Anatomic Pathology Abstracts, 11/16

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Relevance of papillary growth patterns of pulmonary adenocarcinoma

Growth patterns of pulmonary adenocarcinoma have high prognostic impact and are accepted as a novel classification system for this cancer. However, specifically for the papillary pattern, divergent data with respect to prevalence, clinical associations, and prognostic impact have been reported. The authors evaluated 674 resected pulmonary adenocarcinomas, including 308 cases with a papillary component and 101 papillary predominant cases, and documented differences in the morphologic composition of papillary growth patterns. They delineated three types. The various types were correlated with pathologic and clinical data, including survival. Type 3 papillary cases with any or predominant papillary growth were associated with extensive spread through alveolar spaces, high proliferation, higher stage, low rates of *EGFR* mutations, and smoking, whereas type 1 papillary tumors showed the opposite associations. The subclassification of papillary growth revealed type-specific associations for overall and disease-free survival (disease-free survival type 1, 67.1 months; type 2, 56.8 months; type 3, 49.9 months; $P = .025$). The presence of any papillary type 3 pattern was a predominant pattern independent predictor of worse overall survival (hazard ratio, 2.5; $P = .02$). For a future grading system of lung adenocarcinoma, categorization of papillary growth in one category might not be adequate because this pattern contains a heterogenous mix of tumors with divergent prognoses. The authors suggest that papillary pattern types should be separated to further improve the prognostic power of adenocarcinoma growth pattern analysis.

Warth A, Muley T, Harms A, et al. Clinical relevance of different papillary growth patterns of pulmonary adenocarcinoma. *Am J Surg Pathol.* 2016;40(6):818–826.

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HPV involvement in head and neck cancers: assessment of biomarkers

The authors conducted a large international study to estimate fractions of head and neck cancers attributable to human papillomavirus (HPV-AFs) using six HPV-related biomarkers of viral detection, transcription, and cellular transformation. They collected formalin-fixed, paraffin-embedded cancer tissues of the oral cavity, pharynx, and larynx from pathology archives in 29 countries. All samples were subjected to histopathological evaluation, DNA quality control, and HPV DNA detection. Samples containing HPV DNA were further subjected to HPV E6*I mRNA detection and p16INK4a, pRb, p53, and cyclin D1 immunohistochemistry. Final estimates of HPV-AFs were based

on HPV DNA, HPV E6*I mRNA, or p16INK4a results. A total of 3,680 samples yielded valid results: 1,374 pharyngeal, 1,264 oral cavity, and 1,042 laryngeal. HPV-AF estimates based on positivity for HPV DNA and either HPV E6*I mRNA or p16INK4a were 22.4 percent, 4.4 percent, and 3.5 percent for cancers of the oropharynx, oral cavity, and larynx, respectively, and 18.5 percent, 3.0 percent, and 1.5 percent when requiring simultaneous positivity for all three markers. HPV16 was largely the most common type. Estimates of HPV-AF in the oropharynx were highest in South America, Central and Eastern Europe, and Northern Europe, and lowest in Southern Europe. Women showed higher HPV-AFs than men for cancers of the oropharynx in Europe and for the larynx in Central-South America. The authors concluded that HPV contributes substantially to head and neck cancers but is highly heterogeneous by cancer site, region, and gender. This study confirms the important role of HPV in oropharyngeal cancer and drastically downplays the previously reported involvement of HPV in the other head and neck cancers.

Castellsagué X, Alemany L, Quer M, et al; ICO International HPV in Head and Neck Cancer Study Group. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. *J Natl Cancer Inst.* 2016;108:djv403. doi:10.1093/jnci/djv403.

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Distinctive immunoregulatory microenvironment of medullary carcinoma of the colon

Medullary carcinoma of the colon is a unique histologic subtype of microsatellite-unstable colorectal carcinoma but little is known about its tumor-immunoregulatory microenvironment. The authors conducted a study to characterize the immune environment of medullary carcinoma and compare the cancer with other microsatellite-unstable and microsatellite-stable colorectal carcinomas. An initial gene-expression microarray analysis of six cases of medullary carcinoma was used to detect potential differentially expressed genes. The authors extended this analysis, using genomic data from the Cancer Genome Atlas, to compare eight cases of medullary carcinoma with other microsatellite-unstable and -stable carcinomas. Finally, they evaluated the expression of key immune pathway proteins and lymphocyte subsets of a large group of medullary carcinomas (n = 105) and compared these findings with three other carcinoma groups: poorly differentiated, microsatellite-unstable well differentiated, and microsatellite-stable well differentiated. Microarray and Cancer Genome Atlas data analysis identified significant upregulation of several immunoregulatory genes induced by IFNγ, including *IDO-1, WARS* (tRNA[trp]), *GBP1, GBP4, GBP5, PDCD1 (PD-1),* and *CD274* (PD-L1), in medullary carcinoma compared with other microsatellite-unstable and microsatellite-stable tumors. By immunohistochemistry, IDO-1 was expressed in 64 percent (67 of 104) of medullary carcinomas compared with 19 percent (nine of 47) of poorly differentiated carcinomas, 14 percent (three of 22) of microsatellite-unstable carcinomas, and seven percent (two of 30) of microsatellite-stable well-differentiated carcinomas ($P < .0001$). TRNA (trp) was overexpressed in 81 percent of medullary carcinomas, 19 percent of poorly differentiated carcinomas, 32 percent of microsatellite-unstable carcinomas, and three percent of microsatellite-stable well-differentiated carcinomas ($P < .0001$). Medullary carcinoma had higher mean CD8+ and PD-L1+ tumor-infiltrating lymphocytes compared with all other groups ($P < .0001$). This study demonstrates the overexpression of several immunoregulatory genes in microsatellite-unstable colorectal carcinomas and that expression of these genes and proteins is more prevalent in the medullary carcinoma subtype, which may be useful diagnostically and therapeutically.

Friedman K, Brodsky AS, Lu S, et al. Medullary carcinoma of the colon: a distinct morphology reveals a distinctive immunoregulatory microenvironment. *Mod Pathol.* 2016;29:528–541.

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Diagnostic challenges caused by endoscopic biopsy of colonic polyps

Endoscopic mucosal biopsy may result in mucosal elements being misplaced in the submucosa of colonic adenomas, mimicking invasive adenocarcinoma. Biopsy-related misplacement can be more challenging to recognize than typical misplaced epithelium (pseudoinvasion) in pedunculated polyps. The authors compared the features of 16 polyps with biopsy-related misplaced epithelium to those of 10 adenomas with pseudoinvasion and 10 adenomas with invasive adenocarcinoma. They performed Ki67 and p53 immunostaining on all cases. Features of misplaced epithelium in polyps referred to the Bowel Cancer Screening Program Expert Board, in the United Kingdom, were also evaluated for the same morphologic features. Biopsy-related epithelial misplacement occurred in adenomas throughout the colon and often appeared infiltrative (69 percent)—it included epithelial cells singly dispersed within reactive fibroinflammatory stroma or granulation tissue (44 percent). Misplaced epithelium displayed only low-grade cytologic features and was associated with extruded mucin (75 percent), tattoo pigment (63 percent), and misplaced normal glands (38 percent). Scant lamina propria and muscularis mucosae were often present (88 percent and 44 percent, respectively). Cases referred to the Bowel Cancer Screening Program Expert Board also contained infiltrative-appearing misplaced epithelium (91 percent) that was cytologically low grade (72 percent), contained nondysplastic glands (11 percent), and showed other signs of injury. In contrast, misplaced epithelium in pedunculated polyps always had a lobular contour with a rim of lamina propria, hemorrhage, and/or hemosiderin. Invasive carcinomas showed malignant cytology and desmoplasia; most (70 percent) lacked features of trauma. Ki67 and p53 staining was patchy and weak in the misplaced epithelium, whereas invasive carcinomas showed increased staining for one or both markers. The authors concluded that pathologists should be aware that endoscopically manipulated adenomas may contain misplaced epithelium that simulates malignancy.

Panarelli NC, Somarathna T, Samowitz WS, et al. Diagnostic challenges caused by endoscopic biopsy of colonic polyps: A systematic evaluation of epithelial misplacement with review of problematic polyps from the Bowel Cancer Screening Program, United Kingdom. *Am J Surg Pathol.* 2016;40:1075–1083.

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MicroRNA expression profiling and expression of miR-205 in inflammatory breast cancer

Inflammatory breast cancer is the most aggressive form of breast cancer. New biomarkers that can be used as therapeutic targets are urgently needed. Messenger RNA expression profiling studies have indicated that inflammatory breast cancer is a transcriptionally heterogeneous disease, and specific molecular targets for inflammatory breast cancer have not been well established. The authors conducted a study in which they performed microRNA expression profiling in inflammatory breast cancer in comparison with locally advanced noninflammatory breast cancer. Although many micro-RNAs were differentially expressed between normal breast tissue and tumor tissue, most of them did not show differential expression between inflammatory and noninflammatory tumor samples. However, microarray analysis, quantitative RT-PCR, and in situ hybridization showed that microRNA-205 expression was decreased not only in tumor tissue compared with normal breast tissue but also in inflammatory breast cancer compared with noninflammatory breast cancer. Lower expression of micro-RNA-205 correlated with worse distant metastasis-free survival and overall survival in this cohort. A small-scale immunohistochemistry analysis showed both decreased microRNA-205 expression and decreased E-cadherin expression in some ductal tumors. The authors concluded that microRNA-205 may serve as a therapeutic target in advanced breast cancer, including inflammatory breast cancer.

Huo L, Wang Y, Gong Y, et al. MicroRNA expression profiling identifies decreased expression of miR-205 in inflammatory breast cancer. *Mod Pathol.* 2016;29:330–346.

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