Anatomic Pathology Selected Abstracts, 4/14

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Clear cell papillary renal cell carcinoma: diagnosis and immunohistochemical profile

Clear cell papillary renal cell carcinoma is a recently recognized renal neoplasm composed of cells with clear cytoplasm lining cystic, tubular, and papillary structures. These tumors have immunohistochemical and genetic profiles distinct from clear cell renal cell carcinoma and papillary renal cell carcinoma. The authors studied morphologic and immunohistochemical features (cytokeratin 7 [CK7], carbonic anhydrase IX [CAIX], CD10, alpha-methylacyl-CoA racemase [AMACR], smooth muscle actin, desmin, and estrogen and progesterone receptors) in 55 tumors from 34 patients, eight of whom had end-stage renal disease. The tumors comprised three percent of all adult renal cell carcinoma resections over three years. Patients' ages ranged from 33 to 87 years (mean, 61 years). Multiple tumors (two to eight) were present in nine patients. Other renal tumors were present concurrently in four patients and subsequently in two patients, including oncocytoma, clear cell renal cell carcinoma, and multilocular cystic renal cell carcinoma. Sizes ranged from 0.2 to 7.5 cm (mean, 2 cm); 87 percent were Fuhrman grade 2 and 96 percent were stage pT1a. Papillary architecture was usually limited to focal branching papillae (51 percent of 55 tumors) or small, blunt papillae (35 percent). Large areas of extensively branched papillae were present in only 14 percent of tumors. Almost all tumors (98 percent) included cysts, and 18 tumors were extensively (90 percent or greater) cystic. Immunoprofile showed CK7+, AMACR−, CD10−, and CAIX+ in the tubular and papillary components of all tumors. However, CD10 labeled the apical cell membrane of cyst epithelium in 59 percent. The stroma was focally actin positive (94 percent), with infrequent desmin expression (13 percent). Estrogen receptor and progesterone receptor were negative. During a median followup period of 56 months, no patient developed local recurrence or distant or lymph node metastasis or died of cancer. The authors concluded that branched tubules, small papillae, and immunohistochemical and molecular profiles aid in distinguishing clear cell papillary renal cell carcinoma from clear cell renal cell carcinoma and multilocular cystic renal cell carcinoma.

Williamson SR, Eble JN, Cheng L, et al. Clear cell papillary renal cell carcinoma: differential diagnosis and extended immunohistochemical profile. *Mod Pathol.* 2013;26:697–708.

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Breast cancer subtypes defined by ER signaling and prognostic relevance of PR loss

The majority of luminal type breast carcinomas are slow-growing tumors with an overall favorable prognosis. However, a proportion of cases (luminal B tumors) are characterized by coactivation of growth factor receptors or noncanonical estrogen receptor signaling and a poorer clinical outcome. The authors conducted a study to evaluate whether the expression of proteins that are part of the estrogen receptor signaling network may be used to distinguish low-risk from high-risk luminal tumors. Unsupervised hierarchical clustering of a set of proteins involved in estrogen receptor signaling or associated with resistance to endocrine therapy was performed in a series of 443 postmenopausal breast carcinomas. Using this approach, the authors were able to reproduce the established classification with two distinct groups of luminal (estrogen receptor-positive) tumors, one group of HER2-associated tumors, and one group of triple-negative tumors. However, progesterone receptor expression, and not proliferation or expression of one or more of the estrogen receptor cofactors or resistance-associated factors, was identified as the most important stratifier distinguishing between the two luminal groups. Not only

were the four identified clusters shown to be significantly associated with patient outcome, but progesterone receptor expression alone or in combination with Ki-67 stains stratified estrogen receptor-positive tumors into a low-risk and high-risk group. The authors concluded that these data indicate that defining luminal B tumors by the presence of criteria for high risk (loss of progesterone receptor expression or increased proliferation) provides a robust and highly significant stratification of estrogen receptor-positive breast carcinomas into luminal A and B.

Braun L, Mietzsch F, Seibold P, et al. Intrinsic breast cancer subtypes defined by estrogen receptor signaling—prognostic relevance of progesterone receptor loss. *Mod Pathol.* 2013;26:1161–1171.

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Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4

Risk of distant recurrence among women with estrogen receptor-positive early breast cancer is the major determinant of recommendations for or against chemotherapy. It is frequently estimated using the Oncotype DX recurrence score. The PAM50 risk of recurrence (ROR) score provides an alternative approach and also identifies intrinsic subtypes. The authors conducted a study in which the mRNA from 1,017 patients with estrogen receptor-positive primary breast cancer treated with anastrozole or tamoxifen in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial was assessed for ROR using the NanoString nCounter. Likelihood ratio tests and concordance indices (c indices) were used to assess the prognostic information provided beyond that of a clinical treatment score by recurrence score, ROR, or IHC4, an index of risk of distant recurrence derived from immunohistochemical assessment of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and Ki67. The authors found that ROR added significant prognostic information beyond clinical treatment score in all patients (ΔLR-$\chi(2)=33.9$; $P<0.001$). In all four subgroups—node negative, node positive, HER2 negative, and HER2 negative/node negative—more information was added by ROR than by recurrence score. C indices in the HER2-negative/node-negative subgroup were 0.73, 0.76, and 0.78 for clinical treatment score, clinical treatment score plus recurrence score, and clinical treatment score plus ROR, respectively. More patients were scored as high risk and fewer as intermediate risk by ROR than by recurrence score. Relatively similar prognostic information was added by ROR and IHC4 for all patients but more by ROR in the HER2-negative/node-negative group. The authors concluded that ROR provides more prognostic information for endocrine-treated patients with estrogen receptor-positive, node-negative disease than does recurrence score, with better differentiation of intermediate- and higher-risk groups.

Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol.* 2013;31: 2783–2790.

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Margin comments in dermatopathology reports on HDN and re-excision rates

Dermatopathology reports influence clinical management, but it is not clear to what extent comments on margin involvement of histopathologically dysplastic nevi (HDN) influence decisions about re-excision or complete excision. The authors sought to determine if standardized margin comments on HDN influence re-excision rates. By reviewing medical records, they compared re-excision rates of HDN reported with standardized margin comments from May 2011 to December 2012 and without from January 2007 to December 2010. They also surveyed clinicians to assess perceptions of the impact of margin comments on their management of HDN. Of 584 HDN, 302 had margin comments and 282 did not. Re-excision was recommended or performed at a significantly higher rate for patients in the group without comments (51.8 percent; 146 of 282) than in the group with comments (39.4 percent; 119 of 302; P=0.003), regardless of margin status. This difference was observed among HDN diagnosed as mildly and moderately dysplastic but not severely dysplastic. Forty percent of clinicians (16 of 40) responded

that they are more likely to biopsy pigmented lesions with a clinical margin of normal-appearing skin than they were before margin comments were routinely included in dermatopathology reports. As a result of this retrospective study, the authors concluded that re-excision rates were significantly lower in patients who had HDN reported with standardized margin comments. These comments may help reduce re-excision rates and lead to a reduction in health care use, cost, and morbidity.

Comfere NI, Chakraborty R, Peters MS. Margin comments in dermatopathology reports on dysplastic nevi influence re-excision rates. *J Am Acad Dermatol.* 2013;69: 687–692.

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Comparison of two tests for low-grade, ER-positive invasive breast carcinomas

Several molecular tests have been developed to estimate risk of distant recurrence and aid clinical decisionmaking pertaining to adjuvant chemotherapy in patients with early stage breast carcinoma. Oncotype DX, a 21-gene expression profile, and Mammostrat, an immunohistochemistry-based assay, are validated to stratify patients into groups with low, intermediate, and high risk of distant recurrence. However, the tests have not been compared head-to-head, and little data are available regarding their correlation with clinicopathologic tumor features. The authors conducted a study in which they compared clinicopathologic tumor features with risk estimations by Oncotype DX and Mammostrat in 106 low-grade estrogen receptor-positive breast carcinomas. Double immunohistochemical stain for pancytokeratin and Ki-67 was performed to assess cell proliferation in cancer versus stromal/inflammatory cells. Tumors showing intermediate/high risk by Oncotype DX, but not by Mammostrat, showed increased stromal cellularity, presence of inflammatory cells, and increased proliferation in stromal/inflammatory cells. Discrepant cases showing intermediate/high risk by Oncotype DX but low risk by Mammostrat were associated with increased stromal cellularity, presence of inflammatory cells, and increased proliferation in stromal/inflammatory cells compared with concordant cases showing low risk by both assays. These results suggest that low-grade estrogen receptor-positive breast carcinomas with increased stromal/inflammatory cell proliferation may show an increased risk of distant recurrence as assessed by Oncotype DX, which uses RNA extracted from a mixture of tumor and stromal/inflammatory cells in the assay. Mammostrat, which examines cancer cells only, may provide a better estimation of likely tumor behavior in a subgroup of low-grade breast carcinomas.

Acs G, Kiluk J, Loftus L, et al. Comparison of Oncotype DX and Mammostrat risk estimations and correlations with histologic tumor features in low-grade, estrogen receptor-positive invasive breast carcinomas. *Mod Pathol.* 2013;26:1451–1460.

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P53 and BAF250a expression in endometrial clear cell carcinoma

TP53 mutation may be a negative prognostic marker in endometrial cancers, but its relevance in the rarer histologic subtypes, including clear cell carcinomas, has not been delineated. Preclinical studies suggest functional interactions between p53 and the BAF250a protein, the product of the tumor-suppressor gene ARID1A (adenine-thymine-rich interactive domain containing protein 1A), which is frequently mutated in ovarian clear cell carcinoma. The authors conducted a study in which they evaluated the significance of p53 and BAF250a expression, as assessed by immunohistochemistry, in a group of 50 endometrial clear cell carcinomas. Of 50 cases, 17 (34 percent) were p53+, and the remaining 33 cases had a p53 wild-type (p53-wt) immunophenotype. Of the 11 relapses or recurrences in the entire data set, 73 percent were in the p53+ group (P=0.008). On univariate analyses, the median overall survival rate for the p53-wt patients (83 months) was longer than the rate for the p53+ patients (63 months), and the median progression-free survival rate for the p53-wt group (88 months) was significantly longer than the rate for the p53+ group (56 months). On multivariate analyses, p53 expression was not associated with reduced overall or progression-free survival. Furthermore, p53 status was not significantly

associated with pathologic stage or morphologic patterns. Of the 50 cases, 10 (20 percent) showed a complete loss of BAF250a expression. No significant correlation was noted between p53 and BAF250a expression. The p53+/BAF250a–, p53+/BAF250a+, p53-wt/BAF250a+, and p53-wt/BAF250a– composite immunophenotypes were identified in eight percent, 26 percent, 54 percent, and 12 percent of cases, respectively. Neither loss of BAF250a expression nor composite p53/BAF250a expression patterns were associated with reduced overall or progression-free survival. The authors concluded that a significant subset of clear cell carcinomas express p53, and these cases are not definable by their morphologic features. P53 expression may be a negative prognostic factor in this histotype and warrants additional studies. Loss of BAF250a expression has no prognostic significance in endometrial clear cell carcinomas.

Fadare O, Gwin K, Desouki MM, et al. The clinicopathologic significance of p53 and BAF-250a (ARID1A) expression in clear cell carcinoma of the endometrium. *Mod Pathol.* 2013;26:1101–1110.

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