

Infectious Enterocolitides and the Diseases That They Mimic

Clinical, Morphologic, and Laboratory Correlations

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GI Infectious Diseases are Common Throughout the World

- Transplant patients
- Immunocompromised patients
- Immigration/international travel
- Food/water supply issues

Enteric infectious diseases are second leading cause of death worldwide, after cardiovascular disease

Naturally Occurring Foodborne Diseases

CDC Estimates for USA, 2018

- 37 million illnesses/year
- 228,000 hospitalizations/year
- 2600 deaths/year
- Many food-borne outbreaks and sporadic cases unrecognized

http://wwwnc.cdc.gov/eid/article/20/11/13-1316_article

Naturally Occurring Foodborne Diseases

CDC Estimates for USA, 2010-11

Cases with Identified Pathogens

- 47.8 million illnesses/year
 - 9.4 million illnesses/year
- 128,000 hospitalizations/year
 - 55,961 hospitalizations/year
- 5000 deaths/year
 - 1351 deaths/year

Common Etiologic Agents of Infectious Gastroenteritis

- Food-associated

- *Salmonella*
- *S.aureus*
- *Shigella*
- *Campylobacter*
- *C. perfringens*
- *B.cereus*
- STEC

- Water-associated

- Norwalk Virus (norovirus)
- *Giardia*
- *Shigella*
- *Salmonella*
- *Campylobacter*
- *C. parvum*
- STEC



Top Domestically-Acquired Pathogens Contributing to Foodborne Illness, Hospitalization, and/or Death/Year

Foodborne Illness	Foodborne illness-associated hospitalization	Foodborne illness-associated death
Norovirus 5.5 million	<i>Salmonella</i> (nontyphoid) 19K	<i>Salmonella</i> (nontyphoid) 378
<i>Salmonella</i> (nontyphoid) 1 million	Norovirus 14.5K	<i>Toxoplasma</i> 327
<i>C. perfringens</i> 965K	<i>Campylobacter</i> spp 8K	<i>Listeria</i> 255
<i>Campylobacter</i> spp 845K	<i>Toxoplasma</i> 4.4K	Norovirus 149
<i>S. aureus</i> 241K	<i>E. coli</i> O157:H7 2K	<i>Campylobacter</i> spp 76

Foods Commonly Associated with GI Infection

Raw Dairy	Shellfish	Meat
<i>Salmonella</i>	<i>Vibrio</i>	<i>Salmonella</i>
<i>Campylobacter</i>	<i>Hepatitis A</i>	<i>Campylobacter</i>
<i>Brucella</i>	Norovirus	<i>Yersinia</i>
<i>E. coli</i>	Rotavirus	
<i>Listeria</i>	<i>Salmonella</i>	

Naturally-Occurring Food-Borne Outbreaks



- (2010) *Salmonella* + salami: 184 infections; 1.2 million lbs. recalled
- (2009) *E. coli* + ground beef: 26 infections in 8 states; 545,699 lbs. recalled
- (1998) *Listeria* + hotdogs: 17 deaths; 30 million pounds recalled
- (1990s) Raspberries + *Cyclospora*: 2500 infections in 21 states

Enteric Infections Acquired from Animals (rare!)

	Birds	Cats	Dogs	Goats	Ham- sters	Mon- keys	Sheep	Snake	Tur- tle
<i>Aeromonas</i>								X	X
<i>Campylobacter</i>		X	X	X	X		X		X
<i>Salmonella</i>	X	X	X		X	X		X	X
<i>Yersinia</i>	X	X	X						
<i>Crypto- sporidium</i>		X	X	X			X		
<i>Giardia</i>		X	X						
<i>Strongyloides</i>			X						



Challenges for Anatomic Pathologists When Evaluating a Specimen for an Infectious Process

- Everything is in formalin
 - No cultures
 - Limits molecular
- Available resources/techniques that aid in diagnosis may be limited/unavailable, expensive, or unknown to pathologist
- Lack of pertinent history
- Patient given abx before biopsy procedure

Challenges for Pathologists When Evaluating a Specimen for an Infectious Process

- The training that most of us get in ID pathology is at odds with the worldwide frequency of infectious diseases
 - Most pathology training in infectious diseases is in microbiology and divorced from examination of tissue sections
 - Ideal diagnostic environment involves morphology, microbiology, and molecular tests
- Some entities are more easily recognized in tissue than by other means
 - HCV, Pneumocystis jirovecii, coccidians

The Anatomic Pathologist's Goals when Evaluating a GI specimen for Potential Infection

1

Distinguish infectious processes from other processes (ischemia, chronic idiopathic inflammatory bowel disease)

2

Try (enthusiastically!) to identify infectious organism or pattern of infection

- Biopsy often out long before culture result
- Tissue often not preserved for other studies

3

Be aware of resources/techniques that aid in diagnosis

Aids to Diagnosis

- Immunostains
 - Availability
 - Sensitivity/specificity
- Special histochemical stains
 - Gram: hard to tell enteric pathogens from normal commensals
 - Silver impregnation: high background
- Culture
 - Organism may be fastidious
 - Can't tell virulent from nonvirulent strains
 - Patient may have gotten abx

Aids to Diagnosis

- Serologic studies
 - Many cross-reactive organisms
 - Often need acute and convalescent titers
 - False negatives in immunocompromised, very old, or very young patients
- Molecular testing
 - Formalin fixation limits yield
 - Block may be exhausted
 - Stool PCR

The Anatomic Pathologist's Goals when Evaluating a GI specimen for Potential Infection

- Optimize opportunities to intervene and guide the workup:
 - Get material for culture, molecular studies
 - Rapid evaluation techniques
 - Frozen section
 - Touch preps
 - Air dried smears
 - Smears, touch preps, and frozens can be used for same-day special stains

The Anatomic Pathologist's Goals when Evaluating a GI specimen for Potential Infection

- Formulate final anatomic diagnoses that correlate clinical history with
 - Histology
 - Special stains
 - Immunologic studies
 - Molecular studies
 - Cultures (if possible)

Helpful History

- Travel
- Food intake
- Work/environmental exposure
- Animal exposure/zoonoses
- Tick, other vector exposure
- Sexual practices
- Immune status

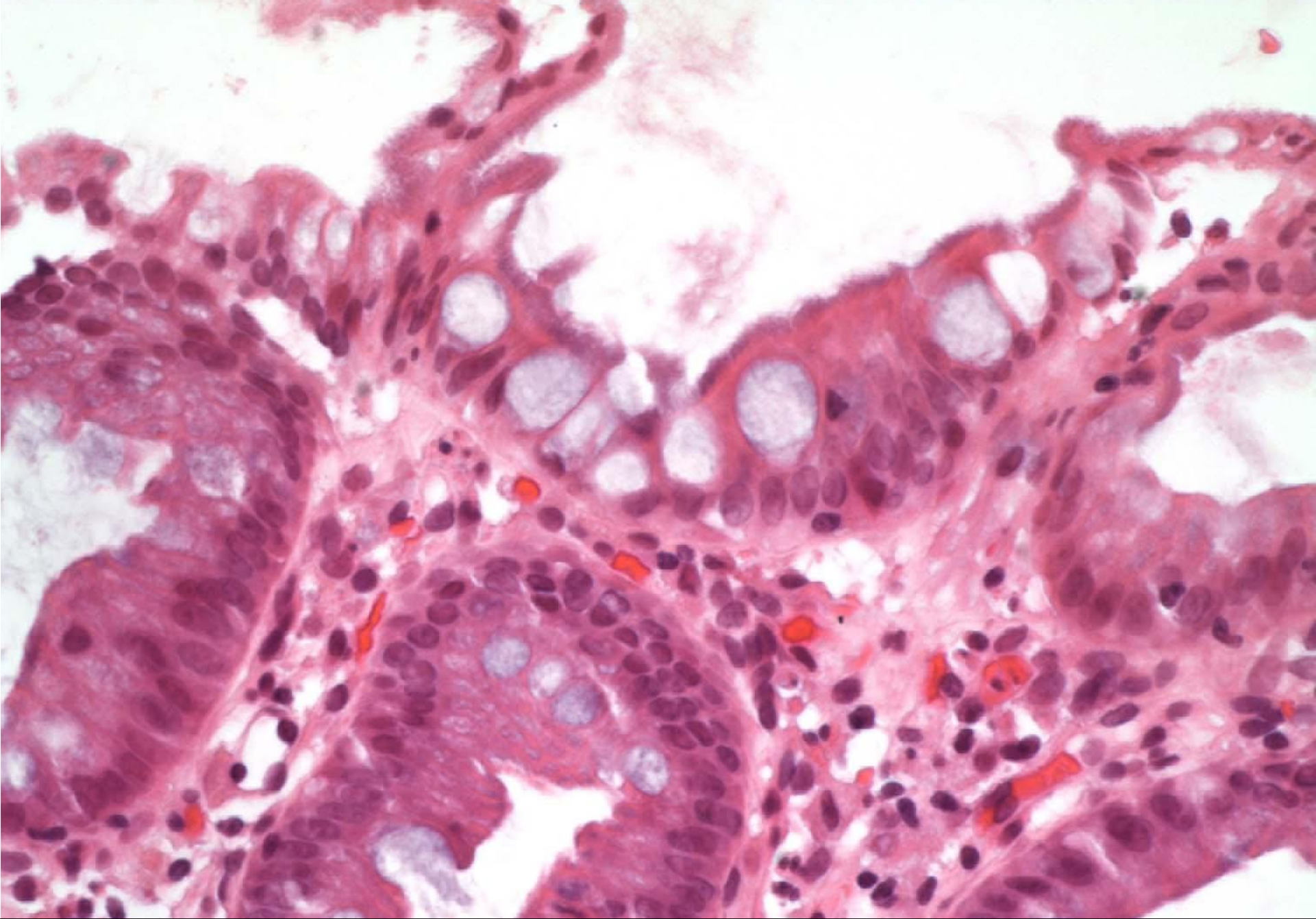
General Classification of Histologic Patterns in Infectious Enterocolitides

- Minimal or no inflammation
- Acute infectious-type enterocolitis/Acute self-limited colitis
- More specific or suggestive patterns:
 - Pseudomembranes
 - Granulomas
 - Diffuse histiocytic infiltrate
 - Architectural distortion
 - Viral inclusions or other visible organisms

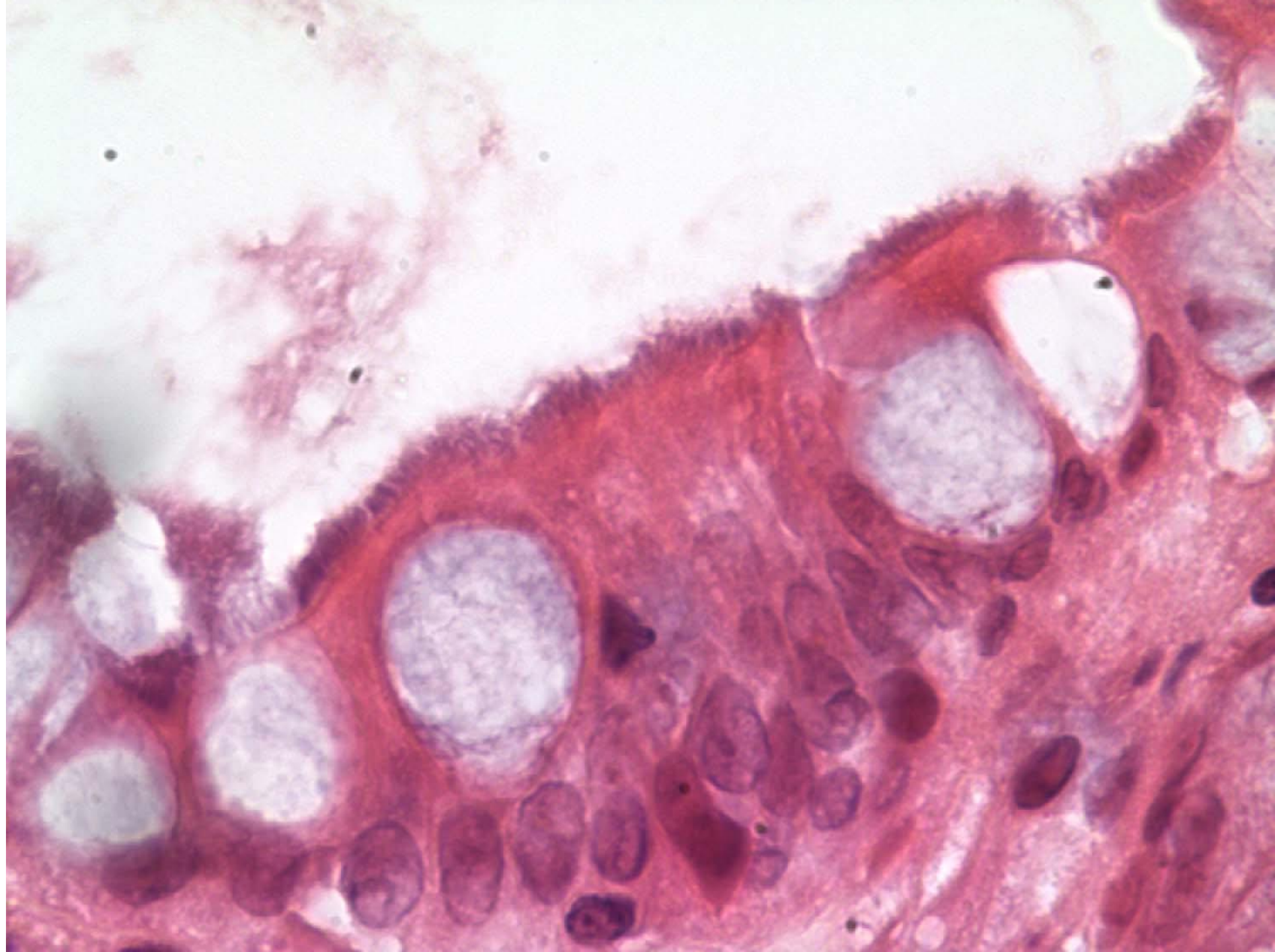
Histologic pattern directs diagnostic algorithm

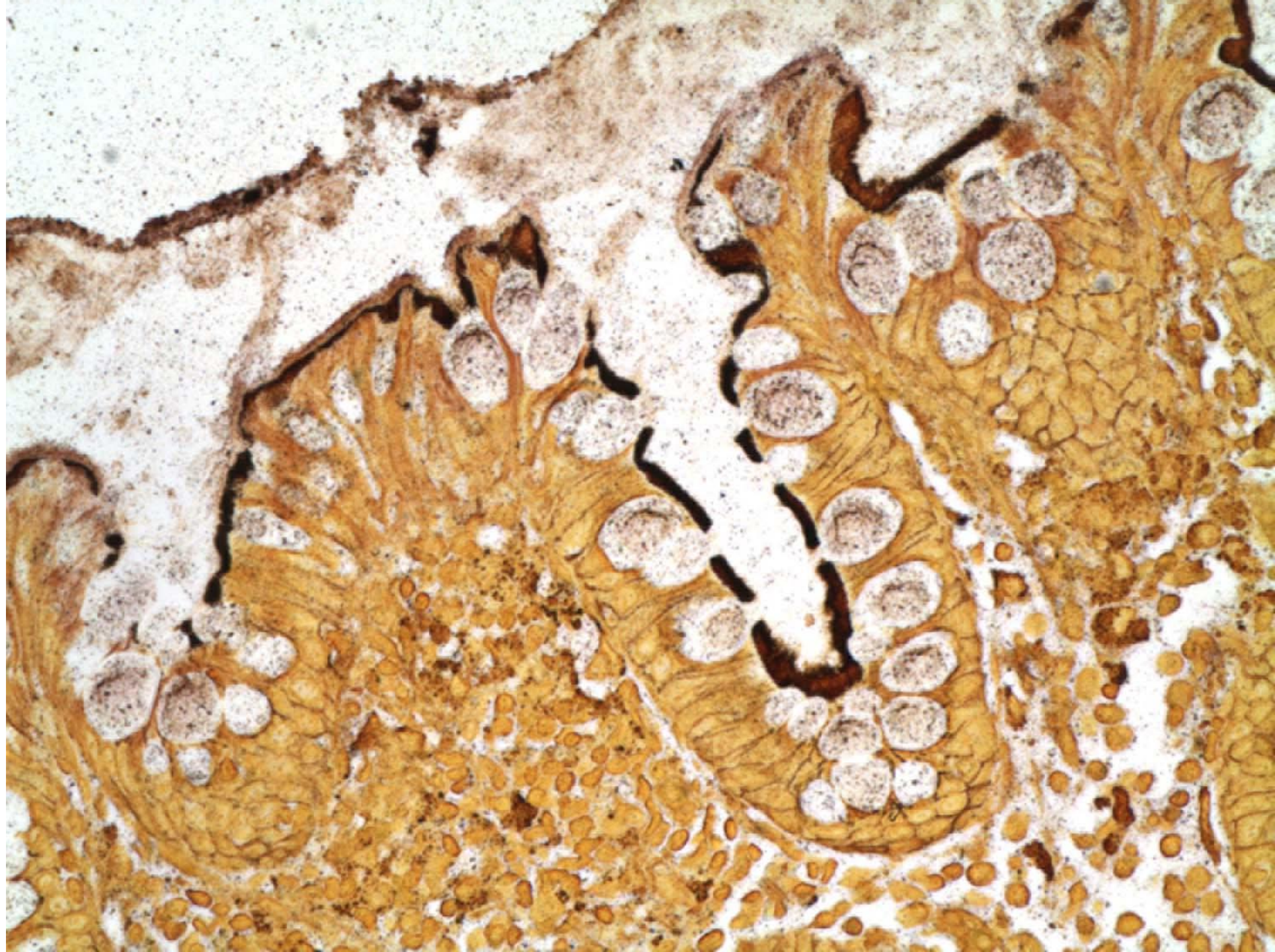
Infections Producing Minimal or No Inflammation

- *Vibrio* and non-*Vibrio cholerae*
- Enteropathogenic and Enteroadherent *E. coli*
- Spirochetosis
- *Neisseria* species
- Many enteric viruses



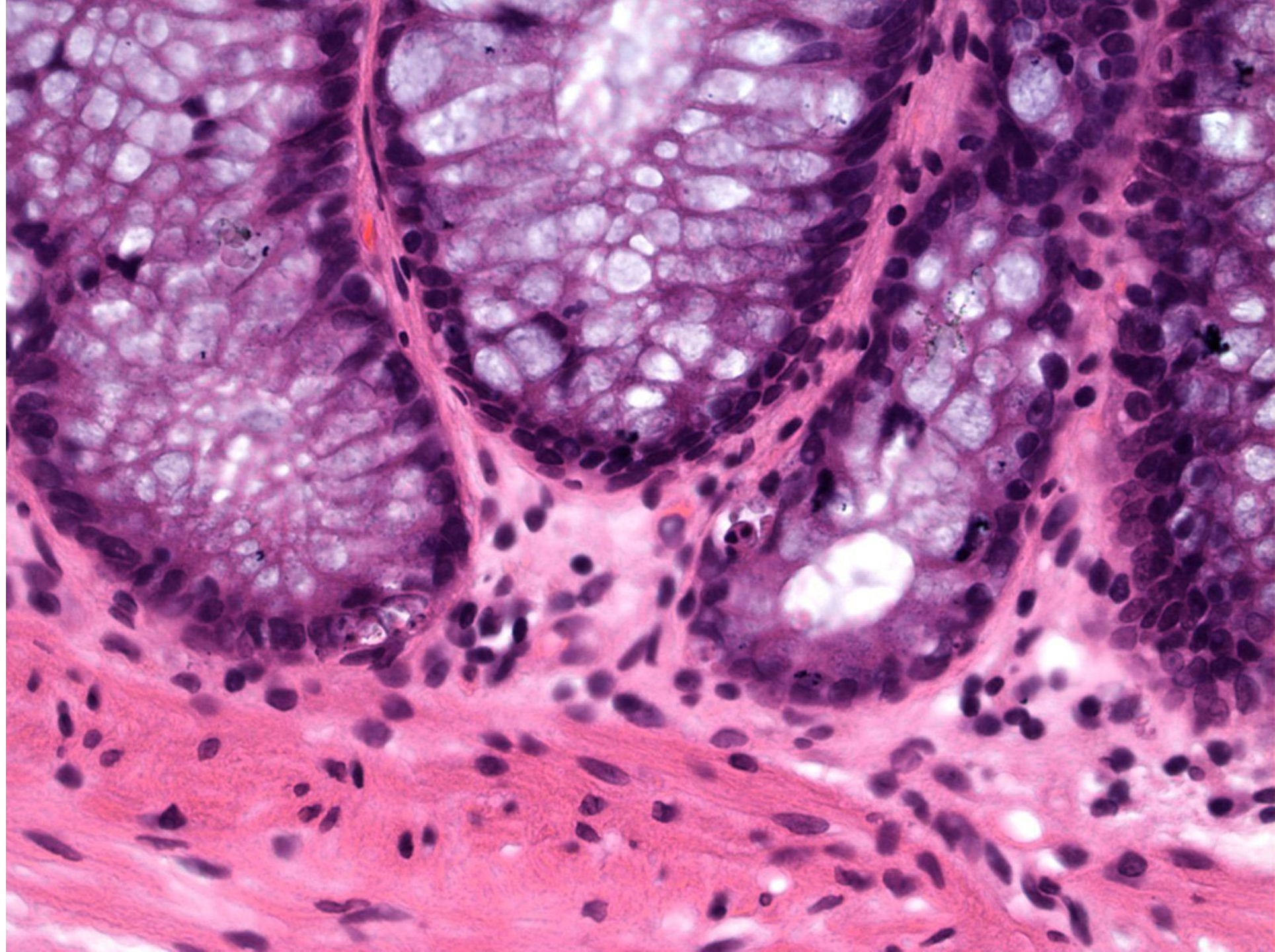
Spirochetosis

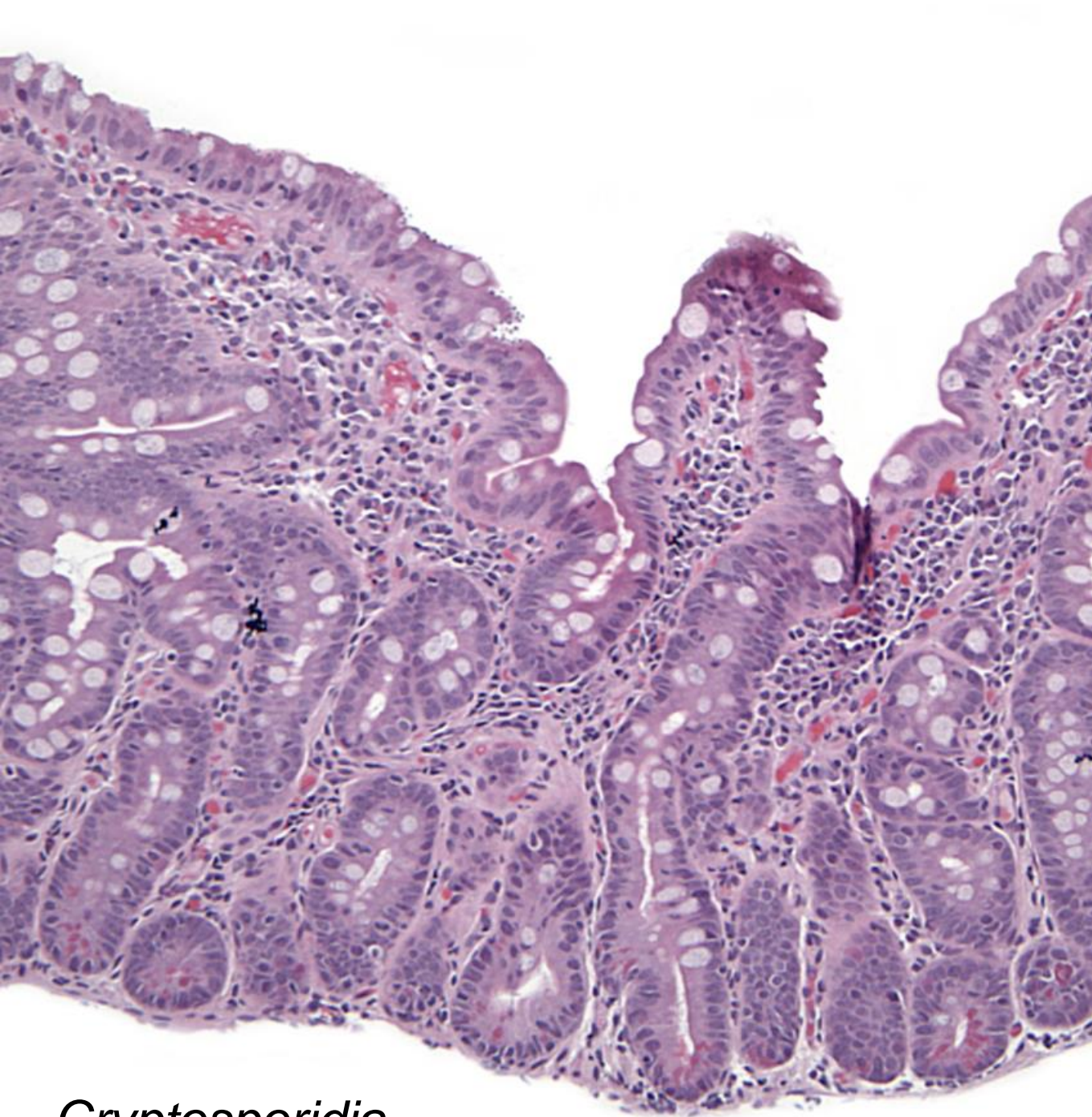




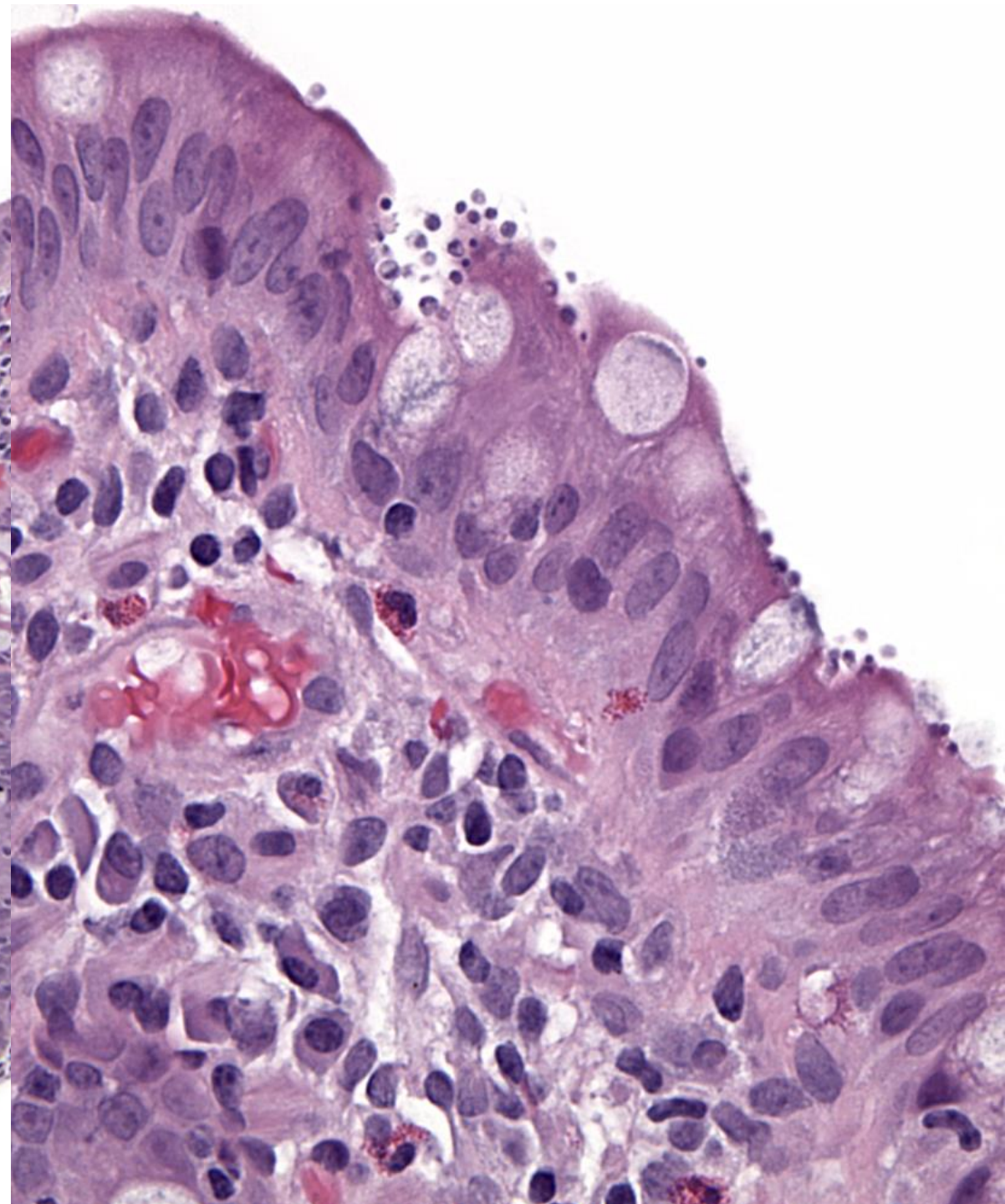


HIV enterocolopathy



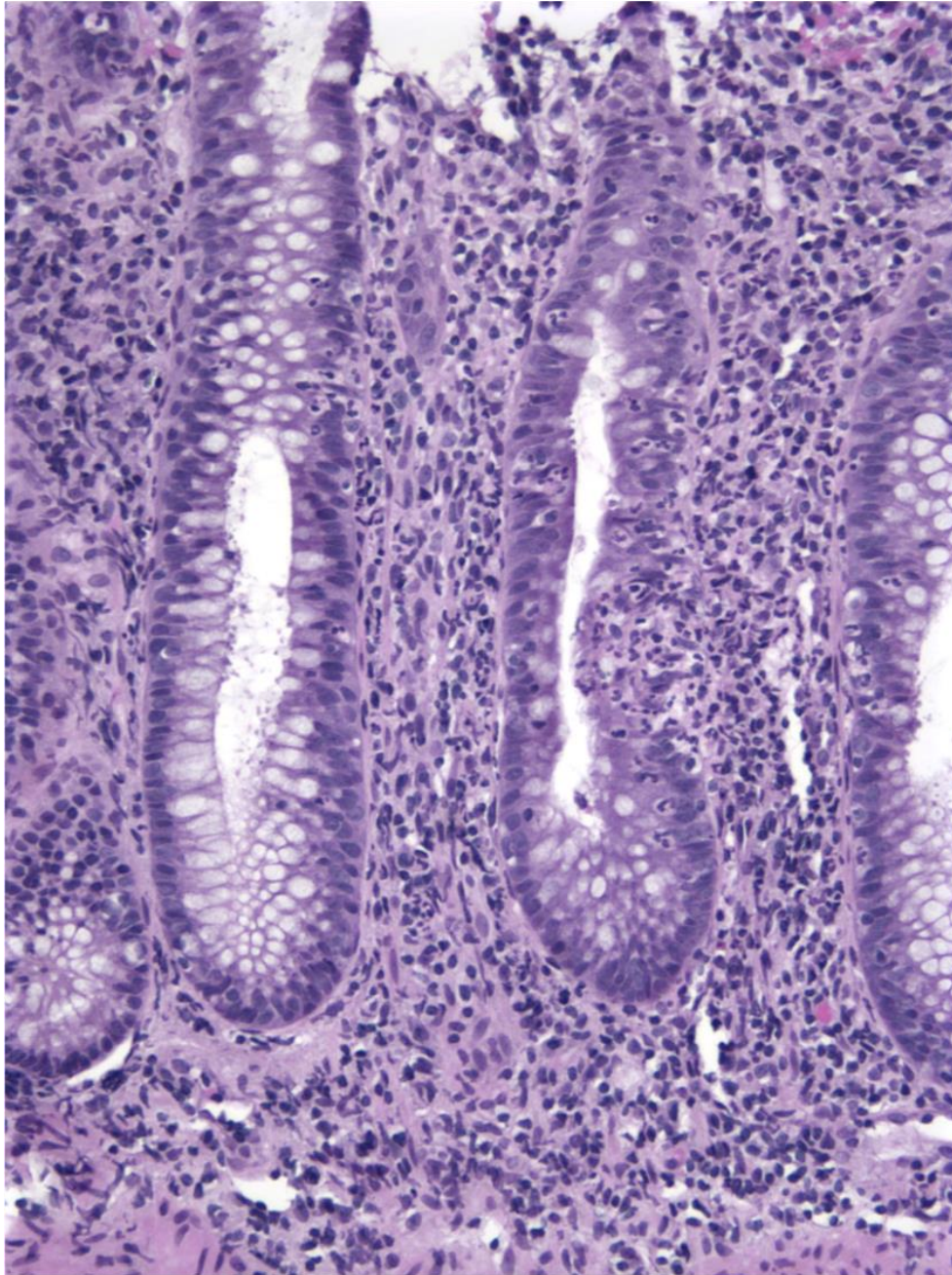


Cryptosporidia



Infections Producing ASLC/AITC Pattern

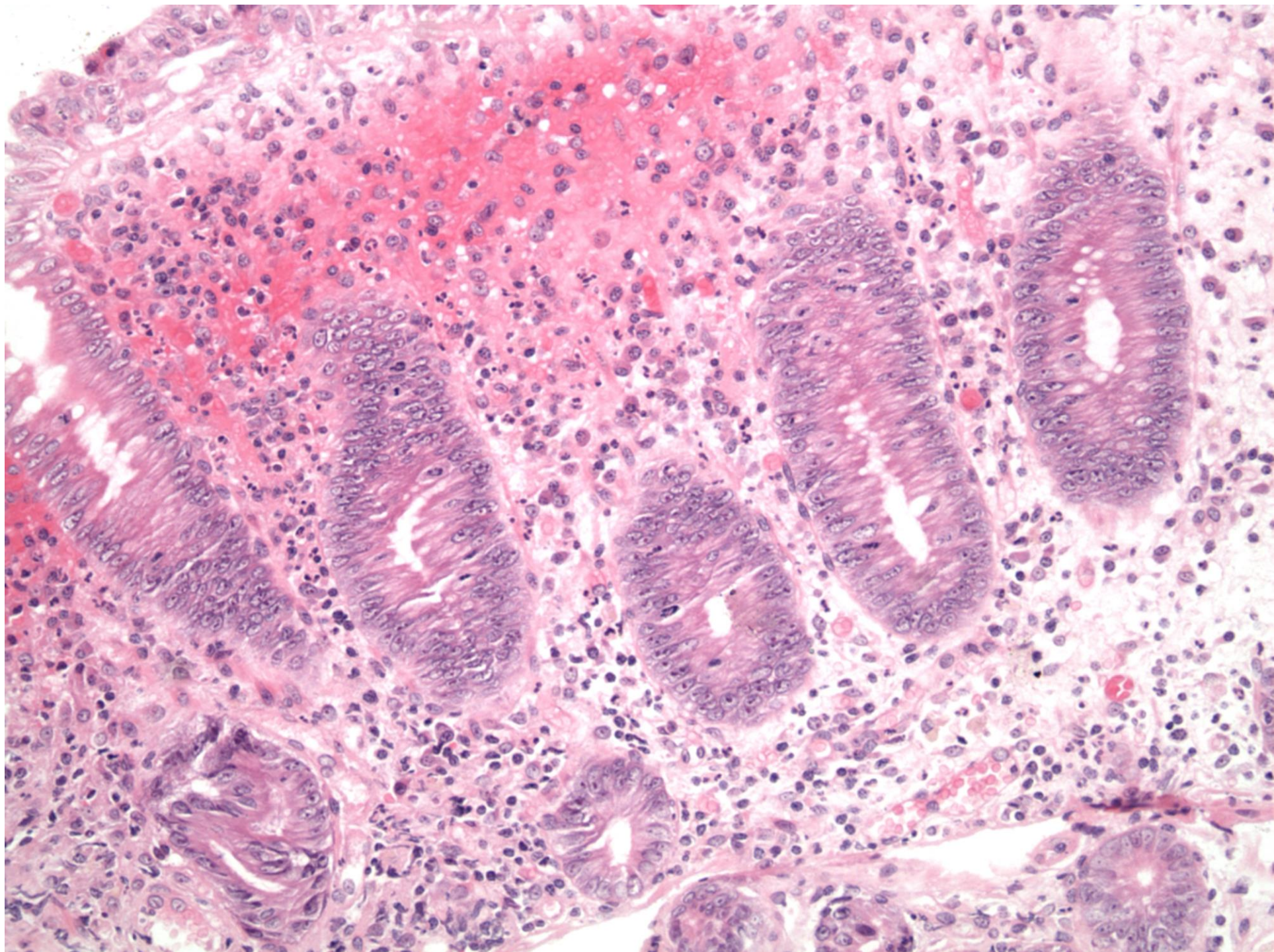
- *Campylobacter* species
- *Shigella*
- *Aeromonas*
- Syphilis (+/- plasma cells)
- Occasionally:
 - *Yersinia*
 - *C. difficile*
 - Non-typhoid *Salmonella*



- Most common histologic pattern in enteric infections

- PMN infiltrate
- Intact architecture

- +/- Crypt abscesses
- No basal plasma cells
- Surface damage



Infections Producing More Specific Diagnostic Features

Pseudo-membranes	Granuloma Formation	Diffuse histiocytic	Architectural Distortion	Inclusions/ Organisms Visible on H&E
<i>C. difficile</i>	<i>Yersinia</i>	<i>R. equi</i>	<i>Salmonella</i>	CMV/HSV
STEC	<i>M. Tb</i>	<i>MAI</i>	<i>Shigella</i>	EAEC
Rarely <i>Shigella</i>	Fungi	Whipple's Disease	Amoeba	Spirochetosis
	Actino-mycosis		Sometimes <i>Aeromonas</i>	Fungi
				Amoeba

GI Infectious Diseases That Mimic Other Processes

Mimics of Crohn's	Mimics of UC	Mimics of Ischemia	Mimics of Normal
<i>Salmonella</i>	<i>Salmonella</i>	STEC	Coccidians
<i>Shigella</i>	<i>Shigella</i>	<i>Aspergillus</i>	Histoplasmosis
<i>Yersinia</i>	<i>E. histolytica</i>	<i>Mucor</i>	EAEC
<i>Campylobacter</i>		CMV	
<i>Aeromonas</i>		<i>C. perfringens</i>	
<i>E. histolytica</i>		<i>C. difficile</i>	
CMV			
<i>M. tuberculosis</i>			
LGV			

Bacteria multiplying on raw kangaroo meat at room temperature over 3 hours

Time	# of bacteria
Start-leave raw meat out	100
20 min	200
40 min	400
60 min	800
80 min	1600
100 min	3200
120 min	6400
140 min	12,800
160 min	25,600
3 hours	51,200



IBD vs. Infection

Specific GI Infectious Disease Examples

- Commonly encountered
 - Responsible for majority of food-related illnesses worldwide
- Mimic other inflammatory conditions

Campylobacter species

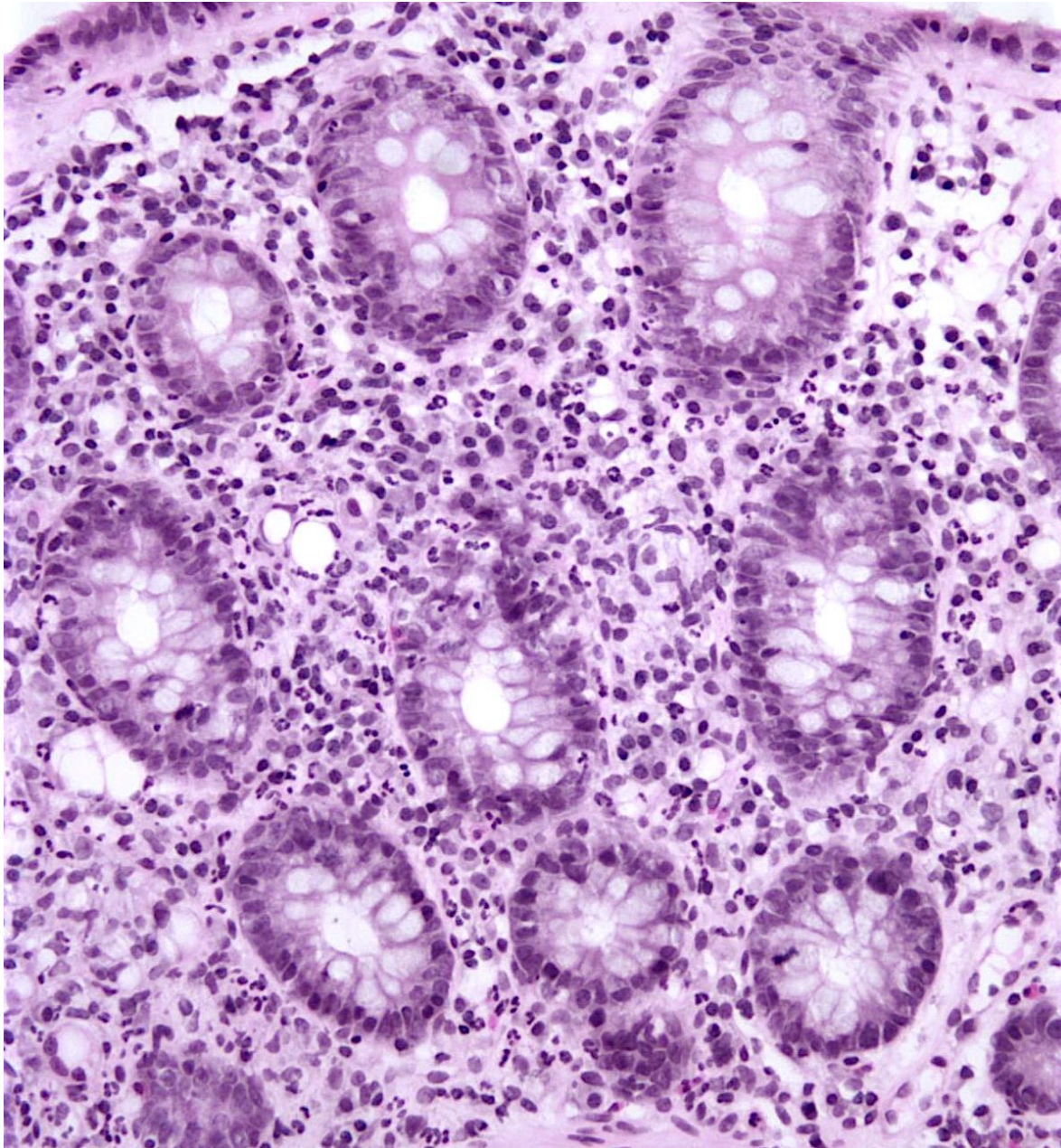
- Most common stool isolate in USA
- Contaminates meat, poultry, water, milk
 - Fecal-oral transmission also possible



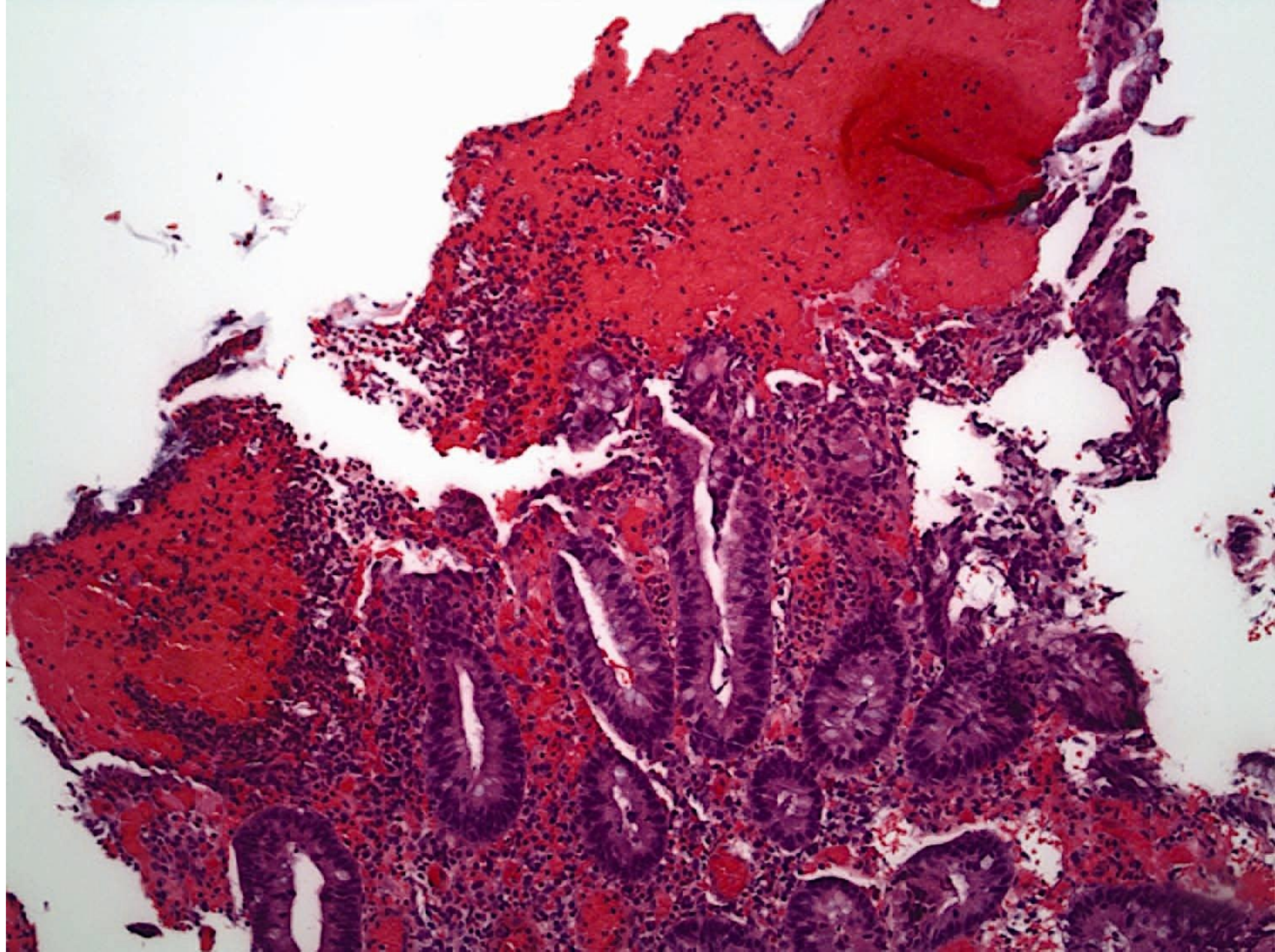
Common Enteric Infections

Clinical Features

	Fever	Diarrhea	Infective Dose	Prognosis	Pattern	Other
Campylobacter spp.	Usually	Yes, +blood, WBC	500 bugs	Usually self-limited; relapse common	AITC	Arthropathy, GBS
Salmonella (Typhoid)	Yes, high	Yes, at 2-3 weeks	1000	Need abx; may cause sepsis	IBD mimic	Rash, leukopenia, HSM
Salmonella (non-Typhoid)	Yes	Yes	1000	Good with abx	AITC; rarely mimics IBD	Milder illness
Shigella spp.	Yes	Yes, +blood, mucus, pus	10-100	Need abx; may cause sepsis, perforation	AITC or IBD mimic	Constitutional sx; HUS



- Lamina propria neutrophils
 - More prominent superficially
- +/- Cryptitis and crypt abscesses
- Preservation of crypt architecture



Campylobacter

- Diagnosis:
 - Stool PCR
 - Culture
 - Patients often on empiric abx therapy prior to biopsy
 - Darkfield examination of stool smears
 - Campy antigens on immunoassay

Salmonella species

Clinical

- Typhoid (*S. Typhi* or *S. Paratyphi*)
 - Rising fever
 - Abdominal pain
 - Rash
 - Leukopenia
 - Hepatosplenomegaly
 - Diarrhea @ 2-3 weeks
- Non-typhoid (e.g., *S. enterica* ser. Typhimurium)
 - Milder illness
 - Nausea
 - Vomiting
 - Milder fever
 - Watery diarrhea

Common Enteric Infections

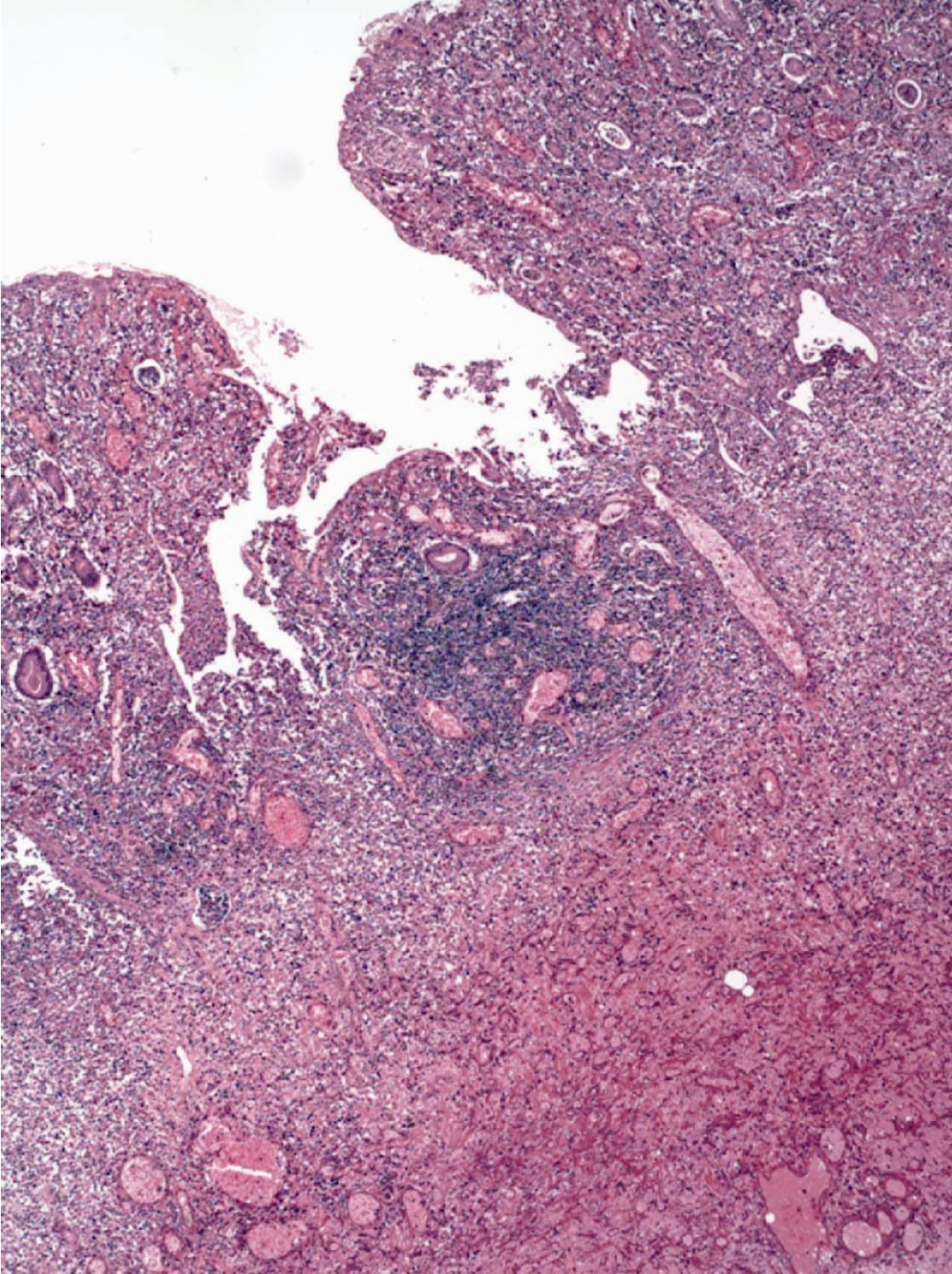
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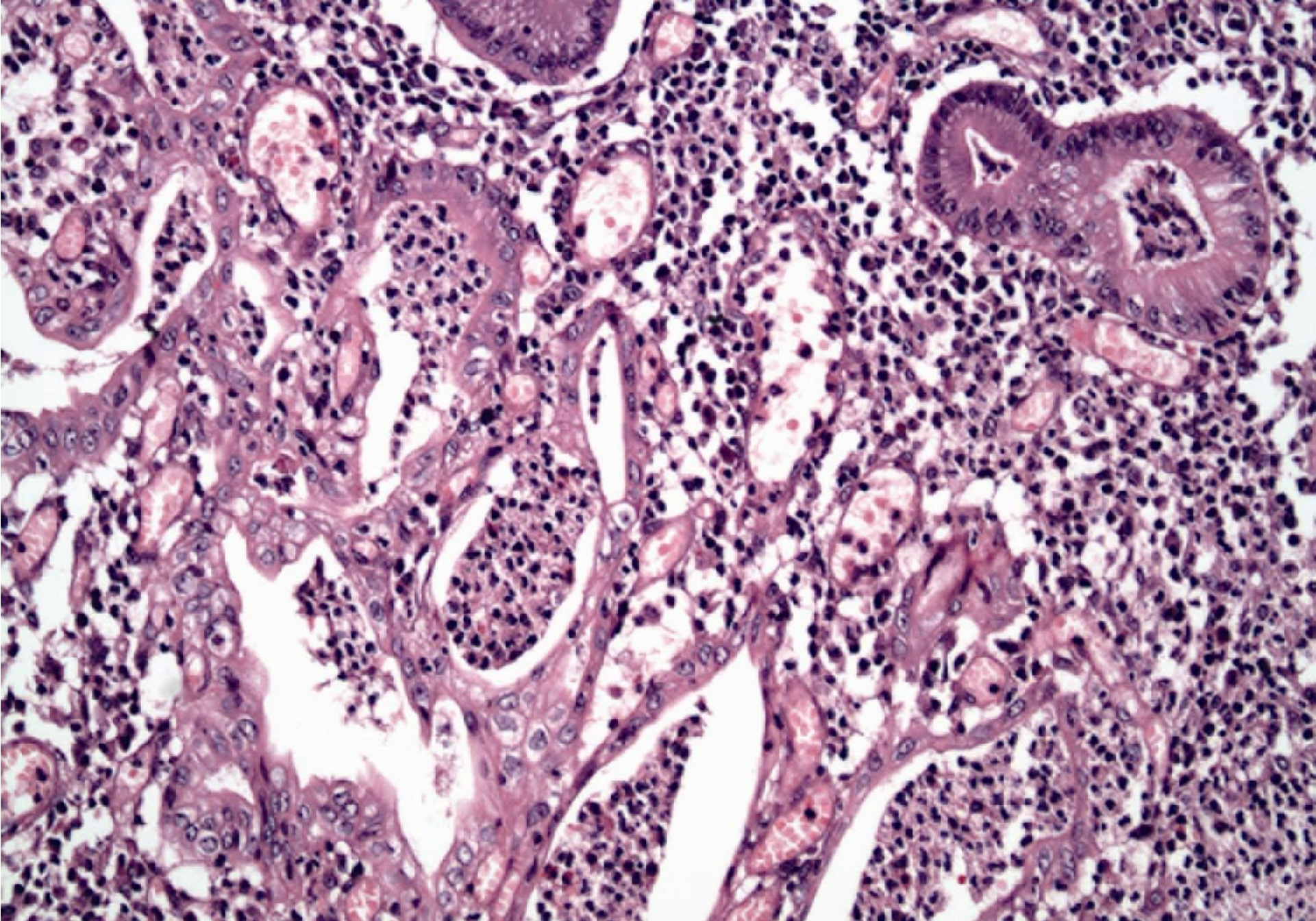
Salmonella species

Gross Pathology

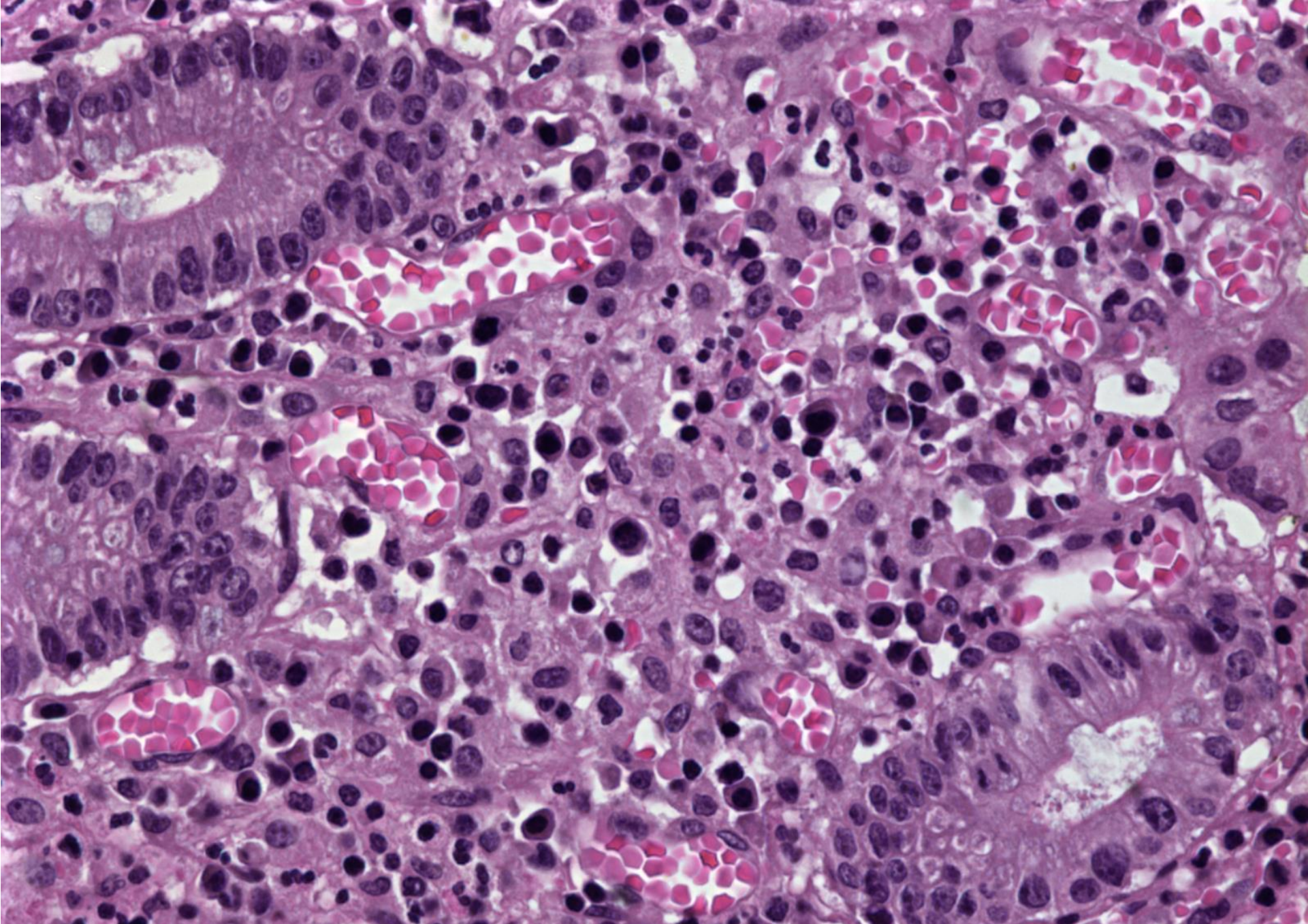
- Favors ileum, appendix, right colon
- Thickened wall, raised nodules over Peyer patches
- Ulceration and necrosis
- Mesenteric adenopathy
- Milder findings in non-typhoid species, but considerable overlap



Ulcers typically occur over Peyer's patches, with necrosis of mucosa



Architectural distortion, crypt abscesses

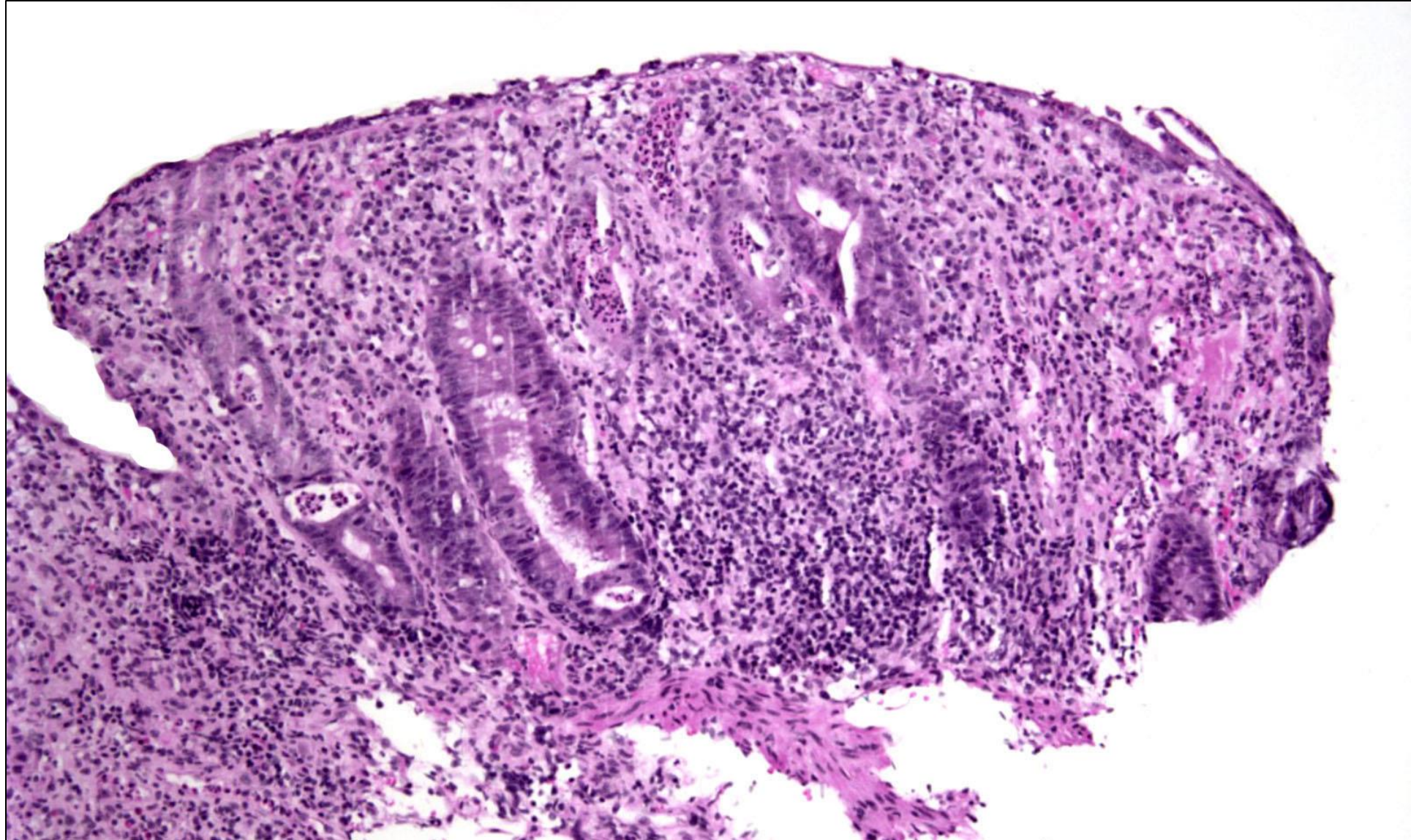


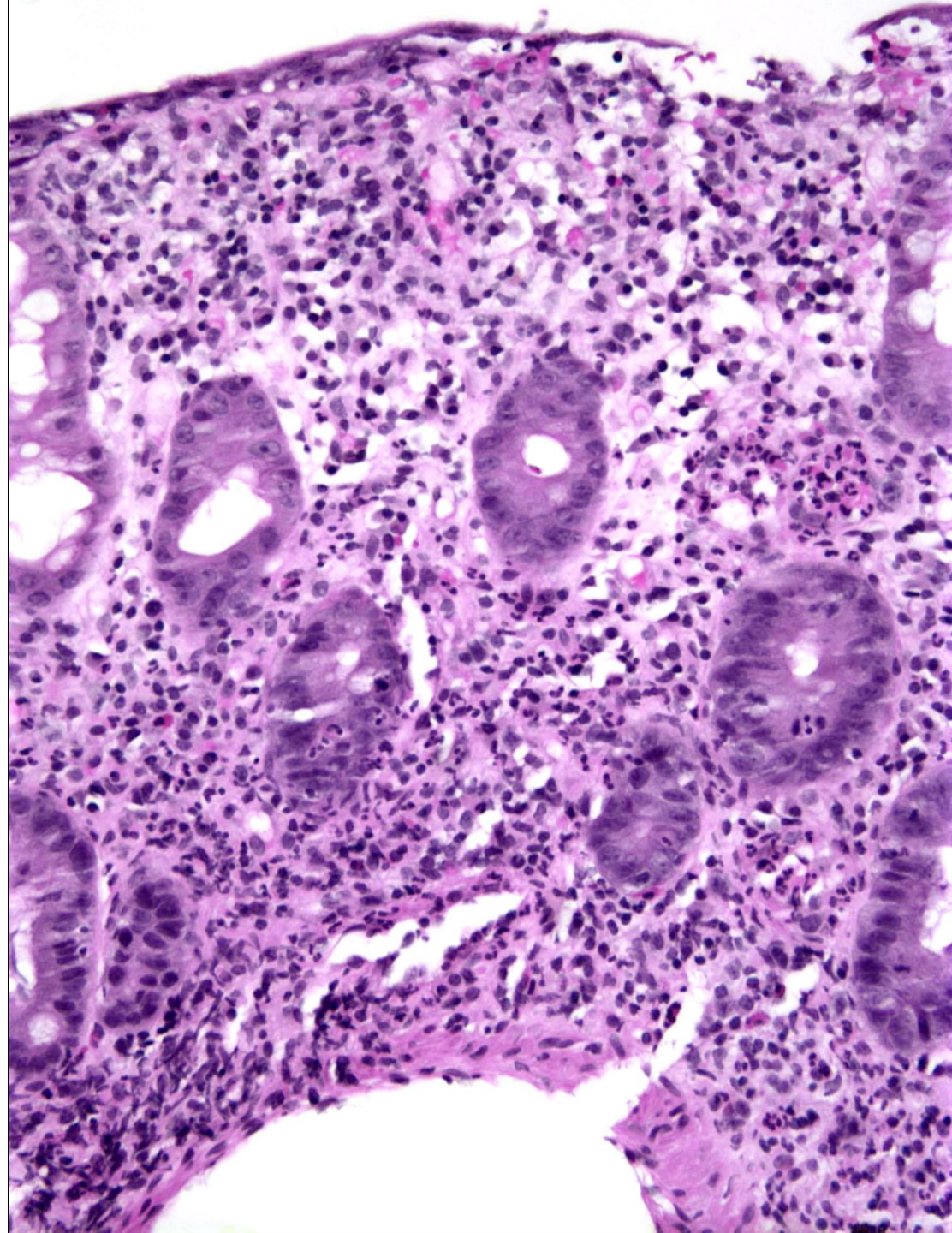
Histiocytes and mononuclear cells are most prominent, with fewer neutrophils

Salmonella

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

Non-typhoid *Salmonella*





Salmonella species

Diagnosis

- Stool PCR
- Stool cultures
- Differential Diagnosis
 - Other enteric pathogens
 - Neutrophils less prominent
 - Granulomas unusual
 - Idiopathic IBD
 - Can see significant crypt distortion

Shigella species

- Invasive, virulent bacteria
- Typically from contaminated water
- Fecal-oral transmission also possible

Common Enteric Infections

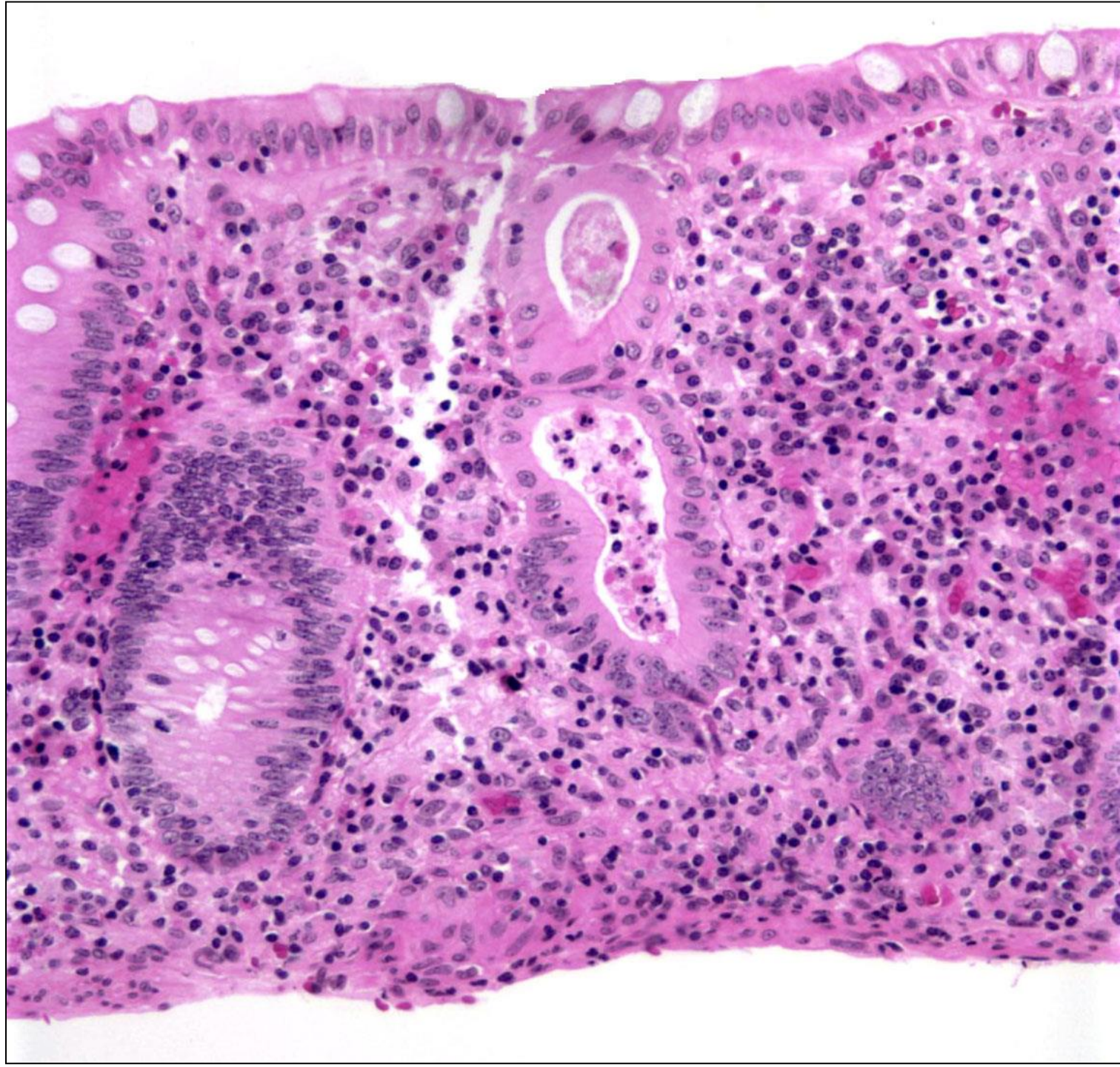
Clinical Features

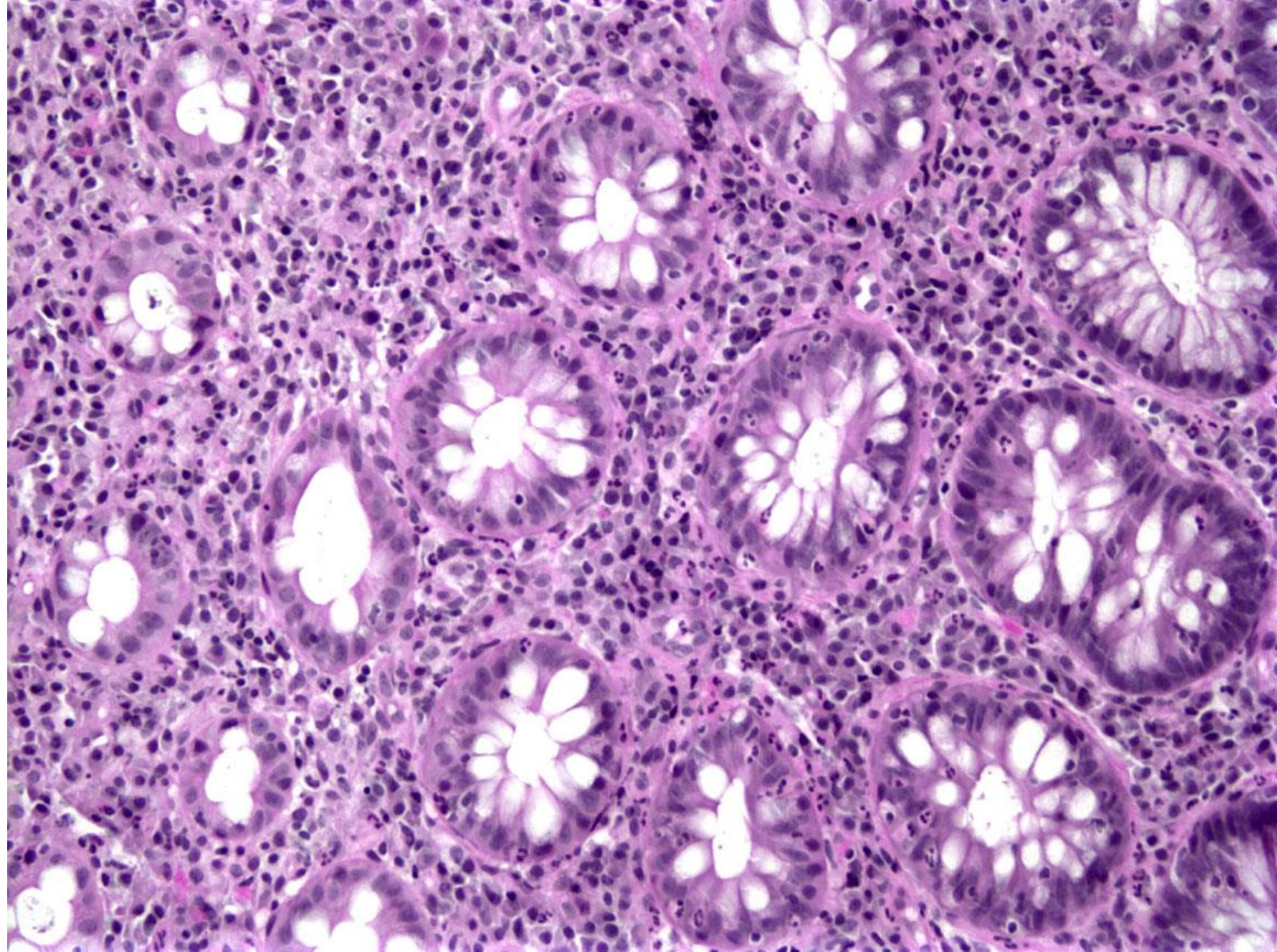
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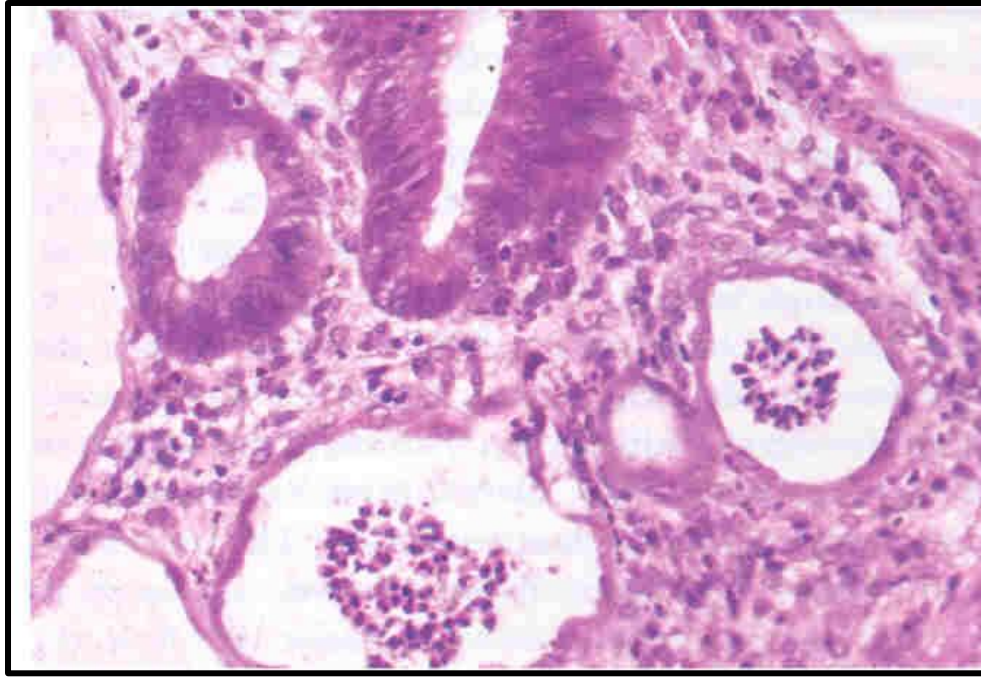
Shigella species

Pathologic Findings

- Favors left colon
 - May endoscopically mimic UC
- +/- pseudomembranes
- Early shigellosis has AITC pattern
- Later in the disease there is often significant mucosal damage, architectural distortion (mimicking UC)

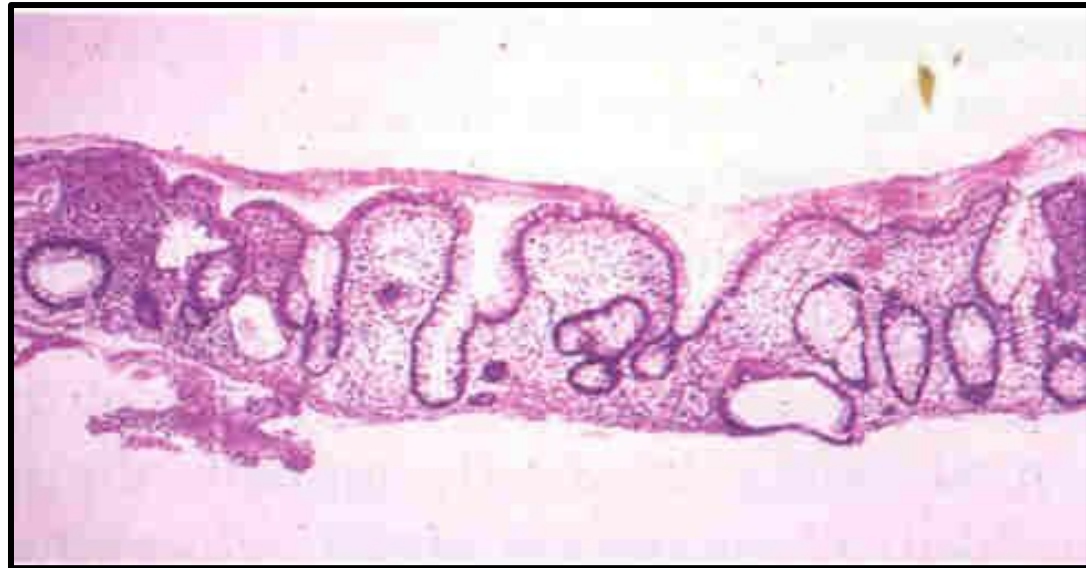


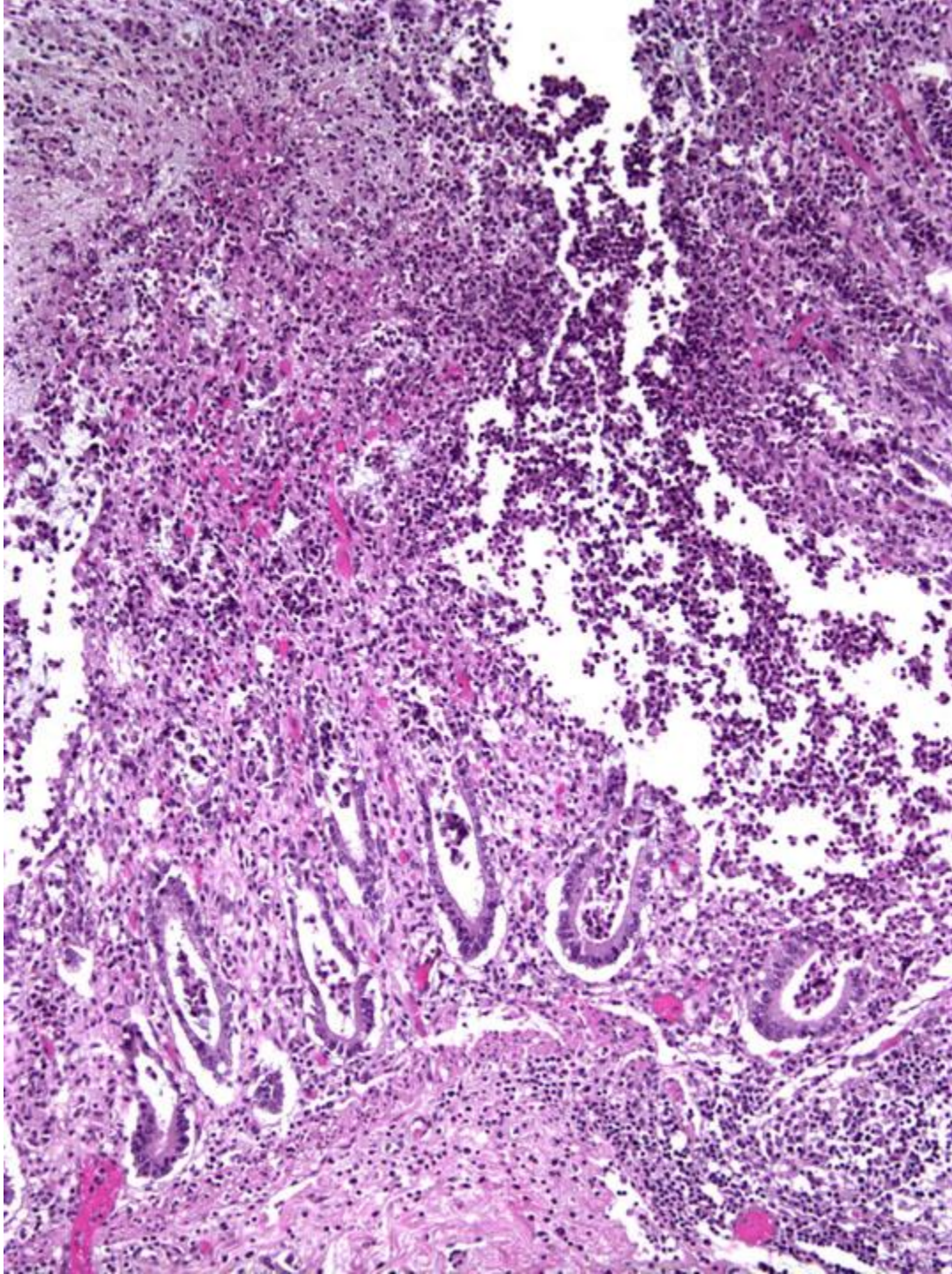




Shigellosis with
marked architectural
distortion

from Riddell, Lewin, and Weinstein:
*Gastrointestinal Pathology and Its
Clinical Implications*





Pseudomembranous Shigellosis

Shigella dysenteriae I: a forgotten cause of pseudomembranous colitis. J Pediatr 1976;89:595-6.

Courtesy Dr. John Hart

Yersinia (enterocolitica and pseudotuberculosis)

- One of the most common causes of bacterial enteritis in N. America and Europe
- Wide variety of acute and chronic GI manifestations
- Contaminates meat, shellfish, poultry, milk and dairy, water

Chitterlings

also Chitlins or Chitlings

- “The small intestines of pigs, especially when cooked and eaten as food.”
 - Probable diminutive of Old English *cieter*, intestines
 - American Heritage Dictionary of the English Language, 3rd ed, 1996.

The Chitterling Data

Tauxe et al

- CDC studied a group of children in Atlanta in 1990 with gastroenteritis secondary to YE (by stool isolate)
- Outbreaks clustered around holidays
- More than 50% exposed to raw pork intestines during household chitterling preparation
- Similar data acquired in Belgium where eating raw and undercooked pork is common

Yersinia

Gross Pathology

- Involves ileum, right colon, and appendix preferentially
- Thickened wall with apthous and linear ulcers
- Associated lymphadenopathy

ENDOSCOPY CENTER

1



2



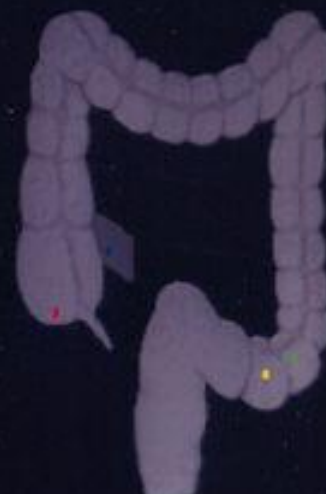
3



4



10/07/2002 COL

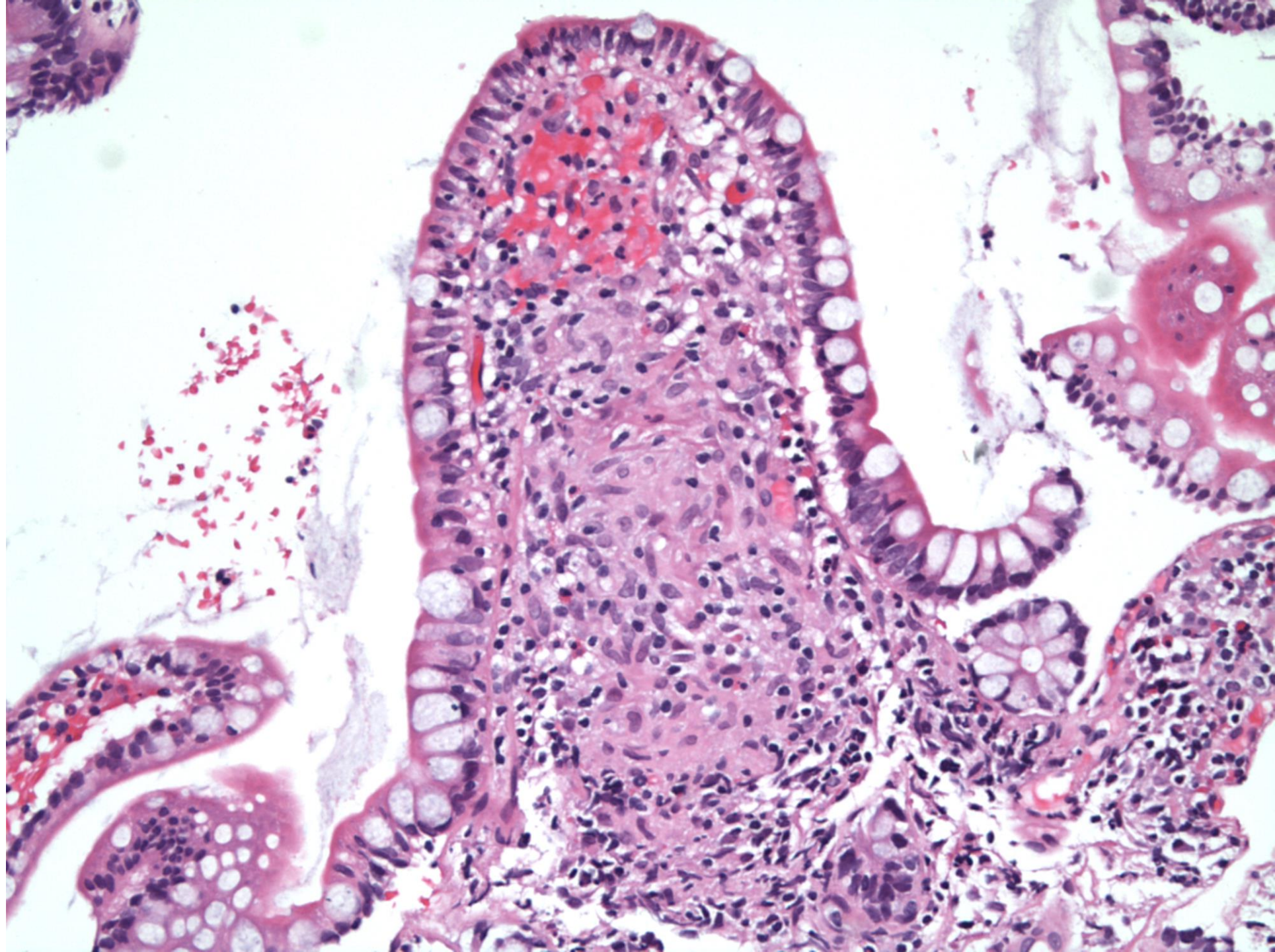


1 cecum

2 TI

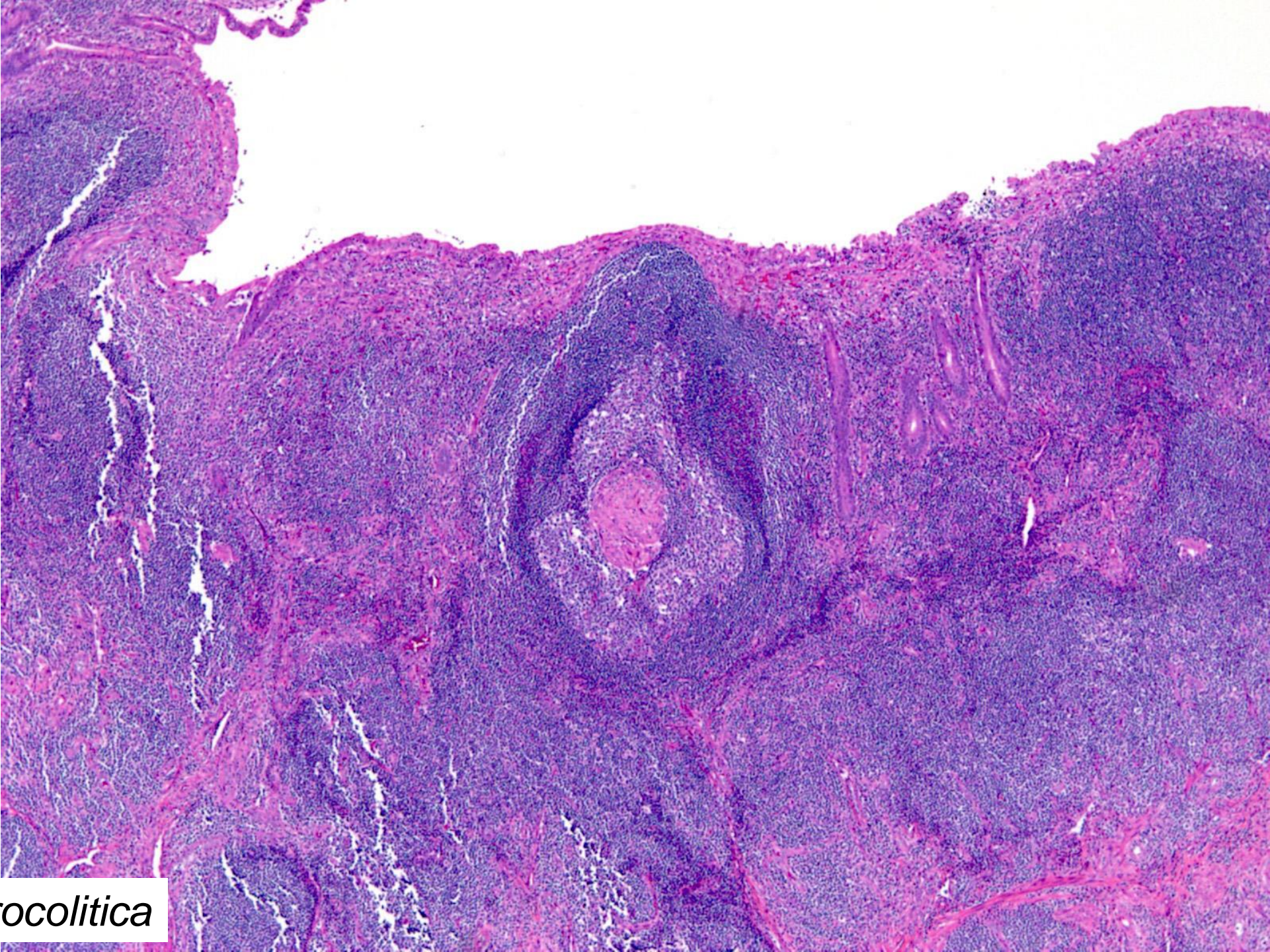
3 Ulcer/Linear Shape

4 narrowed lumen/sigmoid ulcers

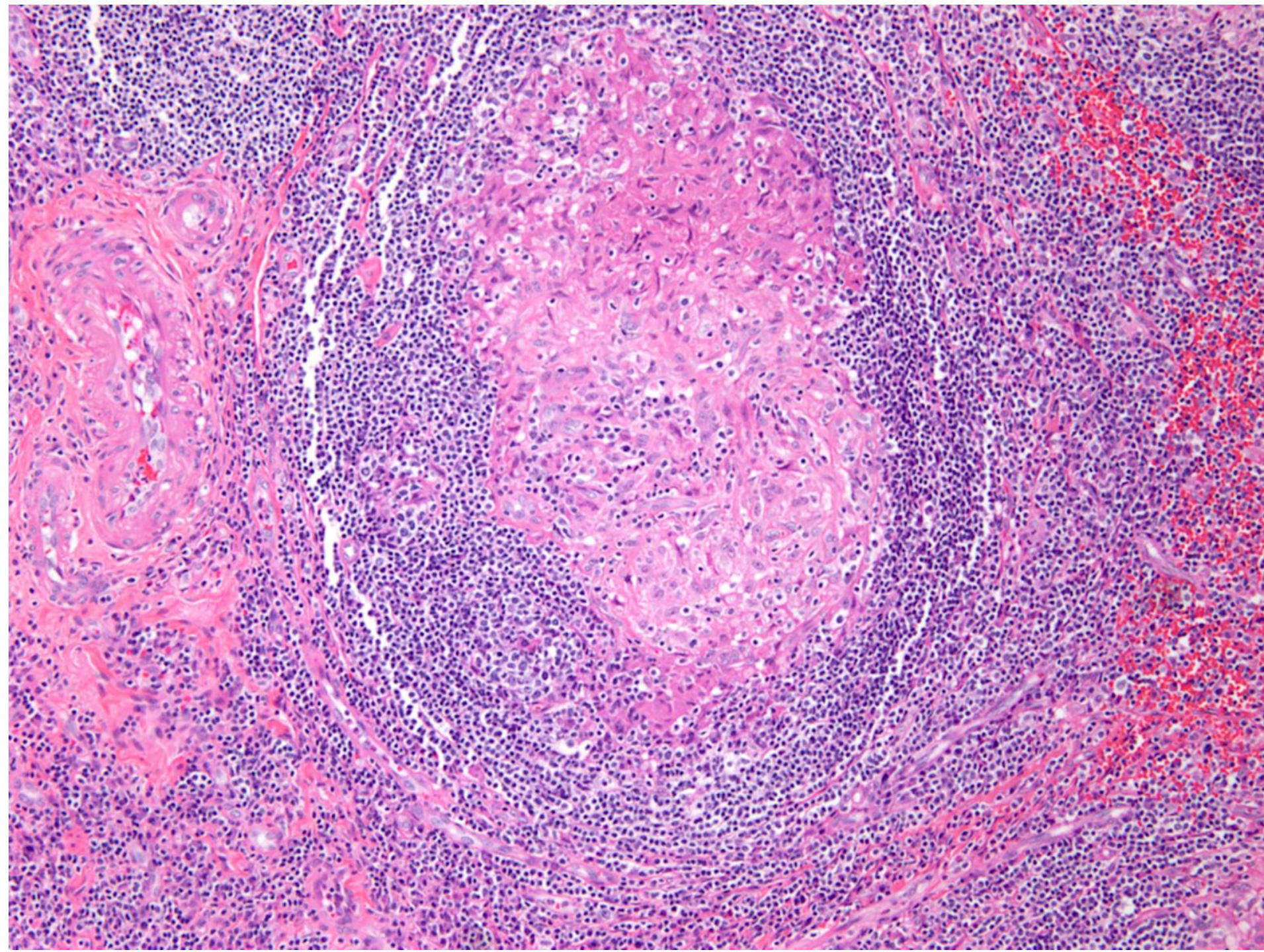


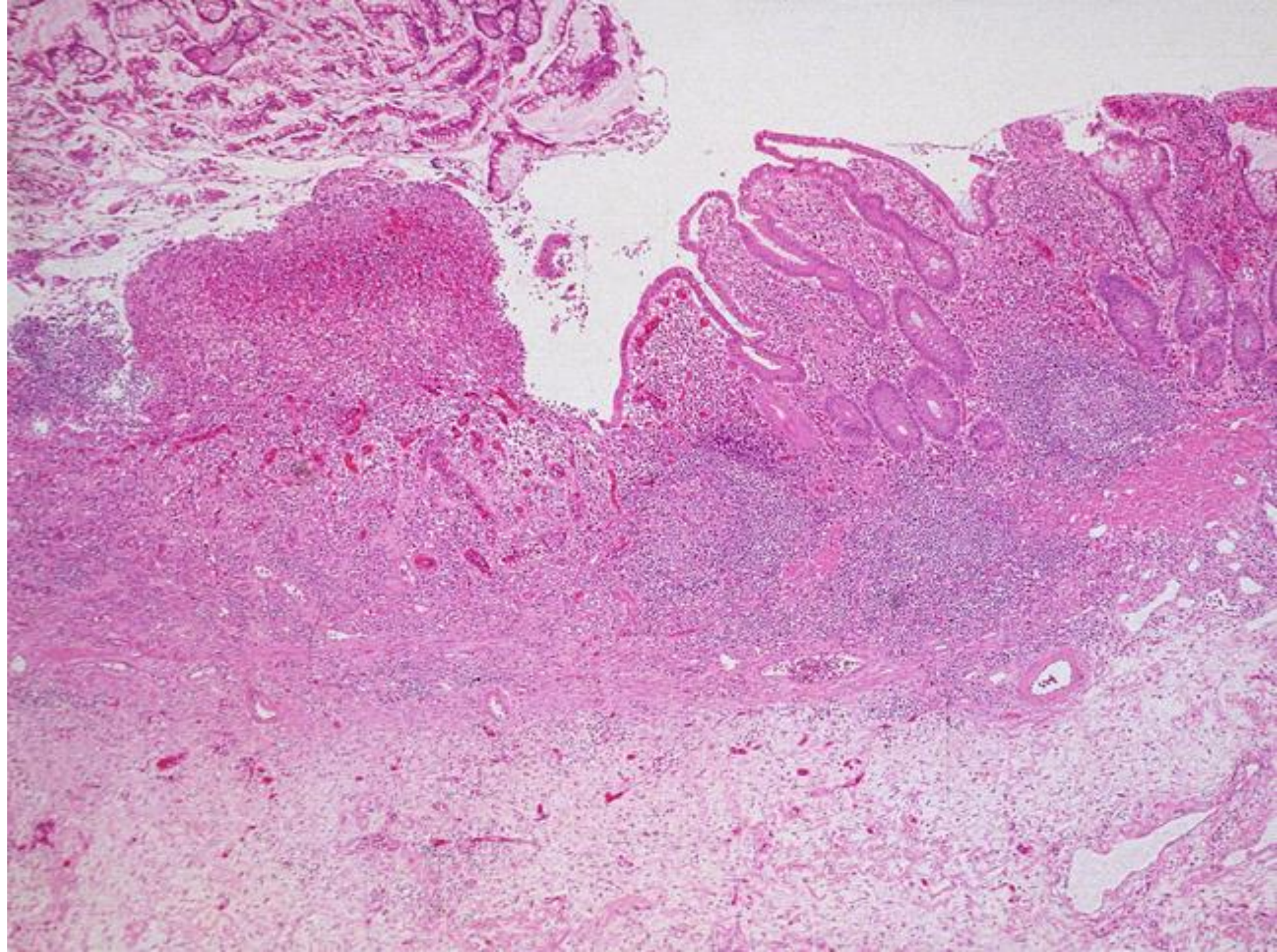
Granulomatous Appendicitis





Y. enterocolitica





Yersinia

Mimic of Crohn's Disease

- **Yersiniosis**

- Isolated appendiceal involvement
- More acute clinical onset

- **Crohn's**

- Disease in multiple sites
- Creeping fat
- Fistulae
- Histologic changes of chronicity

Aeromonas species

- Originally recognized as pathogen in turtles and other water dwelling creatures, but only recently in humans
 - *A. hydrophila*, *A. veronii*, and *A. sobria* now recognized as important to human GI disease
- Associated with water sources, fish, seafood, veggies, raw milk, ice cream, meat

Aeromonas sp.

- Particularly a problem in young children (< one year of age), the elderly, and immunocompromised patients, but can affect anyone
- Summer peak
- *Pleisiomonas* species probably emerging as similar pathogen

Yarze JC. *Aeromonas* as a cause of segmental colitis. *Am J Gastroenterol* 1998; 93:1012-13.
Gracey M, Burke V, Robinson I. *Aeromonas*-associated gastroenteritis. *Lancet* 1982;2(8311): 1304-6.
George WL, Nakata MM, Thompson J, White ML. *Aeromonas*-related diarrhea in adults. *Arch Int Med* 1985; 145:2207-11.

Clinical Findings

- Bloody diarrhea, often mucoid
- Nausea, vomiting, crampy abdominal pain
- May have fever and fecal WBCs
- Duration of symptoms may range from days to much longer

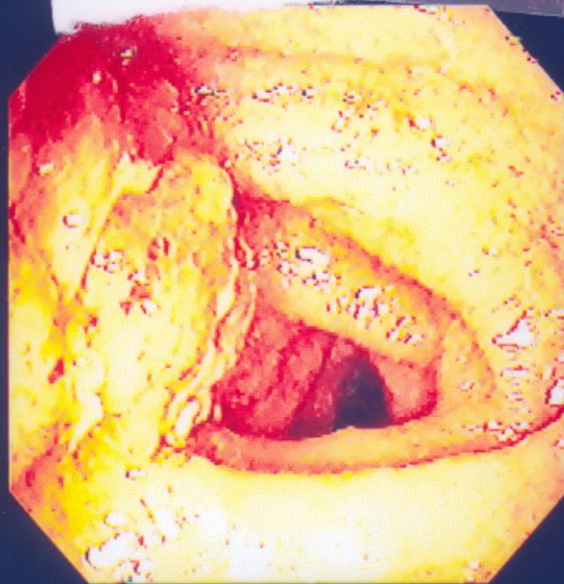
Pathologic Findings

- Often segmental distribution
- Edema, friability, erosions, exudate, loss of vascular pattern
 - DDx: Crohn's disease
- Usually shows AITC pattern
 - Ulceration, focal architectural distortion may be seen, mimicking IBD

6720
M 36
03/10/1968

08/02/2004
12:06:05

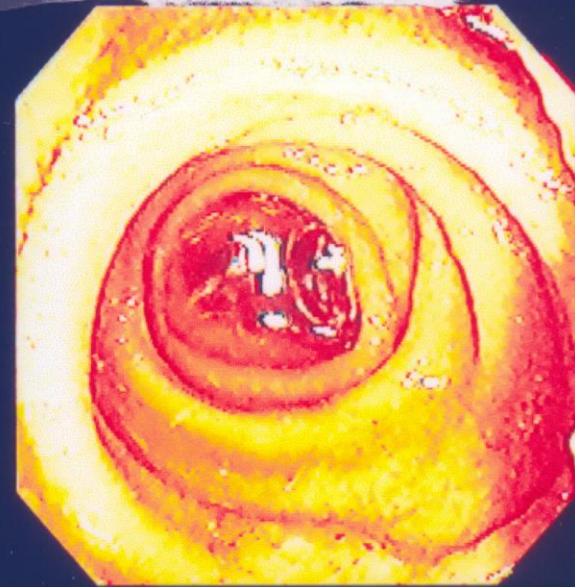
SCV-----1



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03/10/1968

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12:07:01

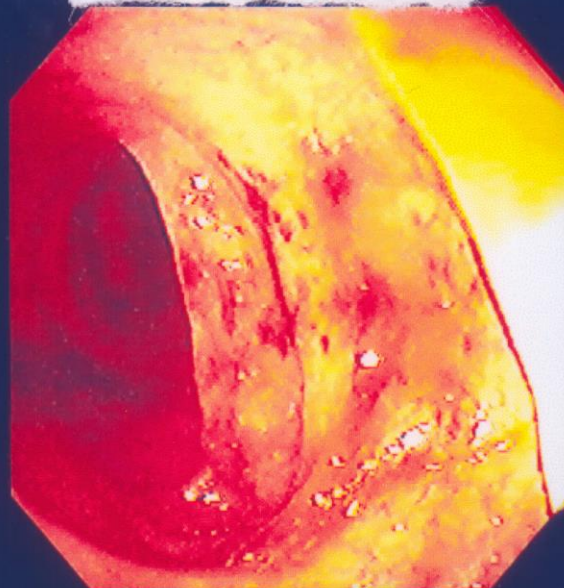
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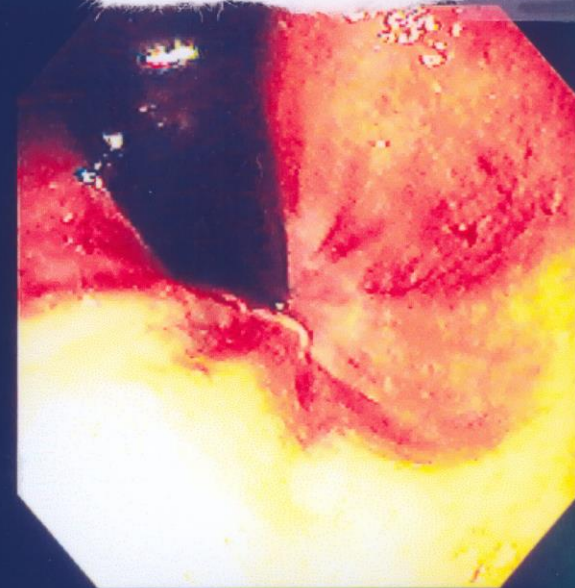
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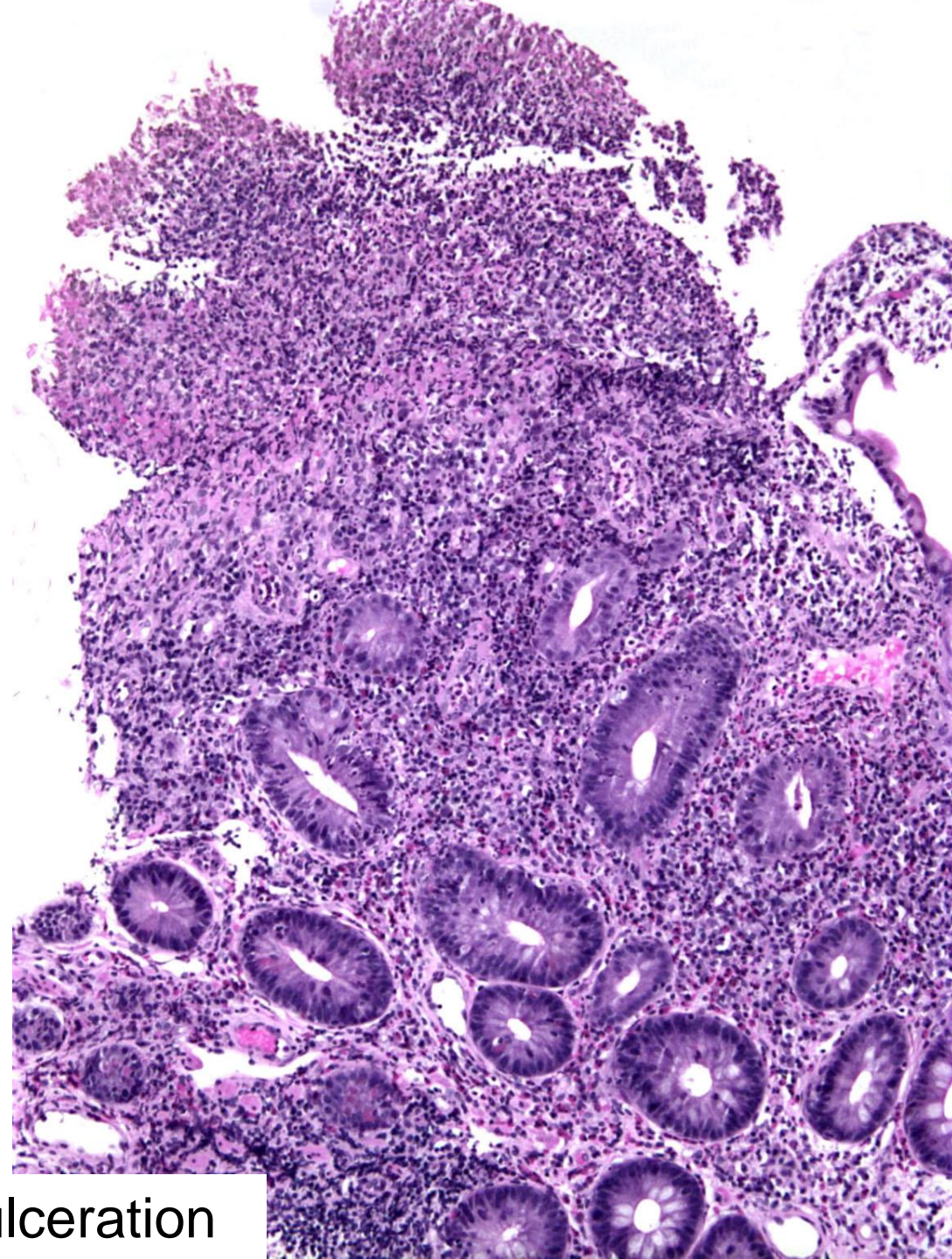


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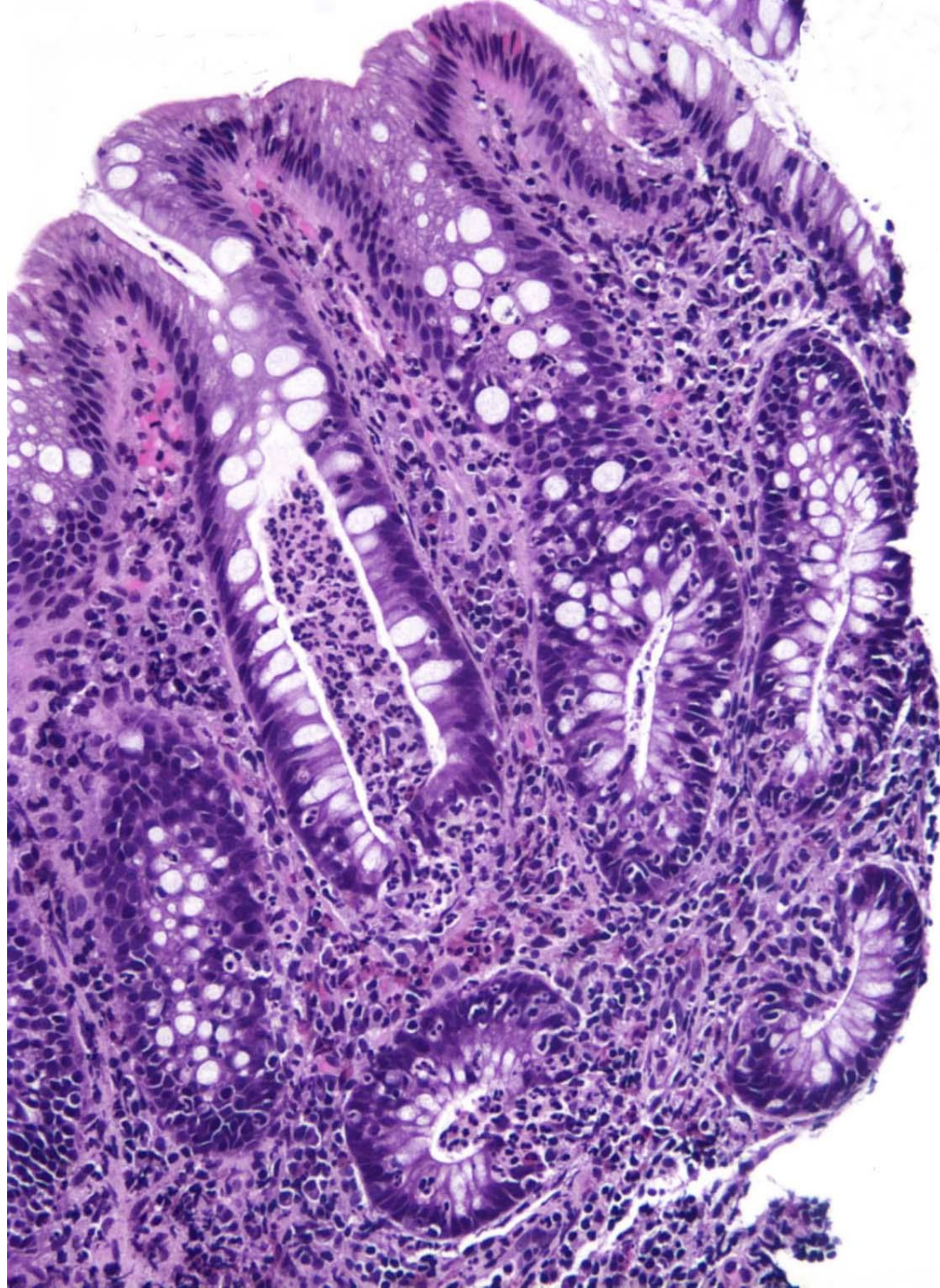
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12:13:31

SCV-----4

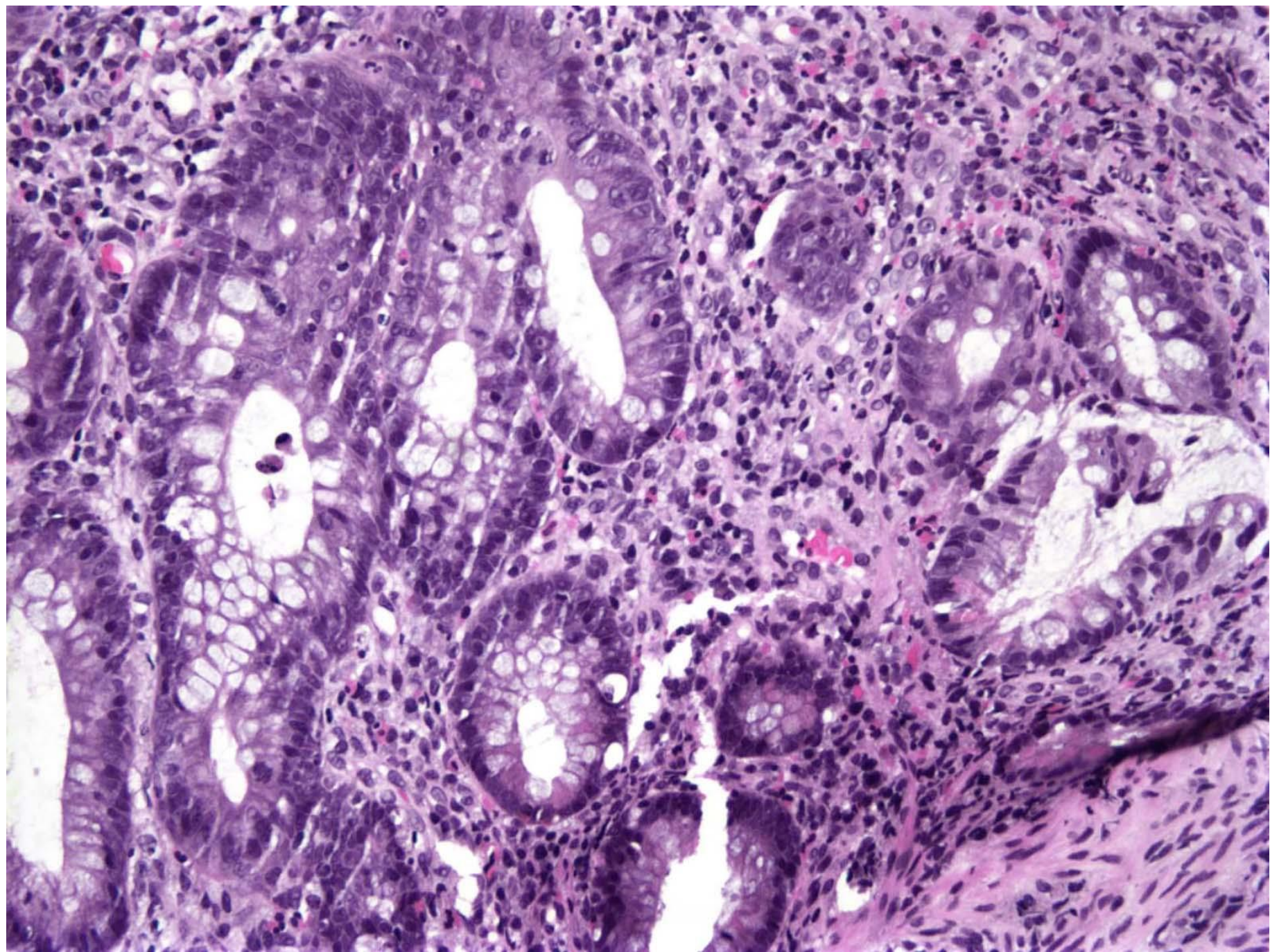




Aeromonas-ileocecal ulceration



Aeromonas



E. histolytica

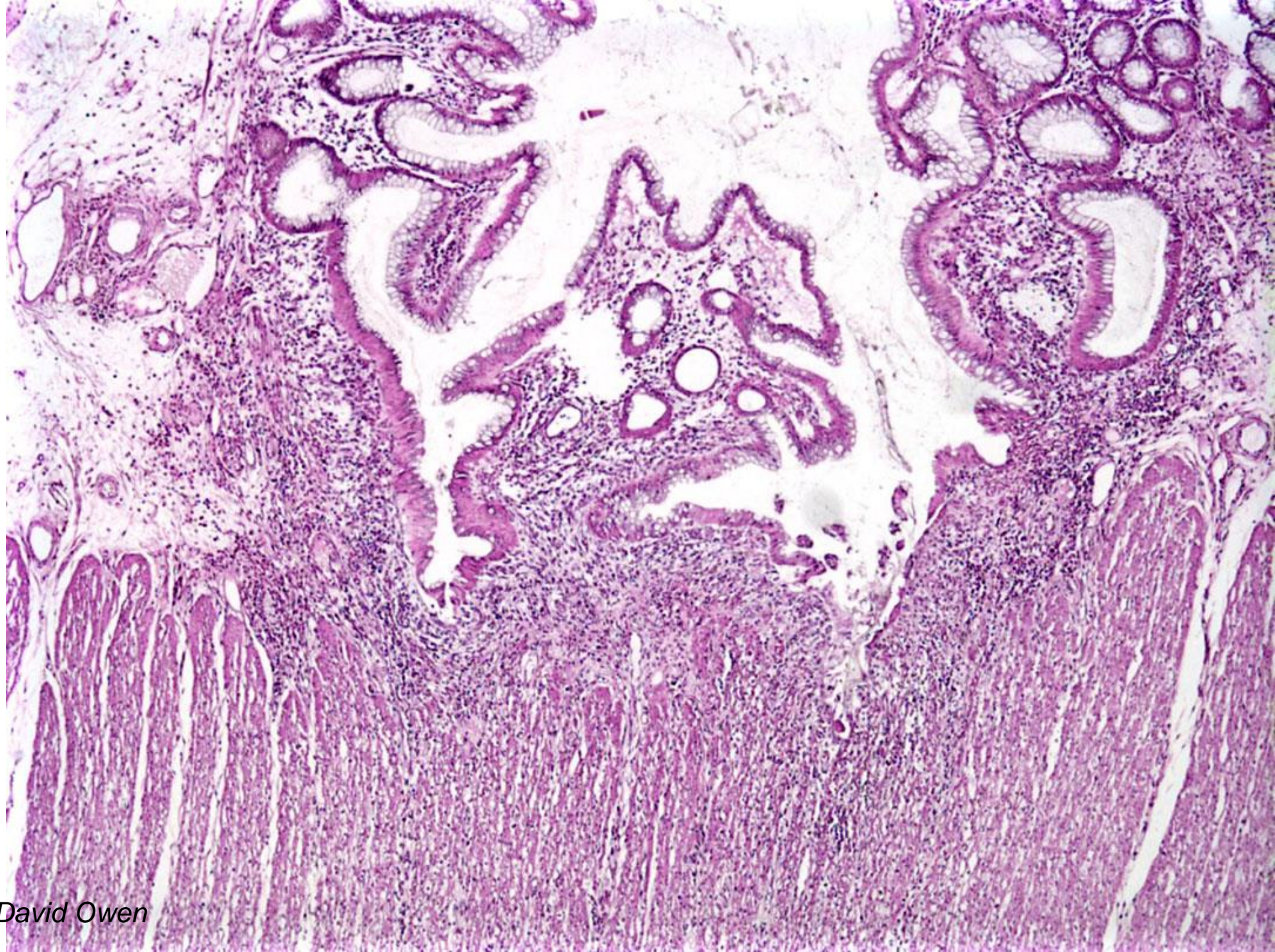
- Infects 10% of world population
- Clinical: ranges from asymptomatic to fulminant colitis
- In industrialized countries, associated with homosexual population and unsanitized water

E. histolytica

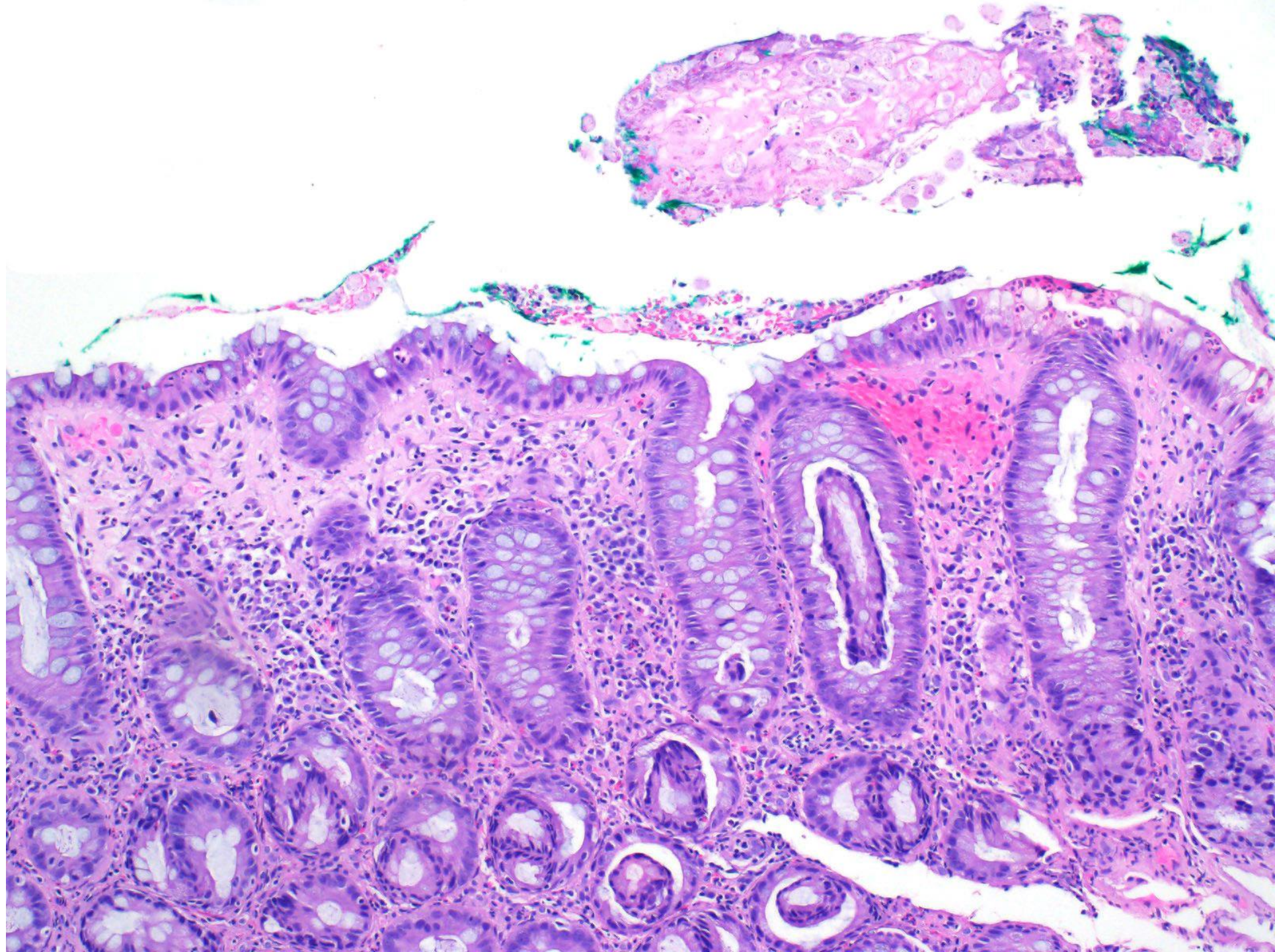
- Typical
 - Flask shaped ulcers
 - Right sided involvement
- Atypical
 - Pseudomembranes
 - Toxic megacolon
 - Crohn' s-like
 - Skip lesions
 - Linear or geographic ulcers
 - Architectural distortion
 - Organisms may be mistaken for macrophages

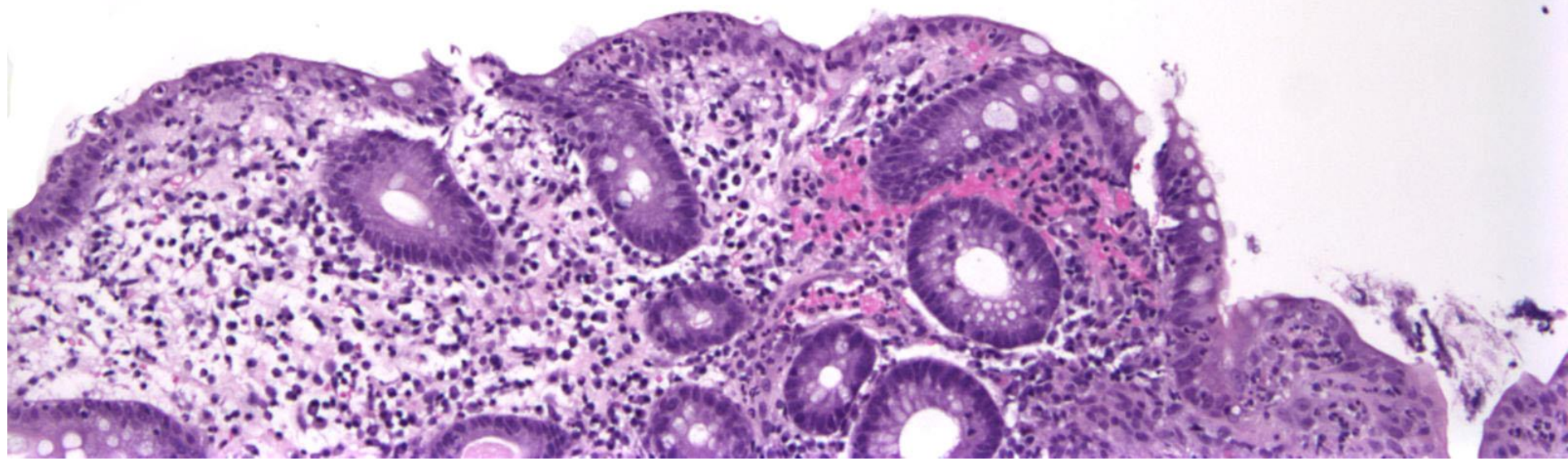
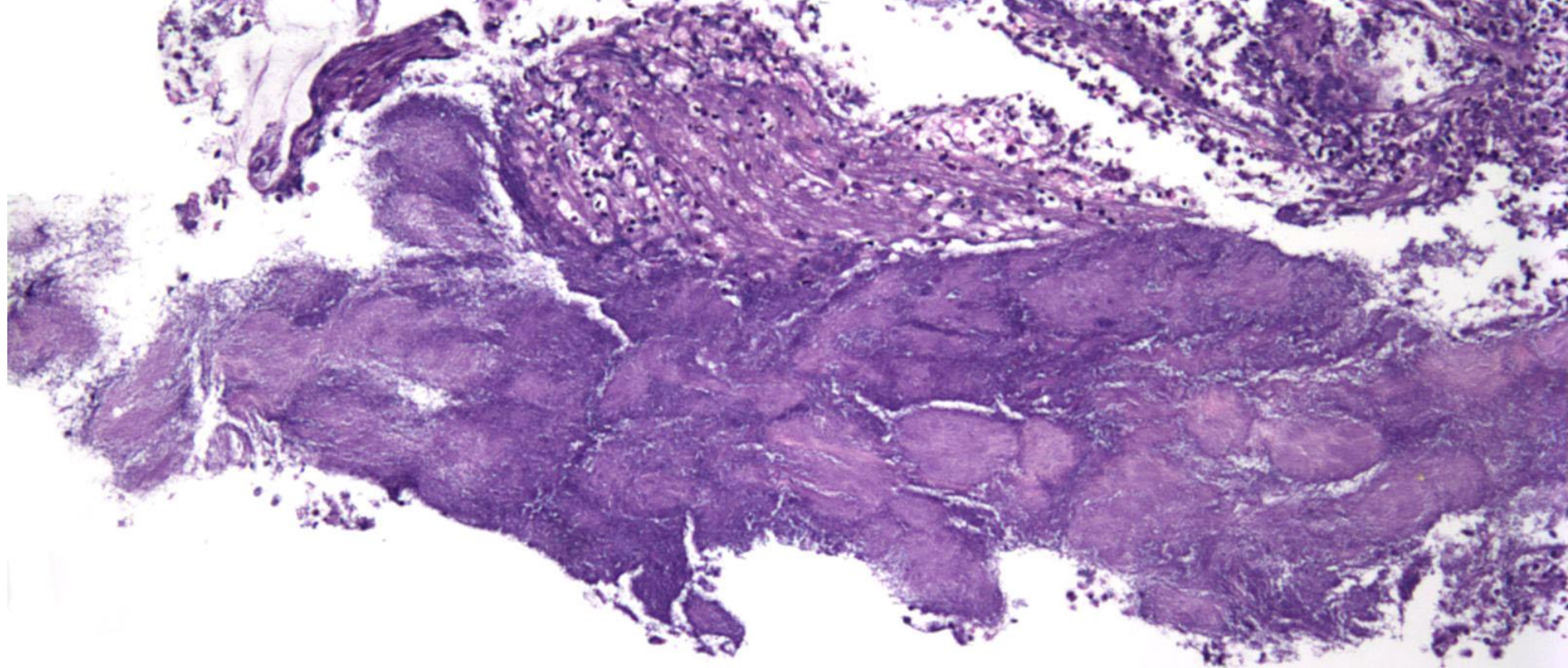


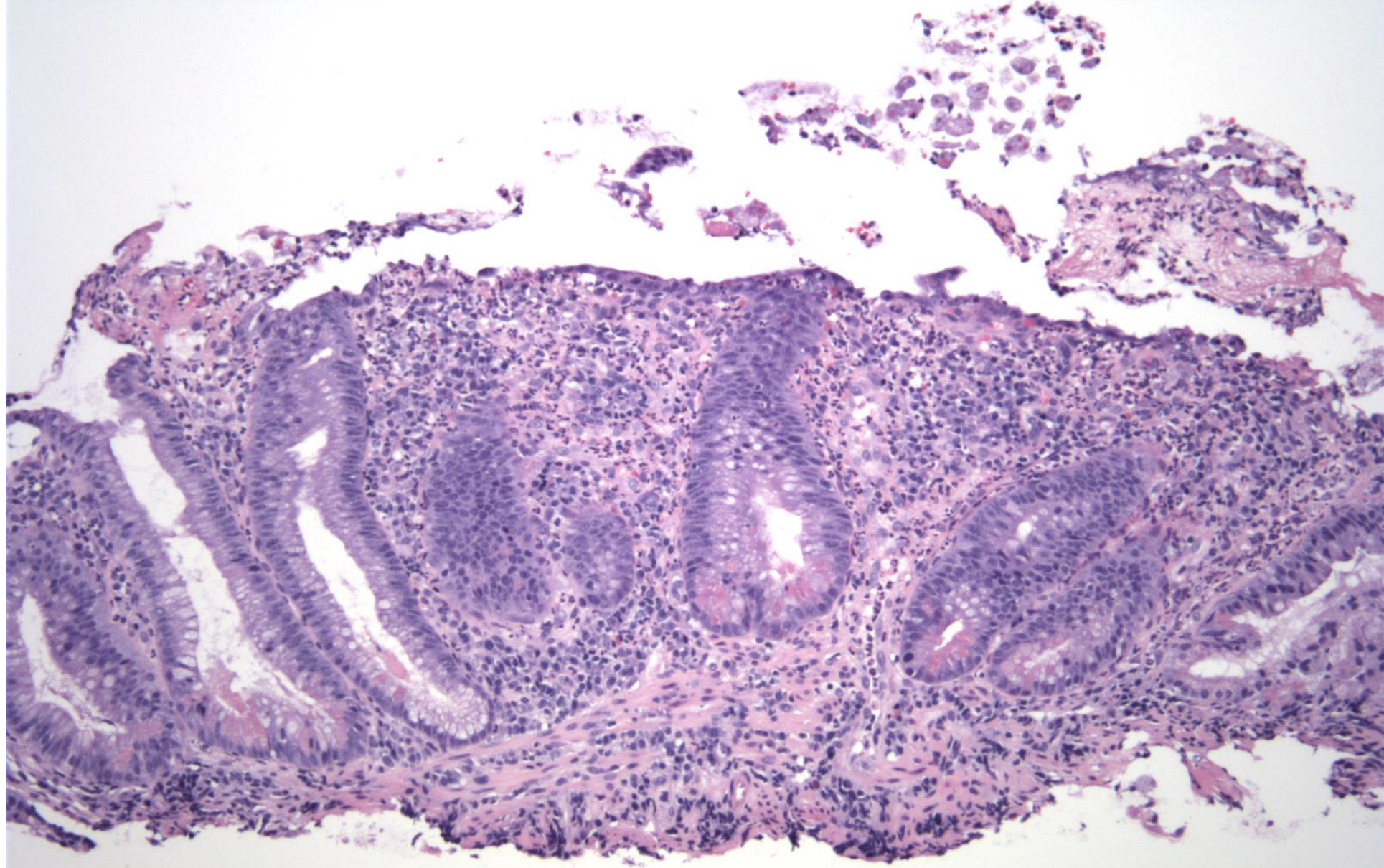
E. histolytica: architectural distortion and skip lesions mimic Crohn's disease



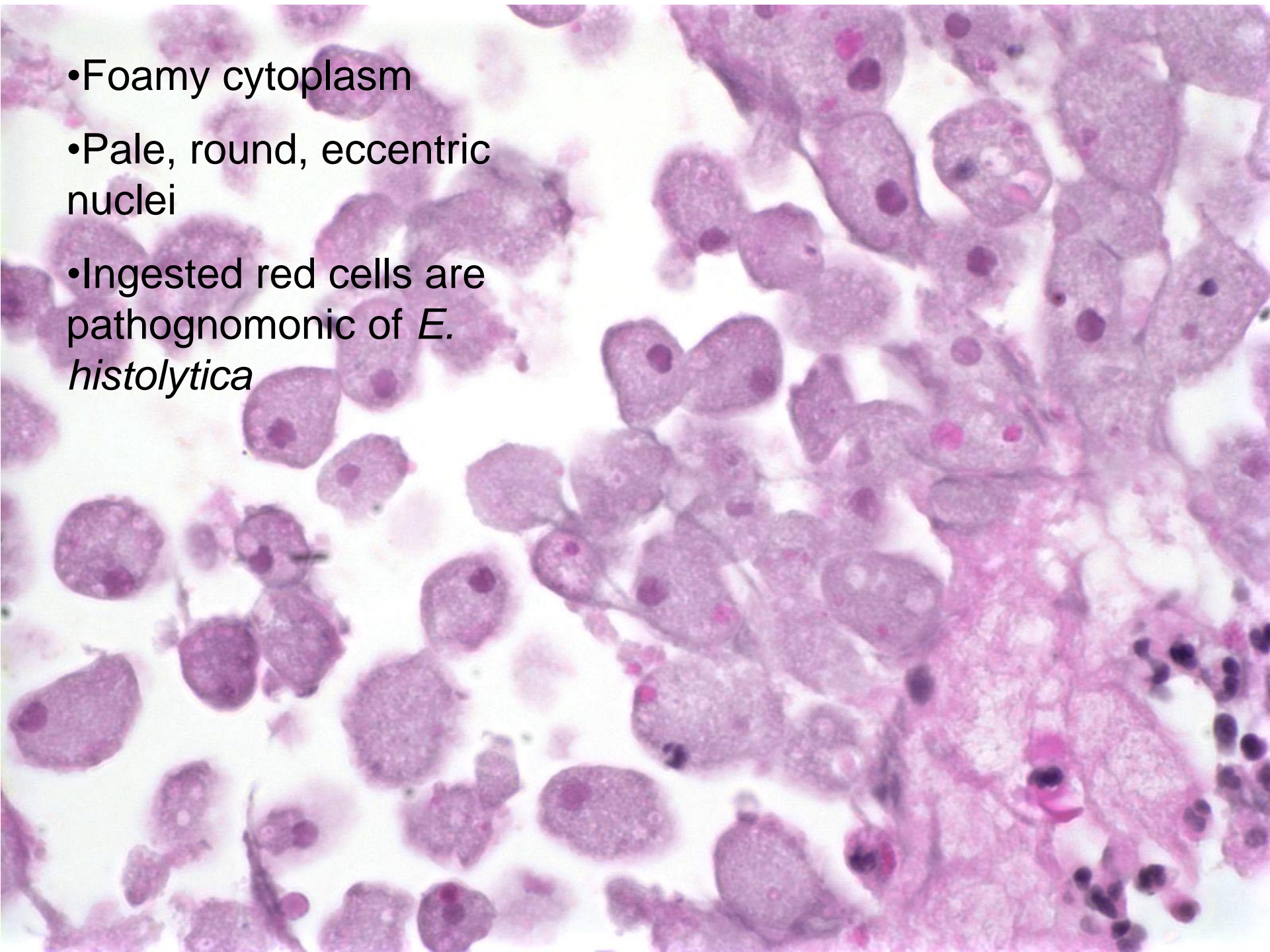
Courtesy Dr. David Owen

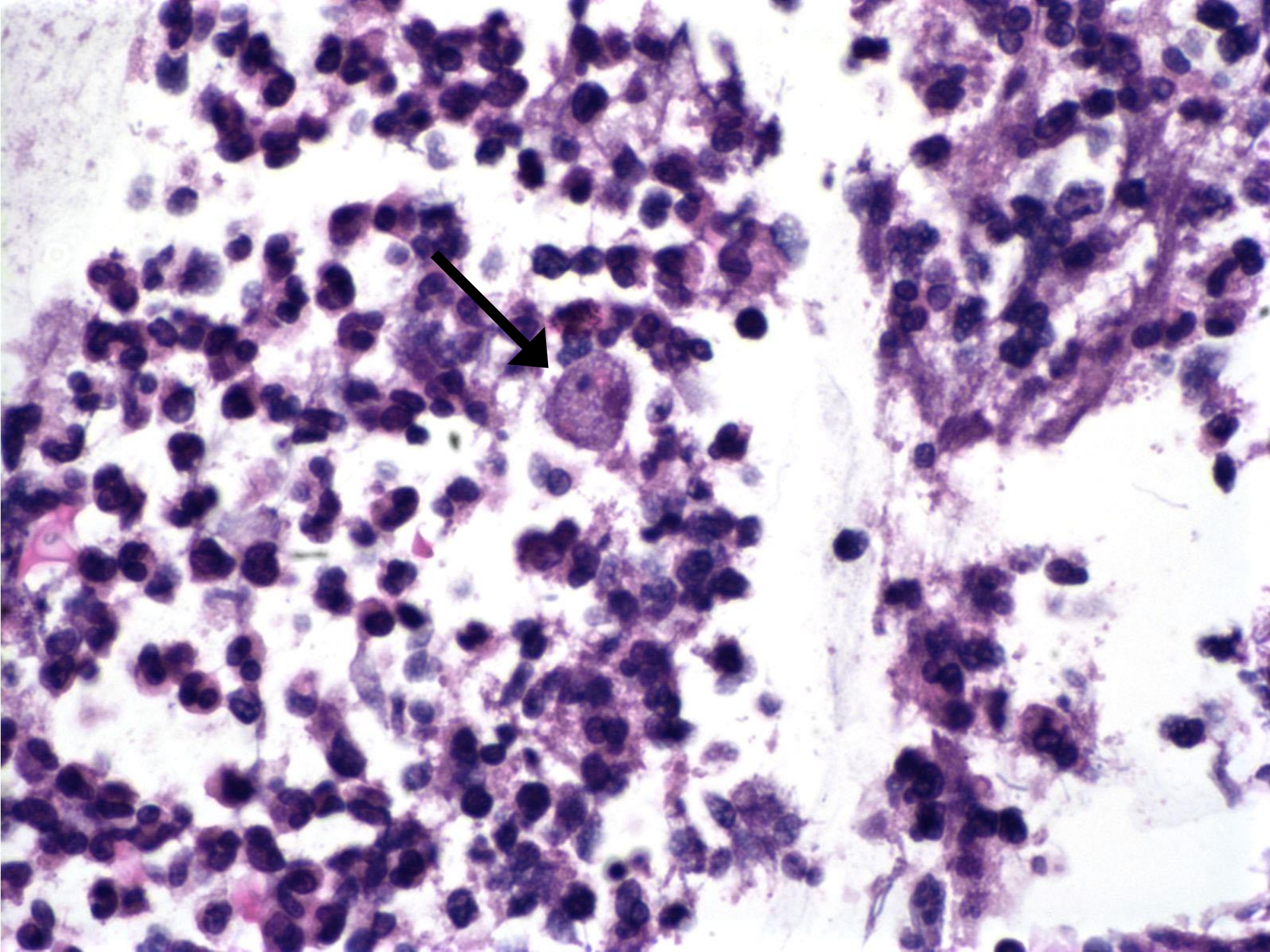


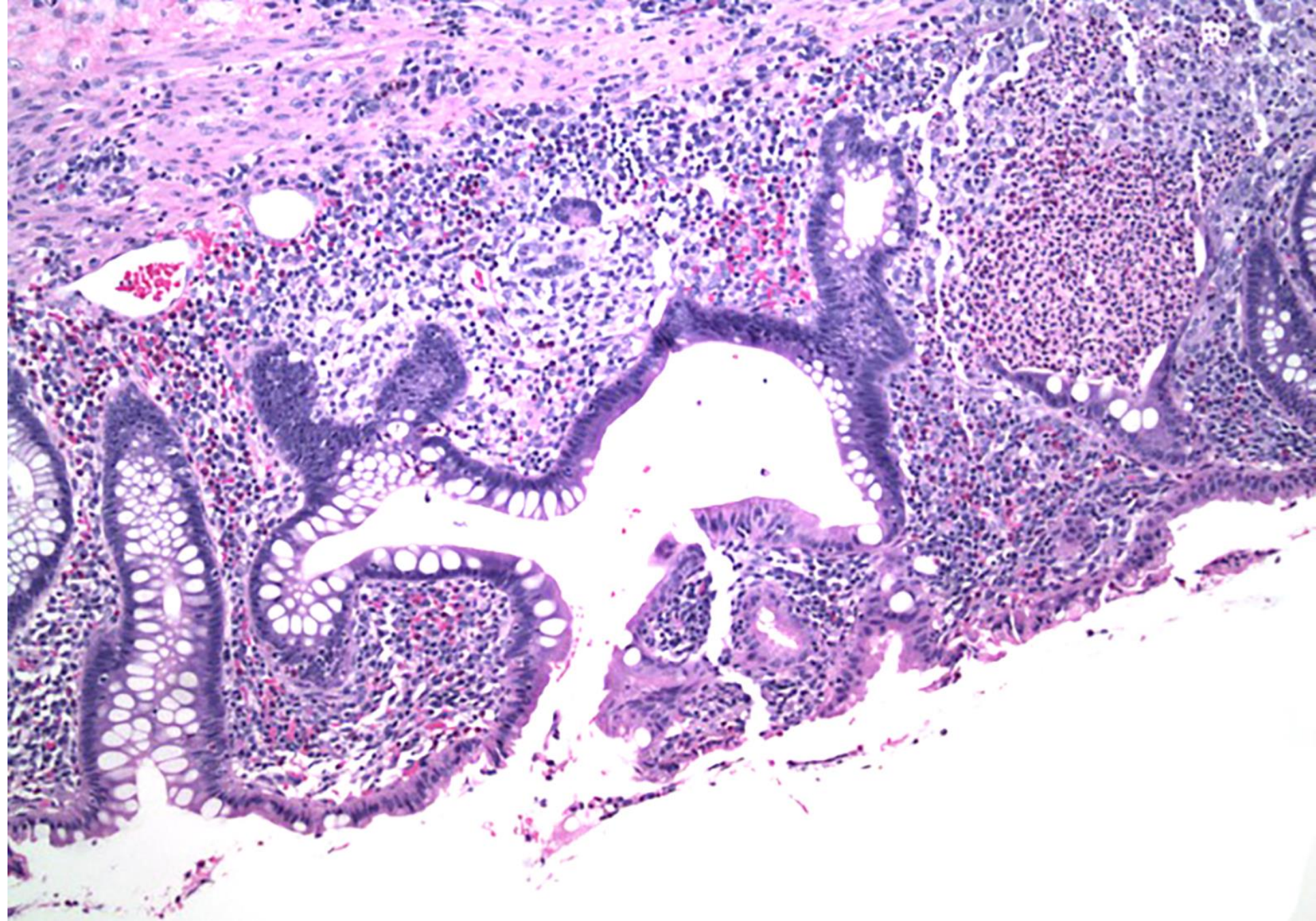




- Foamy cytoplasm
- Pale, round, eccentric nuclei
- Ingested red cells are pathognomonic of *E. histolytica*







Shiga-Toxin Producing (Enterohemorrhagic) *E. coli*

- Usually serotype 0157:H7
- Causes “ischemic-pattern” colitis
 - Shiga-like toxins cause thrombosis
- Contaminates meat, produce, water
- Children and elderly at increased risk
 - TTP, HUS

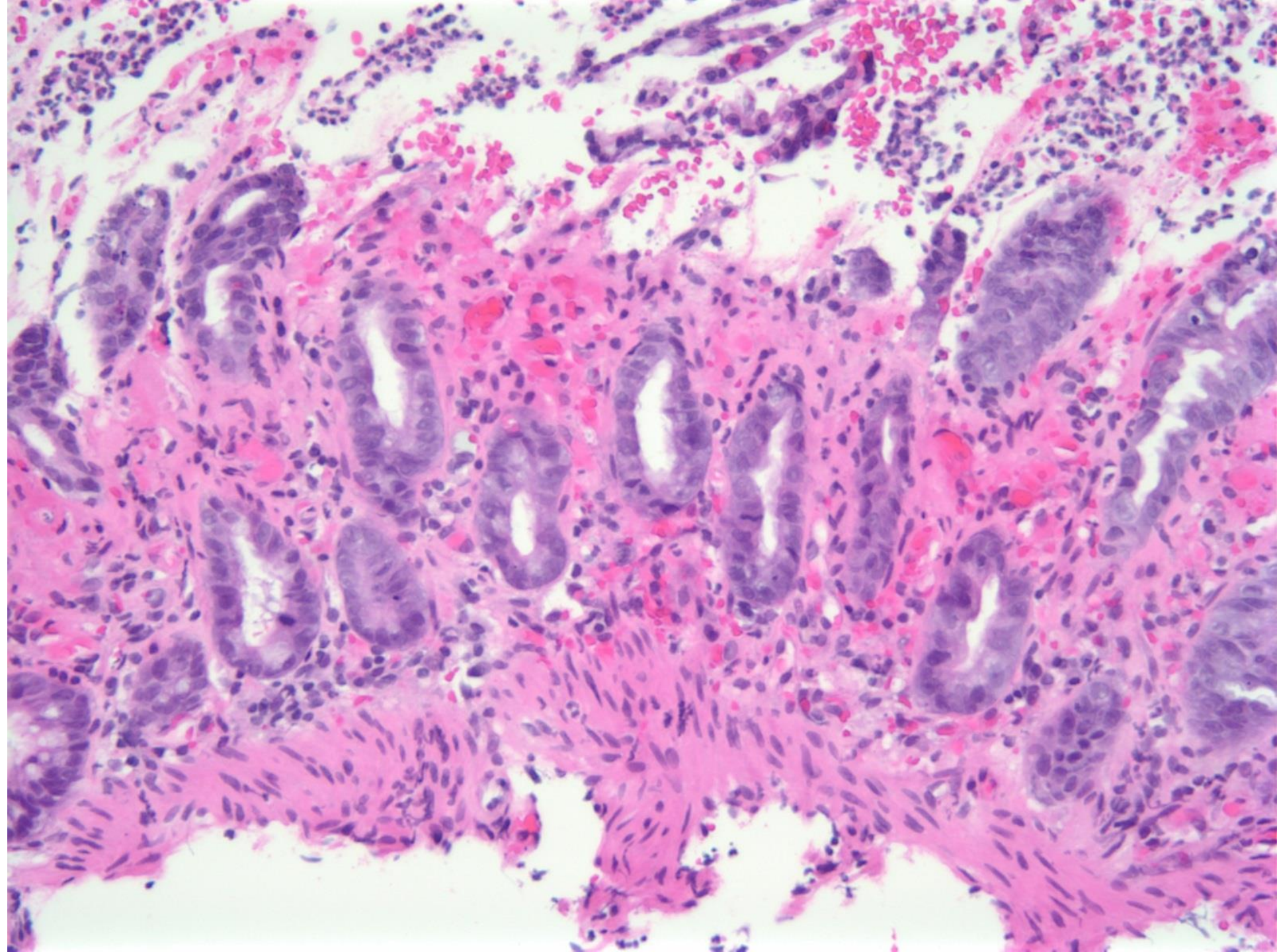
Enterohemorrhagic *E. coli*

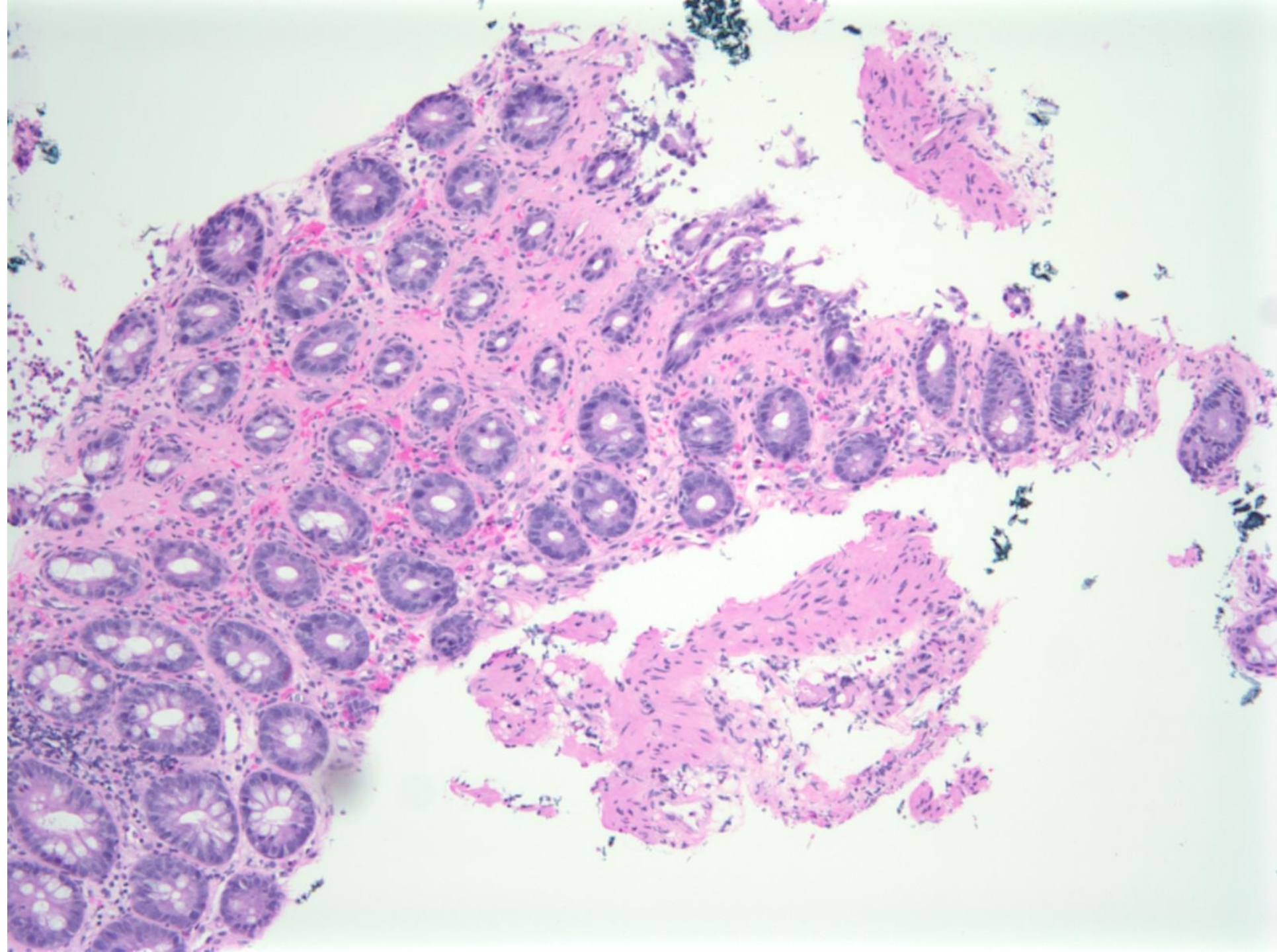
Clinical Features

- Crampy pain, watery and/or bloody diarrhea
- Right sided colitis
- Mild or no fever
- Rare fecal leukocytes
- Stool PCR, culture



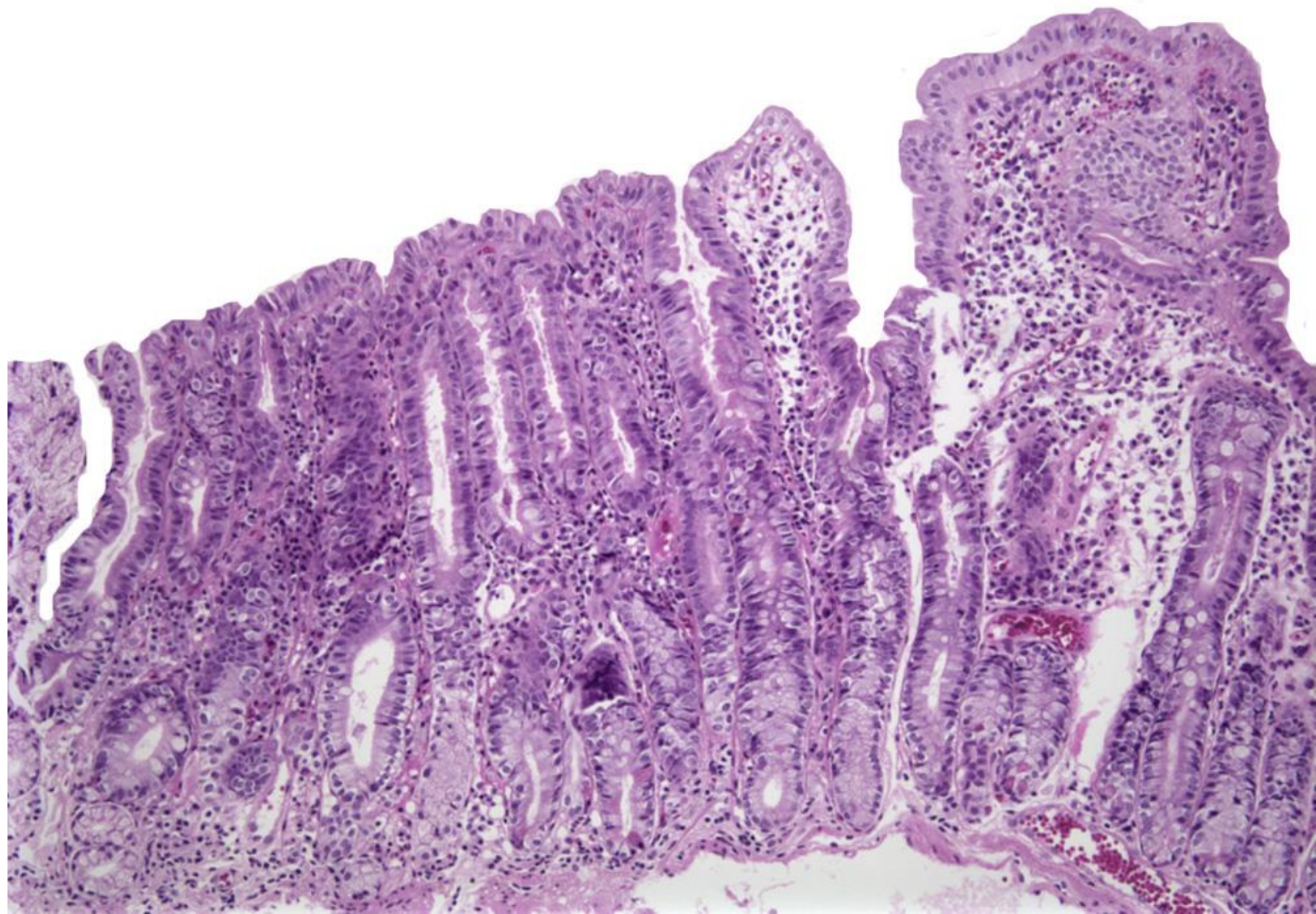
- Hemorrhagic necrosis
- Ulceration with fibrinopurulent exudate

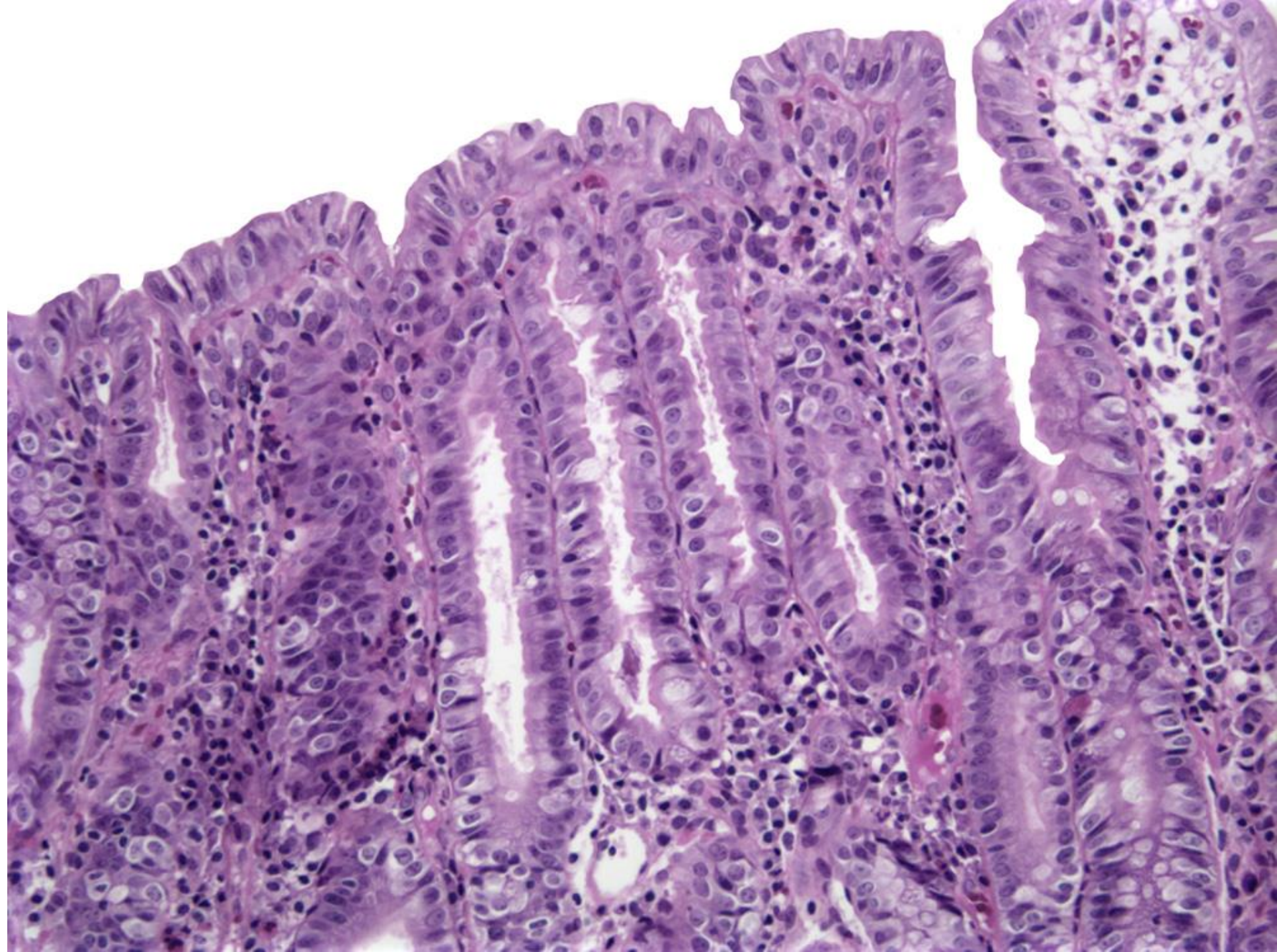


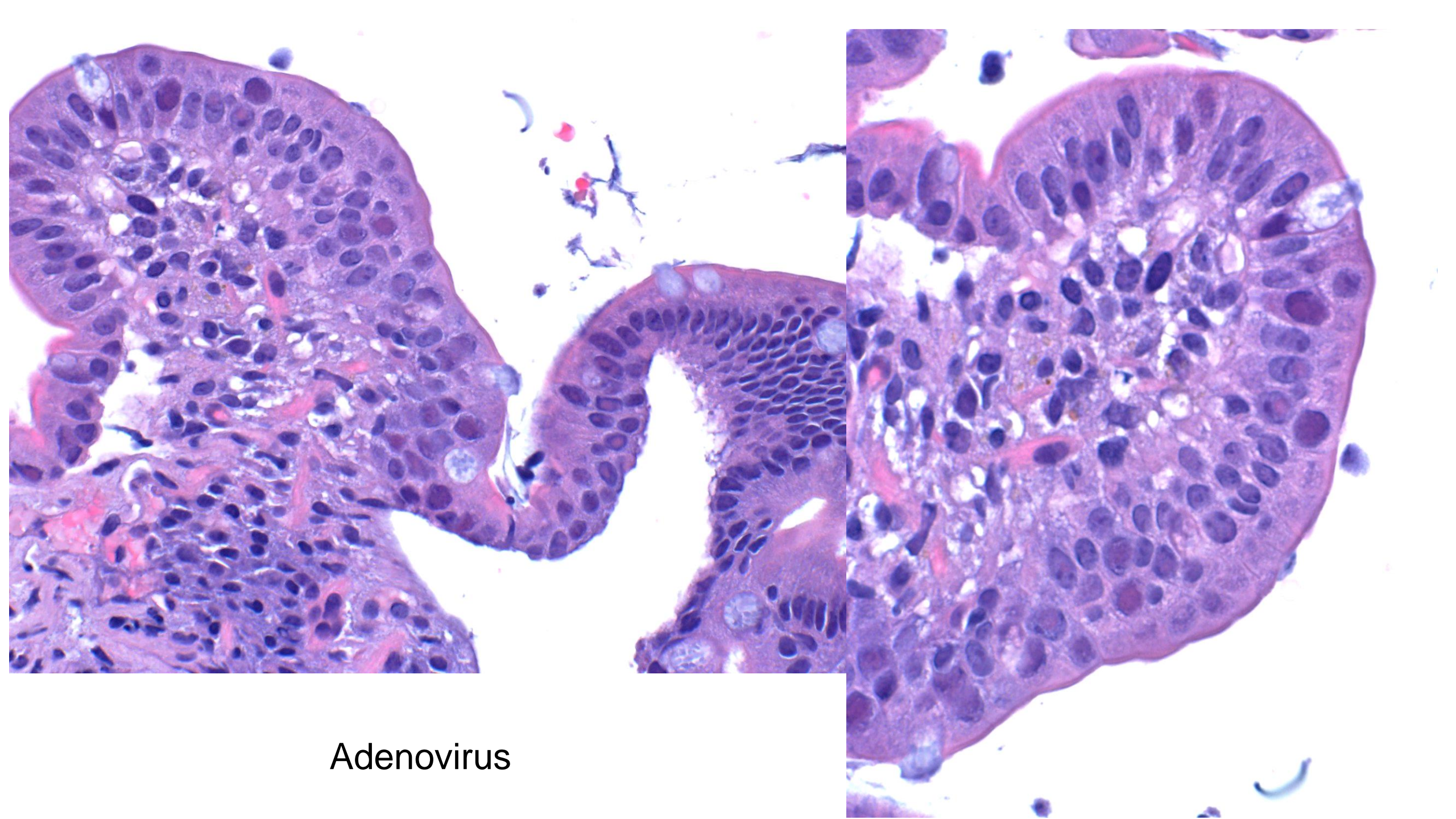


Enteric Viruses

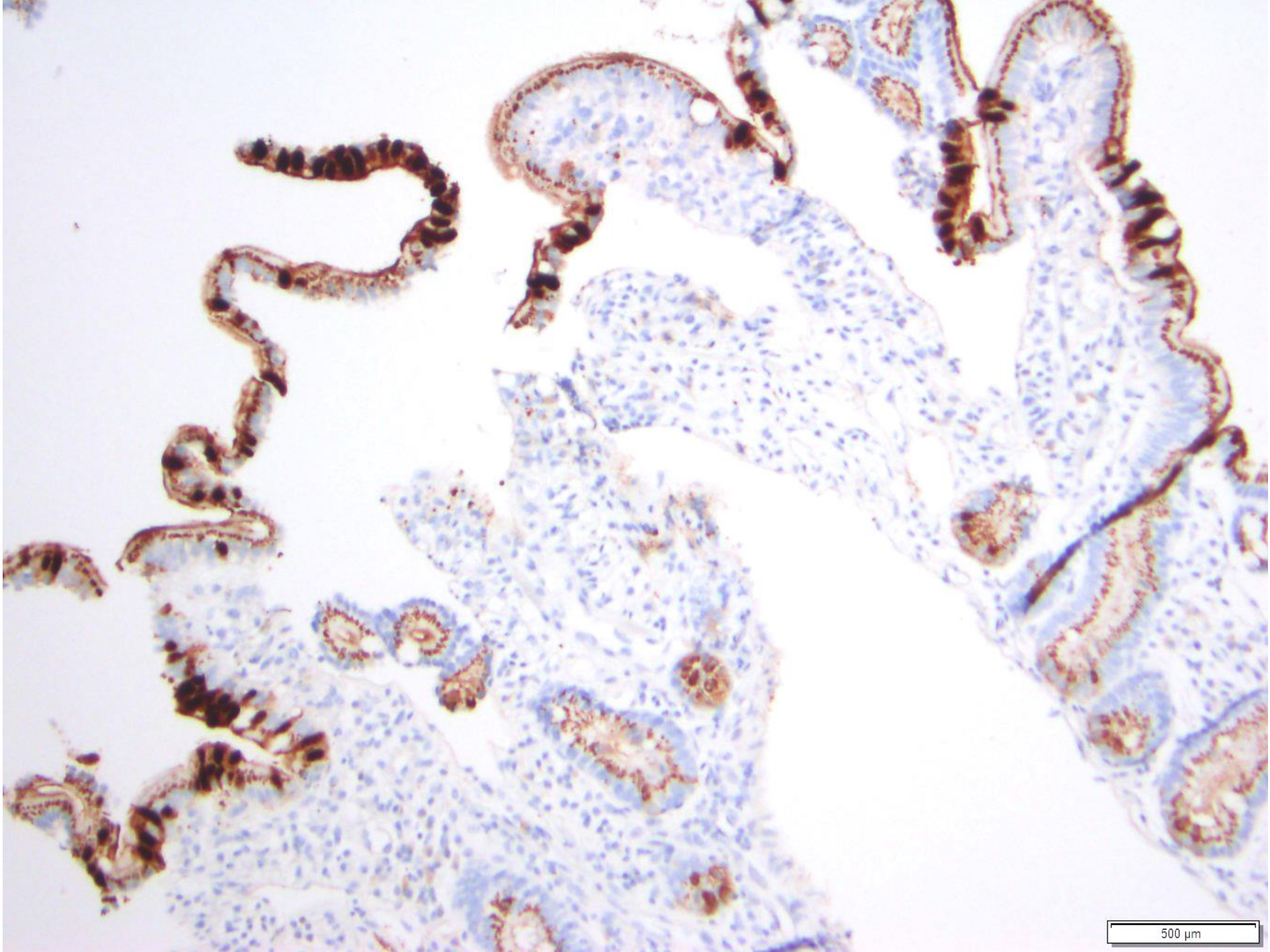
- Rarely biopsied
- Adenovirus, rotavirus, coronavirus, enterovirus
- Diagnosis usually made by stool culture/immunoassay







Adenovirus



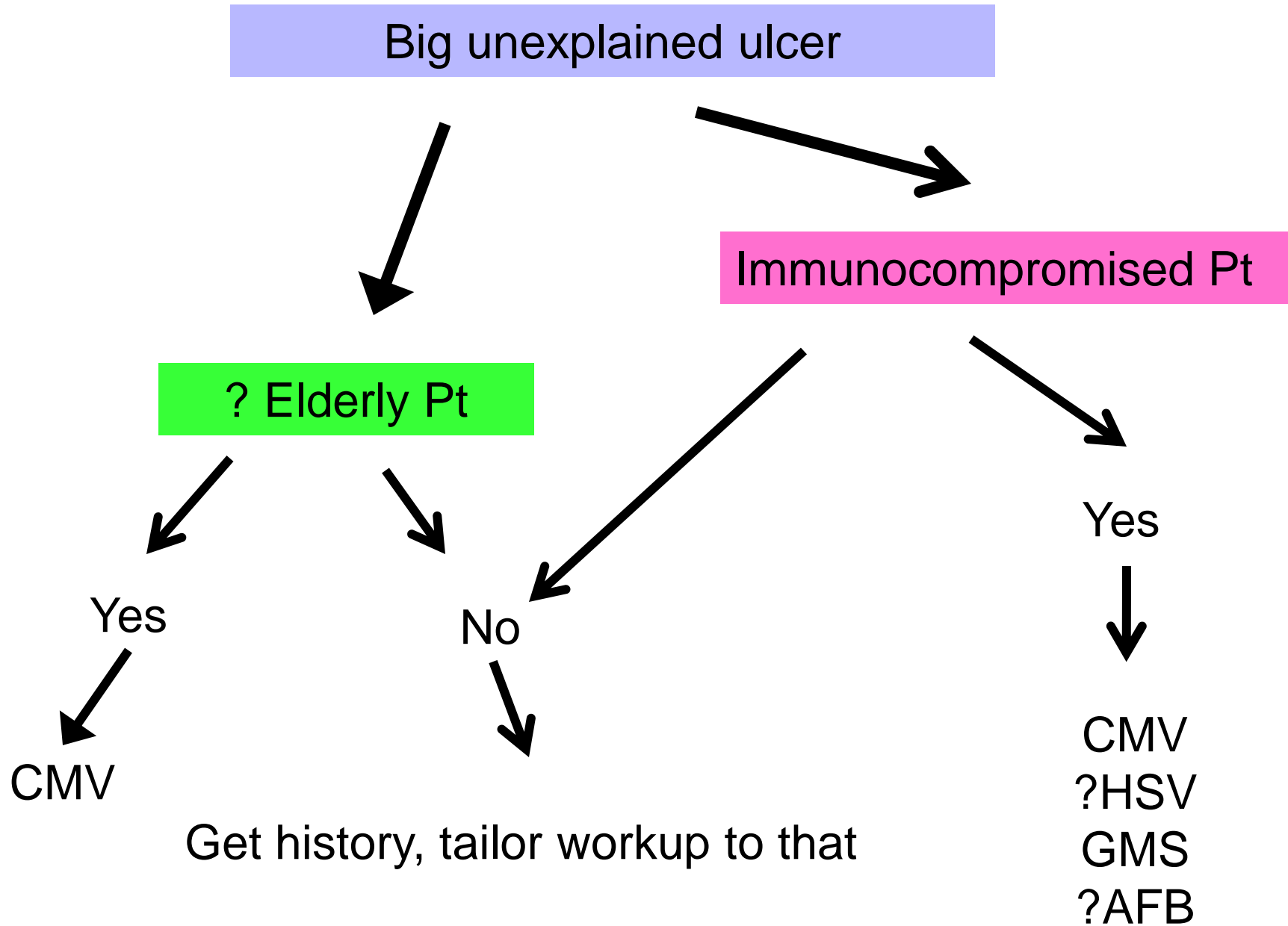
500 μ m

Diagnosis of GI Infectious Diseases

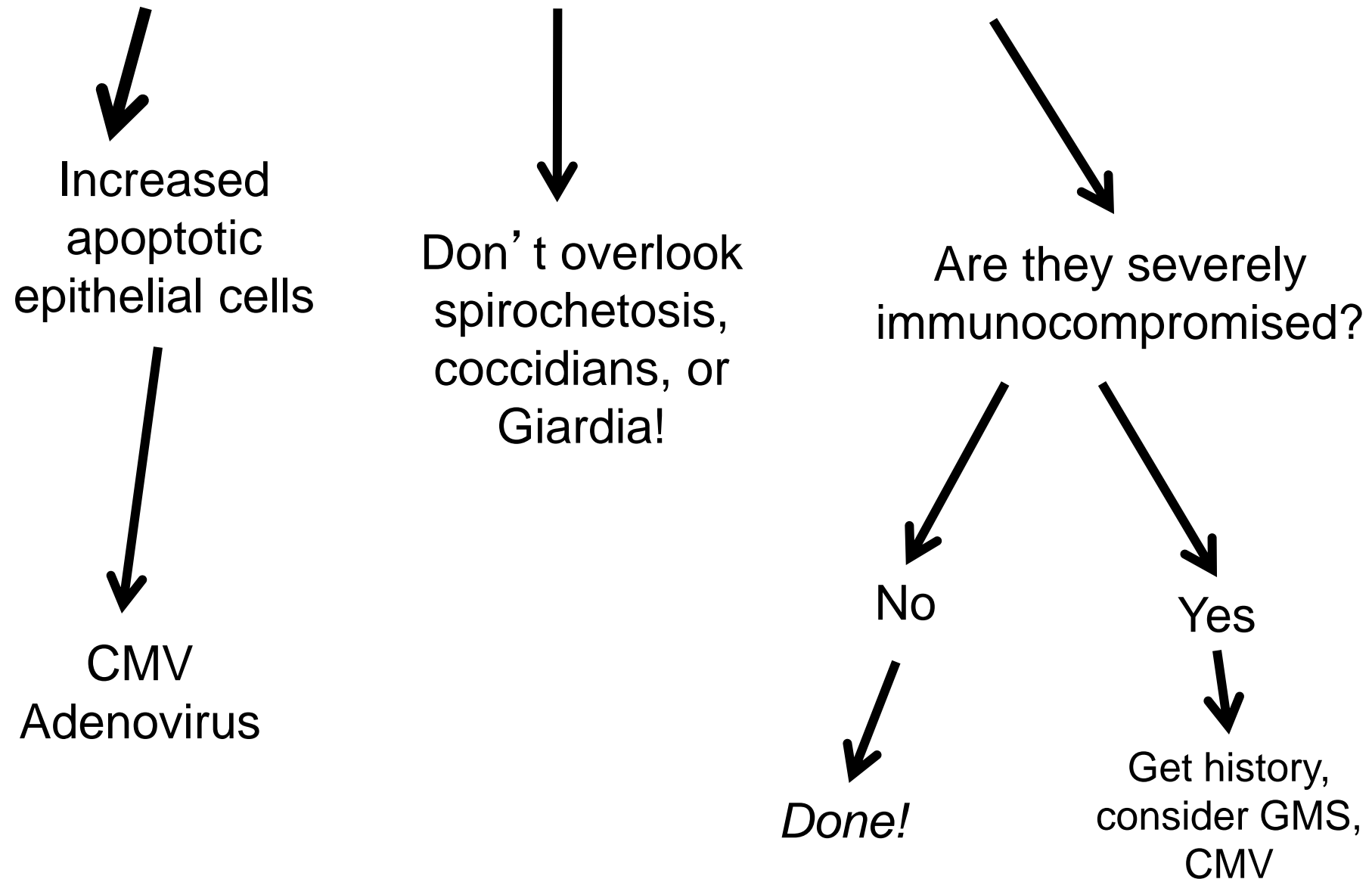
- Many infectious entities are underdiagnosed
 - HIGH INDEX OF SUSPICION!
- Cultures may not be useful/available
 - Patient already got antibiotics
 - Everything is in formalin
- Serologies
 - False negatives
 - Cross-reactivity
- **Molecular testing**

Utility of Special Stains in Evaluation of Biopsies for GI Infections

- Monkemuller et al, AJCP 2000
 - HIV patients
 - 28 months
 - Sensitivity and specificity for CMV diagnosis on H&E were 97% and 100%
 - AFB/GMS stains did not identify previously diagnoses infection in any patient
 - Long-term follow-up revealed no missed infections on H&E
 - Stains doubled cost



Essentially Normal Bx in Immunocompromised Patient



Clinical and Histologic Correlates of the FilmArray BioFire Gastrointestinal Panel

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BACKGROUND

The FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, Utah) is a multiplex PCR assay that tests stool for 22 different GI pathogens, including *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, *Vibrio*, pathogenic *E. coli* subtypes, *P. shigelloides*, *Cryptosporidium*, *Cyclospora*, *Entamoeba*, *Giardia*, *adenovirus*, *astrovirus*, *norovirus*, *rotavirus* and *sapovirus*¹.

Although this assay is used with increasing frequency, the clinical significance of a positive BioFire result is often unclear. The goal of this study was to correlate positive BioFire results with clinical history and histologic findings on GI biopsy. In addition, because of the higher yield using this technology than historically seen with stool cultures, there is an opportunity to study the morphologic features of infections that have not previously been well characterized..

DESIGN



- 3291 stool PCR assays were performed between April 2016 and June 2017.
- Of those, 1192 (36.2%) assays were positive for one or more of the 22 pathogens, and 79 of the 1192 had a colon biopsy within one week of the stool PCR test.
- The 79 biopsies were reviewed by two GI pathologists, and the electronic medical records were reviewed for pertinent clinical findings and laboratory studies.

RESULTS

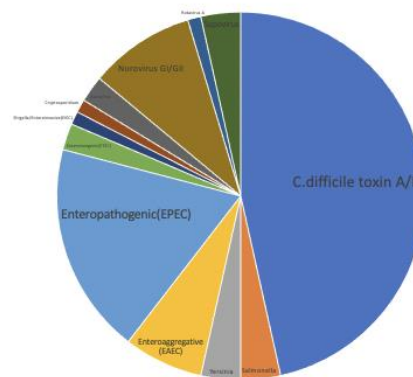


FIGURE 1 Distribution of microorganisms detected by FilmArray BioFire GI panel with colonic biopsies performed concurrently.

- The three most frequently detected pathogens found in the 79 patients who had concomitant biopsies were *C. difficile* (46%), enteropathogenic *E. coli* (19%), and *Norovirus* (9%).
- The majority of patients (94%) in our study who had a positive stool PCR assay had histologic findings on biopsy, although approximately half of these had previous diagnoses of IBD (see Figure 4).
- In patients without IBD, the most common associated histologic pattern was acute infectious-type colitis.

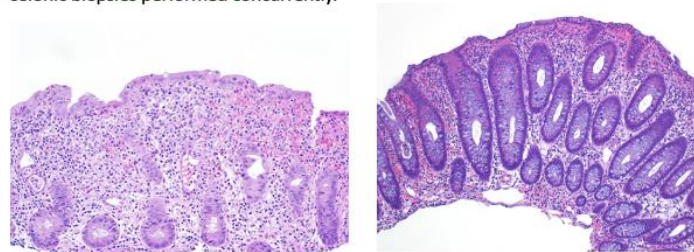


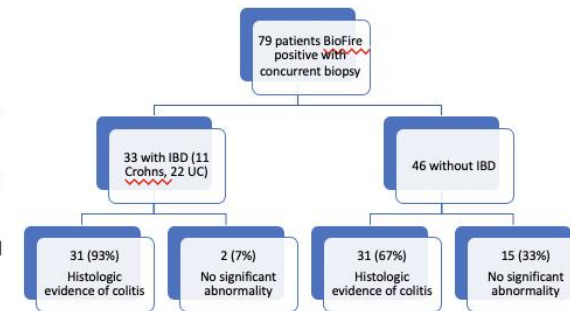
FIGURE 2 Acute infectious colitis in a patient who tested positive for *Salmonella*

FIGURE 3 Acute infectious colitis in a patient who tested positive for *Norovirus*

TABLE 1 Histologic patterns in biopsies who tested positive for select organisms

	Neutrophilic inflammation	Nonspecific ulcers	Negative
EPEC	80%	20%	13%
Norovirus	63%	25%	38%
EAE	67%	33%	0

FIGURE 4 Distribution of histologic evidence of colitis in patients with and without IBD



CONCLUSIONS

- To our knowledge, this is the first study specifically examining the correlation between stool PCR results and concomitant GI biopsy findings.
- Approximately half of patients with positive BioFire results and findings on biopsy had previous diagnoses of IBD, suggesting that pathogenic *E. coli* and *Norovirus*, among others, may be under-recognized causes of IBD flares.
- The clinical significance of a positive BioFire assay in a patient with a negative GI biopsy remains unclear, and is a subject for further study.
- Evaluation of the clinical significance of a positive stool PCR test, and the possible effect on subsequent therapeutic decisions, requires correlation between clinical, molecular, and histologic data.

REFERENCES

1. Buss SN, Leber A, Chapin K, Fey PD, Bankowski MJ, Jones MK, Rogatcheva M, Kanack KJ, Bourzac KM. Multicenter evaluation of the BioFire FilmArray gastrointestinal panel for etiologic diagnosis of infectious gastroenteritis. *J Clin Microbiol*. 2015 Mar;53(3):915-25.

Summary

- Infectious (including food-borne) gastrointestinal disease is common, and probably underdiagnosed
- Microbiological and molecular techniques are invaluable partners to biopsy
- Infectious processes may mimic other types of IBD
- Pathologists and lab workers are essential to evaluating food-borne outbreaks

