Anatomic pathology selected abstracts

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Findings from molecular and immunophenotypic characterization of anal squamous cell carcinoma

October 2021—Squamous cell carcinoma is the most common malignancy of the anal canal and is strongly associated with human papillomavirus (HPV) infection. Characteristic genomic alterations have been identified in anal squamous cell carcinoma (SqCC), but their clinical significance and correlation with HPV status, pathologic features, and immunohistochemical markers are not well established. The authors examined the molecular and clinicopathologic features of 96 HPV-positive and 20 HPV-negative anal SqCC cases. HPV types included 89 HPV16, two combined HPV16/HPV18, and five HPV33. HPV-positive cases demonstrated frequent mutations or amplifications in *PIK3CA* (30 percent; $p = 0.027$) or *FBXW7* mutations (10 percent). HPV negativity was associated with frequent *TP53* (53 percent; $p = 0.00001$) and *CDKN2A* (21 percent; $p = 0.0045$) mutations. P16 immunohistochemistry was positive in all HPV-positive cases and three of 20 HPV-negative cases ($p < 0.0001$; sensitivity, 100 percent; specificity, 85 percent) and was associated with basaloid morphology ($p = 0.0031$). Aberrant p53 IHC staining was 100 percent sensitive and specific for *TP53* mutations ($p < 0.0001$). By the Kaplan–Meier method, HPV negativity, aberrant p53 staining, and *TP53* mutation were associated with inferior overall survival ($p < 0.0001$, $p = 0.0103$, and $p = 0.0103$, respectively) and inferior recurrence-free survival ($p = 0.133$, $p = 0.0064$, and $p = 0.0064$, respectively). *TP53*/p53 status stratified survival probability by HPV status ($p = 0.013$), with HPV-negative/aberrant p53 staining associated with the worst overall survival, HPV-positive/wild-type p53 with the best overall survival, and HPV-positive/aberrant p53 or HPV-negative/wild-type p53 with intermediate overall survival. On multivariate analysis, HPV status ($p = 0.0063$), patient age ($p = 0.0054$), T stage ($p = 0.039$), and lymph node involvement ($p = 0.044$) were independently associated with overall survival. PD-L1 expression (combined positive score of one or more) was seen in 30 percent of HPV-positive and 40 percent of HPV-negative cases. PD-L1 positivity was associated with a trend toward inferior overall survival within the HPV-negative group ($p = 0.064$). The findings suggest that anal SqCC can be subclassified into clinically, pathologically, and molecularly distinct groups based on HPV and *TP53* mutation status. P16 and p53 IHC are clinically useful for predicting these prognostic groups.

Zhu X, Jamshed S, Zou J, et al. Molecular and immunophenotypic characterization of anal squamous cell carcinoma reveals distinct clinicopathologic groups associated with HPV and *TP53* mutation status. *Mod Pathol*. 2021;34:1017–1030.

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SMARCA4- and SMARCA2-deficient carcinoma of the esophagus and gastroesophageal junction

Undifferentiated carcinoma of the esophagus and gastroesophageal junction is a recently recognized entity in the fifth edition of the World Health Organization Classification of Digestive Tumors. It is diagnostically challenging, particularly on small biopsies and in cases without keratin expression. The authors conducted a study to examine the clinical and pathologic features of a series of cases diagnosed as SMARCA4- and SMARCA2-deficient undifferentiated carcinomas of the esophagus and gastroesophageal junction evaluated by SMARCA4 and SMARCA2 immunohistochemistry. *SMARCA4* and *SMARCA2* are chromatin remodeling genes with key roles in oncogenesis. The authors retrieved 14 cases of SMARCA4- and SMARCA2-deficient undifferentiated carcinoma of the gastroesophageal junction and esophagus from their respective institutions. The tumors showed similar

histologic findings: sheet-like proliferation of tumor cells characterized by discohesion, large nuclei, and prominent macronucleoli with many tumor cells exhibiting a rhabdoid appearance. Adjacent specialized intestinal metaplasia was noted in eight cases, and three exhibited adjacent high-grade dysplasia. Immunohistochemically, tumors variably expressed keratins and disclosed loss of expression of SMARCA4 in 12 cases and SMARCA2 in seven. In two cases, SMARCA2 was lost without SMARCA4 loss. A mutant p53 IHC pattern was seen in four of four cases, three of which showed diffuse, strong nuclear expression and one of which displayed a complete loss of nuclear expression of p53. Limited clinical follow-up was available, but three patients died of disease within 0.6, two, and seven months of diagnosis. The authors reported that this was the first case series of undifferentiated carcinomas of the esophagus and gastroesophageal junction characterized by SMARCA4 or SMARCA2 loss, or both. This tumor type likely arises from dedifferentiation of a lower grade carcinoma in some cases and Barrett esophagus and appears to be associated with an aggressive clinical course.

Horton RK, Ahadi M, Gill AJ, et al. SMARCA4/SMARCA2-deficient carcinoma of the esophagus and gastroesophageal junction. *Am J Surg Pathol*. 2021;45:414–420.

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IgG4-related lymphadenopathy: a comparative study of 41 cases

Lymphadenopathy is common in patients with immunoglobulin G4-related disease (IgG4-RD). However, the histopathologic features of IgG4-related lymphadenopathy are largely nonspecific. In an attempt to identify features specific for nodal IgG4-RD, the authors examined the histopathologic features of lymph nodes from 41 patients who had established IgG4-RD and compared them with the features of 60 lymph nodes from patients without known or subsequent development of IgG4-RD. An increase in both IgG4-positive plasma cells greater than 100 per high-power field and IgG4/IgG ratio greater than 40 percent was identified in 51 percent of IgG4-RD cases and 20 percent of control cases. Localization of increased IgG4-positive plasma cells and IgG4/IgG ratio to extrafollicular zones was highly associated with IgG4-RD, particularly when identified in regions of nodal fibrosis ($P < 0.0001$; specificity, 98.3 percent) or in the context of marked interfollicular expansion ($P = 0.022$; specificity, 100 percent). Other features characteristic of IgG4-RD included frequent eosinophils associated with IgG4-positive plasma cells, phlebitis ($P = 0.06$), and perifollicular granulomas ($P = 0.16$). An isolated increase in intrafollicular IgG4-positive plasma cells and IgG4/IgG ratio was more frequent in control cases than in IgG4-RD patients ($P < 0.0001$). This study confirms that an increase in IgG4-positive plasma cells and IgG4/IgG ratio is neither sensitive nor specific for the diagnosis of IgG4-related lymphadenopathy and that most morphologic patterns are nonspecific. In contrast, nodal involvement by IgG4-rich fibrosis akin to extranodal IgG4-RD or diffuse interfollicular expansion by IgG4-positive plasma cells are highly specific features of IgG4-related lymphadenopathy. These findings provide a clinically meaningful approach to evaluating lymph nodes that will assist pathologists in distinguishing IgG4-related lymphadenopathy from its mimics.

Bledsoe JR, Ferry JA, Neyaz A, et al. IgG4-related lymphadenopathy: A comparative study of 41 cases reveals distinctive histopathologic features. *Am J Surg Pathol*. 2021;45(2):178–192.

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Impact of a genomic classifier on indeterminate thyroid nodules

Twenty to 25 percent of thyroid nodules examined are classified as indeterminate thyroid cytology, and the associated risk of malignancy ranges from five to 30 percent. The genomic classifier ThyroSeq, a targeted next-generation sequencing technology, could classify indeterminate thyroid cytology (ITC) nodules as malignant and nonmalignant. The authors characterized their institutional experience with ThyroSeq testing. They retrospectively identified all patients seen from January 2015 through November 2019 who had ITC nodules analyzed with ThyroSeq. The authors reviewed relevant clinical, pathologic, and resection data. For the 133 patients identified, the diagnostic categories included atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS; n = 65; 48.9 percent), suspicious for follicular neoplasm (SFN; n = 48; 36.1 percent), and

suspicious for Hürthle cell neoplasm (n = 20; 15 percent). More than half of the cases of papillary thyroid carcinoma (56.3 percent) and more than one-third of the cases of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP; 37.5 percent) were classified as SFN. Most patients (n = 87; 65.4 percent) did not undergo resection. Of these, 73 (83.9 percent) were negative for all molecular alterations. Of the 54 cases with molecular alterations, isolated *RAS* or *RAS*-like variants were most common (n = 35; 64.8 percent), and nine of the variants (25.7 percent) were identified in papillary thyroid carcinoma and eight (22.9 percent) in NIFTP. *NRAS* was the most common molecular alteration (n = 20; 37 percent), followed by *HRAS* (n = 6; 11.1 percent), which was primarily detected in NIFTP cases (n = 4 of 6; 66.7 percent). The authors concluded that resection was avoided in 73 patients (54.9 percent) because of negative ThyroSeq results. ThyroSeq v2 and v3 provided a more accurate categorization of ITC nodules, improved patient management, and a reduction in unnecessary surgical procedures.

Abdelhakam DA, Mojica RE, Huenerberg KA, et al. Impact of a genomic classifier on indeterminate thyroid nodules: an institutional experience. *J Am Soc Cytopathol*. 2021;10(2):155–163.

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Variability in synoptic reporting of colorectal cancer pT4a category and lymphovascular invasion

Serosal involvement (pT4a category) and lymphovascular invasion have prognostic significance in colorectal carcinoma, but their assessment is subject to interobserver variation. The authors provided a large-scale assessment of interobserver variability in pT4a category and lymphovascular invasion reporting in real-world practice and explored the impact of information from guidelines addressing variability in reporting these features. They analyzed 1,555 consecutive synoptic reports of colorectal carcinoma using multivariate logistic regression. Interobserver variability before and after presenting guideline information was assessed using an image-based survey. Significant differences in the odds of reporting pT4a versus pT3 category, detecting lymphovascular invasion of any type, and detecting large-vessel invasion were identified among hospital sites and for individual pathologists when compared with the median for pathologists at the same site. Consistent with these results, interobserver agreement regarding T4a staging and lymphovascular invasion was only moderate (all $\kappa \leq 0.57$) in the image-based survey. The provision of information from guidelines did not tend to increase interobserver agreement in the survey, although responses in favor of using an elastic stain increased following recommendations supporting their use. However, when observers were provided with elastic-stained images, interobserver agreement remained only moderate ($\kappa = 0.55$). The authors concluded that real-world reporting of pT4a category and lymphovascular invasion shows substantial variability at local and regional levels. This study underscores the need to address features of prognostic significance in quality initiatives and offers a novel method through which synoptic data can be harnessed to monitor reporting patterns and provide individualized feedback.

Naso JR, Yang HM, Schaeffer DF. Variability in synoptic reporting of colorectal cancer pT4a category and lymphovascular invasion. *Arch Pathol Lab Med*. 2021;145(3):343–351. doi:10.5858/arpa.2020-0124-OA

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