A Potpourri of Small Intestinal Neoplasms

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Disclosure Statement

Dr. Montgomery reports no relevant financial relationships with commercial interests.
What about neoplasms
Diagnosis???

Anyone want a special stain?
Duodenal Well-differentiated Neuroendocrine Tumors (Carcinoids)

Can be easily missed and mistaken for inflammation
A special variant of duodenal neuroendocrine tumor

Somatostatinoma in patients with neurofibromatosis (NF1)
Endocrine neoplasm in NF1 patient - Duodenum
Duodenal “somatostatinoma” in NF
Psammoma-like calcifications
Easy carcinoid – the very prominent endocrine granules are a feature of ileal lesions
Endocrine cells
Zollinger-Ellison
MEN-1

**Gene**: Tumor suppressor gene on chromosome 11 (11q13)

**Pituitary**: Prolactinomas, mass effect

**Parathyroid**: Hyperparathyroidism, nephrolithiasis

**Pancreas-duodenum**: Multicentric, gastrinomas, ulcers (PanNETs are leading cause of death)
Klöppel et al,
Klöppel et al,
Gastrin
Another Large Duodenal polyp
Let’s compare the duodenal pyloric gland adenoma to a duodenal tubular or tubulovillous adenoma.
Reactive or neoplastic?
The mucin can be a clue.
Reactive or neoplastic? The gastric mucin can be a clue for reactive
Reactive or neoplastic? The gastric mucin can be a clue for reactive.
Regular old duodenal adenoma with lipid "hang-up"
Regular old duodenal adenoma with lipid “hang-up” – PAS/AB stain – note that the material in the cytoplasm is lipid not mucin.
Real or Fake?
Metaplasia goes for fake
Traditional Serrated Adenoma of Small Bowel

Seem to exist and be rare

Similar molecular profile to that of colorectal lesions

Small bowel TSA
Adenoma or Reactive

Most cases can be resolved
If you do not know, do not pretend.
A diagnosis of ampullary adenoma can prompt a Whipple operation – a bad thing if the biopsy is only reactive
Report the case as “indefinite for adenoma” – it is not so difficult to resample the area
– adenoma
– do not be afraid to report as “indefinite”
Ampullary “Mass”

An endoscopist saw a polyp in the duodenum and performed a polypectomy. He thought the polyp was very firm and told the pathologist that the pathologist should diagnose cancer.
Normal ampulla
Ampulla

Ampulla itself is often a source of difficulty since normal to have ampullary glands are interspersed with disorganized bundles of smooth muscle.

When inflammation is a feature, great caution is advised. The ampulla is not typically biopsied without a compelling reason since pancreatitis may be a severe consequence of performing such biopsies.
Ampullary biopsy
Ampullary Surface – No goblet cells
Small Bowel Adenocarcinomas

Adenocarcinomas are the most common primary malignancies of the small intestine (30-50% of small bowel malignancies).

However, primary adenocarcinomas are still rare lesions accounting 2% of gastrointestinal (GI tract) tumors for 1% of GI tract cancer deaths. Older adults (median 67 years), male predominance, more common in African Americans than Caucasians.
Sporadic ileal adenocarcinoma
Small Bowel Adenocarcinomas

Majority sporadic and share with sporadic colorectal adenocarcinomas both clinical risk factors and development from adenomatous polyps.

Remaining minority syndromic - polyposis syndromes (primarily familial adenomatous polyposis [FAP] but also hereditary nonpolyposis colon carcinoma syndrome (HNPCC, Lynch syndrome), Peutz-Jeghers’ syndrome, and juvenile polyposis syndrome), Crohn’s disease, gluten-sensitive enteropathy, ileostomy, and ileal conduits.
Familial adenomatous polyposis/
FAP – Small intestinal adenocarcinoma
Carcinoma associated with Peutz-Jeghers syndrome
Carcinoma associated with Peutz-Jeghers syndrome
Interesting Lynch Syndrome Variant

Small bowel adenomas and carcinomas are a feature of Lynch syndrome.
Biallelic mismatch repair deficiency syndrome/constitutional mismatch repair deficiency
Tends to be found in populations with consanguinity
Young patient with Trimbath syndrome – germline biallelic loss of PMS2
Small Bowel Adenocarcinomas

Greatest risk of small intestinal adenocarcinomas with FAP.
Relative risk of duodenal adenocarcinoma is striking (relative risk, about 330)
Ampullary adenocarcinoma (relative risk, about 124).
Risk of small intestinal adenocarcinoma in Crohn’s disease and celiac disease are each about 50-100 fold.
Small Bowel Adenocarcinomas

Both for sporadic and predisposing condition associated lesions are most common in the duodenum, with 65 percent periampullary, prevalence decreases progressively through the rest of the small intestine.

Important exception to the proximal location Crohn's disease - 70 percent of adenocarcinomas are ileal, corresponding to the primary site of the inflammatory process in this disease.
CK 7 and CK20 Expression Profile in Normal Small Intestinal Mucosa
CK7 and CK 20 Expression Profile in Sporadic SIA and CRC
CK7 and CK20 Expression in Small Bowel Adenomatous Components
A Loss of CK20 Expression Is Reciprocally Accompanied by An Emergence of CK7 Expression in Some Cases
Comparison of CK7 and CK20 Expression Patterns between Primary SIA and Secondary CRC

<table>
<thead>
<tr>
<th>Pattern</th>
<th>No. Positive (%)</th>
<th>Primary (n=24)</th>
<th>Secondary (n=23)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7+ / CK20-</td>
<td>8 (33)</td>
<td>0</td>
<td></td>
<td>0.0039</td>
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<tr>
<td>CK7- / CK20+</td>
<td>0</td>
<td>21 (91)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CK7+ / CK20+</td>
<td>16 (67)</td>
<td>1 (4)</td>
<td>&lt;0.001</td>
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<tr>
<td>CK7- / CK20-</td>
<td>0</td>
<td>1 (4)</td>
<td>0.4894</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher exact test using S-PLUS system.

Summary

• Alteration of CK7 and CK20 expression profile occurs in early SIA tumorigenesis

• The CK7 positive or CK7 and CK20 double positive pattern may be of diagnostic value in distinguishing primary SIA from secondary CRC
Pitfall 1: Increased CK7 Expression in Normal Appearing Mucosa Near Cancer
Pitfall 2: CK7 Expression in Regenerative Mucosa
Small Bowel Adenocarcinomas

Main differential diagnosis - metastatic disease - small intestine is the most common GI site for metastatic disease.

Features favoring a metastatic tumor include the presence of multiple lesions, the absence of a precursor adenoma, a histologic appearance of tumor being “bottom heavy” or encroaching from below, and lack of ulceration.
An Important Thing to Recall

The small bowel is treacherous since it metastases are so common there and they can “colonize” the surface and mimic an in situ component.
Sarcomatoid carcinoma involving small bowel mucosa
Sarcomatoid carcinoma involving small bowel mucosa
Metastatic sarcomatoid lung carcinoma
Metastatic sarcomatoid lung carcinoma, CAM 5.2
Metastatic sarcomatoid lung carcinoma
Colon carcinoma colonizing small bowel
Unauthorized glands in ampulla
Pancreas cancer spread to ampulla
Small Bowel Adenocarcinomas, Immunohistochemistry

We have found DPC4 (smad4) antibodies helpful in identifying some cases of pancreatic carcinomas since about 60% of pancreatic carcinomas show loss of this marker in their nuclei whereas this is relatively uncommon in colorectal and small intestinal adenocarcinomas.
Loss of DPC4
This metastatic melanoma is very easy to diagnose.
But please always check lacteals
Is this a carcinoid (neuroendocrine tumor)?
If you check lacteals, you will not miss this metastatic breast cancer
Pancreatic ductal carcinoma “colonizing” the duodenum
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Pancreatic ductal carcinoma “colonizing” the duodenum
Pancreatic ductal carcinoma "colonizing" the duodenum, CDX2 staining
Pancreatic ductal carcinoma "colonizing" the duodenum, CDX2 staining
Mucinous neoplasms on duodenal biopsies

You CANNOT tell if they are pancreatobiliary CARCINOMAs or “mucinous neoplasms” extending onto the duodenal surface and you should not try or you will be wrong sometimes

Your report should express the need to correlate with imaging – similar operations will be performed as long as the surgeon has a neoplastic diagnosis!
Ampullary biopsy; mucinous neoplasm
Another Caution

A young male patient presented with vomiting and a duodenal mass was biopsied in about 2005
Small bowel biopsy from a mass; 22 year old male
This is a pankeratin; the lesion was CK7+, CK20-
“Poorly differentiated carcinoma involving the small intestine. Please correlate with imaging to address the possibility of other disease sites”
Another embryonal carcinoma that even suggests an in situ component
Another young male patient with duodenal mass had been reported as Ewing's sarcoma of the duodenum.
Case

Was diagnosed as Ewing’s/PNET based on some CD99 labeling
Another duodenal polyp
Another duodenal polyp
BCL6 highlights the neoplastic follicular cells
BCL2 highlights the abnormal follicles
Cyclin D1 stains proliferating epithelial nuclei but not the follicular lymphoma
BCL2 in a follicular lymphoma – inside the follicles
BCL2 in a reactive lymphoid aggregate – NEGATIVE in the follicles
Most common type of lymphoma that makes “polyposis”: Mantle cell lymphoma
Has a lot of morphologic overlap with follicular lymphoma (but does not make follicles!)
Resection from 1972 for reactive lymphoid polyps
Old resection for diffuse large B cell lymphoma
Isolated Follicular Lymphoma in Small Bowel

Found incidentally on small bowel biopsies performed at time of endoscopy for other indications

Very indolent – treatment is usually OBSERVATION but rare bad actors

Look for paper by Pittman et al with Duffield as last au
Mantle cell lymphoma

Lots of overlap with follicular lymphoma but important to separate
Cyclin D1/BCL1
Enteropathy-Associated T Cell Lymphoma

Rare

About 5% of lymphomas, usually after refractory sprue or ulcerative enteritis/jejunitis

Usually in jejunum

Horrible outcome – 5 y survival 10%
Immunoprofile

Most cases CD3+, CD4-, CD8-, CD7+, CD5-, TIA1+

Can separate into Type A (EATL) and Type B (epitheliotropic lymphoma)

EATL is CD56-, CD30+ and has large pleomorphic cells

Epitheliotropic is CD56+ and has smaller blander cells

Both are ALK-
WHO 2016 classification

Enteropathy-associated T cell lymphoma (EATL). This links with celiac disease and tends to be found in persons of European origin. It tends to have pleomorphic cytologic features. Immunophenotype: CD3+, CD5-, CD7+, CD8 +/-, CD4-, CD56-

Monomorphic epitheliotropic intestinal T cell lymphoma (termed EATL, type 2 in the past) is unassociated with celiac disease and found in Asians and Hispanics. It often has STAT5B mutations, is derived from gamma delta T cells and monomorphic cytologic features. Immunophenotype: CD3+, CD4-, CD8+, CD56+. 
Celiac disease-associated T cell lymphoma resected many years ago (nothing to see and now you shouldn’t see such a resection!)
CD5 – this type of T cell lymphoma is negative
CD8 – loss in lymphoma cells
Enteropathy-associated Lymphoma, Type B; Monomorphic epitheliotropic intestinal T cell lymphoma
Enteropathy-associated lymphoma – Type B; Monomorphc epitheliotropic intestinal T cell lymphoma
Thank you