Anatomic Pathology Selected Abstracts, 10/14

Anatomic pathology abstracts editors: Michael Cibull, MD, professor of pathology, University of Kentucky, Lexington; Rouzan Karabakhtsian, MD, attending pathologist, Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; Thomas Cibull, MD, dermatopathologist, Evanston Hospital, NorthShore University HealthSystem, Evanston, Ill.; and Rachel Stewart, DO, resident physician, Department of Pathology and Laboratory Medicine, University of Kentucky.

Role of STAT6 immunohistochemistry in diagnosis of solitary fibrous tumors

Solitary fibrous tumor is an uncommon fibroblastic neoplasm. Although histologic characteristics and frequent CD34 expression allow for an accurate diagnosis in the majority of solitary fibrous tumor (SFT) cases, a wide histologic spectrum and occasional unexpected immunophenotype may pose diagnostic challenges. Molecular analyses have shown that almost all SFTs harbor a NAB2-STAT6 fusion gene, which is considered specific to this tumor type. Recent studies have suggested that STAT6 immunohistochemistry is a reliable surrogate for detecting the fusion gene. The authors conducted a study to validate these findings by examining a large number of SFT cases and 30 types of non-SFT tumors. Forty-nine SFTs with a range of histologic characteristics and 159 benign or malignant tumors that can mimic SFTs were retrieved and stained for STAT6. All of the 49 SFTs showed STAT6 expression that was restricted in the nucleus, mostly in a diffuse and strong manner, irrespective of tumor sites and histologic patterns. The staining was uniform in most cases but heterogeneous in about 20 percent of the cases in which zonal staining attenuation was observed, likely reflecting variability in fixation or tissue ischemia. In contrast, only four non-SFT tumors (2.5 percent) exhibited weak nuclear STAT6 expression, whereas the remaining 155 cases showed no staining or often weak reactivity in the cytoplasm and nucleus. The authors concluded that nuclear STAT6 immunoreactivity is a highly sensitive and specific marker of SFTs and can be helpful when diagnosis by conventional methods is inconclusive.

Yoshida A, Tsuta K, Ohno M, et al. STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. *Am J Surg Pathol.* 2014;38(4):552–559.

Correspondence email not provided.

Incidence and significance of neuroendocrine differentiation in invasive breast carcinoma

The definition of invasive breast carcinoma with neuroendocrine differentiation and its clinical outcomes have been the focus of controversy. The authors investigated the incidence and clinical significance of neuroendocrine (NE) differentiation in patients with invasive breast carcinoma (IBC). They performed immunohistochemistry for NE markers, chromogranin A, and synaptophysin on 1,428 IBC samples using tissue microarrays and classified cases with NE differentiation into two groups: focal (one to 49 percent of tumor cells positive for any NE marker) and diffuse (50 percent or more tumor cells positive for any NE marker). Fifty-nine cases (4.1 percent) showed NE differentiation immunohistochemically, and the majority did not show typical NE morphology. NE differentiation showed a significant association with positive oestrogen receptor (P=0.001) and progesterone receptor (P=0.008) status. Patients with NE differentiation exhibited worse overall survival and disease-free survival than those without NE differentiation in univariate (P

Kwon SY, Bae YK, Gu MJ, et al. Neuroendocrine differentiation correlates with hormone receptor expression and decreased survival in patients with invasive breast carcinoma. *Histopathol.* 2014;64:647–659.

Correspondence: Y. K. Bae at ykbae@ynu.ac.kr

Venous invasion in oesophageal adenocarcinoma: enhanced detection using elastic stains

In oesophageal adenocarcinoma, detection rates of venous invasion using H&E and elastic stains have not been compared. The authors conducted a study to investigate whether or not elastic stains facilitate the detection of venous invasion and to determine the prognostic significance of venous invasion following review with elastic stains. The authors examined 103 resection specimens containing oesophageal adenocarcinoma (all originally reported as negative for venous invasion) for the presence of venous invasion using H&E and subsequently Movat pentachrome stains. Venous invasion was detected in eight cases with H&E and an additional 66 cases using Movat pentachrome; overall, 72 percent of cases contained venous invasion. Venous invasion was associated with advanced stage, tumor size, lymphatic and perineural invasion, and subsequent distant metastases. Venous invasion, stage, size, grade, lymphatic invasion, and perineural invasion were prognostically significant on univariate analysis. Only tumor stage was independently prognostic. Two of eight patients with venous invasion but no other indication for adjuvant treatment died of recurrent disease. The authors concluded that elastic stains improve detection of venous invasion significantly in oesophageal adenocarcinoma. Venous invasion is associated with multiple adverse clinicopathological features. Its identification may help stratify patients at risk for visceral metastases and disease-related death.

Castonguay MC, Li-Chang HH, Driman DK. Venous invasion in oesophageal adenocarcinoma: enhanced detection using elastic stain and association with adverse histological features and clinical outcomes. *Histopathol.* 2014;64:693–700.

Correspondence: Dr. D. K. Driman at ddriman@uwo.ca

A retrospective comparison of HER2 immunohistochemistry and FISH in breast carcinomas

In 2007, the American Society of Clinical Oncology/College of American Pathologists developed new recommendations for HER2 testing and redefined HER2 positivity. The objective of this study was to analyze results from simultaneous HER2 testing with immunohistochemistry and FISH in 2,590 invasive breast carcinomas between 2002 and 2010 using two scoring systems. Cases from between 2002 and 2006 were scored using original Food and Drug Administration criteria (n=1,138), and those from between 2007 and 2010 were evaluated according to American Society of Clinical Oncology/College of American Pathologists criteria (n=1,452). Concordance between testing methods and clinicopathologic associations were determined. Overall concordance between immunohistochemistry/FISH in the nine-year period was 96.2 percent (κ=0.82), and positive concordance was lower. After 2007, the proportion of HER2/neu-positive and HER2/neu-negative cases was not significantly changed when using immunohistochemistry (10.5 versus 8.9 percent, P=0.22; and 69.4 versus 63 percent, P=0.13, respectively), but the number of equivocal cases was higher (19.9 versus 28 percent, P<0.001). While the proportion of negative cases by FISH remained unchanged after 2007 (86.5 versus 88.2 percent, P=0.76), the number of positive cases was lower (13.4 versus 9.2 percent, P<0.001). Furthermore, 38 cases (2.6 percent) were FISH equivocal, 16 of which were also equivocal by immunohistochemistry. Overall, immunohistochemistry/FISH concordance was 95.9 percent between 2002 and 2006 (κ=0.82) and 96.4 percent after 2007 (κ=0.82). However, an approximately 13 percent lower positive assay concordance was noted in the last period. The authors concluded that application of American Society of Clinical Oncology/College of American Pathologists recommendations is associated with comparable overall immunohistochemistry/FISH concordance, reduced positive concordance, and increased equivocal results.

Schalper KA, Kumar S, Hui P, et al. A retrospective population-based comparison of HER2 immunohistochemistry and fluorescence in situ hybridization in breast carcinomas: impact of 2007 American Society of Clinical Oncology/College of American Pathologists criteria. *Arch Pathol Lab Med.* 2014;138(2):213–219.

Correspondence: Dr. Kurt A. Schalper at kurt.schalper@yale.edu

Interrelationship of intracystic papillary carcinoma of breast with in situ and invasive carcinoma

Whether to classify intracystic papillary carcinoma as invasive or in situ ductal carcinoma is still a matter of debate. The authors conducted a study to explore the genomic relationship of this tumor to its concurrent invasive ductal carcinoma and ductal carcinoma in situ using array comparative genomic hybridization. Intracystic papillary carcinoma cases were classified into three categories: pure, with concurrent ductal carcinoma in situ, or with concurrent invasive ductal carcinoma. Each component underwent laser-capture microdissection. DNA was extracted and array comparative genomic hybridization performed. The test of difference in copy number changes among the three tumors was carried out using CGHMultiArray. Intracystic papillary carcinoma clustered with four of five concurrent ductal carcinoma in situ cases and with two of two invasive ductal carcinoma cases. Intracystic papillary carcinoma showed the highest proportions of genome copy number aberration, followed by ductal carcinoma in situ, and then by invasive ductal carcinoma (P=0.06). Comparing intracystic papillary carcinoma with invasive ductal carcinoma versus without invasive ductal carcinoma, the former had 11q22.1–23.3 loss (P=0.031) and chr5 gain (P=0.085) and was enriched with matrix metalloproteinase genes. Comparing intracystic papillary carcinoma with ductal carcinoma in situ versus without ductal carcinoma in situ, the former had gain in 5q35.3 (P=0.041), 8q24.3 (P=0.041), and 21q13.2 to 21q13.31 (P=0.011). Comparing intracystic papillary carcinoma with ductal carcinoma in situ, the latter acquired a group of genes involved in cell adhesion and motility, whereas intracystic papillary carcinoma differentially expressed genes that are involved in papillary carcinomas of other organs (thyroid and kidney). The authors concluded that the overall molecular change in intracystic papillary carcinoma is closer to ductal carcinoma in situ than to invasive ductal carcinoma, which may explain the indolent behavior of this tumor.

Khoury T, Hu Q, Liu S, et al. Intracystic papillary carcinoma of breast: interrelationship with in situ and invasive carcinoma and a proposal of pathogenesis: array comparative genomic hybridization study of 14 cases. *Mod Pathol.* 2014;27:194–203.

Correspondence: Dr. T. Khoury at thaer.khoury@roswellpark.org or Dr. J. Wang at jianmin.wang@roswellpark.org

Androgen-receptor expression to predict early recurrence in triple-negative breast cancer

Treatment of triple-negative invasive breast cancers, defined by the absence of estrogen and progesterone receptors and c-erbB2 expression, remains challenging. Androgen receptor, a member of the nuclear receptor superfamily involved in signaling pathways regulating cell proliferation, has been implicated in breast tumorigenesis. The authors immunohistochemically examined the expression of androgen receptor, basal markers (CK14 and 34βE12), and EGFR in 699 triple-negative invasive breast cancers in tissue microarrays using the streptavidin-biotin method. They correlated the findings with clinical outcome. Positive androgen-receptor expression was defined as staining of one percent or more of tumor cell nuclei. Survival outcomes were estimated with the Kaplan-Meier method and compared between groups with log-rank statistics. Cox proportional hazards models were used to determine the effect of androgen receptor on survival outcomes. Immunohistochemical positivity was observed in 38 percent of tumors, with the proportion of stained tumor cells ranging from one to 95 percent (mean, 29 percent; median, 10 percent). Androgen-receptor expression was inversely associated with histologic grade and mitotic score. CK14, 34βE12, and EGFR confirmed 85 percent of cases to be basal like, without significant association of basal-like phenotype with androgen-receptor expression. Disease-free survival was significantly better in androgen-receptor–positive triple-negative breast cancer, with a trend for improved overall survival. Decreased recurrence likelihood in triple-negative and basal-like tumors (hazard ratio, 0.704, 95 percent confidence interval [CI], 0.498–0.994, P=0.0464; and hazard ratio, 0.675, 95 percent CI, 0.468–0.974, P=0.0355, respectively) was noted within five years of diagnosis but not thereafter. The authors concluded that this study suggests that loss of androgen receptor in triple-negative breast cancer, including those with basal-like features, portends a worse prognosis. More work in elucidating its relationship with mechanisms of progression, as well as trials of targeted treatment for androgen receptor expressing triple-negative tumors, needs to be performed.

Thike AA, Yong-Zheng Chong L, Cheok PY, et al. Loss of androgen receptor expression predicts early recurrence in triple-negative and basal-like breast cancer. *Mod Pathol.* 2014;27:352–360.

Correspondence: Dr. P. H. Tan at tan.puay.hoon@sgh.com.sg

Surgical margin status in prostatectomy and risk for prostate cancer recurrence

Surgical margin status in prostatectomy is an important predictor of biochemical recurrence. The current convention is to categorize a margin as negative if tumor cells are not at the inked margin, even if they are within a few cells of the margin. The authors hypothesized that cancer within 0.1 mm of the margin confers an increased risk for biochemical recurrence (BCR). They determined the risk for BCR on the basis of surgical margin status in a cohort of 1,588 patients who underwent radical prostatectomy for prostate cancer between 1998 and 2011. Surgical margins were categorized as positive, close (less than 0.1 mm from tumor cells), or negative. Multivariate hazard ratios for BCR were determined by margin status. The authors found that of the 1,588 patients, 193 had prostate cancer recurrence. The margin status was negative in 1,058 (67 percent), close in 232 (15 percent), and positive in 298 (19 percent). Cancer that was close to the margin was a significant and independent predictor of BCR (hazard ratio, 1.53; 95 percent confidence interval [CI], 1.00–2.32) and did not differ statistically from a positive surgical margin (hazard ratio, 2.10; 95 percent CI, 1.48–2.99). The authors concluded that cancer that is within 0.1 mm of the surgical margin in prostatectomy is associated with an increased risk for prostate cancer recurrence. Patients with that margin status may be reasonable candidates for adjuvant local therapy.

Izard JP, True LD, May P, et al. Prostate cancer that is within 0.1 mm of the surgical margin of a radical prostatectomy predicts greater likelihood of recurrence. *Am J Surg Pathol.* 2014;38(3):333–338.

Correspondence email not provided.

Pathologic and molecular factors linked to outcome in resected GI stromal tumor

The ACOSOG (American College of Surgeons Oncology Group) Z9001 (Alliance) study, a randomized, placebo-controlled trial, demonstrated that one year of adjuvant imatinib prolonged recurrence-free survival after resection of primary gastrointestinal stromal tumor. The authors conducted a study to determine the pathologic and molecular factors associated with patient outcome. They assigned 328 patients to the placebo arm of the study and 317 to the imatinib arm. Median patient follow-up was 74 months. A total of 645 tumor specimens were available for mitotic rate or mutation analysis. The authors found that recurrence-free survival (RFS) remained superior in the imatinib arm (hazard ratio, 0.6; 95 percent confidence interval, 0.43–0.75; Cox model-adjusted $P<0.001$). On multivariable analysis of patients in the placebo arm, large tumor size, small bowel location, and high mitotic rate were associated with lower RFS, whereas tumor genotype was not significantly associated with such survival. Multivariable analysis of patients in the imatinib arm yielded similar findings. When comparing the two arms, imatinib therapy was associated with higher RFS in patients with a KIT exon 11 deletion of any type, but not a KIT exon 11 insertion or point mutation, KIT exon 9 mutation, PDGFRA mutation, or wild-type tumor, although some of these patient groups were small. Adjuvant imatinib did not seem to alter overall survival. The authors concluded that tumor size, location, and mitotic rate, but not tumor genotype, are associated with the natural history of gastrointestinal stromal tumor. Patients with KIT exon 11 deletions assigned to one year of adjuvant imatinib had a longer recurrence-free survival rate.

Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol.* 2014;32(15):1563–1570.

Correspondence: Dr. Christopher Corless at corlessc@ohsu.edu