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)
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)
Gastrin

Glucagon

Insulin

PP

Somatostatin

Unclassified

Endocrine tumors

Klöppel et al.,

Another Large Duodenal polyp
Let’s compare the duodenal pyloric gland adenoma to a duodenal tubular or tubulovillous adenoma.
Reactive or neoplastic? The gastric mucin can be a clue for reactive

Regular old duodenal adenoma with lipid “hang-up” – PAS/AB stain – note that the material in the cytoplasm is lipid not mucin

Traditional Serrated Adenoma of Small Bowel
Seem to exist and be rare
Similar molecular profile to that of colorectal lesions
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.

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), 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
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.

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

CK 7 and CK 20 Expression Profile in Sporadic SIA and CRC

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>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>0.0039</td>
</tr>
<tr>
<td>CK7- / CK20+</td>
<td>0</td>
<td>21 (91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK7+ / CK20+</td>
<td>16 (67)</td>
<td>1 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK7- / CK20-</td>
<td>0</td>
<td>1 (4)</td>
<td>0.4894</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.

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

Sarcomatoid carcinoma involving small bowel mucosa

Sarcomatoid carcinoma involving small bowel mucosa

Keratin Cam 5.2

Ampullary biopsy; mucinous neoplasm
Mucinous neoplasms on duodenal biopsies
You CANNOT tell if they are pancreateobiliary 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!

This metastatic melanoma is very easy to diagnose

But please always check lacteals

HMB45 stain
Is this a carcinoid (neuroendocrine tumor)?

Melan-A

If you check lacteals, you will not miss this metastatic breast cancer.

Something is creeping in the submucosa.
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.
Pancreatic ductal carcinoma "colonizing" the duodenum

Another Caution
A young male patient presented with vomiting and a duodenal mass was biopsied in about 2005

This is a pancreatein; 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

CD10

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!)

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
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 and Type B
Type A is CD56-, CD30+ and has large pleomorphic cells
Type B is CD56+ and has smaller blander cells
Both Type A and Type B are ALK-
Enteropathy-associated lymphoma – CD3

CD5 - this type of T cell lymphoma is negative

CD8 - loss in lymphoma cells