

Mimickers in GI Pathology

Lysandra Voltaggio, M.D.

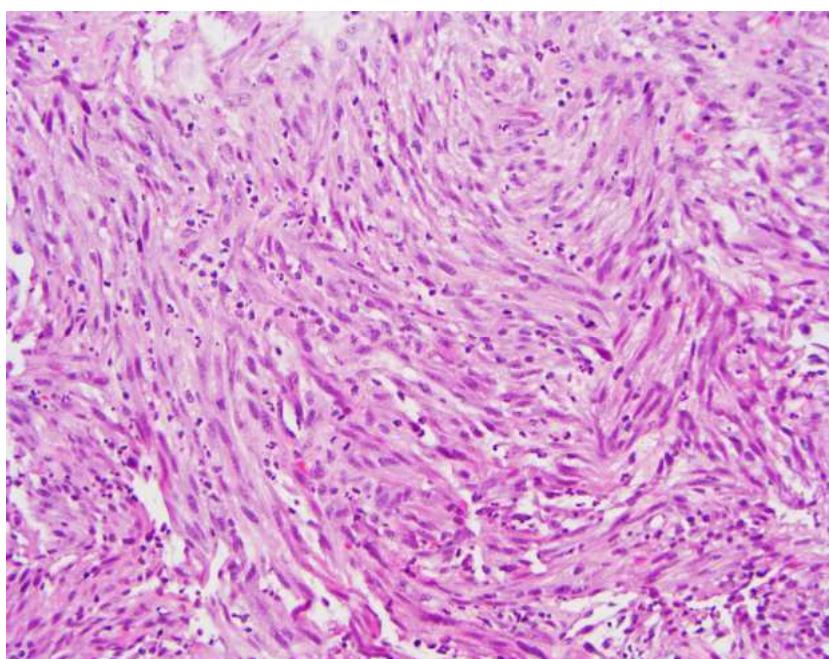
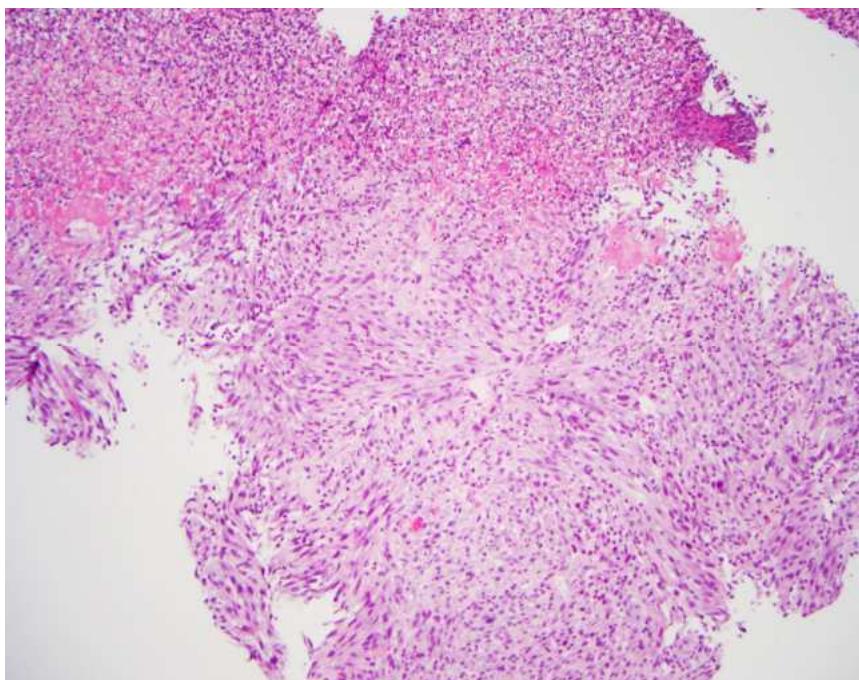
- Disclosures:
 - Salary support: C₂ Therapeutics

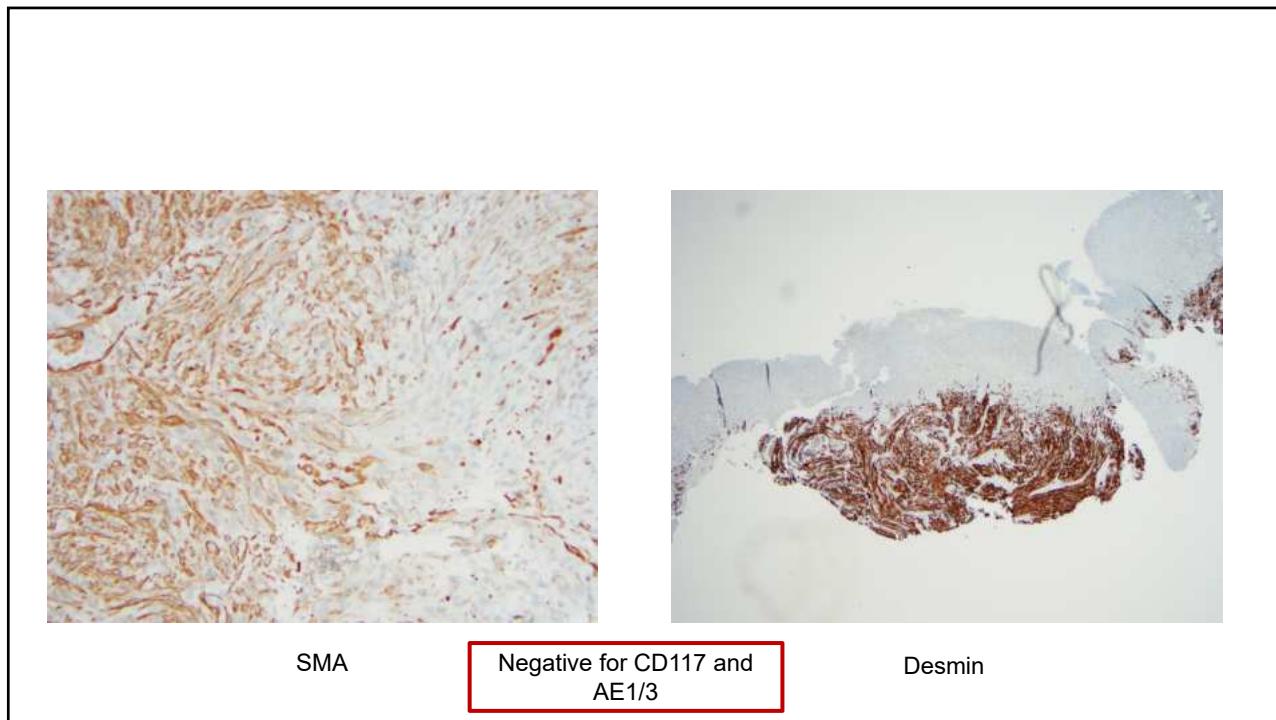
Objectives

- 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



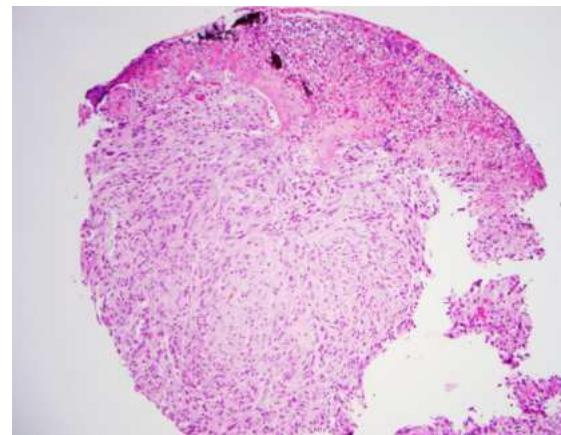
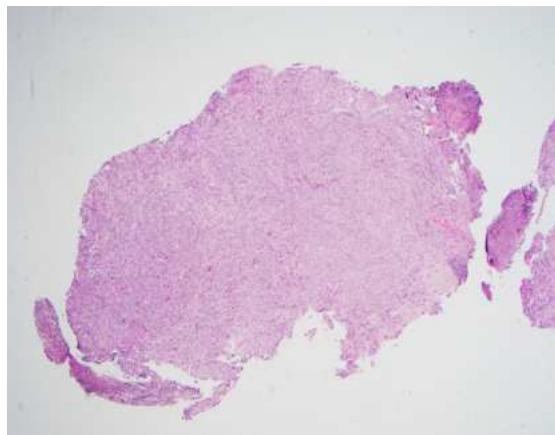


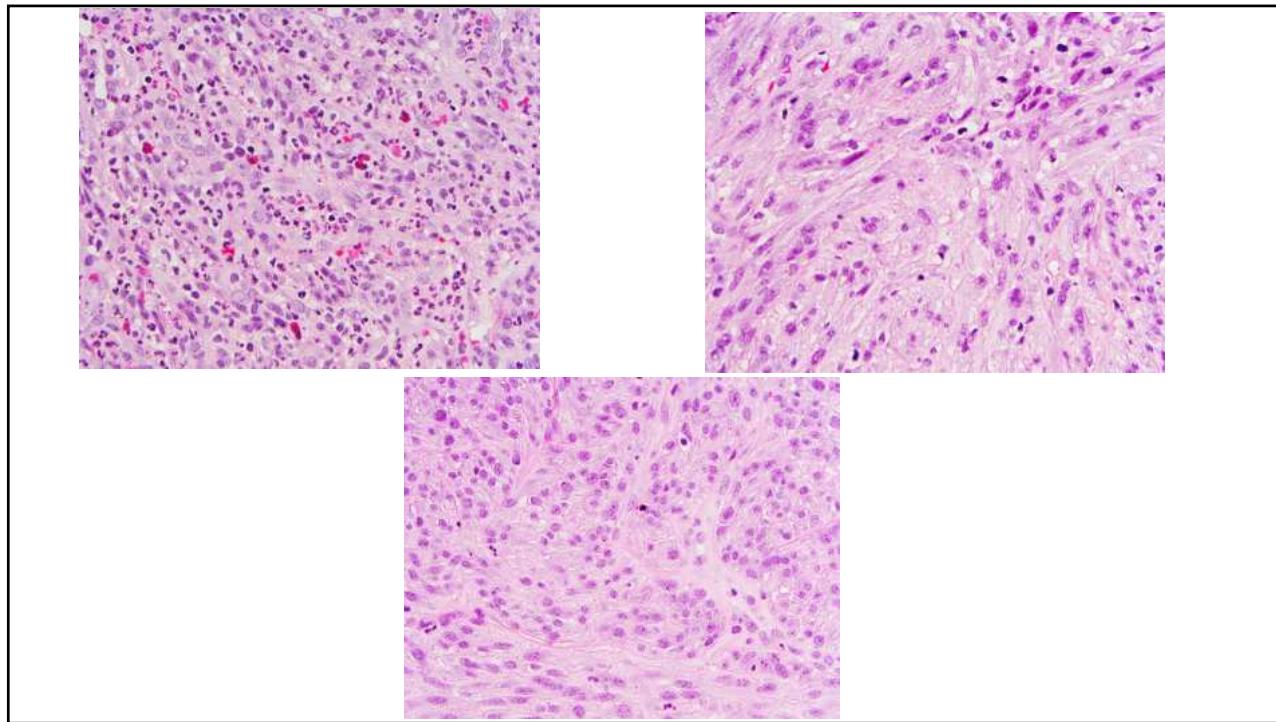
Signed out

- Atypical spindle cell proliferation in a background of extensive fibrinoinflammatory 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



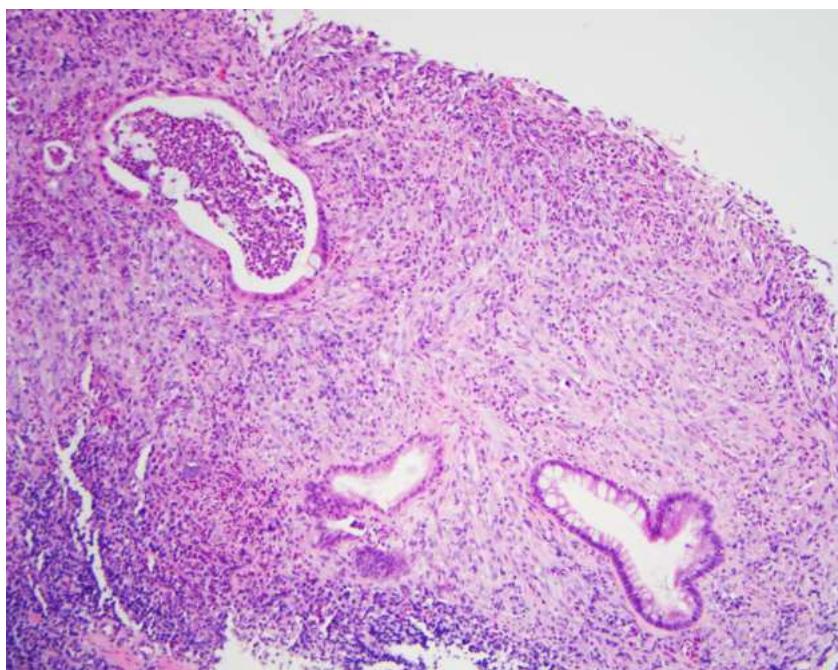


Follow up bx (@ 3 months), sign out

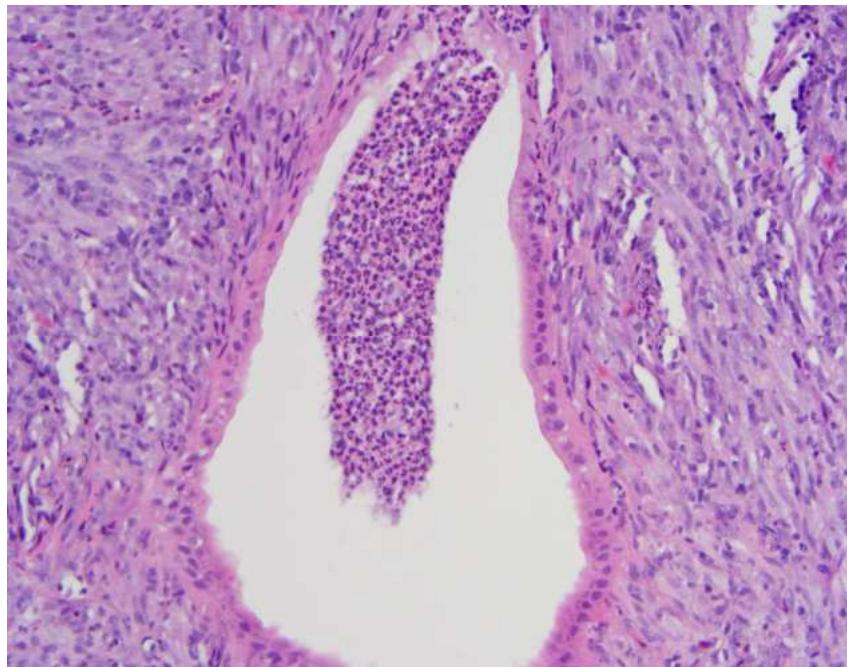
- Exuberant reactive myofibroblastic proliferation associated with ulcer exudate.

Inflammatory Spindle Cell Polyp

Bizarre and Myofibroblastic-like

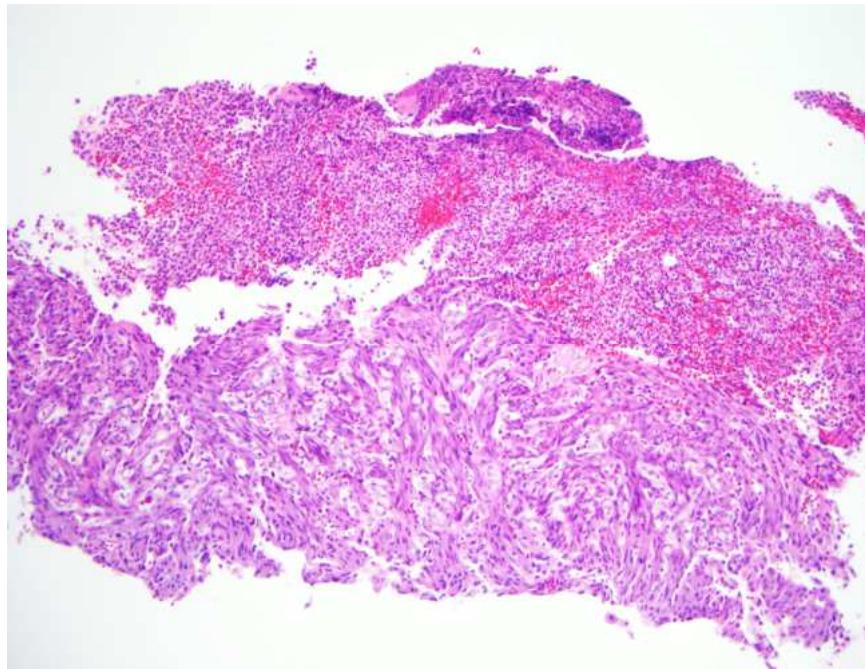
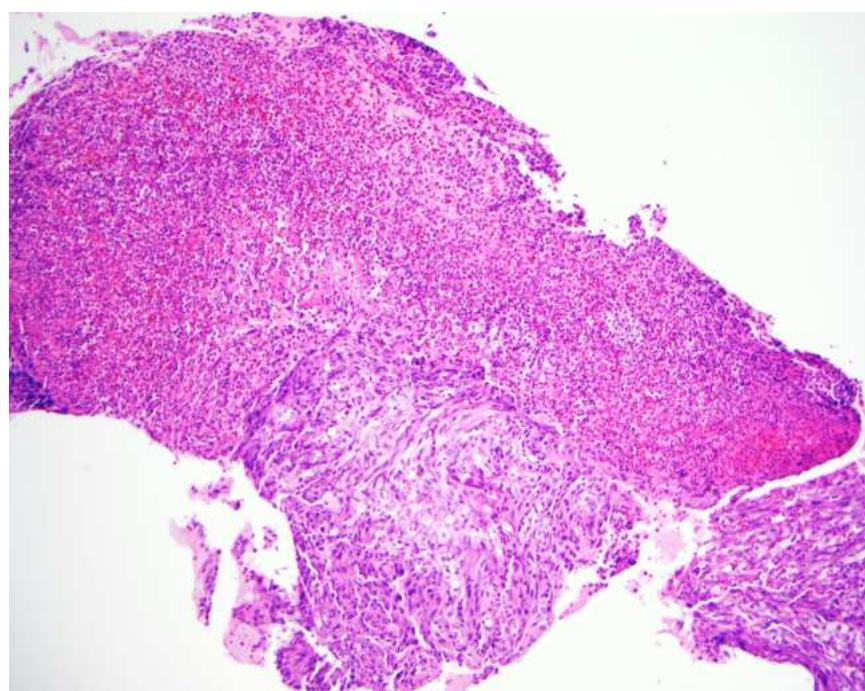


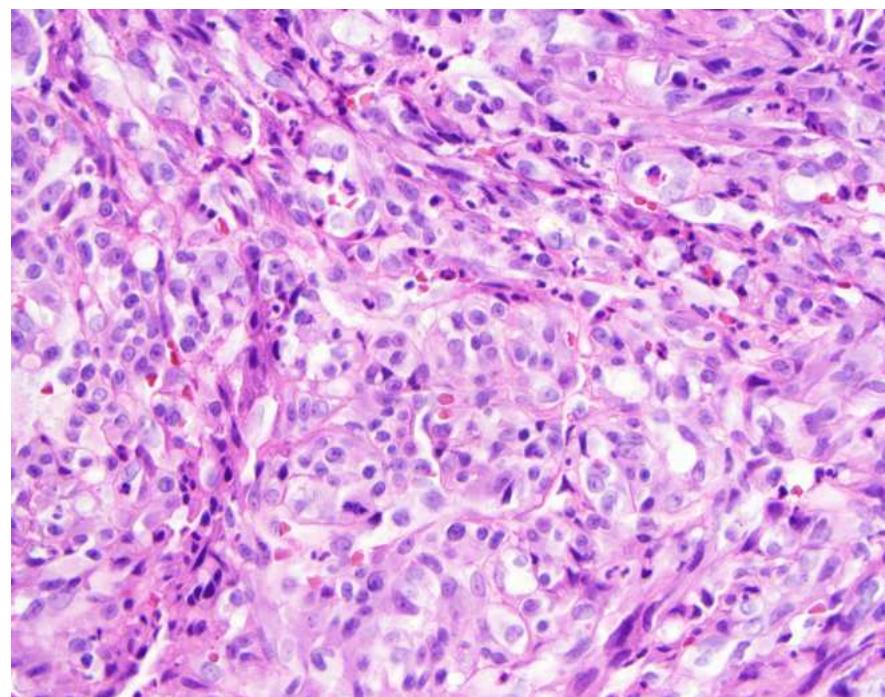
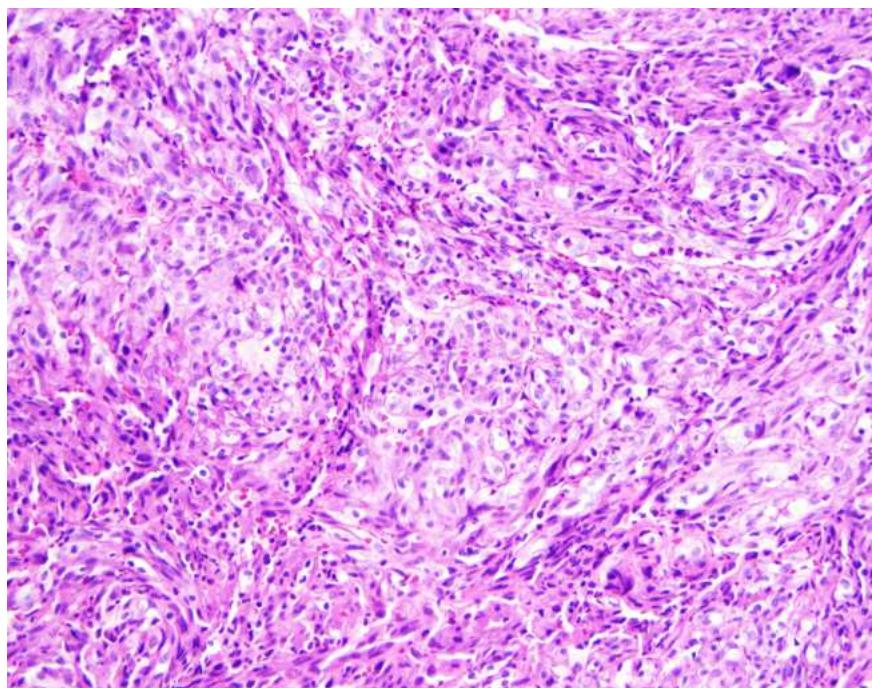
Patient with IBD

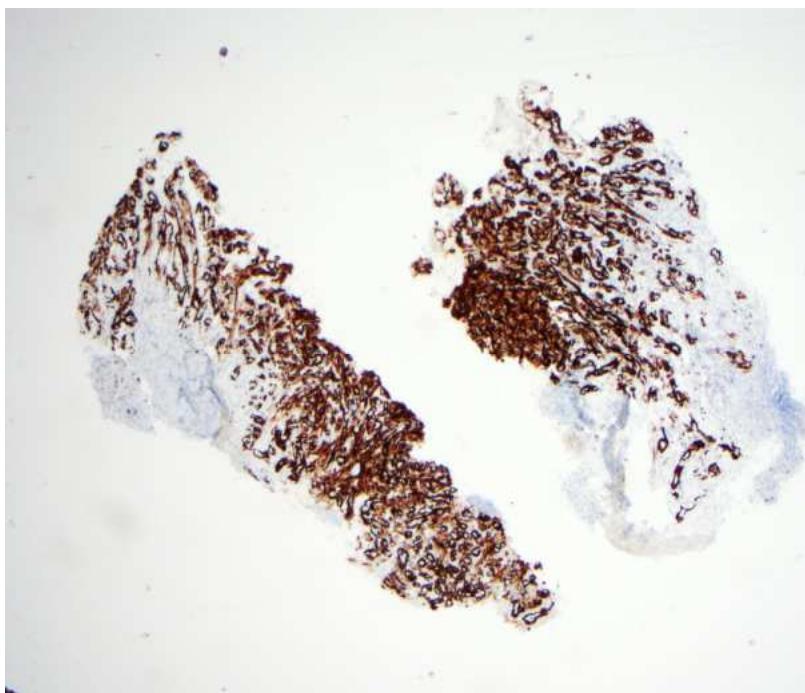


Case

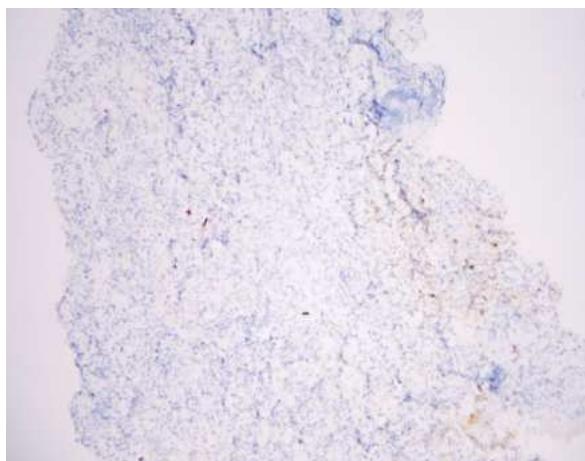
- 78 y/o F with duodenal ulcer
- Hx of metastatic breast cancer, recent oral chemotherapy, and celecoxib intake.
- Impression: poorly differentiated malignant neoplasm



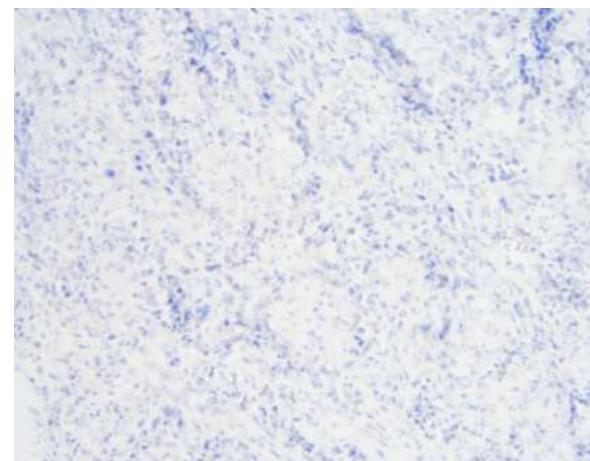




SMA

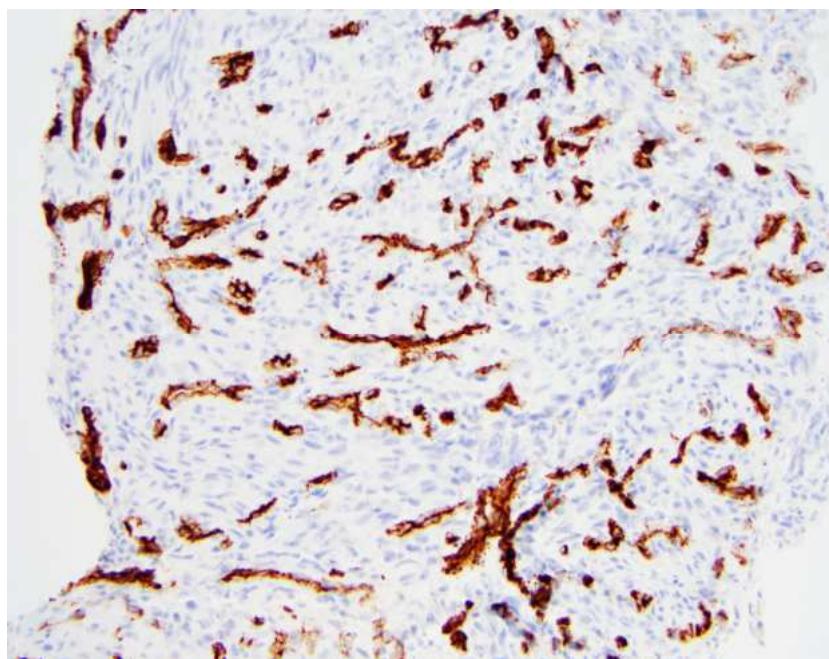


keratin



synaptophysin

negative for AE1/3, S100, synaptophysin, CD117, and HHV8.



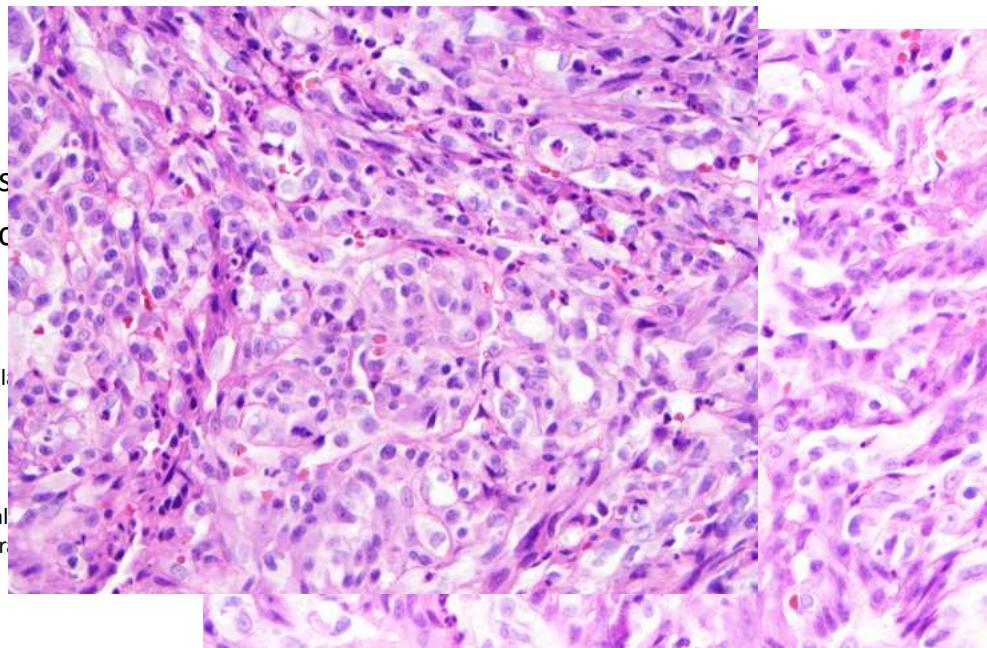
CD34

Case

- No mass
- On celiac

Reactive myofibroblasts

Plump endothelial associated with granular tissue

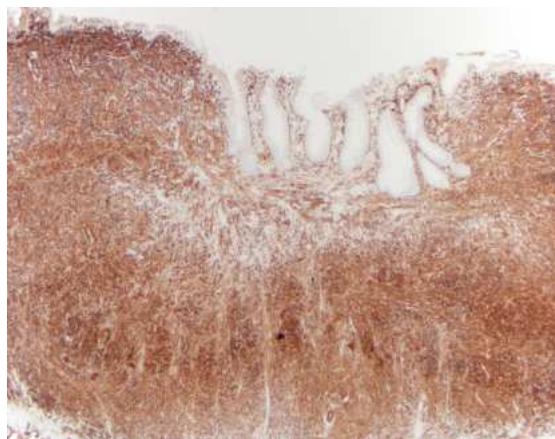
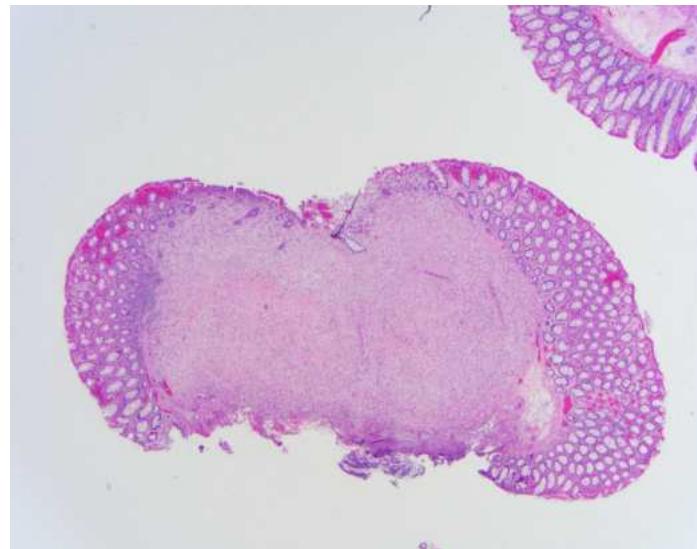


Signed out

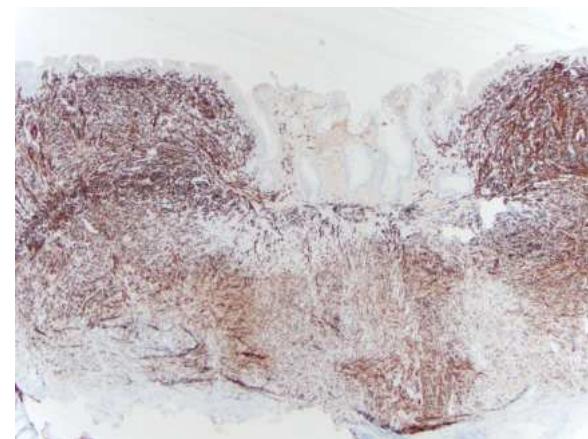
- *Favor exuberant reactive myofibroblastic response in the background of ulceration and granulation tissue. See note.*
- *Slides show a proliferation of spindled cells with abundant, "stretched out" cytoplasm and small delicate vessels lined by plump endothelial cells in a background of acute inflammatory 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?

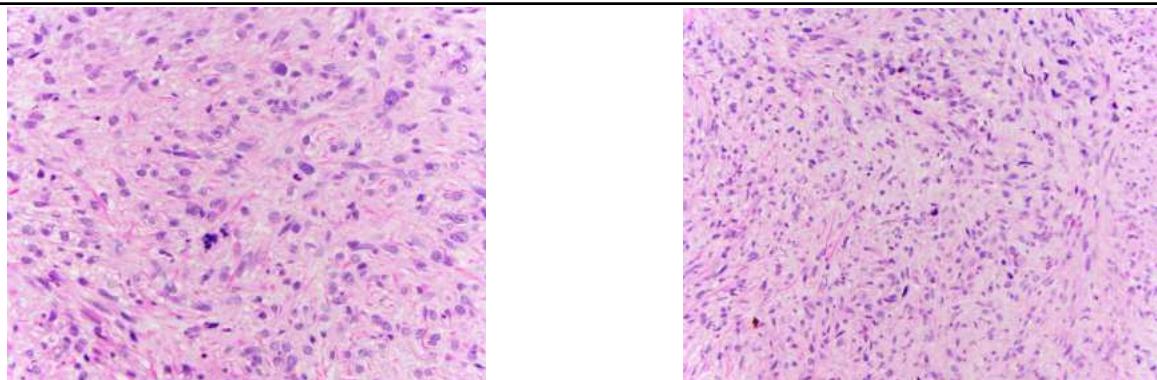
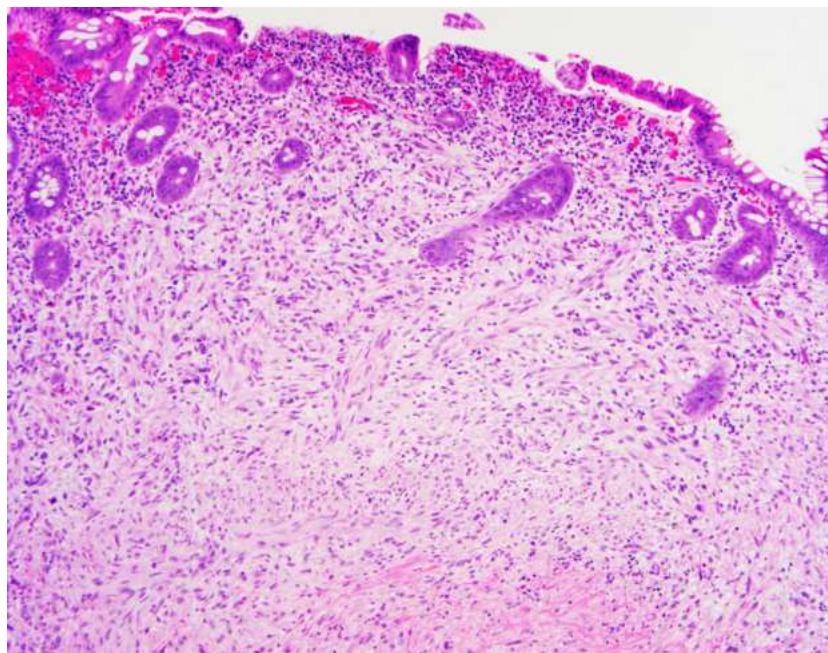
Leiomyosarcoma



SMA

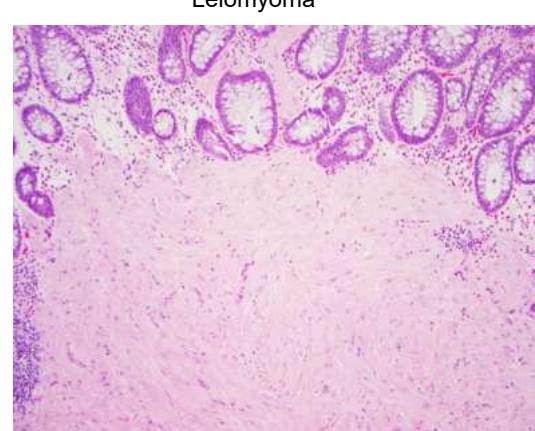
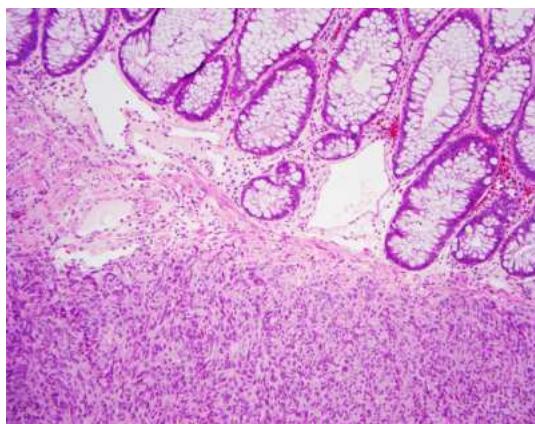


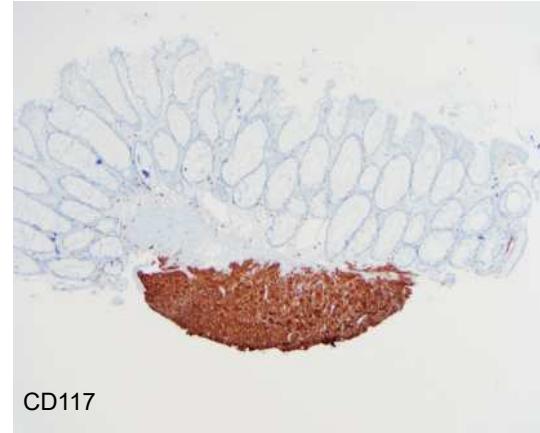
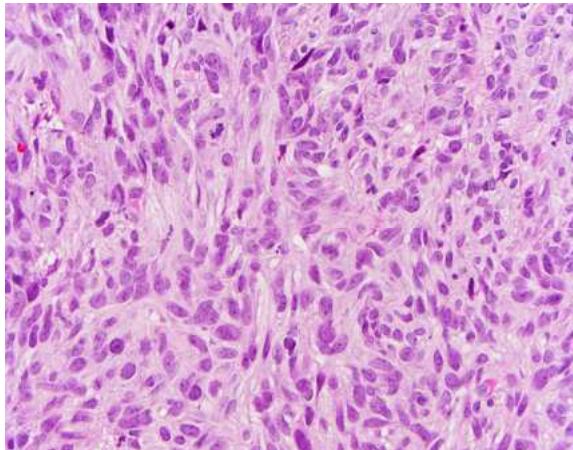
Desmin





Rectal polyp



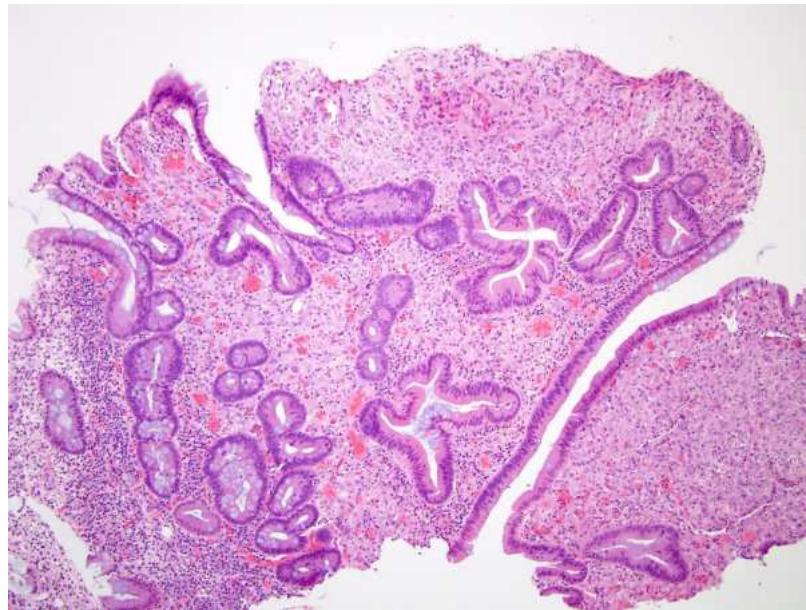


Lesson: Beware of the rare colonic GIST procured via endoscopic biopsy

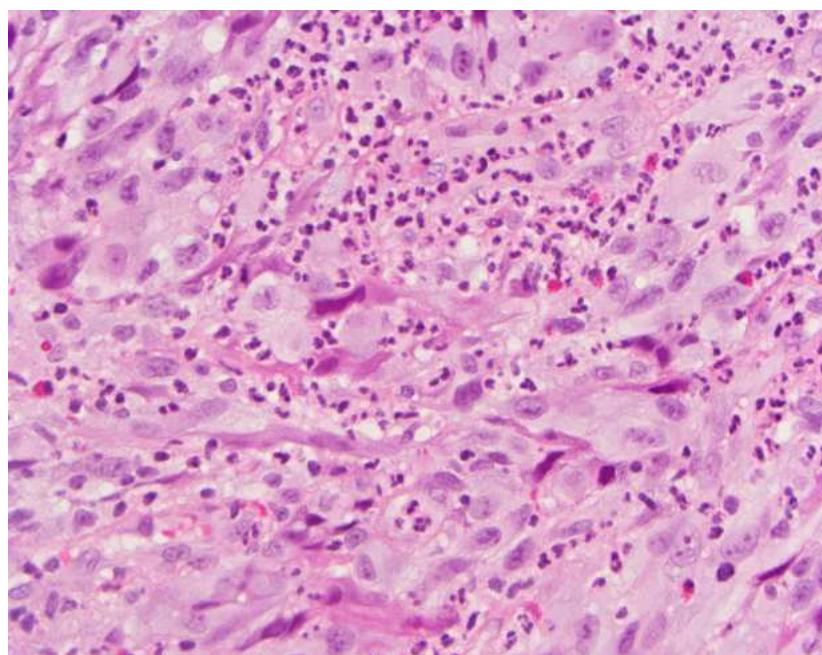
“Bizarre” stromal cells

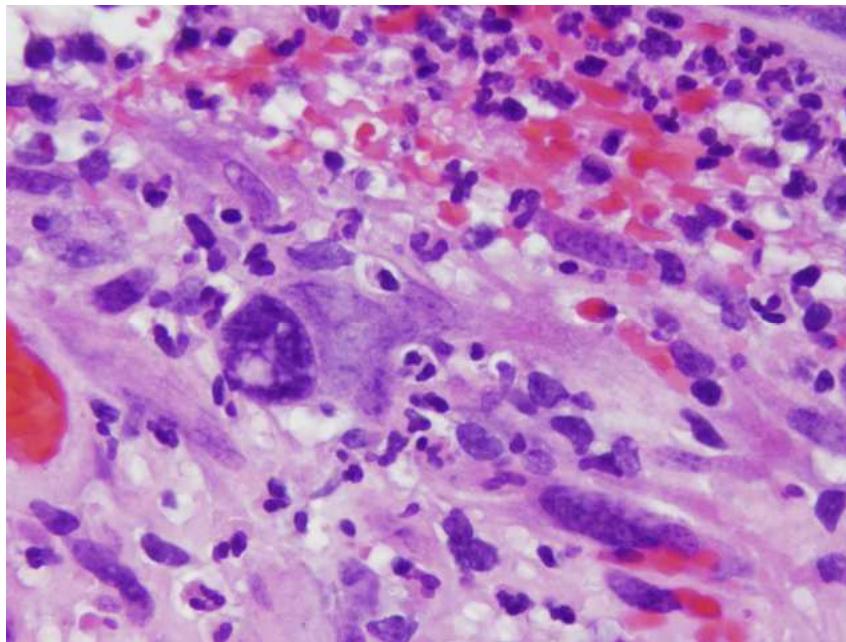
- Ulcers and inflammatory polyps esophagus, GE jx, stomach, colon, anal canal
- Bizarre atypia that can lead to a dx of malignancy
- SMA pos
- Proliferative fasciitis-like ganglion like-cells
 - Abundant, amphophilic cytoplasm, vesicular nuclei, and large eosinophilic, inclusion-like nucleoli.

Shekitka and Helwig. Deceptive bizarre stromal cells in polyps and ulcers of the gastrointestinal tract. *Cancer*. 1991 Apr 15;67(8):2111-7.
Jessurun J, Paplanus SH, Nagle RB, Hamilton SR, Yardley JH, Tripp M. Pseudosarcomatous changes in inflammatory pseudopolyps of the colon. *Arch Pathol Lab Med*. 1986 Sep; (9):833

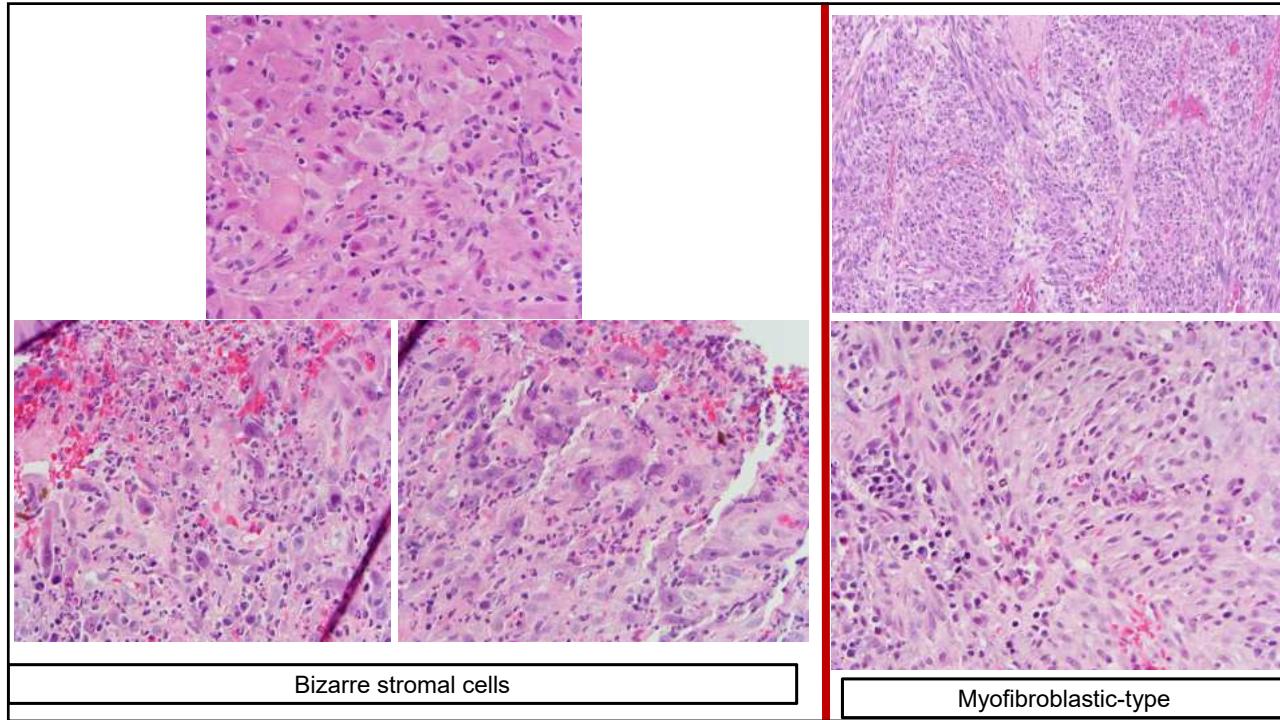


- In a monolayer in an ulcer or polyp





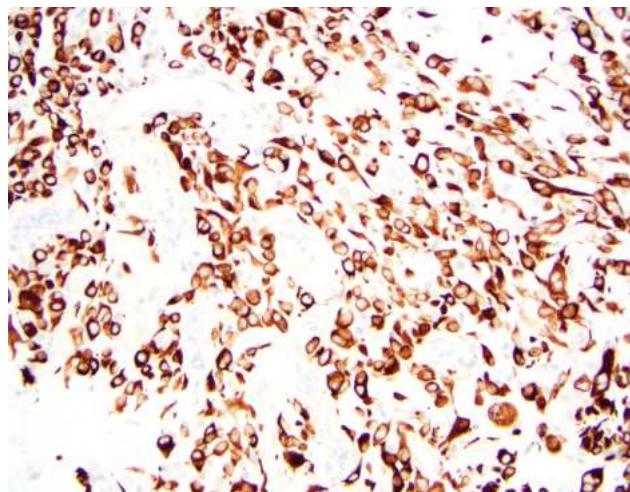
- Large and irregular nuclei
- Prominent nucleoli
- Chromatin typically finely dispersed
- Tons of eosinophilic cytoplasm
- **"Stretched out" reparative look**
- Vimentin-only fibroblasts (some)
- Keratin, S100, CD117, desmin, actin negative



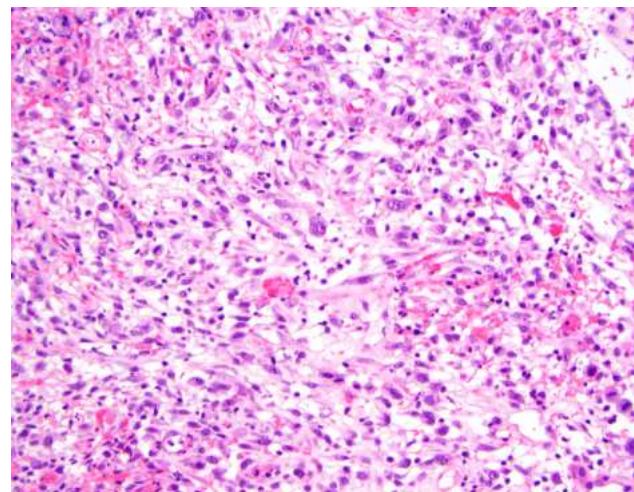
Bizarre stromal cells

Myofibroblastic-type

Pitfall Alert

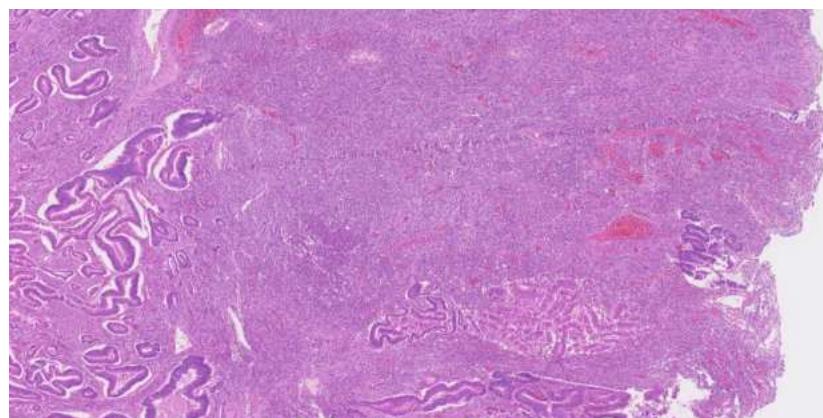


AE1/3

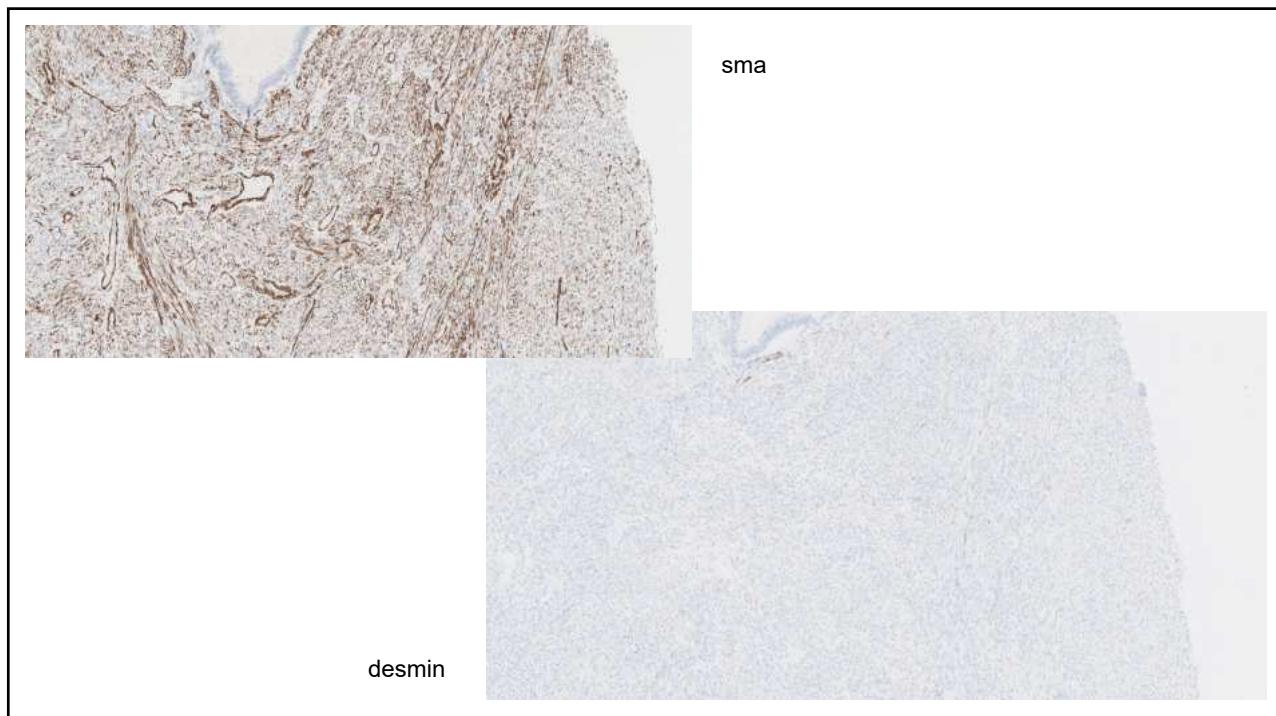
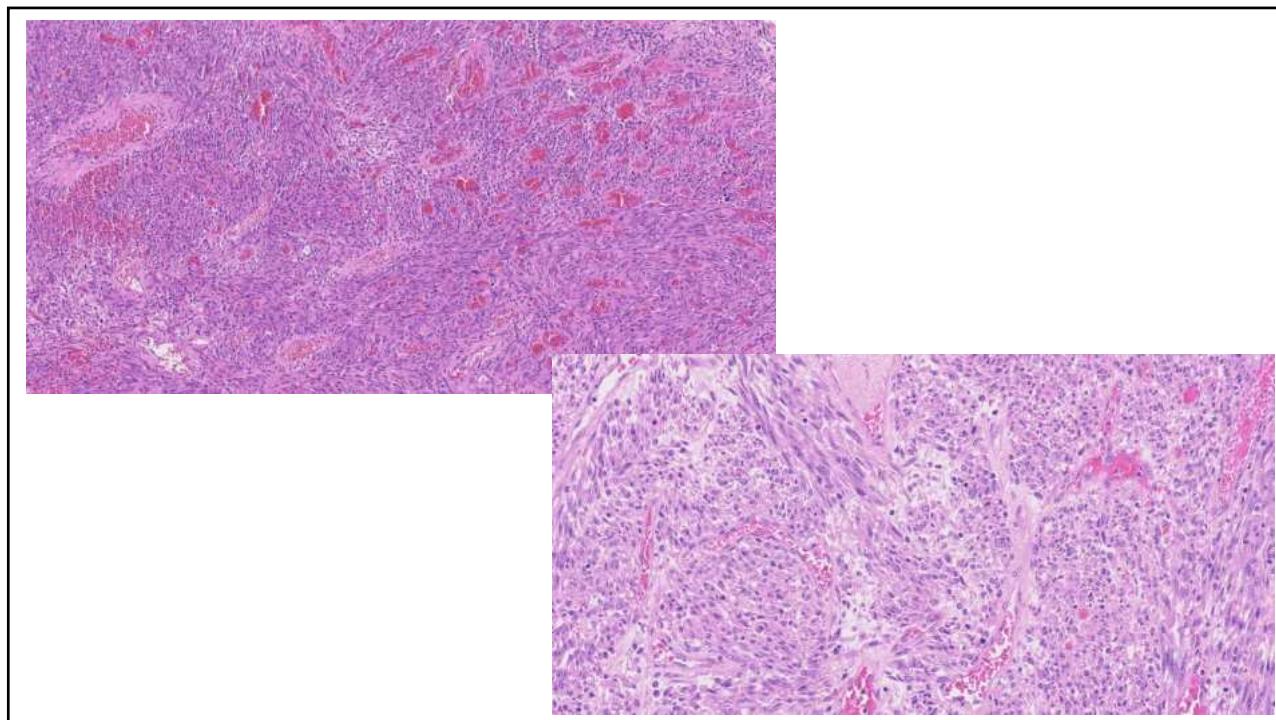


Tamas EF1, Epstein JI. Detection of residual tumor cells in bladder biopsy specimens: pitfalls in the interpretation of cytokeratin stains. Am J Surg Pathol. 2007 Mar;31(3):390-7.

Sometimes Associated with Adenocarcinoma



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

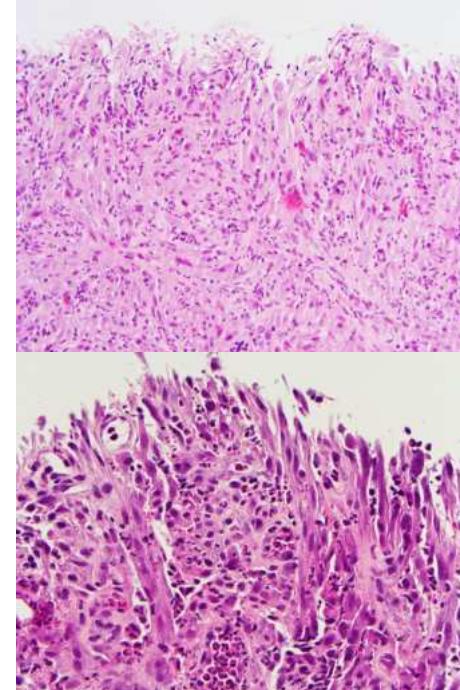




- APC, p53, and KRAS mutation in the carcinoma
- Only a KRAS mutation in the sarcomatoid component (same as in the carcinoma component.)
- No losses or gains in chromosomal copy numbers

Clues that suggest reactive process

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

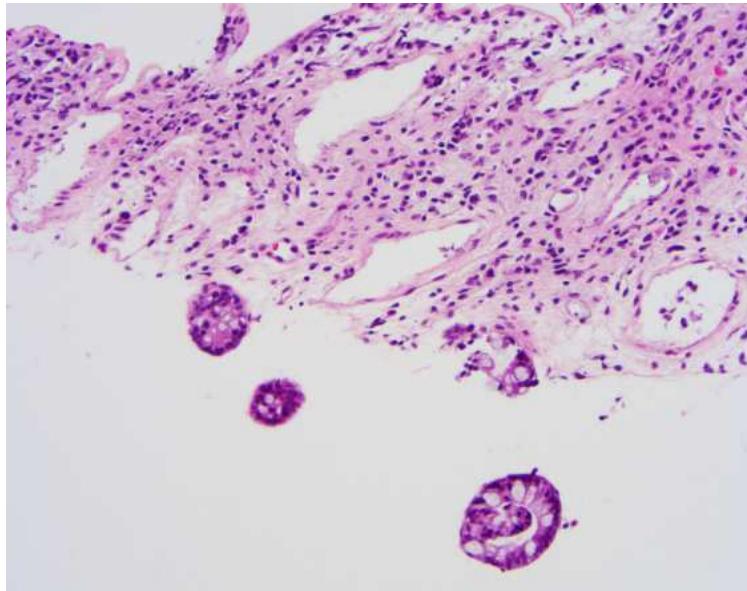


Other Colon

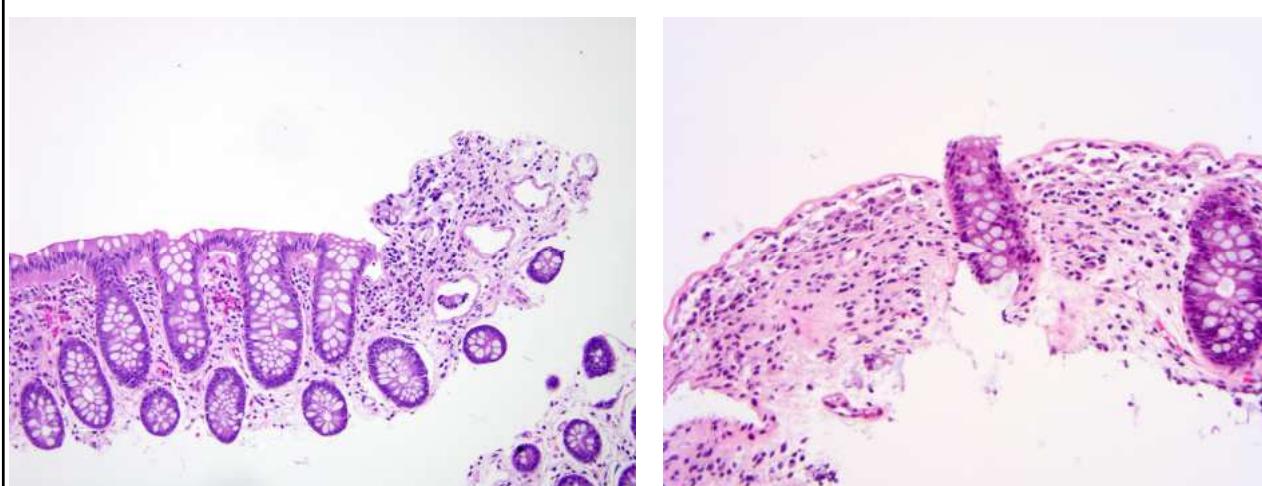


Squeeze Artifact

- Common
- Tissue trauma
- Epithelium is squeezed out of the crypts
- Can be mistaken for ischemia

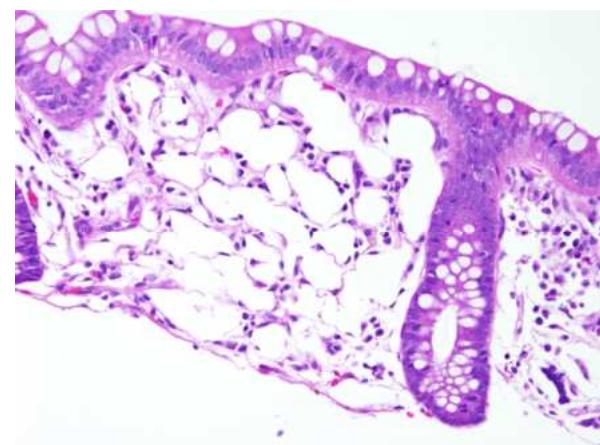
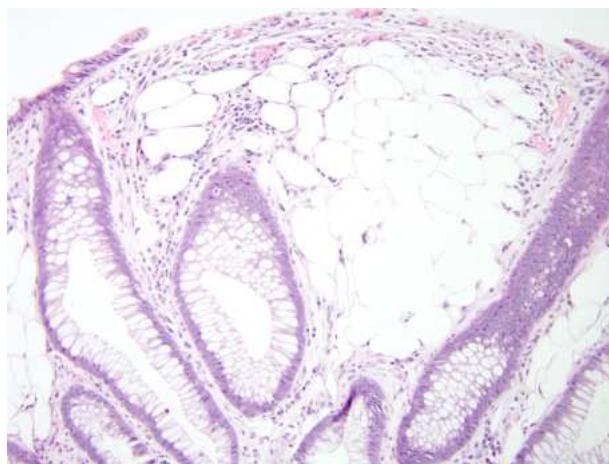


- Squeezed glands sit close to empty crypts
- Glands are not injured
- Lamina propria is not hyalinized

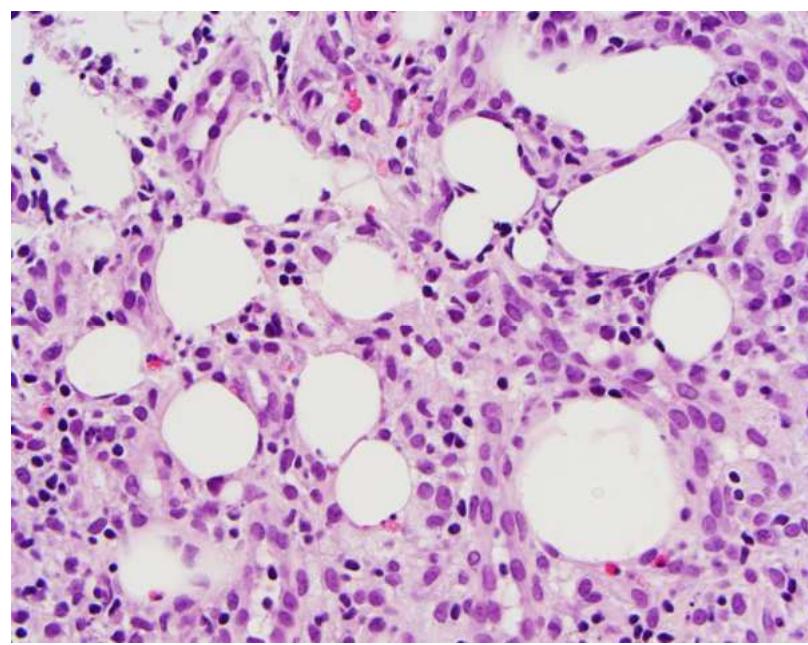
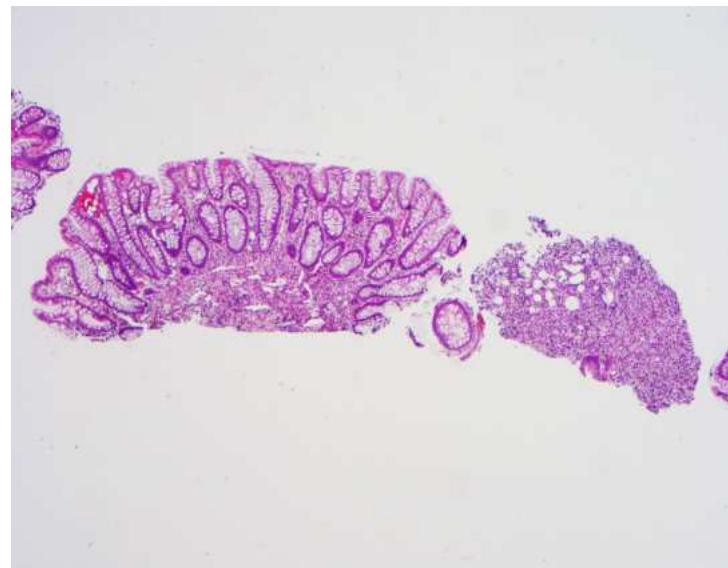


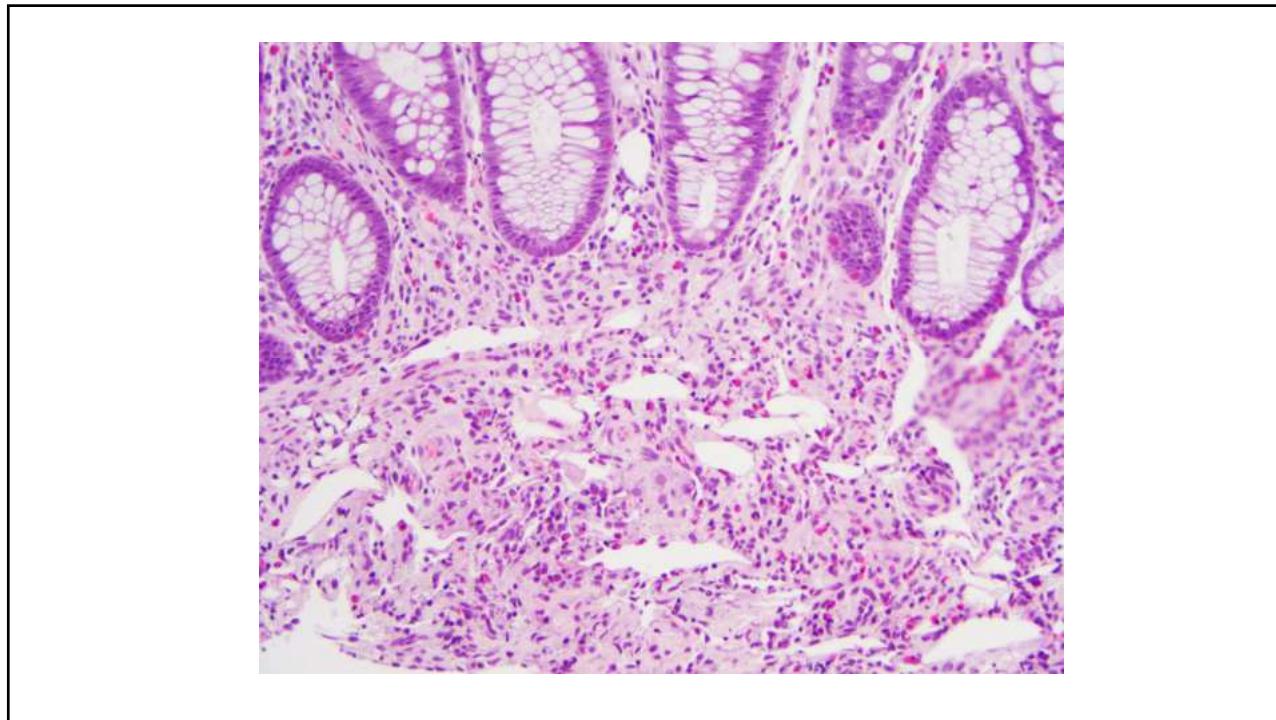
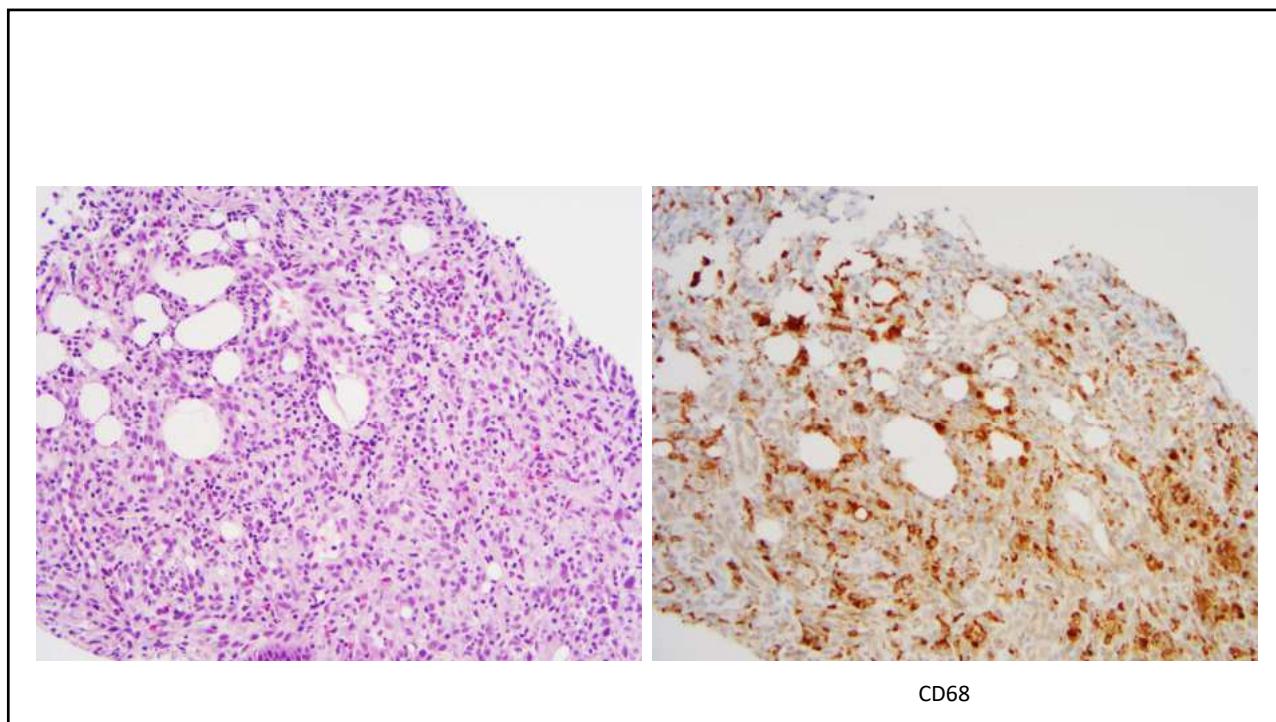
Pseudolipomatosis

- 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



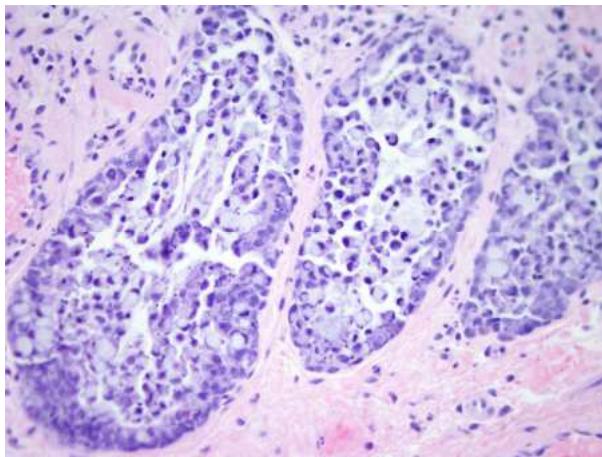
“Air” Polyp





Signet Cell Change

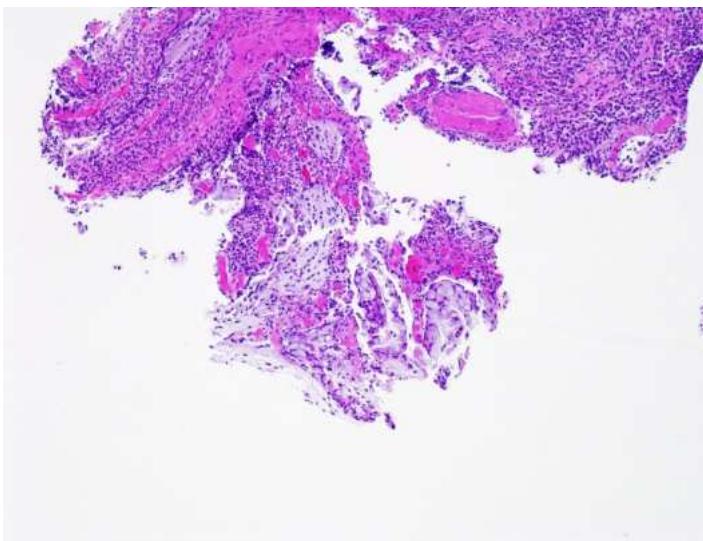
- Epithelium becomes detached and begins to slough



- Cells round up
- Within the basement membrane
- Distended crypts
- Reparative changes = alarming
- Mitoses may be conspicuous
 - Look at intact adjacent gastric mucosa

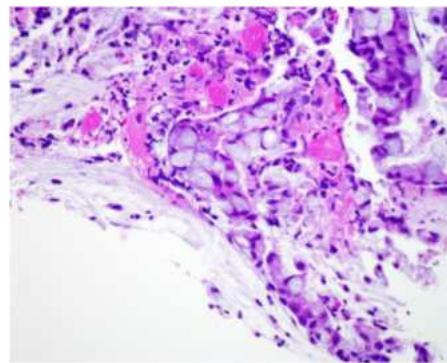
Wang et al. Signet Ring Cell Change vs. Signet Ring Cell Carcinoma. A Comparative Analysis. Am J Surg Pathol. 2003; 27:1429-1433

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

Dhingra and Wang. Nonneoplastic signet-ring cell change in gastrointestinal and biliary tracts: a pitfall for overdiagnosis. Ann Diagn Pathol. 2011 Dec;15(6):490-6



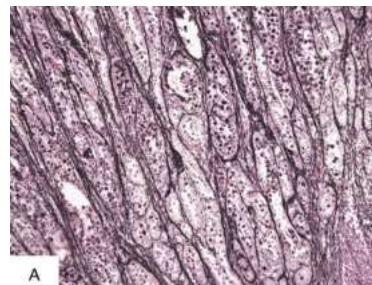
Mucin stain pointless

TABLE 1. Results of Histochemical and Immunohistochemical Stains in Signet-Ring Cell Change and Signet-Ring Cell Carcinoma

Stain	Signet-Ring Cell Change	Signet-Ring Cell Carcinoma
PAS	Strongly positive	Strongly positive
DPAS	Strongly positive	Strongly positive
E-cadherin	100% of cells strongly positive	70–75% of cells weakly positive 25–30% of cells negative
P53	100% of cells negative	>50% of cells strongly positive
Ki-67	100% of cells negative	42–60% of cells positive

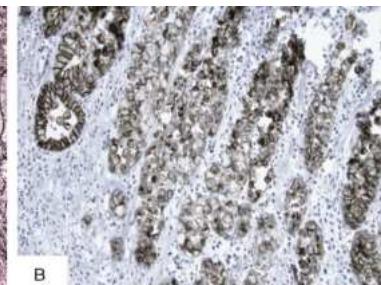
Wang et al. Signet Ring Cell Change vs. Signet Ring Cell Carcinoma. A Comparative Analysis. Am J Surg Pathol. 2003; 27:1429-1433

Reticulin

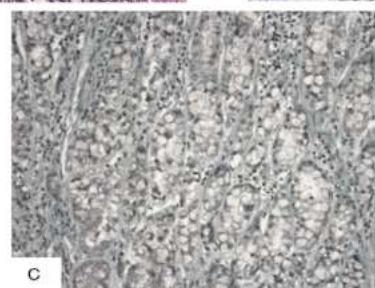


A

Ecadherin

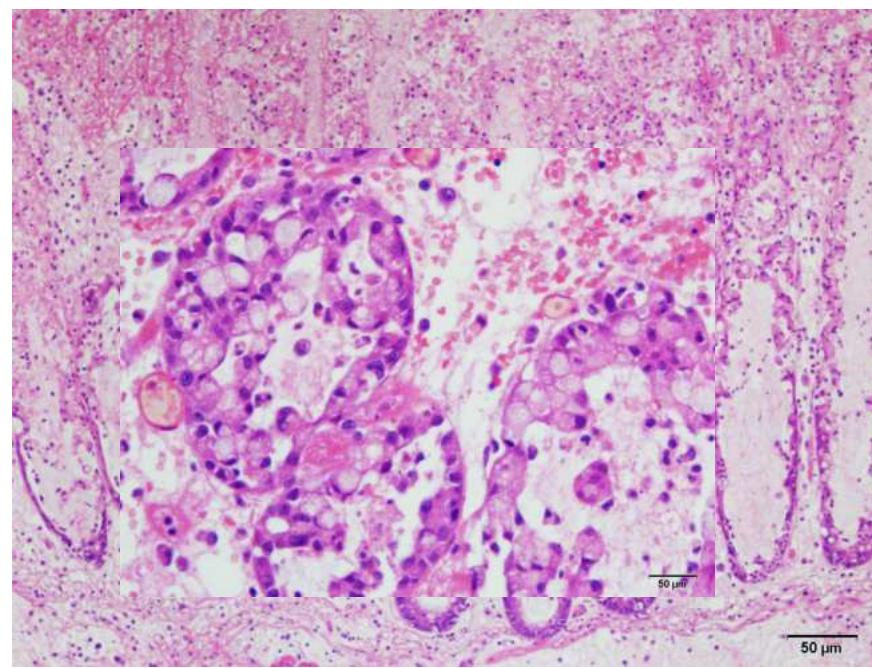
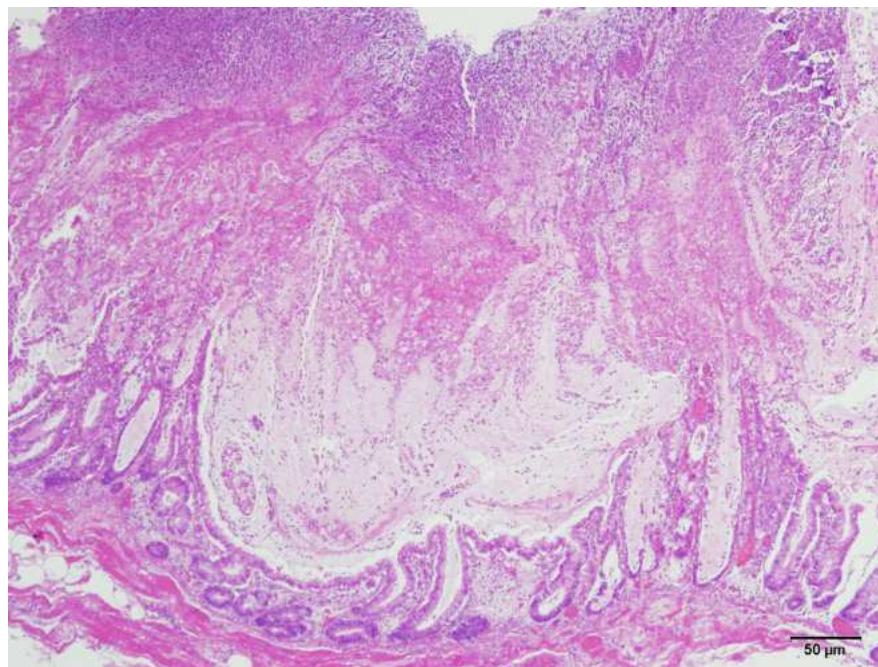


B

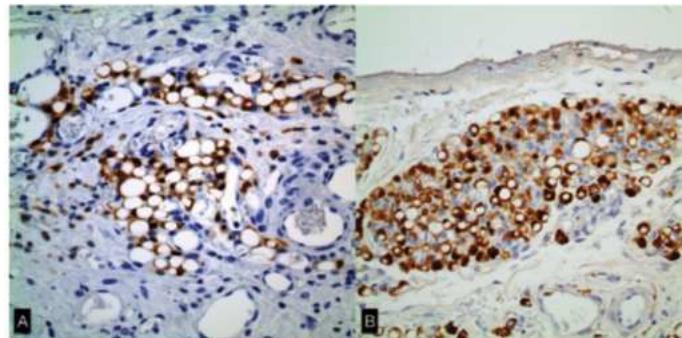
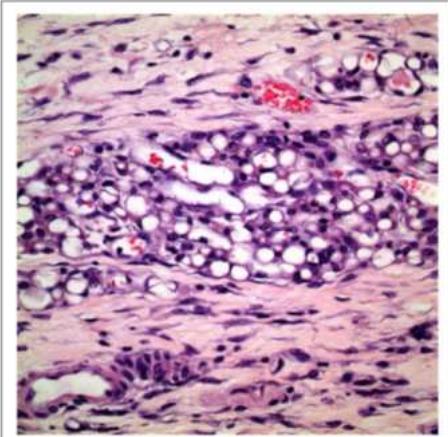


Ki67

Boncher et al. Reticulin staining clarifies florid benign signet ring cell change with mitotic activity in a penetrating gastric ulcer. Am J Surg Pathol. 2011 May;35(5):762-6



Fat atrophy



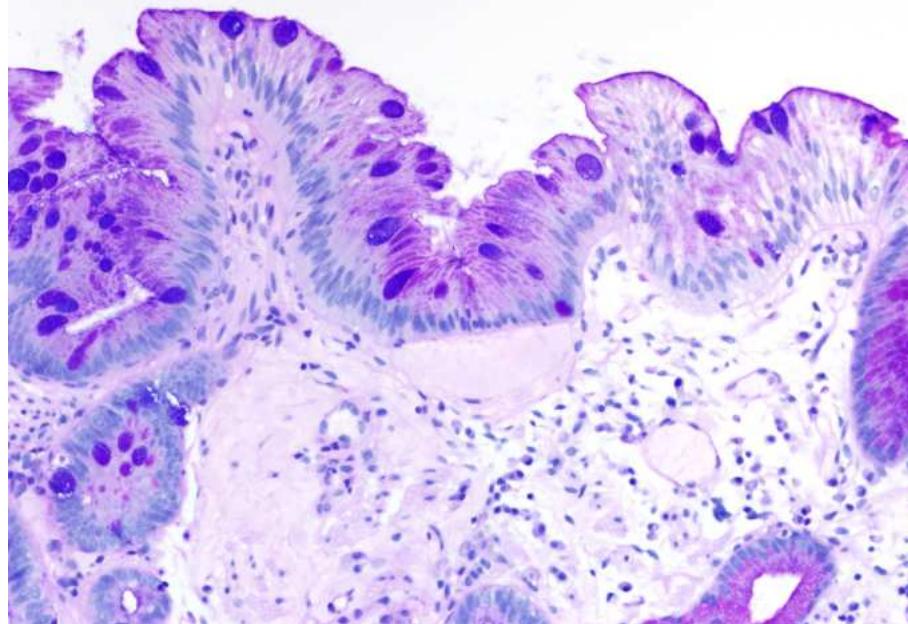
Khan and Ligato. Identification of Signet Ring Cell Change in Colonic Subserosa in the Setting of Clostridium difficile Colitis. Int J Surg Pathol. 2017 Apr;25(2):168-172.

Esophagus

Barrett Esophagus: The Fake Goblet Cell

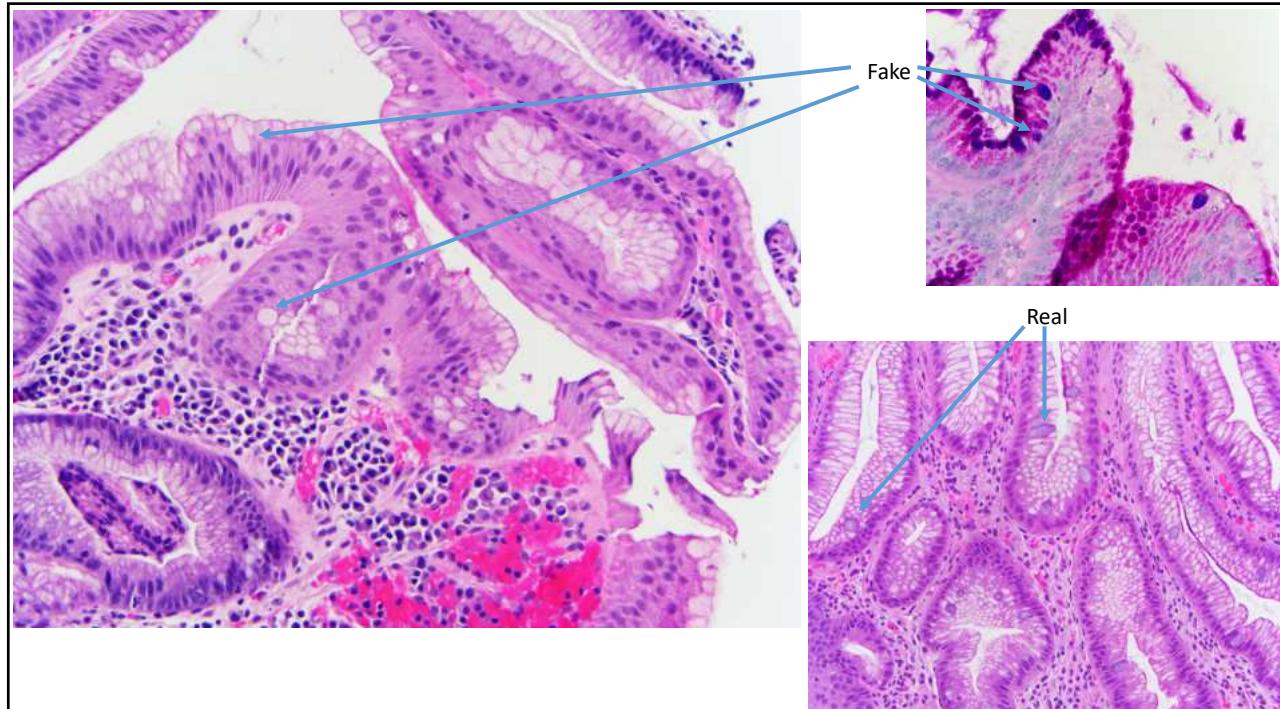
- Some practices use Alcian-Blue or Alcian-Blue/PAS to identify goblet cells
- The acidic sialo- and sulfomucins in goblet cells react with Alcian Blue at pH 2.5
- Alcian-Blue/PAS is a particularly colorful stain that nicely highlights mucin:
 - Goblet cells (acid mucin) are highlighted in purple/deep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



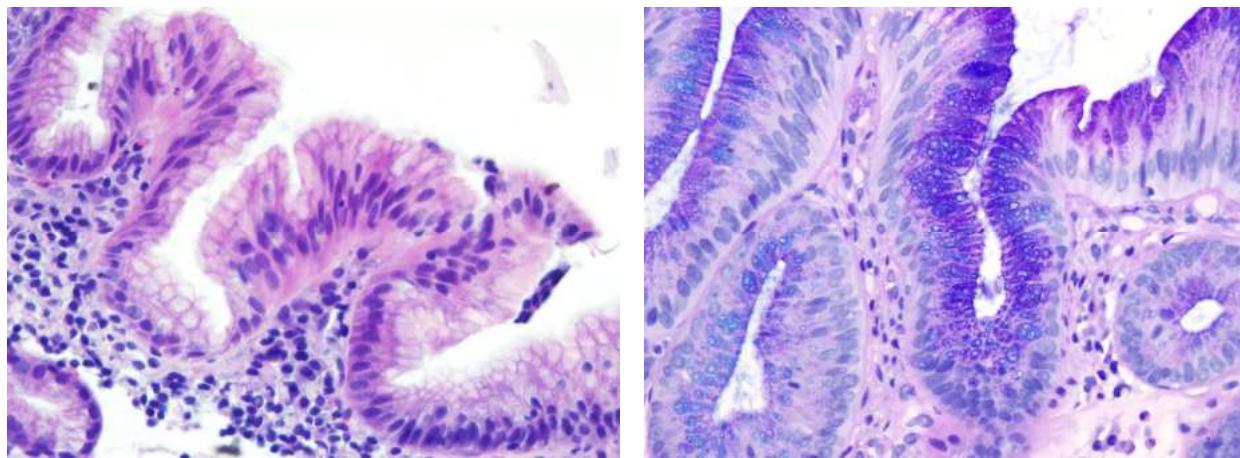
Alcian blue has proclivity to stain small amounts of mucin present in non-goblet cells

- *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**

*Chen et al. *Hum Pathol.* 1999;30:1488–1495. Offner et al. *Hum Pathol.* 1996;27:885–889.

**Genta et al. *Hum Pathol.* 1994;25:915–919. Younes et al. *Arch Pathol Lab Med.* 2007;131:571–575

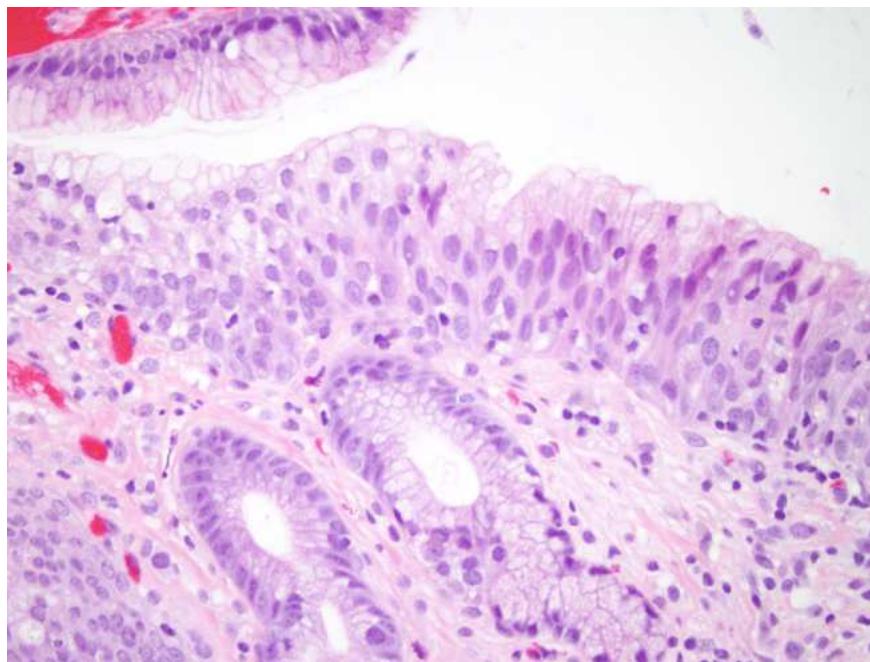
Impostor: Columnar Blues

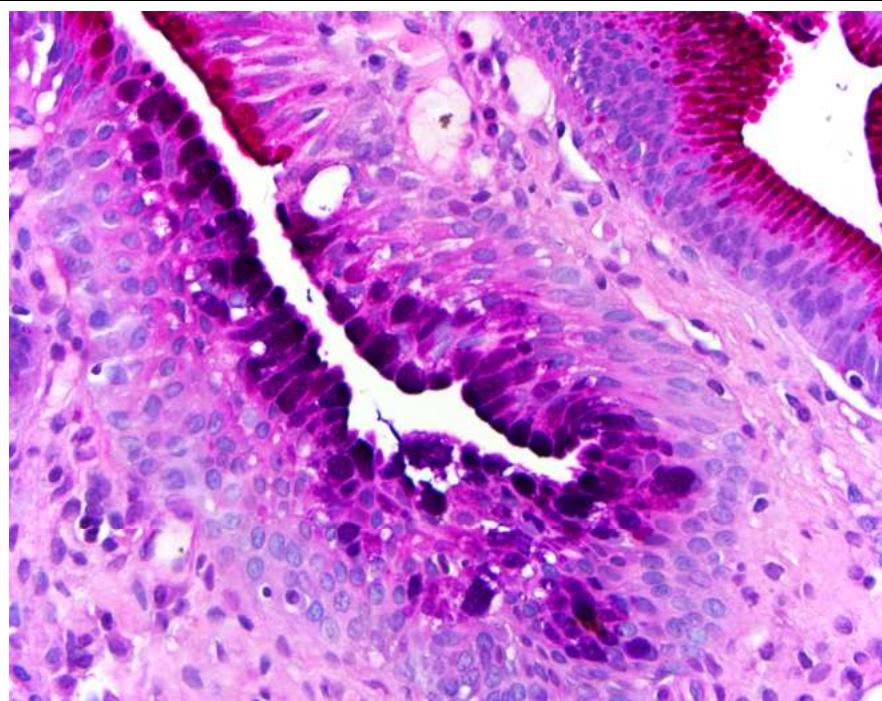
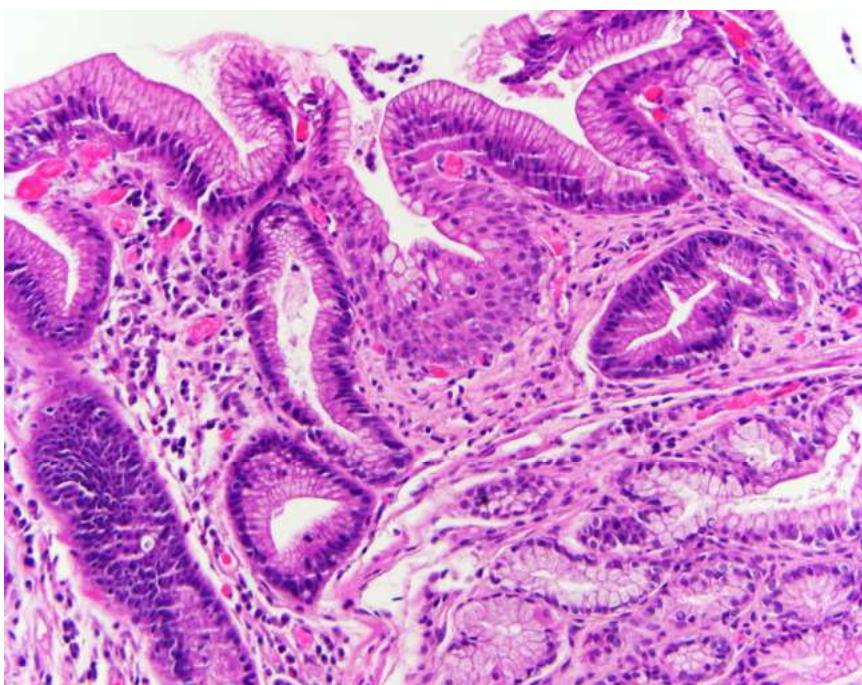


Alcian blue has proclivity to stain small amounts of mucin present in non-goblet cells

- *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

*Glickman et al. Am J Sur Pathol. 2001 May;25(5):569-78. Shields et al. Am J Gastroenterol. 2001 Dec;96(12):3268-73.





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.

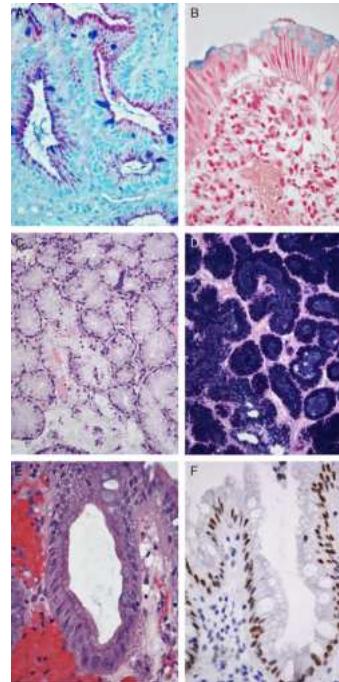
*Johnson et al. *World J Gastroenterol.* 2015;21: 2770–2776

**Hahn et al. *Am J Surg Pathol.* 2009;33:1006-1015

** McIntire et al. *Am J Surg Pathol.* 2011;35:1007-1013

* Groisman et al. *Mod Pathol.* 2004. 2004;17:1282-1288.

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



Pseudogoblet cells



Submucosal glands



CDX2 will stain both goblet and non-goblet cells



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.

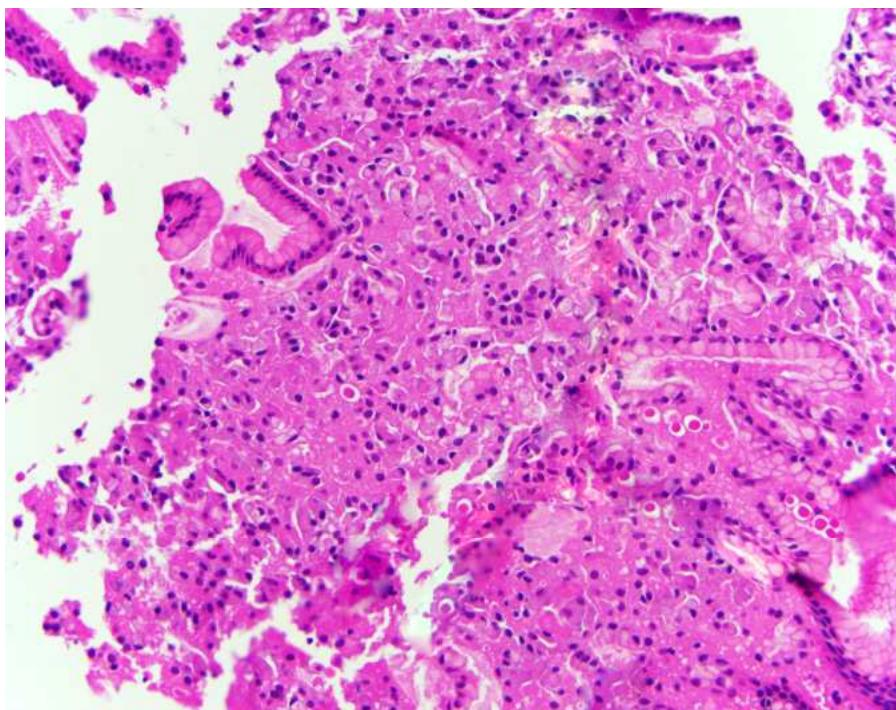
Stomach

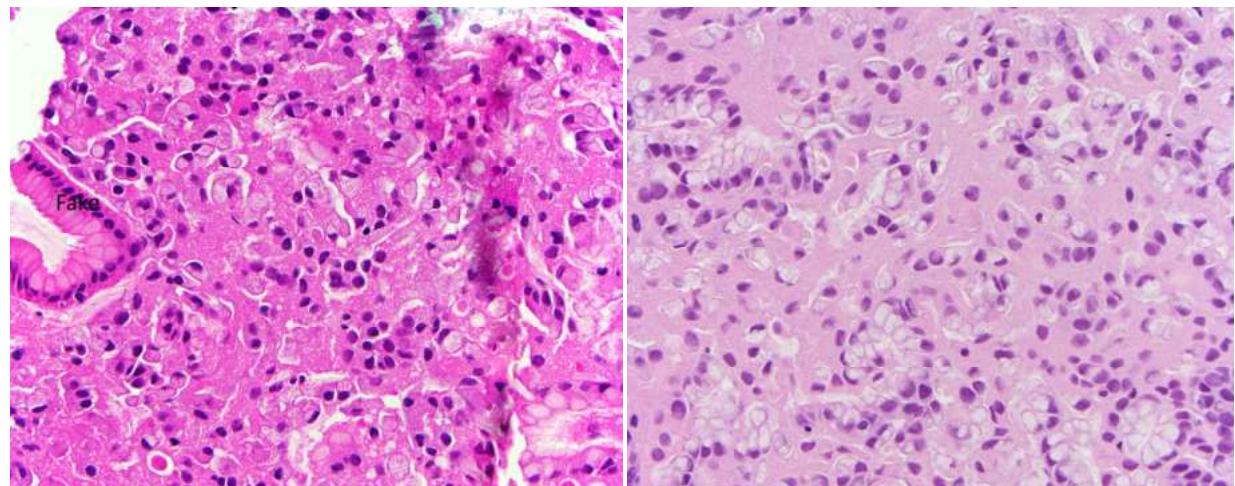
Findings that mimic signet ring cell adenocarcinoma

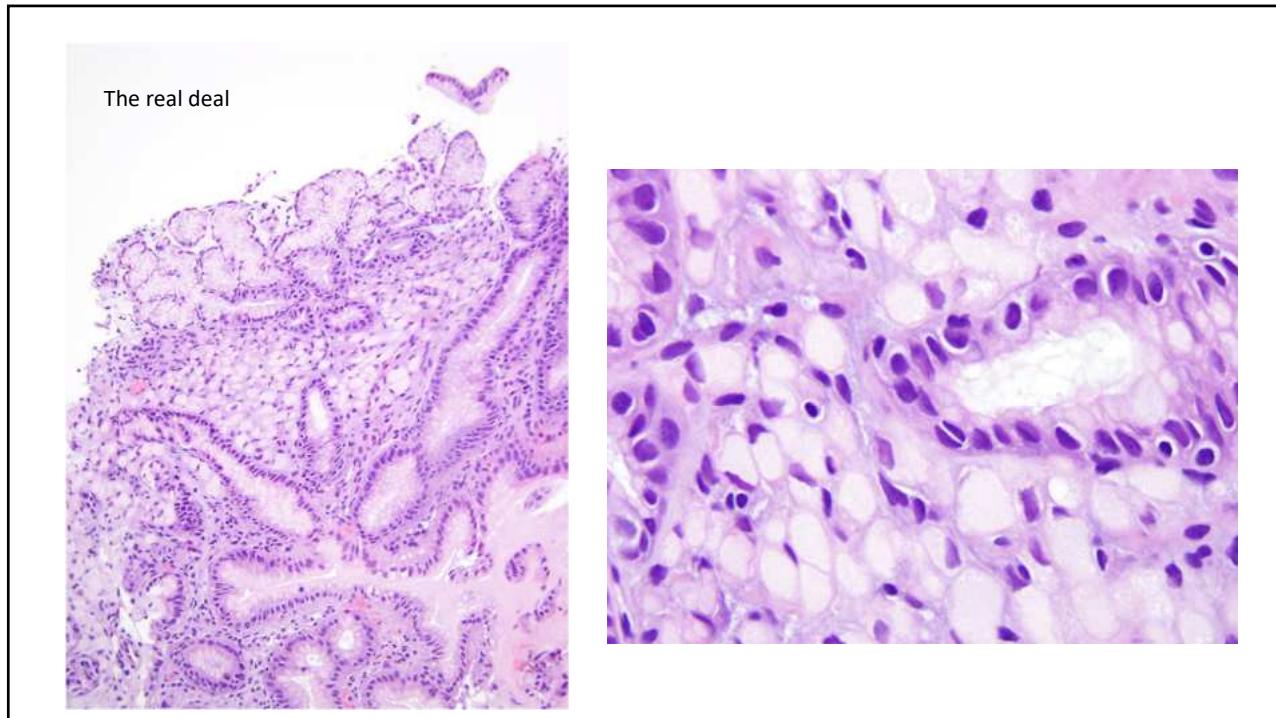
Crushed Oxytic Glands

- If mucous neck cells predominate, they can resemble signet ring cell adenocarcinoma.

Fake



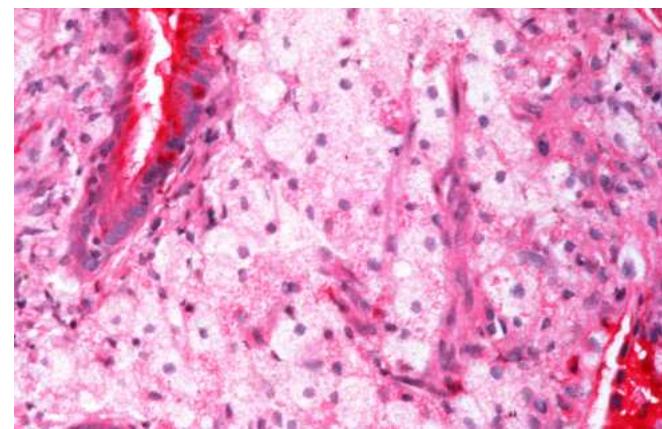
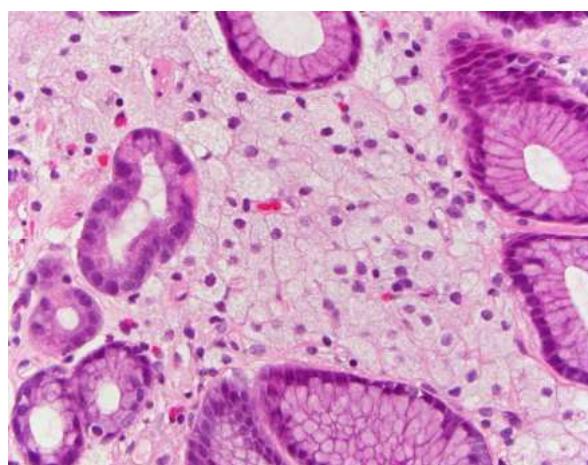
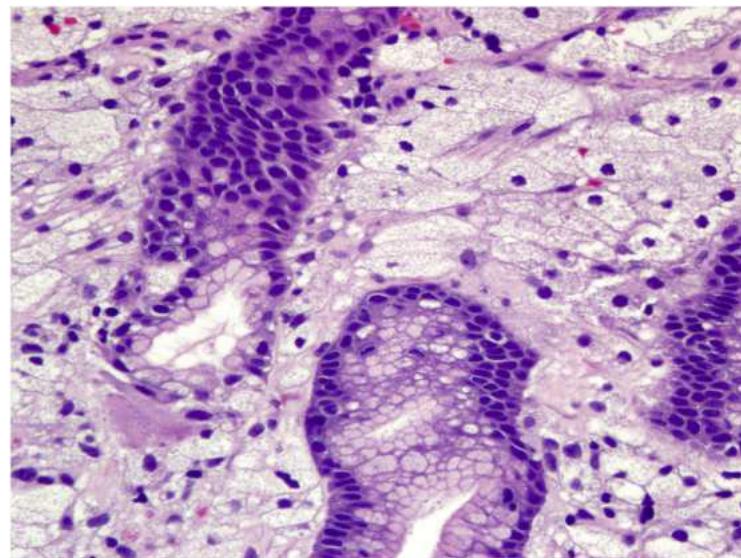




Reassuring Findings that Argue for Dislodged Mucous Neck Cells

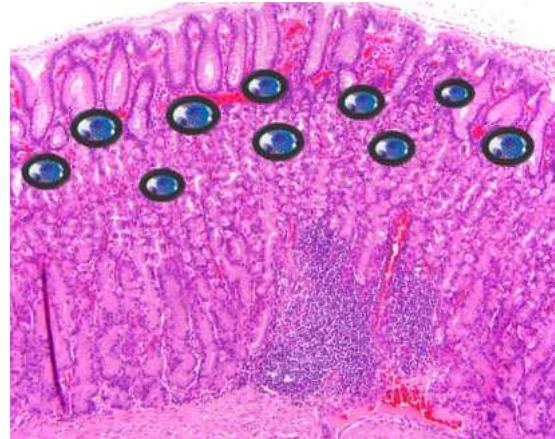
- Tissue is not intact
- Cells dislodged within glandular lumina
- Cells are floating in a sea of extracellular proteinaceous pink material (parietal cell cytoplasmic contents), *not* in lamina propria
- Focally arranged in benign-appearing glandular configurations

Xanthoma



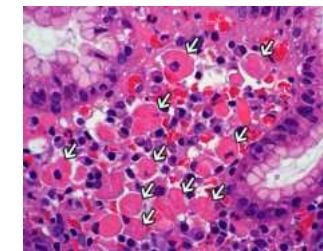
CD68 + and cytokeratin -

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

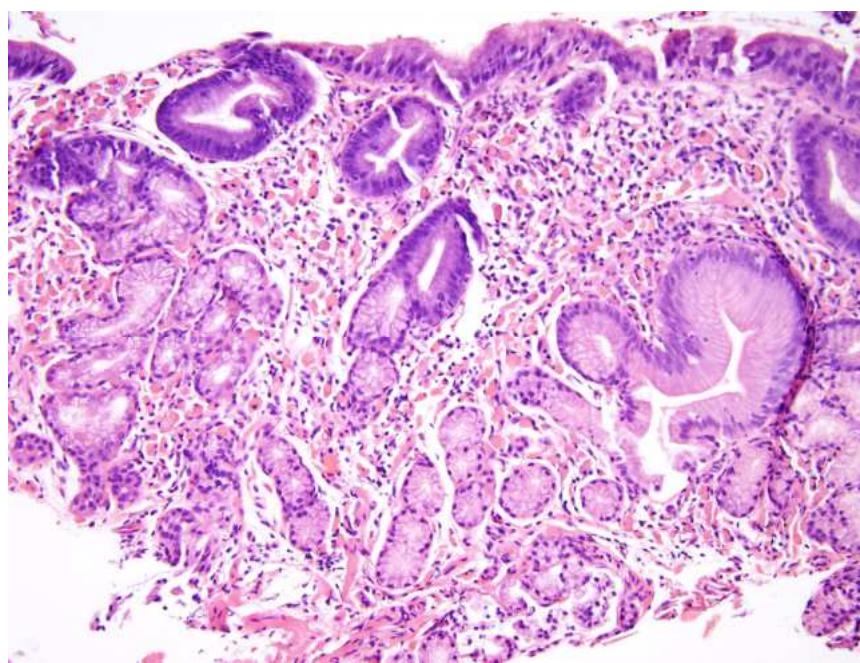


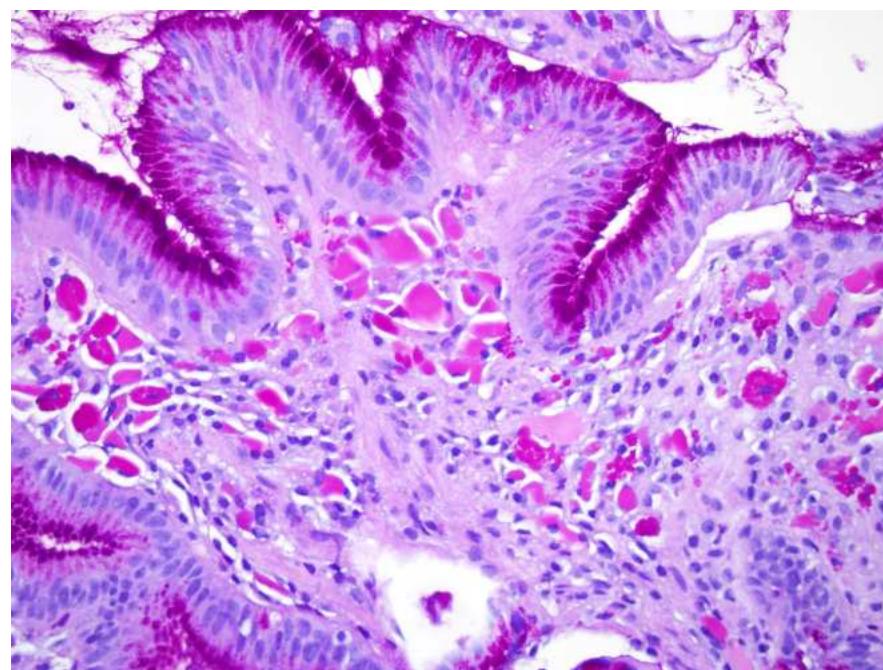
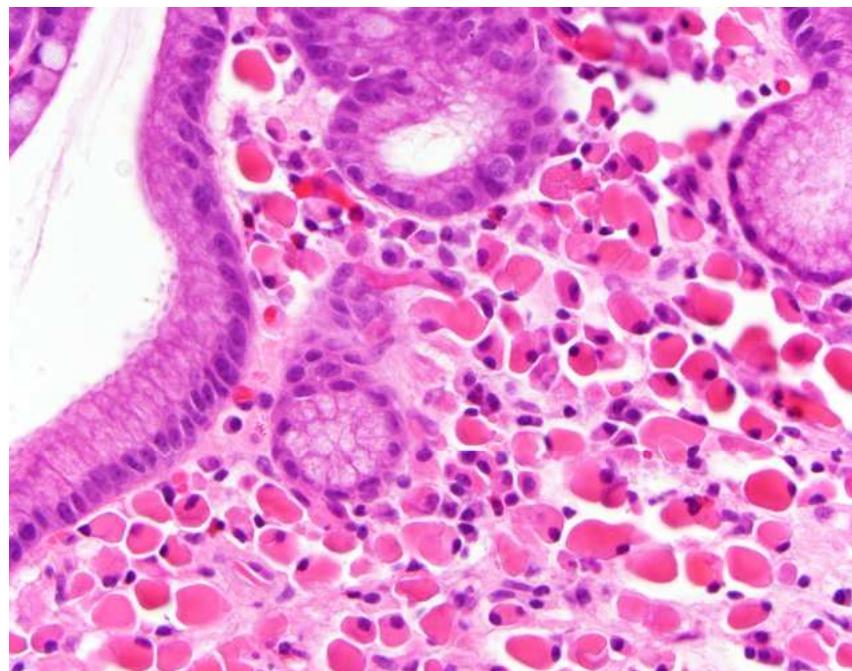
http://niigata-cp.org/?page_id=1342

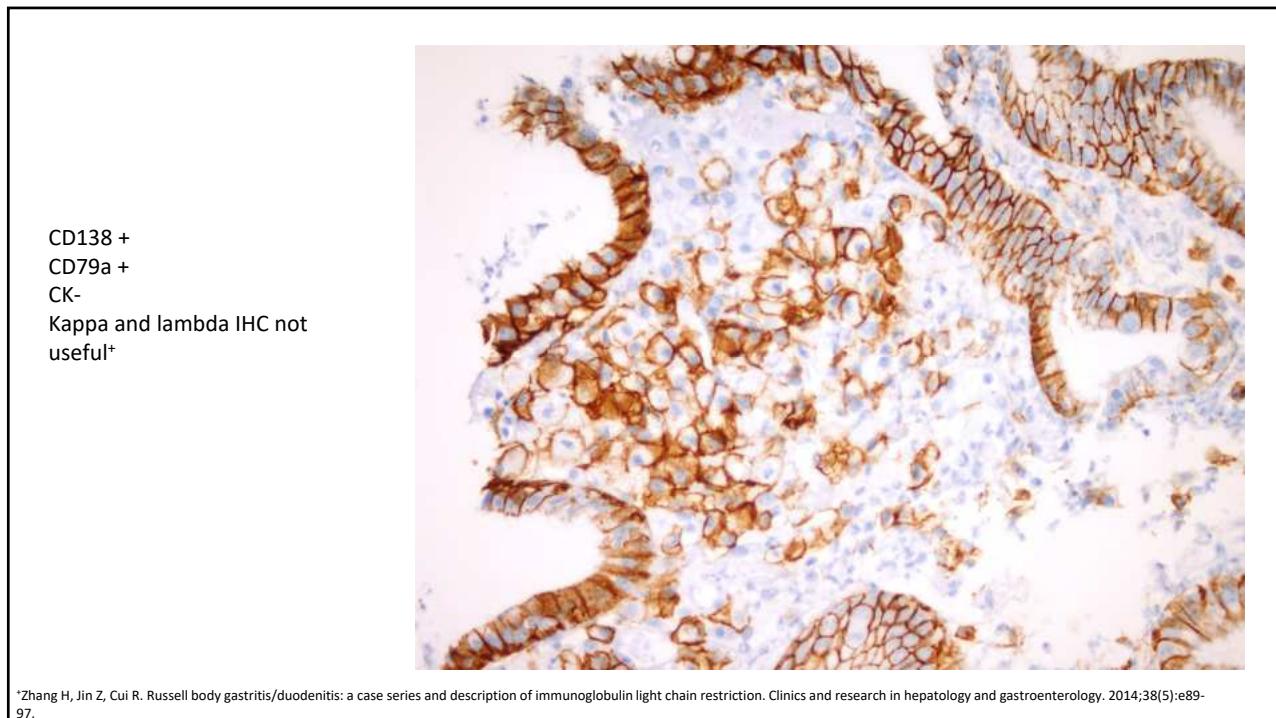
Russell body gastritis



Yorita K, Iwasaki T, Uchita K, Kuroda N, Kojima K, Iwamura S, Tsutsumi Y, Ohno A, Kataoka H. Russell body gastritis with Dutcher bodies evaluated using magnification endoscopy. World J Gastrointest Endosc 2017; 9(8): 417-424



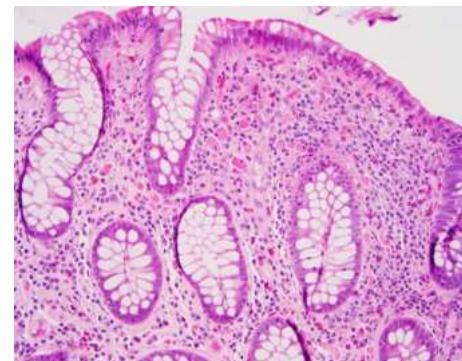
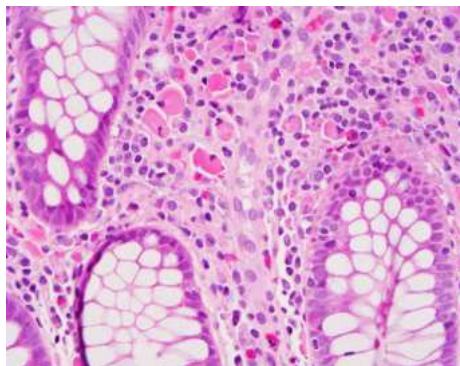




⁺Zhang H, Jin Z, Cui R. Russell body gastritis/duodenitis: a case series and description of immunoglobulin light chain restriction. Clinics and research in hepatology and gastroenterology. 2014;38(5):e89-97.

Russell body gastritis

- Russell body “esophagogastritis”?
 - Esophagus
 - Small bowel
 - Colon

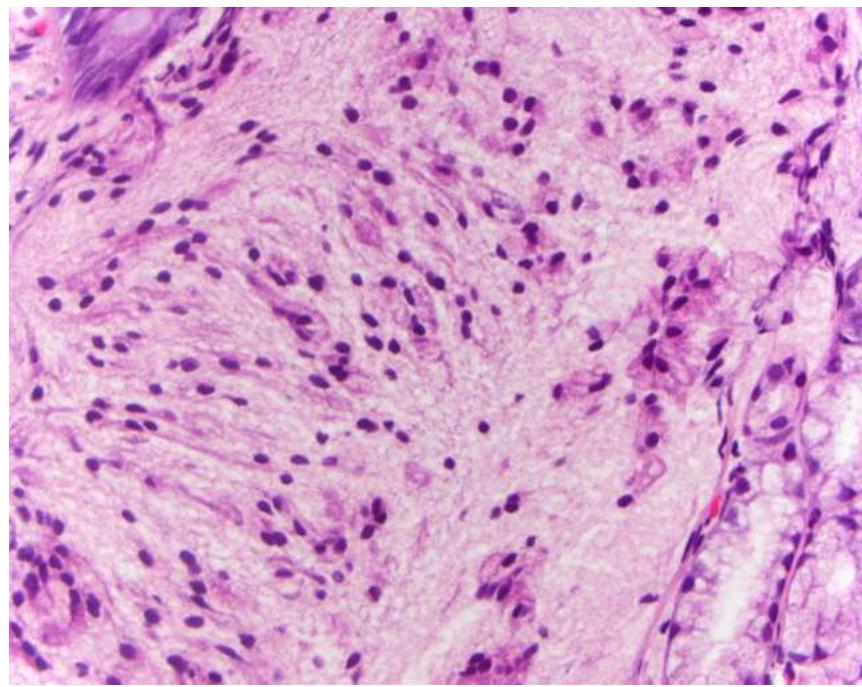
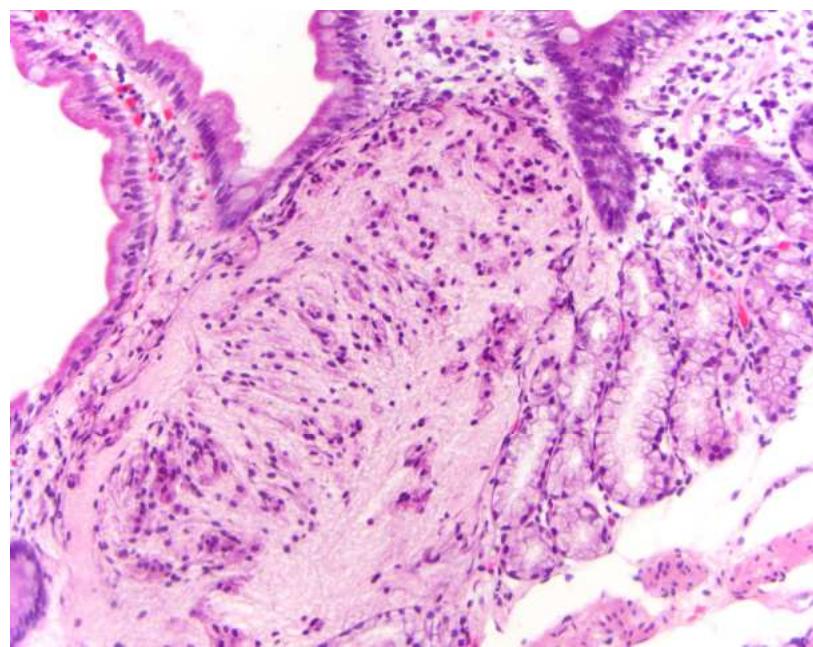


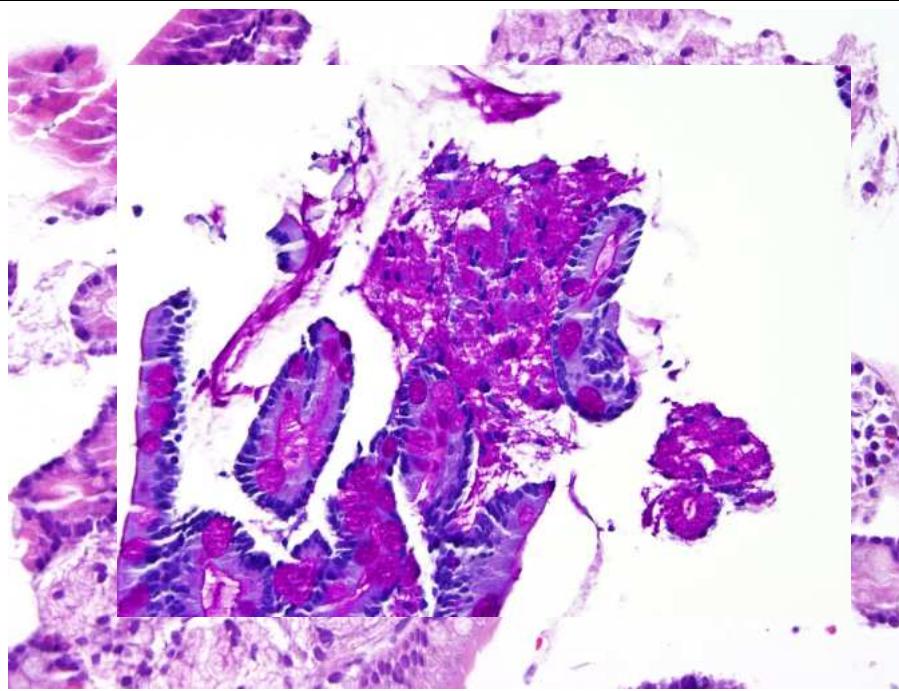
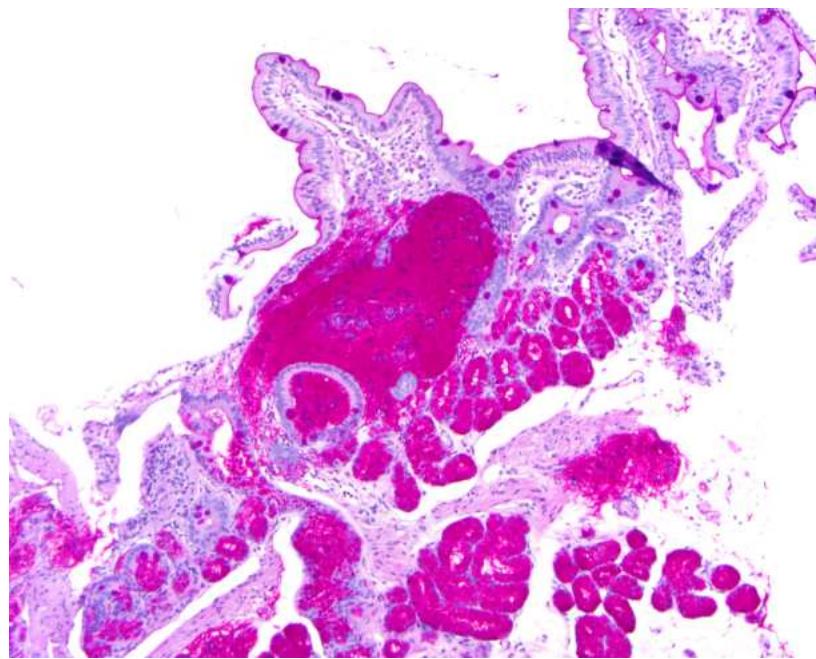
Bhaijee F, Brown KA, Long BW, Brown AS. Russell body gastroenteritis: an aberrant manifestation of chronic inflammation in gastrointestinal mucosa. Case reports in medicine. 2013;2013:797264.
Muthukumarana V, Segura S, O'Brien M, Siddiqui R, El-Fanek H. "Russell Body Gastroenteritis" in a Posttransplant Patient: A Case Report and Review of Literature. International journal of surgical pathology. 2015;23(8):667-72

Duodenum

Crushed Brunner Glands

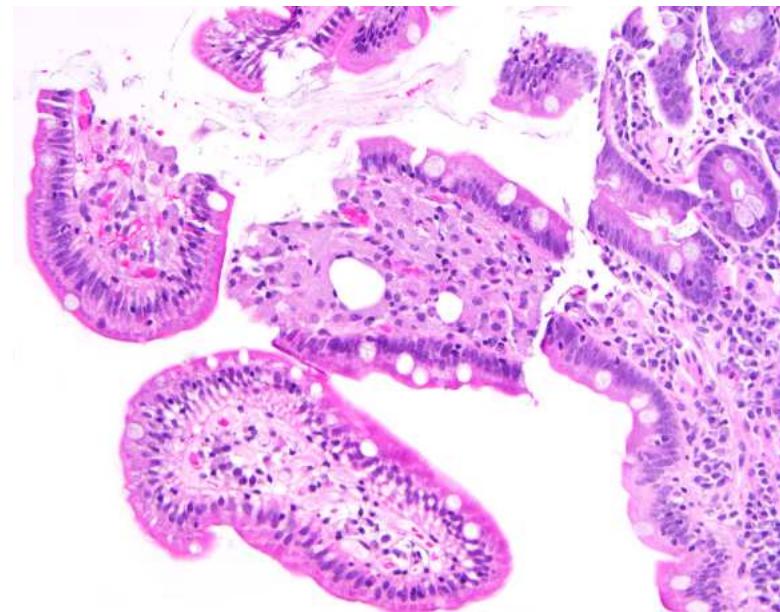
- Often mistaken for
 - Myxoid nerve sheath tumor
 - Whipple disease





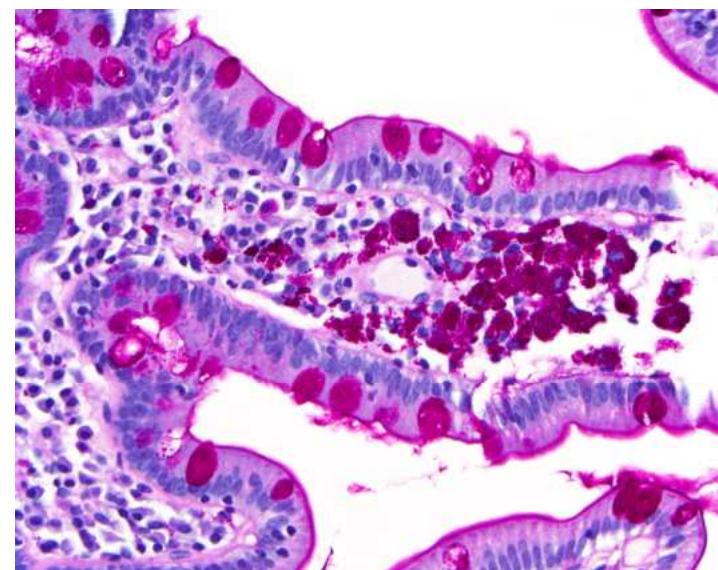
Whipple disease

- Macrophage nuclei
- Lymphangiectasia

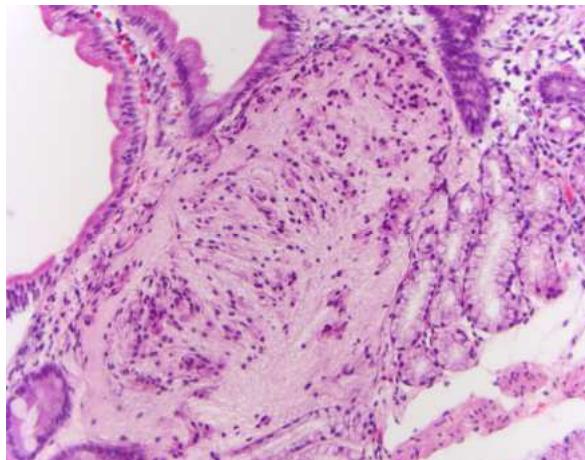


Whipple disease

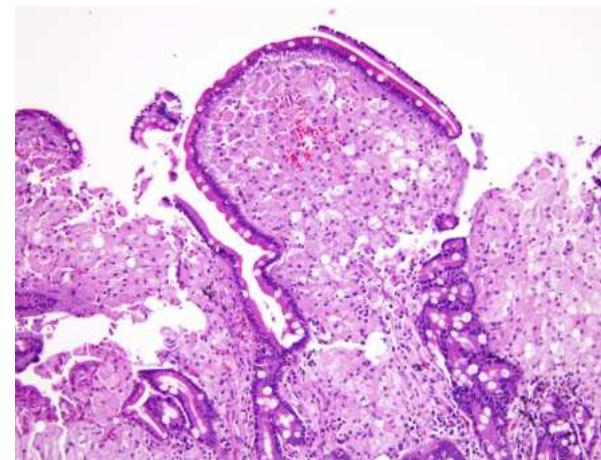
- PAS: Coarse rod/sickle/globular staining



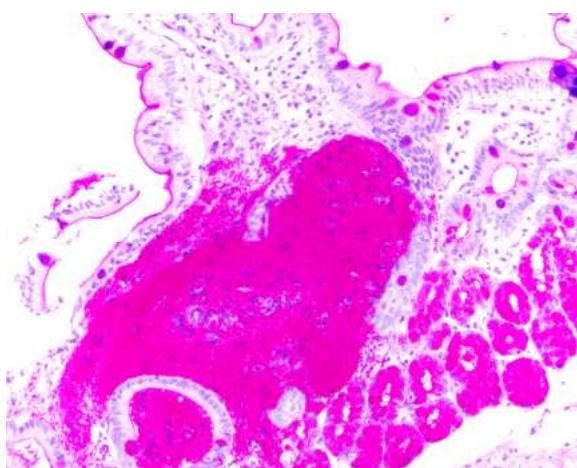
Crushed Brunner Glands



Whipple Disease

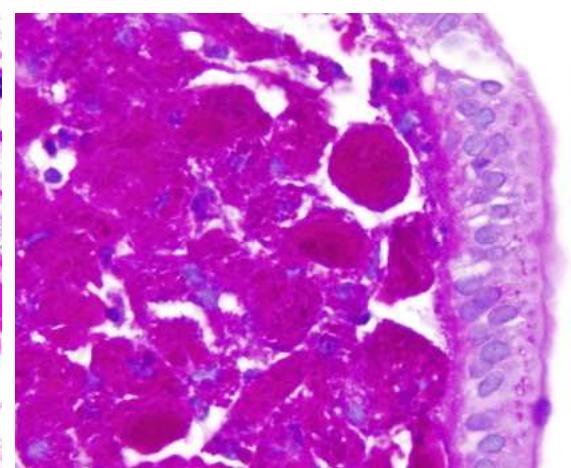


Crushed Brunner Glands



Clump

Whipple Disease

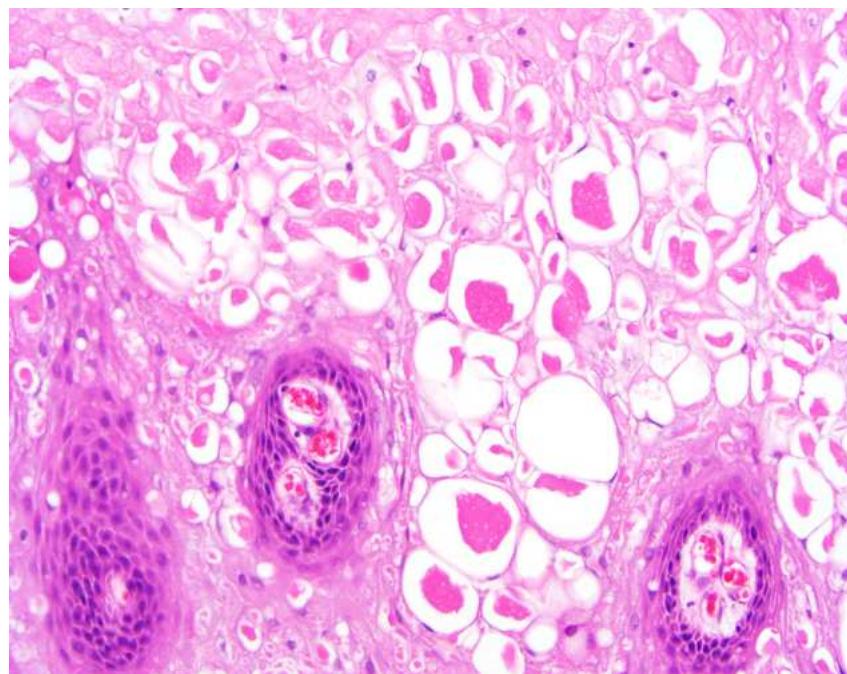
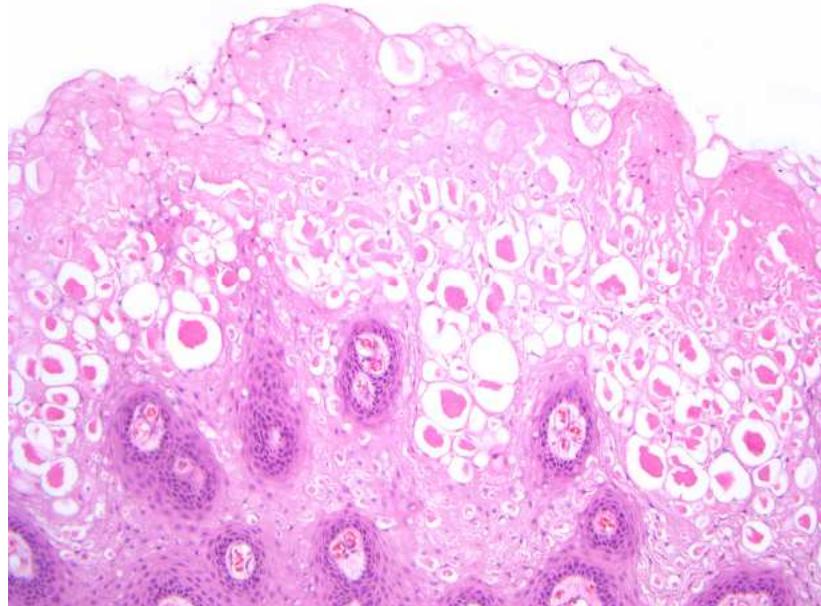


At least some individual cells

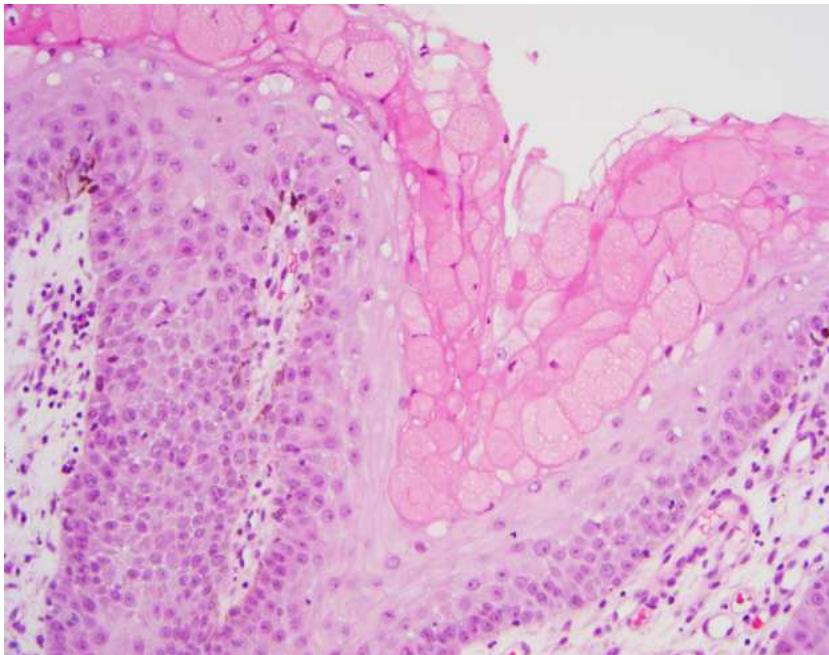
Anus

Pagetoid Dyskeratosis

- Reactive exuberant keratinization in squamous epithelium that may mimic HPV cytopathic changes.

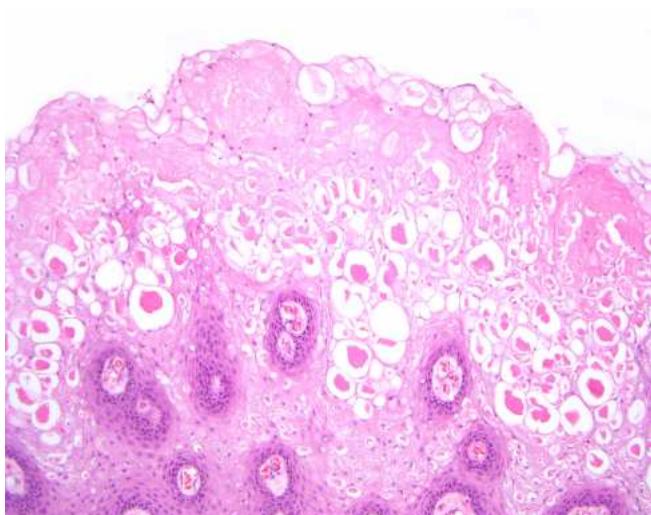


- Keratinocytes are larger than normal
- Pyknotic to hardly visible nuclei
- Clear halo surrounding condensed keratin globs

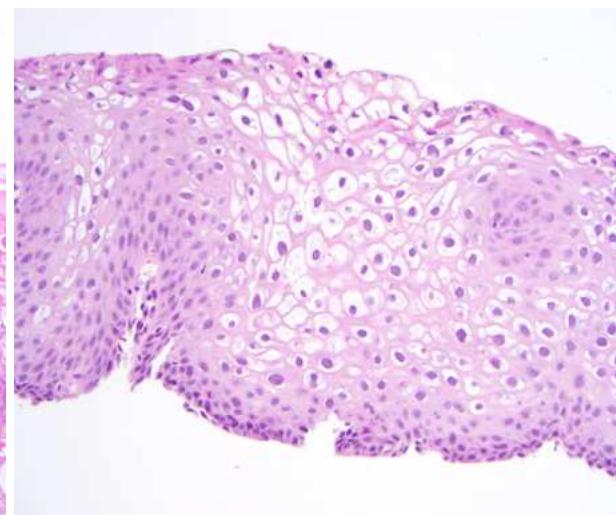


Differential

Condyloma

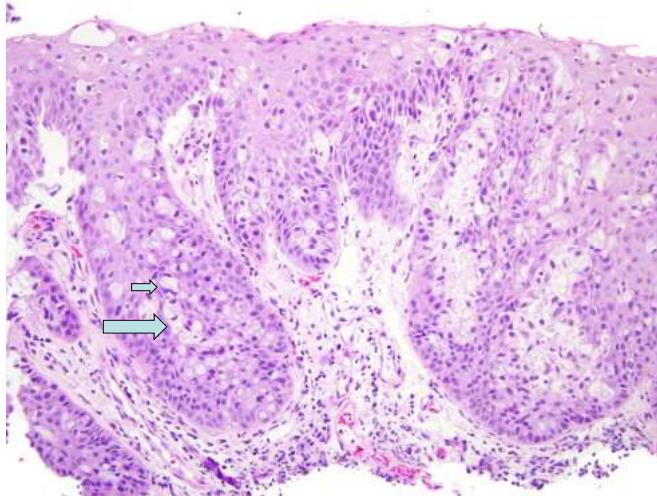


Halo around condensed keratin

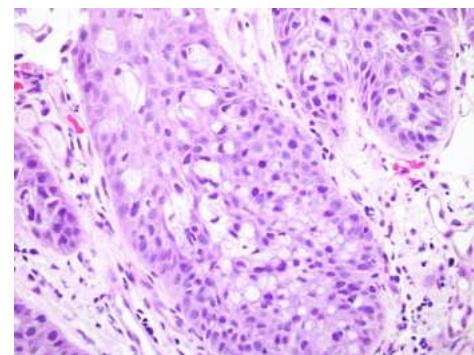


Halo around enlarged, hyperchromatic nuclei

Paget Disease

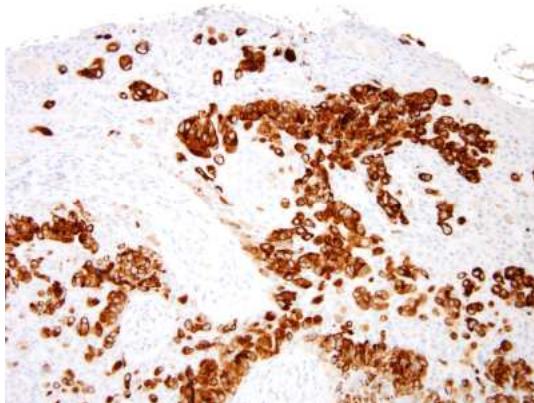


- Large, pale/pink cells
- +/- signet ring cell features



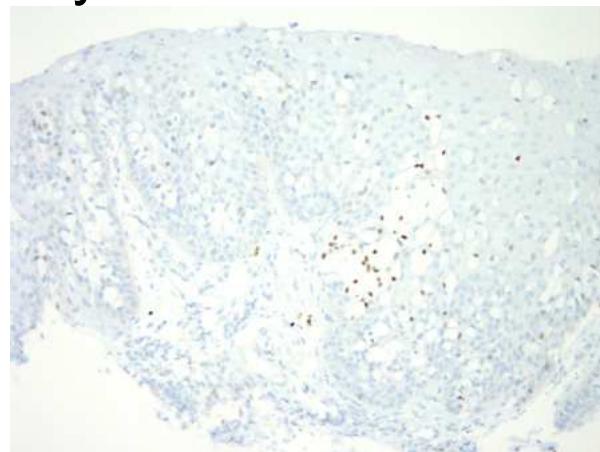
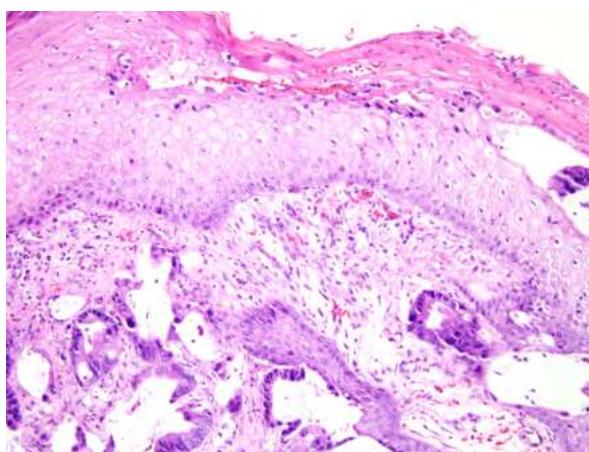
Paget Disease

CK7



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

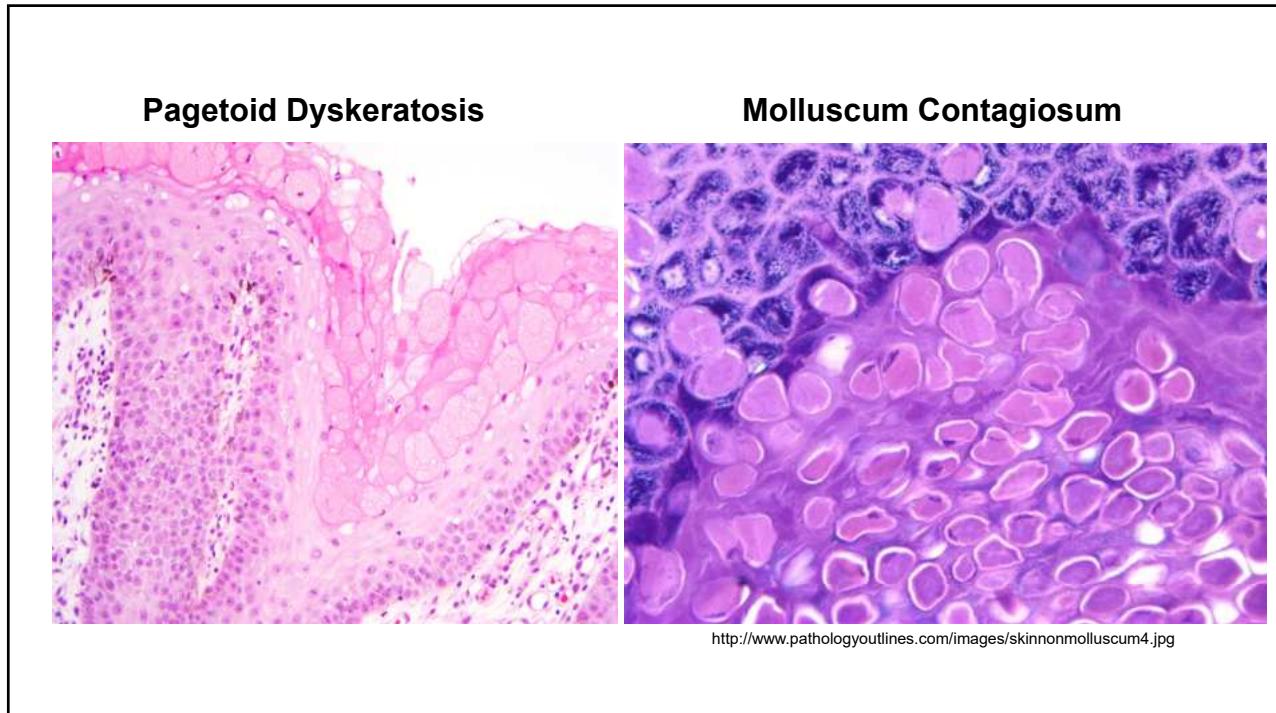
Pagetoid Extension from Colorectal Primary



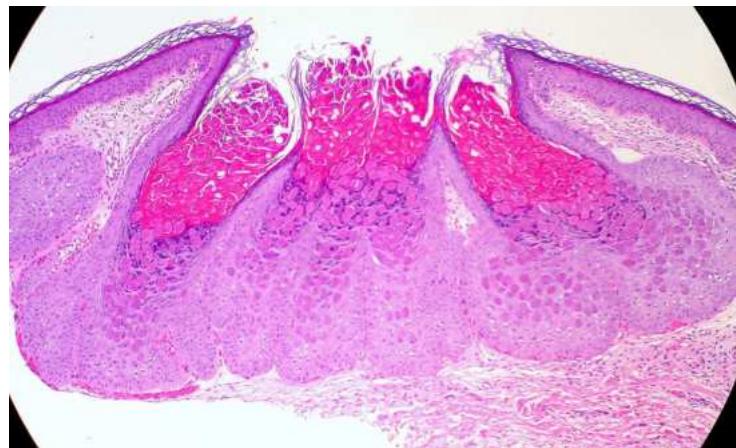
CDX2

IMMUNOHISTOCHEMICAL PROFILES OF INTRAEPITHELIAL NEOPLASTIC LESION OF THE ANUS									
Diagnosis	CK5/6	CEA	GCDFP	CAM 5.2	CK90334 β E12	S100	P16	CK7	CK20/CDX2
SCC/precursors	+	-	-	-	+	-	+	-	-
Paget disease	-	+	+	+	-	-	-	+	Usually -
Pagetoid spread of invasive colorectal adenocarcinoma into perianal skin	-	+	-	+	Usually -	-	-	+/-	+
Melanoma	-	-	-	-	-	+	-	-	-

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.



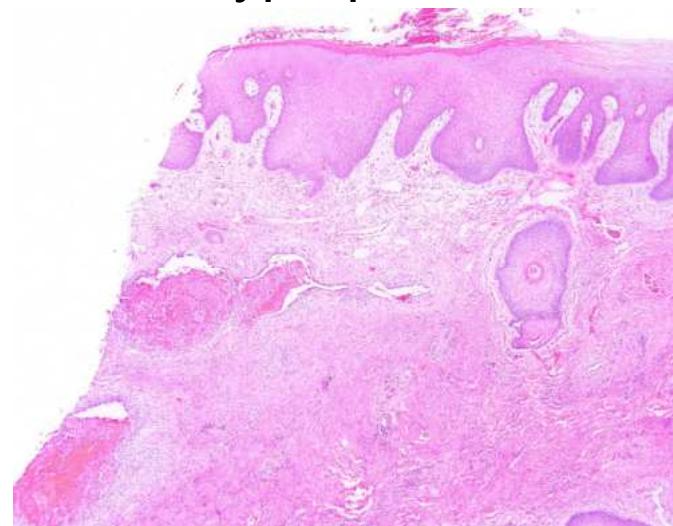
Molluscum Contagiosum

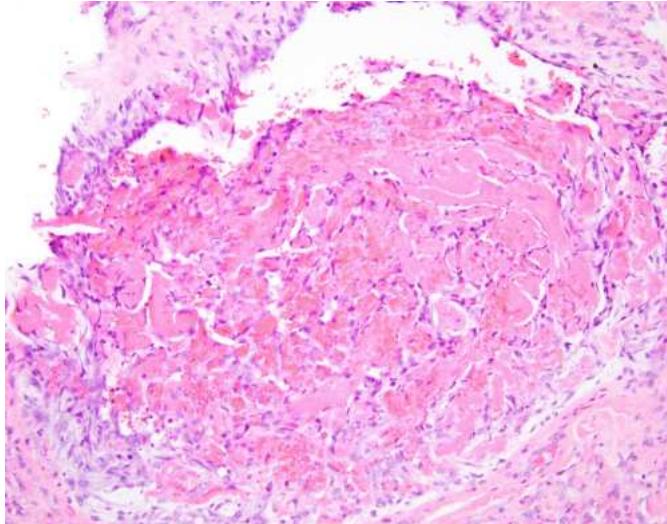


https://upload.wikimedia.org/wikipedia/commons/a/aa/Molluscum_Contagiosum_%283952583713%29.jpg

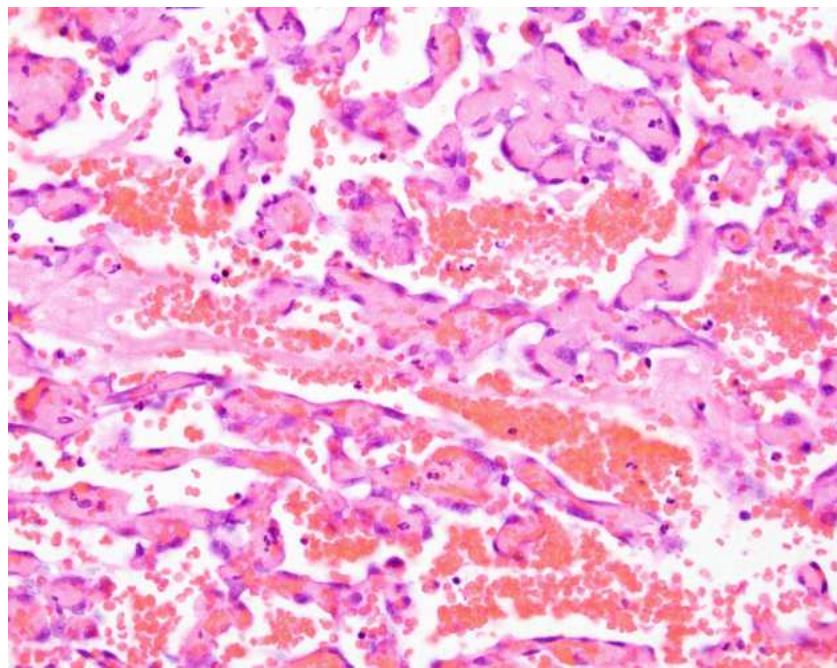
Papillary Endothelial Hyperplasia

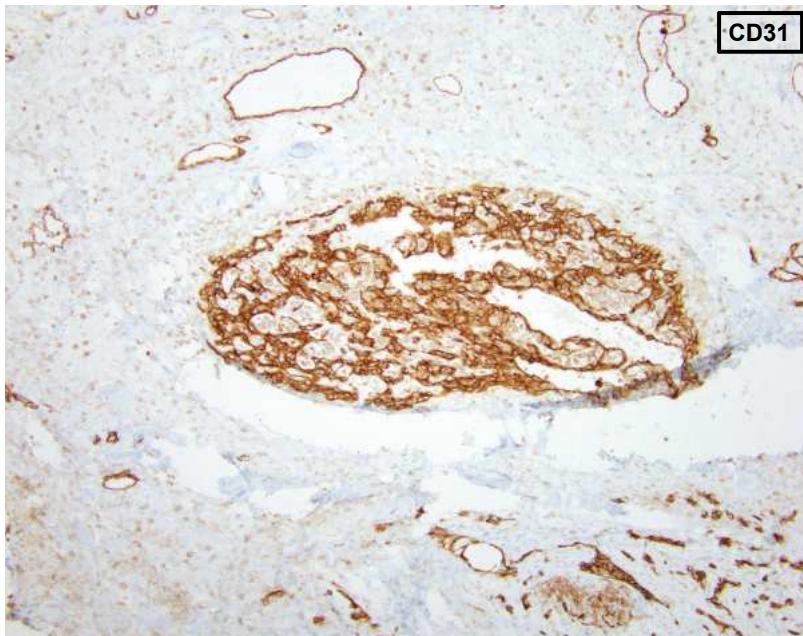
- Exuberant organizing thrombus
- Anywhere in the body
- Solitary superficial, firm, bluish or reddish mass
 - Fingers
 - Head
 - Neck
 - Anorectal area





- Papillary fronds with a fibrin/hyalinized collagenous core lined by single layer of endothelial cells
- No endothelial atypia or mitoses
- Some extravascular extension possible



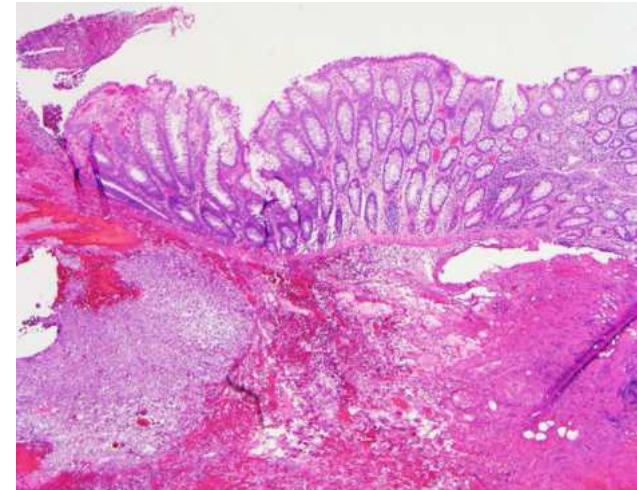


Angiosarcoma of the GI Tract

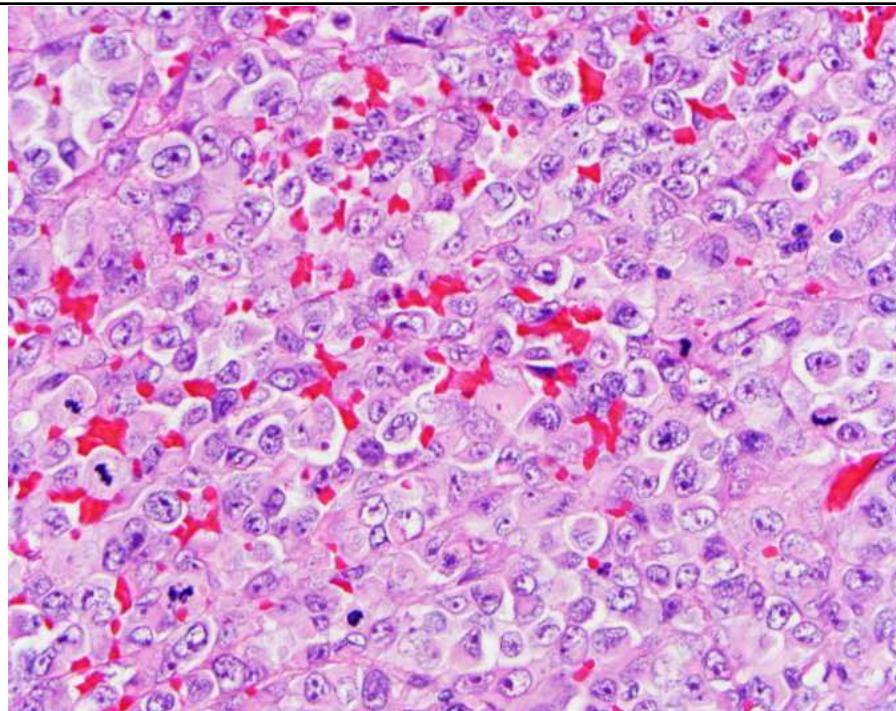
- Small bowel or colon
- Intestinal bleeding, anemia, pain
- Tumors may be primary GI, contiguous spread from adjacent site, or metastatic
- Aggressive

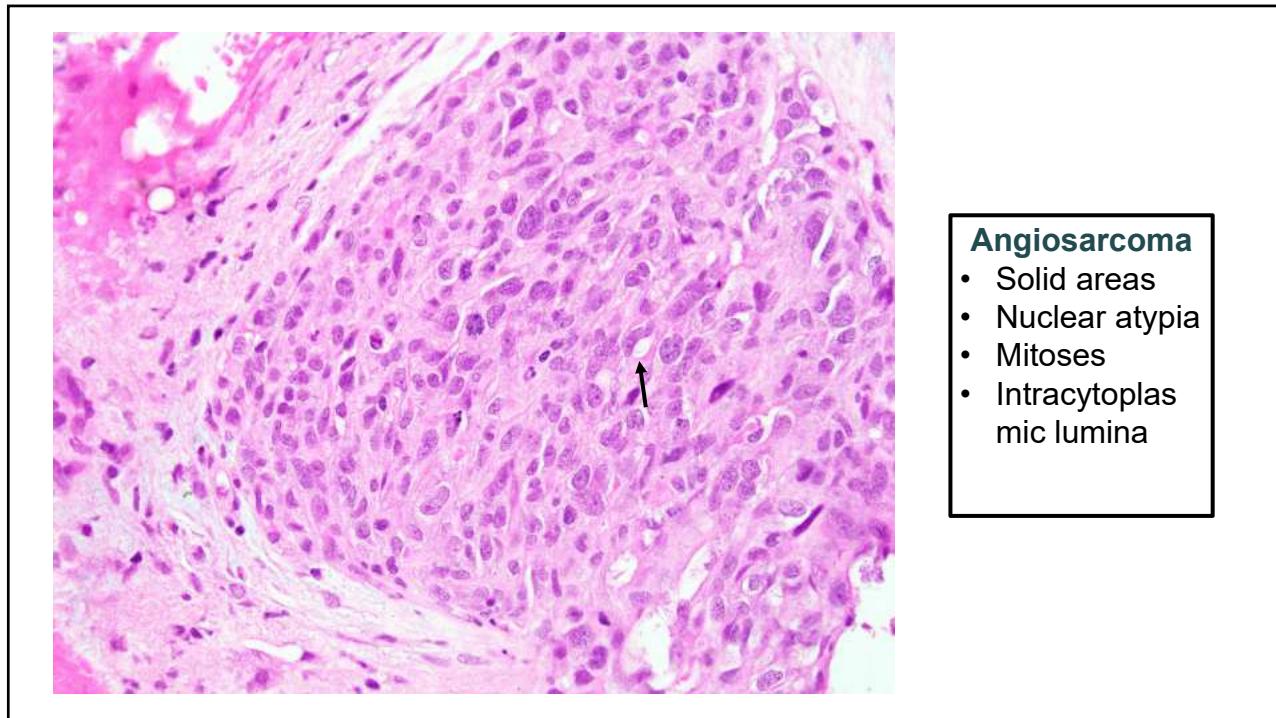
Angiosarcoma of the GI Tract: Epithelioid Morphology Common

- 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

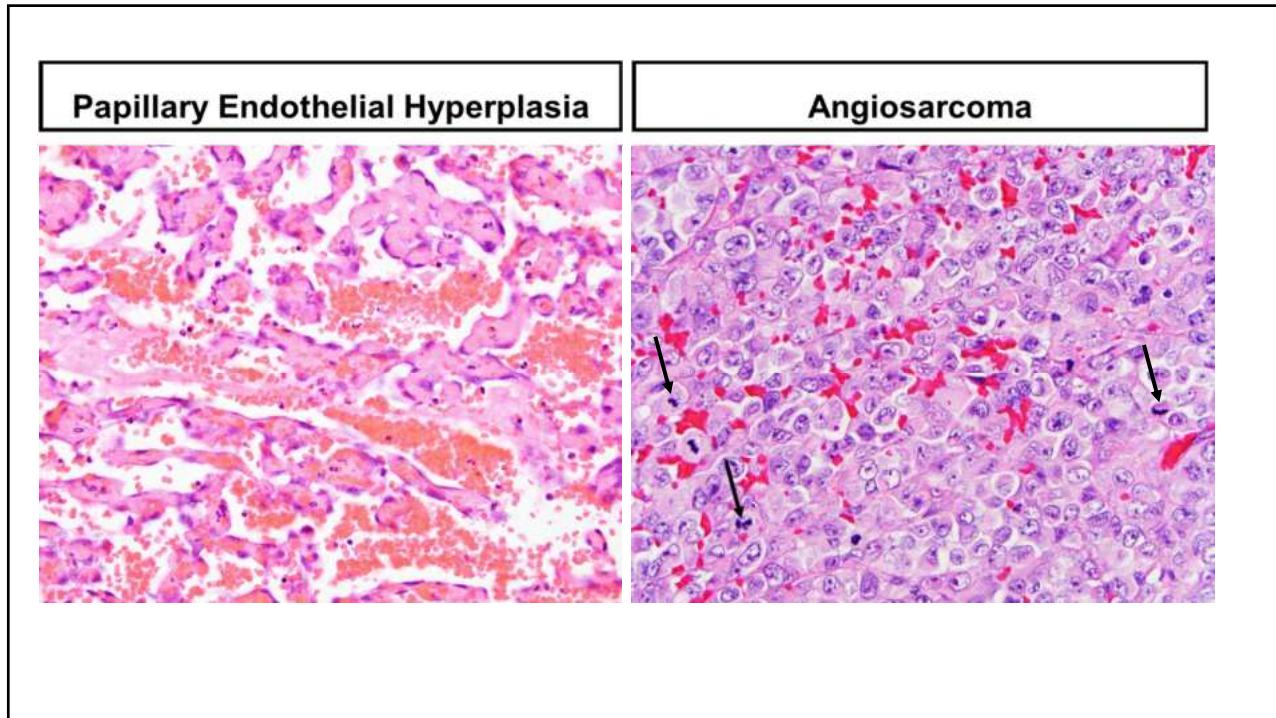


Allison et al. Angiosarcoma involving the gastrointestinal tract: a series of primary and metastatic cases. Am J Surg Pathol. 2004 Mar;28(3):298-307



**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

Clearkin and Enzinger. Intravascular papillary endothelial hyperplasia. Arch Pathol Lab Med. 1976 Aug;100(8):441-4.

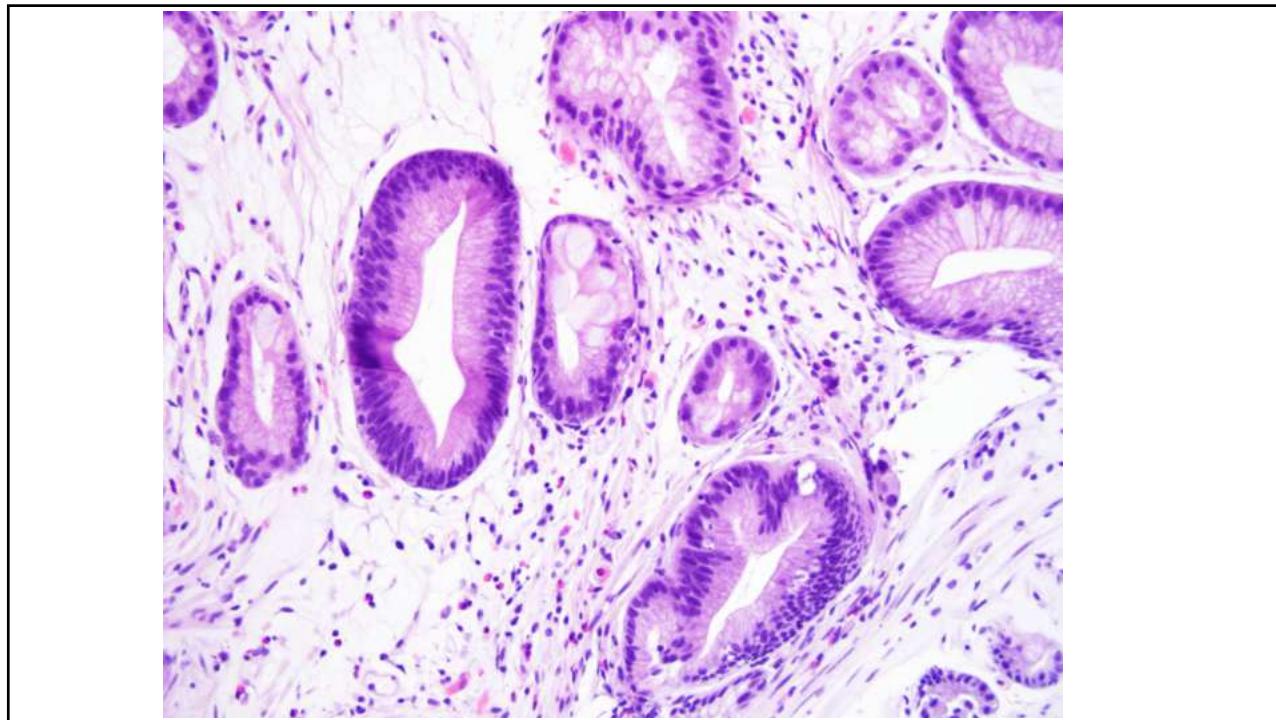
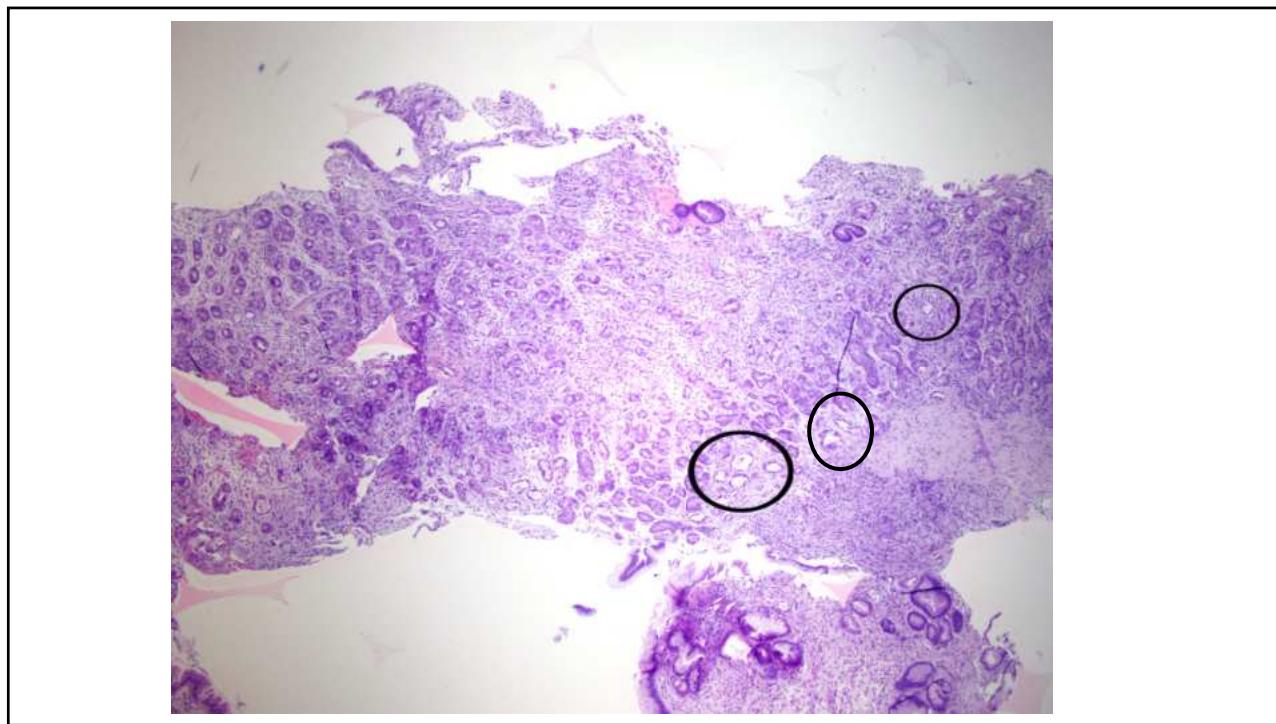
Summary

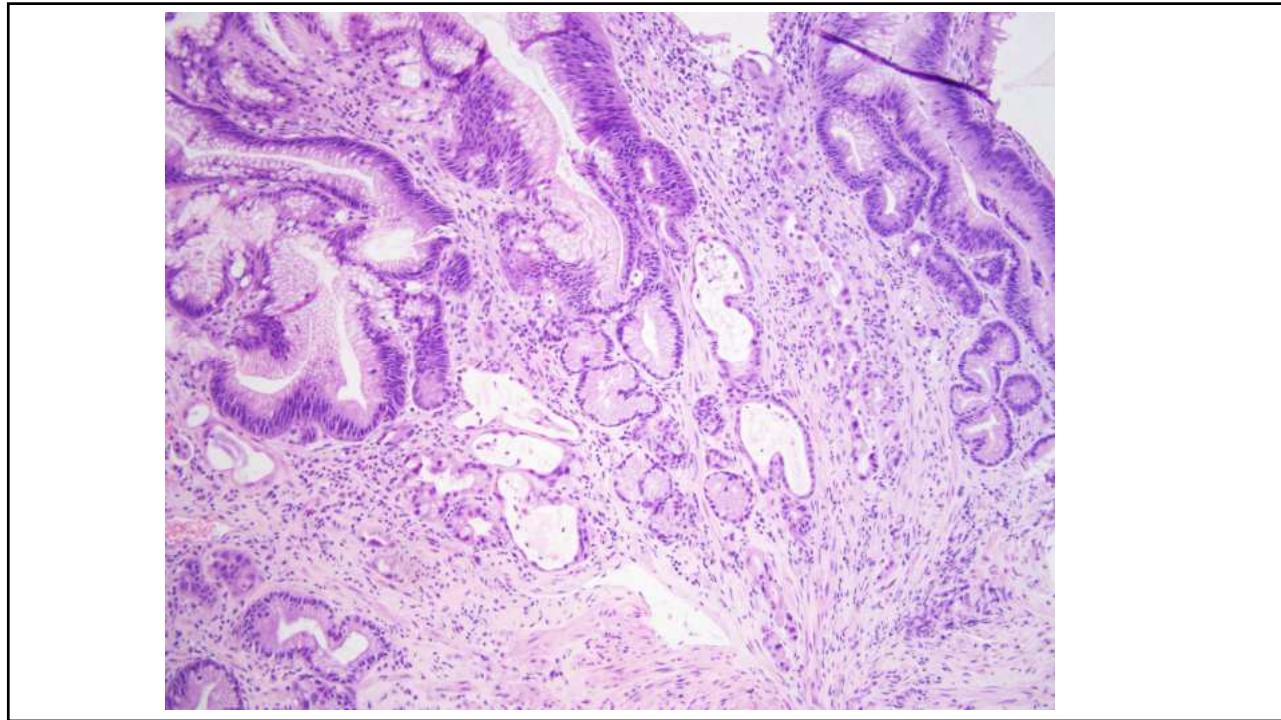
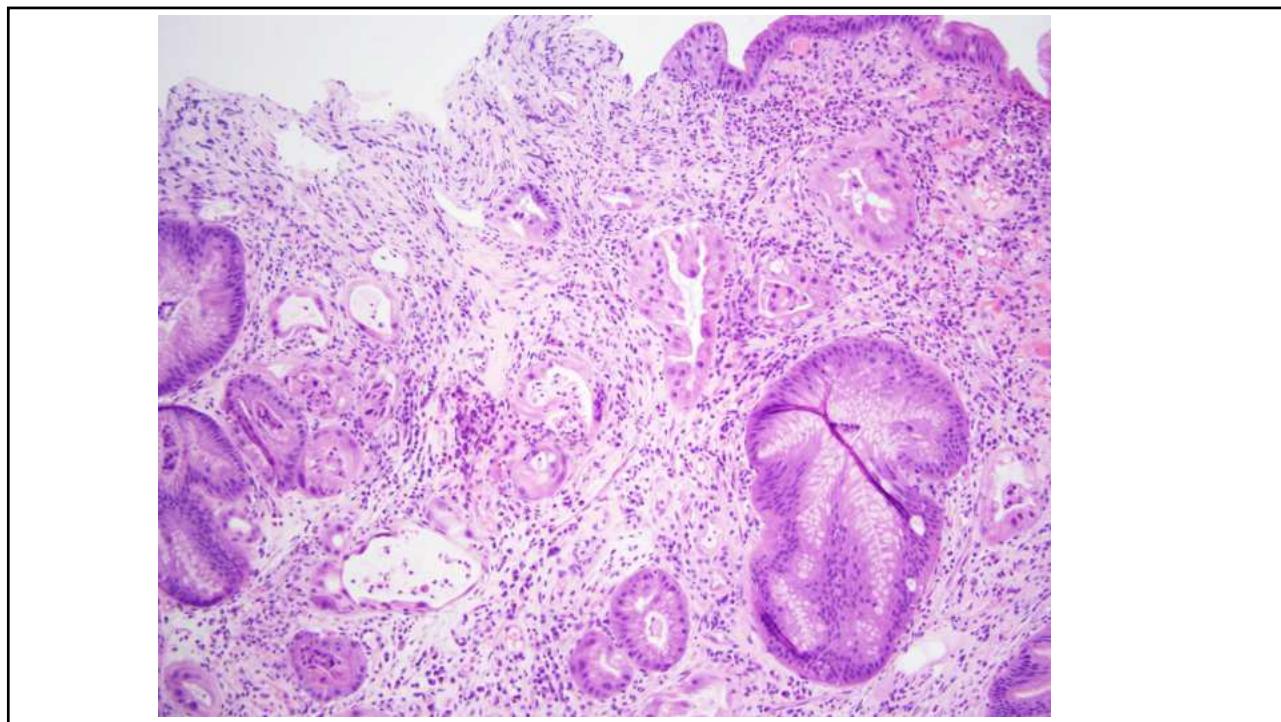
- There are many neoplastic and inflammatory mimics in GI pathology
- Familiarity is important to avoid unnecessary time investment, immunohistochemical panels, and misdiagnoses

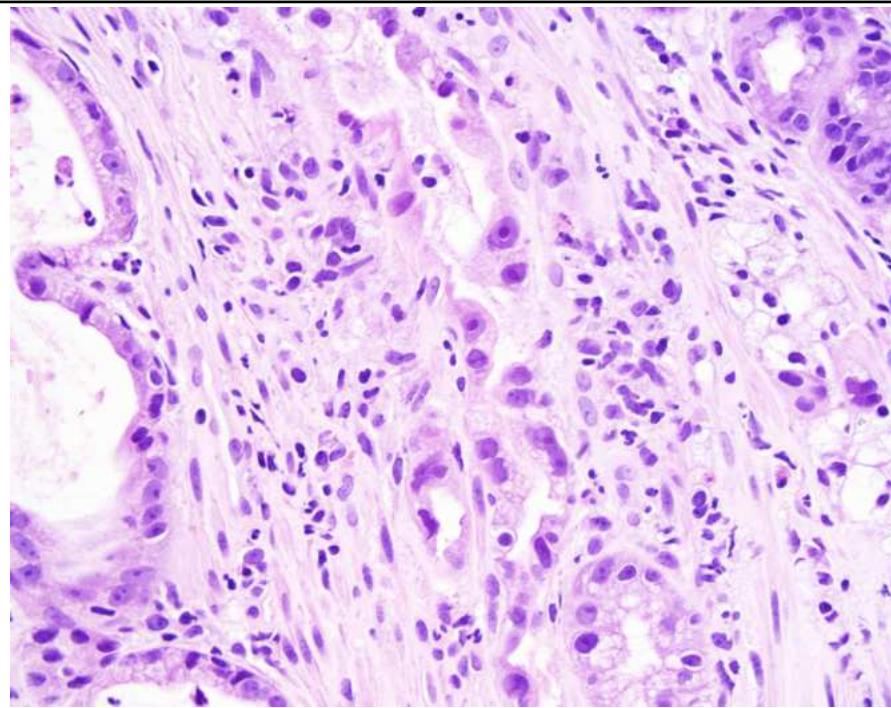
Bonus Case

History

- 55 y/o male
- Esophageal carcinoma
- Small “residual mass” on endoscopy.

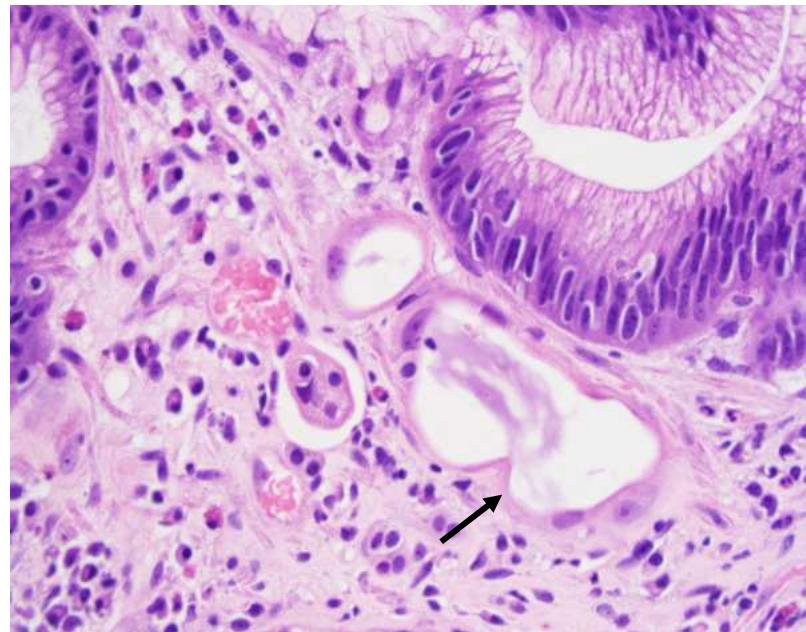




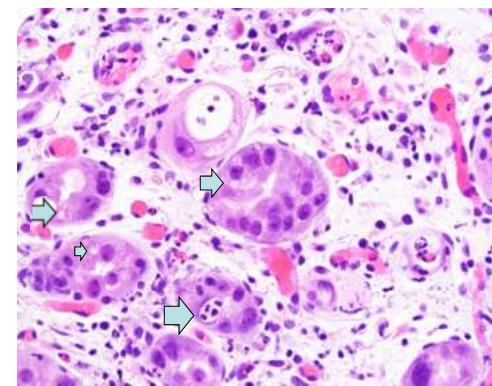
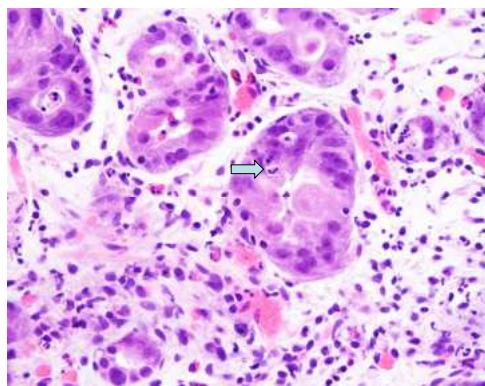


Answer: Radiation Related Changes
Mimicking Neoplasia

Clues



Clues



Clues to Radiation-Related Changes

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