GIPS Journal Watch
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Clinicopathologic features of varicella zoster virus infection of the upper gastrointestinal tract

Mostyka M, Shia J, Neumann WL, Whitney-Miller CL, Feely M, Yantiss RK
Am J Surg Pathol. 2021;45(2):209-214.
https://pubmed.ncbi.nlm.nih.gov/32826528/

Varicella zoster virus (VZV) and herpes simplex virus (HSV) both cause disease in the gastrointestinal tract with a predilection to affect the esophagus. These viruses produce similar viral cytopathic changes with multinucleation, nuclear molding, and brightly eosinophilic (Cowdry A) or basophilic (Cowdry B) intranuclear inclusions. The authors describe the clinicopathologic features of VZV-related upper gastrointestinal tract injury. Six patients with VZV infection involving the upper gastrointestinal tract, in particular the esophagus (n=3), stomach (n=2), or both (n=1) were included and were compared to 14 HSV-related esophagitis controls. All patients were immunocompromised adults, particularly solid organ or stem cell transplant recipients. Five patients had cutaneous and gastrointestinal zoster; 1 had gastrointestinal disease alone. VZV caused hemorrhagic ulcers with nodularity or erythema, whereas HSV produced round, shallow ulcers on a background of nearly normal mucosa. VZV-related ulcers featured fibrin-rich, pauci-inflammatory hemorrhagic exudates compared with the macrophage and neutrophil-rich exudates of HSV. The cytopathic changes of VZV were distributed throughout the epithelial thickness, especially in a peripapillary distribution. In contrast, HSV inclusions were located in the superficial epithelial layers of intact mucosa and detached keratinocytes. Unlike HSV, gastric VZV inclusions were most numerous in the deep glands and pits where they were accompanied by abundant apoptotic debris and gland dropout. The authors conclude that VZV produces unique patterns of gastrointestinal injury that facilitate its diagnosis. Early recognition of gastrointestinal VZV infection is important because it can lead to potentially life-threatening disseminated disease, and can cause significant morbidity and mortality when left untreated.

Do not ignore those chunks: pill fragment-esophageal injury

AbdullGaffar B, Bamakramah K
Int J Surg Pathol. 2021;29(1):73-75.
https://pubmed.ncbi.nlm.nih.gov/32131658/

This is a very brief review intended to draw attention to medication associated esophageal injury. The article is more general in nature and specific entities are not covered.

Disease course and treatment response of eosinophilic gastrointestinal diseases in children with liver transplantation: long-term follow-up

Ozdogan E, Doganay L, Can D, Arikan C
Am J Gastroenterol. 2021;116(1):188-197.
https://pubmed.ncbi.nlm.nih.gov/33065587/

This is a study of children (<18 yo) who were diagnosed with eosinophilic gastrointestinal disorders (EGIDs) following liver transplantation. In their cohort, 39 (44%) patients were diagnosed with post-transplant EGID (29 with eosinophilic esophagitis, 10 with eosinophilic gastroenteritis). In comparison with the non-EGID group, patients with EGID were significantly younger at transplant, transplanted more frequently due to biliary atresia, and had higher rates of pre-transplant allergy. Post-transplant, they had a higher rate of post-transplant lymphoproliferative disorder. Most patients responded to EGID treatment and had symptomatic resolution at 3 months and histologic resolution at 6 months post-diagnosis.

Performance of gastrointestinal pathologists within a national digital review panel for Barrett's oesophagus in the Netherlands: results of 80 prospective biopsy reviews

Klaver E, van der Wel M, Duits L, Pouw R, Seldenrijk K, Offerhaus J, Visser M, Kate FT, Biermann K, Brosens L, Doukas M, Huysentruyt C, Karrenbeld A, Kats-Ugurlu G, van der Laan J, van Lijnschoten I, Moll F, Ooms A, Tijssen J, Meijer S, Bergman J
J Clin Pathol. 2021;74(1):48-52.
https://pubmed.ncbi.nlm.nih.gov/32467320/

The aim of this study was to evaluate the performance of GI pathologists at the eight Barrett's oesophagus (BO) expert centers in the Netherlands, and to expand the current Dutch Barrett's Pathology Review panel. Low- grade dysplasia (LGD) is a risk factor for carcinoma in BO, and interobserver variability has been shown to be poor in diagnosing such by community pathologists in the Netherlands. In their study, the authors included 80 BO cases which were indefinite for dysplasia (IND) or LGD which were previously submitted to the Dutch Barrett's Pathology Review panel. They created 3 benchmark scores to evaluate each participating pathologist, including % of IND, % agreement with consensus diagnosis, % underdiagnosed in comparison to consensus agreement based on review by 8 expert pathologists. The study was conducted in 2 phases: Phase 1 (review of 41 cases by 7 aspirant pathologists), followed by discussion of discrepant cases, then phase 2 (review of 39 cases by 6 aspirant pathologists). In phase 1, 6 pathologists were within benchmark range for % of IND and % underdiagnosed, but only 1 pathologist met all 3 predetermined benchmark scores. This pathologist was added to the core experts to calculate benchmark ranges for phase 2. In phase 2, all 6 pathologists were within range for % IND and % agreement with consensus. Five met all benchmark scores, and were added to the BO review panel. The authors concluded that the number of experts in the review panel could be expanded using benchmark quality criteria.

Tumor regression grading after neoadjuvant treatment of esophageal and gastroesophageal junction adenocarcinoma: results of an international Delph consensus survey

Sliba G, Detlefsen S, Carneiro F, Conner J, Dorer R, Flejou JF, H Hahn H, Kamaradova K, Mastracci L, Meijer SL, Sabo E, Sheahan K, Riddell R, Wang N, Yantiss RK, Lundell L, Low D, Vieth M, Klevebro F
Hum Pathol. 2021;108:60-67.
https://pubmed.ncbi.nlm.nih.gov/33221343/

Currently, histologic tumor regression grading (TRG) for neoadjuvantly treated esophageal adenocarcinoma is not standardized. Various systems in use attempt to measure how much tumor remains in the original tumor bed as estimated by the amount of treatment-related fibrosis present. The authors of this study hoped to reach an international TRG consensus. To that end, they queried 15 experts in gastrointestinal pathology from 12 countries on their opinions regarding TRG in esophageal and gastroesophageal junction adenocarcinoma via a survey that reported answers via a 5-point Likert scale. After 3 rounds of questioning, the majority of the experts supported a 4-tier system of TRG for the primary tumor, and a 3-tier system for defining regression in lymph nodes. Importantly, the panel wanted this system to differentiate between patients who had a complete histopathologic response (no tumor, Grade 1) from patients who had a near-complete histopathologic response (<10% tumor, Grade 2). Additionally, they set >50% tumor as the set point for minimal or no regression (Grade 4). Overall, the authors concluded that a 4-tier TRG system, as proposed, should be easily reproducible in every day practice while still allowing for clinically relevant differentiation of patient prognosis and adjuvant treatment needs.

Updates on World Health Organization classification and staging of esophageal tumors: implications for future clinical practice

Lam AKY
Hum Pathol. 2021;108:100-112.
https://pubmed.ncbi.nlm.nih.gov/33157124/

The purpose of this article is to familiarize the practicing pathologist with the epithelial tumors of the esophagus and the relevant updates to these entities in the most recent WHO blue book (5th edition), which includes the updated staging criteria as defined by the AJCC 8th edition. Some tumor stage groupings have been separated out in these newer editions: esophageal adenocarcinoma and esophageal squamous cell carcinoma have been separated, as have prognostic groups for patients who have received neoadjuvant therapy and those who have not. Also of note is the change in tumor location for esophageal adenocarcinoma, which now requires the epicenter of the tumor to be within 20 mm of the gastroesophageal junction, rather than 50 mm. The clinical relevance of Her2 testing in these esophageal adenocarcinomas is also discussed. In addition to describing some of the less common epithelial tumors of the

esophagus, the review also details esophageal neuroendocrine neoplasia, the classification of which has been standardized throughout the GI tract.

Risk of squamous cell carcinoma and adenocarcinoma of the esophagus in patients with achalasia: a long-term prospective cohort study in Italy

Zagari RM, Marasco G, Tassi V, Ferretti S, Lugaresi M, Fortunato F, Bazzoli F, Mattioli S
Am J Gastroenterol. 2021;116(2):289-295.
https://pubmed.ncbi.nlm.nih.gov/33009050/

The authors conducted a prospective study looking at a cohort of 566 patients with achalasia. The patients were followed for a mean of 15.5 years after diagnosis of achalasia. In the cohort, 20 patients (15M, 5F) developed esophageal cancer (15 squamous cell carcinoma, 5 adenocarcinoma); the risk of cancer development was significantly higher than the general population but the annual incidence rate of cancer was low (<0.5%). The authors conclude that patients with achalasia have excess risk of developing both squamous cell carcinoma and adenocarcinoma, but that the annual incidence rates were rather low, findings that may have implications for endoscopic surveillance in this patient population.

Low GSTM3 expression is associated with poor disease-free survival in resected esophageal squamous cell carcinoma

Yang F, Wen J, Luo K, Fu J
Diagn Pathol. 2021;16(1):10.
https://pubmed.ncbi.nlm.nih.gov/33482859/

This is a retrospective study about the prognostic significance of Glutathione S-transferase mu 3 (GSTM3) expression in R0 esophageal squamous cell carcinoma (ESCC) +/- adjuvant or neoadjuvant therapy. GSTM3 is one the GST enzymes, which are involved in detoxification of potentially carcinogenic compounds. The authors have previously demonstrated low GSTM3 expression in ESCC compared to adjacent benign epithelium using DNA microarray analysis, and sought to study its prognostic significance. Quantitative real-time PCR for GSTM3 RNA levels was performed in 184 ESCC patients (mRNA cohort) and immunohistochemistry for GSTM3 was performed on an additional 247 ESCC cases (protein cohort) with RO resections. Low mRNA expression was seen in 91 patients (49%) using a cutoff value of 0.662, whereas 37.25% had low protein expression with a staining index 0-4. More poorly differentiated tumor, higher risk of recurrence and worse disease free survival were noted in low GSTM3 patients of both cohorts, but GSTM3 expression did not show significant association with patient's age, gender, tumor location, and pathological stage (pT and pN) in either cohort. The authors concluded that GSTM3 is related to tumor differentiation, and it may function as a tumor suppressor in ESCC as it gets downregulated in ESCC.

Comprehensive clinicopathological and molecular analysis of primary malignant melanoma of the oesophagus

Tsuyama S, Kohsaka S, Hayashi T, Suehara Y, Hashimoto T, Kajiyama Y, Tsurumaru M, Ueno T, Mano H, Yao T, Saito T
Histopathology. 2021;78(2):240-251.
https://pubmed.ncbi.nlm.nih.gov/32654197/

Primary malignant melanoma of the esophagus (PMME) is extremely rare. The molecular drivers of PMME, to this point, have not been fully characterized. In this work, the authors attempt to define the clinicopathologic characteristics of PMME in addition to identifying genetic variants in this tumor type that can inform treatment decisions. They investigated a cohort of 13 PMME cases in tandem with 10 cutaneous melanomas (SKMM). For PMME, the mean patient age was 63.2 years. The vast majority of PMME patients were men, and only one tumor involved the proximal esophagus. Lymph node metastasis was a common finding and was present in 8 cases, including in one tumor that was restricted to the mucosa. Distant metastasis was also detected in all but one case following surgery (92.3%). The median overall survival was only 11.9 months. Ten of the 13 cases underwent NGS which identified alterations in *NF1* in 30% of cases, *SF3B1* in 20%, and *KRAS*, *KIT*, *BRCA2*, *TP53*, and *CDKN2A* in a single case. Mutations common to SKMM, including *BRAF*, were not identified and the tumor mutational burden was significantly lower for PMME than for SKMM. RNA sequencing studies also confirmed a different genetic profile between SKMM and PMME, though PMMEs appeared to cluster with other mucosal melanomas. The authors conclude from this work that PMME differs genetically from SKMM and, given the low tumor mutational burden, infrequent PD-L1 expression, and lack of *BRAF* (V600E) alterations, may not respond to therapies proven to be efficacious in their cutaneous counterparts.

Immune checkpoint inhibitor-induced upper gastrointestinal tract inflammation shows morphologic similarities to, but is immunologically distinct from, *Helicobacter pylori* gastritis and celiac disease

Irshaid L, Robert ME, Zhang X
Arch Pathol Lab Med. 2021;145:191-200.
https://pubmed.ncbi.nlm.nih.gov/33501492/

Immune checkpoint inhibitors are increasingly used in the treatment of a range of malignant neoplasms; however, multi-site immune related adverse events can occur, a common site of which is the tubal gut. The authors aimed to describe the morphologic and immunophenotypic features of immune checkpoint inhibitor-induced upper gastrointestinal tract injury, in comparison with *Helicobacter* gastritis, celiac disease, and findings in the lower GI tract. Cases from patients undergoing immune checkpoint inhibitor therapy (8 patients on anti-CTLA-4 therapy and 6 patients on anti-PD-1/PD-L1 therapy) between 2005 and 2018 were included in

the study. *Helicobacter* gastritis (8 cases) stomach and celiac disease (8 cases) duodenal biopsies were used as inflammatory disease controls, while normal gastric and duodenal biopsies were used as normal controls. Immune checkpoint inhibitor gastritis biopsies were characterized by chronic active gastritis with increased intraepithelial lymphocytes, and mixed neutrophilic and lymphoplasmacytic lamina propria infiltrates. Compared to *Helicobacter* gastritis, checkpoint inhibitor induced gastritis was characterized by decreased severity of lamina propria inflammation and lymphoplasmacytosis, increased intraepithelial lymphocytes, and fewer lymphoid follicles, with no significant difference in activity or apoptosis. Checkpoint inhibitor induced duodenitis was characterized by villous blunting, and was distinguished from celiac disease cases by the presence of activity (absent in celiac disease biopsies); there was otherwise no significant difference in degree of lamina propria inflammation, IELs, lymphoid aggregates, crypt hyperplasia, foveolar metaplasia, or apoptosis. In addition, in cases with lower GI tract biopsies, the inflammatory scores were higher in the upper compared to lower tract biopsies. The authors conclude that checkpoint inhibitor-induced upper GI tract inflammation demonstrates some morphologic features that help distinguish it from *Helicobacter* gastritis and celiac disease.

Histologic and cost-benefit analysis of laparoscopic sleeve gastrectomy specimens performed for morbid obesity

Nowak K, Di Palma A, Chieu K, Quereshy F, Jackson T, Okrainec A, Serra S, Chetty R
Arch Pathol Lab Med. 2021;145:365-370.
https://pubmed.ncbi.nlm.nih.gov/32649836/

Laparoscopic sleeve gastrectomy is a common bariatric procedure for treatment of obesity that is unresponsive to medical management. The authors aimed to perform a cost-benefit analysis on the pathologic evaluation of these specimens. The authors collected 572 laparoscopic sleeve gastrectomy cases between 2010 and 2019. For each case, the number of sections taken, gross descriptions, and final diagnoses were compiled. The number of blocks taken for each specimen ranged from 3-8 (mean of 4.87 blocks). Clinically non-actionable findings represented the vast majority of histologic diagnoses, and included cases reported as ‘no significant pathologic abnormalities’, ‘proton pump inhibitor related changes’, and non-*Helicobacter* chronic gastritis. Clinically actionable histologic findings (26 cases) included *Helicobacter* gastritis, intestinal metaplasia, ECL hyperplasia, neuroendocrine microadenoma, gastrointestinal stromal tumor (GIST), intramucosal signet-ring-cell carcinoma, and a well-differentiated neuroendocrine tumor (grade 1). Clinically actionable histologic findings that were not evident on gross exam included 1 case of *Helicobacter* gastritis, 3 cases of ECL hyperplasia, and 2 cases of intestinal metaplasia. In addition, 1 of the 7 GISTS identified in the course of the study was considered to be clinically actionable, as it was >2 cm in dimension. The authors conclude that, since the vast majority of histologic findings are not clinically actionable ones, that sleeve gastrectomy specimens should be submitted for gross examination only, with sections submitted for microscopic evaluation only if grossly evident lesions are present and if there is a valid clinical indication warranting histologic evaluation.

Cell polarity (the 'four lines') distinguishes gastric dysplasia from epithelial changes in reactive gastropathy

Waters KM, Salimian KJ, Assarzadegan N, Hutchings D, Makhoul EP, Windon AL, Wong MT, Voltaggio L, Montgomery EA
Histopathology. 2021;78(3):453-458.
https://pubmed.ncbi.nlm.nih.gov/32841414/

The development of screening and treatment protocols has the potential to reduce the morbidity and mortality associated with gastric cancer. Unfortunately, the identification of dysplasia in precursor lesions is challenging and has less than ideal interobserver agreement. Previously, these authors demonstrated that the identification of maintained surface polarity (the 'four lines') is a useful feature that aids in differentiating non-dysplastic (preserved polarity) from dysplasia in Barrett esophagus (loss of surface polarity). In this study, the authors investigate a cohort of 91 biopsies of gastric dysplasia and compare them with a group of 60 reactive gastropathy cases. The patients with dysplasia were slightly older than those with reactive gastropathy (66.9 years versus 62.6 years). The dysplastic biopsies were also more likely to be derived from Asian or Hispanic patients. While dysplasia was encountered in both the gastric antrum and body, cases of reactive gastropathy were restricted to the gastric antrum. Most cases of dysplasia were intestinal type (64.8%). Foveolar type (15.4%), dysplasia in a fundic gland polyp (15.4%), dysplasia in a pyloric gland adenoma (3.3%), and dysplasia in an oxyntic gland adenoma (1.1%) were all less common. All 88 cases of dysplasia with an evaluable surface component showed disruption of the 'four lines'. In foveolar dysplasia, cells had jumbled nuclei and preserved apical mucin but no consistent cytoplasmic space. In intestinal dysplasia, there was loss of the apical mucin cap and an abrupt transition to non-dysplastic epithelium. Dysplasia in fundic gland polyps resembled that seen in foveolar dysplasia. In contrast, only 2 lines are identifiable in pyloric gland adenomas; apical mucin and a basal line of relatively bland nuclei. While apical mucin was somewhat depleted, and nuclei frequently showed mild to moderate atypia, surface polarity was preserved in all cases of reactive gastropathy with evaluable surface. Focal loss of polarity may, however, be seen in areas immediately adjacent to erosions or fibrinous exudate. The authors conclude that surface cell polarity (the 'four lines') is lost in all cases of gastric dysplasia, but urge caution when evaluating these features adjacent to an erosion.

Diagnostic challenges of intra-operative frozen consultation for gastrointestinal signet ring cell carcinoma

Chen F, Jiang K, Han B
Histopathology. 2021;78(2):300-309.
https://pubmed.ncbi.nlm.nih.gov/32767784/

The evaluation of signet ring cell carcinomas with intraoperative frozen sections is challenging and has a relatively high false negative rate. In this work, the authors investigate factors that contribute to discrepancies between the final diagnosis and that rendered at the time of intraoperative consultation. Their cohort consists of 83 specimens derived from 50 unique patients and consisted of 21 women (mean age 66.8 years) and 39 men (mean age 61.1 years). Intraoperative consultation was requested to exclude metastatic disease for 71.1% of cases, to assess margin status for 21.7% of cases, and for diagnostic confirmation in 7.2% of cases. A false negative diagnosis was rendered during intraoperative consultation in 8.4% of cases, while 6% were deferred. Interpretive error was responsible for the discordant result in 66.6% of cases. The authors cite the presence of clusters of signet ring cells mimicking myxoid stroma, as well as signet ring cells resembling reactive inflammatory or stromal cells, as a common interpretive pitfall. Sampling error (25%) and technical issue related to the preparation of slides (8.3%) were considerably less common. The authors conclude that familiarity with the appearance of signet ring cells on frozen section is essential for reducing the incidence of diagnostic error. Specifically, they recommend paying close attention to abrupt transitions from expected architecture to areas with an inflammatory-like or myxoid appearance.

High miR-324-5p expression predicts unfavorable prognosis of gastric cancer and facilitates tumor progression in tumor cells

Zheng Z, Li J, An J, Feng Y, Wang L
Diagn Pathol. 2021;16(1):5.
https://pubmed.ncbi.nlm.nih.gov/33430926/

This study evaluated the prognostic value of miR-324-5p in gastric cancer (GCa) and evaluated its role in tumor progression. MicroRNAs (miRNAs) are involved in different cellular processes, and studies have demonstrated a diagnostic value of miR-324-5p in other malignancies, such as prostate cancer and rectal cancer. The authors studied the prognostic significance of miR-324-5p in 122 GCa patients from Weifang People's Hospital resected from 2009 to 2013, and performed in vitro studies to assess the role of miR-324-5p on GCa cell lines. miR-324-5p levels were upregulated in GCa compared with normal controls, and 54% had high levels of expression (using a mean value of 2.127). The high- expression group patients had more lymph node metastases, advanced stage, and lower survival in comparison to the low- expression group. There was no association with age, gender, tumor size, and differentiation. In vitro experiments showed that overexpression of miR-324-5p in cell lines promoted cell proliferation, inhibition of apoptosis, induced migration and invasion, and reduced *PTEN* expression. In addition, the effect of miR-324-5p overexpression were reversed by increased expression of *PTEN*. The authors concluded that miR-324-5p overexpression is associated with a poor prognosis in GCa, and may serve as a potential therapeutic target.

YAP1 mediates gastric adenocarcinoma peritoneal metastases that are attenuated by YAP1 inhibition

Ajani JA, Xu Y, Huo L, Wang R, Li Y, Wang Y, Pizzi MP, Scott A, Harada K, Ma L, Yao X, Jin J, Zhao W, Dong X, Badgwell BD, Shanbhag N, Tatlonghari G, Estrella JS, Roy-Chowdhuri S, Kobayashi M, Vykoukal JV, Hanash SM, Calin GA, Peng G, Lee JS, Johnson RL, Wang Z, Wang L, Song S
Gut. 2021;70(1):55-66.
https://pubmed.ncbi.nlm.nih.gov/32345613/

This article looks at yes-associated protein 1 (YAP1) significance in peritoneal carcinomatosis in gastric adenocarcinomas. They looked at the function of YAP1 in vivo and in vitro by immunohistochemistry, immunofluorescence, and RNA sequencing. They found that YAP1 was highly upregulated in peritoneal carcinomatosis tumor cells and appeared to be a metastatic driver. Additionally, they showed that pharmacologic inhibition of YAP1 suppressed tumor growth. Thus, the authors propose that YAP1 inhibition could be a target for patients with advanced gastric adenocarcinoma and carcinomatosis.

Programmed cell death protein 1/programmed death ligand 1 but not HER2 is a potential therapeutic target in gastric neuroendocrine carcinoma

Yamashita S, Abe H, Kunita A, Yamashita H, Seto Y, Ushiku T
Histopathology. 2021;78(3):381-391.
https://pubmed.ncbi.nlm.nih.gov/32767778/

Gastric neuroendocrine carcinomas are rare neoplasms that, like pulmonary small cell carcinomas, are treated with platinum-based chemotherapy protocols, but pursue an aggressive clinical course and have a poor prognosis. To this point, the PD-L1 expression profile of gastric neuroendocrine carcinomas has not been thoroughly investigated utilizing modern techniques known to correlate with response to immune checkpoint blockade with medications such as pembrolizumab. In this study, the authors investigate a cohort of 25 gastric carcinomas with significant poorly differentiated neuroendocrine components. Collectively, 17 of the cases in their cohort were pure neuroendocrine carcinomas, and 8 were mixed adenocarcinoma-neuroendocrine carcinomas (15 showed small cell morphology and 10 showed large cell morphology). Eighteen (72%) of the cases in their cohort exhibited combined positive scores (CPS) greater than or equal to 1. Lymph node metastasis was significantly more frequent in cases with PD-L1 CPS<1. Positive staining for HER2 was not detected in any of the pure neuroendocrine carcinomas or in any of the neuroendocrine components of the mixed neoplasms. However, strong 3+ HER2 staining, or 2+ HER2 staining with positive HER2 FISH, was present in the adenocarcinoma component of 6 of the 15 mixed tumors. Four (16%) of the cases showed complete loss of MLH1 and PMS2 expression, 3 of which showed a CPS greater than or equal to 1. All showed aberrant *MLH1* methylation, while none were *BRAF*-mutated. The authors conclude from this work that therapeutic agents targeting HER2 are unlikely to be an effective treatment for gastric neuroendocrine carcinomas because of the universal absence of HER2 staining in the neuroendocrine carcinoma cells. Immune checkpoint inhibitors may, however, be an attractive target, as a relatively high proportion of cases have a CPS greater

than or equal to 1. Further investigation with clinical trials is recommended to assess this hypothesis.

A comparative study of RTK gene status between primary tumors, lymph-node metastases, and Krukenberg tumors

Wang B, Tang Q, Xu L, Teng X, Ding W, Ren G, Wang X
Mod Pathol. 2021;34(1):42-50.
https://pubmed.ncbi.nlm.nih.gov/32732929/

The authors looked at the frequency of receptor tyrosine kinase (RTK) gene amplification in Krukenberg tumors (KTs) by FISH. Fifty paired samples including primary cancer, lymph node metastasis, and Kts were collected. The authors concluded that the positive rate of RTK gene amplification in KTs was low, and intratumoral heterogeneity was frequent in KTs with RTK amplification.

Loss of SFRP1 expression is a key progression event in gastrointestinal stromal tumor pathogenesis

Liang CW, Yang CY, Flavin F, Fletcher JA, Lu TP, Lai IR, Li Y, Chang YL, Lee JC
Hum Pathol. 2021;107:69-79.
https://pubmed.ncbi.nlm.nih.gov/33186588/

The early genetic changes present in gastrointestinal stromal tumors (GIST), the most common mesenchymal tumor of the GI tract, are well documented. The authors of this study were interested in the genetic changes that take place when a GIST transitions from a low-grade tumor to a high-grade sarcoma. To that end, they focused on 19 GISTs where both a low-grade and a high-grade histologic component (termed "biphasic") were present in the same lesion. All tumors were found to share identical *KIT*/*PDGFRA* mutations between the low- and high-grade areas of the tumor. Using NanoString technology, they analyzed 15 (79%) tumors and found that high-grade regions were more likely to show chromosomal aberrations than their low-grade counterparts. Loss of chromosome 9/9p loss was present in 8 of the high-grade tumors, which appeared to correspond to *CDKN2A* mutations, although confirmatory FISH was not performed on all tumors. The authors also used a NanoString GEP platform to interrogate gene expression profiles of 6 of the study GISTS. Downregulation of *SFRP1* was identified in all tumors, and the authors confirmed that immunohistochemical expression of SFRP1 was decreased or completely lost in the high-grade component of study GISTS but retained in the low-grade regions. Loss of SFRP1 expression was correlated with increasing tumor size and mitotic rate, including in a separate cohort of non-biphasic GISTS. The authors conclude that *SFRP1* downregulation plays a role in GIST transformation to high-grade, high-risk lesions and suggest that, after further study, SFRP1 expression may be a useful biomarker.

Mesenchymal tumors of the gastrointestinal tract with *NTRK* rearrangements: a clinicopathological, immunophenotypic, and molecular study of eight cases, emphasizing their distinction from gastrointestinal stromal tumor (GIST)

Atiq MA, Davis JL, Hornick JL, Dickson BC, Fletcher CDM, Fletcher JA, Folpe AL, Mariño-Enríquez A
Mod Pathol. 2021;34(1):95-103.
https://pubmed.ncbi.nlm.nih.gov/32669612/

The authors report 8 mesenchymal tumors involving the gastrointestinal tract with *NTRK1* or *NTRK3* rearrangements. The tumors occurred in 6 children and 2 adults and involved small intestine (n=4), colon (n=2), rectum (n=1) and mesentery (n=1). The tumors were classified into 3 groups: (1) infantile fibrosarcoma involving the gastrointestinal tract (n=4), enriched for *NTRK3* fusions; (2) low-grade CD34+, S100+ spindle cell tumors associated with *NTRK1* fusions; and (3) unclassified high- grade spindle cell sarcomas with *NTRK* fusions. None of the tumors were positive for SOX10, KIT, or DOG1. Clinical outcomes were variable, ranging from indolent to aggressive disease. The authors conclude that mesenchymal tumors of the GI tract with *NTRK* rearrangements are heterogenous, and few, if any, are related to GIST.

Updated staging and patient outcomes in low-grade appendiceal mucinous neoplasms

Ballentine SJ, Carr J, Bekhor EY, Sarpel U, Polydorides AD
Mod Pathol. 2021;34(1):104-115.
https://pubmed.ncbi.nlm.nih.gov/32728224/

This study of low grade appendiceal mucinous neoplasms (LAMNs) aimed to identify the clinicopathological features associated with patient outcomes as they pertain to the recent changes in AJCC staging guidelines. LAMNs from 192 patients were reviewed. In multivariate analysis, only gross perforation was significantly associated with higher TNM group stage. Higher TNM stage was associated with disease progression. The data support the designation of LAMNs with acellular peritoneal mucin as having an intermediate prognosis between those limited to the appendix and those with intraperitoneal deposits with neoplastic epithelium.

Location but not severity of endoscopic lesions influences endoscopic remission rates in Crohn's disease: a post hoc analysis of TAILORIX

Rivière P, D'Haens G, Peyrin-Biroulet L, Baert F, Lambrecht G, Pariente B, Bossuyt P, Buisson A, Oldenburg B, Vermeire S, Laharie D
Am J Gastroenterol. 2021;116(1):134-141.
https://pubmed.ncbi.nlm.nih.gov/33177349/

The authors conducted a post hoc analysis of the TAILORIX randomized control trial, a study of biologic-naïve patients with active Crohn's Disease (CD) and endoscopic ulcers receiving infliximab therapy, to determine the impact of severity and location of endoscopic ulcers on endoscopic remission. They found that while severity of endoscopic lesions at baseline did not influence healing rates, endoscopic remission rates were lower in the ileum compared with colon and rectum.

Crohn's disease after proctocolectomy and IPAA for ulcerative colitis

Hercun J, Côté-Daigneault J, Lahaie RG, Richard C, Wassef R, Poitras P
Dis Colon Rectum. 2021;64(2):217-224.
https://pubmed.ncbi.nlm.nih.gov/33315714/

This is a retrospective study carried out to estimate the cumulative incidence of a postoperative change of diagnosis from ulcerative colitis (UC) to Crohn`s disease (CD) and its predictive factors in patients with UC who underwent an ileal pouch-anal anastomosis (IPAA) at Centre hospitalier de l'Université de Montréal-Hôpital Saint Luc in Canada. A change of diagnosis from UC to CD can occur in some cases, and surgical IPAA may not be optimal for these patients due to complications including pouch failure. This study included 301 patients who underwent an IPAA (with J-pouch) for UC (1985-2014) with a median follow up of 68 months, and they excluded all CD or indeterminate colitis (IC) patients. A total of 38 patients developed signs of CD following surgery with a change of diagnosis to CD taking a median of 77 months. Of these 38 patients, 16 developed subsequent fistulas. The cumulative incidence of changing diagnoses increased steadily over time, and factors that were significantly associated with a change of diagnosis included tobacco smoking at time of surgery, suspicion of IC, the presence of mouth ulcers, and younger age at diagnosis of IBD. However, duration of disease before surgery, sex, and no smoking history did not reach statistical significance. Extra- intestinal manifestation (skin, liver, eye, and joint disease) did not differ between the two groups. Surgical treatment was required more often in patients with fistulizing disease, and six patients had pouch removal. The authors demonstrated that a diagnosis of CD can occur remotely from the time of IPAA surgery, and they identified risk factors for this diagnosis conversion.

Active margins, plexitis, and granulomas increase postoperative Crohn's recurrence: systematic review and meta-analysis

Tandon P, Malhi G, Abdali D, Pogue E, Marshall JK, van Overstraeten A, Riddell R, Narula N
Clin Gastroenterol Hepatol. 2021;19(3):451-462.
https://pubmed.ncbi.nlm.nih.gov/32801016/

In this meta-analysis, the authors screened 743 cohort studies with intestinal resections for Crohn's disease and analyzed the association of histologic features of the resected bowel with disease recurrence. Results showed that 2481 patients (from 21 studies) with active disease at

resection margins had increased risk of clinical and surgical recurrence of disease compared to patients with negative margins, and a trend of endoscopic recurrence. In 808 patients (from 10 studies) with myenteric plexitis, there was an increased risk of endoscopic recurrence and a trend of clinical recurrence. In 1777 patients (from 19 studies) with granulomas, there was an increased risk of both clinical and endoscopic recurrence and a trend of surgical recurrence. Multivariable analyses were not available or performed in most cohorts, which limited the assessment of one particular risk factor that may be more strongly associated with the recurrence. Although limitations exist in this study, the overall findings from this meta-analysis revealed the importance of histologic features such as positive resection margins, myenteric plexitis, and granulomas in surgical specimens to predict post-operative recurrence of CD.

Discriminant equation using mucosally expressed cytokines and transcription factor for making definite diagnosis of inflammatory bowel disease unclassified

Okuno H, Ogino H, Ihara E, Nishioka K, Tanaka Y, Chinen T, Kohjima M, Oono T, Tanaka M, Goya T, Fujimori N, Iboshi Y, Gotoda T, Ogawa Y
BMC Gastroenterol. 2021;21(1):73.
https://pubmed.ncbi.nlm.nih.gov/33593285/

This study aimed to examine whether the discriminant equation using the mucosally expressed mediators designed in their previous study for IBD could characterize inflammatory bowel disease-unclassified (IBD-U), UC with primary sclerosing cholangitis (PSC-UC), or UC with autoimmune pancreatitis type 2 (AIP-UC). A total of 56 patients including UC (n = 24), CD (n = 15), IBD-U (n = 10), PSC-UC (n = 4), and AIP-UC (n = 3), along with 9 control patients were enrolled in this study. Mucosally expressed inflammatory mediators related to Th1, Th2, Th17, and Treg were measured using quantitative PCR in endoscopic biopsies from the inflamed intestines of the patients. The IBD-U, PSC-UC or AIP-UC were characterized using discriminant and principle component analysis. The study identified 3 markers, IL-13, IL-21 and T-bet, that could diagnose IBD-U patients as either UC or CD with high accuracy. The distribution graph of inflammatory mediators using the principal component analysis revealed that PSC-UC and AIP-UC exhibited CD-like and UC-like features, respectively.

Serrated lesions in inflammatory bowel disease: genotype-phenotype correlation

Brcic I, Dawson H, Gröchenig HP, Högenauer C, Kashofer K
Int J Surg Pathol. 2021;29(1):46-53.
https://pubmed.ncbi.nlm.nih.gov/33030071/

This study was carried out to better elucidate the molecular characteristics of serrated lesions in the setting of IBD. The authors performed molecular studies on a variety of serrated lesions and inflammatory polyps (total of 65 lesions) and found that serrated lesions in the right colon more commonly harbor *BRAF* mutations and in the left colon harbor *KRAS* mutations. No

alterations were detected in the inflammatory polyp cohort. Only one patient with a traditional serrated adenoma progressed to adenocarcinoma after 5 years. The authors conclude that molecular analysis can help distinguish true serrated lesions from reactive pseudopolyps with serrated/hyperplastic epithelial changes.

Variation over time and factors associated with detection rates of sessile serrated lesion across the United States: results form a national sample using the GIQuIC registry

Shaukat A, Holub J, Greenwald D, Eisen G, Schmitt C
Am J Gastroenterol. 2021;116(1):95-99.
https://pubmed.ncbi.nlm.nih.gov/32833735/

The authors used colonoscopies submitted to the GIQuIC registry between 2014 -2017 to examine factors associated with higher detection of sessile serrated lesions (SSLs). They found that the average detection rate for SSL per endoscopist increased from 4.99% to 7.09% over the 3 year study period (p trend <0.001). Clinically significant factors associated with higher rates of SSL detection were longer withdrawal times, adequate preparation, female sex of patient, and use of a specialized pathology group.

An "expressionistic" look at serrated precancerous colorectal lesions

Marra G
Diagn Pathol. 2021;16(1):4.
https://pubmed.ncbi.nlm.nih.gov/33423702/

This study aims to explore the differences between sessile serrated polyps and other precancerous colonic lesions using ISH for transcriptome-based RNA molecules. Genetic alterations in colonic adenoma and colonic adenocarcinoma are known to have different profiles, and previous studies found transcriptome profiling data helpful in differentiating precancerous lesions. In this study from Zurich University Hospital, the author studied 21 mRNA targets (with a focus on 12 targets) in 12 premalignant colorectal tumor samples (3 conventional adenomas [cADNs]; 3 sessile serrated lesions [SSLs]; 3 hyperplastic polyps [HPs]; and 3 traditional serrated adenomas [TSAs]). All polyps were ≥10 mm except one HP. Nine genes were helpful in differentiating SSLs from cADNs (8 were SSL-specific, *VSIG1*, *ANXA10*, *ACHE*, *SEMG1*, *AQP5*, *LINC00520*, *ZIC5*, *FOXD1* and 1 was cADN-specific, *NKD1*). However, none of the genes were helpful in distinguishing SLL from HP, and none of the 9 putatively HP-specific studied markers could be verified to be as such. *VSIG1* was highly expressed in serrated crypts in comparison to the normal colorectal mucosa. The ISH expression patterns of TSAs were heterogeneous and frequently characterized by a mixture of SSL- and cADN-specific staining patterns. The author concluded that ISH can be a promising marker for histologic classification of colonic polyps once the current data is validated in larger scale studies.

Incidental morphologic findings in colorectal adenoma

Dabir PD, van der Post RS, Nagtegaal ID
Histopathology. 2021;78(3):348-357.
https://pubmed.ncbi.nlm.nih.gov/32981102/

In this concise review, the authors discuss colorectal adenomas with distinctive morphologic features, along with the clinical implications, or lack thereof, of these special morphologic findings. Specifically, they discuss adenomas with Paneth cell metaplasia, squamous metaplasia, clear cell metaplasia, osseous metaplasia, neuroendocrine differentiation, and signet-ring cell-like lesions. They discuss the diagnostic pitfalls associated with these metaplastic/degenerative changes, including the over interpretation of neuroendocrine differentiation as infiltrative glands or high-grade dysplasia.

Long-Term incidence and mortality of colorectal cancer after endoscopic biopsy with normal mucosa: a Swedish-matched cohort study

Song M, Emilsson L, Hultcrantz R, Roelstraete B, Ludvigsson JF
Am J Gastroenterol. 2021;116(2):382-390.
https://pubmed.ncbi.nlm.nih.gov/33105194/

This study examined the incidence of colorectal cancer (CRC) after normal colonoscopic screening using a large dataset of Swedish patients (88,798 people) and found that a normal biopsy was associated with lower CRC incidence and mortality for at least 20 years after examination. Therefore the authors suggest that screening intervals after normal colonoscopy could be extended past the current recommended 10 year interval.

Epidemiology of diverticulitis and prevalence of first-ever colorectal cancer postdiverticulitis in adults in the United States: a population-based national study

Jin-Dominguez F, Mansoor E, Panhwar M, Abou-Saleh M, Isenberg G, Wong RCK, Cooper GS
Dis Colon Rectum. 2021;64(2):181-189.
https://pubmed.ncbi.nlm.nih.gov/33044246/

This study aims to describe the incidence of first-ever diverticulitis and the prevalence of first-ever colorectal cancer (CRC) post diverticulitis in the United States. Previous studies have shown variable prevalence of CRC following diverticulitis, and screening for CRC after acute diverticulitis is recommended, but remains controversial. The authors did a retrospective review using Eplorys (large population- based database), identifying adult patients with no prior personal history of CRC or IBD, and no colonoscopy done within 1 year of their first- ever diverticulitis diagnosis. The overall incidence of first-ever diverticulitis was 2.9%, and was more

common in men, seniors, and White patients. The prevalence of post diverticulitis CRC was 0.57% (5200 out of 916,850 patients), which is double the prevalence among patients without a history of diverticulitis (0.3%). A majority of the post diverticulitis CRC cases were diagnosed within the first 6 months after diverticulitis, and almost two thirds were diagnosed in the first two months. The risk of CRC was significantly higher among women, adults, and African Americans, but in an univariate analysis, patients were more likely to be men, African Americans, age >65 years, have type 1 DM, obesity, smoking, type 2 DM, alcohol abuse, or ischemic heart disease. In this study, the authors demonstrated that the prevalence of CRC in diverticulitis patients is twice that of patients without diverticulitis, and they identified some associated risk factors.

Adenoma-like adenocarcinoma: clinicopathologic characterization of a newly recognized subtype of colorectal carcinoma

González IA, Bauer PS, Liu J, Chatterjee D
Hum Pathol. 2021;107:9-19.
https://pubmed.ncbi.nlm.nih.gov/32991929/

In this retrospective study, the authors present the largest cohort of adenoma-like adenocarcinoma with the goal of further elucidating the clinicopatholgic implications of this diagnosis. Adenoma-like adenocarcinoma was included in the 5th edition of the WHO classification of tumors published in 2019; the tumors require at least 50% of the tumor to have a villous-adenoma-like growth pattern with low grade cytology and a pushing border. It has previously been reported that such tumors have a better prognosis than conventional colorectal adenocarcinoma. The authors reviewed 91 cases of adenoma-like adenocarcinoma (AA) and compared clinicopathologic features to 251 cases of adenocarcinoma, NOS. They found that cases of AA were significantly less likely to have lymphovascular space invasion, perineural invasion, intermediate-to-high tumor budding, tumor deposits, and lymph node metastases than conventional adenocarcinoma, NOS. Importantly, AA cases often lacked the immature/myxoid desmoplastic stromal reaction seen in conventional adenocarcinoma. The authors also reviewed the prior biopsies on 23 (35%) of the AA cases, and found that 11 (43%) were interpreted as adenoma only. They confirmed that the stromal changes in the AA biopsies diagnosed as adenocarcinoma were more likely to be dense and eosinophilic rather than loose and/or myxoid. Prior biopsies of adenocarcinoma, NOS cases were not reviewed for comparison. When looking at recurrence-free survival, patients with AA had significantly better RFS than patients with adenocarcinoma, NOS or patients with less than 50% AA features; however, pure AA histology was not found to be an independent prognostic factor. Tumor stage and nodal status remained drivers of patient outcome. Overall, the authors conclude that AA is a distinct morphologic class of colorectal adenocarcinoma associated with better patient prognosis because this tumor type is less likely to have high tumor budding and nodal spread. Cases with 100% AA histology had the best prognosis, and they suggest that keeping the AA category relatively homogeneous will provide better prognostic information for patients and clinicians.

Intraepithelial tumor infiltrating lymphocytes are associated with absence of tumour budding and immature/myxoid desmoplastic reaction, and with better recurrence-free survival in stage I-III colorectal cancer

González IA, Bauer PS, Liu J, Chatterjee D
Histopathology. 2021;78(2):252-264.
https://pubmed.ncbi.nlm.nih.gov/32654226/

There is abundant and accumulating evidence that the presence of tumor budding is associated with a worse prognosis in colorectal adenocarcinomas. Recently, the presence of an immature or myxoid desmoplastic stromal reaction at the tumors infiltrating front has also been proposed to be a histologic feature associated with an adverse prognosis. In contrast, the presence of intraepithelial tumor infiltrating lymphocytes (iTIL) has been linked with a better response to neoadjuvant therapy and a favorable prognosis. In this work, the authors revisit the clinical significance of these histologic parameters and assess their relationship to one another, as well as to other clinicopathologic variables. They investigate a cohort of 372 colorectal adenocarcinomas, excluding stage IV and tumors treated with neoadjuvant therapy. The mean age of the patients in their cohort was 65.7 years, and there was a roughly even split between men and women. Low tumor budding (0-4 per 0.785 mm^2) was identified in 81% of cases. Conversely, the presence of an immature/myxoid desmoplastic reaction (18%) and iTILs (35%) were less frequently encountered histologic parameters. The presence of iTILs was significantly associated with a female gender, low tumor budding, and the presence of non-myxoid, or mature, desmoplastic stroma, among other parameters. The absence of iTILs and the presence of high tumor budding was associated with a worse recurrence free survival (RFS). Similarly, cases with an immature/myxoid desmoplastic reaction had a worse RFS than those with an intermediate or mature desmoplastic stroma. Cases with iTILs and intermediate or mature desmoplastic stroma were associated with a better RFS than those without iTILs and those with an immature or myxoid stroma. Multivariate analysis confirmed the significant association between the presence of iTILS and desmoplastic stroma type on RFS. The authors conclude from this work that like tumor budding, the presence of iTILs and the presence of an immature/myxoid stroma should be included in the pathologic assessment of colorectal adenocarcinoma resections and propose the inclusion of these parameters in risk stratification/prognostic models.

Genotype-phenotype associations in colorectal adenocarcinomas and their matched metastases

Chatzopoulos K, Kotoula V, Koliou GA, Giannoulatou E, Papadopoulou K, Karavasilis V, Pazarli E, Pervana S, Kafiri G, Tsoulfas G, Chrisafi S, Sgouramali H, Papakostas P, Pectasides D, Hytiroglou P, Pentheroudakis G, Fountzilas G
Hum Pathol. 2021;107:104-116.

https://pubmed.ncbi.nlm.nih.gov/33161028/

The purpose of this retrospective study was to investigate the histologic and molecular characteristics shared between a primary colorectal carcinoma and its metastasis. The authors hypothesize that morphologic features can predict not only patient prognosis but also underlying genotypes of colorectal carcinoma. The authors reviewed 85 primary colorectal carcinomas with 85 matched metastatic lesions and specifically recorded budding, tumor infiltrating lymphocytes (TILs), micronecrosis, and mismatch repair protein status. Next-generation sequencing (NGS) data were also available on 66 of the matched pairs of tumors. They found that the number of TILs did not correlate between primary and metastatic lesions. Of the histologic features examined, only micronecrosis in the primary tumor was significantly associated with the amount of metastatic disease burden/higher nodal stage. In the NGS analyses, 56 (85%) cases tested had identifiable mutations, and genomic alterations were shared in 51 (91%) of the matched pairs. Interestingly, the number of TILs in a metastatic lesion was associated with a high mutation rate (>3 genes mutated) and also favorable overall survival rate. The authors conclude that the reporting of TILs in metastatic colorectal carcinoma may be a clinically relevant prognostic indicator for patients.

T3 versus T4a staging challenges in deeply invasive colonic adenocarcinomas and correlation with clinical outcomes

Pantaleon Vasquez R, Arslan ME, Lee H, King TS, Dhall D, Karamchandani DM
Mod Pathol. 2021;34(1):131-140.
https://pubmed.ncbi.nlm.nih.gov/32669613/

In this retrospective study, the authors examined 151 untreated colonic adenocarcinomas staged initially as pT3 or pT4a with available 5 year follow up and re-categorized them as: Group 1 (38 cases): pT4a with tumor at serosa, Group 2 (49 cases): tumor ≤ 1mm from serosa with reactive fibrosis and/or inflammation, and Group 3 (64 cases): pT3 >1mm from serosa. The authors found that colonic adenocarcinomas ≤ 1mm from serosa (Group 2) behaved more akin to “bona fide” pT4a tumors with regards to recurrence free survival and overall survival rates, as well as nodal and distant metastases. They recommend that these tumors be staged as pT4a rather than pT3.

DSG2 expression is low in colon cancer and correlates with poor survival

Yang T, Gu X, Jia L, Guo J, Tang Q, Zhu J, Zhao W, Feng Z
BMC Gastroenterol. 2021;21(1):7.
https://pubmed.ncbi.nlm.nih.gov/33407183/

This study aimed to determine the expression of Desmoglein2 (DSG2) in colon cancer (CC) and its association with CC patients' overall survival (OS). Tissue microarrays containing 587 CC

samples, 41 colitis tissues, and 114 pericarcinomatous tissues were used for DSG2 immunohistochemistry analysis. DSG2 expression was lower in CC tissues than in pericarcinomatous tissues. DSG2 expression was associated with differentiation, lymph node metastasis, distant metastasis, and AJCC stage. Univariate analysis indicated that poor OS in patients with CC was associated with low DSG2 expression, tumor size, lymph node metastasis, distant metastasis, AJCC stage, and venous invasion. In multivariate analysis, low DSG2 expression, distant metastasis, AJCC stage, and venous invasion were independent prognostic factors for CC patients. Bioinformatics analysis also suggested that low DSG2 expression affects protein activation, regulates the P53-related pathway in CC, and activates the EGFR pathway. The authors concluded that DSG2 could be a prognostic biomarker for CC.

Intratumoral budding and automated CD8-positive T-cell density in pretreatment biopsies can predict response to neoadjuvant therapy in rectal adenocarcinoma

Farchoukh L, Hartman DJ, Ma C, Celebrezze J, Medich D, Bahary N, Frank M, Pantanowitz L, Pai RK
Mod Pathol. 2021;34(1):171-183.
https://pubmed.ncbi.nlm.nih.gov/32661298/

The authors assessed CD8+ T cell density and intratumoral budding in 117 pretreatment rectal cancer patient biopsies to determine their utility as predictive biomarkers for response to neoadjuvant therapy and survival. Patients with high CD8+ T cell density on biopsy were significantly more likely to exhibit complete/near complete response to neoadjuvant therapy and low tumor stage (0 or I) on resection compared with patients with low CD8+ T cell density. The presence of intratumoral budding was significantly associated with reduced disease free survival and increased risk of tumor recurrence.

Identifying mismatch repair-deficient colon cancer: near-perfect concordance between immunohistochemistry and microsatellite instability testing in a large, population-based series

Loughrey MB, McGrath J, Coleman HG, Bankhead P, Maxwell P, McGready C, Bingham V, Humphries MP, Craig SG, McQuaid S, Salto-Tellez M, James JA
Histopathology. 2021;78(3):401-413.
https://pubmed.ncbi.nlm.nih.gov/32791559/

The identification of MSI-H colorectal cancers is an essential screening tool for Lynch syndrome, but also has important prognostic and therapeutic implications for sporadic tumors. Reflex testing to identify MSI-H colorectal tumors is performed in many laboratories. There is, however, no consensus as to the preferred method of testing, and laboratories may perform PCR-based MSI testing, MMR immunohistochemistry, or both in their workup. In this study, the authors investigate a cohort of 593 cases from the Northern Ireland Cancer Registry with

known MSI status and MMR IHC results. A total of 136 (22.9%) cases were MSI-H and 135 (22.8%) were MMR-deficient by IHC. Concordance between these two modalities was excellent, with 97.1% of MSH-H cases showing abnormal MMR by IHC, and 97.8% of cases with abnormal MMR IHC being MSI-H by PCR. The authors conclude from these data that MSI-PCR testing and IHC-based studies for the MMR proteins are equally proficient at identifying MSI-H colorectal cancers. The choice should be based upon institutional preference and familiarity with the pitfalls associated with each technique, including the presence of abnormal MMR staining patterns.

'Null-pattern' mismatch repair enzyme immunostaining in a sporadic microsatellite-unstable colorectal carcinoma with biallelic somatic *MSH6* gene aberrations

Hühns M, Prall F
Histopathology. 2021 Jan;78(2):340-342.
https://pubmed.ncbi.nlm.nih.gov/32939843/

This brief letter describes a microsatellite unstable (MSI-H) ascending colon adenocarcinoma. Immunohistochemical staining for MLH1 and PMS2 were lost and associated with the expected *MLH1* hypermethylation and *BRAF* V600E variant frequently found in sporadic microsatellite unstable colorectal adenocarcinomas. The carcinoma unexpectedly also showed loss of MSH2 and MSH6 immunohistochemical staining. NGS studies identified a somatic frameshift mutation in *MSH6* that was subsequently confirmed with Sanger sequencing and demonstrated to involve both alleles. They conclude that this otherwise typical sporadic MSI-H colon adenocarcinoma developed a second hit involving *MSH6*. They are, however, unable to explain the loss of MSH2 by immunohistochemical staining.

Mismatch repair phenotype determines the implications of tumor grade and CDX2 expression in stage II-III colon cancer

Hestetun KE, Aasebø K, Rosenlund NB, Müller Y, Dahl O, Myklebust MP
Mod Pathol. 2021;34(1):161-170.
https://pubmed.ncbi.nlm.nih.gov/32737450/

The authors examined mismatch repair (MMR) status and CDX2 expression in 544 patients with stage II-III colon cancer. They found that for patients with proficient MMR (pMMR) and CDX2 negativity, the hazard ratio for cancer death was 2.93 compared to those with deficient MMR (dMMR) and CDX2 positive tumors. In addition, in those with pMMR tumors, high tumor grade was a significant marker of poor prognosis in the surgery only group, but not in the group receiving chemotherapy. CDX2 expression and tumor grade did not impact prognosis in patients with tumors that had dMMR.

Detection of microsatellite instability in a panel of solid tumours with the Idylla MSI Test using extracted DNA

Pécriaux A, Favre L, Calderaro J, Charpy C, Derman J, Pujals A
J Clin Pathol. 2021;74(1):36-42.
https://pubmed.ncbi.nlm.nih.gov/32513848/

This study aimed to evaluate the Idylla MSI Test (by Biocartis) in comparison to pentaplex PCR and immunohistochemistry. Microsatellite instability (MSI) testing is routinely performed nowadays for potential immunotherapy as well as for Lynch syndrome screening. The Idylla MSI Test is a fully automated system which performs a microsatellite instability analysis within 150 minutes, and it includes PCR amplification followed by analysis of the fusion profiles of seven biomarkers that are frequently mutated genes in MSI tumors. Idylla was performed on 53 colorectal carcinoma (CRC) and 62 non- CRC cases (7 small intestine, 15 duodenal and pancreatic, 16 gastric, 15 endometrial, 5 ovarian and 4 urinary tract), and the results were compared to that of more conventional MSI testing (by PCR and IHC). Using pentaplex PCR as the reference standard, Idylla had only 1 false negative case (1/17 MSI cases), and the specificity was 100%. In the other digestive tract tumors, Idylla sensitivity to detect MSI was 96% (23/24) and its specificity was 100%. Among the 10 MSI endometrial and ovarian cases, one was discrepant with the Idylla system. Among the 2 MSI urinary tract cases, the Idylla result was concordant with PCR and IHC. The authors demonstrated that the Idylla MSI Test is concordant with PCR and/or IHC in approximately 90% of the cases.

Evaluating mismatch repair/microsatellite instability status using cytology effusion specimens to determine eligibility for immunotherapy

Jacobi EM, Landon G, Broaddus RR, Roy-Chowdhuri S
Arch Pathol Lab Med. 2021;145:46-54.
https://pubmed.ncbi.nlm.nih.gov/33367660/

Tumors with mismatch repair deficiency (MMRd) have errors in their replication machinery that result in a high neoantigen burden. Blockade of the PD-1/PD-L1 axis by the anti-PD-1 antibody pembrolizumab has been approved by the FDA for patients who have failed a previous line of therapy. Because these patients often have advanced disease, it is often necessary to assess for biomarkers of interest in scant tissue samples, including cytology effusion specimens. The purpose of this study was to determine the accuracy of mismatch repair protein immunohistochemistry, as performed on cytology effusion specimens. Biopsies and resection specimens of endometrial and colorectal carcinomas with matched effusion cytology specimens with cell blocks were collected. Immunohistochemical stains for mismatch repair proteins were evaluated and classified as retained (any nuclear staining in any percentage of tumor cells), lost (expression lost in tumor, retained in normal cells), suboptimal (questionable staining of tumor cells or focal staining of cells indefinite for tumor), or non-contributory (no staining in internal controls and tumor cells). In the surgical resection specimens, 2 of 53 cases harbored mismatch

repair deficiency (both with MSH2/6 loss). The authors found that MMR results were concordant in 45/53 (85%) of cases, inconclusive in 6/53 (11%) of cases, and discordant in 2/53 (4%) of cases. In the inconclusive cases, MSH6 was difficult to interpret in 5/6 (83%) of cases, and MLH1 and MSH2 accounted for 1/6 (17%) each. The most common cause for an inconclusive result was focal staining in cells indefinite for tumor (4/6; 67% of cases). Of note, only 19.1% of patients in this series were treatment naïve (the remainder having received at least 1 prior chemotherapeutic agent). The authors conclude that effusion cell block specimens may be suitable for determination of MMR status when other specimens are not available; they assert, additionally, that inconclusive cases should be reported with an appropriate diagnostic comment.

SATB2 in neoplasms of lung, pancreatobiliary, and gastrointestinal origins

De Michele S, Remotti HE, Del Portillo A, Lagana SM, Szabolcs M, Saqi A
Am J Clin Pathol. 2021;155(1):124-132.
https://pubmed.ncbi.nlm.nih.gov/32914850/

Special AT-rich binding protein 2 (SATB2) immunohistochemistry (IHC) is known to have high sensitivity and specificity for colorectal adenocarcinoma (CRC). The authors assessed SATB2 expression in a large cohort of adenocarcinomas (total adenocarcinomas n=335, including 35 gastric, 13 small bowel, 46 CRC, 40 lung, 36 ampullary, and 165 pancreatobiliary neoplasms (34 intraductal papillary mucinous neoplasms [IPMNs], 19 pancreatic adenocarcinomas, 112 cholangiocarcinomas). The cases were evaluated for positivity (defined as ≥5% nuclear staining), and an H-score was calculated based on the percentage of SATB2+ cells and staining intensity. SATB2 was found to be positive in 87% colorectal, 17% of gastric, 38% of small bowel, 6% of ampullary, 3% of lung, and 2% of cholangiocarcinomas. All pancreatic adenocarcinomas and IPMNs were negative. The authors conclude that SATB2 is not entirely specific for colorectal origin and can be expressed in a subset of gastrointestinal adenocarcinomas, although SATB2 is most useful in distinguishing CRCs from lung adenocarcinomas and pancreatobiliary neoplasms.

Alterations in Ki67 labeling following treatment of poorly differentiated neuroendocrine carcinomas: a potential diagnostic pitfall

Vyas M, Tang LH, Rekhtman N, Klimstra DS
Am J Surg Pathol. 2021;45(1):25-34.
https://pubmed.ncbi.nlm.nih.gov/33177340/

The authors anecdotally observed 5 cases of poorly differentiated neuroendocrine carcinomas (PD-NECs) with a surprisingly low and heterogeneous Ki67 index status post chemotherapy. They subsequently identified 15 more cases of treated high-grade neuroendocrine neoplasms (HG-NENs) to study the alterations in Ki67 labeling post-therapy. A total of 20 cases status post-

therapy (including 11 PD-NECs, 8 mixed adenoneuroendocrine carcinomas, and 1 well differentiated neuroendocrine tumor (WD- NET), G3) from various anatomic sites (15 gastrointestinal tract, 2 pancreas, 1 larynx, 1 lung, and 1 breast) were included in the study. Topographic heterogeneity in the Ki67 index was expressed using a semi-quantitative score of 0 (no heterogeneity) to 5 (> 80% difference between maximal Ki67 and minimal Ki67 indices). The post-treatment group (n = 20, mean Ki67: 47.7%, range 1% to 90%) showed a significantly lower Ki67 index (18/20 cases) when compared to the pretreatment group (n = 9 available, mean Ki67: 86.3%, range 80% to 100%). Of the 18 cases with a relatively low Ki67 index, 3 cases were homogeneously low, while 15 showed heterogeneous labeling. In 6 cases, the alterations in Ki67 index post-therapy were sufficient to place these HG-NENs in the WHO G1 or G2 grade, potentially leading to a misdiagnosis of WD-NET. Nine cases had sufficient heterogeneity in the Ki67 index to suggest that a limited biopsy could sample an area of low Ki67, despite some hotspot regions with a Ki67 index of > 20%. In 7 cases, the alterations in the Ki67 index were accompanied by morphologic features resembling a WD-NET. The results suggest that there is a potential for misinterpretation of previously treated PD-NECs as WD-NETs, or for assigning a lower grade in G3 WD-NETs. The authors conclude that post-treatment PD-NECs should retain their original pre-therapy diagnostic classification regardless of the Ki67 index and morphologic features post-therapy, until evidence emerges to suggest a change in prognosis based on these treatment-associated alterations.

Perianal Paget's disease as spread from non-invasive colorectal adenomas

Hutchings D, Windon A, Assarzadegan N, Salimian KJ, Voltaggio L, Montgomery EA
Histopathology. 2021;78(2):276-280.
https://pubmed.ncbi.nlm.nih.gov/32705713/

Secondary Paget's disease involving the perianal skin is nearly always associated with an invasive adenocarcinoma of the distal rectum or anal canal. While Paget's disease of the breast is known to arise in the setting of non-invasive mammary carcinomas, only rare case reports have described perianal Paget's disease developing in the setting of colorectal adenomas lacking an invasive component. In this study, the authors present the clinical and pathologic features of a series of four cases of secondary perianal Paget's disease developing in association with non-invasive anorectal neoplasms. The median age of the patients in their cohort was 72 years. One of the adenomas was located in the distal rectum and three were in the anal canal. All showed high-grade dysplasia and one had foci of lamina propria infiltration. Immunohistochemical studies performed on the foci of perianal Paget's disease confirmed intestinal differentiation. Following local excision, 2 patients showed no evidence of disease at 6 and 87 months, 1 had residual perianal Paget's disease at 8 months, and another developed invasive mucinous adenocarcinoma after 36 months. The authors conclude from this work that secondary perianal Paget's disease may develop in the setting of non-invasive anorectal neoplasms. Recognition of this extraordinarily uncommon entity is essential as it may prevent overtreatment of a neoplasm with a variable but frequently indolent clinical course.

Lymphogranuloma venereum (LGV) of the anorectum: evaluation of clinicopathological associations and the utility of a novel RNA in-situ hybridisation stain

Waters KM, Cox BK, Wong MT, Guindi M, Kim SA, Larson BK, Morgan M, Voltaggio L, Balzer BL
Histopathology. 2021 Feb;78(3):392-400.
https://pubmed.ncbi.nlm.nih.gov/32780441/

There has been a resurgence in lymphogranuloma venereum (LGV)-related proctitis, particularly among HIV-positive men who have sex with men. LGV proctitis is histologically indistinguishable from other sexually transmitted forms of proctitis, and coinfection is common. Moreover, the clinical presentation is not entirely specific and may be difficult to discern from idiopathic inflammatory bowel disease. The diagnosis of LGV-infection is frequently made via nucleic acid testing of anorectal swabs, as tissue-based stains are not clinically available. In this work, the authors investigate a cohort of 12 patients with biopsies collected from the distal colorectum or anus within 90 days of a confirmed positive nucleic acid test for *Chlamydia trachomatis*. The average age of the patients in their cohort was 42 years. All were men who have sex with men and 75% were HIV-positive. Biopsies frequently showed mild or moderate acute inflammation (91.7%) and prominent lymphoplasmacytic inflammation (72.7%), while marked crypt architectural distortion was never seen. An investigational RNA ISH probe targeting *Chlamydia trachomatis* was utilized and showed positive foci in 83% of LGV cases, with one case (8%) showing equivocal staining, and another (8%) showing negative reactivity. No positive staining with the LGV probe was seen in any of the negative controls. The authors conclude from this study that there is significant histologic overlap between LGV and other anorectal sexually transmitted infections, which frequently coexist with one another. They demonstrate that the novel RNA ISH probe for *Chlamydia trachomatis* was both sensitive and specific for detecting LGV, and may be useful in situations where nucleic acid testing has not been performed or the results and clinical history are unavailable.

Distribution pattern of tumor infiltrating lymphocytes and tumor microenvironment composition as prognostic indicators in anorectal malignant melanoma

Kim SW, Kim YI, Mustafa B, Kim MJ, Jeong G, Ahn SM, Lim SB, Yu CS, Kim JC, Hong SM, Park IJ
Mod Pathol. 2021;34(1):141-160.
https://pubmed.ncbi.nlm.nih.gov/32709987/

Anorectal malignant melanoma (ARMM) is a rare disease with poor prognosis. The authors assessed the immune profile of 22 cases of ARMM to identify potential prognostic markers. They report that ARMM tumors with high tumor infiltrating lymphocytes (TILs) and high tumor associated macrophages (TAM) had a significantly better overall survival compared to their low TIL and low TAM counterparts. In addition, the presence of CD3+ TILs at the invasive front was an independent favorable prognostic indicator. The authors conclude that TILs have a strong prognostic value in ARMM.

Treatment algorithm and prognostic factors for patients with stage I-III carcinoma of the anal canal: a 20-year multicenter study

Bruyere D, Monnien F, Colpart P, Roncarati P, Vuitton L, Hendrick E, Lepinoy A, Luquain A, Pilard C, Lerho T, Molimard C, Maingon P, Arnould L, Bone-Lepinoy MC, Dusserre L, Martin L, Reynders C, Ancion M, Peiffert D, Leroux A, Hubert P, Delhorme JB, Ghnassia JP, Woronoff AS, Delvenne P, Prétet JL, Bosset JF, Peulen O, Mougin C, Valmary-Degano S, Herfs M
Mod Pathol. 2021;34(1):116-130.
https://pubmed.ncbi.nlm.nih.gov/32728225/

The authors examined a cohort of 372 HIV-negative patients diagnosed with carcinoma of the anal canal over a 20 year period. They found that the incidence of anal cancer peaked during the sixth decade and that females outnumbered males. Uni-multivariate analysis indicated that both negative HPV/p16ink4a status and aberrant p53 expression were better predictors of reduced progression free survival than tumor size and nodal status. Age at diagnosis, p16ink4a status, cTNM classification, and both CD3+ and CD4+ T cell infiltrations within tumor microenvironment were important risk factors for overall survival. The authors conclude that dualistic classification according to the HPV/p53 status should be considered with implications for therapy personalization.

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