GIPS Journal Watch
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Eosinophilic gastroenteritis as a cause of non-*Helicobacter pylori*, non-gastrotoxic drug ulcers in children

Joo JY, Cho JM, Yoo IH, Yang HR
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This retrospective study aimed to analyze the etiology of peptic ulcers in children and the differences in clinical, laboratory, endoscopic, and histopathologic findings of peptic ulcers according to etiology. A total of 255 children with peptic ulcers were included in the study. The subjects were categorized into 5 groups according to the etiology of the ulcer: 1) *H. pylori* infection (n = 51); 2) gastrotoxic drugs (n = 18); 3) idiopathic (n = 144); 4) systemic disease (n = 23); 5) eosinophilic gastroenteritis (EoGE) (n = 19). The result showed that age at diagnosis, ulcer recurrence, atopic dermatitis history, white blood cell count, blood eosinophil count, platelet count, serum albumin level, iron level, erythrocyte sedimentation rate, and C-reactive protein level differed significantly among the 5 groups (all $p < 0.05$). Multiple ulcers and gastric mucosal nodularity under endoscopy also differed among the 5 groups (all $p < 0.05$). The EoGE group has older age ($p = 0.022$), higher rate of ulcer recurrence ($p = 0.018$), atopic dermatitis history ($p = 0.001$), and both blood and tissue eosinophilia (both $p = 0.001$). The authors conclude that EoGE ulcers constituted 10.2% of *H. pylori*-negative and gastrotoxic drug-negative peptic ulcers (HNGN-PU) in pediatric patients. In children with HNGN-PU, peripheral eosinophilia, ulcer recurrence, and atopic dermatitis history might imply EoGE, necessitating thorough investigation of tissue eosinophils during endoscopic biopsy.

Esophageal histological precursor lesions and subsequent 8.5-year cancer risk in a population-based prospective study in China

Wei WQ, Hao CQ, Guan CT, Song GH, Wang M, Zhao DL, Li BY, Bai WL, Hou PY, Wang JW, Jin GL, Lei FH, Li XQ, Xue LY, Wang GQ, Abnet CC, Taylor PR, Dawsey SM, Qiao YL
Am J Gastroenterol. 2020;115(7):1036-1044.
https://pubmed.ncbi.nlm.nih.gov/32618654/

Esophageal squamous dysplasia and carcinoma in situ (CIS) are precursor lesions of esophageal squamous cell carcinoma (ESCC). The authors conducted a prospective cohort study to investigate the natural histories of different pathological diagnoses and precursor lesions of ESCC in a Chinese high risk population. Endoscopic screening was performed on 21,111 participants aged 40-69 years from 3 high risk areas of China in 2005-2009 and the cohort was followed through 2016. During a median follow up of 8.5 years (interquartile range 7.5-10.5 years), 143 new ESCC cases (0.68%) and 62 ESCC deaths (0.29%) were identified. The authors

found that increasing grade of squamous dysplasia was associated with increasing risk of ESCC incidence and mortality. The cumulative incidence rates for severe dysplasia/CIS, moderate dysplasia, and mild dysplasia were 15.5%, 4.5%, and 1.4%, respectively. Older individuals (50-69 years) had 3.1x higher ESCC incidence than younger individuals (40-49 years). Men had 2.4x higher incidence than women. The authors conclude by stating that this study confirms that increasing grades of squamous dysplasia are associated with increasing risk of ESCC and make the following statements: 1. During ESCC screening, it is not necessary to biopsy patients with endoscopically normal mucosa; 2. In high risk areas of China, postponing the start of ESCC screening until 50 years of age is reasonable; 3. Patients with severe dysplasia/CIS or endoscopically worrisome moderate dysplasia should receive endoscopic therapy; 4. In China, patients with endoscopically unremarkable moderate dysplasia can probably undergo surveillance at 3-year intervals; 5. In China, the surveillance interval for patients with mild dysplasia can probably be lengthened to 5 years.

PD-L1 expression in gastroesophageal dysplastic lesions

Fassan M, Brignola S, Pennelli G, G, Valentina Angerilli V, Bressan A, Pellino A, Lanza C, Salmaso R, Lonardi S, Pucciarelli S, Spolverato G, Scarpa M, Realdon S, Farinati F, Luchini C, Rugge M, Loupakis F
Virchows Arch. 2020;477(1):151-156.
https://pubmed.ncbi.nlm.nih.gov/31724072/

This study looks at PD-L1 expression in low grade and high grade dysplastic lesions of the gastroesophageal junction. The authors reported a high prevalence of PD-L1 positivity in dysplastic lesions (~30%). Higher prevalence was seen in high grade lesions (dysplasia and adenocarcinoma) compared to low grade and in lesions with mismatch repair deficiency.

Very low risk of lymph node metastasis in Epstein-Barr virus-associated early gastric carcinoma with lymphoid stroma

Cheng Y, Zhou X, Xu K, Huang J, Huang Q
BMC Gastroenterol. 2020;20(1):273.
https://pubmed.ncbi.nlm.nih.gov/32807085

This is a retrospective study on Epstein-Barr virus-associated early gastric carcinoma with lymphoid stroma (EBV-GCLS). Eight EBV-GCLS cases and 109 conventional early gastric carcinomas, which were divided into intramucosal, SM1, and SM2 subgroups were included. The latter 2 subgroups were classified according to the submucosal invasion depth below or over 500 μm. All 8 EBV-GCLSs occurred in male patients and invaded deep submucosa (SM2) without lymph node metastasis (LNM), four (50%) of which had synchronous non-gastric malignant tumors (3 gastric gastrointestinal stromal tumors and 1 primary clear cell renal cell carcinoma), and four (50%) arose in the proximal stomach. Compared to conventional early

gastric carcinomas, EBV-GCLS was significantly more frequent with SM2 invasion, poor differentiation, and synchronous non-gastric carcinoma tumor. In invasion-depth stratified comparisons in the SM2 subgroup, the frequency of LNM in EBV-GCLS was significantly lower than that in conventional early gastric carcinomas ($p < 0.05$) and the 5-year survival rate of patients with EBV-GCLS was better than that with conventional early gastric carcinomas in 3 subgroups (100% vs 91.5, 85.7, 83.9%, respectively), although the differences did not reach a statistically significant level due to the small sample size. The authors concluded that even with poor differentiation and SM2 invasion, EBV-GCLS showed very low risk of LNM and may be a candidate for endoscopic therapy such as endoscopic submucosal dissection.

Impact of proximal resection margin involvement on survival outcome in patients with proximal gastric cancer

Bochao Zhao, Huiwen Lu, Shiyang Bao, Rui Luo, Di Mei, Huimian Xu, Baojun Huang
Clin Pathol. 2020;73(8):470-475.
https://pubmed.ncbi.nlm.nih.gov/31879270/

The purpose of this study was to evaluate for potential risk factors associated with proximal gastric margin involvement in resections for gastric carcinomas. The authors evaluated 488 cases of proximal gastric carcinoma, 37 of which (7.6%) involved the proximal surgical margin. Involvement of this margin was associated with a number of pathologic features including advanced tumor stage, tumor size, and lymphovascular invasion. Involvement of this margin was found to be associated with a poorer prognosis and was also noted to be an independent prognostic factor by multivariate analysis along with T stage and N stage.

Prognostic perspectives of PD-L1 combined with tumor-infiltrating lymphocytes, Epstein-Barr virus, and microsatellite instability in gastric carcinomas
Choi E, Mee Chang MS, Byeon SJ, Jin H, Jung KC, Kim H, Lee KL, Kim W, Park JH, Kim KH, Kim JS, Choi IS, Han DS, Ahn HS, Heo SC
Ann Diagn Pathol 2020;15(1):69.
https://pubmed.ncbi.nlm.nih.gov/32498695/

In this study, the prognostic significance of PD-L1 status in relationship to tumor infiltrating lymphocytes, microsatellite instability (MSI) and EBV status was studied in ~ 500 patients with stage 2-4a gastric adenocarcinoma who received adjuvant therapy after surgical resection. The authors found that the significance of PDL-1 status is dependent on the tumor environment, EBV and MSI, and recommended combining these factors in evaluating PD-L1 in gastric adenocarcinoma.

An integrative morphomolecular classification system of gastric carcinoma with distinct clinical outcomes

Tsai JH, Jeng YM, Chen KH, Lee CH, Yuan CT, Liau JL
Am J Surg Pathol. 2020;44:1017-1030.
https://pubmed.ncbi.nlm.nih.gov/32568823/

The authors analyzed the morphologic and molecular characteristics in 329 gastric cancer patients using EBV in situ hybridization, immunohistochemistry for mismatch repair proteins, and DNA flow cytometry in an attempt to develop a practical classification scheme that could possibly segregate into prognostically relevant groups. This classification system incorporates molecular features, based on the Cancer Genome Atlas Consortium (TCGA) study. A 4-tier morphologic classification was proposed - diffuse (poorly cohesive signet ring-like cells and/or plasmacytoid cells and/or lymphohistiocytoid –like cells), intestinal (glandular structures, reminiscent of colorectal carcinoma), tubular (irregular tubular, microglandular, or acinar glands of varying diameters) , and lymphoid types (well circumscribed tumor enriched with tumor-associated immune cells present within the tumor reactive stroma, between the tumor islands, and also invading the tumor proper). A strong correlation was identified between the clinicopathologic features and 4 morphologic patterns. Diffuse-type gastric carcinoma showed female predilection and was a decade younger than the other histologic types (59.4 vs. ~69.4y) (both P<0.001). *Helicobacter* infection was significantly associated with tubular-type gastric carcinoma, but less significantly associated with lymphoid histology (P=0.049). Diffuse-type and tubular-type gastric carcinomas were strongly associated with a higher TNM stage, whereas intestinal-type and lymphoid-type gastric carcinomas were associated with a lower TNM stage (P < 0.001). Lymphoid histology strongly associated with EBV infection and PMS2/ MLH1-deficiency (both P < 0.001). HER2 overexpression and SATB2 expression more frequently occurred in intestinal histology (both P < 0.001). Loss of ARID1A expression was strikingly associated with lymphoid histology (P < 0.001). Negative E-cadherin expression was correlated with diffuse histology (P = 0.001). Programmed death-ligand 1 expression was most frequently present in lymphoid-type gastric carcinoma than other histologic subtypes and correlated with the molecular features of PMS2/MLH1-deficiency and EBV infection (all P < 0.001). Aneuploidy was highly correlated with intestinal type and the least with the lymphoid type (P < 0.001). Notably, lymphoid-type gastric carcinoma showed the best outcome, whereas tubular type showed the worst survival rate (P < 0.001). The authors propose a morphomolecular classification system for gastric carcinoma that correlated with the molecular features described in the TCGA study. The distinguishable morphogenetic categories not only differ in clinical and molecular characteristics but also segregate patients into prognostically distinct groups, leading to optimal clinical management.

Clinical and genomic characteristics of mucosal signet-ring cell carcinoma in *Helicobacter pylori*-uninfected stomach

Kiso M, Urabe Y, Ito M, Masuda K, Boda T, Kotachi T, Hata K, Yorita N, Nagasaki N, Abduwali M, Hiyama Y, Oka S, Tanaka S, Chayama K
BMC Gastroenterol, 2020;20(1):243.

https://pubmed.ncbi.nlm.nih.gov/32727394

This study aims to clarify the pathological and genetic features of signet ring cell carcinoma (SRCC) in *H. pylori*-uninfected patients. Seventeen *H. pylori*-uninfected patients with mucosal SRCCs were enrolled and their clinicopathological characteristics were compared with those of *H. pylori*-infected patients with mucosal SRCCs. Seven SRCCs without *H. pylori*-infected, including two invasive SRCCs, and seven *H. pylori*-infected SRCCs were subjected to a genetic analysis using next-generation sequencing. *H. pylori*-uninfected patients with mucosal SRCCs revealed male dominancy and a significantly higher prevalence of smokers as compared with the *H. pylori*-infected patients with SRCC. A *CDH1* mutation (frame shift indel) was detected in one *H. pylori*-uninfected cancer not only in the mucosal SRCC but also in the invasive portion. A *TP53* mutation was detected in one SRCC without *H. pylori*-infected. In the control group, *ARID1A* and *TP53* mutations were detected in one SRCC each. The authors concluded that some SRCCs in *H. pylori*-uninfected patients may have a malignant potential similar to that of SRCCs in *H. pylori*-infected patients. Smoking may not be the main carcinogenic factor for the development of SRCCs among the *H. pylori*-uninfected patients.

Predictors of lymph node metastasis and differences between pure and mixed histologic types of early gastric signet-ring cell carcinomas

Chu Y, Mao T, Li X, Jing X, Ren M, Huang Z, Zhou XB, Chen Y, Tian ZL
Am J Surg Pathol. 2020;44:934-942.
https://pubmed.ncbi.nlm.nih.gov/32149737/

The authors aimed to investigate the differences between pure (> 50% of isolated carcinoma cells containing intracytoplasmic mucin) and mixed (adenocarcinoma with 10% to 50% of isolated carcinoma cells containing intracytoplasmic mucin) signet ring cell carcinomas (SRCCs). They also aimed to identify the factors that predict the successful endoscopic treatment of early gastric cancer (EGC) with signet-ring cell histology. 231 early gastric SRCC patients were included in this study. The overall incidence of lymph node metastases (LNM) in early SRCC was 16.0% (37/231): 6.9% (8/116) and 25.2% (29/115) in patients with pure and mixed SRCC, respectively. On multivariate analysis, the significant independent risk factors for LNM in early SRCC were SM2 (> 500 μm depth of invasion), lymphovascular invasion (LVI), the pathologic pattern of mixed SRCC, the presence of ulcers and a lesion size over 20 mm. The LNM rate was much higher in patients with mixed SRCC (25.2%) than in those with pure SRCC (6.9%) ($P < 0.0001$). Additionally, compared with pure SRCC, the mixed subtype was associated with higher LVI (6.0% vs 20.9%, $P < 0.001$), more perineural invasion (6.0% vs 16.5%, $P= 0.012$), and older age ($P = 0.045$). SM1 and SM2 invasion were less frequent in the pure SRC group than in the mixed SRCC group ($P = 0.009$). Patients with pure SRCC showed significantly longer overall survival ($P = 0.004$) and disease-specific survival ($P = 0.002$) than mixed SRCC patients. The authors propose that the presence of a pure or mixed SRCC component should be reported in daily pathologic practice, especially in cases of early cancers, and such findings should be taken into consideration while making clinical decisions.

The clinicopathologic and molecular analysis of gastric cancer with altered SMARCA4 expression

Huang SC, Ng KF, Yeh TS, Cheng CT, Chen MC, Chao YC, Chuang HC, Liu YJ, Chen TC
Histopathology. 2020;77(2):250-261.
https://pubmed.ncbi.nlm.nih.gov/32343857/

Few studies have investigated alterations in the switch/sucrose non-fermenting chromatin remodeling complex (SWI/SNF) in gastric carcinoma. Alterations in the DNA-binding subunit ARID1A with associated decreased protein expression are detected in a minority of EBV-associated and microsatellite unstable gastric cancers, and decreased SMARCA2 expression has been associated with papillary and poorly differentiated gastric adenocarcinomas. In this study, the authors investigate the prevalence and clinicopathologic features of alterations in SMARCA4 expression in gastric cancers. Microarrays were constructed from 1199 consecutive gastric carcinoma cases regardless of histologic pattern and subjected to immunohistochemical staining for SMARCA4. Twenty-seven cases (2%) showed alterations in SMARCA4 expression including loss of expression in 6 (22%), reduced expression relative to background controls in 9 (33%), and heterogenous expression in 12 (44%). Alterations in SMARCA4 expression were associated with a higher median age, less perineural invasion, and a lower frequency of N3 disease but tendency for regional lymph node recurrence than gastric cancers with retained SMARCA4 expression. While alterations in SMARCA4 occurred more frequently in EBV-positive and MSI gastric carcinomas, 5 of the 6 (83%) gastric cancers showing lost SMARCA4 expression were non-EBV-associated/non-MSI tumors. Concurrent alterations in other SWI/SNF complex components occurred along with SMARCA4 in 17 of the 27 altered cases, regardless of pattern. Five cases with altered SMARCA4 show abnormalities in different SWI/SNF complex components in other areas of the tumor, indicating tumoral heterogeneity. While solid and undifferentiated histologic patterns, including those with rhabdoid morphology, were the most frequently encountered phenotype, tubular and papillary patterns of growth were encountered not infrequently, suggesting that an undifferentiated or rhabdoid phenotype is not entirely specific for SWI/SNF complex disruption. Alterations in SMARCA4 were, however, associated with a worse prognosis in Stage 3 gastric carcinomas, as well as with EBV-associated carcinomas and intestinal type MSI-stable carcinomas. Sequencing studies demonstrated that the incidence of mutations in *SMARCA4* was significantly higher in cases that showed loss of nuclear SMARCA4, while cases with reduced SMARCA4 expression were typically associated with alterations in *ARID1A*. The authors conclude from this work that SMARCA4 alterations are rare overall in gastric carcinomas but show a variety of histologic growth patterns and may be associated with a poor prognosis and inferior response to chemotherapy. While intratumoral heterogeneity exists and is an important consideration, loss of expression of SMARCA4 was frequently associated with deleterious genetic alterations in *SMARCA4* in EBV-negative, MSI-stable gastric cancers. Reduced or heterogenous expression tended to occur in the setting of *ARID1A* alterations.

METTL3-mediated m6A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance

Wang Q, Chen C, Ding Q, Zhao Y, Wang Z, Chen J, Jiang Z, Zhang Y, Xu G, Zhang J, Zhou J, Sun B, Zou X, Wang S
Gut. 2020;69(7):1193-1205.
https://pubmed.ncbi.nlm.nih.gov/31582403/

This study evaluates the prognostic value of METTL3 expression using immunohistochemistry in human gastric cancer along with its biological role in tumor growth and liver metastasis in vitro and in vivo. They found METTL3 is significantly elevated in gastric cancer, associated with poor prognosis and promotes tumor angiogenesis and can potentially be used as a therapeutic target.

Influence of gastrectomy for gastric cancer treatment on faecal microbiome and metabolome profiles

Erawijantari PP, Mizutani S, Shiroma H, Shiba S, Nakajima T, Sakamoto T, Saito Y, Fukuda S, Yachida S, Yamada T
Gut. 2020;69(8):1404-1415.
https://pubmed.ncbi.nlm.nih.gov/31953253/

This study looked at the fecal microbiome of gastrectomy patients compared to controls. They found higher species diversity and richness and greater abundance of aerobes, facultative anaerobes and oral microbes in gastrectomy patients, suggesting an association with postoperative comorbidities.

Retrospective study of the differential diagnosis between cryptogenic multifocal ulcerous stenosing enteritis and small bowel Crohn's disease

Chen D, Liu W, Zhou W, Zheng W, Wu D, Qian J
BMC Gastroenterol, 2020;20(1):252.
https://pubmed.ncbi.nlm.nih.gov/32758146

This retrospective study aims to compare clinical features of cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) to small bowel Crohn's disease (SBCD). Fourteen patients with CMUSE and 61 patients with SBCD were included. Hematochezia, intestinal stenosis, and circumferential ulcers were more frequent in CMUSE patients, while diarrhea, elevated ESR, extra-enteric findings, and longitudinal ulcers were more common in SBCD patients. All ulcers observed in CMUSE patients were within mucosal and submucosal layers, but 8 (44.4%) SBCD patients had deep ulcers that reached beyond submucosal layers (P = 0.003). Ulcers were

located at strictures in 9 (90.0%) CMUSE patients but only in 1 (5.6%) SBCD patient (P = 0.000). The authors concluded that GI symptoms, ESR, imaging, endoscopic, and pathologic features help to distinguish CMUSE from SBCD.

PD-L1 in small bowel adenocarcinoma is associated with etiology and tumor-infiltrating lymphocytes, in addition to microsatellite instability

Giuffrida P, Arpa G, Grillo F, Klersy C, Sampietro G, Ardizzone S, Fociani P, Fiocca R, Latella G, Sessa F, D'Errico A, Malvi D, Mescoli C, Rugge M, Nesi G, Ferrero S, Furlan D, Poggioli G, Rizzello F, Macciomei MC, Santini D, Volta U, De Giorgio R, Caio G, Calabrò A, Ciacci C, D'Armiento M, Rizzo A, Solina G, Martino M, Tonelli F, Villanacci V, Cannizzaro R, Canzonieri V, Florena AM, Biancone L, Monteleone G, Caronna R, Ciardi A, Elli L, Caprioli F, Vecchi M, D'Incà R, Zingone F, D'Odorico A, Lenti MV, Oreggia B, Reggiani Bonetti L, Astegiano M, Biletta E, Cantoro L, Giannone AG, Orlandi A, Papi C, Perfetti V, Quaquarini E, Sandri G, Silano M, Usai P, Barresi V, Ciccocioppo R, Luinetti O, Pedrazzoli P, Pietrabissa A, Viglio A, Paulli M, Corazza GR, Solcia E, Vanoli A, Di Sabatino A
Mod Pathol. 2020;33(7):1398-1409.
https://pubmed.ncbi.nlm.nih.gov/32066859/

The authors investigated PD-L1 and PD-1 expression in small bowel adenocarcinoma (SBA). In this retrospective longitudinal study, 121 surgically resected SBAs, including 34 celiac-associated SBAs, 49 Crohn's disease associated SBAs, and 38 sporadic SBAs were evaluated. PD-L1 positivity was seen in 26% of the cases, with a significantly higher percentage seen in celiac and Crohn's associated SBAs (35%) compared to sporadic SBAs (5%; p=0.001). PD-L1 positivity was also associated with MSI-H cases compared to non-MSI-H (41% vs 18%; p=0.013). PD-L1+ tumors were more frequently medullary in histotype, had higher tumor infiltrating lymphocyte density, and better outcome. The authors suggest that PD-L1 expression, along with MSI status, TIL density and tumor mutation burden should be considered as potential biomarkers of response to PD-1/PD-L1 pathway blockade in clinical trials focused on SBA.

A malignant neoplasm from the jejunum with a *MALAT1-GLI1* fusion and 26-year survival history

Prall OWJ, McEvoy CRE, Byrne DJ, Iravani A, Browning J, Choong DYH, Yellapu B, O'Haire S, Smith K, Luen SJ, Mitchell PLR, Desai J, Fox SB, Fellowes A, Xu H
Int J Surg Pathol. 2020;28(5):553-562.
https://pubmed.ncbi.nlm.nih.gov/31931637/

This is a case report of a malignant tumor of the jejunum with a *MALAT1-GLI1* gene fusion (epithelioid and spindle cell morphology) expressing truncated active GLI1 protein and GLI1 targets, detectable by immunohistochemistry. The tumor recurred multiple times over 26 years.

Histologic characteristics of human intestinal spirochetosis in operatively resected specimens

Ogata S, Shimizu K, Tominaga S, Nakanishi K
Virchows Arch. 2020;477(1):57-63.
https://pubmed.ncbi.nlm.nih.gov/32144538/

This is a retrospective study on human intestinal spirochetosis (HIS) in colectomy or appendectomy specimens obtained in 6 years at a single medical center. They found a heterogeneous distribution of them within the large intestine, an ileal presence, superficial location of HIS-related findings and presence of *Brachyspira* or its derivatives within macrophages in the lamina propria and immune apparatus (lymphoid follicles in superficial wall structures (lamina propria or submucosa) and lymph nodes).

Programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) expression in PD-1 inhibitor-associated colitis and its mimics

Cassol CA, Owen D, Kendra K, Braga JR, Frankel WL, Arnold CA
Histopathology. 2020;77(2):240-249.
https://pubmed.ncbi.nlm.nih.gov/32298485/

Immune-related adverse effects (IRAEs) occurring in the setting of immune checkpoint inhibitor use may involve several organ systems, including the gastrointestinal tract where they can mimic infectious and inflammatory conditions from a clinical and histopathologic perspective. In the kidney, PD-1 blockade can induce acute interstitial nephritis is associated with the increased expression of PD-L1 by renal tubular epithelial cells. In this study, the authors investigate the expression of PD-L1 and PD-1 by colonic epithelial and inflammatory cells in the setting of PD-1 inhibitor-associated colitis (PD1i colitis) and compare the pattern and intensity of reactivity to potential clinical and histologic mimics including 8 normal colon controls derived from ischemic colitis resections, 10 patients with inflammatory bowel disease, and 8 patients with CMV-colitis. Epithelial cell PD-L1 expression was higher in patients with PD1i colitis compared to normal controls. PD-L1 expression by epithelial cells was highest in inflammatory bowel disease cases. In contrast, inflammatory cell PD-1 expression was highest in the setting of infectious colitis, lower in inflammatory bowel disease cases, and minimal to absent in normal colon and in patients undergoing PD-1 inhibition. PD-L1 expression by inflammatory cells was significantly higher in PD1i colitis cases compared with normal colon, but did not differ from that seen in the setting of infection and inflammatory bowel disease. The authors conclude from these data that the increased expression of PD-L1 by epithelial cells seen in PD1i colitis and inflammatory bowel disease may reflect a general mechanism by which the gut mucosa protects itself from immune-mediated injury. They importantly do not endorse the use of PD-L1 and PD-1 immunohistochemical stains to differentiate PD1i colitis from histologic mimics in clinical practice.

Lymphocytic colitis pattern of injury presenting as endoscopic polyps: a case series

Fu Z, Aldyab M, Arslan M, Boguniewicz A, Karamchandani D, Lee H
Hum Pathol. 2020;101:10-17.
https://pubmed.ncbi.nlm.nih.gov/32387106/

In this case series, the authors present 17 patients who were found to have polypoid colonic mucosa endoscopically, but lymphocytic colitis (LC) histologically, without evidence of hyperplastic or adenomatous change to explain the endoscopic appearance. The authors compare the histology and clinical history from these 17 patients to those of 40 control cases of non-polypoid lymphocytic colitis. Overall, patients with polypoid or non-polypoid LC were predominantly women over the age of 50 years. Patients with non-polypoid LC all had a chief complaint of watery diarrhea, as did 10 (59%) patients in the polypoid LC group. Most patients with "polypoid" LC had only one polyp, and the polyps were most often located in the left colon. At least half of the polyps had a sessile appearance, and the colonic background mucosa appeared normal in all but one patient. The histologic features of polypoid LC and non-polypoid LC were essentially identical. In addition, there was no significant difference in comorbidities between the polypoid and non-polypoid LC groups, with the exception of hypertension being more common in the "polypoid" group. The authors suggest that polypoid LC may be part of the spectrum of microscopic colitis.

Chronic active Epstein-Barr virus infection involving gastrointestinal tract mimicking inflammatory bowel disease

Xu W, Jiang X, Chen J, Mao Q, Zhao X, Sun X, Zhong L, Rong L
BMC Gastroenterol. 2020;20(1):257.
https://pubmed.ncbi.nlm.nih.gov/32758149

This retrospective study reviewed 12 cases of chronic active Epstein-Barr virus infection (CAEBV) in immunocompetent patients with gastrointestinal tract involvement. The control group was consisted of twenty-four IBD patients with EBV-DNA value increased in peripheral blood. The clinicopathologic and endoscopic characteristics were reviewed and analyzed. The major clinical presentations of CAEBV patients were intermittent fever, hepatomegaly/ splenomegaly, lymphadenopathy, diarrhea, and hematochezia. Compared with IBD patients, the incidence of intermittent fever and increased level of ferritin were significantly higher among CAEBV patients. The median values for EBV detected in peripheral blood were significantly higher in CAEBV group than in IBD group ($p<0.05$). The main endoscopic findings of CAEBV included multifocal or isolated, irregular, multiform ulcers and diffuse inflammation, lacking of typical cobblestone appearance. Ten patients died within 5 years of disease onset. The average survival time is 21 months. The authors concluded that symptoms such as intermittent fever, increased level of ferritin, and atypical endoscopic findings could be a sign

for CAEBV. Early detections of EBV-DNA in serum and EBV-encoded small nuclear RNA (EBER) by in situ hybridization in intestinal tissue are essential for differential diagnosis between CAEBV and IBD.

Postoperative endoscopic recurrence on the neoterminal ileum but not on the anastomosis is mainly driving long-term outcomes in Crohn's disease

Hammoudi N, Auzolle C, Tran Minh ML, Boschetti G, Bezault M, Buisson A, Pariente B, Treton X, Seksik P, Fumery M, Le Bourhis L, Nancey S, Allez M
Am J Gastroenterol. 2020;115(7):1084-1093.
https://pubmed.ncbi.nlm.nih.gov/32618659/

The authors aimed to evaluate the association between the presence and severity of anastomatic and ileal lesions at early postoperative ileocolonoscopy and long term outcomes in patients with Crohn's disease (CD). This was a prospective multicenter study that included patients operated on for ileal or ileocolonic CD. An ileocolonoscopy was performed 6 months after surgery and an endoscopic score describing the anastamotic and ileal lesions was built. Clinical relapse was defined by CD-related symptoms confirmed by imaging, endoscopy, or therapeutic intensification; CD-related complications; or subsequent surgery. 225 patients were recruited, and long term follow up was available in 193 patients. Median follow up was 3.82 years and median clinical recurrence free survival was 47.6 months. Recurrence free survival was significantly shorter in patients with ileal lesions at early postoperative endoscopy regardless of severity, as compared to those without ileal lesions (p=0.0003). Patients with exclusively ileal lesions had poorer clinical long-term outcomes than patients with exclusively anastamotic lesions (p=0.009). The authors conclude that using an endoscopic score that describes anastamotic and ileal lesions separately might be more appropriate to define postoperative endoscopic recurrence after ileocolonic resection in CD. The authors suggest that patients with ileal lesions could benefit from treatment step up to improve long term outcomes.

Histological and molecular diversity and heterogeneity of precancerous lesions associated with inflammatory bowel diseases

Gui X, Köbel M, Ferraz J, Iacucci M, Ghosh S, Liu S, Ou Y, Perizzolo M, Winkfein RJ, Rambau P, Demetrick DJ
Clin Pathol. 2020;73(7):391-402.
https://pubmed.ncbi.nlm.nih.gov/31801800/

This study reported precancerous lesions in background mucosa in 44 surgically resected bowels of IBD patients including adenomatous and non- adenomatous lesions, and correlated molecular alterations with morphology. The authors found that many of these lesions harbor

common colorectal carcinoma alterations including non- adenomatous lesions, which support their neoplastic nature.

Pathologist experience and concordance in the diagnosis of dysplasia in long-standing inflammatory bowel disease

Jimeno M, Domingo A, Salas I, Sánchez MR, González C, Salas C, Paúles MJ, Sanjuán X, Carballal S, Quintanilla I, Molist G, Cuatrecasas M, Pellisé M
Am J Surg Pathol. 2020;44:955-961.
https://pubmed.ncbi.nlm.nih.gov/32235151/

In this multicenter study, intraobserver and interobserver agreements were assessed among pathologists in the diagnosis of inflammatory bowel disease (IBD)-related dysplasia. Observer characteristics that correlated with concordance deviations in this diagnosis were also analyzed. Eight pathologists evaluated a set of 125 endoscopic biopsy samples from long-standing IBD patients. Two rounds of diagnosis were carried out during a period of 18 months. In total, 1000 diagnoses were obtained in each round (125 samples, 8 observers). Pathologists were grouped on the basis of their experience. Overall interobserver agreement was good (κ=0.73), with an even higher pairwise value (κ=0.86) as well as the intraobserver agreement values (best κ=0.85). The highly prevalent nondysplastic samples were eliminated and the interobserver agreement was still moderate to good (best overall κ=0.50; best paired κ=0.72). There were notable differences between the pathologists working in a high-volume and low-volume practice (best overall κ=0.61 and 0.41, respectively). The authors conclude that the agreement in the diagnosis of dysplasia in IBD endoscopic biopsies may have been undervalued over time and this is the first study evaluating diagnostic robustness of the pathologists' in this field. The authors also suggest that examining a large volume of samples is crucial to increase the consistency in the diagnosis and gradation of IBD-related dysplasia.

Automated quantitation of CD8-positive T cells predicts prognosis in colonic adenocarcinoma with mucinous, signet ring cell, or medullary differentiation independent of mismatch repair protein status

Hartman DJ, Frank M, Seigh L, Choudry H, Pingpank J, Holtzman M, Bartlett D, Bahary N, Pantanowitz L, Pai RK
Am J Surg Pathol. 2020;44:991-1001.
https://pubmed.ncbi.nlm.nih.gov/32205483/

Mucinous, signet ring cell, and medullary differentiation are well-established features of colorectal adenocarcinomas with mismatch repair (MMR) protein deficiency. Still, there are some studies indicating that MMR protein deficiency is not always associated with improved survival in these histologic subtypes, suggesting that additional biomarkers that can predict clinically aggressive disease may be helpful. To this end, the authors used a validated

quantitative digital image analysis platform to evaluate CD8 T-cell density in 259 patients with colonic adenocarcinoma, including 113 patients with tumors demonstrating mucinous, signet ring cell, or medullary differentiation. The CD8-positive T-cell density was correlated with histopathologic variables, MMR status, *KRAS* and *BRAF* mutations, and survival. The authors found that CD8-positive T-cell densities were significantly higher for MMR protein-deficient tumors (P<0.001), *BRAF* V600E mutant tumors (P=0.004), and tumors with medullary differentiation (P<0.001). The CD8-positive T-cell densities did not correlate with mucinous or signet ring cell histology. Only CD8-positive T-cell density and venous invasion were independent predictors of disease-free survival, both within the entire cohort and within the subset of tumors with mucinous, signet ring cell, and medullary differentiation. Increased CD8-positive T-cell density was associated with improved survival both in the entire cohort and in patients with tumors with mucinous, signet ring cell, or medullary differentiation. The prognostic effect of CD8-positive T-cell density was independent of MMR status tumor stage, *KRAS* mutation, and *BRAF* mutation. The authors conclude that the prognostic value of MMR protein deficiency is most likely attributed to increased CD8-positive tumor-associated T cells and that automated quantitative CD8 T-cell analysis in colonic adenocarcinoma may be a better prognostic biomarker of patient survival, particularly for patients with colonic adenocarcinoma with mucinous, signet ring cell, or medullary differentiation.

Tumour infiltrating lymphocyte status is superior to histological grade, DNA mismatch repair and *BRAF* mutation for prognosis of colorectal adenocarcinomas with mucinous differentiation

Williams DS, Mouradov D, Newman MR, Amini E, Nickless DK, Fang CG, Palmieri M, Sakthianandeswaren A, Li S, Ward RL, Hawkins NJ, Skinner I, Jones I, Gibbs P, Sieber OM
Mod Pathol. 2020;33(7):1420-1432.
https://pubmed.ncbi.nlm.nih.gov/32047231/

There are conflicting studies regarding the prognostic impact of mucinous differentiation in colorectal carcinomas. The authors sought to evaluate the prognostic value of tumor classification by mucinous component and examined the changing WHO recommendations regarding whether mucinous CRC should be graded on the basis of defective mismatch repair (dMMR) status (WHO 4th Edition guidelines) or glandular morphology (WHO 5th Edition guidelines). The prognostic interactions between clinico-molecular features and proportion of mucinous component were explored and the prognostic value of TIL status was determined. In a community based cohort of 1643 patients with stage II/III disease, tumor mucinous component, mismatch repair status, *BRAF* mutation, and tumor infiltrating lymphocytes (TILs) were examined. The authors found that tumors with ≤50% mucinous component had similar characteristics to mucinous tumors, such as: female proclivity, proximal location, high grade, TIL-high (≥2 TILs/hpf), dMMR, and *BRAF* mutation. Proportion of mucinous component did not significantly affect disease free survival. In univariate analysis, dMMR status but not histological grade stratified survival for mucinous and mucinous component tumors, but in multivariate analysis dMMR status was not an independent predictor. *BRAF* mutation was associated with

poor prognosis only in non-mucinous microsatellite stable tumors (HR 2.61, 95% CI 1.69-4.03; p<0.001). TILs status was an independent predictor of disease free survival in mucinous/mucinous component tumors (HR 0.40, 95% CI 0.23-0.67; p<0.001), and superior to histological grade, MMR and *BRAF* mutation as a predictor of prognosis. The authors conclude that prognosis for mucinous tumors (with any degree of mucinous differentiation) is strongly associated with TIL status, rather than MMR status, *BRAF* mutation, or histological grade.

Impact on colorectal cancer pathology reporting practice of migration from TNM 5 to TNM 8

Loughrey MB, Kent O, Moore M, Coghlin C, Kelly P, McVeigh G, Coleman HG
Histopathology. 2020;77(2):210-222.
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The classification and reporting of extramural, discontinuous foci of colorectal carcinoma has evolved over the course of different TNM staging systems. While discontinuous foci of mural tumor larger than 3 mm and without evidence of residual nodal tissue were considered to represent nodal disease in TNM5, smaller tumor foci were considered to represent discontinuous invasion of the primary tumor and were interpreted as part of the pT. Many countries, including the UK, did not adopt subsequent TNM staging systems until the introduction of the 8th edition of the UICC classification in 2017. TNM8 refined the concept of tumor deposits introduced in TNM7, which initially defined tumor deposits as discontinuous foci of carcinoma within the pericolorectal fat that lack identifiable nodal tissue. The concept of tumor deposits is retained in TNM8, but now requires the exclusion of extramural venous, lymphatic, and perineural invasion in order to classify a discontinuous focus of carcinoma as a tumor deposit. In this study, the authors investigate changes in reporting practices with regard to extramural venous invasion, perineural invasion, lymph node metastasis, and tumor deposits during the adaptation of TNM8 in their subspecialty gastrointestinal pathology practice. They report a significant increase in the use of ancillary stains (EVG, desmin, S100) following the adaptation of TNM8 (22% of cases versus 41% of cases). There was, however, no change in the proportion of cases that displayed either nodal spread, extramural venous, lymphatic, or perineural spread, with the transition from TNM5 to TNM8. The adaptation of TNM8 did, however, lead to a narrowing of the range amongst individual study pathologists in the reporting of extramural discontinuous tumor (nodal disease, tumor deposits, extramural venous, lymphatic, perineural invasion). Nearly all cases with tumor deposits had one or more other forms of extramural discontinuous tumor growth, including nodal disease and extramural venous invasion, while half of cases lacking tumor deposits had no other extramural regional spread. The authors conclude from this study that TNM8 offers greater reproducibility in documenting discontinuous extramural disease in patients with colorectal cancer than TNM5.

Morphological consistency of desmoplastic reactions between the primary colorectal cancer lesion and associated metastatic lesions
Ao T, Kajiwara Y, Yonemura K, Shinto E, Mochizuki S, Okamoto K, Kishi Y, Ueno H

Virchows Arch. 2020;477(1):47-55
https://pubmed.ncbi.nlm.nih.gov/31932918/

This study looked at the features and prognostic implications of the desmoplastic reaction in lymph nodes and liver metastases compared to the primary lesion of colorectal adenocarcinoma. They classified the desmoplastic reaction as mature, intermediate, or immature, based on keloid-like collagen and myxoid stroma. They found that the desmoplastic reaction in the lymph node and liver metastases correlated with the primary lesion and concluded that they can be classified in the same manner.

Tumor proportion in colon cancer: results from a semiautomatic image analysis approach

Martin B, Banner BM, Schäfer EM, Mayr P, Anthuber M, Schenkirsch G, Märkl B
Virchows Arch. 2020;477(2):185-193.
https://pubmed.ncbi.nlm.nih.gov/32076815/

The authors investigated the tumor stroma ratio (TSR) as prognostic biomarker in colon cancer. They divided cases in low, medium and high TSR. They report that high and low tumor proportions were associated with an adverse overall survival in comparison to medium ones.

Comparison of tissue molecular biomarker testing turnaround times and concordance between standard of care and the Biocartis Idylla platform in patients with colorectal cancer

Tsongalis GJ, Al Turkmani MR, Suriawinata M, Babcock MJ, Mitchell K, Ding Y, Scicchitano L, Tira A, Buckingham L, Atkinson S, Lax A, Aisner DL, Davies KD, Wood HN, O'Neill SS, Levine EA, Sequeira J, Harada S, DeFrank G, Paluri R, Tan BA, Colabella H, Snead C, Cruz-Correa M, Ramirez V, Rojas A, Huang H, Mackinnon AC, Garcia FU, Cavone SM, Elfahal M, Abel G, Vasef MA, Judd A, Linder MW, Alkhateeb K, Skinner WL, Boccia R, Patel K
Am J Clin Pathol. 2020; 154:266-276.
https://pubmed.ncbi.nlm.nih.gov/32525522/

This was a multicenter study in which a fully integrated Idylla automated system (Biocartis) using the *KRAS*, *NRAS*, and *BRAF* cartridges (research use only) were compared to standard-of-care assays used by 20 participating laboratories with a total of 874 enrolled colorectal cancer cases. Idylla average time to results was 4.9 days with a range of 0.4 to 13.5 days. Standard testing had an average turnaround time of 11 days. In-house polymerase chain reaction (PCR) had an average testing turnaround time of 5.6 days, send-out PCR of 22.5 days, in-house Sanger sequencing of 14.7 days, send-out Sanger of 17.8 days, in-house next-generation sequencing (NGS) of 12.5 days, and send-out NGS of 20.0 days. This multicenter study demonstrated that the Idylla system significantly improves genetic biomarker testing turnaround times, requires minimal sample input and is robust with respect to the accurate identification of clinically actionable variants in the *KRAS*, *BRAF*, and *NRAS* genes. Its performance is reproducible in a

variety of testing institutions. The authors conclude that this cartridge-based system offers rapid and reliable testing of clinically actionable mutation in colorectal cancer specimens directly from formalin-fixed, paraffin-embedded tissue sections.

STAT3 activation through IL-6/IL-11 in cancer-associated fibroblasts promotes colorectal tumour development and correlates with poor prognosis

Heichler C, Scheibe K, Schmied A, Geppert Ci, Schmid B, Wirtz S, Thoma OM, Kramer V, Waldner MJ, Büttner C, Farin HF, Pešić M, Knieling F, Merkel S, Grüneboom A, Gunzer M, Grützmann R, Rose-John S, Koralov SB, Kollias G, Vieth M, Hartmann A, Greten FR, Neurath MF, Neufert C
Gut. 2020;69(7):1269-1282
https://pubmed.ncbi.nlm.nih.gov/31685519/

This study evaluated the role of STAT3 activation in cancer-associated fibroblasts in colorectal cancer development. They found out that STAT3 expression is negatively correlated with survival in colorectal cancer patients. The authors also report a critical role of STAT3 activation in fibroblasts in driving colorectal tumourigenesis in vivo.

HIV-positive women with anal high-grade squamous intraepithelial lesions: a study of 153 cases with long-term anogenital surveillance

Liu Y, Prasad-Hayes M, Ganz EM, Poggio JL, Lenskaya V, Malcolm T, Deshmukh A, Zheng W, Sigel K, Gaisa MM
Mod Pathol. 2020;33(8):1589-1594.
https://pubmed.ncbi.nlm.nih.gov/32152521/

The authors sought to characterize the relationship between anal and genital disease in a retrospective cohort of 153 women living with HIV (WLHIV) with biopsy-proven anal high grade squamous intraepithelial lesions (AHSIL), and long term evaluable cervical/vaginal/vulvar histopathology. Based on the presence or absence of genital HSIL, subjects were categorized as having isolated AHSIL or multicentric HSIL. Of the 153 WLHIV, the authors found that 110 (72%) had isolated AHSIL, while 43 (28%) had multicentric HSIL (28 cervical, 16 vulvar, 8 vaginal). Cervical HPV 16/18 infection was associated with multicentric disease (p=0.001). 53% of multicentric cases had genital HSIL preceding AHSIL with a median interval of 13 y (range 2-23). Paired anal and cervical high-risk HPV results within 12 months of AHSIL were available in 60 patients. Of these, 30 (50%) had anal infection alone, while 30 (50%) had anal and cervical infection by HPV 16/18 at both sites (15%), non-16/18 at both sites (13%), or different types (anal HPV 16/18 combined with cervical non-16/18, 22%). The authors conclude by saying that these findings support anal cancer screening for WLHIV irrespective of prior genital disease.

COVID-19 and the digestive system

Ma C, Cong Y, Zhang H
Am J Gastroenterol. 2020;115(7):1003-1006.
https://pubmed.ncbi.nlm.nih.gov/32618648/

Although COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is principally defined by its respiratory symptoms, it is now clear that the virus can also affect the digestive system. This review (received March 18, 2020; accepted April 15, 2020; with most of the data coming from studies in China) focuses on the clinical findings and potential underlying mechanisms of COVID-19 gastrointestinal pathogenesis. Research has shown that angiotensin converting enzyme (ACE2) is the functional receptor of SARS-CoV and is critical to the cellular entry of SARS-CoV. ACE2 is widely distributed in various human organs, and it is reported that ACE2 expression is ~100x higher in the gastrointestinal system (particularly the colon) than in the respiratory system. Positive detection of SARS-CoV-2 in the stool suggests that the virus can replicate and exist in the digestive tract. Digestive symptoms are reported among a clinically important subset of COVID-19 patients, often with concurrently elevated liver enzymes. They include diarrhea, nausea, vomiting, and diminished appetite. In some cases digestive symptoms are reported as the initial presentation of COVID-19, and in one study, 3% of the COVID-19 cases exhibited only digestive symptoms. In a study by Guan et al, patients with severe disease were found to have a higher incidence of diarrhea, nausea or vomiting compared to those with non-severe disease. Intestinal damage caused by SARS-CoV-2 has been verified by autopsy and biopsy. A case report of a patient who underwent gastrointestinal endoscopy found damage to the esophageal mucosa, and lymphoplasmacytic infiltrates in the stomach, duodenum, and rectum. Viral nucleocapsid protein was detected in the cytoplasm of these sites. Another case report found acute hemorrhagic colitis in a COVID-19 patient with primarily digestive symptoms. Abnormal liver function and liver enzymes have been positively associated with COVID-19 severity. Elevated liver enzymes can be seen in up to 43% of patients. Liver damage in COVID-19 tends to be secondary to hypoxia, as autopsy examinations have found moderate microvascular fatty degeneration and inflammation hepatic lobular portal region. The authors in this review conclude that digestive symptoms should be noted in the early stage of COVID-19, and monitoring of liver function and cytokines is imperative to reduce the complications and mortality of COVID-19. The detection of SARS-2-CoV in fecal samples should be considered, particularly in patients with atypical symptoms and may be performed with COVID-19 patients leave the hospital to confirm viral clearance.

Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake

Meslier V, Laiola M, Roager HM, De Filippis F, Roume H, Quinquis B, Giacco R, Mennella I, Ferracane R, Pons N, Pasolli E, Rivellese A, Dragsted LO, Vitaglione P, Ehrlich SD, Ercolini D
Gut. 2020;69(7):1258-1268.
https://pubmed.ncbi.nlm.nih.gov/32075887/

This is a randomized study on the effects of an isocaloric Mediterranean diet intervention on metabolic health, gut microbiome and systemic metabolome in subjects with risk factors for metabolic disease. In summary, switching to a Mediterranean diet while maintaining the same energy intake reduces blood cholesterol and causes multiple favorable changes in microbiome.

Major trends in gastroenterology and hepatology between 2010 and 2019: an overview of advances from the past decade selected by the editorial board of the American Journal of Gastroenterology

Bajaj JS, Brenner DM, Cai Q, Cash BD, Crowell M, DiBaise J, Gallegos-Orozco JF, Gardner TB, Gyawali CP, Ha C, Holtmann G, Jamil LH, Kaplan GG, Karsan HA, Kinoshita Y, Lebwohl B, Leontiadis GI, Lichtenstein GR, Longstreth GF, Muthusamy VR, Oxentenko AS, Pimentel M, Pisegna JR, Rubenstein JH, Russo MW, Saini SD, Samadder NJ, Shaukat A, Simren M, Stevens T, Valdovinos M, Vargas H, Spiegel B, Lacy BE
Am J Gastroenterol. 2020;115(7):1007-1018.
https://pubmed.ncbi.nlm.nih.gov/32618649/

The Associate Editors of the The American Journal of Gastroenterology published this review of advances in Gastroenterology and Hepatology over the past decade in 8 major areas (endoscopy, esophagus, colorectal, small intestine, disorders of gut-brain interaction, hepatology, pancreatology, and inflammatory bowel disease). While much of the article is clinically focused (ie. endoscopy and therapeutic treatments), this summary will concentrate on the advances relevant to gastrointestinal pathology.

Endoscopy - *1.* Interventional endoscopic ultrasound (EUS) has evolved tremendously, with one of the major advances being lumen-opposing stents (LAMS) which enable pancreatic pseudocyst drainage, bile duct drainage, gastroenterostomy, and creation of transgastric fistula to access the excluded stomach in Roux-en-Y anatomy. *2*. Third space endoscopy/submucosal endoscopy: Gastrointestinal lumen is considered the primary or “first space.” Improvements in devices and techniques have allowed endoscopists to gain access to the peritoneal cavity (“second space”). In the past decade these advances have enabled access to the “third space” (submucosal space). Since the introduction of the mucosal flap safety valve (SEMF) technique in 2007, submucosal endoscopy has been used in a variety of gastrointestinal diseases including per oral endoscopic myotomy (POEM) for achalasia, submucosal tunnel endoscopic resection for submucosal tumors, gastric POEM for gastroparesis, and submucosal tunneling endoscopic septum division for Zenker diverticulum. In addition, endoscopic submucosal dissection, which does not use the SEMF technique, has rapidly progressed from an uncommon technique to a well established, routinely performed procedure involving endoscopic en bloc removal of gastrointestinal epithelial lesions.

Gastroesophageal Disorders - *1.* Endoscopic therapy for Barrett esophagus and early esophageal neoplasia began in the 2000s and led to a management revolution in the 2010s. Guidelines shifted from recommending surveillance for low grade dysplasia to considering

endoscopic therapy, from surveillance of esophagectomy for high grade dysplasia to endoscopic therapy, and from esophagectomy to endoscopic therapy for pT1a adenocarcinoma. *2.* The prevalence of *H. pylori* infection and peptic ulcer disease has decreased over the past decade due to better antibiotic and PPI regimens. *3.* Gastric intestinal metaplasia remains a significant issue in clinical practice, endoscopic grading of gastric mucosa remains an important determinant of early gastric cancer. In patients who underwent eradication of *H. pylori* infection, mucosal atrophy was identified to be a critical risk factor for the development of gastric cancer. *4.* Eosinophilic gut disease has been recognized as a significant clinical issue over the past decade. Within the field of eosinophilic esophagitis, PPI responders were demonstrated to have similar demographic, clinical, and molecular characteristics as PPI nonresponders, prompting guidelines against requiring PPI nonresponse as a criterion for EoE diagnosis.

Colorectal - *1.* The past decade has witnessed significant advances in our understanding of familial predisposition to colorectal cancer (CRC) and hereditary syndromes. Individuals with a family history of CRC are at increased risk for developing CRC, the increased risk depends on the degree of biological relationship and the age at which the relatives were diagnosed with CRC. 10-15% of individuals with CRC have pathogenic cancer susceptibility genes that involve both high and moderate penetrance. Healthcare insitutions have begun to adopt universal tumor screening for microsatellite instability to identify patients most likely to have Lynch Syndrome. Advances in technology have made multigene panels affordable. In addition, precision therapy options linked to the genomic basis of CRC are on the rise. *2.* Carcinoid tumors have been renamed neuroendocrine tumors and increased recognition of these tumors has occurred in part due to imaging improvements. *3.* Increased emphasis on high quality colonoscopy – has been a key advancement, and includes monitoring quality metrics and advanced techniques.

Small Intestinal Diseases - *1.* Celiac Disease – Our understanding of celiac disease epidemiology has evolved over the past decade. Cohort and case control studies have found that a higher quantity of gluten consumed during the first 2 years of life was associated with a modest increase in the risk of celiac disease, suggesting that the quantity (rather than the timing) of gluten intake may be a key factor. The burden of the gluten free diet has been documented in recent years, with self-reported treatment for celiac disease rated as more burdensome than that reported by individuals with diabetes mellitus or congestive heart failure.

Inflammatory Bowel Disease (IBD) - *1.* In the past decade there has been a rise in incidence of IBD in newly industrialized countries in Asia, Africa, and Latin America. By contrast, the incidence of IBD has begun to stabilize or decline in North America, Europe and Oceania. However, countries of the Western world are experiencing compounding prevalence and the IBD population is aging. One of the most important changes is the shift away from using clinical symptoms to assess treatment response toward endpoints of mucosal healing.

Next-generation sequencing in high-sensitive detection of mutations in tumors: challenges, advances, and applications

Singh R
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This article reviews next-generation sequencing of tumors, with an emphasis on difficulties in differentiating mutations with low allele fraction from artifacts. As such, the range of reported limit of detection (defined as the minor allele frequency at with 95% of tested samples will be reliably detected) ranges from 2% to 15%. The article provides an overview of the different kinds of artifacts that can be introduced at various stages in the process, including sample and DNA processing (including limitations of FFPE material), PCR amplification, sequencing, and sequencing data analysis. In addition, orthogonal (non-NGS) platforms such as real-time PCR (limit of detection of 0.0002%) and digital droplet PCR (0.001% to 0.1%) are discussed as alternatives when high sensitivity is needed (with the limitation that fewer markers can be assessed simultaneously). Finally, techniques in NGS used to ameliorate errors at low allele fraction are reviewed, including template tagging (i.e. tagging each strand of DNA with a molecular barcode prior to amplification), duplex sequencing (i.e. tagging of both strands of the DNA duplex), and single molecule sequencing (i.e. unamplified single DNA strands in the sample are sequenced individually). Finally, applications for detection of minimal residual disease and detection of circulating tumor DNA are discussed.

Malakoplakia of the gastrointestinal tract: clinicopathologic analysis of 23 cases

Lee M, Ko HM, Rubino A, Lee H, Ryan Gill R, Lagana SM
Diagn Pathol. 2020;15(1):97.
https://pubmed.ncbi.nlm.nih.gov/32709245/

This multi-institutional study evaluated the clinical and pathologic features of gastrointestinal malakoplakia. The authors collected 23 cases with the most common site being the sigmoid colon or rectum (n=10). Other sites of involvement included the descending colon (n=4), stomach/gastroesophageal junction (n=4), appendix (n=2), cecum (n=1), small bowel (n=1), and the peri-anal area (n=1) with most (65%) presenting as polyps or masses. Most patients found to have malakoplakia were immunocompromised (91%).

Unexpected high prevalence of lymphocytic infiltrates in myenteric ganglions in intestinal inertia

Rais R, Chai J, Blaney E, Liu TL
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Intestinal inertia is a form of severe gut dysmotility disorder with prolonged stool transit in the gastrointestinal tract, and represents ∼15% to 30% of constipated patients. The authors aimed to discern if intestinal inertia can be attributed to the lack of myenteric ganglion cells or inflammatory ganglionitis. Resection specimens from 27 intestinal inertia and 28 colon cancer patients were evaluated. All hematoxylin and eosin (H&E) sections were blindly reviewed for evidence of ganglion cell loss, the presence of neuronal hypertrophy and the presence of acute and chronic inflammatory infiltrate. Histologically, ganglionitis was defined by the presence of any inflammatory cell types within the ganglion (neutrophils, lymphocytes, monocytes, eosinophils, and plasma cells). CD3, CD8, and CD20 immunohistochemistry was used to quantify T and B lymphocytes, along with subtyping the T-lymphocyte population by CD8. A hot spot approach with 5 HPFs was used for quantifying inflammatory cells. None of the intestinal inertia nor control cases showed the absence of myenteric ganglion cells. Fifteen (55.6%) of the intestinal inertia cases showed inflammatory cell infiltration in the myenteric ganglion cells, when compared to 3.6% (1/28) control cases ($P<0.0001$). The inertia cases with inflammatory infiltrates were all associated with T lymphocytes (100%), including 1 case with a subset of concurrent B lymphocytes. Three cases (11.1%) had concurrent eosinophil infiltration, and 1 case (3.7%) had concurrent neutrophil infiltration. The average CD3 count was 3.8 cells/HPF. CD8 immunohistochemical stain showed positive staining in 12 of the 15 cases (80%). In contrast, the only control case with lymphocytic ganglionitis showed mixed B and T lymphocytes and eosinophils. The study demonstrates that a significant subset of patients that present with intestinal inertia possess T-cell–associated myenteric ganglionitis, and recognizing these findings may be helpful in the diagnosis of intestinal inertia.

Neuroendocrine cells are commonly absent in the intestinal crypts in autoimmune enteropathy

Lee HE, Lin Yuan L, Wu T
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Autoimmune enteropathy (AIE) in small bowel biopsy is characterized by partial or complete blunting of the villi, deep crypt lymphocytosis, increased crypt apoptosis, minimal surface intraepithelial lymphocytosis, active inflammation with neutrophilic cryptitis/crypt abscess, and absence of goblet cells and/or Paneth cells. The authors aimed to determine the status of neuroendocrine (NE) cells in AIE, as this has not been systematically evaluated in the literature. In this retrospective study, biopsies from 18 AIE patients (baseline [18 small bowel and 8 colon]; and 15 follow-up [11 duodenum and 4 colon] biopsies in 11 patients) and control groups [33 common variable immunodeficiency (CVID) patients (30 small bowel and 16 colon), 15 inflammatory bowel disease patients (5 duodenum and 10 colon), 13 immunoglobulin A deficiency patients (13 duodenum and 5 colon), and 10 normal controls (5 colon and 5 duodenum)] were assessed for villous atrophy, intraepithelial lymphocytosis, acute inflammation, crypt apoptosis, and absence or presence of goblet cells, Paneth cells and plasma cells. Chromogranin immunostain was performed to assess for NE cells, and cases were graded

as absent (≤ 3 NE cells per 10 consecutive, well-oriented crypts), markedly decreased (≤ 15 per 10 consecutive, well-oriented crypts), and intact (> 15 per 10 consecutive, well-oriented crypts). The NE cell status was correlated with histologic features. The median age of 18 AIE patients was 38.5 years (range: 11 to 74 y) and 78% patients were male. Fourteen of 18 (78%) patients (12/18 small bowel and 6/8 colon baseline biopsies) showed loss (absent or markedly decreased) of NE cells. Follow-up biopsies available in 11 patients, showed that 85%(6/7 patients) who showed loss of NE cells in the initial biopsies recovered NE cells in the follow-up biopsies, but 1 patient continued to show loss of NE cells. Four patients who showed intact NE cells in the baseline remained unchanged in the follow-up. Among the control groups, 9% (3/33) CVID patients showed loss of NE cells. NE cells were not lost in any of the biopsies from other controls. NE cell loss was significantly associated with increased crypt apoptosis and loss of goblet cells but not with other histologic findings. The authors conclude that NE cells are frequently lost in the intestinal crypts of the small bowel and colon in patients with AIE, and regained after treatment, and NE cells may be the target cells in addition to enterocytes and goblet cells in the pathogenesis of AIE. Evaluating NE cell status can be used as an adjunct histologic feature to diagnose AIE.

Loss of switch/sucrose non-fermenting complex protein expression in undifferentiated gastrointestinal and pancreatic carcinomas

Tessier-Cloutier B, Schaeffer DF, Bacani J, Marginean CE , Kalloger S, Köbel M, Lee CH
Histopathology. 2020;77(1):46-54.
https://pubmed.ncbi.nlm.nih.gov/32413172/

Loss of function of the switch/sucrose non-fermenting chromatin remodeling complex (SWI/SNF) has been reported in undifferentiated carcinomas of several sites and is associated with rhabdoid features in some instances, as well as an aggressive clinical course. In this study, the authors investigate the expression of the SWI/SNF complex units encoded by *SMARCA4*, *SMARCA2*, *SMARCB1*, *ARID1A*, and *ARID1B*, as well as the mismatch repair proteins MLH1, PMS2, MSH2, and MSH6 in undifferentiated carcinomas of the gastrointestinal and pancreatobiliary tracts. They perform a retrospective review of their pathology archives and identify 31 cases that were initially classified as undifferentiated carcinoma. Review of these cases resulted in 12 being reclassified as poorly differentiated carcinoma. The remaining 19 showed no specific cytologic or architectural pattern of differentiation and were classified as undifferentiated. Eight of these undifferentiated carcinomas were colonic, six gastric, three pancreatic, one appendiceal, and one duodenal in origin. Loss of expression of one of the SWI/SNF complex proteins was seen in 11 of the 19 cases. However, loss of core SWI/SNF complex components (SMARCA4, SMARCB1, co-loss of ARID1A and ARID1B) that disrupts the function of the complex was only seen in 5 of the 19 cases (26%). Over half of the undifferentiated carcinomas were MMR-deficient, with two also exhibiting loss of SWI/SNF core complex components. None of the reclassified poorly differentiated carcinomas showed loss of core SWI/SNF complex proteins by immunohistochemistry. The authors conclude that undifferentiated carcinomas of the gastrointestinal and pancreas frequently show loss SWI/SNF

complex core components and advocate for the use of a limited panel of immunohistochemical stains (SMARCA4, SMARCB1, ARID1B) to support a diagnosis of undifferentiated carcinoma and accurately classify patients for clinical trial inclusion.

Smooth muscle tumors of the gastrointestinal tract: an analysis of prognostic features in 407 cases

Alpert L, Al-Sabti R, Graham RP, Pai RK, Gonzalez RS, Zhang X, Smith V, Wang HL, Westbrook L, Goldblum JR, Bakhshwin A, Shetty S, Klimstra DS, Shia J, Askan G, Robert ME, Thomas C, Frankel WL, Alsomali M, Hagen C, Mostafa ME, Feely MM, Assarzadegan N, Misdraji J, Shih AR, Agostini-Vulaj D, Meis JM, Tang S, Chatterjee D, Kang LI, Hart J, Lee SM, Smith T, Yantiss RK, Hissong EM, Gao ZH, Wu J, Resnick MB, Wu EY, Pai RK, Zhao L, Doyle LA, Chopra S, Panarelli NC, Hu S, Longacre TA, Raghavan SS, Lauwers GY, Ghayouri M, Cooper HS, Nagarathinam R, Bellizzi AM, Kakar S, Hosseini M, Rong J, Greenson JK, Lamps LW, Dong Z, Bronner MP
Mod Pathol. 2020;33(7):1410-1419.
https://pubmed.ncbi.nlm.nih.gov/32051556/

Authors from 31 institutions sought to analyze a large cohort of smooth muscle tumors in the GI tract in order to identify potential prognostic features. A total of 407 immunohistochemical stain confirmed cases were identified: esophagus (n=97, 24%), stomach (n=180, 44%), small bowel (n=74, 18%), and colorectum (n=56, 14%). The mean patient age was 55 y (range 19-92 y), 57% were female. The mean tumor size was 5.4cm (range 0.5-29cm). Post-surgical disease progression (local recurrence, metastasis, or disease related death) occurred in 56 patients (14%). Colorectal tumors were most likely to progress (43%) followed by small bowel (24%), and gastric (8%). None of the esophageal tumors progressed. Tumor size, mitotic activity, moderate to severe atypia, high cellularity, abnormal differentiation, tumor necrosis, mucosal ulceration, lamina propria involvement, and serosal involvement were all significantly associated with progression, However, age, sex, and margin status were not significantly associated with progression. A risk assessment table was created based on tumor site, size, and mitotic count. Receiver operating characteristic method was used to determine the optimal cutoff for tumor size and mitotic activity. Based on the cutoffs, cases were divided into subgroups. Kaplan-Meier analysis for each subgroup revealed progression-based tiers. The authors conclude that non-esophageal gastrointestinal smooth muscle tumors >10cm and/or showing ≥3 mitoses/5mm2 may behave aggressively and warrant close follow-up.

Colonic neurogenic lesion: an admixture of mucosal neurofibromatous lesion and submucosal ganglioneuromatous lesion with transition

Hashimoto H, Koda H, Horiuchi H, Takayama M, Toyoda J, Momiyama M, Harihara Y, Morikawa T
Int J Surg Pathol. 2020;28(5):563-568.
https://pubmed.ncbi.nlm.nih.gov/32028811/

This is a case report of an unclassifiable neural lesion (mucosal neurofibromatous and submucosal ganglioneuromatous lesions) of the sigmoid colon, incidentally detected in a 68-year-old man treated with laparoscopic low anterior resection for an advanced carcinoma.

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American Journal of Surgical Pathology
Annals of Diagnostic Pathology
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