Beyond Acute Appendicitis:
Fascinating Lesions of the Vermiform Appendix

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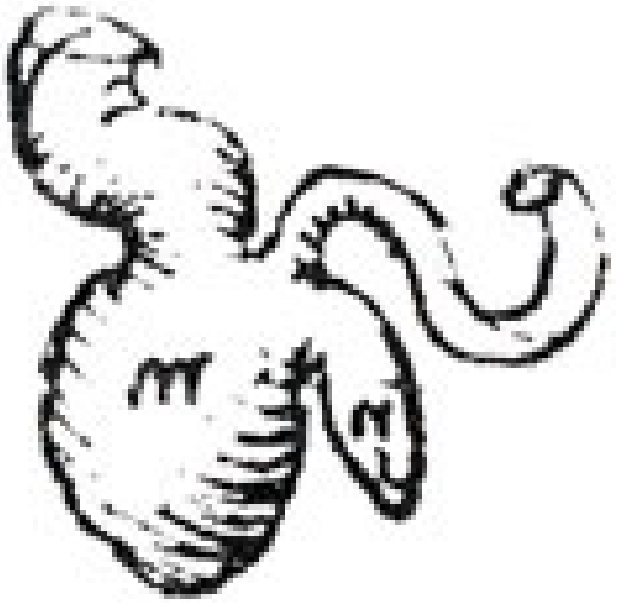
The Appendix: historical perspectives

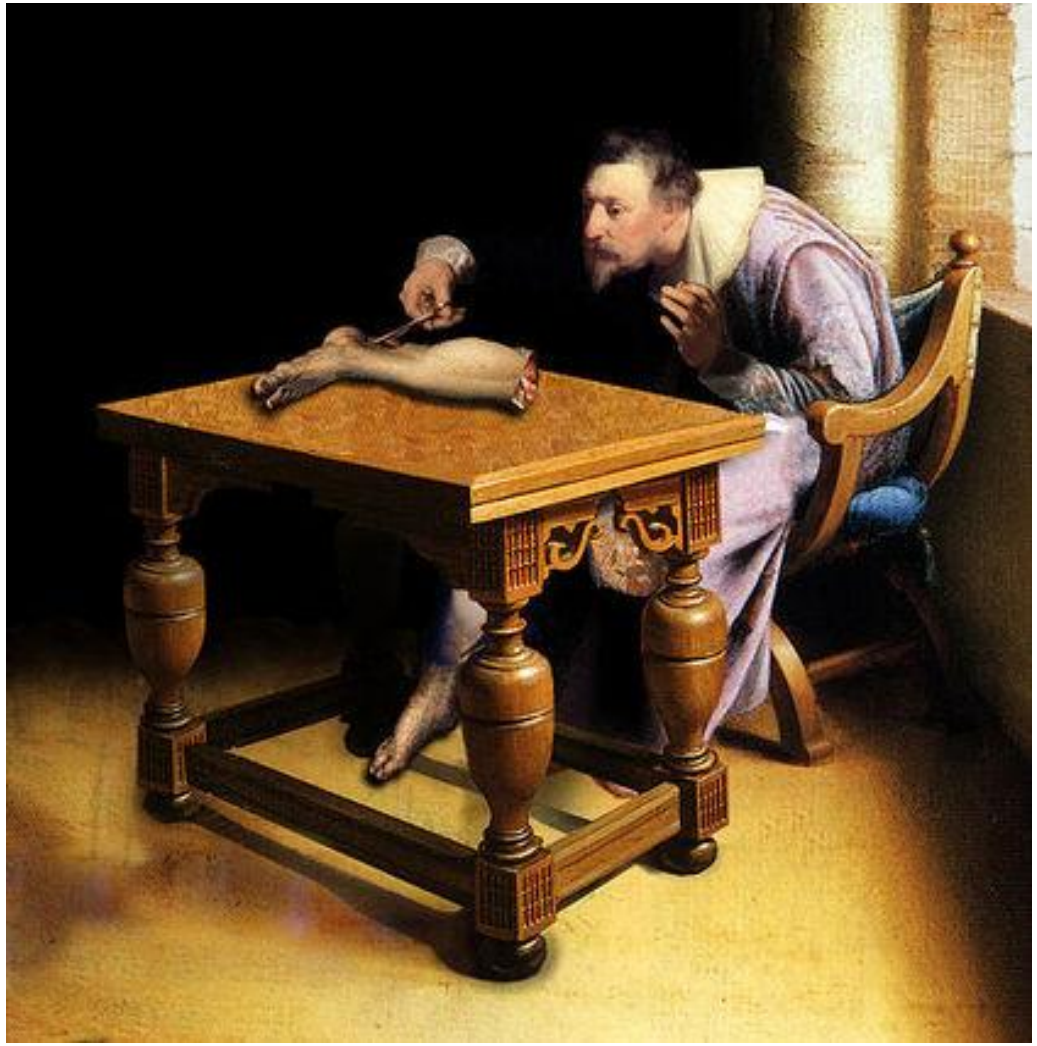
- Probably first noted by Egyptians around 3000 B.C.
- First sketched by da Vinci around 1500
  - Used term “orecchio,” or “ear,” to describe
- Formally described by da Capri (1521) and Vesalius (1543)



da Vinci, 1504-6

The Appendix: historical perspectives

Phillippe Verheyen, a Belgian anatomist/surgeon, coined the term “appendix vermiformis” in 1710.



The Appendix: historical perspectives

- Appendix thought unable to cause disease on its own
  - 1759: first recorded case documenting disease in appendix (Mestivier)
    - 45 year old man with “tumor” on right side of umbilicus
    - Fluctuant, a “pint of pus” removed
    - Patient died; autopsy revealed acute inflammation of appendix, peritonitis, and large rusty pin in appendix

The Appendix: historical perspectives

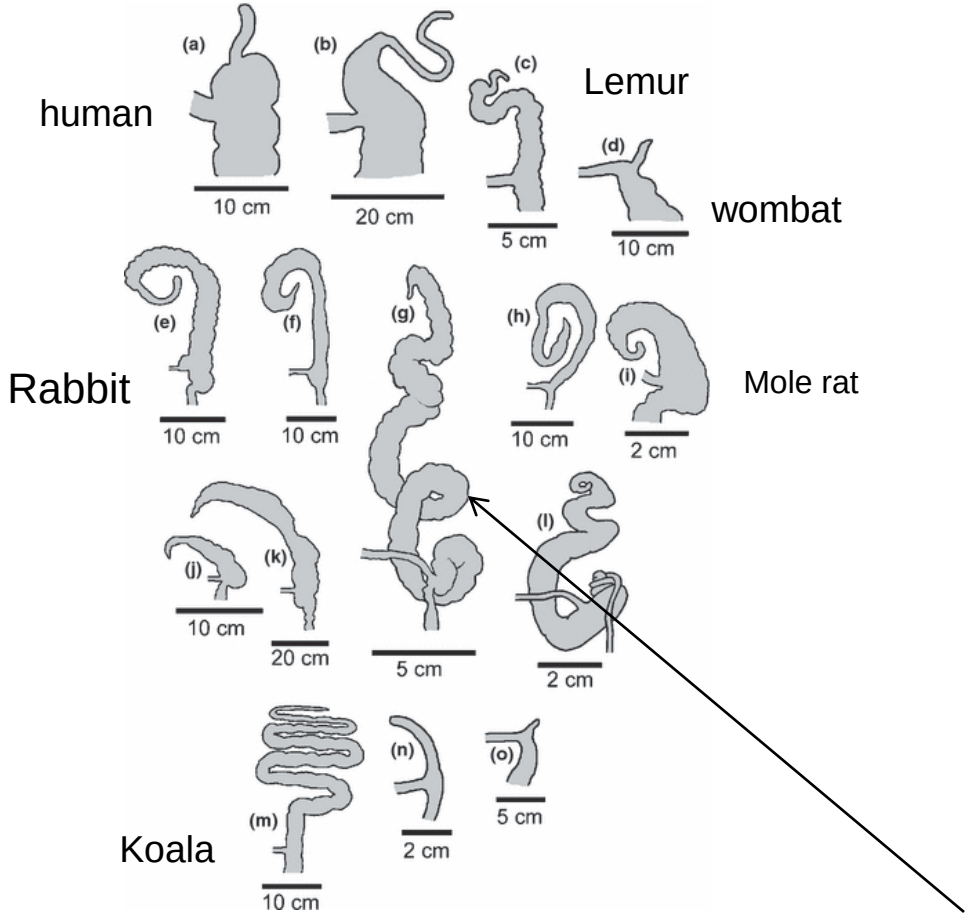
- 1830s: Englishmen Bright and Addison wrote seminal text "Inflammation of the Cecum and Appendix Vermiformis," clearly describing and documenting the appendix as a source of disease

- Similar work published by Voltz in Germany in 1846

Appendix
Comparative Anatomy

- An embryologic continuation of the cecum
- Present in all hominoid apes, some monkeys, a few other mammals (such as wombats)
- Absent in dogs, wolves, lions, tigers
- Larger structure in strict herbivores

Comparative anatomy and phylogenetic distribution of the mammalian cecal appendix

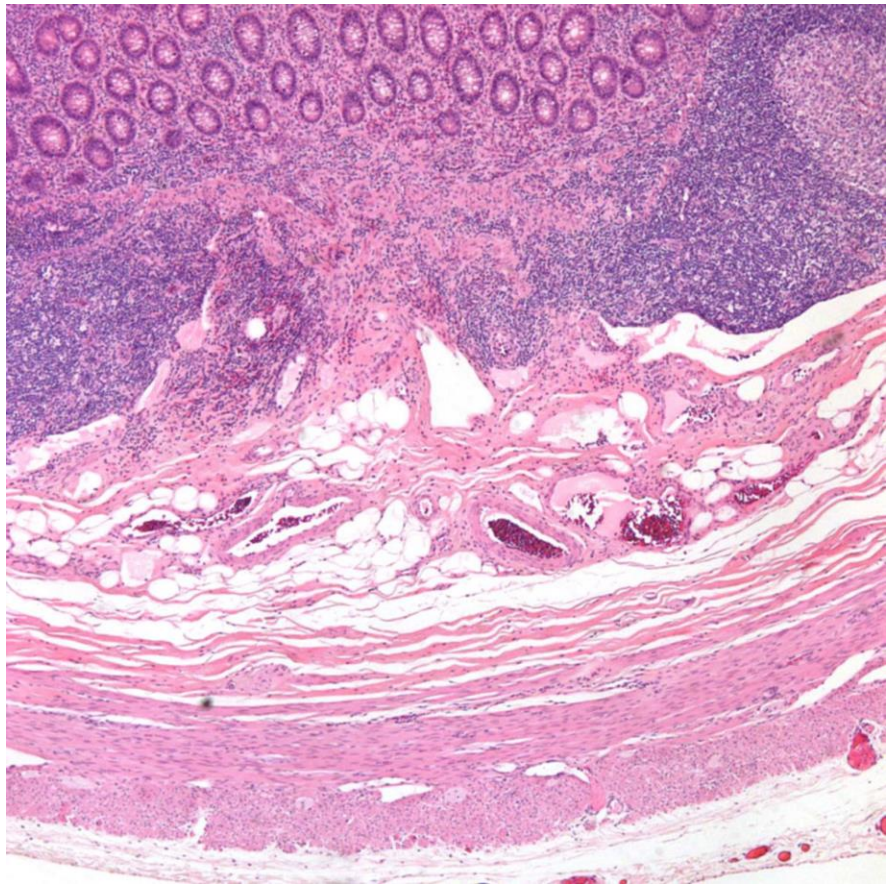


Journal of Evolutionary Biology
Volume 22, Issue 10, pages 1984-1999, 12 AUG 2009 DOI: 10.1111/j.1420-9101.2009.01809.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1420-9101.2009.01809.x/full#f1

Anatomy/Histology

Same basic structure as the colon with a few exceptions:

- Muscular wall development more irregular
- Muscularis mucosae may be discontinuous
- Prominent lymphoid tissue
- Abundant ganglion cells and neuroendocrine cells



Williams RA and Myers P. *Pathology of the Appendix and Its Surgical Treatment*. London: Chapman and Hall Medical, 1994.

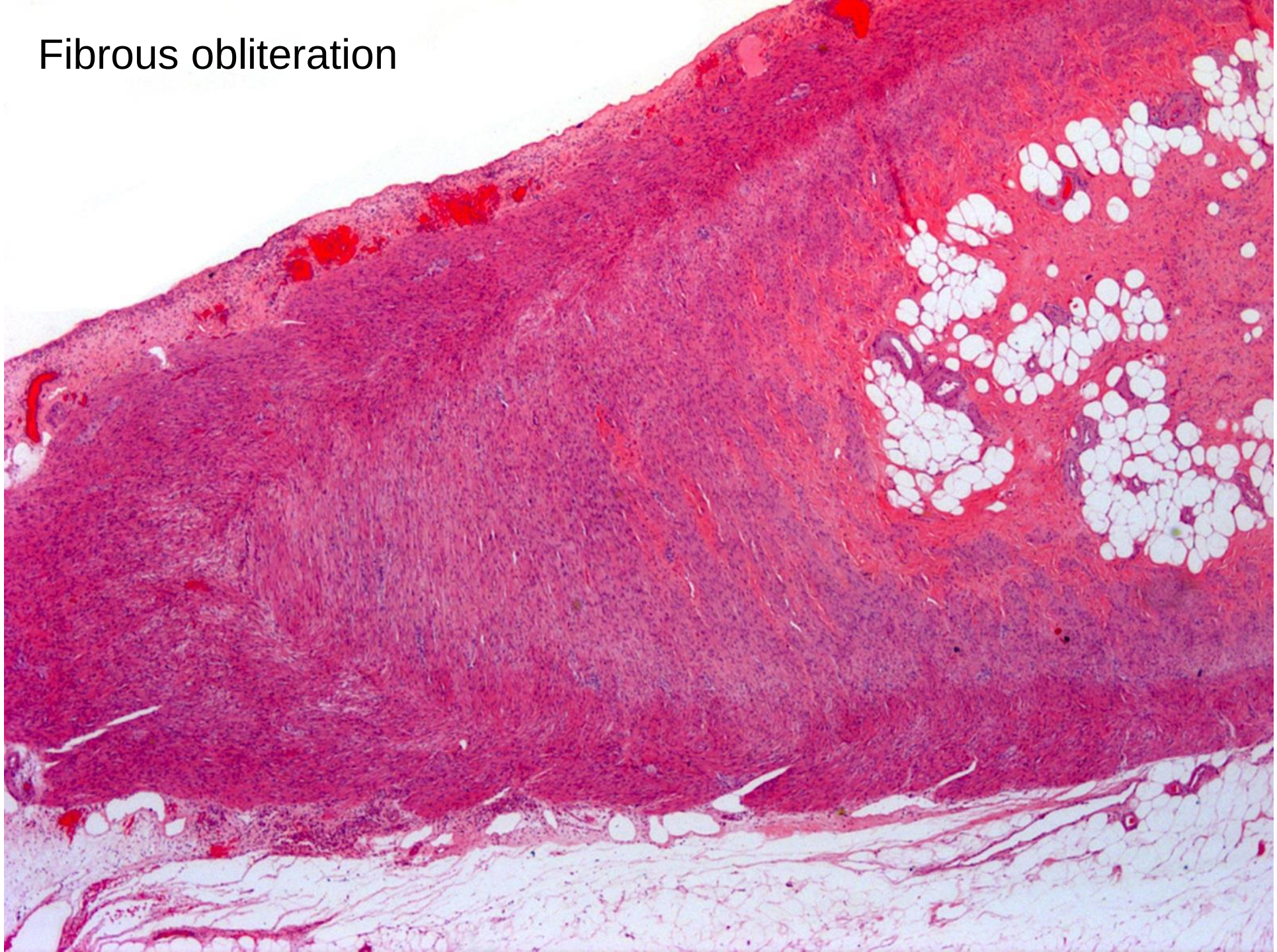
Handling of Appendectomy Specimens

- A few pointers:
  - Noting mucin on the outside of the appendix or in the mesoappendix is key
    - Be wary of contaminating mucin on the cutting board
  - Transverse section of proximal margin is essential
  - If a mucinous neoplasm is a consideration, put the entire thing in

Anatomy/Histology

- Age -related changes
  - Is largest in childhood
    - Maximum diameter at age 4
    - Shrinks throughout adult life
  - Lymphoid tissue diminishes after age 25
  - Fibrous tissue increases (especially after age 40)
    - Fibrous obliteration of the appendiceal tip

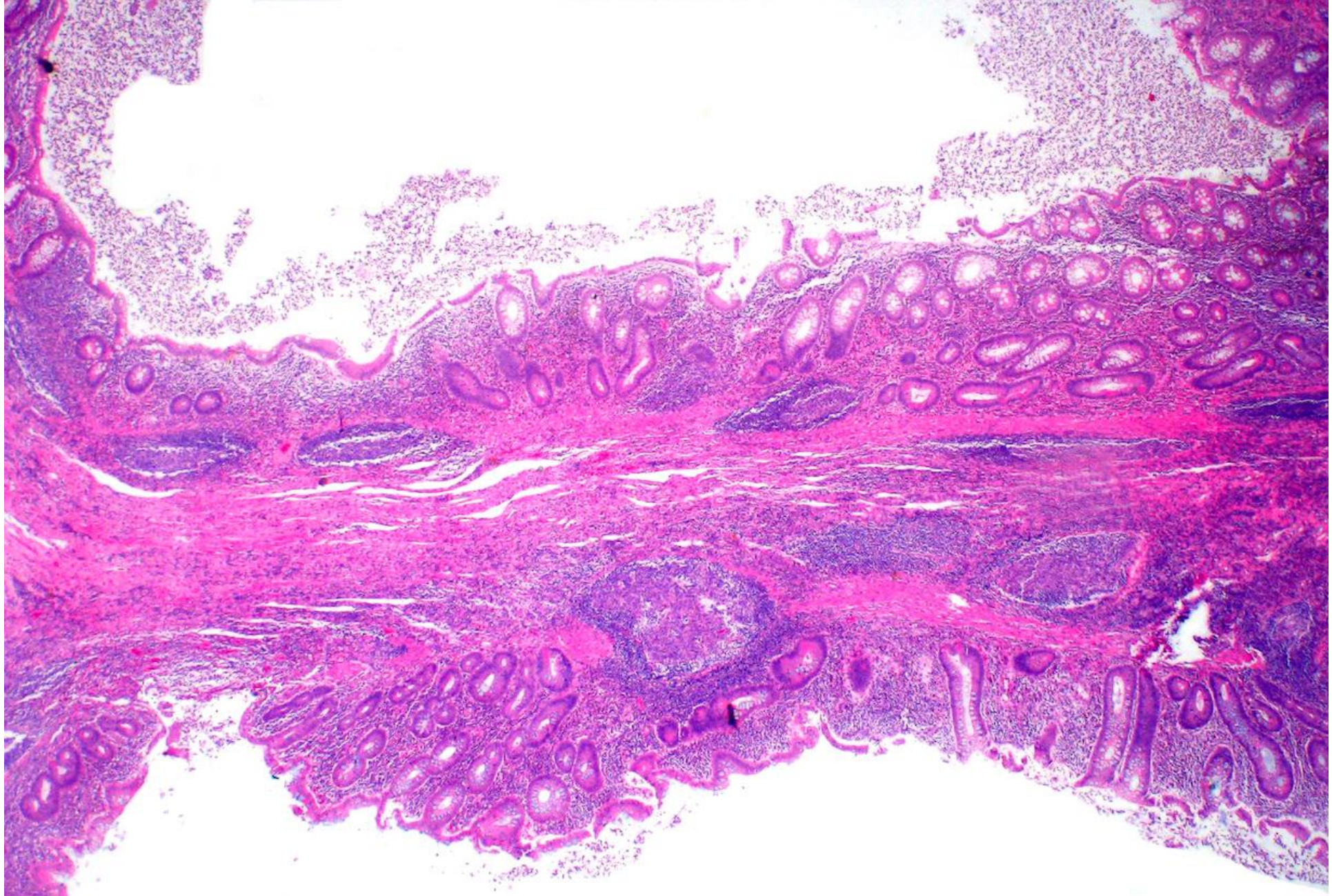
Fibrous obliteration



Other Odd Lesions

- Melanosis
- Heterotopic stomach and esophagus
- Congenital abnormalities
  - Agenesis
  - Duplication
  - Congenital diverticula
  - Septa

Melanosis



Duplication

Inflammatory Processes in the Appendix

- Appendicitis
  - Acute nonspecific appendicitis
  - Granulomatous appendicitis
  - Interval appendicitis
- Infections of the appendix
  - Viral
  - Bacterial
  - Parasitic
- Miscellaneous
  - Malakoplakia
  - Appendiceal diverticula
  - Mullerian lesions

Acute “nonspecific” appendicitis

- Most common intra-abdominal surgical emergency
- Peak incidence 2nd-3rd decades
- Perforation more common in children and very elderly
- Tumors associated with appendicitis in older adults

Carr NJ. The pathology of acute appendicitis. Ann Diag Pathol 2000;4:46-58.
Butler C. Surgical pathology of acute appendicitis. Hum Pathol 1981; 12:870-8.

Acute Appendicitis-pathogenesis

- Rarely foreign bodies
- Obstruction
- Infection
- Vascular compromise
- No single theory can explain all cases

The First Appendectomy

- Performed by Claudius Amyand, surgeon to King George II, December 6, 1735, at St. George's Hospital in London
  - "Not a man of genius, but one of solid worth"
- Patient was Hanvil Anderson, age 11
- Presented with inguinal hernia and fecal fistula tract draining in the groin

The First Appendectomy

- No anesthesia
  - "Tis easy to conceive that this operation was as painful to the patient as laborious to me."
    - *Philosophical Transactions of the Royal Society, 1736*
  - Perforated appendix was found within a hernia sac (Amyand's hernia)
  - Supposedly caused by ingested pin that lodged in the appendix

Most Famous Appendectomy

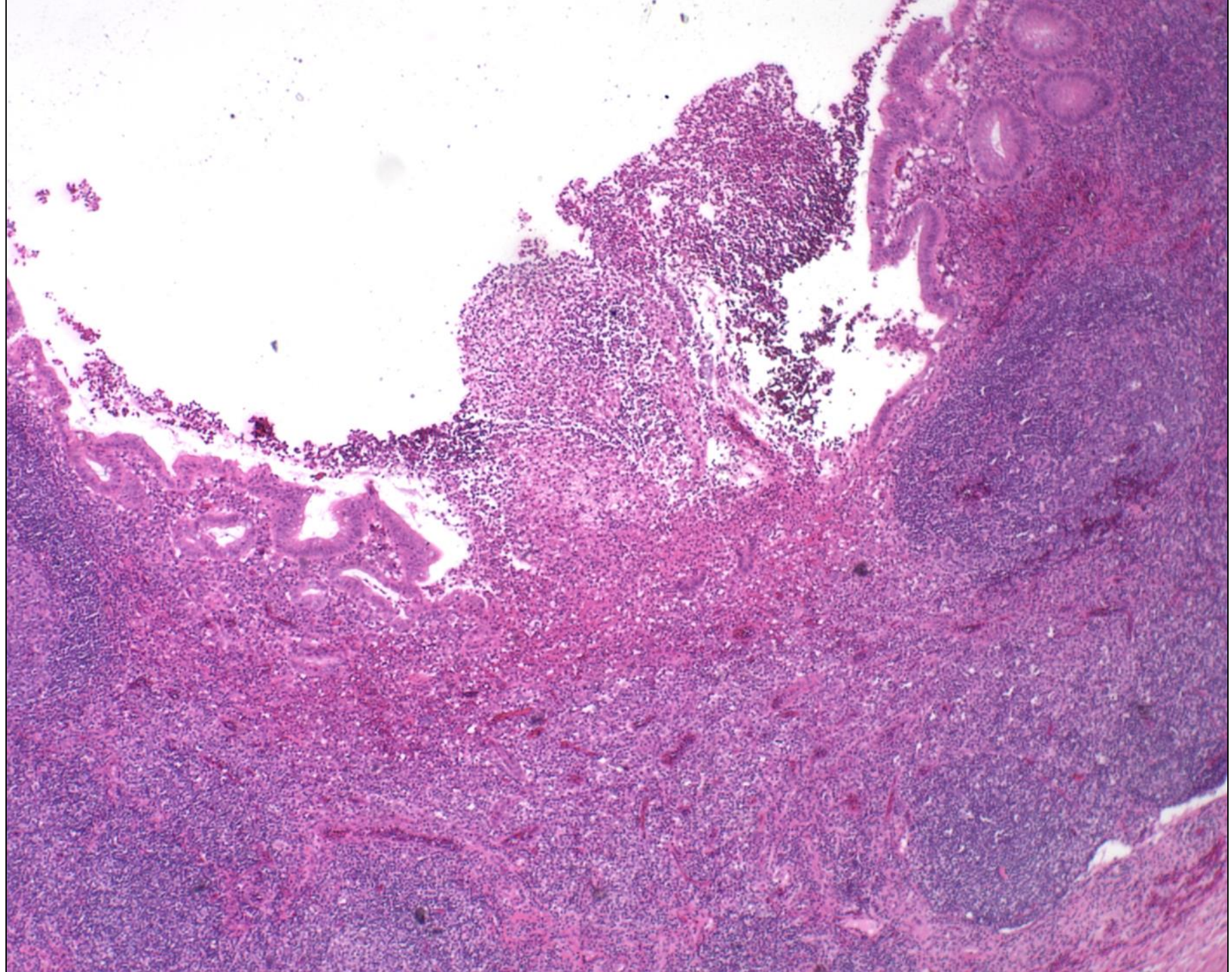
- Prince Edward VII, son of Queen Victoria
- Became ill two weeks before coronation in 1902
- Treves finally convinced him to undergo the operation, which lasted less than an hour and was successful

Earliest changes: serosal dullness, injection of vessels

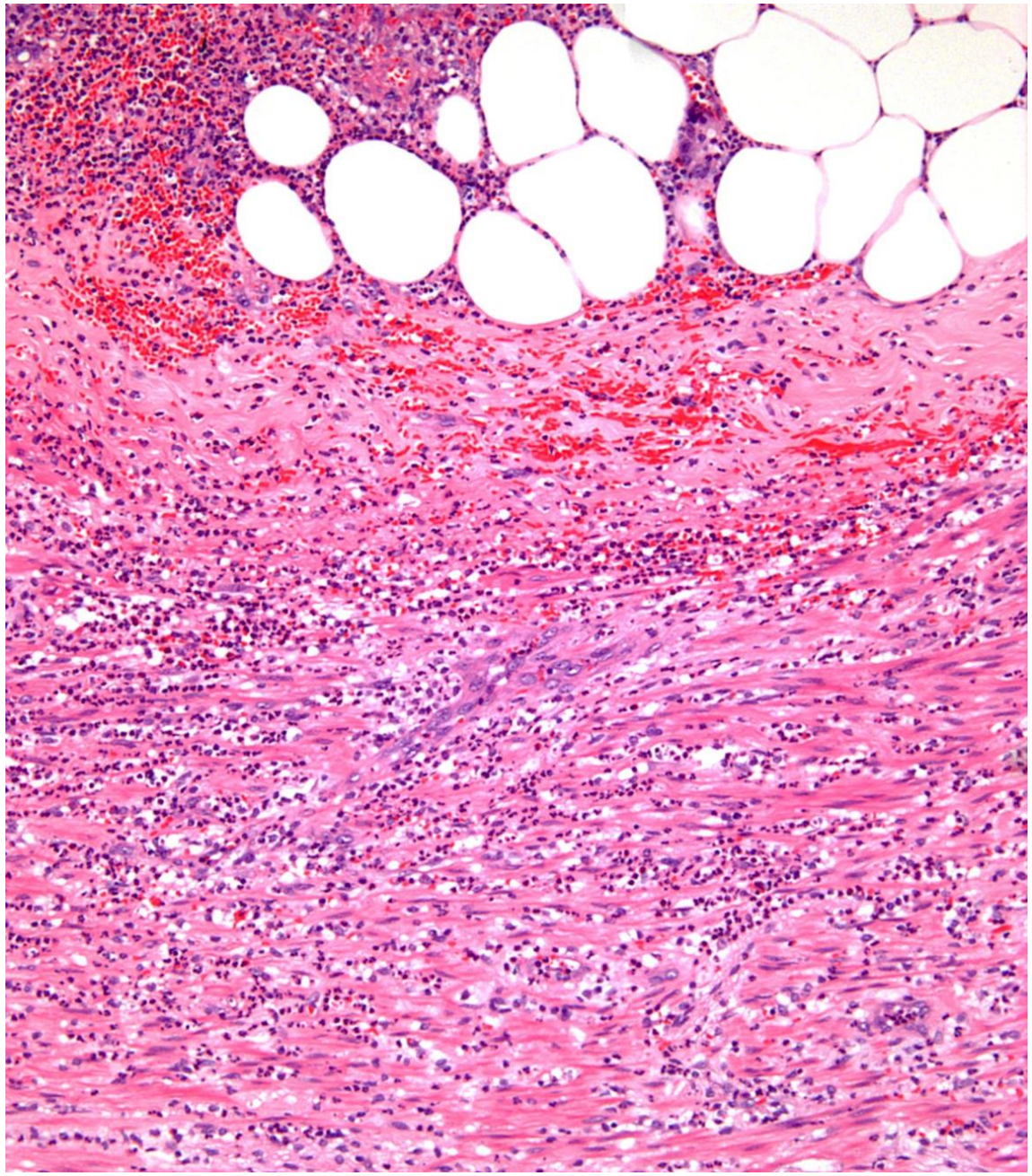
Increased serosal dullness and early hyperemia/exudate

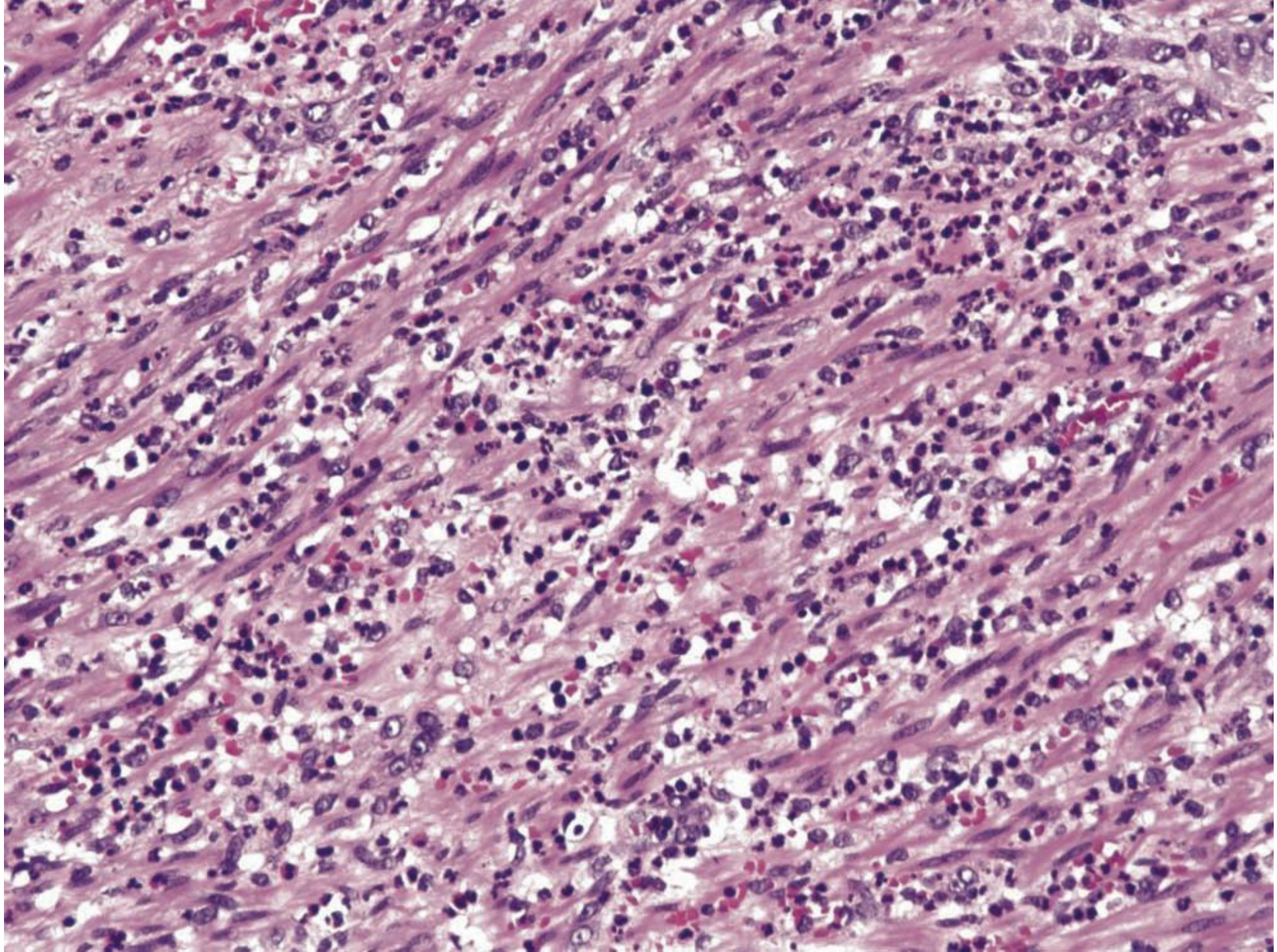
Over time, increasing hyperemia develops…..

……..and purulent exudate.

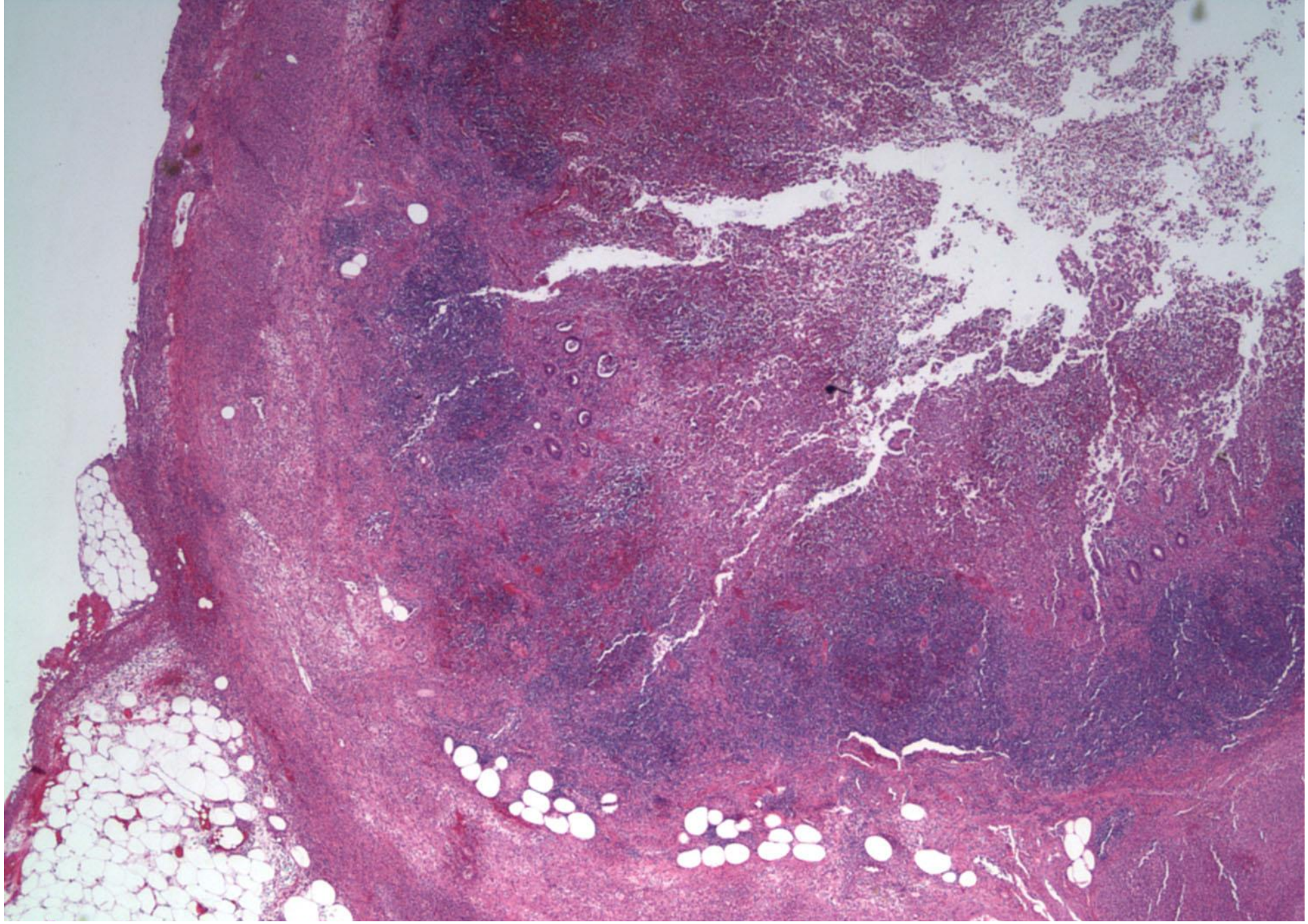


Edema and extension of the neutrophilic infiltrate across the muscularis mucosa into the submucosa, and eventually into muscularis propria





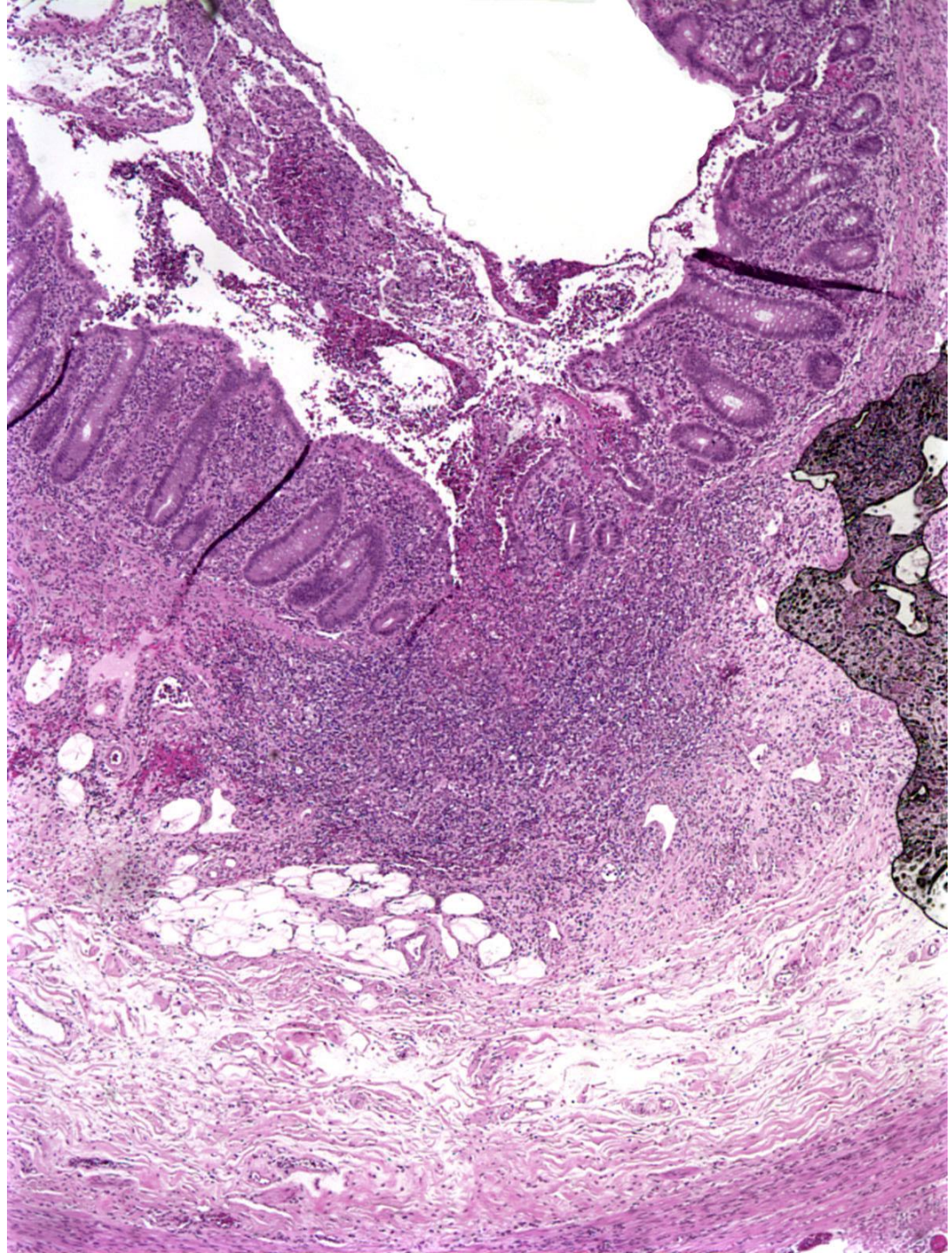
Gangrenous appendix with green-gray mural discoloration

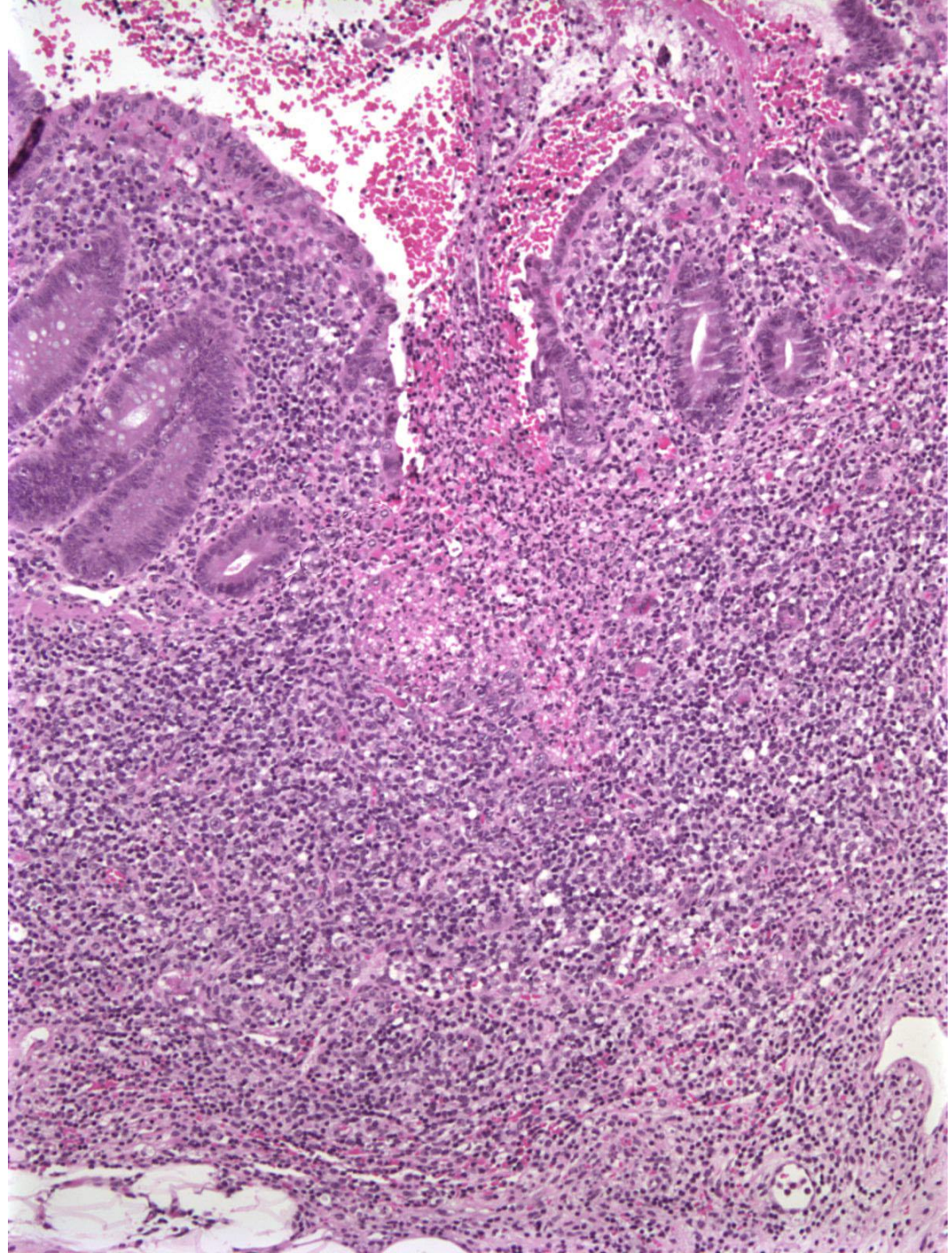


Eventual progression to transmural neutrophilic inflammation and necrosis

Acute Appendicitis
"minimal diagnostic criteria"

- Is acute inflammation limited to mucosa/superficial submucosa enough to diagnose acute appendicitis?
  - Also seen with fecaliths, infections
- Stated another way, does it explain the patient's symptoms?



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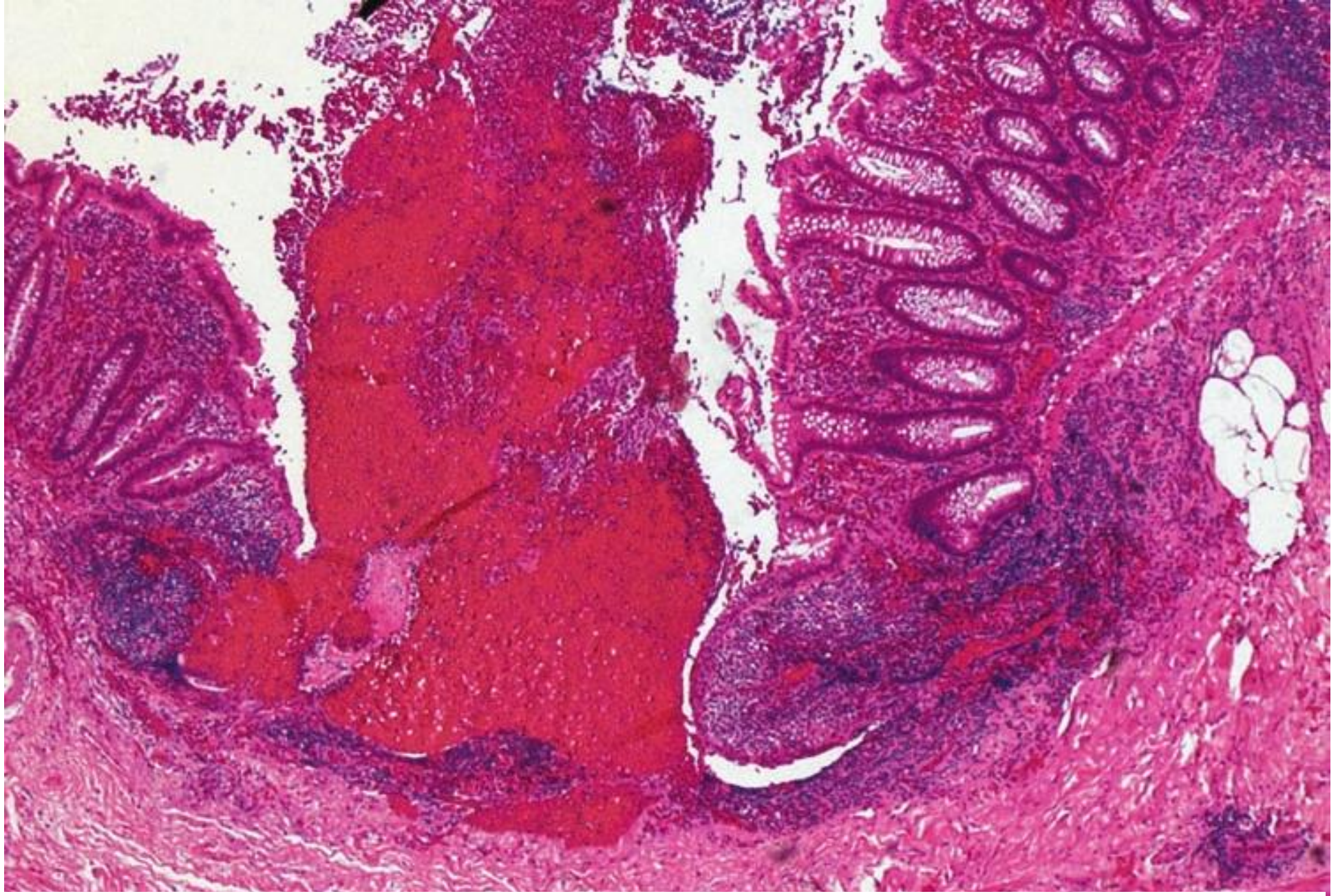


Campylobacter infection involving appendix

What does the literature say?
Back to the Bucket

- Williams and Myers study
  - More than 1000 appendectomies
  - Detailed correlation of clinical, surgical, and pathological information
  - Found that mucosal neutrophilic infiltrates (usually with cryptitis or ulceration) represented the early stage of acute suppurative appendicitis, and that more sections usually led to finding neutrophils in wall

Acute Nonspecific Appendicitis
Differential Diagnosis

- Periappendicitis/extra-appendiceal cause of inflammation
  - Pelvic inflammatory disease
  - Other intra-abdominal disease processes
- Infection
- Vasculitis

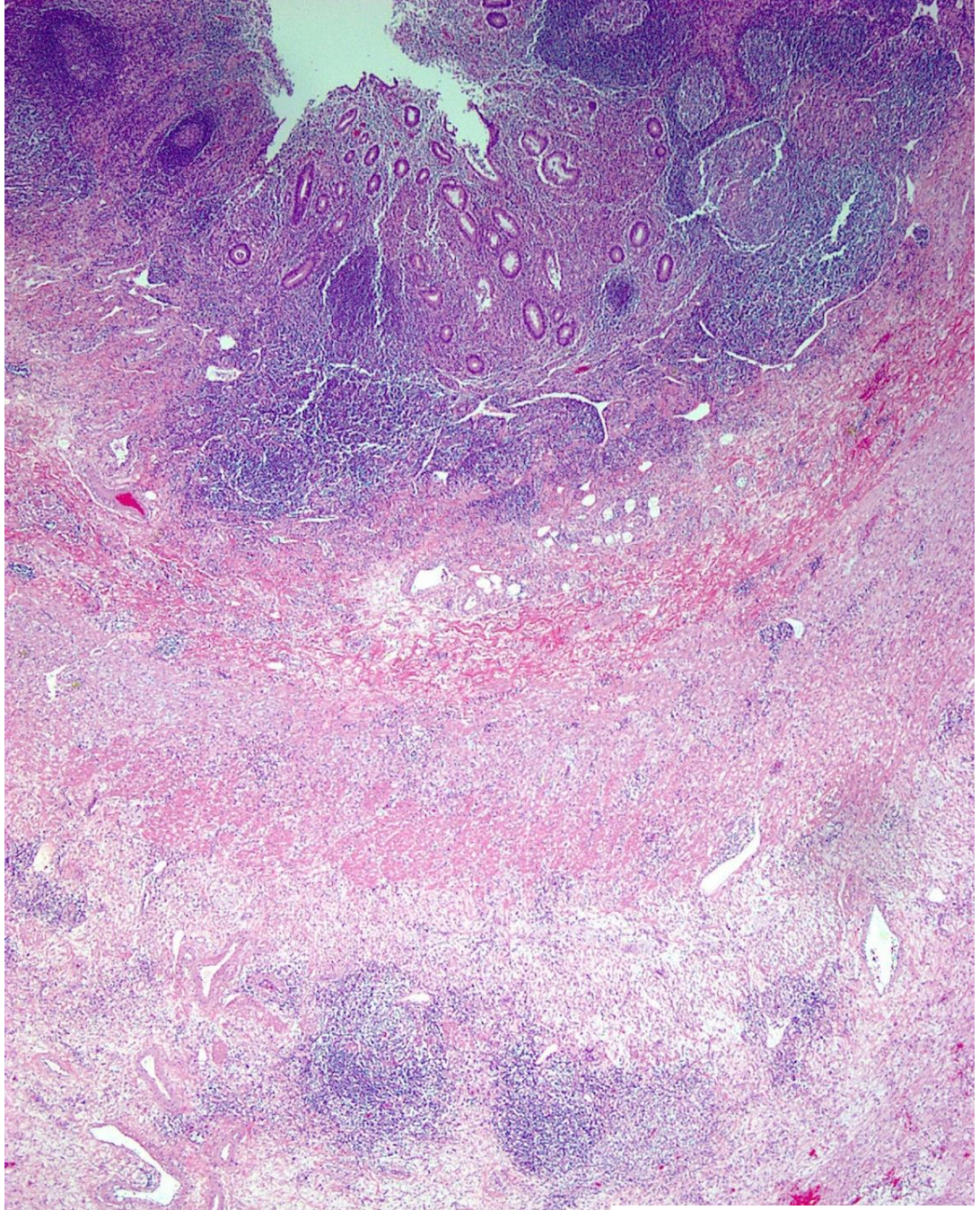
Acute Nonspecific Appendicitis
Differential Diagnosis

- Appendiceal diverticula/diverticulitis
- Chronic idiopathic inflammatory bowel disease
  - Ulcerative colitis
    - Usually contiguous from cecum
    - May have appendiceal “patch”
  - Crohn’s disease
    - 40% of patients with ileocecal disease have appendiceal involvement

Bronner MP. Granulomatous appendicitis and the appendix in idiopathic inflammatory bowel disease. Sem Diag Pathol 21:98-107, 2004.

Ulcerative colitis, appendix

Normal appendix



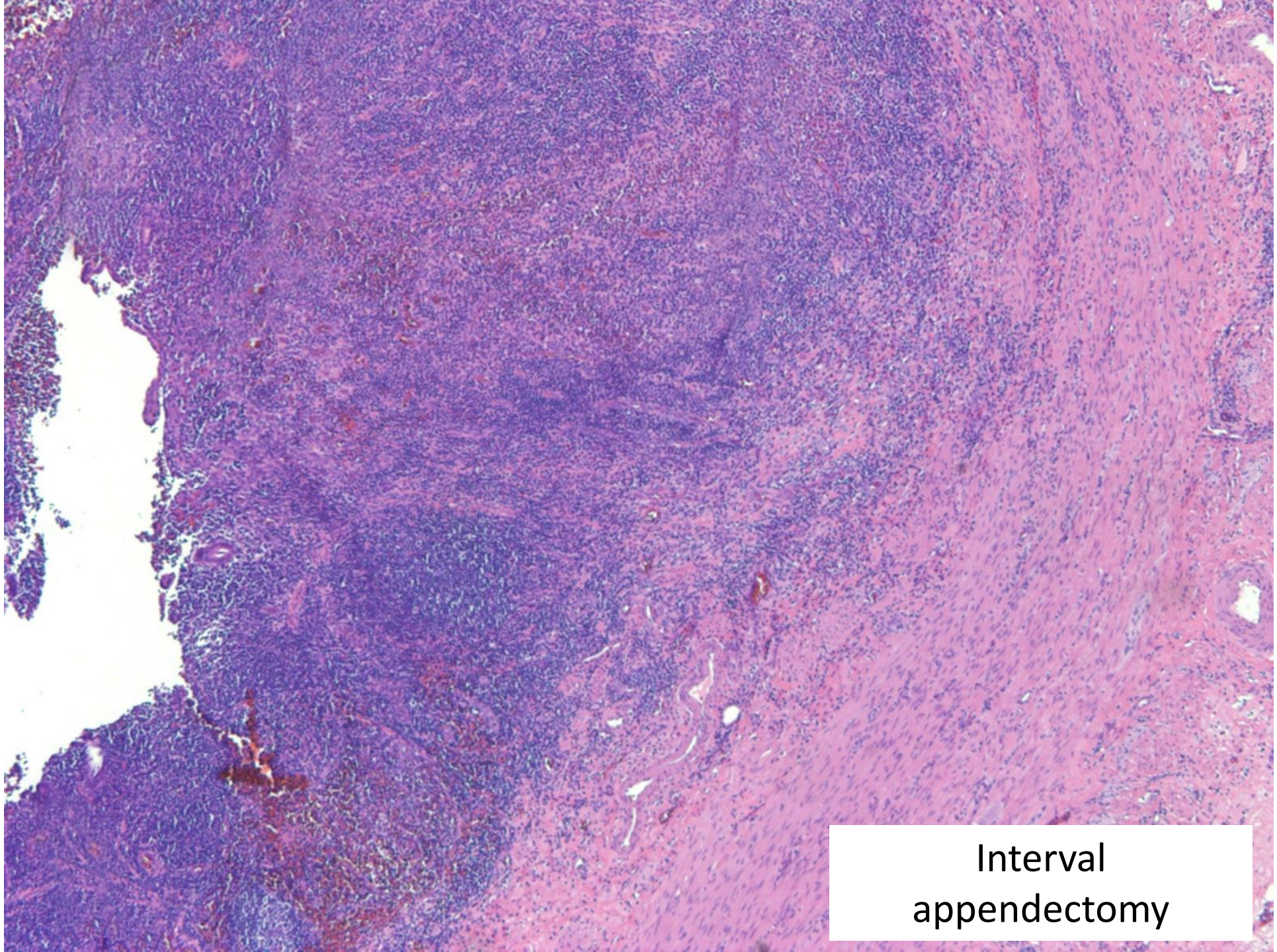
Crohn’s disease, appendix

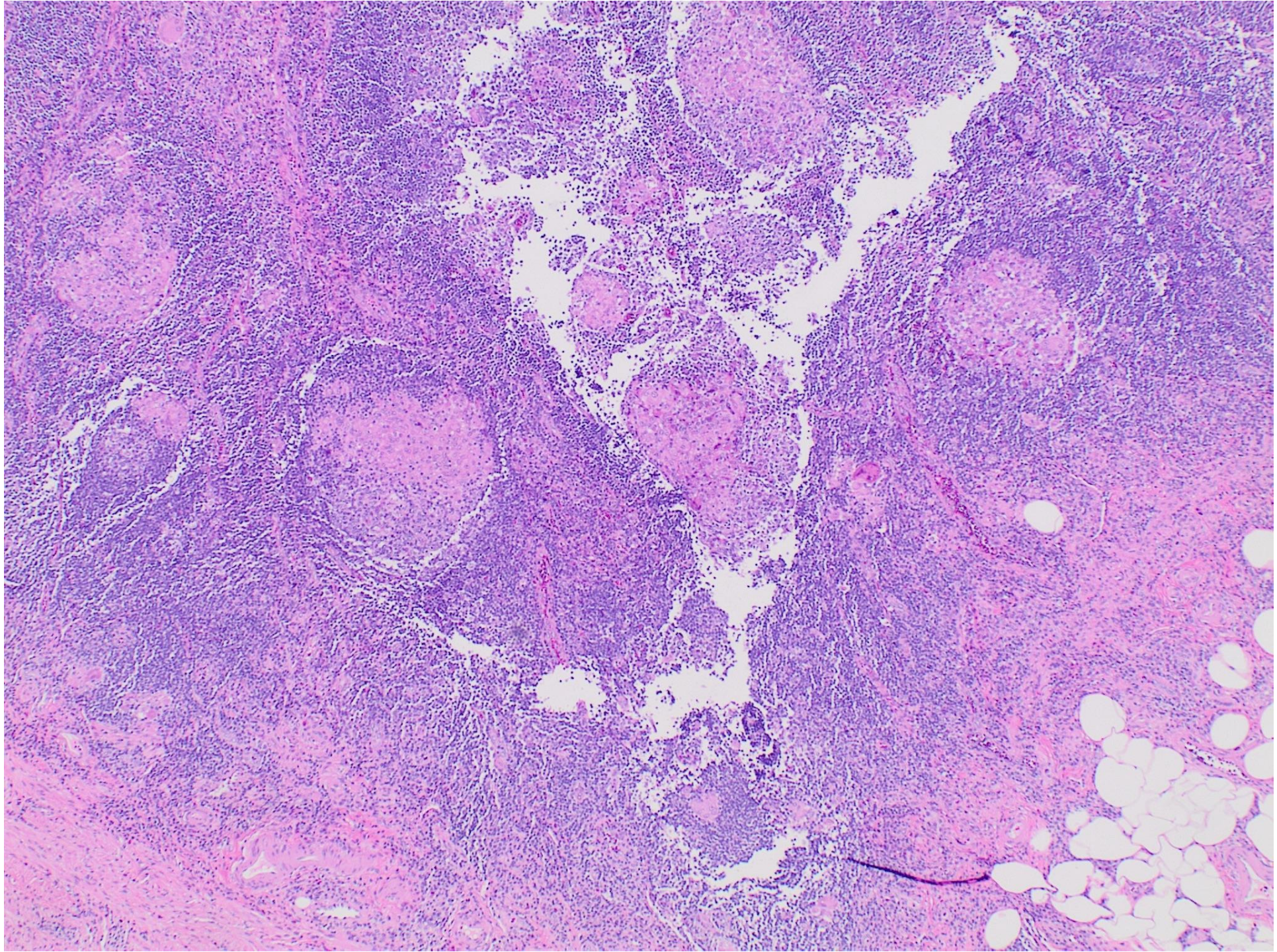

I think my caterpillar has appendicitis.

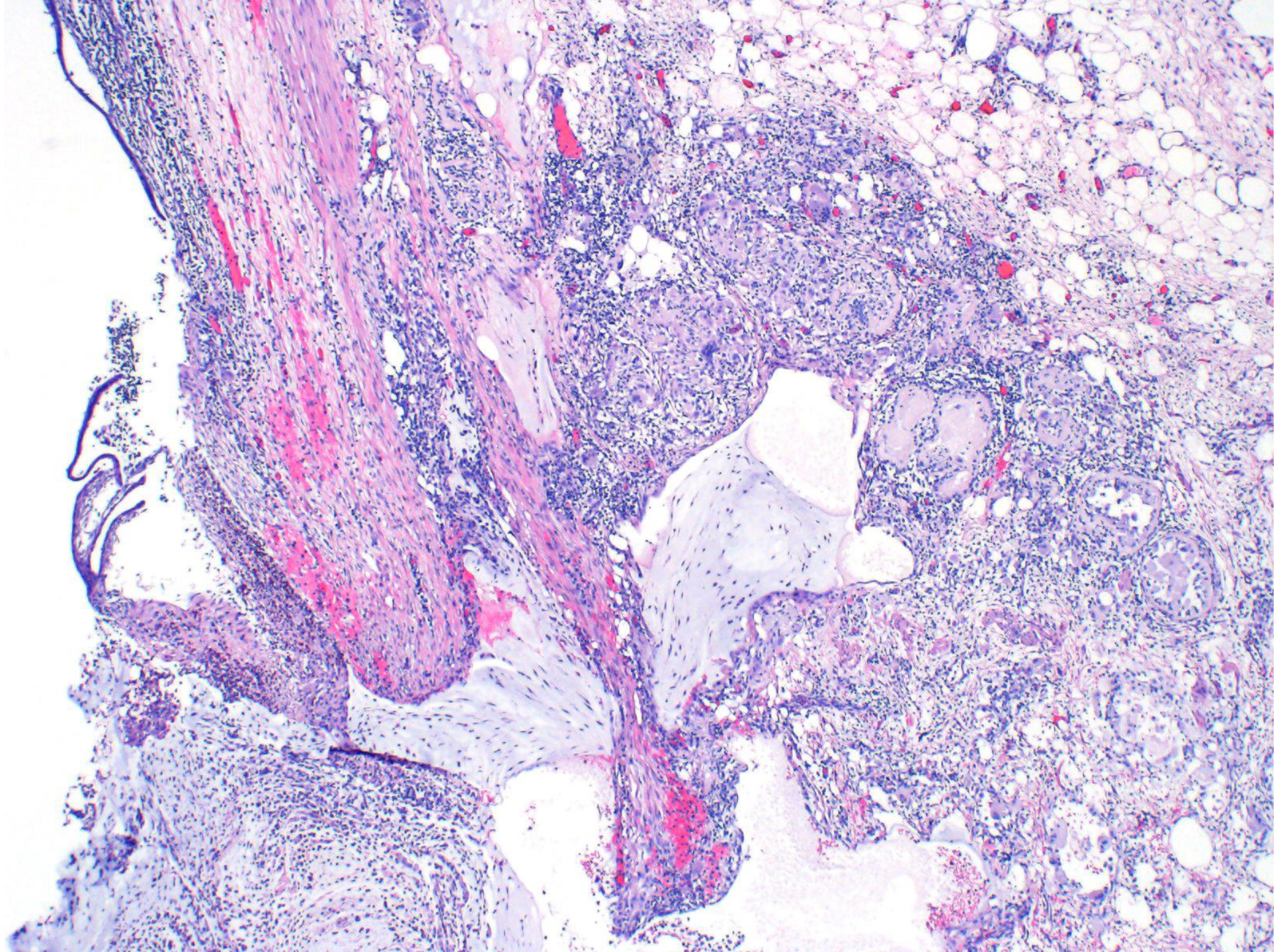
What about "chronic appendicitis?"

- There are chronic appendiceal infections (e.g. tuberculosis)
- Some patients have recurrent or smoldering AA before resection
  - Appendix with scarring, plasmacytic infiltrate-probably resolving or ongoing AA
- Interval/delayed appendectomies show chronic changes
- Primary chronic appendicitis should not be used
  - Luminal fibrosis with mild chronic inflammation is not chronic appendicitis

Guo G, Greenson JK. Histopathology of interval (delayed) appendectomy specimens. Am J Surgical Pathol 27:1147-51, 2003.


Interval
appendectomy






Just don’t get her started on that infectious stuff. She’ll never stop.

Selected Infectious Agents Affecting the Appendix

Parasites	Bacteria	Viruses
Pinworms	*Yersinia*	Adenovirus
Amoeba	*Campylobacter*	EBV
Schistosomes	*Actinomyces*	CMV
Strongyloides stercoralis	Tb/atypical mycobacteria	Measles
Other helminths	*Salmonella* *Shigella*	

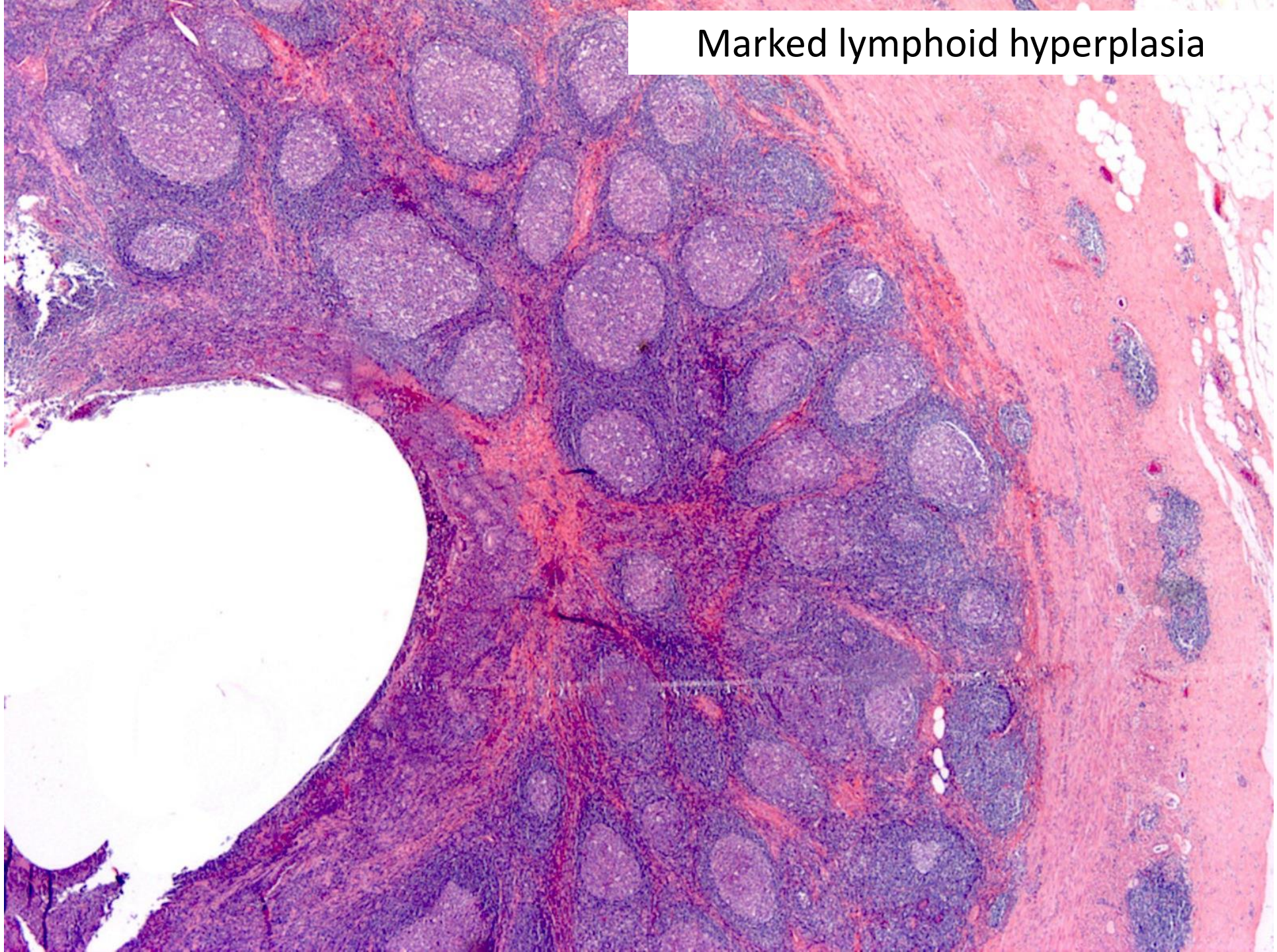
Appendix-Viral Infections

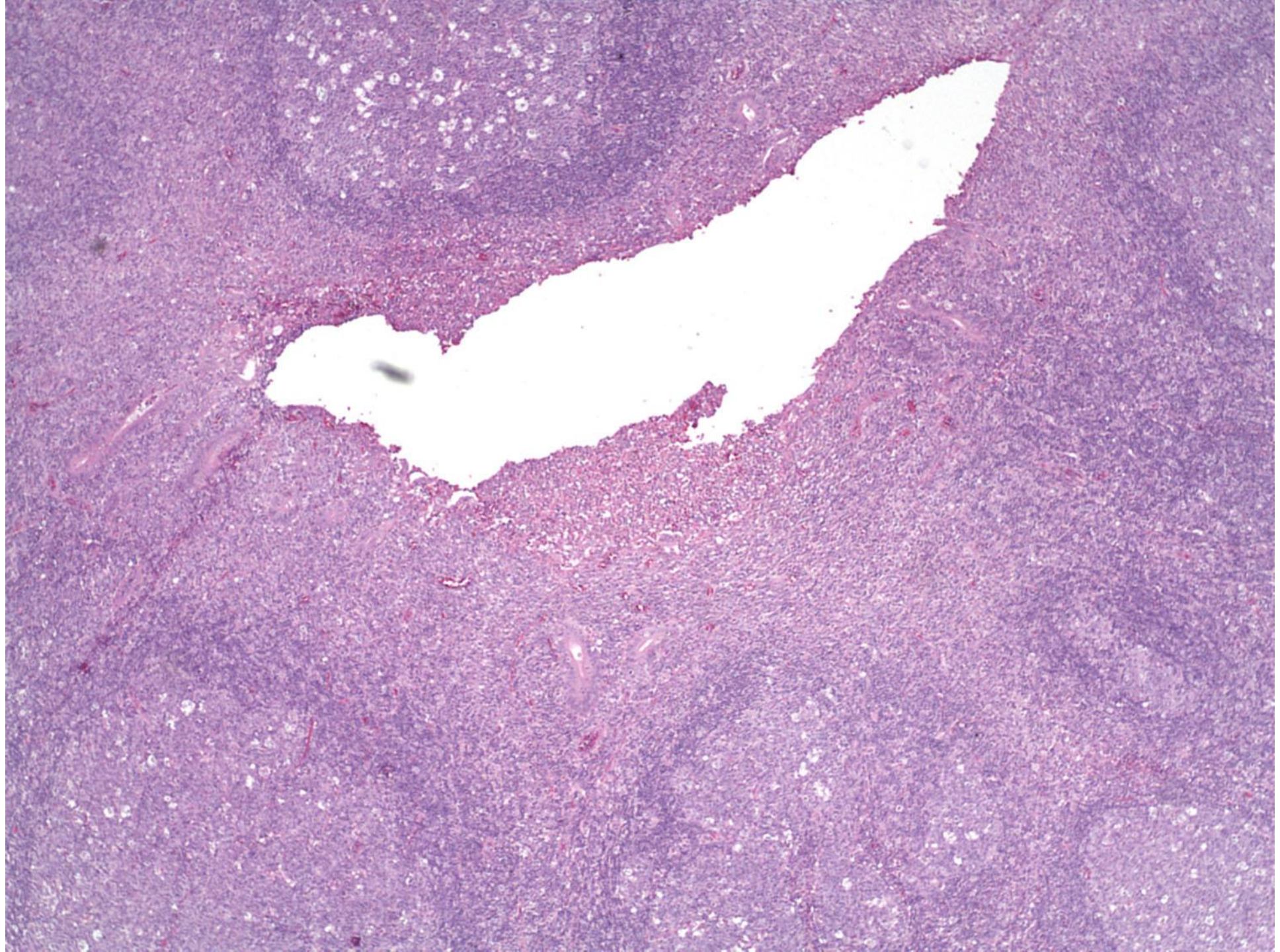
- Adenovirus
- Measles
  - May precede prodrome and rash
- CMV
  - Almost always AIDS patients
- Epstein-Barr virus
  - Usually in context of mononucleosis

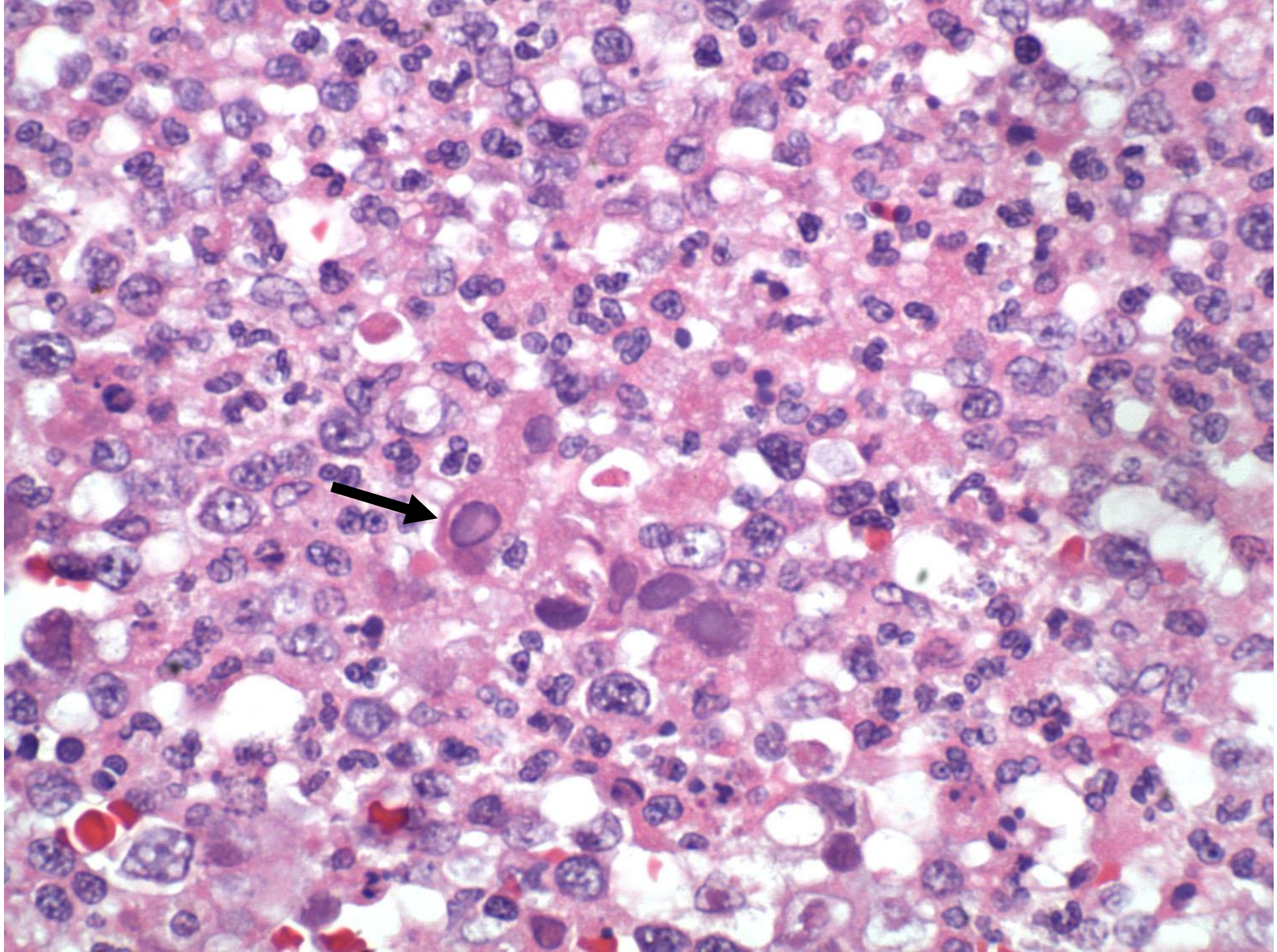
Adenovirus in the Appendix

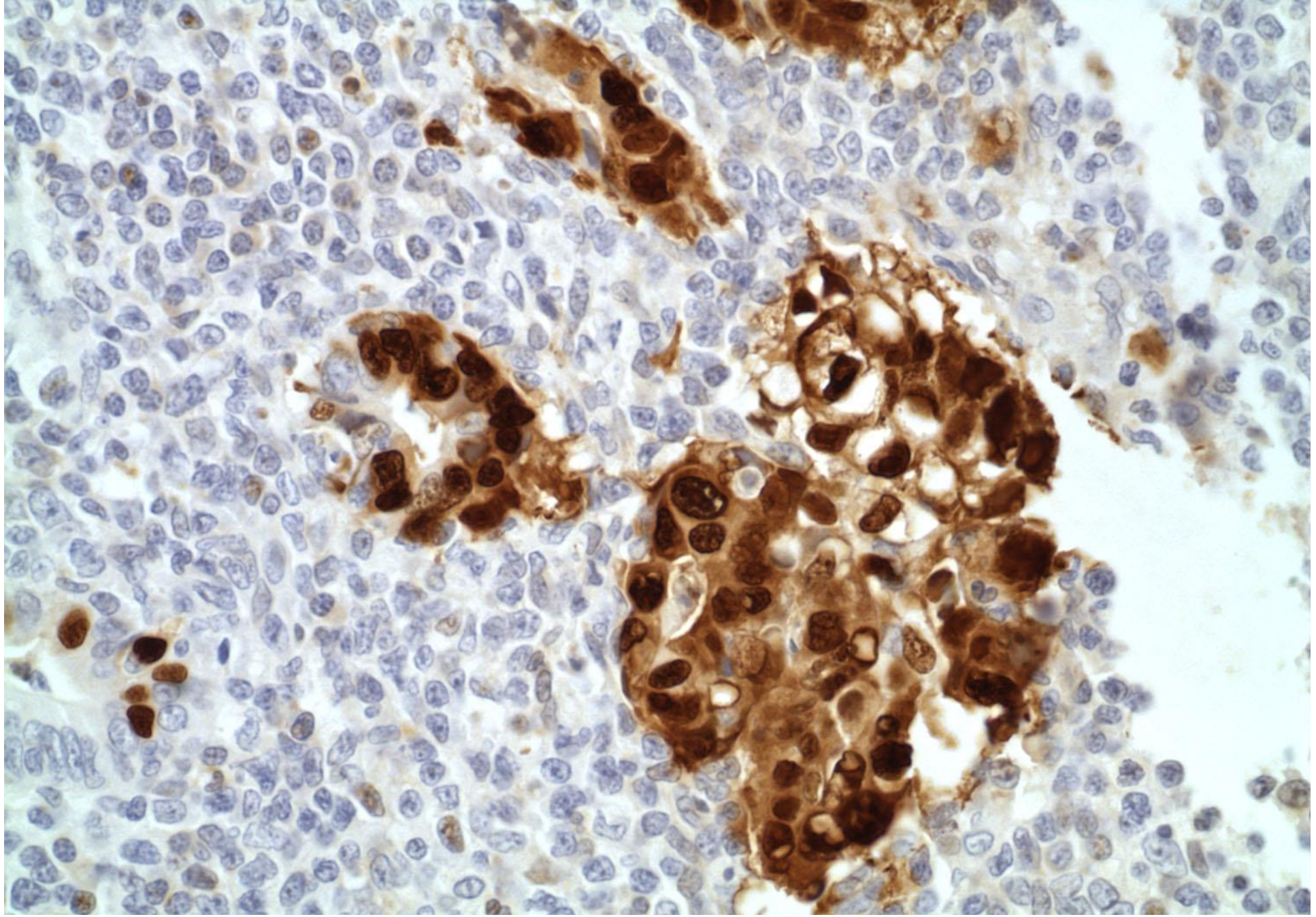
- Associated with ileal and cecal intussusception
- Most often in children
- Patients usually do not have signs and symptoms of acute appendicitis

Yunis EJ, Atchison RW, Michaels RH, DeCicco FA. Adenovirus and ileocecal intussusception. Lab Invest 33:347-51, 1975.

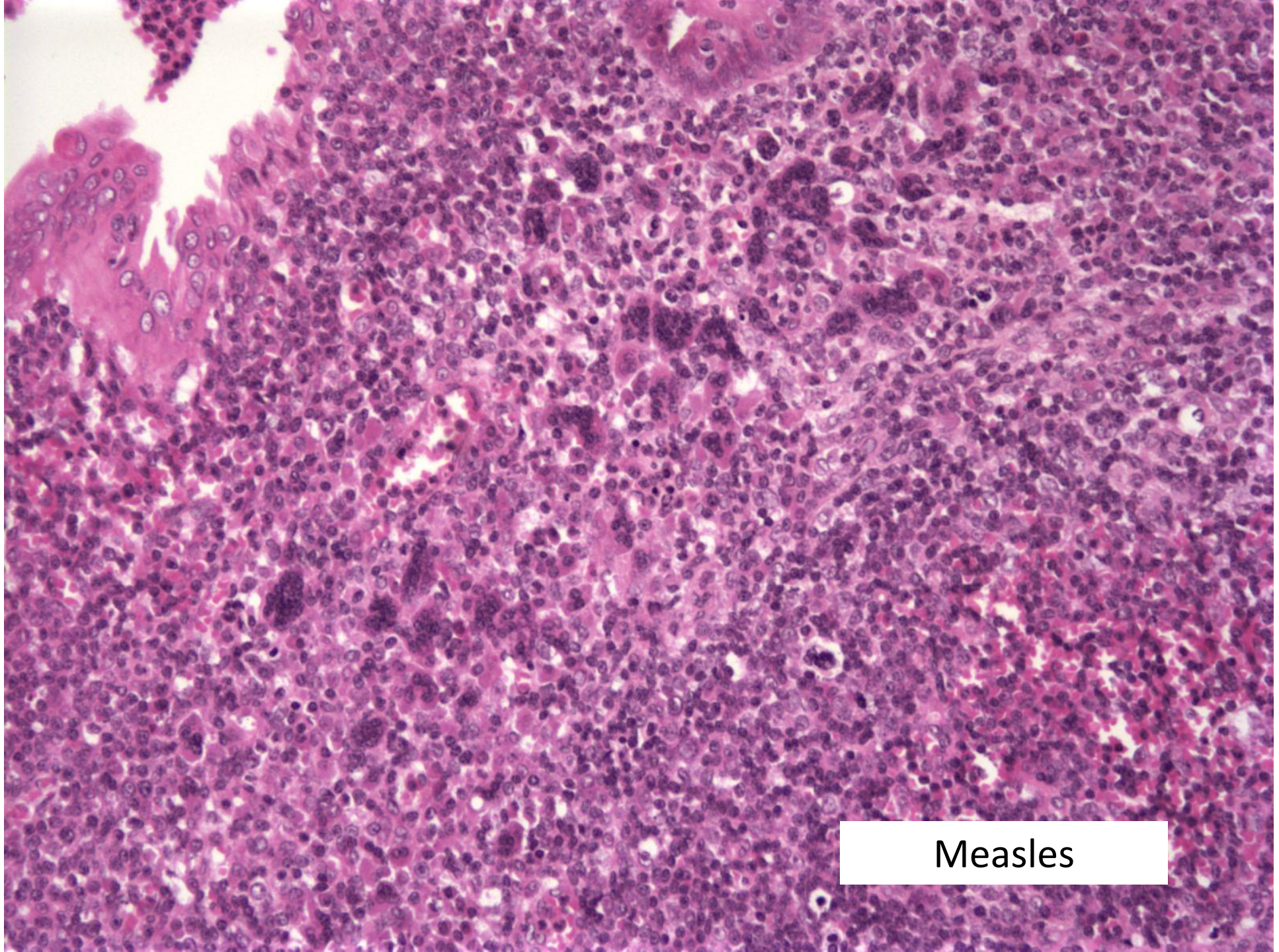

Marked lymphoid hyperplasia

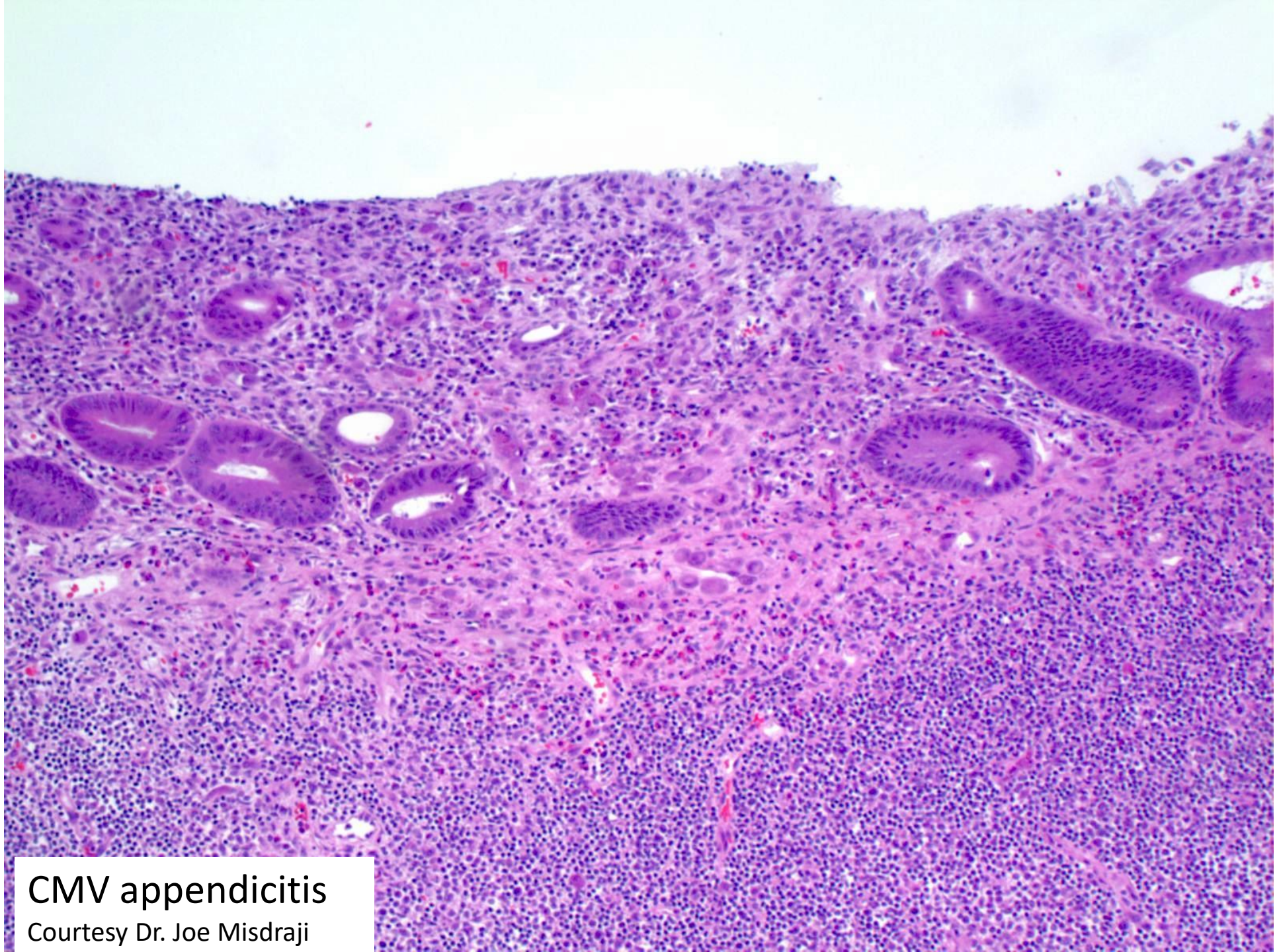






Adenovirus immunostain highlights intra-epithelial inclusions


Measles



CMV appendicitis

Courtesy Dr. Joe Misdraji

Appendix-Bacterial Infections

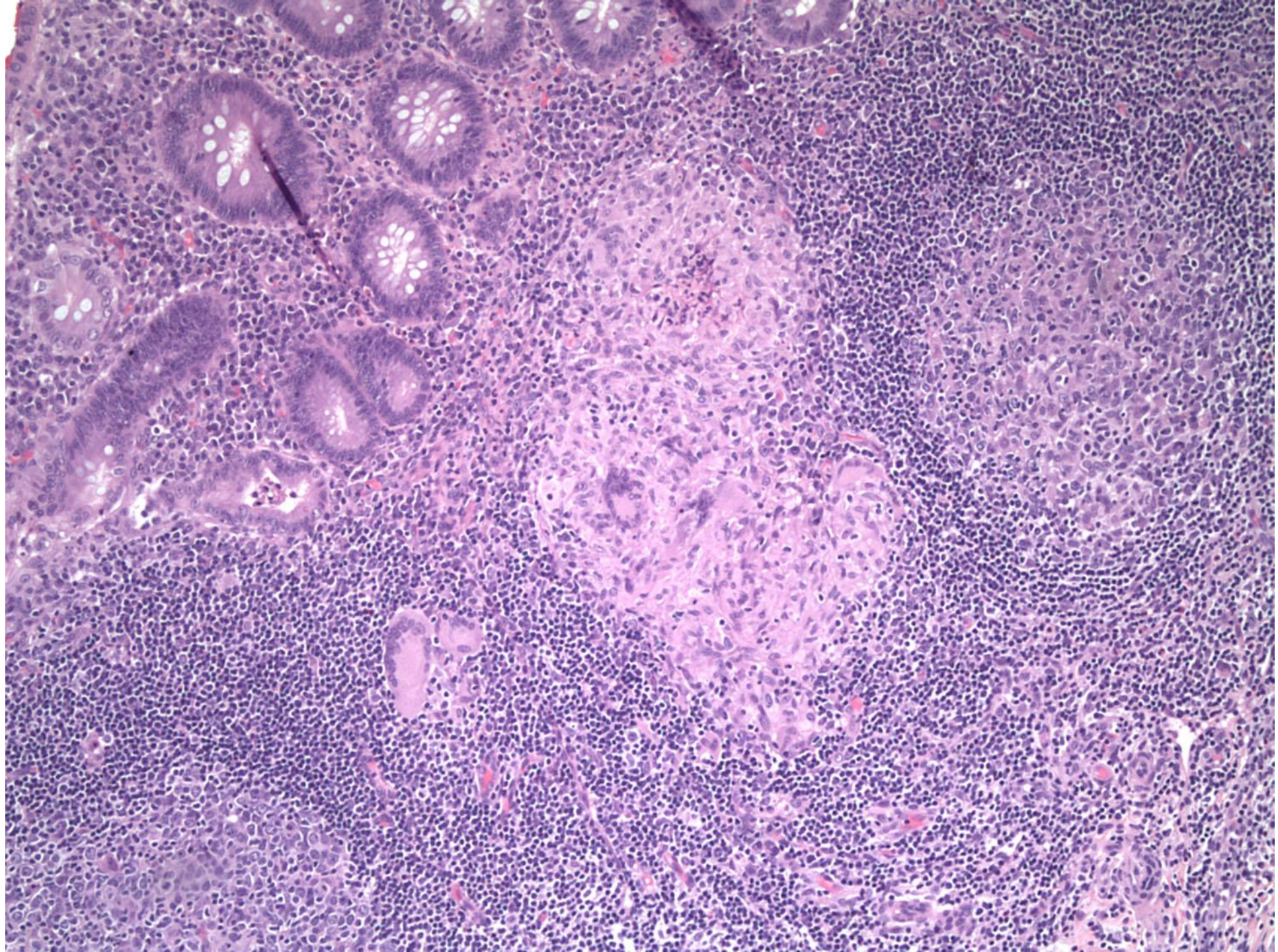
- *Yersinia* species
- *Actinomyces israelii*
- Tuberculosis
- Enteric infections from colon
  - Rare; *Salmonella, Shigella, Campylobacter*
- *C. difficile*

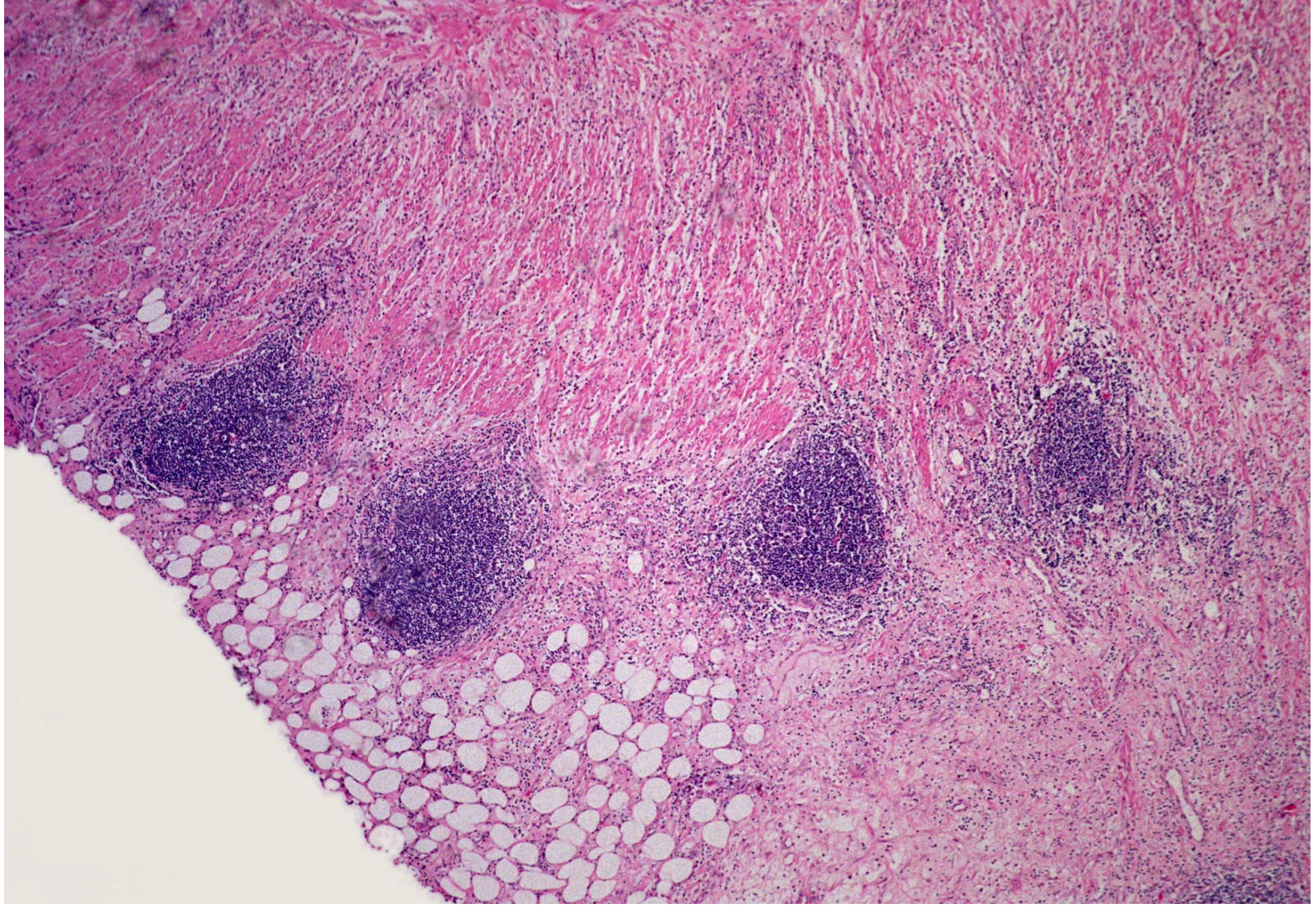
Yersinia Appendicitis

- Gram negative bacilli cause wide range of GI diseases
- Present in many food sources
- *Yersinia* (*enterocolitica* and *pseudotuberculosis*) responsible for about 25% of granulomatous appendicitis
- Usually self limited
- Diagnosis:
  - PCR and high index of suspicion
  - Culture and serologies less useful

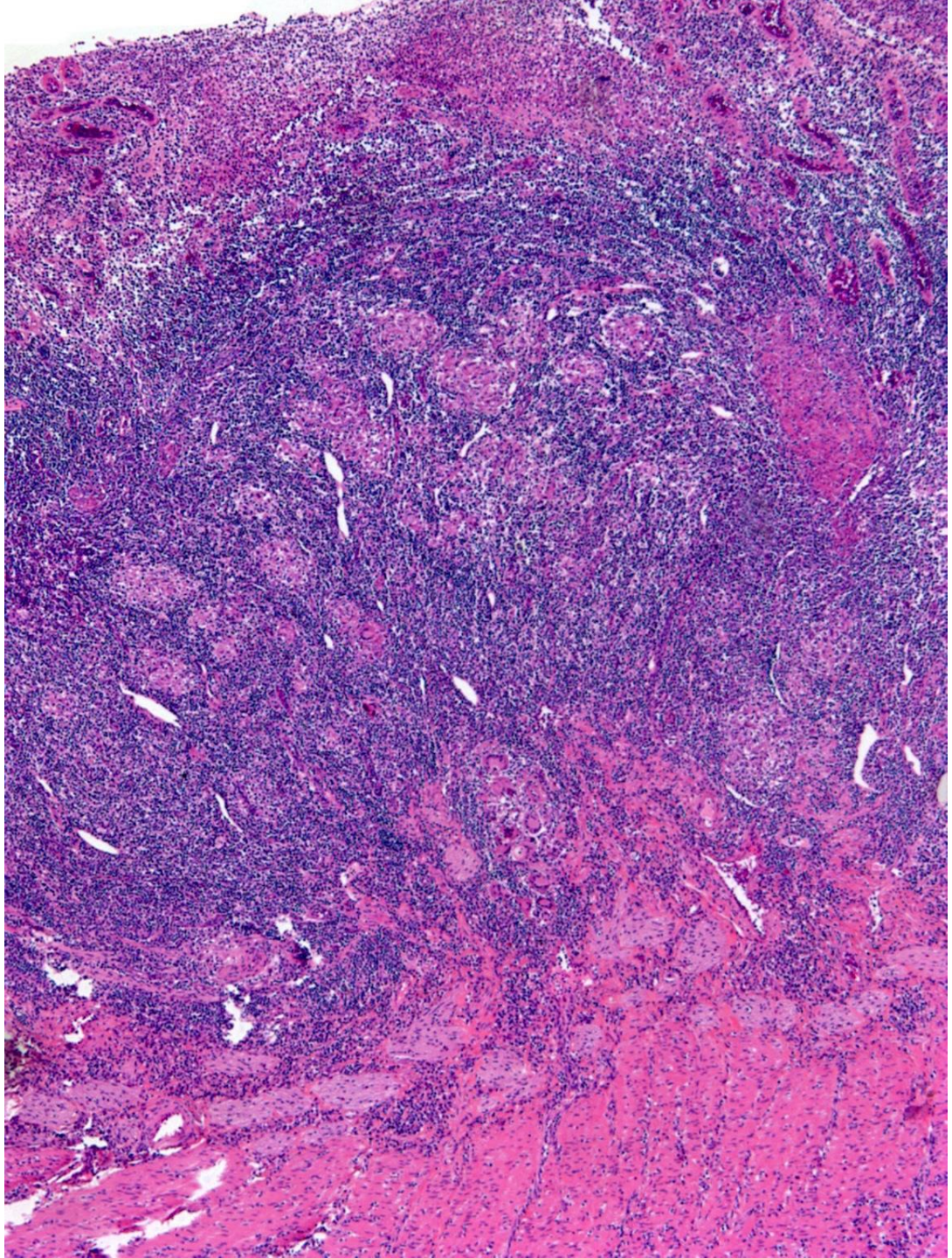
Nodular mucosa overlying thickened wall

Lymphoid hyperplasia and epithelioid granulomas





Linear array of lymphoid aggregates



Crohn’s disease is main entity in differential diagnosis

Isolated granulomatous appendicitis is Crohn’s disease less than 10% of the time

Dudley TH, Dean PJ. Idiopathic granulomatous appendicitis, or Crohn's disease of the appendix revisited. Hum Pathol 24:595-601, 1993.

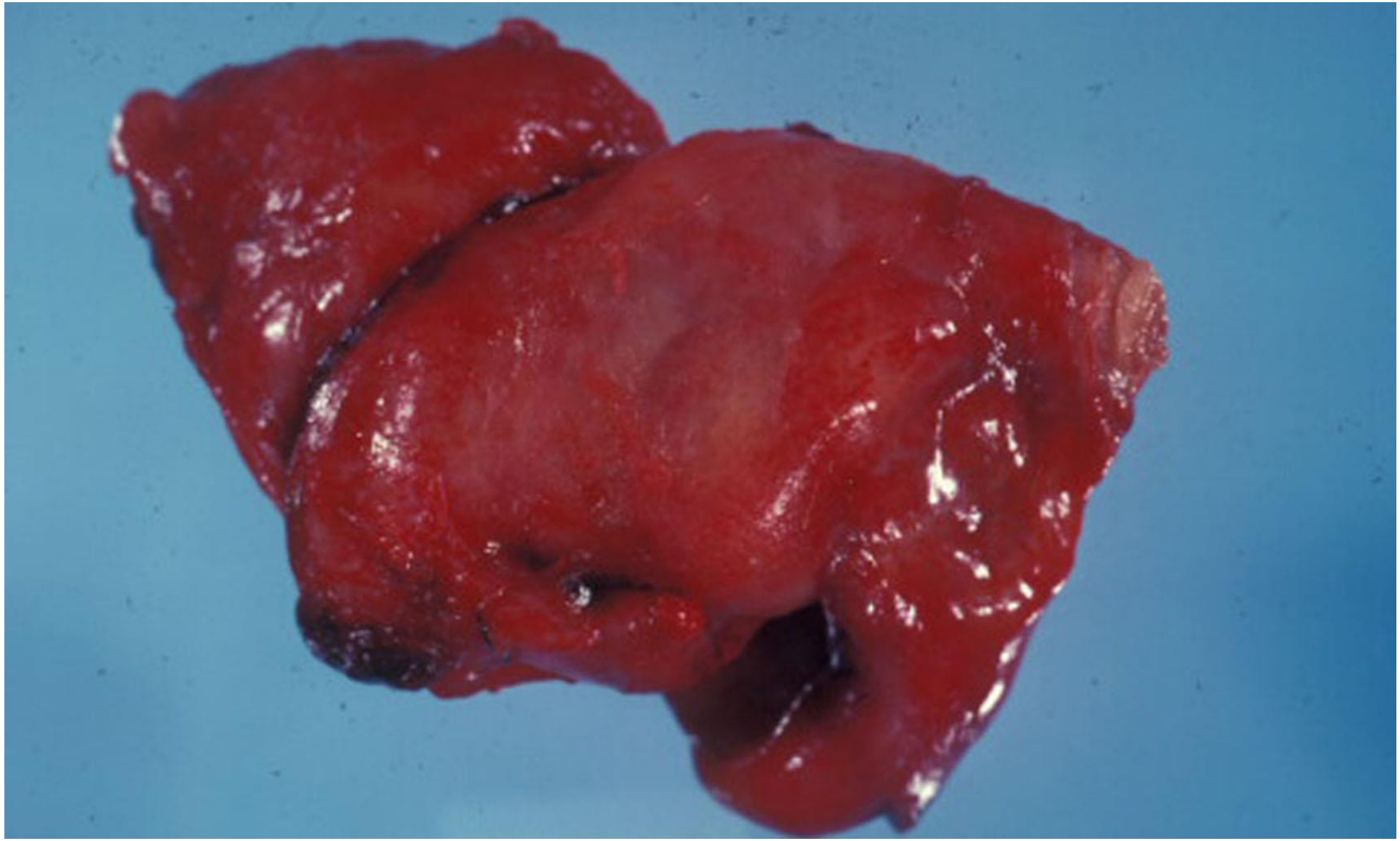
Lamps LW, Madhusudhan KT, Greenson JK, et al. The role of *Y. enterocolitica* and *Y. pseudotuberculosis* in granulomatous appendicitis: a histologic and molecular study. Am J Surg Pathol 25:508-15, 2001.

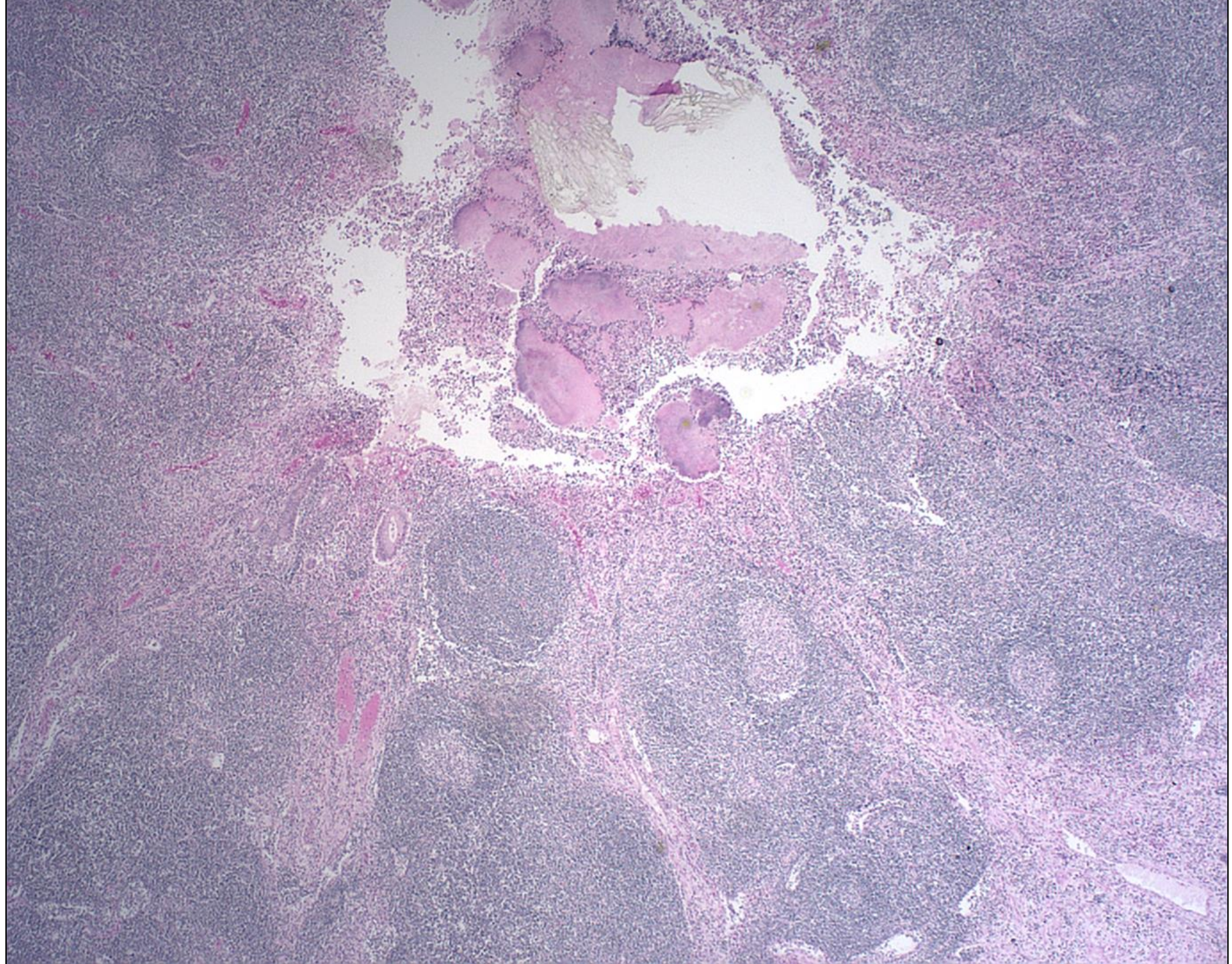
Huang JC, Appelman HD. Another look at chronic appendicitis resembling Crohn's disease. Mod Pathol 9(10):975-981, 1996.

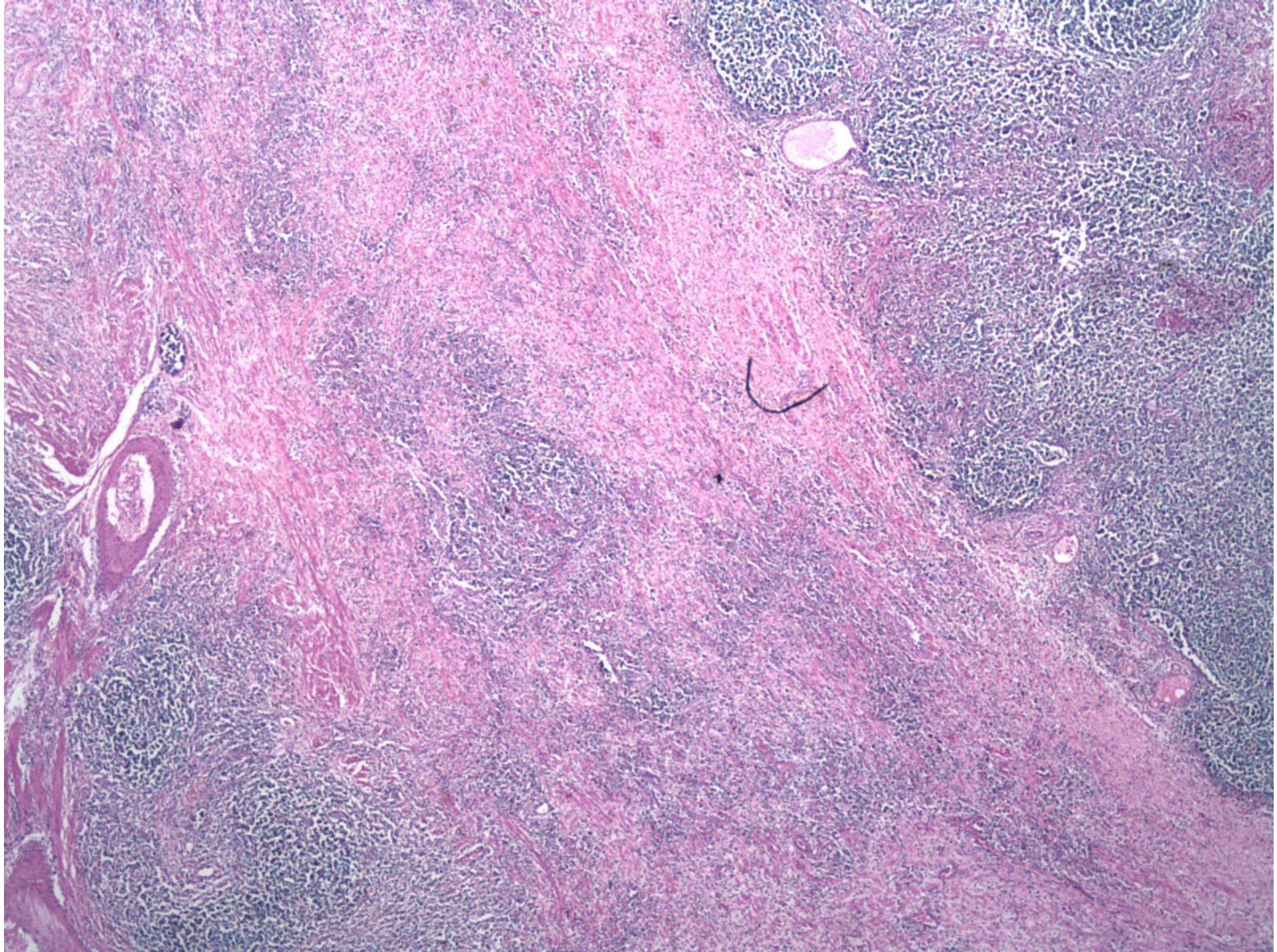
Actinomycosis: *Actinomyces israelii*

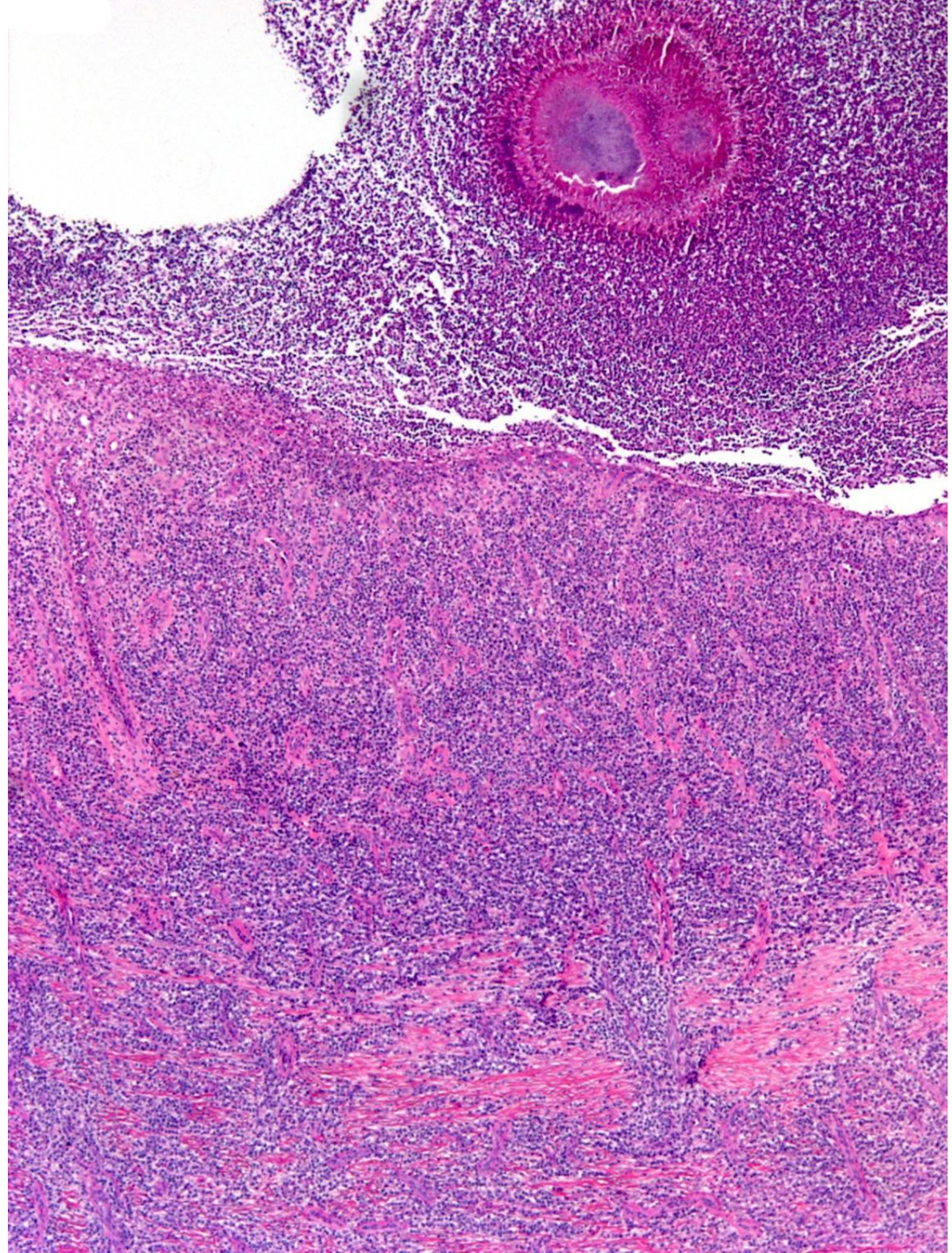
- Normal commensal
- Any level of GI tract
- Usually solitary mass, invading adjacent structures
  - Sometimes associated with diverticulosis
- Symptoms:
  - Acute appendicitis
  - Fever, abdominal pain
  - +/- palpable mass

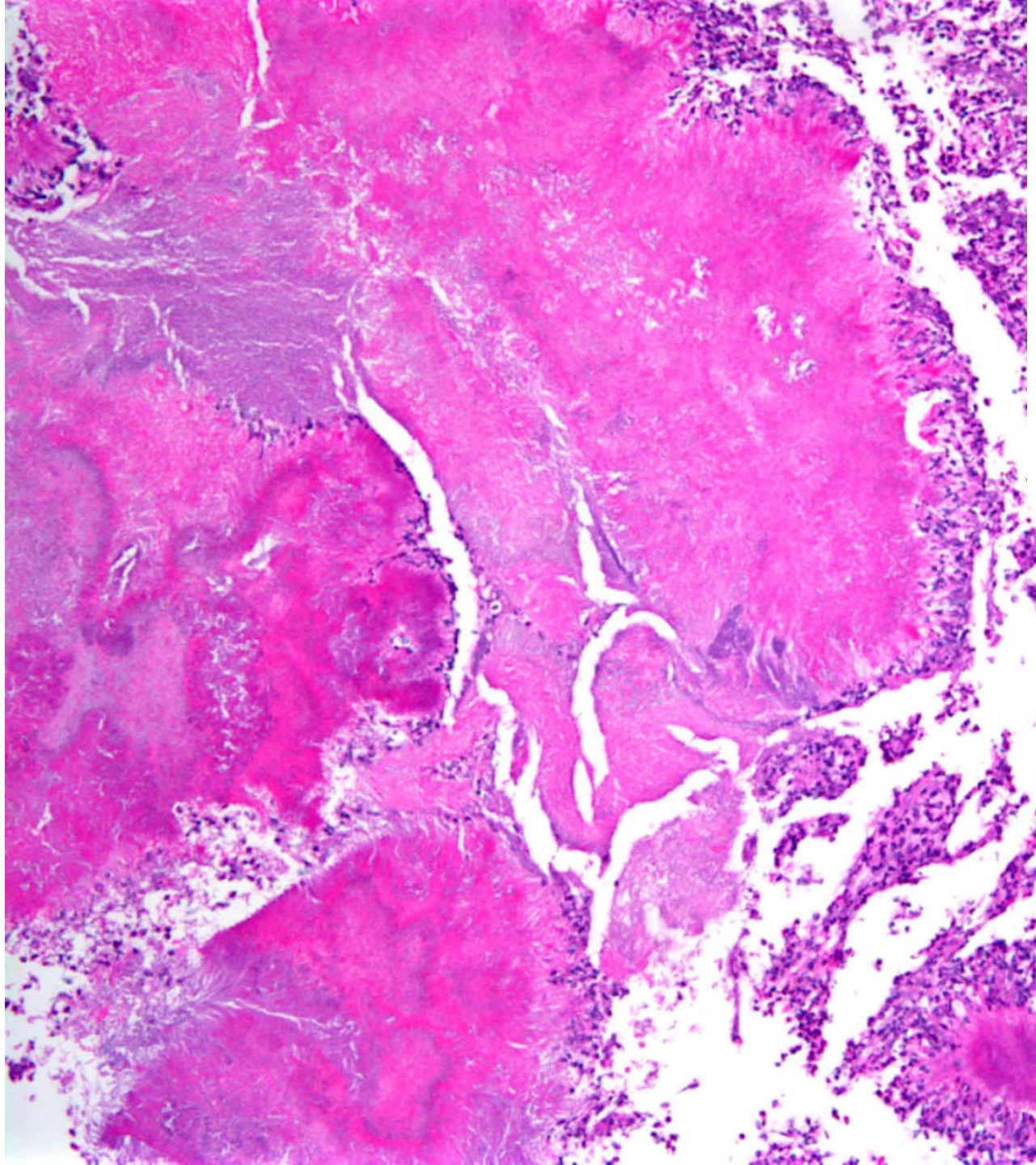
Horvath BA, Maryamchik E, et al. Actinomyces in Crohn's-like appendicitis. Histopathology 2019;75:486-95.







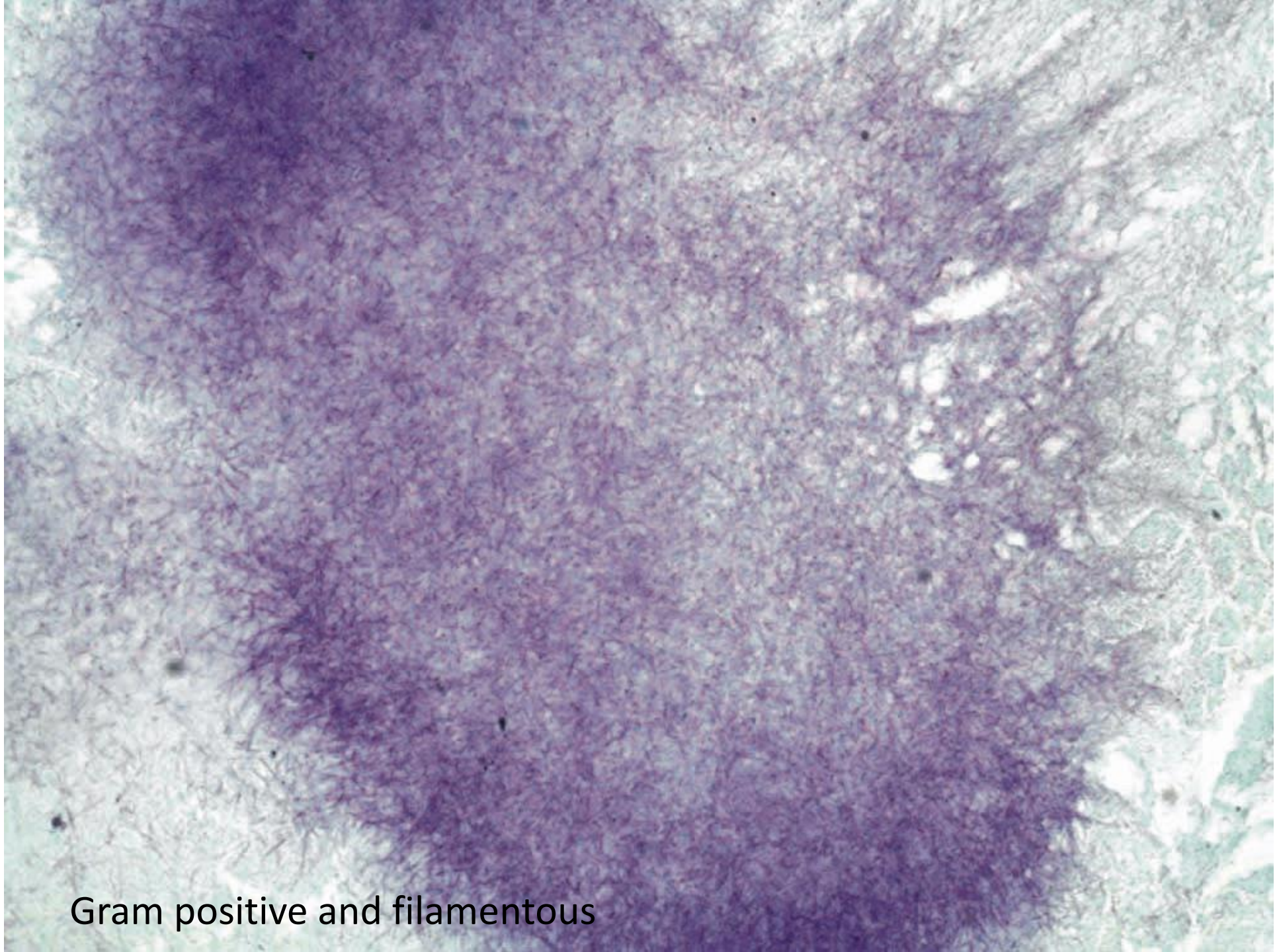




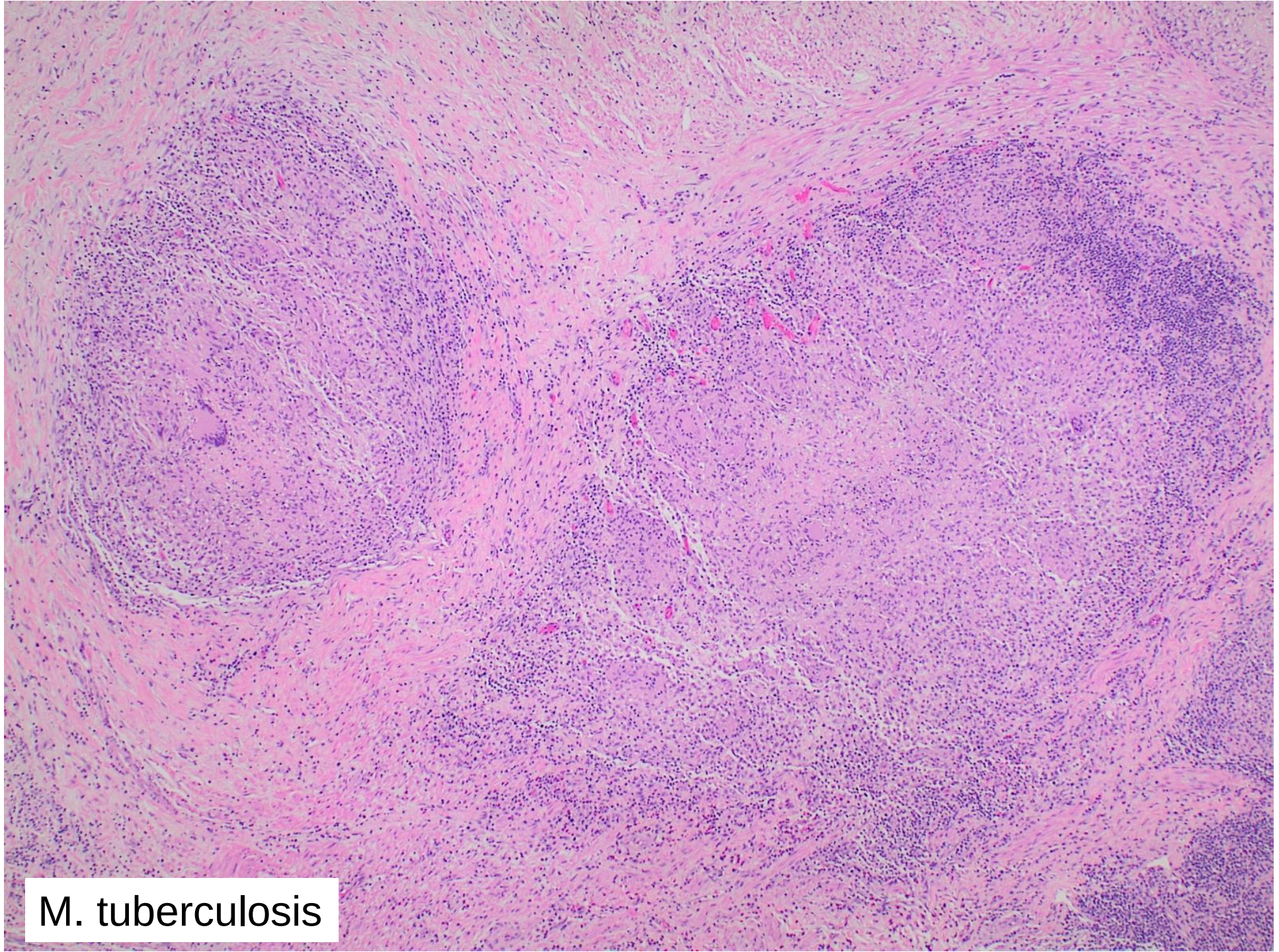
DDx:
Nocardia (partially acid fast)

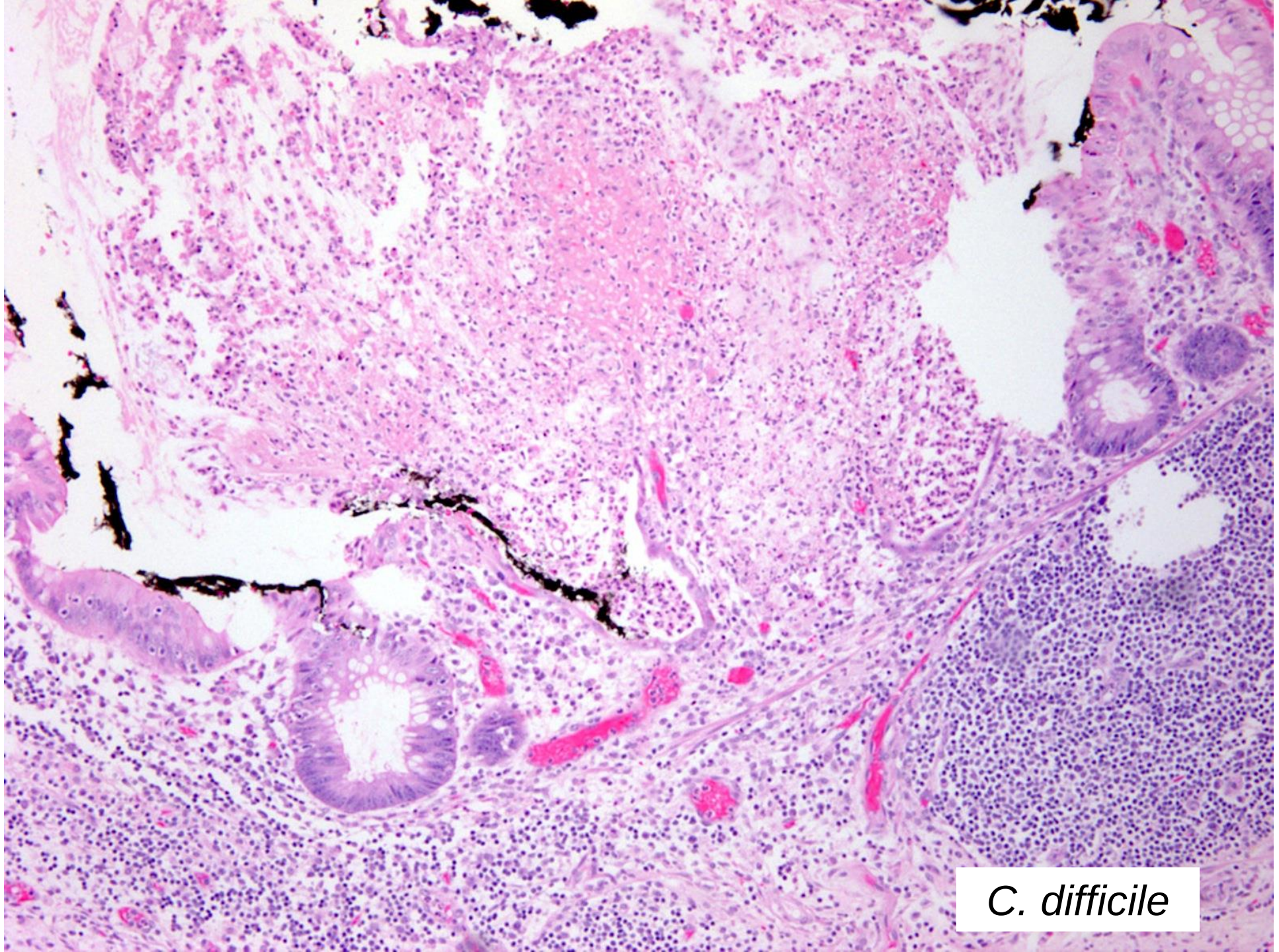
Other bacteria that form clusters or chains, but are not truly filamentous, e.g. *Pseudomonas, E. coli*

Splendore-Hoeppli protein is helpful



Gram positive and filamentous


M. tuberculosis


C. difficile

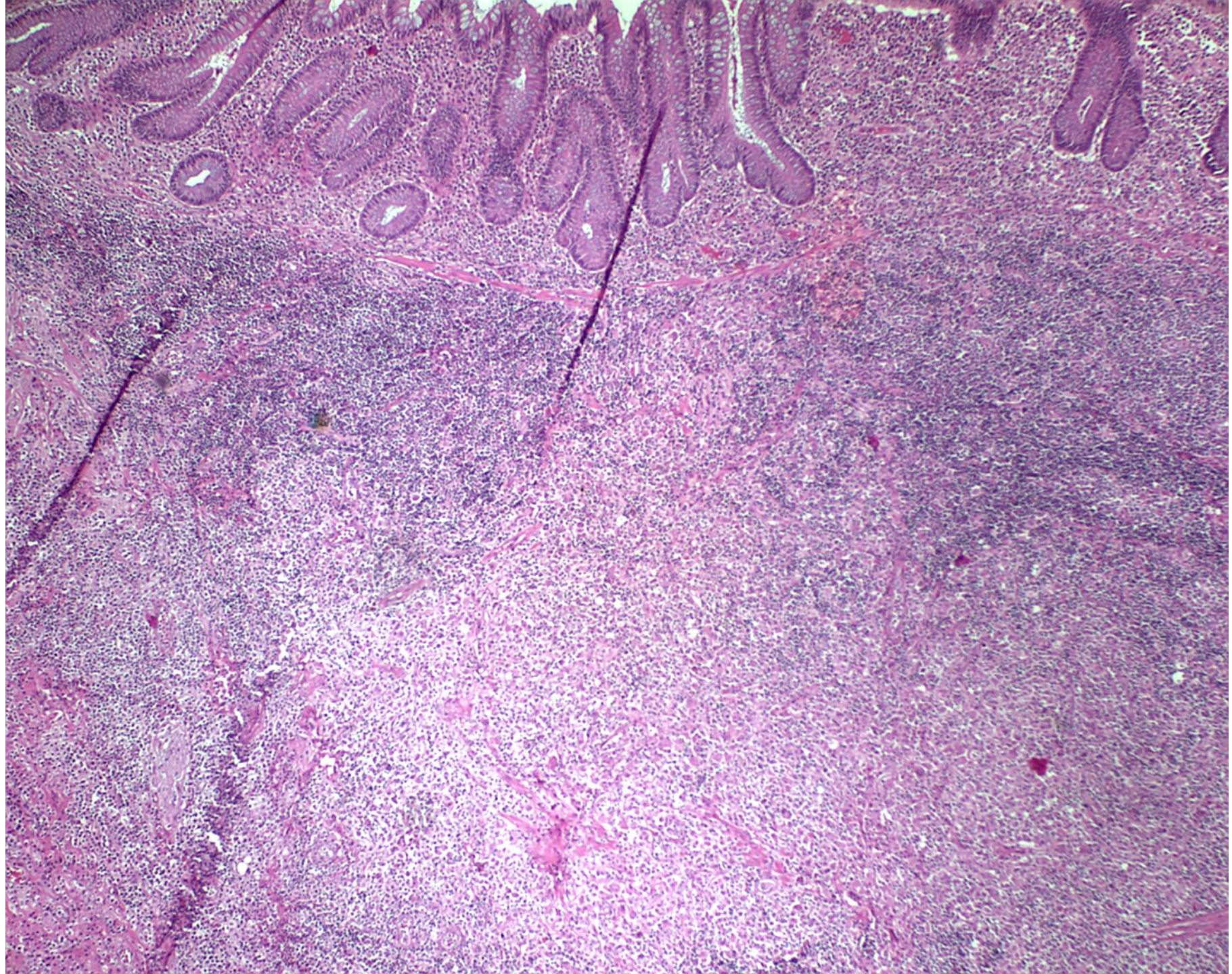
Appendiceal Malakoplakia

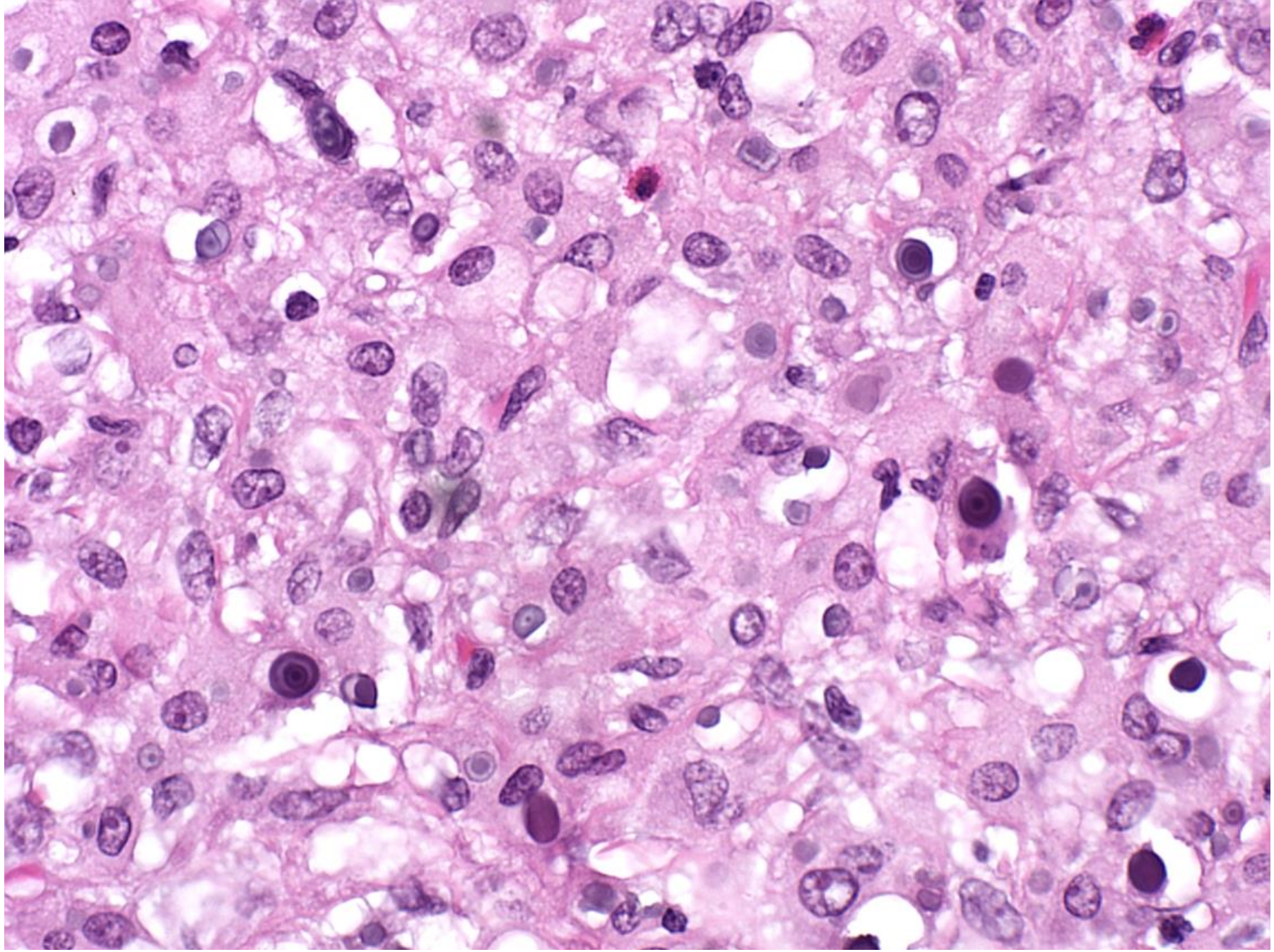
- Malakoplakia
  - “malakos” = soft
  - “plakion” = plaque
- Rare granulomatous disease of uncertain etiology
- Originally described in 1902 (Michaelis & Gutmann)

Zhang Y, Byrnes K, et al. Gastrointestinal Malakoplakia: clinicopathologic analysis of 26 cases. Am J Surg Pathol 2020;44:1251-58.

Appendiceal Malakoplakia

- Sometimes associated with colorectal adenocarcinoma
- Many patients have some form of underlying immunocompromise
- Soft yellow-tan plaques or masses may infiltrate wall or nodes
- May cause bleeding, obstruction, diarrhea, mass





M-G bodies iron and calcium positive

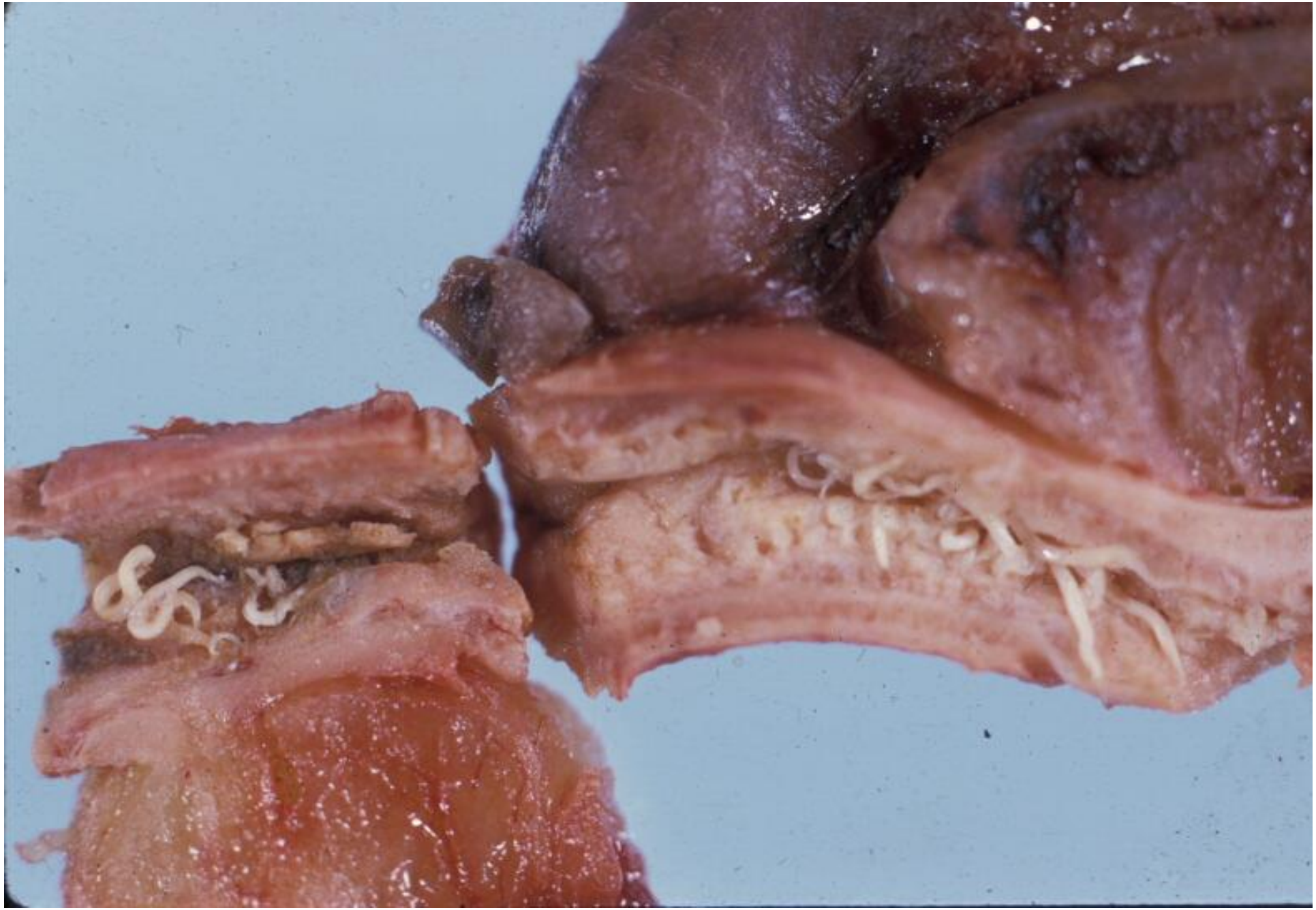
Appendix-Parasitic Infections

- *Enterobius vermicularis* (pinworm)
- *Strongyloides stercoralis*
- Schistosomiasis
- *Cryptosporidium*
- Roundworms (*Ascaris*)
- Whipworms (*Trichuris*)

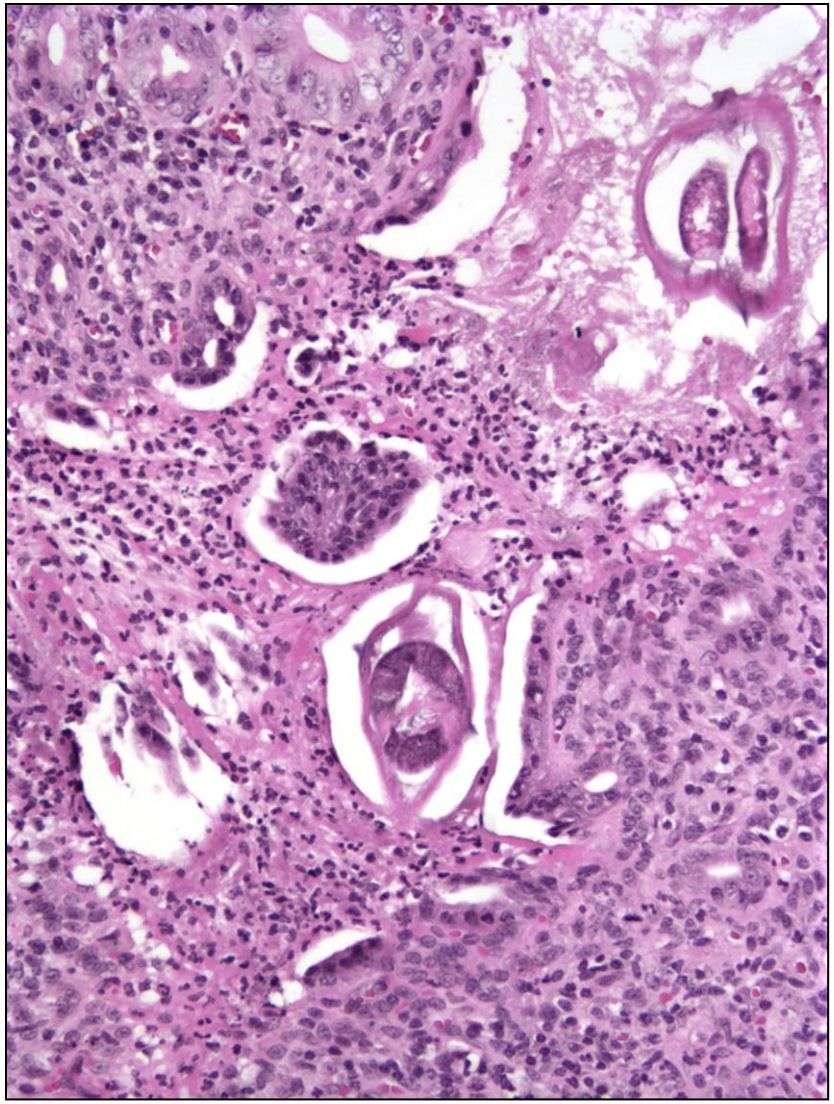
Enterobius vermicularis -Pinworms

- One of the most common human parasites
  - Most common appendiceal parasite
  - Present in 0.6-13% of appendectomies
- Prevalent in developed countries
- Generally infects children and adolescents

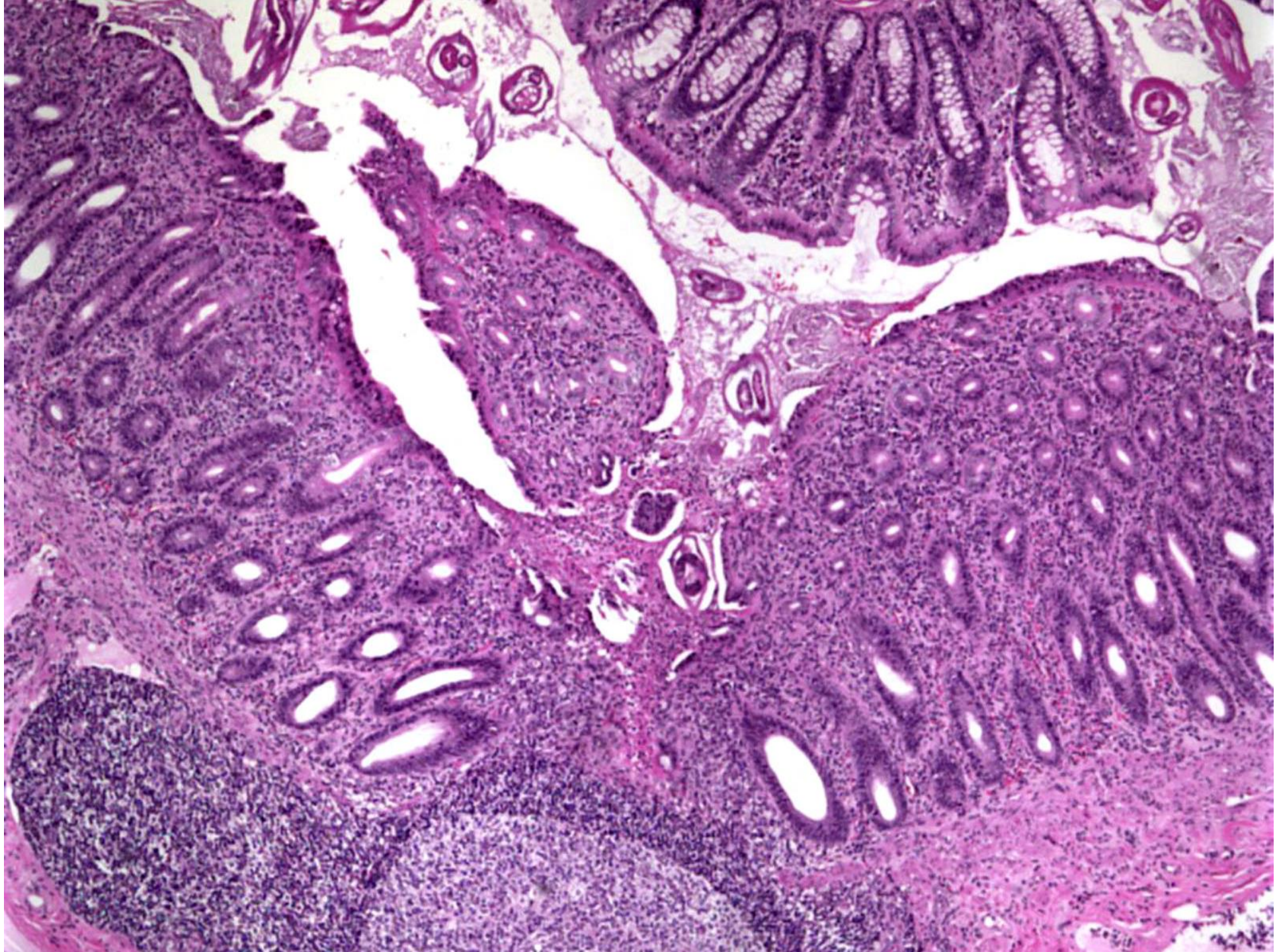
Sinniah B, Leopairut RC, Connor DH. Voge M. . Enterobiasis: a histopathological study of 259 patients. Ann Trop Med Parasitol 85: 625-35, 1991.
Wiebe BM. Appendicitis and *Enterobius vermicularis*. Scan J Gastroenterol 26;336-8, 1991.



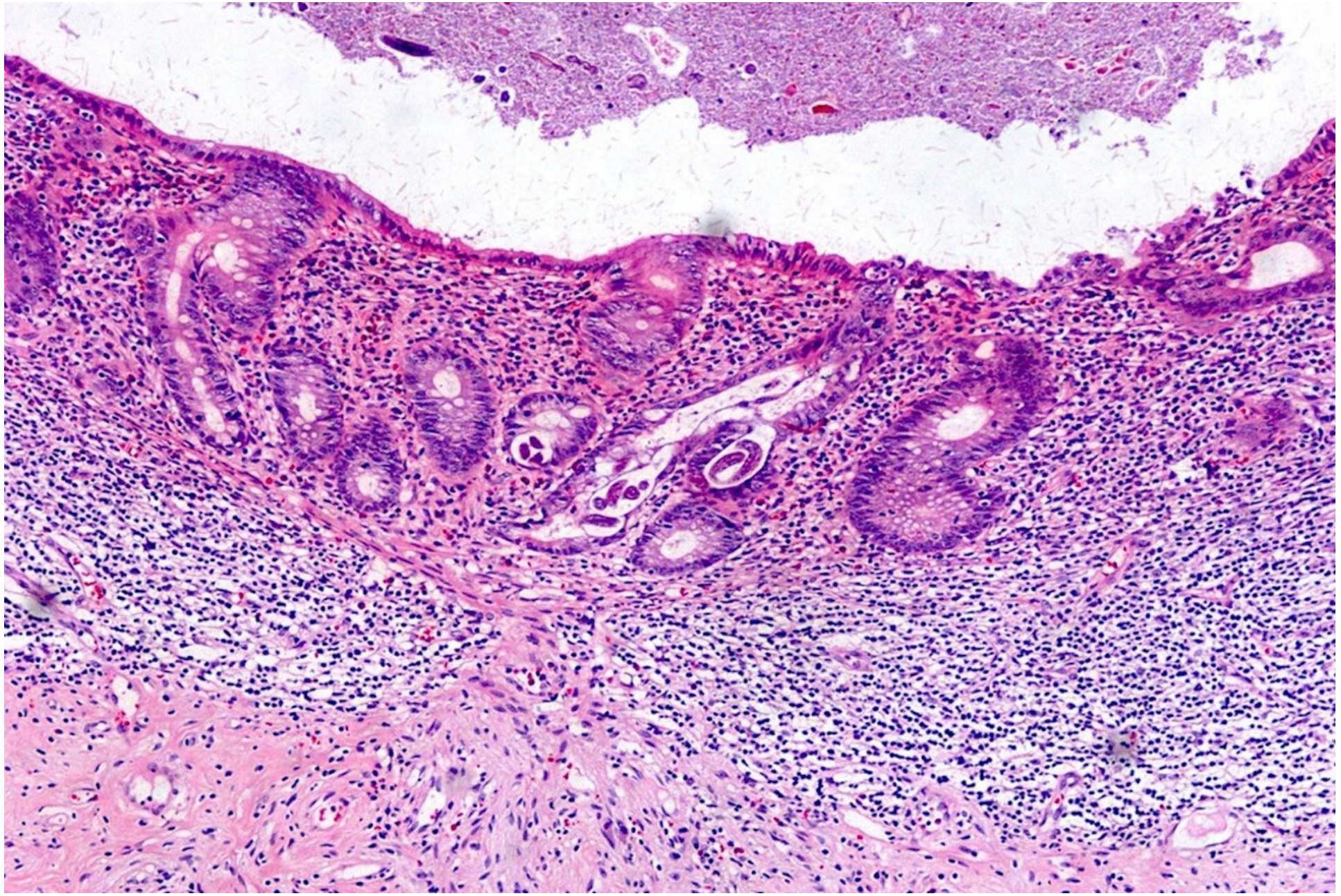
Can enterobius invade?

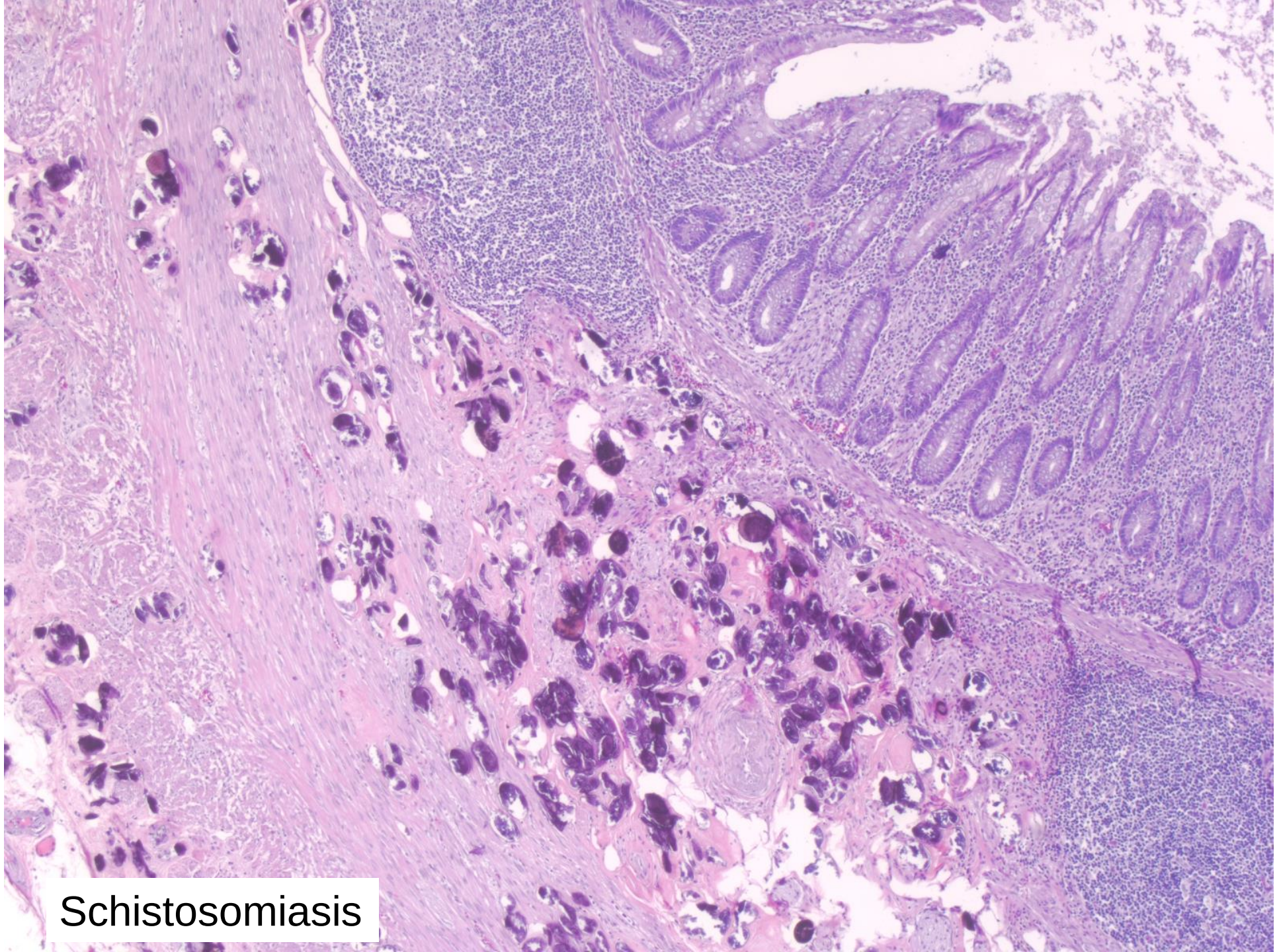


- Ability to actually cause mucosal damage/inflammation is hotly debated
- Rarely observed invasion, ulceration, inflammation in appendix, colon, female genital tract, and peritoneum
- Some believe they invade peri- appendectomy

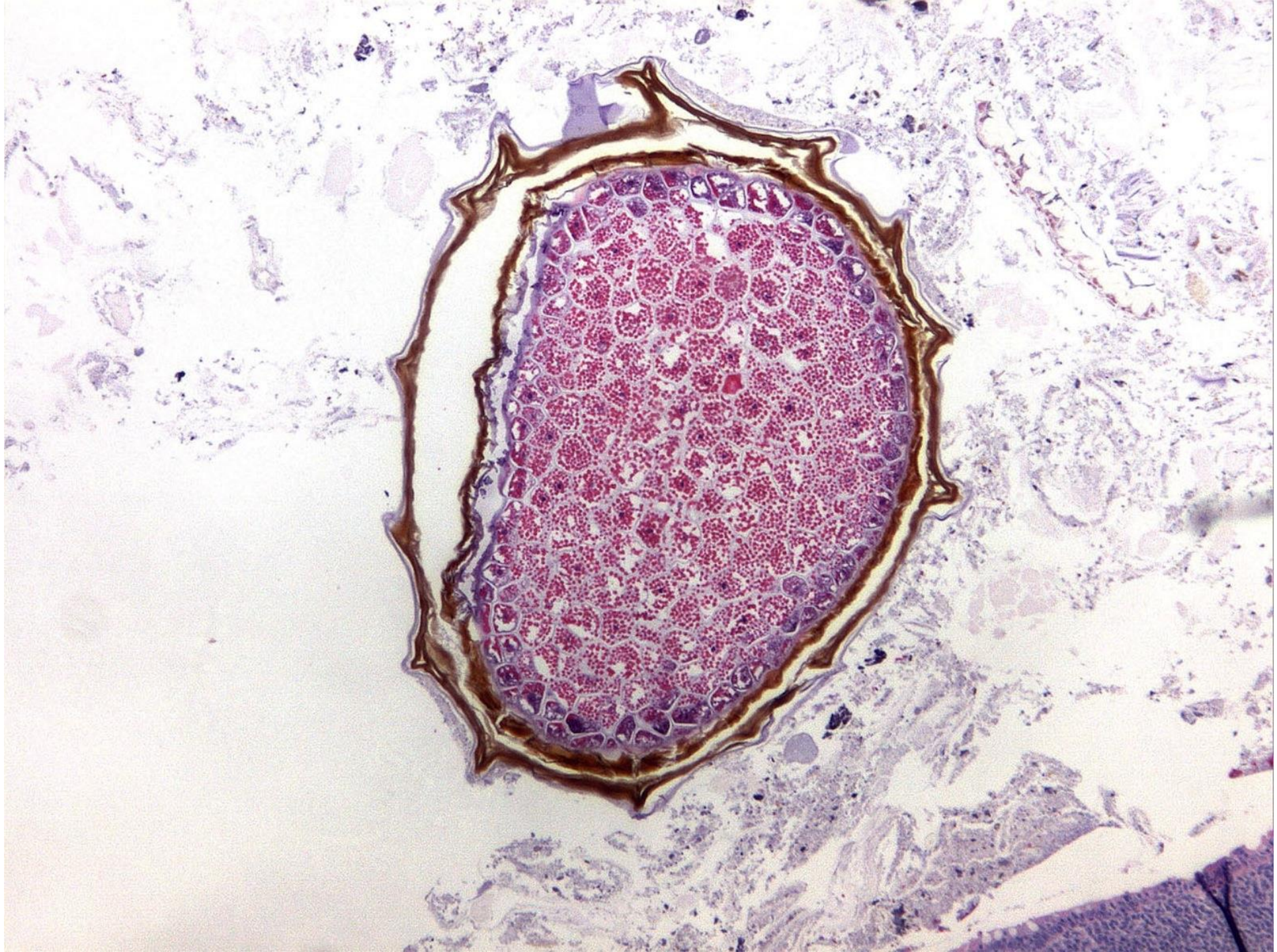


Strongyloides





Schistosomiasis



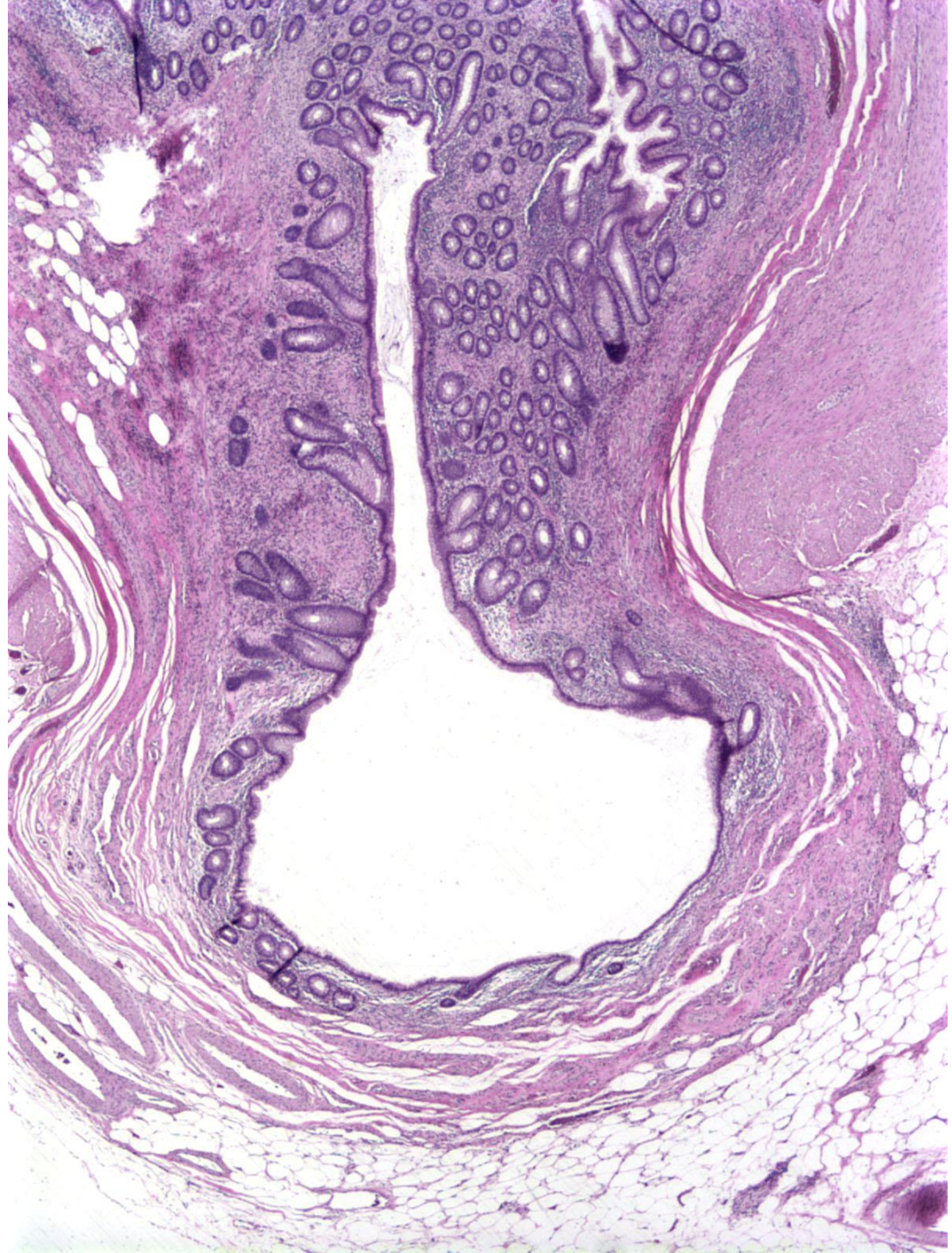
Appendiceal Diverticula

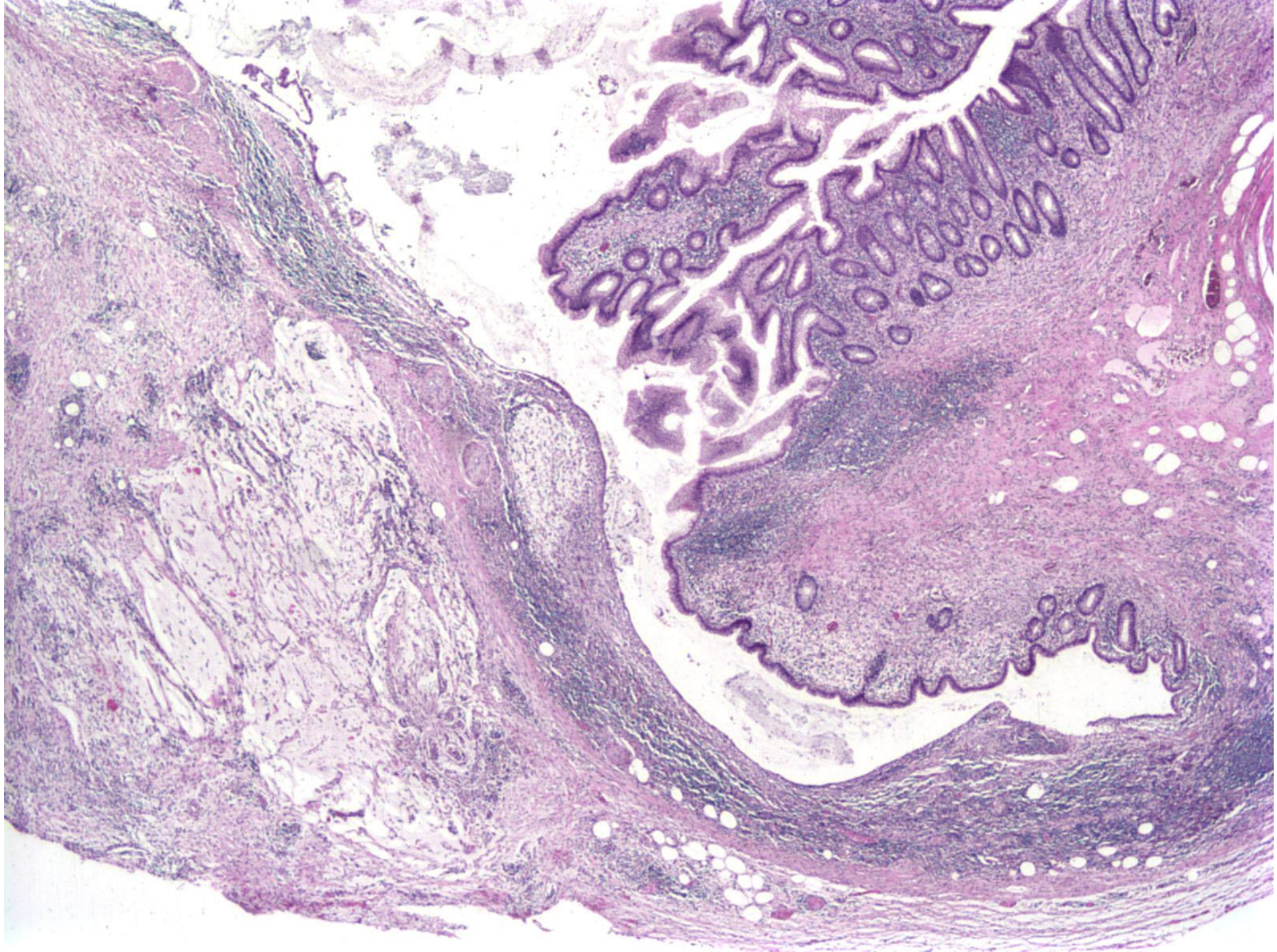
- 10% congenital, 90% acquired
- Acquired diverticula present in 0.4 - 2% appendectomies
- Probably underreported
- Associated with numerous conditions:
  - Neoplastic epithelial lesions
  - Neuromas
  - Cystic fibrosis

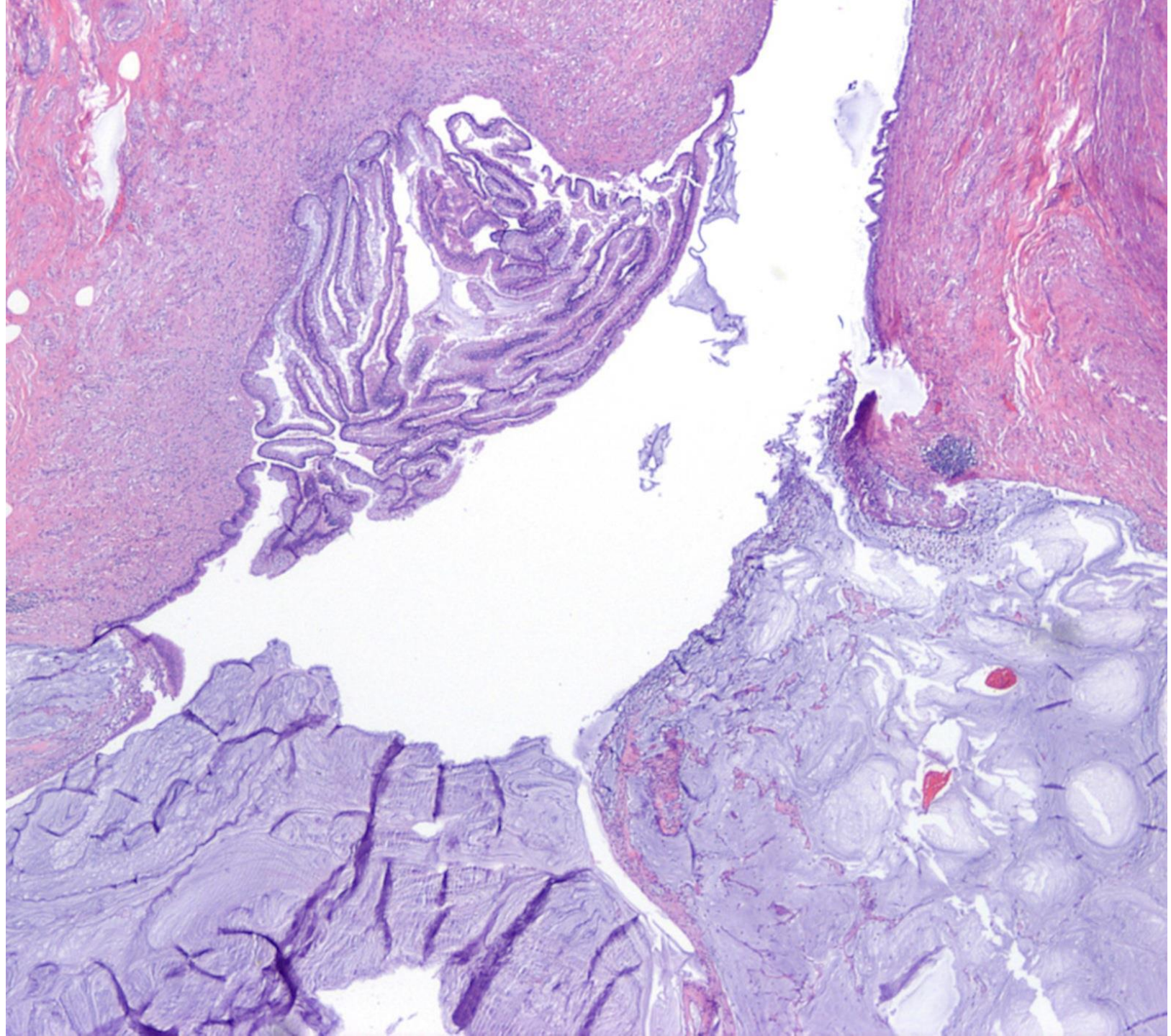
Payan HM. Diverticular disease of the appendix. Dis Col Rect 20: 473-6, 1977.
Trollope ML, et al. Diverticulosis of the appendix: a collective review. Dis Col Rect 17:200-18, 1974.

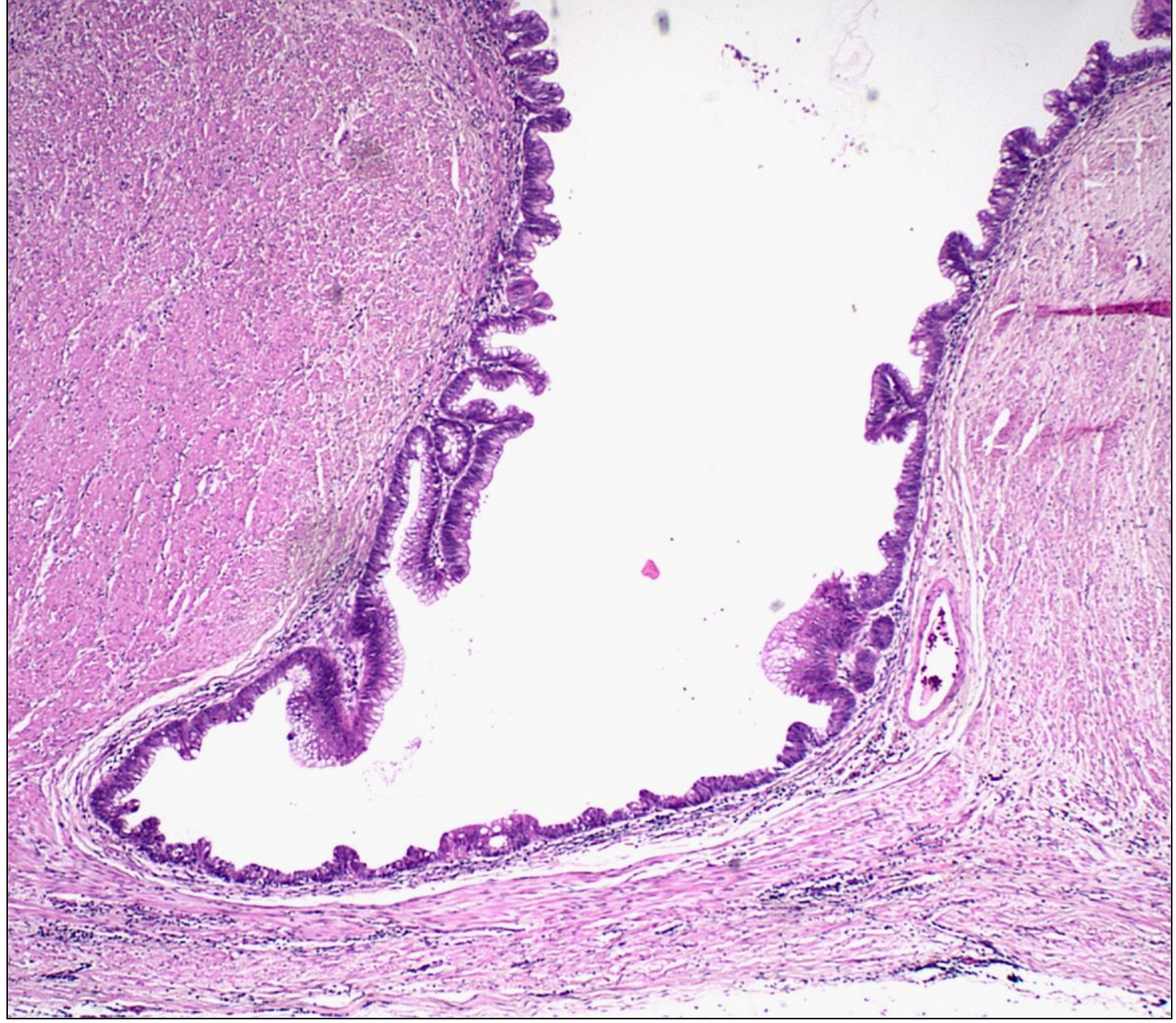
Appendiceal Diverticula

- Single or multiple
- Often less than 5mm
- On mesenteric or antimesenteric border
- 25% at tip



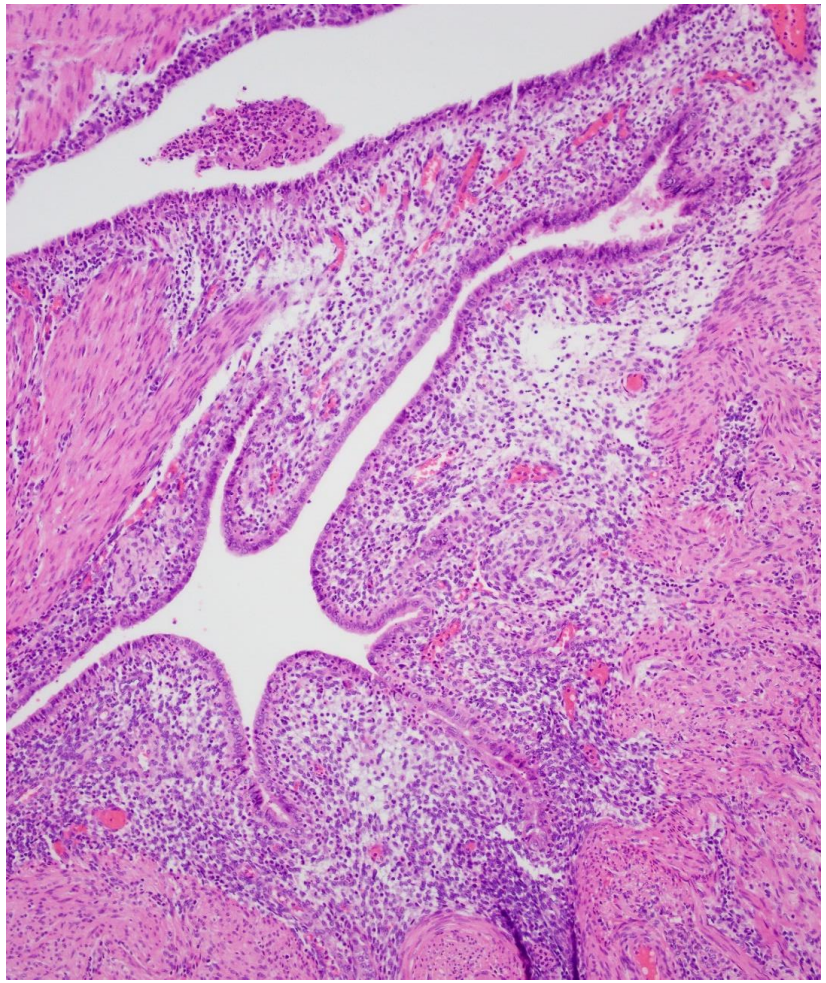




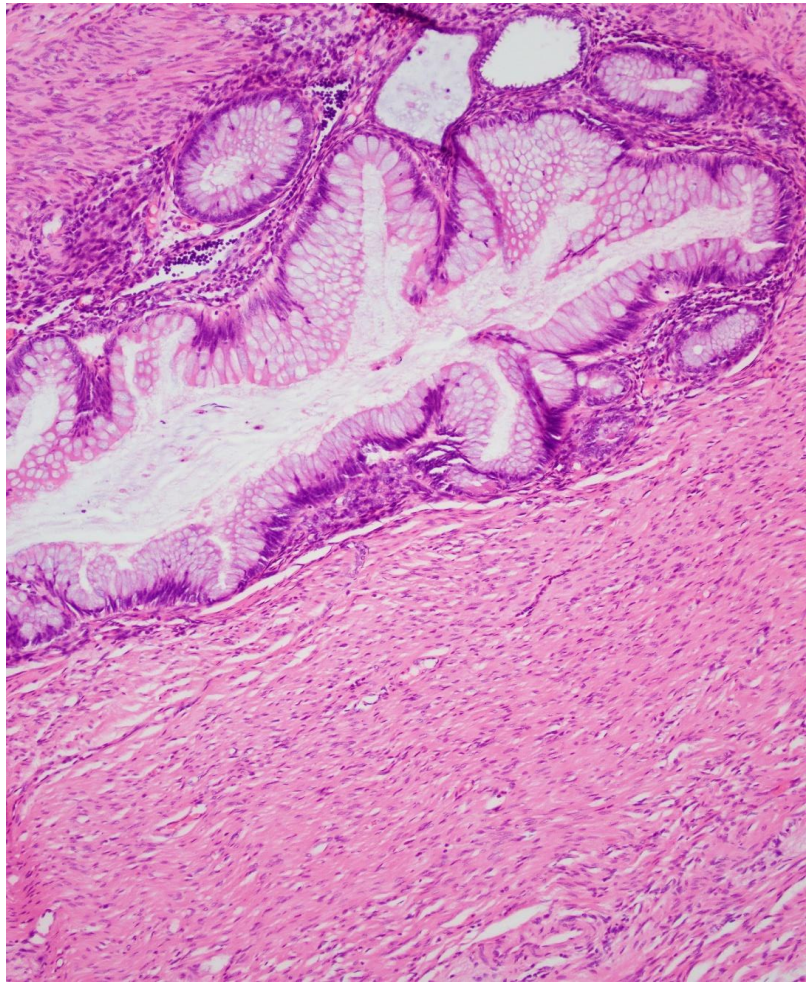


Mullerian Lesions

Endometriosis



Endometriosis with Intestinal metaplasia



Courtesy Dr. Zaid Mahdi

THANK YOU!