity patterns of 5-hydroxymethylcytosine in the full spectrum of melanocytic lesions to further validate the potential practical application of this epigenetic marker. They evaluated 175 cases: 18 benign nevi, 20 dysplastic nevi (10 low-grade and 10 high-grade lesions), 10 atypical Spitz nevi, 20 borderline tumors, five melanomas arising within nevi, and 102 primary melanomas. Progressive loss of 5-hydroxymethylcytosine from benign dermal nevi to high-grade dysplastic nevi to borderline melanocytic neoplasms to melanoma was observed. In addition, an analysis of the relationship of nuclear diameter with 5-hydroxymethylcytosine staining intensity within lesional cells revealed a significant correlation between larger nuclear diameter and decreased levels of 5-hydroxymethylcytosine. Furthermore, borderline lesions exhibited a diverse spectrum of staining of each individual case. The authors concluded that this study further substantiates the association of 5-hydroxymethylcytosine loss with dysplastic cytomorphologic features and tumor progression and supports the classification of borderline lesions as a biologically distinct category of melanocytic lesions.

Larson AR, Dresser KA, Zhan Q, et al. Loss of 5-hydroxymethylcytosine correlates with increasing morphologic dysplasia in melanocytic tumors. *Mod Pathol.* 2014;27:936–944.

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Frequent CCNE1 amplification in endometrial intraepithelial carcinoma and uterine serous carcinoma

Uterine serous carcinoma accounts for only 10 percent of all uterine epithelial cancers but is the leading cause of death among them. The pathogenesis of this aggressive neoplasm has been largely elusive, until recently, when comprehensive genome-wide analyses of uterine serous carcinoma were performed. The cancer-related gene CCNE1, encoding for cyclin E1, is frequently amplified in uterine serous carcinoma. The authors conducted a study in which they used FISH to determine CCNE1 copy number in uterine serous carcinoma and concurrent endometrial intraepithelial carcinoma, the noninvasive component of uterine serous carcinoma, and correlated the results with clinicopathological and molecular features. They found that 20 of 44 (45 percent) uterine serous carcinomas and 11 of 27 (41 percent) endometrial intraepithelial carcinomas showed CCNE1 amplification. Overall, the authors found high concordance in CCNE1 copy number in concurrent uterine serous carcinoma and endometrial intraepithelial carcinoma pairs (P=0.0003). No correlation was observed between CCNE1 copy number and clinicopathological features, as well as common mutations previously reported in uterine serous carcinoma. The authors concluded that this study confirms that amplification of CCNE1 is a frequent molecular genetic change in uterine serous carcinoma. Moreover, the identification of CCNE1 amplification in many endometrial intraepithelial carcinomas suggests that this genetic event occurs early in tumor progression.

Kuhn E, Bahadirli-Talbott A, Shih IM. Frequent CCNE1 amplification in endometrial intraepithelial carcinoma and uterine serous carcinoma. *Mod Pathol.* 2014;27:1014–1019.

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Tubal origin of ovarian endometriosis

Endometriosis is a puzzling and debilitating disease that affects millions of women worldwide. The ovary is the most common organ site involved by the disease. Despite various hypotheses about its cell of origin, uncertainty remains. On the basis of their clinicopathologic observations, the authors hypothesized that the fallopian tube may contribute the histogenesis of ovarian endometriosis. To examine if this hypothesis has scientific supporting evidence, they identified, through a gene differential assay study, a set of novel genes that are highly expressed in the normal fallopian tube or endometrium. FMO3 and DMBT1 were selected as the initial biomarkers to test the hypothesis. These biomarkers were then validated in ovarian sections with foci of endometriosis by comparing their expression levels in the fallopian tube and endometrium of the same patients using real-time PCR, Western blot, and immunohistochemistry analysis. FMO3 was highly expressed in the tubal epithelia and low in the paired endometrium. In contrast, DMBT1 was high in the endometrium but low in the fallopian tube. In 32 ovarian endometriosis cases analyzed by real-time PCR, 18 (56 percent) showed a high level of FMO3 and a low level of DMBT1 expression. However, 14 (44 percent) endometriosis cases showed a reversed expression pattern with these two markers. Similar results were generated using Western blot and immunohistochemistry. The findings suggest that approximately 60 percent of the cases of ovarian endometriosis in the study may have been derived from the fallopian tube, whereas about 40 percent of the cases may have been of endometrial origin. Fallopian tube epithelia may represent one of the tissue sources contributing to ovarian endometriosis. Such novel findings, which require confirmation, may have significant clinical impact in searching for alternative ways to prevent and treat endometriosis.

Yuan Z, Wang L, Wang Y, et al. Tubal origin of ovarian endometriosis. *Mod Pathol.* 2014;27:1154–1162.

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