Anatomic Pathology Abstracts, 10/15

CD117 expression in phyllodes tumors: correlation with adverse pathologic parameters

CD117 (c-Kit) is a type III receptor tyrosine kinase encoded by the KIT gene. Deregulation of expression and mutations in the gene are implicated in various tumors. Reports of CD117 expression in phyllodes tumors have generated controversy. The authors investigated the protein expression of CD117 and mutations in the KIT gene in phyllodes tumors and correlated the findings with pathological parameters and clinical outcome. A total of 272 cases were included in the study. CD117 expression was investigated by immunohistochemistry on tissue microarray sections. Toluidine blue staining was performed to indicate mast cells. Overall, 28 (10 percent) cases were CD117 positive. CD117 expression was significantly associated with tumor grade ($P<0.001$), increased stromal hypercellularity ($P=0.003$), stromal atypia ($P=0.01$), stromal mitotic activity ($P<0.001$), permeative microscopic margins ($P=0.002$), and presence of hemorrhage ($P=0.001$). Expression was also associated with poorer overall survival ($P=0.003$). Nineteen cases were further selected for mutation screening through the Affymetrix OncoScan platform. No mutation of the KIT gene was found. The authors concluded that despite a lack of mutations in the gene, CD117 protein expression is associated with unfavorable pathological parameters and poor prognosis, suggesting an underlying role in the biology of phyllodes tumors.

Tan WJ, Thike AA, Tan SY, et al. CD117 expression in breast phyllodes tumors correlates with adverse pathologic parameters and reduced survival. *Mod Pathol.* 2015;28:352–358.

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Clear cell carcinoma of the ovary: evaluation of prognostic parameters

The authors evaluated the clinicopathological features of ovarian clear cell carcinomas to identify which, if any, are prognostically significant and to determine whether there is value in grading these tumors. They reviewed 100 tumors with clinical follow-up. Features evaluated included age, preoperative/intraoperative rupture, size, architectural patterns, presence of oxyphilic cells, degree of cytological atypia, nucleolar grade, mitoses, background precursor, and stage. Survival differences were analyzed using the log-rank test and Kaplan-Meier estimator. Stage and lymph node status were the only parameters that were statistically significant ($P<0.0001$). Patients with stage I disease (71 percent) had a 92 percent five-year survival rate compared to a 31 percent five-year survival rate for advanced stage disease (29 percent). Those with negative lymph nodes (92 percent) had an 80 percent five-year survival rate compared to a 22 percent five-year survival rate for those with positive nodes (eight percent). The authors concluded that stage and lymph node status are the only prognostically significant parameters in patients with ovarian clear cell carcinoma. Furthermore, most patients with clear cell carcinoma present with disease confined to the ovary and have an excellent prognosis. Grading ovarian clear cell carcinomas based on morphological features is not recommended.

Bennett JA, Dong F, Young RH, et al. Clear cell carcinoma of the ovary: evaluation of prognostic parameters based on a clinicopathological analysis of 100 cases. *Histopathology.* 2015;
66:808–815.

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Analysis of natural history of low-grade DCIS to reaffirm proclivity for local recurrence

Opportunities to study the natural history of ductal carcinoma in situ are rare. A few studies of incompletely excised lesions in the premammographic era, retrospectively recognized as ductal carcinoma in situ, have demonstrated a proclivity for local recurrence in the original site. The authors reported a follow-up study of 45 women with low-grade ductal carcinoma in situ treated by biopsy only, recognized retrospectively during a larger review of surgical pathology diagnoses and original histological slides for 26,539 consecutive breast biopsies performed at Vanderbilt, Baptist, and St. Thomas hospitals in Nashville, Tenn., from 1950 to 1989. Long-term follow-up was previously reported on 28 of the women. Sixteen (36 percent) women developed invasive breast carcinoma, all in the same breast and quadrant as their incidental ductal carcinoma in situ. Eleven invasive breast carcinomas were diagnosed within 10 years of the ductal carcinoma in situ biopsy. Subsequent cases were diagnosed at 12, 23, 25, 29, and 42 years. Seven women, including one who developed invasive breast cancer 29 years after her ductal carcinoma in situ biopsy, developed distant metastasis, resulting in death one to seven years after diagnosis of invasive breast carcinoma. The natural history of low-grade ductal carcinoma in situ may extend more than four decades, with invasive breast cancer developing at the same site as the index lesion. This protracted natural history differs markedly from that of patients with high-grade ductal carcinoma in situ or any completely delimited ductal carcinoma in situ excised to negative margins. The study reaffirms the importance of complete margin evaluation in women treated with breast conservation for ductal carcinoma in situ, as well as balancing recurrence risk with possible treatment-related morbidity for older women.

Sanders ME, Schuyler PA, Simpson JF, et al. Continued observation of the natural history of low-grade ductal carcinoma in situ reaffirms proclivity for local recurrence even after more than 30 years of follow-up. *Mod Pathol.* 2015;28:662–669.

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PTEN loss linked to upgrading prostate cancer from biopsy to radical prostatectomy

When distinguishing between indolent and potentially harmful prostate cancers, the Gleason score is the most important variable, but it may be inaccurate in biopsies due to tumor under-sampling. The authors investigated whether a molecular feature, PTEN protein loss, could help identify which Gleason score six tumors on biopsy are likely to be upgraded at radical prostatectomy. Seventy-one patients with Gleason score six tumors on biopsy upgraded to Gleason score seven or higher at prostatectomy were compared with a control group of 103 patients with Gleason score six on both biopsy and prostatectomy. A validated immunohistochemical assay for PTEN was performed, followed by fluorescence in situ hybridization (FISH) to detect PTEN gene deletion in a subset. PTEN protein loss and clinical-pathologic variables were assessed by logistic regression. The upgraded patients were older than the controls (61.8 versus 59.3 years), had higher preoperative prostate-specific antigen (PSA) levels (6.5 versus 5.3 ng/mL), and had a higher fraction of involved cores (0.42 versus 0.36). PTEN loss by immunohistochemistry was found in 18 percent (13 of 71) of upgraded cases compared with seven percent (seven of 103) of controls (P=0.02). Comparison between PTEN immunohistochemistry and PTEN FISH showed the assays were highly concordant, with 97 percent (65 of 67) of evaluated biopsies with intact PTEN protein lacking PTEN gene deletion, and 81 percent (13 of 16) of the biopsies with PTEN protein loss showing homozygous PTEN gene deletion. Tumors with PTEN protein loss were more likely to be upgraded at radical prostatectomy than those without loss, even after adjusting for age, preoperative PSA, clinical stage, and race (odds ratio, 3.04; 1.08–8.55; P=0.035). The authors concluded that PTEN loss in Gleason score six biopsies identifies a subset of prostate tumors at increased risk of upgrading at radical prostatectomy. The data provide evidence that a genetic event can improve Gleason score accuracy and highlight a path toward the clinical use of molecular markers to augment pathologic grading.

Lotan TL, Carvalho FL, Peskoe SB, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. *Mod Pathol.* 2015;28:128–137.

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Papillary and neuroendocrine breast lesions: the WHO stance

The authors highlighted adaptations in the World Health Organization 2012 classification of papillary and neuroendocrine breast lesions as compared with the 2003 version. Consensus criteria for distinguishing atypical ductal hyperplasia from ductal carcinoma in situ within an intraductal papilloma were proposed. The absence of myoepithelial cells around the wall of an encapsulated papillary carcinoma, although raising consideration of an indolent tumor with minimal invasion, is regarded as in situ disease for staging purposes. The majority of solid papillary carcinomas are classified as in situ tumors, but lesions with irregular tumor islands within desmoplastic stroma may be considered invasive. The diagnosis of solid papillary carcinoma without further qualification as either in situ or invasive disease is discouraged. When invasive papillary carcinoma is seen in the breast, metastatic papillary carcinoma from other organ sites needs to be excluded. WHO 2012 classifies a neuroendocrine breast tumor as a well-differentiated neuroendocrine tumor, small-cell carcinoma, and invasive breast carcinoma with neuroendocrine differentiation. There is no clinical impact from identifying neuroendocrine differentiation in conventional invasive breast carcinomas, apart from acknowledging its frequent occurrence in such subtypes as the hypercellular variant of mucinous carcinoma and solid papillary carcinoma.

Tan PH, Schnitt SJ, van de Vijver MJ, et al. Papillary and neuroendocrine breast lesions: the WHO stance. *Histopathology.*2015;66(6):761–770.

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Use of cribriform growth to predict outcomes in Gleason score seven prostate cancer

Patients with Gleason score seven prostate cancer at radical prostatectomy demonstrate a wide range of clinical outcomes. Gleason grade four prostate cancer encompasses a heterogenous group of tumor growth patterns, including fused, ill-defined, cribriform, and glomeruloid glandular structures. The authors sought to determine the prognostic value of various Gleason grade four growth patterns. They performed a nested case-control study among 535 patients with Gleason score seven prostate cancer at radical prostatectomy who were treated between March 1985 and July 2013 at a university hospital in the Netherlands. The authors analyzed 52 cases (with metastasis, disease-specific mortality, or both) and 109 controls matched for age, prostate-specific antigen level, and pT stage. Presence of the following Gleason grade four patterns was recorded: fused, ill-defined, cribriform, and glomeruloid. Intraductal carcinoma of the prostate and tertiary Gleason grade five were also assessed. Outcomes were metastasis-free survival and disease-specific survival. The authors used Cox proportional hazards regression to determine the predictive value of Gleason grade four patterns for survival time. The overall prevalence of Gleason grade four patterns was fused, 75 percent (n=121); ill-defined, 64 percent (n=102); cribriform, 48 percent (n=83); and glomeruloid, 25 percent (n=40). Cribriform was the only pattern with an unequal distribution between cases and controls. Forty-two of 52 (81 percent) cases had cribriform growth pattern versus 41 of 109 (38 percent) controls. In multivariate analysis, presence of cribriform growth was an adverse independent predictor for distant metastasis-free survival (hazard ratio [HR], 8.0; 95 percent confidence interval [CI], 3.0–21; P<0.001) and disease-specific survival (HR, 5.4; 95 percent CI, 2.0–15; P=0.001). The authors concluded that cribriform growth in Gleason grade four is a strong prognostic marker for distant metastasis and disease-specific death in patients with Gleason score seven prostate cancer at radical prostatectomy.

Kweldam CF, Wildhagen MF, Steyerberg EW, et al. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod Pathol.* 2015;28:457–464.

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Usefulness of colonic mast cell counts in chronic diarrhea of unknown etiology

Mastocytic enterocolitis is a recently described entity defined by chronic diarrhea of unknown etiology and normal colon biopsy results with increased mast cells seen on special stains. These patients may benefit from mast cell stabilizers; however, the clinical utility of mast cell counts remains unknown. The authors conducted a study to determine the clinical utility of colonic mast cell counts on normal biopsies in patients with chronic diarrhea of unknown etiology. Blinded mast cell counts using a c-Kit stain were performed in 76 consecutive patients with chronic diarrhea of unknown etiology who had normal colon biopsy results and in 89 consecutive control patients presenting for screening colonoscopy. Mast cells were counted per single high-power field in the highest density area. A t-test was used to compare the counts, and receiver operating characteristic curves were generated to examine sensitive and specific cutoff values. Overall, mast cell counts averaged 31 mast cells per high-power field in the study group versus 24 mast cells per high-power field in the control group (P<0.0001). When stratified by location, a significant increase was seen in biopsies from the left colon only. Receiver operating characteristic analysis revealed that overall mast cell counts, left-sided mast cell counts, and difference between right- and left-sided mast cell counts did not yield discriminatory cutoff values (area under the curve, 0.68, 0.74, and 0.81, respectively). The authors found that mast cell counts were increased, primarily in the left colon, in patients with chronic diarrhea of unknown etiology. However, receiver operating characteristic analysis demonstrated no discriminatory cutoff values. Quantitative mast cell stains yield little useful diagnostic information.

Sethi A, Jain D, Roland BC, et al. Performing colonic mast cell counts in patients with chronic diarrhea of unknown etiology has limited diagnostic use. *Arch Pathol Lab Med.* 2015;139:225–232.

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Esophageal eosinophilia in patients undergoing upper endoscopy

The variability of eosinophilic infiltrates in eosinophilic esophagitis is not well described. The authors conducted a prospective study to determine the distribution of esophageal eosinophilia and the utility of histologic cut-points for eosinophilic esophagitis diagnosis in adults undergoing outpatient endoscopy. Research protocol esophageal biopsies were obtained from all subjects. Incident cases of eosinophilic esophagitis were diagnosed per consensus guidelines. Biopsies were interpreted following a validated protocol, and maximum eosinophil counts (eosinophils per high-power field [EOS/HPF]) were determined. Histologic analyses were performed on a per patient, per biopsy, and per HPF basis. There were 213 patients, yielding 923 esophageal biopsies with 4,588 HPFs. Overall, 48 (23 percent) patients, 165 (18 percent) biopsy fragments, and 449 (10 percent) HPFs had 15 or more EOS/HPF; most subjects had no eosinophils or low levels of eosinophils. In the eosinophilic esophagitis cases, 119 (63 percent) biopsy fragments and 332 (36 percent) HPFs had 15 or more EOS/HPF. There was a mean 104-fold difference between the lowest and highest HPF eosinophil count for the eosinophilic esophagitis patients; 85 percent of the biopsies from eosinophilic esophagitis cases also had at least one HPF with fewer than 15 EOS/HPF. The cut-point of 15 EOS/HPF had a sensitivity of 100 percent and specificity of 96 percent for the diagnosis of eosinophilic esophagitis. The authors concluded that most patients have little to no esophageal eosinophilia. In patients with eosinophilic esophagitis, there was marked variability in the eosinophil counts by biopsy and by HPF within a given biopsy. Additionally, the 15 EOS/HPF cut-point was highly sensitive and specific for eosinophilic esophagitis. Multiple esophageal biopsies from different locations should be obtained to optimize eosinophilic esophagitis diagnosis.

Dellon ES, Speck O, Woodward K, et al. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. *Mod Pathol.* 2015;28:383–390.

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Comparative effectiveness of screening strategies for Lynch syndrome

Colorectal cancer is the second leading cause of cancer death in the United States, and approximately three percent of colorectal cancers are associated with Lynch syndrome. Controversy exists regarding the optimal screening strategy for the disorder. Using an individual level microsimulation of a population affected by Lynch syndrome over several years, the authors compared the effectiveness and cost-effectiveness of 21 screening strategies. Modeling assumptions were based on published literature, and sensitivity analyses were performed for key assumptions. The study used a two-step process that measured the number of Lynch syndrome diagnoses (step one) and life-years gained as a result of foreknowledge of Lynch syndrome in otherwise healthy carriers (step two). The optimal strategy was sequential screening for probands starting with a predictive model, then immunohistochemistry for mismatch repair protein expression, followed by germline mutation testing (incremental cost-effectiveness ratio [ICER], $35,143 per life-year gained). The strategies of IHC + BRAF followed by germline testing for positive results and universal germline testing of colon cancer probands had ICERs of $144,117 and $996,878, respectively. This analysis suggests that the initial step in screening for Lynch syndrome should be the use of predictive models in probands. Universal tumor testing and general population screening strategies are not cost-effective. When family history is unavailable, alternate strategies are appropriate. Documentation of family history and screening for Lynch syndrome using a predictive model may be considered a quality-of-care measure for patients with colorectal cancer.

Barzi A, Sadeghi S, Kattan MW, et al. Comparative effectiveness of screening strategies for Lynch syndrome. [published online ahead of print March 20, 2015]. *J Natl Cancer Inst.* doi: 10.1093/jnci/djv005.

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