Mimickers in GI Pathology

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• Disclosures:
  • Salary support: C₂ Therapeutics
Objectives

- Review histologic mimickers of neoplasia commonly encountered in GI pathology
- Discuss a practical approach to identify these mimickers and differentiate them from true neoplasia
- Review a few mimickers of non-neoplastic processes

Case

- 79 y/o female with anemia and colon lesion
- Described as large and “fibrotic”; could not be lifted after submucosal injection
- Status post laparoscopic ileocolonic resection of large villous adenoma with HGD
- Polyp was at anastomotic site
Signed out

- Atypical spindle cell proliferation in a background of extensive fibrino-inflammatory exudate. Minute fragment of benign epithelium. See note.

- *Note: Though we believe this represents a florid myofibroblastic response at the anastomotic site, we recommend close patient follow-up to ensure eventual resolution.*
Case follow up

• Findings at f/u colonoscopy
  – Polypoid lesion at anastomosis, decreased in size, soft to touch
Follow up bx (@ 3 months), sign out

- Exuberant reactive myofibroblastic proliferation associated with ulcer exudate.
Inflammatory Spindle Cell Polyp

Bizarre and Myofibroblastic-like

Patient with IBD
Case

- 78 y/o F with duodenal ulcer
- Hx of metastatic breast cancer, recent oral chemotherapy, and celecoxib intake.
- Impression: poorly differentiated malignant neoplasm
negative for AE1/3, S100, synaptophysin, CD117, and HHV8.
Case

- No mass lesion
- On celecoxib

Plump endothelial cells associated with granulation tissue

Reactive myofibroblasts
Signed out

- Favor exuberant reactive myofibroblastic response in the background of ulceration and granulation tissue. See note.

- Slides show a proliferation of spindled cells with abundant, "stretched out" cytoplasm and small delicate vessels lined by plump endothelial cells in a background of acute inflammatory cells and overlying ulceration. Though some of the spindled cells show hyperchromatic nuclei, others show hypochromasia with visible but small nucleoli (JHH recut reviewed). Rare mitotic figures are present. Submitted immunostains show that spindle cells are immunoreactive for SMA and negative for CD34, CD31, AE1/3, S100, synaptophysin, CD117, and HHV8. CD31 and CD34 highlight vessels. We repeated synaptophysin and added a chromogranin and those are negative. The patient’s history of metastatic breast cancer, recent oral chemotherapy, and celecoxib intake is noted from the submitted paperwork. Though we suspect this is a florid myofibroblastic proliferation associated with new vessels of granulation tissue, the findings are sufficiently striking to suggest close patient follow up to assure resolution.

Differential?
Leiomyosarcoma

SMA

Desmin
Rectal polyp

Leiomyoma
Lesson: Beware of the rare colonic GIST procured via endoscopic biopsy

“Bizarre” stromal cells

- Ulcers and inflammatory polyps esophagus, GE jx, stomach, colon, anal canal
- Bizarre atypia that can lead to a dx of malignancy
- SMA pos
- Proliferative fasciitis-like ganglion like-cells
  - Abundant, amphophilic cytoplasm, vesicular nuclei, and large eosinophilic, inclusion-like nucleoli.

- In a monolayer in an ulcer or polyp
• Large and irregular nuclei
• Prominent nucleoli
• Chromatin typically finely dispersed
• Tons of eosinophilic cytoplasm
• “Stretched out” reparative look
• Vimentin-only fibroblasts (some)
• Keratin, S100, CD117, desmin, actin negative

Bizarre stromal cells

Myofibroblastic-type
Pitfall Alert

Sometimes Associated with Adenocarcinoma

Courtesy of Dr. Brosens and Dr. Offerhaus, University Medical Center Utrecht, Netherlands
Caldesmon

- APC, p53, and KRAS mutation in the carcinoma
- Only a KRAS mutation in the sarcomatoid component (same as in the carcinoma component.)
- No losses or gains in chromosomal copy numbers

Clues that suggest reactive process

- Neutrophils peppered in the backdrop
- School of fish/stretched out cells that tend to run perpendicular to an ulcerated surface
- Abundant cytoplasm
- Open chromatin pattern with visible nucleoli, *typically* no macronucleoli
Other Colon

Squeeze Artifact

• Common
• Tissue trauma
• Epithelium is squeezed out of the crypts
• Can be mistaken for ischemia
• Squeezed glands sit close to empty crypts
• Glands are not injured
• Lamina propria is not hyalinized
Pseudolipomatosis

• Colon is insuflated during colonoscopy for visualization
• Gas may infiltrate tissue and appear as small, clear, fat-like spaces in the mucosa or superficial submucosa, often associated with lymphoid aggregates.
• No clinical significance
“Air” Polyp
Signet Cell Change

- Epithelium becomes detached and begins to slough
  - Cells round up
  - Within the basement membrane
  - Distended crypts
  - Reparative changes = alarming
  - Mitoses may be conspicuous
    - Look at intact adjacent gastric mucosa


Signet Ring Cell Change (SRCC)

- Pseudomembranous colitis
  - Classic association
  - 28% cases of PC show variable numbers of SRCs
  - Inflammatory bowel disease
  - Ischemic injury
  - H. pylori gastritis
  - Reported in many organs
    - Endometrium
    - Prostate
    - Bladder


<table>
<thead>
<tr>
<th>Stain</th>
<th>Signet-Ring Cell Change</th>
<th>Signet-Ring Cell Carcinoma</th>
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<tr>
<td>PAS</td>
<td>Strongly positive</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>DPAS</td>
<td>Strongly positive</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>100% of cells strongly positive</td>
<td>70-75% of cells weakly positive</td>
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<tr>
<td>P53</td>
<td>100% of cells negative</td>
<td>&gt;50% of cells strongly positive</td>
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<tr>
<td>Ki-67</td>
<td>100% of cells negative</td>
<td>42-60% of cells positive</td>
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</table>

Fat atrophy


Esophagus
Barrett Esophagus: The Fake Goblet Cell

- Some practices use Alcian-Blue or Alcian-Blue/PAS to identify goblet cells
- The acidic sialo- and sulfomucins in goblet cells react with Alcian Blue at pH 2.5
- Alcian-Blue/PAS is a particularly colorful stain that nicely highlights mucin:
  - Goblet cells (acid mucin) are highlighted in purple/deep blue
  - Gastric-type mucin (neutral mucin) is highlighted in magenta

The real deal
Alcian blue has proclivity to stain small amounts of mucin present in non-goblet cells

- *Pseudogoblet cells* are distended foveolar cells with “pinkish” intracytoplasmic mucin.
  - Frequently seen in inflamed cardia-type epithelium
  - Typically present contiguously/in clusters one after the other.
  - Typically stain magenta on AB/PAS but can occasionally have a blue hue.
  - They tend to stain blue on AB alone
Alcian blue has proclivity to stain small amounts of mucin present in non-goblet cells

- *Columnar blues* are **non-goblet shaped/non-distended** foveolar cells
  - May stain blue with AB alone
  - May be seen in multilayered epithelium
  - Though some have proposed they are a precursor to IM*, others disagree**

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Alcian blue has proclivity to stain small amounts of mucin present in non-goblet cells

- *Multilayered epithelium* consists of basally located immature-appearing squamous cells underneath acid mucin-containing columnar cells
  - Proposed by some as a precursor to BE*
  - Columnar cells stain deep blue/purple-magenta on AB/PAS
  - On AB stain alone the columnar cells stain blue

Alcian blue has proclivity to stain small amounts of mucin present in non-goblet cells

- Alcian blue has similar sensitivity but lower specificity when compared to H&E examination*
- PPV of AB for detecting goblet cells has been reported at 72% by one study*.
- Some argue that (and some practices employ) MUC2 and CDX2 are better options to help identify goblet cells but
  - These can stain non-goblet cells.
  - CDX2 stains 38*-43%** of samples from patients without goblet cells.
- What does this non-goblet cell staining mean for the patient?
  - Though this may potentially identify patients at risk for IM**, studies addressing this and also risk of dysplasia are lacking.


The real deal: Intensely blue, discrete goblet cells in a background of foveolar cells with magenta cytoplasm

CDX2 will stain both goblet and non-goblet cells

Pseudogoblet cells

Submucosal glands

Panarelli and Yantiss. Do Ancillary Studies Aid Detection and Classification of Barrett Esophagus? 
Am J Surg Pathol. Volume 40(8), August 2016, p e83–e93
In summary

• Special stains are not necessary in the diagnosis of BE.

Stomach

Findings that mimic signet ring cell adenocarcinoma
Crushed Oxyntic Glands

- If mucous neck cells predominate, they can resemble signet ring cell adenocarcinoma.
Reassuring Findings that Argue for Dislodged Mucous Neck Cells

• Tissue is not intact
• Cells dislodged within glandular lumina
• Cells are floating in a sea of extracellular proteinaceous pink material (parietal cell cytoplasmic contents), not in lamina propria
• Focally arranged in benign-appearing glandular configurations
Xanthoma

CD68 + and cytokeratin -
The biopsy with prominent Mott cells

Russell body gastritis

- Benign and typically incidental
- Mucosal accumulation of plasma cells with intracytoplasmic, eosinophilic globules (a.k.a. Mott cells) composed of immunoglobulins (Russell bodies)
- Chronic inflammation
- *H. pylori* infection is a common though not universal association
- Significance:
  - Do not confuse with signet ring cell gastric carcinoma

[Image: http://niigata-cp.org/?page_id=1342]
Russell body gastritis

CD138 +  
CD79a +  
CK-  
Kappa and lambda IHC not useful*  


Russell body gastritis

• Russell body “esophagogastroenteritis”?  
  • Esophagus  
  • Small bowel  
  • Colon  

Duodenum

Crushed Brunner Glands

- Often mistaken for
  - Myxoid nerve sheath tumor
  - Whipple disease
Whipple disease

- Macrophage nuclei
- Lymphangiectasia

Whipple disease

- PAS: Coarse rod/sickle/globular staining
Crushed Brunner Glands

Whipple Disease

Clump

At least some individual cells
Anus

Pagetoid Dyskeratosis

- Reactive exuberant keratinization in squamous epithelium that may mimic HPV cytopathic changes.
- Keratinocytes are larger than normal
- Pyknotic to hardly visible nuclei
- Clear halo surrounding condensed keratin globs
Differential
Condyloma

Halo around condensed keratin

Halo around enlarged, hyperchromatic nuclei

Paget Disease

- Large, pale/pink cells
- +/- signet ring cell features
Paget Disease

- Apocrine differentiation
  - CAM5.2+
  - CEA+
  - GCDFP+
  - CK7+
  - Mucin+

Pagetoid Extension from Colorectal Primary

CDX2
### IMMUNOHISTOCHEMICAL PROFILES OF INTRAEPITHELIAL NEOPLASTIC LESION OF THE ANUS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CK5/6</th>
<th>CEA</th>
<th>GCDFP</th>
<th>CAM 5.2</th>
<th>CK90334E12</th>
<th>S100</th>
<th>P16</th>
<th>CK7</th>
<th>CK20/CDX2</th>
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<tbody>
<tr>
<td>SCC/precursors</td>
<td>+</td>
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<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Paget disease</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Usually –</td>
</tr>
<tr>
<td>Pagetoid spread of invasive colorectal adenocarcinoma into perianal skin</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Usually –</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+/–</td>
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<tr>
<td>Melanoma</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CEA, carcinoembryonic antigen; GCDFP, gross cystic disease fluid protein; *A subset of squamous carcinoma in situ that appears Pagetoid can express CK7, so a panel is warranted.

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**Pagetoid Dyskeratosis**

**Molluscum Contagiosum**

http://www.pathologyoutlines.com/images/skinnonmolluscum4.jpg
Molluscum Contagiosum

https://upload.wikimedia.org/wikipedia/commons/a/aa/Molluscum_Contagiosum_%283952583713%29.jpg

Papillary Endothelial Hyperplasia

- Exuberant organizing thrombus
- Anywhere in the body
- Solitary superficial, firm, bluish or reddish mass
  - Fingers
  - Head
  - Neck
  - Anorectal area
• Papillary fronds with a fibrin/hyalinized collagenous core lined by single layer of endothelial cells
• No endothelial atypia or mitoses
• Some extravascular extension possible
Angiosarcoma of the GI Tract

- Small bowel or colon
- Intestinal bleeding, anemia, pain
- Tumors may be primary GI, contiguous spread from adjacent site, or metastatic
- Aggressive
Angiosarcoma of the GI Tract: Epithelioid Morphology Common

- Sheets of epithelioid cells
- Hemorrhage
- Subtle areas with cleft-like spaces
- Pos for CD31, CD34, ERG, Factor VIII, AE1/3 (most), CK7 (small subset), Cam5.2 (65%), and CK19 (65%)
- Neg for CK20, S100

**Angiosarcoma**
- Solid areas
- Nuclear atypia
- Mitoses
- Intracytoplasmic lumina
Papillary Endothelial Hyperplasia
- Confined to vascular lumen
- No nuclear atypia
- Endothelium in a monolayer
- No or few mitoses
- No necrosis
- Intimate association of the proliferated tuft-like structures with thrombotic material

Angiosarcoma
- Infiltrative
- Endothelial atypia common (though not universal)
- Mitoses common
- Necrosis possible
- In GI tract typically epithelioid morphology

Summary
- There are many neoplastic and inflammatory mimics in GI pathology
- Familiarity is important to avoid unnecessary time investment, immunohistochemical panels, and misdiagnoses
Bonus Case

History

- 55 y/o male
- Esophageal carcinoma
- Small “residual mass” on endoscopy.
Answer: Radiation Related Changes Mimicking Neoplasia
Clues

Clues

Clues
Clues to Radiation-Related Changes

• Bizarre atypia
• Flattened, stretched glands
• Intracytoplasmic vacuolation
• Intracytoplasmic neutrophils
• May be seen anywhere in the GI tract