Anatomic pathology selected abstracts

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Thymoma: a clinicopathological correlation of surgical resection cases

September 2018—The authors presented 1,470 surgical resections for thymoma from the pathology files of 14 institutions in 11 countries with the purpose of determining and correlating a simplified histological classification of thymoma and pathological staging with clinical outcome. The study population comprised 720 men and 750 women between the ages of 12 and 86 years (average, 54.8 years). Clinical information about the presence of myasthenia gravis, other autoimmune disorders, and other neoplasia obtained for 807 patients showed that 137 (17 percent) patients had a history of myasthenia gravis, 31 (3.8 percent) patients had another autoimmune disease, and 55 (6.8 percent) patients had another neoplastic process. The remaining patients presented with nonspecific symptoms. Surgical resection was performed in all patients. Histologically, 1,284 (87.13 percent) cases were thymomas (World Health Organization types A, B1, and B2, and mixed histologies), and 186 (12.7 percent) were atypical thymomas (World Health Organization type B3). Of the entire group, 630 (42.9 percent) were encapsulated thymomas and 840 (57.9 percent) were invasive thymomas in different stages. Follow-up information was obtained for 1,339 (91 percent) patients, who subsequently were analyzed by univariate and multivariate statistical analysis. Follow-up ranging from one to 384 months (mean, 69.2 months) showed tumor recurrence in 136 (10.1 percent) patients. Two hundred and twenty-seven patients died—64 (28.2 percent) due to tumor and 163 (71.8 percent) due to other causes. Statistical analysis showed that separating these tumors into thymoma and atypical thymoma is statistically significant ($P=.001$), and tumor staging into the categories of encapsulated, minimally invasive, and invasion into adjacent organs offers a meaningful clinical assessment ($P=.038$). The authors concluded that the findings suggest that their simplified histological schema and pathological staging system are excellent predictors of clinical outcome.

Weissferdt A, Kalhor N, Bishop JA, et al. Thymoma: a clinicopathological correlation of 1470 cases. *Hum Pathol.* 2018;73:7–15.

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Detection and treatment of thyroid neoplasms in Carney complex patients

The initial description of Carney complex in 1985 included myxomas; spotty skin pigmentation; and endocrine overactivity of the adrenal gland, pituitary gland, and testis. In 1997, thyroid neoplasms were found in three patients with Carney complex and involvement of the gland in the syndrome was apparent. The authors described the clinical, pathologic, and follow-up findings in 26 patients with Carney complex and a disorder of the thyroid gland. The patients were predominantly middle-aged women with an asymptomatic thyroid mass. Four patients had hyperthyroidism, which was caused by follicular hyperplasia in two patients and toxic adenoma in two others. Pathologic findings included benign lesions—follicular hyperplasia, nodular hyperplasia, and follicular adenoma—in 16 patients and carcinomas—follicular or papillary—in 10 patients. The follicular carcinomas had unusual features, multifocality, bilaterality, and lymph node metastasis. A tumor of three centimeters or more in diameter was fatal in three of four patients. One patient had an unusual multifocal microscopic follicular hyperplasia. The authors concluded that detection and treatment of thyroid neoplasms in patients with Carney complex requires long-term follow-up of patients with the syndrome.

Carney JA, Lyssikatos C, Seethala RR, et al. The spectrum of thyroid gland pathology in Carney complex: The

importance of follicular carcinoma. *Am J Surg Pathol.* 2018;42(5):587–594.

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Association between *RAS* mutation and clinicopathologic characteristics in colorectal cancer

In colorectal cancer, *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) mutations are associated with resistance to antiepidermal growth factor receptor monoclonal antibodies, and *BRAF* mutation is a molecular marker of poor prognosis. *KRAS* exon 2 and *BRAF*-mutated colorectal cancers have well-known distinct clinicopathologic characteristics. The authors conducted a study in which they compared tumors with different RAS status (exons 2, 3, and 4 of KRAS and NRAS) based on their clinicopathologic characteristics. The observational retrospective study included all colorectal cancer patients who underwent RAS and BRAF testing from 2011 to 2015. Patient and tumor characteristics were collected and correlation with RAS and BRAF status was evaluated. A total of 1,735 patients with colorectal cancer were included in the study. *RAS*-mutated colorectal cancers (n=1,002), compared with *RAS* wild-type colorectal cancers (n=733), were significantly associated with male gender, classical adenocarcinoma subtype, well/moderately differentiated tumors, and microsatellite stable phenotype. *KRAS* codon 13-mutated colorectal cancers (n=171), compared with *RAS* wild-type colorectal cancers, more frequently presented a classical adenocarcinoma subtype and microsatellite stable phenotype. In comparison with other *RAS* mutations, *KRAS* exon 3-mutated colorectal cancers (n=23) were associated with mucinous/rare histological subtypes and were most likely to be located in the rectum. *KRAS* exon 4-mutated colorectal cancers (n=33) were more frequently associated with mucinous/rare histological subtypes. No significant association between *NRAS* mutation (n=37) and clinicopathologic features was found. The authors concluded that colorectal cancers are associated with different clinicopathologic features according to the type of *RAS* mutation. Consequently, these characteristics must be considered when assessing the prognostic value of *RAS* status in colorectal cancer.

Rimbert J, Tachon G, Junca A, et al. Association between clinicopathological characteristics and RAS mutation in colorectal cancer. *Mod Pathol.* 2018;31:517–526.

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Histologic features of gastrointestinal tract biopsies in IgA vasculitis

Immunoglobulin A vasculitis, formerly called Henoch-Schönlein purpura, typically occurs in the pediatric population, although rare cases also occur in adults. Gastrointestinal involvement is common. The classic histologic finding in IgA vasculitis is leukocytoclastic vasculitis (LCV); other histologic features in biopsies of IgA vasculitis have been described only rarely. The pathology archival files at the authors' institution were searched for GI biopsies from patients with IgA vasculitis. Slides were retrieved and histologic and clinical features reviewed. The authors identified 16 patients (adult and pediatric) with IgA vasculitis who had a GI biopsy series available. The most common histologic abnormality was lamina propria hemorrhage (all cases), with many cases also showing lamina propria fibrin deposition with red cell sludging and nuclear debris (seven cases). Twelve of the 16 duodenal biopsies had acute duodenitis, three of which were severe and erosive. Several also had an eosinophilic infiltrate. Seven of the nine jejunal or ileal biopsies, or both, had acute jejunitis or ileitis. An acute colitis or proctitis was observed in nine of 12 colorectal biopsies. Four biopsies contained LCV; in each of these cases, the involved vessels were small capillaries within the lamina propria. Only one biopsy contained deeper submucosal vessels, but these were uninvolved. Sites involved by LCV included the colorectum (two cases), colorectum and terminal ileum, terminal ileum only, duodenum, and jejunum (one case each). All patients presented with abdominal pain, and 13 of 16 developed a rash—one following the index biopsy. Other presenting symptoms included diarrhea or hematochezia, or both (eight cases); nausea/vomiting (five cases); and intussusception (one case). Four patients had concurrent skin biopsies showing LCV. Only one of these patients had LCV on GI biopsy. Indications for biopsy included nonspecific presenting symptoms, absence of rash at presentation, or failure to respond adequately to steroid therapy. Biopsies are commonly performed on patients with or without suspected IgA vasculitis to rule out

infection, inflammatory bowel disease, and, less commonly, vasculitis. Vasculitis is not typically observed in GI biopsies of patients with IgA vasculitis, and the spectrum of findings includes neutrophilic infiltrate within the small bowel and colon, with the duodenum most commonly affected. While the clinical and histologic findings may mimic early inflammatory bowel disease, the presence of predominant small bowel involvement, especially erosive duodenitis, should raise suspicion for IgA vasculitis. Biopsies should be obtained before initiating steroid therapy, if possible.

Louie CY, Gomez AJ, Sibley RK, et al. Histologic features of gastrointestinal tract biopsies in IgA vasculitis (Henoch-Schönlein purpura). *Am J Surg Pathol.* 2018;42(4):529–533.

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Fibroma-like PEComa: a tuberous sclerosis complex-related lesion

Perivascular epithelioid cell tumors, which are mesenchymal tumors morphologically characterized by epithelioid cells, co-express melanocytic and muscle markers. The authors described a heretofore undescribed tuberous sclerosis complex (TSC)-related neoplasm morphologically resembling a soft tissue fibroma-like lesion but showing an immunophenotype resembling perivascular epithelioid cell tumor (PEComa). They identified three soft tissue fibroma-like lesions in individuals with TSC. They also evaluated six TSC-related periungual fibromas and a range of non-TSC fibroma-like lesions (n=19). Immunohistochemistry for HMB-45, desmin, smooth muscle actin, TFE3, and S100 was performed on the TSC-related fibromas. Periungual fibromas and non-TSC fibroma-like lesions were also stained for HMB-45. All three TSC patients were female, ranging in age from four to 51 years (mean, 26.7 years). Two tumors were located in extremities and one on the chest wall. The tumors showed elongated to stellate spindle-shape cells and prominent collagenous background, and they lacked mitotic activity and cytologic atypia. Immunohistochemically, all three tumors were positive for HMB-45; smooth muscle actin or desmin was positive in both tumors tested. TFE3 was negative. All patients were alive with no evidence of disease at a median follow-up of 55 months (range, six–131 months). Non-TSC fibroma-like lesions and oral and periungual fibromas were negative for HMB-45. The authors concluded that fibroma-like PEComa, a newly recognized soft tissue tumor that has a strong association with TSC, mimics soft tissue fibroma but shows reactivity with melanocytic markers.

Larque AB, Kradin RL, Chebib I, et al. Fibroma-like PEComa: a tuberous sclerosis complex-related lesion. *Am J Surg Pathol.* 2018;42(4):500–505.

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Use of molecular classification to group grade 3 endometrioid endometrial carcinomas

The authors investigated whether molecular classification can be used to refine prognosis in grade 3 endometrioid endometrial carcinomas. Grade 3 EECs were classified into four subgroups: p53 abnormal, based on mutant-like immunostaining (p53abn); mismatch repair deficient, based on loss of mismatch repair protein expression (MMRd); presence of *POLE* exonuclease domain hotspot mutation (*POLE*); and no specific molecular profile, in which none of these aberrations were present (NSMP). Overall survival and recurrence-free survival rates were compared using the Kaplan-Meier method (log-rank test) and univariable and multivariable Cox proportional hazard models. The study included 381 patients who were a median age of 66 years (range, 33–96 years). Federation Internationale de Gynecologie et d'Obstetrique stages (2009) were IA, 171 (44.9 percent); IB, 120 (31.5 percent); II, 24 (6.3 percent); III, 50 (13.1 percent); and IV, 11 (2.9 percent). The tumors were classified as 49 (12.9 percent) *POLE*, 79 (20.7 percent) p53abn, 115 (30.2 percent) NSMP, and 138 (36.2 percent) MMRd. The median follow-up of patients was 6.1 years (range, 0.2–17 years). Compared to patients with NSMP, those with *POLE*-mutant grade 3 EEC had a significantly better prognosis (overall survival: hazard ratio [HR], 0.36 [95 percent confidence interval, 0.18–0.70]; $P = .003$; recurrence-free survival: HR, 0.17 [0.05–0.54]; $P = .003$), while those with p53abn tumors had a significantly worse recurrence-free survival rate (HR, 1.73 [1.09–2.74]; $P = .021$), and those with MMRd tumors showed a trend toward better recurrence-free survival. Estimated five-year overall survival rates were *POLE*, 89

percent; MMRd, 75 percent; NSMP, 69 percent; and p53abn, 55 percent (log rank, $P = .001$). Five-year recurrence-free survival rates were *POLE*, 96 percent; MMRd, 77 percent; NSMP, 64 percent; and p53abn, 47 percent ($P = .000001$), respectively. In a multivariable Cox model that included age and Federation Internationale de Gynecologie et d'Obstetrique stage, *POLE* and MMRd status remained independent prognostic factors for better recurrence-free survival, and p53 status was an independent prognostic factor for worse recurrence-free survival. Molecular classification of grade 3 EECs reveals that these tumors are a mixture of molecular subtypes of endometrial carcinoma rather than a homogeneous group. The addition of molecular markers allows identification of prognostic subgroups, with potential therapeutic implications.

Bosse T, Nout RA, McAlpine JN, et al. Molecular classification of grade 3 endometrioid endometrial cancers identifies distinct prognostic subgroups. *Am J Surg Pathol*. 2018;42(5):561–568.

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