Anatomic Pathology Selected Abstracts, 8/13

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Endometrium as a primary site of origin of pelvic high-grade serous carcinoma in BRCA1 or BRCA2 mutation carriers

Serous endometrial intraepithelial carcinoma has been proposed to be a potential precursor lesion of pelvic high-grade serous carcinoma. If true, an increased incidence of uterine papillary serous carcinomas would be expected in BRCA1 and BRCA2 mutation carriers, who are at high risk of developing pelvic high-grade serous carcinoma. The authors conducted a study in which they explored the occurrence of uterine papillary serous carcinoma, as well as other endometrial cancers, following risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 germline mutation who were treated at a tertiary multidisciplinary clinic in the Netherlands. A consecutive series of women with a BRCA1 or BRCA2 mutation who had undergone risk-reducing salpingo-oophorectomy without hysterectomy at the University Medical Center Groningen from January 1996 until March 2012 were followed prospectively. They were crossed with the histopathology list of endometrial cancer diagnoses reported by the Dutch nationwide pathology database PALGA. To assess the risk of endometrial cancer, a standardized incidence ratio was calculated comparing the observed with the expected number of endometrial cancer cases. Overall, 201 BRCA1 and 144 BRCA2 mutation carriers who were a median age of 50 years (range, 32–78 years) were analyzed. After a median followup of six years after risk-reducing salpingo-oophorectomy, two cases of endometrial cancer were diagnosed, whereas the expected number was 0.94 cases (standardized incidence ratio, 2.13; 95 percent confidence interval, 0.24–7.69; P=.27). Both endometrial cancer cases were of the endometrioid histological subtype. The authors showed that the incidence of endometrial cancer following risk-reducing salpingo-oophorectomy, especially uterine papillary serous carcinoma, in women at high risk of developing pelvic high-grade serous carcinoma is not increased. On the basis of these data, the hypothesis of serous endometrial intraepithelial carcinoma being an important precursor lesion of pelvic high-grade serous carcinoma seems unlikely. The authors concluded that it is not necessary to add a prophylactic hysterectomy to risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers.

Reitsma W, Mourits MJ, de Bock GH, et al. Endometrium is not the primary site of origin of pelvic high-grade serous carcinoma in BRCA1 or BRCA2 mutation carriers. *Mod Pathol.* 2013;26:572–578.

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Criteria and pitfalls in diagnosis of lymphovascular invasion in prostatectomy specimens

Lymphovascular invasion is an independent prognostic factor in prostate cancer. The authors conducted a study to describe reliable morphologic features for identifying lymphovascular invasion in prostatectomy specimens and avoiding misinterpretation of its mimickers. A total of 364 foci of lymphovascular invasion were analyzed in 264 slides from 170 prostatectomies. The average tumor volume was 25.5 percent. Tumor emboli were seen inside the tumor (eight percent), at the front edge of the tumor (30 percent), separated from the tumor (32 percent), and distant from the tumor (30 percent). Tumor emboli were more frequent per case and more often in an extraprostatic location in lymph node-positive cases (P<.05). One hundred thirty-four emboli were in a single thin-walled vessel; 227 were in a thin-walled vessel next to an artery; and three were inside an artery. Twenty-eight tumor emboli were attached to a vessel wall; 18 had proteinaceous material in the vascular lumen; and 14 were surrounded by erythrocytes. The following mimickers were seen: retraction artifact and perineural invasion—all cases; cancer impinging upon vascular space—45 foci; tangential sections of endothelium—10 foci; displacement of benign and collapsed malignant glands—16 and 27 foci, respectively; retraction with erythrocytes—three cases;

intravascular degenerating tumor cells—3 foci; malignant glands in atrophic ducts—four foci; and myofibroblastic proliferation in thrombosed vessels—two foci. In 50 stained blocks, CD31 and D2-40 immunostaining studies confirmed all lymphovascular invasions diagnosed by hematoxylin-and-eosin staining and demonstrated emboli in 47 lymphatic and 16 blood vessels. This study identifies features of true lymphovascular invasion and how to distinguish them from mimickers on routine hematoxylin-and-eosin sections.

Kryvenko ON, Epstein JI. Histologic criteria and pitfalls in the diagnosis of lymphovascular invasion in radical prostatectomy specimens. *Am J Surg Pathol.* 2012;36(12):1865–1873.

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An interobserver study of reproducibility in subtyping pulmonary adenocarcinomas

Histological subtyping of pulmonary adenocarcinoma has been updated based on predominant pattern, but data on reproducibility are required for validation. The authors conducted a two-part study in which they assessed reproducibility in subtyping adenocarcinomas and then assessed further the distinction between invasive and non-invasive (wholly lepidic) patterns of adenocarcinoma among an international group of pulmonary pathologists. Two ring studies were performed using a microphotographic image-based method, evaluating selected images of lung adenocarcinoma histologic patterns. In the first study, 26 pathologists reviewed representative images of typical and "difficult" histologic patterns. A total number of scores for the typical patterns combined (n=94) and the difficult cases (n=21) were 2,444 and 546, respectively. The mean kappa score (± standard deviation) for the five typical patterns combined and for difficult cases were 0.77±0.07 and 0.38±0.14, respectively. Although 70 percent of the observers identified 12 percent to 65 percent of typical images as single pattern, highest for solid and least for micropapillary, the predominant pattern was recognized in 92 percent to 100 percent of the images, except for micropapillary pattern (62 percent). For the second study on invasion, which was identified as a key problem area from the first study, 28 pathologists submitted and reviewed 64 images representing typical and difficult examples. The kappa score for typical and difficult cases was 0.55±0.06 and 0.08±0.02, respectively, with consistent subdivision by the same pathologists into invasive and non-invasive categories due to differing interpretations of terminology defining invasion. In pulmonary adenocarcinomas with classic morphology, which comprise the majority of cases, there is good reproducibility in identifying a predominant pattern and fair reproducibility in distinguishing invasive from in situ (wholly lepidic) patterns. However, more precise definitions and better education relative to interpreting existing terminology are required to improve recognition of purely in situ disease, an area of increasing importance.

Thunnissen E, Beasley MB, Borczuk AC, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. *Mod Pathol.* 2012;25(12):1574–1583.

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Value of PAX8, PAX2, claudin-4, and h-caldesmon in identifying peritoneal epithelioid mesotheliomas

Distinguishing between peritoneal epithelioid mesotheliomas and papillary serous carcinomas involving the peritoneum can be difficult using routine histological preparations, but this differential diagnosis can be facilitated using immunohistochemistry. Recent investigations have indicated that the immunohistochemical markers PAX8, PAX2, claudin-4, and h-caldesmon can help distinguish between these two malignancies. However, much of the published information about the value of these markers is insufficient or contradictory. The authors conducted a study to resolve some of the controversies and to determine the practical value of these markers for assisting in the differential diagnosis of peritoneal mesotheliomas and serous carcinomas. They investigated 40 peritoneal epithelioid mesotheliomas and 45 serous carcinomas (15 primary and 30 metastatic to the peritoneum). PAX8 and PAX2 nuclear positivity was demonstrated in 42 (93 percent) and 25 (56 percent) of the serous carcinomas,

respectively, whereas none of the mesotheliomas expressed either marker. Forty-four (98 percent) of the serous carcinomas exhibited claudin-4 reactivity along the cell membrane, whereas none of the mesotheliomas were positive for this marker. All of the serous carcinomas and mesotheliomas were negative for h-caldesmon. The authors concluded that PAX8 and claudin-4 have a higher sensitivity and specificity for helping discriminate between peritoneal epithelioid mesotheliomas and serous carcinomas when compared with all other positive carcinoma markers that are recommended for inclusion in the immunohistochemical panels used in this differential diagnosis. Even though it is highly specific, PAX2 has low sensitivity, so it is of little practical value in diagnosing peritoneal epithelioid mesotheliomas. H-caldes-mon is not useful.

Ordóñez NG. Value of PAX8, PAX2, claudin-4, and h-caldesmon immunostaining in distinguishing peritoneal epithelioid mesotheliomas from serous carcinomas. *Mod Pathol.* 2013;26:553–562.

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Clinicopathologic study of cutaneous digital papillary adenocarcinoma

Aggressive digital papillary adenocarcinoma is a rare tumor predominantly involving the distal end of digits. The authors examined 31 cases of this distinctive tumor for clinicopathologic, immunohistochemical, and followup data when available. Males who were a mean age of 43 years (range, 14 to 67 years) were predominantly affected (n=29). Three lesions were reported in patients younger than 20 years old. All cases involved a finger (n=26) or a toe (n=5), with most involving the distal portion of the digit (n=29). Two lesions involved the base of the digit, or web space. Histopathologically, all tumors involved the dermis, with subcutaneous extension in 14 cases. The lesions demonstrated a multinodular solid or cystic pattern, or both, with focally infiltrative architecture in 21 cases. Papillary projections were prominent (n=10), focal (n=15), or not identified (n=6). Within the solid component, tubular structures were present, at least focally, in all cases. Cytologic atypia ranged from mild (n=8) to moderate (n=20) but was focally severe in three cases. Mitotic count ranged from less than one to 18 per millimeter. Focal necrosis was seen in six cases. Immunohistochemically stained sections were available for review in eight cases. Tumor cells were diffusely positive for MNF116 (three of three). Carcinoembryonic antigen and epithelial membrane antigen highlighted the luminal border of tubules (eight of eight). Smooth muscle actin (five of six) and calponin (six of six) highlighted a myoepithelial layer around tubular/glandular structures, as did p63 (two of two) and podoplanin (five of five). Followup after excision or amputation (n=23; range, two months to 21 years) revealed local recurrence (n=5) and metastatic disease (n=6; lymph node in one, lungs in four, and both lymph node and lung in one). Metastases were noted at presentation in two cases (lymph node in one and lung in one), but presented as late as 14 and 20 years in lymph node and lung, respectively. Only one patient died of metastatic disease six years after initial diagnosis, after multiple recurrences and lung metastases. Three patients were alive with progressive disease up to 24 months after developing lung metastases. Histopathologic features did not predict outcome. The presence of tumor-associated myoepithelial cells histologically and immunohistochemically was not synonymous with benign-ity. Wide excision and partial digit amputation significantly reduced recurrence and metastatic rates. The authors concluded that a delayed occurrence of metastases and a protracted course despite metastatic disease necessitates long-term followup. And because the name implies a malignant neoplasm, the rubric “aggressive” is unnecessary.

Suchak R, Wang WL, Prieto VG, et al. Cutaneous digital papillary adenocarcinomas: a clinicopathologic study of 31 cases of a rare neoplasm with new observations. *Am J Surg Pathol.* 2012;36(12):1883–1891.

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