

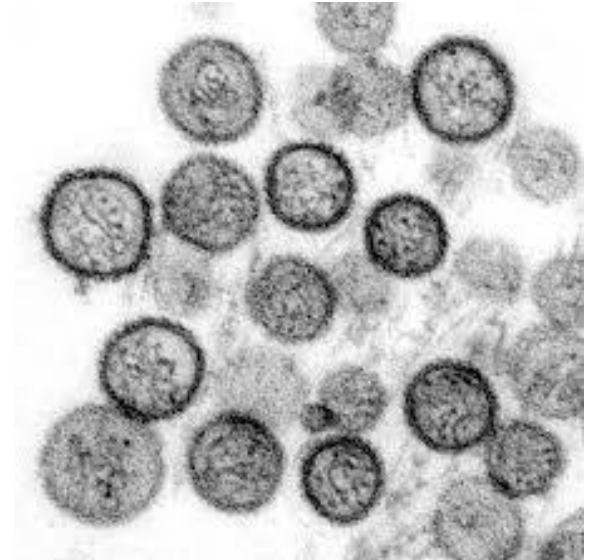
Emerging Infections: historical perspectives, precipitating factors, and pathologic diagnosis

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What is an “emerging” infectious disease?

- A totally new or previously unrecognized organism:
 - HIV
 - Hantavirus
 - SARS
 - Hepatitis C



What is an “emerging” infectious disease?

- A previously recognized organism that has been recently identified as a true pathogen:
 - *H. pylori*
 - *Aeromonas* spp



What is an “emerging” infectious disease?

- A known pathogen that has undergone changes such that it is increasing in incidence or geographic range:
 - Basidiobolomycosis (unknown)
 - Schistosomiasis (dam building)
 - Lyme disease (reforestation favoring ticks and deer near homes)
 - Cryptosporidium (contaminated surface water, faulty water purification)

Factors that contribute to “emerging” infectious diseases

- Antibiotic resistance
- New (permissive) environment
 - Transportation, travel, migration
 - Urbanization with new exposure to pathogens or vectors
 - Food/water contamination
- New (vulnerable) host population
 - Immune deficiency

Vulnerable Host Populations

Who is immunocompromised?

- AIDS
- Chemotherapy
- Solid organ and bone marrow transplants

Vulnerable Host Populations

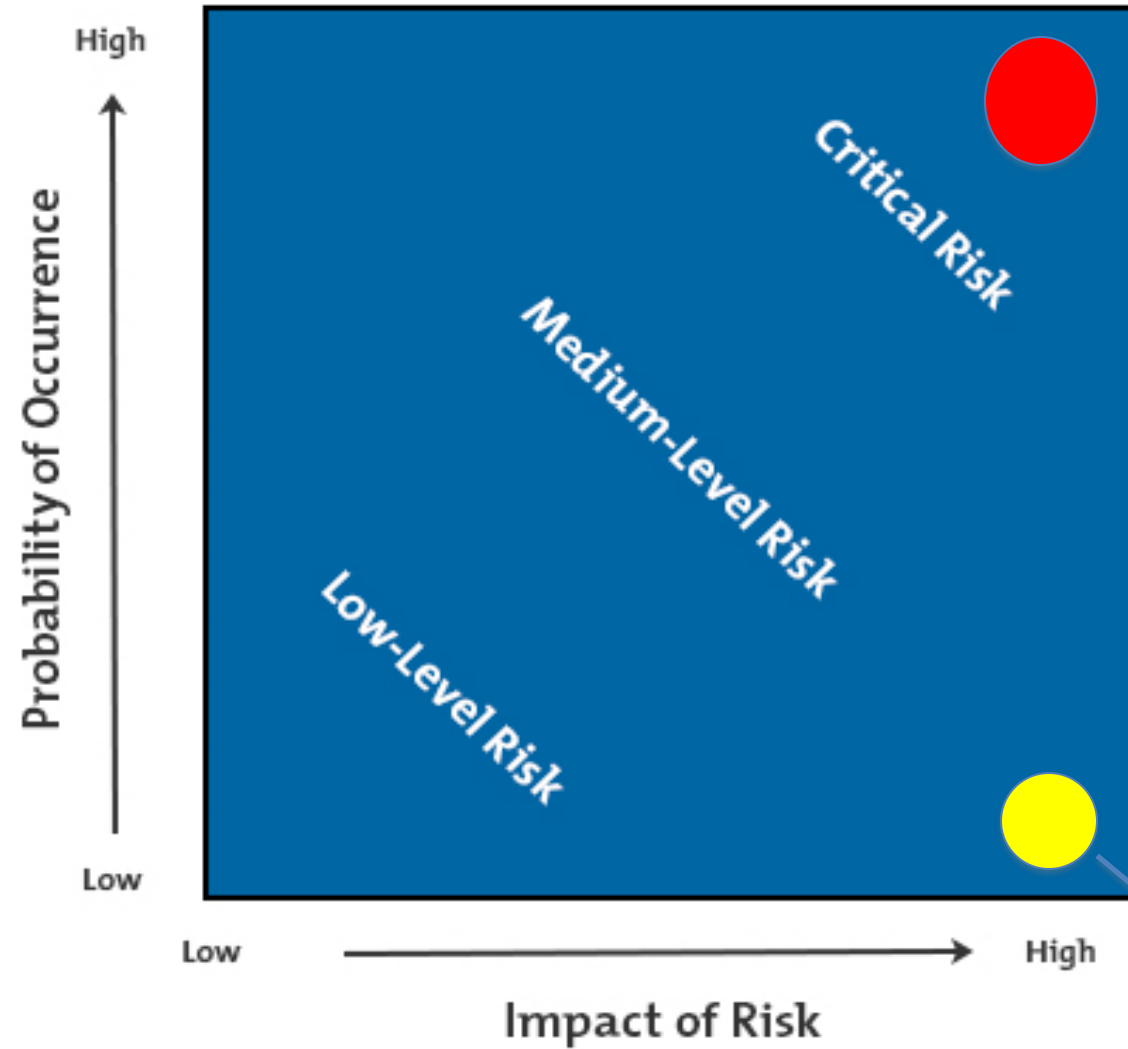
Who is immunocompromised?

- Elderly patients
- Young children
- Patients with CIIBD, autoimmune disease on chronic immunomodulator therapy
- Corticosteroid use

Vulnerable Host Populations

Who is immunocompromised?

- Diabetics
- Patients without spleens
- Chronic alcoholism
- Malnutrition
- Any chronic debilitating disease



Risk impact/probability chart

Many of the
cases for
discussion today

Lessons from a Volcano

Case study: The infamous Eyjafjallajökull volcano belched out tons of ash in 2010. The ash from that volcanic eruption caused tens of thousands of trans-Atlantic airline flights to be canceled, wreaking travel havoc worldwide.

- Low probability, high impact events are areas of vulnerability in diagnostic anatomic pathology.
- We can learn from the study of this matrix in other sectors of science and technology.

What can we learn from an ash cloud?

- Rare things by definition are rare, but neither nonexistent or impossible
 - This requires preparation for things that it's hard to even conceive of
- Local things rarely remain local anymore
 - Infections that spread through food, travel
 - Weird patterns of metastasis
 - Weird distribution of vasculitis

What can we learn from an ash cloud?

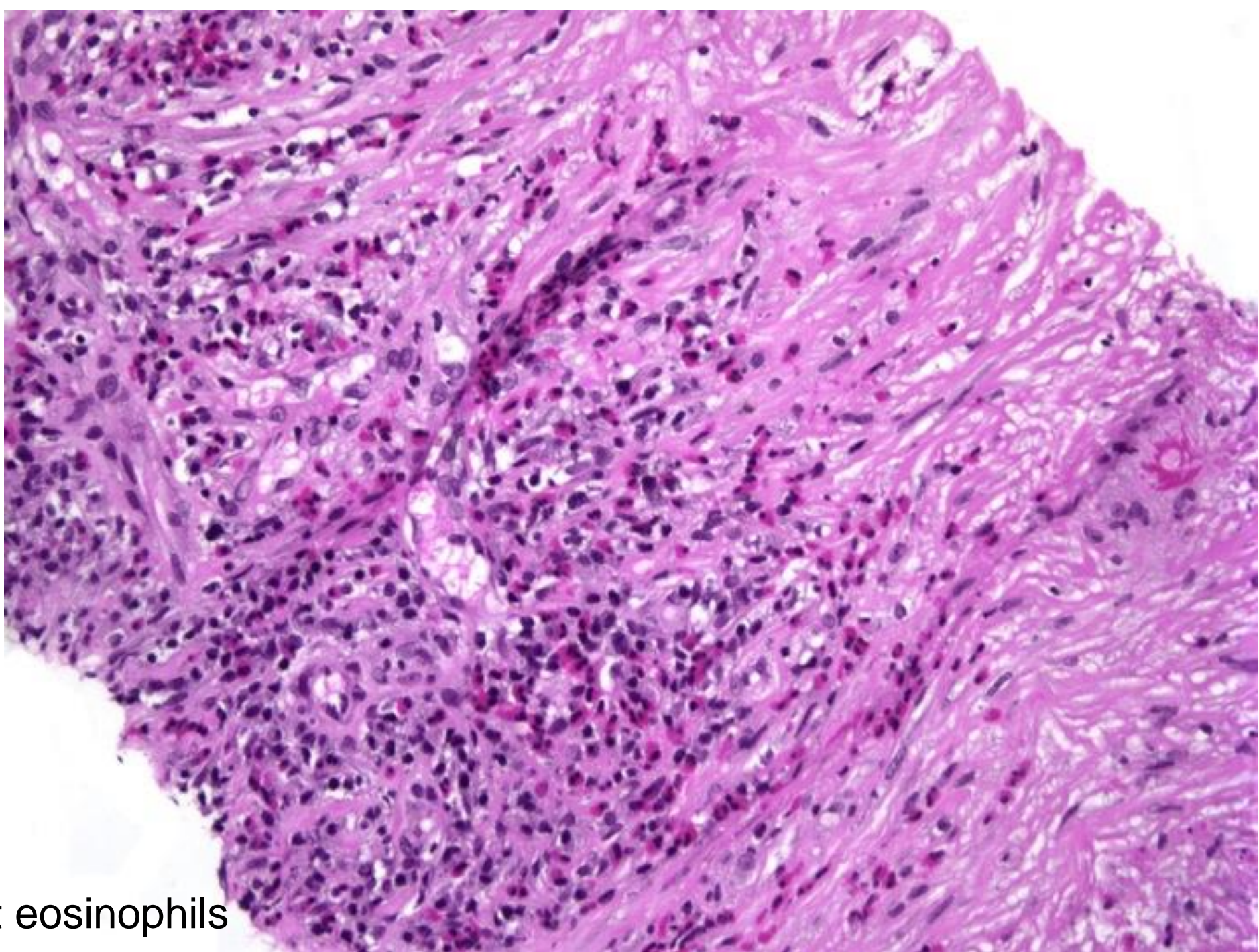
- Collect all the information you can about events (cases), and communicate with others who have information.
- Establish and be aware of best practices.
- Know the literature (“build up a library of observations that can be drawn on when preparing for similar shocks in the future”).

Give us the
chicken. We'll
check it for
Salmonella.



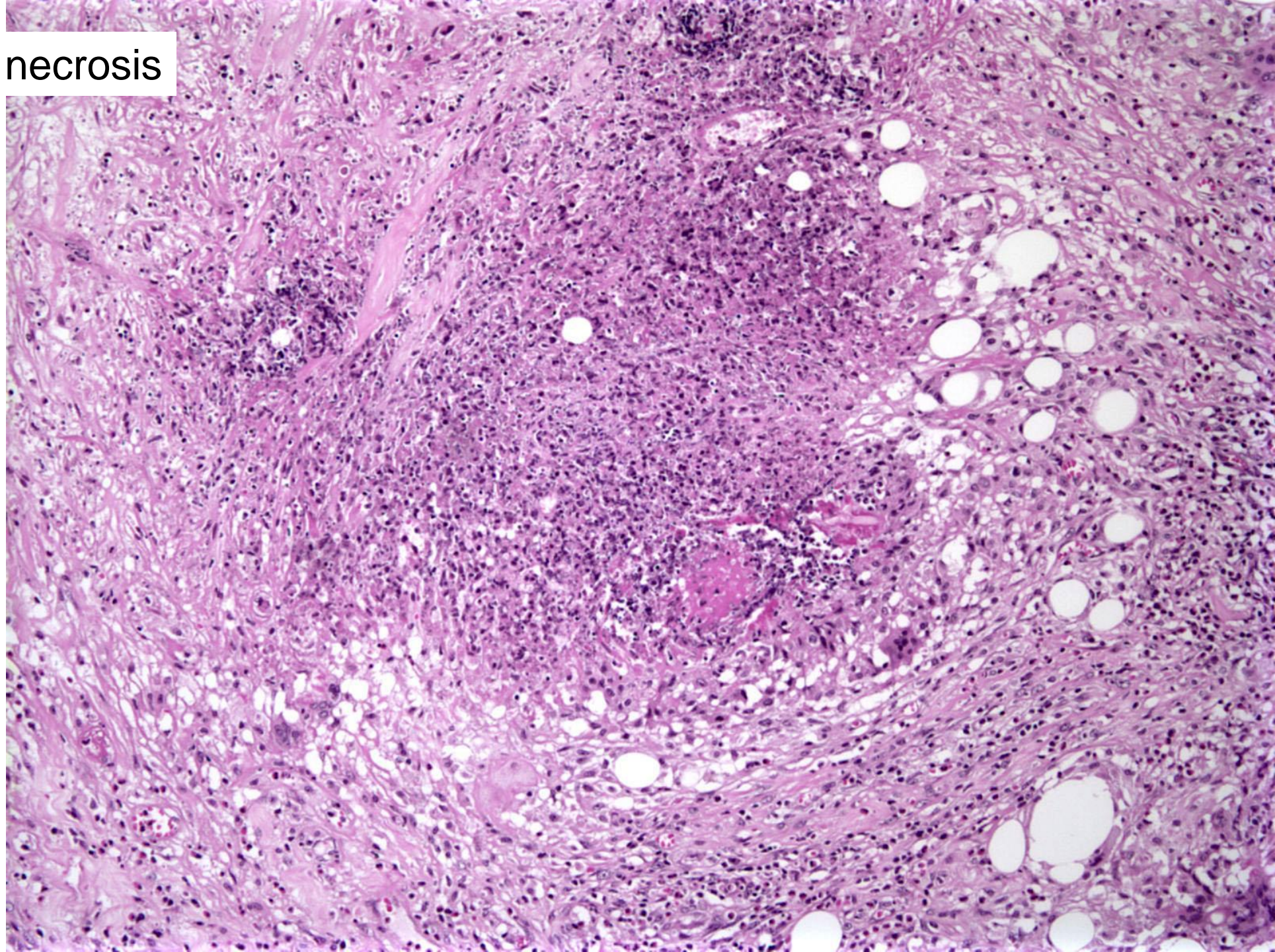
Case Example #1

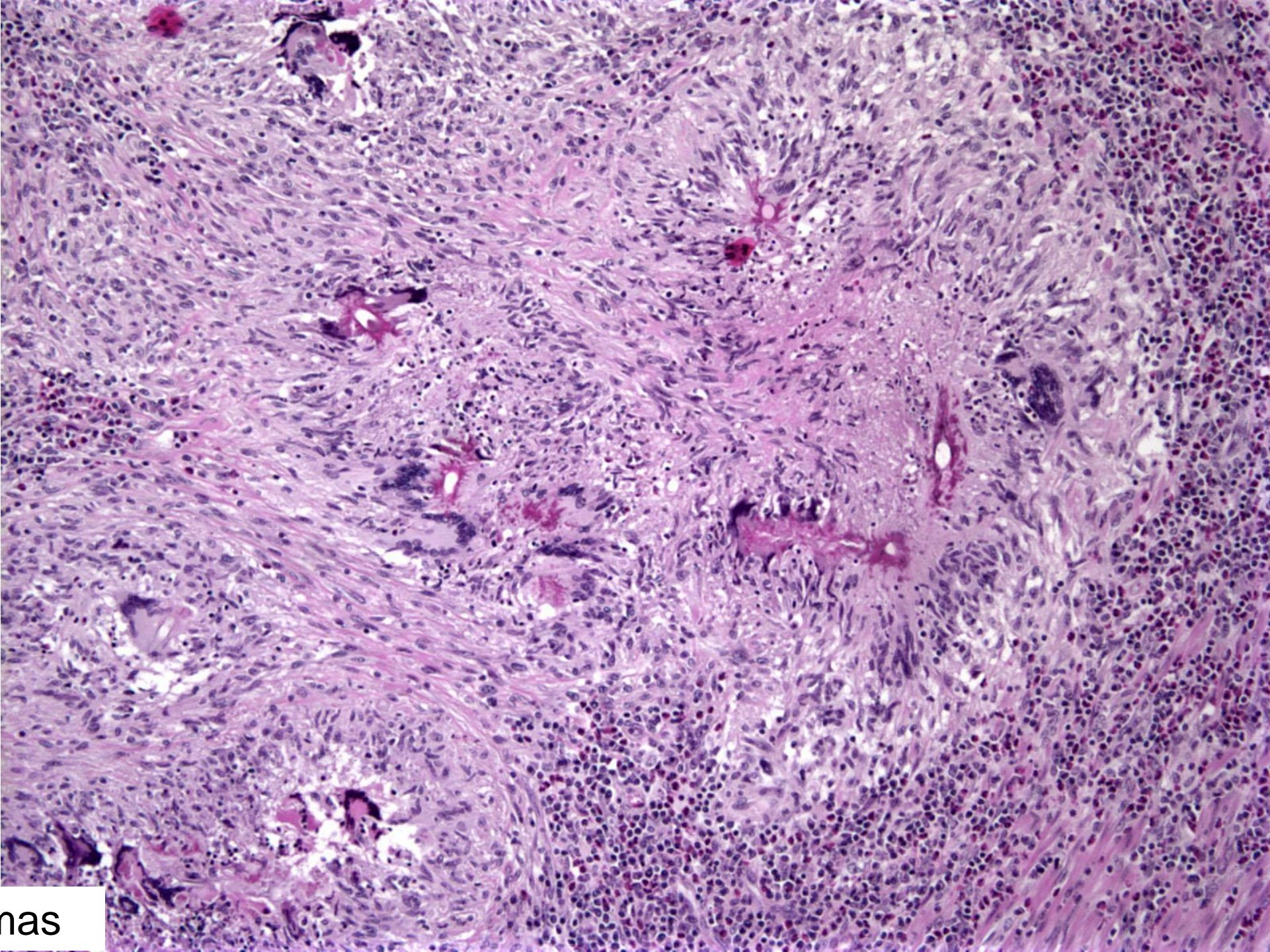
- A 45 year old migrant worker, currently employed in Arizona, presented with severe abdominal pain. Imaging studies showed a large near-obstructing colonic/paracolic mass that was suspicious for malignancy. A segmental resection was performed.



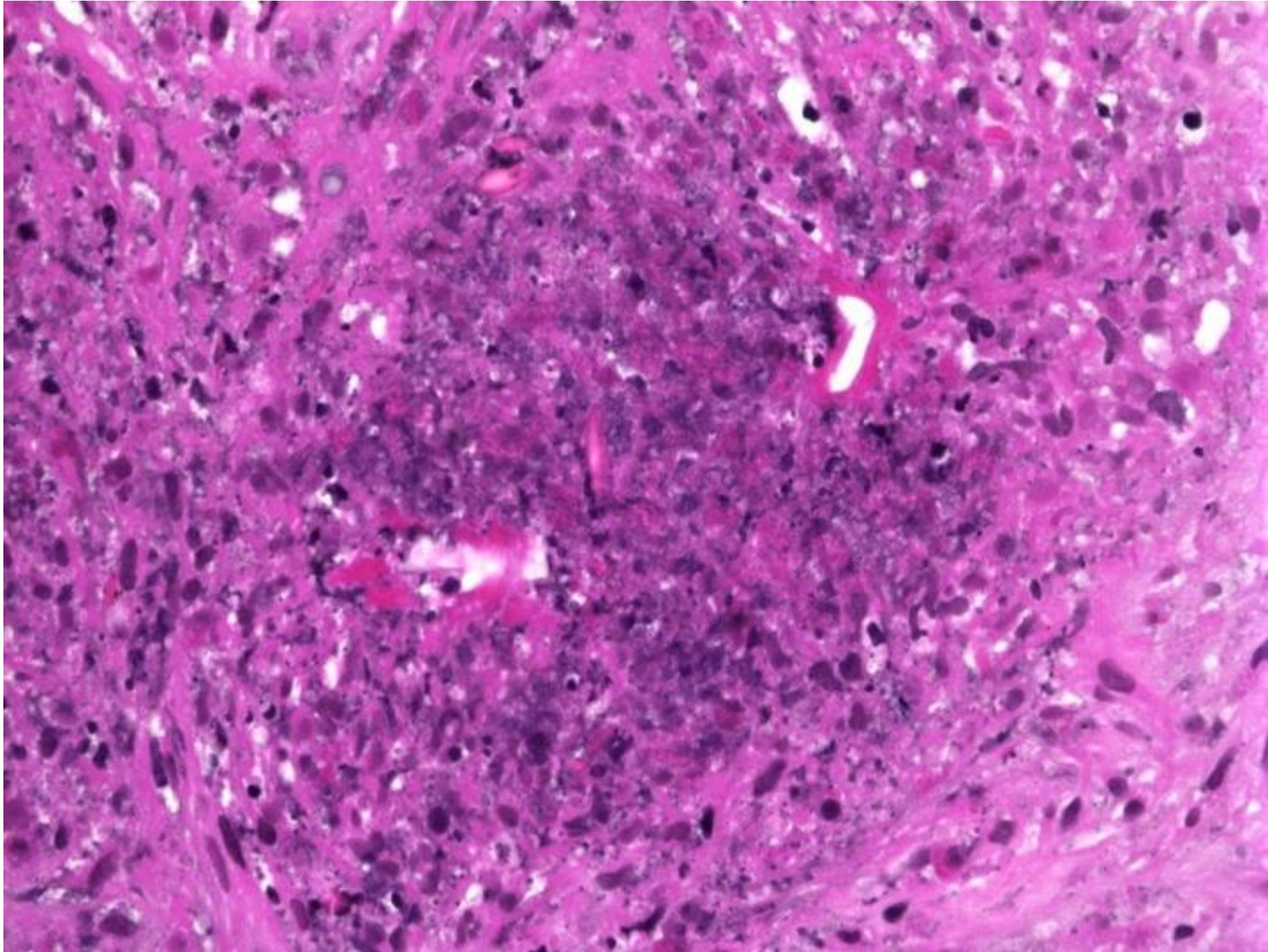
Prominent eosinophils

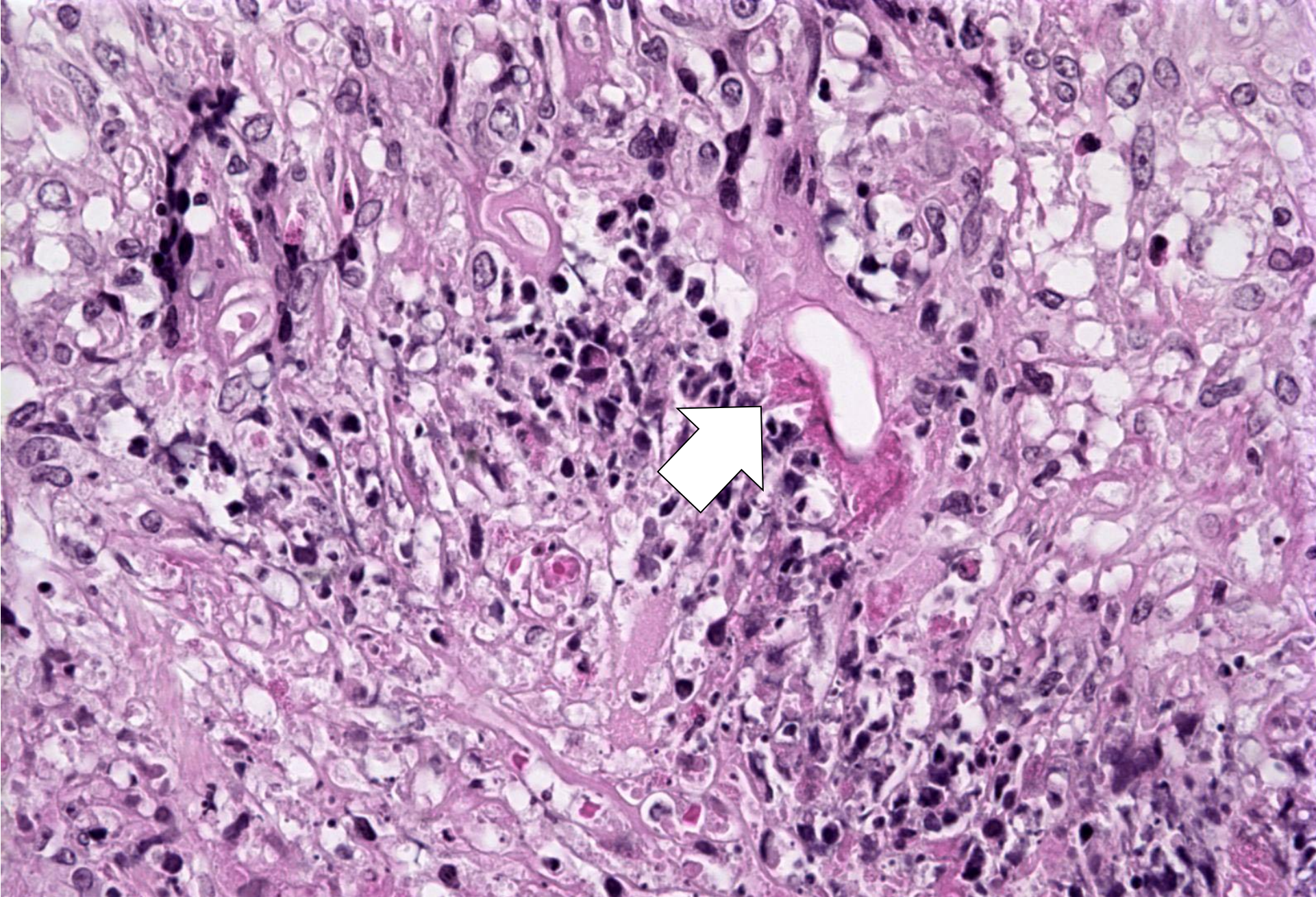
Extensive necrosis



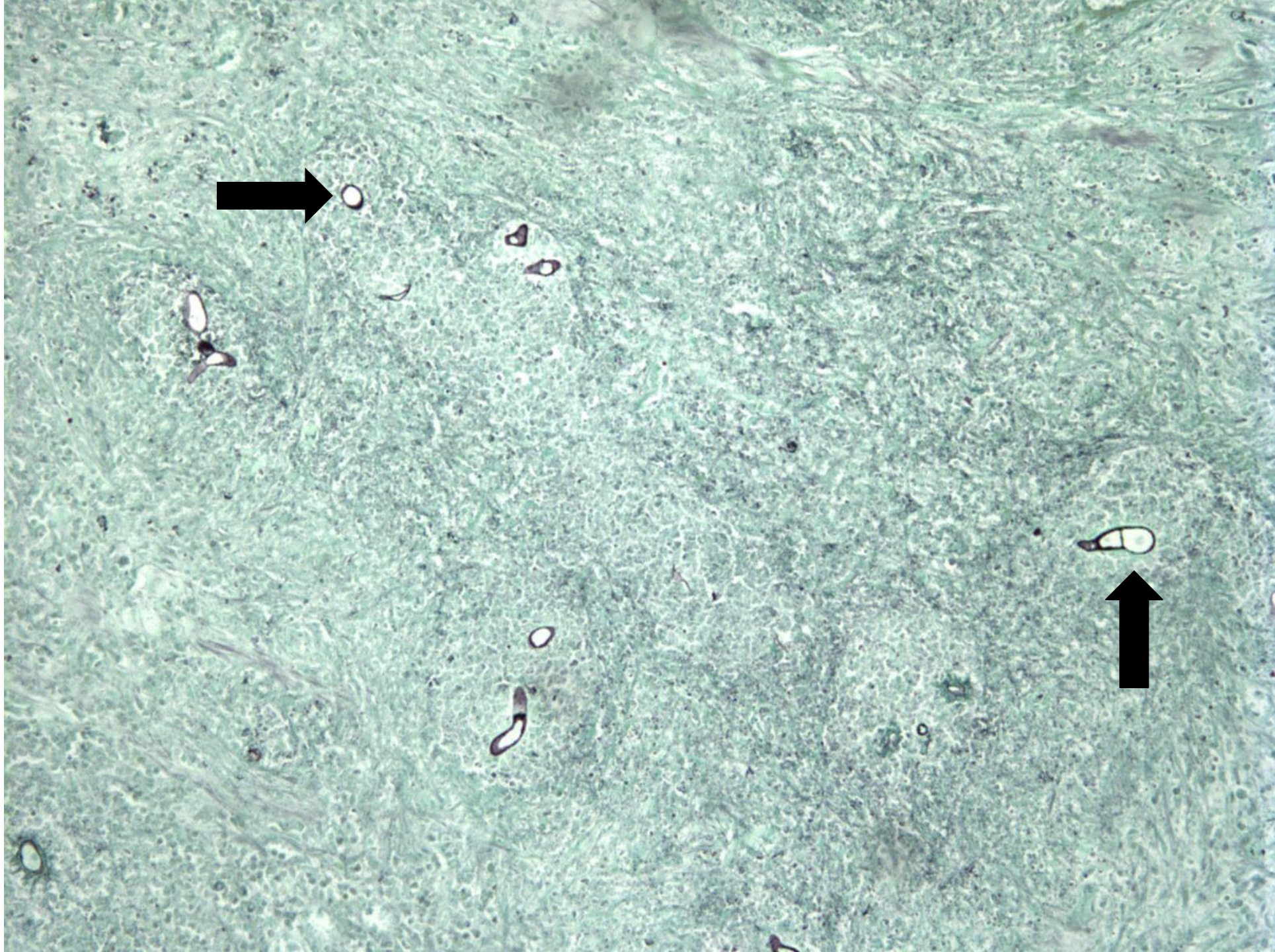


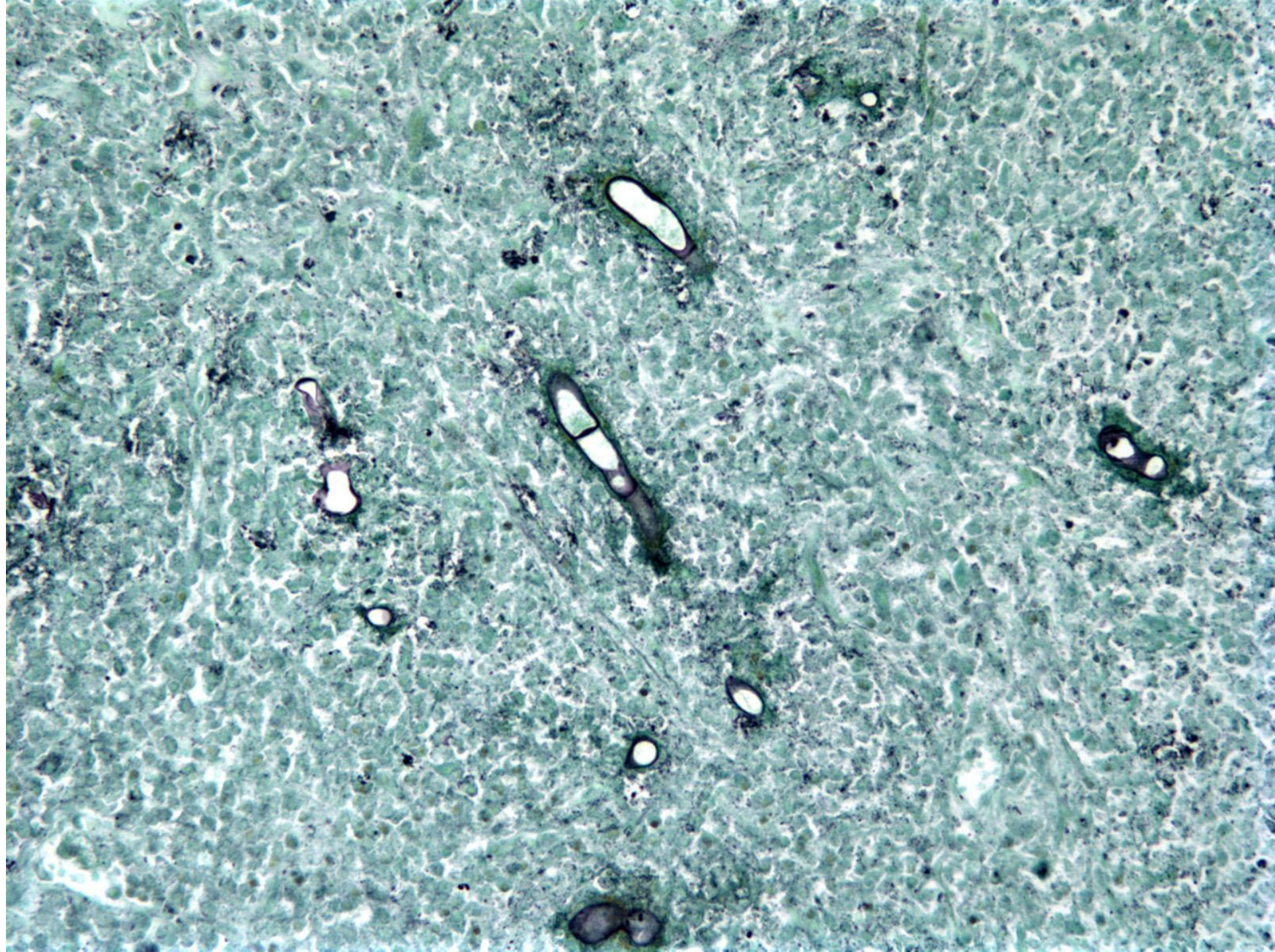
Granulomas

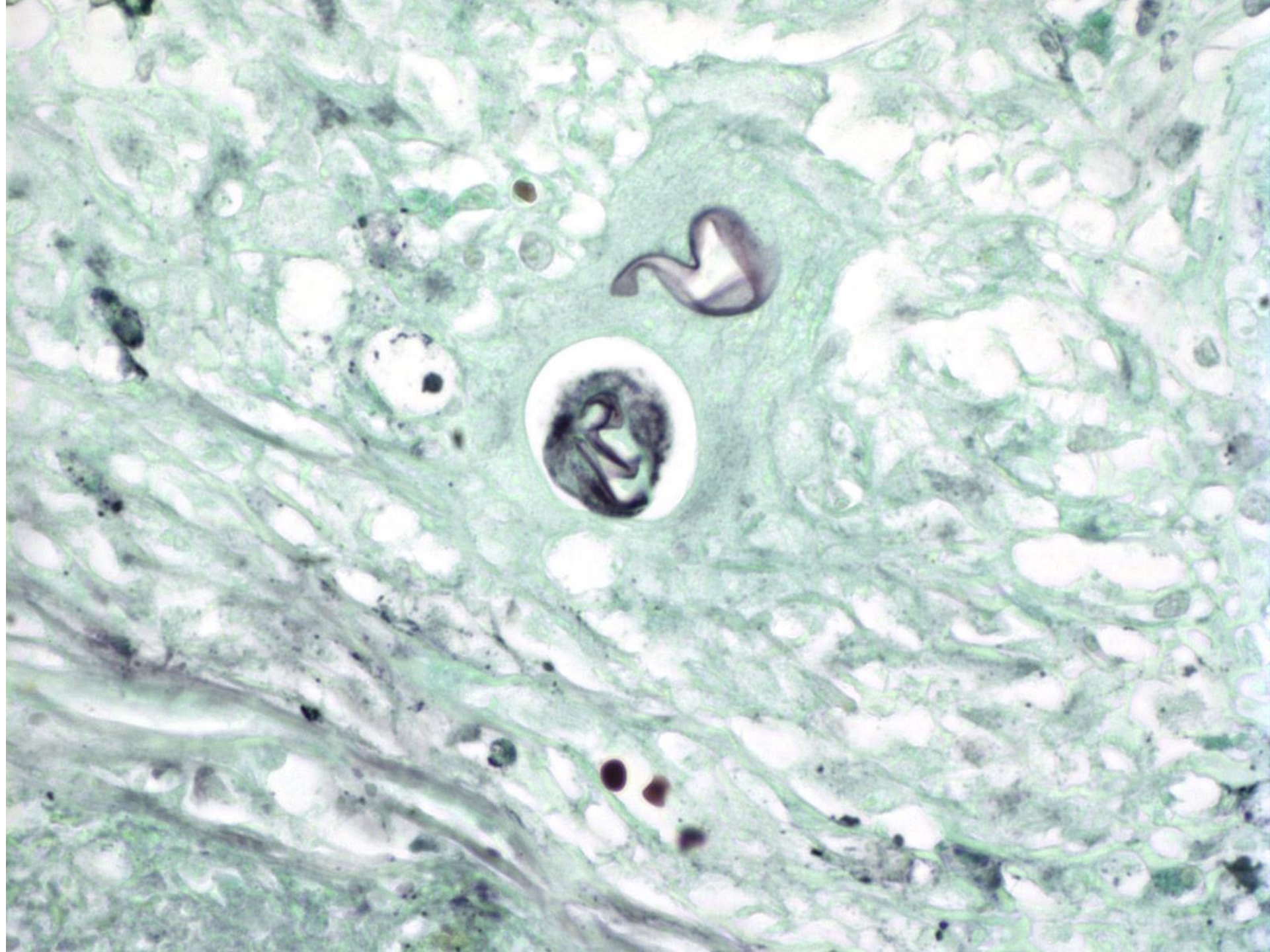




Organisms are rare, not angioinvasive, and associated with Splendore-Hoeppli material







Emerging Infection: Basidiobolomycosis

- *Basidiobolus ranarum*, closely related to *Mucorales* (Entomophthorales)
- Worldwide soil saprophyte
 - Until recently, primarily considered a subcutaneous infection (site changing)
 - Most cases reported in Saudi Arabia, Africa, South America; current cohort of cases in Arizona (geography changing)

Gastrointestinal Basidiobolomycosis

- GI cases can mimic malignancy, idiopathic inflammatory bowel disease
- Most cases respond to long-term antifungal therapy, but colonic perforation, dissemination, and death are well-documented

Basidiobolomycosis

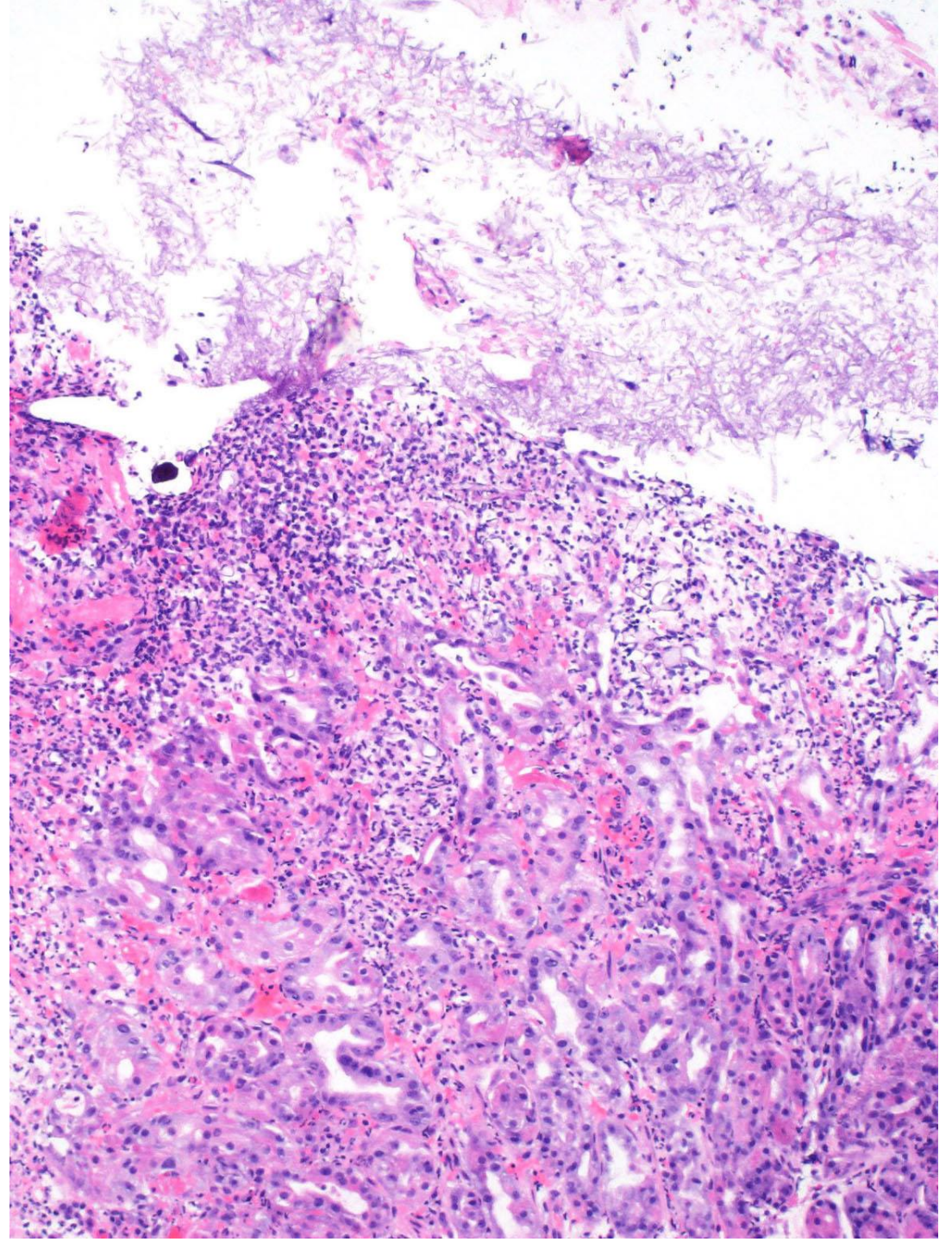
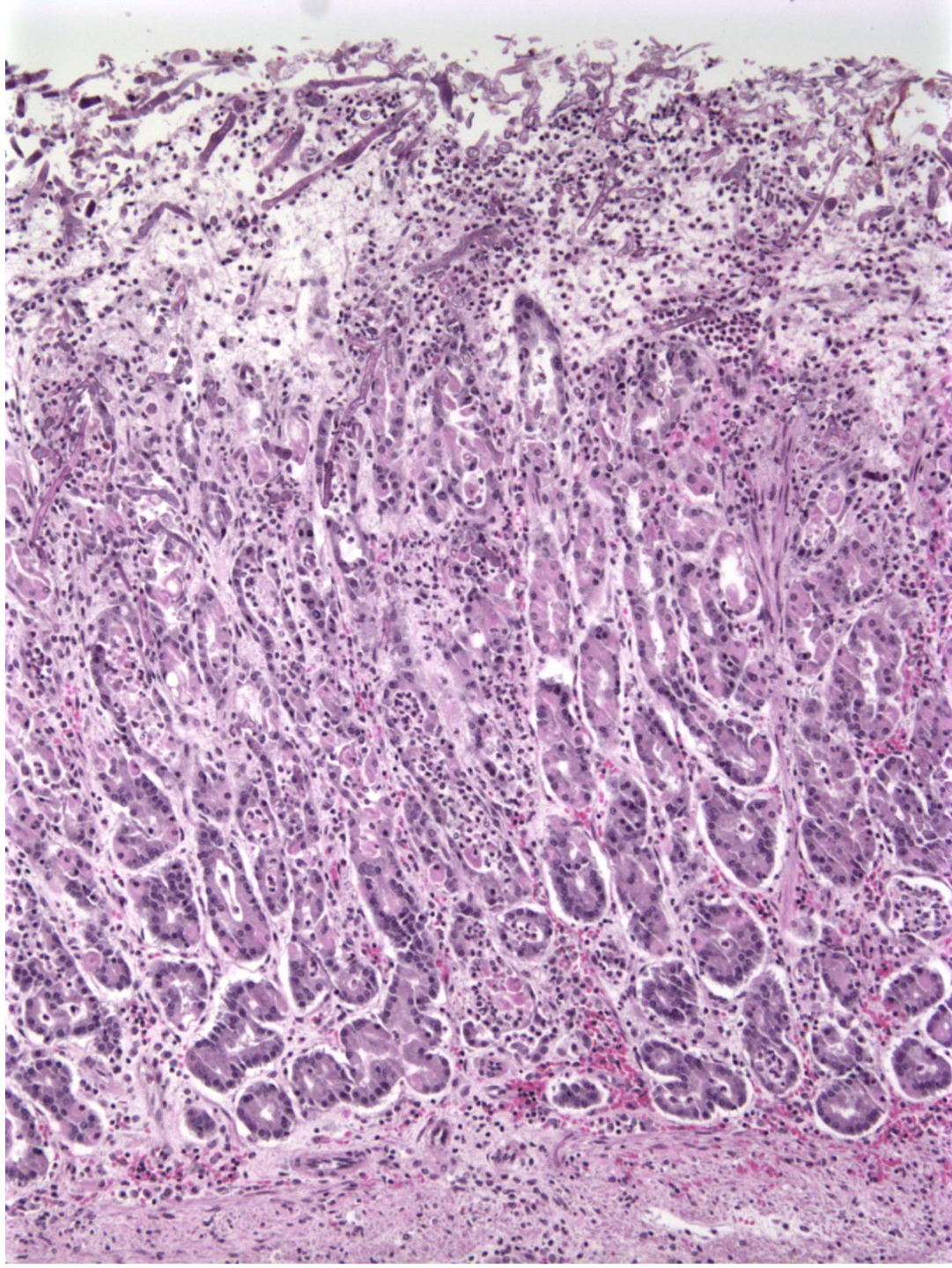
- Vulnerable populations:
 - Children
 - Peptic ulcer disease
 - Diabetes
 - Pica
 - Ranitidine use
 - Living in an endemic area

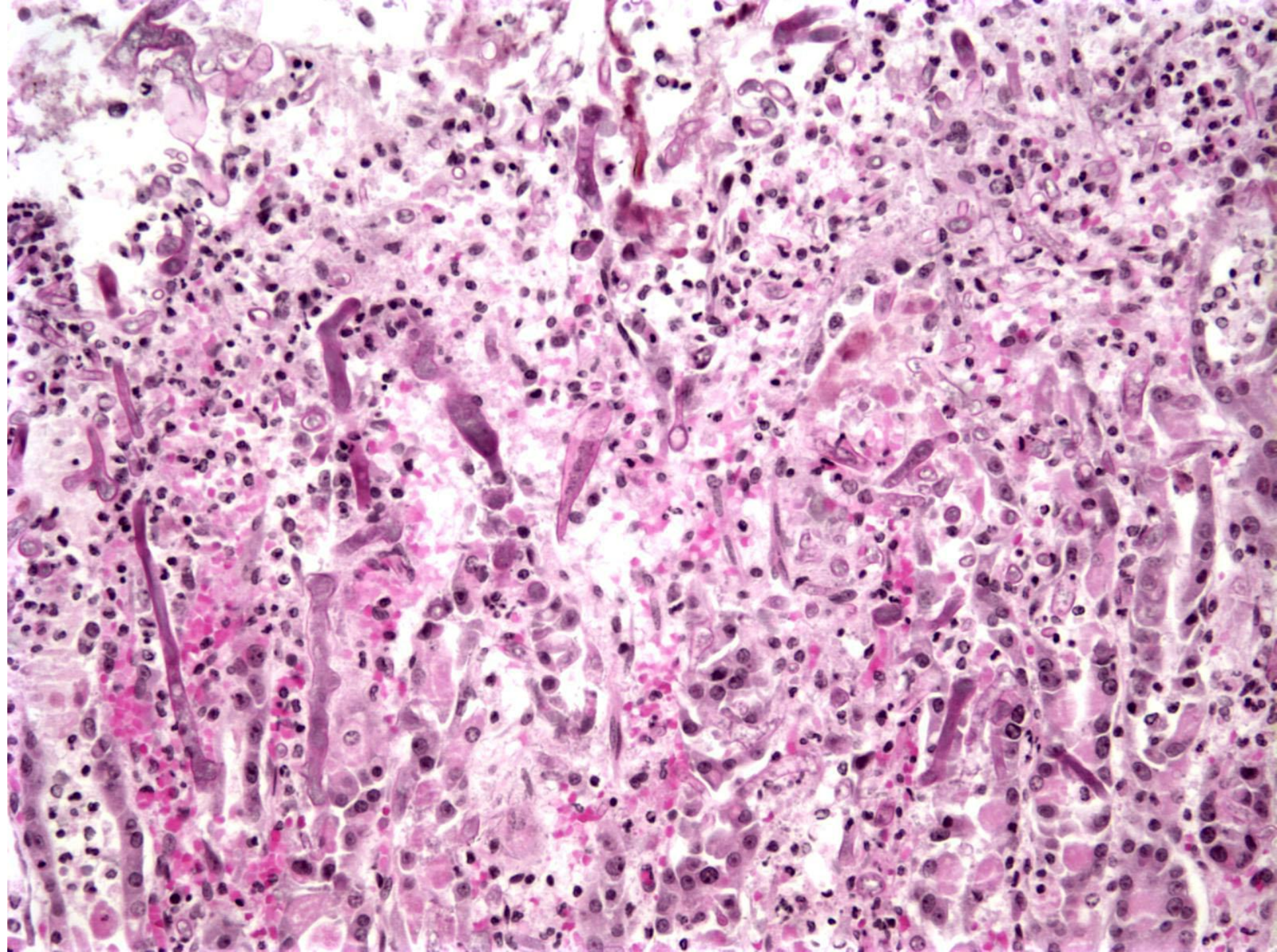
Low probability, high impact event

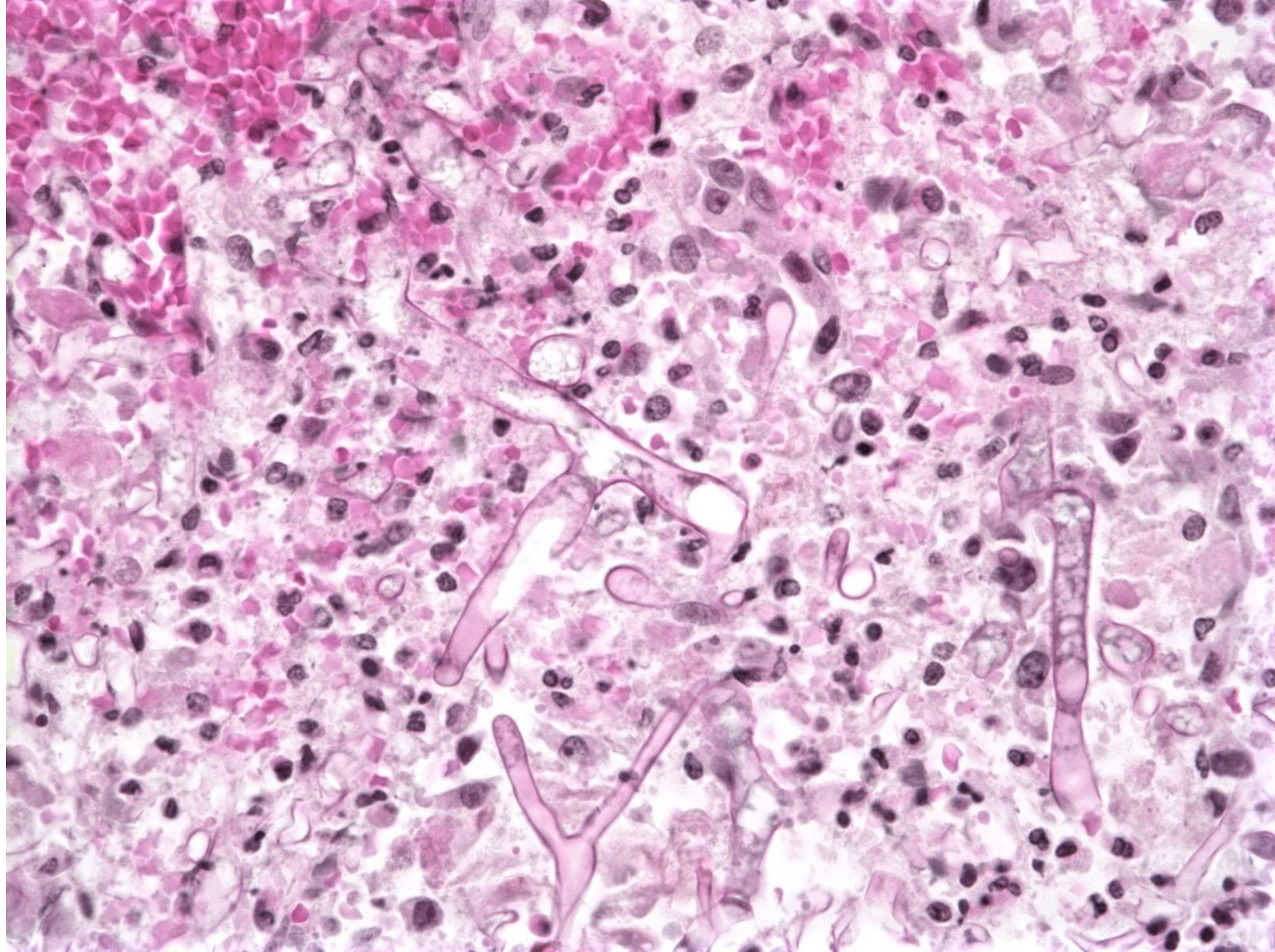
- We report here the case of a 55-year-old man from Mali, who presented with abdominal pain. Radiological exploration revealed an ileo-colonic mass surrounding the appendix. A biopsy was taken and on histology, transmural granulomatous inflammation of numerous eosinophils, lymphocytes, plasmocytes and giant cells was seen. **Tuberculosis was suspected clinically and an antibiotic treatment was initiated. Two months later, the patient died of septic complications.** *Basidiobolus ranarum* was identified by PCR. Pathogens were retrospectively highlighted on biopsies. Gastro-intestinal basidiobolomycosis is rare and presents considerable diagnostic difficulty. This infection needs to be diagnosed because surgical resection and prolonged antifungal treatment are curable in most cases.

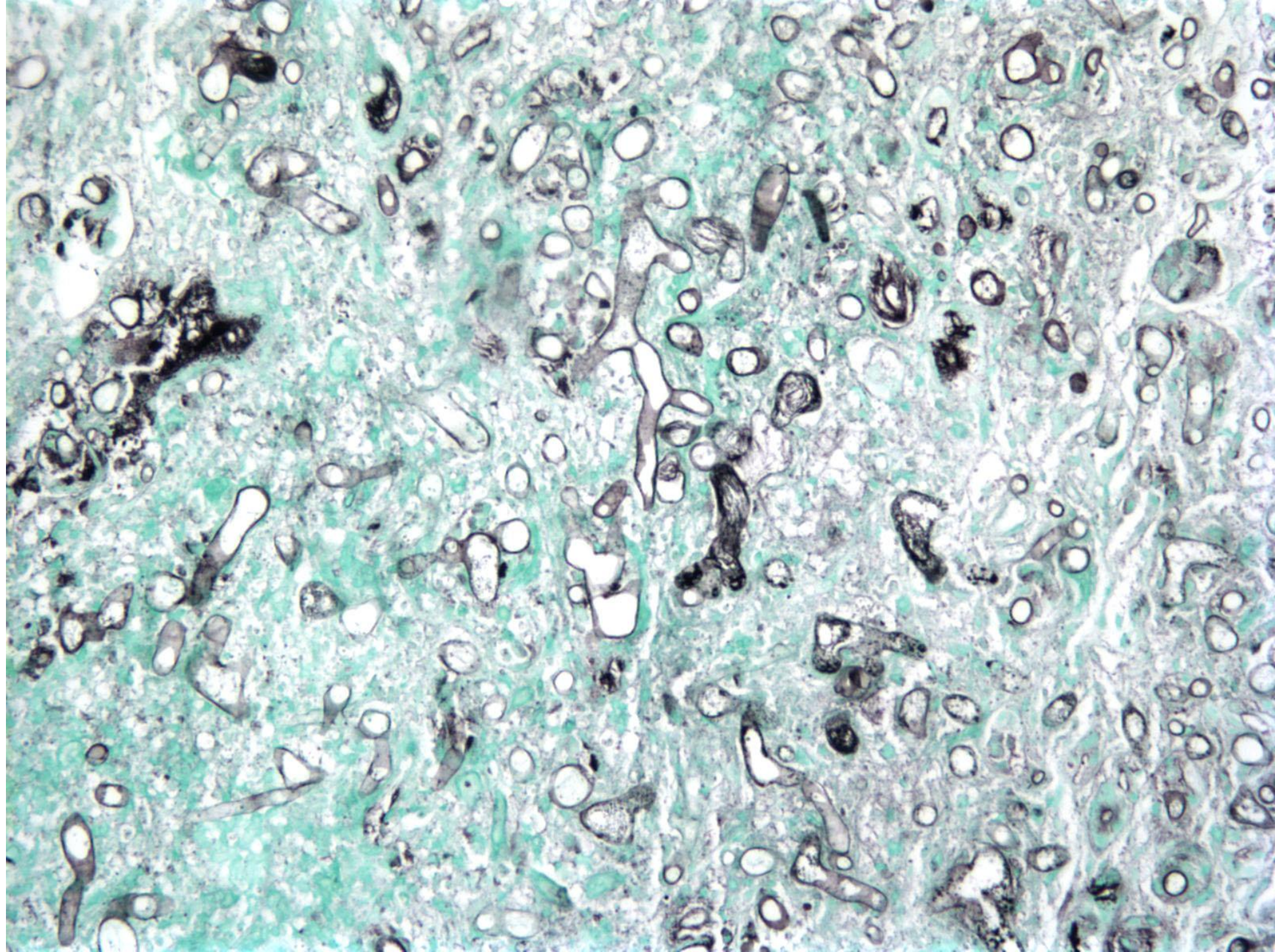
GI Mucormycosis

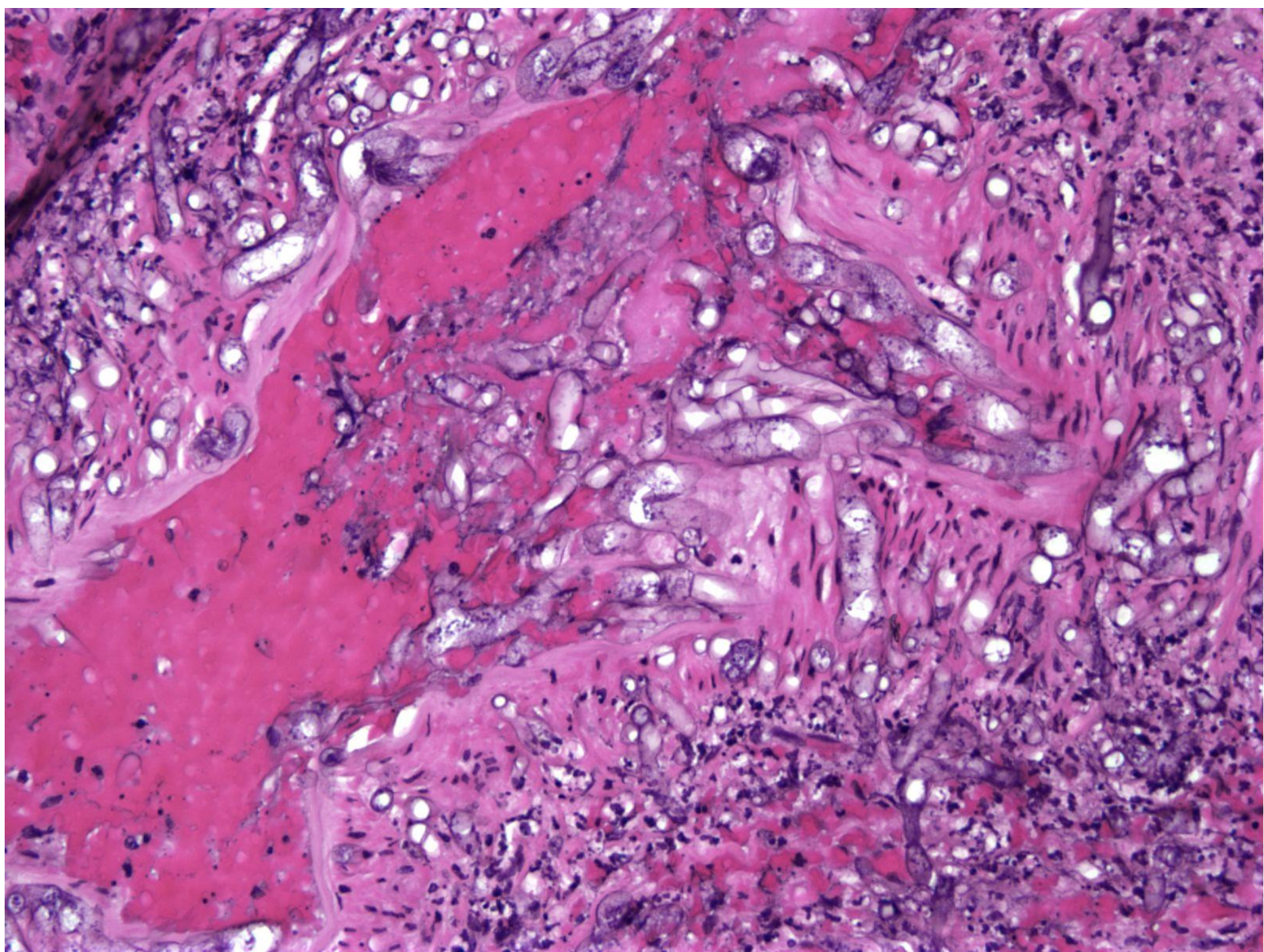
- Often caused by colonization of ulcers
- Stomach and colon are most frequently involved sites
- Ulcers often have heaped-up, rolled edges that mimic malignancy grossly
- Pathologic features very similar to aspergillosis











Mucor vs. Basidiobolomycosis

Mucor

- Angioinvasive
- Abundant organisms
- No Splendore-Hoeppli
- Necrosis
- Not eosinophilic
- Diabetics, ketoacidosis

Basidiobolomycosis

- Not angioinvasive
- Fewer organisms
- Splendore-Hoeppli
- Necrosis and granulomas
- Markedly eosinophilic
- Farm workers, desert dwellers

Summary

- Basidiobolomycosis resembles Mucor, but is not angioinvasive and has a different tissue reaction
- Suspect in patients from endemic areas with paracolonc masses
- Patients often not immunocompromised
- Mucor in the sinonasal tract is a medical emergency

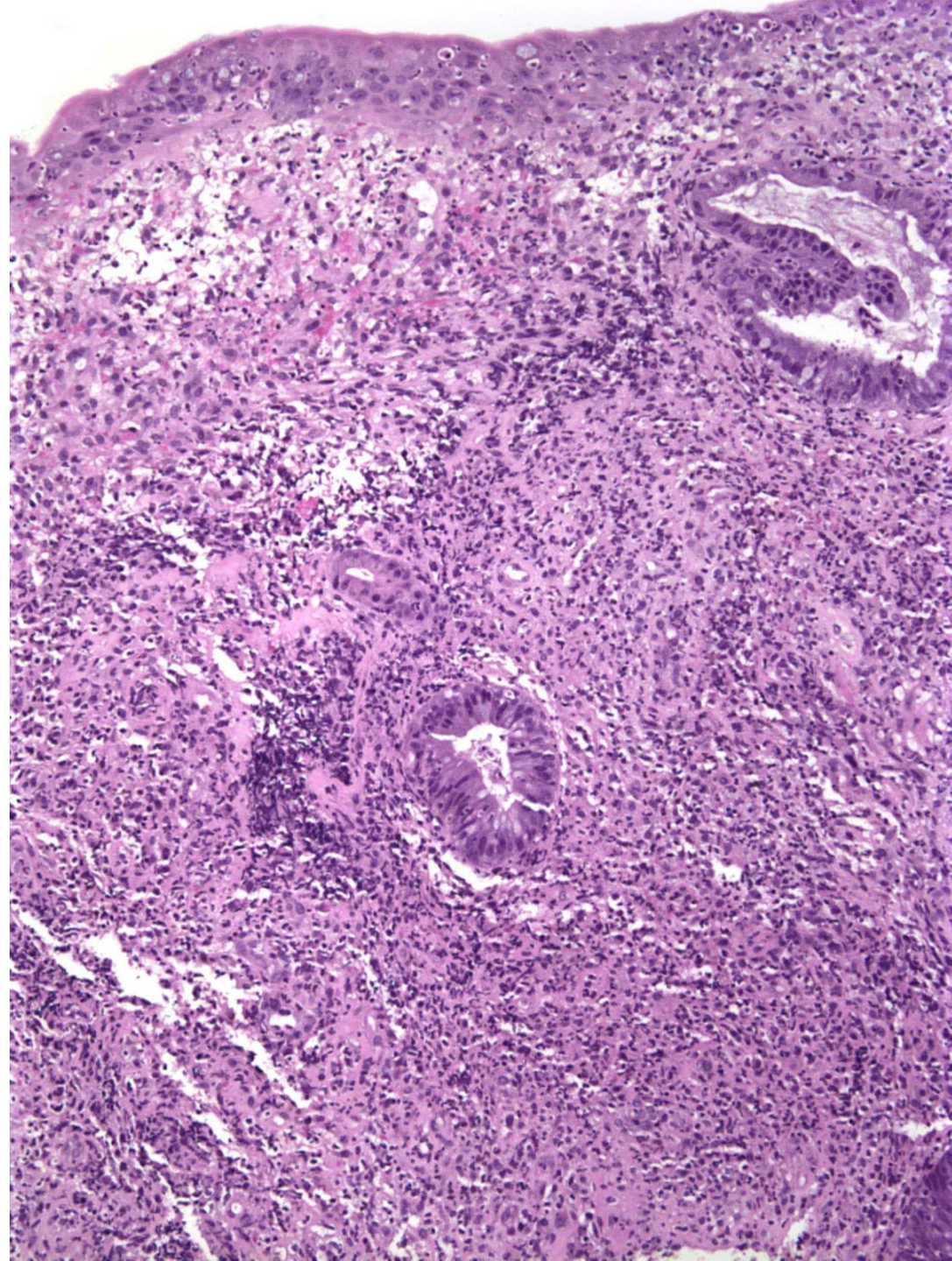
Thomson SR et al. Gastrointestinal mucormycosis. Brit J Surg 78; 952-4, 1991.
Smilack JD. Gastrointestinal basidiobolomycosis. Clin Infect Dis 27; 663-4, 1998.
Yousef OM et al. Gastrointestinal basidiobolomycosis. Morphologic findings in a cluster of six cases. Am J Clin Pathol 112(5):610-6, 1999.

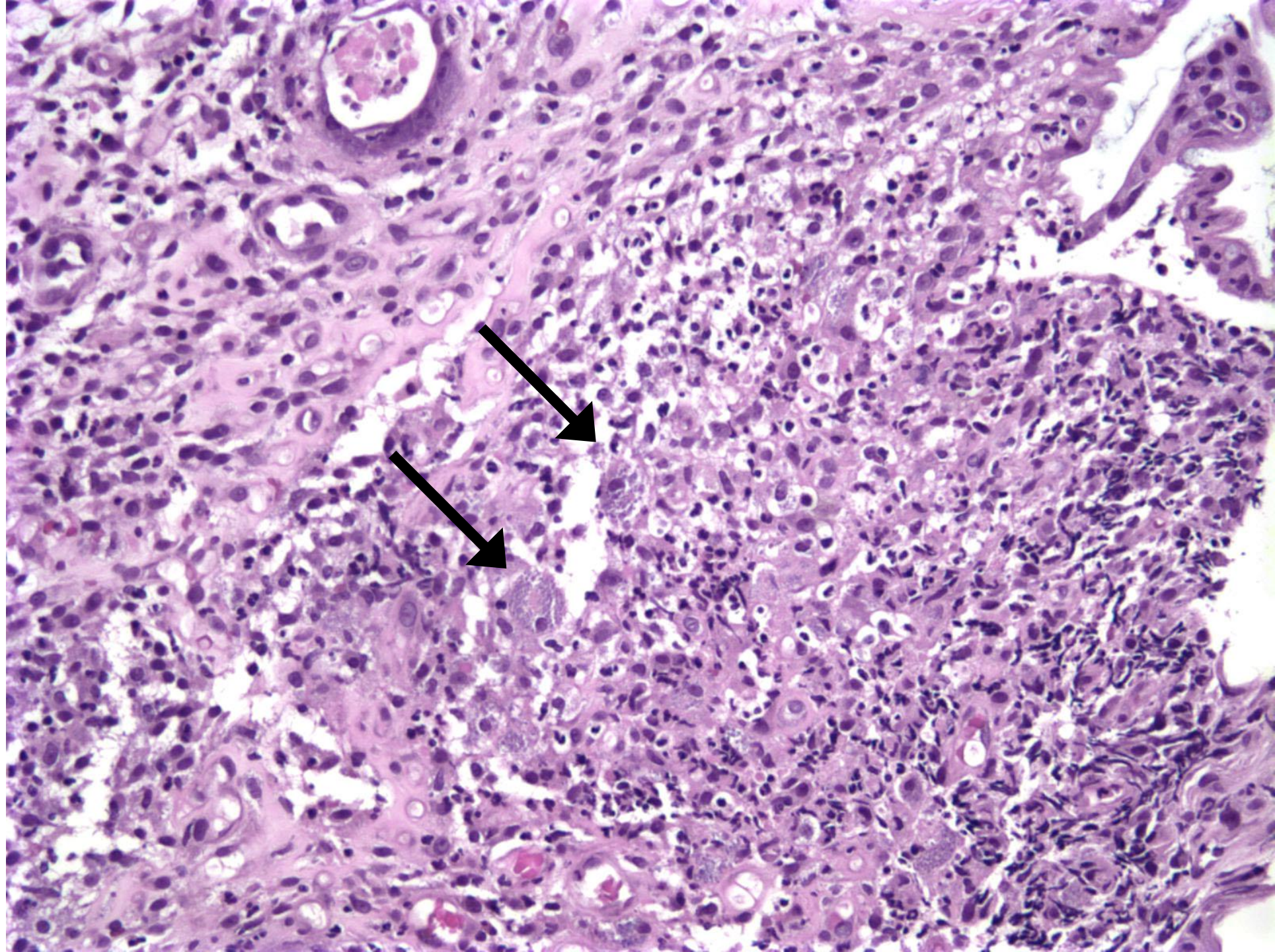
Alys searches for soil saprophytes.

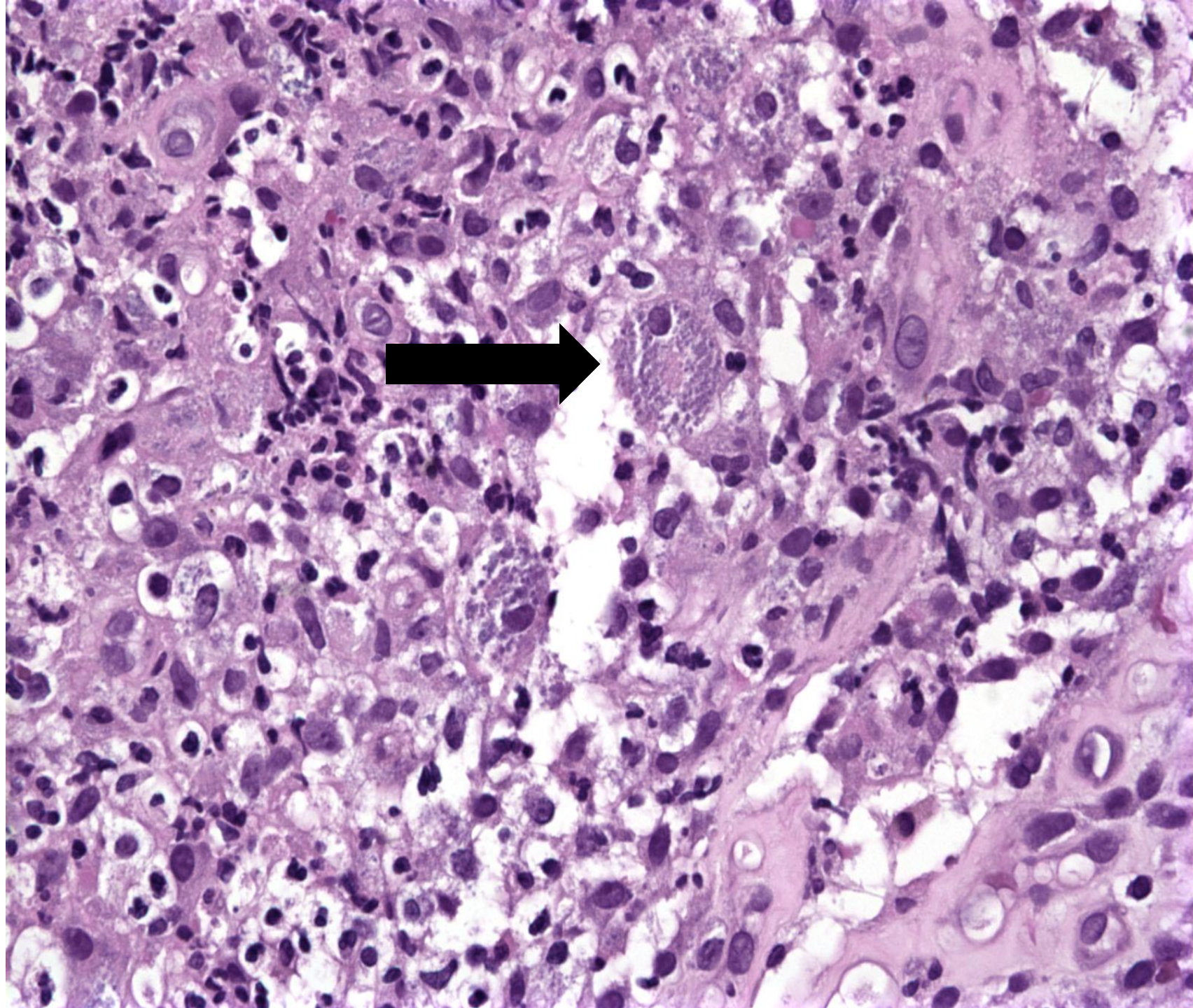


Case Example #2

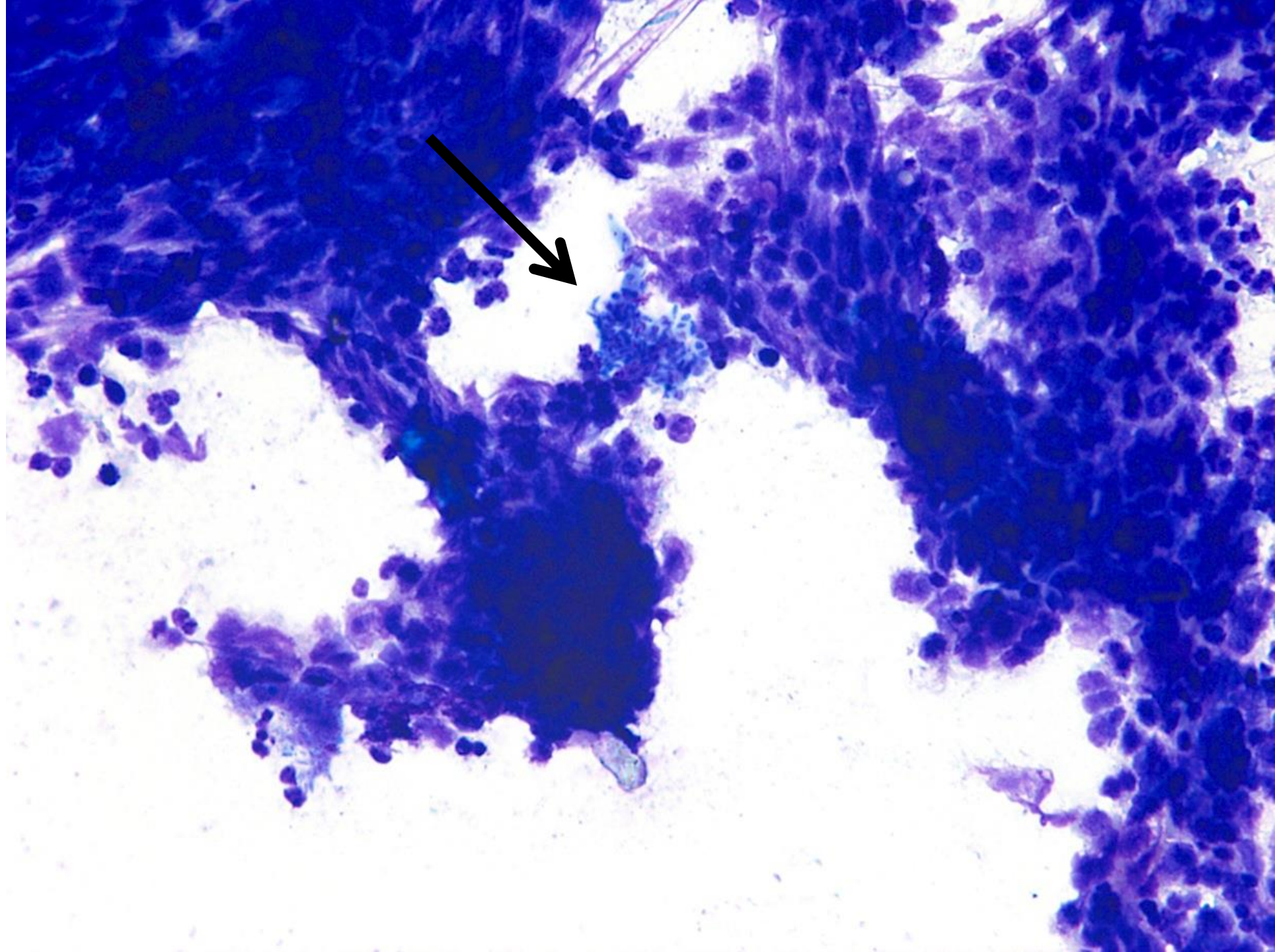
- A 25 year old Chinese exchange student, living in Arkansas, presented with diarrhea and lower GI bleeding. CT scan showed a thickened colon and liver lesions. Colonoscopy showed areas of friable mucosa. Biopsies were obtained.











Emerging Infection: *Talaromyces* (*Penicillium*) *marneffe*

- Dimorphic fungus
- Endemic in Southeast Asia and Far Eastern Asia
- Most commonly involves lungs and liver, followed by GI tract

Emerging Infection: *Penicillium (Talaromyces) marneffe*

- Now one of the most common opportunistic infections in Asian patients with AIDS
- In Western countries, associated with:
 - Travel/immigration
 - Immunocompromise

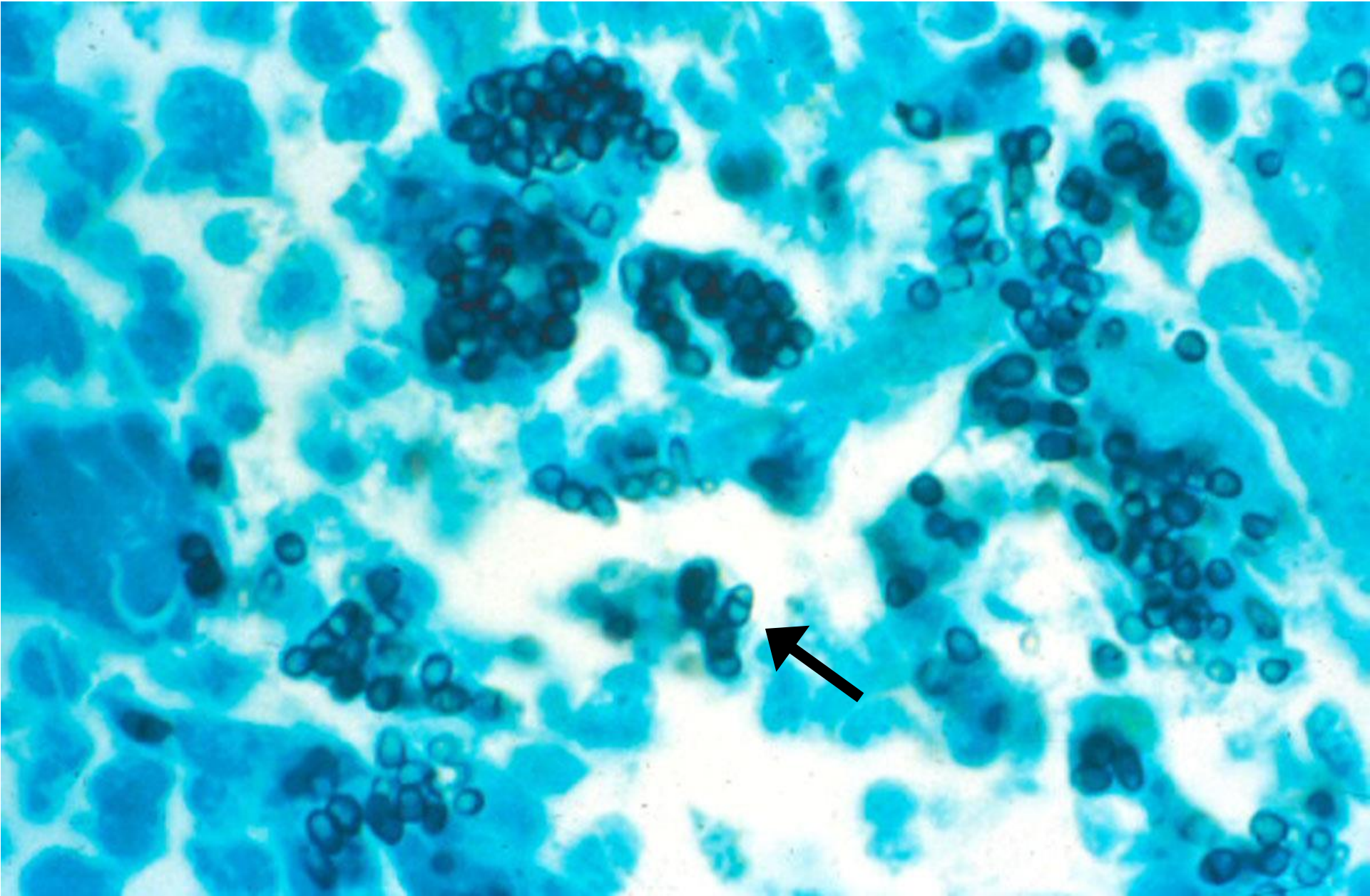
T. marneffe

- Inflammatory response is granulomatous, suppurative, or mixed
- Yeast forms are septate (“pill capsule”) and similar to histoplasmosis, but they do not bud
 - Occasional elongated “sausage” forms with prominent septum
- Require months of antifungal therapy, and dissemination can be rapidly fatal

Low probability, high impact event

- Results: A total of 47 AIDS-associated penicilliosis were confirmed by fungal culture, which accounted for 4.8% of 981 AIDS-related admissions. Two independent predictors for early mortality (death within 12 weeks) of the patients (21.3%, 10/47) were a delayed diagnosis and no treatment with antifungal therapy.

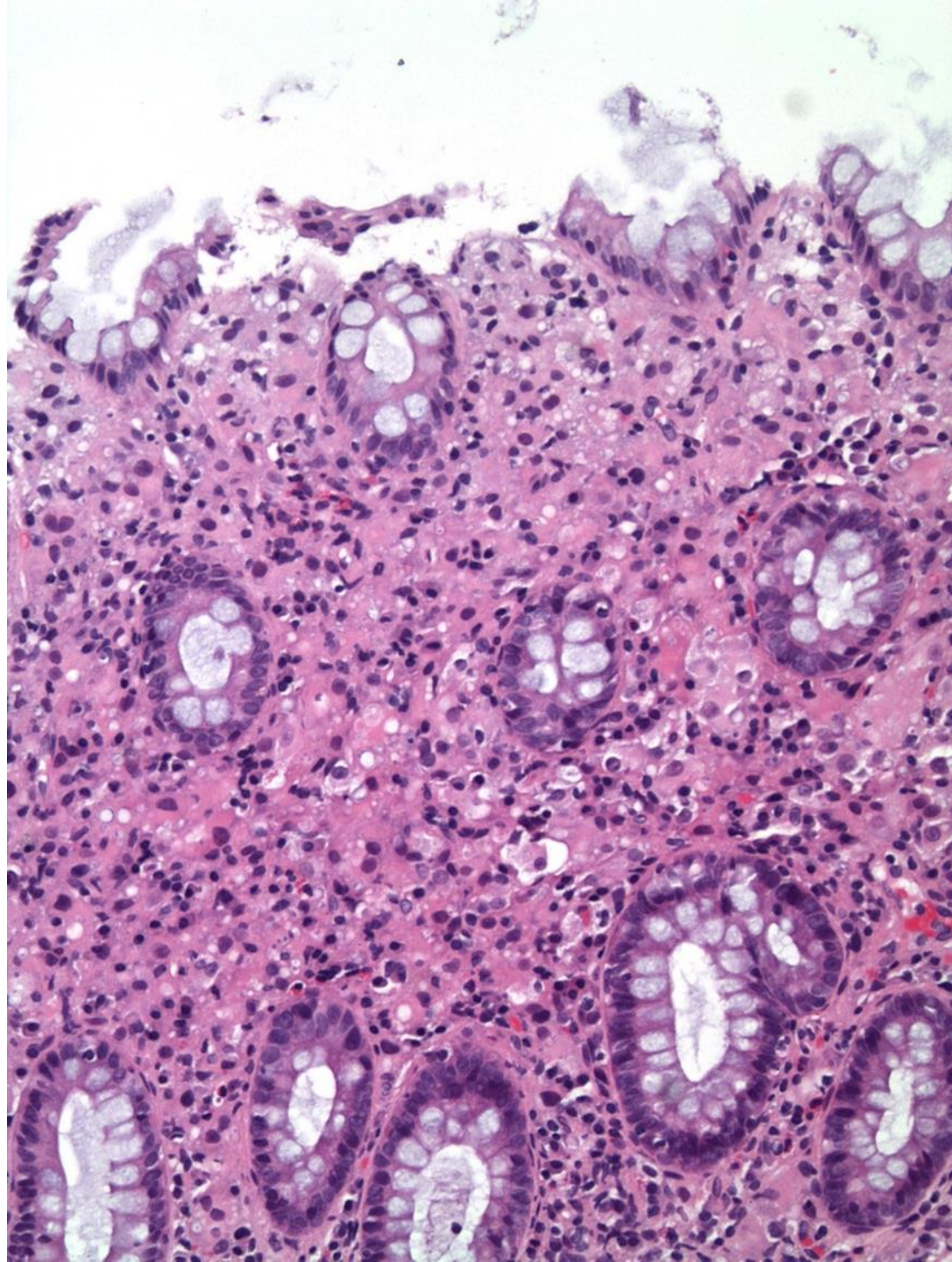
- Zheng et al. A clinical study of AIDS-associated *Penicillium marneffe*i infection from a non-endemic area in China. PLoS One June 17 2015

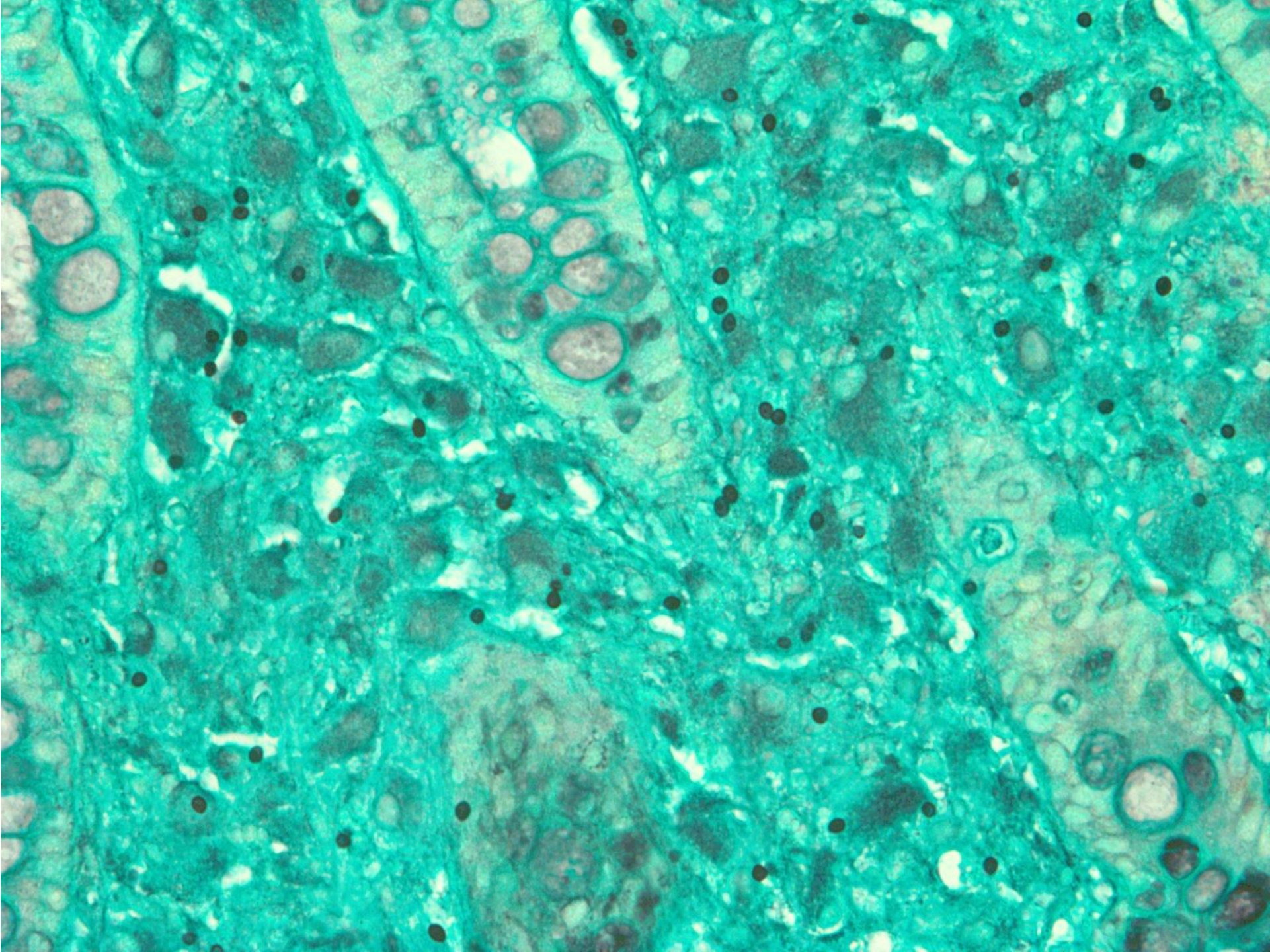


Courtesy Dr. David Walker

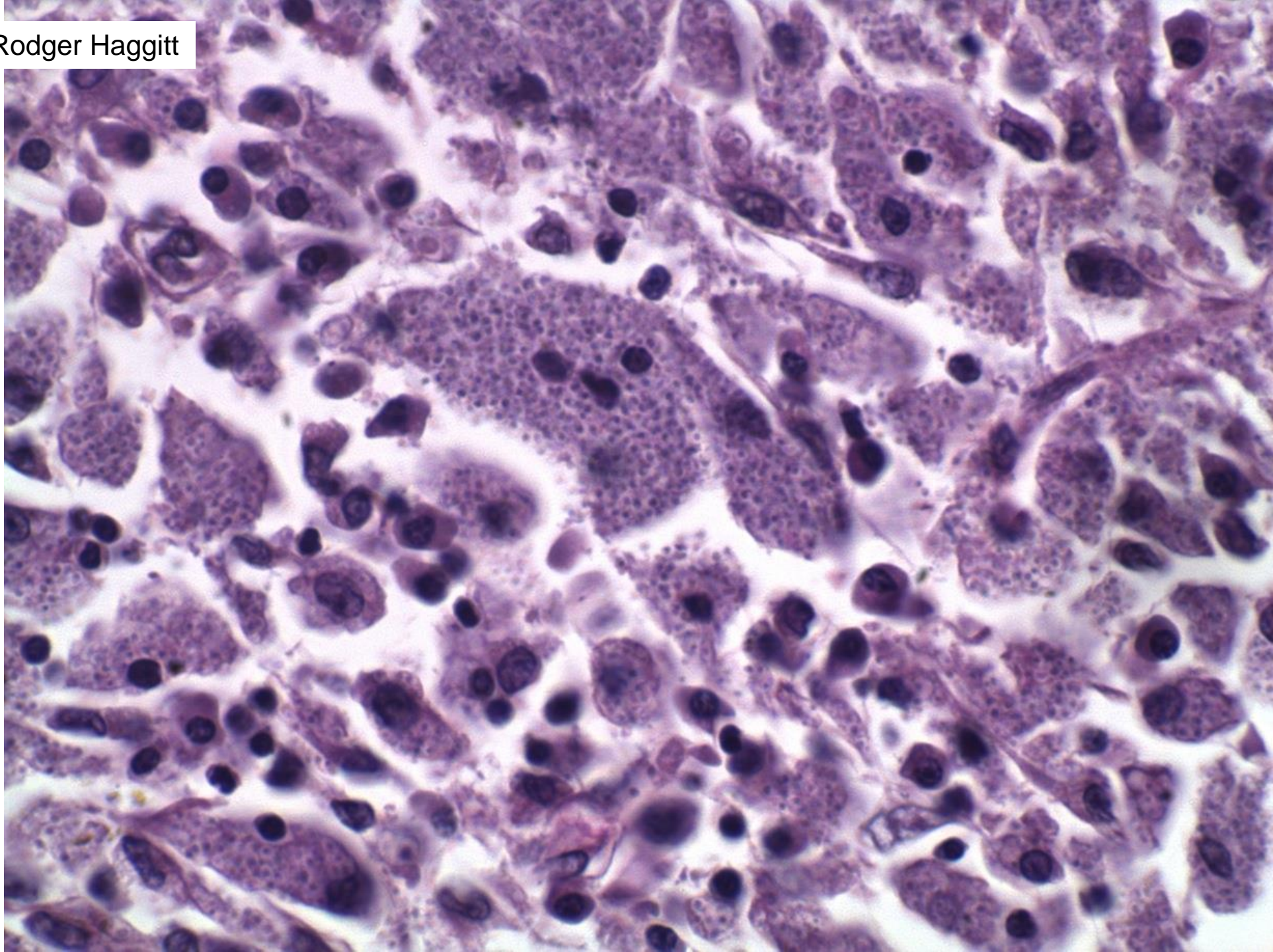
Characteristics of Yeast in Tissue Sections

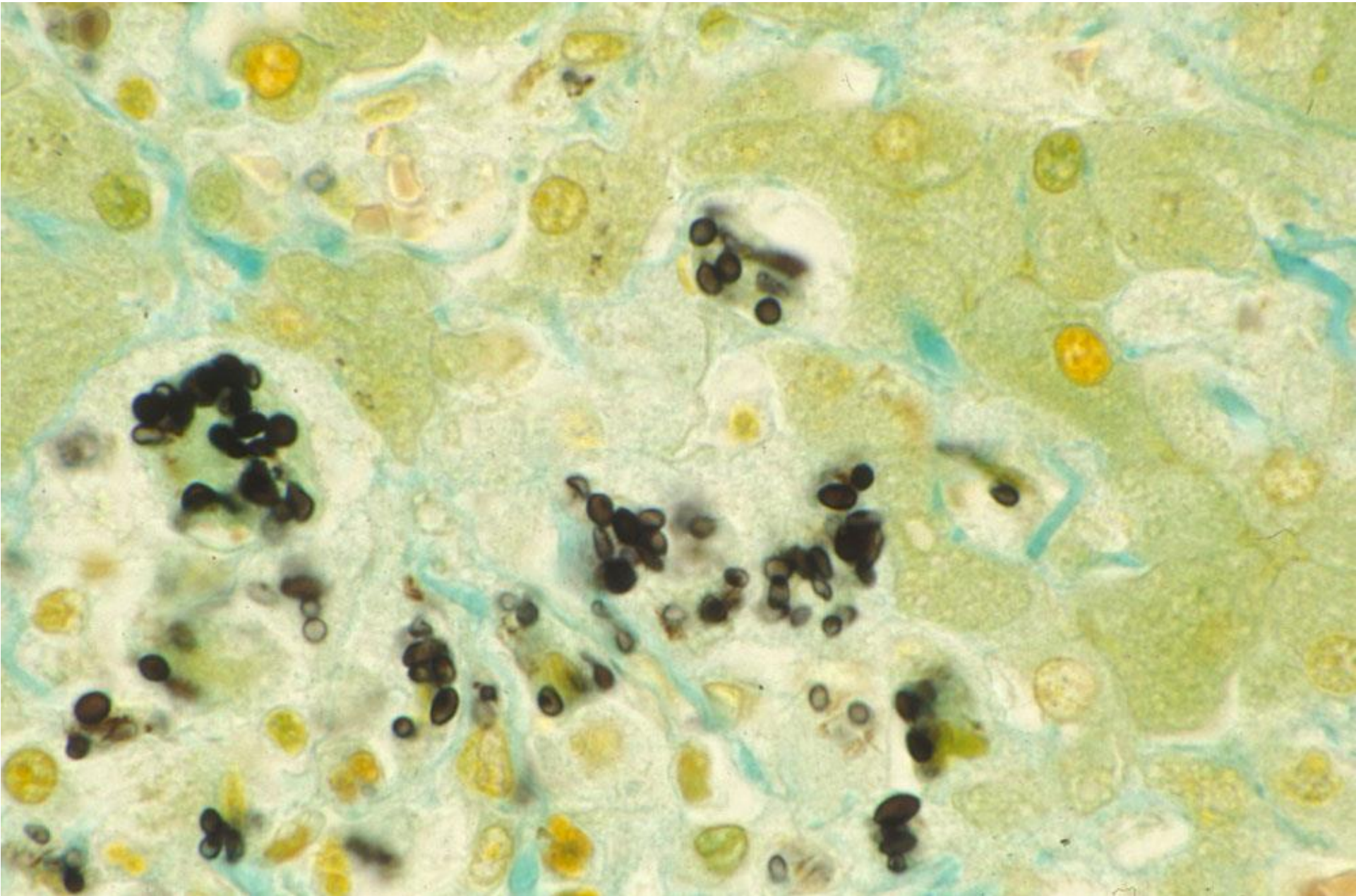
Fungus	Exposure	Histology	Stains
<i>Histoplasma capsulatum</i>	Ohio/MS river valleys	Uniformly small oval yeast with buds at pointed pole; “Halo” in tissue Usually in macrophages	GMS PAS
<i>T. marnefei</i>	Asia	Small nonbudding septated yeast	GMS PAS
<i>Cryptococcus neoformans</i>	Worldwide	Variably sized yeast with narrow based buds	GMS, PAS Melanin Mucicarmine
<i>Blastomyces dermatitidis</i>	Ohio and MS river valleys Great Lakes NW Ontario	Large yeast with broad based buds	GMS PAS Gram negative
<i>Candida torulopsis</i>	Worldwide	Small budding yeast Often extracellular No hyphae	GMS, PAS



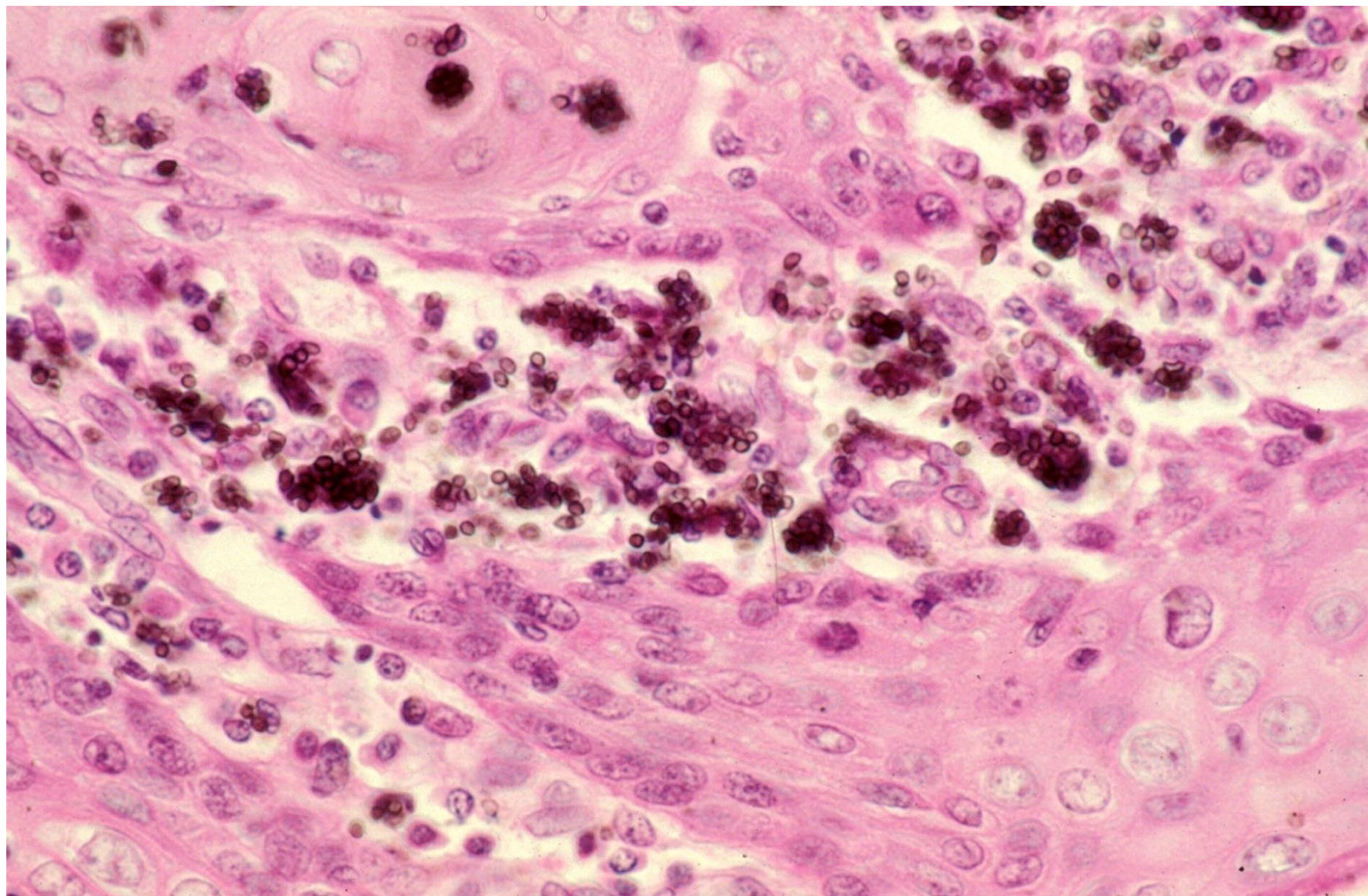


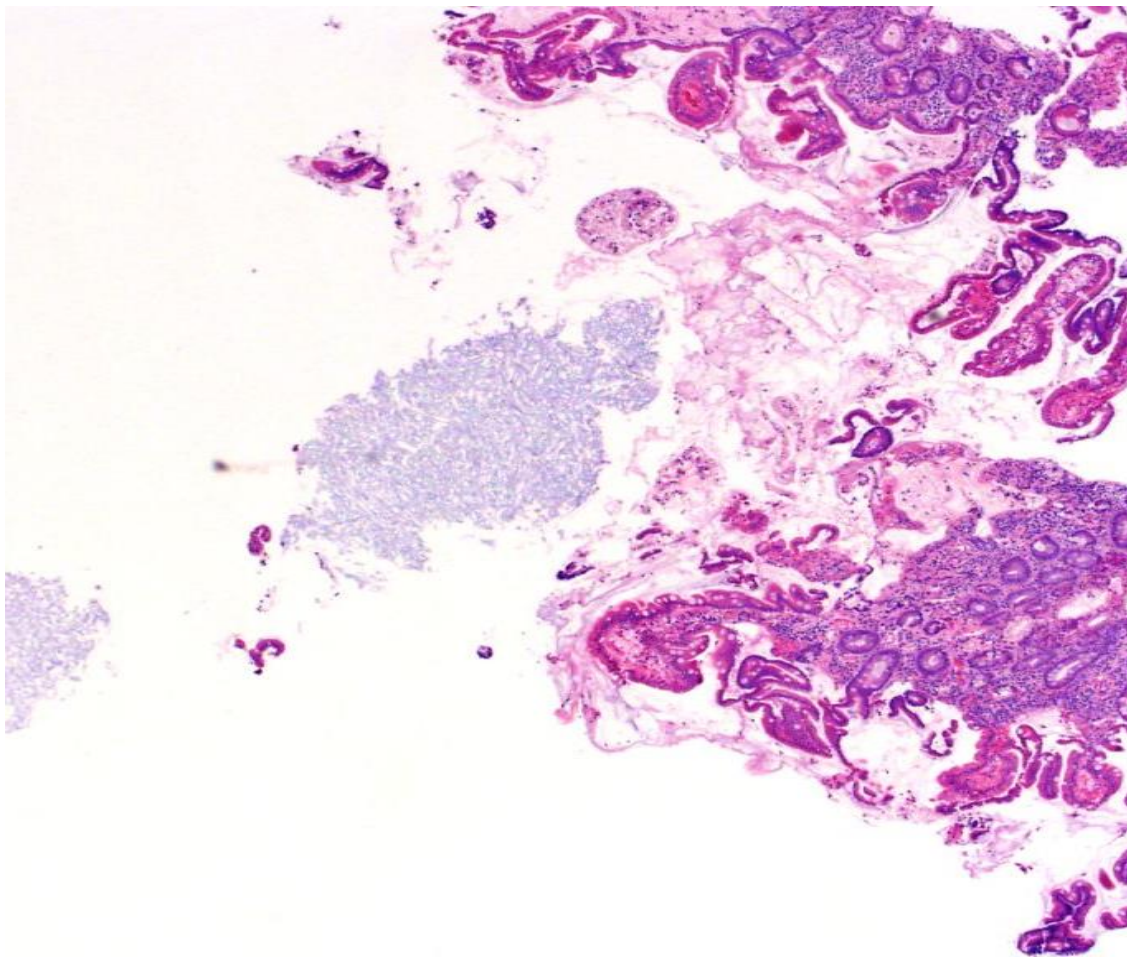
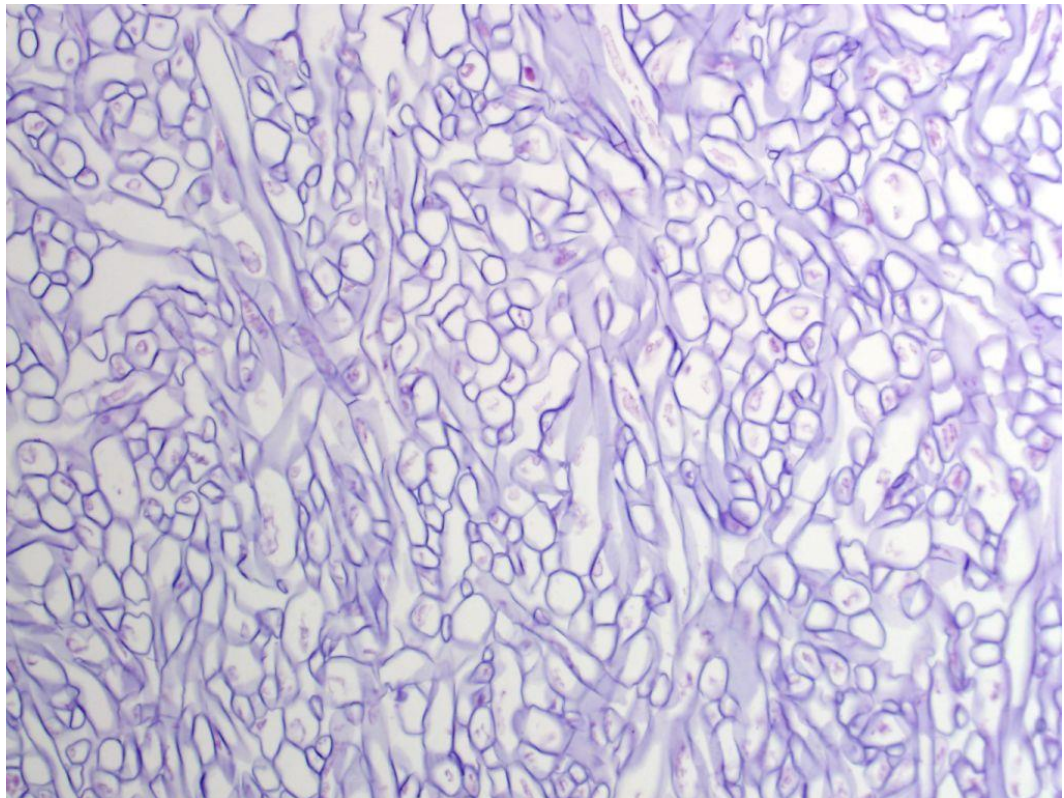
Courtesy Dr. Rodger Haggitt





Courtesy Dr. Brian West







Courtesy Dr. Bobbi Pritt

Summary

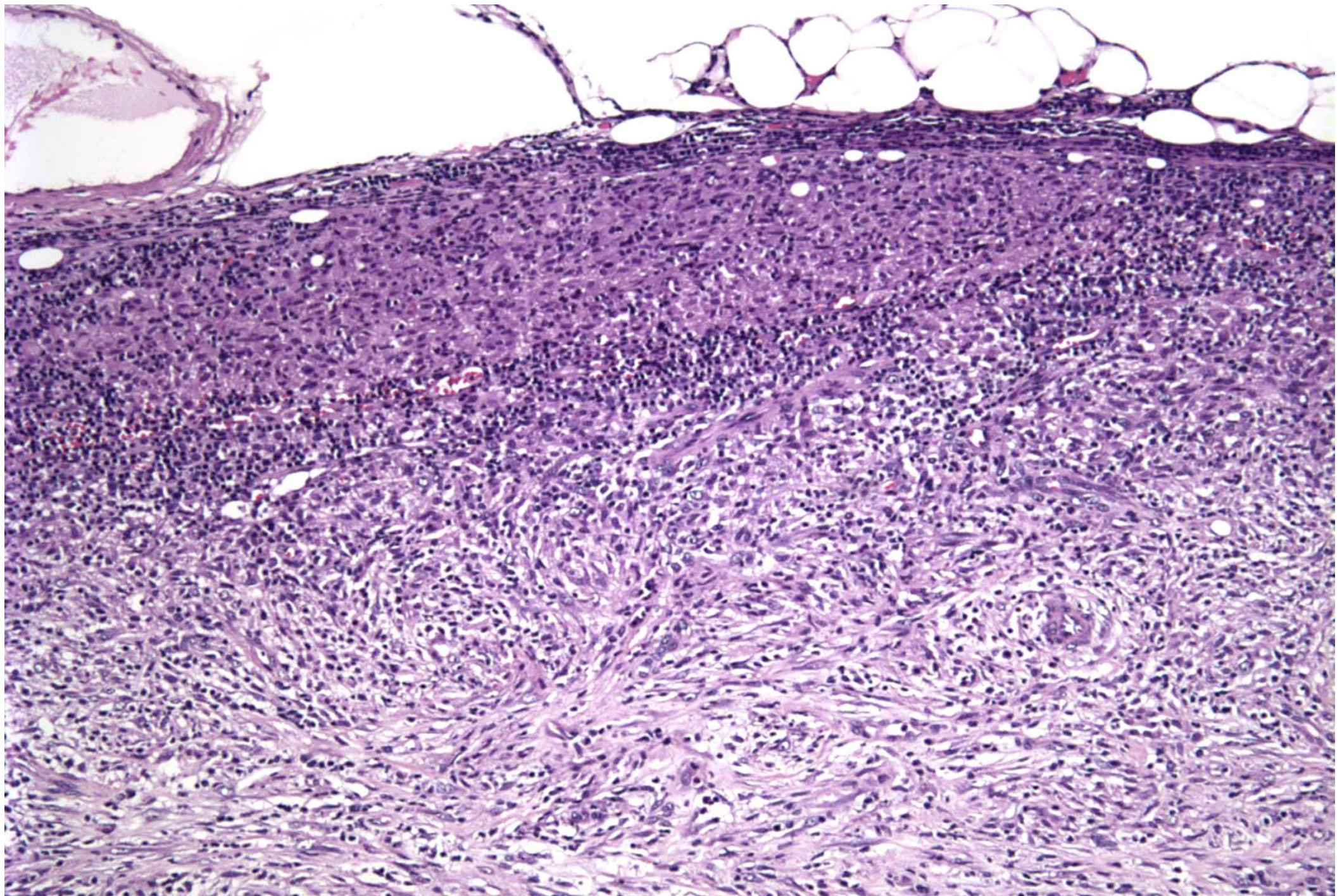
- *T. marneffe* is now one of the most common infectious diseases among Asian AIDS patients
- Given travel and immigration, seen more and more in the USA
- Must be distinguished from other small intracellular fungi, particularly histoplasmosis

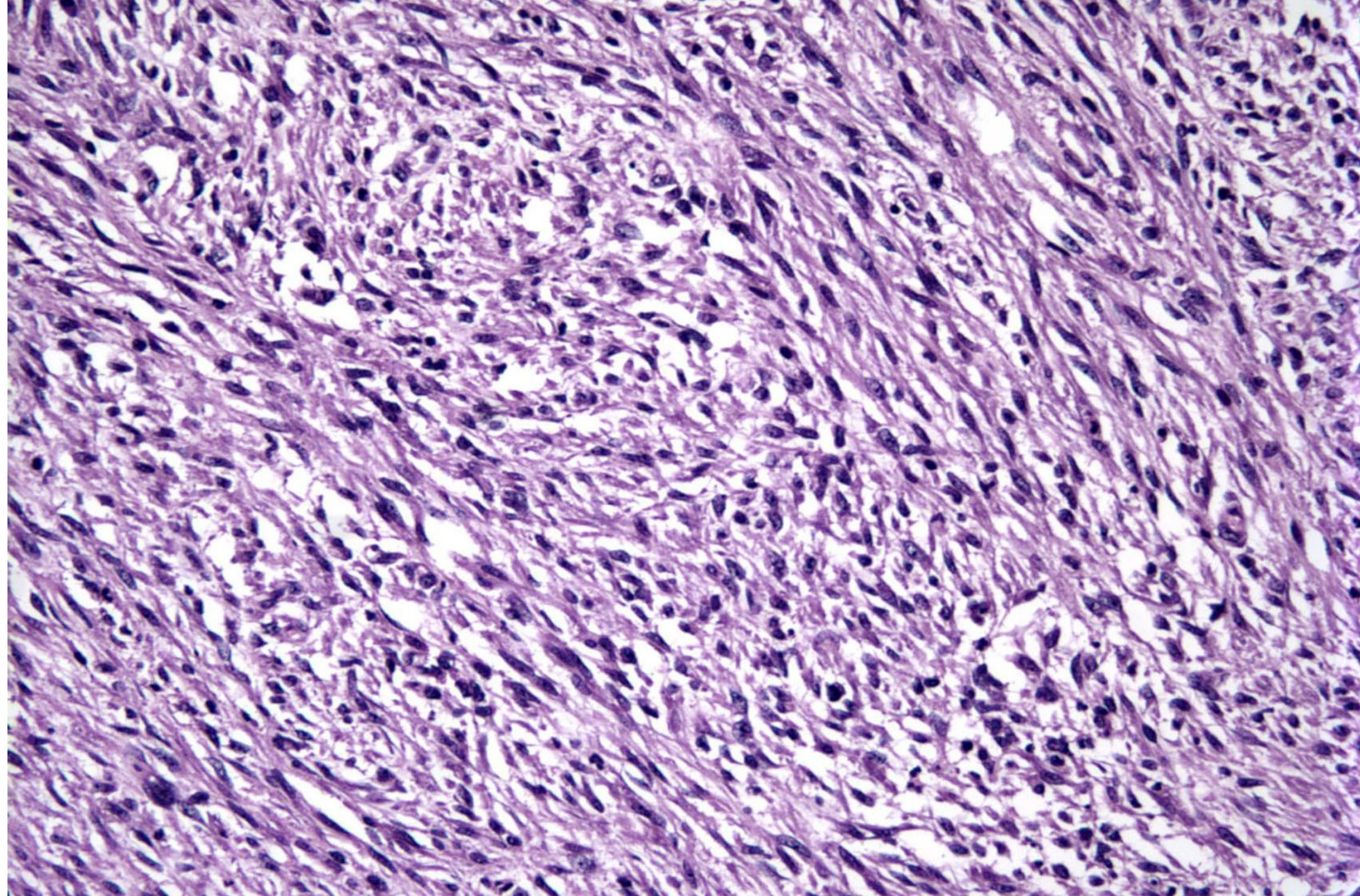


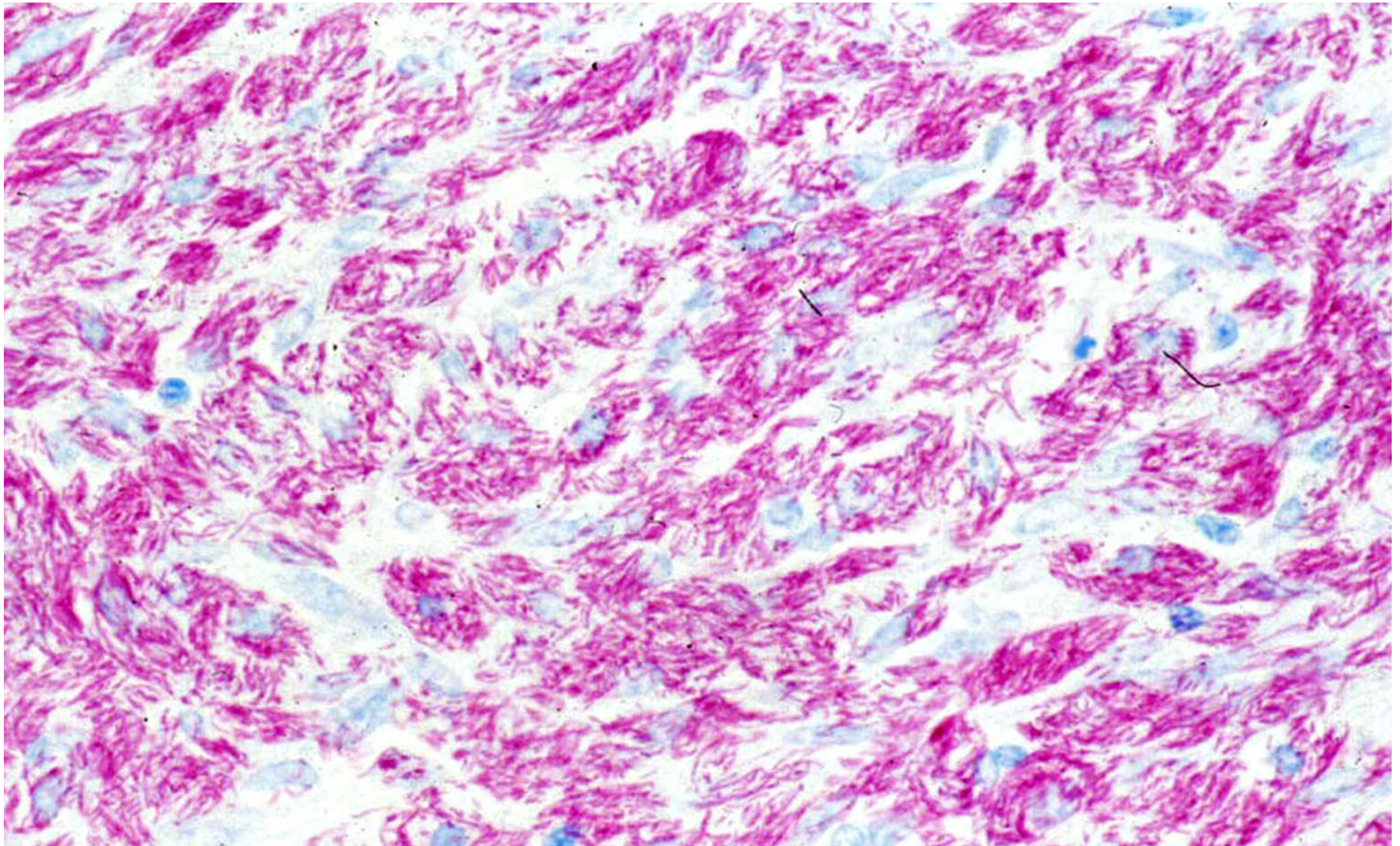
It really irritates us when they rename organisms for no apparent reason.

Case Example #3

- A 46 year old HIV-positive man presented with fever and weight loss.
- CT scan showed mesenteric lymphadenopathy. A mesenteric lymph node biopsy was performed.







Mycobacteria (MAI) –associated spindle cell pseudotumor

Emerging Infection: Atypical (non-Tubercular) Mycobacteria

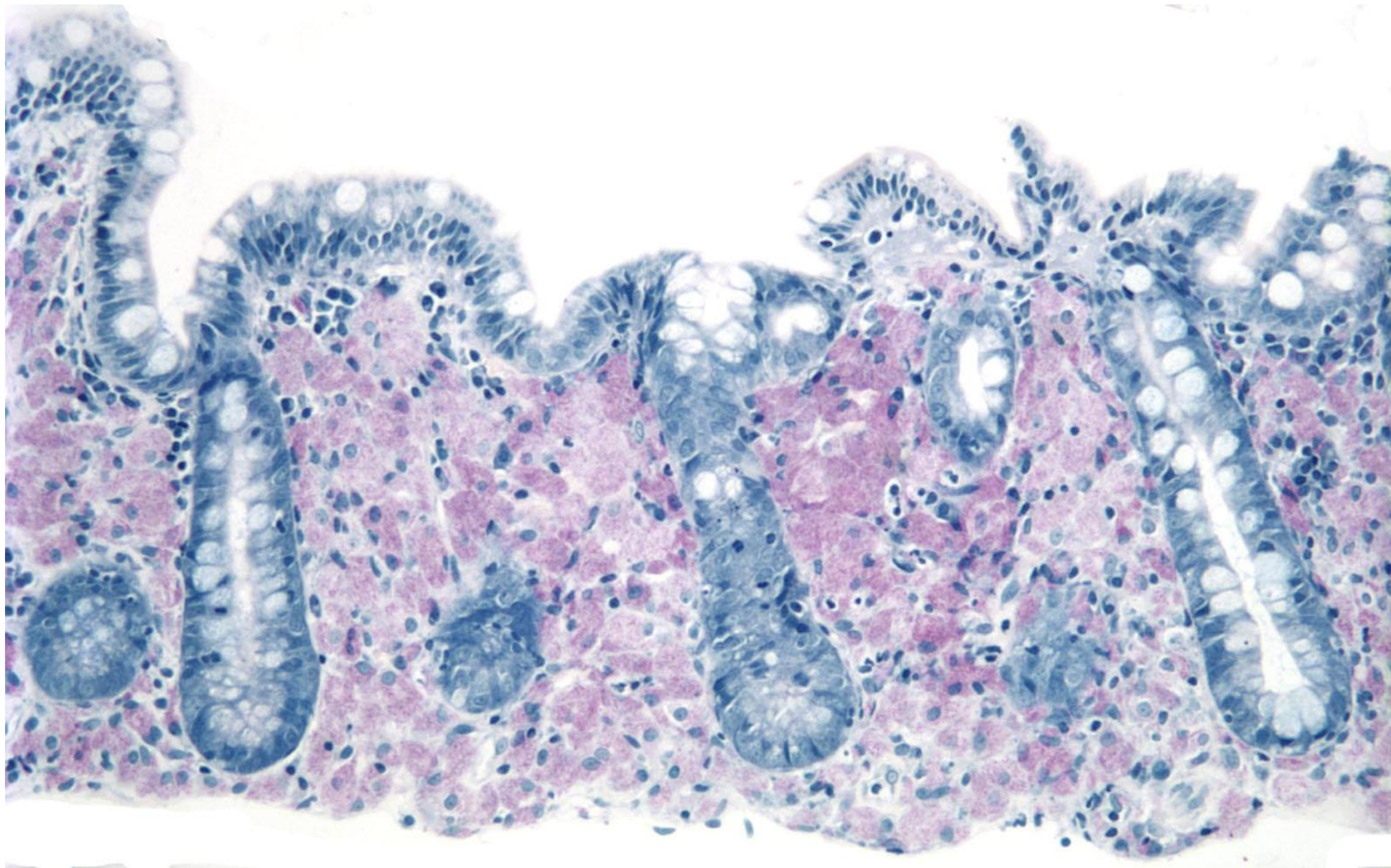
- MAI is most commonly encountered
- Widespread throughout nature, pretty much everywhere
 - Ubiquitous soil, milk, food, and water inhabitants
- Increasing in patients without AIDS
- Increasing in patient populations with chronic pulmonary disease, immunosuppressive medications and comorbid diseases
 - 25% of patients in one large study had no known risk factors

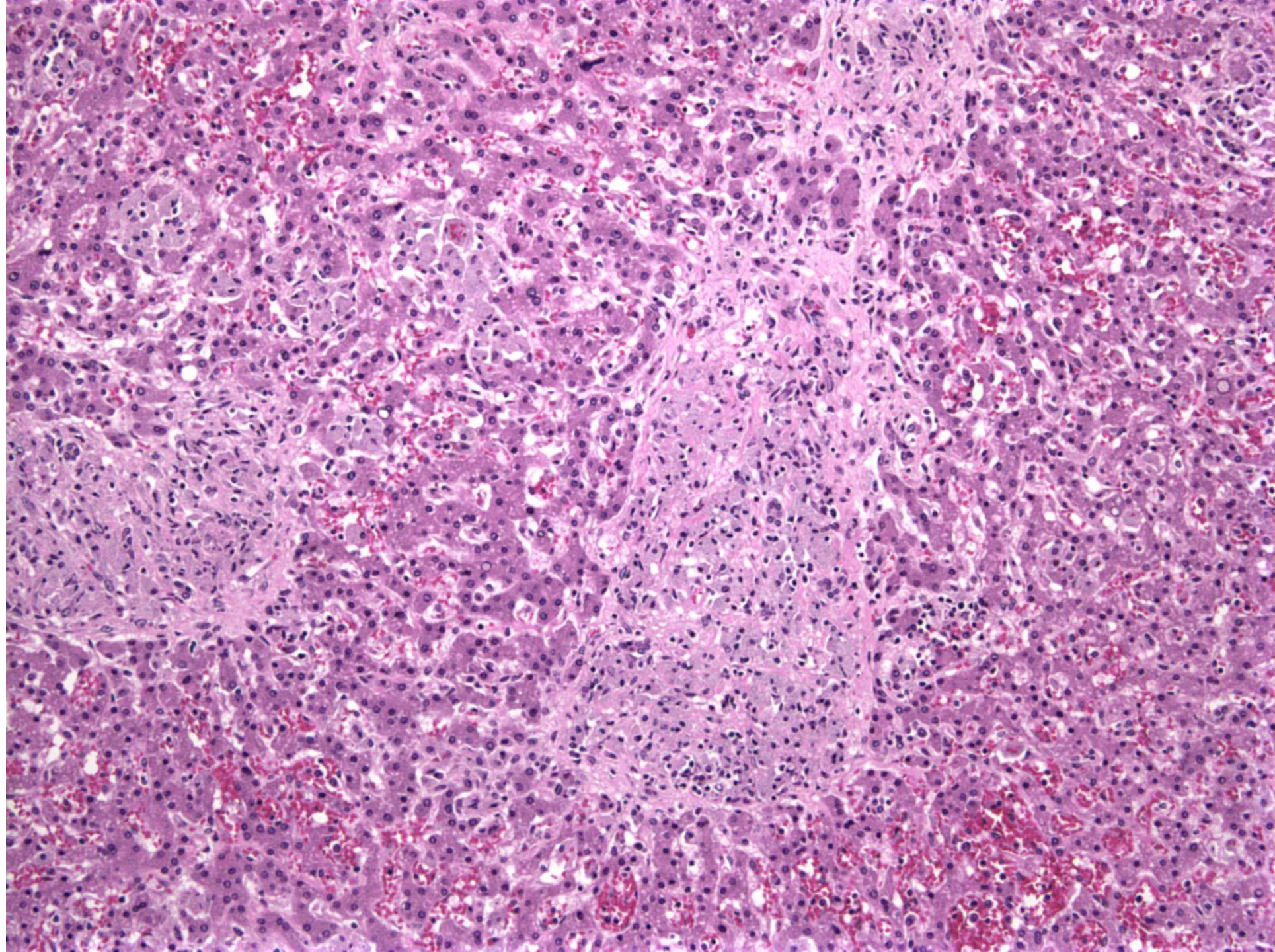
Selected sites of atypical mycobacterial infection

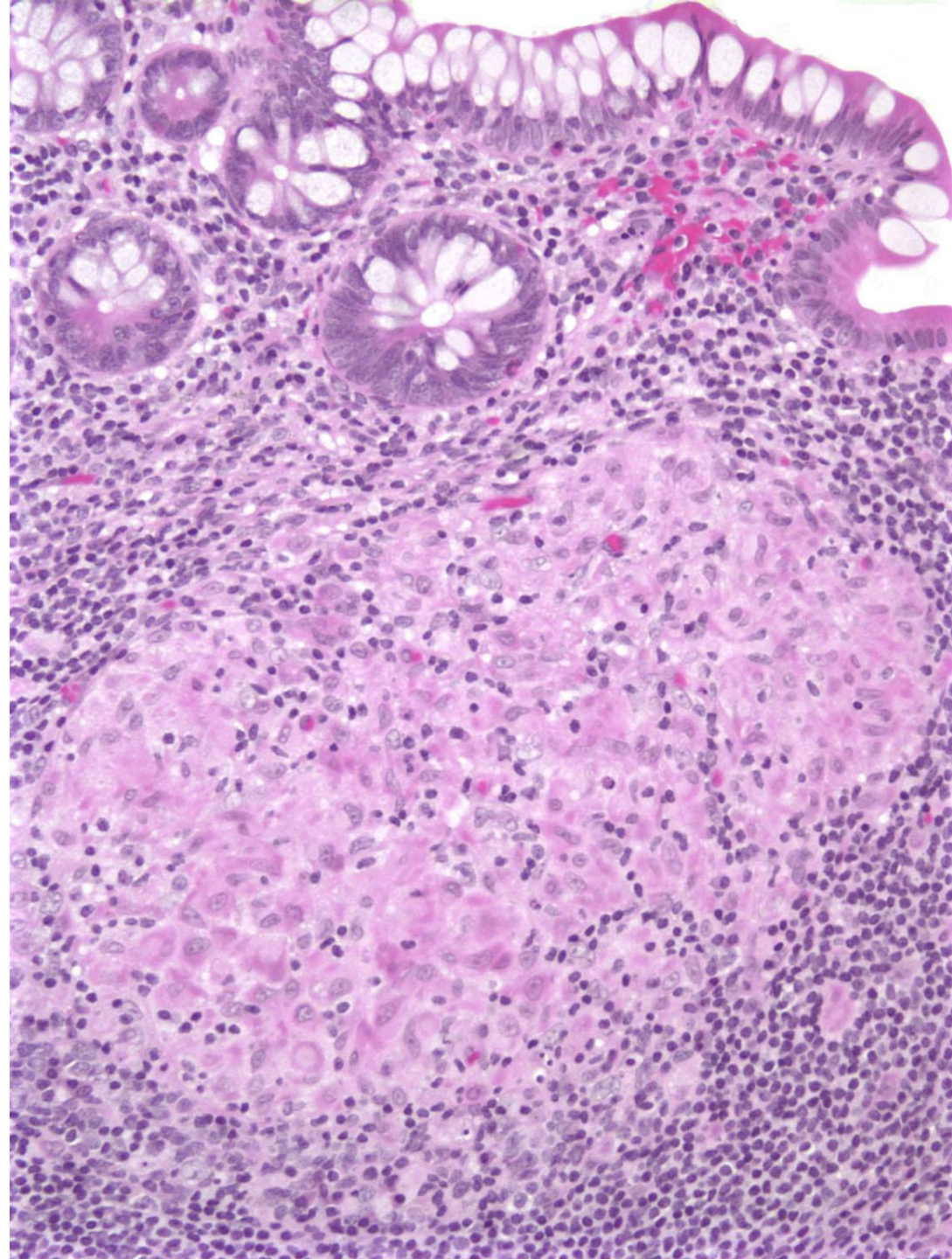
	MAI	M. kansasii	M. abscessus	M. fortuitum	M. smegmatis	M. chelonae	M. marinum	M. ulcerans	M. szulgai
Lung	X	X	X	X	X				
GI	X								
Spindle cell nodule	X								X
Bone/ soft tissue	X	X	X	X		X	X	X	
Liver	X	X							

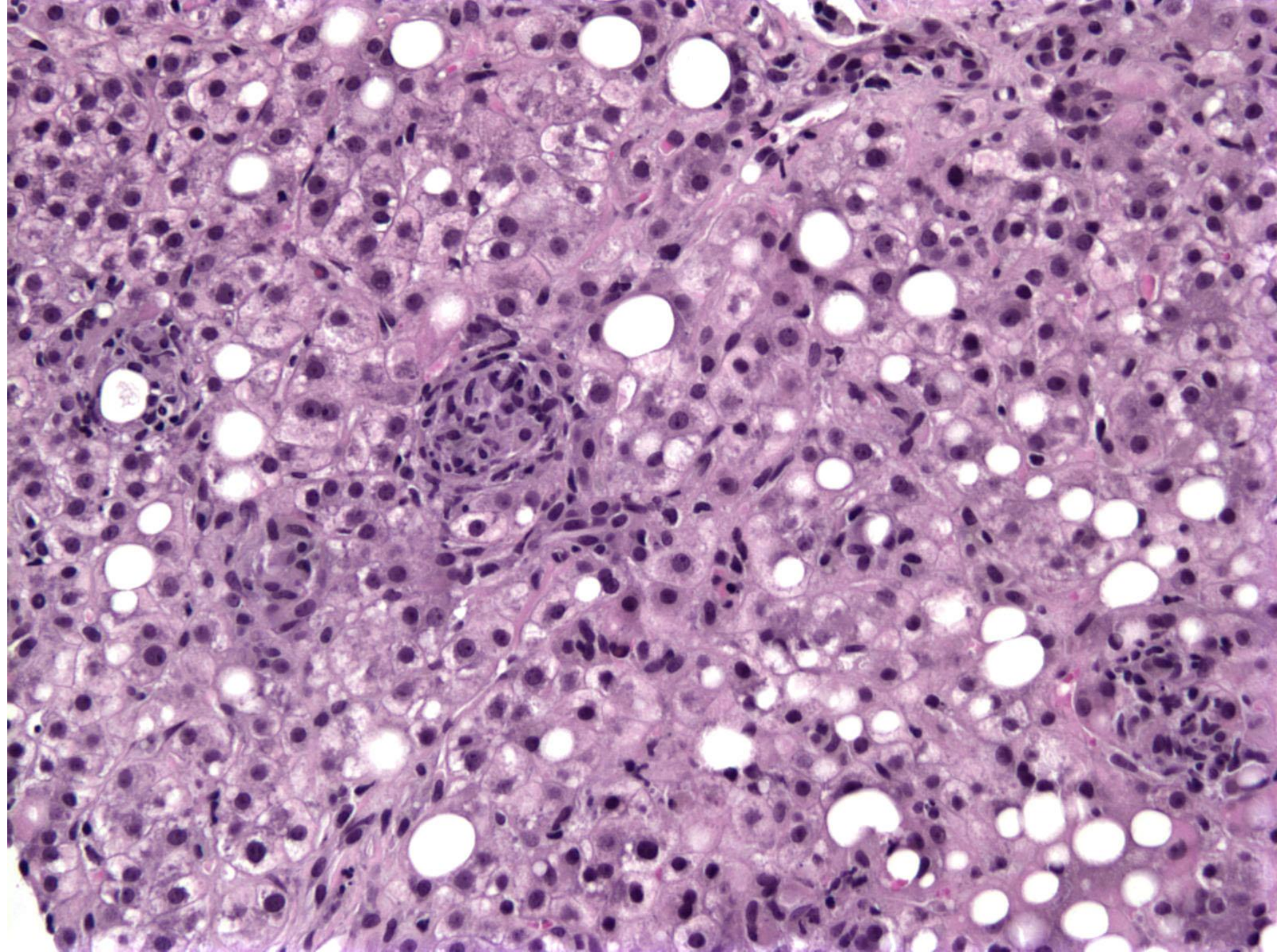
MAI

- Inflammatory reaction very variable:
 - Site of infection
 - Immune status of host
 - Patterns:
 - Foamy histiocyte infiltrate
 - Epithelioid granulomas
 - Spindle cell nodule
 - Fibrin ring granuloma







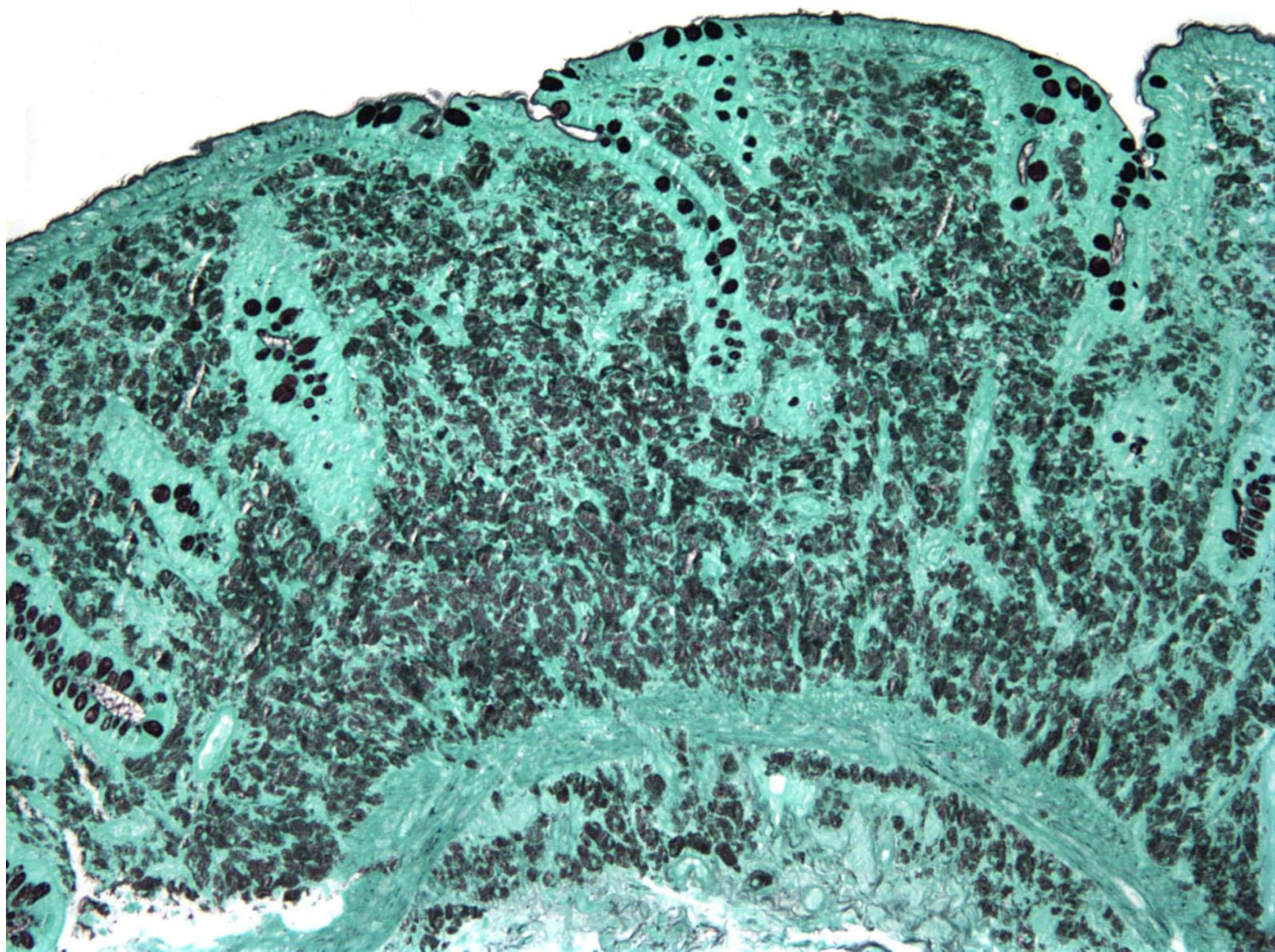


Low probability, high impact event

- The FNA revealed cohesive, dense cellular fragments consisting of spindle cells with elongated nuclei and ill-defined, pale cytoplasm....scattered spindle cells showed cytologic atypia, including enlarged, rounded nuclei with prominent nucleoli. Poorly formed granulomas comprised of epithelioid histiocytes and lymphocytes were also present....Aspirated material was sent for mycobacterial culture due to the presence of granulomatous inflammation. The diagnosis was rendered descriptively....a neoplasm was favored due to the presence of atypical spindle cells. Due to the presence of cellular atypia possibly representing a neoplasm, the patient underwent surgical resection. The histologic material revealed extensive subcutaneous necrotizing granulomatous inflammation consistent with an infectious process. Cultures collected at the time of the FNA subsequently grew *Mycobacterium chelonae*.

MAI-Differential Diagnosis

- *M. tuberculosis*
 - Culture, PCR
 - Different inflammatory reaction (usually)
- Other atypical mycobacteria
- Other neoplasms (spindle cell nodule)
 - AFB stain
 - CD68
 - Mycobacteria will stain with desmin, actin, keratin



Summary

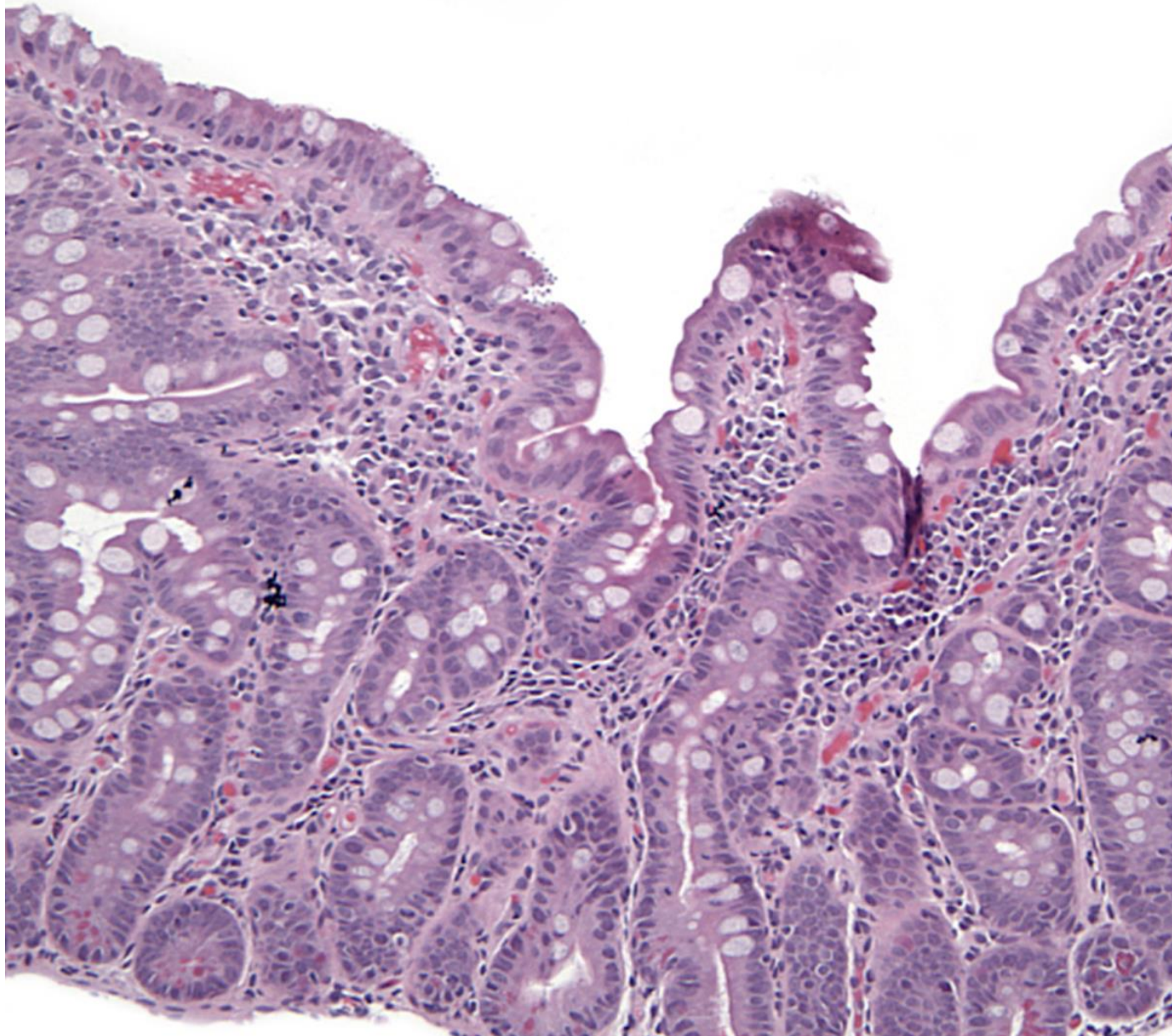
- We are seeing atypical mycobacteria in a wider variety of clinical scenarios
- Histology may vary with immune status
- Therapy varies by species
- If you see organisms but PCR is negative, doesn't mean you hallucinated, just that block is exhausted



Watching for emerging infectious diseases. They can come from anywhere.

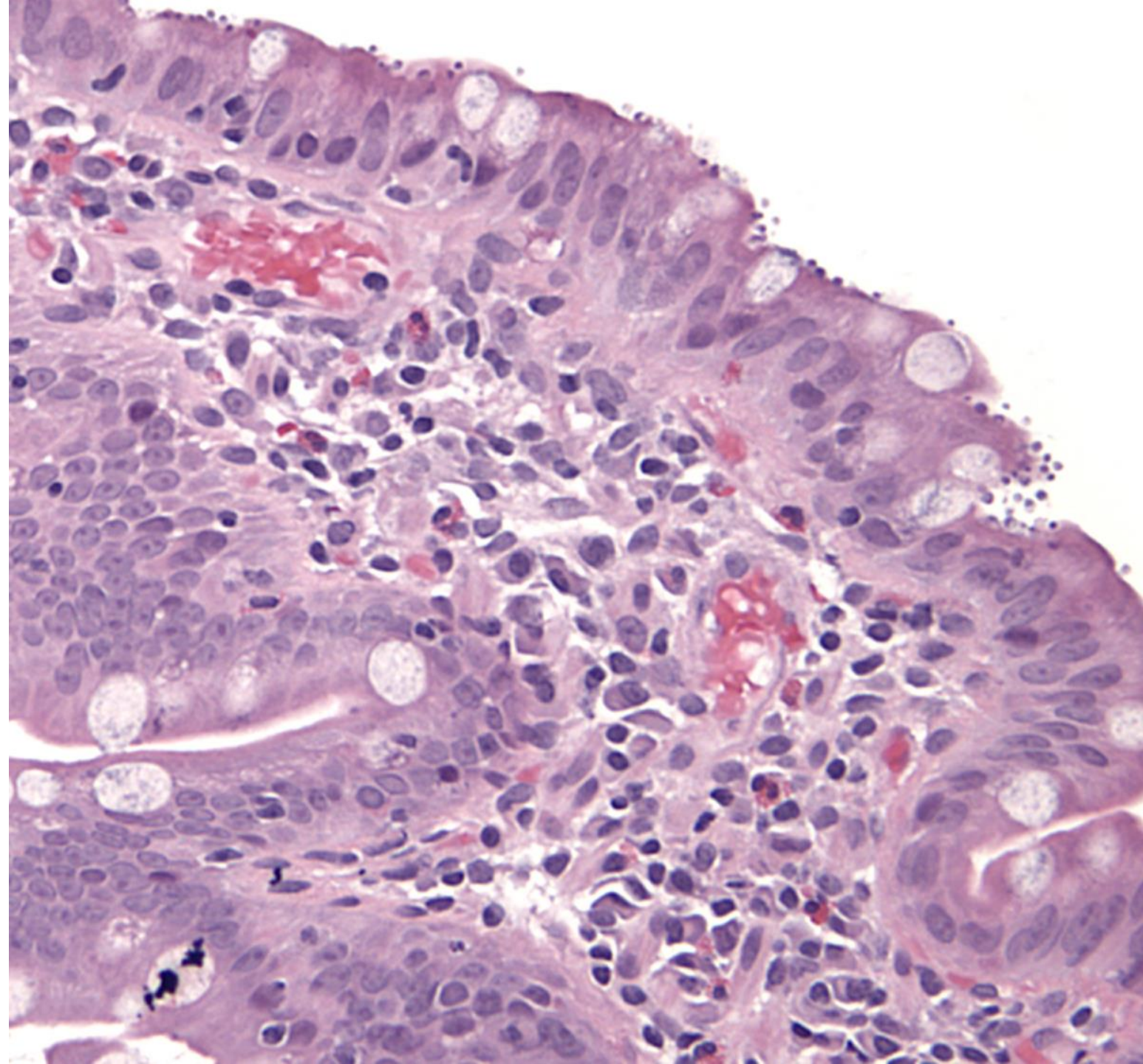
Case Example #4

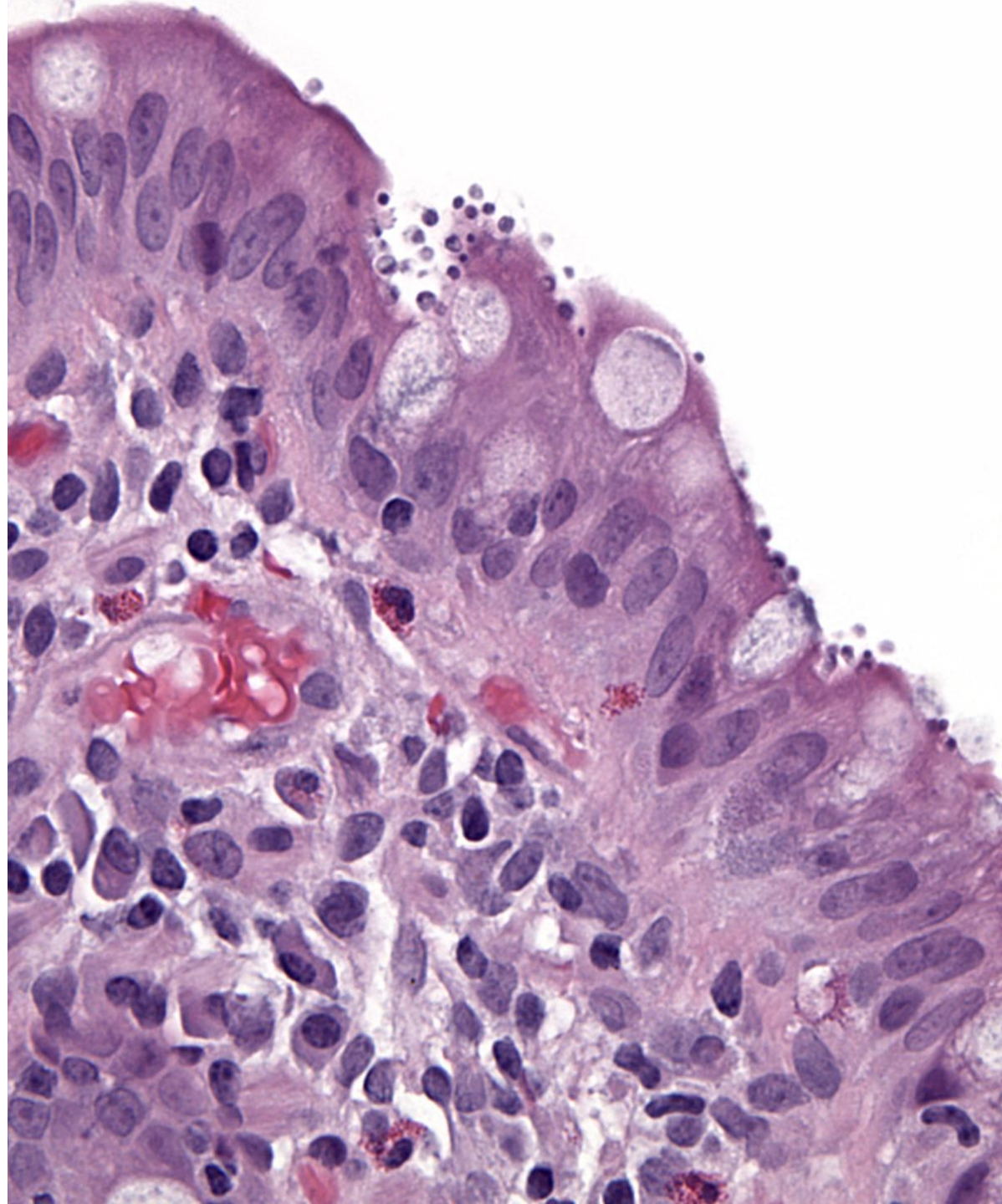
- 40 year old man with chronic watery diarrhea. Patient had unintentional 25 pound weight loss in previous month.
- Colonoscopy and EGD essentially normal, but biopsies taken.

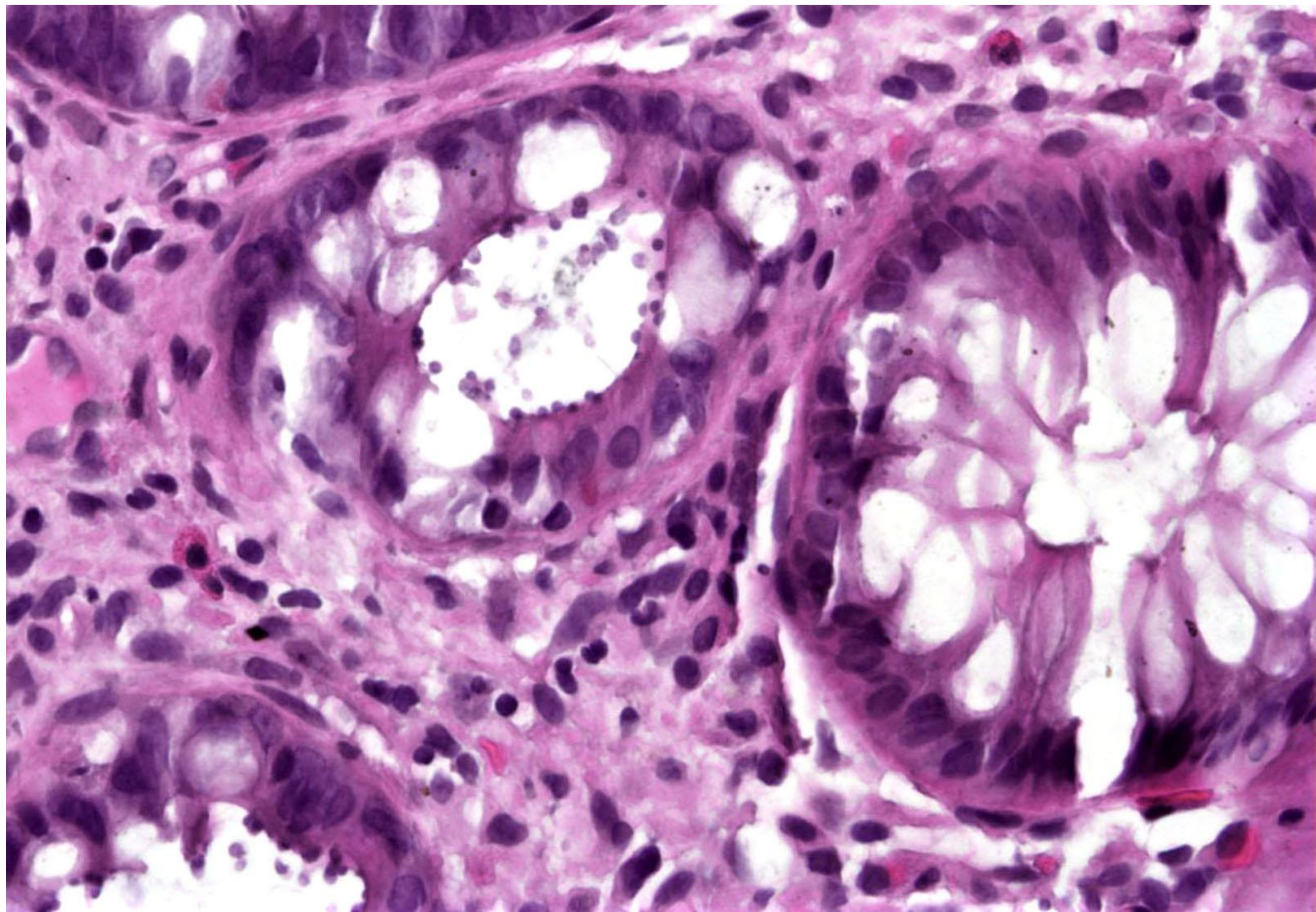


Villous blunting and crypt elongation

Picture courtesy of Dr. Joel Greenson







Coccidians in the News

- 2014: Cryptosporidiosis outbreak in public water supply in Sweden
- 2011: Firefighting episode in Indiana leads to cryptosporidiosis
- Summer, 2015: Texas Cyclospora outbreak

Coccidians

- Parasites (and one fungus) that cause diarrhea in both immunocompromised and immunocompetent patients
 - More serious diarrhea, malabsorption in immunocompromised
 - Often asymptomatic in immunocompetent
- Transmitted through food, water, person-to-person

Coccidians

- Endoscopic exam usually normal
- Useful stool studies require special stains
- Mucosal biopsies very effective for dx
- ELISA, IHC, PCR available but not widely used

Implications of easily overlooked pathogens

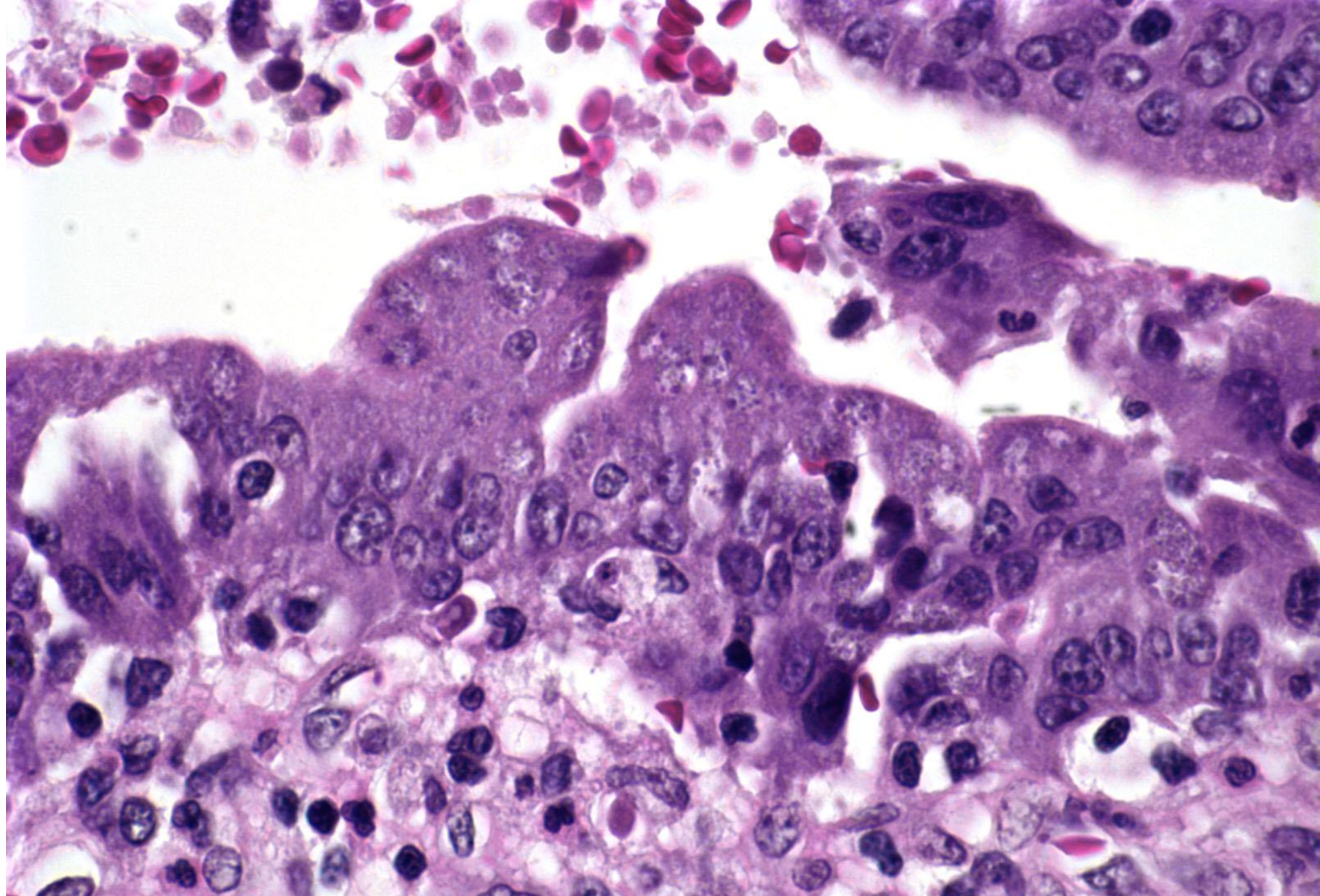
- Thirty three consecutive patients infected by human immunodeficiency virus type 1 (HIV1) with persistent diarrhoea which remained undiagnosed after microbiological examination of six stool samples and rectal histology were investigated for malabsorption. All had xylose and Schilling tests, distal duodenal biopsy, comprehensive barium studies, microbiological examination of six further stool samples, and repeat rectal histology. A microbiological or histological diagnosis of infection was made in 12 patients (multiple organisms in three). Cryptosporidia were identified on five occasions, cytomegalovirus on four, Giardia lamblia on two, and herpes simplex, Campylobacter jejuni, Salmonella enteritidis, and Entamoeba histolytica once each. Pathogens were identified in nine of 13 patients (69%) with weight loss greater than 10 kg and stool volume more than 800 ml/day.

Comparison of Enteric “Coccidians”*

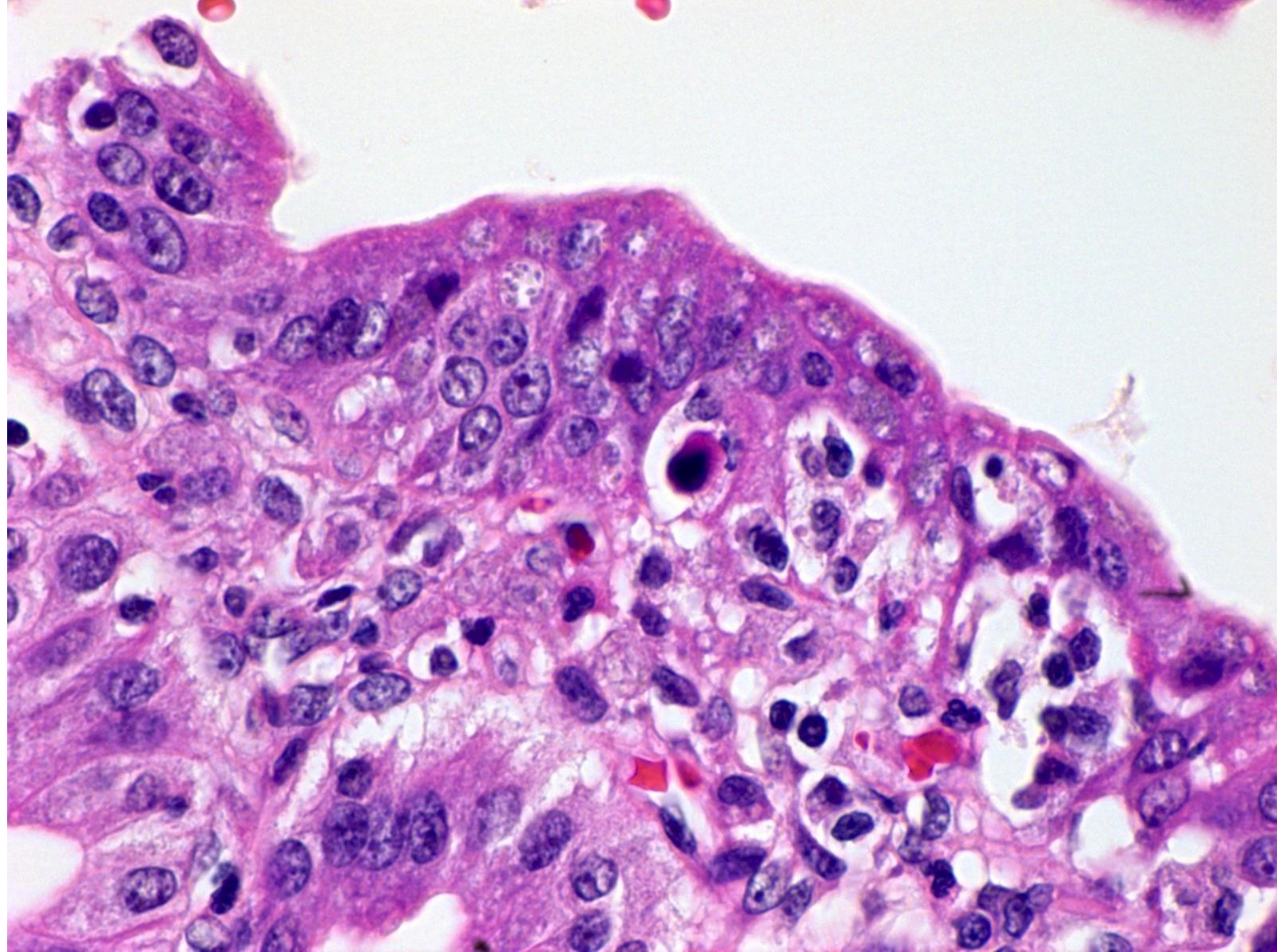
Feature	Microsporidia	Cryptosporidia	Cyclospora	Cystoisospora
Size	2-3μ (smallest)	2-5 μ	2-3μ schizonts 5-6μ merozoites	15-20μ (largest)
Location	Epithelial cells	Apical surface	Upper epithelium	Epithelium Macrophages
Staining	Mod trichrome Giemsa Gram W-S PAS	Giemsa Gram	Acid fast Auramine	Giemsa Gram PAS GMS
Other	Birefringent under polarized light	Bulges out of luminal apex of enterocyte	Parasitophorous vacuole	Parasitophorous vacuole Eosinophils

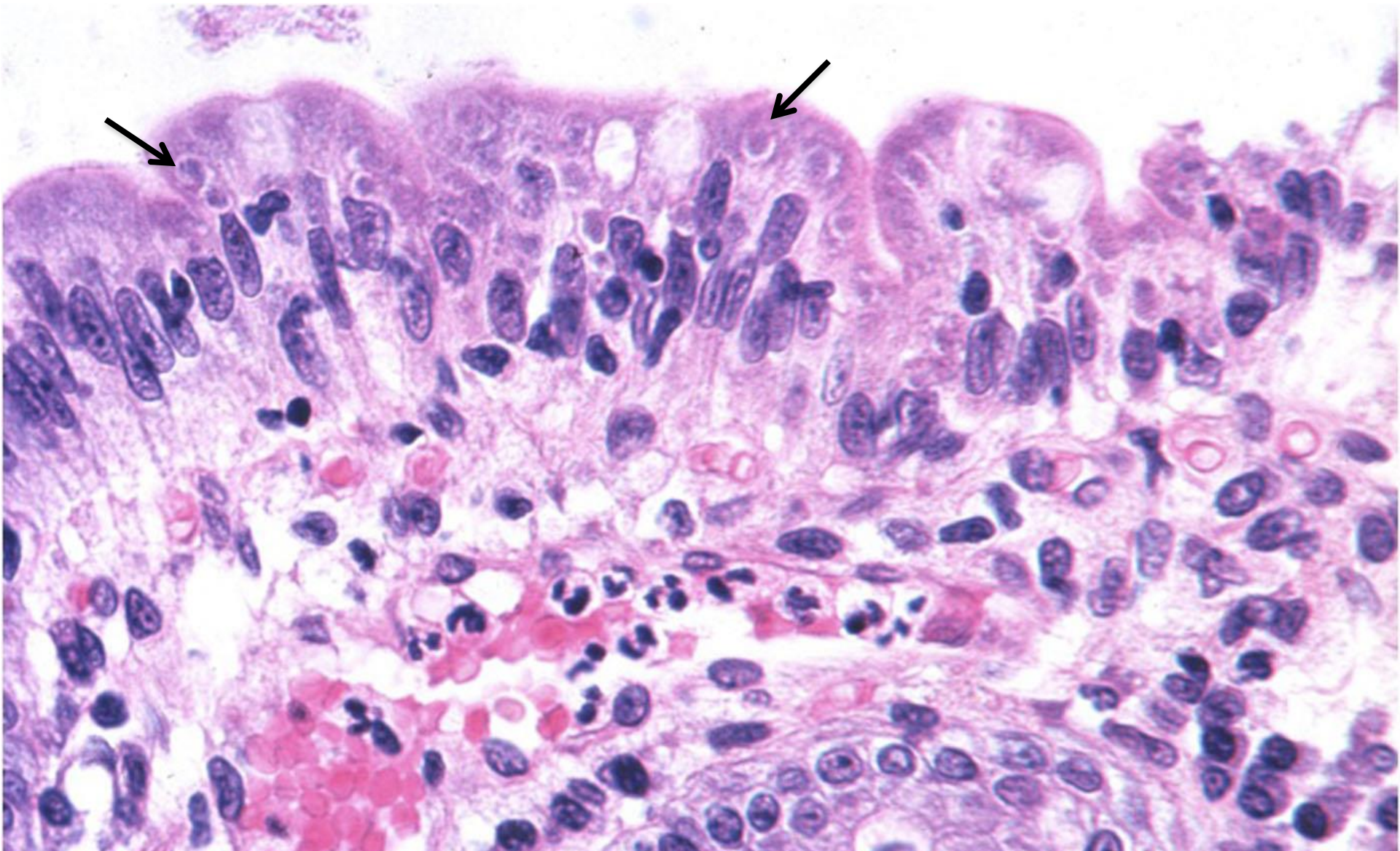
*Microsporidia are now classified as fungi

Cryptosporidia are still parasites, but gregarines, not coccidia



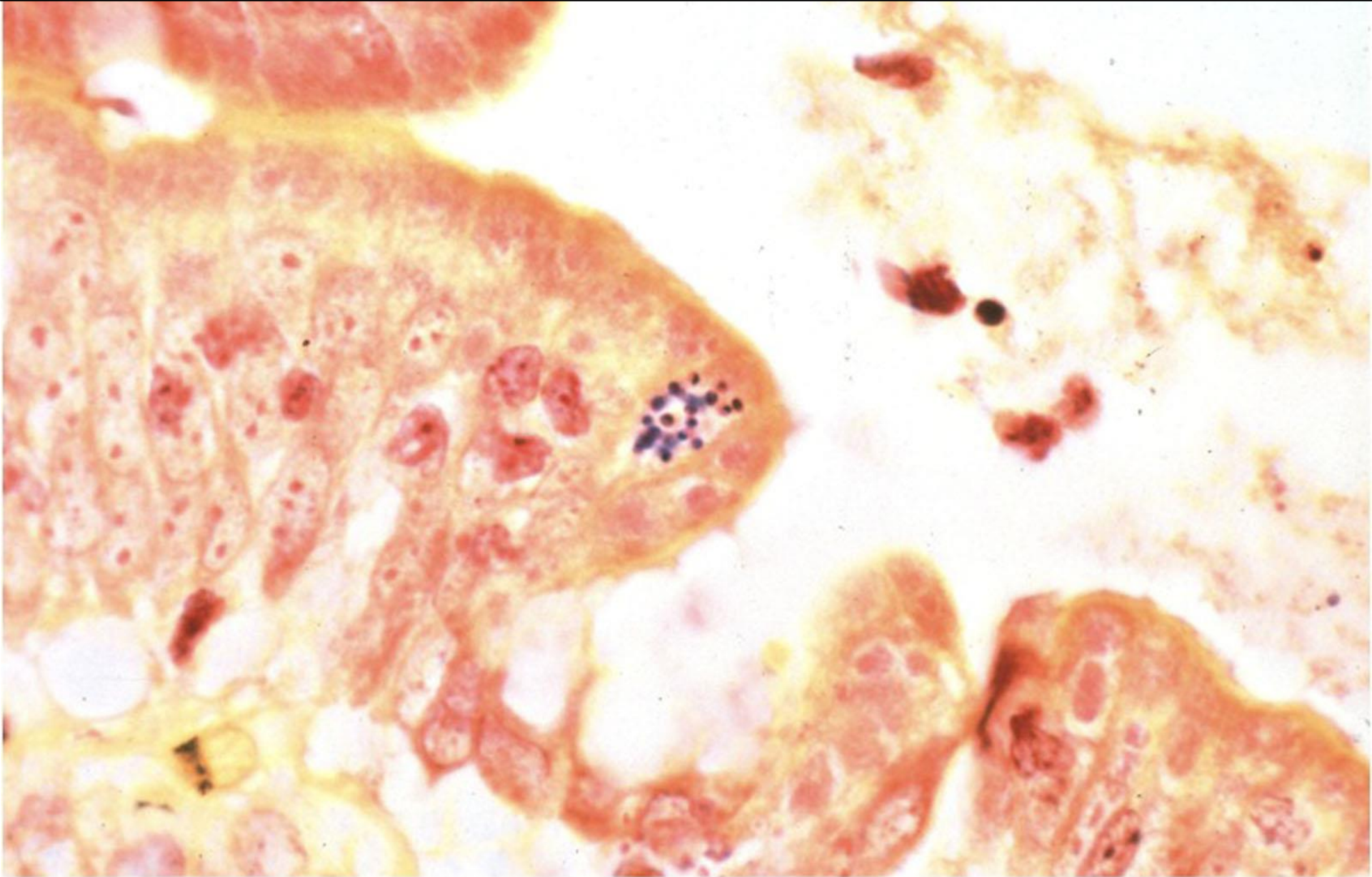
Microsporidia: Surface epithelial cell disarray and vacuolization

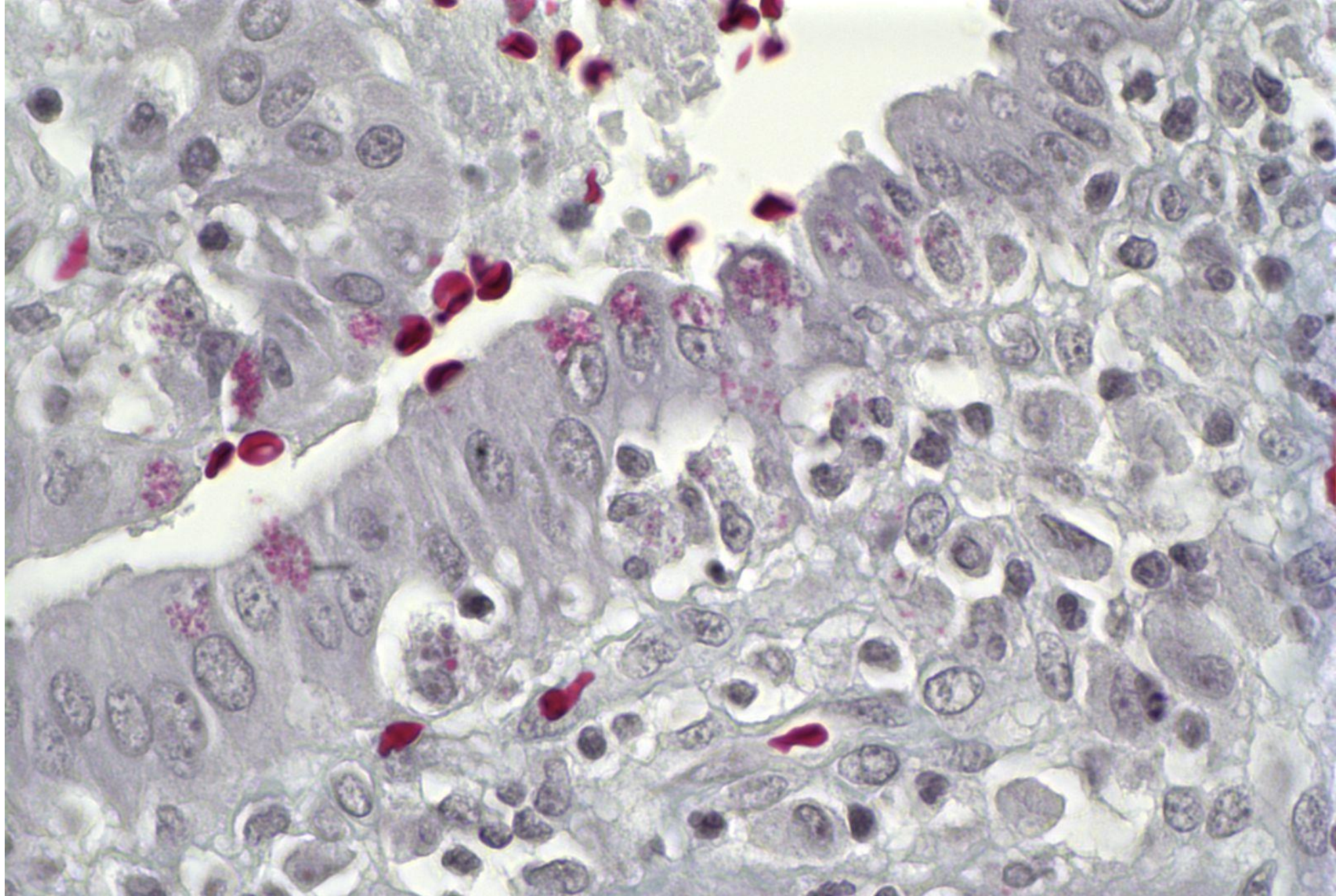




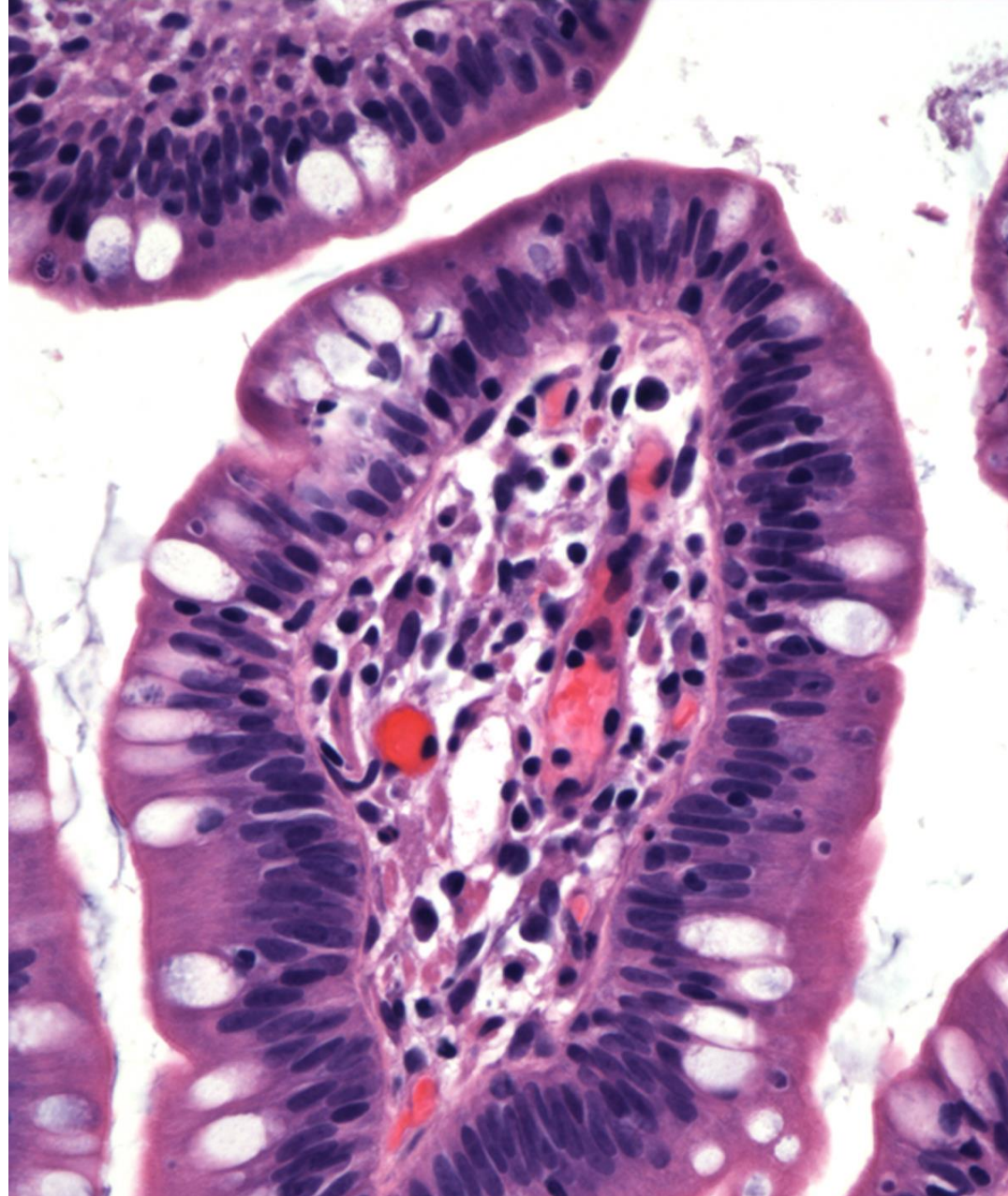
Either spores or plasmodia may be present
Picture courtesy of Dr. Joel Greenson

Gram stain highlights spores
Picture courtesy of Dr. Joel Greenson

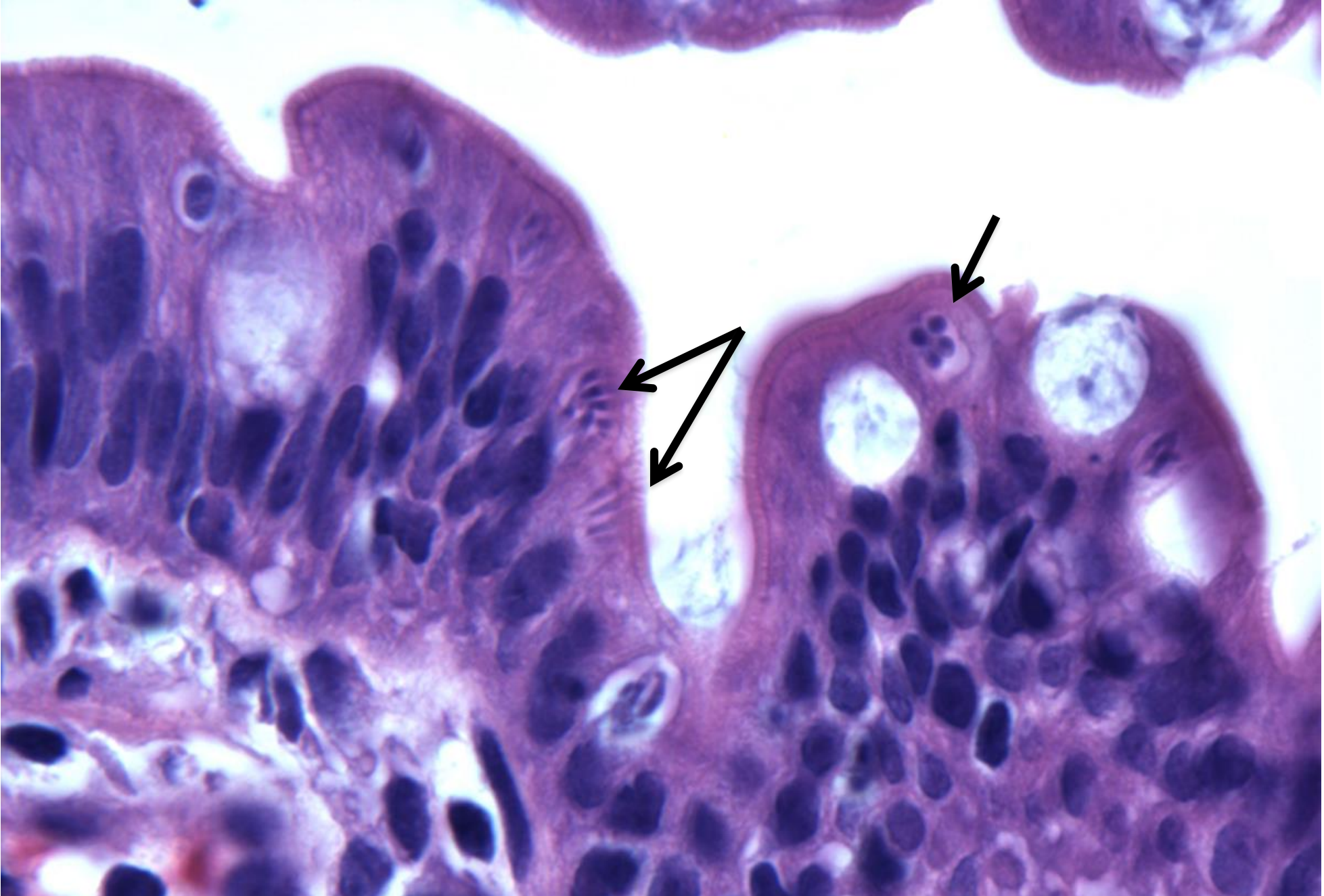




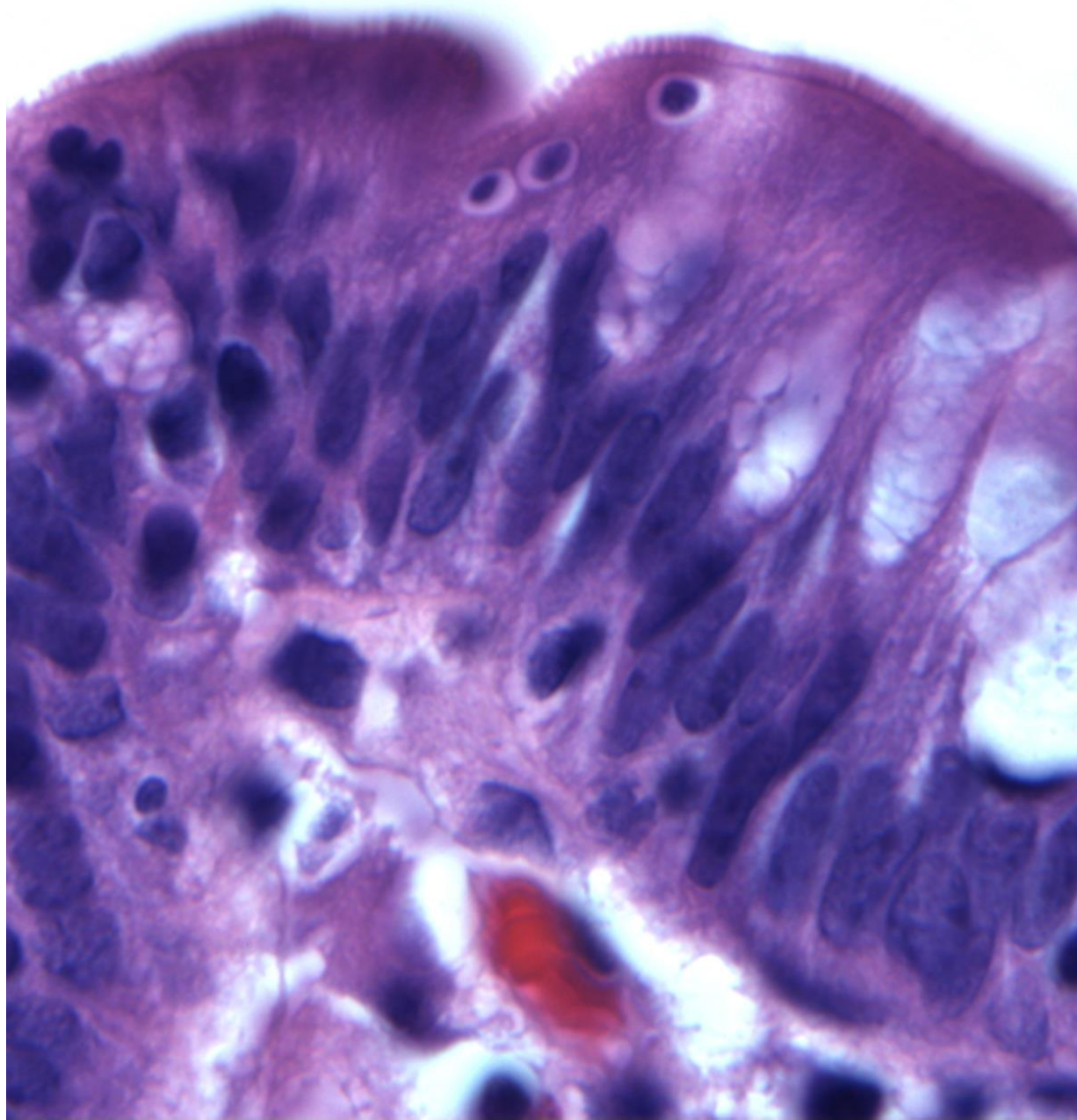
Modified trichrome stain highlights organisms

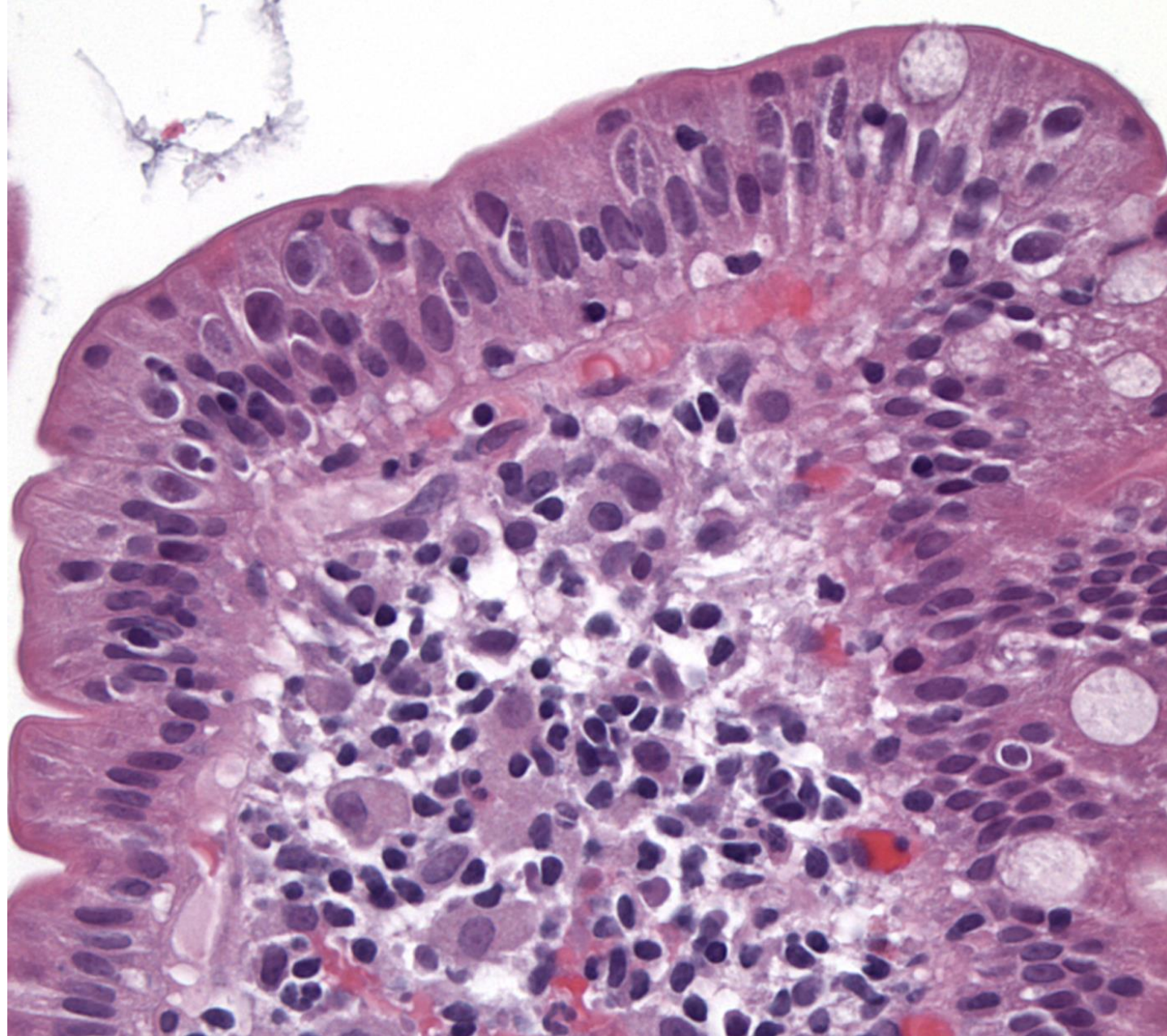


Cyclospora: surface epithelial cell disarray
Case and pictures courtesy of Dr. Rhonda Yantiss

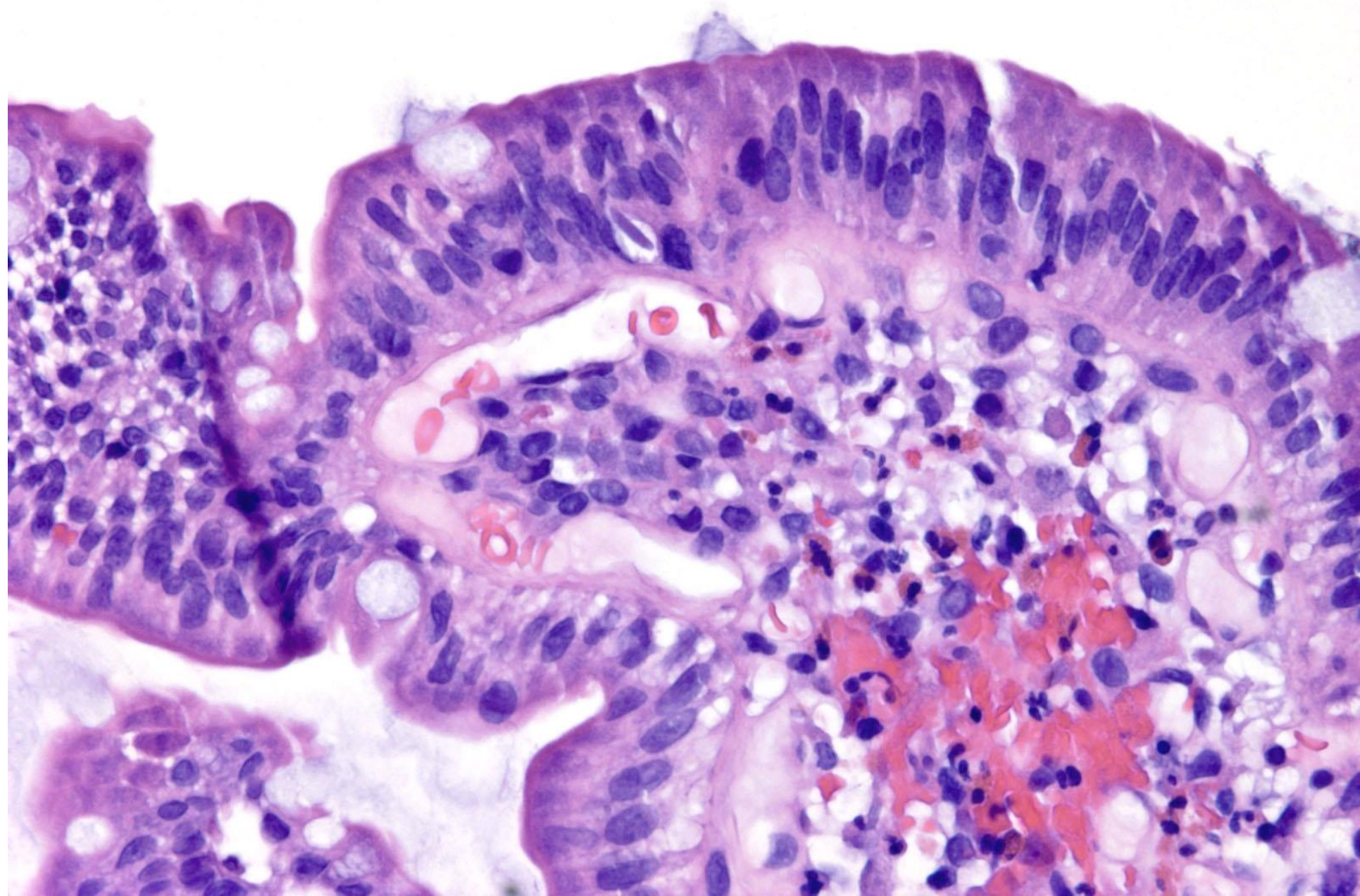


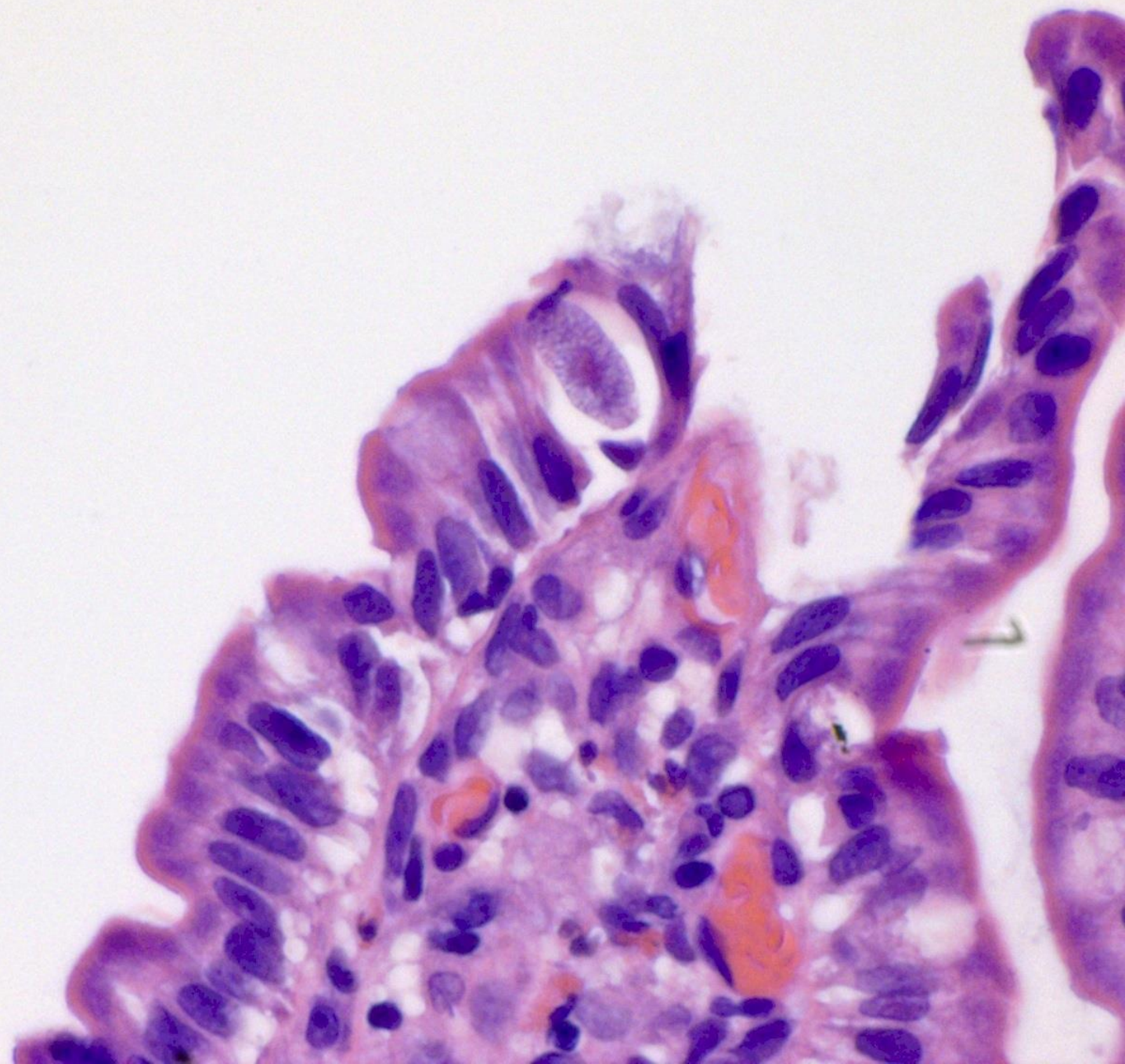
Round schizonts and banana shaped merozoites in parasitophorous vacuoles





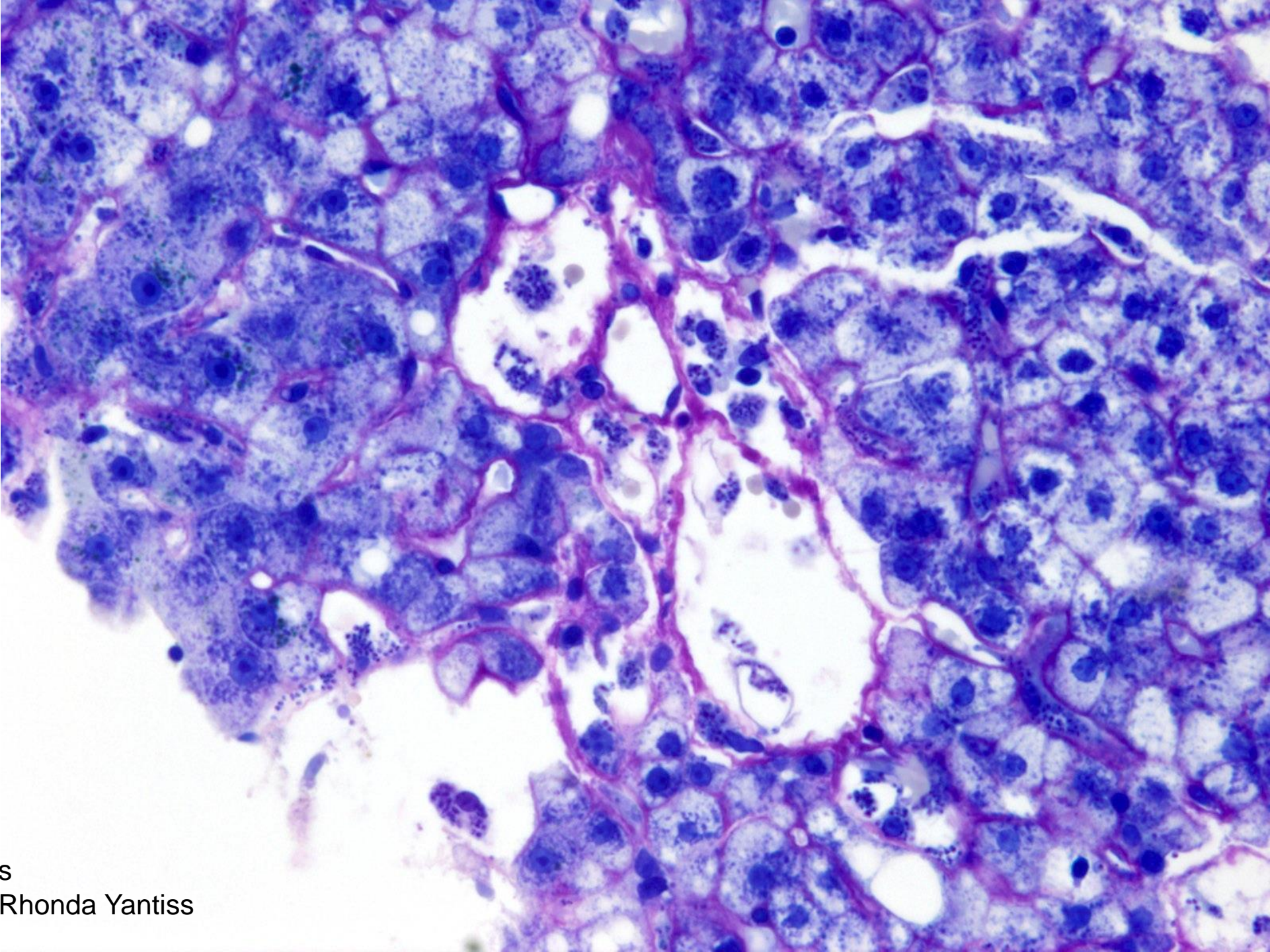
Cystoisospora: Schizonts and merozoites with parasitophorous vacuoles and epithelial cell disarray
Picture courtesy of Dr. Joel Greenson





Enteric “Coccidians” Differential Diagnosis

- Almost all other intracellular organisms will be within macrophages, and not at the luminal surface
 - Leishmania
 - Toxoplasmosis
 - Fungi (Histoplasmosis, *T. marneffe*)



Leishmaniasis
Courtesy Dr. Rhonda Yantiss

Summary

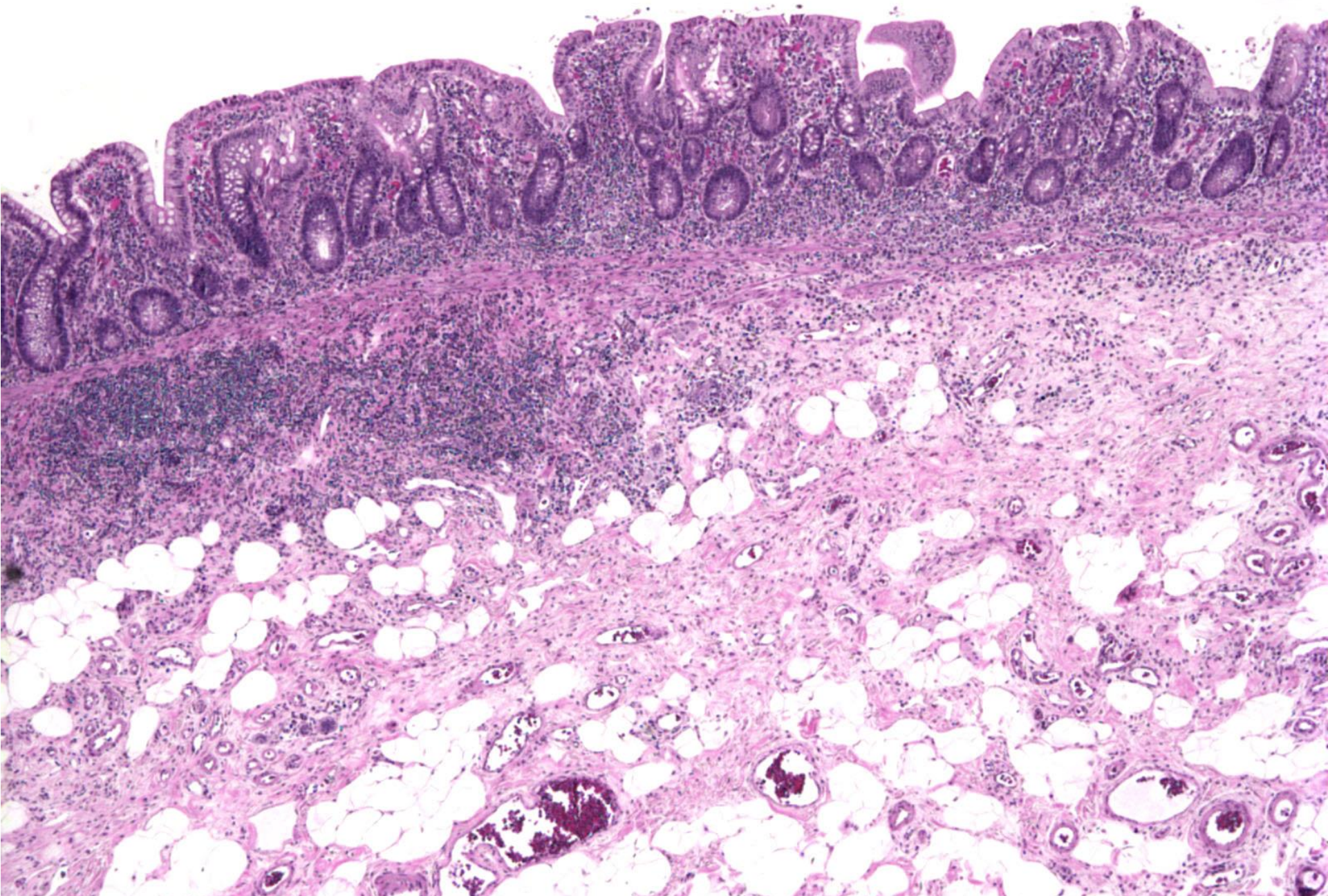
- Infection by coccidians not limited to immunocompromised
- Mucosal biopsy +/- special stains is best for diagnosis
- Stool studies can be helpful with special stains
- May have minimal associated tissue reaction, so remember to look for them

Shouldn't
have had
that last
beer...

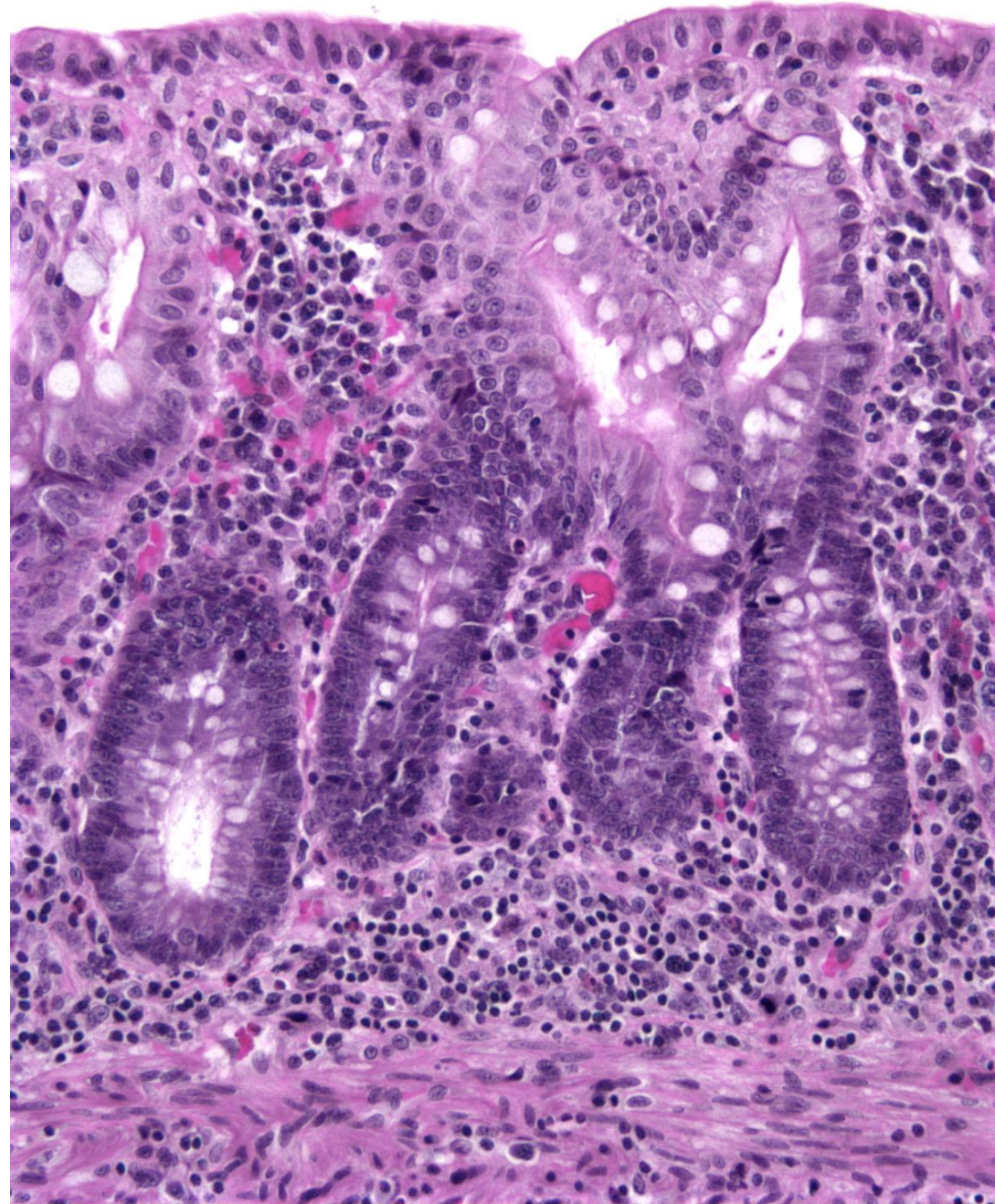


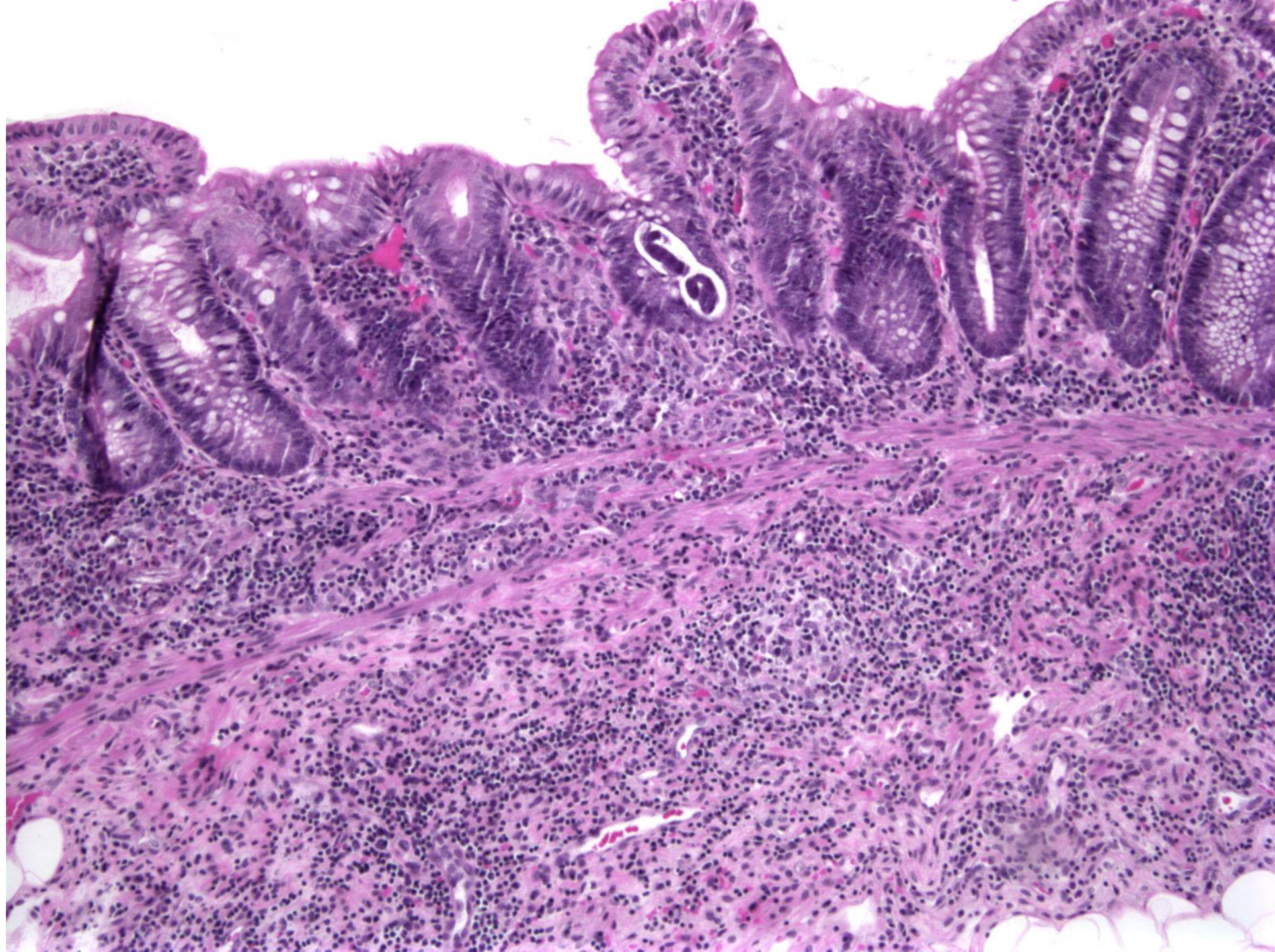
Case Example #5

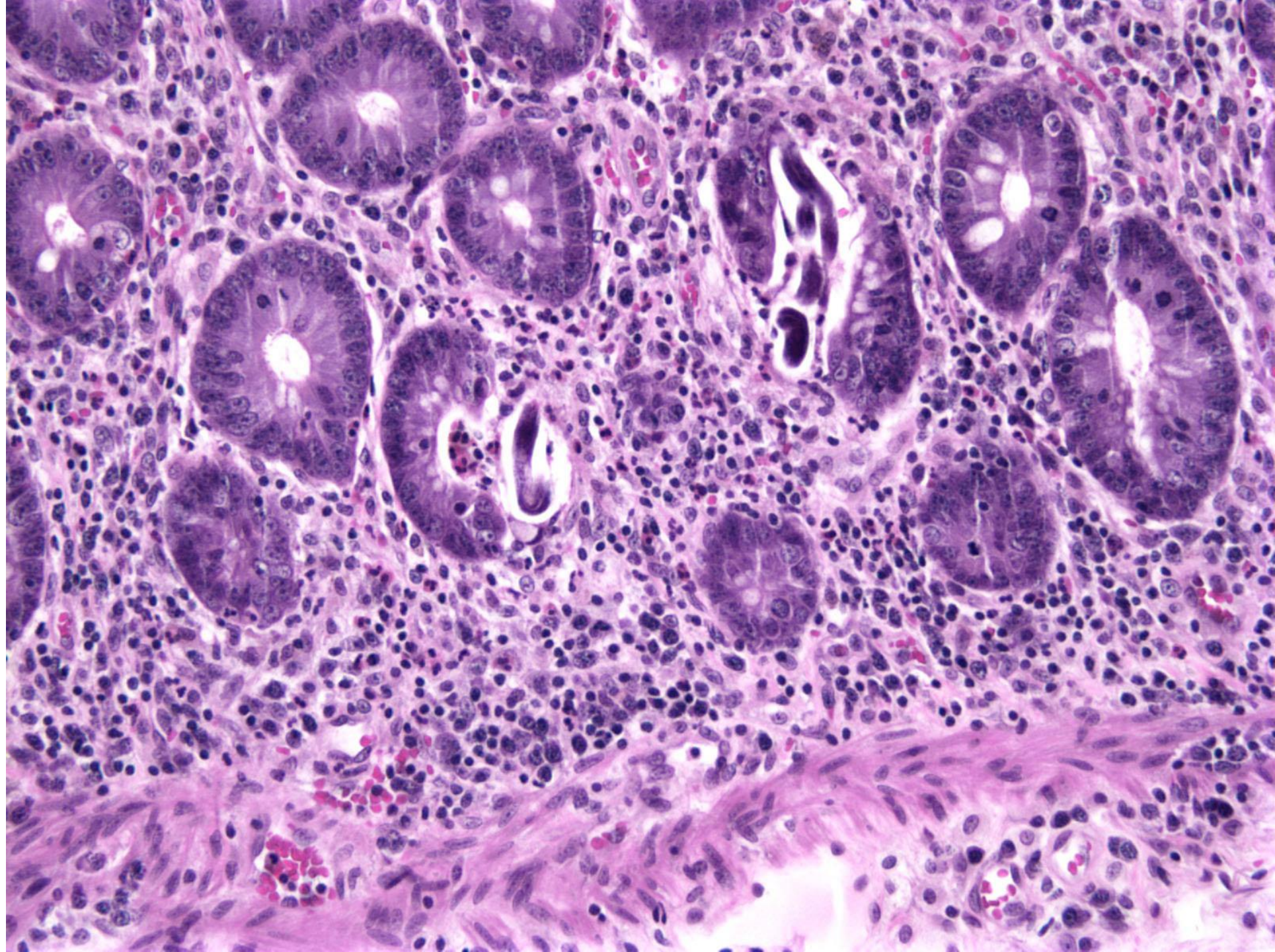
- 50 year old woman with reported history of Crohn's disease was taken to emergency surgery for disease flare
- Patient had been on several weeks of steroids with no improvement
- Following right colectomy, patient clinically decompensated, developed pneumonia, and was intubated

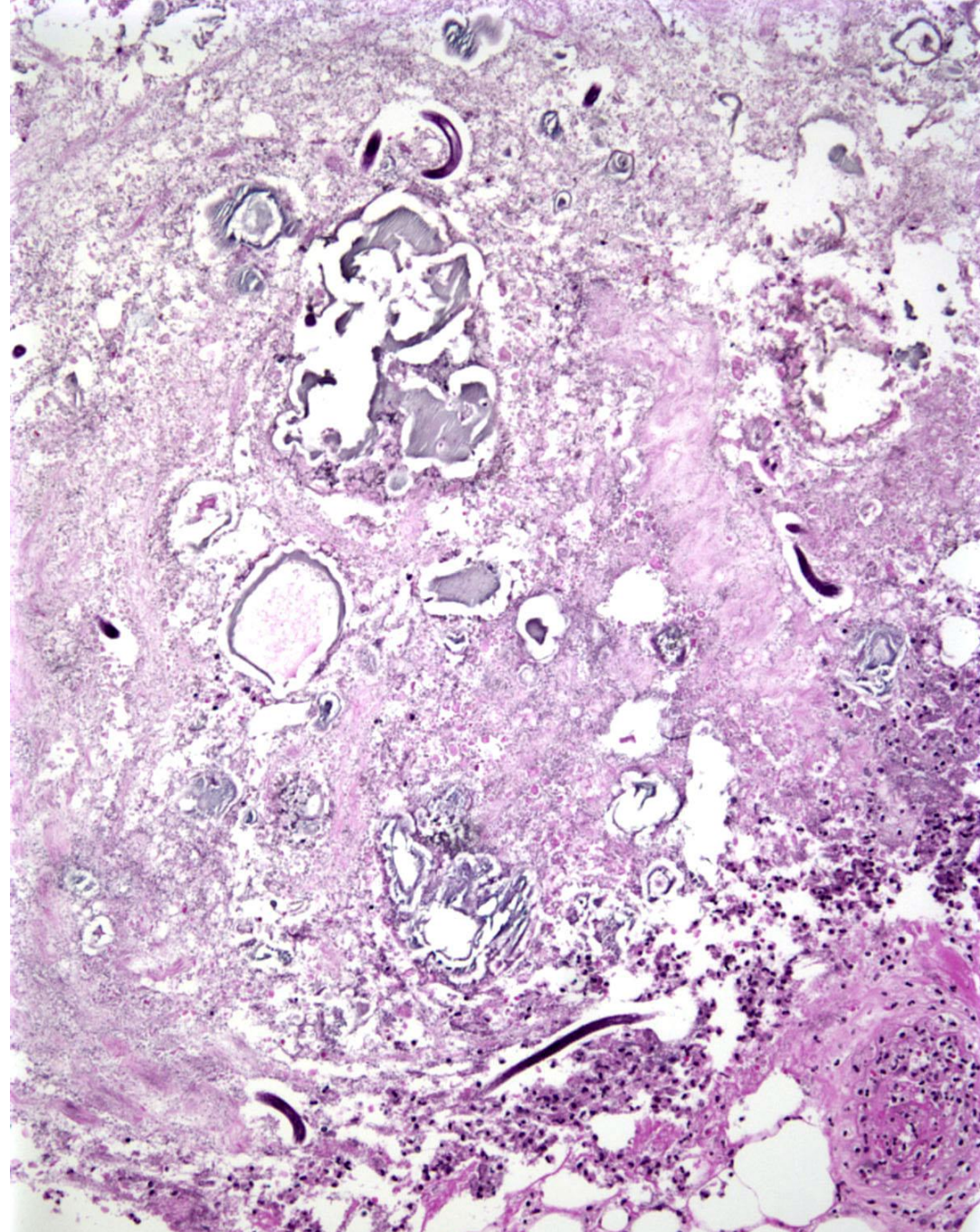


Chronic, active colitis with architectural distortion and basal plasmacytosis

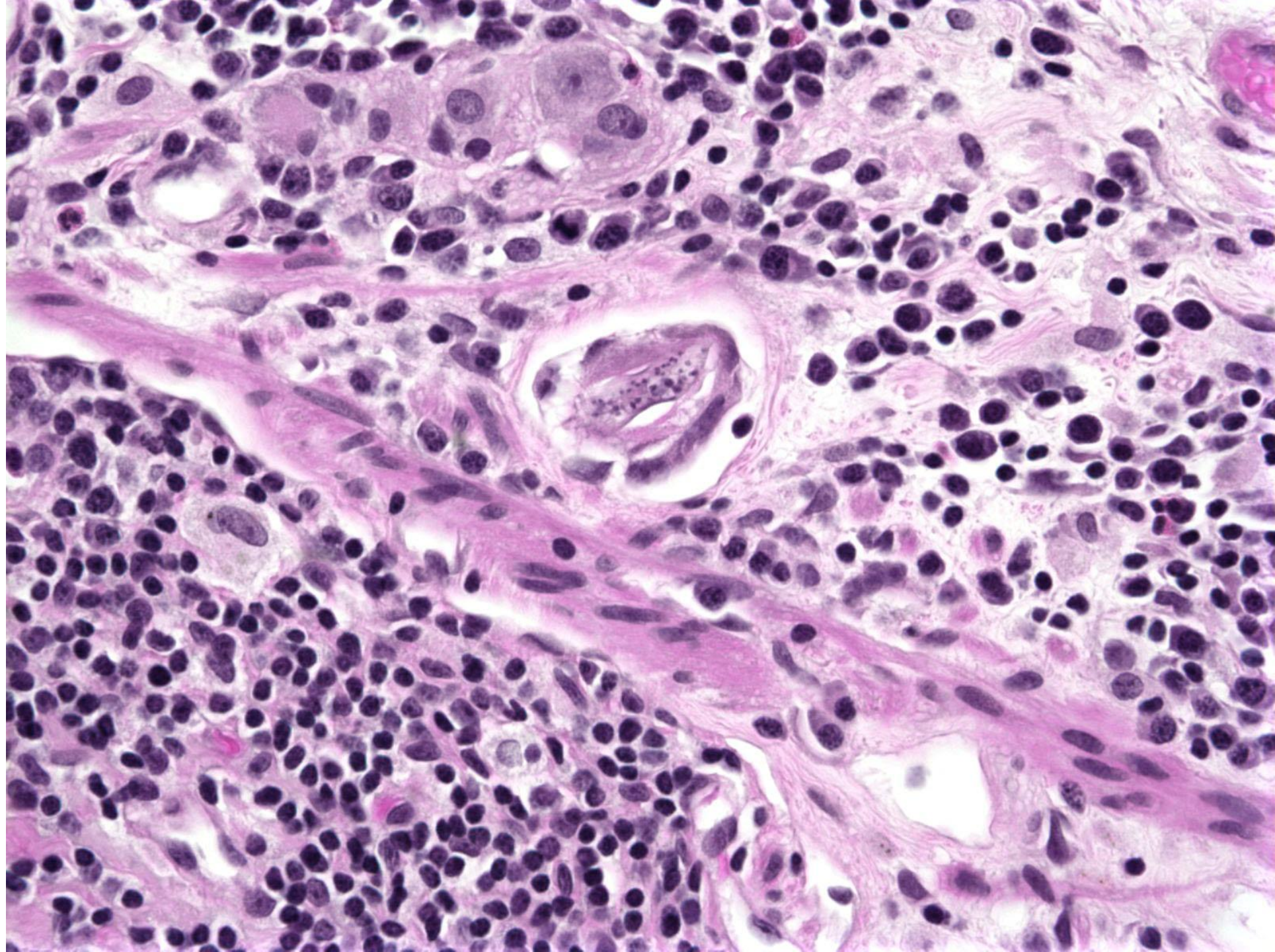


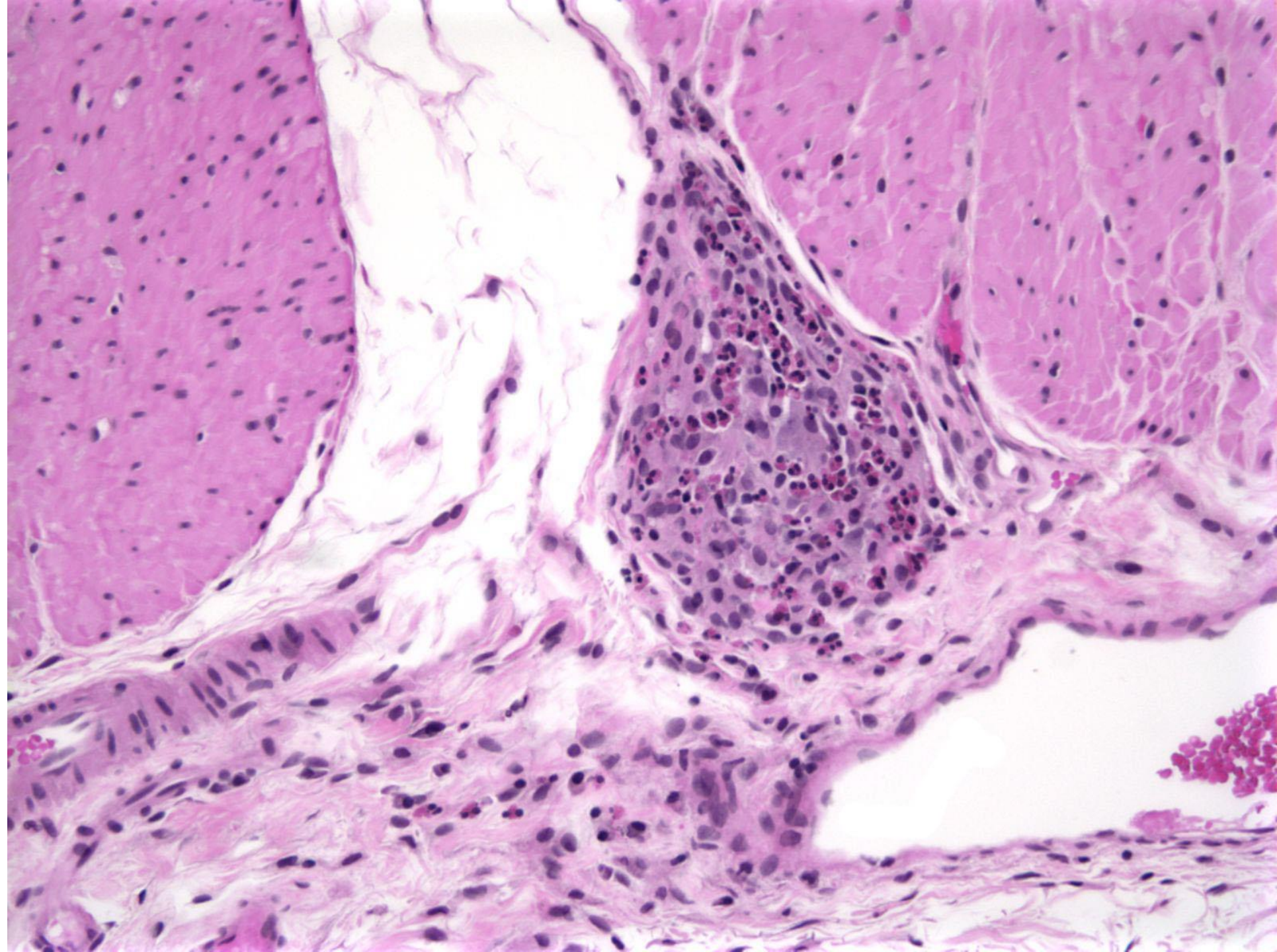


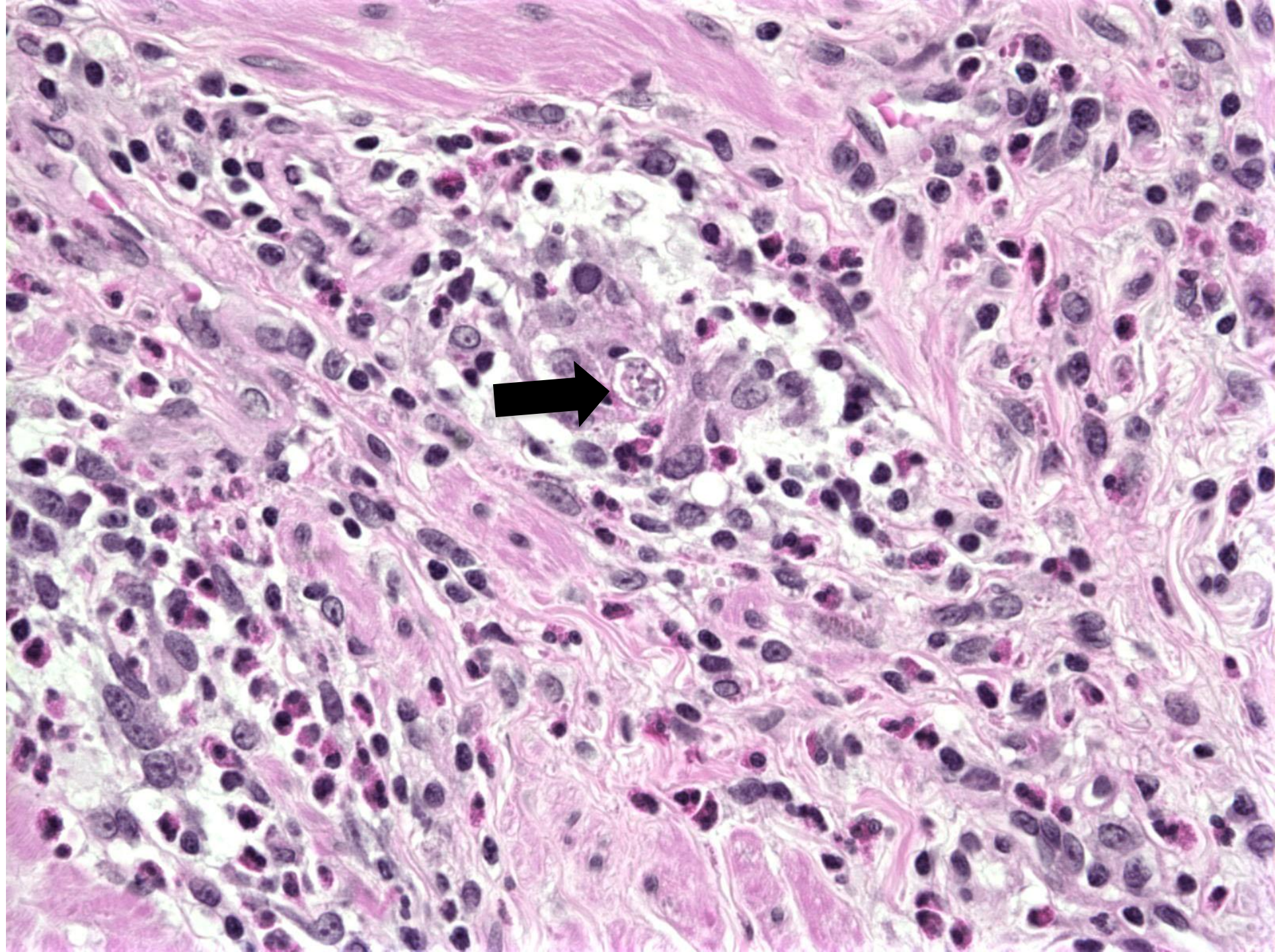


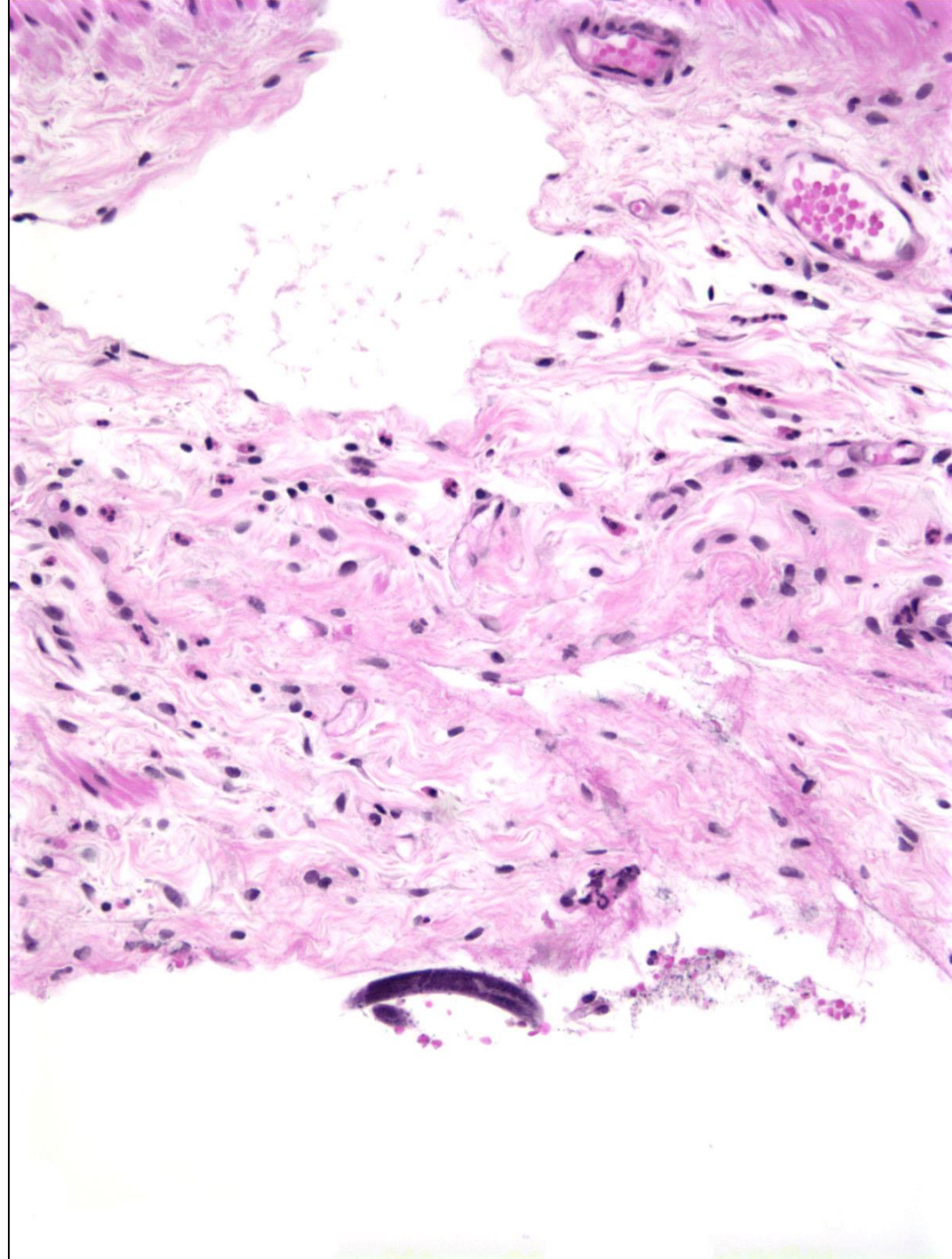


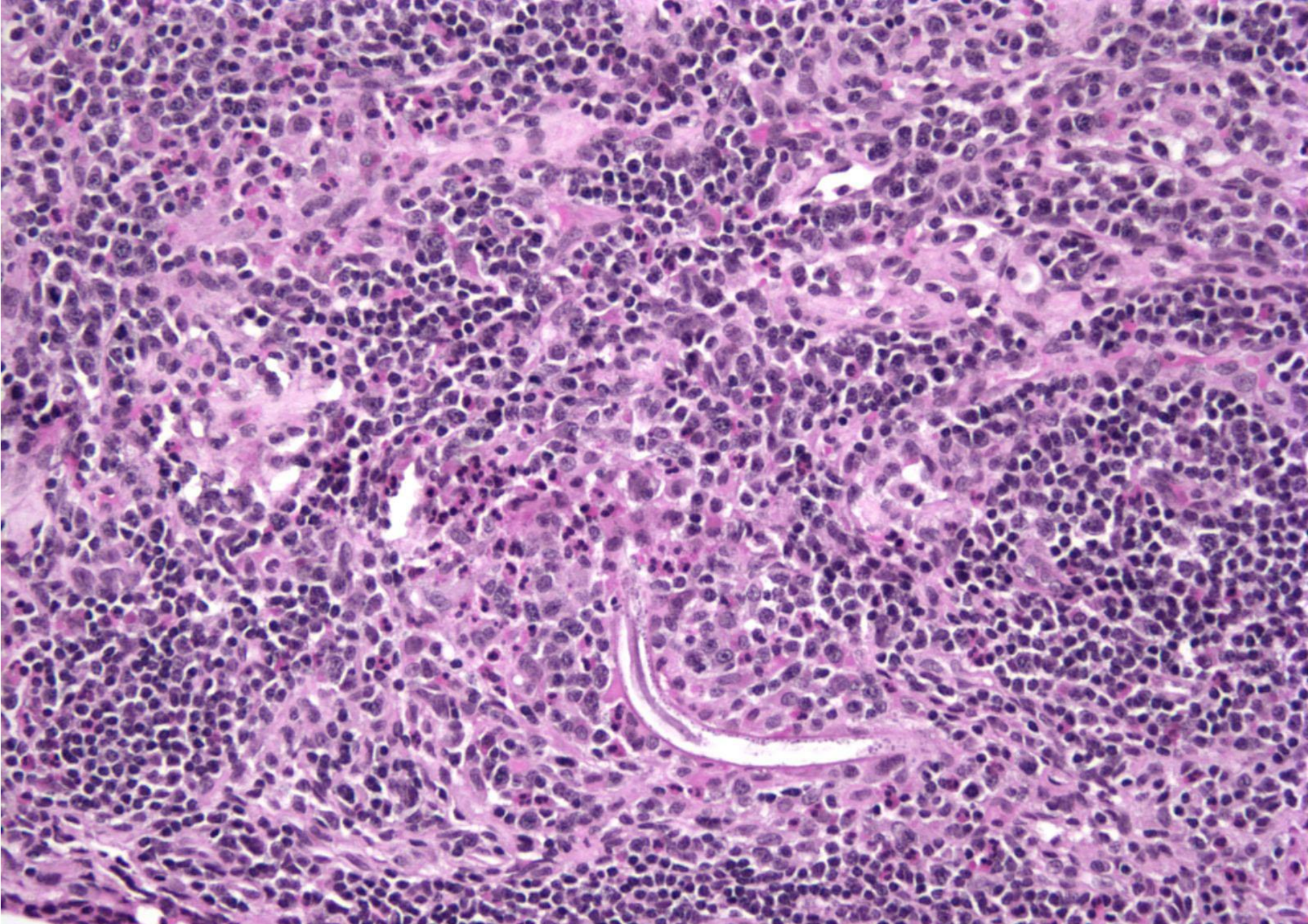
Deep areas of ulceration with inflammatory exudate



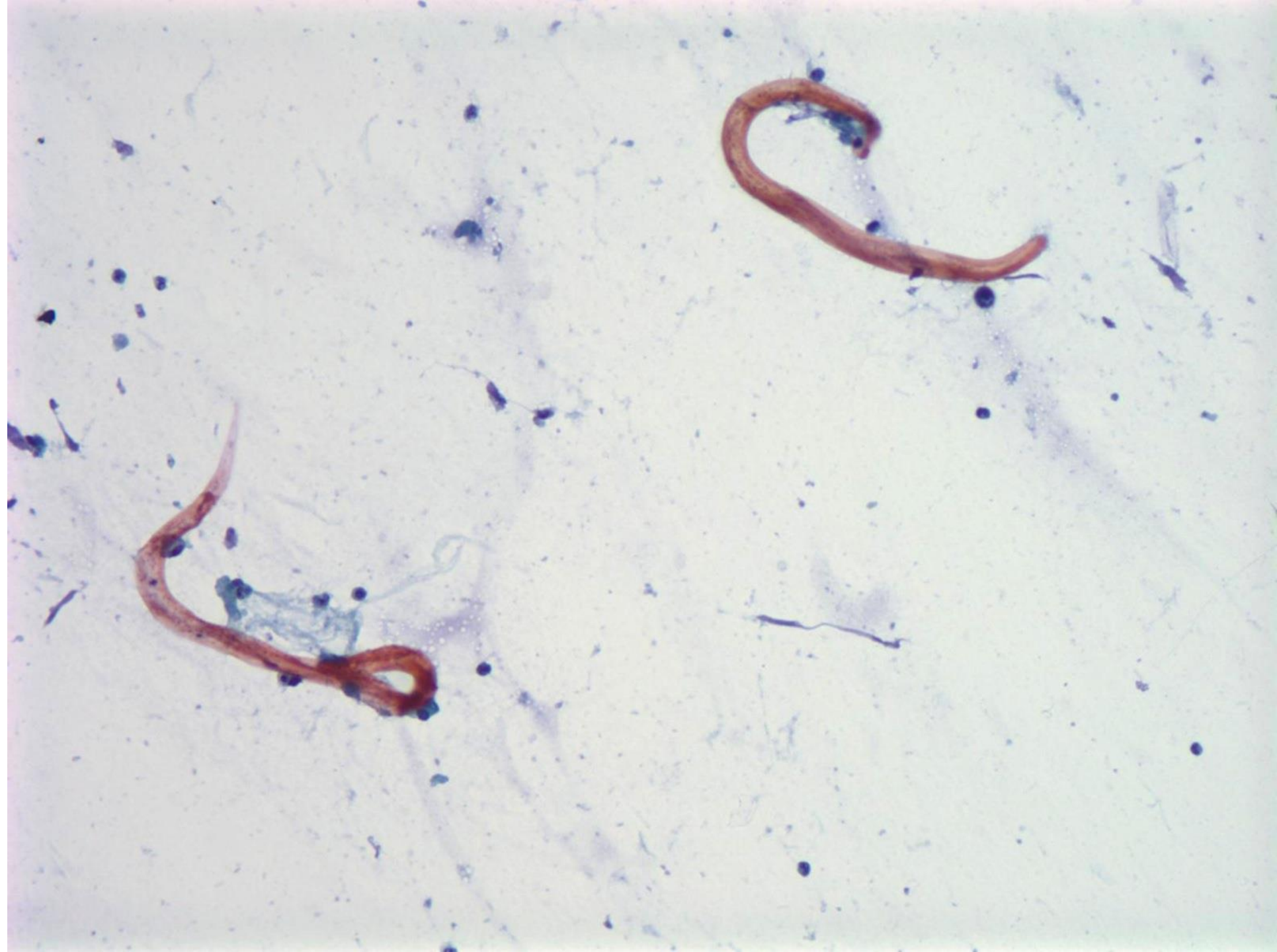








Mesenteric lymph node



Emerging Infection: Strongyloidiasis

- Soil nematode with worldwide distribution, endemic in southeast USA
- Autoinfective capability allows them to live in the small bowel for up to 30 years or more
- **Steroids** cause the conversion of chronic, low grade disease into fulminant infection in many cases

Low probability, high impact event

- Strongyloides stercoralis colitis is a severe, but easily curable, form of strongyloidiasis that carries a high mortality rate if untreated. ..Our experience with 4 cases of Strongyloides colitis prompted us to assess the clinical outcome of the disease by literature review. In this case series, the misdiagnosis and resultant mortality rates of Strongyloides colitis are 52% and 39.1%, respectively. A low index of suspicion and morphologic resemblance to ulcerative colitis were the main sources of diagnostic error. Ulcerative colitis alone accounted for 38.5% of the erroneous diagnoses. Features of Strongyloides colitis that contrast with those of ulcerative colitis include (1) skip pattern of the inflammation, (2) distal attenuation of the disease, (3) eosinophil-rich infiltrates, (4) relative intact crypt architecture, and (5) frequent involvement of submucosa. We also found that history of steroid therapy, chronic colitis refractory to conventional immune-modifying management, and endoscopic finding of distal attenuation of the colitis are helpful clues. It is also our experience that if Strongyloides colitis is included in the differential diagnosis, the correct diagnosis can usually be made. Current therapy with ivermectin or albendazole is very effective at a cure rate greater than 98%. We believe that the misdiagnosis and mortality rates of this curable, but often, unnecessarily deadly, infectious disease are alarming and warrant efforts to increase the awareness of the disease.

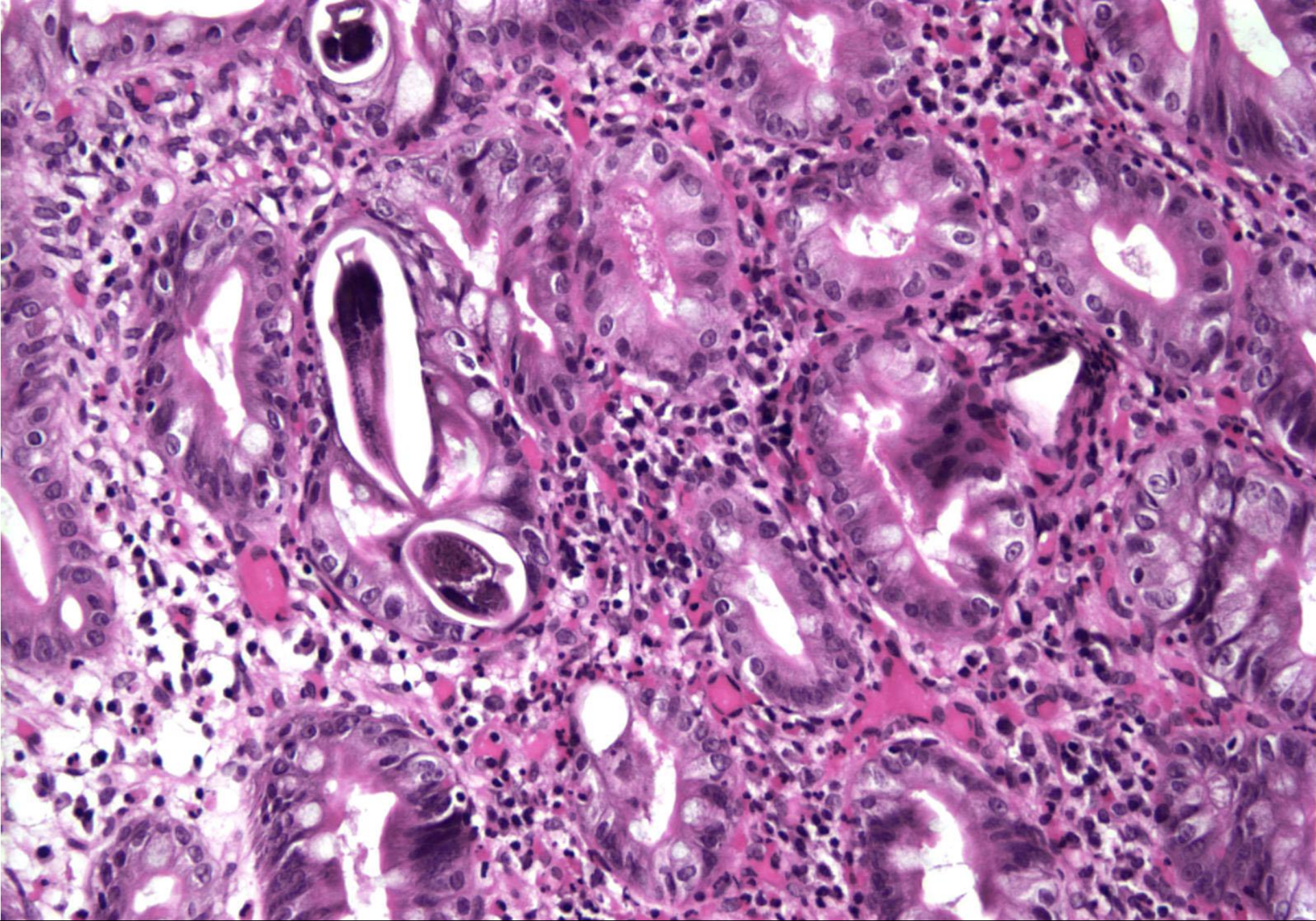
Strongyloidiasis-Clinical

- Many patients asymptomatic
- When symptomatic, presentation is very variable
 - Diarrhea, abdominal pain, GI bleeding
- Extra-GI manifestations include rash, mesenteric adenopathy, eosinophilia
- Complications include strictures, bowel obstruction

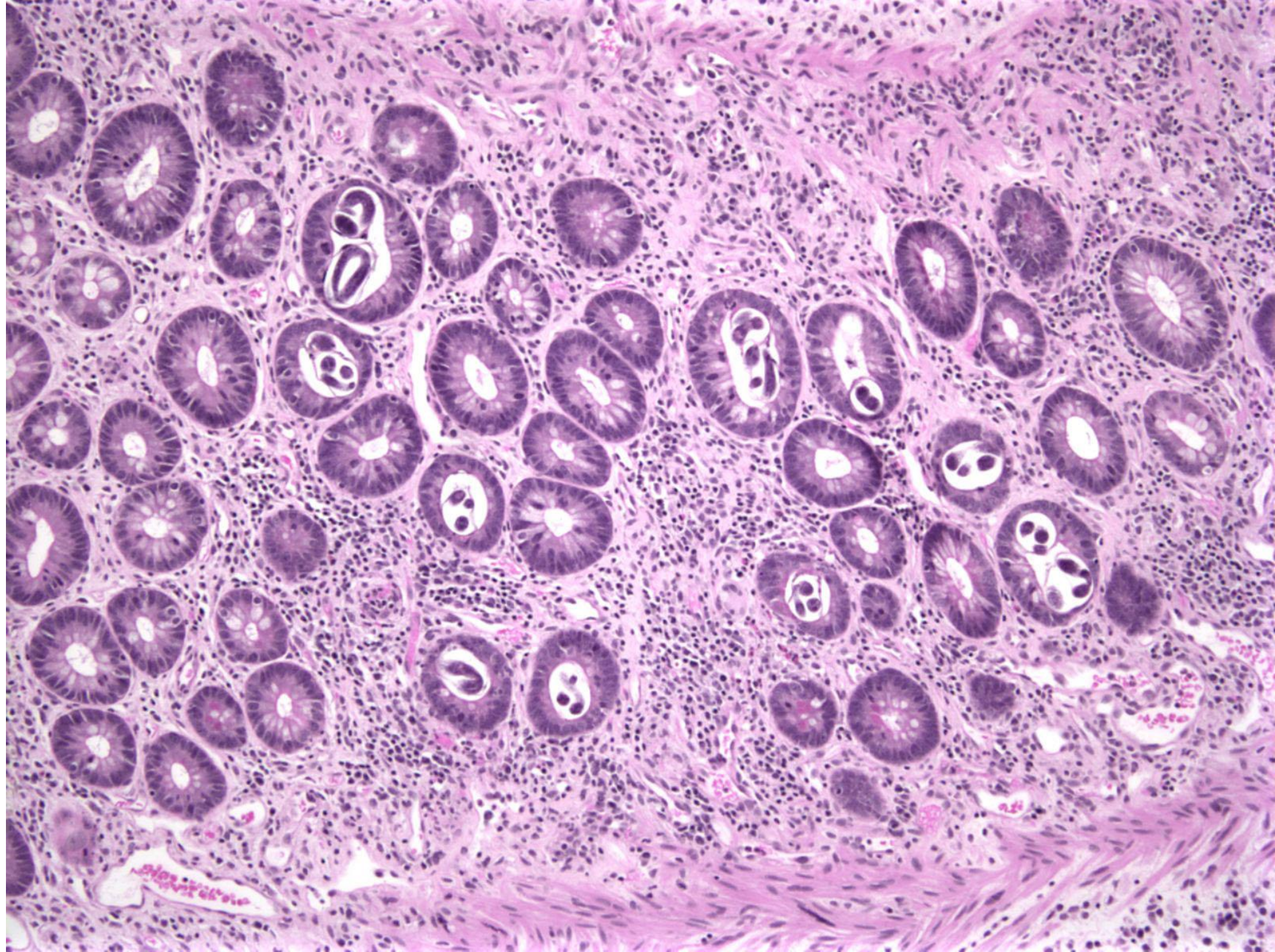
Strongyloidiasis

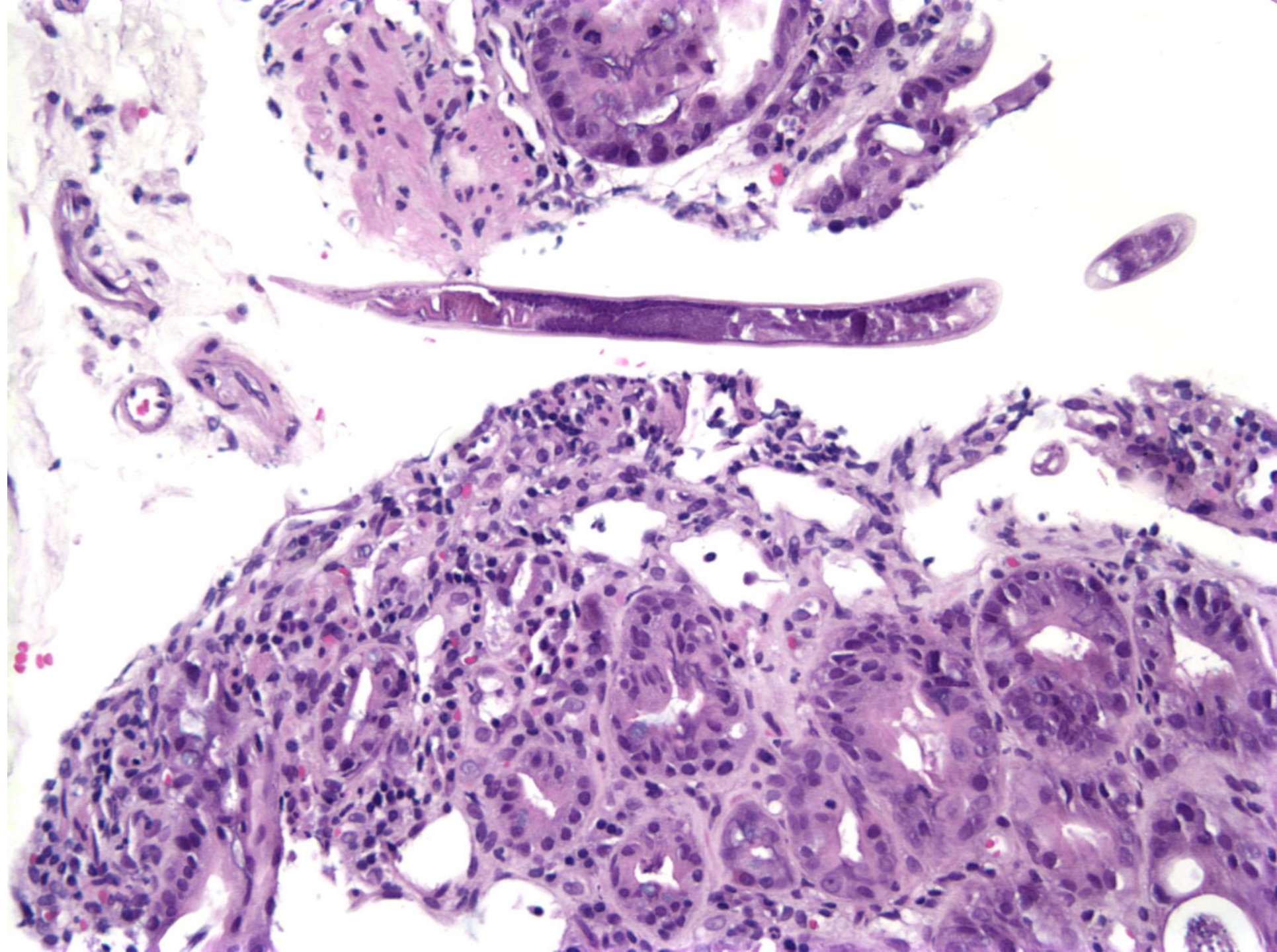
Pathology

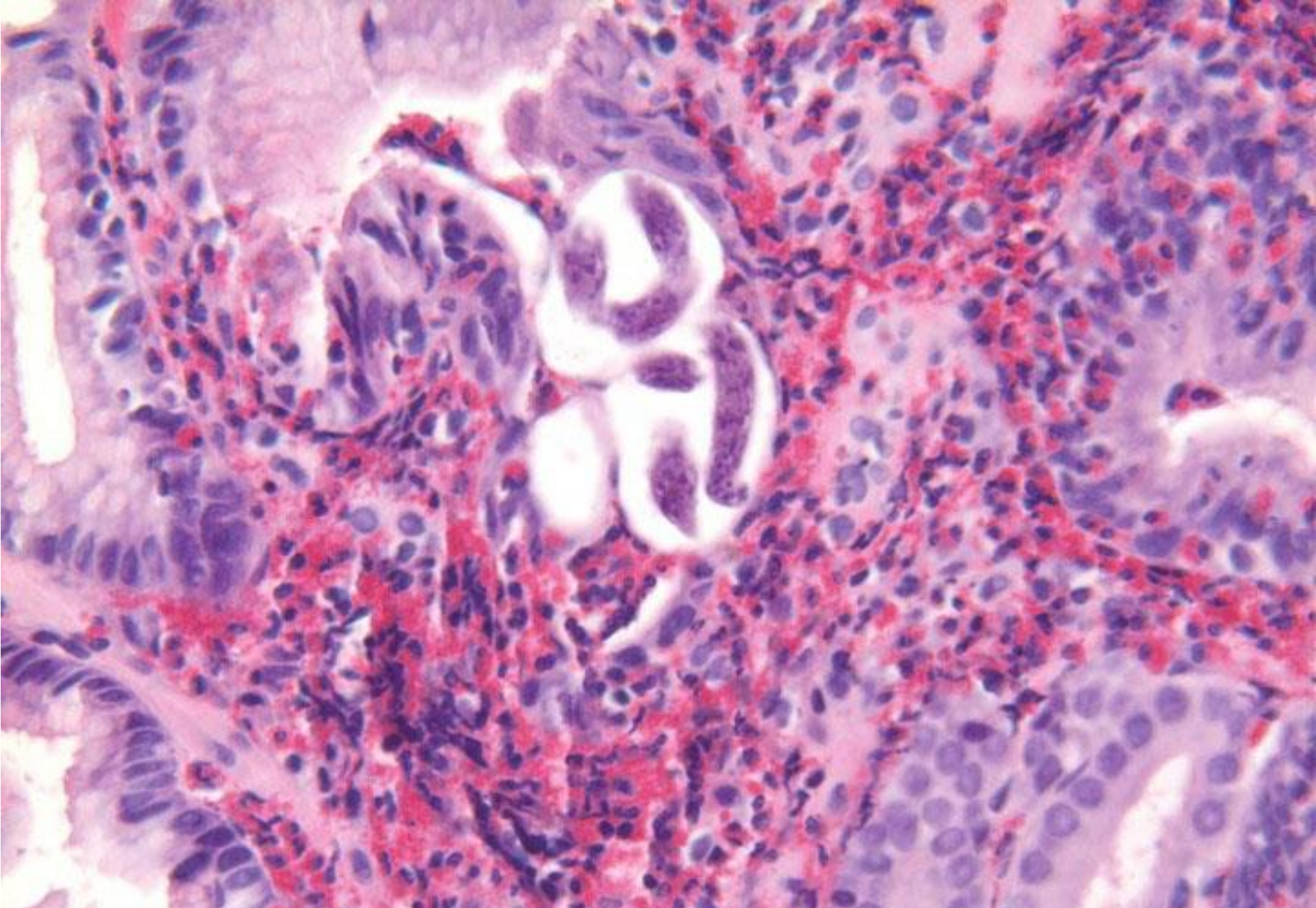
- Found anywhere in stomach, small bowel, or colon
- May have minimal inflammatory reaction
- Some patients have neutrophilic/eosinophilic infiltrate, granulomas, ulceration, villous blunting



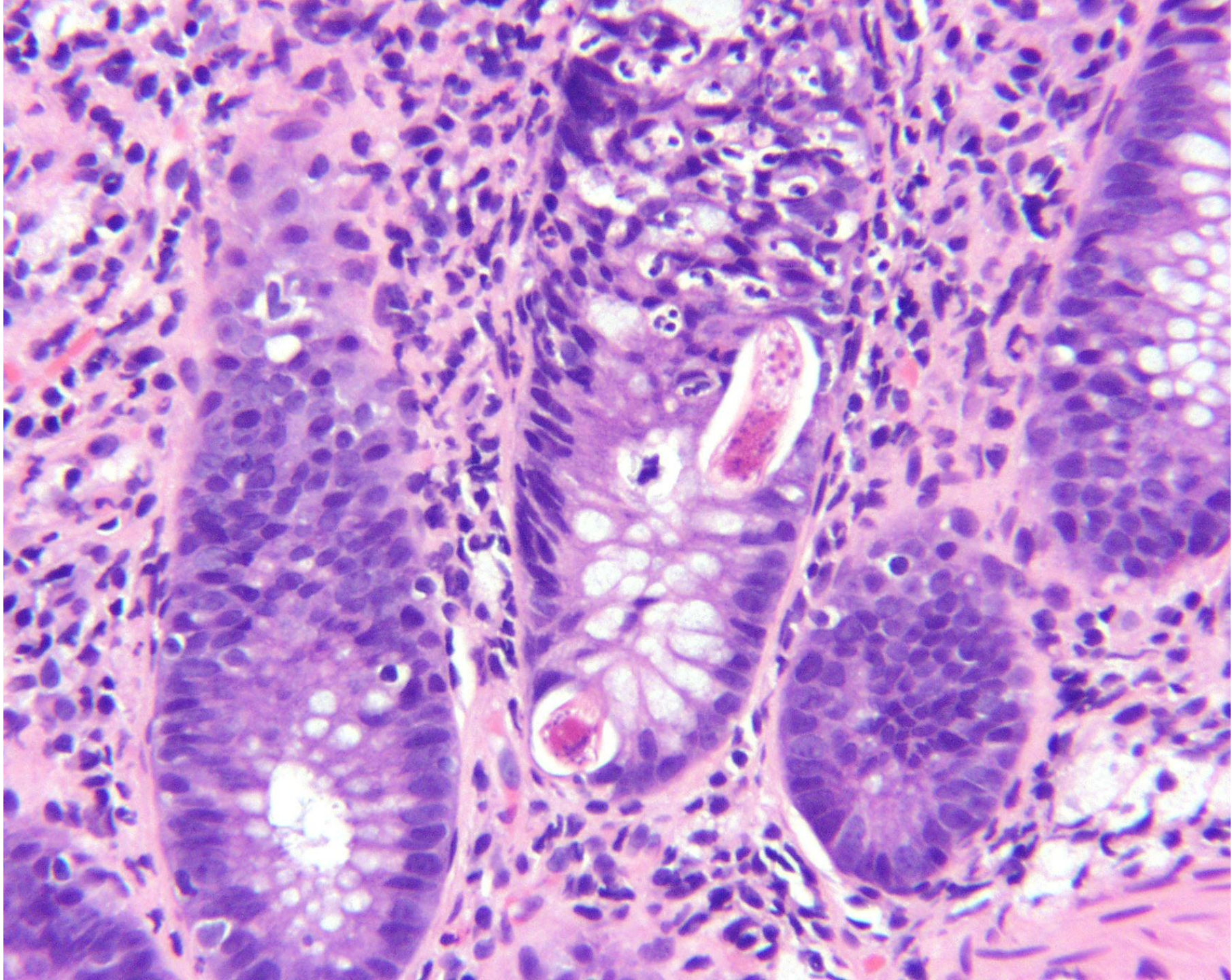
Worms have sharply pointed, often curved tails and are found in crypts

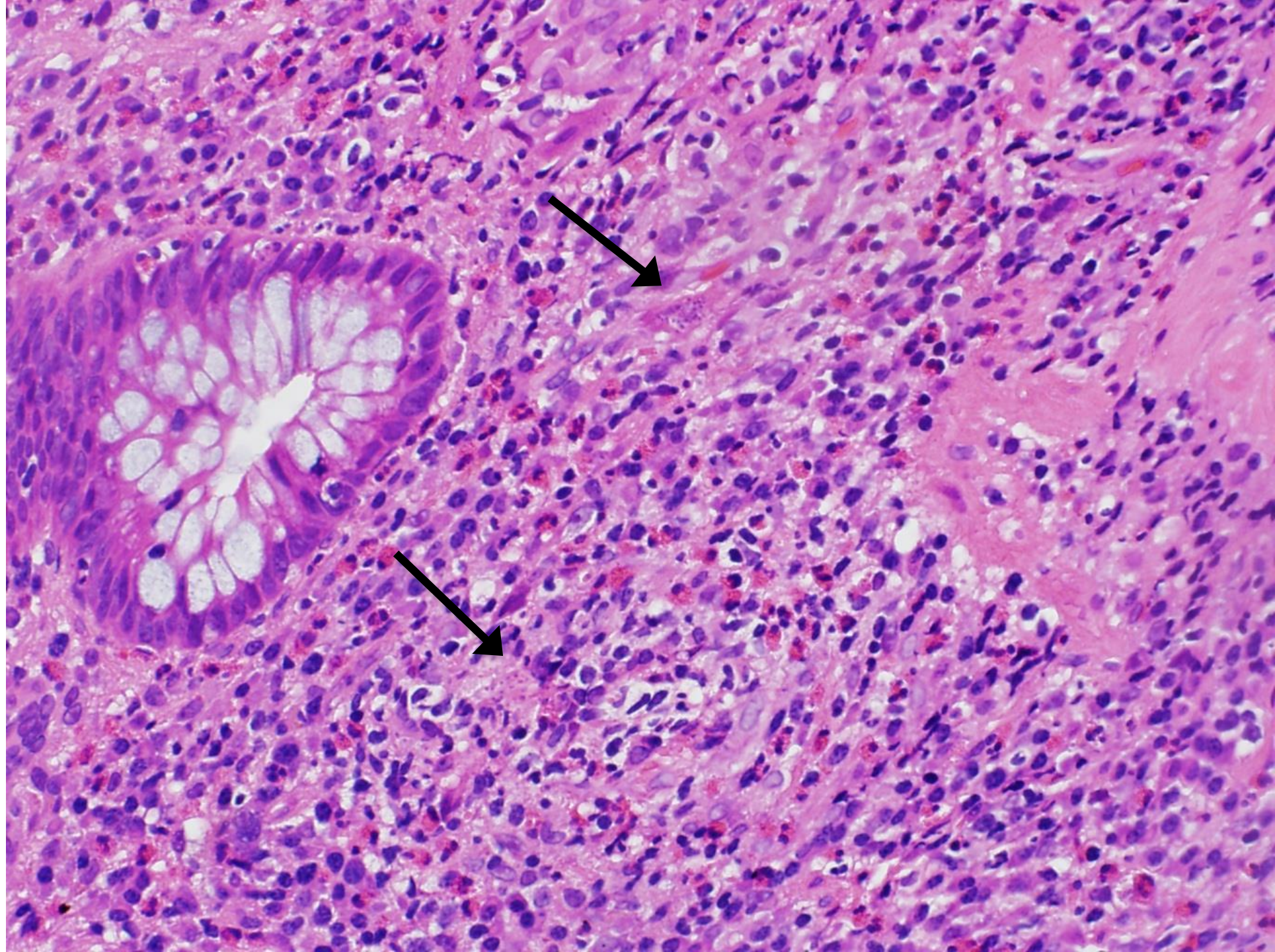


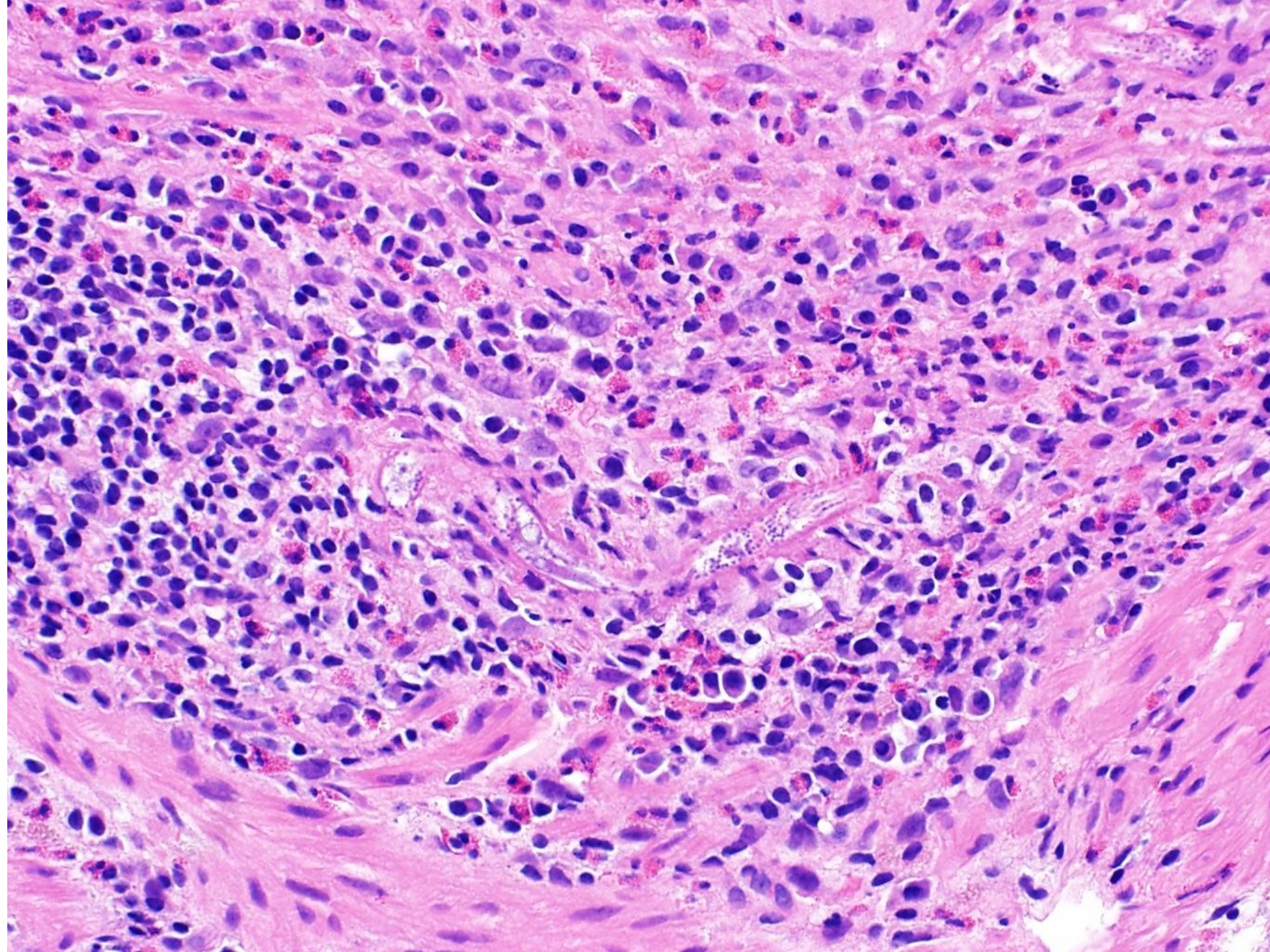




A neutrophilic or eosinophilic infiltrate can be seen in association with the parasite







Differential Diagnosis

- Larvae/worms with sharply pointed tails within epithelium is essentially diagnostic
 - In the proper geographic setting, capillariasis could mimic strongyloidiasis
- Schistosomiasis: eggs, not worms
- Enterobius: too big, in lumen
- Anisakiasis: huge, in stomach, sushi

Summary

- Almost always a history of steroid use
- Fulminant infection can mimic chronic idiopathic inflammatory bowel disease
- If you see pockets of eosinophils on biopsy, consider recuts to look for strongyloides
- Stool exam for O&P, serologies can be helpful

In closing...

- Pathogens (particularly emerging ones, as their characteristics are changing) are important and often under-recognized
 - History, food intake, risk factors, environmental exposure often critical

In closing.....

- In the GI tract, emerging infections are a clinically significant problem
 - Particularly in immunocompromised patients
 - Immunocompromised means lots of things
- **Although cultures/molecular are gold standard, morphology can be extremely helpful in directing therapy, especially early on**



Where are the
snacks?