

Iatrogenic and Infectious Mimics of Chronic Idiopathic Inflammatory Bowel Disease

PRESENTED BY

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USCAP 108TH ANNUAL MEETING

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Laura W. Lamps reported no relevant financial relationships.

Dr. Lamps

83% Excellent

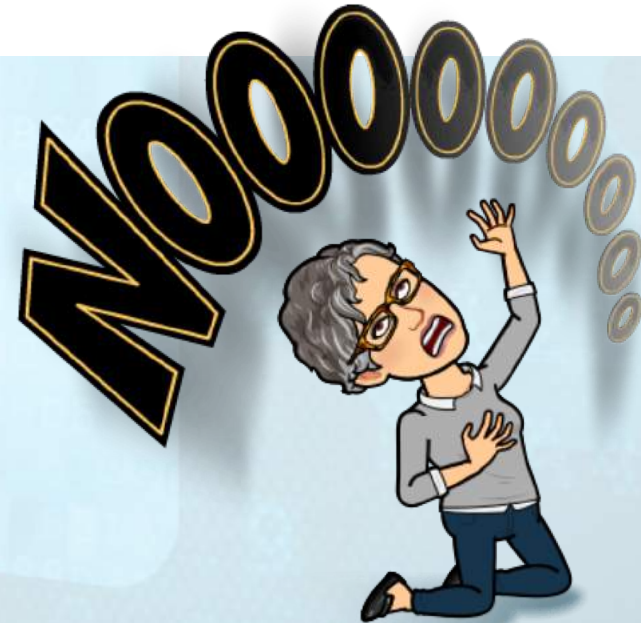
17% Good

(0%) Fair

Comments:



- A bit too much information was covered in too short a time frame here.
- Very fast talker.



**Colon
Specimen**

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graph TD; A[Colon Specimen] --> B[IBD]; A --> C[NOT IBD];
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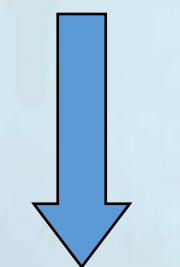
A flowchart with a light blue background featuring faint, repeating patterns of padlocks and alphanumeric strings. At the top center is a blue rounded rectangle containing the text 'Colon Specimen'. Two red arrows originate from the bottom corners of this rectangle and point downwards and outwards to two separate blue rectangles. The rectangle on the left contains the text 'IBD', and the rectangle on the right contains the text 'NOT IBD'.

IBD

NOT IBD

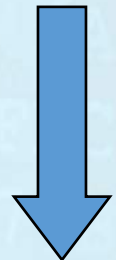
Colitis

ASLC
AITC



Infection

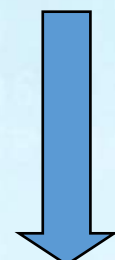
FAC



Infection
NSAID
Rarely Crohn's

CHRONICITY
Architectural distortion
Basal plasmacytosis
Left sided Paneth cells
Pyloric metaplasia

Other



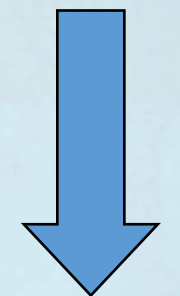
Diversion colitis
Diverticular
disease-
associated
segmental
colitis

Microscopic
Colitis



Lymphocytic colitis
Collagenous colitis

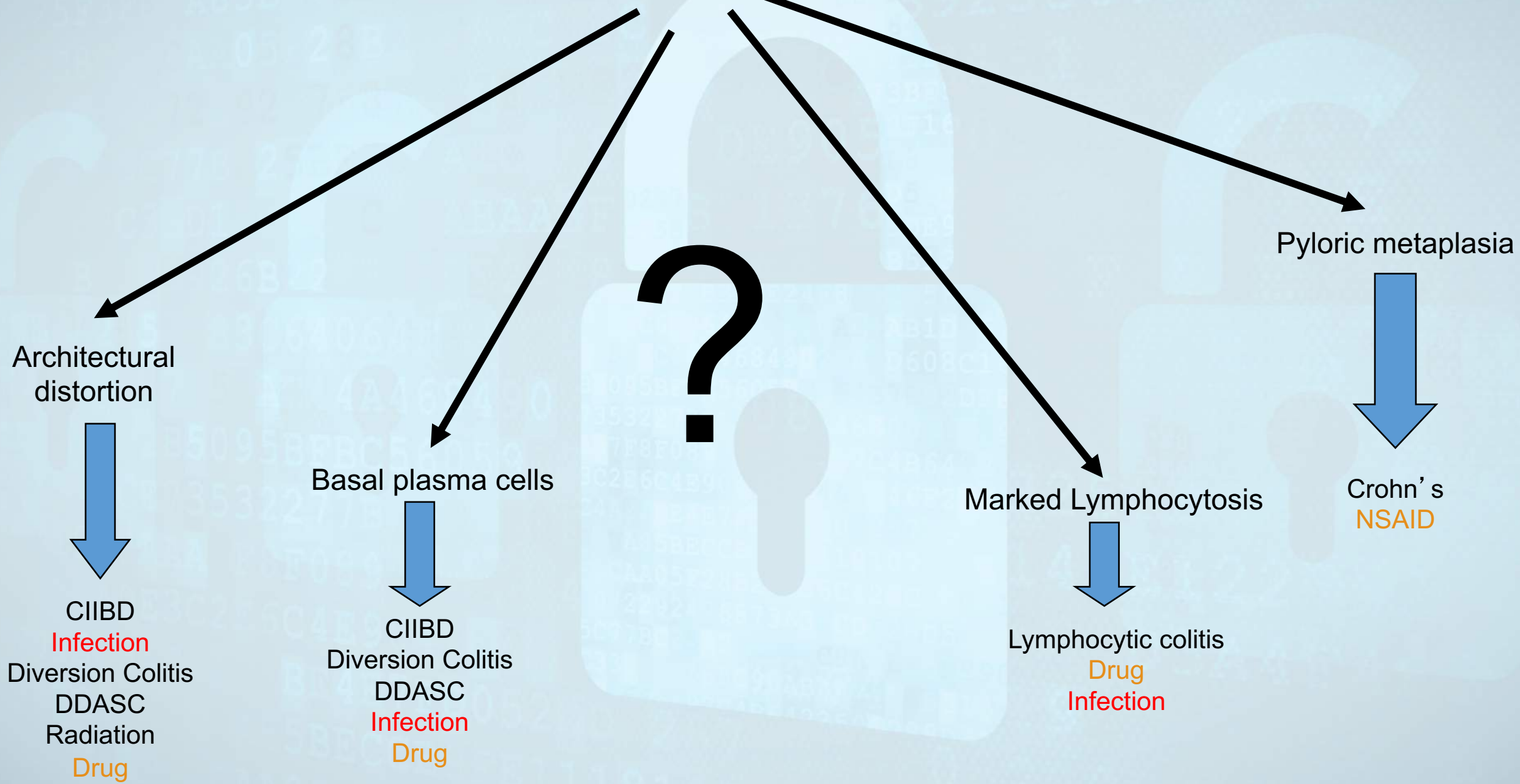
CIIBD



Crohn's
UC

Surawicz et al. *Gastroenterol* 1994;107:755-63
Greenson et al. *Hum Pathol* 1997;28:729-33
Volk et al. *Mod Pathol* 1998;11:789-94
Shetty et al. *Histopathology* 2011;59:850-6

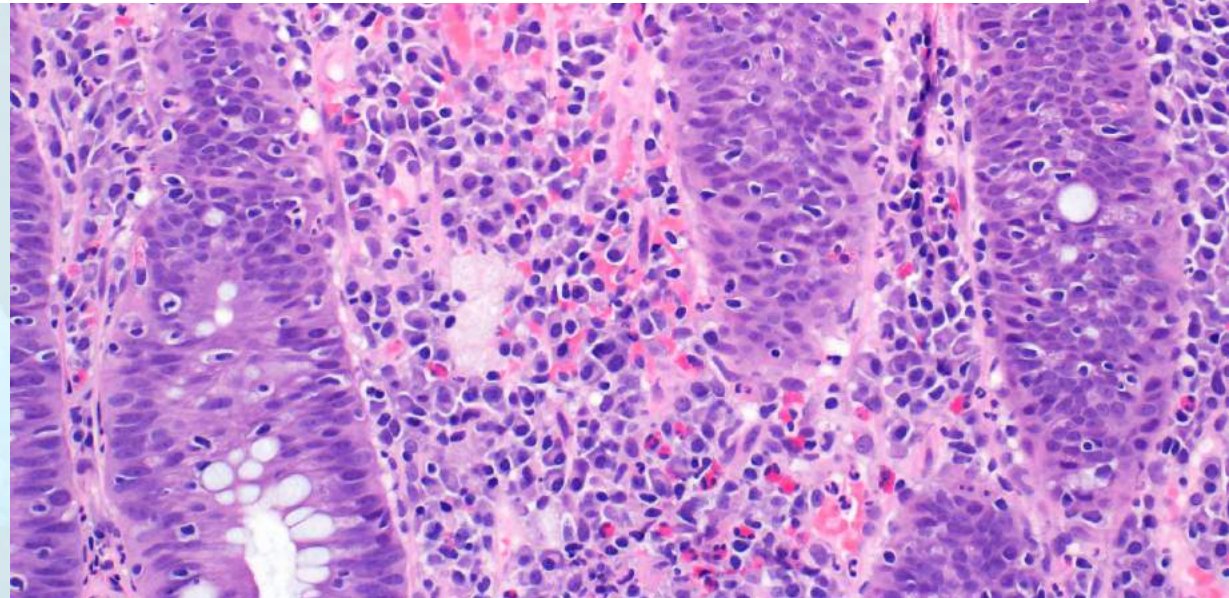
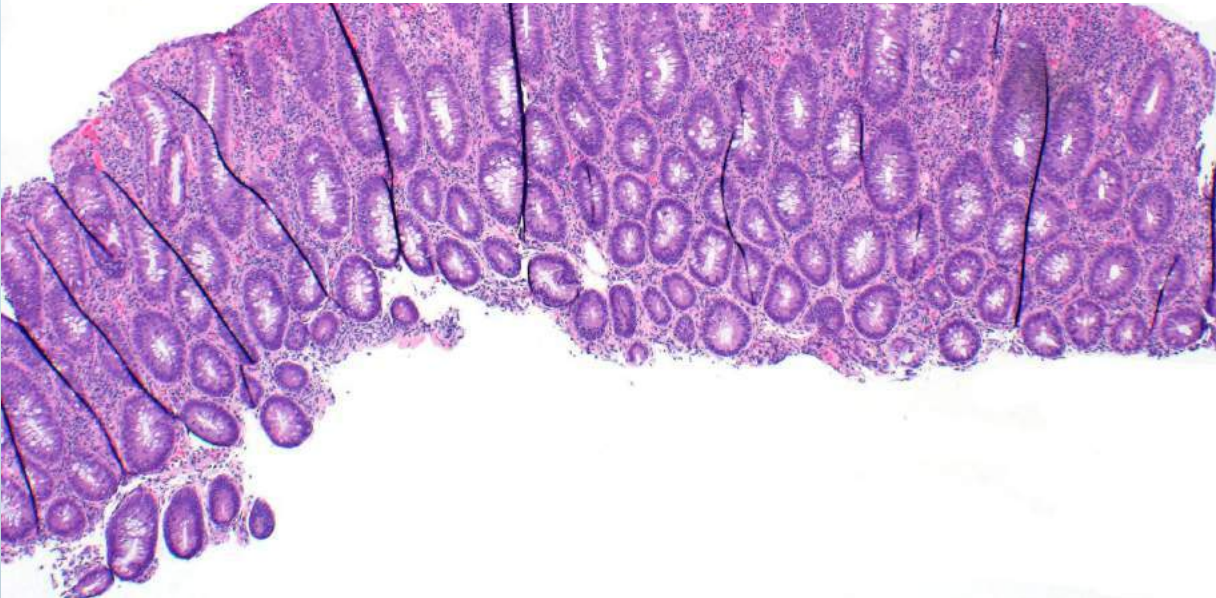
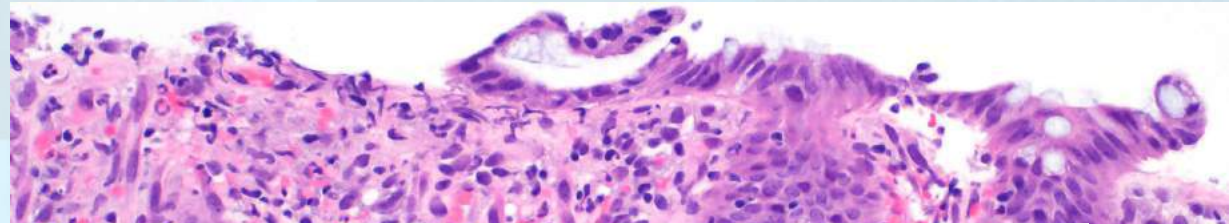
Colitis



58 year old man with diarrhea

- Endoscopy: “mild to moderate inflammation in colon”
- Requisition: “diarrhea”

Widely metastatic Merkel cell carcinoma; Avelumab started three months ago



Drugs and Chemicals that Mimic Chronic Colitis

Immune Checkpoint Inhibitors

- Mimic CIIBD, lymphocytic colitis, or autoimmune enterocolitis

NSAIDS

- Mimic Crohn disease

Mycophenolate

- Mimics CIIBD, GVHD

Olmesartan

- Mimics microscopic colitis or autoimmune enterocolitis

Bowel prep injury

- Mimics Crohn disease

Immune checkpoint-inhibitors

GI Toxicity

Clinical	Agent	Treatment
<ul style="list-style-type: none">• Most common reported adverse side effect (~1/3 patients)• Typically involves colon, sometimes small bowel and stomach• May take 5-10 weeks to develop• Colonoscopy usually abnormal but not always	<ul style="list-style-type: none">• CTLA-4 inhibitors (ipilimumab) more likely to cause GI problems than PD-1/PD-L1 inhibitors• Combination of the two increases risk	<ul style="list-style-type: none">• Steroids are first line therapy• Infliximab if steroid-resistant or very severe• Superimposed infection common with steroid therapy

Table 1 Food and Drug Administration-approved immune checkpoint inhibitors

Drug	Trade name	Target	Indications
Ipilimumab	Yervoy (2011)	Cytotoxic T-lymphocyte antigen 4	Melanoma
Nivolumab	Opdivo (2014)	Programmed cell death-1	Melanoma Non-small-cell lung carcinoma Renal cell carcinoma Hepatocellular carcinoma Classic Hodgkin's lymphoma Squamous cell carcinoma of head and neck Urothelial carcinoma Colorectal cancer with microsatellite instability or mismatch-repair deficiency
Pembrolizumab	Keytruda (2014)	Programmed cell death-1	Melanoma Non-small-cell lung carcinoma Classic Hodgkin's lymphoma Squamous cell carcinoma of head and neck Urothelial carcinoma Gastric cancer Solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	Tecentriq (2016)	Programmed cell death ligand-1	Non-small-cell lung carcinoma Urothelial carcinoma
Avelumab	Bavencio (2017)	Programmed cell death ligand-1	Merkel cell carcinoma Urothelial carcinoma
Durvalumab	Imfinzi (2017)	Programmed cell death ligand-1	Urothelial carcinoma

Table 2 Summary of key histological features of various immunotherapeutic agents

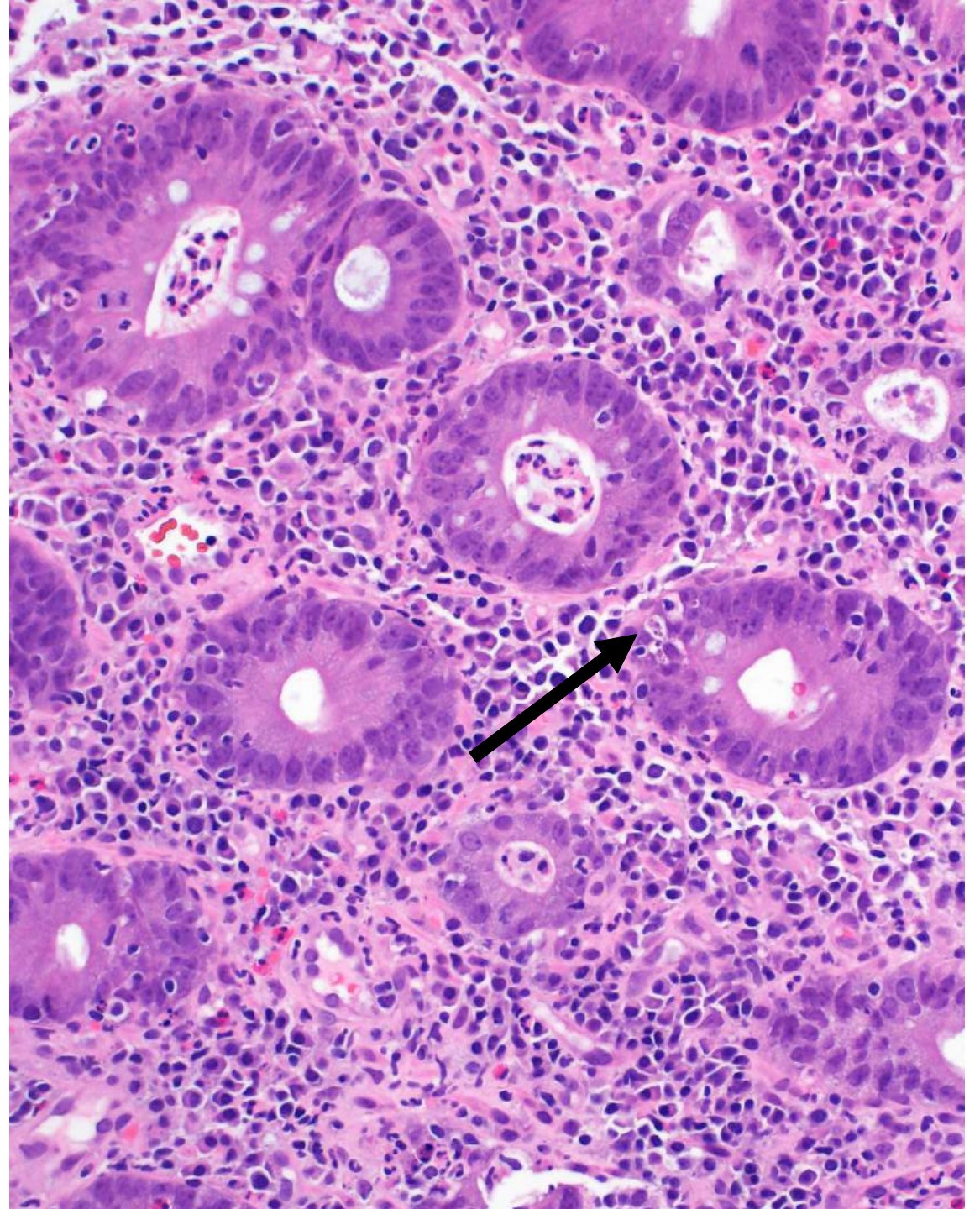
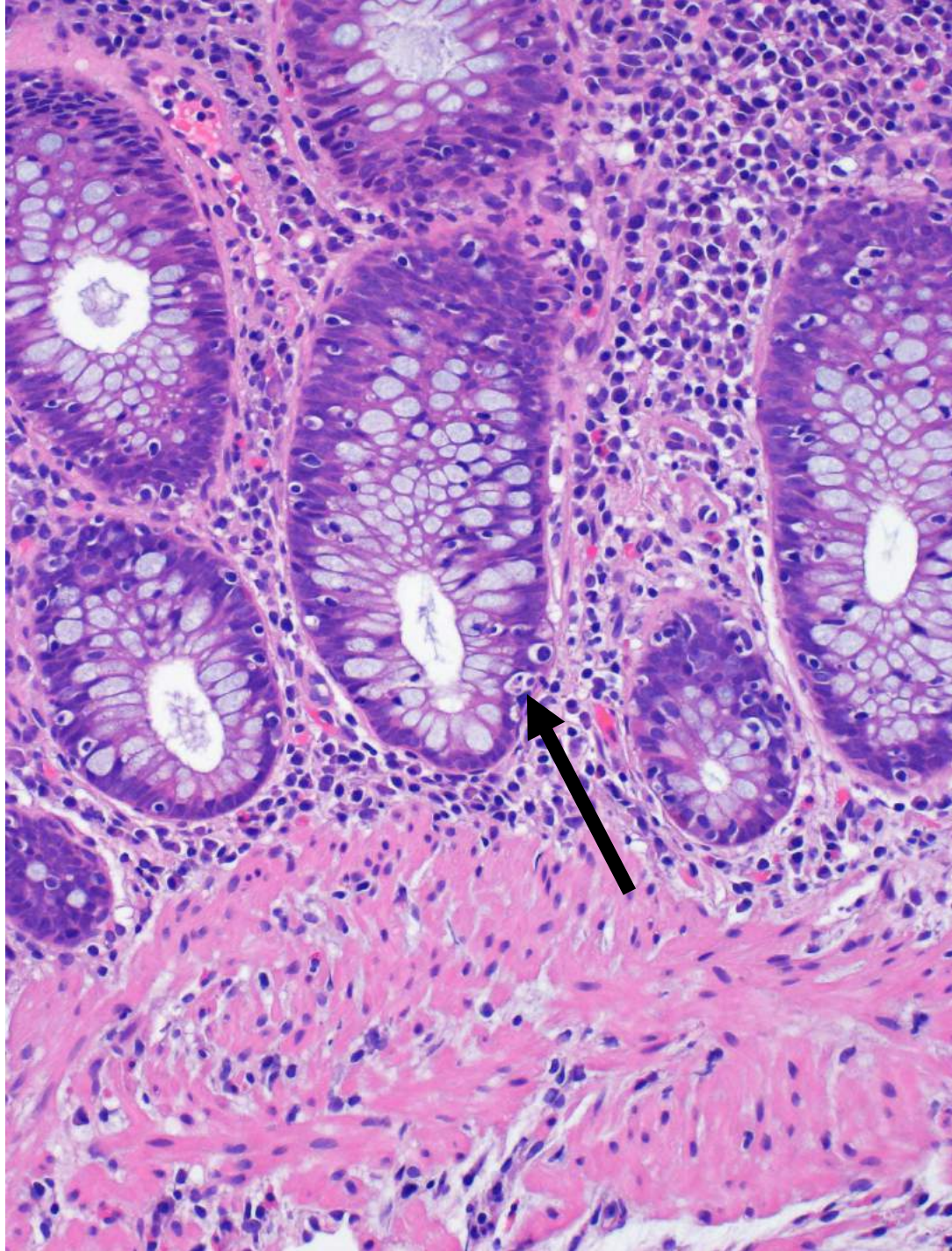
CTLA4 inhibitors (ipilimumab)	<i>Autoimmune-like</i> enterocolopathy: <ul style="list-style-type: none">– Lymphoplasmocytic expansion of lamina propria– Increased apoptosis and intraepithelial lymphocytes– Cryptitis and crypt elongation– Lack of basal plasmocytosis
PD1 inhibitors (pembrolizumab and nivolumab)	<ul style="list-style-type: none">– <i>Active colitis pattern</i> with increased apoptosis– <i>Lymphocytic colitis pattern</i>– Features of chronicity in recurrent cases– Ruptured granuloma
PI3K δ isoform inhibitor (idelalisib)	“ <i>Triad</i> ” of: <ul style="list-style-type: none">– Intraepithelial lymphocytosis– Epithelial cell apoptosis– Neutrophilic cryptitis



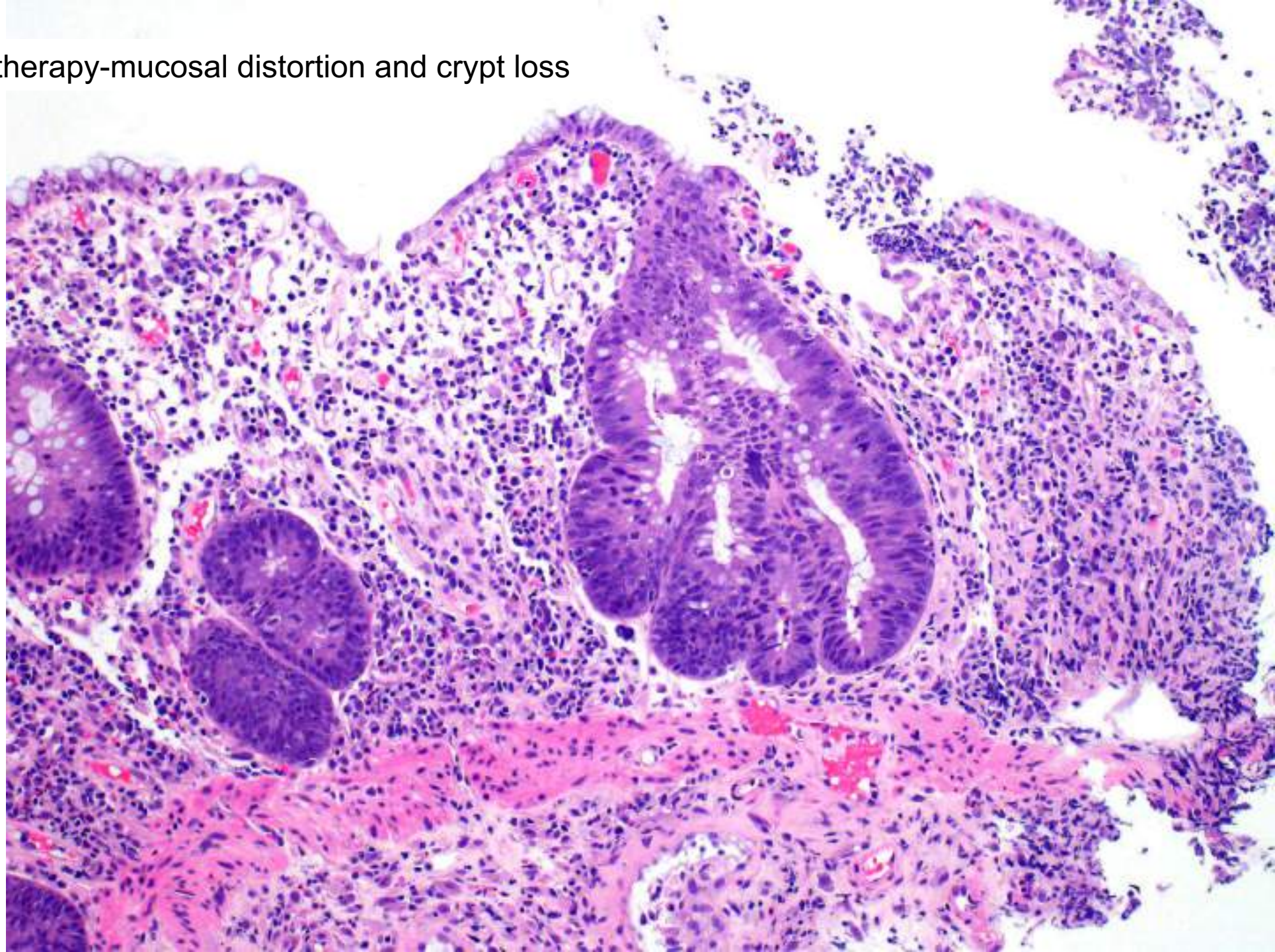
Pembrolizumab – Lymphocytic colitis pattern

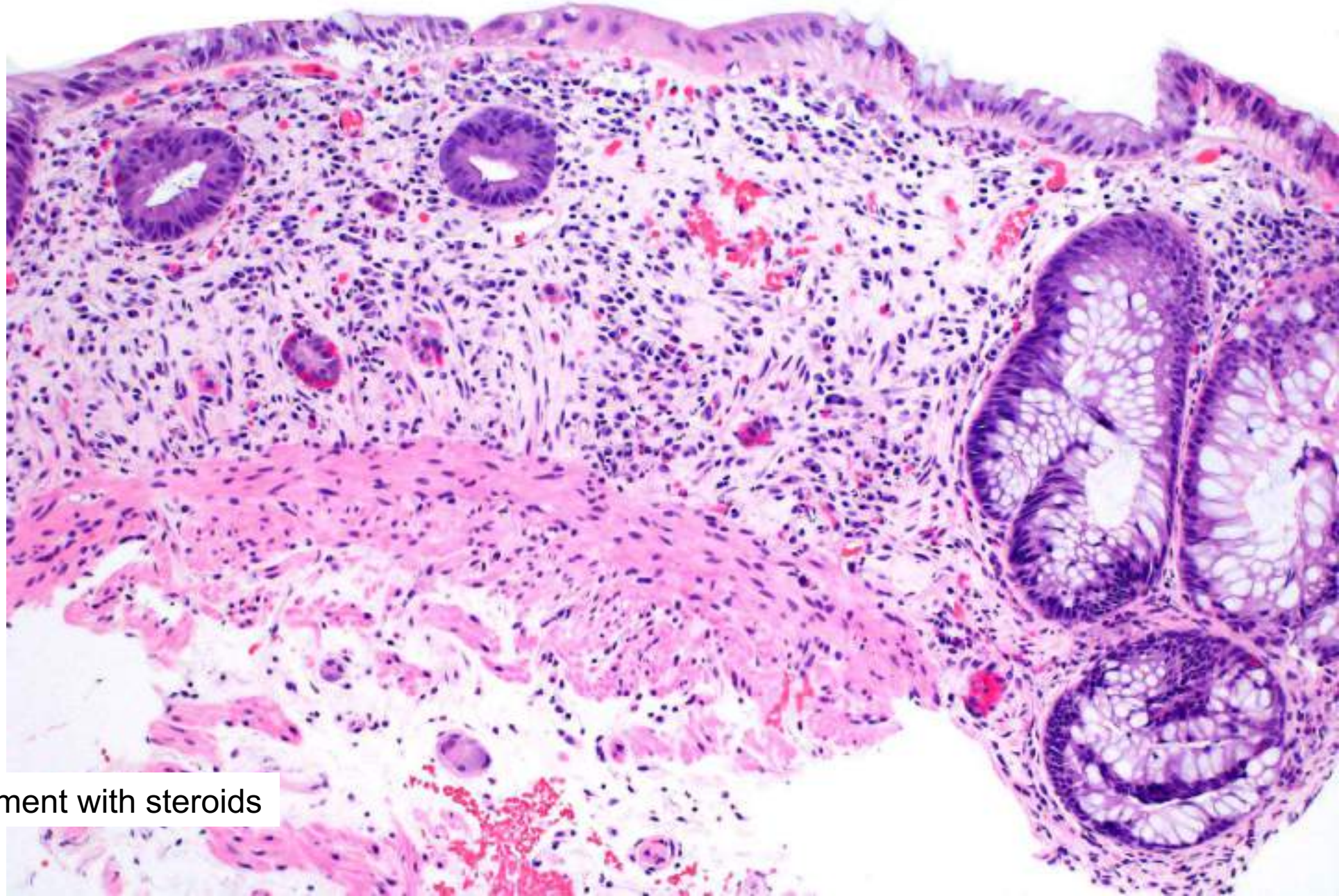


PDL1 inhibitor – Active colitis pattern



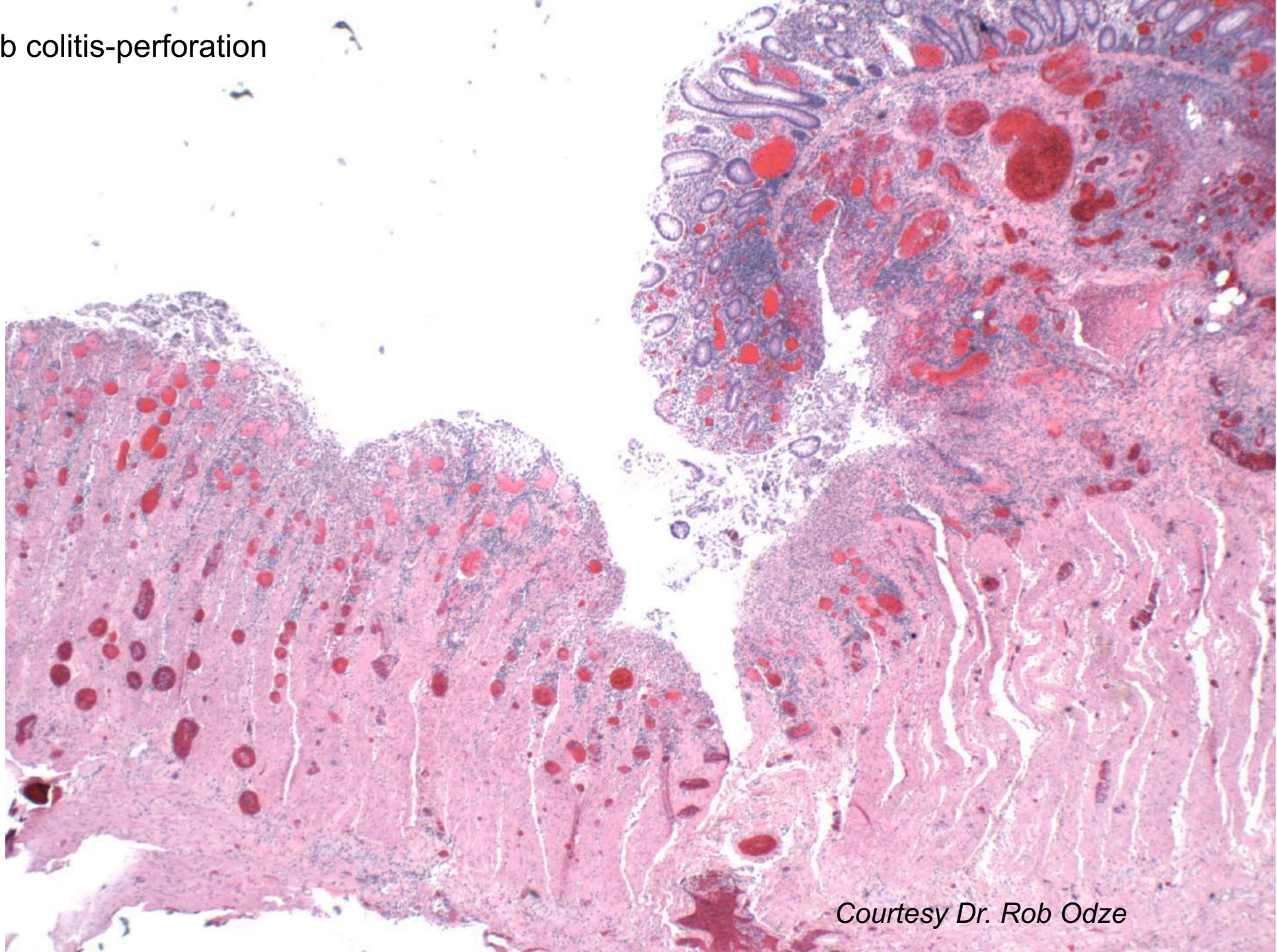
Combination therapy-mucosal distortion and crypt loss





S/P treatment with steroids

Ipilimumab colitis-perforation



Courtesy Dr. Rob Odze

Mycophenolate mofetil (Cellcept)

Use

- Maintenance immunosuppression, usually solid organ transplants

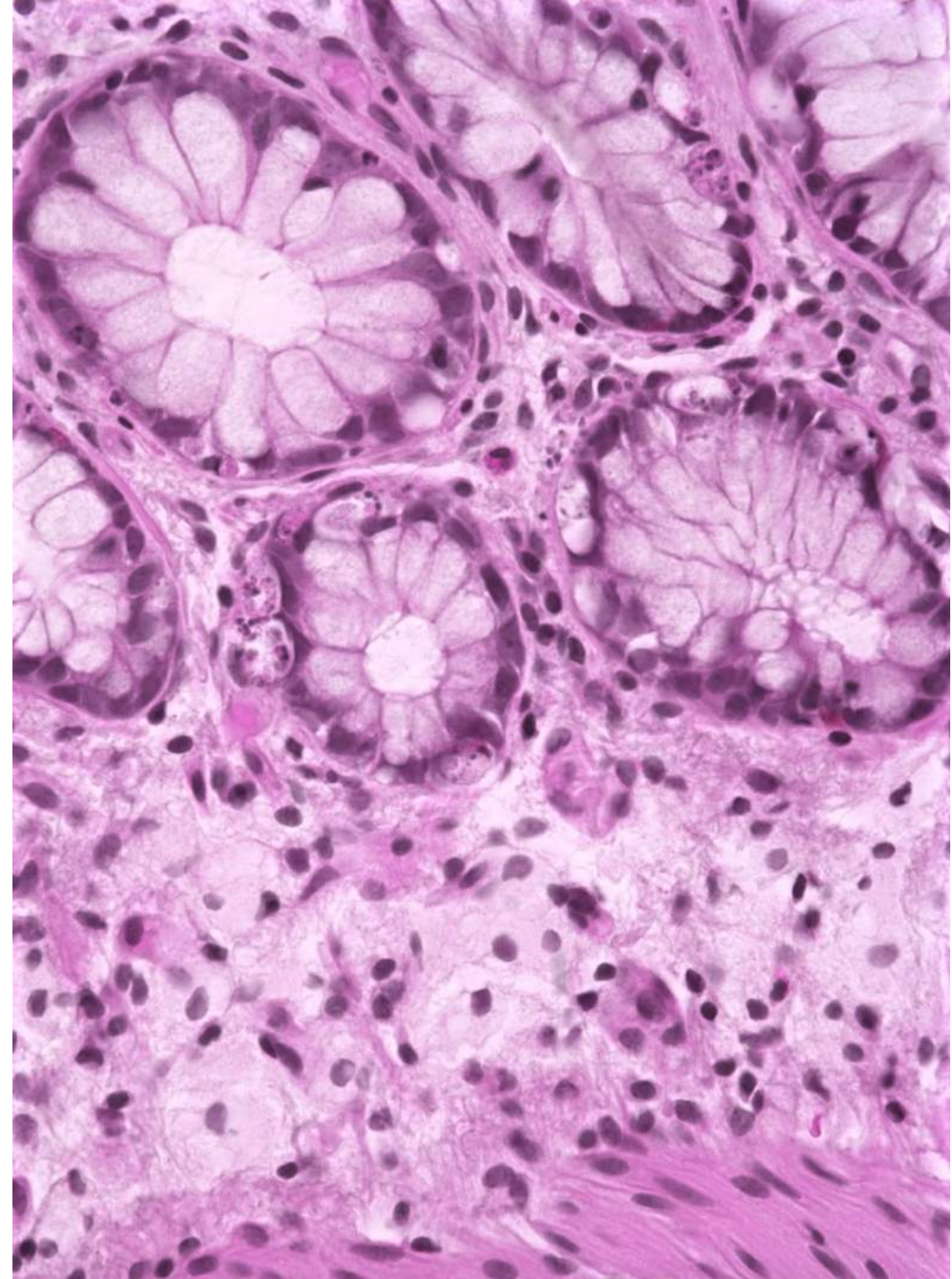
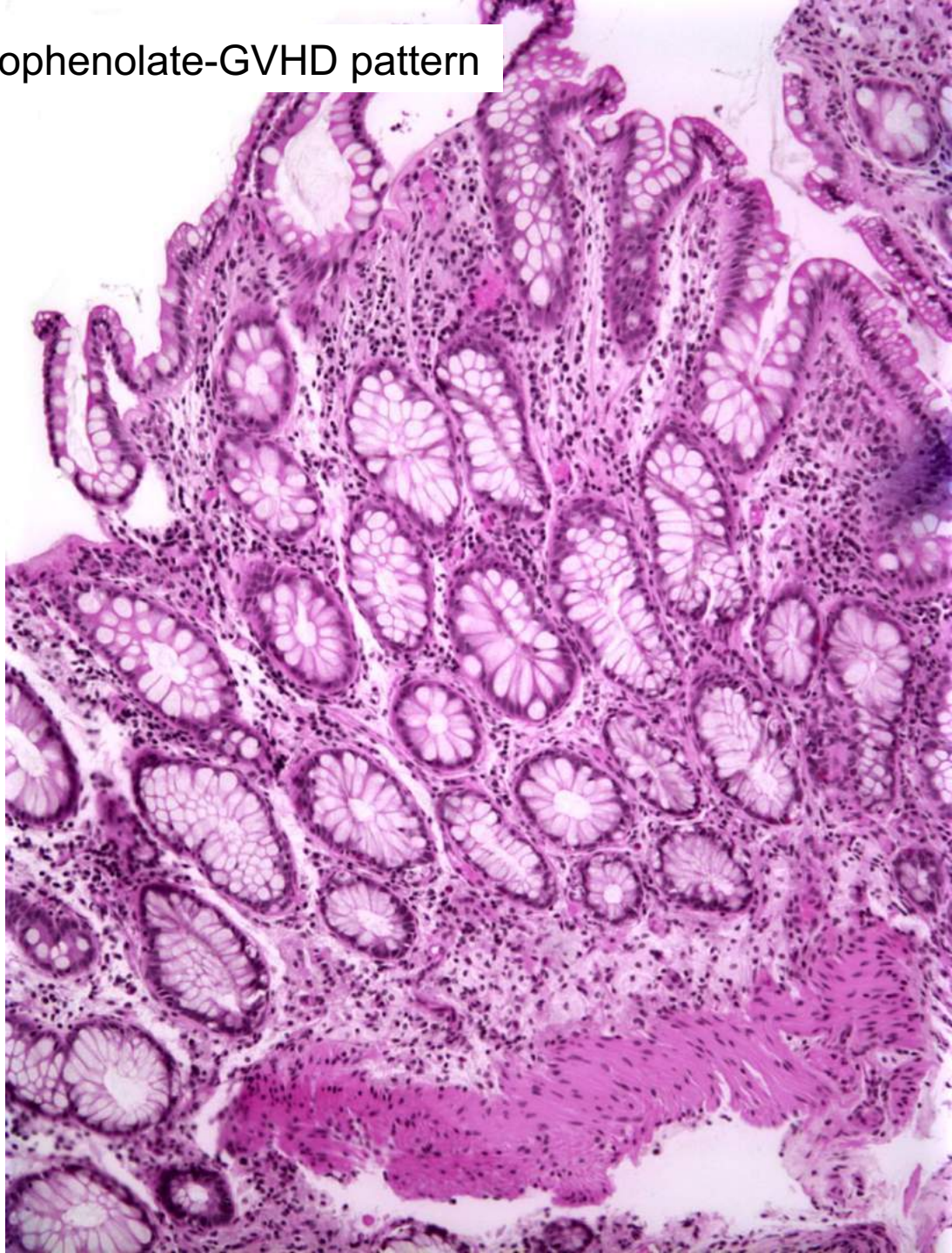
GI Toxicity

- Most common side effect
- Not dose dependent
- Worse with higher creatinine

Clinical

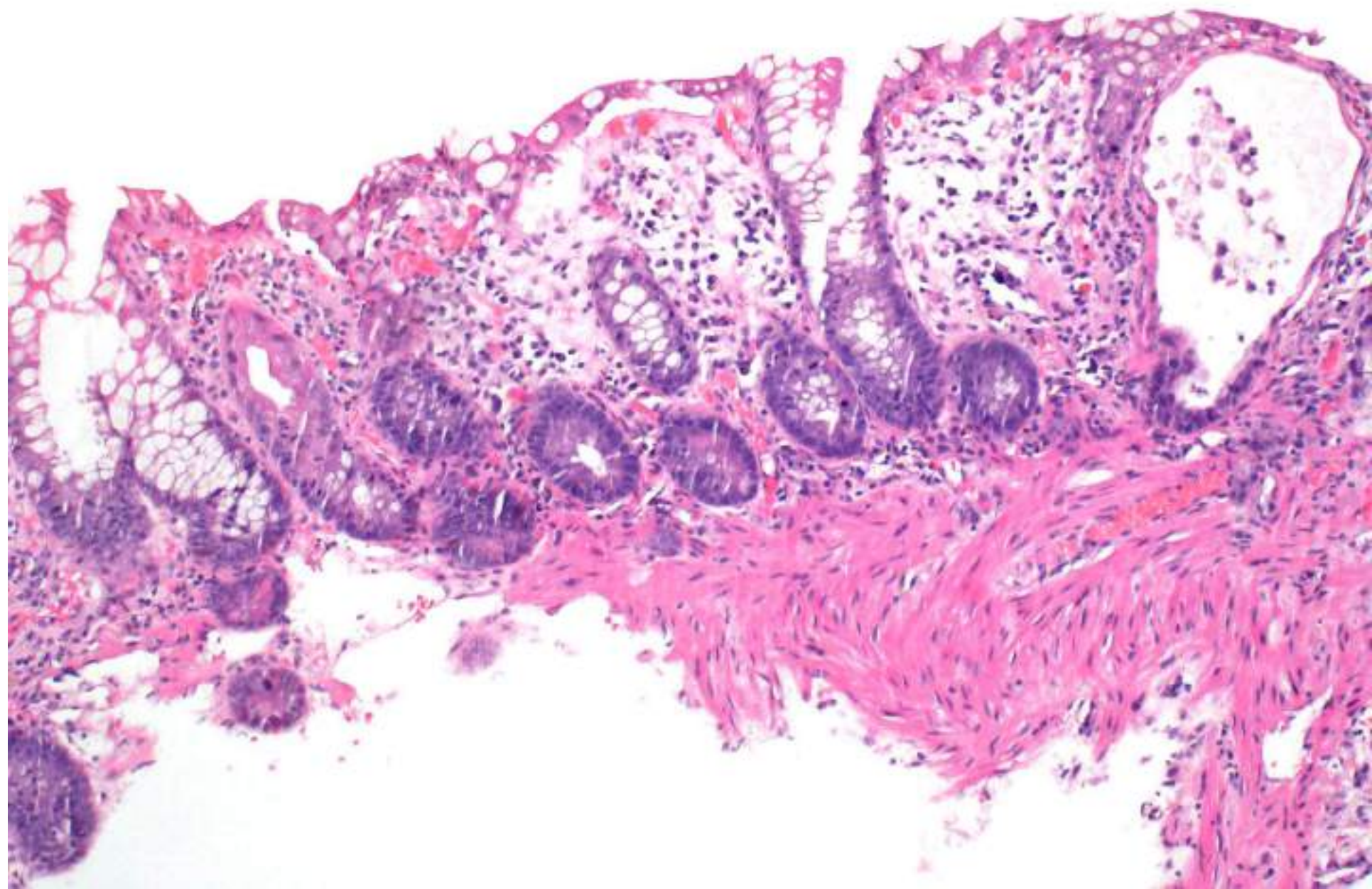
- Any part of gut
- Not dose dependent

Mycophenolate-GVHD pattern



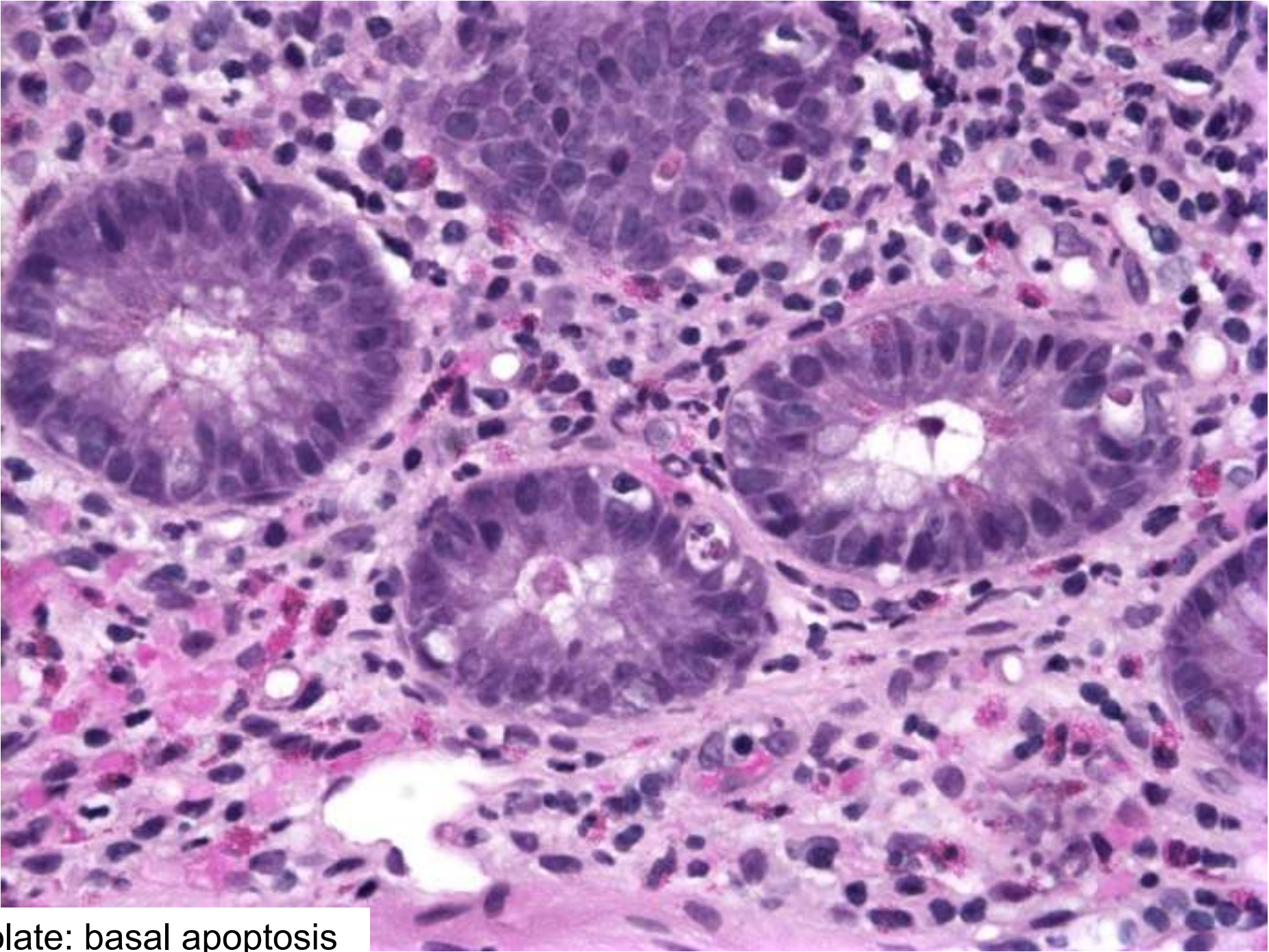


Mycophenolate-mild crypt distortion and dropout

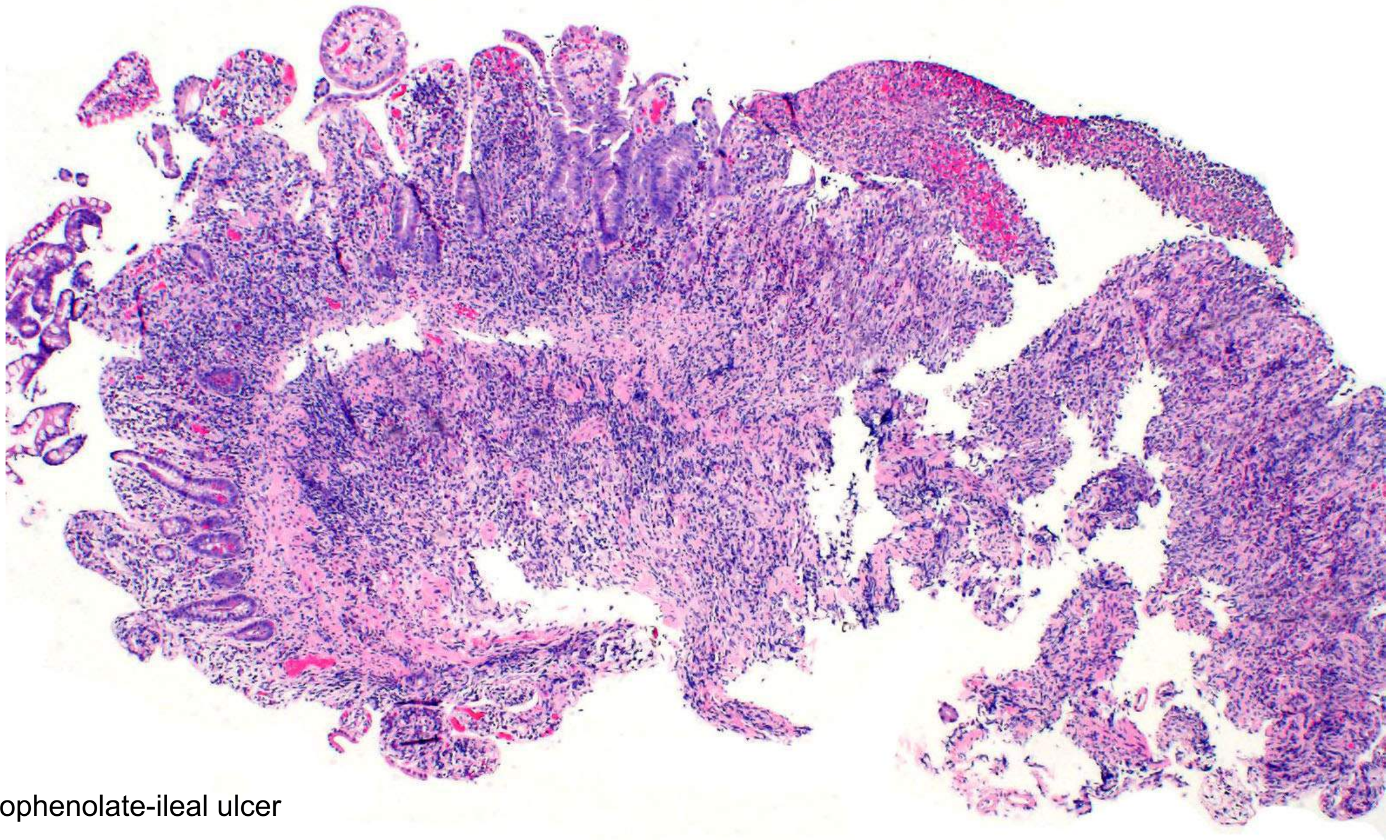


Mycophenolate: significant architectural distortion





Mycophenolate: basal apoptosis



Mycophenolate-ileal ulcer

Olmesartan

Clinical

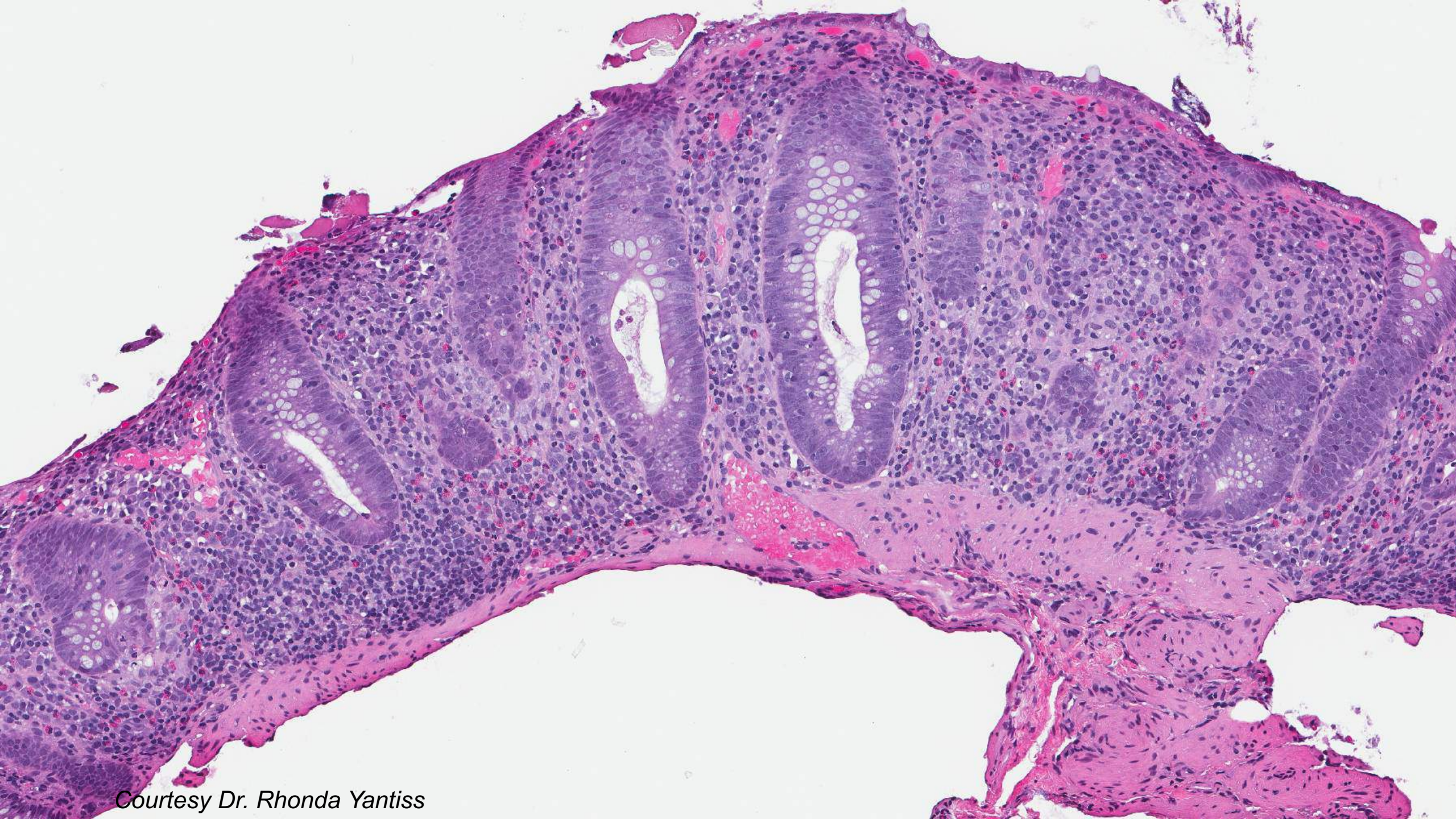
- Chronic nonbloody diarrhea
- Abdominal pain, nausea, vomiting
- Anemia, hypoalbuminemia

Onset

- Months to years after initiation of drug

Macroscopic

- Often normal exam
- Duodenum can mimic celiac disease



Courtesy Dr. Rhonda Yantiss

NSAID injury

Clinical

- May occur after only weeks of use
- Abdominal pain, cramps, bloody stool
- Massive bleeding, perforation

Other Risk Factors

- Older age
- Duration
- Polypharmacy

Macroscopic

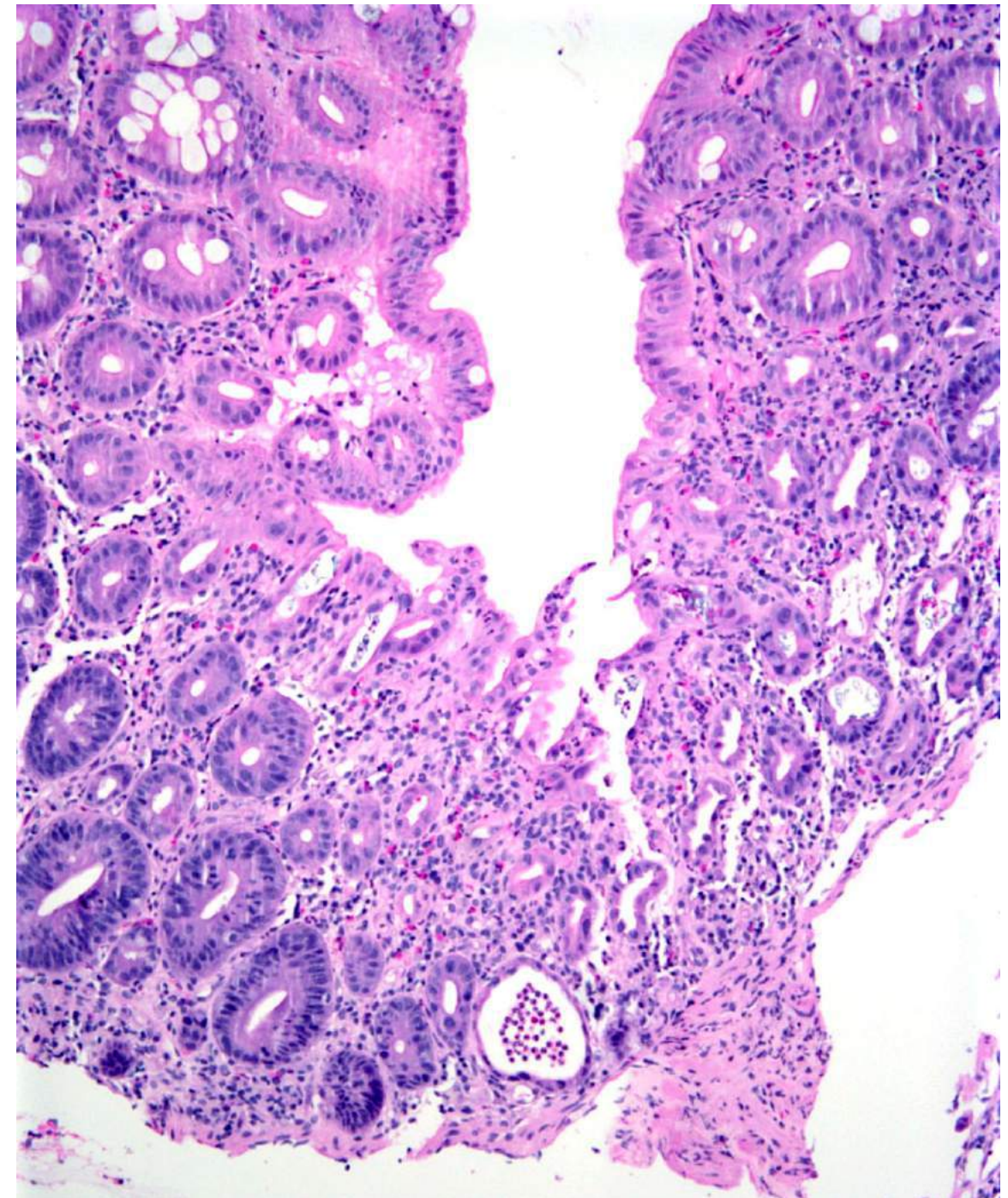
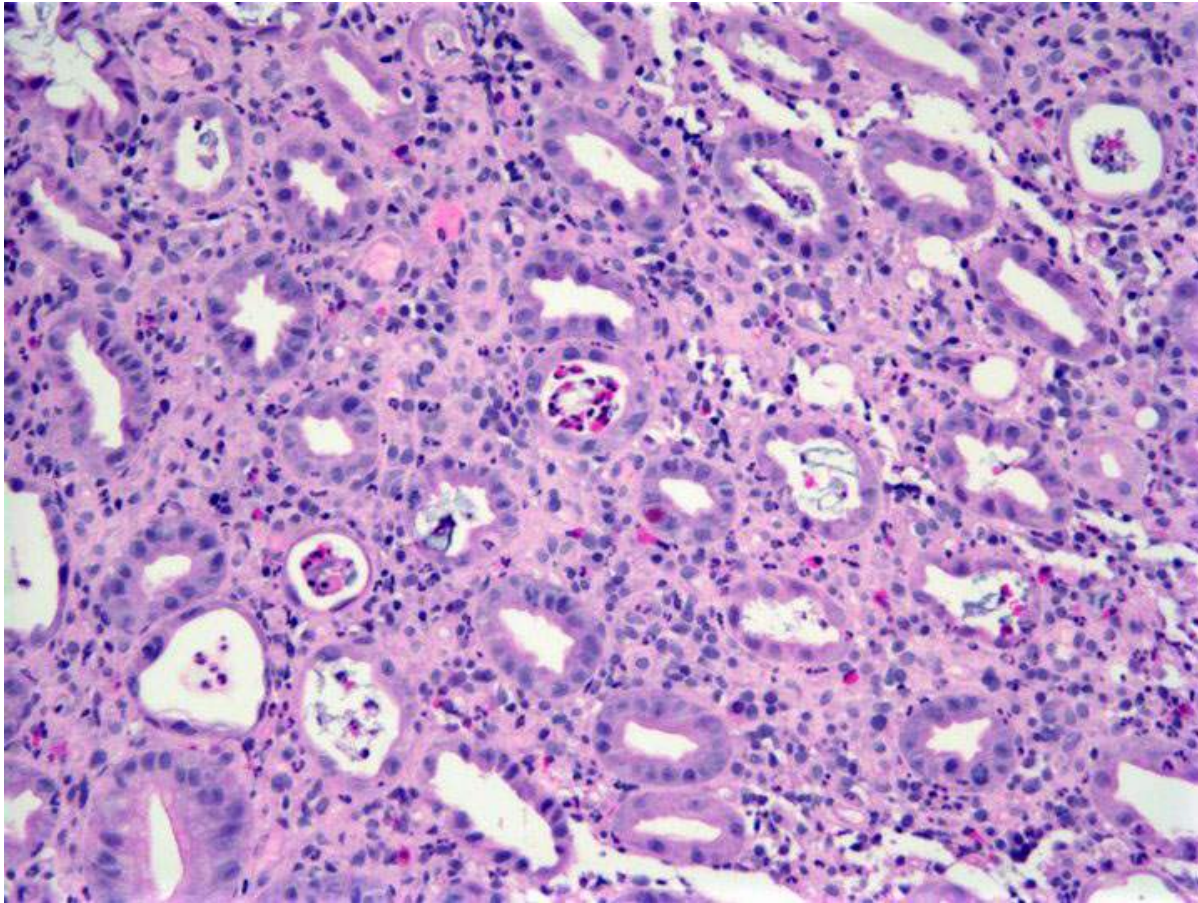
- Any part of gut but ileum most common
 - Friability
 - Ulcers
 - Diaphragm disease

Features that mimic IBD:

Patchy active colitis

Ileocecal ulcers/erosions

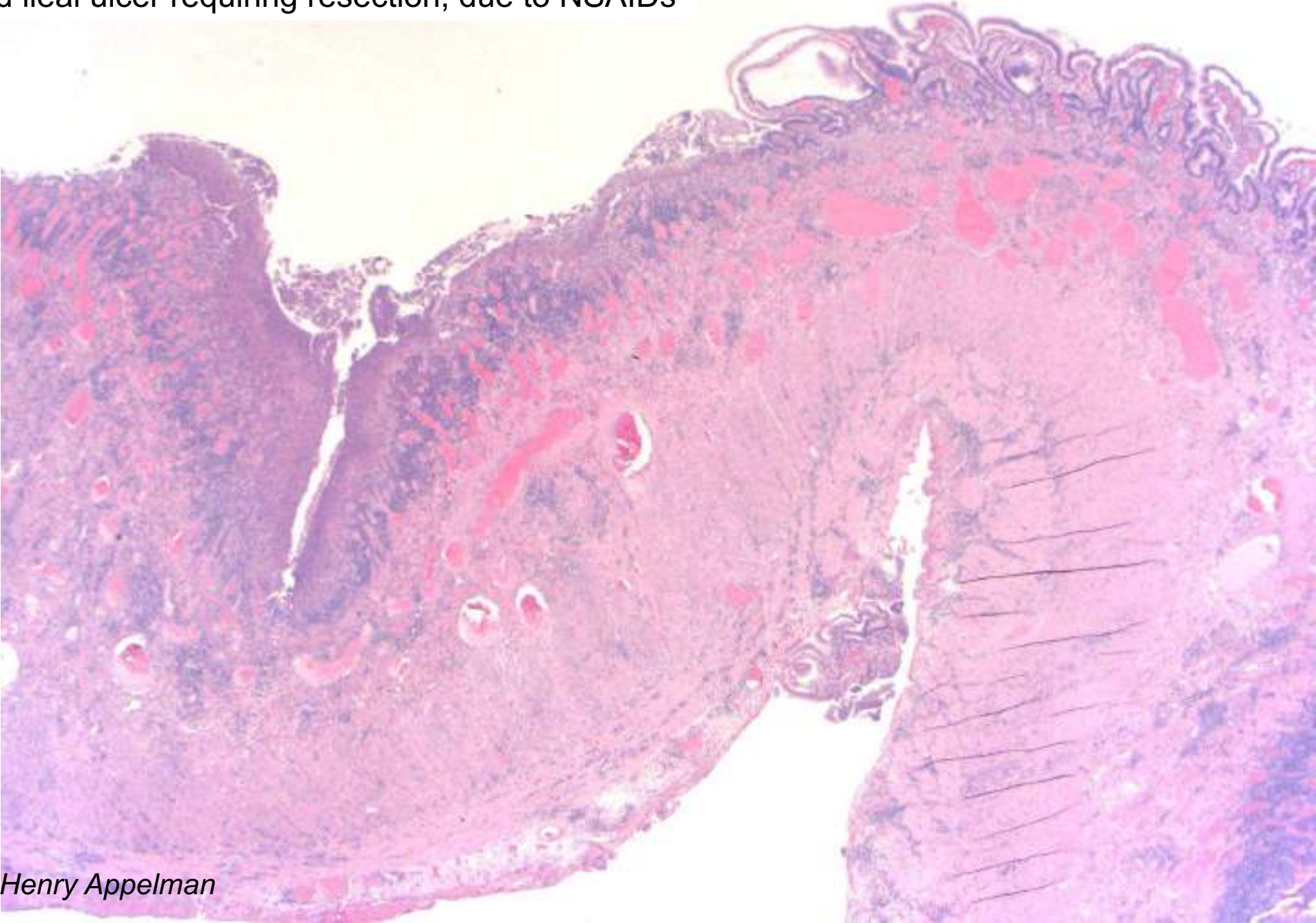
Focal architectural distortion



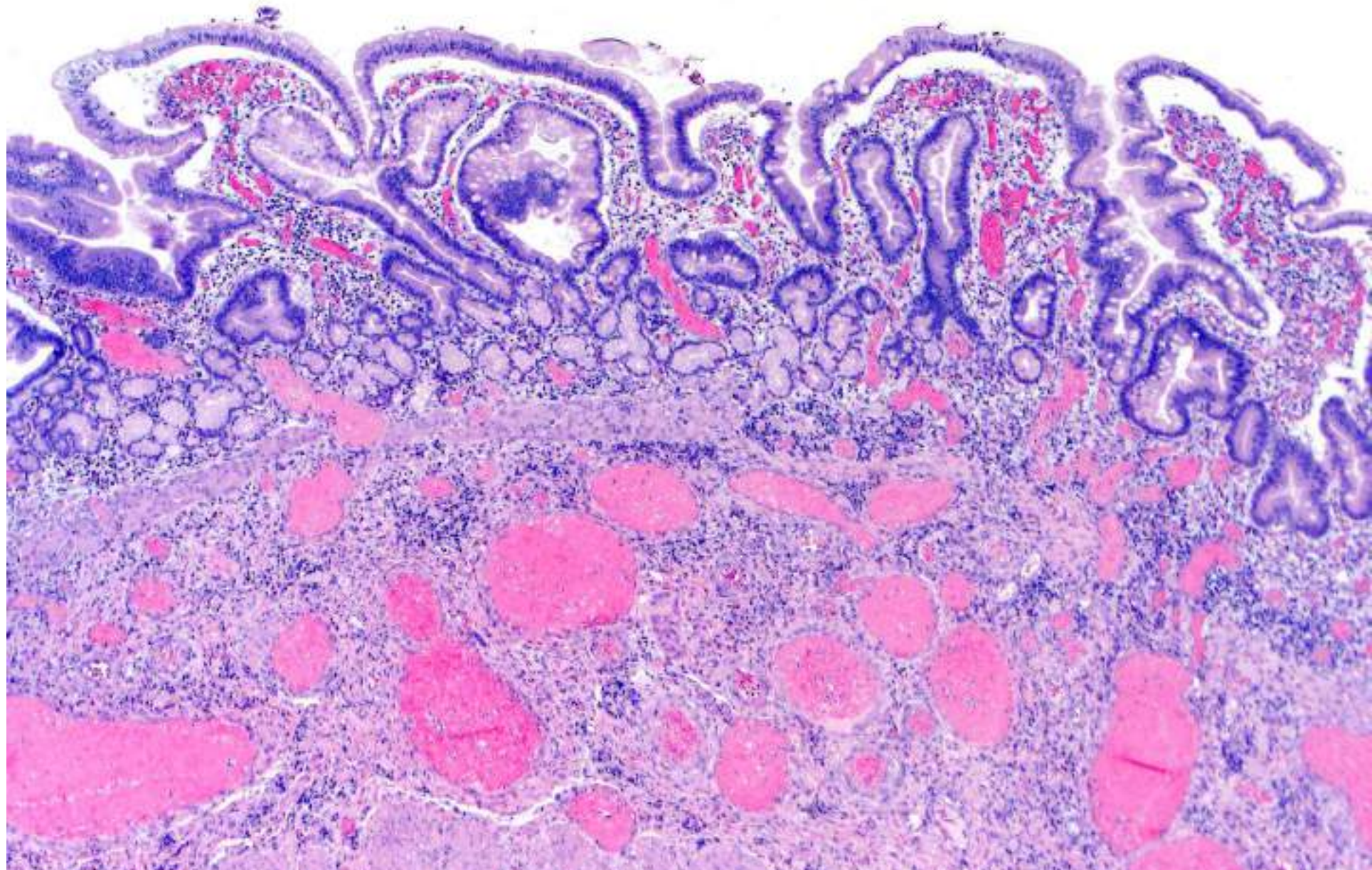
The isolated ileal ulcer

- What are the clinical implications?
 - About one-third of patients eventually develop Crohn's
 - Two-thirds are NSAID, infection, or idiopathic but they get better on their own
- Features that help diagnose Crohn's (which are almost never there)
 - Granulomas
 - Fibrosis
 - Architectural distortion
 - Pyloric gland metaplasia
 - **Persistent histologic abnormalities over time**

Large isolated ileal ulcer requiring resection, due to NSAIDs



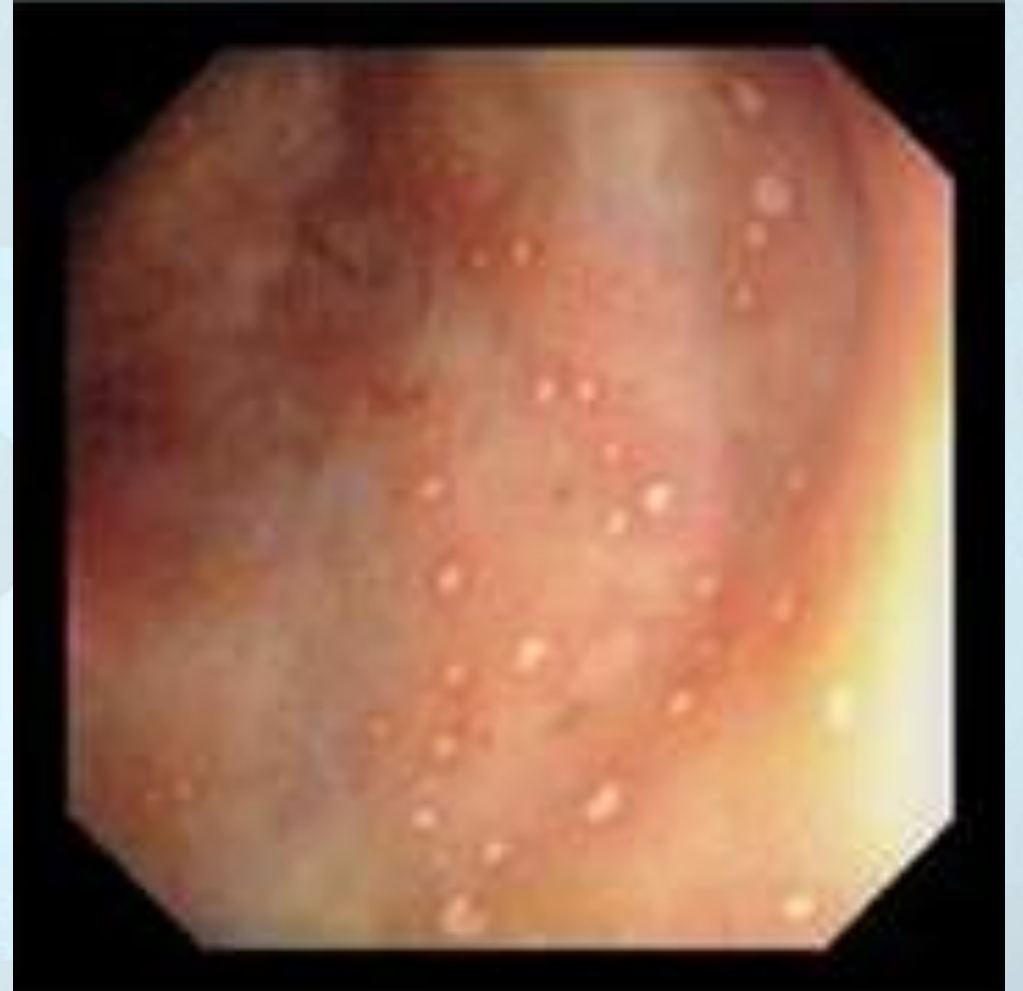
Courtesy Dr. Henry Appelman



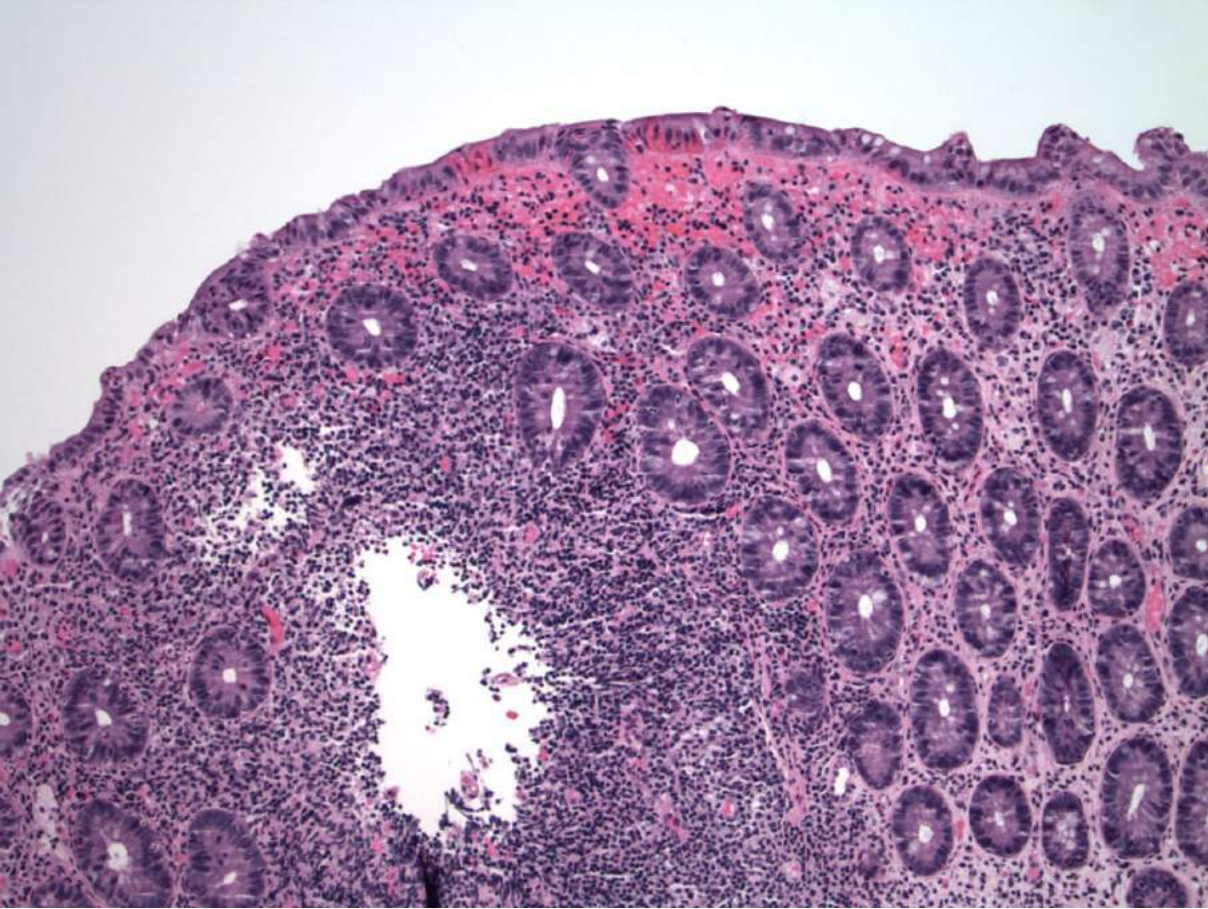
Lengeling RW et al. Ulcerative ileitis encountered at ileo-colonoscopy: likely role of nonsteroidal agents. Clin Gastroenterol Hepatol 2003;1:160-9.

Remember the bowel prep artifacts!

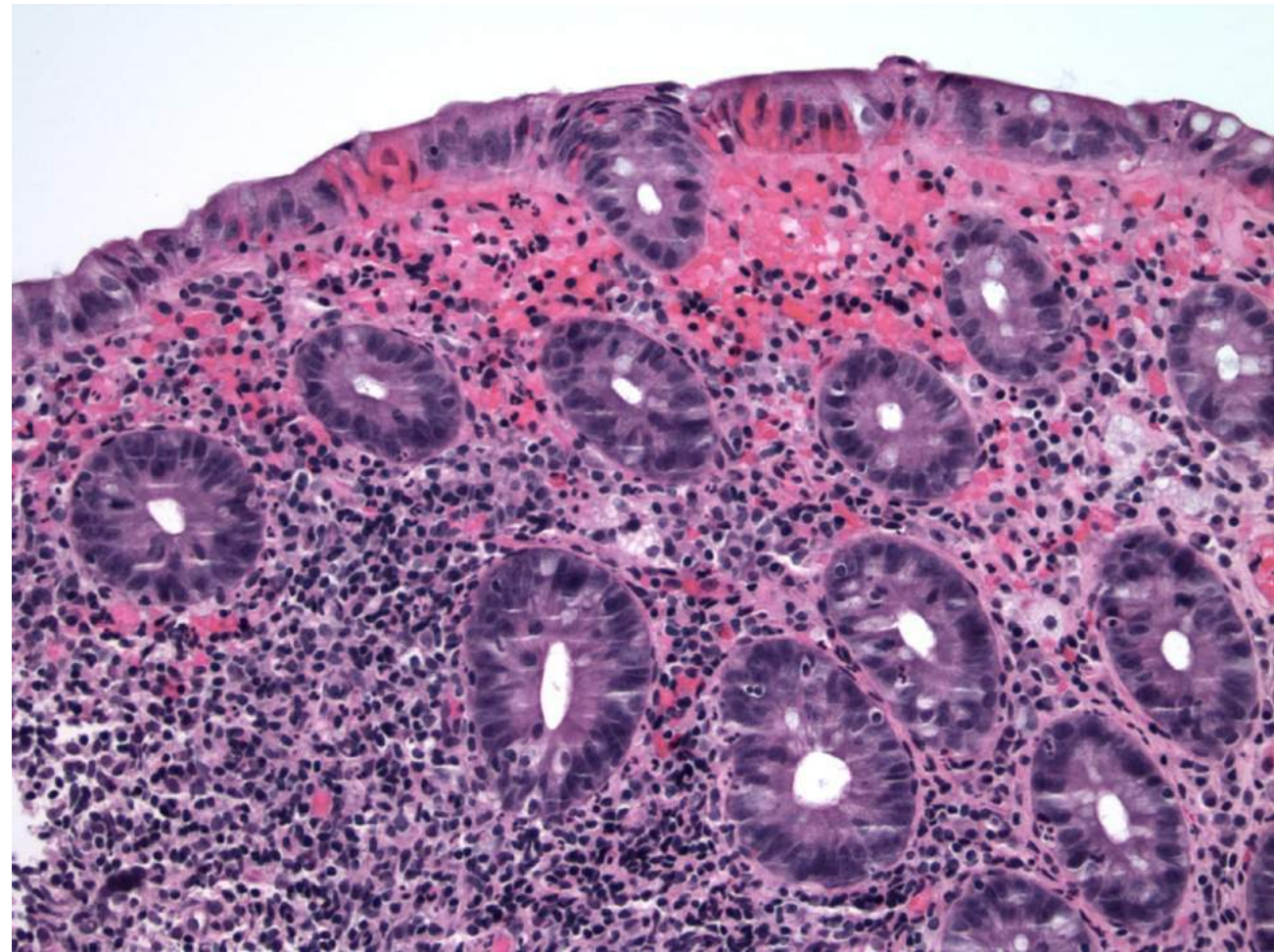
- Aphthous ulcers
- Cryptitis
- Superficial hemorrhage
- Apoptotic debris at surface



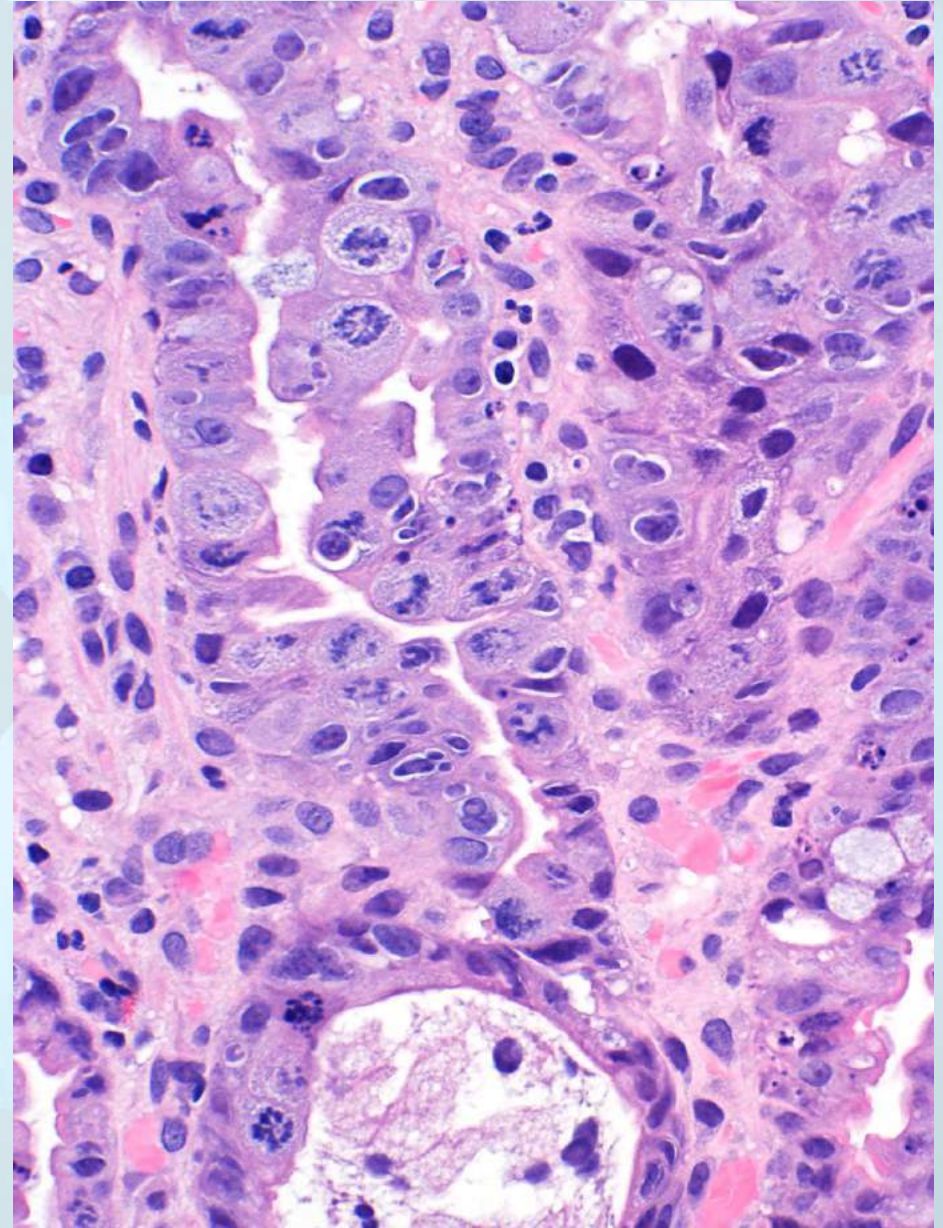
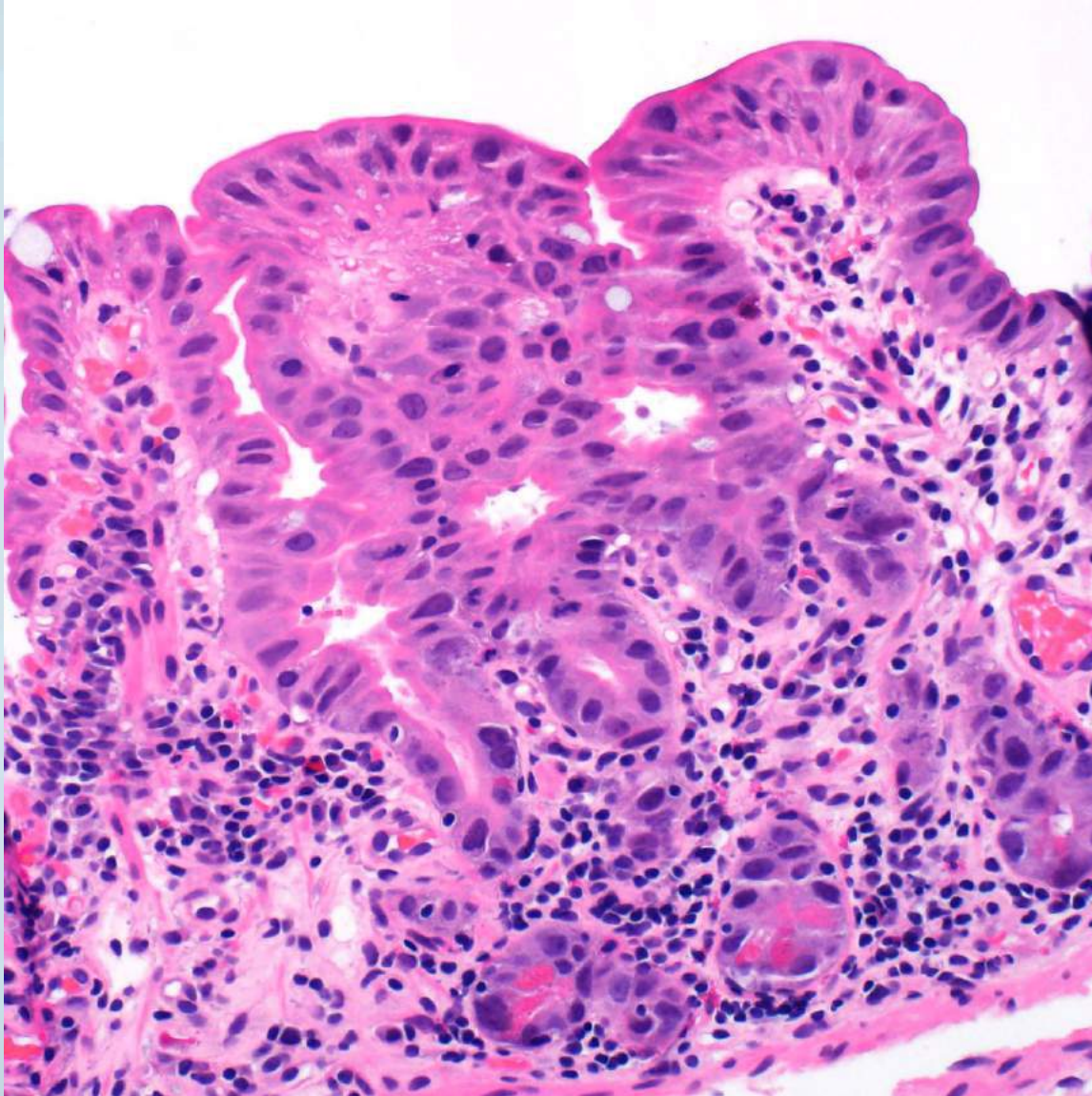
Courtesy Dr. Joel Greenson



Bowel prep artifact



Warning: Chemotherapy can mimic dysplasia

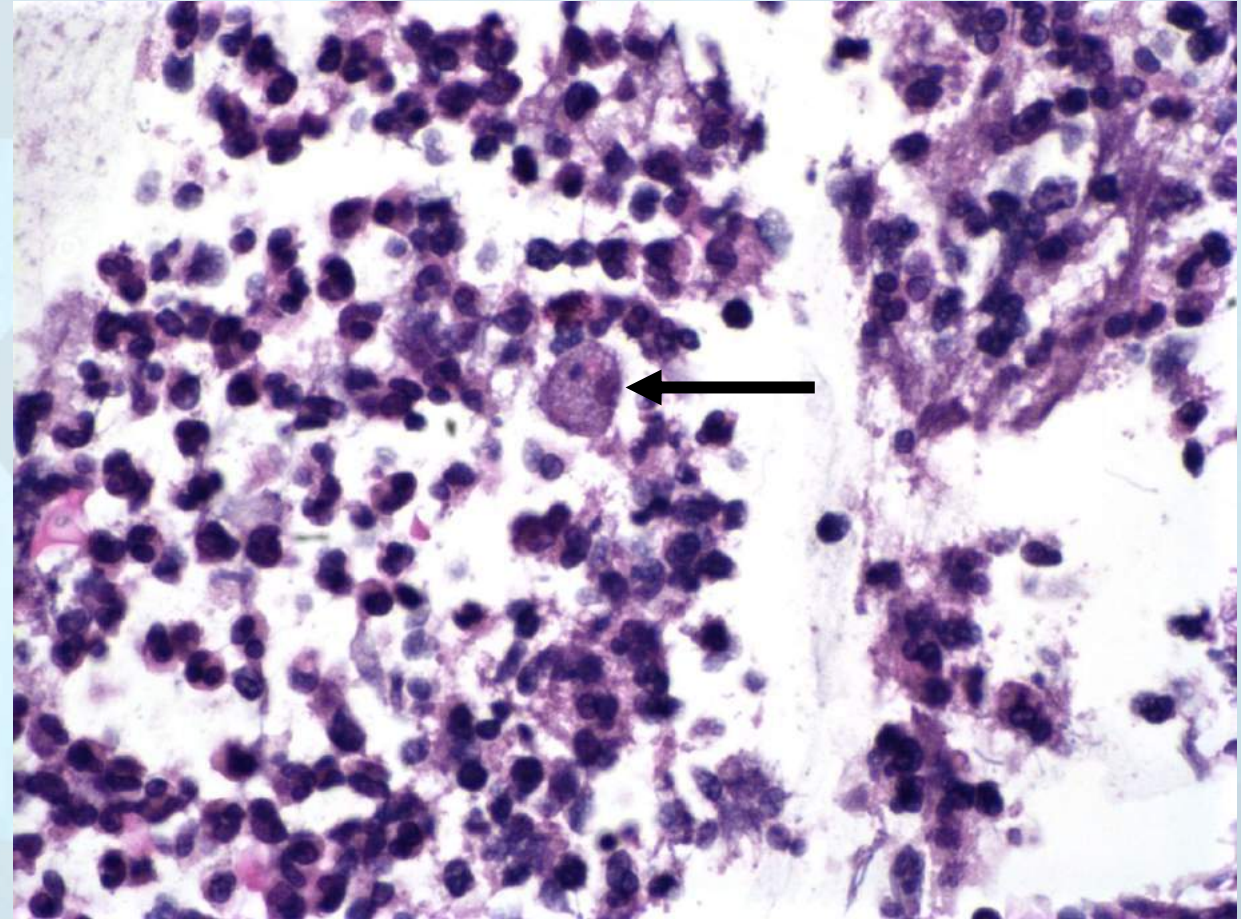




Alys ponders the diagnostic nuances of inflammatory bowel disease.

35 year old woman with diarrhea

- Endoscopy: "Colitis"
- Requisition: "Diarrhea"
- Path report: "Nonspecific chronic inflammation"



Amoebiasis in industrialized countries

- It happens
 - Well water
 - Immigrants
 - Homosexual male population
- Can mimic both Crohn's and ulcerative colitis
- Often mimics macrophages in colon biopsies



Classic amebiasis:

Flask shaped ulcers

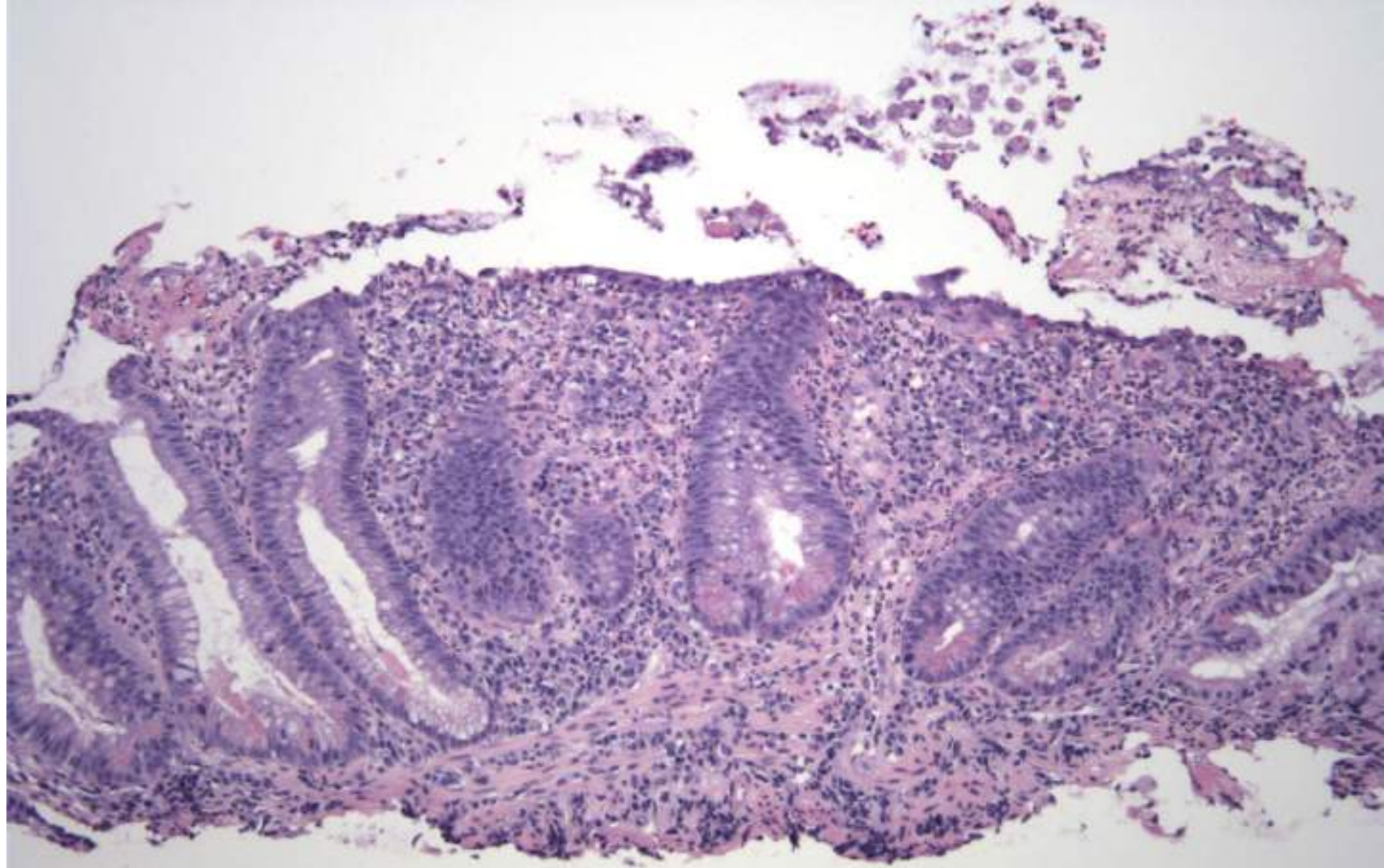
Right side

Atypical patterns:

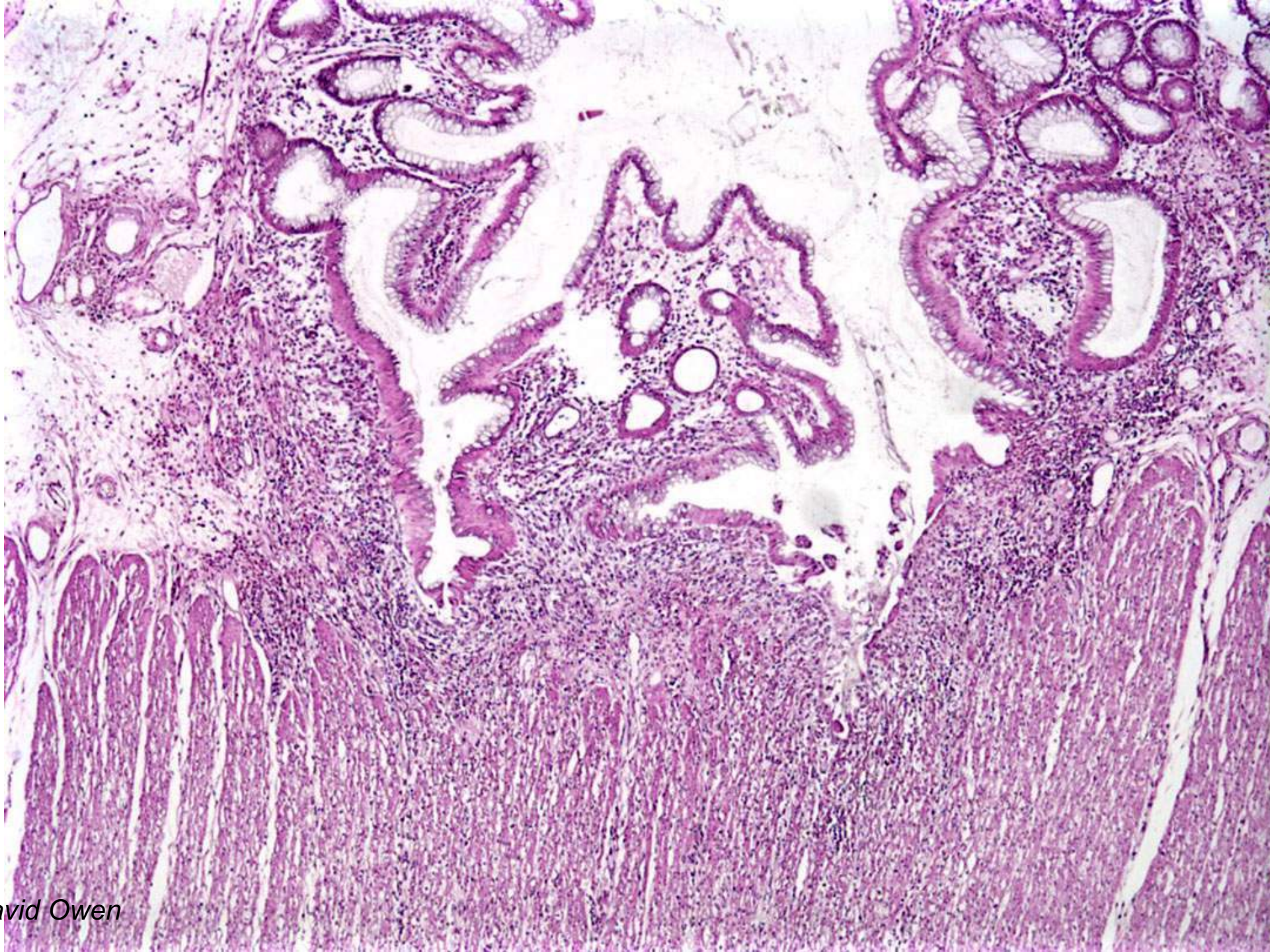
Pseudomembranous

Toxic megacolon

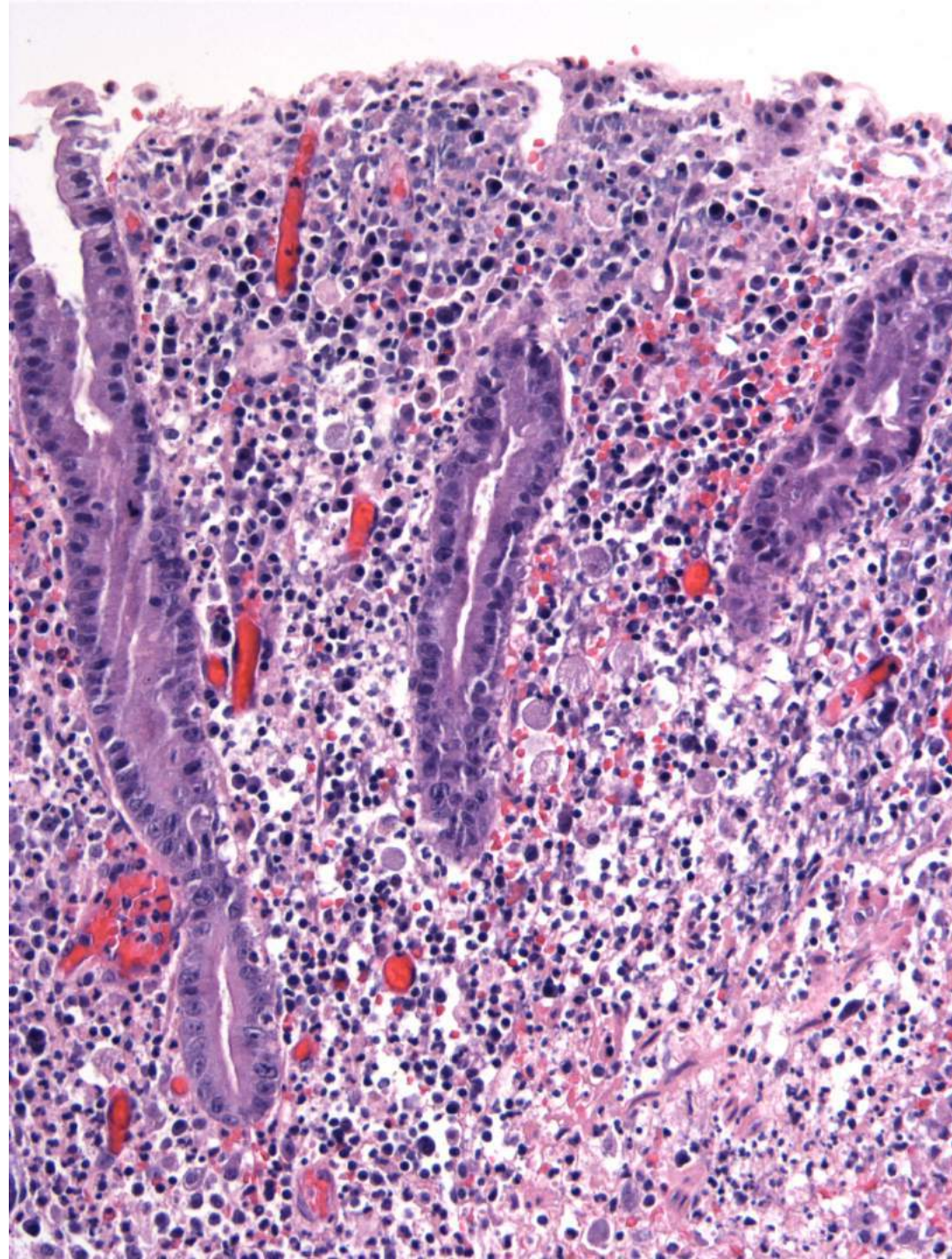
Crohn's- like



Courtesy Dr. Rhonda Yantiss



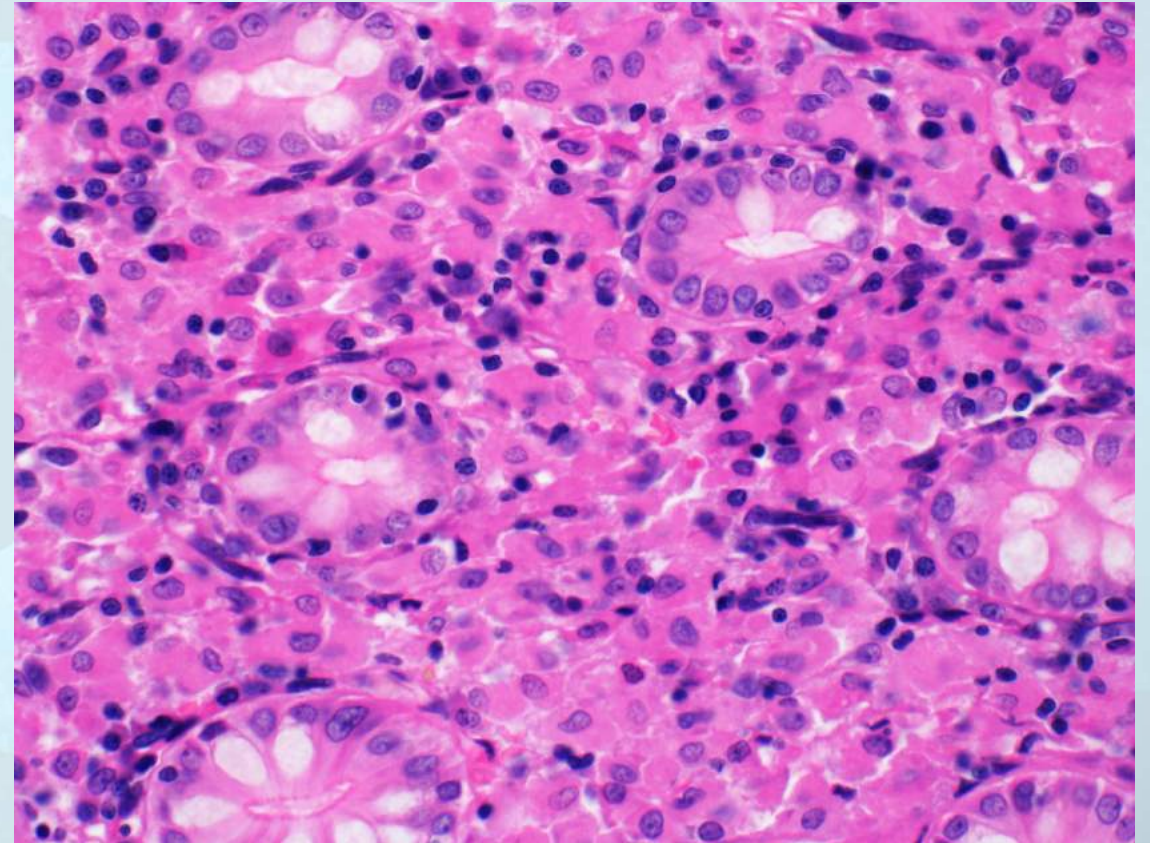
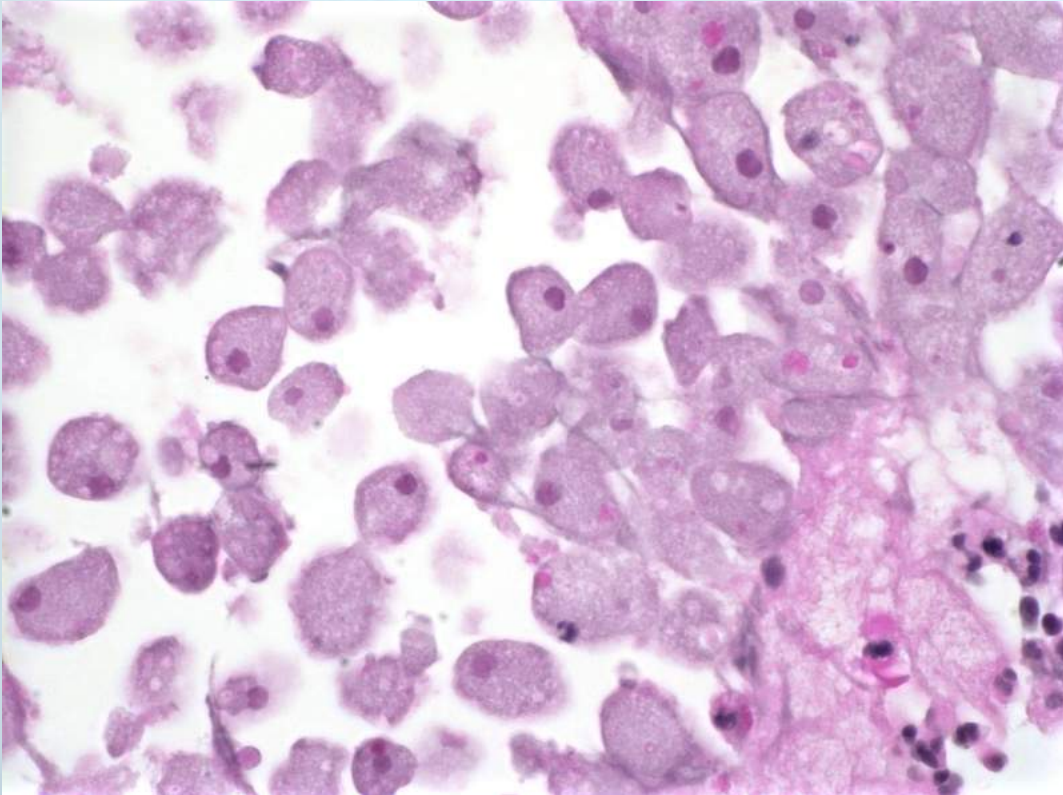
Courtesy Dr. David Owen



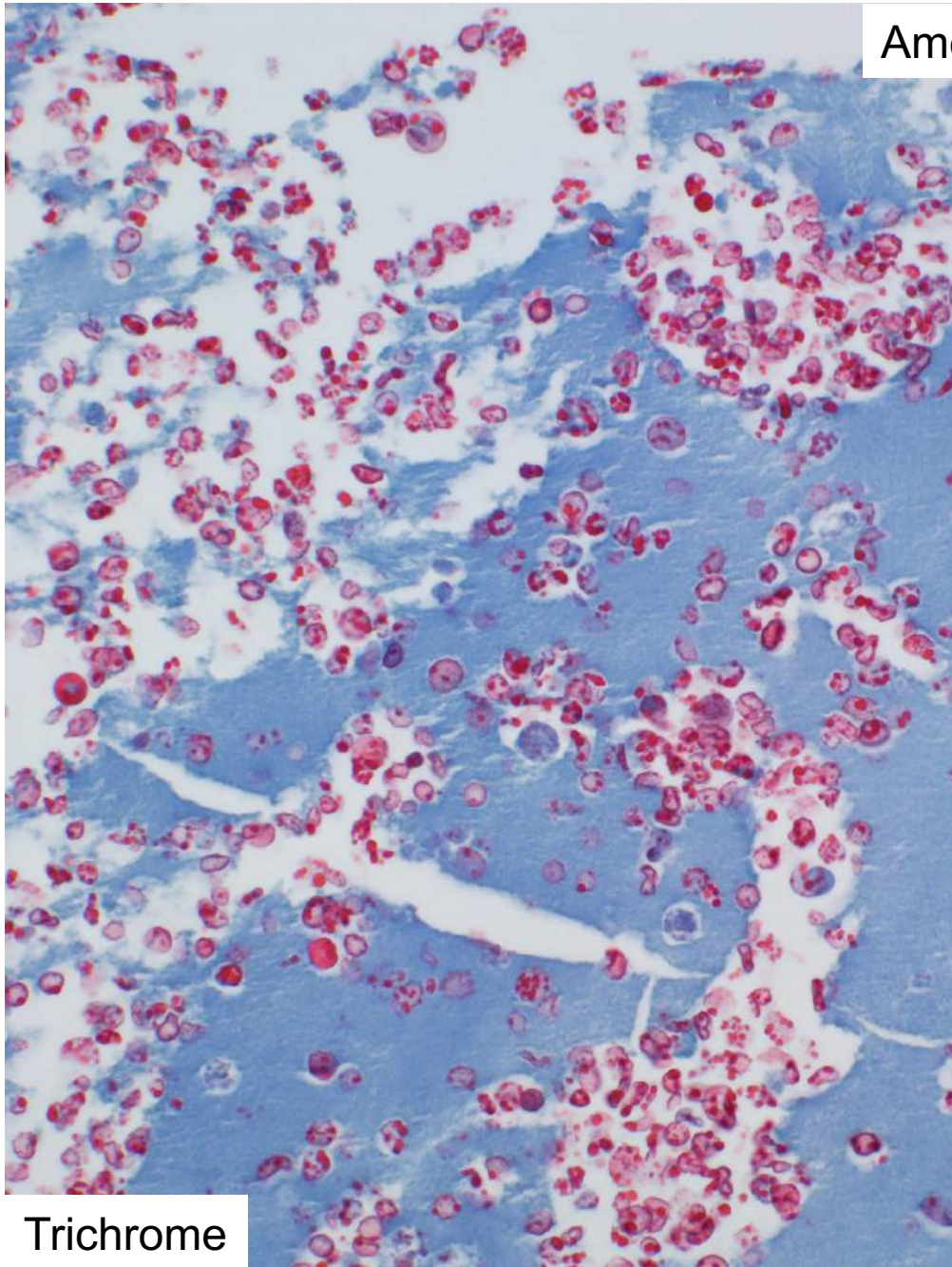
Courtesy Dr. Rhonda Yantiss

Amoebas vs. Macrophages

- Foamy cytoplasm
- Pale, round, eccentric nuclei with open chromatin
- Trichrome, PAS +
- CD68, CD163+
- Irregular, grooved nuclei
- Nucleoli



Amebic abscess



Trichrome



CD163

GI Infectious Diseases That Mimic Chronic Idiopathic Inflammatory Bowel Disease

More likely to mimic ulcerative colitis

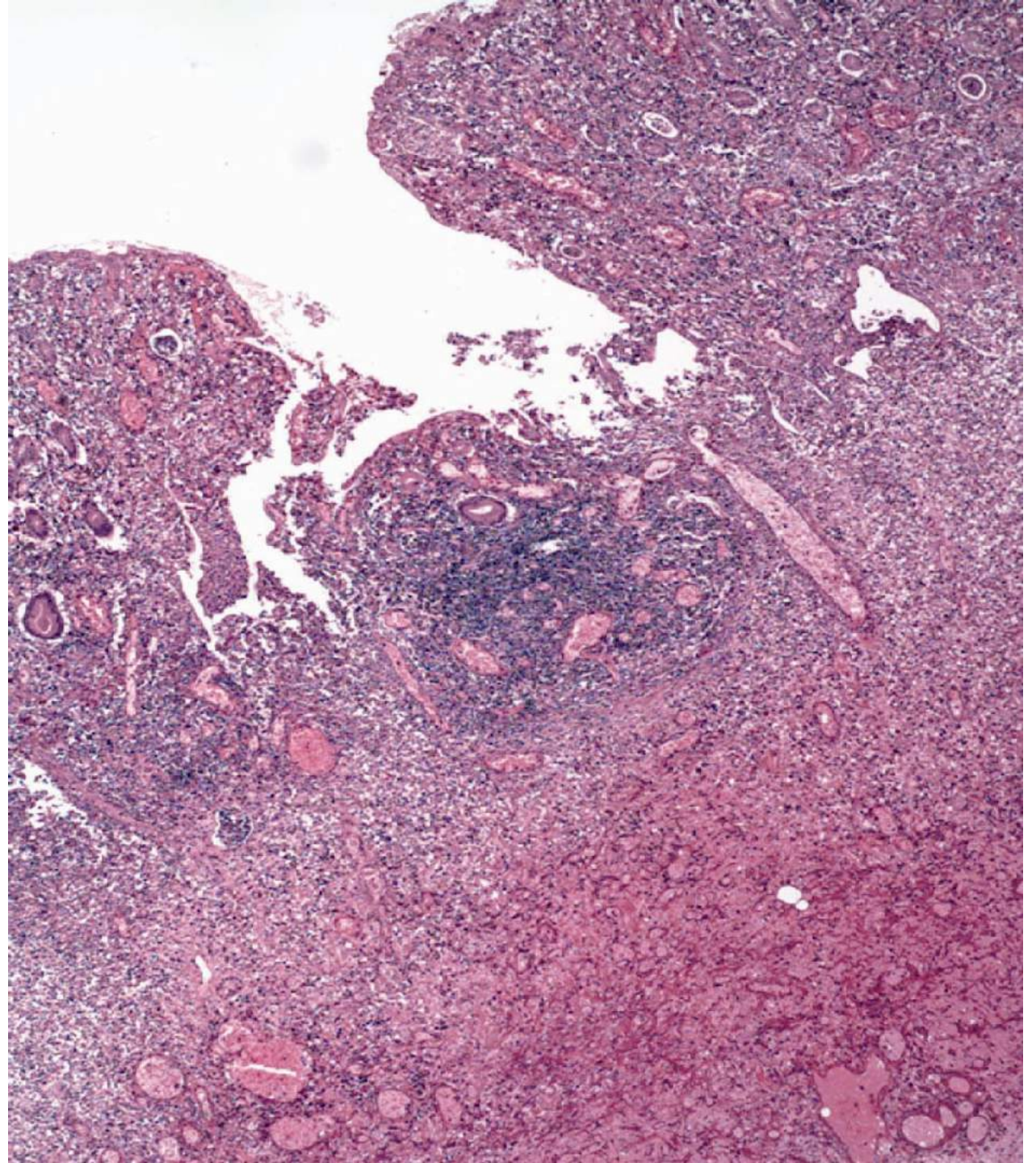
- Architectural distortion:
 - ***Salmonella*, *Shigella***
- Other histologic signs of chronicity
 - **Syphilis, LGV**
- Contiguous left side colorectal distribution
 - **All of the above**

More likely to mimic Crohn's disease

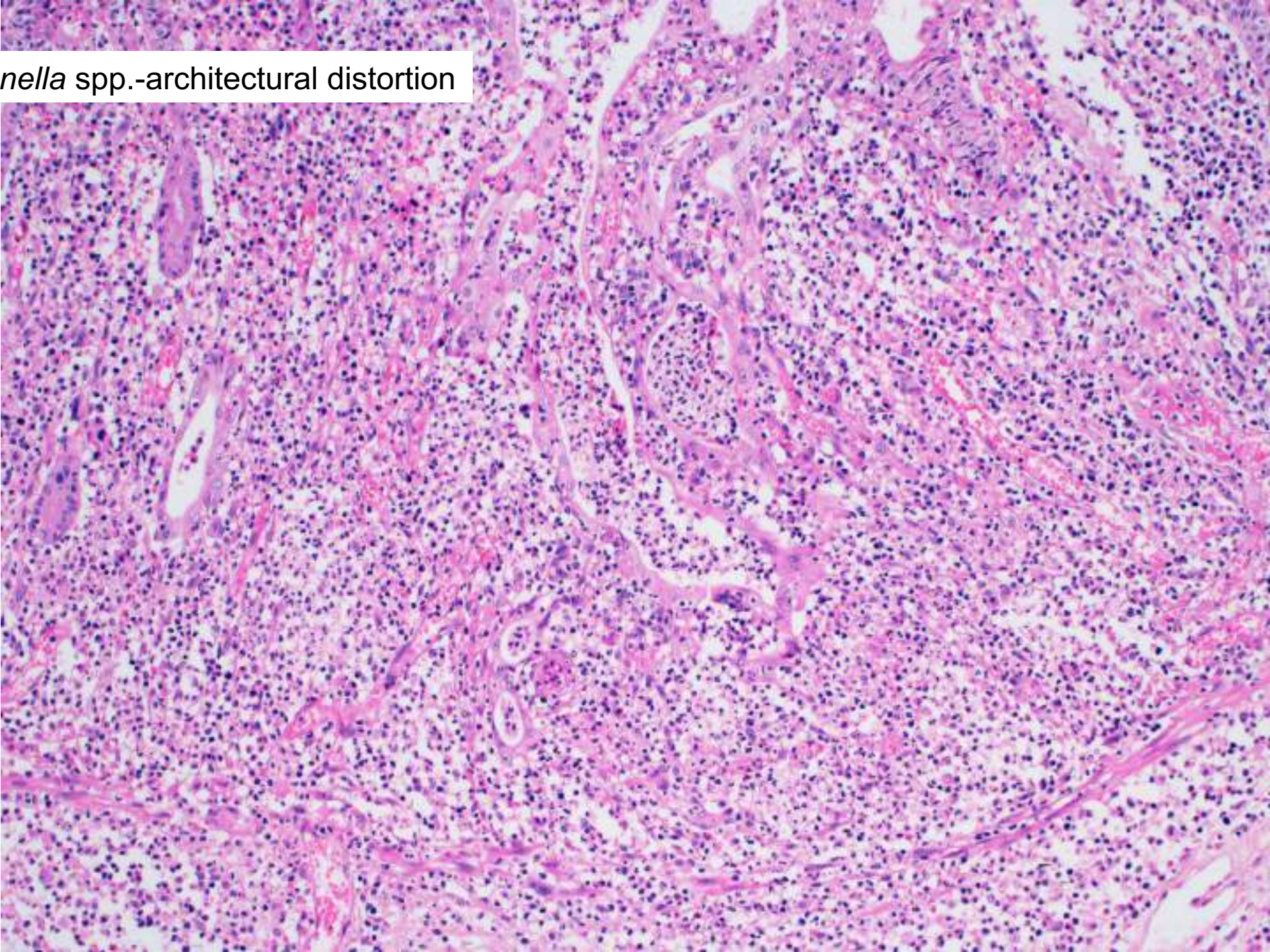
- Significant histologic overlap
 - ***Yersinia*, *Salmonella***
- Right side distribution
 - ***Yersinia*, *Salmonella*, *MTb*, *Aeromonas***
- Patchy architectural distortion
 - ***Salmonella*, *Aeromonas*, *Campylobacter***
- Granulomas
 - ***MTb*, *Yersinia***
- Skip lesions, deep ulcers
 - ***E. histolytica*, CMV**

Salmonella spp

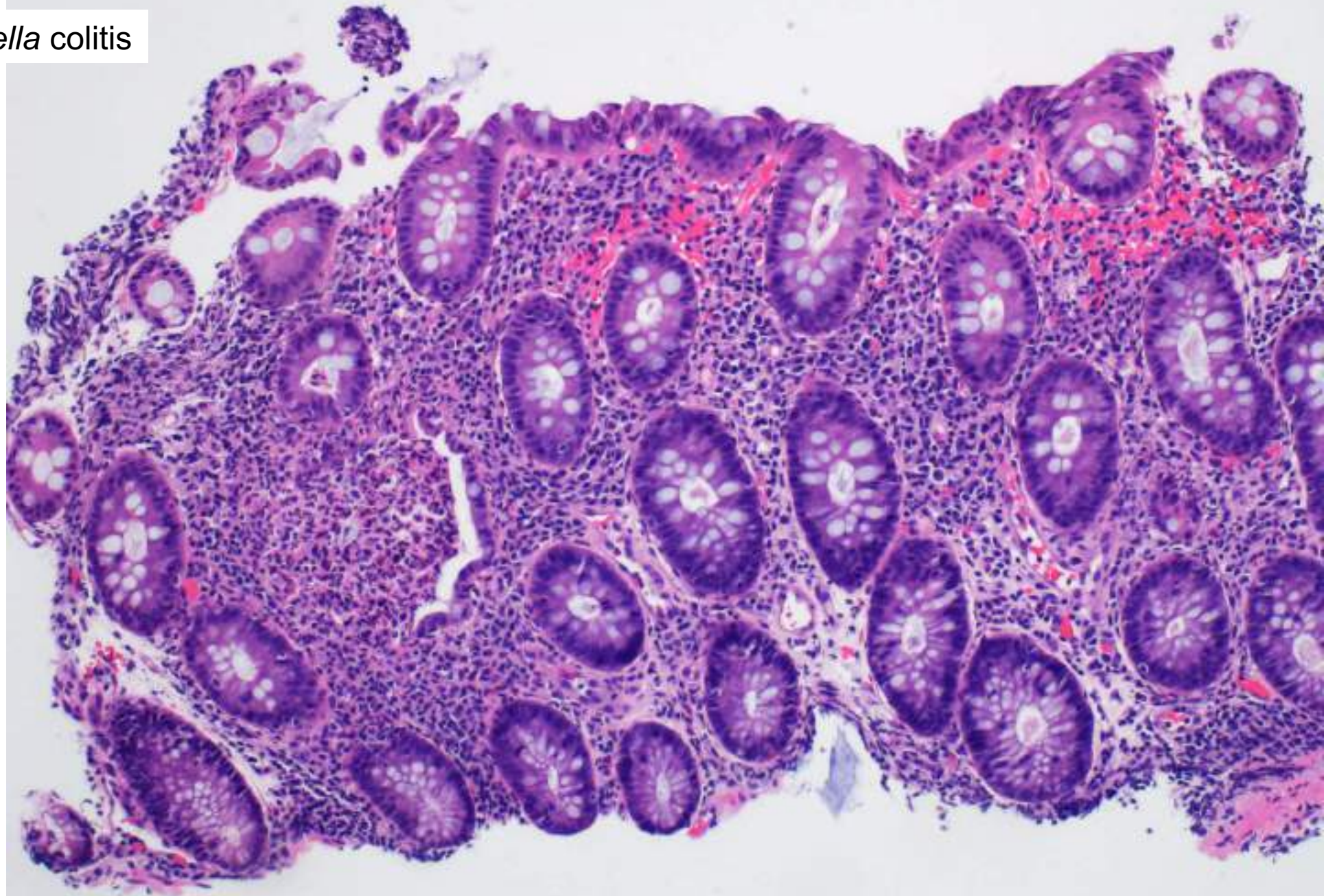
- Features that mimic CIIBD:
 - Aphthous, linear, and/or deep ulcers
 - Transmural inflammation
 - Crypt distortion
 - Right side distribution with ileal involvement may mimic Crohn's in particular

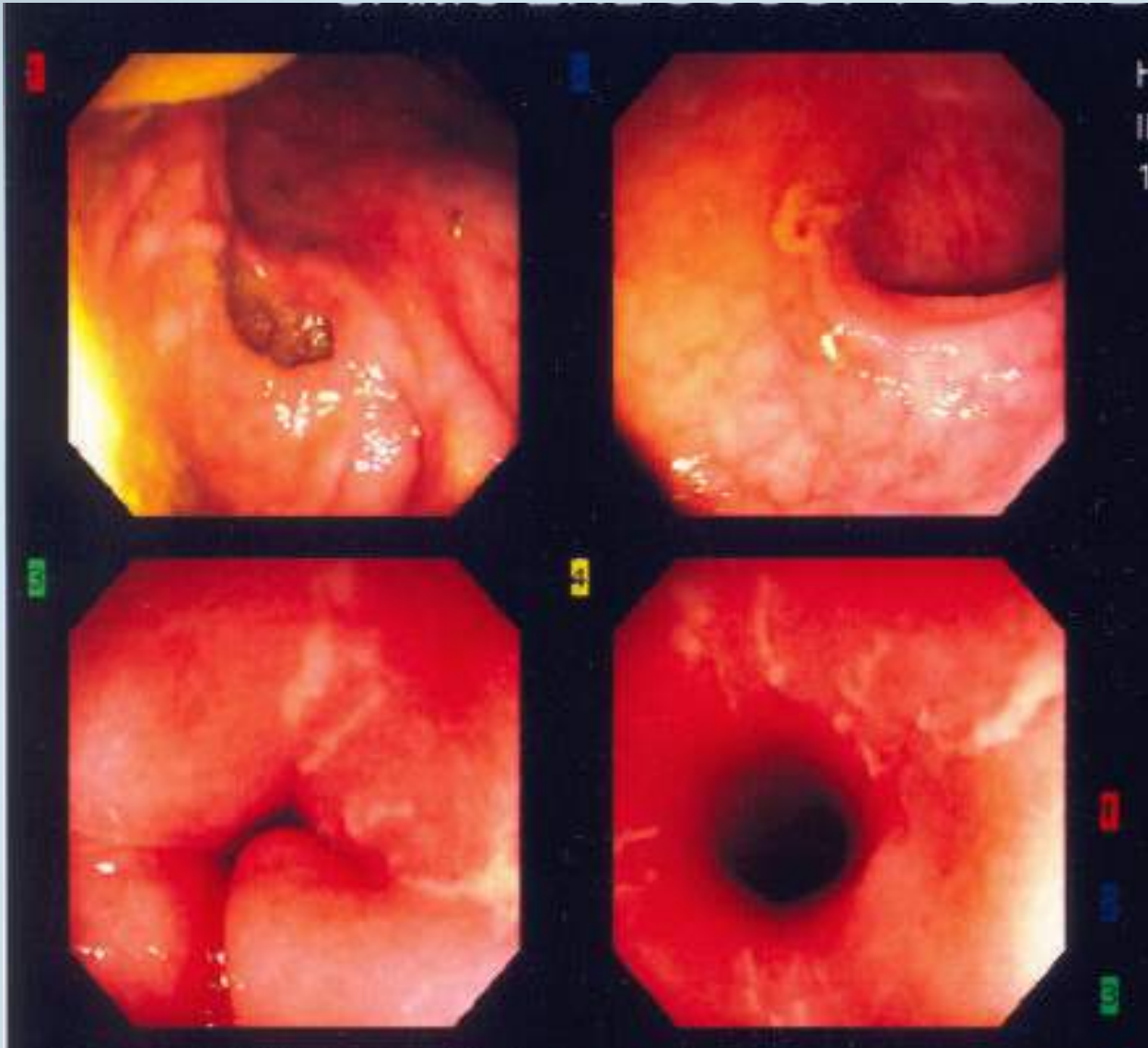


Salmonella spp.-architectural distortion



Salmonella colitis





Yersinia spp

One of the most common causes of bacterial enterocolitis in North America and Europe

Food and water borne; loves cold temps

Favors *Yersinia*:

Isolated
appendiceal
involvement

Acute onset of
symptoms

Favors Crohn's:

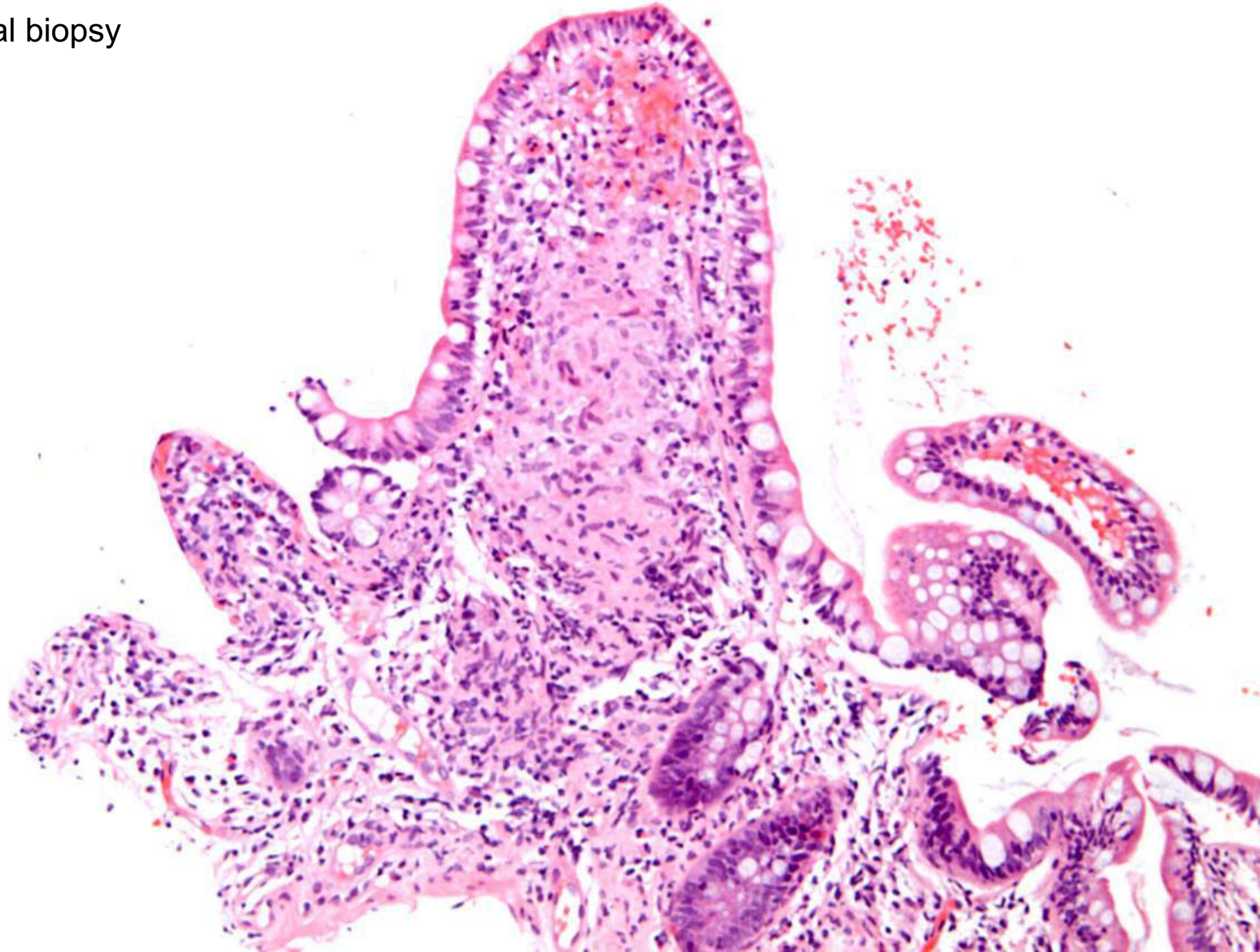
Fistulas

Multiple sites of involvement

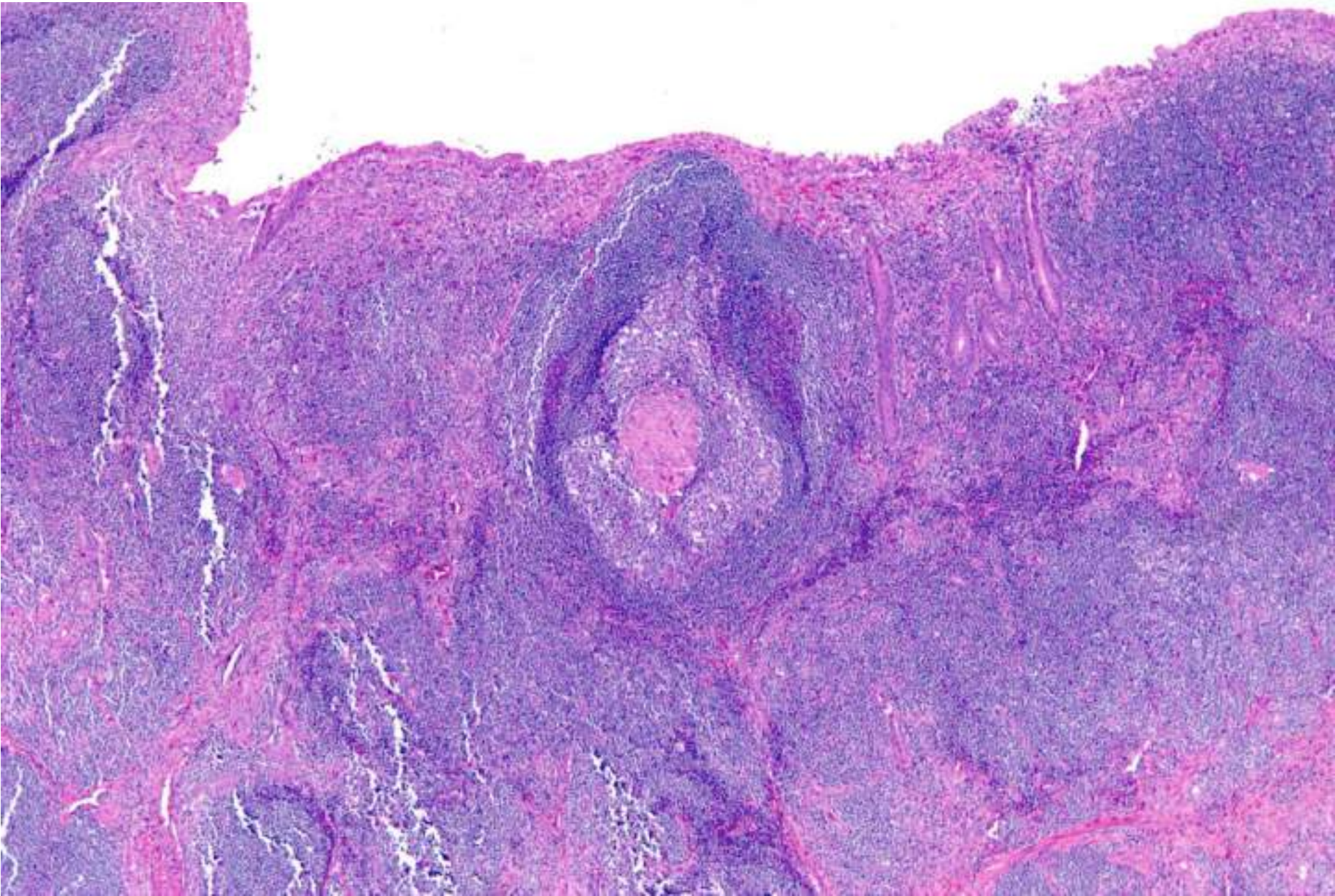
Chronic symptoms

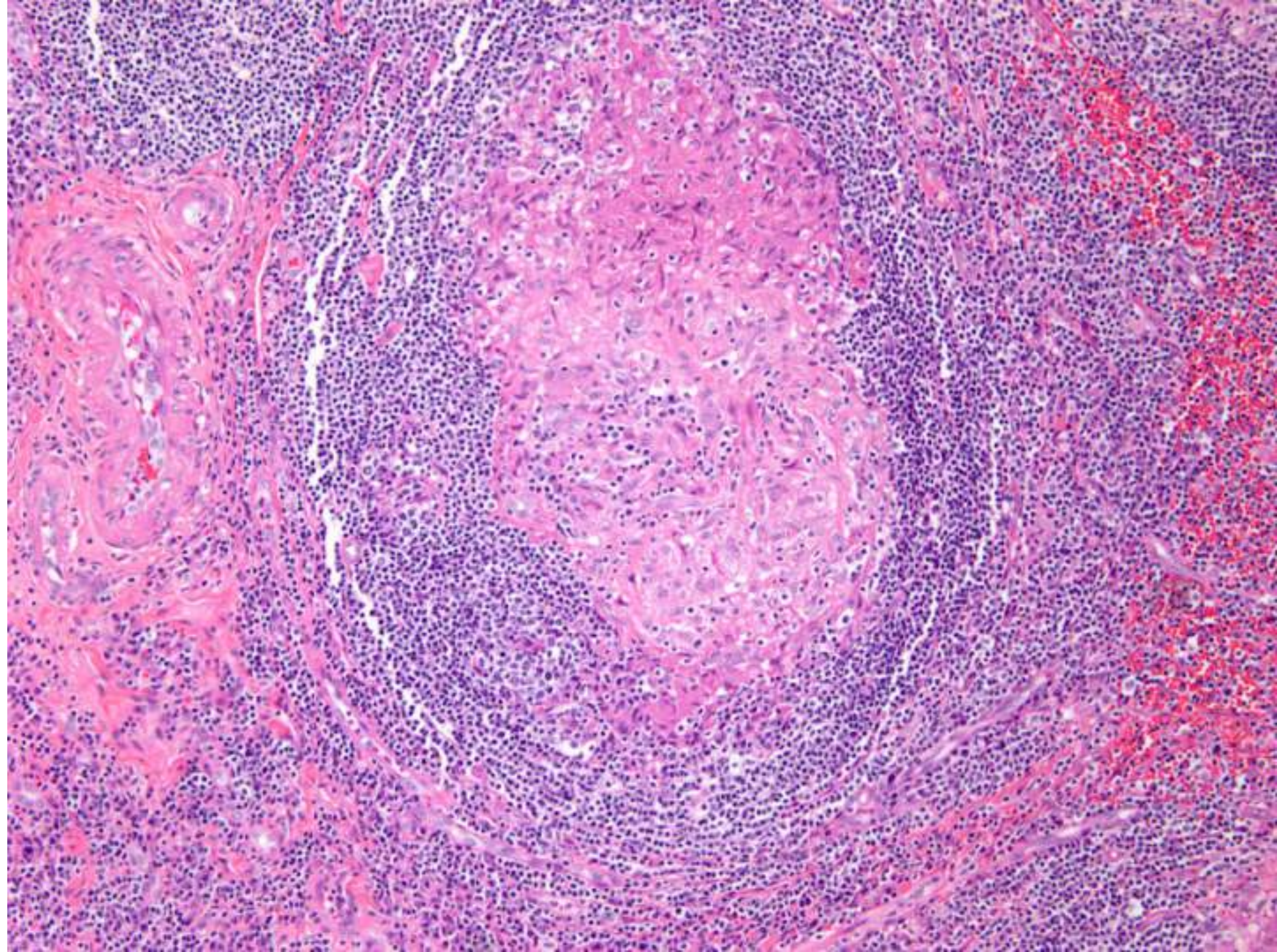
- 60M with diarrhea, abdominal pain; ileal and right side patchy inflammation and ulcers

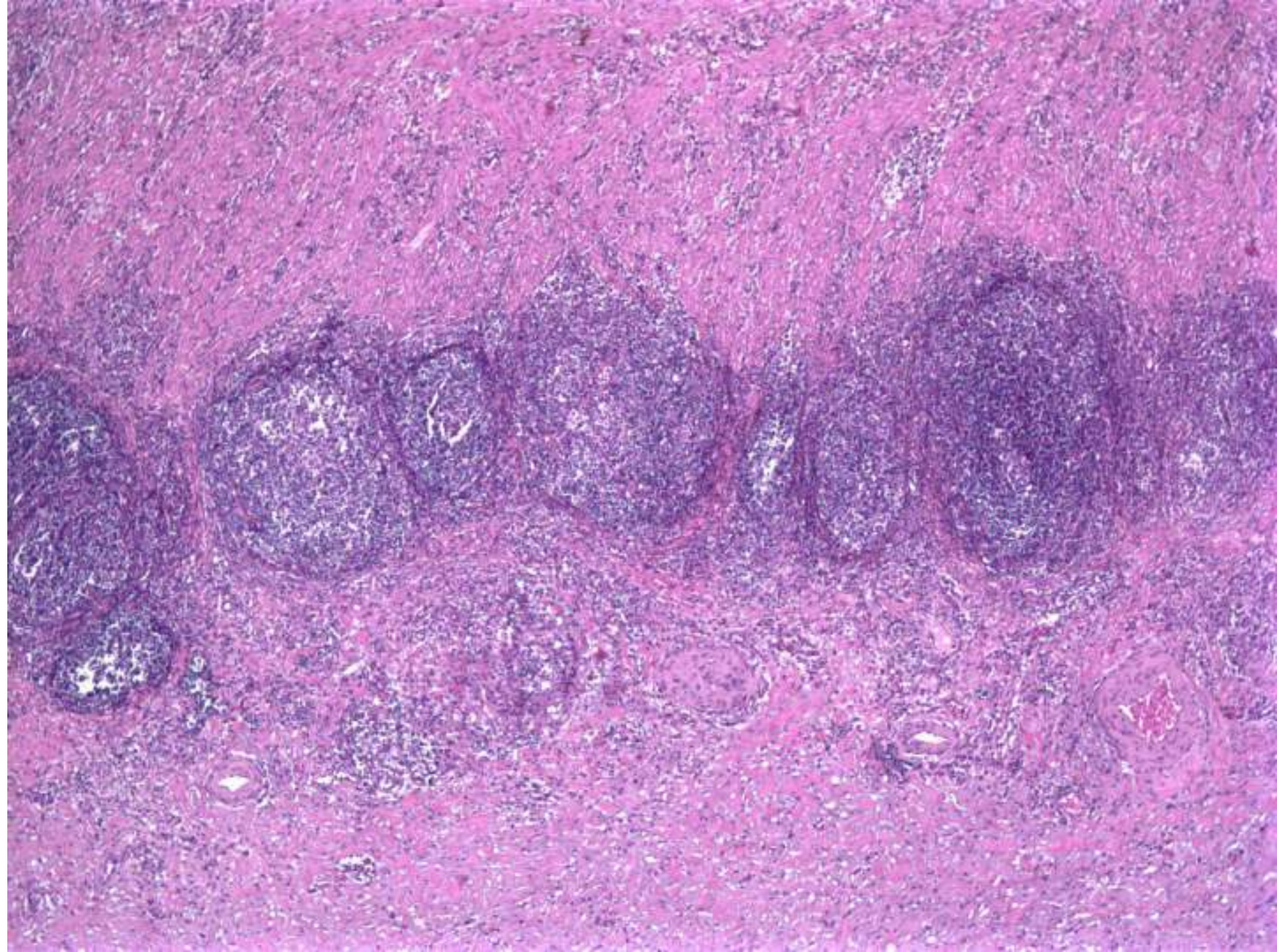
Yersinia-ileal biopsy



Yersinia enterocolitica enterocolitis



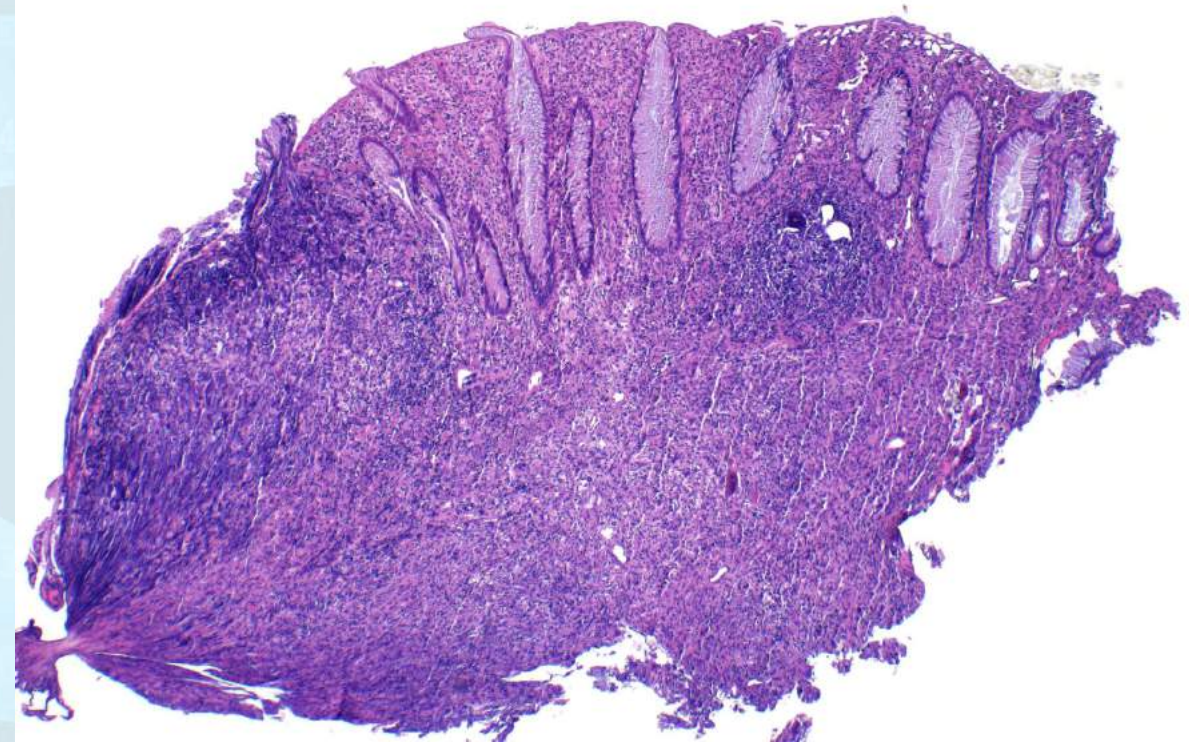
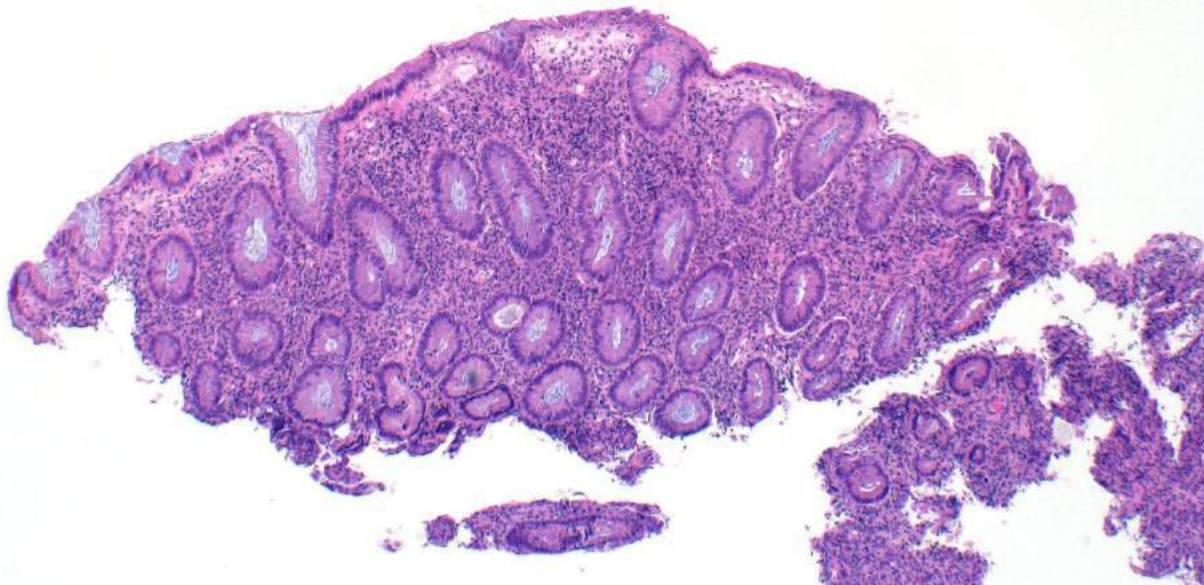


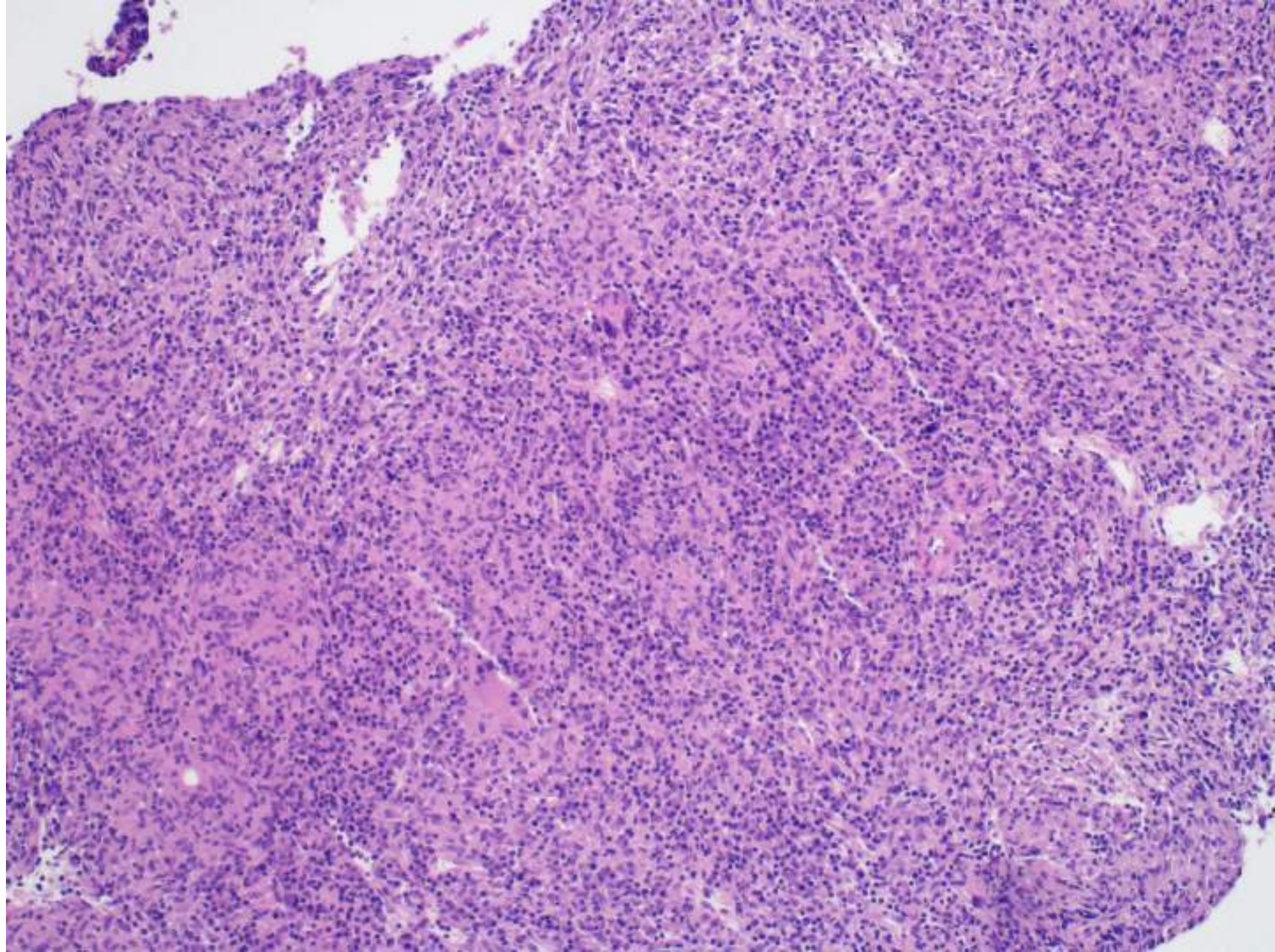


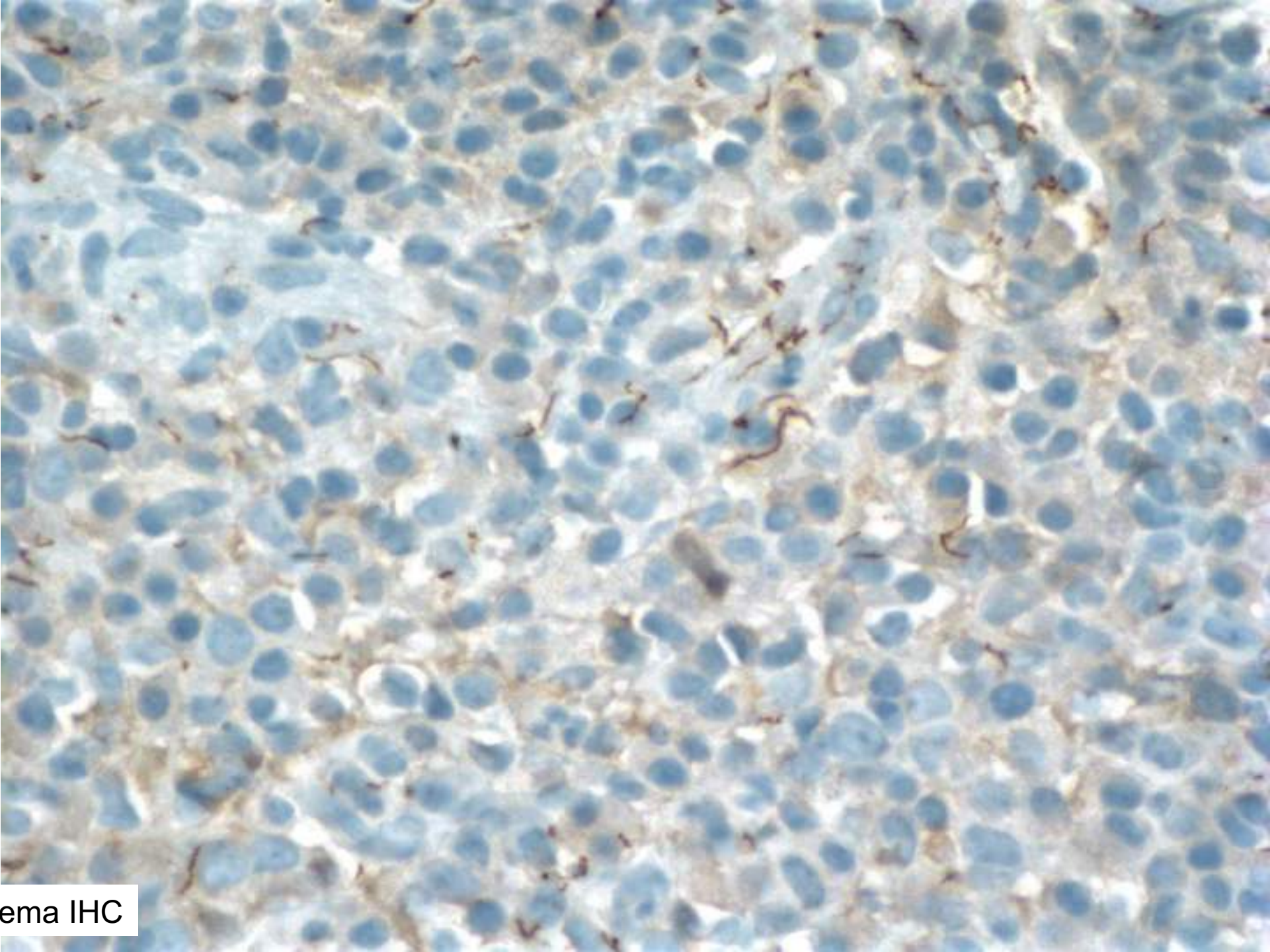
45 year old man

One week history of bright red blood per rectum

On colonoscopy looked like distal left-sided ulcerative colitis







Treponema IHC

Sexually transmitted bacterial infections

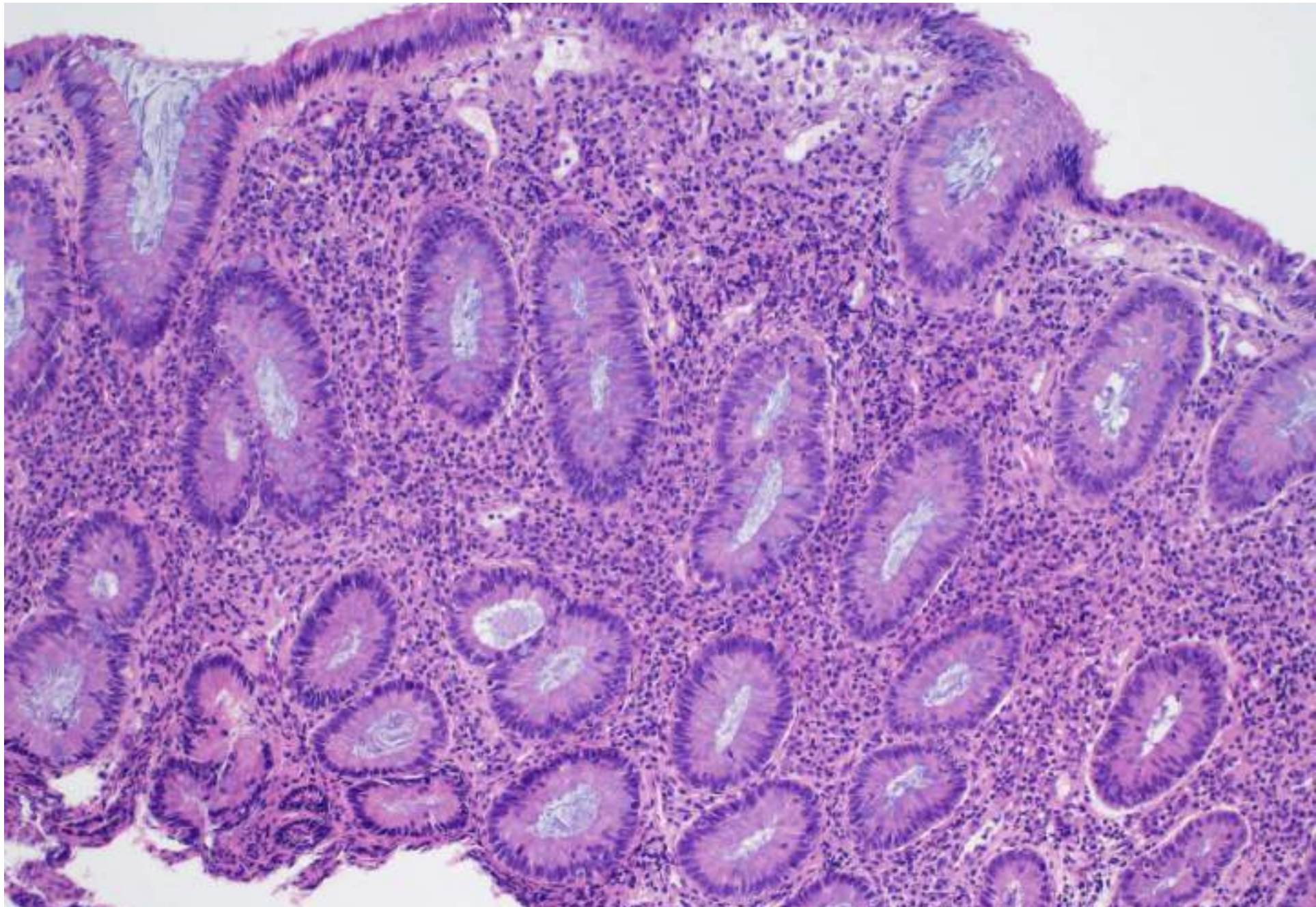
- Gonorrhea
- Chlamydia (LGV)*
- Shigella*
- Chancroid (*H. ducreyi*)
- Granuloma inguinale

* ***Most likely to mimic IBD***

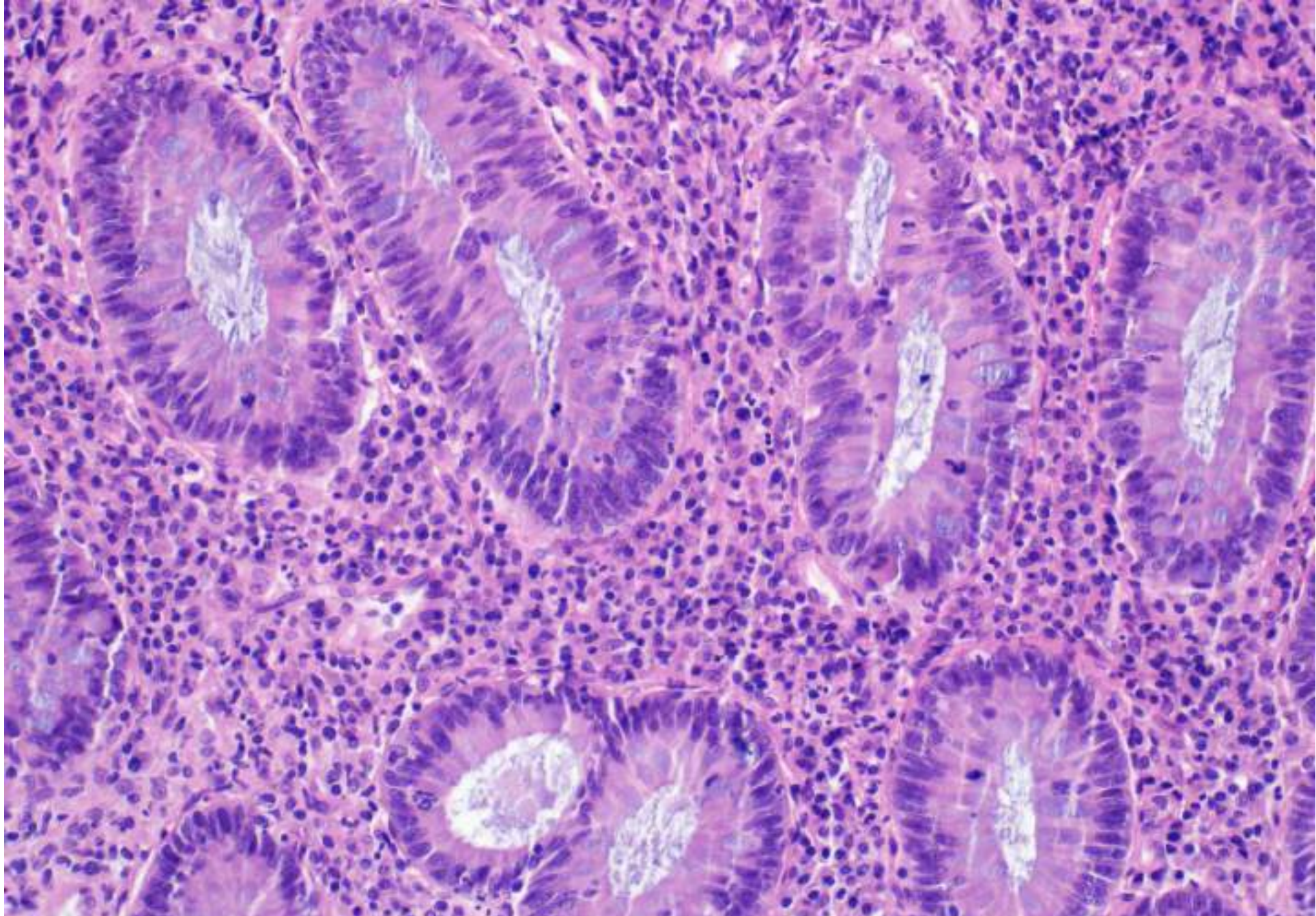
- Syphilis*
 - 228.8/100,00 persons in the MSM population (2013)
 - Rates approaching those last seen in 1982
 - Fairly constant low level infection (0.9/100,000) for women and congenital cases

Anorectal syphilis

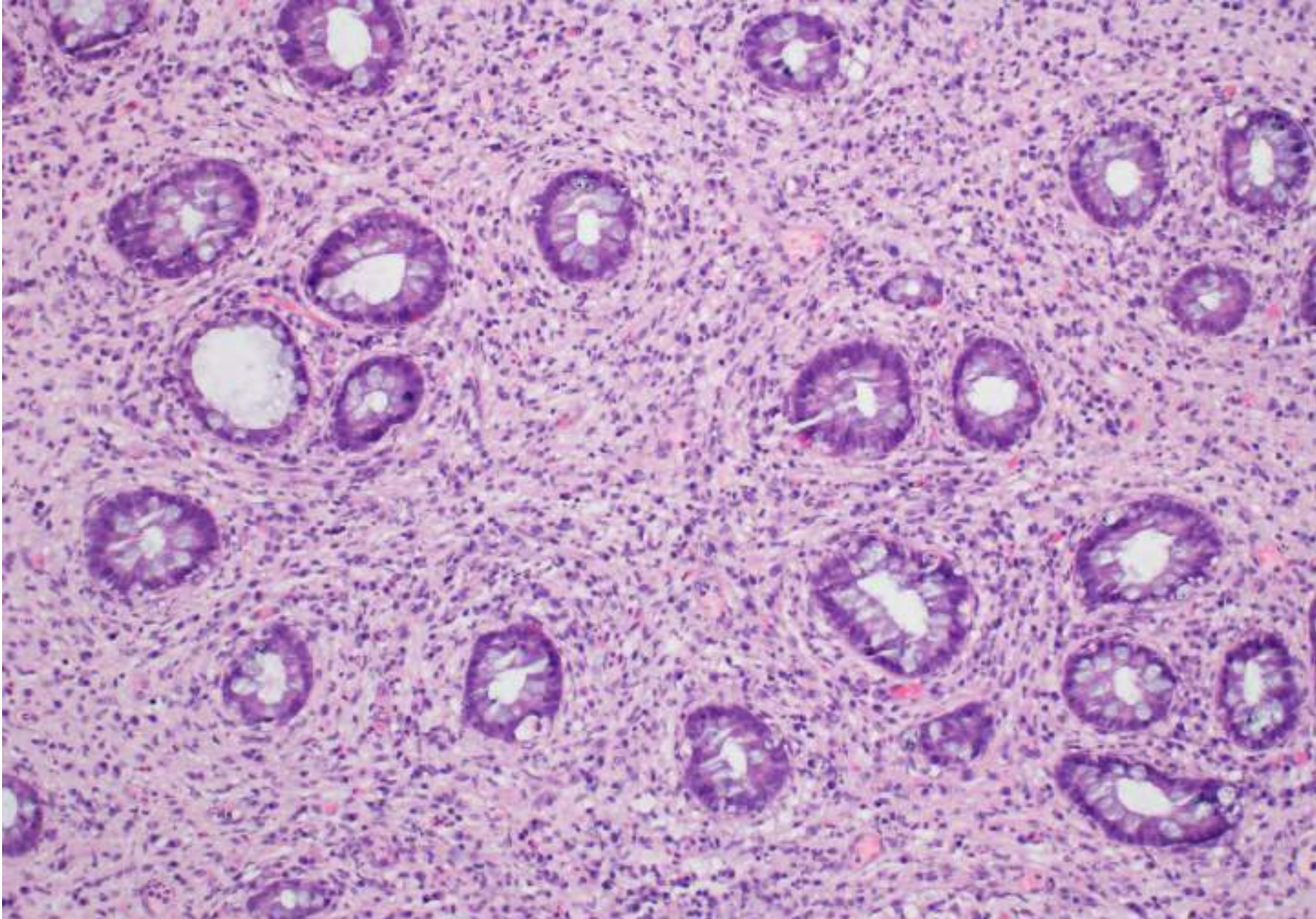
- Histologic features
 - Intense lymphohistiocytic and plasmacytic infiltrate
 - Out of proportion to acute inflammation
 - Eosinophils rare
 - Crypt distortion mild, Paneth cells rare
 - Occasional granulomas, stromal and submucosal fibrosis, reactive endothelial cells



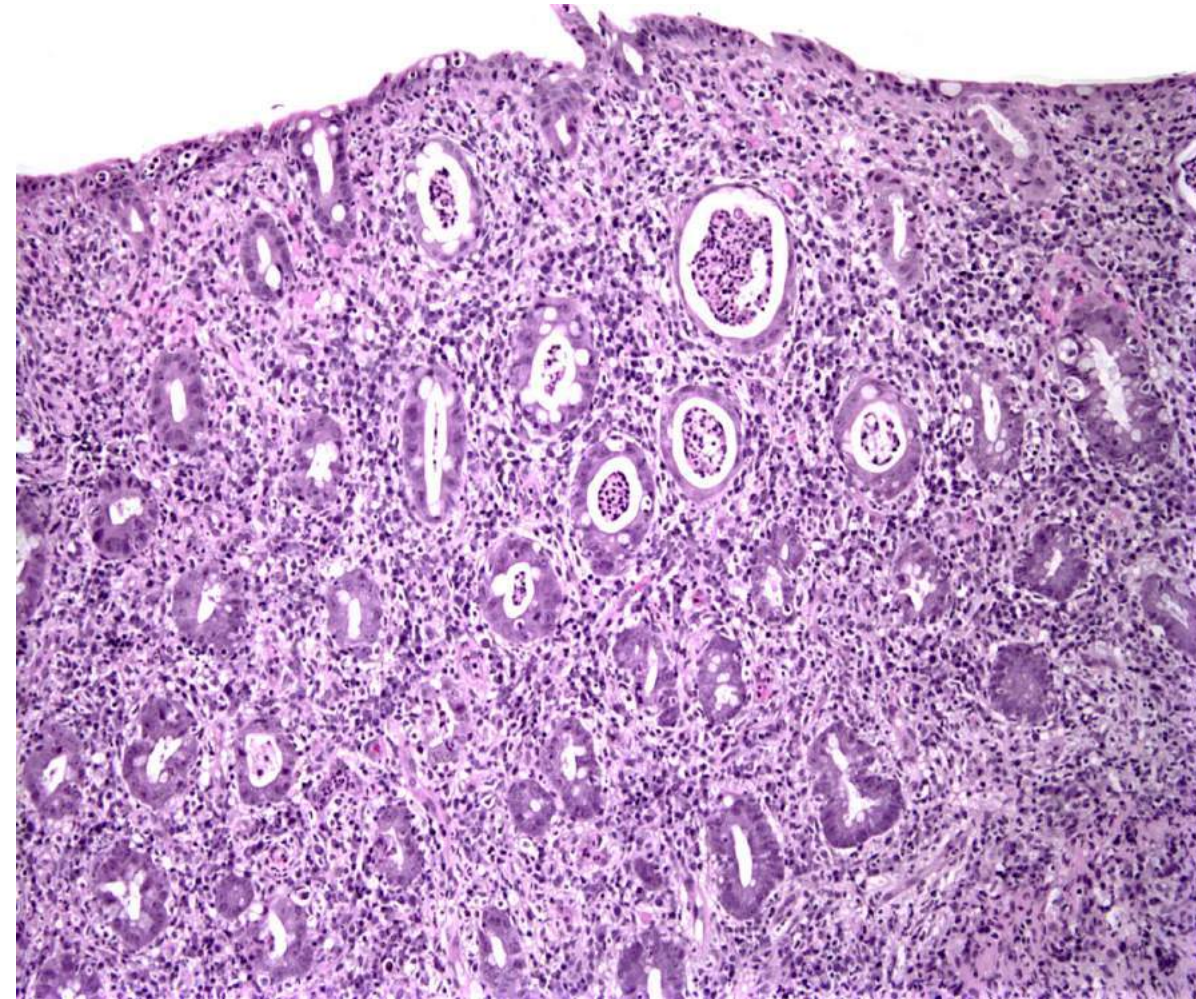
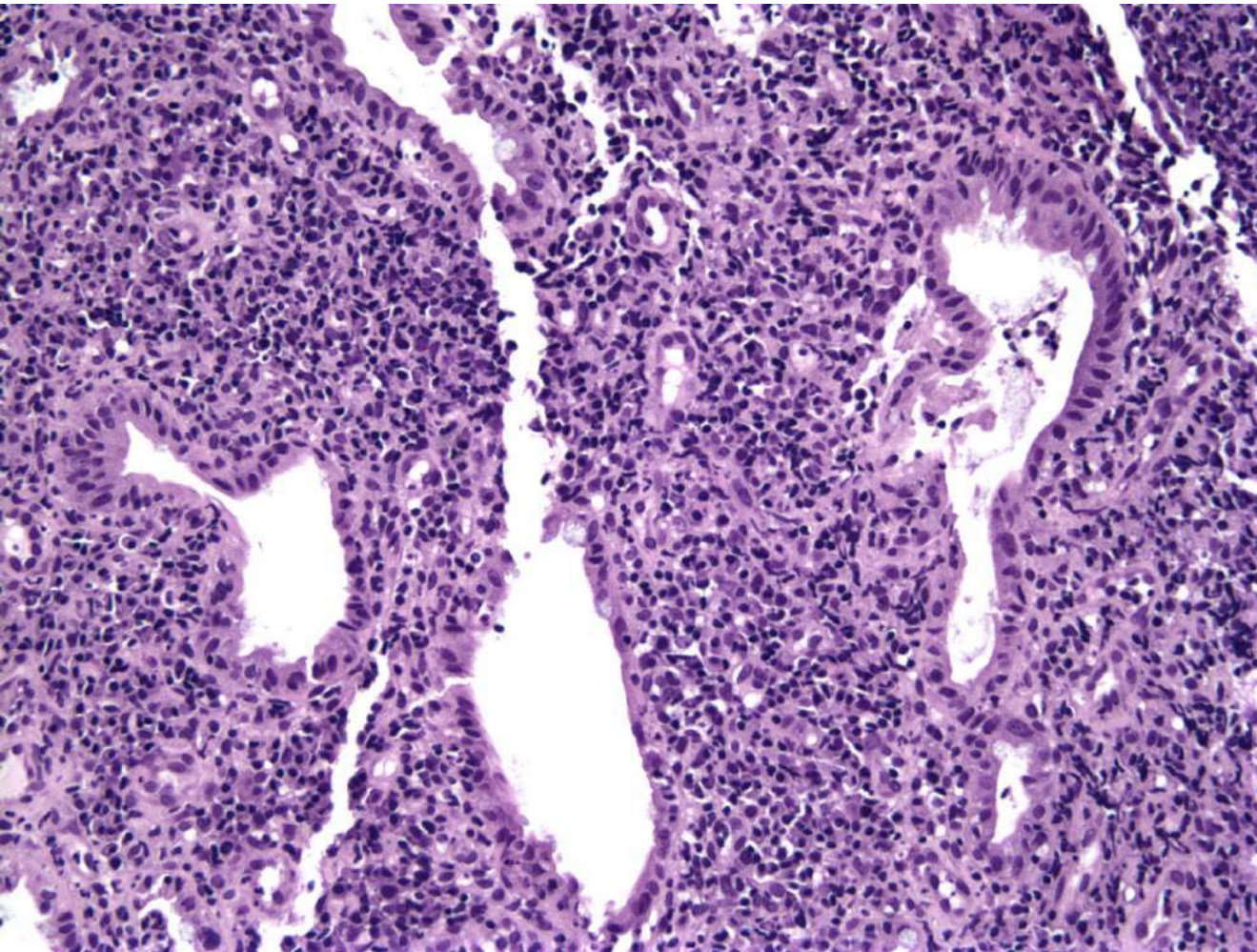
Typically less overt architectural distortion than ulcerative colitis



Dense plasmacytic infiltrate (although not always)



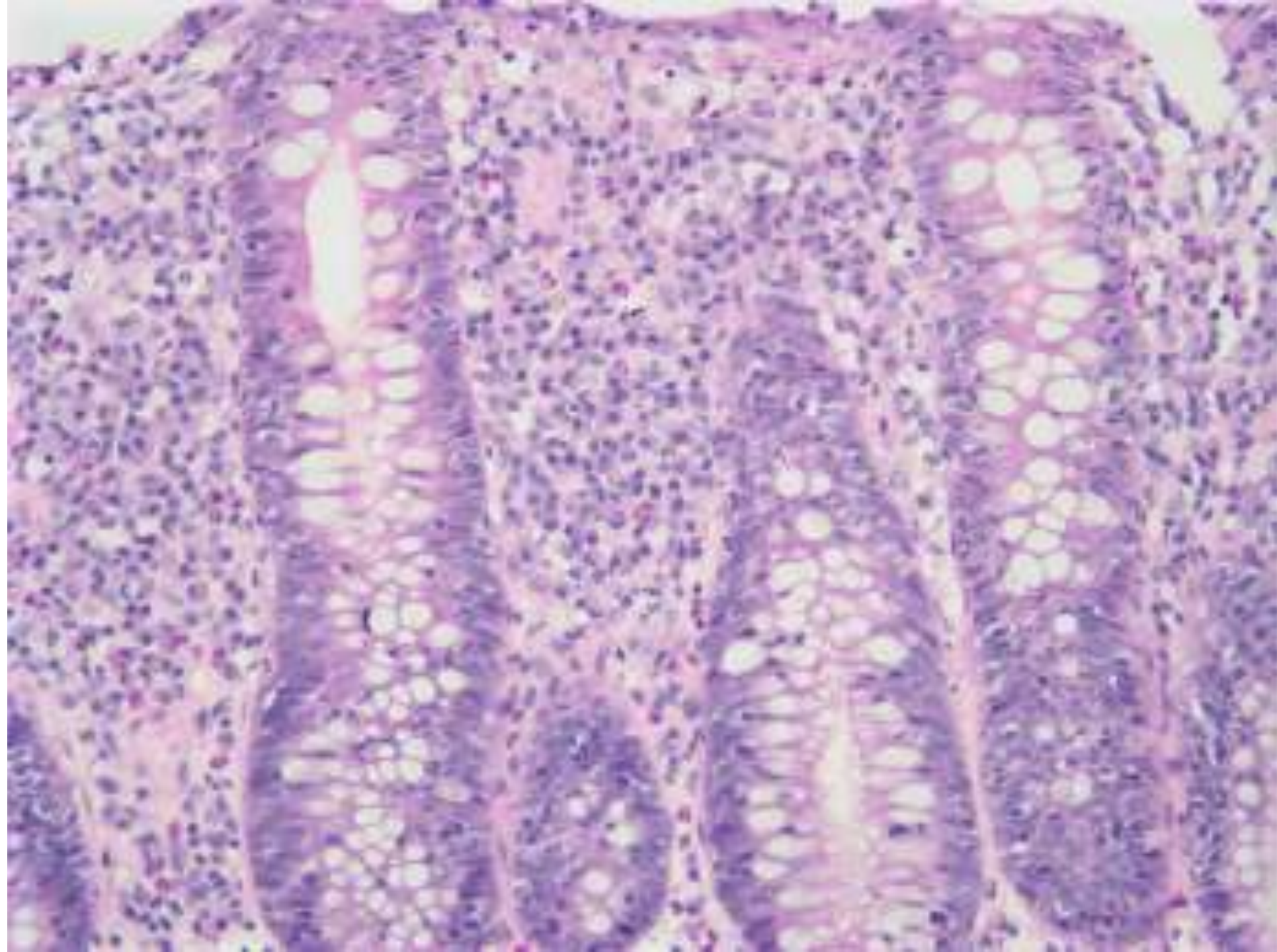
Prominent stromal reaction in lamina propria



Syphilis-marked architectural distortion and prominent activity are rare but do happen

Resolving bacterial infection





CMV



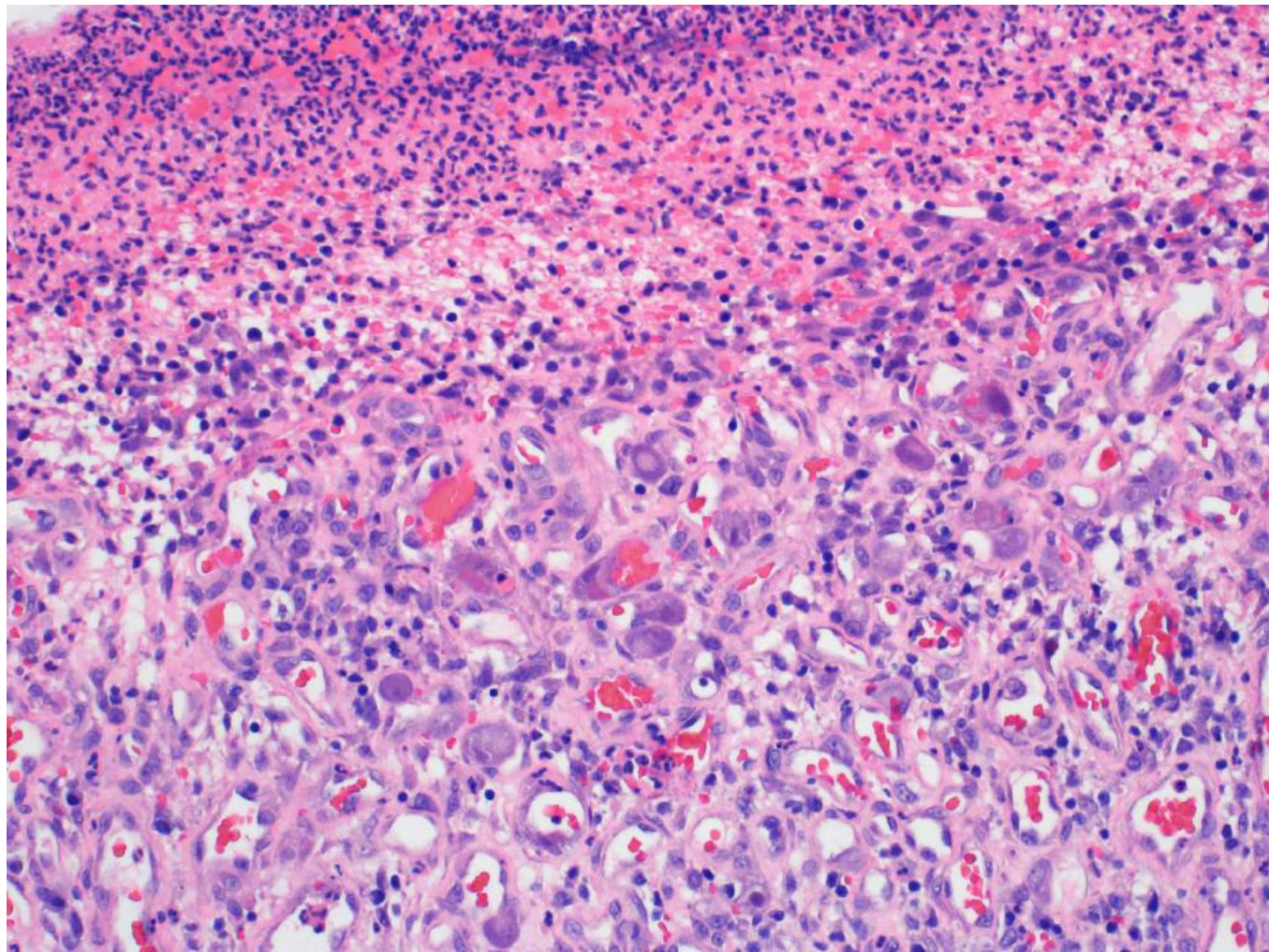
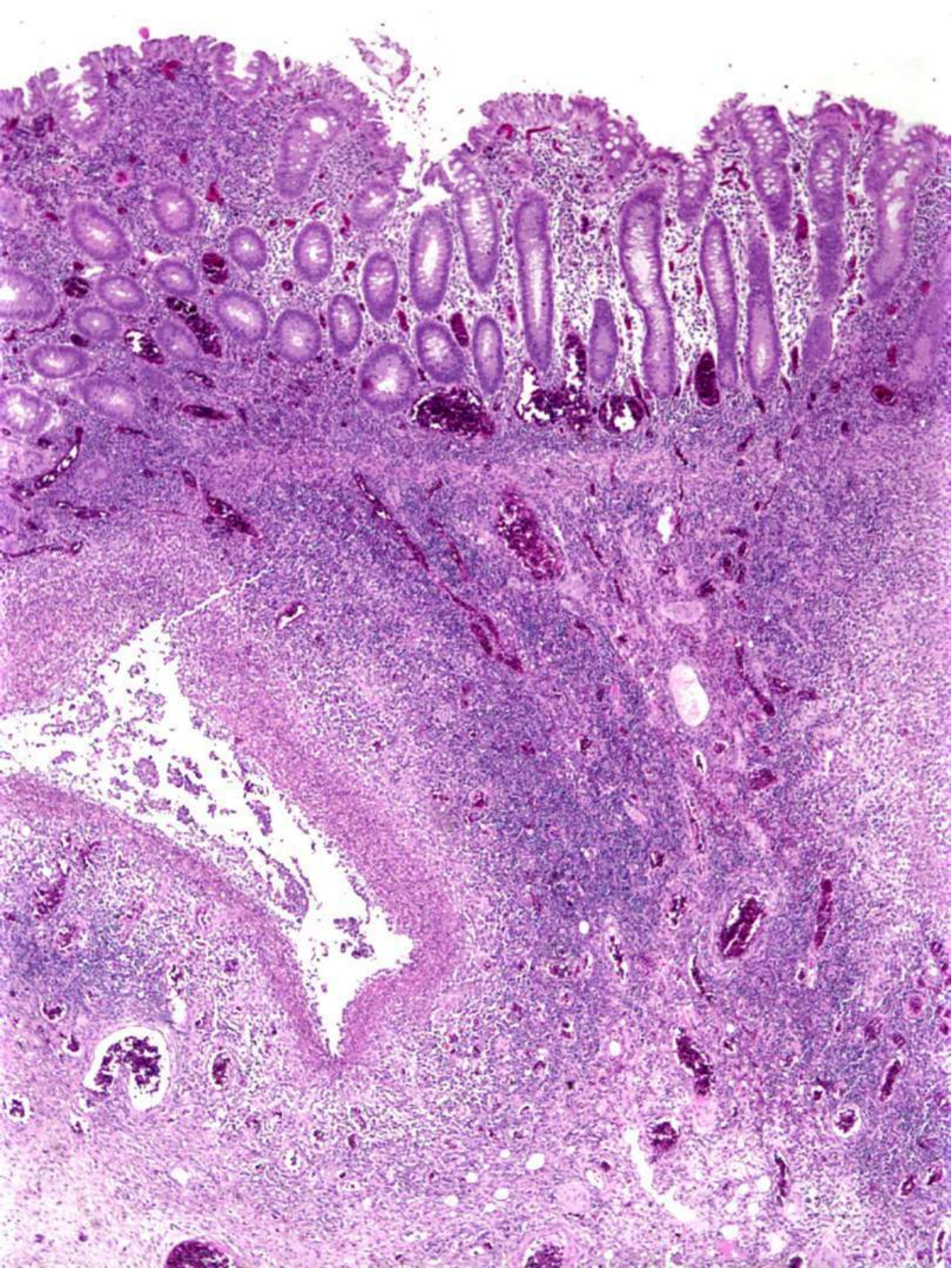
45M Renal Tx Patient

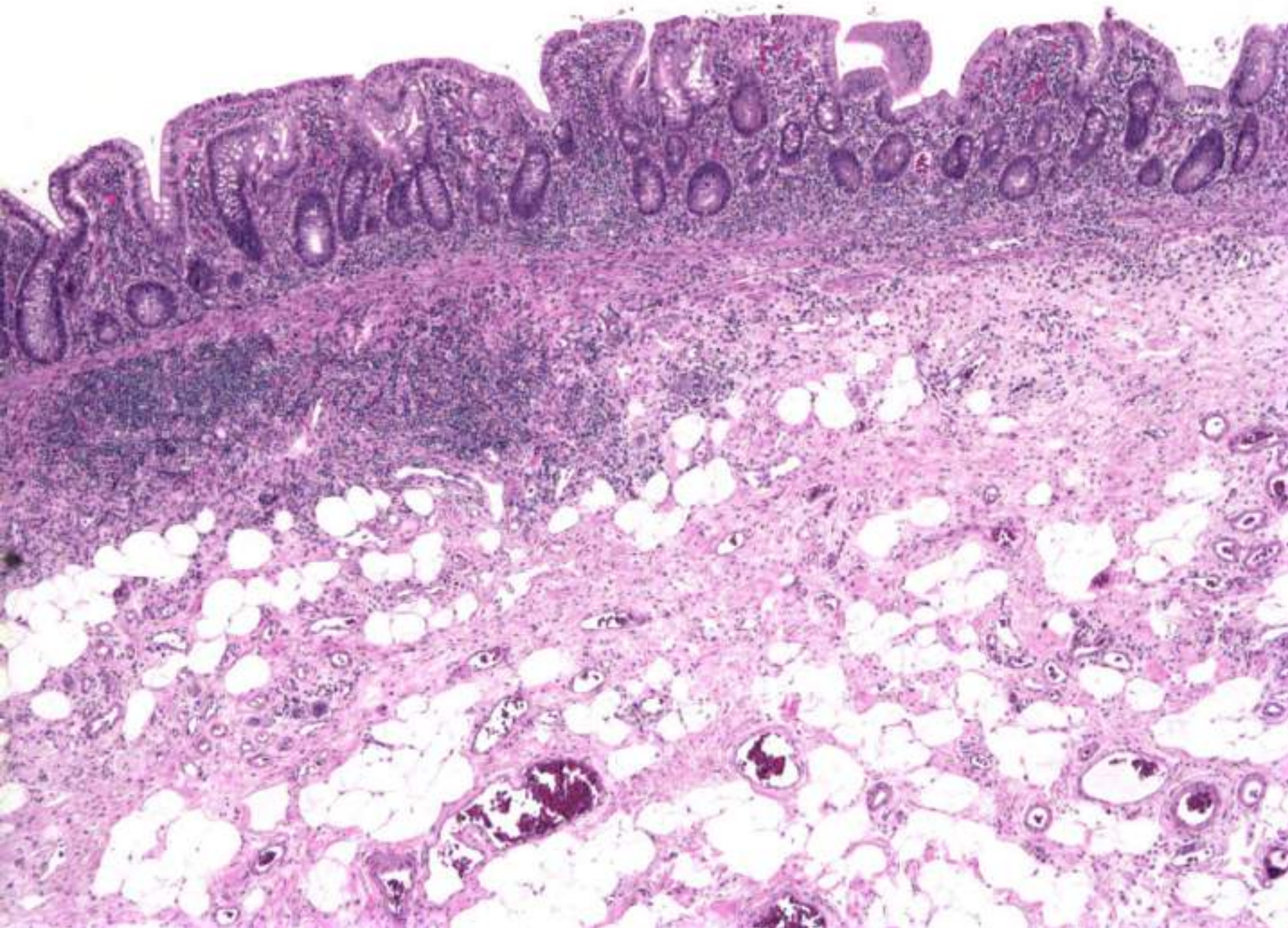
Characteristic CMV Infection

- Ulceration and active inflammation
- “Owl’s eye” inclusions deep within ulcer bases

Atypical CMV Infection

- Ischemic
- Crohn’s-like
- GVHD-like
- Hypertrophic gastropathy

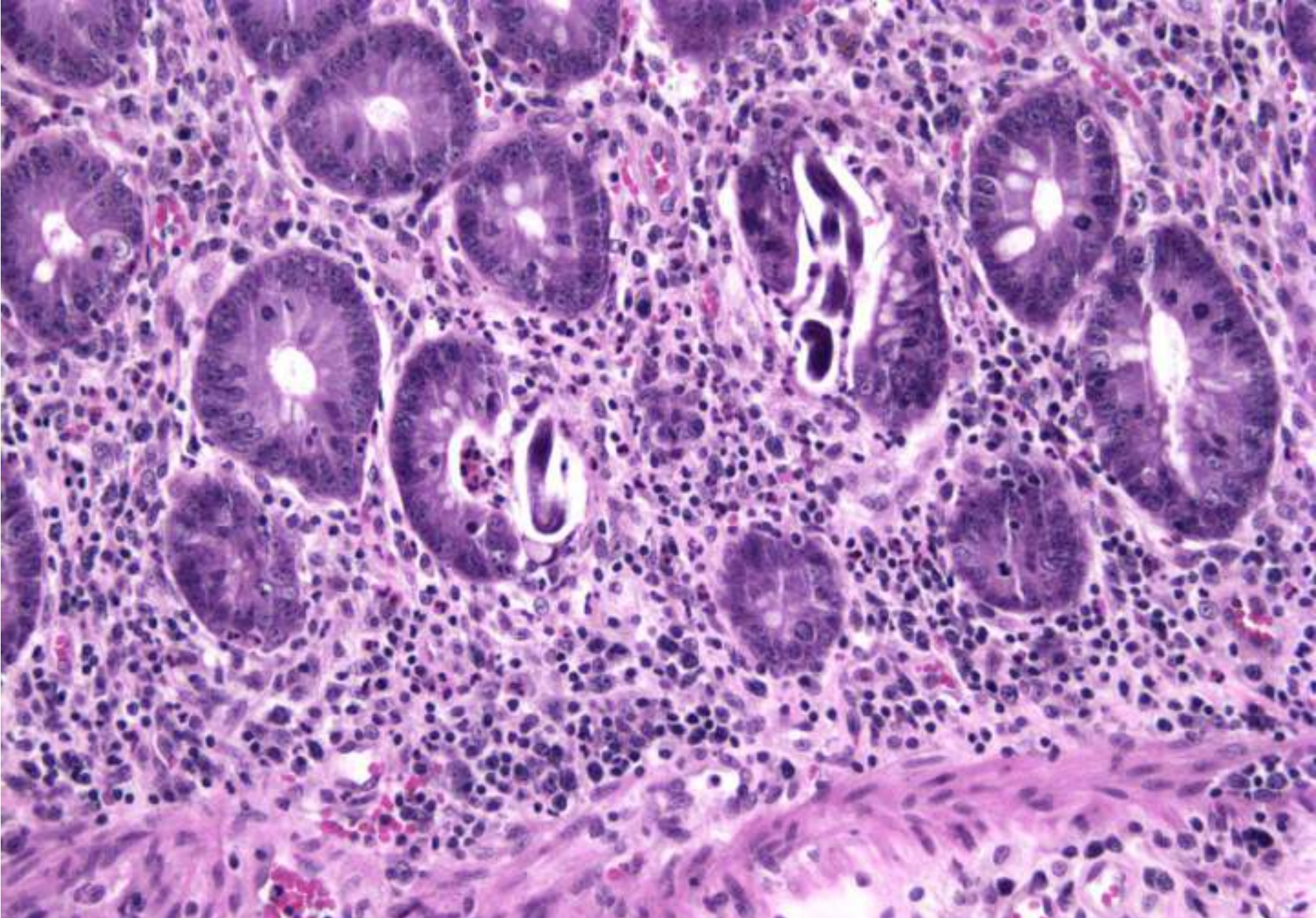




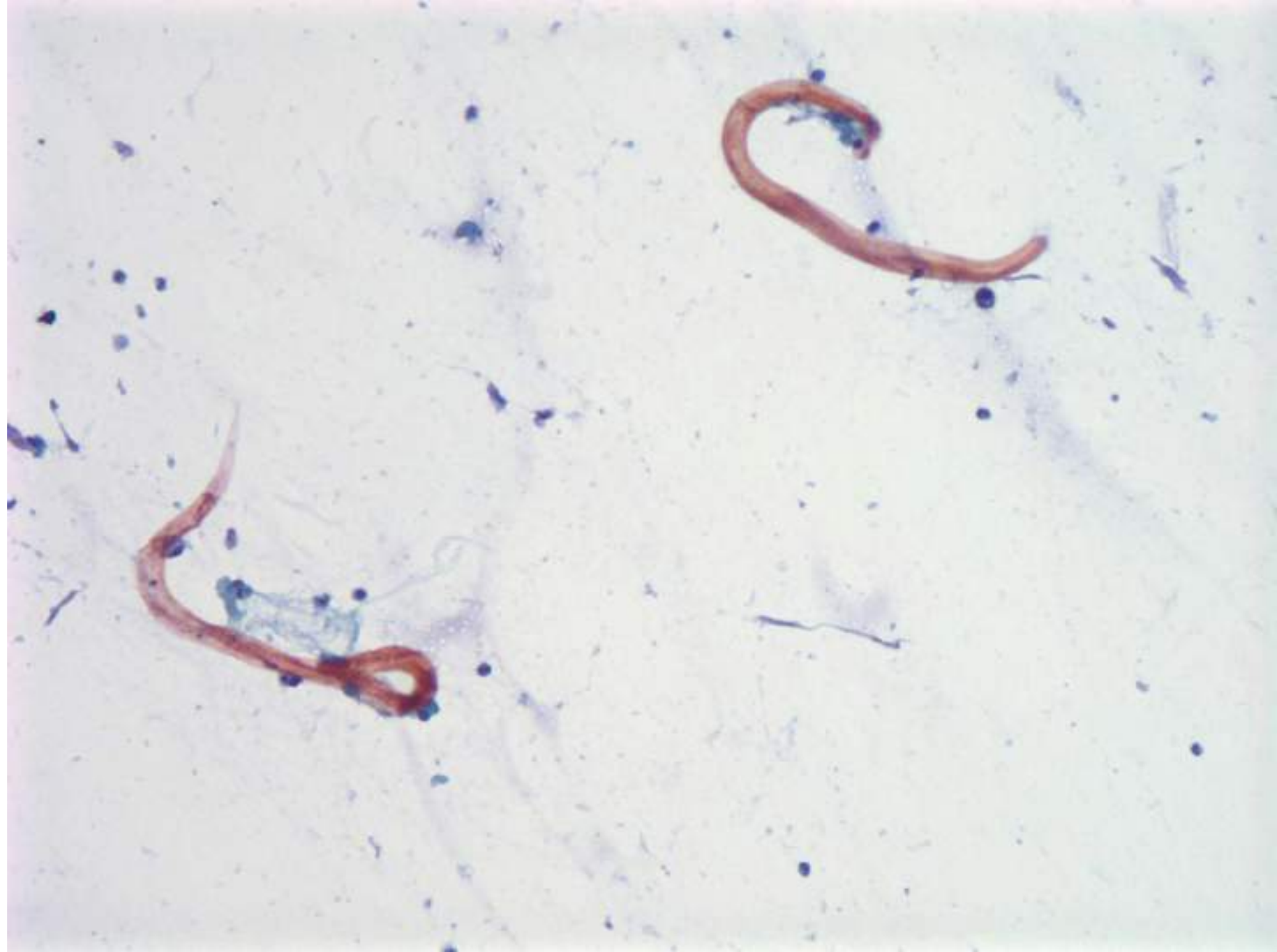
50 year old woman with reported history of Crohn's disease was taken to emergency surgery for disease flare

Patient had been on several weeks of steroids with no improvement

Following right colectomy, patient clinically decompensated, developed pneumonia, and was intubated



Qu Z et al. *Strongyloides* is a lethal mimic of ulcerative colitis. *Hum Pathol* 2009;40:572-7





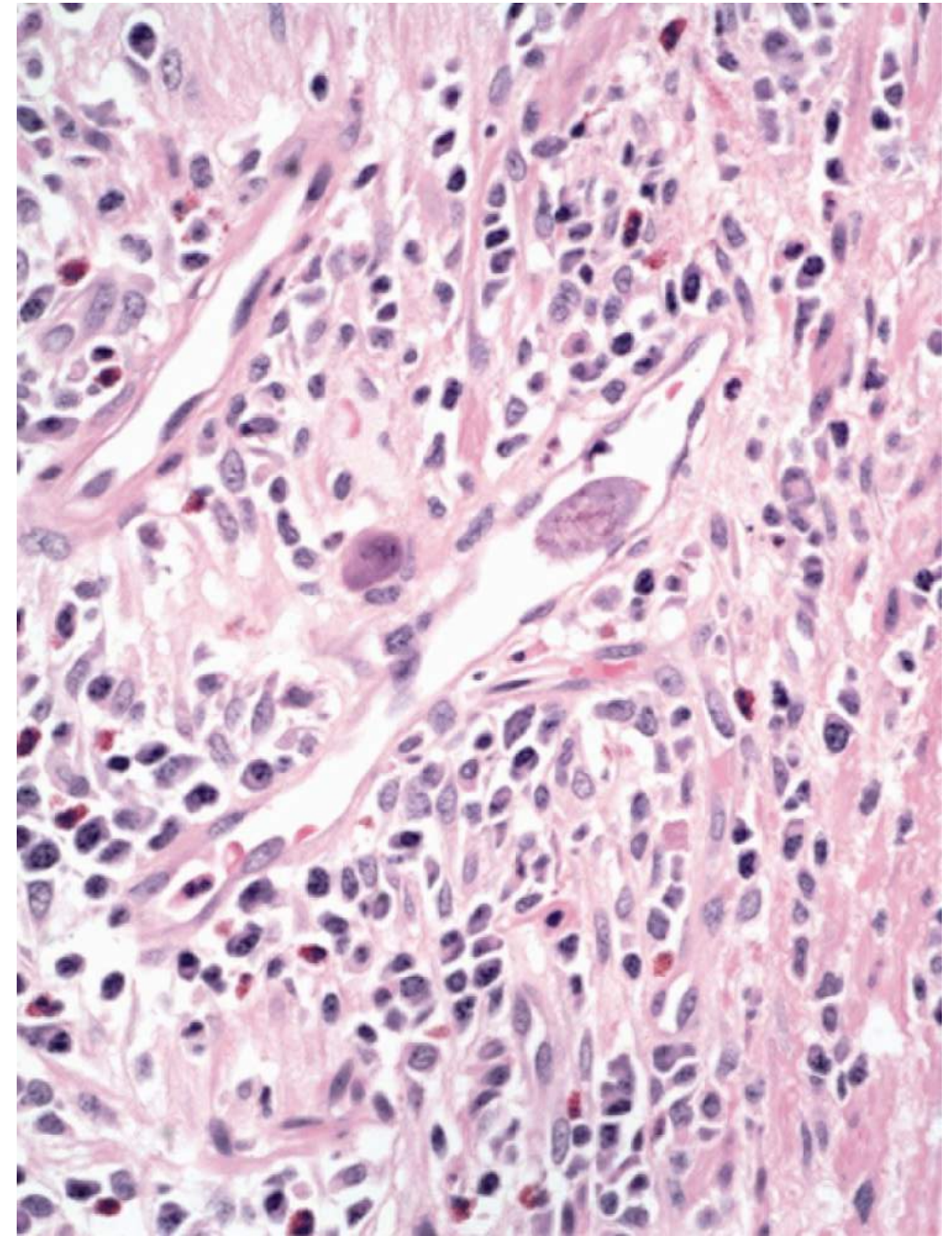
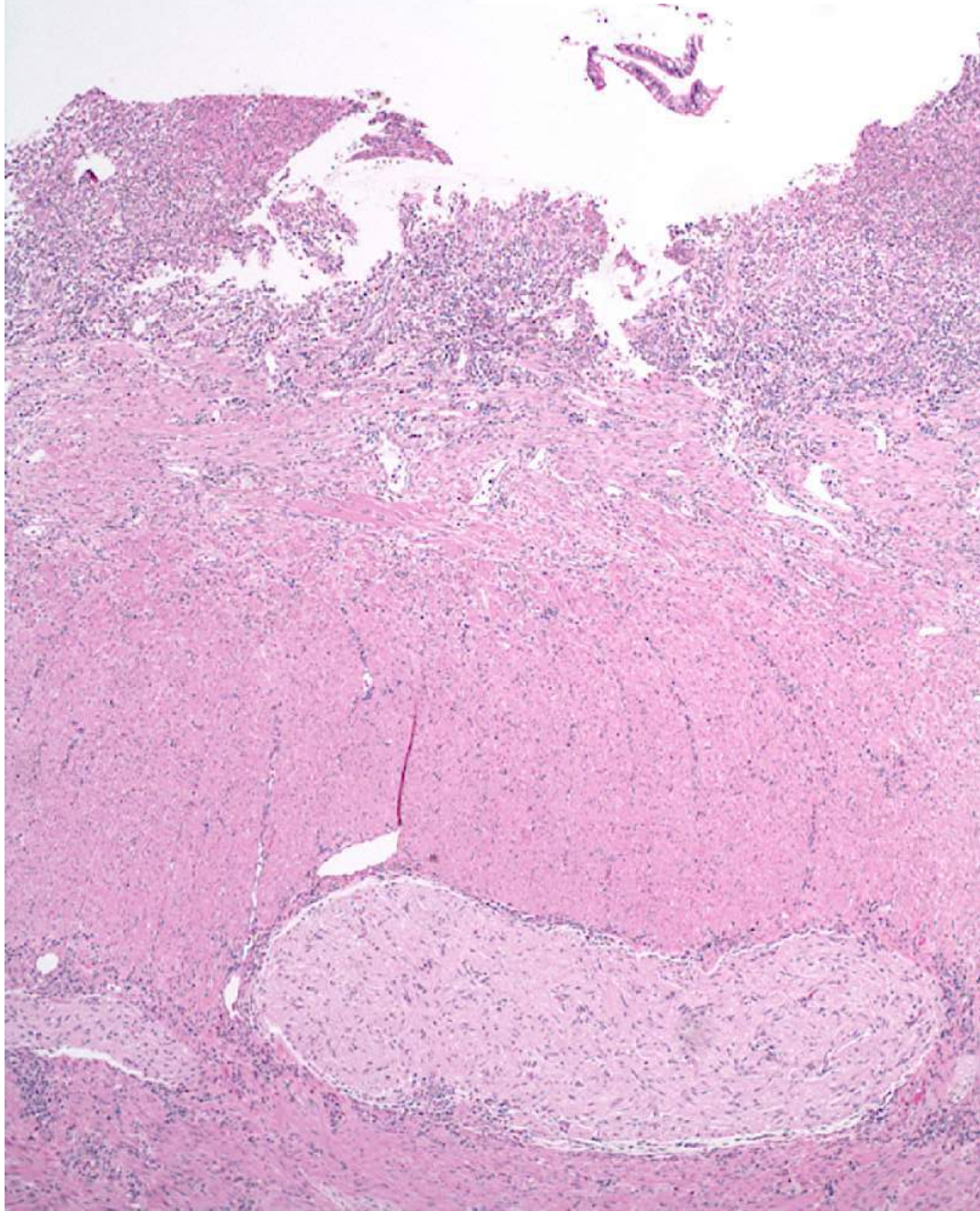
Alys digs for diagnostic clues.

Infections superimposed on CIIBD

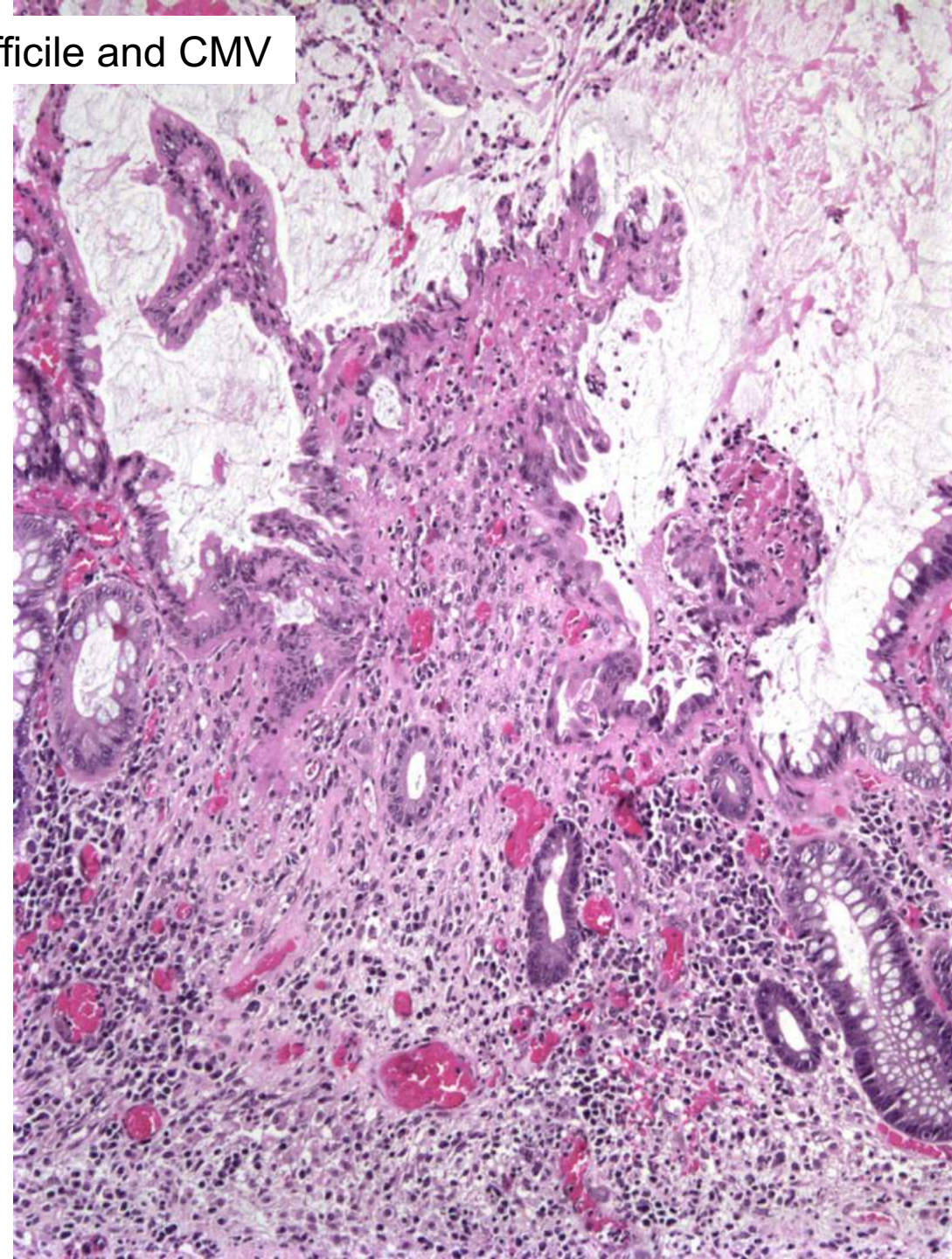
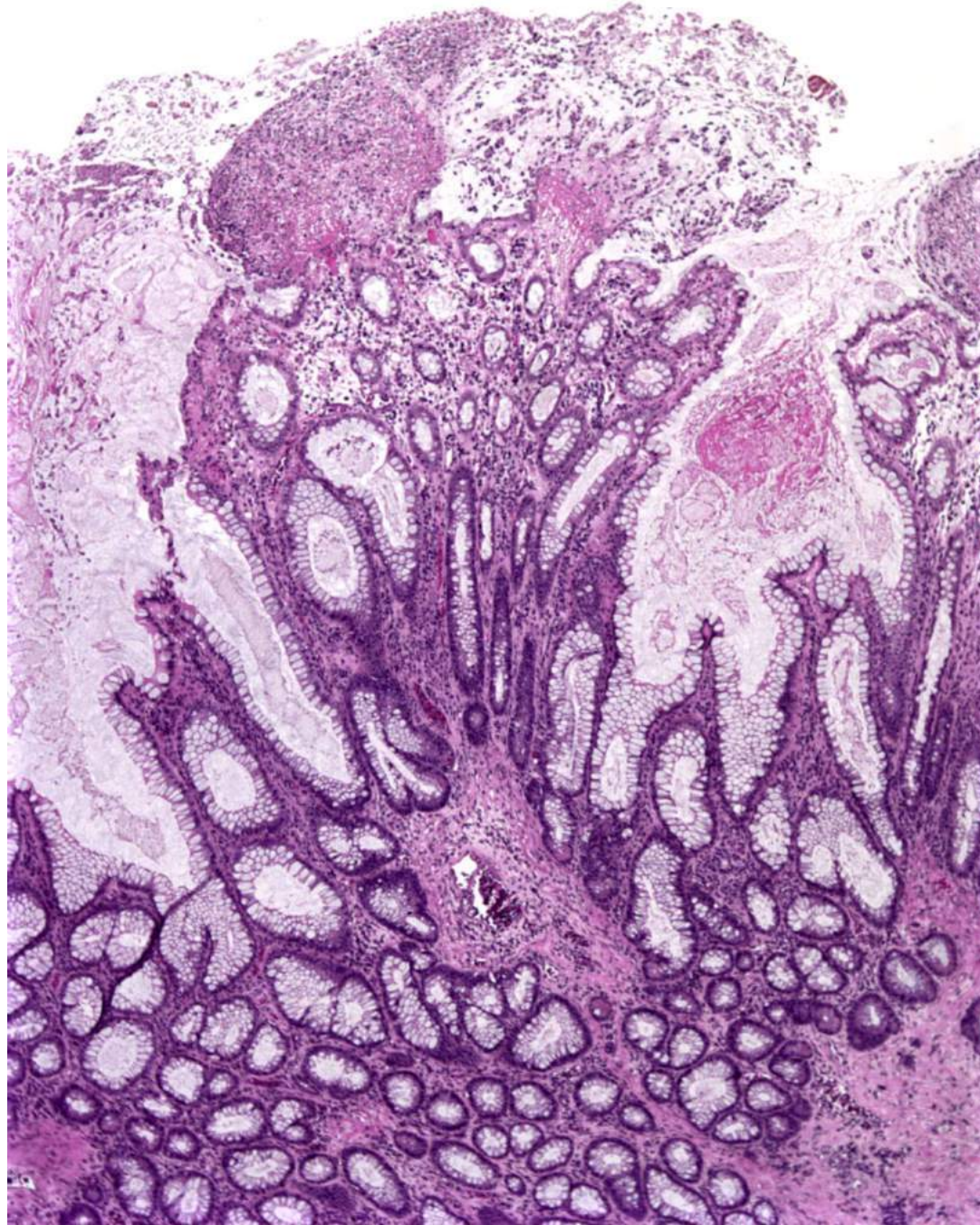
- CMV
- *C. difficile*
- Food-borne enterics

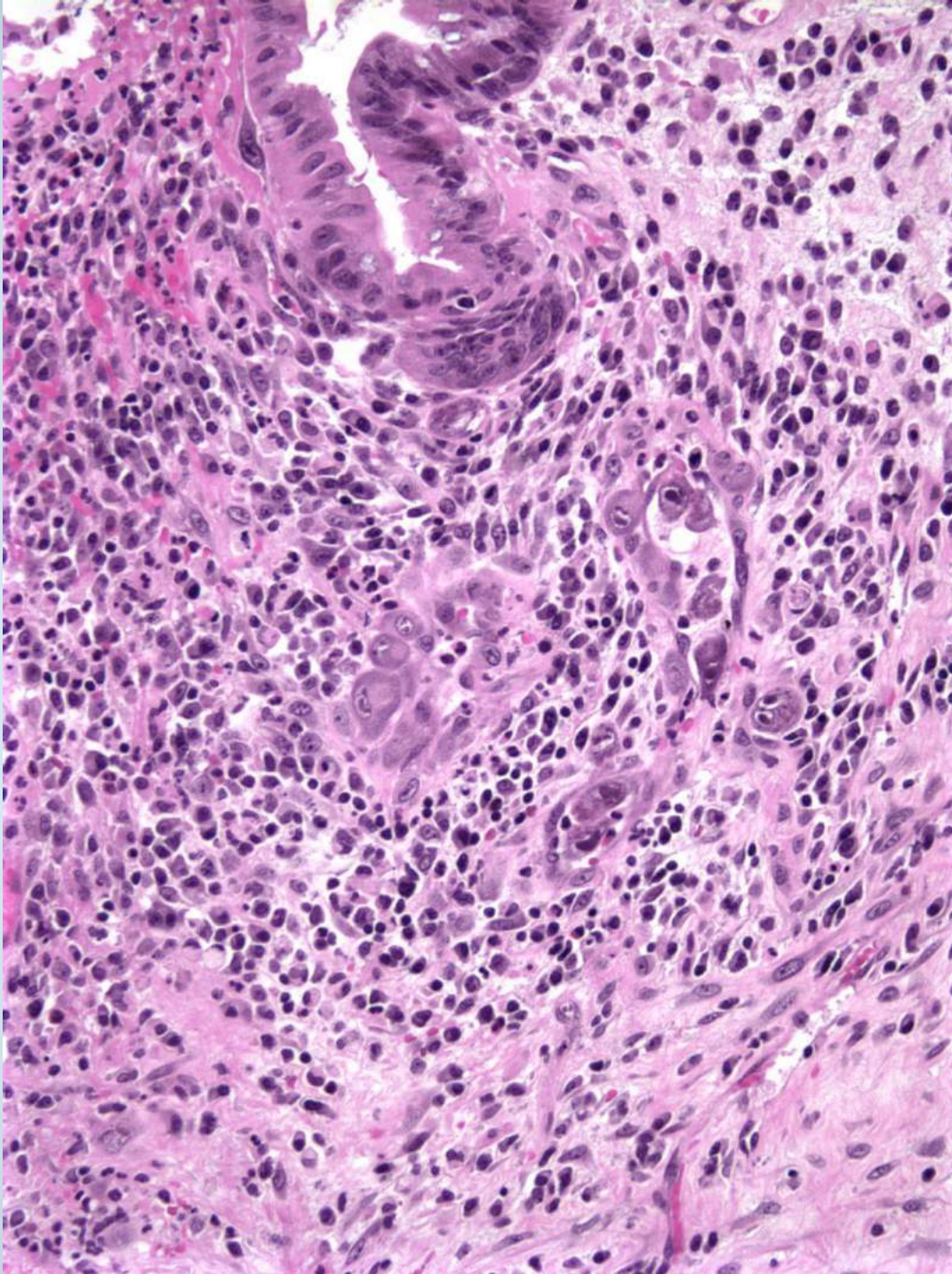


Crohn's disease patient with flare leading to resection



UC patient with *C. difficile* and CMV





Of note:

C. diff is more common in IBD patients with CMV, and outcomes are worse

UC patients with *C. diff* often don't show the classic histologic findings

Wang T et al. Histologic findings and clinical characteristics in acutely symptomatic ulcerative colitis patients with superimposed *C. difficile* infection. *Am J Clin Pathol* 2013;140:831-7.

McCurdy JD et al. Increased rates of *Clostridium difficile* infection and poor outcomes in patients with IBD and cytomegalovirus. *Inflamm Bowel Dis* 2016;22:2688-93.

Diagnostic Help

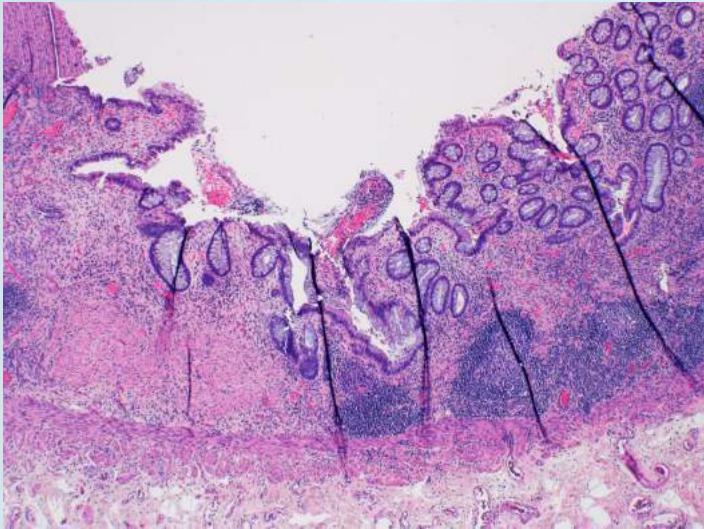
- CMV
 - IHC, PCR from tissue or serum
- Enteric bacteria
 - Stool PCR platforms
 - Require liquid stool
 - Stool culture
 - History: travel, food intake, length of symptoms
- Amoeba
 - History
 - Stool O&P
- Syphilis
 - Treponemal and non-treponemal serologies
- Strongyloides
 - Serologies

I think you're boring me.

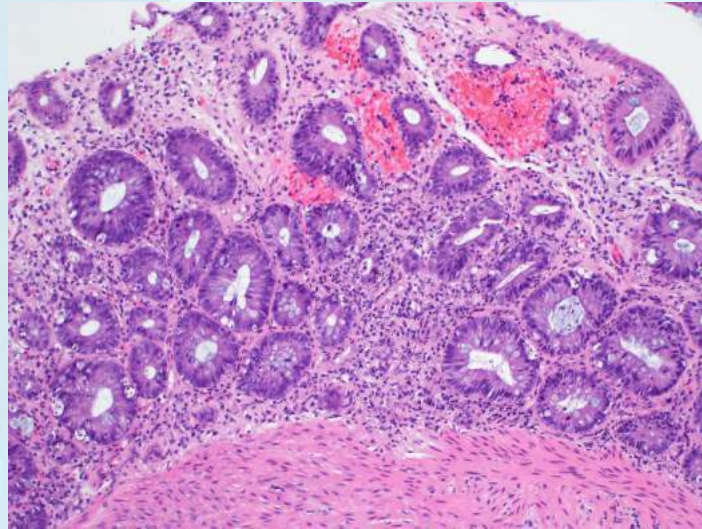
Do you think it's infection or a drug reaction?



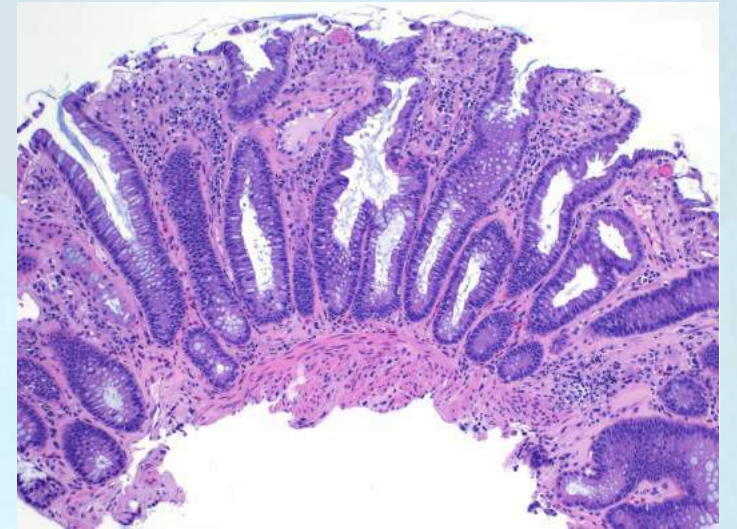
Iatrogenic Mimics of CIIBD



**Diversion
colitis**



GVHD



**Radiation
colitis**

Diversion colitis

Occurs in diverted segment of bowel that is *not exposed to fecal stream*

Symptoms occur with increasing duration of diversion:

Bloody/mucoid discharge

Abdominal pain

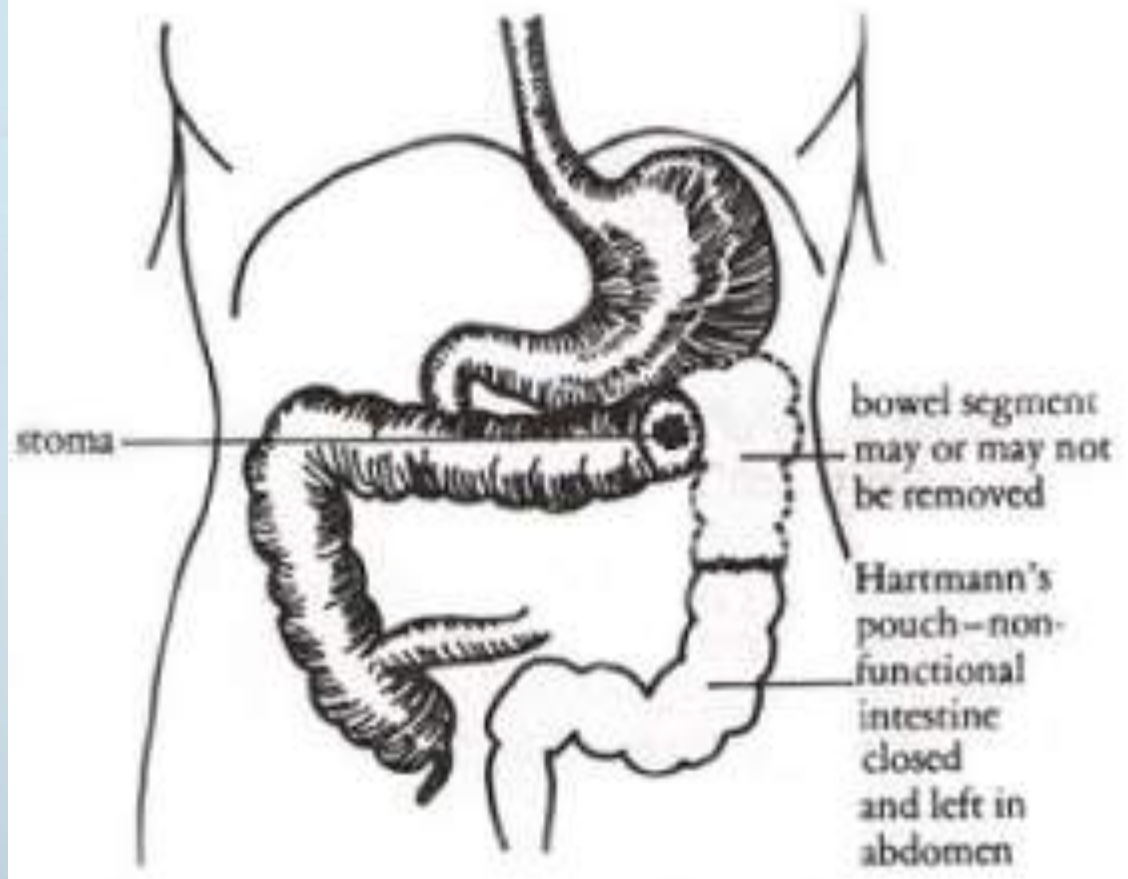
Tenesmus

Cured by surgical reversal; sometimes fatty acid enemas work

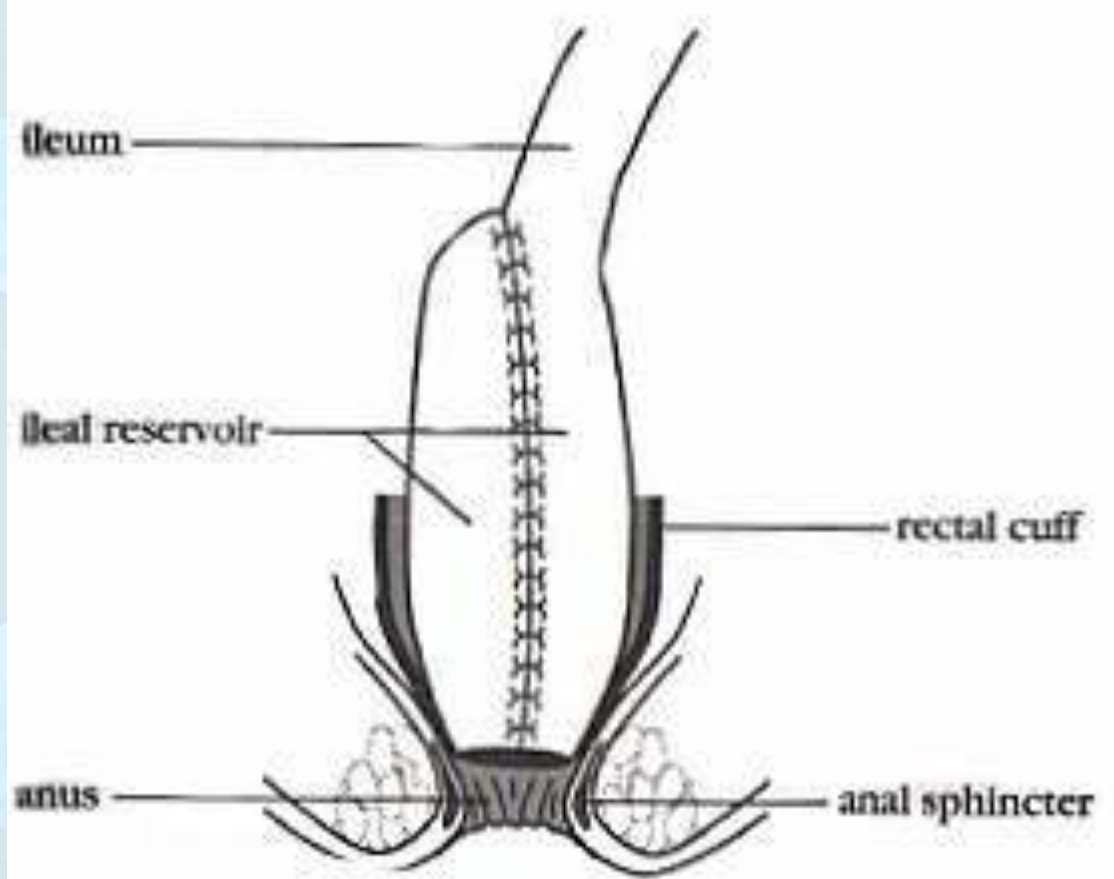
Can mimic IBD both clinically and histologically

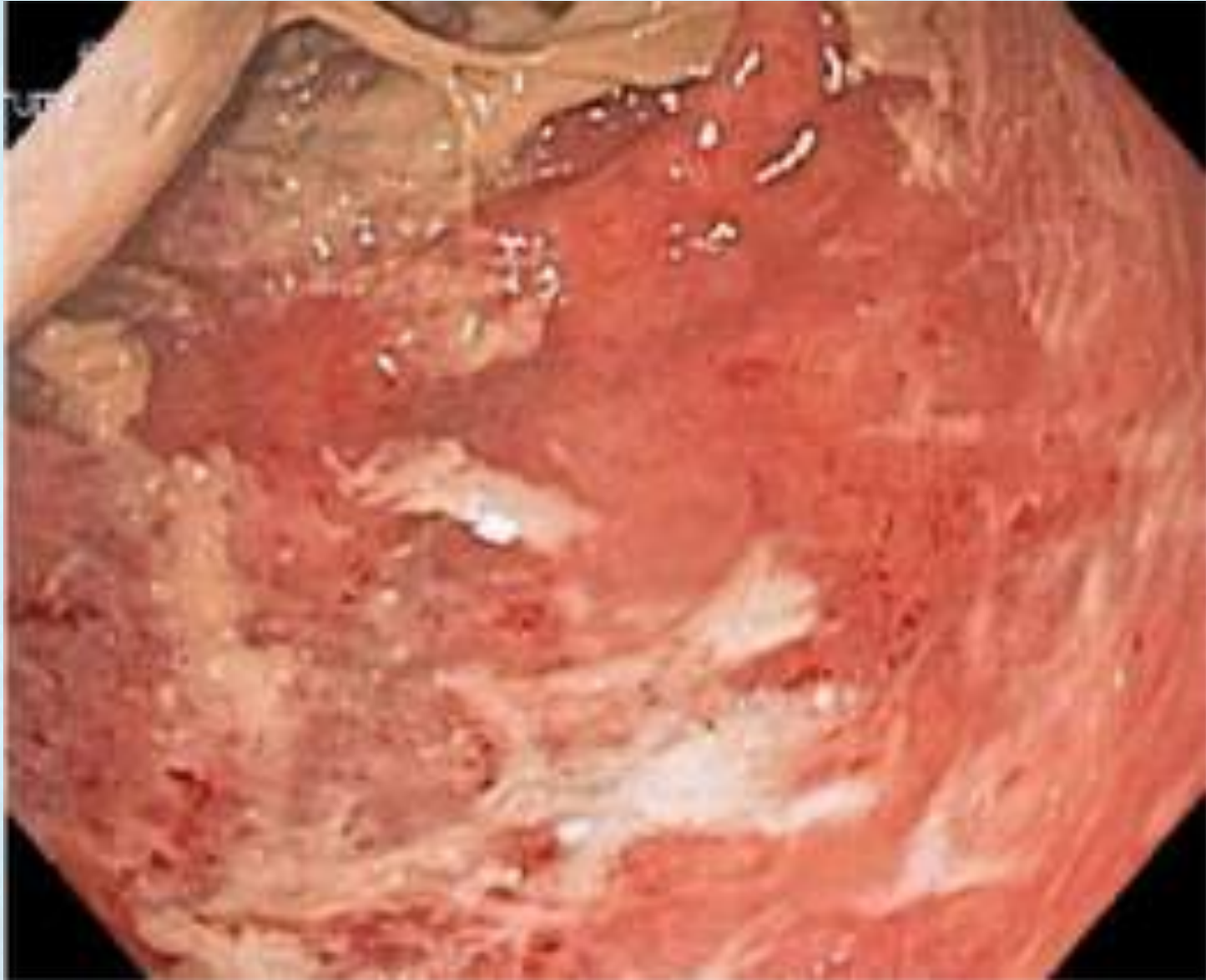
It's the Surgeon's Fault!

END OSTOMY AND HARTMANN'S POUCH — one stoma



Ileoanal anastomosis with reservoir



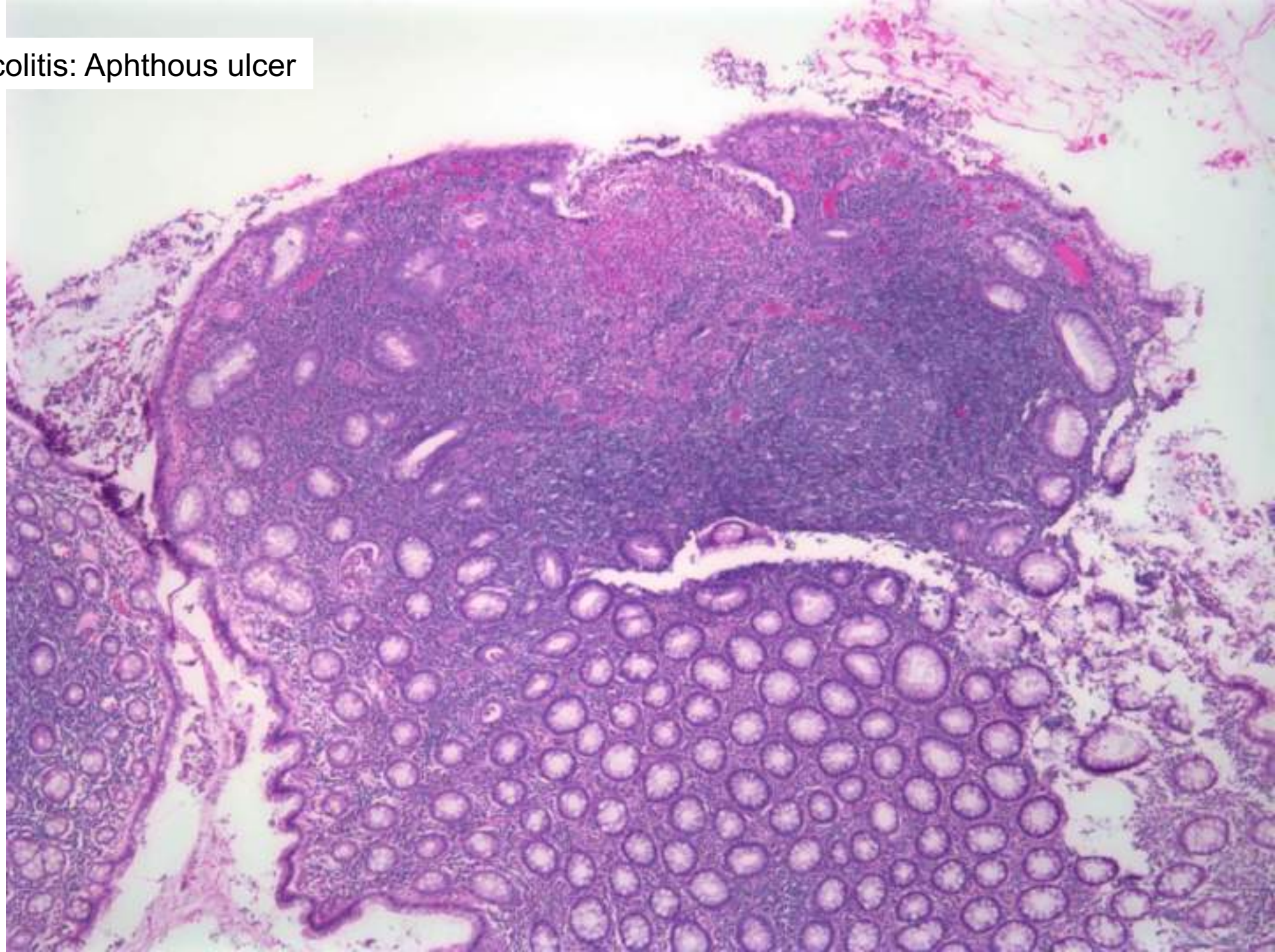


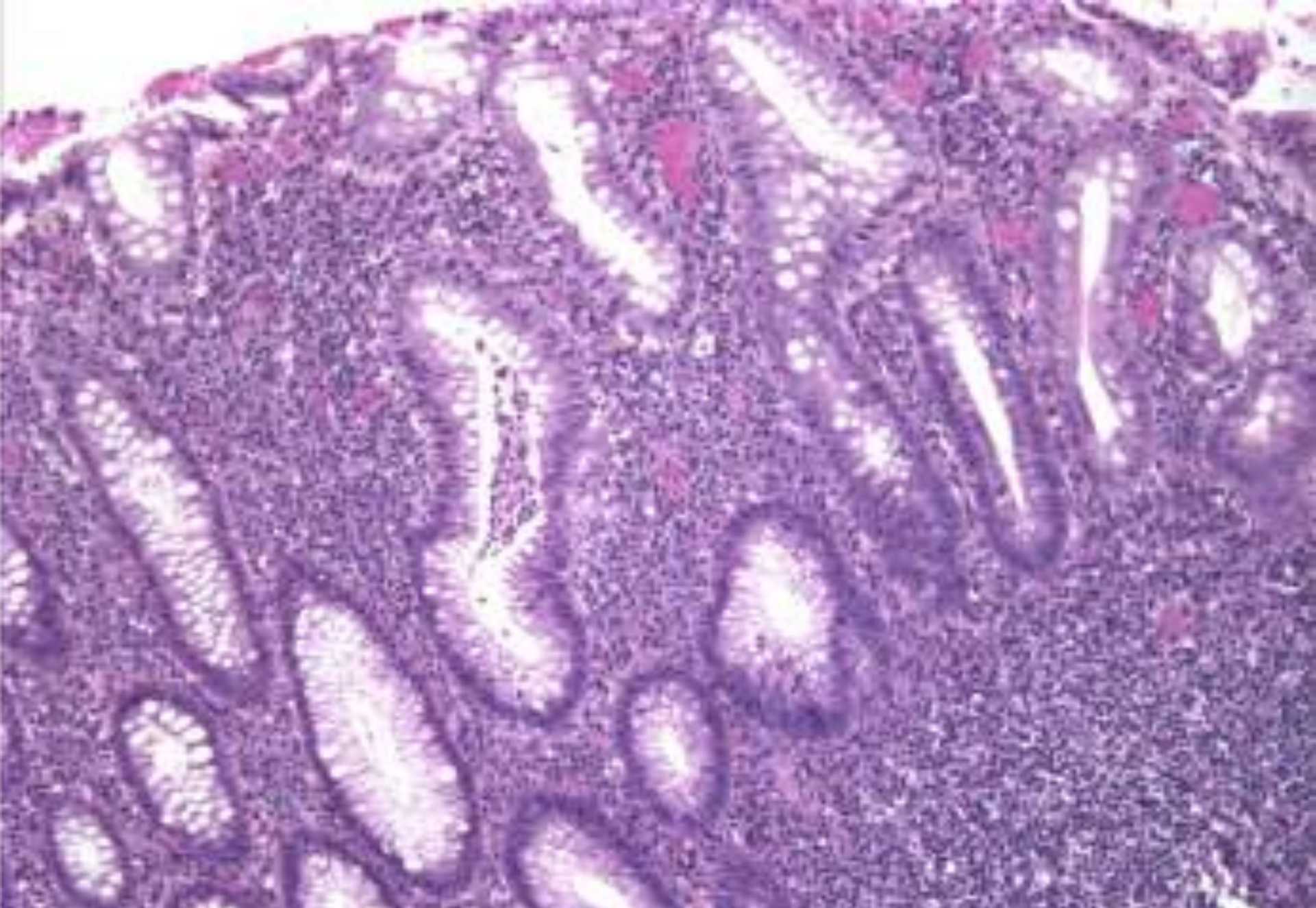
Courtesy Dr. Nathan Lee

Diversion colitis: Prominent lymphoid aggregates



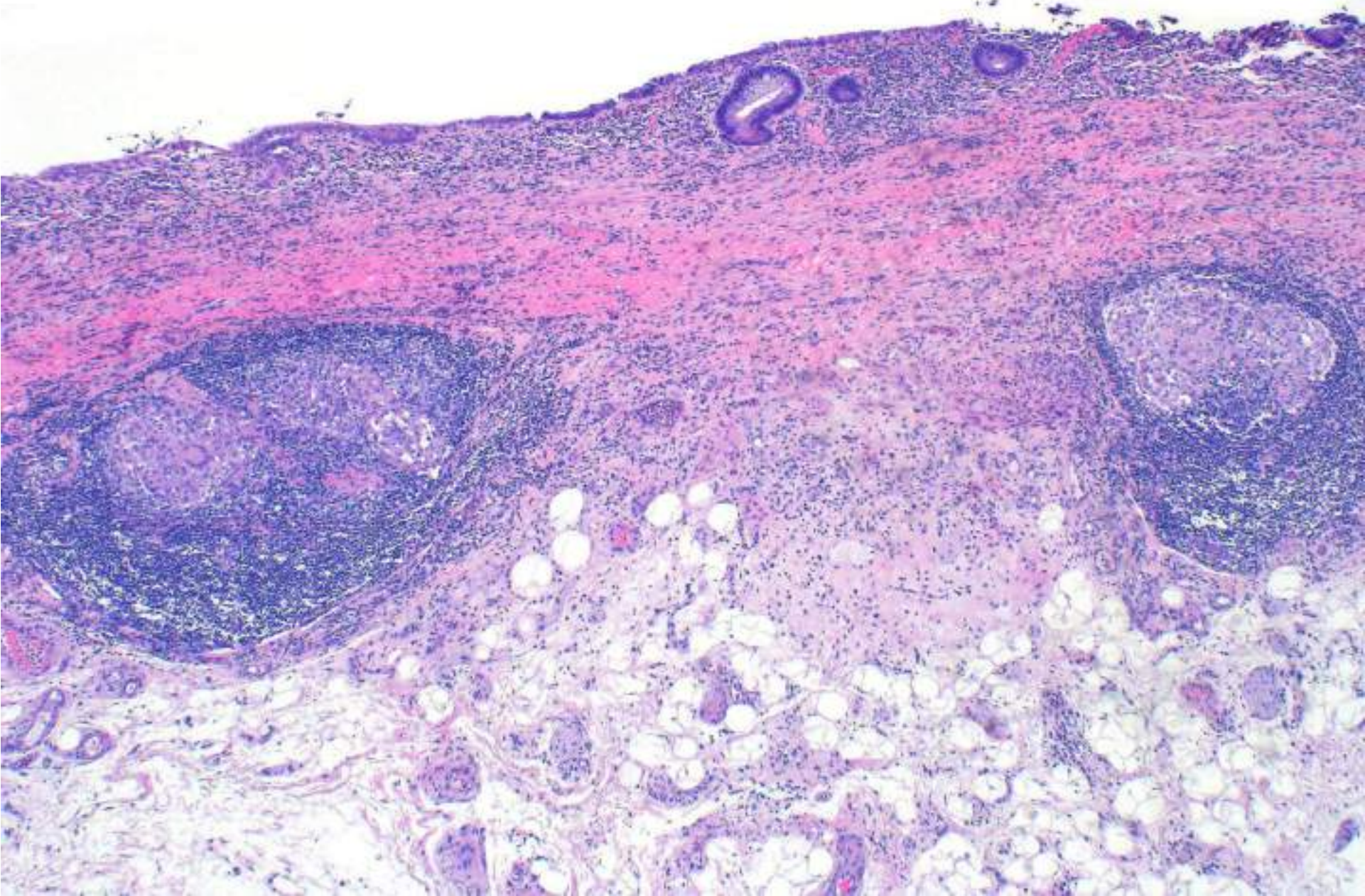
Diversion colitis: Aphthous ulcer





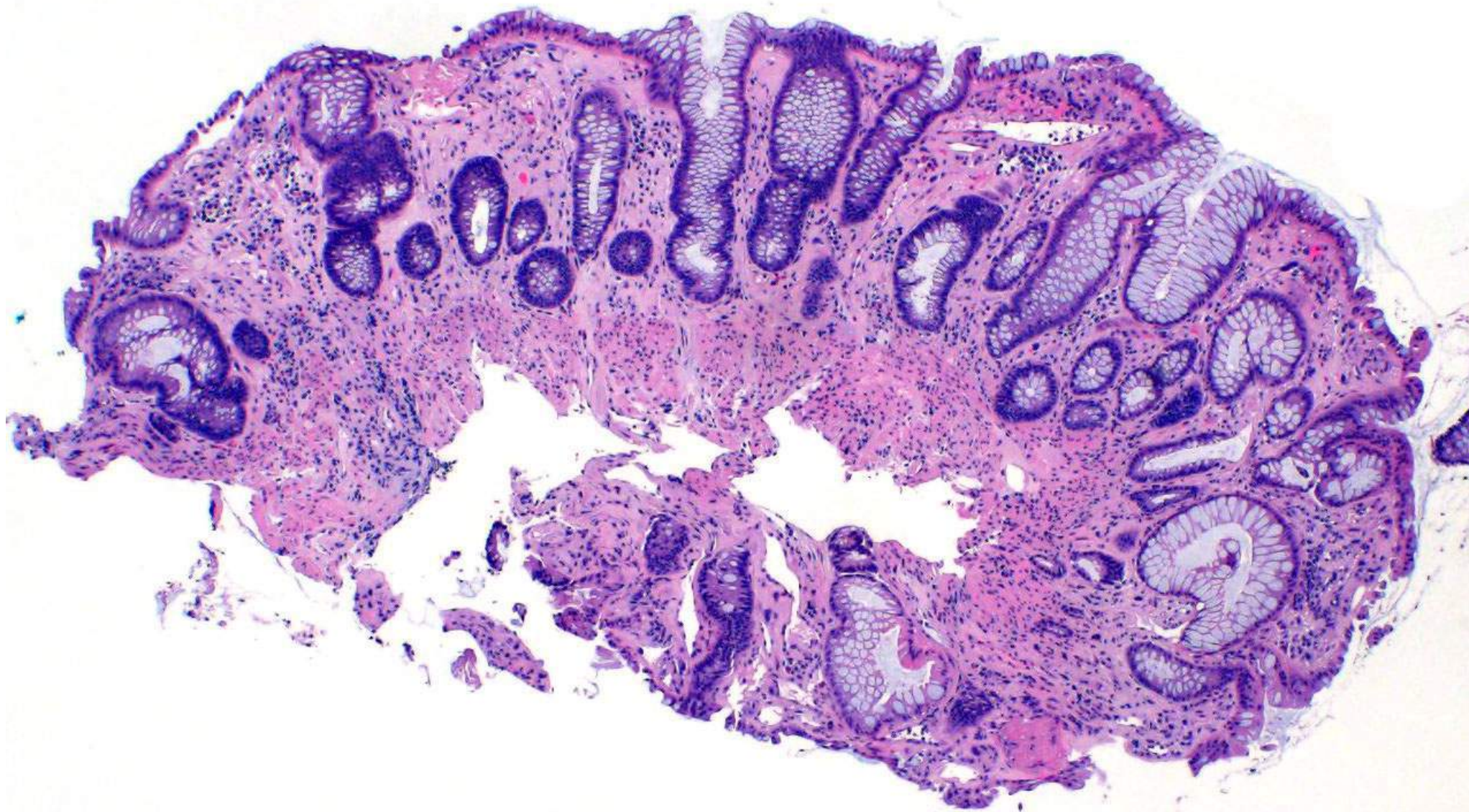
Diversion colitis: Cryptitis, crypt abscesses, and mild architectural distortion

Crohn's like diversion colitis





Chronic GVHD



Chronic radiation colitis: architectural distortion



Avoiding Diagnostic Misadventures with Mimics of CIIBD

- **High index of suspicion**
 - Patients who are immunocompromised rarely develop de novo chronic idiopathic inflammatory bowel disease
- Length of symptoms
- Critical clinical information:
 - Exact distribution of disease
 - History of diversion
 - Food, travel intake
 - Drug history
- Recommend microbial workup liberally

Live Content Slide

When playing as a slideshow, this slide will display live content

**Poll: The following drug is known to
mimic autoimmune enterocolitis:**

The following drug is known to mimic autoimmune enterocolitis:

- Answer: C, ipilimumab, an immune checkpoint-inhibitor, can mimic autoimmune enterocolitis.

Assarzadegan, Montgomery, and Anders: Immune checkpoint inhibitor colitis: the flip side of the wonder drugs. Virch Arch 2018;472:125-133



I think we're done here.

