Anatomic pathology selected abstracts

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Triple-positive breast carcinoma: histopathologic features and response to neoadjuvant chemotherapy

December 2021—It is unclear whether $HER2^+$ tumors expressing estrogen receptor and progesterone receptor—that is, triple-positive breast carcinomas—show unique morphologic and clinical features and response to neoadjuvant chemotherapy. The authors conducted a study of the morphologic and immunohistochemical features of triple-positive breast carcinomas (TPBC) in patients who underwent neoadjuvant chemotherapy. They retrospectively reviewed the core biopsy and post-neoadjuvant chemotherapy slides of 85 TPBCs. H-scores were calculated for estrogen receptor (ER) and progesterone receptor (PR). HER2 slides and FISH reports were reviewed. The residual cancer burden was calculated for post-neoadjuvant chemotherapy specimens. Eighty-one of the 85 (95.3 percent) tumors showed ductal histology. Three (3.5 percent) were invasive lobular carcinomas and one (1.2 percent) showed mixed ductal and lobular features. A subset showed mucinous (n = 7, 8.2 percent), apocrine (n = 5, 5.9 percent), and/or micropapillary (n = 4, 4.7 percent) differentiation. Fifty-four (63.5 percent) TPBCs showed high ER expression (H-score greater than 200), including 27 (31.8 percent) with high ER and PR expression. Fifty-two (61.1 percent) tumors showed HER2 3^+ staining. The mean HER2/CEP17 ratio by FISH was 3.6 (range, 2–12.2) and mean HER2 signals per cell was eight (range, 3.7–30.4). The pathologic complete response (pCR) rate was 35.3 percent (30 of 85). HER2 3^+ staining was the only significant predictor of pCR on multivariate analysis (odds ratio, 9.215; 95 percent confidence interval [CI], 2.401–35.371; $P < .001$). The ER/PR expression did not correlate with response to therapy. The authors concluded that TPBCs are heterogeneous, with some showing mucinous, lobular, or micropapillary differentiation. The pCR rate of TPBCs is similar to that reported for $ER^+/PR^-/HER2^+$ tumors. HER2 overexpression by IHC was associated with significantly better response to therapy and may help in selecting patients for treatment in the neoadjuvant setting.

Zeng J, Edelweiss M, Ross DS, et al. Triple-positive breast carcinoma: Histopathologic features and response to neoadjuvant chemotherapy. *Arch Pathol Lab Med*. 2021;145(6):728–735.

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Categorization of HER2 FISH results from invasive breast cancer patients treated with HER2-targeted agents

HER2 (ERBB2) gene status serves as a strong predictive marker of response to HER2-targeted agents in invasive breast cancers, albeit with heterogeneous response. The authors conducted a study to determine the distribution and prognosis of HER2 groups by FISH using the updated 2018 American Society of Clinical Oncology–College of American Pathologist (ASCO–CAP) guidelines, which contain five in situ hybridization categories. They identified 226 patients who had equivocal or positive HER2 FISH invasive breast cancer (interpreted by ASCO–CAP guidelines at the time of reporting) and who received HER2-targeted agents from 2006 to 2017. The authors subcategorized group one (a broad group and the dominant category in terms of number of patients in the authors' cohort) into three subgroups: low amplified (HER2/CEP17 ratio ≥ 2.0–2.99, mean HER2 per cell 4.0–5.9), amplified (HER2/CEP17 ratio ≥ 2.0–2.99, mean HER2 per cell ≥ 6), and excessive amplification (HER2/CEP17 ratio ≥ 3, mean HER2 per cell ≥ 4). They recorded the outcomes of recurrence, metastasis, second breast primary, disease-free survival, and overall survival. Univariate analysis showed that the five categories of HER2 FISH were significantly associated with overall survival ($p < .01$) and that higher HER2 amplification was associated with fewer deaths. HER2 FISH status

also was statistically significantly related to disease-free survival ($p < .01$) and metastasis ($p = .01$) but not to recurrence or second breast primary. Multivariate analysis showed that tumor type and HER2 ISH groups were independent predictors for overall survival and disease-free survival in the HER2-treated cohort. The group one subcategories were significantly associated with overall survival ($p < .01$) and disease-free survival ($p < .01$), and excessive HER2 amplification was associated with longer median survival. The Cox regression models showed better survival outcomes for the excessive amplification subgroup than the low-amplified subgroup with regard to overall survival (hazard ratio = 0.63; 95 percent confidence interval [CI], 0.42–0.93) and disease-free survival (hazard ratio = 0.55; 95 percent CI, 0.37–0.83). The authors demonstrated that in HER2 FISH group one patients, high HER2 amplification was significantly associated with longer overall and disease-free survival. Furthermore, these patients seemed to benefit more from HER2-targeted regimens. The authors recommend reporting these group one subcategories when assessing HER2 FISH.

Alhamar M, Alkamachi B, Mehrotra H, et al. Clinical significance of quantitative categorization of HER2 fluorescent in situ hybridization results in invasive breast cancer patients treated with HER2-targeted agents. *Mod Pathol*. 2021;34:720–734.

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Outcomes of the Milan system categories nondiagnostic and nonneoplastic for salivary gland FNA

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) specifies six categories with estimated risks of malignancy and suggested management. The estimated risk of malignancy is 25 percent for the nondiagnostic and 10 percent for the nonneoplastic categories. The authors conducted a study to investigate the histopathologic and clinical outcomes of the MSRSGC categories nondiagnostic and nonneoplastic at the authors' institution. Cytopathology fine-needle aspiration (FNA) reports from 2008 to 2020 were searched for the words salivary, parotid, and submandibular. Cases fitting the nondiagnostic and nonneoplastic categories were identified. Follow-up cytopathology/histopathology and clinical data were extracted. There were 43 nondiagnostic and 46 nonneoplastic cases. The average patient age was 58.3 years. Neoplastic lesions were found in 13 of 43 (30 percent) nondiagnostic and three of 46 (6.5 percent) nonneoplastic cases. The rate of malignancy was 14 percent (six of 43) in the nondiagnostic category and zero (of 46) in the nonneoplastic category. Four (9.3 percent) cases that were nondiagnostic and six (13 percent) that were nonneoplastic had no neoplasm and instead had an underlying reactive condition, such as chronic sialadenitis, or inflammatory lesion, such as lymphoepithelial cyst, on histologic follow-up. There was no follow-up pathology in 46.5 percent (20 of 43) of nondiagnostic and 82.6 percent (38 of 46) of nonneoplastic cases. However, no lesions were apparent clinically with a mean follow-up of three years and 1.5 years, respectively. The authors concluded that the MSRSGC categories nondiagnostic and nonneoplastic are helpful for reporting salivary gland FNA results. With proper clinical and radiologic correlation, risk of malignancy in the nonneoplastic group is low. Yet risk of malignancy in the nondiagnostic group remains significant. Repeat FNA after clinical and radiologic correlation for nondiagnostic cases seems prudent as neoplasms and malignancies may have gone undetected.

Johnson DN, Antic T, Reeves W, et al. Histopathologic and clinical outcomes of Milan system categories "non-diagnostic" and "non-neoplastic" of salivary gland fine needle aspirations. *J Am Soc Cytopathol*. 2021;10(4):349–356.

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Use of targeted NGS to assess serrated epithelial change as a precursor to IBD-associated colorectal neoplasia

Serrated epithelial change manifests in patients with long-standing inflammatory bowel disease and is characterized by disorganized crypt architecture, irregular serrations, and goblet cell-rich epithelium. The serrated nature of serrated epithelial change (SEC) is reminiscent of serrated colorectal polyps, which frequently harbor

KRAS/BRAF mutations. However, SEC is not only histologically distinct from sporadic serrated polyps but also associated with colorectal neoplasia. Whether SEC is a precursor to inflammatory bowel disease-associated neoplasia remains unclear. To further define the relationship of SEC with serrated colorectal polyps and inflammatory bowel disease-associated neoplasia, the authors performed targeted next-generation sequencing (NGS) on colorectal specimens that included SEC without dysplasia/neoplasia (n = 10), SEC with separate foci of associated dysplasia/adenocarcinoma from the same patients (n = 17), and uninvolved mucosa (n = 10) from 14 patients. In addition, they molecularly profiled specimens that were sessile serrated lesion (SSL)-like or serrated lesion, not otherwise specified (SL-NOS), from 11 patients who also had inflammatory bowel disease. This control cohort included SSL-like/SL-NOS without dysplasia/neoplasia (n = 11), SSL-like/SL-NOS with associated low-grade dysplasia (n = 2), and uninvolved mucosa (n = 8). Using NGS, the most frequently mutated gene in SEC without neoplasia and associated dysplasia/adenocarcinoma from separate foci in the same patients was determined to be *TP53*. Recurrent *TP53* mutations were present in 50 percent of SEC specimens without dysplasia/neoplasia. Alterations in *TP53* were detected at a prevalence of 71 percent in low-grade dysplasia, 83 percent in high-grade dysplasia, and 100 percent in adenocarcinoma. Paired sequencing of SEC and associated neoplasia revealed identical *TP53* missense mutations in three patients. In contrast, 91 percent of SSL-like/SL-NOS specimens without dysplasia/neoplasia harbored *KRAS/BRAF* mutations, which were conserved in associated low-grade dysplasia. No genomic alterations were found in uninvolved mucosa from patients with SEC or patients with SSL-like/SL-NOS. Based on these findings, the authors concluded that SEC is distinct from SSL-like serrated colorectal lesions in patients with inflammatory bowel disease and an early precursor to inflammatory bowel disease-associated neoplasia that warrants colonoscopic surveillance.

Singhi AD, Waters KM, Makhoul EP, et al. Targeted next-generation sequencing supports serrated epithelial change as an early precursor to inflammatory bowel disease associated colorectal neoplasia. *Hum Pathol*. 2021;112:9–19.

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Breast implant-associated ALCL: clinical follow-up and analysis of specimens of untreated patients

Breast implant-associated anaplastic large cell lymphoma (ALCL) is a distinctive type of T-cell lymphoma that arises around textured-surface breast implants. In a subset of patients, this disease can involve surrounding tissue, spread to regional lymph nodes, and rarely metastasize to distant sites. The authors conducted a study to assess sequential pathologic specimens from patients with breast implant-associated ALCL to better understand the natural history of early stage disease. To achieve this goal, they searched their files for patients who had breast implant-associated ALCL and who had undergone earlier surgical intervention with assessment of biopsies or cytologic specimens. They then focused on the patient subset in whom a definitive diagnosis was not established and, therefore, did not receive current standard-of-care therapy. The authors created a study group of 10 patients who had breast implant-associated ALCL and for whom pathologic specimens were collected 0.5 to four years before a definitive disease diagnosis was established. A comparison of these serial biopsy specimens showed persistent disease without change in pathologic stage in three patients, progression in five, and persistence versus progression in two. Six patients eventually had their implants removed via complete capsulectomy and four had partial capsulectomy. Seven patients also received chemotherapy because of invasive disease, of whom three received radiation therapy, two brentuximab vedotin after chemotherapy failure, and one allogeneic stem cell transplant. Eight patients achieved complete remission and two had partial remission after definitive therapy. At the time of last follow-up, six patients were alive without disease, one had evidence of disease, one had died of disease, and two had died of unrelated cancers. The authors concluded that this analysis of sequential specimens from patients with breast implant-associated ALCL suggests these neoplasms persist or progress over time if not treated with standard-of-care therapy.

Evans MG, Medeiros LJ, Marques-Piubelli ML, et al. Breast implant-associated anaplastic large cell lymphoma: clinical follow-up and analysis of sequential pathologic specimens of untreated patients shows persistent or progressive disease. *Mod Pathol*. 2021. https://doi.org/10.1038/s41379-021-00842-6

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