Anatomic Pathology Selected Abstracts, 1/14

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Flat pattern of nephrogenic adenoma unveiled using PAX2 and PAX8 immunohistochemistry

Nephrogenic adenoma is a benign lesion of the urinary tract, particularly the urinary bladder. It is a gross and microscopic mimicker of urothelial neoplasm or metastatic carcinoma. Several histological patterns—tubular, tubulocystic, polypoid, papillary, and fibromyxoid—have been recognized, but a flat pattern has not been described. Histologically, nephrogenic adenoma consists of tubules, cysts, or papillae lined by flat to polygonal cells with frequent hobnail appearance. The stroma is often edematous or has a granulation tissue-like appearance with acute or chronic inflammation. By immunohistochemistry, nephrogenic adenomas are positive for the renal epithelial markers CK7, CD10, and alpha-methylacyl-coenzyme A racemase and negative for bladder urothelium or prostate markers. Recent studies have shown that nephrogenic adenomas are positive for PAX2 and PAX8. The authors encountered an interesting case of tubular nephrogenic adenoma with adjacent areas suspicious of flat urothelial atypia. Immunohistochemistry for PAX2 and PAX8 were positive in these areas, unveiling a flat pattern of nephrogenic adenoma. This case prompted the authors to study 15 cases of nephrogenic adenoma to determine additional instances of flat pattern and to assess the value of PAX2 and PAX8 immunoreactivity in diagnosing nephrogenic adenoma. PAX2 and PAX8 immuno-staining was positive in 14 of 15 and 15 of 15 cases, respectively. The flat pattern was present at least focally adjacent to tubular, polypoid, and papillary areas in eight of 15 cases of nephrogenic adenoma. The authors concluded that the flat pattern is a common finding in nephrogenic adenomas but easily underrecognized by morphologic examination, and it may be confused with flat urothelial lesions with atypia. Immunostains for PAX2 and PAX8 are useful in detecting nephrogenic adenomas and unveil those nephrogenic adenomas with a flat pattern.

Piña-Oviedo S, Shen SS, Truong LD, et al. Flat pattern of nephrogenic adenoma: previously unrecognized pattern unveiled using PAX2 and PAX8 immunohistochemistry. *Mod Pathol.* 2013;26:792–798.

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Managing borderline atypical ductal hyperplasia/ductal carcinoma in situ on breast needle core biopsy

The differential diagnosis of low-nuclear grade intraductal epithelial proliferations of the breast includes atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS). This distinction can be difficult on core needle biopsy but can have significant clinical ramifications. The authors examined the clinical course of patients diagnosed with borderline ADH/DCIS lesions (marked ADH [MADH]) via core needle biopsy at their institution. Seventy-four patients were diagnosed with MADH on core needle biopsy and underwent an excisional biopsy. The majority of the core needle biopsies reviewed at outside hospitals had been classified as DCIS. Twenty patients (27 percent) had benign findings or lobular neoplasia in their excisional biopsy, 18 (24 percent) had ADH, 33 (45 percent) had DCIS, and three (four percent) had DCIS and invasive ductal carcinoma. None of the 38 patients who were not diagnosed with DCIS or invasive ductal carcinoma on excisional biopsy underwent further surgery or radiation postoperatively. Thirty-seven of these 38 patients had no recurrences, and one patient developed a recurrence that on our review was likely residual localized MADH. The mean followup for these patients was 54 months. Of the 36 patients diagnosed with DCIS or invasive ductal carcinoma on excisional biopsy, fewer than 20 percent required mastectomy. On review, MADH involving an intermediate-sized duct on core needle biopsy and the amount of

residual lesion on imaging were significantly associated with DCIS or invasive ductal carcinoma on excisional biopsy. Conversely, MADH involving columnar cell lesions and calcification on core needle biopsy were significantly associated with benign pathology on excisional biopsy. The authors concluded that their study provides preliminary data that justify a conservative approach to managing borderline ADH/DCIS lesions on core needle biopsy—that is, diagnose as MADH and treat by conservative excision.

Vandenbussche CJ, Khouri N, Sbaity E, et al. Borderline atypical ductal hyperplasia/low-grade ductal carcinoma in situ on breast needle core biopsy should be managed conservatively. *Am J Surg Pathol.* 2013;37(6):913–923.

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Classic lobular neoplasia on core biopsy: a clinical and radiopathologic study with followup excision biopsy

No consensus guidelines exist for managing lobular neoplasia diagnosed on core biopsy as the highest risk factor for cancer. The authors conducted a study to assess the risk of upgrade (invasive carcinoma or ductal carcinoma in situ) at the site of the lobular neoplasia and any clinical, radiological, or pathologic factors associated with the upgrade. They reviewed all cases with a diagnosis of lobular neoplasia on core biopsy from June 2006 to June 2011. Any cases with radiopathologic discordance, coexistent lesion that required excision (atypical ductal hyperplasia, flat epithelial atypia, duct papilloma or radial scar), or nonclassic variant of lobular carcinoma in situ (pleomorphic, mixed ductal and lobular, lobular carcinoma in situ with necrosis) were excluded from the study. Core biopsy indications included calcification in 35 cases (40 percent), non-mass–like enhancement in 19 (22 percent), mass lesion in 31 (36 percent), and mass as well as calcification in two (two percent). Followup excisions were studied for upgrades. The study cohort included 87 cases and showed an upgrade of 3.4 percent (95 percent confidence interval, 1–10 percent). Three cases showed an upgrade—one ductal carcinoma in situ and two invasive cancers. All upgraded cases were a breast imaging-reporting and data system score of four or greater and associated with atypical ductal hyperplasia or in situ or invasive cancer in prior or concurrent biopsies in either breast. The number of cores and lobules involved, pagetoid duct involvement, presence of microcalcification in lobular neoplasia, needle gauge, and number of cores obtained showed no correlation with upgrade. The results suggest that with radiopathologic concordance and no prior biopsy-proven risk for breast cancer, a core biopsy finding of lobular neoplasia as the highest risk lesion can be managed appropriately and safely with clinical and radiologic followup as an alternative to surgical excision.

Chaudhary S, Lawrence L, McGinty G, et al. Classic lobular neoplasia on core biopsy: a clinical and radio-pathologic correlation study with follow-up excision biopsy. *Mod Pathol.* 2013;26:762–771.

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Intestinal-type endocervical adenocarcinoma in situ: a subset of AIS affecting older women

Conventional endocervical adenocarcinoma in situ (cAIS) is typically strongly and diffusely positive for p16 and has a high Ki67 index consistent with its frequent association with high-risk human papillomavirus (HPV) infection. The intestinal variant (iAIS) is less common, and its relationship to HPV infection has not been thoroughly examined. The authors compared the clinicopathologic features, frequency of HPV infection, and expression of CDX2 and surrogate biomarkers of HPV infection (p16, Ki67) in cAIS with those of iAIS. They identified 86 cases with a diagnosis of AIS (49 iAIS, 37 cAIS) from their multi-institutional files. Of these, 13 iAIS and 20 cAIS cases had slides and tissue available for histopathologic review, immunohistochemical analysis, and molecular tests. All 86 cases were used to evaluate clinical parameters. However, HPV DNA analysis and immunohistochemical analysis for p16, MIB-1, CDX2, and p53 were performed only on those cases for which slides or paraffin blocks were available. The average age at diagnosis was significantly higher in iAIS than in cAIS (44.5 versus 32.6 years; P=0.0001). All 20 cAIS cases showed moderate to strong and diffuse p16 staining, but only nine of 13 iAIS cases showed this degree

of p16 staining, and four of 13 iAIS cases showed weak and patchy distribution (P<0.02). Only six of nine iAIS cases were positive for HPV type 18 (five cases) or 33 (one case), in contrast to 11 of 11 conventional cAIS cases (P=0.04). Similarly, 12 of 14 cAIS but only five of 13 iAIS cases showed a high Ki67 proliferative index. CDX2 was positive in all iAIS cases and p53 was negative. The authors concluded that most iAIS cases are positive for high-risk HPV and show moderate to strong and diffuse p16 staining. However, a subset of iAIS shows variable staining with p16 and Ki67, is not associated with HPV, and occurs in a distinctly older age group, suggesting an alternative pathogenesis. Recognizing that iAIS can show variable staining for p16 and Ki67 is important when resolving problematic endocervical lesions, particularly in small biopsies with unusual p16 staining patterns.

Howitt BE, Herfs M, Brister K, et al. Intestinal-type endocervical adenocarcinoma in situ: an immunophenotypically distinct subset of AIS affecting older women. *Am J Surg Pathol.* 2013;37:625–633.

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Oncotype DX recurrence score: use of pathology-generated equations from linear regression analysis

Oncotype DX is a commercial assay frequently used to make decisions about chemotherapy in estrogen receptor-positive breast cancers. The result is reported as a recurrence score ranging from zero to 100 and divided into low-risk (<18), intermediate-risk (18–30), and high-risk (≥31) categories. The authors conducted a pilot study that showed that recurrence score can be predicted by an equation that incorporates standard morphoimmunohistologic variables (referred to as the original Magee equation). Using a data set of 817 cases, the authors formulated three additional equations (referred to as new Magee equations one, two, and three) to predict the recurrence score category for an independent set of 255 cases. The concordance between the risk category of Oncotype DX and the authors' equations was 54.3 percent, 55.8 percent, 59.4 percent, and 54.4 percent for the original Magee equation and new Magee equations one, two, and three, respectively. When the intermediate category was eliminated, the concordance increased to 96.9 percent, 100 percent, 98.6 percent, and 98.7 percent for the original Magee equation and new Magee equations one, two, and three, respectively. Even when the estimated recurrence score fell in the intermediate category with any of the equations, the actual recurrence score was intermediate or low in more than 80 percent of the cases. The authors concluded that any of the four equations can be used to estimate the recurrence score, depending on available data. If the estimated recurrence score is clearly high or low, oncologists should not expect a dramatically different result from the Oncotype DX test, and the test may not be needed. Conversely, an Oncotype DX result that is dramatically different from what is expected based on standard morphoimmunohistologic variables should be thoroughly investigated.

Klein ME, Dabbs DJ, Shuai Y, et al. Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis. *Mod Pathol.* 2013;26:658–664.

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Neuroendocrine carcinoma of the stomach: characteristics and prognosis

Neuroendocrine carcinoma of the stomach has been recognized as a highly malignant tumor. However, because it is rare, limited information is available regarding its clinicopathologic characteristics. The authors investigated the morphologic and immunohistochemical features and prognoses of 51 cases of gastric neuroendocrine carcinoma. Histologically, 40 lesions were large cell type and 11 were small cell type. The vast majority of the tumors exhibited a solid growth pattern (94 percent), with subsets of tumors showing trabecular (18 percent), scirrhous (10 percent), or tubular (six percent) growth patterns. Thirty-six cases (71 percent) had adenocarcinoma components or dysplasia, or both. Of those, 26 cases (51 percent) were associated with intramucosal adenocarcinoma or dysplasia. Immunohistochemically, synaptophysin, chromogranin A, and CD56 were diffusely expressed in 48 (94 percent), 44 (86 percent), and 24 (47 percent) cases, respectively. Two recently reported neuroendocrine markers, ASH1 and NKX2.2, were diffusely positive in 12 (24 percent) and 17 (33 percent) cases,

respectively. The diffuse or focal expression of TTF-1 was observed in 19 cases (37 percent). Among the 41 patients who underwent curative resection, 16 patients (39 percent) developed radiologic recurrences, and the liver was the most frequent site of recurrence (11 patients; 27 percent). The three- and five-year overall survival rates were 57.8 percent and 44.7 percent, respectively. None of the histologic subclassifications, including small cell versus large cell types and the presence versus absence of adenocarcinoma components and/or dysplasia, were significant with regard to patient outcome. Curative surgery was identified as the sole independent prognostic factor in a multivariate analysis (P=0.03). The authors concluded that although gastric neuroendocrine carcinomas exhibit significant morphologic diversity, their histologic subclassification is unlikely to be of immediate clinical relevance.

Ishida M, Sekine S, Fukagawa T, et al. Neuroendocrine carcinoma of the stomach: morphologic and immunohistochemical characteristics and prognosis. *Am J Surg Pathol.* 2013;37(7):949–959.

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Interobserver reproducibility in diagnosis of high-grade endometrial carcinoma

Patients with high-grade subtypes of endometrial carcinoma—grade 3 endometrioid, serous, clear cell, or carcinosarcoma—have a relatively poor prognosis. The specific subtype may be used to guide patient management, but little information exists regarding the reproducibility of subtype diagnoses in cases of high-grade endometrial carcinoma. Consequently, the authors undertook a study in which 56 cases diagnosed as a high-grade subtype of endometrial carcinoma were identified from the pathology archives of Vancouver (Canada) General Hospital. All slides for each case were reviewed independently by three pathologists, who diagnosed the specific tumor subtypes and assigned the percentage of each subtype for mixed tumors. Agreement between observers was categorized as major or minor. Major disagreement was no consensus for low-grade endometrioid versus high-grade carcinoma (any subtype) or no consensus with respect to the predominant high-grade subtype present. Minor disagreement was when a consensus was reached about the cell type of the predominant component of a mixed tumor but there was disagreement about the subtype of the minor component. A tissue microarray was constructed from these cases and immunostained for p16, estrogen receptor, progesterone receptor, PTEN, and p53. In 35 of 56 cases (62.5 percent), there was agreement between all three reviewers regarding the subtype diagnosis of the exclusive (in pure tumors) or predominant (in mixed tumors) high-grade component. Minor disagreement occurred in four of the cases (7.1 percent). In 20 of 56 cases (35.8 percent), there was major disagreement. In 17 (30.4 percent) of the latter, there was no consensus about the major subtype diagnosis, and in three cases (5.4 percent), there was disagreement about whether a component of high-grade endometrial carcinoma was present. All three reviewers diagnosed the final case as low-grade endometrioid carcinoma, disagreeing with the original diagnosis of high-grade carcinoma. The most frequent areas of disagreement were serous versus clear cell (seven cases) and serous versus grade 3 endometrioid (six cases). Immunostaining results using the five-marker immunopanel were then used to adjudicate in the six cases in which there was disagreement between reviewers with respect to serous versus endometrioid carcinoma. These supported a diagnosis of serous carcinoma in four of six cases and endometrioid carcinoma in two of six cases. With regard to pairwise comparisons between the reviewers for the 20 cases classified as showing major disagreement, reviewers one and two agreed in five of 20 cases, reviewers one and three agreed in seven of 20 cases, and reviewers two and three agreed in eight of 20 cases, indicating that disagreements were not because of a single reviewer with outlier opinions. Diagnostic consensus among the three reviewers about the exclusive or major subtype of high-grade endometrial carcinoma was reached in only 35 of 56 cases (62.5 percent), and in four of the cases there was disagreement about the minor component present. This poor reproducibility did not reflect systematic bias on the part of any one reviewer. The authors concluded that molecular tools are needed to aid in the accurate and reproducible diagnosis of high-grade endometrial carcinoma subtype.

Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. *Am J Surg Pathol.* 2013;37(6):874–881.

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Features associated with metastatic potential in invasive adenocarcinomas of the lung

The International Association for the Study of Lung Cancer (IASLC) recently reclassified adenocarcinomas of the lung on the basis of histologic patterns. However, consensus about a grading system for these tumors is lacking. The authors studied a series of invasive lung adenocarcinomas and correlated histologic features with lymph node and distant metastases. A series of invasive lung carcinomas resected over a five-year period were retrospectively reviewed and classified by the IASLC system. The proportion of each histologic subtype was estimated at five percent increments, and cytologic features were blindly recorded and subsequently correlated with lymph node and distant metastases. The 125 tumors were classified on the basis of the predominant pattern as lepidic predominant (n=9), acinar (n=71), solid (n=23), papillary (n=11), and mucinous (n=11). The acinar pattern was heterogeneous in that a cribriform subgroup (n=34) was significantly more likely to demonstrate lymph node metastases compared with a tubular subgroup (n=37) and had a higher mitotic rate and rate of necrosis, as well as vascular invasion and prominent nucleoli. Mucinous tumors were lepidic predominant (n=3), tubular (n=4), and cribriform predominant (n=4). The rate of lymph node metastasis was greatest in the solid type (P=0.02), and the rate of distant metastasis was greatest in the mucinous and solid groups (P<0.02). Mitotic activity (one high-power field or greater), desmoplasia greater than 20 percent of the tumor, prominent nucleoli, and vascular invasion, along with a solid growth pattern of 20 percent or more, were independently associated with metastatic potential and considered poor prognostic histologic features. A three-tiered grading system separated tumors into well differentiated (predominantly lepidic predominant, papillary, and tubular patterns), moderately differentiated (predominantly cribriform tumors), and poorly differentiated (20 percent or greater solid growth pattern). Tumors in the well-differentiated group were elevated to moderately differentiated if they had poor prognostic histologic features. Using this system, there was a stepwise increase in the rate of lymph node metastasis (P<0.0001) and distant metastasis (P=0.0004) from well-differentiated, moderately differentiated, to poorly differentiated tumors, the rate being 40, 46, and 39, respectively. Application of the IASLC classification in this series resulted in a predominance of acinar adenocarcinomas. The authors concluded that to stratify tumors into clinically relevant grades, it is useful to grade by pattern (tubular, cribriform, solid), mitotic activity, and nuclear features.

Xu L, Tavora F, Burke A. Histologic features associated with metastatic potential in invasive adenocarcinomas of the lung. *Am J Surg Pathol.* 2013;37(7):1100–1108.

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