

Persistent basal cell hyperplasia is associated with clinical and endoscopic findings in patients with histologically inactive eosinophilic esophagitis

Whelan KA, Godwin BC, Wilkins B, Elci OU, Benitez A, DeMarshall M, Sharma M, Gross J, Klein-Szanto AJ, Liacouras CA, Dellon ES, Spergel JM, Falk GW, Muir AB, Nakagawa H
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Peak intraepithelial eosinophil count ≥ 15 eos/HPF remains the histological criteria for the diagnosis of eosinophilic esophagitis (EOE). However, when monitoring disease activity after the treatment, eosinophil count may not correlate with persistent clinical symptoms and endoscopic findings. In this study, the authors investigated epithelial changes including basal cell hyperplasia (BCH) and spongiosis in patients with EOE, and the association of these epithelial changes with clinical symptoms and endoscopic findings. Among 243 study patients, 196 were confirmed with the diagnosis of EOE, 48 patients were active EOE (≥ 15 eos/HPF), 148 were inactive EOE (< 15 eos/HPF), and 47 formed a non-EOE control group. Dysphagia (50%) and abdominal pain (51%) were the most common symptoms in active EOE and non-EOE patients, respectively. In the inactive EOE group, 19.7% had dysphagia and 19.7% had abdominal pain. Endoscopic findings were reported in 87.2%, 44.1%, and 2.1% of active EOE, inactive EOE, and non-EOE patient groups, respectively. BCH was found in 29.1% of inactive EOE patients, 97.9% of active EOE, and 5.8% of the non-EOE group, respectively. BCH but not spongiosis or peak intraepithelial eosinophils was significantly associated with clinical symptoms and endoscopic findings in the inactive EOE group. This finding was further validated in a second cohort of EOE patients, showing BCH was present in 26% and 84% of therapeutic responders (< 15 eos/HPF) and non-responders, respectively. These findings suggest that BCH is an indicator of disease activity in patients with EOE, and may impact future clinical practice to include BCH in histological evaluation especially in patients < 15 eos/HPF after therapy.

Verruciform xanthoma of the esophagus: two case reports with review of the literature

Noguchi H, Kitazono I, Hamada K, Tanaka T, Tasaki T, Shirahama H, Yamamoto Y, Tanimoto A
Int J Surg Pathol. 2020 May;28(3):302-305.
<https://pubmed.ncbi.nlm.nih.gov/31594440/>

This is a report of two cases of verruciform xanthoma of the esophagus, of disease of which the authors note only 5 prior cases appear in the literature. These lesions have verrucous and papillomatous epithelial hyperplasia associated with numerous foamy histiocytes infiltrating the elongated papillae. It has been suggested that these benign lesions are secondary to prior trauma or localized therapy such as radiation.

Mucosal Schwann cell hamartoma of the gastroesophageal junction: a series of 6 cases and comparison with colorectal counterpart

Li Y, Beizai P, Russell JW, Westbrook L, Nowain A, Wang HL
Ann Diagn Pathol. 2020 Apr 28;47:151531.
<https://pubmed.ncbi.nlm.nih.gov/32460039/>

The authors describe the clinicopathologic features of 6 gastroesophageal junction Schwann cell hamartomas. Patients comprised an admixture of adult males and females (mean 70.2 years, range 57-76). Of note, no endoscopic polyp or nodule was noted in any of their cases, and the sizes of the lesions were small (mean 2.8 mm, range 2-4 mm). Similar to colorectal mucosal Schwann cell hamartomas, there was no association with inherited syndromes.

Independent blinded validation of a tissue systems pathology test to predict progression in patients with Barrett's esophagus

Davison JM, Goldblum J, Grewal US, McGrath K, Fasanella K, Deitrick C, DeWard AD, Bossart EA, Hayward SL, Zhang Y, Critchley-Thorne RJ, Thota PN
Am J Gastroenterol. 2020 Jun;115(6):843-852.
<https://pubmed.ncbi.nlm.nih.gov/32079863/>

The authors sought to independently validate a test that predicts risk of progression to high grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) in Barrett's esophagus (BE) patients with nondysplastic (ND), indefinite for dysplasia (IND), and low grade dysplasia (LGD). This was a single-blinded, case-control study to stratify patients as low, intermediate, or high risk of progression to HGD/EAC within 5 years. Patients with BE who progressed to HGD/EAC after >1 year (n=58) were matched to patients undergoing surveillance without progression (n=210, median surveillance 7 years). The authors found that the risk prediction test stratified patients with BE based on the progression risk. The high-risk group had a 4.7 fold increased risk for HGD/EAC compared with the low risk group (95% CI 2.5-8.8, p<0.0001). The high risk class and male sex provided predictive power that was independent of pathologic diagnosis age, segment length, and hiatal hernia. The prevalence adjusted PPV was 23%, meaning that 23% of patients who scored high risk would progress to HGD/EAC within 5 years. The authors suggest that the risk prediction test offers advantages over traditional pathology methods. They point out that confirmation of LGD is challenging and agreement is poor even among expert GI pathologists. In addition, the patients with ND BE who scored in high risk progressed at a higher rate (26%) than patients with subspecialty pathologist confirmed LGD (21.8%) at 5 years. The authors conclude that this risk prediction test identifies patients with ND BE who are at high risk for progression and may benefit from early endoscopic therapy or increased surveillance.

Histopathologist features predictive of diagnostic concordance at expert level among a large international sample of pathologists diagnosing Barrett's dysplasia using digital pathology

van der Wel MJ, Coleman HG, Bergman JJGHM, Jansen M, Meijer SL; BOLERO working group
Gut. 2020 May;69(5):811-822.

<https://pubmed.ncbi.nlm.nih.gov/31852770/>

This is a study to evaluate the concordance rates among pathologists diagnosing Barrett's esophagus (BE). 51 Pathologists from 20 countries assessed 55 BE biopsies before and after viewing matched p53 labelling and compared to a reference diagnosis of a review panel (n=4) of experienced Barrett's pathologists. They found excellent concordance (>70%) for non-dysplastic and high-grade dysplasia, and intermediate concordance for low-grade dysplasia (42%) and indefinite for dysplasia (23%). Major diagnostic errors were found in 8.8% of diagnoses, which reduced to 8.3% after viewing p53 labelled slides. They found that at least 5 years of professional experience was protective against major diagnostic errors for H&E slide review. Working in a non-teaching hospital was associated with increased odds of major diagnostic error, however, this was neutralized when pathologists viewed p53 labelled slides. Notably, neither case volume nor self-identifying as an expert predicted diagnostic proficiency. Their data suggests that 92.3% of major diagnostic errors are due to overinterpreting non-dysplastic BE.

Surface Ki-67 expression improves reproducibility of dysplasia diagnosis in Barrett's esophagus

Yousaf H, Hayat U, Manivel J, Iwamoto C, Peltola J, Hanson B, Larson W, Dachel S, Gravely A, Mesa H

Am J Clin Pathol. 2020;153(5):695-704.

<https://pubmed.ncbi.nlm.nih.gov/32076708/>

Histologic grading of dysplasia on H&E stain remains the gold standard marker for grading dysplasia in Barrett's esophagus (BE). However, there is significant interobserver variability among pathologists for diagnosing Barrett's dysplasia. The authors aimed to study the markers involved in cell-cycle (cyclin D1, Ki-67, P16), differentiation/cell-cell interaction (β -catenin, SATB2 CD44, OCT4) and senescence (γ H2AX) in reactive versus dysplastic processes by evaluating a micrograph album of 40 H&E cases and corresponding immunostains. These were evaluated independently by 3 pathologists. Expression was scored separately in the surface, isthmus, and base regions of the glands. Significant differences between the 2 groups were found in the surface compartment for Ki-67, γ -H2AX, CD44, and CyD1; in the neck compartment for Ki-67, γ -H2AX, and CD44; and in the base only for γ -H2AX. No significant differences were noted in the expression of P16, β -catenin, SATB2, or OCT4 in any compartments. Among the evaluated markers, surface Ki-67 showed the best discriminative power, with the largest mean difference, the largest mode difference, and the smallest P value. At less than 5% expression, surface Ki-67 showed sensitivity of 100%, specificity of 31%, positive

predictive value (PPV) of 69%, and negative predictive value (NPV) of 100%. At a cut-off level of more than 5%, PPV increased to 91% and NPV declined to 82%; at a cutoff of more than 50%, PPV remained at 91% but NPV declined to 74%. κ correlation between pathologists improved from substantial to almost perfect (0.70-0.95) using ancillary surface Ki-67. The authors conclude that any surface Ki-67 expression in BE epithelium should be considered abnormal and is associated with high odds risk of progression, and the use of ancillary surface Ki-67 improved the κ correlation between pathologists and improved correlation with outcome.

Immunohistochemical analysis of the expression of cancer-associated fibroblast markers in esophageal cancer with and without neoadjuvant therapy

Galván JA, Wiprächtiger J, Slotta-Huspenina J, Feith M, Ott K, Kröll D, Seiler CA, Langer R
Virchows Arch. 2020 May;476(5):725-734.
<https://pubmed.ncbi.nlm.nih.gov/31828432/>

This is a retrospective study to evaluate the impact of cancer-associated fibroblasts (CAFs) in esophageal carcinomas using immunohistochemistry (COL11A1, SPARC, and CD90 immunostains). They had two groups of esophageal carcinomas: 164 cases treated with resection and 256 cases receiving chemotherapy before resection (nTX-treated). Presence of COL11A1 and SPARC in fibroblasts was associated with unfavorable variables such as higher T category and lymphatic invasion. The presence of COL11A1-positive CAFs was associated with worse survival in resected cases. They conclude that CAFs are an important factor of tumor promotion and can serve as potential future therapeutic target.

Use of immunostaining for the diagnosis of lymphovascular invasion in superficial Barrett's esophageal adenocarcinoma

Hosono I, Miyahara R, Furukawa K, Funasaka K, Sawada T, Maeda K, Yamamura T, Ishikawa T, Ohno E, Nakamura M, Kawashima H, Yokoi T, Tsukamoto T, Hirooka Y, Fujishiro M
BMC Gastroenterol, 2020 Jun 5; 20(1):175.
<https://pubmed.ncbi.nlm.nih.gov/32503448>

This retrospective study aimed to assess the usefulness of immunostaining in determining the extent of lymphovascular invasion (LVI) in superficial Barrett's esophageal adenocarcinoma (BEA). A total of 41 patients who underwent endoscopic resection or surgery between January 2007 and July 2018 were included. All cases were stained for H&E, D2-40, and CD31. Two specialized gastrointestinal pathologists blinded to clinical information, independently evaluated the extent of LVI from these specimens. H&E staining alone identified LVI in 7 patients (positivity rate: 17.1%). Immunostaining for D2-40 and CD31 identified LVI in 10 patients (positivity rate: 24.4%). The authors conclude that combined H&E staining and immunostaining is useful in diagnosing LVI in superficial BEA, particularly in endoscopically resected specimens.

Evaluation of the lower histologic threshold for gastric graft versus host disease

Mostafa M, Hartley CP, Hagen CE
Mod Pathol. 2020 May;33(5):962-970.
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The authors aimed to review a cohort of gastric biopsies taken to evaluate for graft-versus-host-disease (GVHD) to determine a lower diagnostic threshold for gastric GVHD by correlating histologic findings with clinical and endoscopic evidence of GVHD as well as biopsy findings from other locations. The maximum number of apoptotic bodies per 10 gastric pits, presence of ≥ 1 apoptotic body per biopsy (NIH guidelines), and presence of gastric pit drop out and/or ulceration were recorded. 60 gastric biopsies from non-stem cell transplant patients were used as a control group. 65 gastric biopsies from 52 stem cell transplant patients were included in the study group. When NIH guidelines were combined with the presence of at least two apoptotic bodies per 10 contiguous gastric pits, this cutoff point was significantly associated with treatment for GVHD (OR=9.4, 95% CI 1.7-176.7, $p = 0.04$) and evidence of extraintestinal GVHD (OR= 3.2, 95% CI 1.1-10.7, $p = 0.04$). The diagnostic specificity for the proposed cutoff value is 94%. The authors conclude by stating that their newly proposed cutoff is a lower diagnostic threshold of gastric GVHD, but provides higher specificity than NIH guidelines alone and is correlated with clinical evidence of GVHD.

Proton pump inhibitor use and risk of gastric, colorectal, liver, and pancreatic cancers in a community-based population

Lee JK, Merchant SA, Schneider JL, Jensen CD, Fireman BH, Quesenberry CP, Corley DA
Am J Gastroenterol. 2020 May;115(5):706-715.
<https://pubmed.ncbi.nlm.nih.gov/32205645/>

Proton pump inhibitors (PPIs) increase systemic gastrin levels and there is concern about their carcinogenicity. The authors sought to evaluate the association between PPI use and gastrointestinal (GI) cancers. This was a nested case-control study conducted within Kaiser Permanente Northern California (KPNC), in a large community-based integrated healthcare setting. Case patients were KPNC members with initial gastric ($n=1,233$), colorectal ($n=18,595$), liver ($n=2,329$), or pancreatic cancer ($n=567$) diagnoses between 1996-2016. For each eligible case, up to 10 controls were randomly selected using incidence density sampling and matching by sex, race, medical facility, age, and enrollment duration. For the primary analysis, PPI exposed patients had a ≥ 2 year cumulative PPI supply dispensed before index cancer date. Unexposed patients had no record of PPI use. Associations were evaluated using conditional logistic regression and adjusted for multiple confounders. In secondary analyses, the associations with GI cancers stratified separately by mean daily PPI dose and duration of use.

The authors found that PPI use ≥ 2 years was not associated with the risks of gastric, colorectal, liver, or pancreatic cancers compared to non-users. Exploratory analyses examining PPI intensity of use found elevated cancer risks in those with ≥ 10 years of PPI use, however, there were no consistent associations found for increasing PPI dose and/or duration of use. The authors conclude that PPI use ≥ 2 years was not associated with increased risks of GI cancers. Cancer risks associated with PPI use ≥ 10 years requires further studies.

Surveillance of gastric intestinal metaplasia

Shah SC, Gawron AJ, Li D

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The authors state that gastric intestinal metaplasia (GIM) is increasingly recognized as an important premalignant diagnosis, but there is an unmet need to standardize the endoscopic GIM surveillance practices. In an article geared toward endoscopists, the authors detail their approach to the endoscopic surveillance of individuals diagnosed with GIM and highlight the importance of risk stratification. 1. Evaluate for and eradicate *H. pylori* in patients with GIM. The authors state that if gastric biopsies are negative for *H. pylori*, stool or urease breath tests can be performed. They note that *H. pylori* colonization of gastric mucosa may be patchy/absent in areas with GIM. 2. Patient selection for GIM surveillance. Risk depends on multiple factors and the authors recommend a shared decision-making process regarding surveillance. 3. Endoscopic techniques. The authors recommend endoscopists perform a careful inspection with high resolution white light endoscopy. 4. Biopsy protocol, histologic reporting and documentation. The two main goals are to rule out neoplasia and to determine the GIM extent and histologic subtype. Extensive GIM, defined as any involvement of the corpus, is associated with $>2x$ increased risk of gastric cancer compared with limited GI defined as only antral involvement (+/- incisura). The authors recommend that pathologists perform histological subtyping of GIM into complete vs incomplete because the latter is associated with a 3.3x higher risk of gastric cancer based on limited but consistent data. Biopsies should be targeted as well as nontargeted (utilizing the Sydney protocol of 5 biopsies in separate jars), but state that if cost is a concern, nontargeted biopsies can be placed in two jars labeled "body" and "antrum/incisura." Targeted biopsies should be in separately labeled jars. The authors conclude that magnitude and pace of progress on the subject of GIM is limited by the dearth and heterogeneity in the literature, particularly when generalizing findings from populations with different gastric cancer incidence and risk factor profiles. Endoscopic surveillance protocols will undergo modifications as more data are generated. Regardless, adjunctive risk reduction interventions, patient selection based on stratification by cancer risk, and adequate mucosal visualization/assessment will remain the foundational elements of GIM management and surveillance.

Impact of lymphovascular invasion on survival outcome in patients with gastric cancer

Mei D, Zhao B, Zhang J, Luo R, Lu H, Xu H, Huang B
Am J Clin Pathol. 2020;153(6):833-841.
<https://pubmed.ncbi.nlm.nih.gov/32146483/>

Lymphovascular invasion (LVI), defined as the infiltration of tumor cells in the vascular and/or lymphatic vessel wall or the presence of tumor emboli with an endothelial-lined space, is an important pathway for the spread of tumor cells. In this retrospective study, the authors aimed at exploring the risk factors for LVI and evaluating the impact of LVI on long-term survival outcome in a cohort of 1,720 consecutive patients (72.0% men, 28.0% women, median age: 60 years) who underwent curative gastrectomy for gastric cancer. LVI was detected in 21.3% (366/1720) of all patients, 5.9% (15/255) of early GC patients, 24.0% (351/1,465) of advanced GC patients. The frequency of LVI in the patients with and without lymph node metastasis was 30.2% (322/1,065) and 6.7% (44/655), respectively. The presence of LVI was significantly associated with female sex, larger tumor size, more extended involvement of the stomach, undifferentiated type, infiltration growth pattern, more frequent serosal invasion and lymph node metastasis, and more advanced pathologic TNM stage. Tumor size, differentiated type and the depth of tumor invasion were independent predictive factors for LVI. Irrespective of tumor stage or lymph node metastasis, LVI-positive patients had a poorer survival outcome than LVI-negative patients, and the presence of LVI was an independent prognostic factor. The authors conclude that LVI provided additional prognostic information for patients with GC, and those GC patients with LVI should be considered candidates for adjuvant chemotherapy, irrespective of tumor stage or lymph node metastasis.

Lymphovascular invasion in early gastric cancer: impact of ancillary D2-40 and elastin staining on interobserver agreement

Takada K, Yoshida M, Aizawa D, Sato J, Ono H, Sugino T
Histopathology. 2020;76(6):888-897.
<https://pubmed.ncbi.nlm.nih.gov/31989674/>

Lymphovascular invasion is a strong risk factor for lymph node metastasis in the setting of gastric cancer. While early gastric cancers are potentially cured with endoscopic submucosal dissection (ESD), treatment decisions are made based upon the presence or absence of lymphovascular invasion in ESDs, but this histologic finding has less than perfect interobserver agreement. In this study, the authors investigate whether the use of an immunohistochemical stain for D2-40 and an elastin special stain improve the identification of lymphatic and vascular invasion, respectively, in gastric cancer. The authors retrospectively identify 100 ESD specimens with submucosally invasive gastric cancer. D2-40 and elastin stains were performed on tissue sections with the deepest invasion. Expert, intermediate, and trainee gastrointestinal pathologists first reviewed H&E-stained sections for each of the cases for lymphatic and vascular invasion. Subsequently, these pathologists reviewed these same cases with the aid of the D2-40 immunostain and the elastin special stain. The expert and intermediate-level

pathologists had very good agreement regarding the detection of lymphatic invasion based upon the evaluation of H&E-stained sections alone ($k=0.78$), which improved slightly with the addition of D2-40-stained sections ($k=.85$). There was only fair agreement between the expert and intermediate-level pathologist regarding the detection of vascular invasion ($k=0.25$), which improved dramatically following review of elastin-stained sections ($k=0.63$). Similar improvements to interobserver agreement were noted when comparing the performance of the expert pathologist with the trainee. The detection rates for lymphatic and vascular invasion improved with the addition of the ancillary studies for pathologists of all three experience levels, though the effect was most dramatic for the trainee. The authors conclude that the use of ancillary D2-40 immunostains and elastin stains may improve interobserver agreement on lymphatic and vascular invasion in specimens derived from patients with early gastric cancer, which can potentially lead to better risk stratification.

Clinicopathologic characteristics, diagnostic clues, and prognoses of patients with multiple sporadic gastrointestinal stromal tumors: a case series and review of the literature

Yan-Ying Shen , Xin-Li Ma, Lin-Xi Yang, Wen-Yi Zhao , Lin Tu, Chun Zhuang, Bo Ni, Qiang Liu, Ming Wang, Hui Cao

Diagn Pathol. 2020 May 14;15(1):56.

<https://pubmed.ncbi.nlm.nih.gov/32408889/>

This retrospective study reports the clinicopathologic of 27 patients diagnosed with multiple sporadic GISTs in 1660 consecutive cases, and multiplicity was determined by gross examination with or without mutational analysis. Most cases were in the stomach and were low- grade with spindle cell morphology. In addition, no relapses were reported. The authors concluded that the prognosis of single and multiple sporadic GISTs appear to be similar.

Counting intraepithelial lymphocytes: a comparison between routine staining and CD3 immunohistochemistry

Cooper R, Papworth NJ, Harris C, Horne J, Lai J, Rajak R, Valentine KM, Gaya SO, Carr NJ
Int J Surg Pathol. 2020 Jun;28(4):367-370.

<https://pubmed.ncbi.nlm.nih.gov/31847634/>

This study compares the intraepithelial lymphocytes (IEL) counts in duodenal biopsies using H&E and CD3 IHC, and examines the interobserver variability. CD3 IHC was associated with significantly higher IEL counts than H&E. Some cases with normal H&E counts had elevated counts with CD3. They found lack of concordance between CD3 and H&E IEL counts suggesting that counts derived from the 2 methods may not be comparable to each other and should not be considered equivalent. They found no significant improvement in interobserver variability with CD3 IHC.

Small-bowel carcinomas associated with celiac disease: transcriptomic profiling shows predominance of microsatellite instability-immune and mesenchymal subtypes

Rizzo, F, Vanoli, A, Sahnane, N, Cerutti, R, Trapani, D, Rinaldi, A, Sellitto, A, Ciacci, C, Volta, U, Villanacci, V, Calabrò, A, Arpa, G, Luinetti, O, Paulli, M, Solcia, E, Di Sabatino, A, Sessa, F, Weisz, A, Furlan, D
Virchows Arch 2020 May;476(5):711-723.
<https://pubmed.ncbi.nlm.nih.gov/31696360/>

This retrospective study is a gene expression analysis of 13 cases of small-bowel carcinomas associated with celiac disease and comparing them to the four Consensus Molecular Subtypes (CMS) of colorectal carcinoma. They found two main subtypes: MSI-immune and a mesenchymal subtype (subtypes 1 and 4). The first and predominant subset was commonly microsatellite unstable, and exhibited CIMP and high T cell infiltration and was indolent. However, cancers falling in subtype 4 showed prominent transforming growth factor- β activation and were characterized by complement-associated inflammation, cancer-associated stroma production, and angiogenesis and had a worse prognosis.

Poorly cohesive (signet ring cell) carcinoma of the ampulla of Vater

Tuncel D, Basturk O, Bradley KT, Kim GE, Xue Y, Reid MD, Balci S, Erbarut I, Adsay V
Int J Surg Pathol. 2020 May;28(3):236-244.
<https://pubmed.ncbi.nlm.nih.gov/31612756/>

This is a retrospective study of 9 cases of signet ring cell carcinoma of the ampulla of Vater (signet ring cell morphology constituting >50% of the tumor). They found that these tumors constitute 2.4% of adenocarcinomas from this region and present as advanced tumors with poor prognosis. These tumors tended to express upper-gastrointestinal immunoprofiles with frequent MUC5AC labeling. The authors suggest that this protein expression may be helpful in identifying subtle infiltration in the surface mucosa since MUC5AC is not normally expressed in the ampullary mucosa.

Low-grade appendiceal mucinous neoplasms: a single institution experience of 64 cases with clinical follow-up and correlation with the current (eighth edition) AJCC Staging

Wong M, Barrows B, Gangi A, Kim S, Mertens RB, Dhall D
Int J Surg Pathol. 2020 May;28(3):252-258.
<https://pubmed.ncbi.nlm.nih.gov/31645160/>

This is a retrospective study of LAMN from a single institution. They looked at 64 LAMN cases which presented over a 22 year period and found that a majority of their cases were pTis with

an excellent prognosis and recurrence was observed in only 2 patients (both with pT4aM1b disease).

Post-inflammatory mucosal hyperplasia and appendiceal diverticula simulate features of low-grade appendiceal mucinous neoplasms

Hissong E, Goncharuk T, Song W, Yantiss RK
Mod Pathol. 2020 May;33(5):953-961.
<https://pubmed.ncbi.nlm.nih.gov/31857681/>

The authors sought to identify the clinicopathologic and molecular features that distinguish appendiceal mucinous neoplasms from non-neoplastic mimics. 37 low grade appendiceal mucinous neoplasms and 55 non-neoplastic examples of mucosal hyperplasia/diverticulosis were retrospectively identified. The authors found that non-neoplastic appendices were smaller ($p < 0.05$) and more likely to present with appendicitis ($p < 0.05$) when compared to neoplasms. Twenty non-neoplastic mucinous lesions were subjected to *KRAS* mutational analysis, of which 6 (30%) contained *KRAS* mutations, which the authors speculate could arise via mechanisms similar to those of other proliferative lesions with known associations with *KRAS* mutation such as goblet rich hyperplastic polyps. The authors conclude that the distinction between neoplastic and non-neoplastic mucinous appendiceal lesions requires recognition of key morphologic features. *KRAS* mutational testing cannot be used to assess biologic risk or confirm a diagnosis of neoplasia.

Impact of referral center pathology review on diagnosis and management of patients with appendiceal neoplasms

Jedrzkiwicz J, Tateishi Y, Kirsch R, Conner J, Bischof D, McCart A, Riddell R, Pollett A, Taylor EL, Govindarajan A
Arch Pathol Lab Med. Jun 2020; 144: 764-768.
<https://pubmed.ncbi.nlm.nih.gov/31714810/>

The purpose of this study was to evaluate whether pathology review by gastrointestinal pathologists at a tertiary care center resulted in changes to clinical management. The authors evaluated a series of 145 appendiceal lesions (including low-grade appendiceal mucinous neoplasms (LAMNs), invasive adenocarcinomas, goblet cell carcinomas, among others) reviewed as consult cases. Discrepancies were divided into “change in categorical interpretation” (neoplastic to neoplastic or benign to malignant), “change within the same category” (goblet cell carcinoid to adenocarcinoma ex goblet cell carcinoid), and “change in threshold” (changes in wording – atypical, suspicious, favor, etc.). They noted that almost a quarter (24.8%) of cases underwent one or more changes to the diagnosis; in 28% of these patients, the discrepancy resulted in a significant change in management. The most common changes to result in changes to management include changes within the same category (poorly

differentiated signet ring cell carcinoma to carcinoma ex GCC), changes of category (LAMN to non-dysplastic serrated polyp or reactive changes), and grade, with a subset showing multiple discrepancies.

Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study

Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L

Am J Gastroenterol. 2020 May;115(5):766-773.

<https://pubmed.ncbi.nlm.nih.gov/32287140/>

The authors aimed to investigate the prevalence and outcomes of COVID-19 patients with digestive symptoms in Hubei, China. This was a descriptive cross-sectional, multicenter study. Patients with COVID-19 who presented between January 18, 2020 to February 28, 2020 were enrolled. All patients were confirmed by PCR testing and clinical characteristics, laboratory data, and treatment were analyzed. Patients were followed up until March 18, 2020. 204 COVID-19 patients were analyzed, 107 men and 97 women, with an average age of 52.9 years (SD± 16). While most patients presented with respiratory symptoms, 103 patients (50.5%) reported digestive symptoms. 81 (78.6%) had loss of appetite, 35 (34%) had diarrhea, 4 (3.9%) had vomiting, and 2 (1.9%) had abdominal pain. 17% of patients with COVID-19 reported loose stools on the initial presentation. Patients with digestive symptoms had significantly longer time from onset to admission than patients without digestive symptoms (9.0 days vs 7.3 days). 6 of the 103 cases had digestive symptoms without respiratory symptoms. As severity of disease increased, digestive symptoms became more pronounced. Patients with digestive symptoms had higher mean liver enzyme levels, longer prothrombin time, lower monocyte count, and received more antimicrobial treatment than those without digestive symptoms. The authors conclude that digestive symptoms are common in COVID-19 patients and that diarrhea may be one of the presenting features of COVID-19.

Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection

Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H

Gut. 2020 Jun;69(6):997-1001.

<https://pubmed.ncbi.nlm.nih.gov/32241899/>

The authors analyzed data of 95 cases of SARS-CoV-2 and did Real-time RT-PCR to detect the presence of the virus in feces and GI tissues. 58 cases exhibited GI symptoms of which 11% did so on admission and 49% developed during hospitalization. Diarrhea, anorexia and nausea were the main symptoms. A majority of patients developed diarrhea during hospitalization, potentially aggravated by drugs including antibiotics. Six patients underwent endoscopy,

revealing esophageal bleeding with erosions/ ulcers in one severe patient. SARS-CoV-2 RNA was detected in specimens from two severely affected patients. In contrast, only one of the four non-severe patients had detectable virus in their GI tissue.

Brown bowel syndrome: a multi-institutional case series

Arnold CA, Burke AP, Calomeni E, Mayer RC, Rishi A, Singhi AD, Stashek K, Voltaggio L, Tondon R

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<https://pubmed.ncbi.nlm.nih.gov/31985498/>

Brown bowel syndrome (BBS), also termed “intestinal lipofuscinosis” or “smooth muscle myopathy of mitochondrial origin” is characterized by brown discoloration of the bowel due to massive lipofuscin accumulation in the smooth muscle cells of the muscularis propria, the underlying defect being vitamin E deficiency. The authors present a series of eight BBS cases (M: F=5:3; mean age=58.6 y). Seven of these were surgical resections and one was an autopsy case; 5 cases were small bowel only (terminal ileum = 3, jejunum = 2); 2 were terminal ileum with right colectomy; and the findings in the autopsy case were most prominent in the duodenum. The associated comorbidities included bariatric surgery, malnourishment, Crohn’s disease, cystic fibrosis, alcohol and cocaine abuse, and prior small bowel resections. The clinical symptoms included abdominal pain, bleeding, nausea and vomiting, and unresponsiveness. Imaging studies were often abnormal: 3 cases with thickened bowel wall (of which 1 was concerning for a mass), 2 with small bowel obstruction, and 2 with edematous and dilated bowel wall. Two specimens were grossly mahogany in color, and 1 case had a perforation. Histologic sections showed finely granular, brown cytoplasmic pigment in the smooth muscle cells of slightly disorganized appearing muscularis propria. The pigment was also identified in the smooth muscle of intermediate-sized arteries in the submucosa. Although this pigment was difficult to appreciate at scanning magnification, it was easily perceptible on intermediate power. The pigment was more conspicuous in the small bowel, compared with the colon. The pigment was highlighted with Fontana- Masson, carbol lipofuscin, Periodic acid-Schiff, and Periodic acid-Schiff with diastase, and was negative on Prussian blue and von Kossa stain. The mean clinical follow-up was 208 weeks- 1 patient died of complications of encephalitis, the others were alive and well. BBS is a worthwhile consideration in patients with chronic malabsorption of any underlying etiology, and has been described in patients with celiac disease, gastrointestinal tract bypass surgery, chronic pancreatitis, inflammatory bowel disease, alcoholism, intestinal lymphangiectasia, and intestinal atresia. Treatment of BBS is aimed at optimizing the patient’s overall nutritional status, including correcting the vitamin E deficiency and identifying and managing the cause of the underlying malabsorption.

Young-onset ischemic colitis: a condition of elusive etiology frequently associated with immune dysregulation

Byrnes K, Khararjian A, Mannan AASR, Arnold M, Voltaggio L
Int J Surg Pathol. 2020 Jun;28(4):361-366.
<https://pubmed.ncbi.nlm.nih.gov/31870209/>

This is retrospective study of 31 cases of ischemic colitis in young patients (<40 years). In 43% of cases no association was found. The remaining showed associations in with immune dysregulation such as lupus, dermatomyositis, vasculitis (21%) and poorly controlled HIV/AIDS (18%), cocaine and cigarette use and premature atherosclerosis. While rare before 20 years of age, ischemic colitis in teenagers was related to mechanical issues.

Elderly-onset vs adult-onset ulcerative colitis: a different natural history?

Zammarchi I, Lanzarotto F, Cannatelli R, Munari F, Benini F, Pozzi A, Lanzini A, Ricci C
BMC Gastroenterol, 2020 May 12; 20(1):147.
<https://pubmed.ncbi.nlm.nih.gov/32398011>

This study aimed to characterize ulcerative colitis (UC) in elderly-onset patients and compare with adult-onset UC. A total of 94 patients with UC diagnosed after the age of 65 years (elderly group) were identified and matched 1-1 according to gender and calendar year of diagnosis with patients diagnosed with UC at age 40-64 years (adult age). The study found that Comorbidity Index and mortality was higher, and surgery was more frequently performed for elderly UC patients. Weight loss, complications, left colitis, and proctitis was more common in the elderly group. Symptoms at presentation, therapy and clinical behavior, and time to first relapse were similar between the two groups. However, abdominal pain and extraintestinal manifestations were more common in adults, and biological therapy was used more often in adults. The authors conclude that the elderly are more fragile because of comorbidities, increased risk of infections and disease-related complications. However, the presentation and behavior of UC is similar between elderly and adults.

Inflammatory polyps occur more frequently in inflammatory bowel disease than other colitis patients

Ashktorab H, Brim H, Hassan S, Nourai M, Gebreselassie A, Laiyemo AO, Kibreab A, Aduli F, Latella G, Brant SR, Sherif Z, Habtezion A
BMC Gastroenterol, 2020 Jun 5; 20(1):170.
<https://pubmed.ncbi.nlm.nih.gov/32503428>

This study aimed to determine the prevalence of colorectal polyps in a predominantly African American population with inflammatory bowel disease (IBD) and Non-IBD/Non-Infectious Colitis (NIC). A total of 485 patients were included in the study: 70 IBD and 415 NIC. Seventy-three percent of the NIC patients and 81% of the IBD patients were African Americans. The prevalence of polyps was 15.7 and 8.2% in the IBD and NIC groups, respectively (P = 0.045). The

prevalence of inflammatory polyps was higher in the IBD group (55%) compared to the NIC group (12%). After adjusting for age, sex and race, odds ratio of inflammatory polyps in IBD patients was 6.0 (P = 0.016). Adenoma prevalence was 4.3% (3/70) in IBD patients and 3.9% (16/415) in NIC patients (p = 0.75). The polyps occur predominantly in the colitis field regardless of colitis type. More polyps were present in ulcerative colitis patients when compared to Crohn's disease patients (27% vs. 5%, P < 0.001) within the IBD group. The authors conclude that inflammatory polyps are more common in IBD patients comparing to NIC patients and most polyps were in the same location as the colitis.

Characterization of novel injectable lifting agents used in colonic polyp removal: an emerging amyloid mimic

Pezhouh MK, Burgart LJ, Chiu K, Cohen DA, Hutchings DA, Sanderson SO, Shirazi M, Stanich PP, VandenBussche CJ, Voltaggio L, Willhoit ED, Xue Y, Arnold CA
Am J Surg Pathol. 2020;44(6):793-798.
<https://pubmed.ncbi.nlm.nih.gov/31934919/>

The newer submucosal lifting agents, namely, Eleview (Cosmo Technologies, 2015, also known as SIC-8000) and Orise (Boston Scientific, 2018) offer the advantage of immediate availability for use without requiring media preparation during the procedure, in contrast to the traditional agents, and are increasingly being used for polypectomies. The study cases consisted of 1 polypectomy and 8 colon resections (6 had a history of Orise injection and 3 used Eleview) from 9 patients (male: female = 3:6; mean age=64 y); the median time interval between injection and resection was 16 weeks. Resection of a polyp immediately after injection of the lifting agent showed basophilic, amorphous, and bubbly-extracellular material with prominent hemorrhage. Resection of a polyp 1 day after lifting agent injection showed infiltrating neutrophils and a more solid and less bubbly texture. Resection of a polyp 3 months after lifting agent injection showed a white-tan firm submucosal mass grossly. Histologic sections showed prominent hyalinized, pink-amorphous ribbons and globules with a foreign body giant cell reaction and fibrosis with an epicenter in submucosa. The material was neither refractile nor polarizable. The authors also confirmed that a histologically processed Orise aliquot from the manufacturer showed similar histology to that seen in the specimens from patients with confirmed Orise injection. Five cases were stained with Congo Red, and all cases were negative. Awareness of the morphology of these new lifting agents is important for accurate diagnosis and to avoid the diagnostic pitfall of amyloid and pulse granulomas. These lesions are negative on a Congo red stain and hence can be definitively distinguished from amyloid in conjunction with a corroborating history. The authors affirm that the diagnosis can be rendered on H&E alone, without special stains, assuming the morphology is characteristic and the history of lifting agent injection is confirmed.

Lifting Agent Granuloma

Westbrook LM, Henn PA, Cornish TC
Am J Clin Pathol. 2020; 153:630-638.
<https://pubmed.ncbi.nlm.nih.gov/31875886/>

The authors describe the histologic findings after endoscopic resection using the newer submucosal lifting agents. These newer synthetic submucosal lifting agents are more expensive; however, appear to maintain submucosal fluid cushions longer than other available products, leading to fewer repeat injections and decreased procedure duration. Four cases were identified based on the histologic presence of ORISE gel- two with tissue collected at 0 days postinjection, one at approximately 2 months post- injection, and one with tissue from both 0 days and 2 months postinjection. Immediately after injection, the gel had an appearance similar to a mucin- like substance within the submucosa on H&E stain and showed mucicarmine positivity but was negative for periodic acid-Schiff stain and Alcian blue. At 2 months, the histologic sections were characterized by a homogenous eosinophilic material with a robust foreign body-type giant cell reaction; also termed by the authors as “lifting agent granuloma”. The immediate phase could be mistaken for a mucinous tumor and in cases of mucinous adenocarcinoma can complicate the assessment of margins and depth of invasion. The aged material may be mistaken for amyloid or a pulse (legume) granuloma; however, the material seen with the submucosal lifting agent was negative on Congo red stain (unlike amyloid) and has a different clinical history and distribution in the tissue from those of a pulse granuloma. The authors affirm that it is important to be aware of the histologic appearance of these new submucosal lifting agents over a varying time interval, so that they are accurately diagnosed and not mistaken for other entities.

Nonconventional dysplasia in patients with inflammatory bowel disease and colorectal carcinoma: a multicenter clinicopathologic study

Choi WT, Yozu M, Miller GC, Shih AR, Kumarasinghe P, Misdraji J, Harpaz N, Lauwers GY
Mod Pathol. 2020 May;33(5):933-943.
<https://pubmed.ncbi.nlm.nih.gov/31822800/>

While conventional (intestinal) dysplasia is the most recognized form of dysplasia, nonconventional dysplasia can occur in the setting of inflammatory bowel disease (IBD) and includes at least 6 subtypes: hypermucinous, goblet cell deficient, terminal differentiation/crypt cell dysplasia, traditional serrated adenoma (TSA)-like, sessile serrated lesion (SSL)-like and serrated lesion not otherwise specified (NOS). The authors aimed to define the morphologic features of nonconventional dysplasia in a cohort of IBD patients with colorectal carcinoma and determine the characteristics of these patterns including their association with conventional dysplasia and/or colorectal carcinoma. 58 patients with IBD related colorectal cancer from 5 institutions were included. The cancer resection specimens and available preoperative biopsies were reviewed to identify dysplastic or serrated lesions which were type as conventional or non-conventional. 106 lesions from 58 patients were identified. 36 cases of nonconventional dysplasia were identified in 26 (45%) of the cohort. The most common subtype of

nonconventional dysplasia was hypermucinous dysplasia (n=15; 42%), either pure type or mixed with other dysplastic subtypes. Nonconventional dysplasia was in the same segment or in the immediately adjacent segment to the colorectal cancer 85% of the time, similar to conventional dysplasia. Nonconventional dysplasia was more likely to be low grade (29/81, 81%) than conventional dysplasia (26/70, 37%), p=0.003. However, colorectal cancer in patients with only nonconventional dysplasia was more likely to be poorly differentiated compared with colorectal cancer in patients with conventional dysplasia (p=0.026). Mucinous features were more frequently associated with colorectal cancers in patients with conventional dysplasia versus those with nonconventional dysplasia (p=0.024). In summary, the findings suggest that nonconventional dysplasia is common in patients with IBD, it can be associated with conventional dysplasia, and seems to carry at least a similar colorectal cancer risk as conventional dysplasia.

Revisiting the distinct histomorphologic features of inflammatory bowel disease-associated neoplastic precursor lesions in the SCENIC and post-DALM era

Gui X, Iacucci M, Ghosh S, Ferraz JGP, Lee S
Hum Pathol. 2020 June;100-24-37.
<https://pubmed.ncbi.nlm.nih.gov/32387105/>

The purpose of this retrospective study was to better define the histologic features of colitis-associated dysplasia in patients with inflammatory bowel disease. The authors reviewed 52 carcinoma-related lesions, 34 endoscopically visible but non-polypoid lesions, 57 polypoid and adenoma-like lesions in areas of colitis, 32 sporadic conventional adenomas in patients with IBD, and 60 sporadic conventional adenomas in patients without a history of colitis. They found that 40% of lesions in the carcinoma-related and visible but non-polypoid group were best classified as “nonconventional” and therefore had a mucinous, serrated, eosinophilic, or differentiated cytology and patterns of growth. Conventional or adenomatous cytology and architecture was the most common finding across all groups, but adenomatous lesions in the “carcinoma-related” group often had peculiar histologic features, such as significant inflammatory debris or crypt drop-out. The authors conclude that description and classification of these lesions is most useful for the non-polypoid lesions because these are more likely to be associated with carcinoma, with the exception of the “peculiar” adenomas. Straightforward, conventional adenoma-like lesions in colitis are morphologically and genetically similar to sporadic adenomas. The authors also provide a table with recommendations for approaching these lesions in a clinically relevant way.

Re-examining the 1-mm margin and submucosal depth of invasion: a review of 216 malignant colorectal polyps

Berg KB, Telford JJ, Gentile L, Schaeffer DF
Virchows Arch. 2020 Jun;476(6):863-870.

<https://pubmed.ncbi.nlm.nih.gov/31915959/>

This a retrospective cohort of 216 malignant polyps. They found that positive margin at cautery was associated with significantly increased rates of lymph node metastases compared to a margin of greater than 0 mm. Polyps with a margin of greater than 0 mm had no risk of residual carcinoma. A submucosal depth of ≥ 2 mm had an increased rate of lymph node metastases compared to < 2 mm. Their suggestion is to report the submucosal depth of invasion and refine the cut-off for positive margin.

Switch/sucrose nonfermenting nucleosome complex-deficient colorectal carcinomas have distinct clinicopathologic features

Villatoro TM, Ma C, Pai RK

Hum Pathol. 2020 May;99:53-61.

<https://pubmed.ncbi.nlm.nih.gov/32222462/>

The authors of this retrospective study aim to correlate the IHC expression of SMARCB1, SMARCA2, ARID1A, and SMARCA4 in colorectal adenocarcinoma, as assessed on a tissue microarray, with other histopathologic features, MMR status, mutation status, and patient survival. Their cohort includes 338 patients with resected colorectal adenocarcinoma, 107 of whom had MMR-deficient tumors. Overall, 23 (7%) cases demonstrated IHC loss of at least one of the switch/sucrose nonfermenting (SWI/SNF) nucleosome complex proteins that were tested: 16 with deficiency of ARID1A and 11 with deficiency of SMARCA2. The cases with ARID1A loss were more likely to have a corresponding MMR deficiency and to demonstrate medullary growth with loss of CDX-2 than SMARCA2 deficient cases or SWI/SNF-proficient cases. Cases with isolated SMARCA2 loss (n=7) all had conventional gland-forming growth. Differences in *KRAS* and *BRAF* mutations were not significantly different between the SWI/SNF-proficient and deficient adenocarcinomas. In this cohort, there was no difference in disease-specific or disease-free survival between the two groups. The authors conclude that SWI/SNF-deficient colorectal carcinomas with ARID1A loss have distinct histologic growth patterns and are more likely to be MMR-deficient than SWI/SNF-proficient cases. The prognostic significance of these mutations in colorectal carcinoma remains unclear. At least in this cohort, survival did not seem to be impacted by SWI/SNF status.

Retained mismatch repair protein expression occurs in approximately 6% of microsatellite instability-high cancers and is associated with missense mutations in mismatch repair genes

Hechtman JF, Rana S, Middha S, Stadler ZK, Latham A, Benayed R, Soslow R, Ladanyi M, Yaeger R, Zehir A, Shia J

Mod Pathol. 2020 May;33(5):871-879.

<https://pubmed.ncbi.nlm.nih.gov/31857677/>

Immunohistochemistry (IHC) for mismatch repair (MMR) protein expression usually correlates with the presence of microsatellite instability high status in DNA. The authors sought to examine the sensitivity of immunohistochemistry for microsatellite instability-high status. Germline/somatic mutation types were classified as truncating versus missense, with the theory that missense mutations are a potential cause for retained MMR protein expression in microsatellite instability high cases. 29,530 clinical cases were sequenced with MSK-IMPACT assay to reveal 582 (2%) microsatellite instability-high status. 443 of these cases had available MMR protein immunohistochemistry. Review of these cases identified 32 (7.2%) with discrepant immunohistochemistry results. The 32 tumors included 17 colorectal carcinomas and 9 endometrial carcinomas. 4 additional microsatellite instability-high colorectal carcinoma research cases that had discordant IHC were also examined. Of the 36 microsatellite instability-high cases with discordant IHC, 30 were MMR proficient, 6 (5 MLH1 and one MSH2) retained expression of the defective MMR protein and lost its partner. 69% (25/36) cases had pathogenic germline or somatic missense mutations, as opposed to only 19% (7/36) in a matched microsatellite instability-high group with concordant IHC ($p=0.0007$). The authors conclude that approximately 6% of microsatellite instability-high cases have retained MMR protein expression and would be missed by IHC based testing. Another 1% of microsatellite instability-high cases show isolated loss of defective gene's dimerizing partner. The majority of these cases harbor missense mutations and often express MMR proteins in a lower percentage of tumor cells.

Detection of microsatellite instability from circulating tumor DNA by targeted deep sequencing

Cai Z, Wang Z, Liu C, Shi D, Li D, Zheng M, Han-Zhang H, Lizaso A, Xiang J, Lv J, Wu W, Zhang Z, Zhang Z, Yuan F, He S, Sun J
J Mol Diagn. Jul 2020; 22(7): 860-870.
<https://pubmed.ncbi.nlm.nih.gov/32428677/>

Assessment of microsatellite instability is increasingly important as a predictive marker for response to immunotherapy in addition to its traditional role in cancer risk counseling. However, acquisition of tissue can be difficult in certain subsets of patients. The authors developed a next-generation sequencing based algorithm to detect MSI from blood in patients with colorectal cancer. In comparison to cell lines and in silico simulation experiments, MSI status determination showed 98% sensitivity and 100% specificity at a minimum 1% circulating DNA content and a 91.8% sensitivity and 100% specificity at a 0.4% circulating DNA content. These results were verified in a validation cohort of colorectal carcinoma patients who had orthogonal MSI testing performed; a sensitivity of 94% and specificity of 100% was achieved for samples with a circulating DNA content of $>0.4\%$.

External quality assessment schemes for biomarker testing in oncology: comparison of performance between formalin-fixed, paraffin-embedded tissue and cell-free tumor DNA in plasma

Casteren KV, Keppens C, Schuurin E, Deans ZC, Normanno N, Patton SJ, Dequeker EMC
J Mol Diagn. Jun 2020; 22(6): 736-747.
<https://pubmed.ncbi.nlm.nih.gov/32205291/>

The purpose of this study was to compare formalin-fixed, paraffin-embedded (FFPE) tissue and plasma cell-free DNA in evaluating for variants. The authors found that, compared to tissue, plasma DNA analysis had lower overall performance and higher error rates; performance in plasma was decreased for variants with an allele frequency of 1%, compared to those with an allele fraction of 5%. These results suggest that results of circulating tumor DNA testing (particularly negative results) may need to be verified before treatment decisions are made based off those results.

High mutational burden in colorectal carcinomas with monoallelic *POLE* mutations: absence of allelic loss and gene promoter methylation

Hühns M, Nürnberg S, Kandashwamy KK, Maletzki C, Bauer P, Prall F
Mod Pathol. 2020 Jun;33(6):1220-1231.
<https://pubmed.ncbi.nlm.nih.gov/31857678/>

Hypermutator type colorectal carcinomas are microsatellite stable and have point mutations of *POLE* or *POLD1* and ultrahigh tumor burden (TMB). These tumors are thought to be associated with enhanced antitumor immunity and affect younger patients. The authors performed *POLE* and *POLD1* exonuclease domain Sanger sequencing in 271 unselected colorectal cancers and identified four microsatellite stable tumors, two with somatic *POLE* p.P286R variants, and two with *POLE* p.V411L, all had ultrahigh TMBs. Two of the 4 tumors were from patients <50 years old, and there was a prominent T-cell infiltration noted in 3 of the 4. In addition, a *POLE* p.A465T was found in a Lynch associated tumor and focal somatic *POLE* and *POLD1* mutations were found in 2 other tumors with low TMBs. The mutations in *POLE* or *POLD1* were found to be monoallelic, without evidence of a “second hit” by allelic loss or promoter methylation. Therefore, a 50% reduction of *POLE* dosage caused by these mutations is enough to confer ultrahigh TMBs in sporadic colorectal carcinomas. Taken together, the authors conclude that *POLE* variants p.P286R and p.V411L define a separate class. Though they are not identified in a straightforward fashion on histology, they are likely to be “immunoreactive” and thus the *POLE* hotspots should be included in sequencing panels.

A novel group of HPV-related adenocarcinomas of the lower anogenital tract (vagina, vulva, and anorectum) in women and men resembling HPV related endocervical adenocarcinomas

Voltaggio L, McCluggage WG, Iding JS, Martin B, Longacre TA, Ronnett BM
Mod Pathol. 2020 May;33(5):944-952.
<https://pubmed.ncbi.nlm.nih.gov/31857682/>

The authors report a series of 9 HPV-related adenocarcinomas of the lower anogenital tract, distal to cervix. All tumors were strongly positive for p16 immunostain. Of the 9 tumors, 3 were cancers of the anorectum (the remaining 6 consisted of 4 in vagina and 2 in vulva). Two of the 3 cases of anorectal cases involved men. The morphological features of these tumors closely resemble high risk HPV associated endocervical adenocarcinoma. The most characteristic morphologic finding was the presence of a papillary or villiform/villoglandular architecture. One anal tumor featured abundant intracytoplasmic mucin that was multivacuolated in some areas imparting a clear cell like appearance. The authors report that this is the first series of high risk HPV related adenocarcinomas of the lower anogenital tract, and that the tumors are rare but morphologically distinctive.

An update on the role of immunohistochemistry in the evaluation of gastrointestinal tract disorders.

Robertson S, Patil DT
Adv Anat Pathol. 2020 May;27(3):193-205.
<https://www.ncbi.nlm.nih.gov/pubmed/30234501>

In this comprehensive review article, the authors tackle the topic of immunohistochemistry and its appropriate uses in the luminal gastrointestinal tract. They begin with gastritis, explaining why reflex staining for *H. pylori* is not recommended and how gastrin can aid in the diagnosis of autoimmune metaplastic atrophic gastritis. They end with anal lesions, specifically discussing p16 staining in squamous intraepithelial lesions and a panel of IHC that may aid in the distinction between basal cell carcinoma and basaloid squamous cell carcinoma. The bulk of the review is a nice overview of IHC in gastrointestinal malignancies, and this section covers undifferentiated malignancies, AFP-producing carcinomas, the emergence of SATB2 as a potential marker, SMARC-deficient tumors, and neuroendocrine tumors of unknown primary. Representative figures accompany detailed text.

Practical application of lineage-specific immunohistochemistry markers: transcription factors (sometimes) behaving badly

Lou SK, Adeyi OA
Arch Pathol Lab Med. May 2020; 144: 626-643.
<https://pubmed.ncbi.nlm.nih.gov/31385722/>

This review paper summarizes uses and pitfalls of ubiquitous transcription factors used for primary site assignment. In addition to the transcription factor infidelity noted with poorly

differentiated neuroendocrine carcinomas, this review discusses TTF-1, GATA3, CDX2, PAX8, PAX5, SF-1, OCT4, SALL4, NKX3.1, SOX2, and SOX10, and the importance of using a panel of immunohistochemical stains in primary site determination. Of particular relevance to gastrointestinal pathologists, aberrant expression of TTF-1 has been reported in a small fraction of colorectal adenocarcinomas, gastric adenocarcinoma, and metastatic cholangiocarcinomas to the lung. GATA3 can be strongly positive in squamous cell carcinomas of the skin; a smaller subset of anal, cervical, and lung squamous cell carcinomas can also be positive, as can squamous components of adenosquamous carcinomas. GATA3 is also expressed in a subset of pancreatic adenocarcinomas. In addition, CDX2, a commonly used marker of enteric (and, to a lesser extent, pancreaticobiliary) carcinomas can be positive in endometrioid carcinomas of the ovary and uterus, prostatic adenocarcinomas, urachal adenocarcinomas, hepatocellular carcinomas, and lung adenocarcinomas, in addition to mucinous adenocarcinomas of any site. Moreover, in addition to the known CDX2 positivity in intestinal type sinonasal adenocarcinomas, CDX2 can be positive in oropharyngeal undifferentiated carcinomas, and various testicular germ cell tumors. Notably, CDX2 is also positive in 90% of acute myeloid leukemias in some series. Markers of germ cell tumors also can be aberrantly positive in gastrointestinal carcinomas including Oct-4 positivity in esophageal and pancreatic carcinomas and SALL4 positivity in gastric, pancreatic, rectal, and hepatocellular carcinomas. The authors also discuss the expression of PAX8 in well-differentiated neuroendocrine tumors of the pancreas, rectum, appendix, stomach, and duodenum.

INSM1 is a highly specific marker of neuroendocrine differentiation in primary neoplasms of the gastrointestinal tract, appendix, and pancreas

McHugh KE, Mukhopadhyay S, Doxtader EE, Lanigan C, Allende DS
Am J Clin Pathol. 2020 ;153(6):811-820.
<https://pubmed.ncbi.nlm.nih.gov/32128564/>

INSM1 (insulinoma-associated protein 1) is a zinc- finger transcription factor and has been described as a sensitive and specific neuroendocrine marker. The authors aimed to determine the utility of INSM1 as a marker of neuroendocrine differentiation in primary gastrointestinal tract, appendiceal, and pancreatic neuroendocrine neoplasms. 110 neuroendocrine neoplasms and controls were stained with INSM1, synaptophysin, chromogranin, CD56, and Ki-67. INSM1 was positive in 80.9% (89/110) primary gastrointestinal, appendiceal, and pancreatic neuroendocrine neoplasms (and neoplasms with neuroendocrine differentiation), including 94.1% gastric (16/17), 94.4% pancreatic (17/18), 72.2% small bowel (13/18), 81.0% colonic (17/21), and 72.2% appendiceal neoplasms (26/36). INSM1 was positive in 82.9% (58 /70) well-differentiated neuroendocrine tumors, 85.0% (17/20) poorly differentiated neuroendocrine carcinomas, 72.7% (8/11) low-grade goblet cell adenocarcinomas (grade 1) and 66.7% (6/9) high-grade goblet cell adenocarcinomas (grade 2/3). The sensitivity of INSM1 for neuroendocrine neoplasms as a group (80.9%) was lower than that of synaptophysin (99.1%), chromogranin (88%), and CD56 (95.3%); specificity was higher than all 3 traditional neuroendocrine markers (95.7% vs synaptophysin: 86.0%; CD56: 86.0%; chromogranin: 87.3%).

The authors concluded that INSM1 is a reliable marker of neuroendocrine differentiation in gastrointestinal neuroendocrine and mixed neuroendocrine neoplasms and may be a useful adjunct to traditional neuroendocrine markers, with the main benefits being crisp nuclear staining and high specificity for neuroendocrine differentiation. Other notable findings included the combination of good sensitivity and excellent specificity for poorly differentiated neuroendocrine carcinomas of the GI tract and the utility of INSM1 in identifying neuroendocrine differentiation in up to two-thirds of goblet cell adenocarcinomas.

A reappraisal of sclerosing nodular and/or polypoid lesions of the gastrointestinal tract rich in IgG4-positive plasma cells

Chetty R

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<https://pubmed.ncbi.nlm.nih.gov/31919879/>

This brief article investigates a cohort of 5 cases of fibrosing/sclerosing nodules and polyps of the gastrointestinal tract, their relationships with systemic IgG4-related disease, and recommends reporting guidelines for these lesions. The author of this study retrospectively identified 5 cases over a 10 year period, which included two submucosal gastric nodules, one submucosal cecal nodule, one submucosal rectal nodule, and a single serosal-based ileal lesion. Immunohistochemical stains for CD34, CD117, DOG-1, S100, neurofilament, desmin, SMA, caldesmon, CK AE1/AE3, IgG, and IgG4 were performed on all cases. Regardless of site, the lesions had a similar histologic appearance, characterized by hyalinized, keloidal-type fibrosis without a storiform appearance. A lymphoplasmacytic inflammatory infiltrate was described in all cases, along with occasional lymphoid aggregates. No cases exhibited obliterative phlebitis. There was focal reactivity for SMA in stromal cells in three of the cases, but the remaining immunohistochemical stains were negative. Greater than 10 IgG4 plasma cells per HPF were identified in all 5 cases, and the IgG4/IgG ratio was greater than 0.4. None of the 5 patients in the cohort had clinical features of IgG4-related disease at other sites or elevated serum IgG4 during the study period. The author suggests that IgG4-related lesions of the tubular gastrointestinal tract are only rarely associated with classical IgG4-related disease of other sites. They advocate for the terminology "IgG4-positive nodule or polyp with probable histologic features of IgG4-related disease" after the exclusion of other tumors of known lineage and the performance of immunohistochemical stains for IgG and IgG4.

Pathological assessment of endoscopic resections of the gastrointestinal tract: a comprehensive clinicopathologic review

Kumarasinghe MP, Bourke MJ, Brown I, Draganov PV, McLeod D, Streutker C, Raftopoulos S, Ushiku T, Lauwers GY

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<https://pubmed.ncbi.nlm.nih.gov/31907377/>

Endoscopic resection (ER) is used for the treatment of Barrett's related early carcinomas and dysplasias, as well as low risk submucosal invasive carcinomas and laterally spreading adenomas of the colon. It offers potential cure for early stage luminal malignancies and organ preservation. A systematic approach for handling and assessing ER specimens is recommended. Technically, ERs can be simple polypectomies or endoscopic mucosal resections (EMRs), or endoscopic submucosal dissections. EMRs in particular can be performed with various techniques including "inject and lift", "cap EMR", "band EMR", and "underwater EMR".

Pathological aspects: intraepithelial neoplasms (ie. adenoma) and early invasive carcinoma are the two major groups of lesions evaluated by pathologists in assessing ERs. Histologic examination serves to 1. Confirm the pre-procedure diagnosis; 2. Prognosticate/stage lesions. For non-invasive lesions, complete resection is curative. Therefore confirmation, subtyping, and comments on lateral margins are appropriate. For invasive lesions, histological factors predict two main outcomes: risk of lymph node metastasis and risk of residual disease. The adverse histological factors are poor differentiation, lymphovascular invasion (LVI), depth of infiltration, high tumor budding, and margin involvement. The authors recommend pinning out a specimen and floating the specimen upside down in formalin. This allows proper orientation and sectioning. Documenting the size and number of fragments received is important. If identifiable, the distance from the lesion to the nearest margin must be recorded. Sections should be at intervals of 2-3mm and embedded "en face". The authors state that two to three H&E levels per block can facilitate microscopic evaluation. When appropriate, ribbons between levels can be preserved for ancillary stains. A recommended approach to reporting is as follows: type of lesion, histological subtype if invasive carcinoma, size of lesion, and for invasive lesions: depth of invasion (in microns), margin status (lateral and deep), LVI, perineural invasion, histologic grade and tumor budding, and any additional findings. Site specific issues (ie. duplication of the muscularis mucosae in the esophagus) should be considered. The authors conclude by saying that the pathological processing and evaluation of ERs should be carefully undertaken to allow optimal patient care.

Journals Reviewed May-June 2020

Advances in Anatomic Pathology
American Journal of Clinical Pathology
American Journal of Gastroenterology
American Journal of Surgical Pathology
Annals of Diagnostic Pathology
Archives of Pathology and Lab Medicine
BMC Gastroenterology
Clinical Gastroenterology Hepatology
Diagnostic Pathology
Diseases of the Colon and Rectum

Gastrointestinal Endoscopy
Gut
Histopathology
Human Pathology
International Journal of Surgical Pathology
Journal of Clinical Pathology
Journal of Molecular Diagnostics
Journal of Pathology
Modern Pathology
Virchows Archiv