

GIPS JOURNAL WATCH, MAR-APR 2014

Gastroenterology, Mar 2014

Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch repair deficiency in Lynch syndrome like tumors.

Mensenkamp AR, et al. Gastroenterology. 2014; 146(3):643-646.

Some sporadic colorectal cancers with MSI do not have germline mutations in mismatch repair genes and do not have MLH1 promoter methylation. In this study, 25 MSI-positive tumors were screened for somatic mutations in MLH1 and MSH2 genes. In 13 of 25 tumors (8 MLH1-deficient and 5 MSH2-deficient tumors), somatic mutations were identified in these genes. The authors conclude that MMR-deficiency in the absence of germline mutations or promoter methylation may be related to somatic mutation.

<http://www.ncbi.nlm.nih.gov/pubmed/24333619>

Hum Pathol, Mar 2014

Evidence that gastric pit dysplasia like atypia is a neoplastic precursor lesion.

Agoston AT, et al. Hum Pathol. 2014; 45(3):446-55.

This study introduces the concept of dysplasia-like atypia (DLA) in the gastric pit epithelium but without involvement of the surface epithelium. DLA was found in 49% of resected gastric adenocarcinoma specimens adjacent to conventional dysplasia or carcinoma. DLA in gastric cancer cases was associated with intestinal-type adenocarcinoma, low-grade, stage 1, and a higher rate of chronic gastritis, intestinal metaplasia, atrophy, and conventional dysplasia. DLA was identified in 14% of biopsies with chronic gastritis and 6.8% of normal control biopsies. The authors conclude that DLA represents a precursor lesion in gastric carcinogenesis.

<http://www.ncbi.nlm.nih.gov/pubmed/24529328>

SOX9 a useful marker for pancreatic ductal lineage of pancreatic neoplasms.

Shroff S, et al. Hum Pathol. 2014; 45(3):456-63.

SOX9 plays an important role in pancreatic ductal development. This study shows that nuclear expression of SOX9 is seen in centroacinar cells and ductal cells in non-neoplastic pancreas, but not in acinar or endocrine cells. Focal or diffuse SOX9 expression was detected in all PanINs, IPMNs, mucinous cystic neoplasms, and serous cystadenomas, and in 89% of pancreatic ductal adenocarcinomas, 2.6% pancreatic neuroendocrine tumors, 11.1% acinar cell carcinomas, and 0% solid pseudopapillary neoplasms. The authors conclude that SOX9 can be a useful marker to demonstrate pancreatic ductal lineage.

<http://www.ncbi.nlm.nih.gov/pubmed/24418153>

Immunohistochemical detection of BRAF V600E mutant protein using the VE1 antibody in colorectal carcinoma is highly concordant with molecular testing but requires rigorous antibody optimization.

Kuan SF, et al. Hum Pathol. 2014; 45(3):464-72.

A monoclonal antibody (VE1) is directed against the BRAF V600E mutant protein, and has yielded variable results in different studies. In this series, all 74 cases with BRAF V600E mutation showed cytoplasmic staining with VE1 antibody (95% cases with moderate to strong staining). 51/54 BRAF V600E mutation-negative cases did not stain with VE1; 3 cases showed weak cytoplasmic staining. The sensitivity and specificity of VE1 was 100% and 94%, respectively. The authors conclude that moderate to strong staining with VE1 is a useful for the detection of the BRAF V600E mutation in colorectal cancer, while weak staining must be evaluated by PCR analysis to exclude a false positive outcomes.

<http://www.ncbi.nlm.nih.gov/pubmed/24529329>

MUC2 expression is an adverse prognostic factor in superficial gastroesophageal adenocarcinomas.
Davison JM, et al. *Hum Pathol.* 2014; 45(3):540-8.

Based on 142 resected, superficial esophageal adenocarcinomas (T1), this series shows that MUC2 positivity (intestinal" phenotype) was associated with a worse outcome, independent of lymph node metastasis.

<http://www.ncbi.nlm.nih.gov/pubmed/24290360>

Pancreatic ductal adenocarcinoma with autoimmune pancreatitis like histologic and immunohistochemical features.

Zhang X, et al. *Hum Pathol.* 2014; 45(3):621-7.

Autoimmune pancreatitis (AIP) often manifests as a mass lesion causing obstructive jaundice, clinically mimicking pancreatic carcinoma. A diagnosis of AIP may obviate the need for surgical resection, as most patients respond to steroid treatment. However, it is not clear whether these 2 conditions can coexist. In this study, 105 specimens resected for pancreatic ductal adenocarcinoma (PDAC) that also have changes of chronic pancreatitis were examined for features considered to be characteristic of AIP. In a study of 105 cases of pancreatic ductal adenocarcinoma, 10 cases showed concomitant histologic features of autoimmune pancreatitis (AIP): extensive fibrosis, lymphoplasmacytic infiltration, obliterative phlebitis, granulocytic epithelial lesions. More than 20 IgG4+ plasma cells per high-power field were seen in 7 cases, and KRAS mutation was seen in 3 cases in benign areas resembling AIP. The authors conclude that AIP-like lesions may occur in a small number of pancreatic ductal adenocarcinoma and suggest that some adenocarcinomas may arise in the setting of AIP. Hence caution should be exercised in treatment AIP based on needle biopsy of AIP, and close follow-up is necessary in these cases.

<http://www.ncbi.nlm.nih.gov/pubmed/24457081>

Gut, Mar 2014

Endoscopic versus histological characterisation of polyps during screening colonoscopy

Schachschal G et al. *Gut* 2014;63:458-465.

Can endoscopic assessment of small polyps replace biopsy interpretation by a pathologist? Ten experienced private practice endoscopists in Germany assessed all polyps identified in >1000 screening colonoscopies. Diagnostic accuracy of in vivo polyp assessment (by endoscopist) was measured for adenomatous vs. hyperplastic polyp. Also assessed were: differences between

conventional or latest-generation HDTV endoscopy were assessed, reliability of image-based follow-up recommendations, and blinded post-hoc analysis of polyps by photographs. For all polyps (n=675) accuracy of diagnosis was 76.6%, with highest accuracy of 96.1% for polyps >10 mm (n=51) and/or pedunculated (90.4%, n=94). There was no difference in diagnostic accuracy for right-sided vs. left-sided (n=236 vs. 437, respectively; accuracy of 72.5% vs. 78.7%). Overall, adenoma detection rate was not significantly different across endoscopy technologies (some subtleties are discussed in the paper). Using endoscopic decision-making, follow-up interval was incorrectly assigned for ~30% of patients overall for polyps up to 10 mm in size. Overall, there was no benefit to post-hoc polyp image analysis as inter-physician agreement was low (kappa of 0.45 for all five examiners, 0.55 for three private practice endoscopists involved in other parts of the study, 0.53 for two hospital endoscopists not involved in other parts of the study but with expertise in image analysis). University endoscopists were better at diagnosing adenomas correctly (p<0.001). The authors do not exclude the possibility of a "resect and discard" strategy for small colon polyps in future.

<http://gut.bmj.com/content/63/3/458.abstract>

AJSP, Mar 2014

[The Histopathology of PRSS1 Hereditary Pancreatitis](#)

Singhi A et al. *Am J Surg Pathol.* 38(3):346-353.

Most cases of hereditary pancreatitis, which is inherited as an autosomal dominant disease, are due to mutations in serine protease 1 (cationic trypsinogen gene, PRSS1). Ten pancreas specimens from PRSS1 patients are described. Patients range from 9-66 years in age with a history of intermittent abdominal pain. Pediatric patients (n=4) tended to retain normal lobular architecture but show variation in lobular size and shape due to patchy loss of acini and ducts. Loose fibrosis is present. At most PanIN-1A was present (n=1). Specimens from young adults (ages 28-30, n=2) show increased loss of acini and ducts and loose fibrosis with intermixed adipocytes. In older adults (ages 45-66, n=4) the pancreas is soft and shrunken with marked atrophy, fat replacement, duct dilatation, and intraductal calcifications. Mature adipose tissue replaces most of the pancreatic parenchyma and fibrosis is mostly periductal. PanIN-1 and -2 are present.

[GNAS Sequencing Identifies IPMN-specific Mutations in a Subgroup of Diminutive Pancreatic Cysts Referred to as "Incipient IPMNs"](#)

Matthaei H et al. *Am J Surg Pathol.* 38(3):360-363.

In contrast to PanIn (microscopic) and IPMNs (defined as >1 cm in maximum diameter), "incipient IPMNs" are cystic lesions <1 cm in diameter with epithelial features similar to IPMNs (long finger-like papillae, prominent mucin). Due to histologic similarity, the authors speculate that incipient IPMNs may be in the IPMN pathway. 21 incipient IPMNs were studied, of which 8 were found in association with pancreatic ductal adenocarcinoma and 3 in association with ampullary adenocarcinoma. 14 cases showed intermediate-grade dysplasia and 11 showed a gastric-foveolar epithelial subtype. All lesions studied showed at least 1 KRAS codon 12 mutation.

AJSP, Apr 2014

[Poorly Differentiated Neuroendocrine Carcinomas of the Pancreas: A Clinicopathologic Analysis of 44 Cases](#)

Basturk et al. Am J Surg Pathol. 38(4):437-447.

Poorly differentiated neuroendocrine (NE) carcinoma of the pancreas, defined as small cell or large cell NE carcinoma, is rare. 107 resections were identified with an original diagnosis suggesting poorly differentiated NE carcinoma. Cases were reclassified after immunohistochemistry for NE markers, trypsin, chymotrypsin, CD99, Ki67 and several eliminated as acinar cell carcinoma or morphologically well-differentiated NET. Of the 44 cases characterized in detail here, 27 were large cell (mean 37 mitoses per 10 hpf, mean Ki67 index of 66%) and 17 were small cell (mean 51 mitoses per 10 hpf, mean Ki67 index of 75%). 8 tumors had combined components including adenocarcinoma. 2 tumors had components of well-differentiated NET. The majority (88%) of patients had nodal or distant metastasis at the time of presentation. Most patients died within a year (median survival of 11 months for 33 patients who died of disease of 43 for whom follow-up was available).

[Whipple Made Simple For Surgical Pathologists: Orientation, Dissection, and Sampling of Pancreaticoduodenectomy Specimens For a More Practical and Accurate Evaluation of...Pancreatic,](#)

Distal Common Bile Duct, and Ampullary Tumors

Adsay NV et al. Am J Surg Pathol. 38(4):480-493.

Comprehensive multi-center guidelines and images for the approach to the Whipple specimen, including tips on maximizing lymph node retrieval.

[Immunohistochemistry for Annexin A10 Can Distinguish Sporadic From Lynch Syndrome-associated Microsatellite-unstable Colorectal Carcinoma](#)

Pai RK et al. Am J Surg Pathol. 38(4):518-525.

Lynch syndrome accounts for 2-3% of all CRC, and most cases of Lynch are MSI-High. However, ~75% of MSI-H CRC are sporadic, due to hypermethylation of the MLH1 promoter's CpG islands (CIMP-high), and not due to Lynch. These hypermethylated tumors may also contain BRAF V600E mutations, which are rare in Lynch-associated tumors, but 35-55% of sporadic MSI-H tumors show wild-type BRAF. Most Lynch-associated CRC stem from tubular and tubulovillous adenomas, but most sporadic MSI-H CRC stem from sessile serrated adenomas/polyps. The authors examine annexin A10 (ANXA10, expressed in SSA/Ps) as a way to distinguish between sporadic and Lynch-associated MSI-H tumors. 75 sporadic MSI-H and 56 Lynch-associated CRCs were studied. ANXA10 was expressed at higher levels (quantitative real-time rtPCR and immunohistochemistry) in sporadic vs. Lynch-associated tumors. Overall, 43% of BRAF-mutated sporadic cases were positive for ANXA10 by immunohistochemistry, compared to 41% of wild-type BRAF, MLH1 promoter hypermethylated cases. The authors point out ANXA10 use may be limited in biopsy specimens as expression can be focal; ANXA10 expression may decrease as dysplastic cases progress to carcinoma. The proposed algorithm is to add IHC for ANXA10 after initial MMR ihc, with cases positive for ANXA10 likely being sporadic tumors. In those cases, germline MLH1 promoter hypermethylation testing can be added if there is persistent suspicion for Lynch syndrome. In cases negative or equivocal for ANXA10, BRAF analysis can be

performed followed by MLH1 promoter studies as needed to further distinguish between sporadic tumors and cases of Lynch syndrome.

[Adenocarcinoma of the Minor Duodenal Papilla and Its Precursor Lesions: A Clinical and Pathologic Study](#)

Shia J et al. Am J Surg Pathol. 38(4):526-533.

Nine cases of the rare entity of adenocarcinoma of the minor duodenal papilla are characterized in detail, including patient demographics, gross features of tumor, association with IPMN-like precursor lesion (seen in 5 cases), immunoprofile (generally positive for CK20, CDX2, MUC2, B72.3 in intestinal-type and positive for CK7, MUC1, B72.3, CA125 in pancreatobiliary-type), MMR profile, and clinical follow-up information. Overall these lesions are similar to ampullary or IPMN-associated pancreatic carcinomas with intestinal, colloid, or pancreatobiliary phenotype.

Arch Pathol Lab Med, Mar 2014

Summary of Microsatellite Instability Test Results From Laboratories Participating in Proficiency Surveys: Proficiency Survey Results From 2005 to 2012

Boyle TA et al. Arch Pathol Lab Med 138:363-370, Mar 2014.

[Abstract](#)

CAP proficiency testing for 16 surveys from 2005-2012 is analyzed. In the most recent survey, 104 laboratories participated, most of whom use 5 markers (including a panel from Promega). Average correct classification rate is 95.4%. Some cases may be misclassified as MSI-L or MSS when the tumor content in the sample is below the limit of detection of the assay. In one particular survey from 2011, 14 labs misidentified specimens as MSS; 6 of these 14 did not use microdissection, whereas of 75 labs that did use microdissection, only 13 misclassified the tumor (P=0.03). There is no clear consensus on the minimum percentage of neoplastic cellularity.

Modern Pathology, April 2014

Pediatric autoimmune enteropathy: an entity frequently associated with immunodeficiency disorders

Singhi, A, et al. Mod Pathol APR 2014 27: 543-553; advance online publication, September 20, 2013

In this article the pathological and clinical features of a series of pediatric patients with a diagnosis of autoimmune enteropathy are discussed. The classic description of autoimmune enteropathy, the most frequent diagnosis in pediatric patients with intractable diarrhea, includes intractable diarrhea in patients less than 6 months in age (male predominance), circulating gut autoantibodies and histologic classic histologic features of the small bowel (villous blunting, crypt hyperplasia, expansion of the lamina propria by a mononuclear inflammatory infiltrate, and crypt apoptosis). More recently, the article states, reports of adults with autoimmune enteropathy describe a wider range of pathologic changes, including celiac like histology. In this current series, selected by a search of the University of Pittsburg Medical center electronic medical records, the classic histologic features were seen in 11 of 14 of the patients; however 3 cases were noted to have celiac-like histology. In addition it was note that 50% of the cases had

significant acute inflammation that masked the presence of apoptosis. Another finding was that crypt apoptosis in the colon and in the stomach were also seen as early findings, and the authors suggest that, especially in the colon, this may be an important diagnostic clue and should not be overlooked.

<http://www.ncbi.nlm.nih.gov/pubmed/24051695>

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