GIPS Journal Watch November & December 2017

Occurrence of IgG4 in Esophageal Lichen Planus.
Podboy AJ, Alexander JA, Smyrk TC, Halland M, Ravi K, Geno DM, Murray JA, Katzka DA.
Clin Gastroenterol Hepatol. 2017 Dec;15(12):1975-1977.
https://www.ncbi.nlm.nih.gov/pubmed/28606847

In this brief article, the authors sought to examine the presence of tissue IgG4 in cases of esophageal lichen planus. The authors note that recent work has documented the presence of IgG4 in the epithelium of eosinophilic esophagitis cases but has never been examined in esophageal lichen planus, another disease which leads to stricture formation. From their institution archives the authors were able to identify 29 patients with esophageal lichen planus which had sufficient material for review. The median patient age was 63 years and patients were predominately female (75%) and Caucasian (100%). A majority of patients, 76% (22/29), demonstrated evidence of extra-esophageal lichen planus with involvement of the genitals, mouth, or skin. Seven patients had disease seemingly limited to the esophagus. Immunohistochemistry for IgG4 was performed and quantified as the number of IgG4 positive plasma cells in a high-power field (hpf) (400x). The distribution of IgG4 staining was also noted. The authors describe the presence of IgG4 staining in 41% (12/29) of cases with most staining occurring within cells of the lamina propria. Acellular IgG4 staining within the squamous epithelium was also noted. The number of positive IgG4 cells counted varied widely (0-100/hpf) with the median number of positive cells being significantly higher in the cases categorized as being severe lichen planus. The authors conclude that IgG4 can be demonstrated in a subset of esophageal lichen planus cases and tends to be more pronounced in severe cases. The potential application of IgG4-related disease therapies, such as rituximab or systemic steroids, was discussed for such cases of lichen planus.

Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia.
Singhi AD1, Arnold CA2, Lam-Himlin DM3, Nikiforova MN1, Voltaggio L4, Canto MI4, McGrath KM1, Montgomery EA4.
Mod Pathol. 2017 Nov;30(11):1613-1621.
https://www.ncbi.nlm.nih.gov/pubmed/28731047

This study set out to characterize esophageal epidermoid metaplasia, a recently described condition usually involving the proximal or mid esophagus, in a study set using next generation sequencing. Esophageal epidermoid metaplasia is described grossly as a patch or plaque of white-tan mucosa having sharp demarcation and microscopically as having a thickened basal layer, midzone acanthosis, a prominent granular cell layer, and superficial hyperorthokeratosis. The lesion is associated with similar risk factors as with squamous cell carcinoma and previous studies show the condition is associated with concurrent squamous dysplasia and carcinoma. In this study the authors performed targeted next generation sequencing of epidermoid metaplasia and uninvolved mucosa in a set of cases from a total of 18 patients. In a subset of the patient's samples synchronous and metachronous high grade dysplasia and carcinoma were also evaluated and the authors

identified shared genetic alterations suggesting a clonal relationship. No genetic alterations were found in the uninvolved mucosa. The authors conclude that esophageal epidermoid metaplasia is a precursor lesion for in situ and invasive esophageal neoplasia.

Submucosal Invasive Depth Predicts Lymph Node Metastasis and Poor Prognosis in Submucosal Invasive Esophageal Squamous Cell Carcinoma.
Kadota T, Yano T, Fujita T, Daiko H, Fujii S.
Am J Clin Pathol. 2017. Nov 2;148(5):416-426.
https://www.ncbi.nlm.nih.gov/pubmed/29069275

The purpose of this study was to identify histopathologic features that might help predict lymph node metastasis in submucosal invasive squamous cell carcinoma. The retrospective study included 108 patients who did not have neoadjuvant therapy and underwent esophagectomy and lymph node dissection at a single institution. In multivariate analysis of the cases, tumor size of 35 mm or more, submucosal invasive depth (SID) and lymphatic invasion were all significantly correlated with lymph node metastasis. Tumor size greater than 35 mm and submucosal invasive depth greater than 2 mm, defined as the vertical distance from the muscularis mucosa (or a line formed by connecting the nearest smooth muscle fibers) to the deepest portion of invasive tumor, were found to also be associated with poorer recurrence-free survival.

A new model system identifies epidermal growth factor receptor-human epidermal growth factor receptor 2 (HER2) and HER2-human epidermal growth factor receptor 3 heterodimers as potent inducers of oesophageal epithelial cell invasion.
Fichter CD, Przypadlo CM, Buck A, Herbener N, Riedel B, Schäfer L, Nakagawa H, Walch A, Reinheckel T, Werner M, Lassmann S.
J Pathol. 2017 Dec;243(4):481-495.
https://www.ncbi.nlm.nih.gov/pubmed/28940194

This study sought to explore the role of ErbB family of kinases, including EGFR, HER2, and HER3, had on the morphology, cell migration, and tendency for invasion of esophageal squamous cells. The authors note that both squamous cell carcinoma and adenocarcinoma of the esophagus can demonstrate amplification of these receptors with EGFR overexpression being more common in the former and HER2/HER3 overexpression being more frequently encountered in the latter. Despite this basic understanding, studies investigating the effects of specific EGFR, HER2, and HER3 dimers on esophageal squamous cells are lacking. By transducing non-neoplastic esophageal squamous cells with various ErbB dimers and heterodimers, the authors were able to demonstrate that cells containing HER2 dimers showed increased cell migration velocity. An increased propensity for cell invasion was also noted in induced HER2-HER3 heterodimer cells. Using three dimensional organo-typic cultures, control cells grew as superficial sheets while cells transduced with HER2 homodimers demonstrated invasive features with extension of cells into the underlying model matrix. The authors conclude that controlled activation of ErbB dimers and heterodimers leads to increased migration and invasion in esophageal squamous cells and these kinases may play an important role in the carcinogenesis of esophageal squamous cell carcinoma.

Prevalence and significance of HMGA2 expression in oesophageal adenocarcinoma.
Mito JK, Agoston AT, Dal Cin P, Srivastava A.
Histopathology. 2017 Dec;71(6):909-917.
https://www.ncbi.nlm.nih.gov/pubmed/28710822

This study focuses on high mobility group AT-hook 2 (HMGA2) expression in esophageal adenocarcinoma (EAC). HMGA2 immunohistochemistry was performed in 91 primary EAC resections without neoadjuvant treatment, with FISH in a subset of tumors to identify alterations at the HMGA2 locus. HMGA2 expression was present in 25 of 91 (27.4%) tumors. HMGA2-expressing cells were present in solid, poorly differentiated areas at the invasive tumor front, or as single infiltrating cells. FISH showed that three to four copies of HMGA2 are frequently present in EAC regardless of HMGA2 protein expression and that high level HMGA2 amplification is rare. HMGA2 expression was associated with numerous adverse clinicopathological parameters, including higher T- and N-stage, the presence of lymphovascular invasion and with a worse recurrence-free and overall survival.

Gastrointestinal stromal tumours of the oesophagus: a clinicopathological and molecular analysis of 27 cases.
Kang G, Kang Y, Kim KH, Ha SY, Kim JY, Shim YM, Heinrich MC, Kim KM, Corless CL.
Histopathology. 2017 Nov;71(5):805-812.
https://www.ncbi.nlm.nih.gov/pubmed/28644569

Esophageal GISTs are rare; the authors summarize the clinical, pathological and molecular characteristics of 27 primary esophageal GISTs, the largest such series to be published.
DNA was extracted and exons 9, 11, 13 and 17 of KIT, exons 12, 14 and 18 of PDGFRA and exon 15 of BRAF were amplified and sequenced. Patients included 14 men and 13 women ages 22 to 80 years (mean: 56 years). All 27 cases were immunohistochemically positive for KIT, and 92 and 47% co-expressed CD34 or smooth muscle actin, respectively. Fifteen (71% of analyzed cases) contained KIT exon 11 mutations and one case each had a mutation in KIT exon 13 (K642E) or BRAF exon 15 (V600E). Long-term follow-up data (median, 96.5 months) for 20 cases showed that two patients had metastases at presentation and seven had developed local recurrence and/or metastasis after surgery. Features associated with recurrence and metastasis are: large tumor size (≥ 10 cm), high mitotic rate (> 5/5 square mm), presence of a deletion mutation in KIT exon 11 involving codons 557-558, and a positive microscopic margin. The KIT mutations identified in esophageal GISTs were found to be similar to those observed in gastric GISTs. The authors propose that surgical resection with clear margins is recommended, and that genotyping can aid in diagnosis and management of esophageal GIST.

Two staging systems for gastrointestinal stromal tumors in the stomach: which is better?
Park CH, Kim GH, Lee BE, Song GA, Park DY, Choi KU, Kim DH, Jeon TY.
BMC Gastroenterol. 2017 Dec 6;17(1):141.
https://www.ncbi.nlm.nih.gov/pubmed/29207963

This study aims to compare the clinical efficacy of 2 staging systems, the National Institutes of Health (NIH) consensus criteria (very low, low, intermediate, and high risk group) and the 7th Union for International Cancer

Control/American Joint Committee on Cancer (UICC/AJCC) tumor-node-metastasis (TNM) staging system (stage IA, IB, II, IIIA, and IIIB), for risk stratification of patients with gastric gastrointestinal stromal tumor (GIST). A retrospective study of 145 patients with a median follow up of 44 months (6-144 months) from a single institution (Pusan National University Hospital, Busan, Korea) who underwent surgical resection for gastric GIST between February 2001 and June 2012 was performed. Recurrence and 5-year RFS were analyzed. Tumor size, mitotic count, and epithelioid and mixed pathological types were significantly associated with recurrence. Comparing the 2 risk stratification models based on the 2 staging systems using model fit statistics, the 7th UICC/AJCC TNM staging system appears to be a better model to predict patient prognosis.

Surgical Pathology of Gastrointestinal Stromal Tumors: Practical Implications of Morphologic and Molecular Heterogeneity for Precision Medicine
Gregory W. Charville, MD, PhD and Teri A. Longacre, MD
Adv Anat Pathol. 2017 Nov;24(6):336-353.
https://www.ncbi.nlm.nih.gov/pubmed/28820749

This review article covers a range of topics on the surgical pathology of GIST. The article is geared towards the general surgical pathologist with practical recommendations on how to approach and sign out GISTs. The authors list the pathologist's roles and provide guidance for each step of the process: establish a diagnosis, evaluate margins, assess prognostic features, order/perform molecular studies, consider syndromic etiologies, and confirm recurrence. More in depth discussion is available on topics such as variations in morphology (with numerous high quality images), differential diagnosis, use of IHC (CD34, CKIT/CD117, DOG1, etc.), discussion of the cell of origin, and molecular aspects such as mutations in KIT/CD117, PDGFRα, NF1, succinate dehydrogenase complex, and BRAF. Also discussed are the clinical management, prognostic features, and the morphology of post-treatment GIST.

DIMT1 overexpression correlates with progression and prognosis in gastric carcinoma.
Liu G, Peng X, Cai Y, Cheng A, Zha L, Wang Z.
Hum Pathol. 2017 Dec;70:35-42.
https://www.ncbi.nlm.nih.gov/pubmed/28601661

This immunohistochemical and Western blot study looked at the expression of dimethyladenosine transferase 1 homolog (DIMT1) in human gastric carcinoma and compared expression to both normal gastric tissue and tissue adjacent to tumor. The authors found that DIMT1 was expressed more commonly in gastric cancer than noncancerous tissue. High expression of DIMT1 correlated with poor differentiation, invasion, lymph node metastasis, distant metastasis, and advanced TNM stage. The authors suggest that DIMT1 can be used to predict gastric tumor progression and prognosis.

Gastric Carcinomas With Lymphoid Stroma: Categorization and Comparison With Solid-Type Colonic Carcinomas.

Gonzalez RS, Cates JMM, Revetta F, McMahon LA, Washington K.
Am J Clin Pathol. 2017 Nov 20;148(6):477-484.
https://www.ncbi.nlm.nih.gov/pubmed/29126141

The purpose of this study was to determine if histologic features of gastric carcinomas with a solid pattern can be used to distinguish microsatellite instable (MSI) "medullary carcinomas" from EBV related "lymphoepithelioma-like carcinomas" or those with neither. The study set included 17 solid gastric carcinomas (8 EBV-associated tumors, 5 MSI tumors, and 4 non-EBV non-MSI tumors). A set of colorectal solid-type carcinomas were also included for comparison. There was found to be morphologic overlap, but some statistically significant differences were identified: EBV-associated tumors were found to more often have intratumoral germinal centers, more eosinophils, and lacked necrosis compared to MSI and "neither" tumors; however, the authors noted that ancillary testing (EBV-EBER ISH and immunohistochemistry for DNA mismatch repair proteins) was more reliable in identifying EBV and MSI associated tumors.

Norovirus Loads in Stool Specimens of Cancer Patients with Norovirus Gastroenteritis

He T, McMillen TA, Qiu Y, Chen LH , Lu H, Pang X, Kamboj M, Tang Y
J Mol Diagn. 2017 Nov;19(6):836-842.
https://www.ncbi.nlm.nih.gov/pubmed/28807813

These authors developed a rapid real time quantitative PCR, lab developed, assay to determine genogroup-specific Norovirus (NoV) loads in stools. Although NoV is usually of short duration and self limited in immunocompetent patients, those with compromised immune systems can suffer complications from NoV related gastroenteritis. This study also looked at the association between NoV stool loads and the severity of acute illness at initial diagnosis. Utilizing the Luminex xTAG Gastrointestinal Pathogen Panel 6918 diarrhea stool specimens from 4345 patients with malignancies were tested. Ultimately 25 patients tested positive for genogroup I (GI) and 127 patients tested positive for genogroup II (GII). To grade severity modified Vesikari scores were implemented (mild, moderate and severe): 1) Diarrhea duration, 2) Maximal diarrheal stools per 24-hour period, 3) Vomiting duration, 4) Maximal vomiting episodes per 24-hour period, 5) Maximal recorded temperature >38^{o}C, 6) Hospital visits within 90 days, and 7) Rehydration times during hospitalization. Higher stool loads correlated significantly with more severe clinical symptoms, including clinically significant dehydration and ICU admissions. In conclusion, the authors state that immunocompromised patients, such as those with malignancies, are highly vulnerable to NoV infections, and suggest NoV monitoring in high-risk populations.

ROC-king onwards: intraepithelial lymphocyte counts, distribution & role in coeliac disease mucosal interpretation.

Rostami K, Marsh MN, Johnson MW, Mohaghegh H, Heal C, Holmes G, Ensari A, Aldulaimi D, Bancel B, Bassotti G, Bateman A, Becheanu G, Bozzola A, Carroccio A, Catassi C, Ciacci C, Ciobanu A, Danciu M, Derakhshan MH, Elli

L, Ferrero S, Fiorentino M, Fiorino M, Ganji A, Ghaffarzadehgan K, Going JJ, Ishaq S, Mandolesi A, Mathews S, Maxim R, Mulder CJ, Neefjes-Borst A, Robert M, Russo I, Rostami-Nejad M, Sidoni A, Sotoudeh M, Villanacci V, Volta U, Zali MR, Srivastava A.
Gut. 2017 Dec;66(12):2080-2086.
https://www.ncbi.nlm.nih.gov/pubmed/28893865

This multi-center study addresses the range of intraepithelial lymphocytes (IEL) in a diagnosis of celiac disease (CD), as there is no prior definition of a normal IEL range. More than 400 duodenal mucosal biopsies were reviewed (198 patients with Marsh III histology and 203 controls) and receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off between normal and CD (Marsh III lesion). Reviewers counted IEL per 100 enterocytes in well-oriented biopsies, with mean patient age of 45.5 years in CD patients and controls 38.3 years. Mean IEL count was 54±18/100 enterocytes in CD and 13±8 in normal controls (p=0.0001). ROC analysis indicated an optimal cut-off point of 25 IEL/100 enterocytes, with 99% sensitivity, 92% specificity and 99.5% area under the curve. This is proposed as the cutoff for optimal discrimination between normal control and CD biopsies. No differences in IEL counts were found between Marsh III a, b and c lesions.

The Role of an IgA/IgG-Deamidated Gliadin Peptide Point-of-Care Test in Predicting Persistent Villous Atrophy in Patients With Celiac Disease on a Gluten-Free Diet.
Lau MS, Mooney PD, White WL, Rees MA, Wong SH, Kurien M, Trott N, Leffler DA, Hadjivassiliou M, Sanders DS.
Am J Gastroenterol. 2017 Dec;112(12):1859-1867.
https://www.ncbi.nlm.nih.gov/pubmed/29016564

This study examined the potential for a point of care test (POCT) based on IgA/IgG-deamidated gliadin peptide as a surrogate maker for persistent villous atrophy in celiac disease patients. The authors note that persistent villous atrophy is associated with an increased risk of celiac disease complications such as small bowel lymphoproliferative disorders and that currently there is no reliable surrogate marker for evaluating these villous changes beyond biopsy. A total of 217 celiac disease patients were included in this study, all of which were maintained on a gluten free diet. All patients had IgA-endomysial (EMA) antibodies, IgA-tissue transglutaminase (TTG) antibodies, and POCT performed as well as duodenal biopsies. Histologic villous atrophy was evaluated using the modified Marsh criteria. Patients having Marsh scores of 0-2 were considered to be in histologic remission. Eighty-five (39.2%) patients had persistent villous atrophy histologically and the sensitivities of the aforementioned laboratory testing modalities in detecting these patients was 67.1% for POCT, 44.7% for TTG, and 37.7% for EMA. Specificities for those various methodologies were 59.1%, 86.4%, and 89.4% respectively. The authors concluded that while the POCT performed superiorly to other surrogate markers, the sensitivity of this testing is not sufficient for it to be used in isolation.

The Apoptotic Crypt Abscess: An Underappreciated Histologic Finding in Gastrointestinal Pathology.
Talmon G, Manasek T, Miller R, Muirhead D, Lazenby A.
Am J Clin Pathol. 2017 Nov 20;148(6):538-544.
https://www.ncbi.nlm.nih.gov/pubmed/29140405

This study looks at the differences between “apoptotic crypt abscesses” (ACA), “neutrophilic crypt abscesses” (NCA), and “mixed crypt abscesses” (MCA) and examines whether the differences may be diagnostically useful in determining the underlying disease state. It was noted that NCAs tend to occur in necroinflammatory injury and in a background of active inflammation while ACAs tend to be in pathologic states that involve cell mediated immune response. The authors suggest that their findings support a potential diagnostic use to suggest the etiology of colitis: when only NCAs are identified IBD is likely; when only ACAs are identified another diagnosis such as drug injury or viral infection (in the non-transplant setting) is more likely.

Histologic Grade 1 Is Associated With Increased Nonrelapsed Mortality in Lower Gastrointestinal Graft Versus Host Disease.

Im JS, Abraham SC, Saliba RM, Rondon G, Ross WA, Rashid A, Shpall EJ, Popat U, Qazilbash MH, Hosing C, Oran B, Shah N, Tewari P, Nieto Y, Kebriaei P, Champlin RE, Alousi AM.

Am J Surg Pathol. 2017 Nov;41(11):1483- 1490.

https://www.ncbi.nlm.nih.gov/pubmed/28834808

The authors of this study aimed to study the prognostic significance of histologic grade 1 GI GVHD in 309 consecutive patients who underwent an initial endoscopic biopsy for suspected GI GVHD within 6 months from transplantation. Overall, histologic grade 1 GVHD was the most common finding in these patients and occurred in 101 of 309 cases (33%). Correlating with the clinical stage, histologic grade 1 was seen in patients with all clinical stages: 43 of 112 isolated upper GI GVDH (38%), 10 of 33 stage 0 (30%), 27 of 77 stage 1 (35%), 9 of 35 stage 2 (26%), 3 of 17 stage 3 (18%), and 9 of 35 (26%) patients with stage 4 lower GI GVHD manifestations. In patients with isolated upper GI GVHD symptoms, the presence of histologic grade 1 did not predict higher nonrelapse mortality (NRM) when compared with negative biopsy. In patients with lower GI GVHD symptoms, histologic grade 1 was associated with increased NRM (hazard ratio=2.6, p=0.02) when compared with negative biopsy. Multivariate analysis confirmed that histologic grade 1 is an independent predictor of NRM among patients with clinical stages 0 to 2 (HR= 2.7; P= 0.044). In patients with clinically advanced lower GI GVHD (stage 3 and 4), there was no statistical difference in NRM between patients with histologic grade 1 and higher histologic grade 3 or 4. Based on these findings authors concluded that histologic grade 1 is associated with higher NRM in patients with lower GI GVHD with clinical stages 0 to 2 suggesting that it is an important prognostic factor independent of the clinical stage. Additionally, histologic grade 1 is not synonymous with mild GVHD as it does not lessen the adverse impact of higher clinical stage 3 or 4 in patients with lower GI GVHD.

Targeted Gene Panel Sequencing for Early-onset Inflammatory Bowel Disease and Chronic Diarrhea.

Petersen BS1, August D, Abt R, Alddafari M, Atarod L, Baris S, Bhavsar H, Brinkert F, Buchta M, Bulashevska A, Chee R, Cordeiro AI, Dara N, Dückers G, Elmarsafy A, Frede N, Galal N, Gerner P, Glocker EO, Goldacker S, Hammermann J, Hasselblatt P, Havlicekova Z, Hübscher K, Jesenak M, Karaca NE, Karakoc-Aydiner E, Kharaghani MM, Kilic SS, Kiykim A, Klein C, Klemann C, Kobbe R, Kotlarz D, Laass MW, Leahy TR, Mesdaghi M, Mitton S, Neves JF, Öztürk B, Pereira LF, Rohr J, Restrepo JLR, Ruzaike G, Saleh N, Seneviratne S, Senol E, Speckmann C, Tegtmeyer D, Thankam P, van der Werff Ten Bosch J, von Bernuth H, Zeissig S, Zeissig Y, Franke A, Grimbacher B.

Inflamm Bowel Dis. 2017 Dec;23(12):2109-2120.
https://www.ncbi.nlm.nih.gov/pubmed/28930861

This multinational study included 71 patients diagnosed before age 10 with early-onset Crohn's disease (n=24), ulcerative colitis (n=19), indeterminate colitis (n=19), suspected early onset inflammatory bowel disease (n=6), and early-onset chronic diarrhea (n=3), all with previously unknown genetic background. Targeted gene panel was performed in these patients, which included 23 genes known to cause disease with intestinal inflammation or chronic diarrhea, plus an additional 5 genes shown in genome-wide association studies to be strongly associated with IBD. 25 patients also underwent whole-exome sequencing. At a quarter of the cost of whole-exome sequencing, targeted gene panel testing is also effective and yields high quality data. Defects in genes in the IL10 signaling pathway accounted for most of the abnormalities in the patients in this study. The authors also identified dyskeratosis congenita as a possible underlying cause of early onset IBD, as well as several X-linked conditions.

Histologic Correlates of Clinical and Endoscopic Severity in Children Newly Diagnosed With Ulcerative Colitis.
Boyle B, Collins MH, Wang Z, Mack D, Griffiths A, Sauer C, Markowitz J, LeLeiko N, Keljo D, Rosh J, Baker SS, Pfefferkorn M, Heyman M, Patel A, Baldassano R, Noe J, Rufo P, Kugathasan S, Walters T, Denson L, Hyams J; PROTECT Study Group.
Am J Surg Pathol. 2017 Nov;41(11):1491-1498.
https://www.ncbi.nlm.nih.gov/pubmed/28863076

The goal of this study was to characterize the rectal histologic findings and to evaluate the relationship of histologic findings to clinical indices of disease severity in a prospective cohort of children newly diagnosed with ulcerative colitis (UC) enrolled in the PROTECT (Predicting Response to Standardized Pediatric Colitis Therapy) Study. Baseline rectal biopsies from 369 patients (mean age, 12.9± 3.1 y, M:F-1:1) were reviewed. The biopsies were evaluated for acute and chronic inflammation, eosinophilic inflammation, and chronic architectural and nonarchitectural changes and correlated with clinical indices of disease severity such as Mayo endoscopy subscore (MSS) and Pediatric Ulcerative Colitis Activity Index (PUCAI). Crypt atrophy/distortion was the most common finding seen in 98% of specimens while ulceration/erosion was uncommon (4%). Cryptitis was found in 65%, crypt abscesses in 25% and eosinophilic inflammation (>32/hpf without intraepithelial eosinophils) in 58%. Higher grades of acute and chronic inflammation were significantly associated with chronic changes such as basal plasmacytosis (P<0.0001), basal lymphoid aggregates (P<0.0001), and surface villiform changes (P<0.0001). The distribution of MSS differed across grades of acute and chronic inflammation (P<0.03). However, this relationship was not linear as 51% of biopsies with severe histologic inflammation (grade IV/ V) had endoscopic subscore 2 of 3. Significant association of severe PUCAI scores was noted with absence or mild eosinophilic inflammation (P<0.03) and presence of surface villiform changes (P<0.005). Based on these findings the authors have concluded that acute and chronic inflammation, eosinophilic inflammation, and chronic architectural/nonarchitectural changes are common in the rectal biopsies of newly diagnosed pediatric UC patients. Association of severe clinical disease and histologic findings of surface villiform changes and low eosinophilic count (<32/hpf) requires further study.

Peripheral Eosinophilia in Patients With Inflammatory Bowel Disease Defines an Aggressive Disease Phenotype.

Click B, Anderson AM, Koutroubakis IE, Rivers CR, Babichenko D, Machicado JD, Hartman DJ, Hashash JG, Dunn MA, Schwartz M, Swoger J, Barrie Iii A, Wenzel SE, Regueiro M, Binion DG.
Am J Gastroenterol. 2017 Dec;112(12):1849-1858.
https://www.ncbi.nlm.nih.gov/pubmed/29112200

This registry analysis of a large institutional inflammatory bowel disease (IBD) cohort sought to examine the relationship of peripheral blood eosinophilia (PBE) to disease activity and clinical outcomes in IBD patients. The authors note that previous studies have established that PBE is largely associated with ulcerative colitis and active disease. Given the lack of literature regarding the long-term impact of PBE on disease course in IBD patients, the authors examined their experience in a large IBD cohort which was followed over a course of 6 years. Within the institutional registry, 19.2% of IBD patients developed PBE with 26.7% of those individuals having eosinophilia at their initial IBD presentation and 73.2% developing PBE subsequently. PBE was significantly associated with a number of factors including younger age and concurrent diseases such as asthma, rheumatologic disease, adrenal insufficiency, and primary sclerosing cholangitis. PBE was also significantly associated with ulcerative colitis, extensive colitis, and short disease duration. Patients with PBE were more likely to have active disease and increased healthcare utilization, including IBD surgery, and aggressive medical therapies, such as prednisone and anti-TNF therapy. Even on multivariate analysis, PBE remained significantly associated with hospitalization and surgery in both Crohn disease and ulcerative colitis patients. The authors conclude that PBE may identify a distinct IBD subgroup with increased risk for worse clinical outcomes.

What Is the Risk of Anastomotic Leak After Repeat Intestinal Resection in Patients With Crohn's Disease?

Johnston WF, Stafford C, Francone TD, Read TE, Marcello PW, Roberts PL, Ricciardi R.
Dis Colon Rectum. 2017 Dec;60(12):1299-1306.
https://www.ncbi.nlm.nih.gov/pubmed/29112566

This retrospective review evaluated the increased risk of anastomotic leaks within in 30 days in patients with Crohn's disease undergoing repeat resections. Given that approximately one third of Crohn's patients who undergo repeat resections require multiple repeat resections, the authors hypothesized that there would be a higher risk of anastomotic leak compared to those patients undergoing initial resection. An internal database was queried from 2007-2016 to include any patient with a diagnosis of Crohn's disease who underwent resection. Exclusion criteria included those with anastomosis with fecal diversion and patients only undergoing loop ileostomy closure. Variables related to anastomotic leak were recorded such as preoperative serum albumin, intra-abdominal abscess or fistula at the time of surgery, ASA score, preoperative use of immune-altering medications, type of resection, duration of surgery, blood loss, type of anastomosis (stapled vs handsewn) and surgeon. The authors' definition of clinical anastomotic leak was "intestinal luminal contents outside of the bowel coming from the surgical junction". A clinical leak combined radiographic evidence with clinical signs of inflammation. Of the 523 patients identified, 206 met the final study criteria, including 123 with previous resection and 83 without previous resection. Overall, 20 of 206 patients (10%) presented with anastomotic leaks; 14 leaks (17%) occurring in the previous resection group and 6 (5%) in the no previous

resection group. The OR of anastomotic leak between the two groups was 3.5 (95% CI, 1.3–9.4). There also appeared to be a direct correlation between the number of repeat resections and the rate of clinically apparent anastomotic leaks. However, the etiology for the increased risk is currently unclear. In conclusion, the authors recommend that previous resection be included as a risk factor in the algorithm for management of patients with Crohn's, due to the increased risk for anastomotic leak.

Impact of Histological and Endoscopic Remissions on Clinical Recurrence and Recurrence-free Time in Ulcerative Colitis.

Ponte A, Pinho R, Fernandes S, Rodrigues A, Alberto L, Silva JC, Silva J, Rodrigues J, Sousa M, Silva AP, Proença L, Freitas T, Leite S, Carvalho J.

Inflamm Bowel Dis. 2017 Dec;23(12):2238-2244

https://www.ncbi.nlm.nih.gov/pubmed/28991857

Current therapeutic targets in ulcerative colitis (UC) are clinical and endoscopic remission, but not histologic healing. Histologic healing is, however, associated with improved clinical outcomes in UC. This retrospective study included 60 adult UC patients in clinical and endoscopic remission (measured by the partial Mayo score, and the Mayo endoscopic subscore, respectively) and not on corticosteroids, who underwent biopsy to determine the impact of endoscopic recurrence and histologic activity (measured by the Nancy score) on clinical recurrence of UC (defined as partial Mayo score ≥2, therapy escalation, hospitalization, or colectomy) and on recurrence-free survival time. Of the 19 patients (31.7%) with clinical recurrence during the study period, 12 (52.2%) had histologic activity (Nancy score 2-3) which was significantly associated with recurrence (P = 0.007). Endoscopic remission score of 1 was also significantly associated with recurrence (P = 0.02); however, only histologic activity (P = 0.03) was an independent predictor of recurrence. Similar findings were identified for recurrence-free survival time. Therefore, due to histologic activity being an independent predictor of clinical recurrence and recurrence-free survival time in UC, the authors propose that histology has a role in improving clinical outcome predictions in UC.

A Pilot Study of the Prevalence of Anal Human Papillomavirus and Dysplasia in a Cohort of Patients With IBD.

Cranston RD, Regueiro M, Hashash J, Baker JR, Richardson-Harman N, Janocko L, McGowan I.

Dis Colon Rectum. 2017 Dec;60(12):1307-1313

https://www.ncbi.nlm.nih.gov/pubmed/29112567

Human papilloma virus (HPV) infection is controlled by cell-mediated immunity. Therefore, patients with inflammatory bowel disease who undergo immunosuppressive therapy may be at an increased risk of HPV-associated disease, including warts, dysplasia, and ultimately anogenital cancer. This prospective study assessed anal/vaginal HPV and anal dysplasia prevalence in patients with IBD. One of the limitations of this study is the lack of a control group. Inclusion criteria included men and non-pregnant sexually active women older than 18 years old with biopsy proven IBD. Low risk and high risk HPV strains were detected by an Eva green intercalating dye assay. Anal cytology was graded according to 2001 Bethesda guidelines for cervical cytology. Anal biopsies

were graded as normal, condyloma, anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. Ultimately 46 patients were enrolled in the study (25 men and 21 women), 31 of which had Crohn's disease (CD), 14 ulcerative colitis (UC) and one diagnosis of indeterminate colitis. 23 of CD patients and 12 of UC patients were taking immunosuppressive medication. 28 patients undergoing anal biopsy showed dysplasia, 4 of which were high grade. 41 participants tested positive for HPV, many with multiple low and high risk strains. High risk strain HPV 16 was the most common strain identified. Similar results were discovered in 19 out of 21 female vaginal swabs. Carcinoma was not seen in any of the participants. Overall, the authors conclude that the rate of HPV infection in this patient population is high and comparable to those of an HIV positive population. However, the authors urge the findings to be taken with caution for several reasons: 1) lack of control group, 2) use of a research HPV assay ,and 3) lack of information on sexual practices. They emphasize the need to perform additional studies to assess HPV and anal dysplasia prevalence in this population.

Inflammatory Bowel Disease and Small Bowel Cancer Risk, Clinical Characteristics, and Histopathology: A Population-Based Study.

Bojesen RD, Riis LB, Høgdall E, Nielsen OH, Jess T.
Clin Gastroenterol Hepatol. 2017 Dec;15(12):1900-1907.e2.
https://www.ncbi.nlm.nih.gov/pubmed/28694132

The goal of this study was to report on a nationwide cohort of inflammatory bowel disease (IBD) associated small bowel carcinoma (SBC) and provide the clinical, histological, and molecular features of such cases. The authors note that while a considerable amount of work has examined the colorectal carcinomas that arise in IBD patients, due to their rarity, far less is known about SBC arising in this same patient population. Using a nationwide registry consisting of 6,985,185 patients over the age of 16, diagnosis codes relevant to Crohn disease (CD) and ulcerative colitis were applied followed by further linking with national cancer and pathology registries. This resulted in an initial population of 277 patients. Further scrutiny of the associated medical records and pathologic material from these cases resulted in 40 cases of confirmed IBD-SBC. Adenocarcinomas and malignant neuroendocrine tumors were included while lymphomas and neuroendocrine tumors indefinite for malignancy were excluded. Examination of the resulting data demonstrated that CD patients had a 14-fold increased risk for small bowel adenocarcinomas and a 9-fold increased risk of neuroendocrine tumors. While rare cases of SBC were identified in ulcerative colitis patients, the prevalence was not any higher than the non-IBD population. Among the CD patients, the median age of CD and cancer diagnoses was 45 and 53 years respectively. A majority of the CD patients with SBC had IBD involvement of the upper gastrointestinal tract (91%) with a majority also demonstrating internal fistulas and abscesses. Complete histological examination of specimens from 14 CD patients demonstrated that a majority of adenocarcinomas arose in a background of inflammation and associated dysplasia. While the authors note that the rate of microsatellite instability in colorectal carcinomas in IBD patients is relatively high, only 2/14 (14%) of adenocarcinomas in the current series demonstrated those findings. The authors conclude that CD patients are at an increased risk for SBC of both adenomatous and neuroendocrine types, with the former typically arising in the background of IBD related changes. They also note that the molecular features of SB adenocarcinomas appear to differ from colorectal adenocarcinomas arising in CD patients.

Grading and staging mucinous neoplasms of the appendix: a case series and review of the literature.
Umetsu SE, Shafizadeh N, Kakar S.
Hum Pathol. 2017 Nov;69:81-89.
https://www.ncbi.nlm.nih.gov/pubmed/28970138

The article encompasses several topics related to appendiceal mucinous neoplasms (AMNs). It briefly summarizes the new staging of AMNs found in the AJCC 8th edition and describes the differences between WHO 2010 and AJCC 8th edition histologic grading (i.e. 2-tier vs 3-tier). The authors then review 33 cases of AMNs with available follow-up data and also perform a comprehensive literature review.

Among all cases confined to the muscularis propria (21 in their series and 43 in the literature), none had peritoneal disease. Among all cases with *epithelium* beyond the muscularis propria, 64% had peritoneal disease at diagnosis or follow-up. The authors feel these data support the use of pTis as outlined in AJCC8 staging of LAMN:

pTis - LAMN confined by muscularis propria. Acellular mucin or mucinous epithelium may I nvade into the muscularis propria
pT1 - Not used for LAMN
pT2 - Not used for LAMN
pT3 - *Acellular mucin or mucinous epithelium* extends into subserosa
pT4a - *Acellular mucin or mucinous epithelium* extends to involve serosa
pT4b - *Acellular mucin or mucinous epithelium* directly invades or adheres to adjacent organs

The authors note that rare instances of peritoneal disease may occur even though the primary tumor is classified as pTis. Since labelling such a tumor "in situ" seems inappropriate, they recommend staging them pTx.

The authors also investigate the use of a two-tiered (WHO 2010) vs three-tiered (AJCC8) histologic grading system, with a focus on disseminated AMNs. Based on literature review, they find significant differences in five-year survival using the three-tiered grading scheme, supporting the AJCC8.

G1: Low grade cytologic atypia without signet rings or infiltrative invasion
G2: High grade cytologic atypia or any infiltrative invasion, but no signet ring cells
G3: High grade cytologic atypia, usually with signet ring component

Many other points are addressed within this article, including overviews of the 7 key studies leading up to the current grading scheme and photomicrograph examples of each grade. For GIPS members looking for a historical perspective and an update, this article will be valuable reading.

The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei.
Carr NJ, Bibeau F, Bradley RF, Dartigues P, Feakins RM, Geisinger KR, Gui X, Isaac S, Milione M, Misdraji J, Pai RK, Rodriguez-Justo M, Sobin LH, van Velthuysen MF, Yantiss RK.
Histopathology. 2017 Dec;71(6):847-858.
https://www.ncbi.nlm.nih.gov/pubmed/28746986
This is a review article of interest.

Sessile serrated adenomas with dysplasia: morphological patterns and correlations with MLH1 immunohistochemistry.
Liu C, Walker NI, Leggett BA, Whitehall VL, Bettington ML, Rosty C.
Mod Pathol. 2017 Dec;30(12):1728-1738.
https://www.ncbi.nlm.nih.gov/pubmed/28752838

This study aims to better characterize the spectrum of dysplasia in sessile serrated adenomas (SSAs). The authors believe that the 2010 WHO classification that includes only two types of dysplasia – that resembling conventional adenomas and serrated dysplasia – does not adequately describe the types of dysplasia in SSAs. Specifically, the authors are of the opinion that a "minimal deviation dysplasia", which is characterized by minimal architectural and cytological changes, is difficult to distinguish histologically but frequently harbors loss of MLH-1 by immunohistochemistry supportive of progression to dysplasia. Overall the authors divide dysplasia in SSAs into minimal deviation, serrated, adenomatous, and not otherwise specified. They suggest that MLH1 immunohistochemistry is helpful to support a diagnosis of dysplasia in cases suggestive of minimal deviation dysplasia (although not in cases of unequivocal architectural or cytological dysplasia).

Smoking is associated with hypermethylation of the APC 1A promoter in colorectal cancer: the ColoCare Study.
Barrow TM, Klett H, Toth R, Böhm J, Gigic B, Habermann N, Scherer D, Schrotz-King P, Skender S, Abbenhardt-Martin C, Zielske L, Schneider M, Ulrich A, Schirmacher P, Herpel E, Brenner H, Busch H, Boerries M, Ulrich CM, Michels KB.
J Pathol. 2017 Nov;243(3):366-375.
https://www.ncbi.nlm.nih.gov/pubmed/28791728

This study investigated how epigenetic factors may be associated with the development of colorectal carcinoma in smokers. The authors note that while smoking tobacco is a known risk factor for the development of colorectal carcinoma, the mechanism by which this association occurs is not well established. Studies in healthy smokers as well as tumor derived tissue from smokers has implicated the role of epigenetic modification of gene expression through DNA methylation in other tumor types such as lung and bladder carcinomas. In this study, which utilized patient data and tissue from a large colorectal carcinoma consortium, epigenomic-wide analysis of DNA methylation was performed on tumors and adjacent normal mucosa from groups of never-smokers, former smokers, and active smokers. While 21 CpG sites were identified where methylation was significantly different between tumors of active smokers and never-smokers, the most notable differences were found in the

APC promoter region 1A. Such promoter methylation was identified in 19% (7/36) of never-smoker tumors and 62% (8/13) of active smokers. Analysis of adjacent normal mucosa did not demonstrate these methylation differences in either groups suggesting these changes were limited to tumor. Furthermore, promoter methylation in *APC* positively correlated with duration of smoking. The authors postulate that smoking may contribute to the development of colorectal carcinoma through hypermethylation of the tumor suppressor *APC*.

Association of Aneuploidy and Flat Dysplasia With Development of High-Grade Dysplasia or Colorectal Cancer in Patients With Inflammatory Bowel Disease.
Tsai JH, Rabinovitch PS, Huang D, Small T, Mattis AN, Kakar S, Choi WT.
Gastroenterology. 2017 Dec;153(6):1492-1495.e4.
https://www.ncbi.nlm.nih.gov/pubmed/28843957

The authors detected aneuploidy by flow cytometry in 15 of 37 (40.5%) samples of paraffin embedded tissue that was histologically diagnosed as flat low grade dysplasia (fLGD) in patients undergoing surveillance for IBD. Among patients with aneuploidy detected, the univariate hazard ratio for subsequent HGD or colorectal carcinoma was 5.3 (mean follow-up time 37 months). By comparison, aneuploidy was detected in 93% (14 of 15 samples) of flat HGD and only 4% (2 of 45 samples) of negative for dysplasia showed aneuploidy. The authors conclude that the detection of aneuploidy in fLGD can identify patients at increased risk for HGD or colorectal cancer. Flow cytometry for aneuploidy may also provide support for histologic diagnosis of dysplasia.

Clinicopathologic and endoscopic features of early-stage colorectal serrated adenocarcinoma.
Hirano D, Oka S, Tanaka S, Sumimoto K, Ninomiya Y, Tamaru Y, Shigita K, Hayashi N, Urabe Y, Kitadai Y, Shimamoto F, Arihiro K, Chayama K.
BMC Gastroenterol. 2017 Dec 12;17(1):158.
https://www.ncbi.nlm.nih.gov/pubmed/29233113

Serrated adenocarcinoma (SAC) is a distinct colorectal adenocarcinoma variant that accounts for approximately 7.5% of all advanced colorectal carcinomas. The clinicopathologic features of early-stage SAC are unclear. This study therefore aimed to determine the clinicopathologic and endoscopic characteristics of early-stage SACs. A total of 40 consecutive early-stage (Tis and T1) SAC cases from a single institution (Hiroshima University Hospital) were reviewed. SACs were classified into epithelial and non-epithelial serration groups. Serrated adenomas were divided into 4 groups: sessile serrated adenomas (SSA), traditional serrated adenoma (TSA), unclassified, and non-serrated adenoma. There were significant differences in tumor size (27.6 vs. 43.1 mm), incidences of T1 carcinoma (71% vs. 13%), and having the same color as normal mucosa (47% vs. 17%), respectively ($p < 0.01$) between SAC with epithelial and non-epithelial serration. In larger SACs (>20 mm), the incidence of T1 carcinoma was significantly greater in SAC with epithelial serration than that in SAC with non-epithelial serration (70% vs 13%) ($p < 0.05$). The average TSA-type tumor size (42.6 mm) was significantly larger than that of the SSA (17.2 mm) and non-serrated component types (18.3 mm). The incidences of submucosal invasion in SSA- (80%), unclassified- (100%), and non-serrated-type (100%) tumors were significantly higher than

that in the TSA type (11%). The authors concluded that epithelial serration in the cancerous area and a non-TSA background indicated aggressive behavior in early-stage SACs.

Prognostic significance of CDX2 immunoexpression in poorly differentiated clusters of colorectal carcinoma
Luca Reggiani Bonetti, Simona Lionti, Enrica Vitarelli, Valeria Barresi
Virchows Arch 2017 Dec 471(6):731–741
https://www.ncbi.nlm.nih.gov/pubmed/28819729

Poorly differentiated clusters (PDCs) were defined as clusters of at least five neoplastic cells, with no glandular formation, at the invasive front or within the tumor stroma of colorectal cancer (CRC). By counting PDC under a ×20 objective lens, CRC can be classified into three grades, which has been shown predictive of metastatic disease and worse prognosis in patients with CRC. In this study, the authors investigated the prognostic significance of CDX2 expression in PDC and corresponding main tumor in 42 CRCs graded as PDC G3 (≥ 10 PDCs) with a follow-up time of at least 5 years. Positivity for CDX2 was scored as 1 (≥20% of cells stain), while negativity was scored as 0. All cases were subdivided in two three groups: 1) score 0 (PDC and main tumor both negative for CDX2), 2) score 1 (PDC or main tumor positive for CDX2), and 3) score 2 (PDC and main tumor both positive for CDX2). Results showed that 12% main tumors were CDX-2 negative, and 69% PDC were CDX-2 negative. Using CDX2-staining score, 4 cases were scored as 0, 26 were scored as 1, and 12 were scored as 2. Loss of CDX2 expression in the main tumor was significantly associated with high WHO grade, recurrence, and death from CRC. Loss of CDX2 expression in PDC was significantly associated with tumor size ≥3 cm, high pTNM stage, and recurrence. Loss of CDX2 expression in both main tumor and PDC was significantly associated with tumor size ≥3 cm, high WHO grade, development of recurrence, and death from CRC. Multivariate analysis demonstrated that CDX2-staining score and LVI were significant and independent prognostic variables for disease-free survival and cancer-specific survival.

Desmoplastic Pattern at the Tumor Front Defines Poor-prognosis Subtypes of Colorectal Cancer.
Ueno H, Kanemitsu Y, Sekine S, Ishiguro M, Ito E, Hashiguchi Y, Kondo F, Shimazaki H, Mochizuki S, Kajiwara Y, Shinto E, Yamamoto J.
Am J Surg Pathol. 2017 Nov;41(11):1506-1512.
https://www.ncbi.nlm.nih.gov/pubmed/28877064

This multi institutional study aimed to investigate the prognostic significance of desmoplastic response (DR) in 821 patients with stage II and III colorectal cancer and a R0 resection. DR was classified based on the presence of keloid like collagen and myxoid stroma at the extramural desmoplastic front. DR was classified as mature when fibrotic stroma did not contain keloid like collagen or myxoid stroma. When the mature stroma is intermingled with keloid like collagen it was classified as intermediate. If the stroma showed myxoid changes it was classified as immature. Of the 821 cases, 325 (39.6%), 282 (34.3%), and 214 (26.1%) cases were classified into mature, intermediate, and immature groups, respectively. The incidence of immature stroma was higher in the rectum than in colon. Tumors with immature stroma showed significantly correlation with conventional high risk pathologic prognostic markers such as higher T and N stages, tumor budding, and lymphatic and venous

invasion. Inversely, the mature stroma was associated with low-risk pathologic markers. Five-year recurrence free survival (RFS) was 85.7%, 77.3%, and 50.4% in the mature, intermediate, and immature groups, respectively ($P < 0.0001$). There was significant higher rate of site specific recurrence in immature group when compared to other groups. Similarly disease-specific survival was most favorable in mature group, followed by intermediate and immature groups. Multivariate analysis demonstrated DR as an independent prognostic factor along with T and N stages. Additionally, on the basis of Harrell's concordance index, the prognostic power of DR categorization (0.67) in stratifying RFS was greater than any other conventional prognostic factors, including TNM (0.64), N (0.62) and T stages (0.59), venous invasion (0.59), and tumor grade (0.54). Based on these findings authors suggested that histologic characterization of DR may be the most significant prognostic factor than other conventional tumor factors.

Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non–Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors
Shona Hendry, MBBS, Roberto Salgado, MD, Thomas Gevaert, MD, et al
Adv Anat Pathol. 2017 Nov;24(6):311-335.
https://www.ncbi.nlm.nih.gov/pubmed/28777143

This article is part 2 of 2, addressing a standardized method to assess tumor-infiltrating lymphocytes in solid tumors. Published by the International Immuno-Oncology Biomarkers Working Group, Part 1 contained the proposal for applying TIL assessment, as extrapolated from guidelines for invasive breast carcinoma. Part 2, linked above, contains the available evidence for prognostic and predictive value of TILs in lung, GI, GU, GYN, H&N, neuro, meso, and melanoma. Of the 25 page document, 2 pages are spent discussing the current knowledge of TILs in colorectal and upper GI cancers, including some brief historical context, association with microsatellite instability and EBV.

Journals Reviewed (November & December 2017)

- **Advances in Anatomic Pathology**
- **American Journal of Clinical Pathology**
- **American Journal of Gastroenterology**
- **American Journal of Pathology**
- **American Journal of Surgical Pathology**
- **Archives of Pathology and Lab Medicine**
- **BMC Gastroenterology**
- **Cancer Cytopathology**
- **Clinical Gastroenterology Hepatology**
- **Diseases of the Colon and Rectum**
- **Gastroenterology**
- **Gastrointestinal Endoscopy**
- **Gut**
- **Histopathology**
- **Human Pathology**
- **Inflammatory Bowel Diseases**
- **Journal of Clinical Pathology**
- **Journal of Gastrointestinal Surgery**
- **Journal of Molecular Diagnostics**
- **Journal of Pathology**
- **Modern Pathology**
- **Virchows Archiv**