Envoi
SPECIALIST PATHOLOGISTS
inside insights

Envoi Specialist Pathologists' Challenging Case Highlights

Dr Ian Brown
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‘I did not know that’

Dr Ian Brown

Overview

- Diagnosis
- Background to the condition
- Presentation of case
- GIT manifestation of the disease

Common Variable ImmunoDeficiency (CVID)

- autoimmune variant

Immune dysregulation in the GIT

- Inherited (childhood)
  - Monogenic/polygenic/unknown at present

- Acquired (adult)
  - Checkpoint inhibitors
  - Sartans
  - Thymoma
  - Other

Common features in GIT

- Any site
- Variable severity
- Not all sites involved in all cases

- Patterns
  - Lymphocytic
  - Collagenous
  - Eosinophil rich
  - Apoptosis rich
  - Granulomas
  - Combinations of everything

- Often have manifestations outside the GIT**

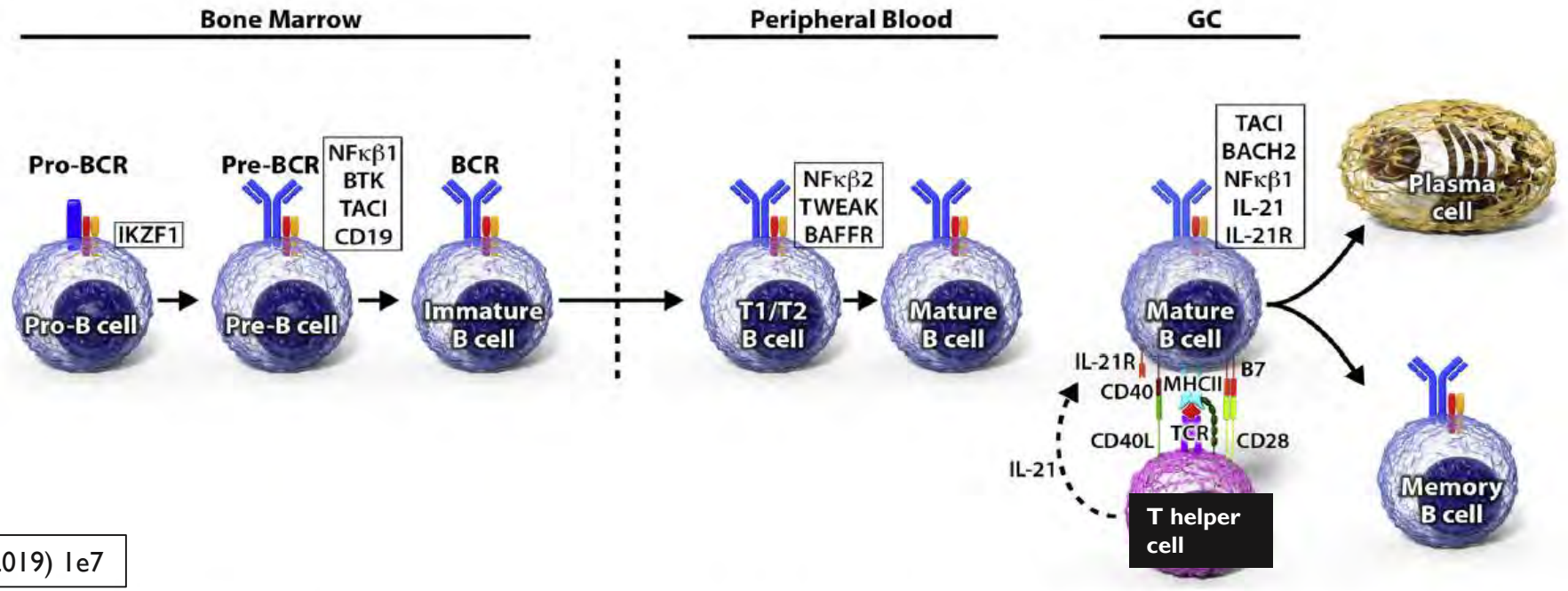
Defect and Causes	Gene Defect	Inheritance	Histology	Special Stains/Test
B cell/antibody defects				
• Agammaglobulinaemia		X linked recessive or AR	Reduced or absent plasma cell	Absent serum gamma globulins
• Selective IgA deficiency		Variable	numbers, lymphoid follicles, villous blunting	Absent serum IgA
• Common variable immunodeficiency		Variable	Variable features ranging from reduced plasma cell numbers through to mucosal inflammation resembling coeliac disease. Granulomas may occur	Reduced serum gamma globulins
• Hyper IgM syndrome	various	Mostly AR	can mimic coeliac disease	
T cell defects				
• Immune dysfunction, polyendocrinopathy, enteropathy, X linked (IPEX)	FOXP3	X linked	Autoimmune enteropathy	
• Autoimmune - candidiasis – polyendocrinopathy - ectodermal - dystrophy (APECED)	AIRE	AR	Autoimmune enteropathy	
Also (CD25 deficiency, STAT5b deficiency, STAT 1 over activity, ITCH deficiency)				
Combined T cell and B cell defects				
• Severe combined immunodeficiency	Various	Variable	Villous blunting; hypocellular lamina propria, without plasma cells or lymphocytes.	
• Wiskott-Aldrich syndrome	WASP	X-linked recessive	Ulcerative colitis like	
Neutrophil defects				
• Chronic granulomatous disease	various	X linked or AR	Granulomas	
• Also (leukocyte adhesion deficiency, glycogen storage disease 1b, severe congenital neutropenia)				
Miscellaneous				
• Interleukin 10 deficiency	Various	AR	Early onset inflammatory bowel disease	
• ADAM17 deficiency	ADAM17	AR	Villous blunting, crypt hyperplasia, lamina propria chronic inflammation	
• CD55 deficiency (CHAPLE syndrome)	CD55		Intestinal lymphangiectasia; variable mucosal inflammation	

CVID

- 2-4/100,000 (may be as high as 1/10,000)
- GIT manifestations in >50% (not the 10-20% often quoted)
- NOT a single disease
- A cluster of diseases characterised by recurrent infections, autoimmunity, and lymphoproliferation (including granulomas) with laboratory evidence of hypogammaglobulinaemia

CVID

Biologic defect	CVID-associated genes
Impaired B-cell development and Survival	IKZF1, BAFFR (IL21), TWEAK (IL21R), NFKB2, CD27 (TACI), IRF2BP2, STAT1 GOF
Impaired class switch recombination/ somatic hypermutation	BACH2, BAFFR (IL21), TWEAK (IL21R),
Excessive lymphoproliferation	CD81 (CTLA4), LRBA, PIK3CD, PIK3R1, STAT3 GOF
Impaired B-cell activation and tolerance	NFKB1, CD27 (TACI), CD19, CD21, CD81 (CTLA4), , CD20 (ICOS), BLK, PLCG2

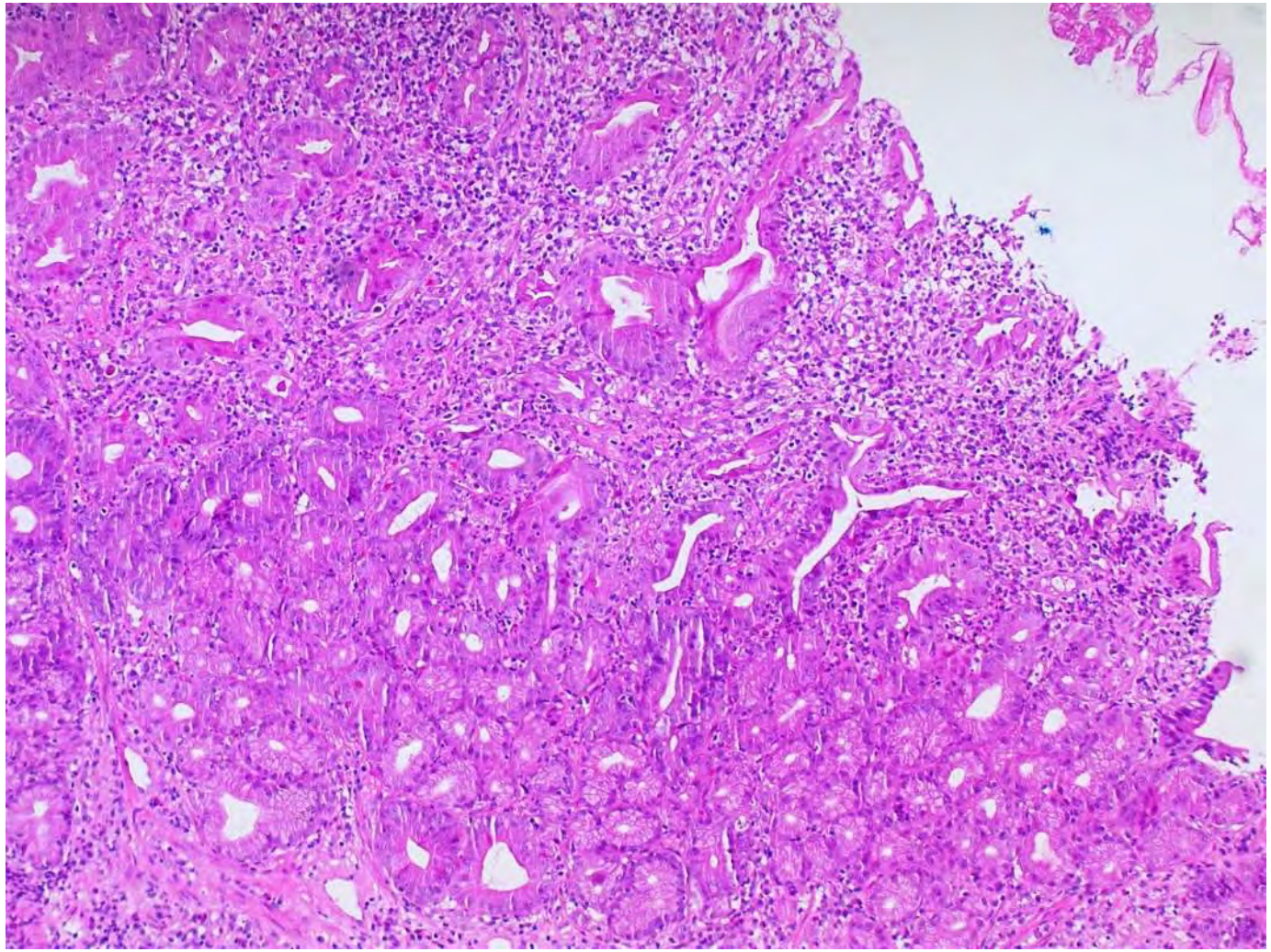


Ann Allergy Asthma Immunol xxx (2019) 1e7

Case history

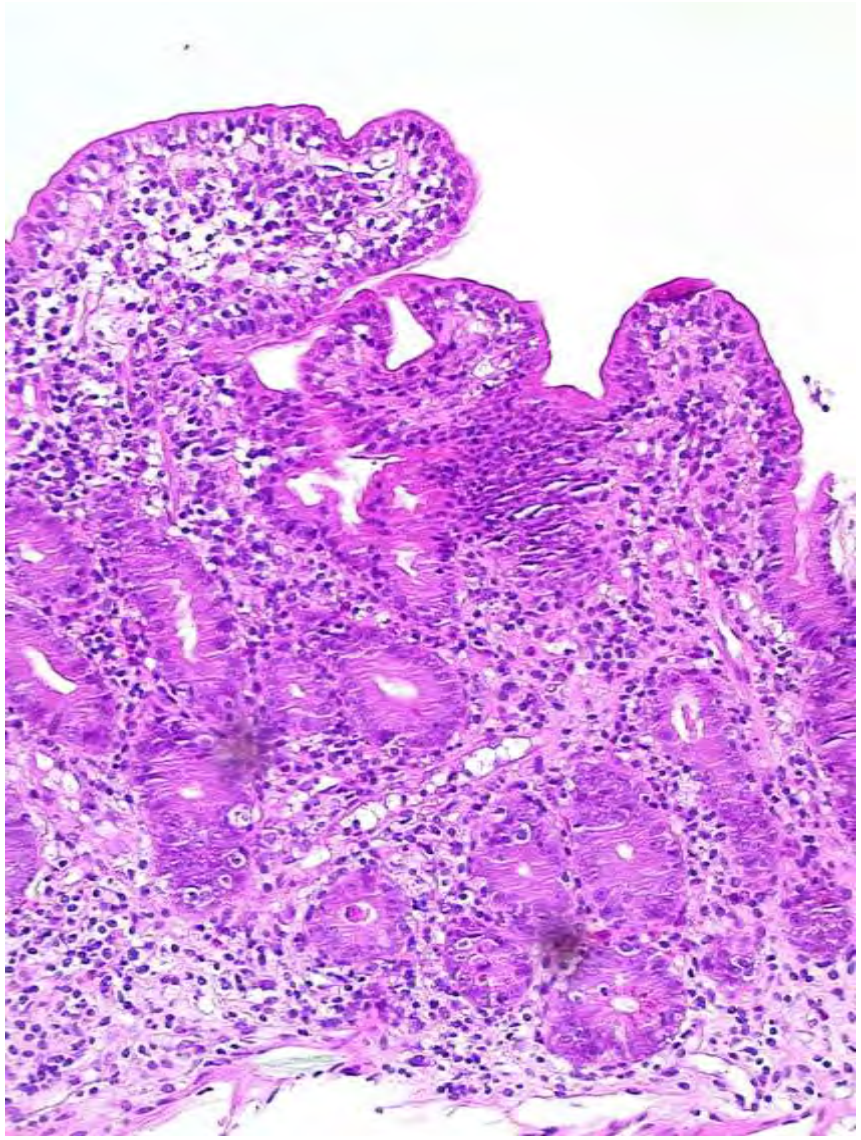
- 35 female
- Autoimmune enteropathy diagnosed at 18 months
  - Responded to cyclosporin treated to age 13 years then ceased
  - Recurred at age 23 years (post partum), again responded to cyclosporin
  - Ceased cyclosporin 2 years ago and AIE recurred
- Bronchiectasis
- Splenomegaly
- Monthly Ig injections

Gastric body

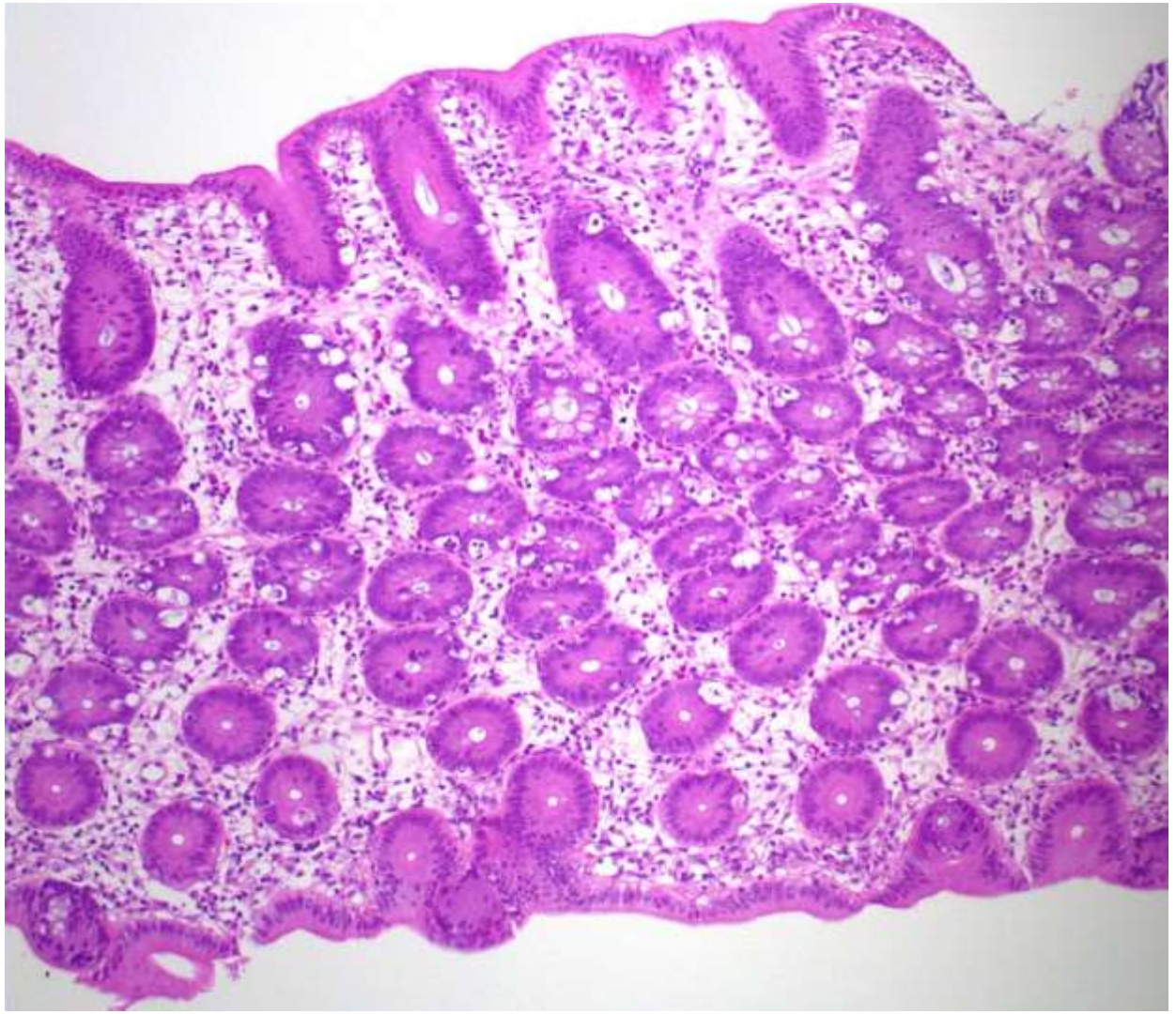


Helicobacter were never identified in any gastric biopsy

Duodenum



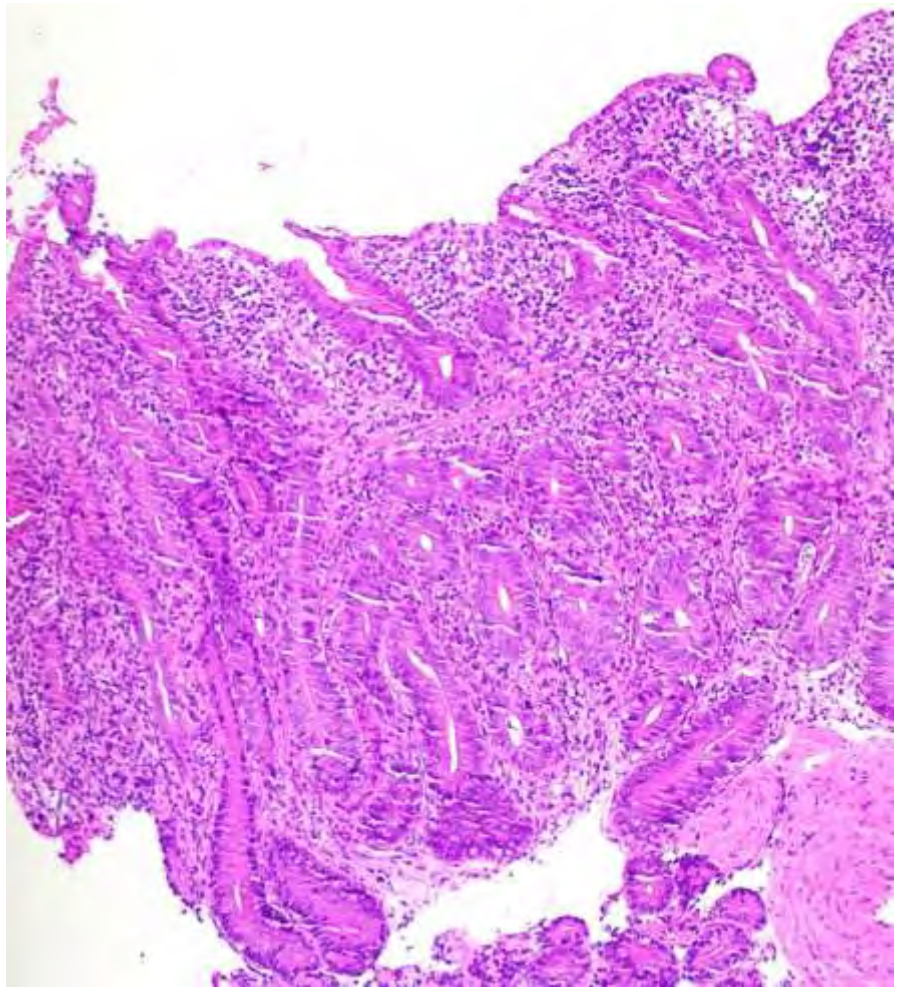
Colon

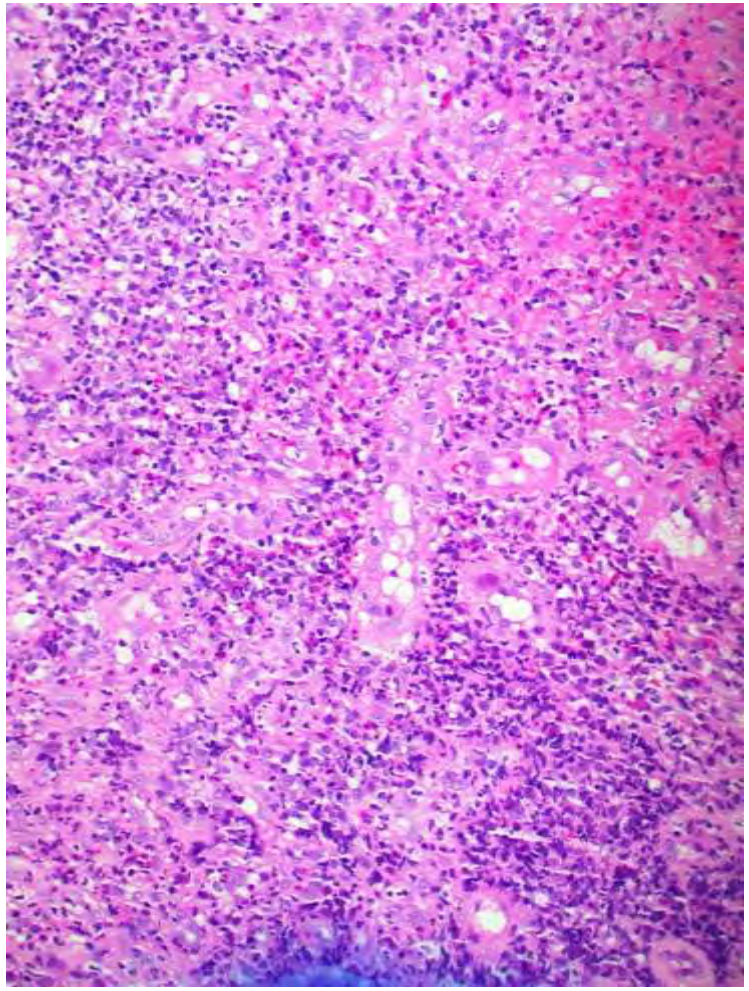


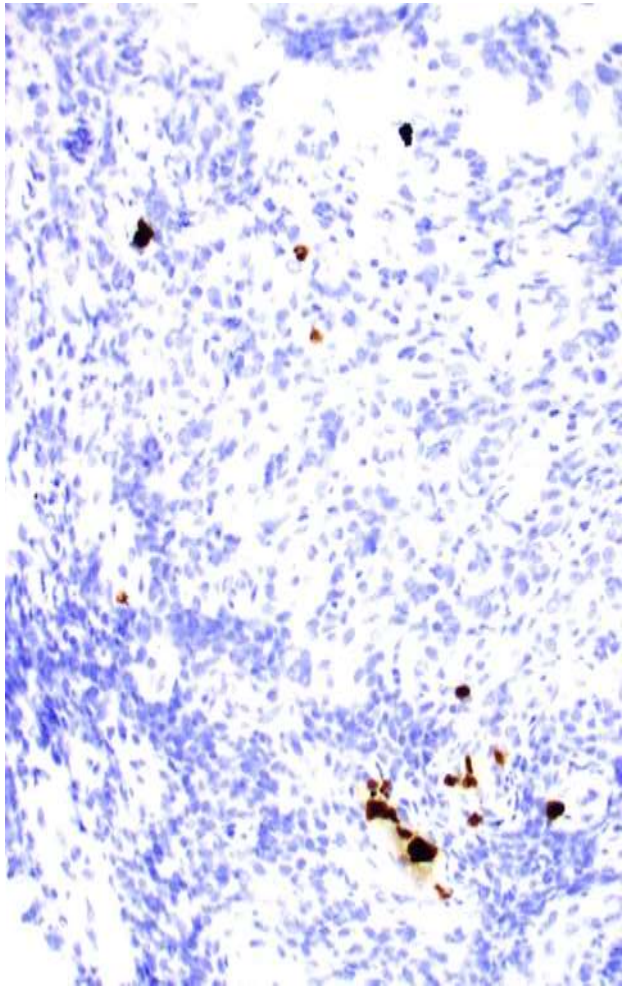
Stomach never ‘healed’

- Reasonably common to autoimmune enteropathy (in my experience)
- If it is the worst gastritis you have seen – think of immune dysregulation disorders
- [always need to exclude H.pylori infection]

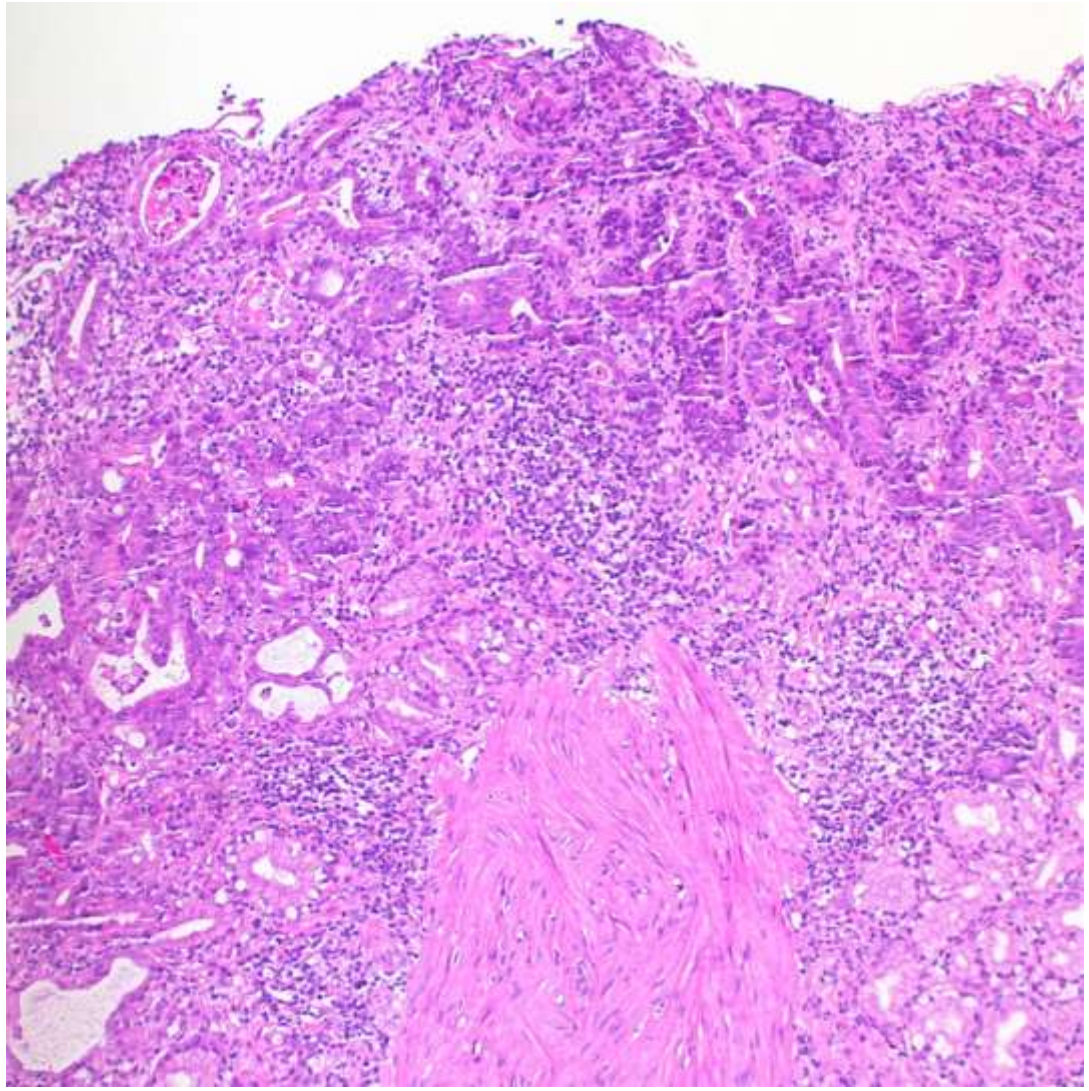
Follow up gastric biopsies



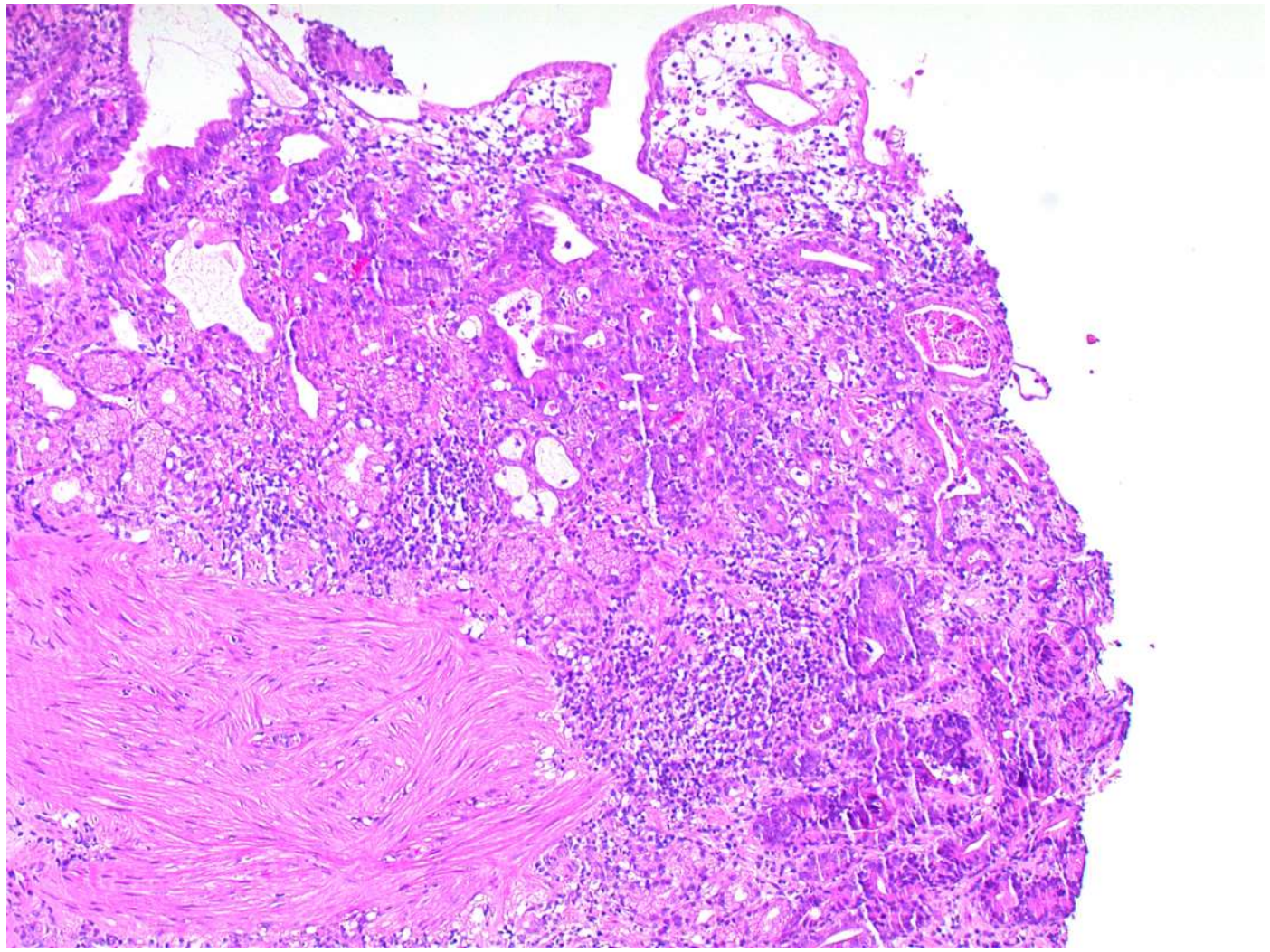


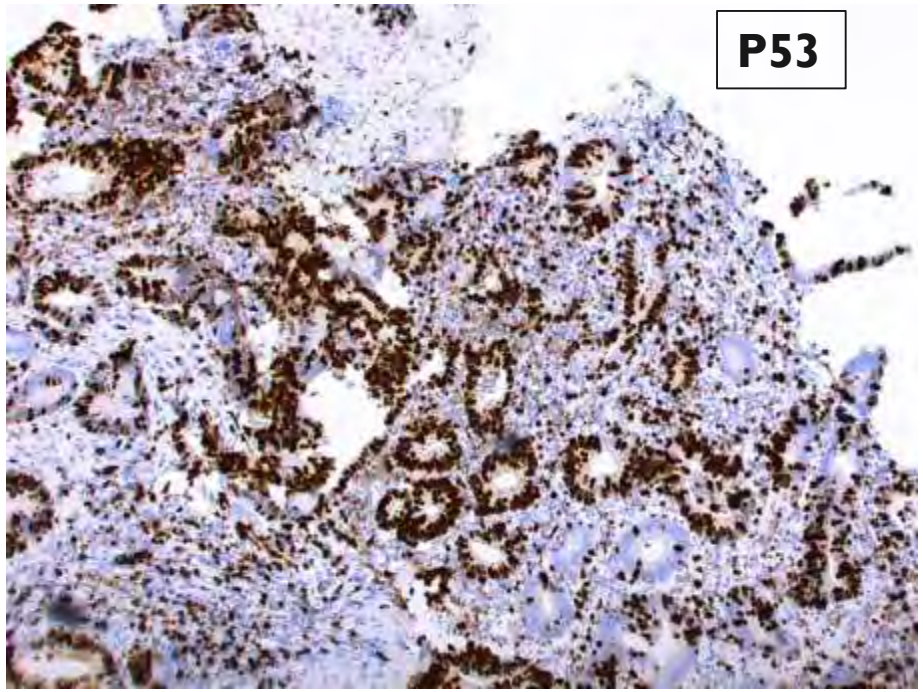


Follow up gastric biopsies



Follow up gastric biopsies





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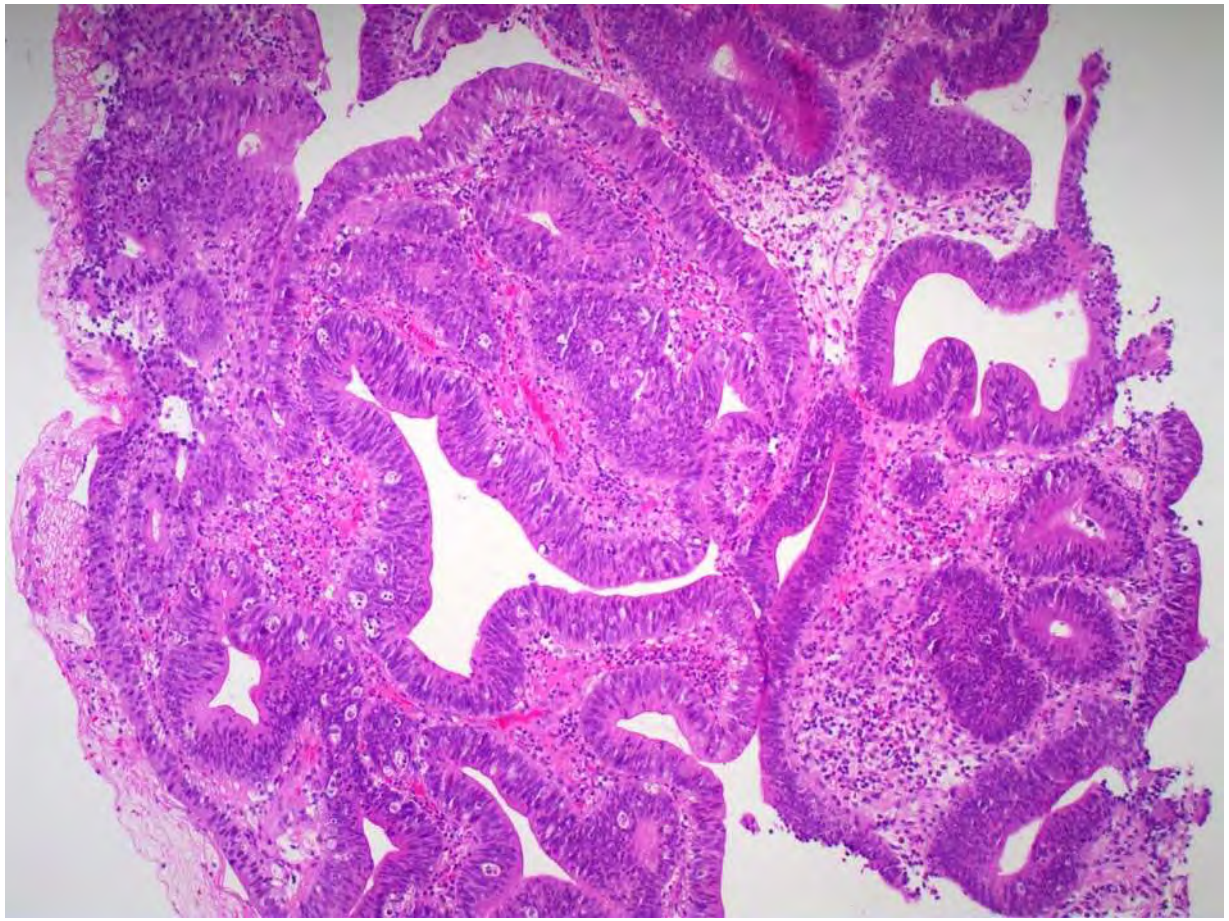

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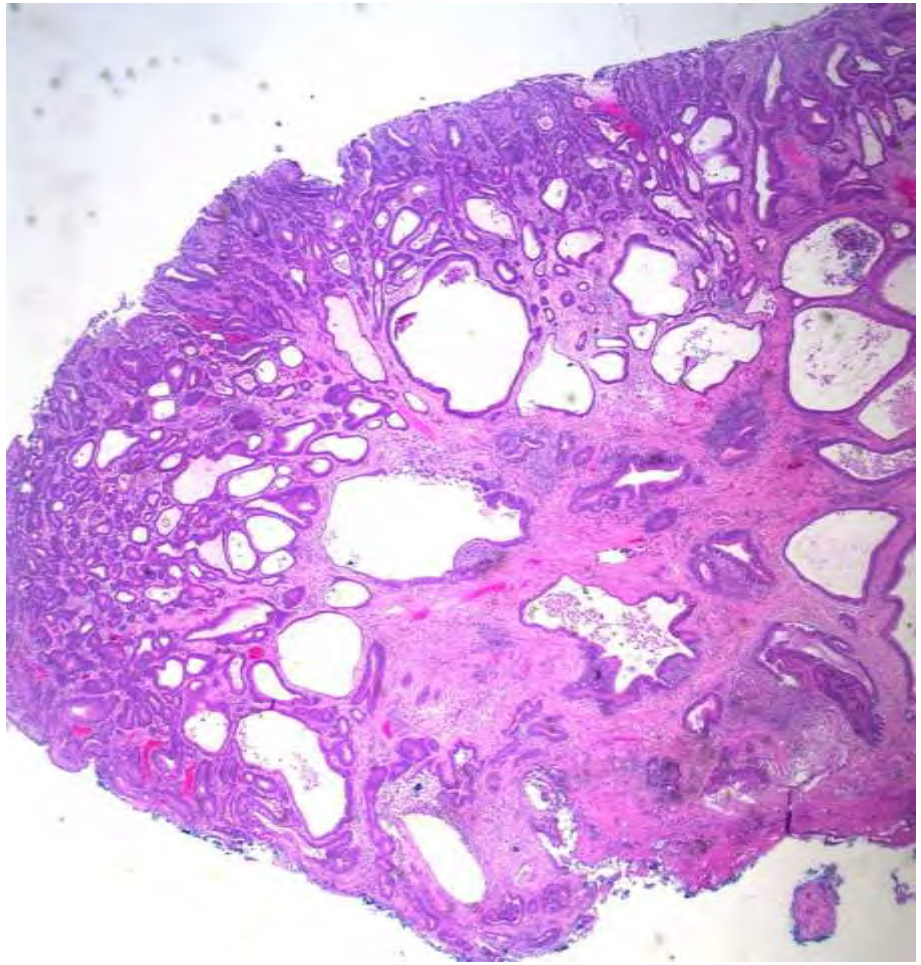
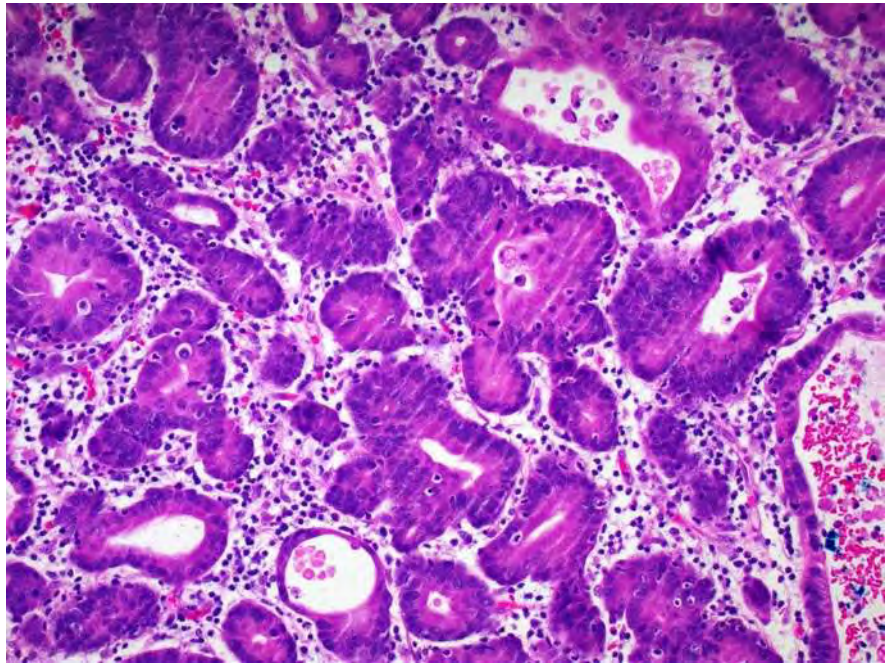
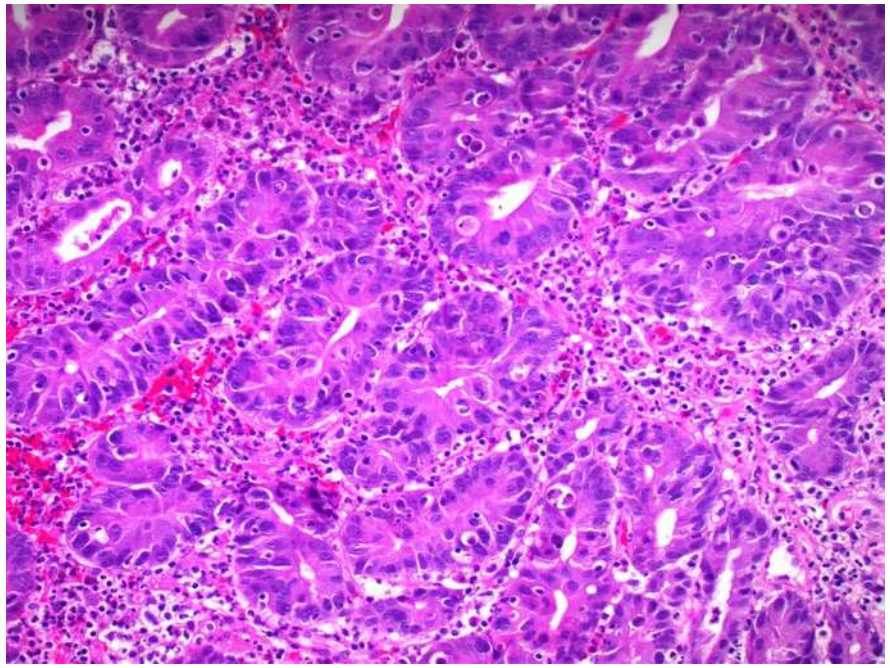
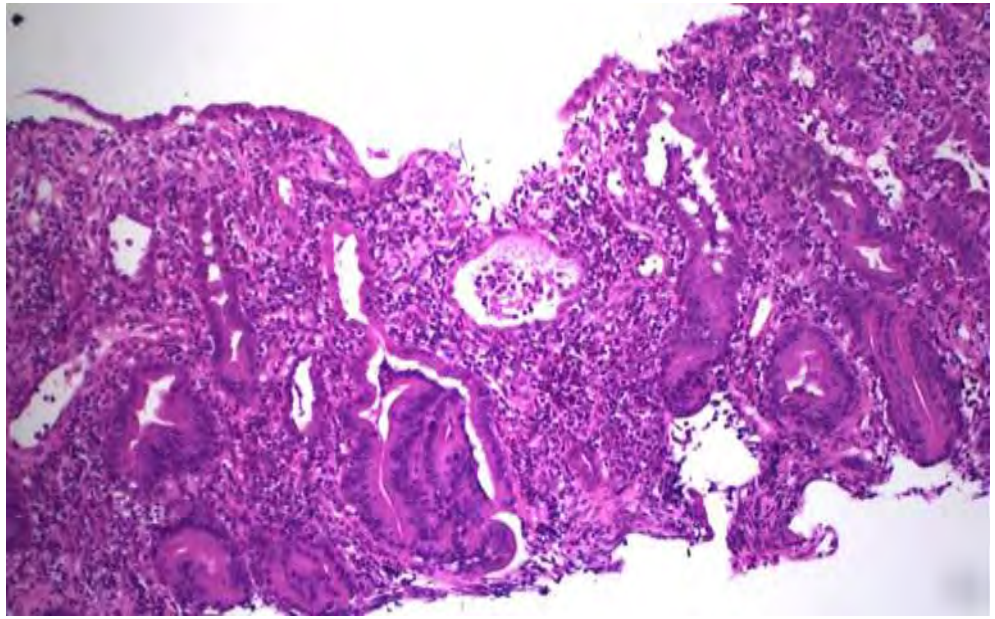
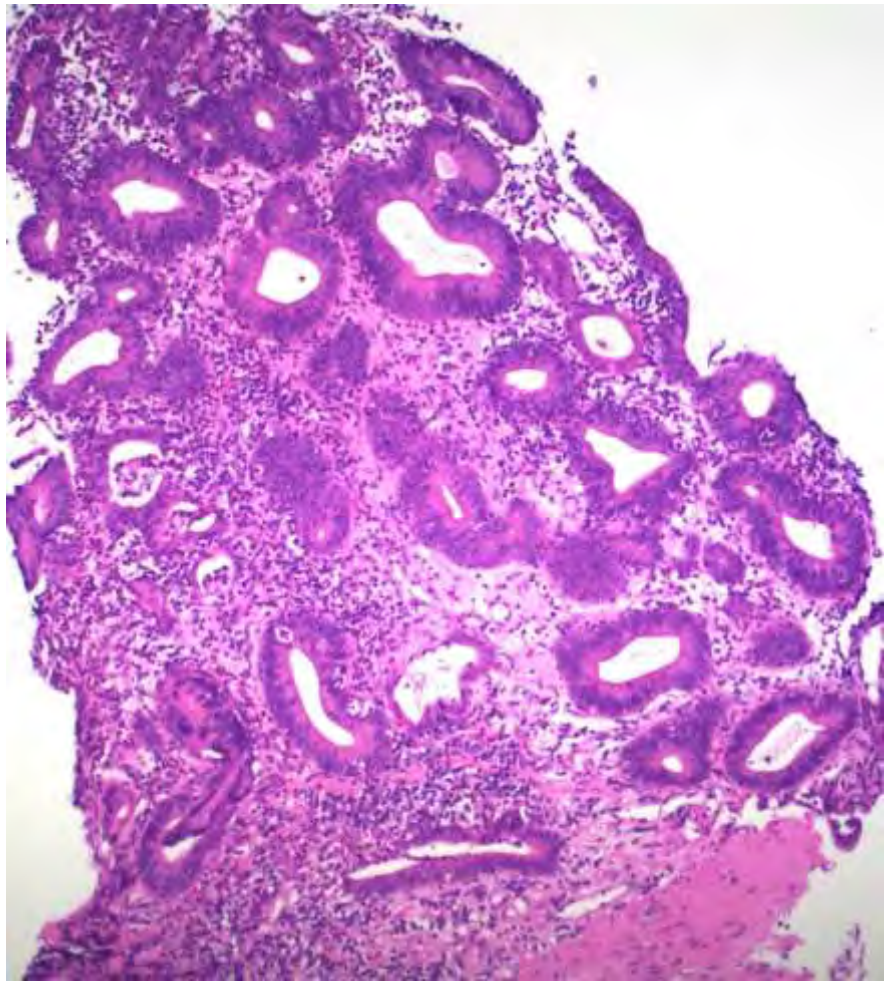






Follow up gastric biopsies





frontiers in Immunology

ORIGINAL RESEARCH
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Gastric Cancer Is the Leading Cause of Death in Italian Adult Patients With Common Variable Immunodeficiency

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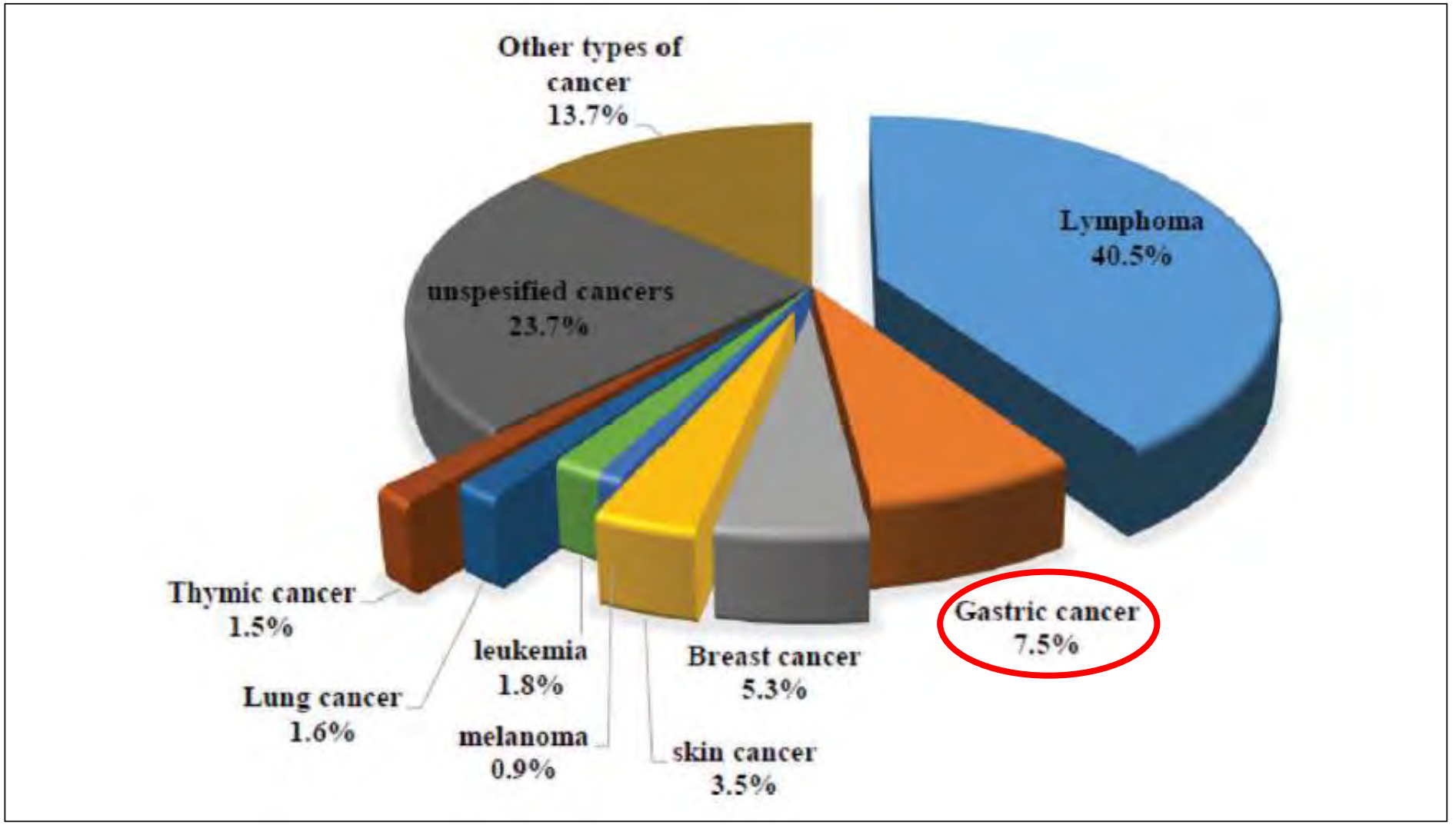
What I learnt that I did not know!!!

Pooled frequency of malignancy in **8123 CVID patients**

- Kiaee F et al Malignancy in common variable immunodeficiency: a systematic review and meta-analysis. Expert Rev Clin Immunol. 2019 Sep 15:1-9



CVID in GIT

1) Infectious (including SIBO)

2) T cell immune mediated
   - IELosis (70%)
   - Active chronic inflammation
   - Granulomas (up to 20%)
   - Collagenosis
   - Apoptosis

3) Neoplasia
   - Lymphomas
   - Epithelial neoplasms

Plasma cells are not always absent

Histologic Findings	Esophagus	Stomach	Small Intestine	Colon
Decreased plasma cells	N/A	12/18 (67%)	13/19 (68%)	10/16 (63%)

Am J Surg Pathol 2007;31:1800–1812

Am J Gastroenterol 2016; 111:1467–1475

Histological abnormality in 60%

Stomach

- Atrophic gastritis (18%)
- Gastric metaplasia in duodenal bulb (26%)
- Fibrosis in the gastric mucosa (26%)
- Intestinal metaplasia in gastric mucosa (12%)
- Subacute inflammation (4%)

Small intestine

- IELs +/- atrophy duodenum (46%)
- Reduced number of plasma cells (62%)
- Lymphoid hyperplasia (38%)

Colon

- GVHD-like (2%)
- Eosinophilic inflammation (8%)
- Lymphocytic enteritis/colitis (8%)
- Collagenous enteritis/colitis (6%)
- Granulomatous inflammation (6%)

Am J Gastroenterol. 114(4):648-655.

GIT manifestations in 60-70%

Oesophagus

- Candida oesophagitis (5%)
- Reflux oesophagitis (4%)
- oesophageal ulceration (3%)
- Barrett oesophagus (1%)

Stomach

- Chronic gastritis (15%)
- Gastritis with H. Pylori (3%)
- Atrophic gastritis (17%)
- Atrophic gastritis with H.Pylori (5%)
- Benign polyps (5%)
- **Gastric carcinoma (3%)**

Small bowel

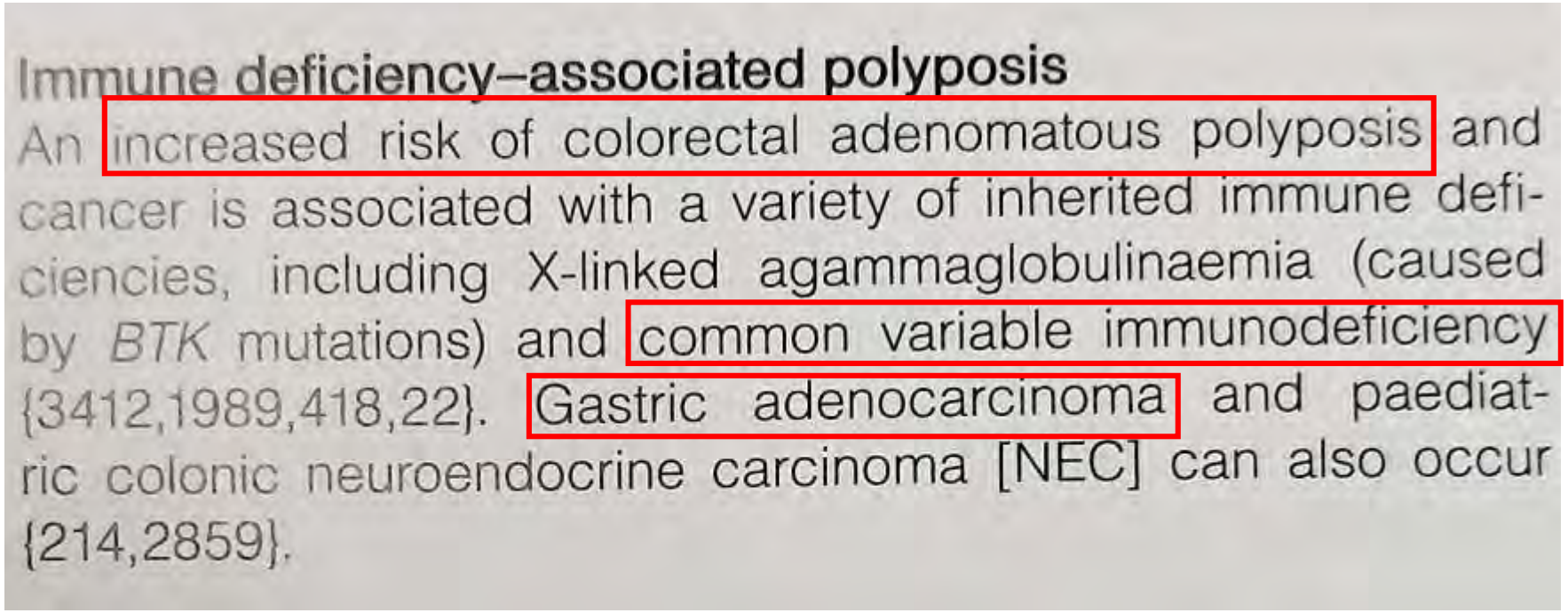
- Enteropathy (villous blunting and increased IEL) (10%)
- Nodular lymphatic hyperplasia (4%)
- Inflammatory stricture (ileum) (3%)

Colon

- Ulcerative colitis (8%)
- Crohn's disease (2%)
- Unspecific ileocolitis (2%)
- Collagenous colitis (2%)
- Lymphocytic colitis (8%)
- Unspecific colitis (related to CVID) (15%)
- CMV colitis (colectomy) (2%)
- HSV colitis (2%)
- Malignancy of colon (3%)
- Benign polyp (31%)

WHO 5th edition

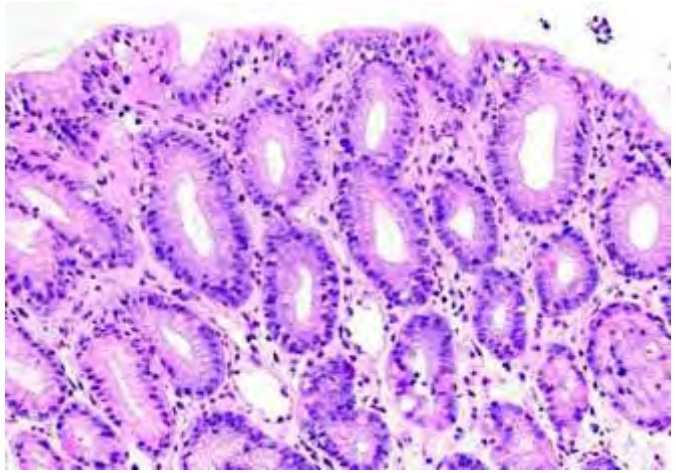
- Chapter "Other adenomatous polyposes"
  - Page 531

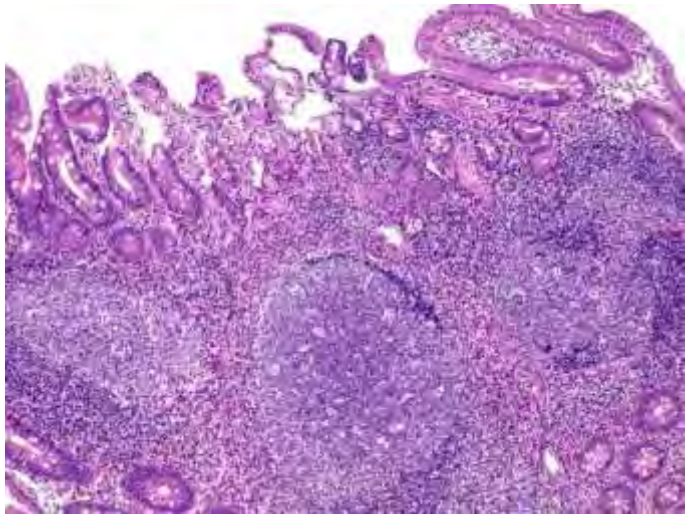


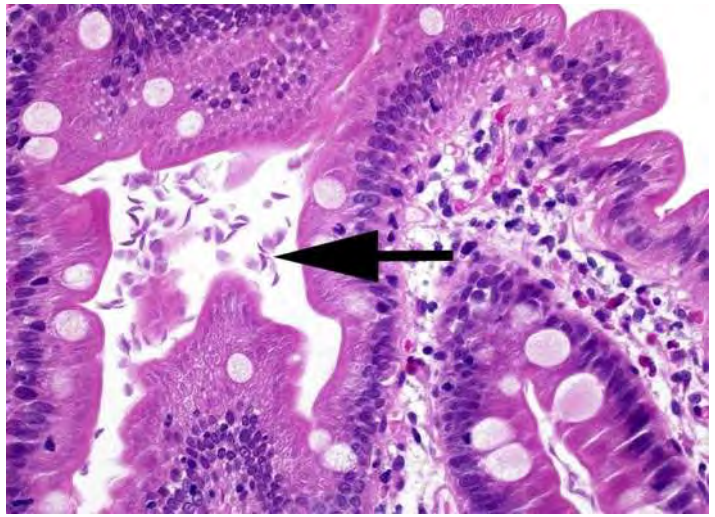
Immune deficiency–associated polyposis

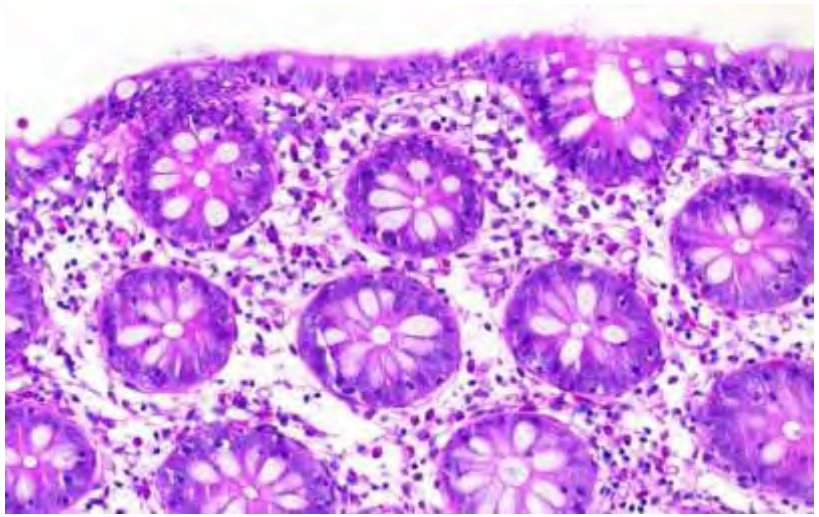
An increased risk of colorectal adenomatous polyposis and cancer is associated with a variety of inherited immune deficiencies, including X-linked agammaglobulinaemia (caused by *BTK* mutations) and common variable immunodeficiency {3412,1989,418,22}. Gastric adenocarcinoma and paediatric colonic neuroendocrine carcinoma [NEC] can also occur {214,2859}.

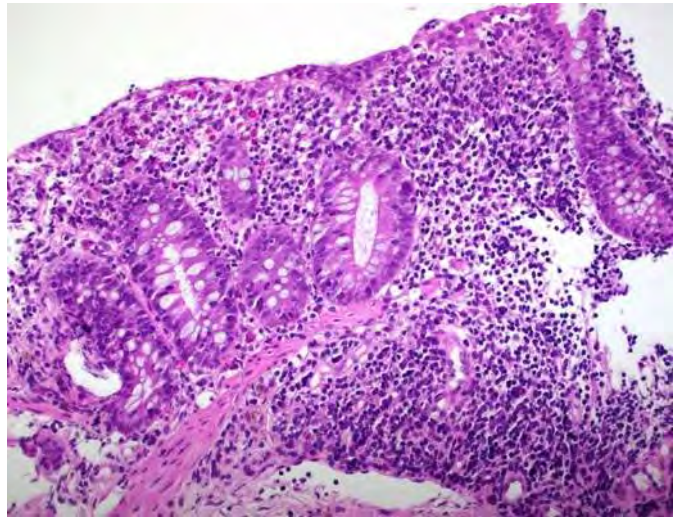
Envoi cases of CVID



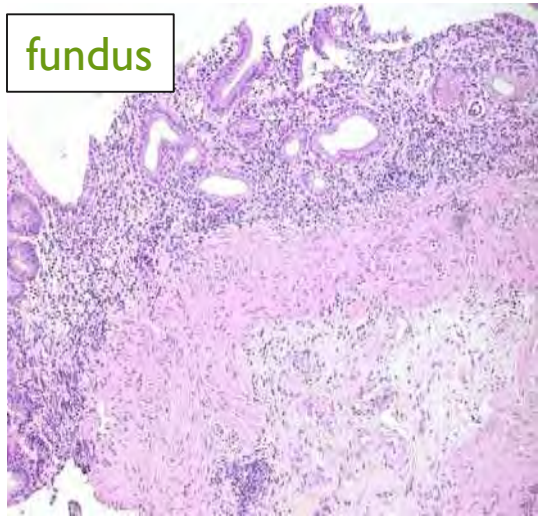


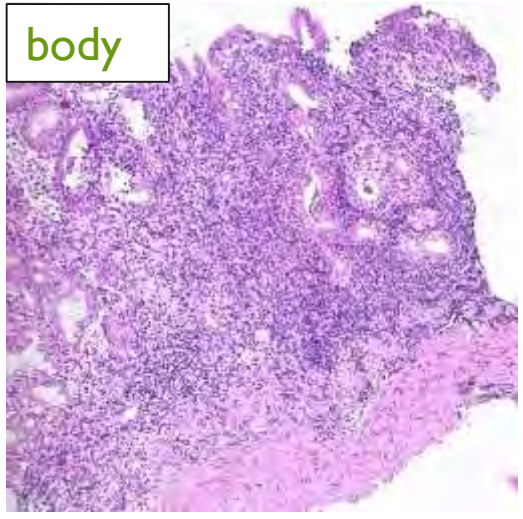


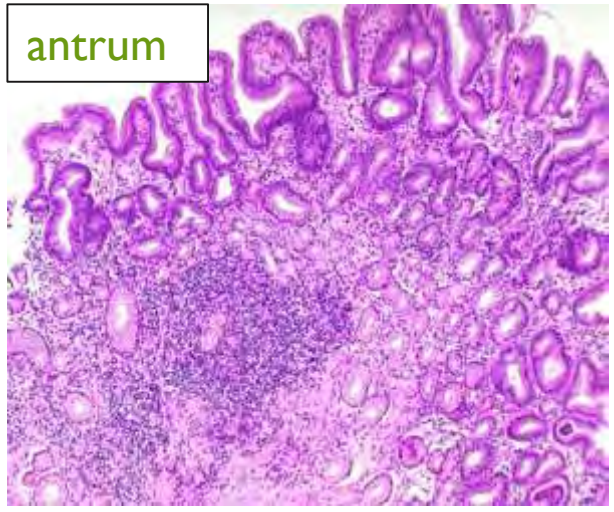


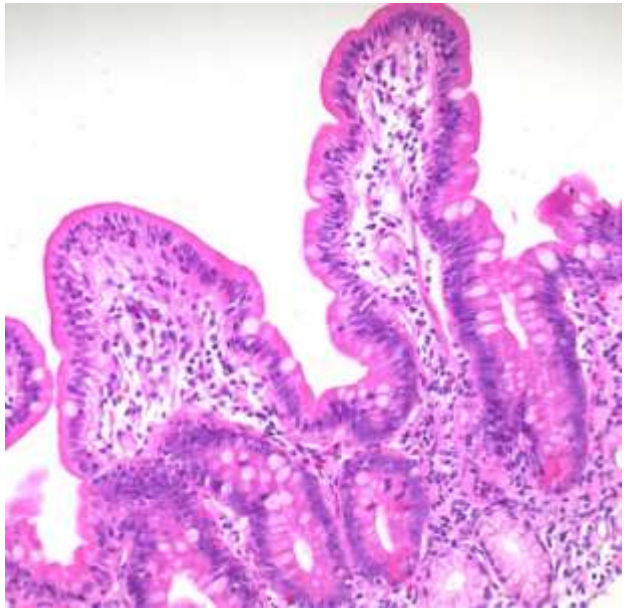


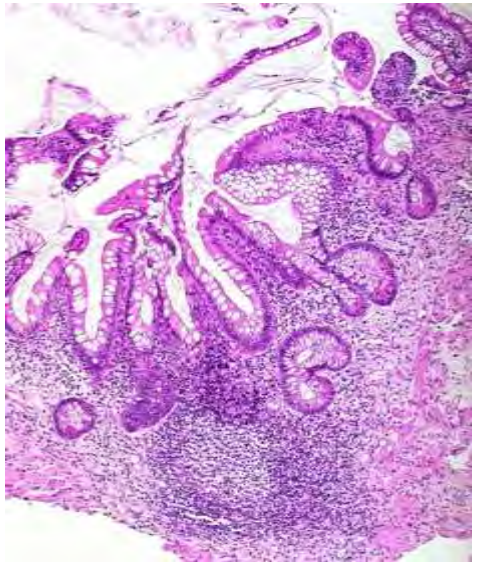
Envoi cases of CVID

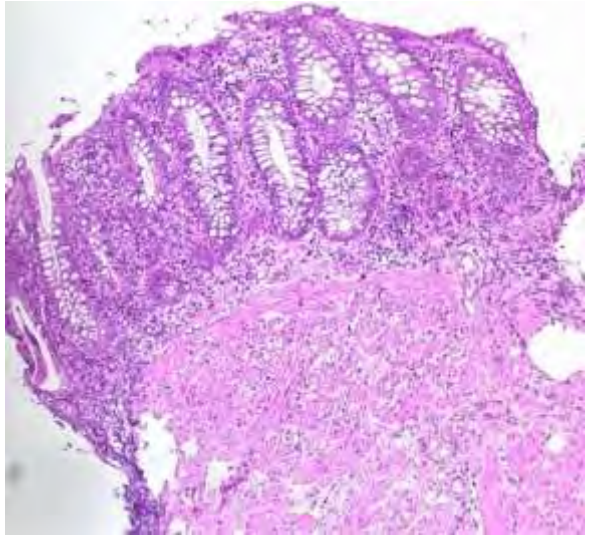


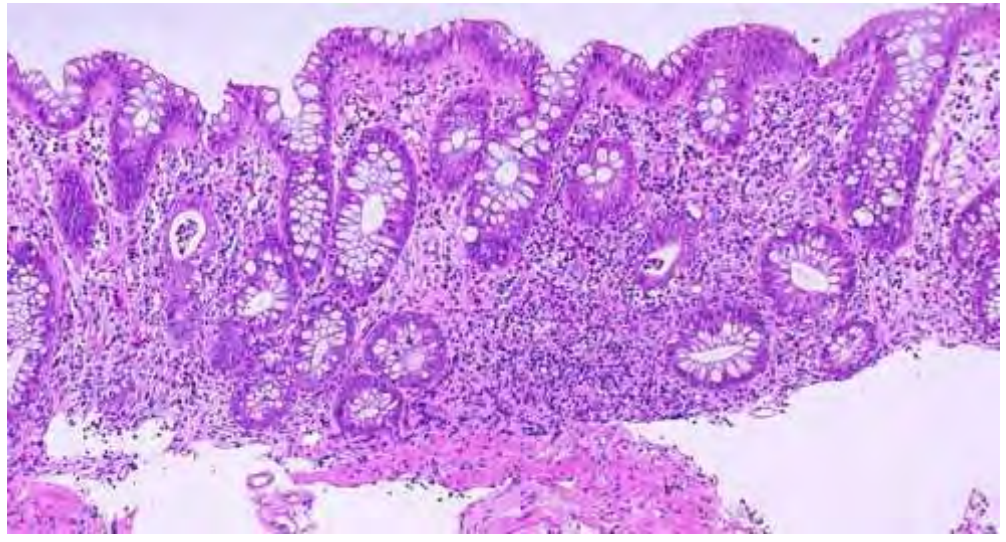












Take home messages

- Think of CVID when you have
  - Difficult to characterize GIT inflammation (various patterns, just doesn't fit right)
  - Severe gastritis (with architectural disturbance/atrophy)
  - Gastric dysplasia/cancer in a young patient

Envoi
SPECIALIST PATHOLOGISTS
inside insights

Low anterior resection for….something

Dr Mark Bettington

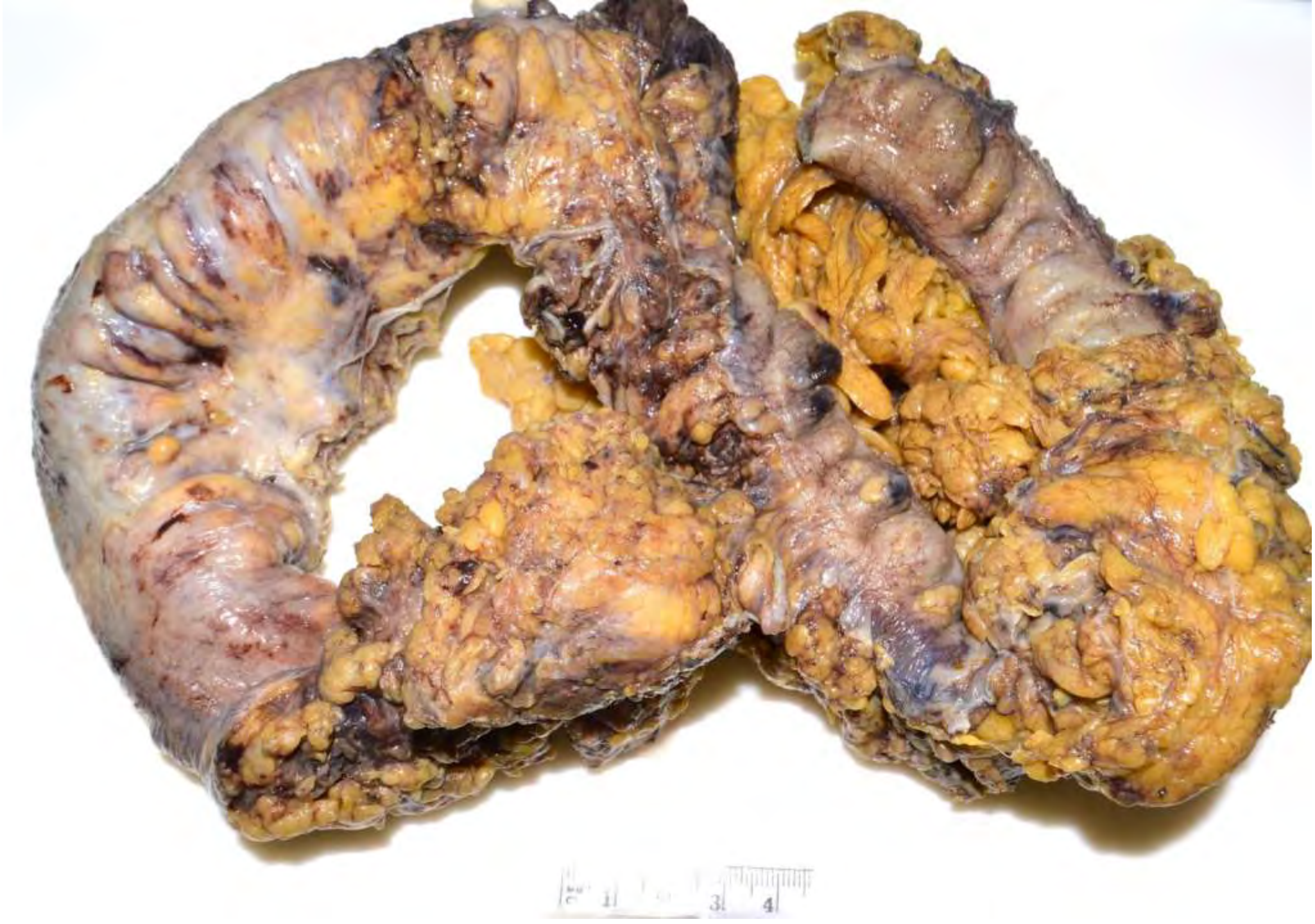
Patient details / specimen request form

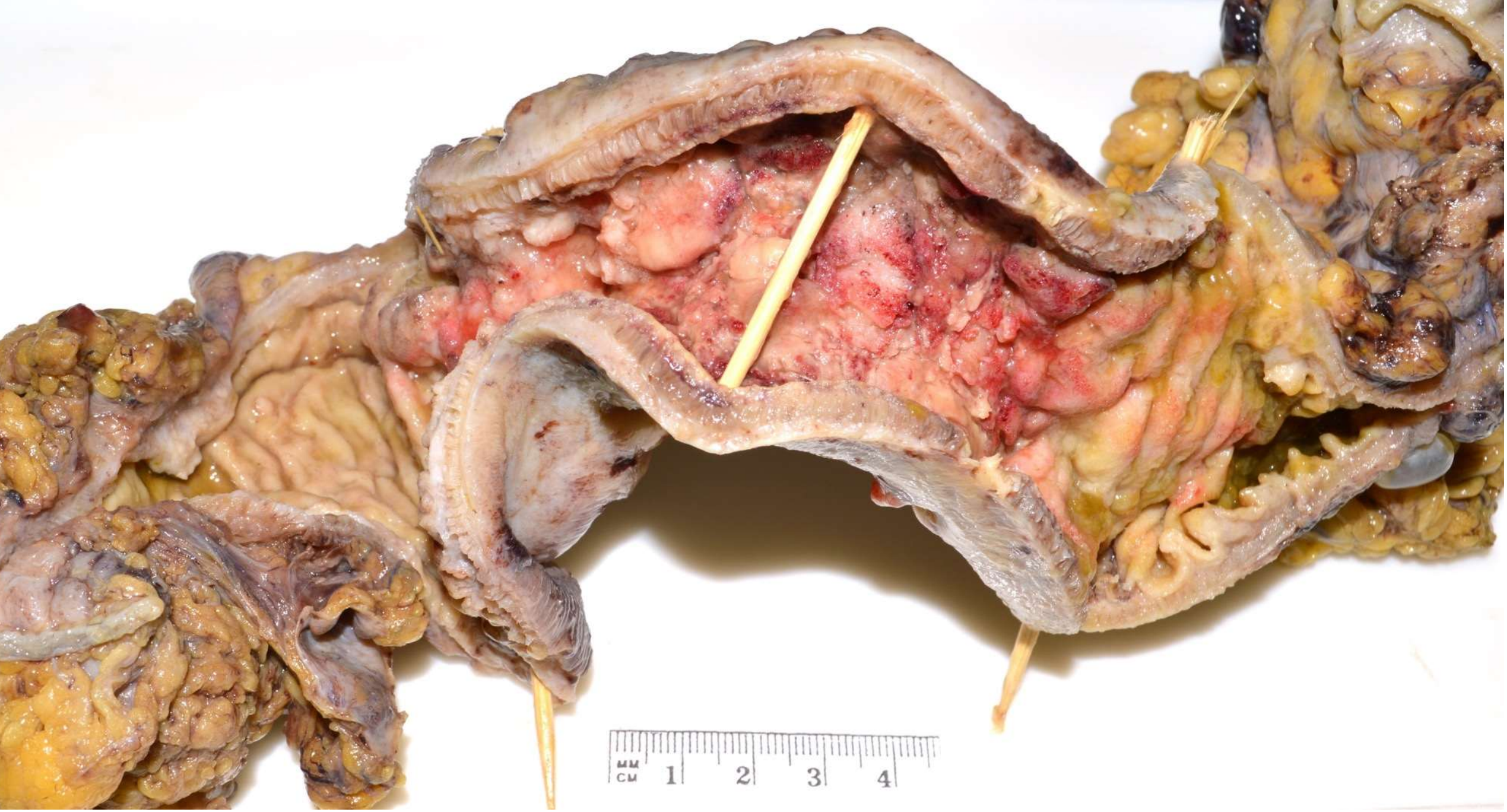
- Female
- 90 years old
- From central coast of Queensland
- No previous pathology on our system

Clinical notes:

“Ultra-low anterior extended Hartmann’s”

Macroscopic

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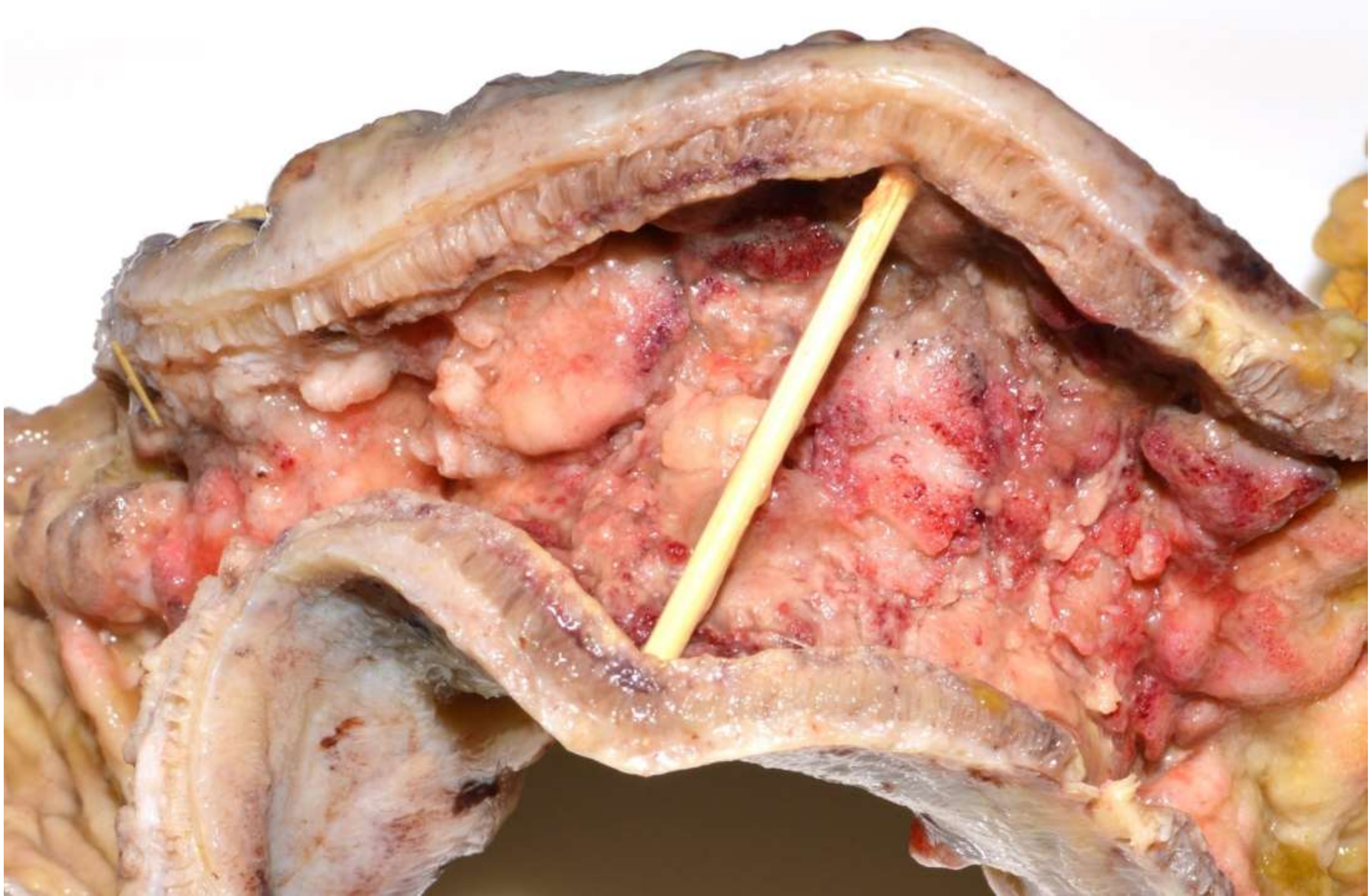
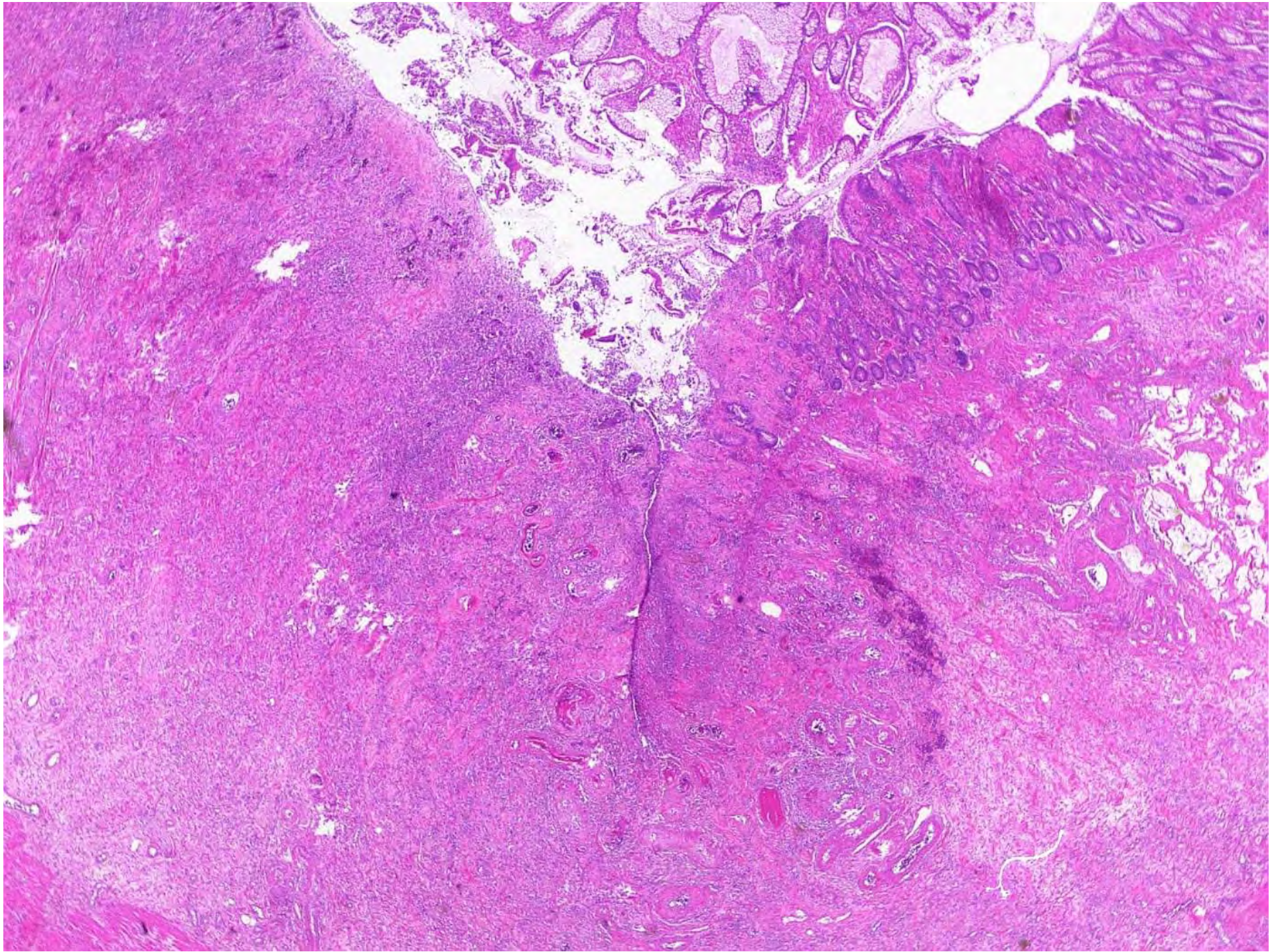
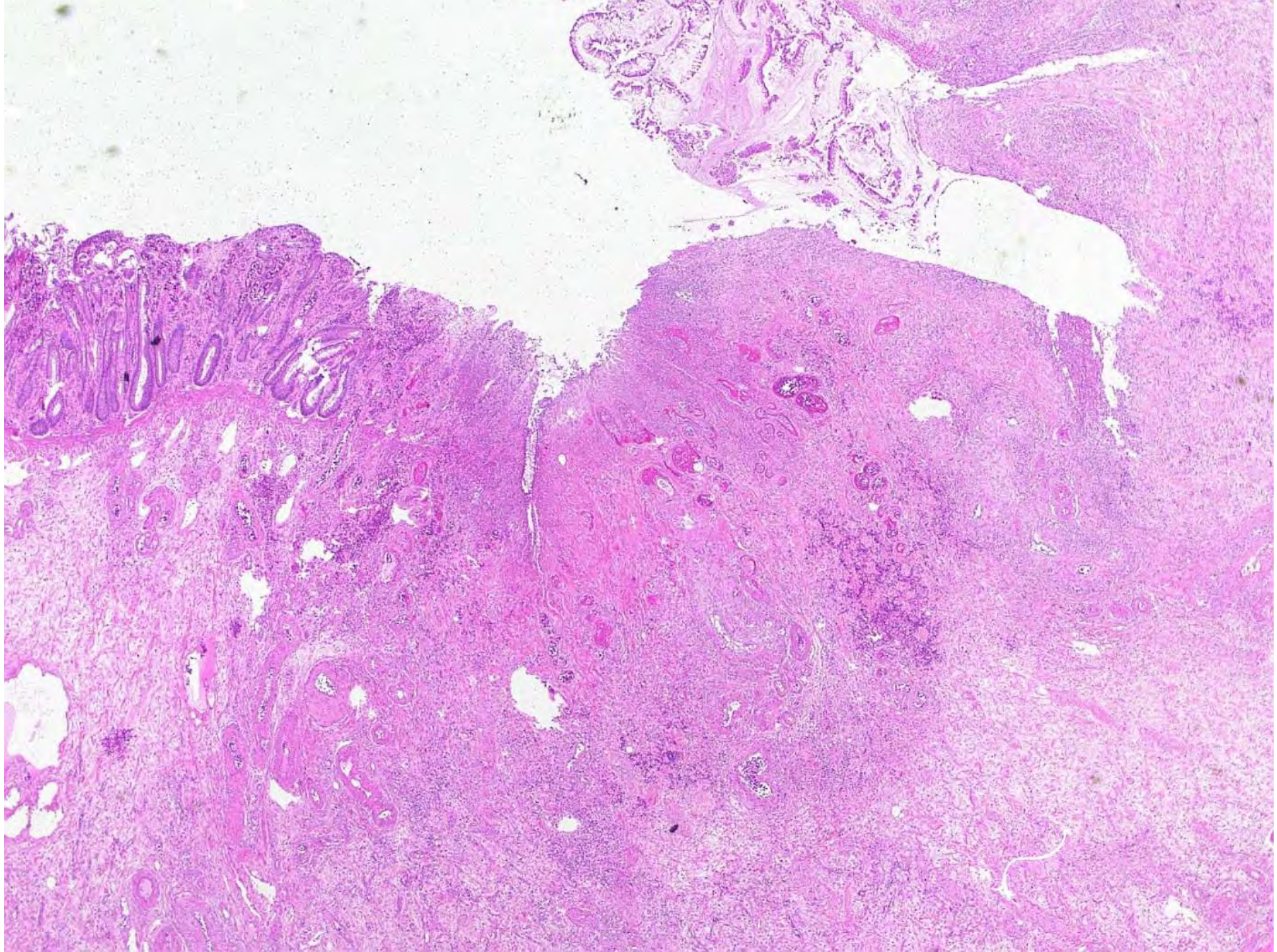


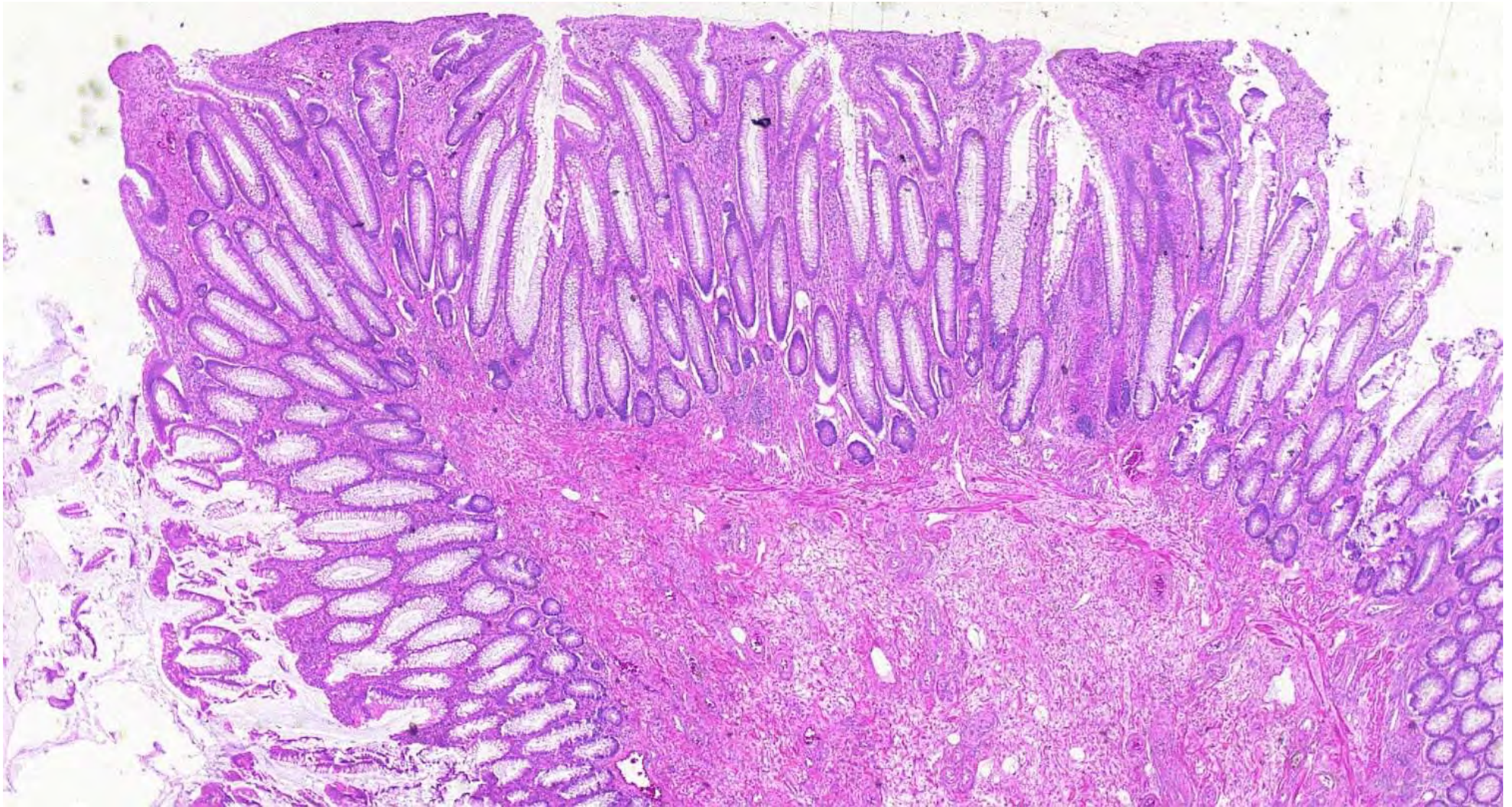
Macroscopic differential diagnosis?

- Cancer
- Not cancer

Microscopic







Microscopic differential diagnosis?

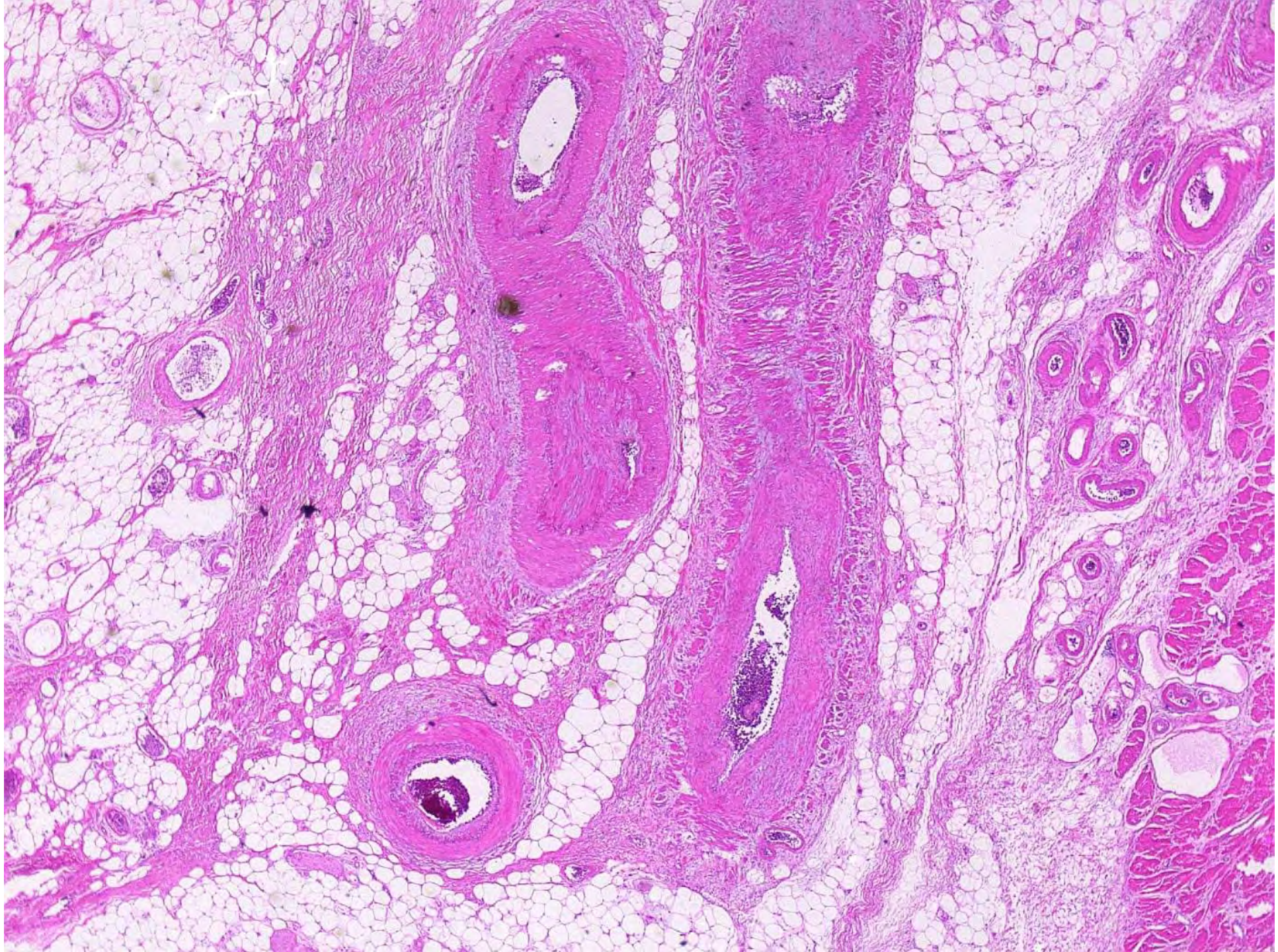
- Not cancer
- Ischaemic colitis
- Infectious colitis
- Radiation colitis

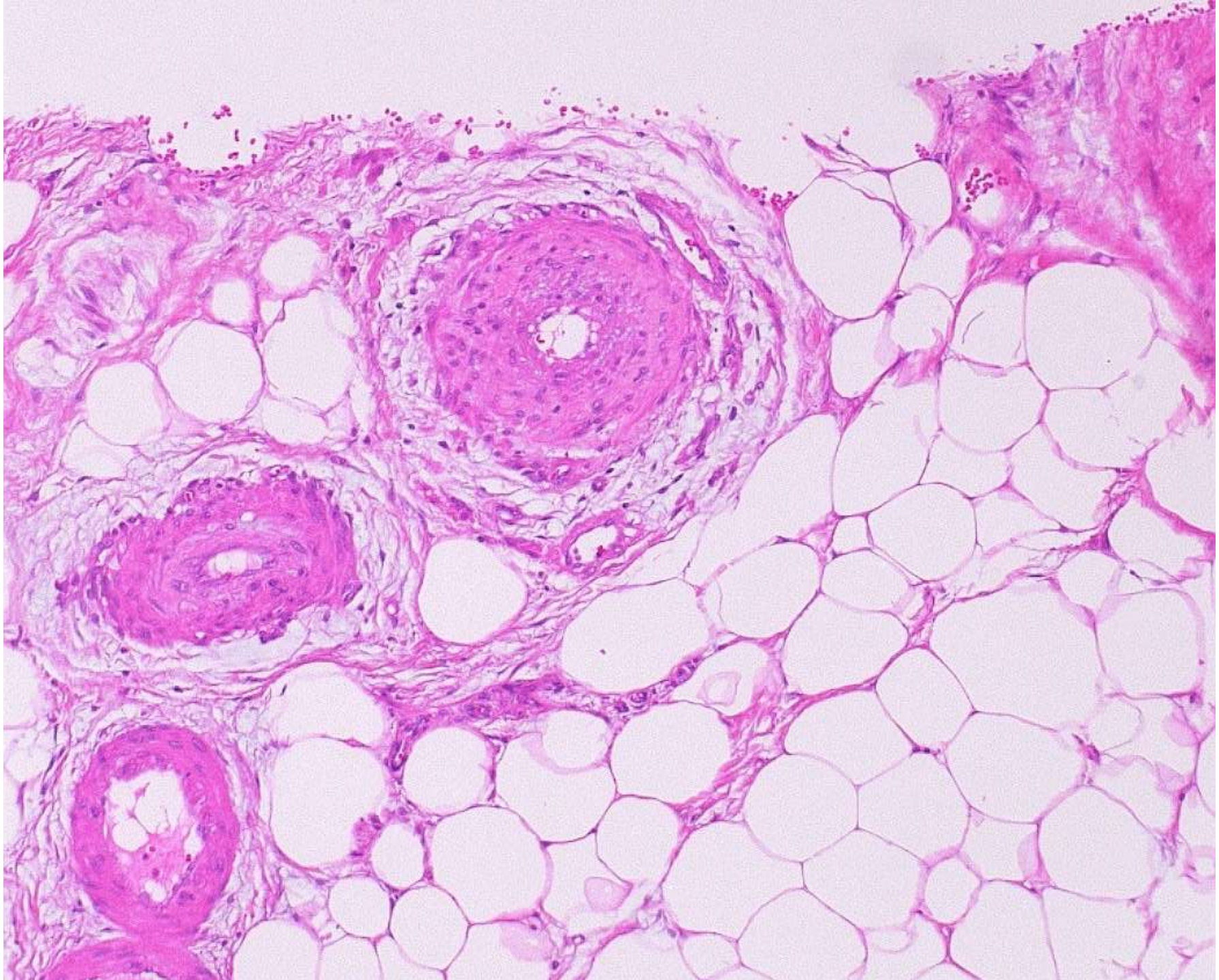
Phone a friend

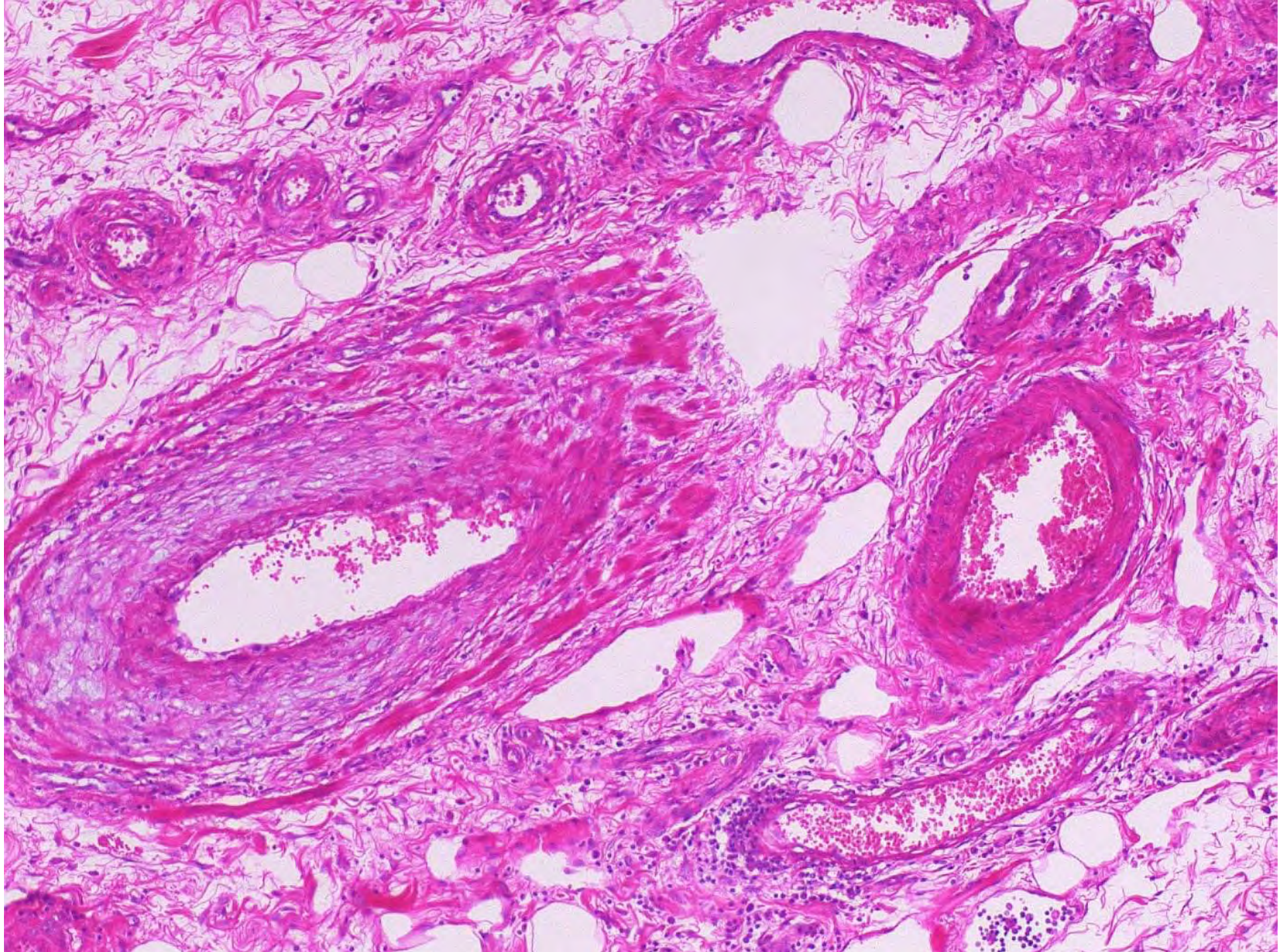
Further clinical history

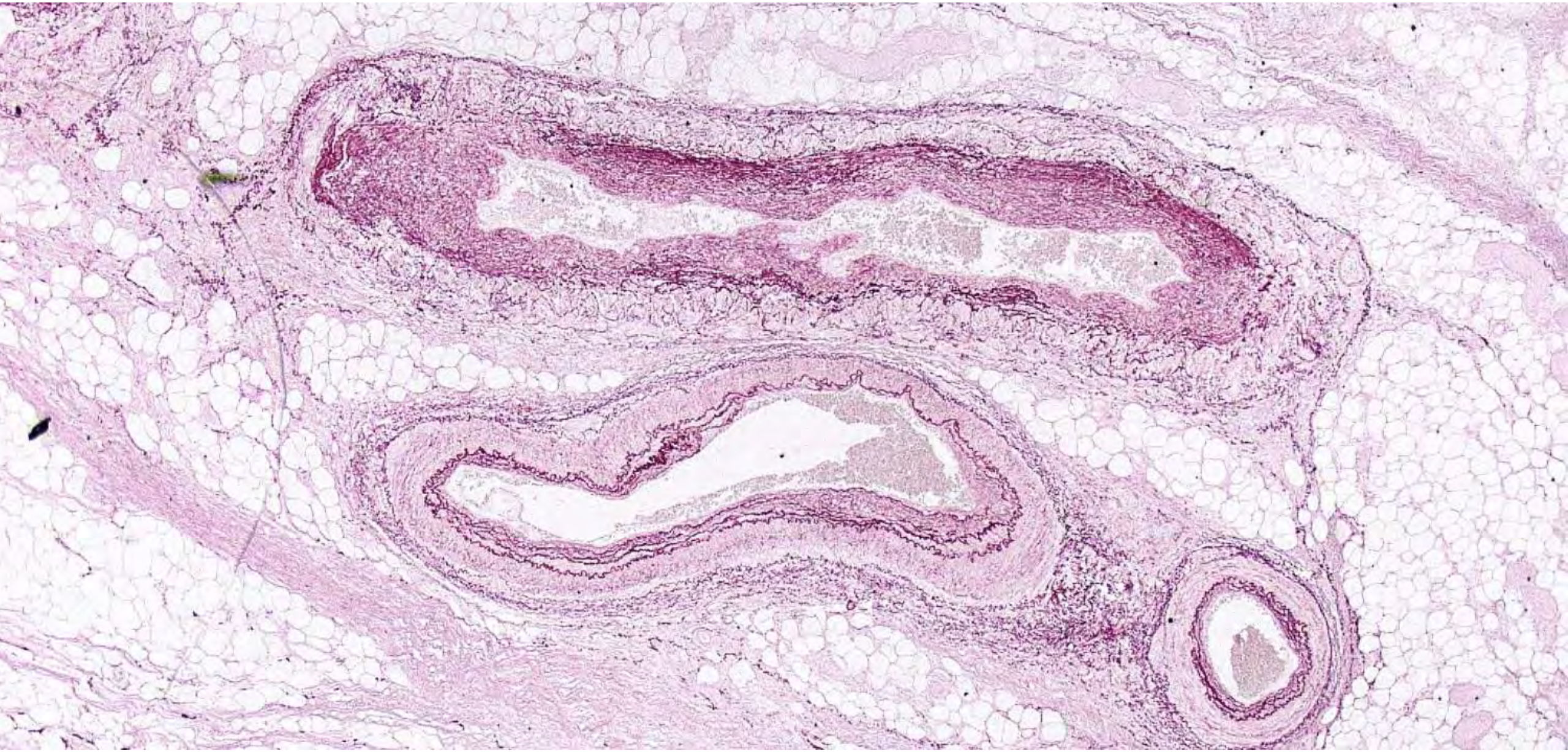
- Several weeks to months of intermittent pain and PR bleeding
- Getting worse
- No cancer diagnosis (pre-op colonoscopy done peripherally reported as non-specific ulceration)
- No radiation

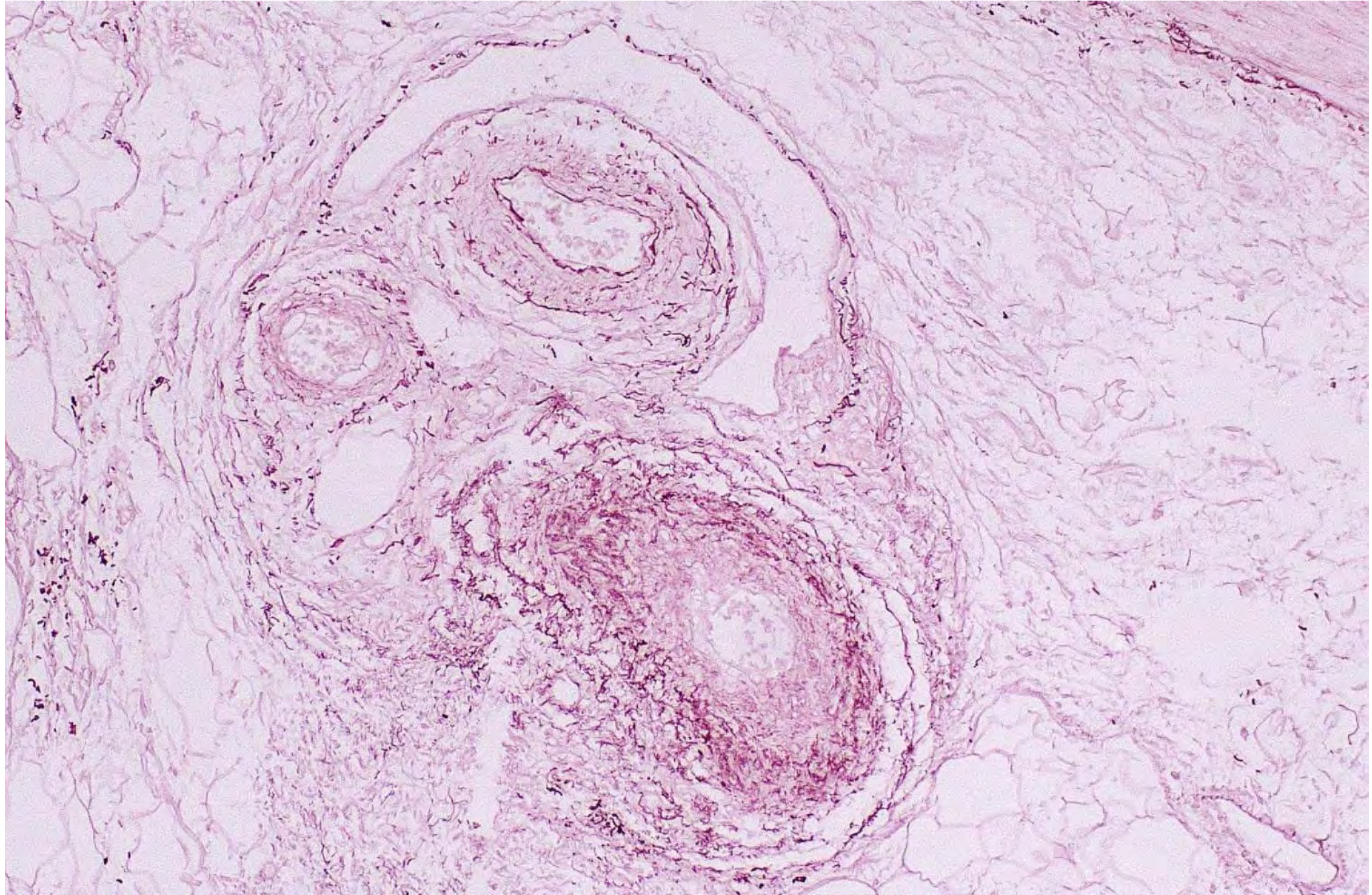
More helpful microscopic images

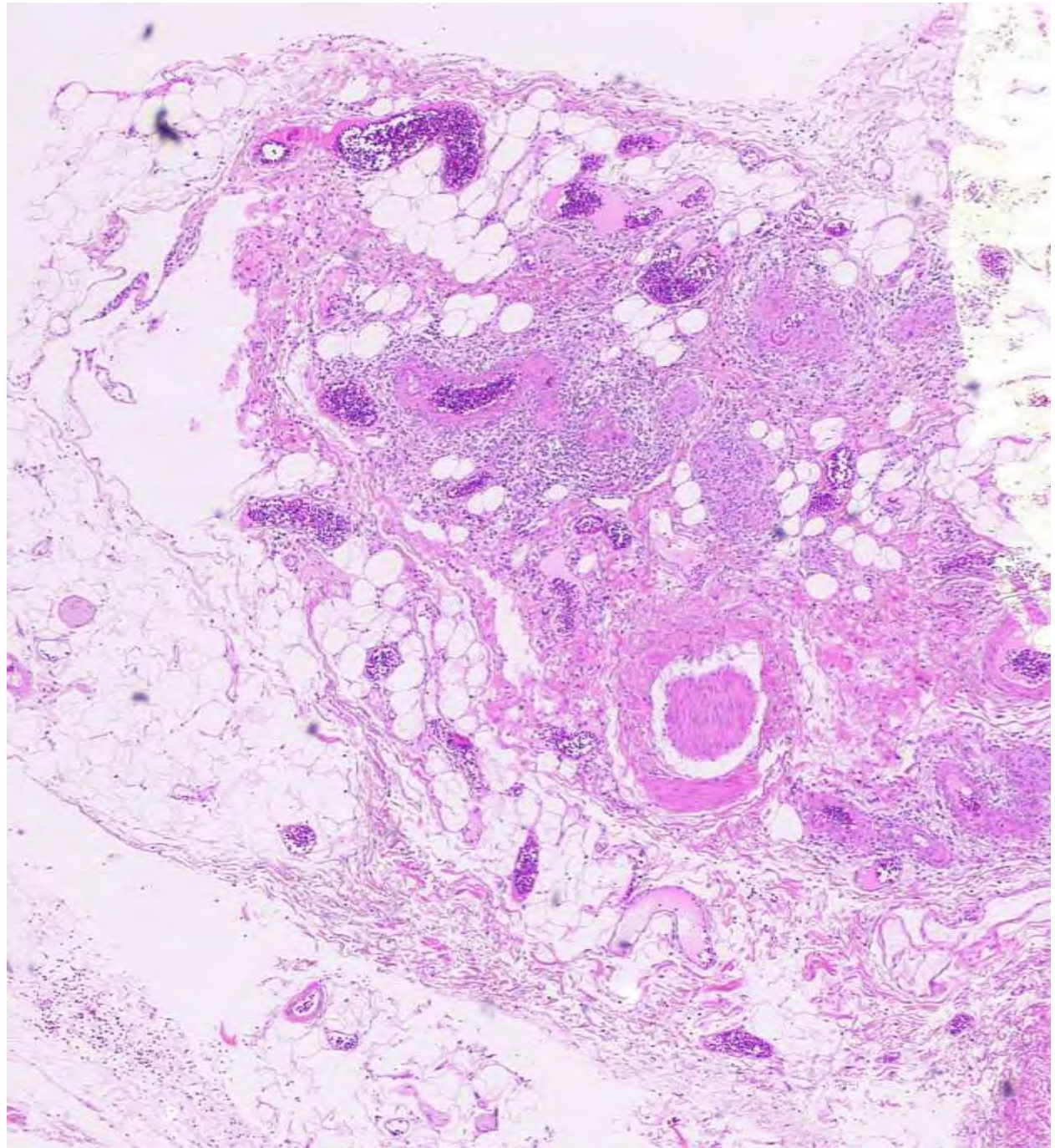


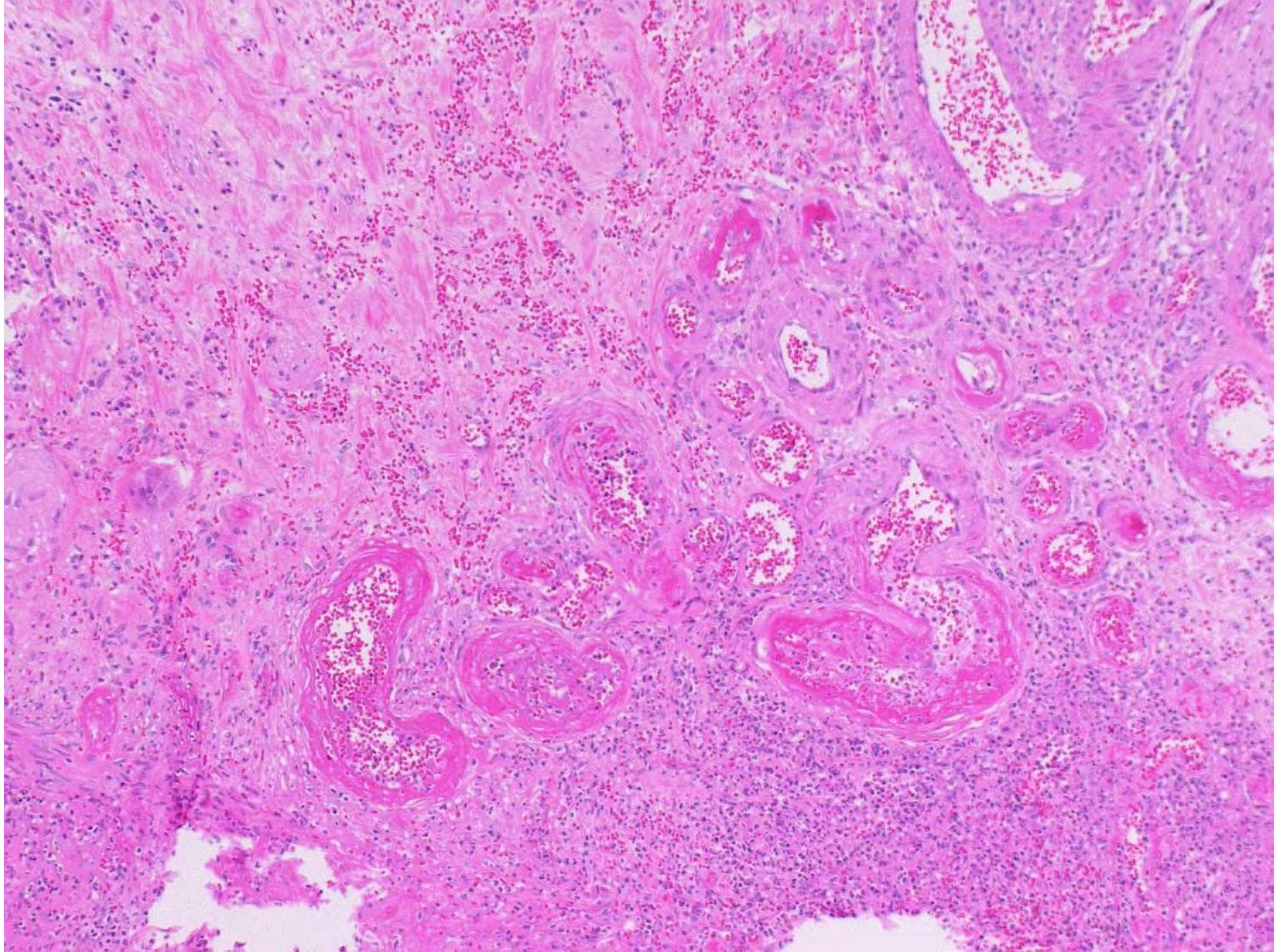


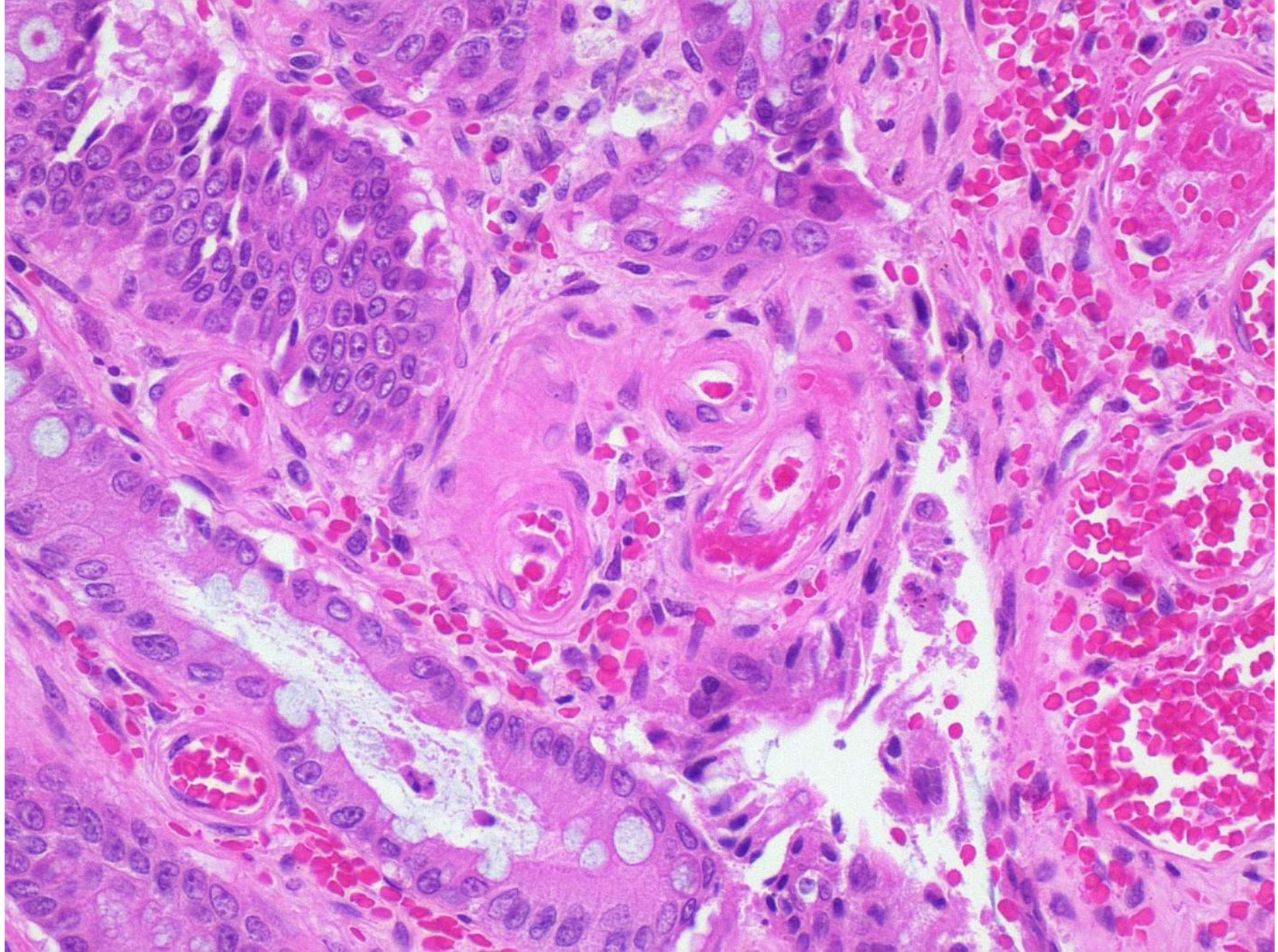


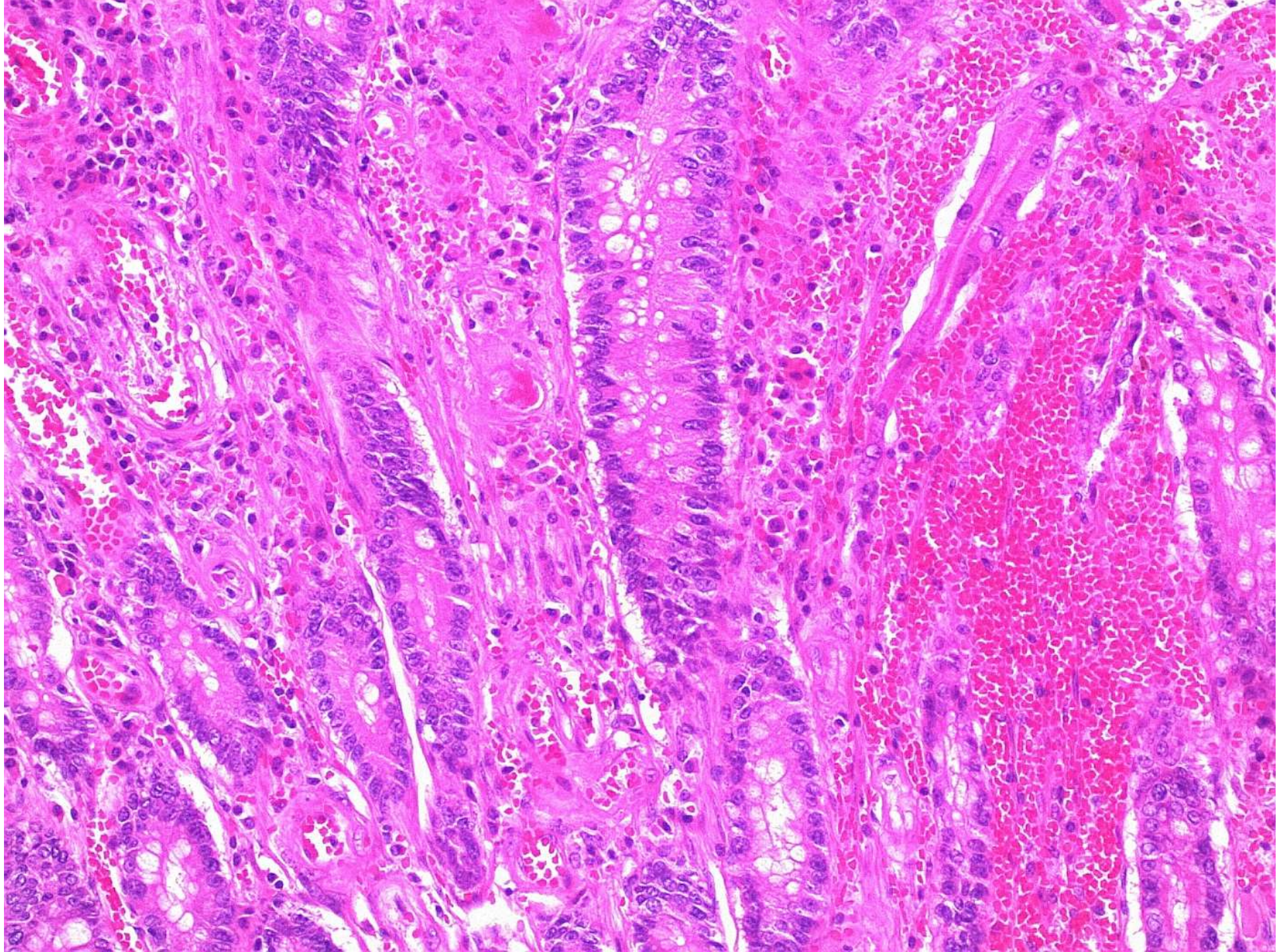












Idiopathic myointimal hyperplasia of mesenteric veins

- IMHMV is a rare condition first described in 1991 by Drs Genta and Haggitt and is characterised by non-inflammatory obliteration of medium to large mesenteric veins
- Initially thought to be most common in young men, it is now recognised to be most prevalent in the elderly
- Sigmoid colon is the most common location, but other areas can also be affected
- The aetiology is not well-defined but it may be secondary to chronic traction on the mesenteric veins
- Presents with intermittent pain and bloody diarrhoea
- Surgical resection is curative

Differential diagnosis

- Inflammatory bowel disease
  - more often the clinical impression than the histopathological impression
- Ischaemic colitis
  - not incorrect as the result is an ischaemic colitis
  - the venous changes are the best discriminating feature
- Radiation colitis
  - history is probably most important
  - radiation injury should be fairly limited in the sigmoid colon
- Diverticular disease associated colitis
- Mesenteric inflammatory veno-occlusive disease
  - this may be part of the spectrum of IMHMV but may be a separate disease
  - has a wider distribution (stomach, small bowel, proximal colon)
  - inflammatory changes around the veins
  - some reports of relationship to previous CMV, vasculitis, etc

Diagnosis

- The obliterative venous changes are the key feature, however some authors have suggested the diagnosis can be made on biopsy specimens
- The constellation of subendothelial fibrin deposition, fibrin thrombi and arteriolisation of the lamina propria capillaries are features that are reported as specific for IMHMV in mucosal biopsies
- Hyalinisation of the lamina propria, crypt loss, architectural distortion, ulceration all occur but are not specific
- We have raised the possibility a few times (some of us are more enthusiastic in this regard than others), but none have gone on to surgery so we have no confirmed mucosal diagnoses at this time

Summary

- Idiopathic myointimal hyperplasia or mesenteric veins is very rare
- Should be considered when presented with a sigmoid colectomy with ischaemic pattern of injury
- The diagnosis on endoscopic biopsy specimens is possible but requires a high index of suspicion and fully develop features

Envoi
SPECIALIST PATHOLOGISTS
inside insights

It's not a Tumour – Colonic Polyps that mimic carcinoma

Dr Gregory Miller

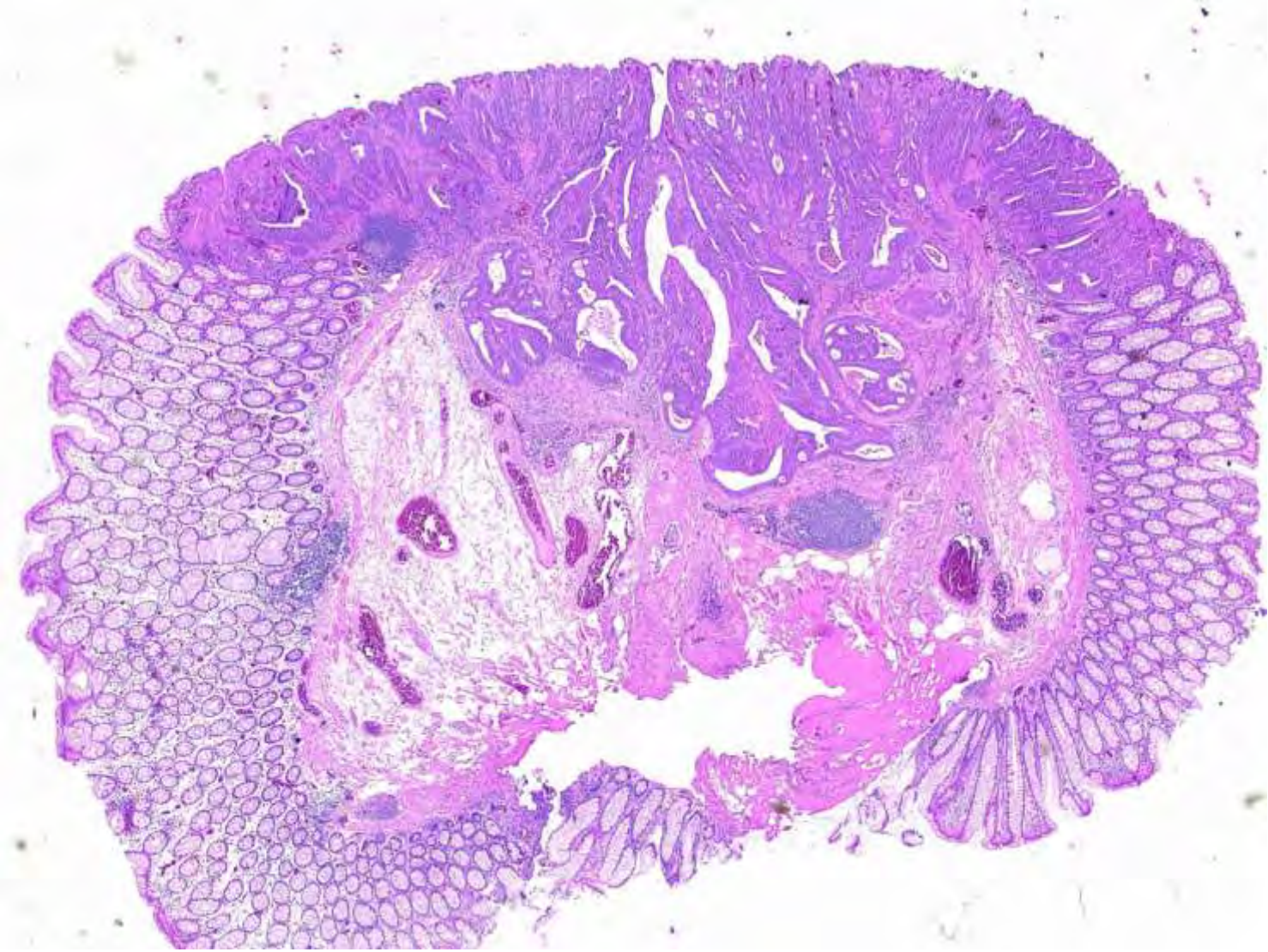
Outline

- Criteria for invasion in the colon
- Misplaced epithelium/pseudoinvasion
- Other problematic polyps

Criteria for Invasion in the colon

- Abnormal gland architecture and cellular cytology (malignant glands)
- Invasion through the muscularis mucosae into submucosal
- Usually associated with a desmoplastic stromal response

- All 3 are usually present and necessary for the diagnosis of adenocarcinoma in the colon

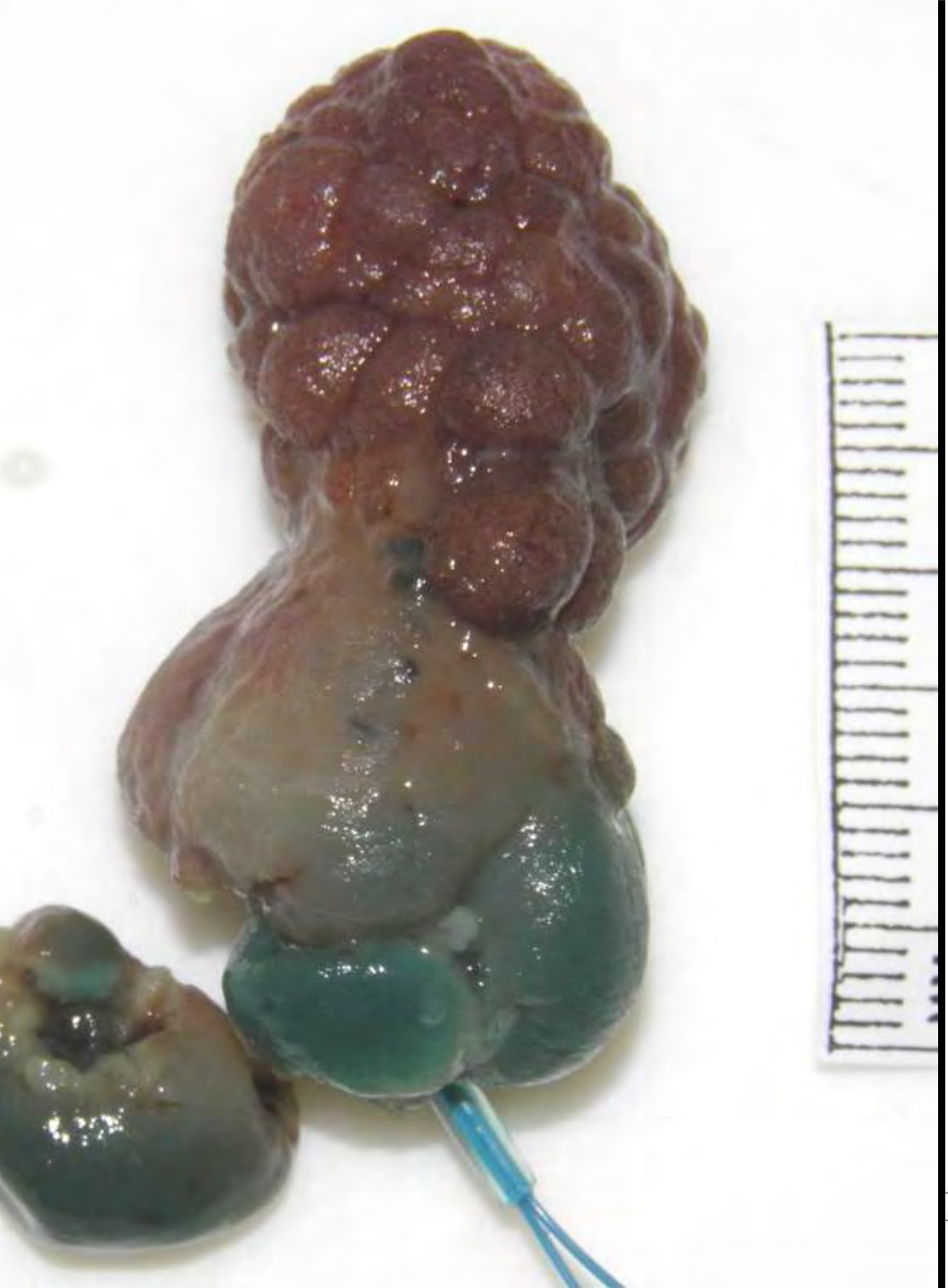


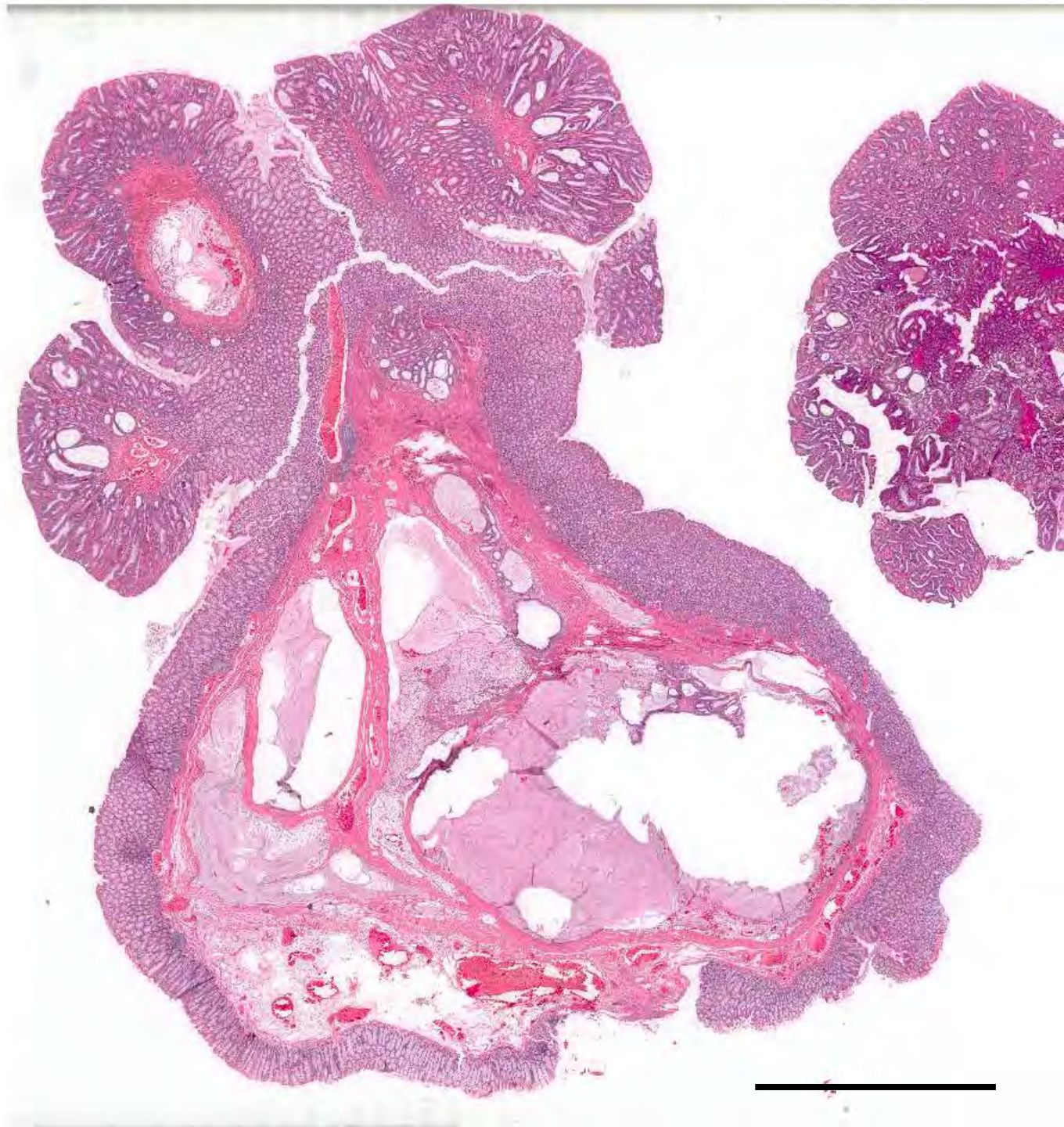
Cases with some features of invasion

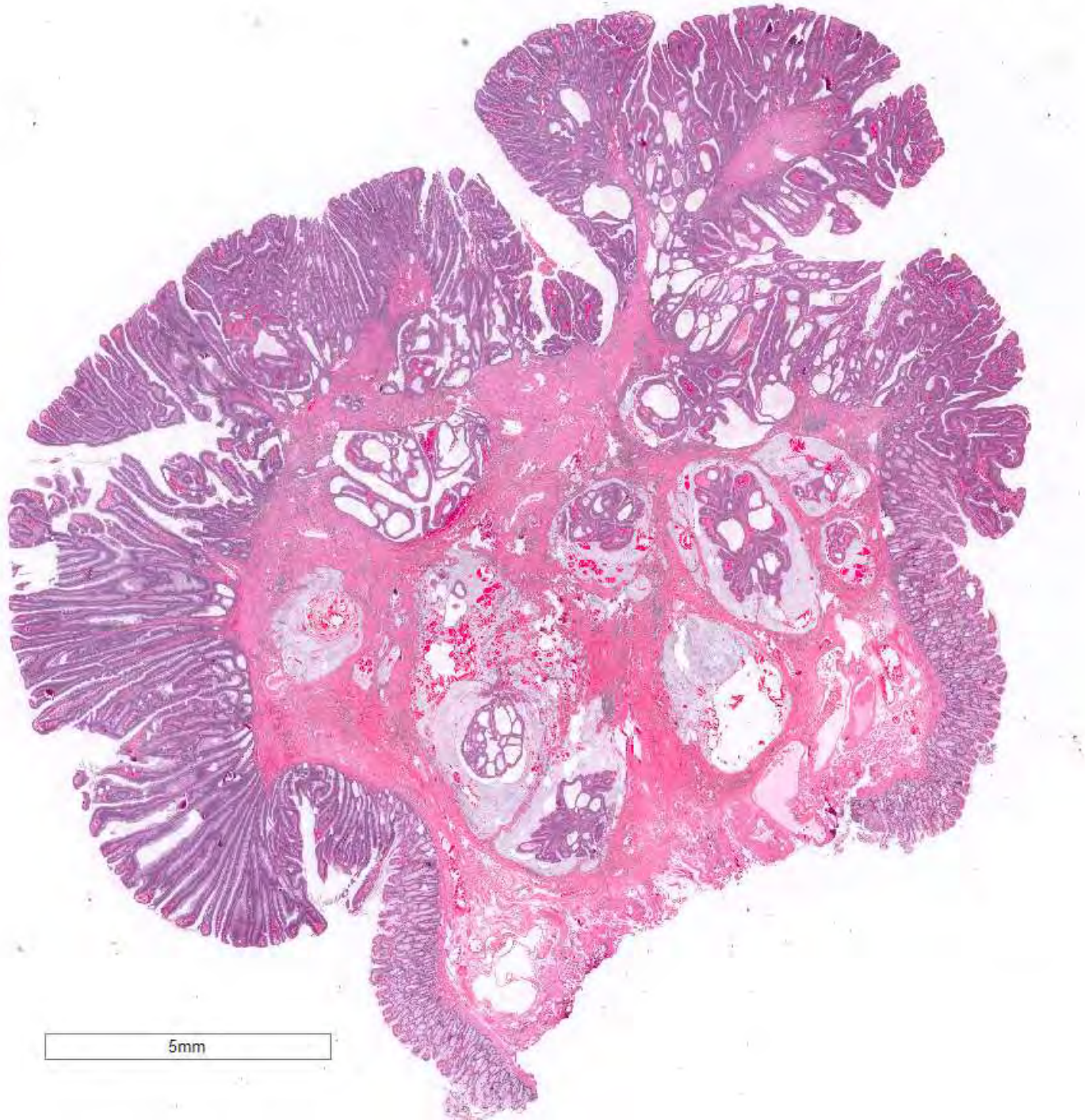
- Misplaced epithelium in a pedunculated polyp
- Inverted growth of sessile serrated lesions
- Involvement of lymphoglandular complexes

- Biopsy site reactions

- “Intramucosal” Adenocarcinoma
- Non-invasive lesions with lymphatic invasion



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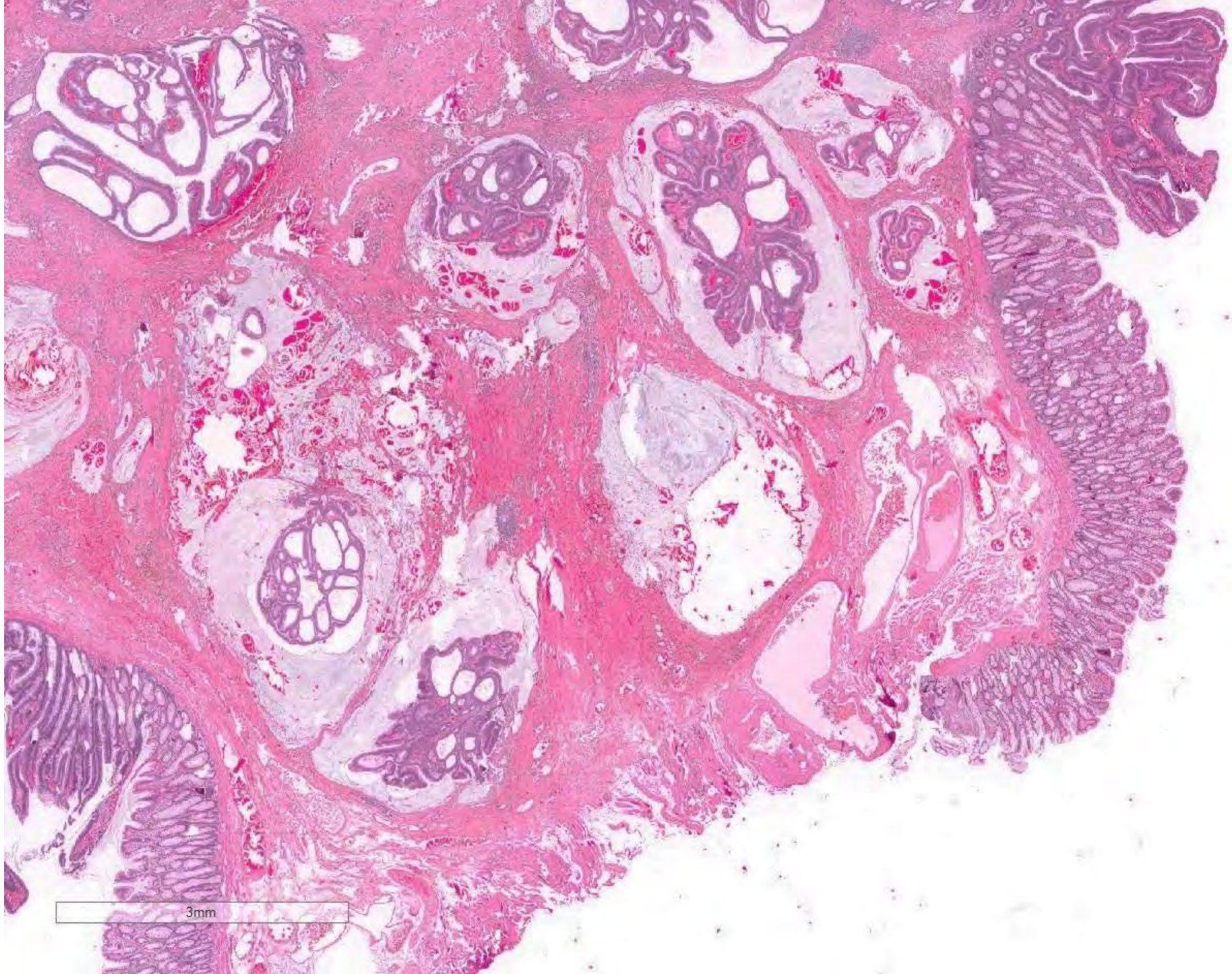
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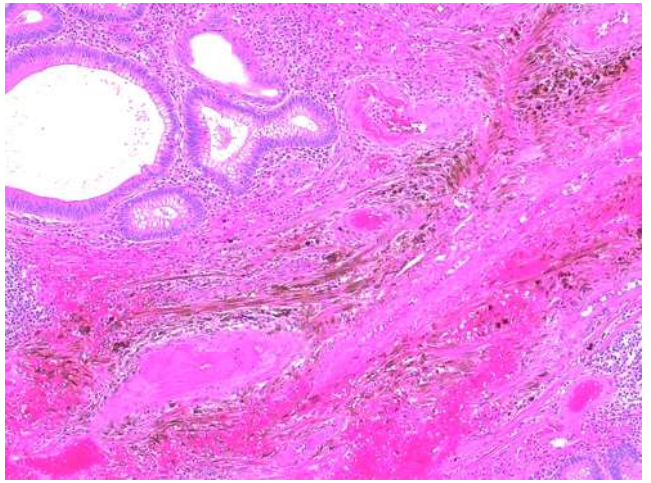
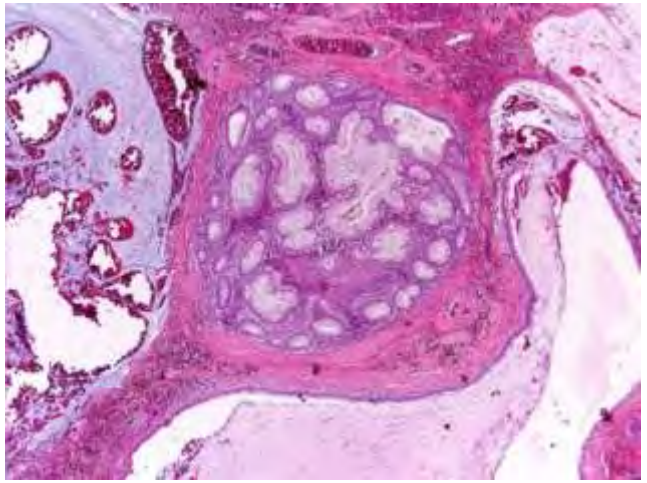
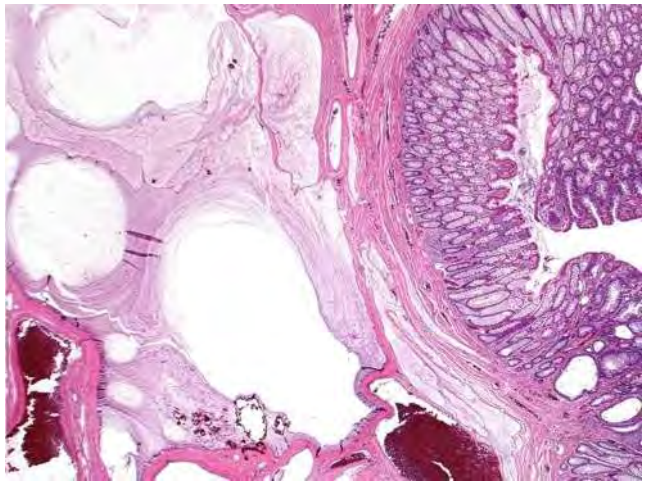
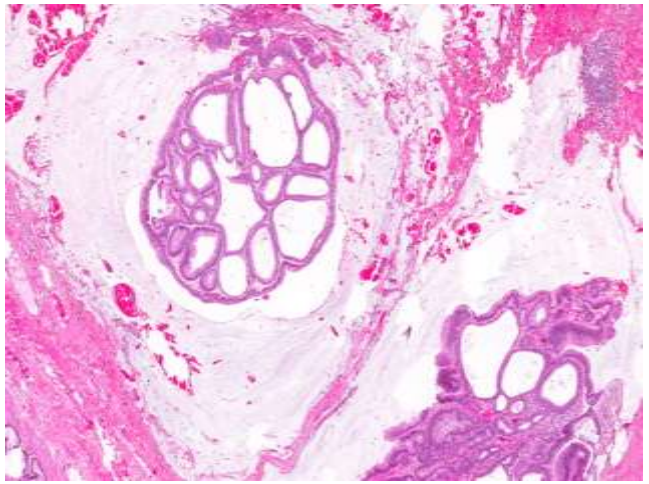
Misplaced epithelium / Pseudoinvasion

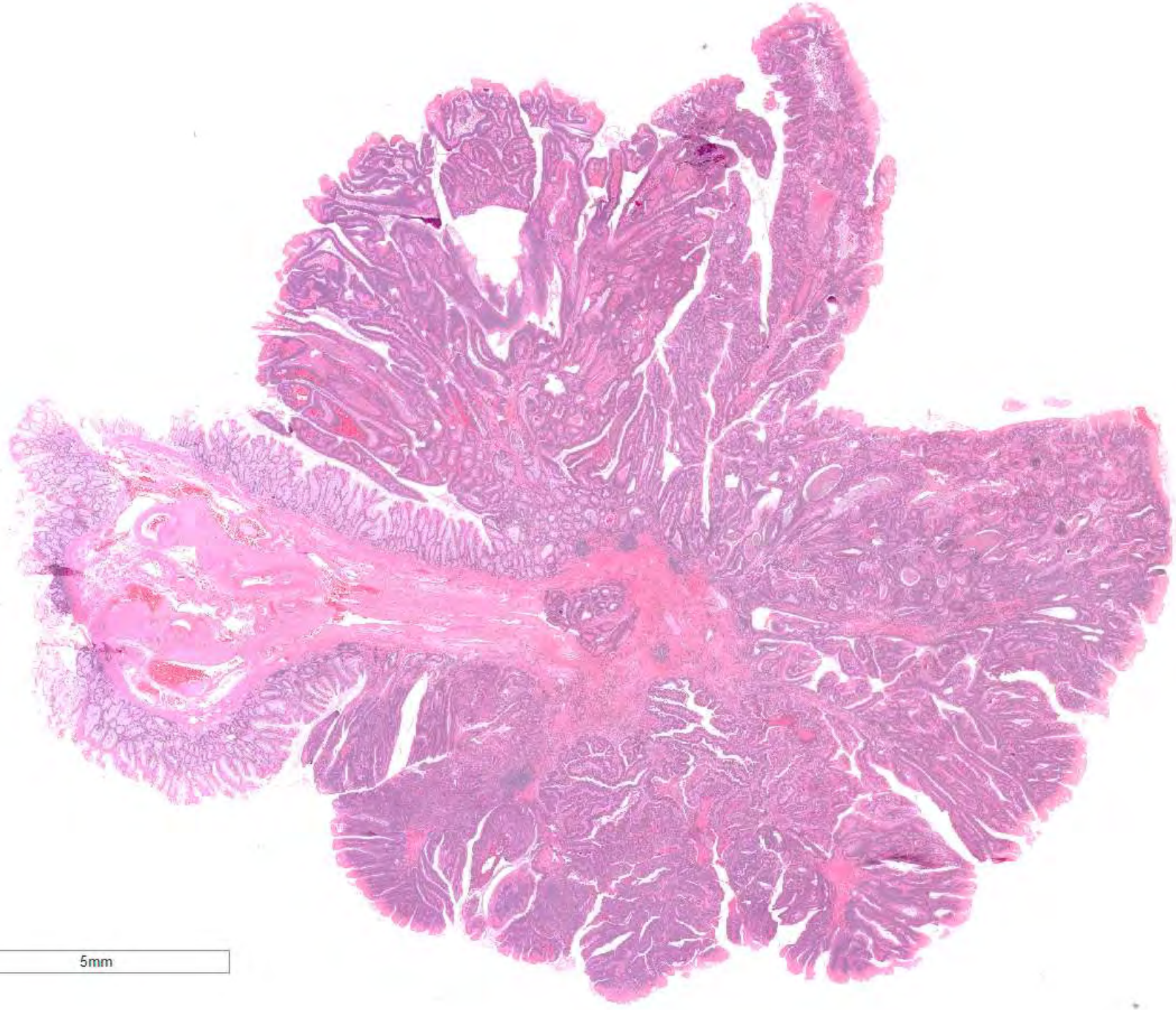
- Helpful criteria
  - Haemorrhage and haemosiderin
  - Rounded gland contours
  - Lamina propria surrounding glands
  - Mucin pools in submucosa
  - Normal glands/glands resembling overlying epithelium







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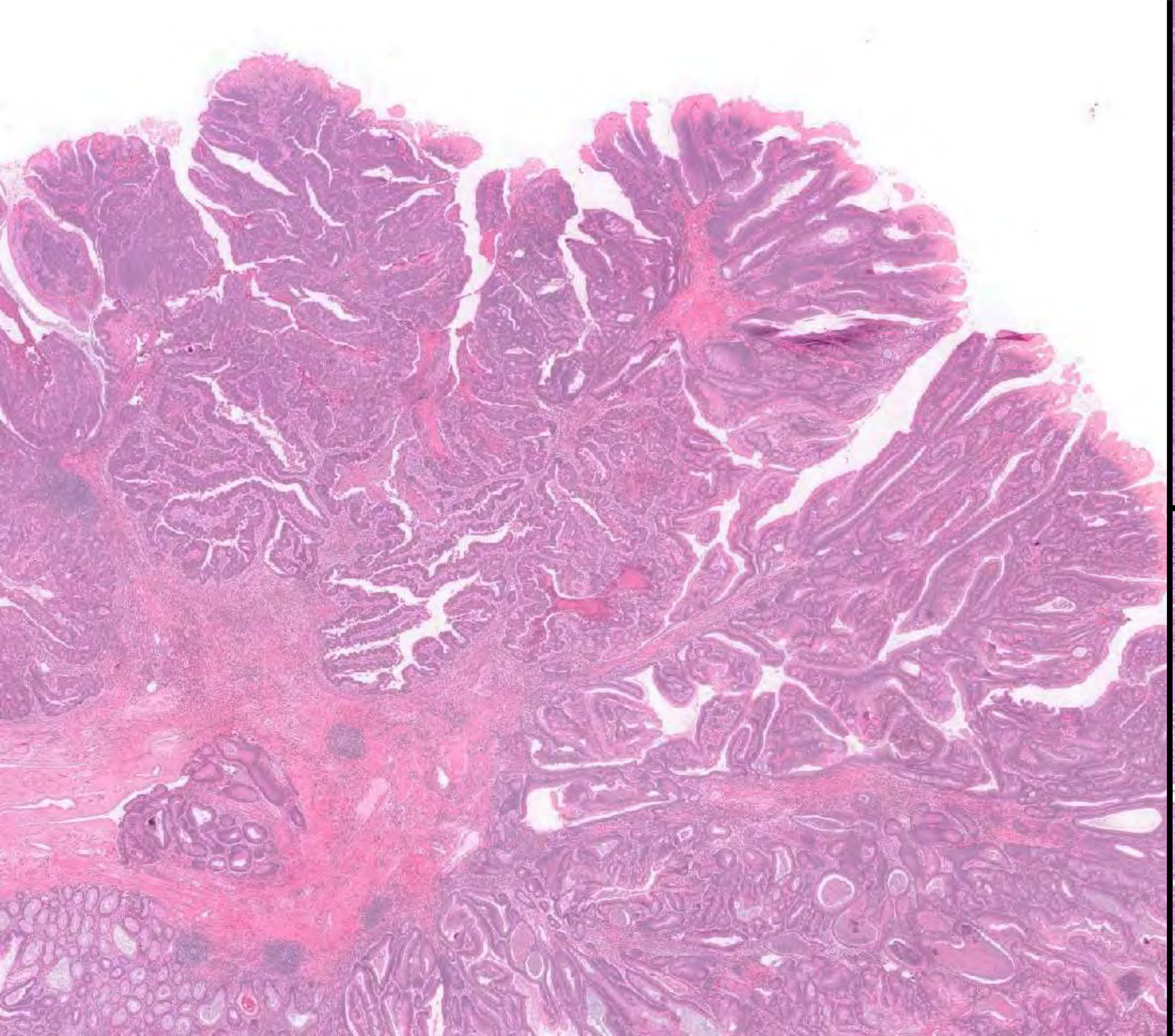
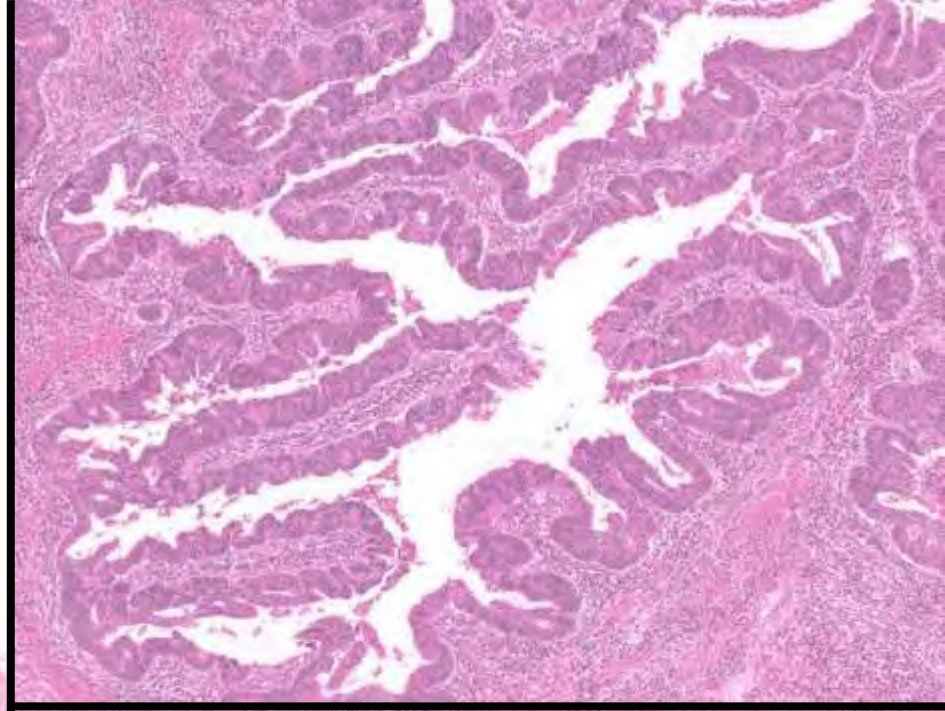
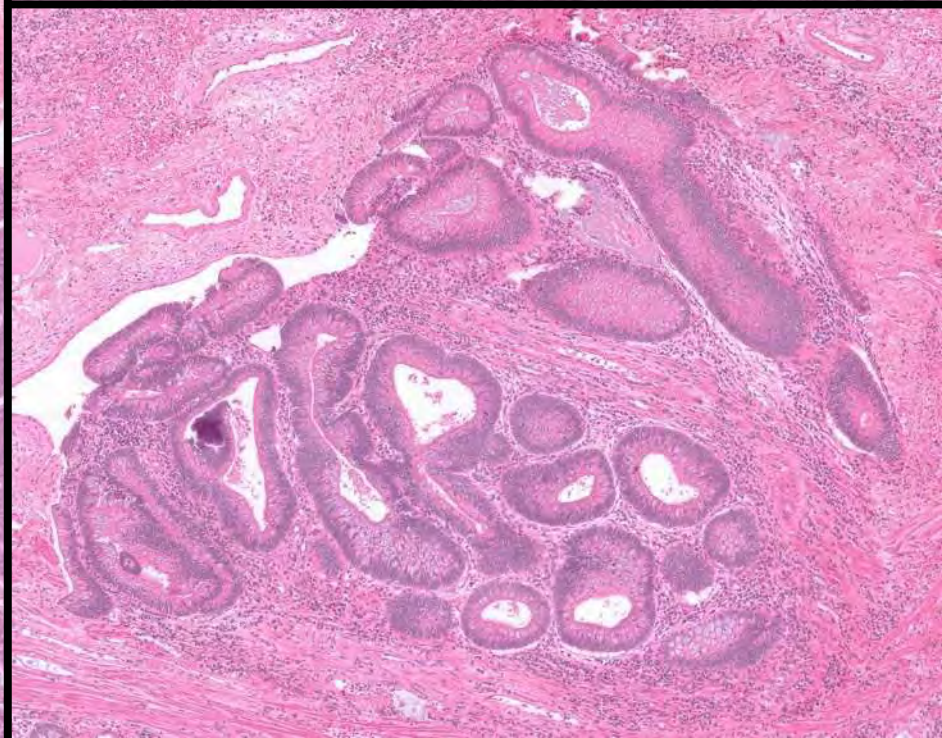
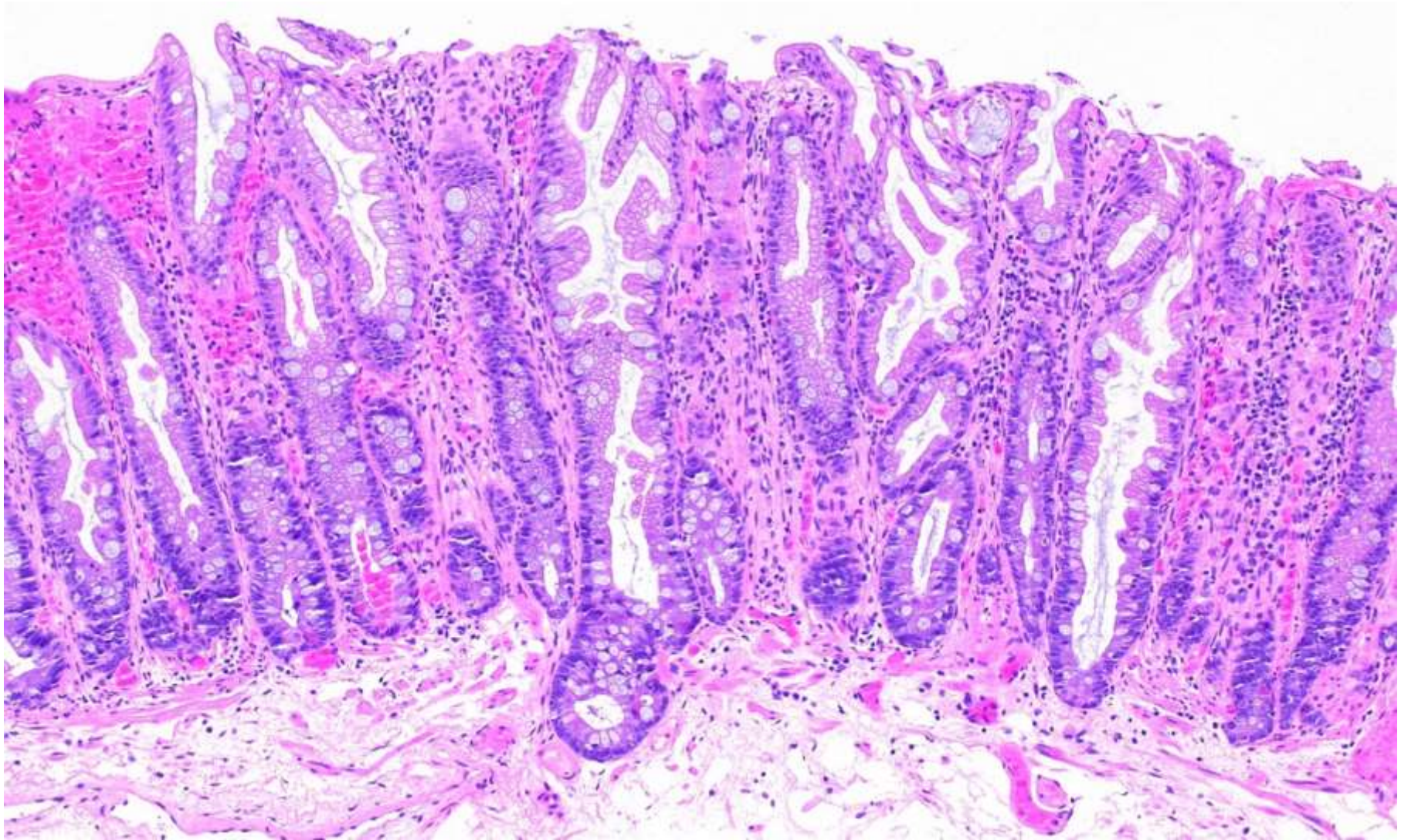
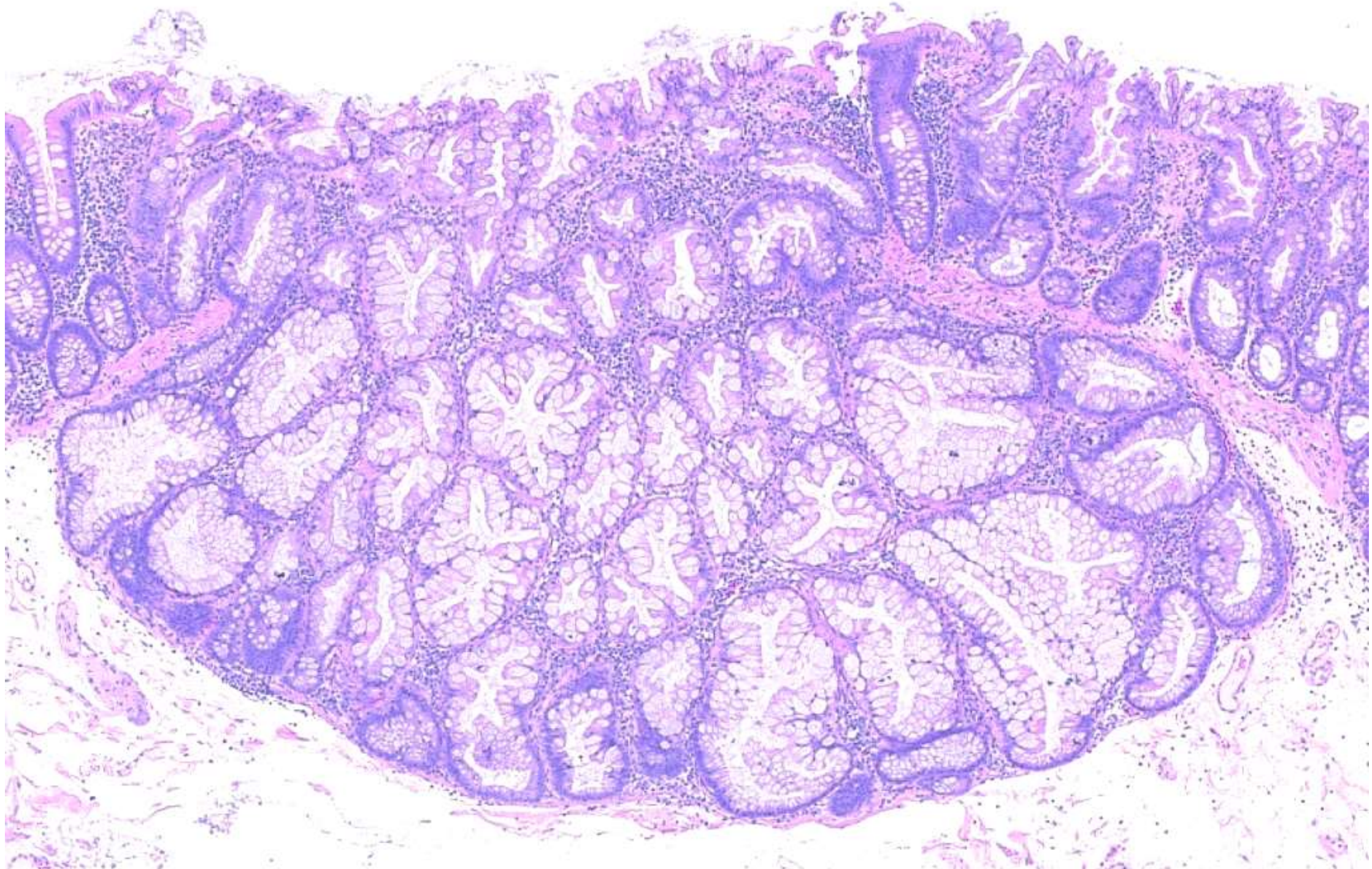




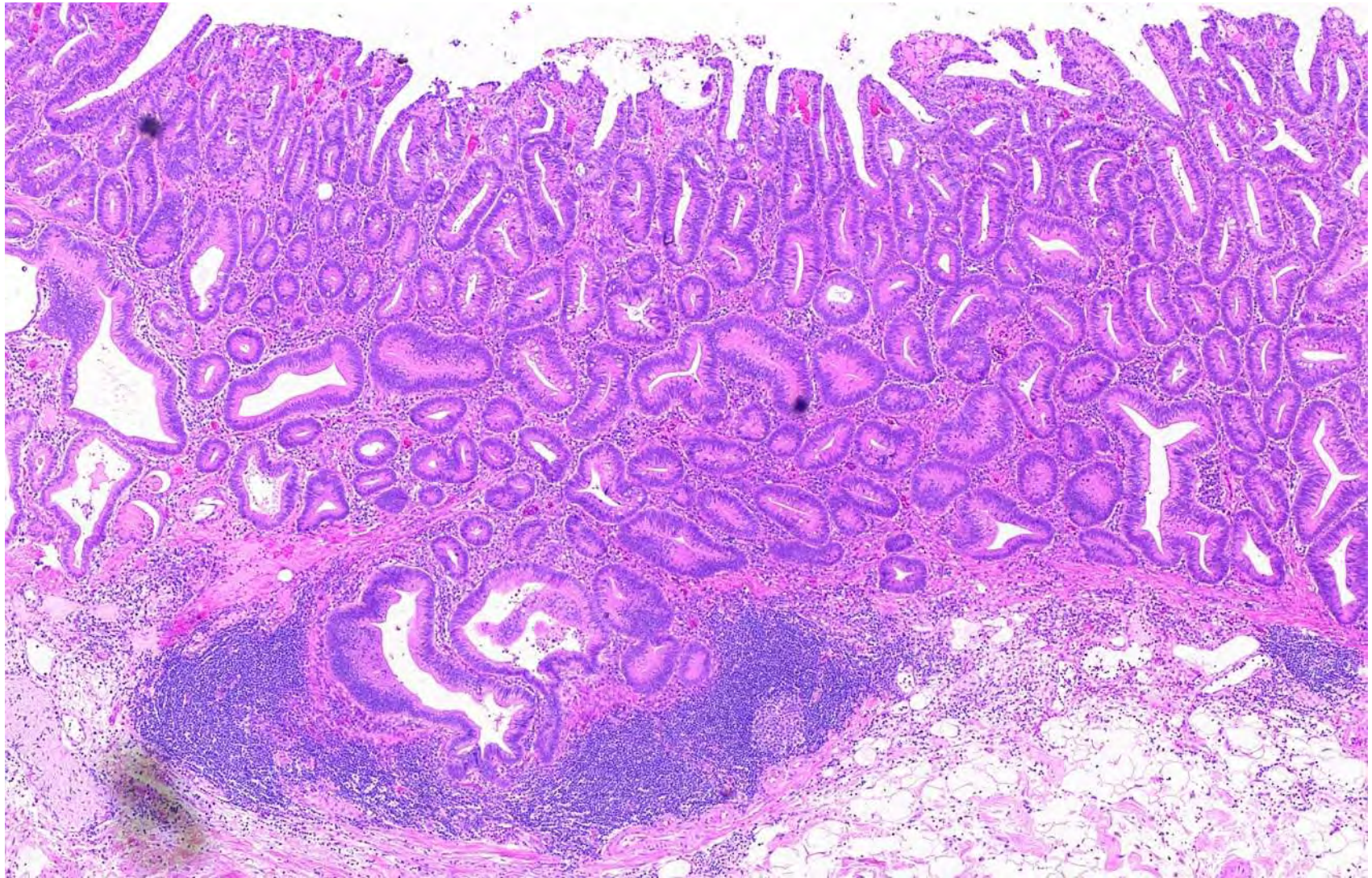


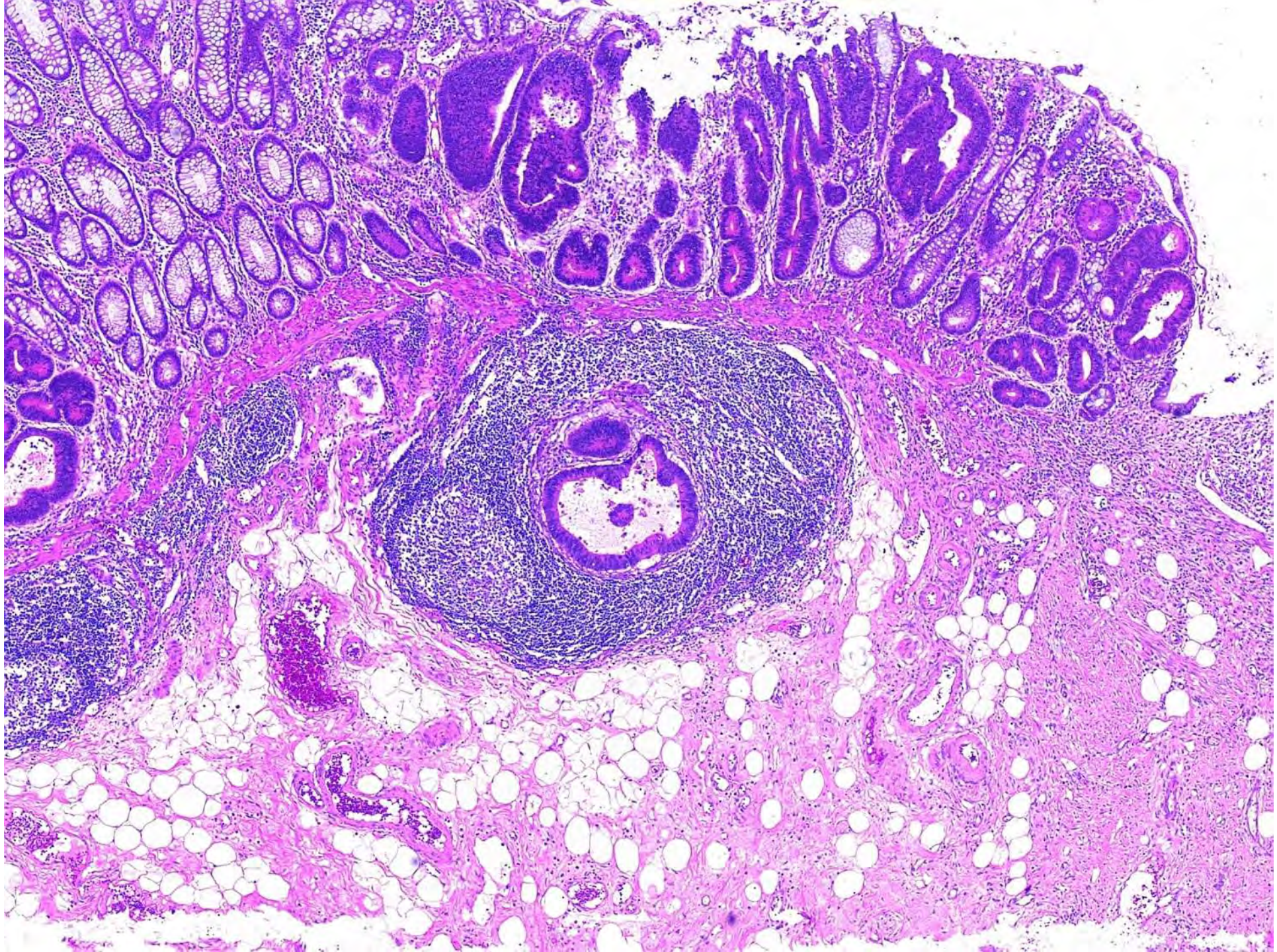
Inverted growth

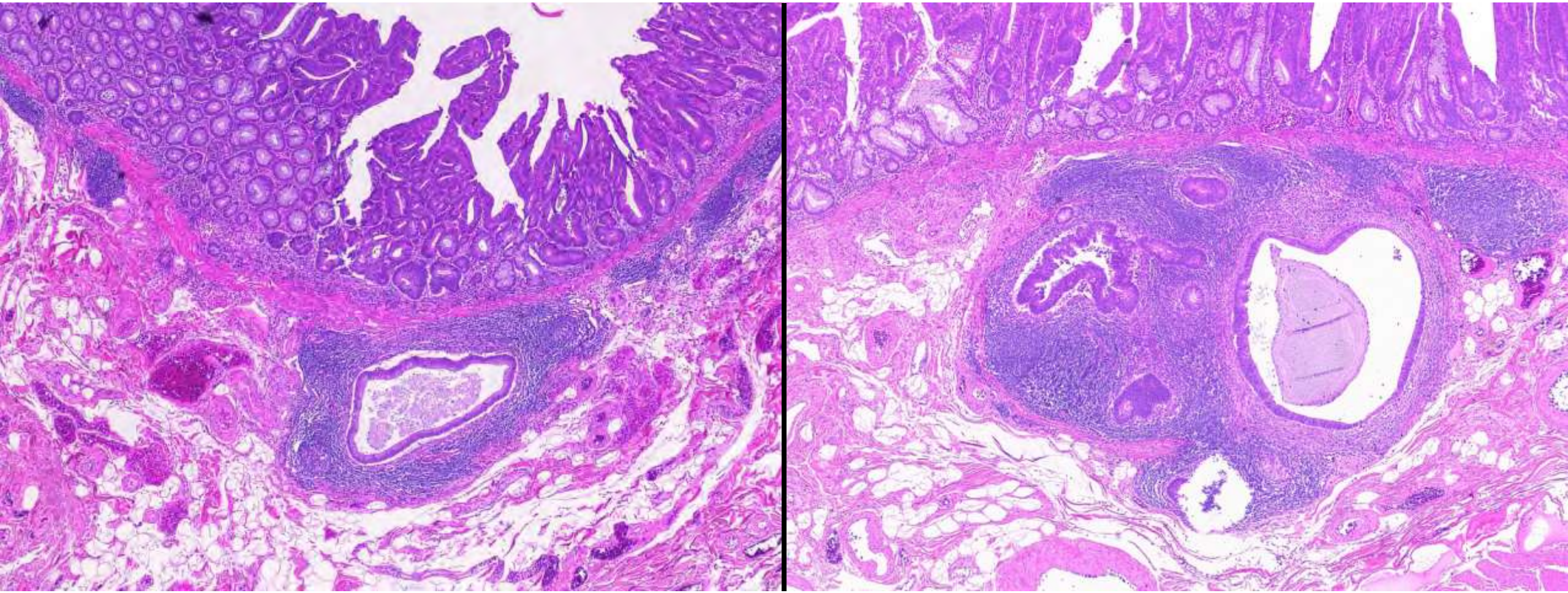


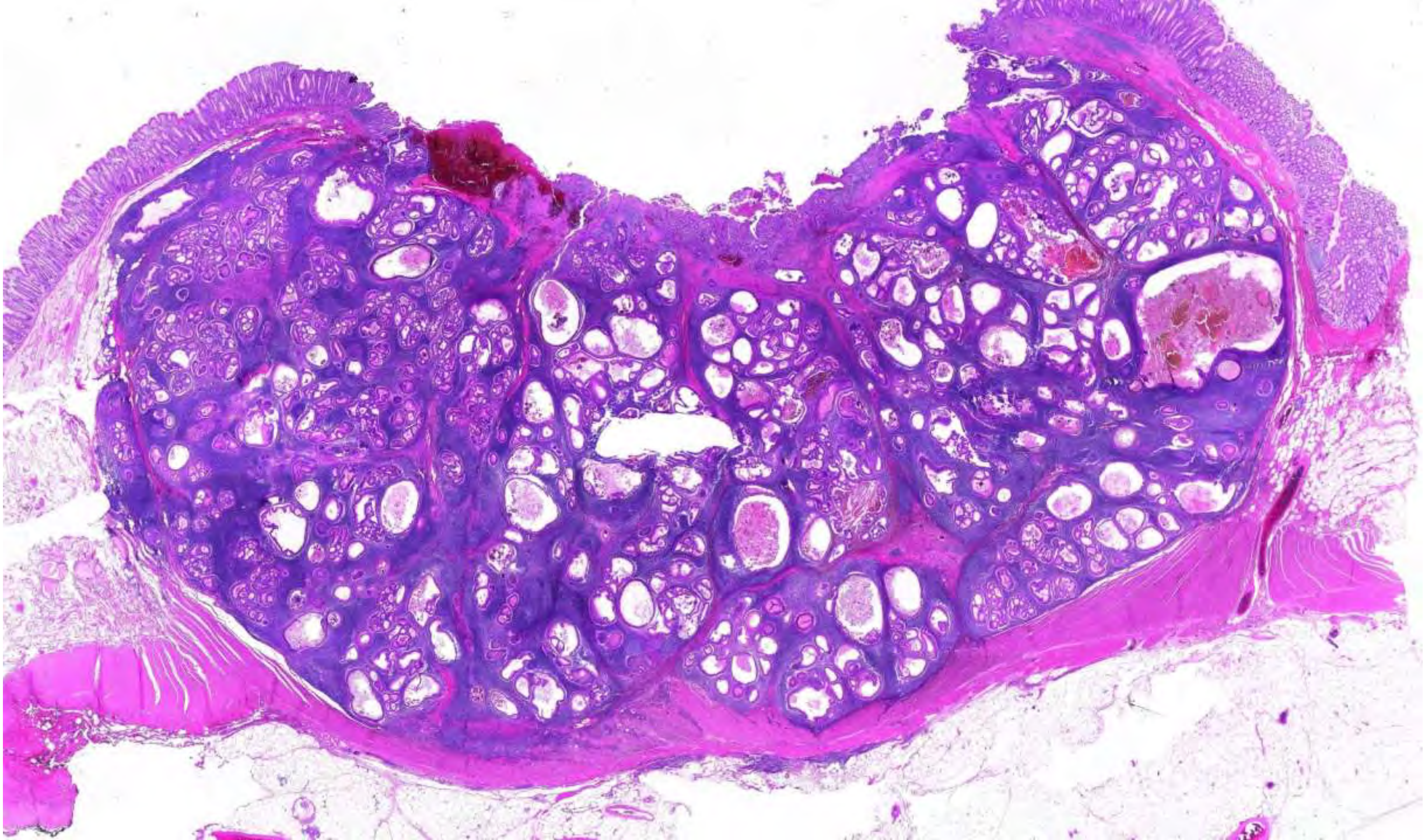


Lymphoglandular complex involvement

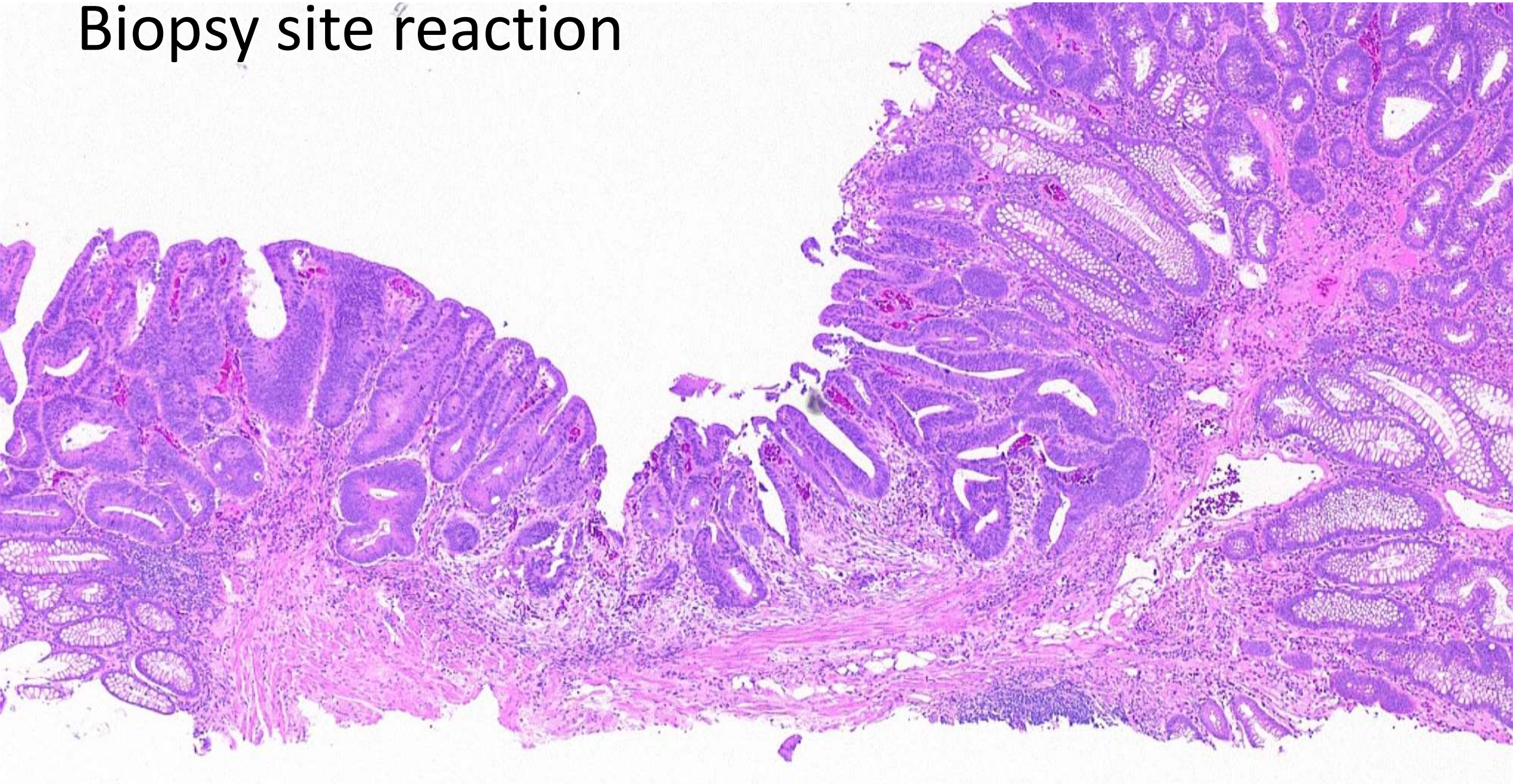


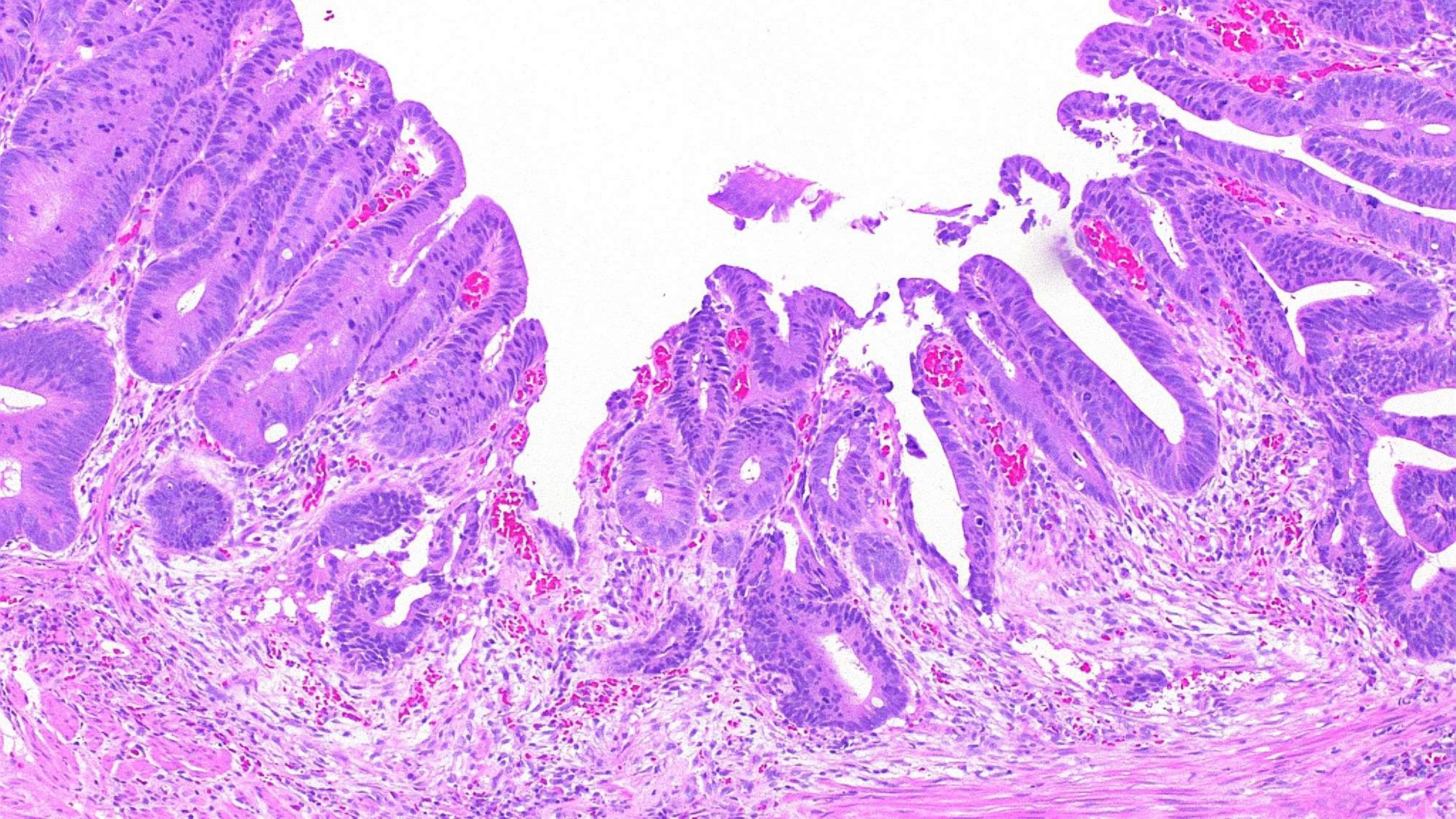


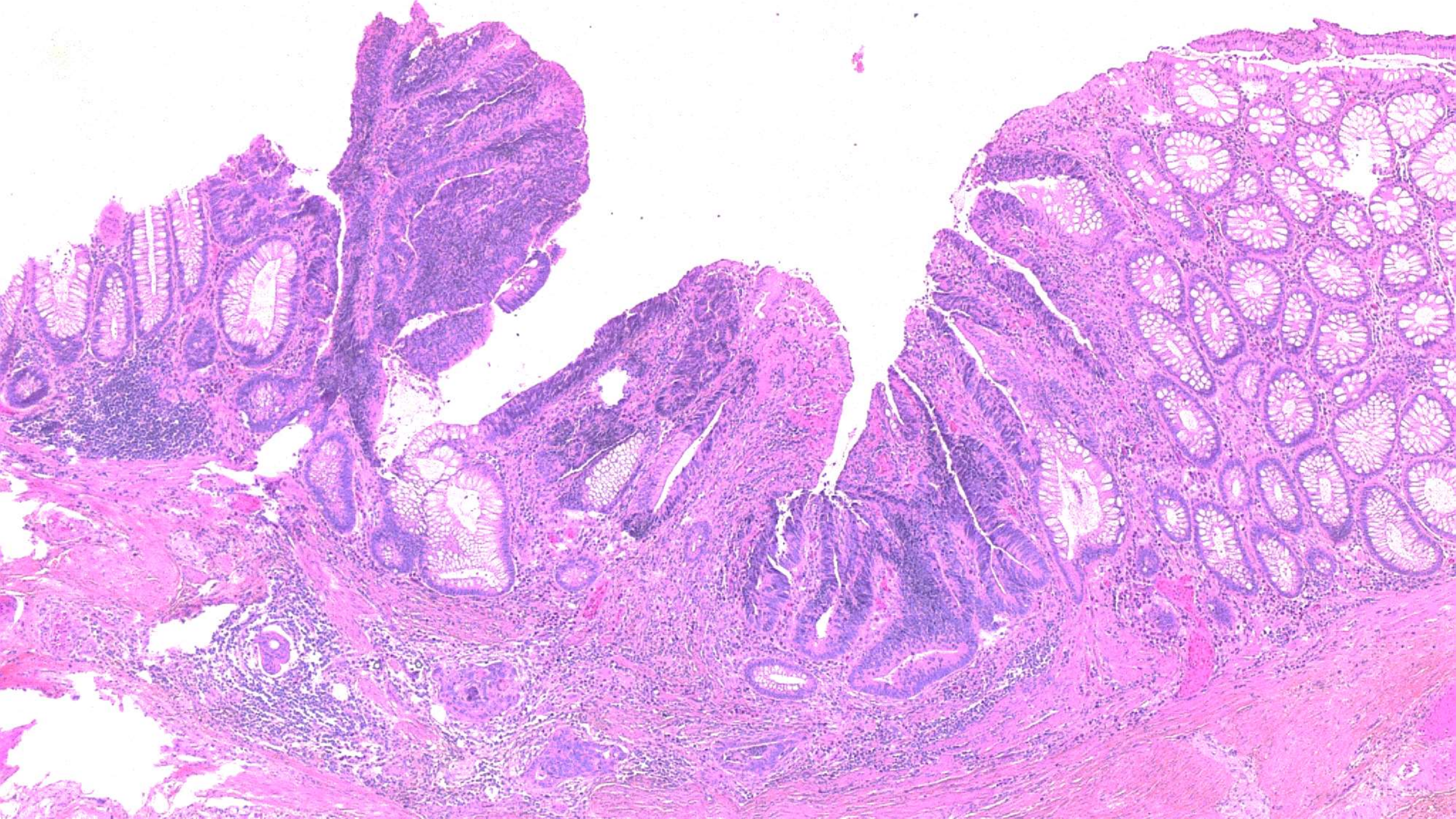


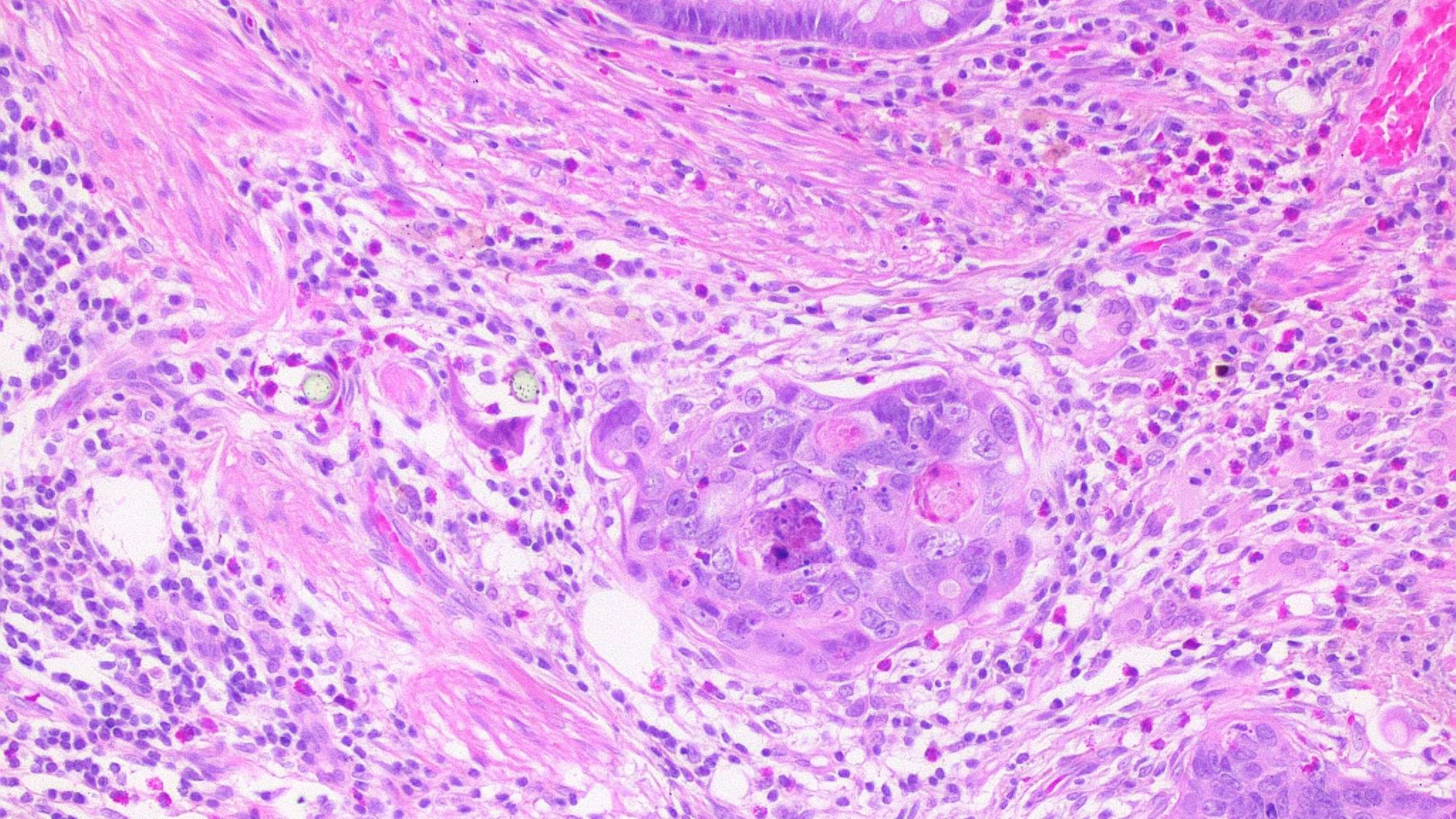


Biopsy site reaction

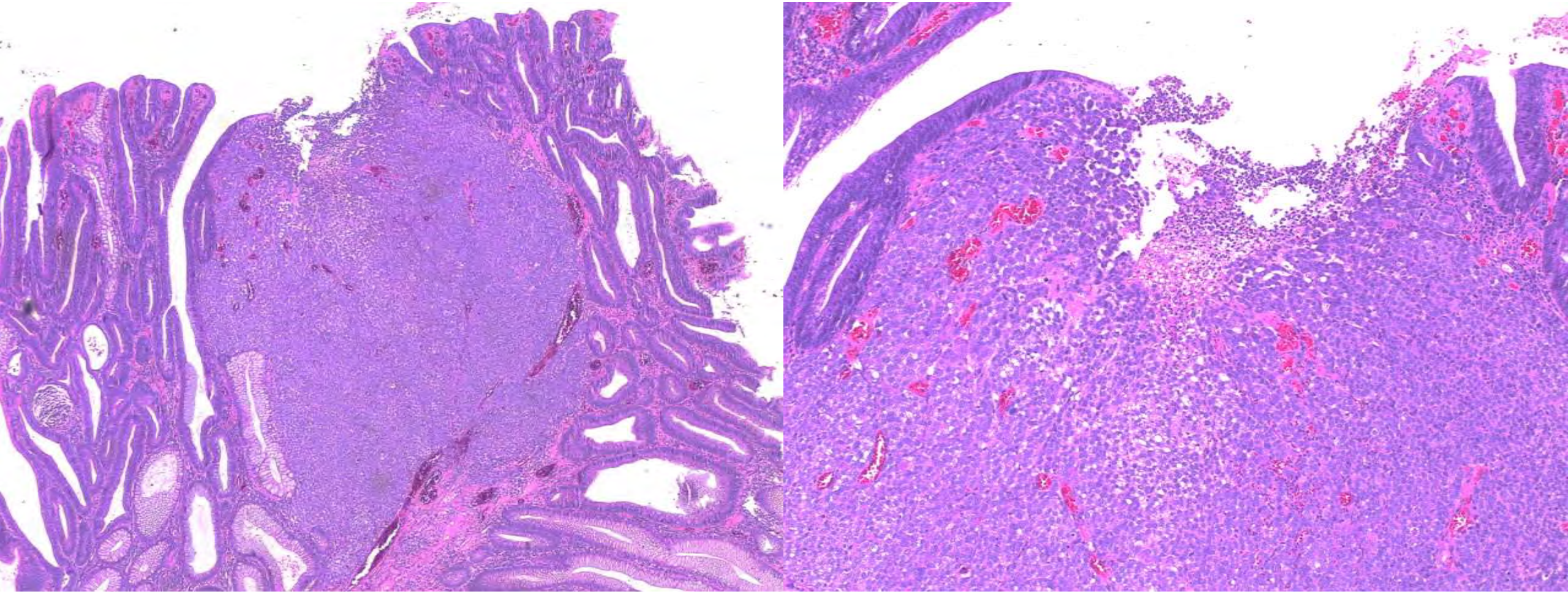


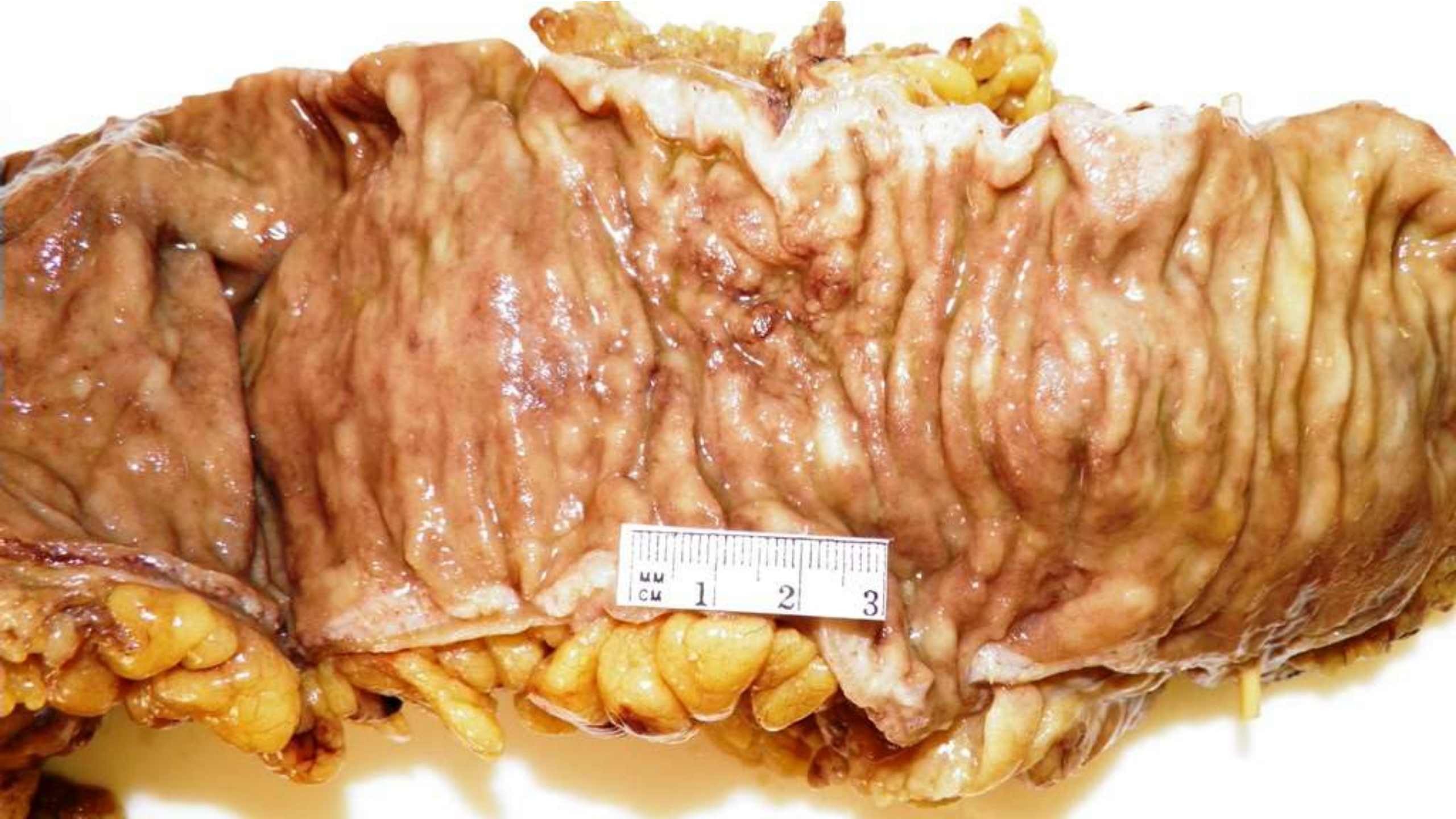






Intramucosal adenocarcinoma

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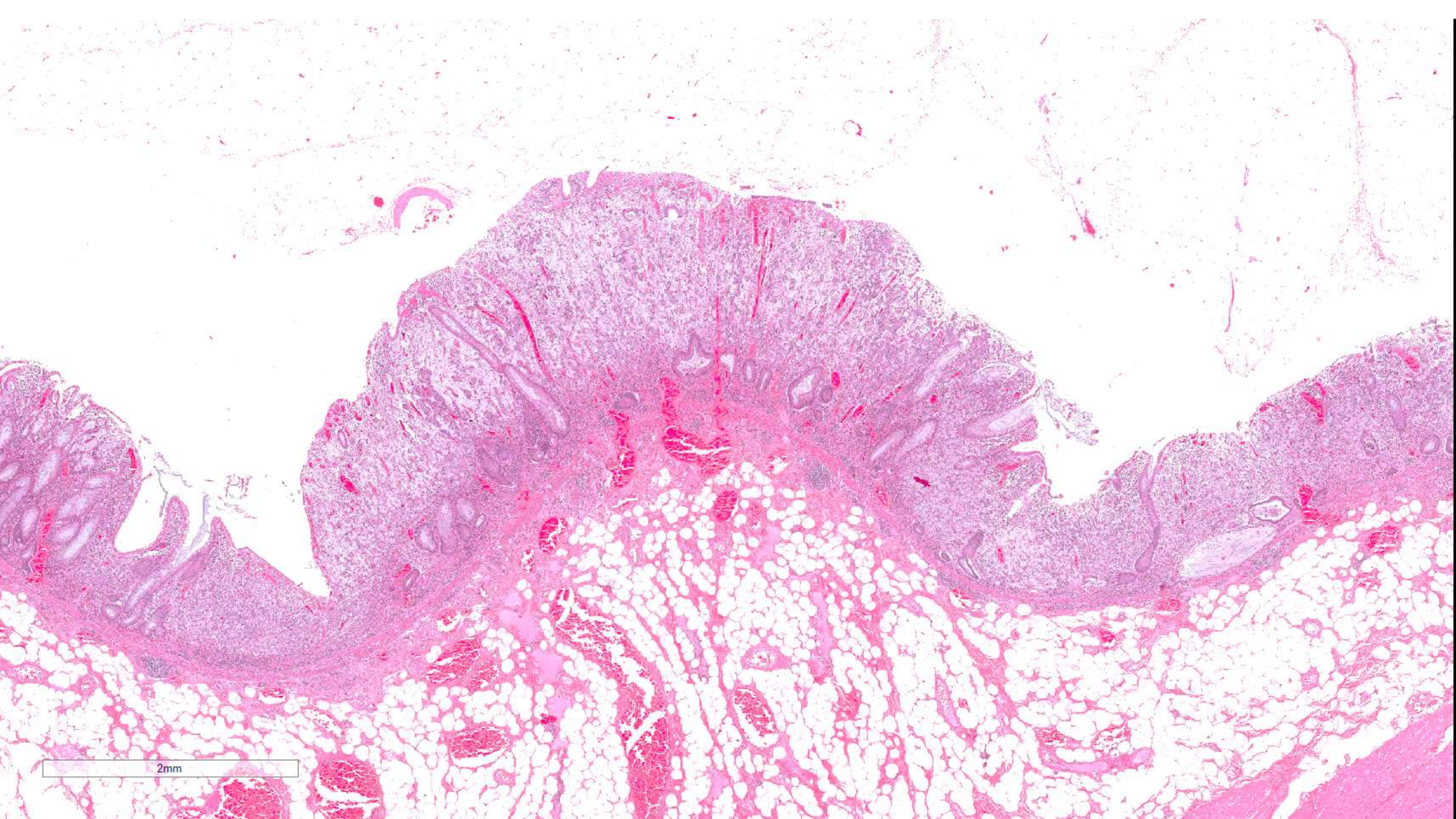
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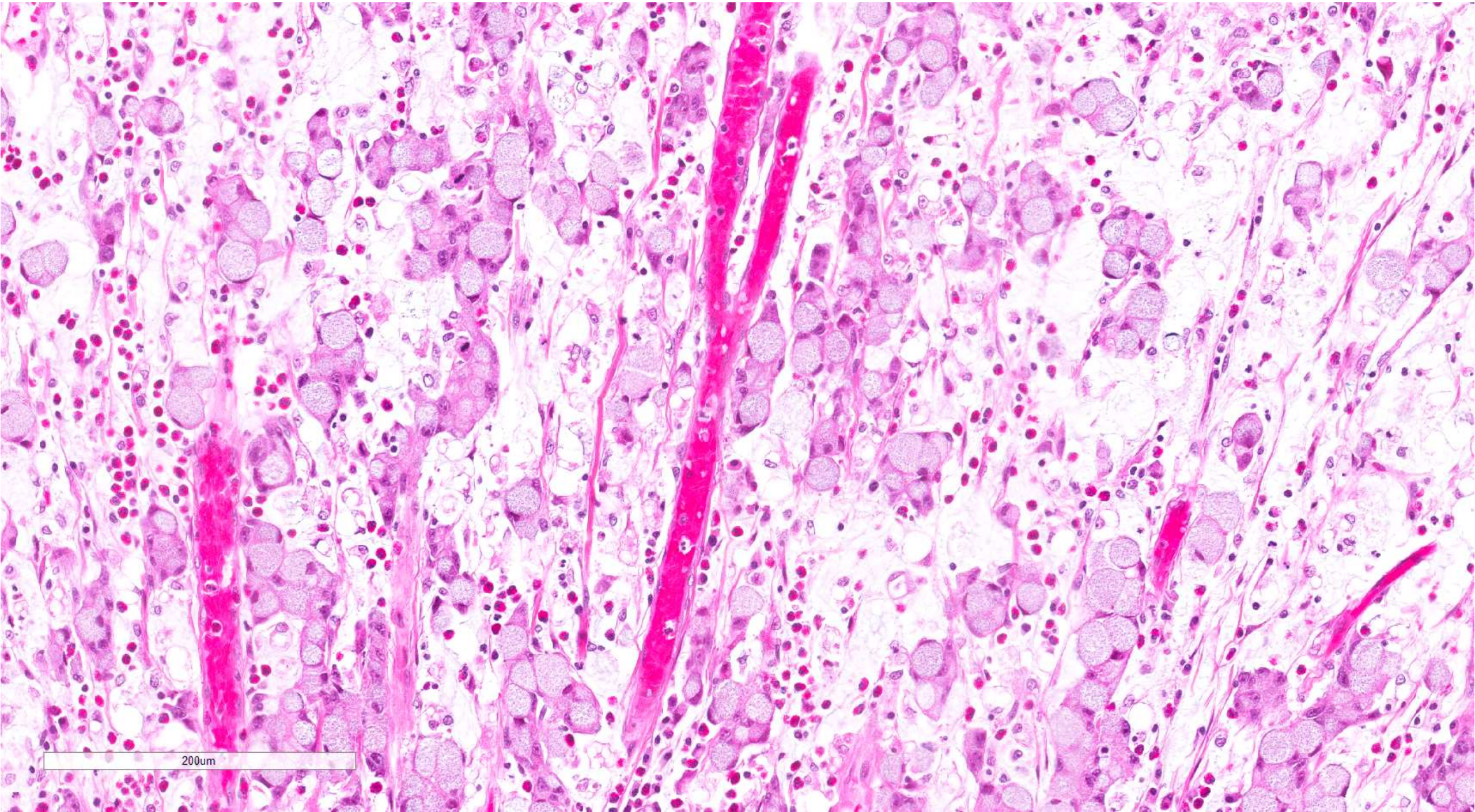
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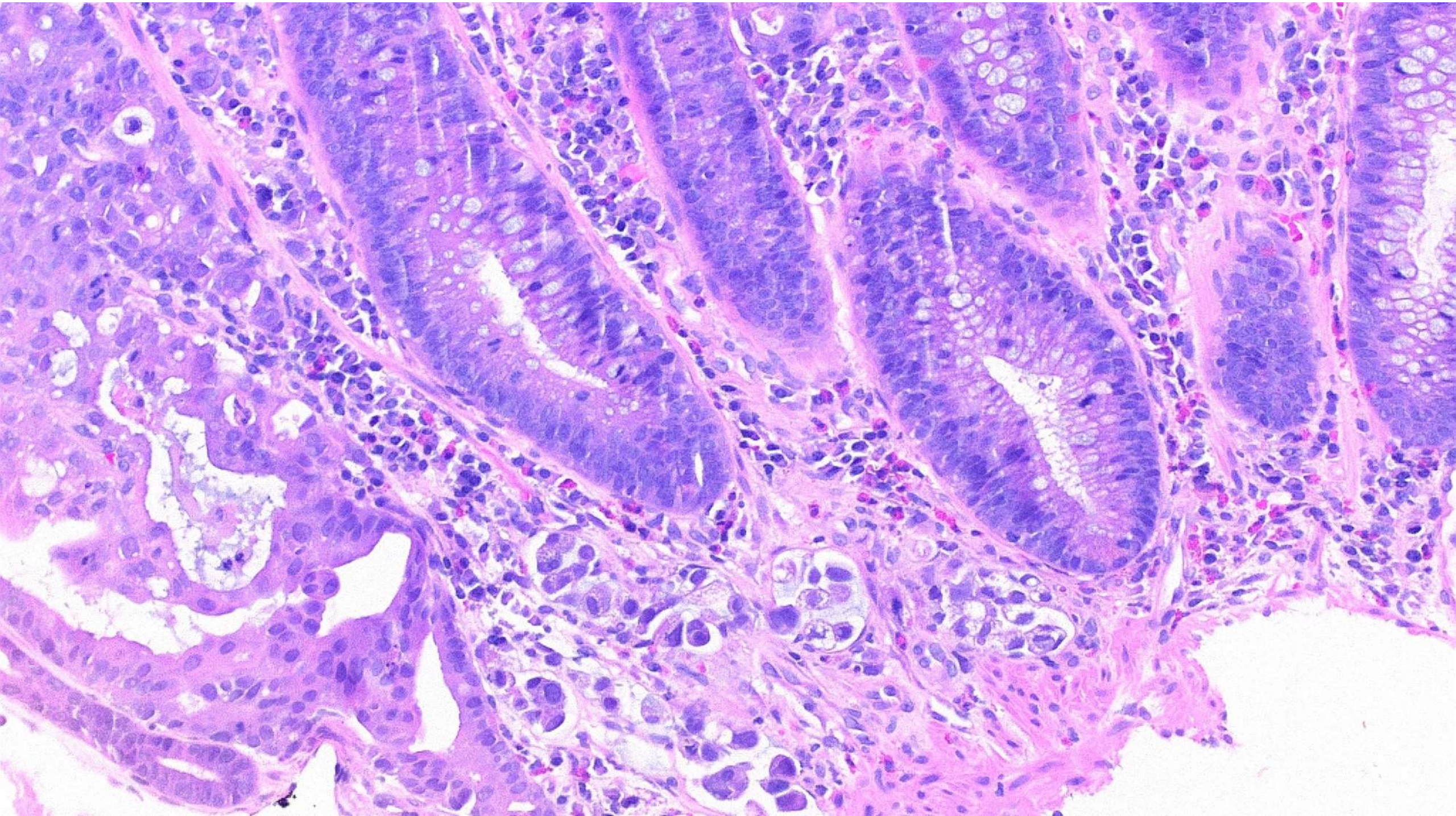

Summary

- Some colorectal polyps have features that can make the assessment of invasive adenocarcinoma difficult

- Morphological features on H&E are the best discriminants of benign and malignant lesions
  - IHC has limited role in these problematic lesions

- If in doubt, get more sections and show a friend