Journal Watch – January and February, 2015

Colonic spirochetosis is associated with colonic eosinophilia and irritable bowel syndrome in a general population in Sweden.

Walker MM, Talley NJ, Inganäs L, Engstrand L, Jones MP, Nyhlin H, Agréus L, Kjellstrom L, Öst Å, Andreasson A.

Hum Pathol 2015; 46(2):277-83.

http://www.ncbi.nlm.nih.gov/pubmed/25540866

This is a random population-based study including 745 adults who underwent colonoscopy with biopsy of ileum, cecum, transverse colon, sigmoid colon, and rectum to determine the prevalence of colonic spirochetosis and whether the presence of spirochetosis was linked to other histologic features or clinical symptoms. Seventeen subjects (2.28%) had histologic evidence of colonic spirochetosis, most often identified in the sigmoid. There was no ileal spirochetosis, and no association with age, gender, or NSAID use. The presence of spirochetosis was associated with statistically significant eosinophilia in the transverse colon, sigmoid colon, and rectum, and with the presence of lymphoid follicles at any site. A more than 3-fold increased risk of irritable bowel syndrome was found in subjects with spirochetosis.

Association between molecular subtypes of colorectal cancer and patient survival.

Phipps AI, Limburg PJ, Baron JA, Burnett-Hartman AN, Weisenberger DJ, Laird PW, Sinicrope FA, Rosty C, Buchanan DD, Potter JD, Newcomb PA.

Gastroenterology 2015; 148(1):77-87.e2.

http://www.ncbi.nlm.nih.gov/pubmed/25280443

This population-based study included 2706 patients diagnosed with invasive colorectal cancer between 1998 and 2007 and determined their survival in 2012, correlated to their tumor subtype (sampled in 2050 patients) as defined by the proposed etiologic pathways. The authors concluded that most of the patients had type 4 tumors (MSS or MSI-low, non-CIMP, negative for *BRAF* and *KRAS* mutations). Disease specific mortality was lowest among patients with type 5 tumors (MSI-high, non-CIMP, negative for *BRAF* and *KRAS* mutations), followed by patients with type 1 tumors (MSI-high, CIMP-positive, positive for *BRAF* mutation, negative for *KRAS* mutation). Disease specific mortality was highest among patients with type 2 tumors (MSS or MSI-low, CIMP-positive, positive for *BRAF* mutation, negative for *KRAS* mutation), followed by patients with type 3 tumors (MSS or MSI-low, non-CIMP, negative for *BRAF* mutation, positive for *KRAS* mutation).

Molecular markers identify subtypes of stage III colon cancer associated with patient outcomes.

Sinicrope FA, Shi Q, Smyrk TC, Thibodeau SN, Dienstmann R, Guinney J, Bot BM, Tejpar S, Delorenzi M, Goldberg RM, Mahoney M, Sargent DJ, Alberts SR.

Gastroenterology 2015; 148(1):88-99.

http://www.ncbi.nlm.nih.gov/pubmed/25305506

This study looked at survival of patients with stage III colon cancer using prospectively collected tumor samples to subtype the tumors based on mutations in *BRAF* or *KRAS,* as well as MMR status. The five tumor subtypes included: 1. Proficient MMR with nonmutated BRAF and KRAS, 2. Proficient MMR with mutant KRAS and non-mutated BRAF, 3. Proficient MMR with mutant BRAf and non-mutant KRAS, 4. Deficient MMR (sporadic) with mutant BRAF or MLH1 hypermethylation and any KRAS, and 4. Deficient MMR (familial) with nonmutated BRAF, unmethylated MLH1, and any KRAS. The authors also performed a validation study of their subtype classification on an independent cohort of 783 Stage III colon cancer patients. Subtype 1 tumors comprised almost half of those tested, and these patients had a favorable prognosis, similar to patients with subtypes 4 and 5 (MMR deficient tumors). Patients with subtypes 2 and 3 had poorer survival. The authors also provide a summary table of clinical characteristics highlighting differences between the 5 subtypes. The authors conclude that their classification system has prognostic value for these patients.

Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers

Lagana SM, Braunstein ED, Arguelles-Grande C, Bhagat G, Green PHR, Lebwohl B

J Clin Pathol 2015; 68:29-32.

http://www.ncbi.nlm.nih.gov/pubmed/25342757

There has been considerable recent interest in severe sprue-like enteropathy caused by Olmesartan in patients presenting with severe diarrhea and weight loss. This paper describes duodenal histology in patients taking Olmesartan who presented for upper endoscopy solely for evaluation of abdominal pain. Mild sprue-like histologic features (villous blunting, increase intraepithelial lymphocytes etc.) were evident in the duodenal biopsies from 10 of the 20 patients compared to 4 of 20 matched control patients with abdominal pain but not taking Olmesartan.

Comparative validation of assessment criteria for Crohn-like lymphoid reaction in colorectal carcinoma.

Kim JH, Kim KJ, Bae JM, Rhee YY, Cho NY, Lee HS, Kang GH.

J Clin Pathol 2015; 68(1):22-8.

http://www.ncbi.nlm.nih.gov/pubmed/25322692

A Crohn-like reaction (CLR) at the edge of an invasive colorectal adenocarcinoma has been shown to be associated with a more favorable clinical outcome and also is a valuable predictor of microsatellite instability-high status. However, the clinical significance of the presence or absence of a Crohn-like reaction within the subset of MSI-high tumors has not been explored. The authors of this report classified 212 MSI-high colorectal cancer as either CLR positive or negative based on three published sets of criteria, and examined the reproducibility of each system and the impact on patient prognosis. Statistical analysis demonstrated that an intense CLR was correlated with early stage, and CLR was also associated with favorable prognosis.

Pathogenesis of necrotizing enterocolitis: modeling the innate immune response.

Tanner SM, Berryhill TF, Ellenburg JL, Jilling T, Cleveland DS, Lorenz RG, Martin CA.

Am J Pathol 2015; 185(1):4-16.

http://www.ncbi.nlm.nih.gov/pubmed/25447054

This review article discusses the role of the innate immune system in the patrogenesis of necrotizing enterocolitis.

A rule for determining risk of colorectal cancer in patients with inflammatory bowel disease.

Lutgens M, Vermeire S, Van Oijen M, Vleggaar F, Siersema P, van Assche G, Rutgeerts P, Oldenburg B, Dutch Initiative on Crohn and Colitis.

Clin Gastroenterol Hepatol 2015; 13(1):148-54.

http://www.ncbi.nlm.nih.gov/pubmed/25041864

The investigators performed a multivariate analysis to identify factors predictive of the development of colorectal cancer among patients with inflammatory bowel disease. The factors analyzed included: gender, IBD type, smoking behavior, microscopic disease extent > 50%, PSC, presence of inflammatory polyps, presence of DALM, adenoma-like mass, flat LGD,

flat HGD, colonic stenosis, mesalamine use, methotrexate use, surveillance, any prior colonic resection, age < 19 years, and age > 37 years. The statistical analysis identified ulcerative colitis, PSC, extent of disease > 50% and inflammatory polyps as features predictive of the future risk of colorectal cancer which the authors felt could be used to stratify patients for the purposes of surveillance colonoscopy. The results were validated in a second retrospective cohort of patients. The authors conclude that the following patients groups should be regarded as high risk: 1) any IBD patient with PSC; 2) Crohn disease patients with > 50% colonic involvement and inflammatory polyps; and 3) Ulcerative colitis patients with either > 50% colonic involvement or inflammatory polyps. Ulcerative colitis and Crohn disease patients without PSC and with disease affecting < 50% of the colon and without inflammatory polyps they regard as low risk.

Autoimmune features are associated with chronic antibiotic-refractory pouchitis

Seril DN, Yao Q, Lashner BA, Shen B

Inflamm Bowel Dis 2015; 21(1):110-120.

http://www.ncbi.nlm.nih.gov/pubmed/25437817

The authors investigated associations between various immune mediated disease, autoimmune serologic markers, and the presence of IgG4-positive plasma cells infiltrates in patients with chronic antibiotic refractory pouchitis. They found statistically significant associations between chronic antibiotic refractory pouchitis and primary sclerosing cholangitis, the presence of serum autoantibodies (particularly antimicrosomal antibodies), ileal pouch mucosal infiltration by >10 IgG4-positive plasma cells, and the presence of more than one immune-mediated disease or serum marker.

Risk for colorectal neoplasia in patients with inflammatory bowel disease and mucosa indefinite for dysplasia

Lai KK, Horvath B, Xie H, Wu X, Lewis BL, Pai RK, Plesec T, Patil DT, Gordon IO, Wang Y, Shen B, Goldblum JR, Liu X.

Inflamm Bowel Dis 2015; 21(2): 378-84.

http://www.ncbi.nlm.nih.gov/pubmed/25569733

The authors studied the prevalence and incidence of neoplasia in a cohort of 93 patients with inflammatory bowel disease and a biopsy diagnosis of indefinite for dysplasia. Prevalence was estimated in 22 patients who underwent colectomy within six months of the diagnosis of indefinite for dysplasia. Six (22%) patients had foci of dysplasia in their colectomy specimens: one was low-grade and five were high-grade. Incidence was estimated in 71 patients who had colonoscopic surveillance, 18 (25%) of whom had subsequent neoplasia (10 with low-grade

dysplasia, five with high-grade dysplasia, and three with adenocarcinoma). The progression rate to any neoplasia (low- and high-grade dysplasia or carcinoma) was 3.2 cases per 100 person years, whereas the progression to advanced neoplasia (high-grade dysplasia or carcinoma) was 1.5 cases per 100 person years. The latter groups was also compared to a control group diagnosed as negative for dysplasia, which showed a progression rate to any neoplasia of 4.9 cases per 100 person years and progression to advanced neoplasia rate of 0.7 cases per 100 person years. The differences between these groups were not statistically significant.

Upfront special staining for Helicobacter pylori in gastric biopsy specimens Is not indicated

Chitkara Y.

Am J Clin Pathol 2015; 143(1):84-8.

http://www.ncbi.nlm.nih.gov/pubmed/25511146

The purpose of this study was to assess the value of upfront special stains for the identification of H. pylori (HP) organisms in gastric biopsies. A total of 570 biopsies from 568 patients were evaluated by H&E and either Diff-Quick or immunohistochemistry for HP. The biopsies were classified by modified Sydney criteria into the following subgroups: normal; minimal chronic gastritis (or near normal); mild chronic gastritis; moderate chronic gastritis; and severe chronic gastritis. The presence or absence of active inflammation was also recorded. The author found that 386 (67.7%) were normal, near normal, or had mild chronic inactive gastritis and HP was not identified in any of these biopsies. Given these findings the author suggests that it may be more cost effective to order special stains selectively in gastric biopsies, specifically in cases with any active inflammation and cases with moderate inactive colitis (although there is also some discussion about the ability to identify HP by H&E alone). By using Medicare allowable rates and using the proposed algorithm, the author calculates a theoretical savings of 40% over routine up front special stains for the cases in this study.

Pathologic diagnostics of HER2 positivity in gastroesophageal adenocarcinoma

Koopman T, Louwen M, Hage M, Smits M, Imholz A.

Am J Clin Pathol 2015; 143(2):257-64.

http://www.ncbi.nlm.nih.gov/pubmed/25596252

This study aims to validate current scoring guidelines for Her2 immunohistochemistry in gastroesophageal adenocarcinoma using the criteria of Hoffman with additional guidelines of Ruschoff. The authors state that gastroesophageal adenocarcinoma has the potential for greater interobserver variability than breast carcinoma due to greater tumor heterogeneity and irregular membrane staining. The study set of 323 cases was reviewed by three pathologists

who, prior to the study, were familiar with breast Her2 scoring but had no experience with gastroesophageal tumor scoring. The study pathologists completed training on scoring of gastroesophageal adenocarcinoma through an internet site and were given the additional guidelines by Ruschoff. Following the training interobserver variability was found to be good, similar to previously published studies with well-trained pathologists experienced with gastroesophageal Her2 scoring. It was noted that, as to be expected, there was more disagreement among pathologists for 2+ immunohistochemistry and in cases of diffuse or mixed (Lauren type) adenocarcinoma.

Familial colorectal cancer type X: genetic profiles and phenotypic features.

Dominguez-Valentin M, Therkildsen C, Da Silva S, Nilbert M.

Mod Pathol 2015; 28(1):30-6.

http://www.ncbi.nlm.nih.gov/pubmed/24743215

This review article focuses on a subset of cancers in patients with so called familial colorectal cancer type X (FCCTX) syndrome. FCCTX is defined as occurring in patients who, by clinical features, fulfill the Amsterdam criteria for hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, but have microsatellite stable tumors and no DNA mismatch repair mutations. The authors include an overview of hereditary influences in colorectal cancer and note that it is estimated that 20% of cases are thought to have some hereditary factors, although most factors are not well understood. Hereditary syndromes are broadly divided into polyposis syndromes (FAP, MAP, PJ, and JP) and non-polyposis syndromes (HNPCC), which are heterogeneous and include a subset of the Lynch syndrome (it is noted that only 1/3 of Lynch patients fulfill the Amsterdam criteria), Lynch-like syndrome (Amsterdam criteria and MMR gene function defects but no known MMR gene mutation), and FCCTX. Details of the genomic profiles of FCCTX tumors are discussed and it is stated that the tumors generally resemble sporadic MMR-proficient colorectal cancer. Morphologic features are, non-specific and generally show a “sporadic phenotype” including moderate differentiation, glandular and infiltrating patterns, and dirty necrosis. The authors note that because of the non-specific clinical presentation and phenotype of the tumors, it is difficult to identify patients with FCCTX syndrome without a detailed clinical history; however, there is hope that with additional investigation genetic and epigenetic findings may help in diagnosis and targeted intervention in the future.

Do serrated neoplasms of the small intestine represent a distinct entity? Pathological findings and molecular alterations in a series of 13 cases.

Rosty C, Campbell C, Clendenning M, Bettington M, Buchanan DD, Brown IS.

Histopathology 2015; 66(3):333-42.

http://www.ncbi.nlm.nih.gov/pubmed/24894811

This series of 13 serrated adenomas of the small intestine showed CDX2-positive phenotype in all tumors and subsets with abnormal beta-catenin staining, p53 expression, KRAS mutation, or CpG island methylator phenotype. Eight of 13 showed diffuse Ki67, associated with high-grade dysplasia. No BRAF V600E mutation or loss of MLH1 expression was seen, in contrast to colorectal serrated polyps.

Application of immunohistochemistry in gastrointestinal and liver neoplasms: new markers and evolving practice.

Chen ZE, Lin F.

Arch Pathol Lab Med 2015; 39(1):14-23.

http://www.ncbi.nlm.nih.gov/pubmed/25549141

This review article discusses new immunohistochemical stains useful in the workup of gastrointestinal and hepatic tumors. The authors highlight the role of predictive markers, including EGFR2, and mutation-specific markers, including BRAF V600E, in guiding clinical management.

Utility of immunohistochemistry in the pancreatobiliary tract.

Lin F, Chen ZE, Wang HL.

Arch Pathol Lab Med 2015; 139(1):24-38.

http://www.ncbi.nlm.nih.gov/pubmed/25549142

This review article presents an update in immunohistochemical stains useful in the workup of pancreatic tumors. The authors review effective antibodies and recommend an algorithm for approach to pancreatic neoplasms.

Histopathology Annual Review Issue: Intestinal Pathology.

Shepherd NA, Lauwers GY (Eds)

Histopathology 2015; 66(1): 1-160.

http://onlinelibrary.wiley.com/doi/10.1111/his.2015.66.issue-1/issuetoc

This annual review issue is entirely devoted to gastrointestinal pathology and is free to access online. It is divided into three sections: intestinal inflammation, polyps, and intestinal cancer.

Journals Reviewed (January and February 2015 Issues)

Histopathology

Archives of Pathology and Lab Medicine

Modern Pathology

American Journal of Clinical Pathology

Journal of Pathology

Journal of Clinical Pathology

American Journal of Pathology

Human Pathology

Cancer Cytopathology

American Journal of Surgical Pathology

Advances in Anatomic Pathology

Journal of Molecular Diagnostics

Gastrointestinal Endoscopy

Gastroenterology Clinics of North America

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