Anatomic Pathology Abstracts, 8/16

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Use of HSP70 and glutamine synthetase to diagnose hepatocellular carcinoma

Well-differentiated hepatocellular carcinoma can mimic high-grade dysplastic nodule in cirrhotic liver and hepatocellular adenoma in noncirrhotic liver. The authors evaluated the efficacy of combined use of heat-shock protein 70 (HSP70), glutamine synthetase, and glypican-3 in this setting. Immunohistochemistry for these three markers was performed in 17 typical hepatocellular adenomas, 15 high-grade dysplastic nodules, 20 atypical hepatocellular neoplasms (14 clinically atypical and six pathologically atypical), 14 very well-differentiated hepatocellular carcinomas, and 43 well-differentiated hepatocellular carcinomas. All three markers were negative in typical adenomas. HSP70 was positive in 10, 71, and 67 percent of atypical neoplasms, very well-differentiated hepatocellular carcinoma, and well-differentiated hepatocellular carcinoma, respectively, while glutamine synthetase was positive in 60, 50, and 60 percent of atypical neoplasms, very well-differentiated hepatocellular carcinoma, and well-differentiated hepatocellular carcinoma, respectively. Glypican-3 was negative in all atypical neoplasms and very well-differentiated hepatocellular carcinomas and was positive in 27 percent of well-differentiated hepatocellular carcinomas. Positive staining with HSP70 or glutamine synthetase, or both, was seen in 85 percent of very well-differentiated hepatocellular carcinomas, which was similar to what was seen in well-differentiated hepatocellular carcinomas (78 percent; P=.4) and pathologically atypical cases (100 percent; P=.5) but significantly higher than what was seen in clinically atypical cases (43 percent; P=.03), and not seen with typical adenomas (P<.001). Positive staining with glutamine synthetase and HSP70 was seen significantly more often in hepatocellular carcinoma compared with atypical neoplasms (45 versus 10 percent; P=.004). Both of these markers were also expressed more often in very well-differentiated hepatocellular carcinomas compared with atypical cases (38 versus 10 percent; P=.06). The authors concluded that the combined use of glutamine synthetase and HSP70 can be useful in the diagnosis of very well-differentiated hepatocellular carcinoma. These stains can also help distinguish typical adenoma from atypical hepatocellular neoplasms. Glypican-3 has low sensitivity and is not useful in this setting.

Nguyen TB, Roncalli M, DiTommaso L, et al. Combined use of heat-shock protein 70 and glutamine synthetase is useful in the distinction of typical hepatocellular adenoma from atypical hepatocellular neoplasms and well-differentiated hepatocellular carcinoma. *Mod Pathol.* 2016;29:283–292.

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Recurrence of benign and low-grade fibroepithelial neoplasms of the breast

Breast phyllodes tumors are uncommon fibroepithelial neoplasms with a range of histologic features. Surgical excision is the primary management, but the need for excision to negative margins in benign and borderline phyllodes tumors is unclear. The authors conducted a study in which they reviewed the surgical-management patterns and outcomes of 90 patients with benign and low-grade fibroepithelial lesions of the breast treated at their institution. The lesions included 19 borderline phyllodes tumors, 52 benign phyllodes tumors, and 19 representative neoplasms with overlapping features of fibroadenoma and benign phyllodes tumors, which were classified as fibroadenomas with phyllodal features. Fifty-two (58 percent) had positive surgical margins on the first excision, and of these, 17 (33 percent) underwent re-excision to achieve negative margins. Residual tumor was identified in three (18 percent) re-excisions. Patients with fibroadenoma with phyllodal features were more likely to have a positive surgical margin than were those with benign phyllodes tumors or borderline phyllodes tumors (89 versus 49 percent; *P*=.0015) and were less likely to undergo re-excision for positive margins (12 versus 43 percent; *P*=.031). There were three (three percent) recurrences, with one per fibroadenoma with phyllodal features, benign phyllodes tumor, and borderline phyllodes tumor. No statistically significant difference in recurrence rates between patients with positive or negative margins, or between patients with positive margin with or without re-excision, were noted. The extent of the positive margin did not predict recurrence. The authors concluded that the recurrence rate of benign and low-grade fibroepithelial lesions is low and is not associated with original margin status. Patients with fibroadenomas with phyllodal features, benign phyllodes tumors, or selected borderline phyllodes tumors and positive margins on initial excision may be managed conservatively, with close follow-up and timely re-excision of any potential recurrence.

Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. *Mod Pathol.* 2016;29:259–265.

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Lobular neoplasia detected in MRI-guided core biopsy: a high risk for upgrade

Certain criteria support surgical excision for lobular neoplasia diagnosed in mammographically detected core biopsy. The authors conducted a study to explore the rate of upgrade of lobular neoplasia detected in magnetic resonance imaging (MRI) guided biopsy and to investigate the clinicopathological and radiological features that could predict upgrade. They reviewed 1,655 MRI-guided core biopsies yielding 63 (four percent) cases of lobular neoplasia and recorded key clinical features. They also recorded MRI findings, including mass versus nonmass enhancement, and the reason for biopsy. An upgrade was defined as the presence of invasive carcinoma or ductal carcinoma in situ in subsequent surgical excision. The overall rate of lobular neoplasia in MRI-guided core biopsy ranged from two to seven percent, with an average of four percent. Fifteen (24 percent) cases had an upgrade, including five cases of invasive carcinoma and 10 cases of ductal carcinoma in situ. Pure lobular neoplasia was identified in 34 cases, 11 (32 percent) of which had an upgrade. In this group, an ipsilateral concurrent or past breast cancer was found to be associated with a higher risk of upgrade (six of 11, 55 percent) than contralateral breast cancer (one of 12, eight percent; *P*=.03). To the authors' knowledge, this is the largest series of lobular neoplasia diagnosed in MRI-guided core biopsy. The incidence of lobular neoplasia is relatively low. Lobular neoplasia detected in MRI-guided biopsy carries a high risk for upgrade warranting surgical excision. However, more cases, from different types of institutions, are needed to verify these results.

Khoury T, Kumar PR, Li Z, et al. Lobular neoplasia detected in MRI-guided core biopsy carries a high risk for

upgrade: a study of 63 cases from four different institutions. *Mod Pathol.* 2015;29:25–33.

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Use of microsatellite instability, MLH1 methylation analysis, IHC to identify Lynch syndrome

The best screening practice for Lynch syndrome in endometrial cancer is unknown. The authors sought to determine whether tumor microsatellite instability typing along with immunohistochemistry (IHC) and MLH1 methylation analysis can help identify women with Lynch syndrome. Endometrial cancers from GOG-210 study patients were assessed for microsatellite instability, MLH1 methylation, and mismatch repair (MMR) protein expression. Each tumor was classified as having normal MMR, defective MMR associated with MLH1 methylation, or probable MMR mutation—that is, defective MMR but no methylation. The authors compared cancer family history and demographic and clinical features for the three groups and performed Lynch mutation testing for a subset of women. Their analysis of 1,002 endometrial cancers suggested possible MMR mutation in 11.8 percent of tumors. The number of patients with a family history suggestive of Lynch syndrome was highest among women whose tumors were classified as probable MMR mutation (P=.001). Lynch mutations were identified in 41 percent of patient cases classified as probable mutation (21 of 51 tested). One of the MSH6 Lynch mutations was identified in a patient whose tumor had intact MSH6 expression. Age at diagnosis was younger for mutation carriers than noncarriers (54.3 versus 62.3 years; P<.01), with five carriers diagnosed at age greater than 60 years. The authors concluded that a combination of microsatellite instability, methylation, and IHC analysis may prove useful in Lynch screening in endometrial cancer. Twenty-four percent of mutation carriers presented with such cancers at age greater than 60 years, and one carrier had a microsatellite instabilty-positive tumor with no IHC defect. Restricting Lynch testing to women diagnosed at age younger than 60 years or to women with IHC defects could result in a substantial fraction of genetic disease not being diagnosed.

Goodfellow PJ, Billingsley CC, Lankes HA, et al. Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for Lynch syndrome screening in endometrial cancers from GOG210: an NRG oncology and gynecologic oncology group study. *J Clin Oncol.* 2015;3:4301–4308.

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Differential diagnosis of bladder versus colorectal adenocarcinoma

The authors conducted a study to evaluate immunohistochemical markers for the differential diagnosis of primary bladder adenocarcinoma (BAC) from secondarily involving colorectal adenocarcinoma (CAC). Additional staining of putative precursor lesions (cystitis cystica et glandularis [CC] and intestinal metaplasia) offers insights into metaplastic cell development and aberrant differentiation in tumors. Tissue microarray sections of formalin-fixed, paraffin-embedded tissues from clinically verified BACs (11), CACs (11), invasive urothelial carcinomas (18), normal urothelium samples (22), CCs (25), and intestinal metaplasias (15) were stained for keratin 7, 5/6, 5/14, and 20, β-catenin, e-cadherin, cadherin 17, cdx2, uroplakin II and III, CD10, androgen receptor, S100P, MUC2, MUC5AC, and GATA3 expression. Data were analyzed using Kruskal–Wallis/Dunn's multiple comparison test and Fisher's exact test. A significant difference (P<.05) between all three tumor groups was observed for keratin 7 only. A significant difference between BAC and CAC was found for GATA3 and nuclear β-catenin staining. BAC-positive/CAC-negative markers without significance were p63, keratin 5/6, 5/14, uroplakin II and III, and androgen receptor. CC showed a urothelial phenotype (p63+, GATA3+, S100P+, uroplakin+ in single cells) with initial signs of intestinal differentiation (single cells cdx2+ or cadherin 17+). Intestinal metaplasia displayed a full intestinal phenotype (p63–, all urothelial markers–, cdx2/MUC2/MUC5AC+, cadherin17+). The authors concluded that the differential diagnosis of BAC and CAC remains difficult, but positive staining for keratin 7 in nuclear β-catenin-negative tumors

argues for BAC. Additional markers like GATA3 and p63 may be added, as positivity in some cases may be helpful. However, knowledge of comprehensive clinical data is still essential for reliable histological diagnosis.

Broede A, Oll M, Maurer A, et al. Differential diagnosis of bladder versus colorectal adenocarcinoma: keratin 7 and GATA3 in positivity in nuclear β-catenin-negative glandular tumours defines adenocarcinoma of the bladder. *J Clin Pathol.* 2016;69:307–312.

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Enhanced expression of PD L1 in CIN and cervical cancers

Programmed death ligand 1 expression can reduce the immune response in infectious diseases and cancers. Therefore, the authors examined programmed death ligand 1 (PD L1) expression in cervical intraepithelial neoplasias (CINs) and cancers because each reflects infection by human papillomavirus (HPV). PD L1 protein was not evident by immunohistochemistry in histologically normal cervical epithelia (zero of 55) even when adjacent to CIN or cancer. PD L1 expression was much increased in CINs (20 of 21; 95 percent) and cervical squamous cell cancer (56 of 70; 80 percent) and localized to the dysplastic/neoplastic squamous cells and mononuclear cells, respectively. A significant increase (each, $P<.001$) in PD L1 detection in mononuclear cells was also found when comparing cervical squamous cell cancers to endometrial (22 of 115; 19 percent) and ovarian adenocarcinomas (five of 40; 13 percent). Co-expression analyses showed that the primary inflammatory cell that contained PD L1 was the CD8+ lymphocyte that strongly concentrated around the dysplastic CIN cells and nests of invasive squamous cancer cells. These data show that PD L1 is a solid biomarker of productive HPV infection of the cervix and is significantly upregulated in both the carcinoma and surrounding inflammatory cells in cervical cancer when compared with other gynecologic malignancies. This suggests that anti-PD L1 therapy may play a role in the treatment of cervical cancer.

Mezache L, Paniccia B, Nyinawabera A, et al. Enhanced expression of PD L1 in cervical intraepithelial neoplasia and cervical cancers. *Mod Pathol.* 2015;28:1594–1602.

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