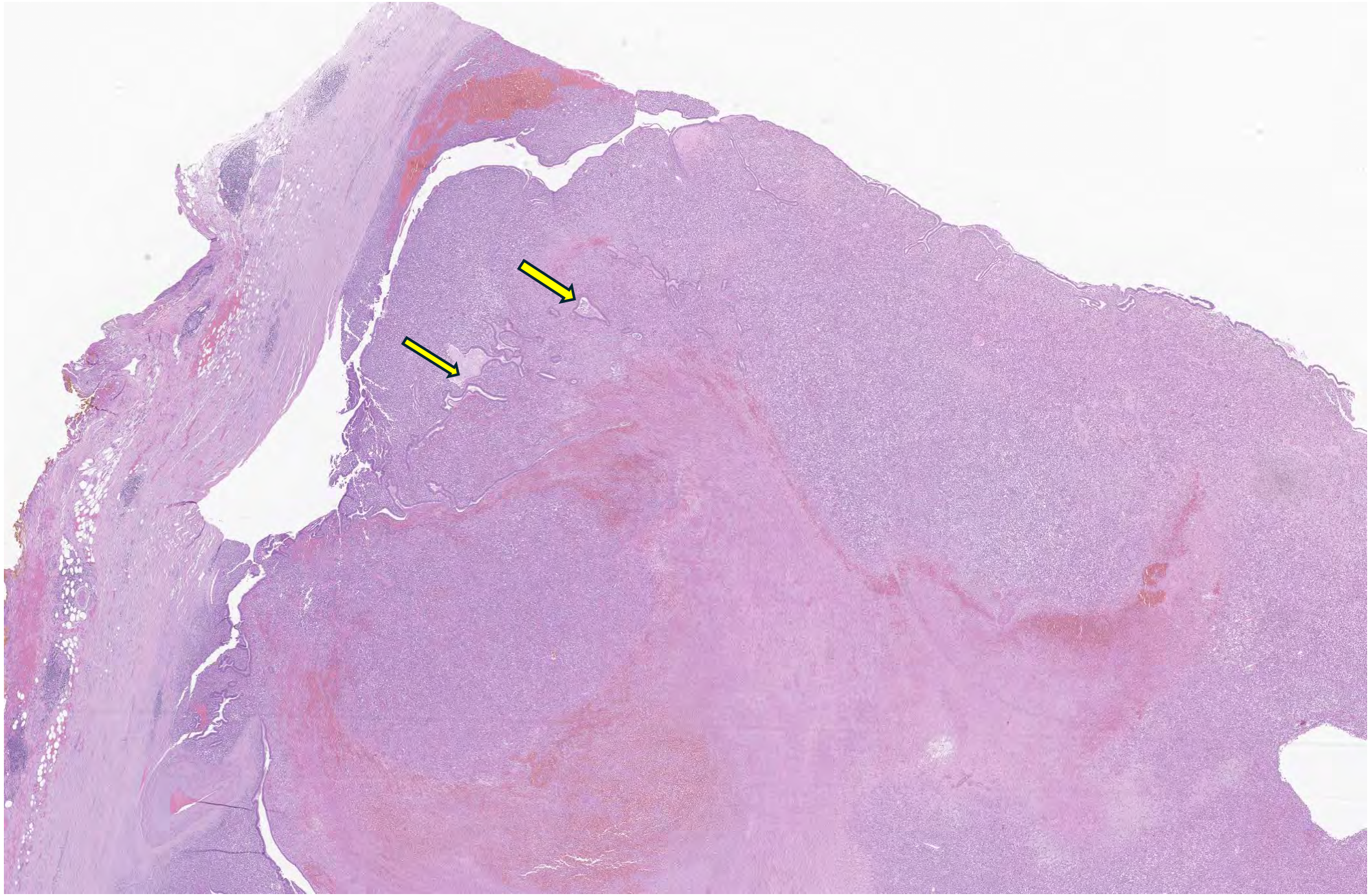
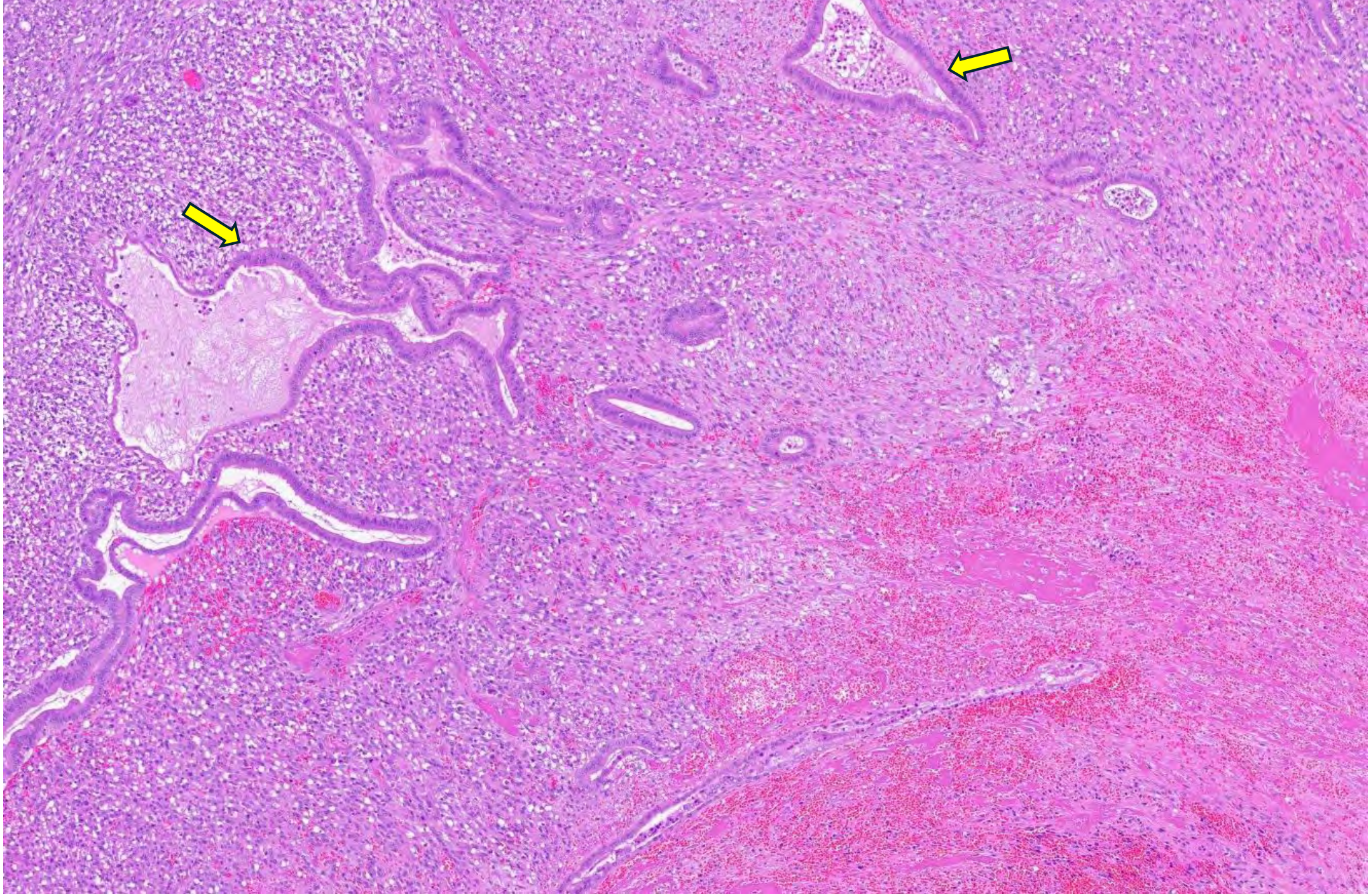
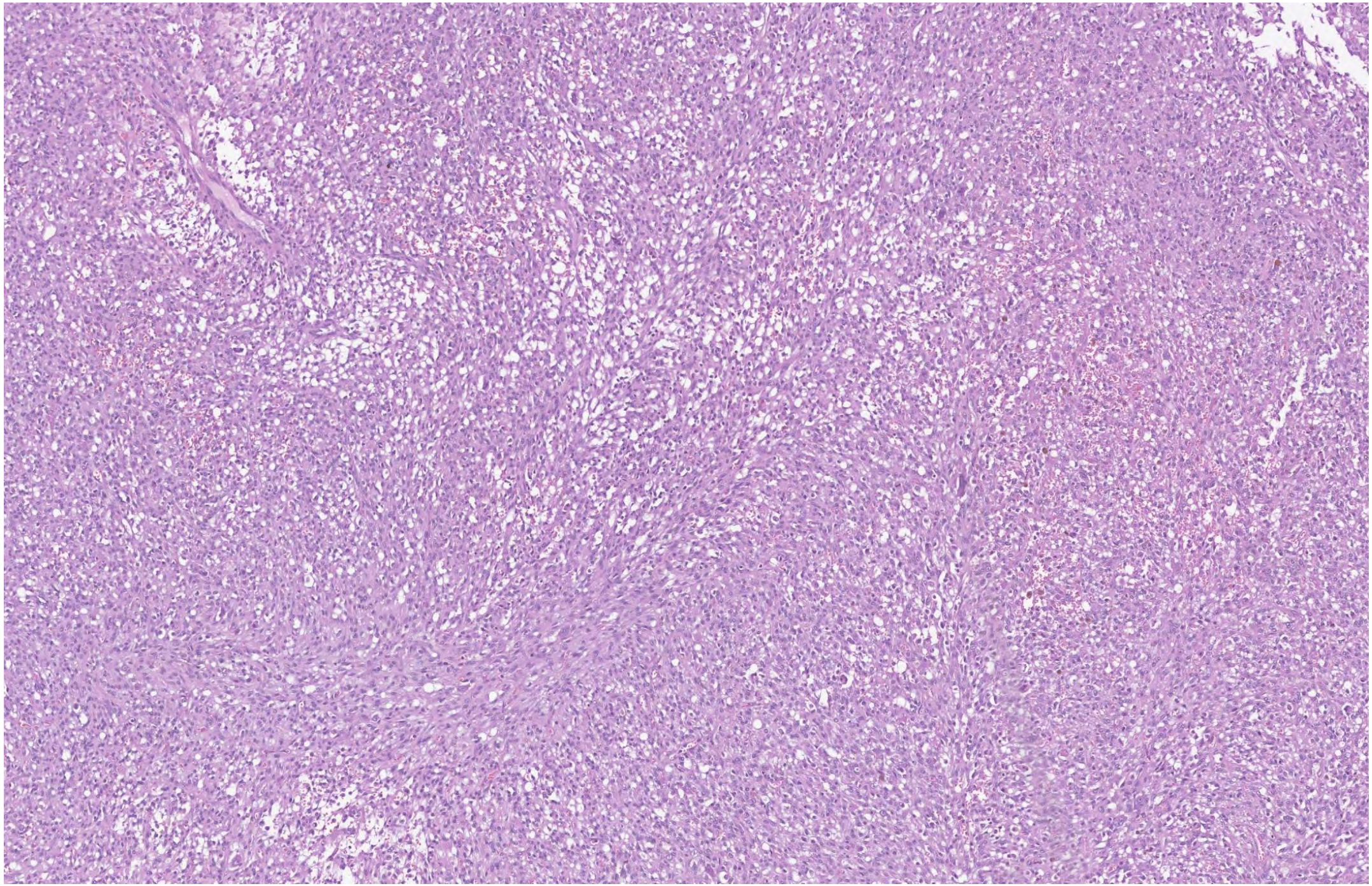
Case of the month
Feb. 2025

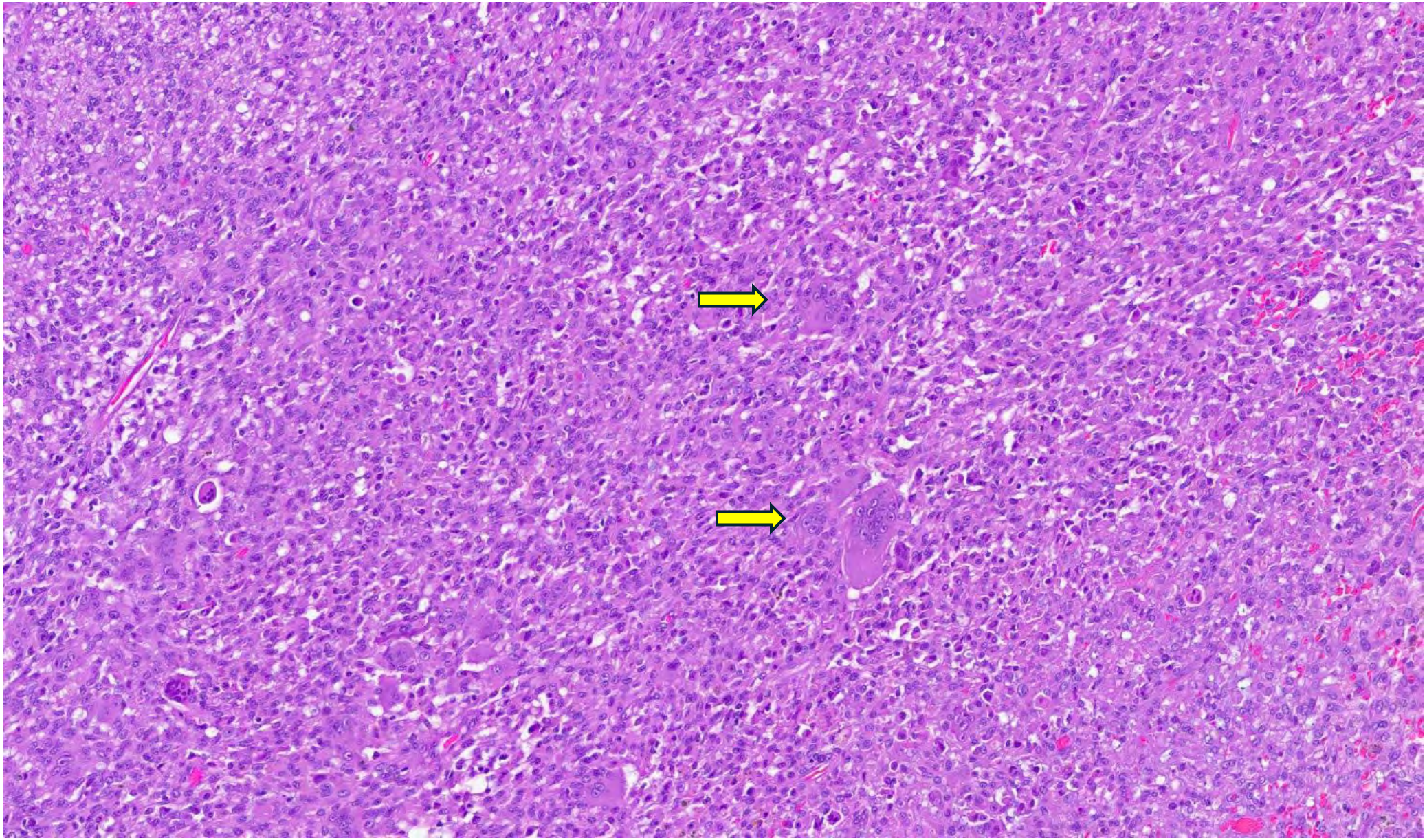
Dilshad Dhaliwal, MD-PGY3 resident

Celia Marginean, MD-Program Director

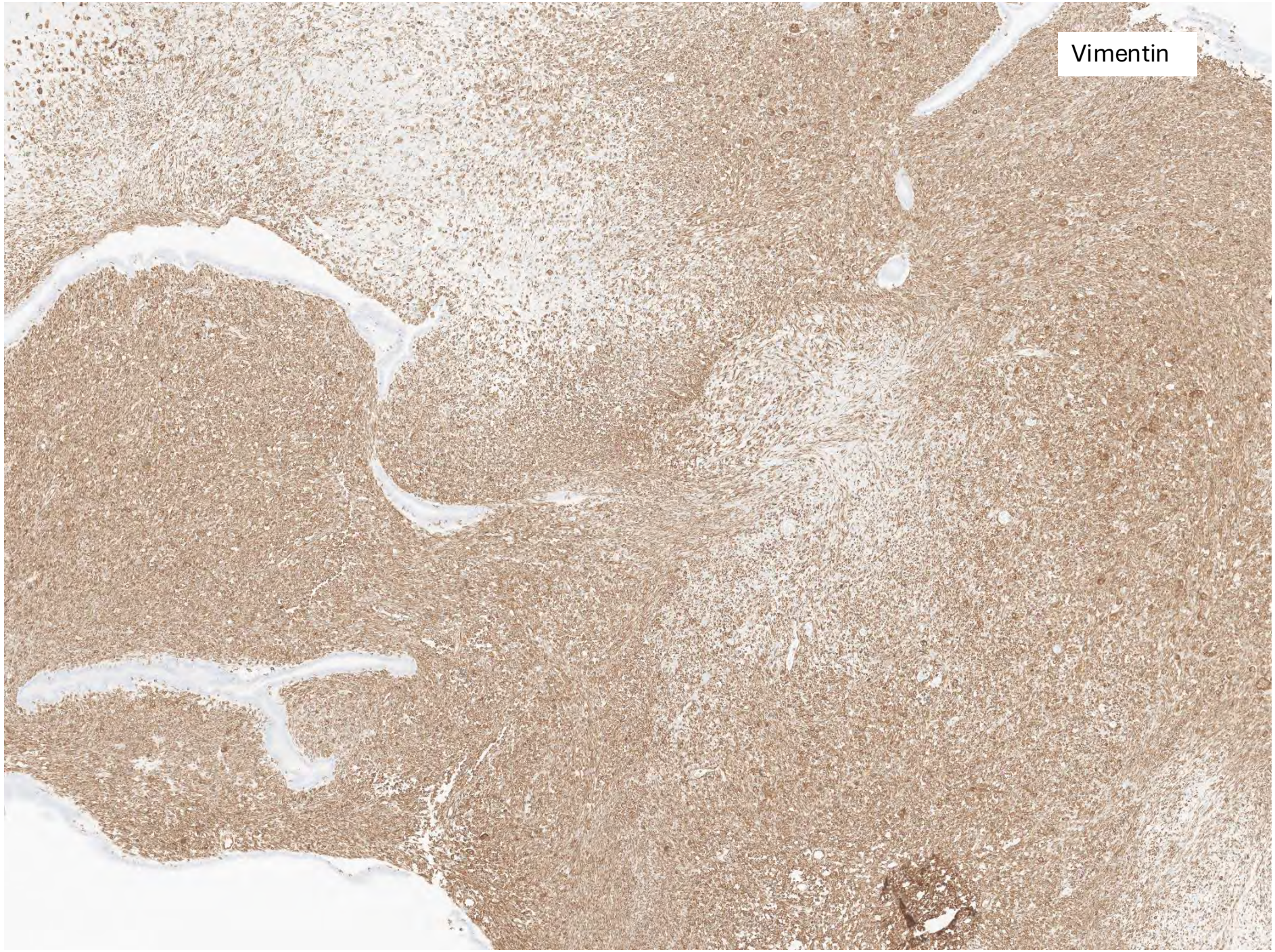


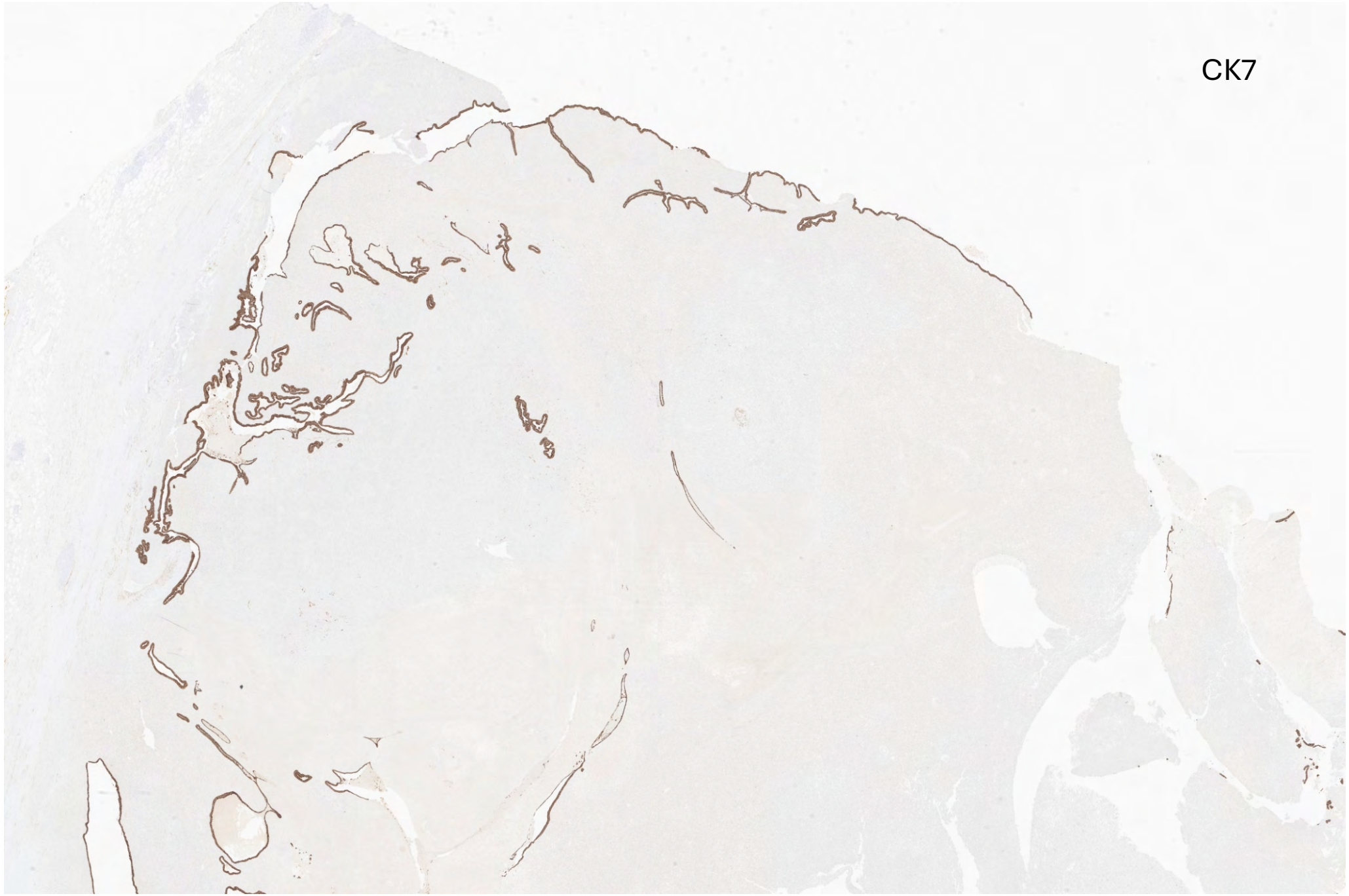


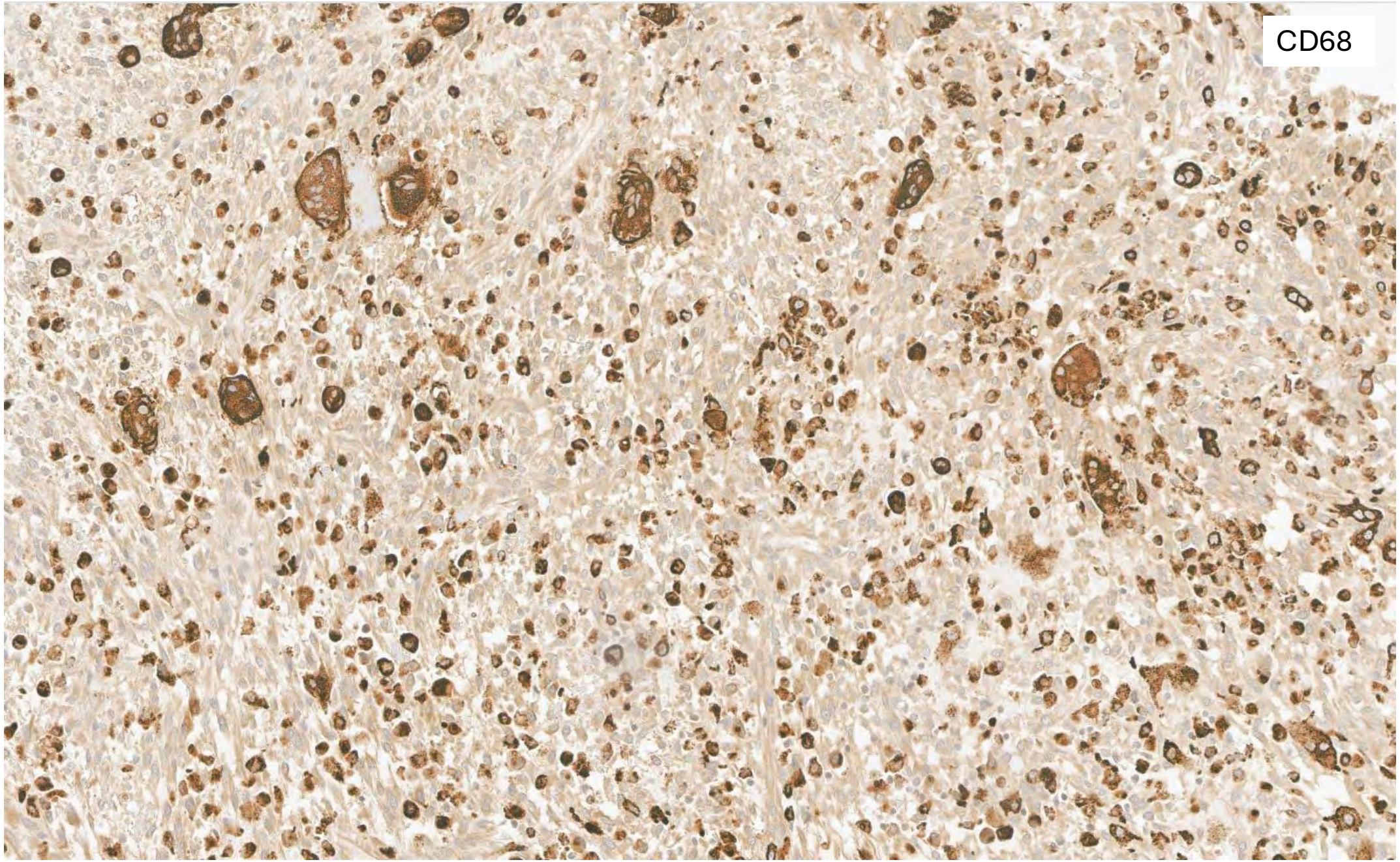




The tumor is composed of sheets of spindle cells, admixed with epithelioid cells and numerous multinucleated osteoclast like giant cells.


Vimentin


CK7


CD68

Case of the month

Feb 2025

Dilshad Dhaliwal, E. Celia Marginean

Resected pancreatic mass, 63 yo F. Which of the following is a poor prognostic factor associated with this neoplastic entity?

A. Presence of >20% undifferentiated component
B. Number of osteoclast giant cells
C. GLI3 mutation
D. Association of conventional ductal adenocarcinoma
E. Stromal desmoplasia more than >75% of tumor

Answer: **D. Association of conventional ductal adenocarcinoma.**

- **Explanation**: The diagnosis is Undifferentiated Carcinoma with Osteoclast-like giant cells (UCOGC) associated with a well differentiated ductal adenocarcinoma (PDAC).
- In this case, PDAC is present predominantly at the periphery of the tumor, see images. (arrows).

- UC-OGC is a rare, aggressive tumor, representing less than 1% of all pancreatic malignancies. In the new WHO classification is recognized as a variant of ductal adenocarcinoma (PDAC).
- According to the 5th edition of WHO classification, UC-OGC contains three cell types: osteoclast-like multinucleated giant cells (considered non-neoplastic), mononuclear histiocytes, and neoplastic mononuclear cells. There is no definite percentage cutoff for the undifferentiated component. Osteochondroid differentiation, osteoid and bone formation can be observed. UC-OGC can be pure or associated with another pancreatic neoplasm like intraductal papillary mucinous neoplasm, pancreatic mucinous cystic neoplasm, adenosquamous carcinoma, cystadenocarcinoma, and conventional ductal adenocarcinoma.
- Molecular alterations: activating mutations in the oncogene *KRAS* and inactivating mutations in the tumor suppressor genes *CDKN2A*, *TP53* and *SMAD4*. This finding supports current WHO classification as variant of pancreatic ductal adenocarcinoma. Rare cases showed mutations in *SERPINA3 and GLI3*.
- Immunohistochemically, most of the neoplastic mononuclear cells express vimentin, some express keratin, and some label with antibodies to p53. Osteoclast-

like giant cells and a subset of the mononuclear histiocytic cells express CD68, CD163, vimentin and CD45, but are negative for keratin. PDAC component is positive for CK7 and negative for vimentin.

- ***PDL-1 expression by tumor cells is associated with poor prognosis***[1]**.**
- **Concurrent associated conventional ductal adenocarcinoma is a poor prognostic factor** [1,2,3–6]

References:

1. Demetter P, Maréchal R, Puleo F, et al. Undifferentiated Pancreatic Carcinoma With Osteoclast-Like Giant Cells: What Do We Know So Far? *Front Oncol*. 2021;11:630086. doi:10.3389/fonc.2021.630086

2. Hrudka J, Kalinová M, Ciprová V, Moravcová J, Dvořák R, Matěj R. Undifferentiated Carcinoma with Osteoclast-like Giant Cells of the Pancreas: Molecular Genetic Analysis of 13 Cases. *Int J Mol Sci*. 2024;25(6):3285. doi:10.3390/ijms25063285

3. Bergmann F, Esposito I, Michalski CW, Herpel E, Friess H, Schirmacher P. Early undifferentiated pancreatic carcinoma with osteoclastlike giant cells: direct evidence for ductal evolution. *Am J Surg Pathol*. 2007;31(12):1919-1925. doi:10.1097/PAS.0b013e318067bca8

4. Luchini C, Pea A, Lionheart G, et al. Pancreatic undifferentiated carcinoma with osteoclast-like giant cells is genetically similar to, but clinically distinct from, conventional ductal adenocarcinoma. *J Pathol*. 2017;243(2):148-154. doi:10.1002/path.4941

5. Maksymov V, Khalifa MA, Bussey A, Carter B, Hogan M. Undifferentiated (anaplastic) carcinoma of the pancreas with osteoclast-like giant cells showing various degree of pancreas duct involvement. A case report and literature review. *JOP J Pancreas*. 2011;12(2):170-176.

6. Muraki T, Reid MD, Basturk O, et al. Undifferentiated Carcinoma With Osteoclastic Giant Cells of the Pancreas: Clinicopathologic Analysis of 38 Cases Highlights a More Protracted Clinical Course Than Currently Appreciated. *Am J Surg Pathol*. 2016;40(9):1203-1216. doi:10.1097/PAS.0000000000000689

Case of the month
March 2025

Jacky Akhter, MD, GI Fellow (PGY-6)

Kalyani Patel, MD, Associate Professor,

Site Director for GI/Hepatobiliary Pathology Fellowship, Texas Children's Hospital

Q1: 10-day old female presented with abdominal distention, bilious emesis with concern for bowel obstruction, and lack of stools for six days, previously normal, ultrasound negative for pyloric stenosis, underwent rectal suction biopsy.

Which of the following is an adequate biopsy specimen for the diagnosis of this condition?

A) 2 cm above the anal verge, showing transitional mucosa, and all biopsy specimen showing at least 50% submucosal tissue, 20 sections are given for microscopic review

B) 2, 3, and 4 cm above the anal verge, all biopsy exhaustively sectioned, most biopsy sections include at least 50% submucosal tissue, showing colonic mucosa

C) 2, 3, 4 cm above the anal verge, maximum up to 40 sections cut per biopsy specimen, showing minimal sub-mucosal tissue with overlying colonic epithelium

D) 5 cm proximal to the transition zone, with presence of ganglion cells and does not show submucosal nerve hypertrophy or myenteric hypoganglionosis

Q2: Which of the following features define the transition zone?

A) Partial circumferential aganglionosis

B) Myenteric hypoganglionosis

C) Submucosal nerve hypertrophy

D) A, B, and C (all 3 necessary)

E) A, B, or C (any one of these features)

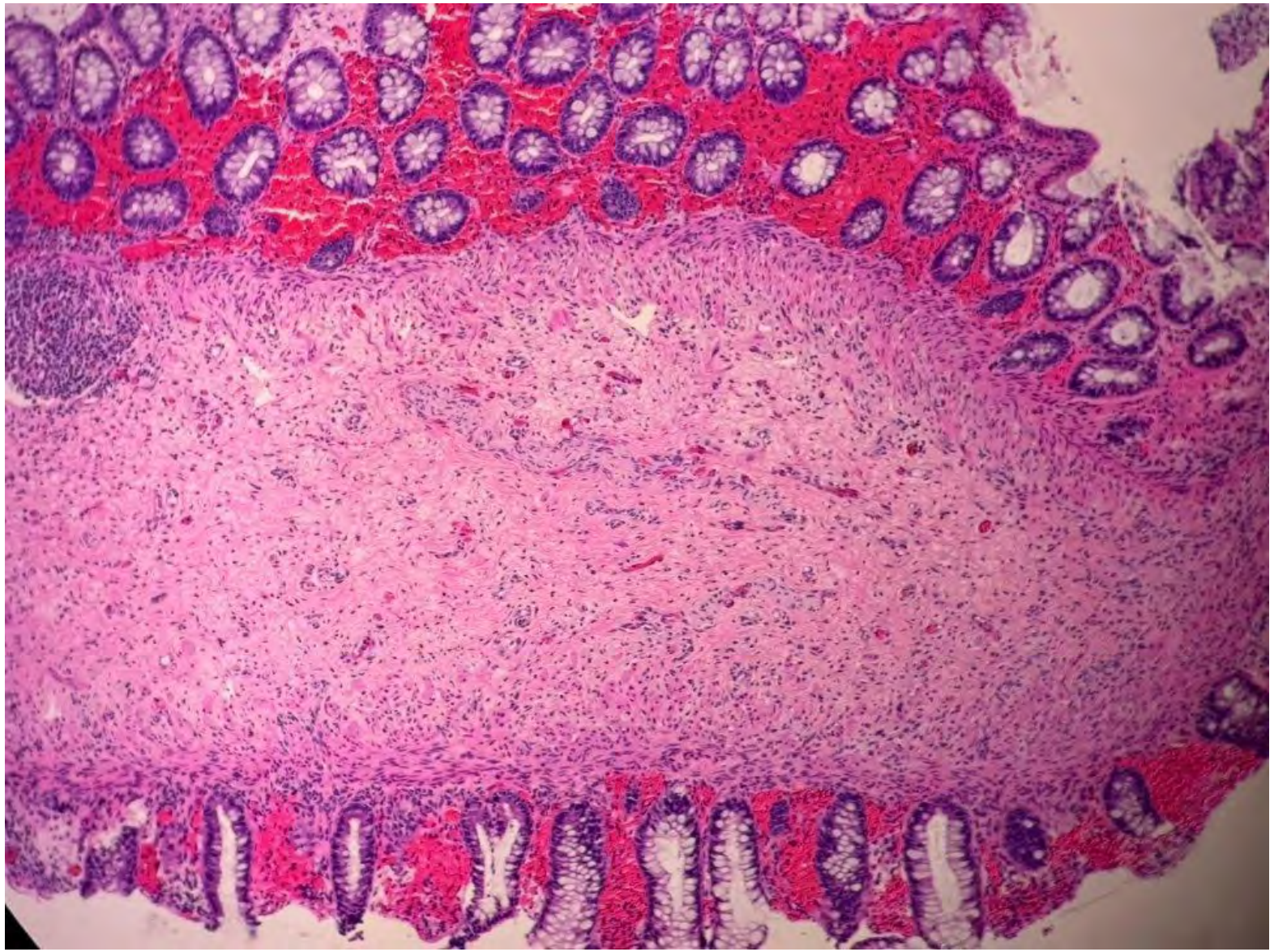
Explanations:

Q1:

- Answer: **B) 2, 3, and 4 cm about the anal verge, all biopsy exhaustively sectioned, most biopsy sections include at least 50% submucosal tissue, showing colonic mucosa**
- **Explanation:**
  - In suspected HD, the biopsy must be adequate to diagnose or rule out HD. An adequate biopsy must have tissue from multiple areas (conventionally taken 2, 3, and 4 cm above the anal verge), and each biopsy must show at least 50% submucosa in most of the sections. Biopsies from 2.0 cm can sometimes show transitional mucosa, however, colonic mucosa is typically considered reassuring for adequacy. Finally, adequate sections must be examined to confidently rule out HD, ranging from 40 to >100.

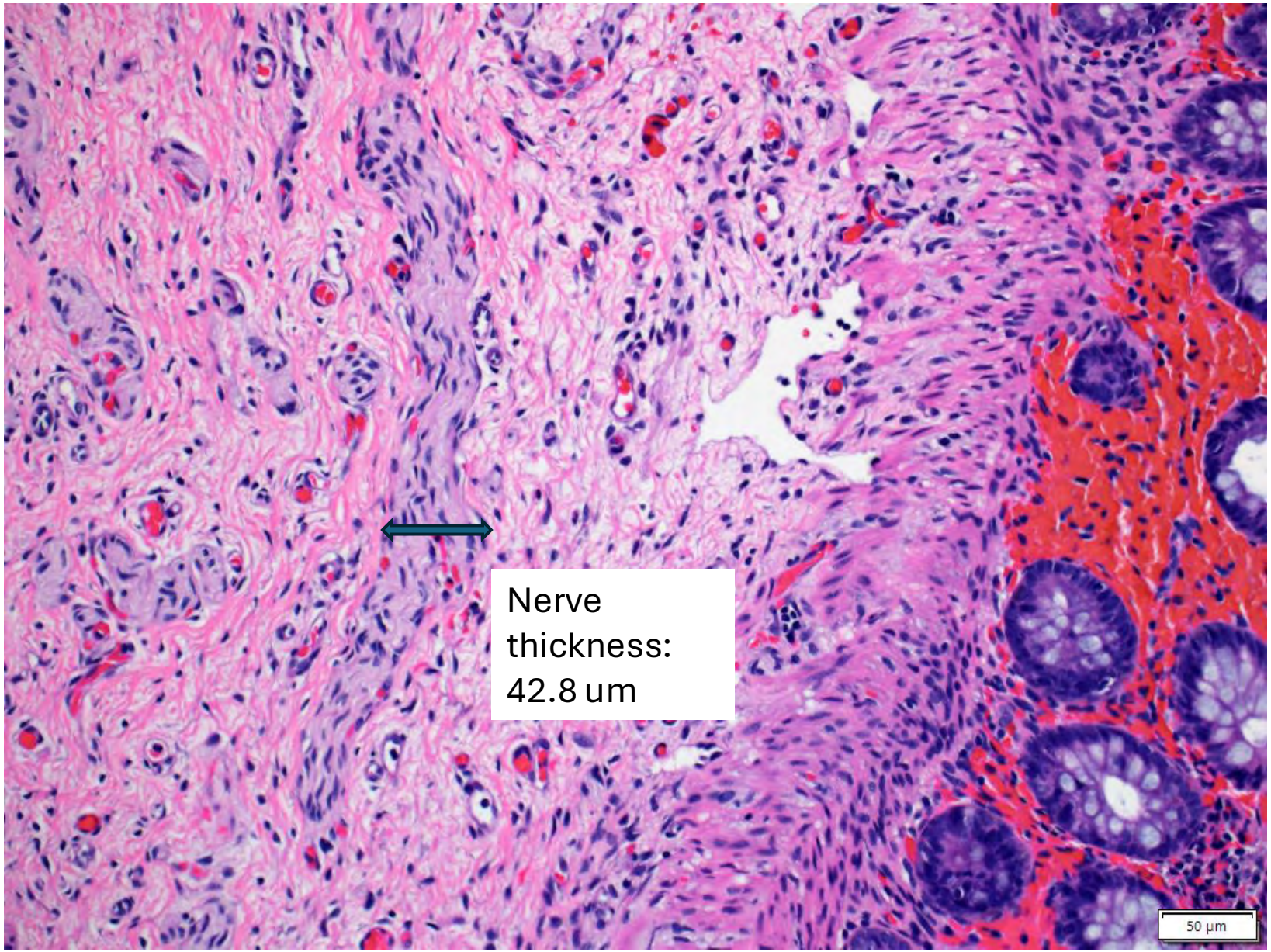
Q2:

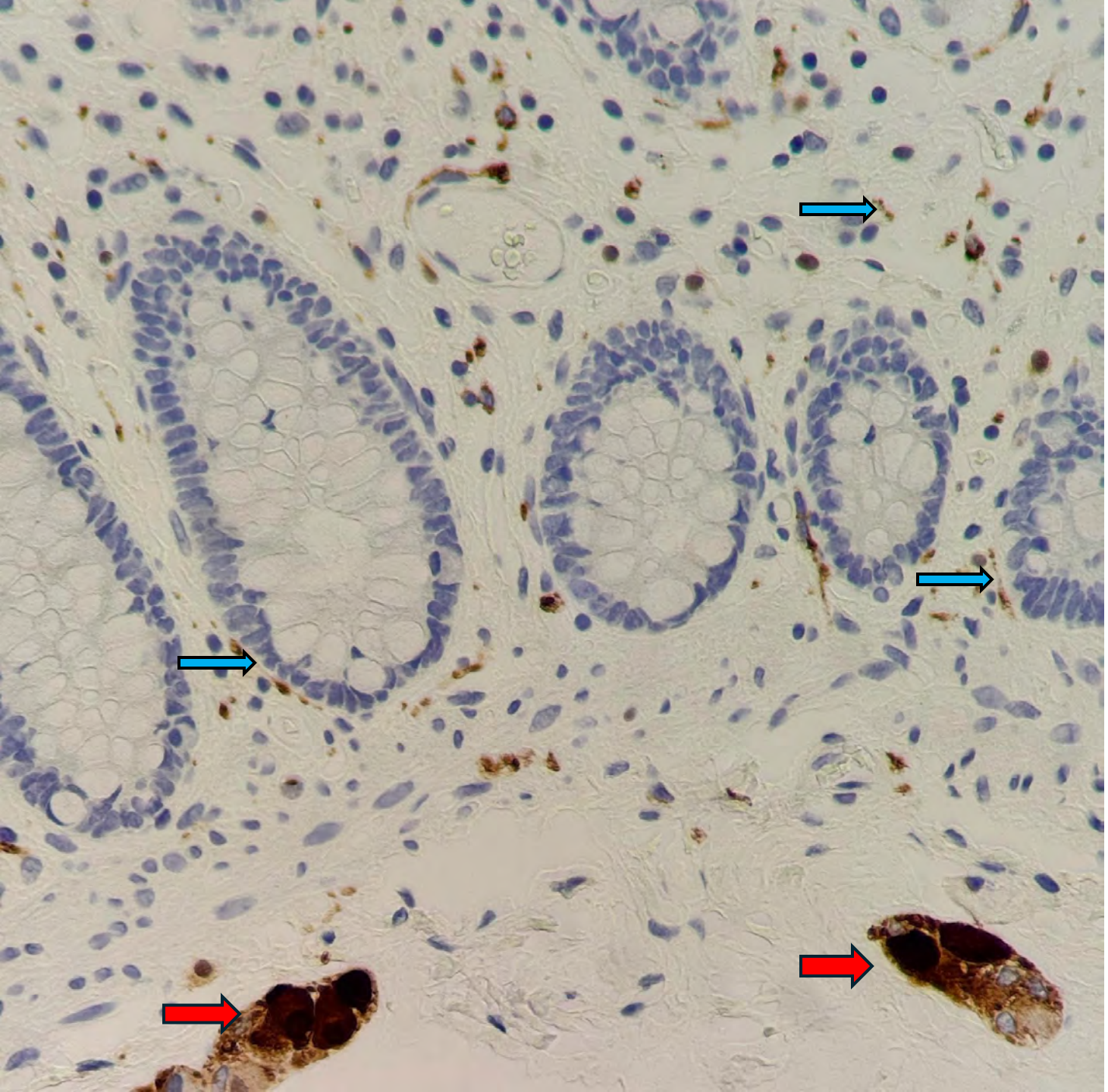
- **Answer: E) A, B, or C, if any of these features are present, this is considered diagnostic of transition zone**
- **Explanation:**
  - The transition zone (TZ) is the intestinal segment immediately proximal to the aganglionic bowel, leading to more proximal euganglionic tissue. The presence of any of these features is diagnostic of TZ. Intraoperative recognition of TZ at the proximal margin of the pull-through specimen is necessary to ensure that the anastomosis does not contain aganglionic or TZ tissue.



Rectal suction biopsy:
Colonic mucosa with abundant submucosal tissue

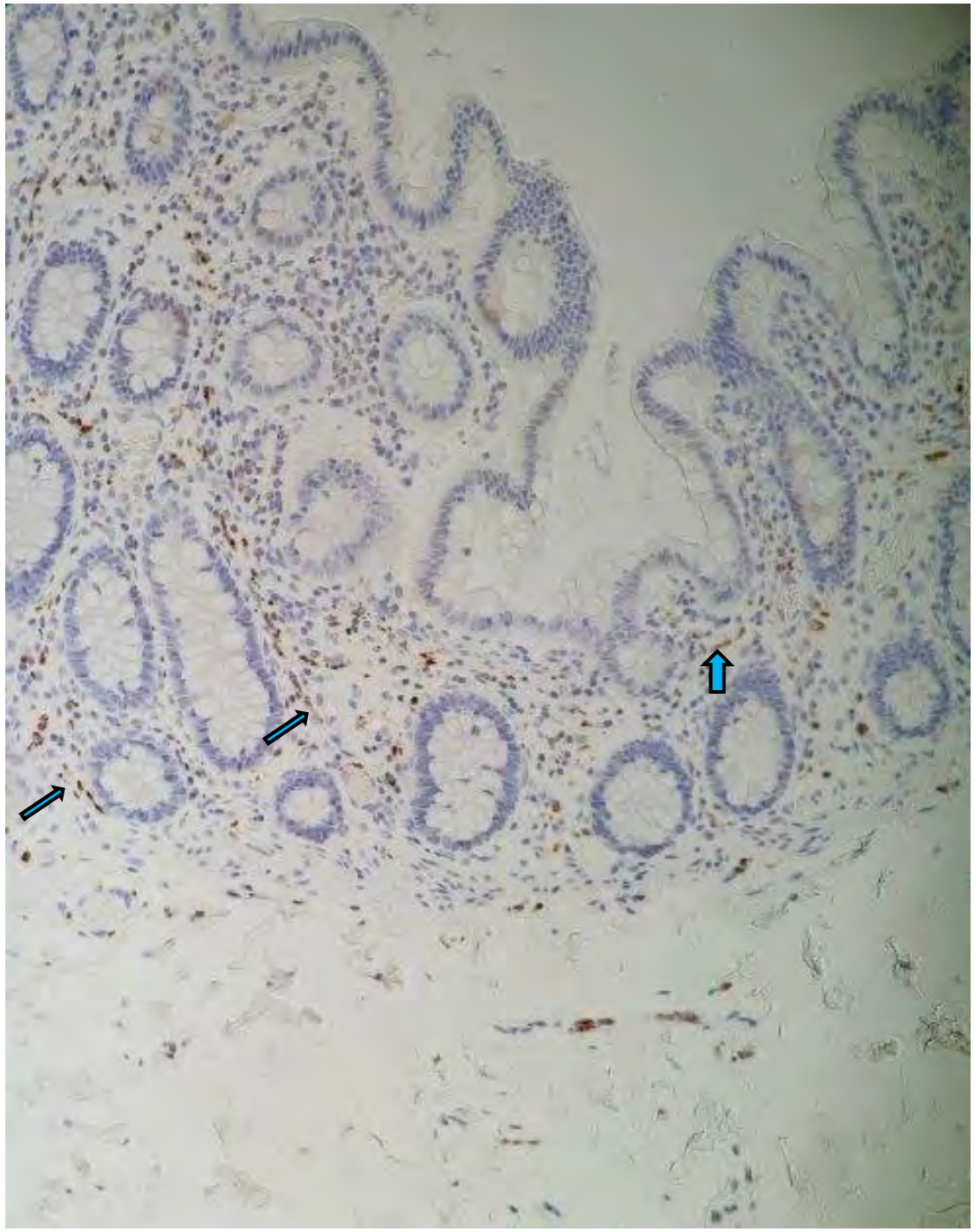
Rectal suction biopsy at 2.0 cm (H&E, 200x)



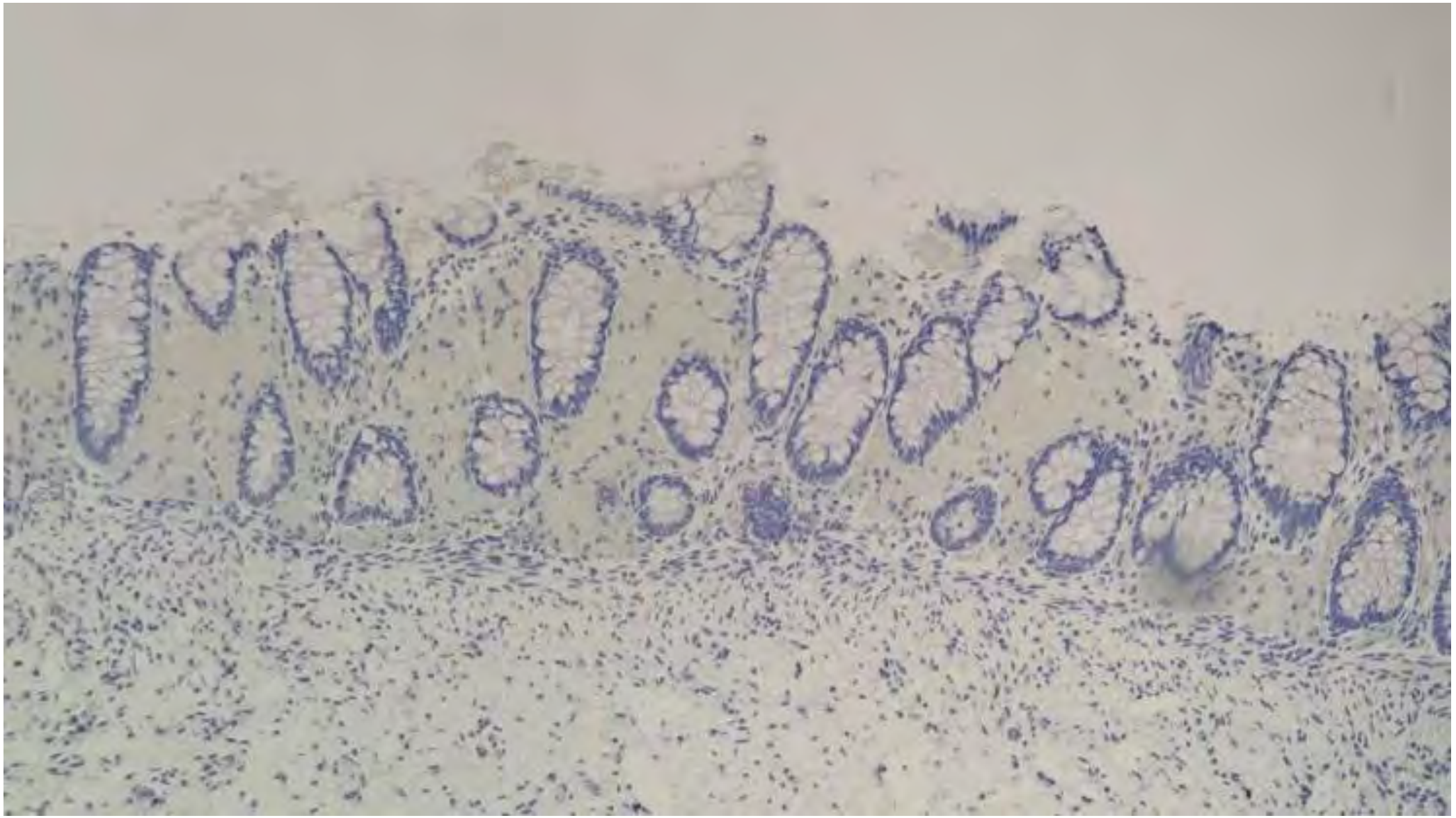


Calretinin:

Normal (expected) stain- submucosal ganglion cells (red arrow) and mucosal neurites in lamina propria (blue arrow)

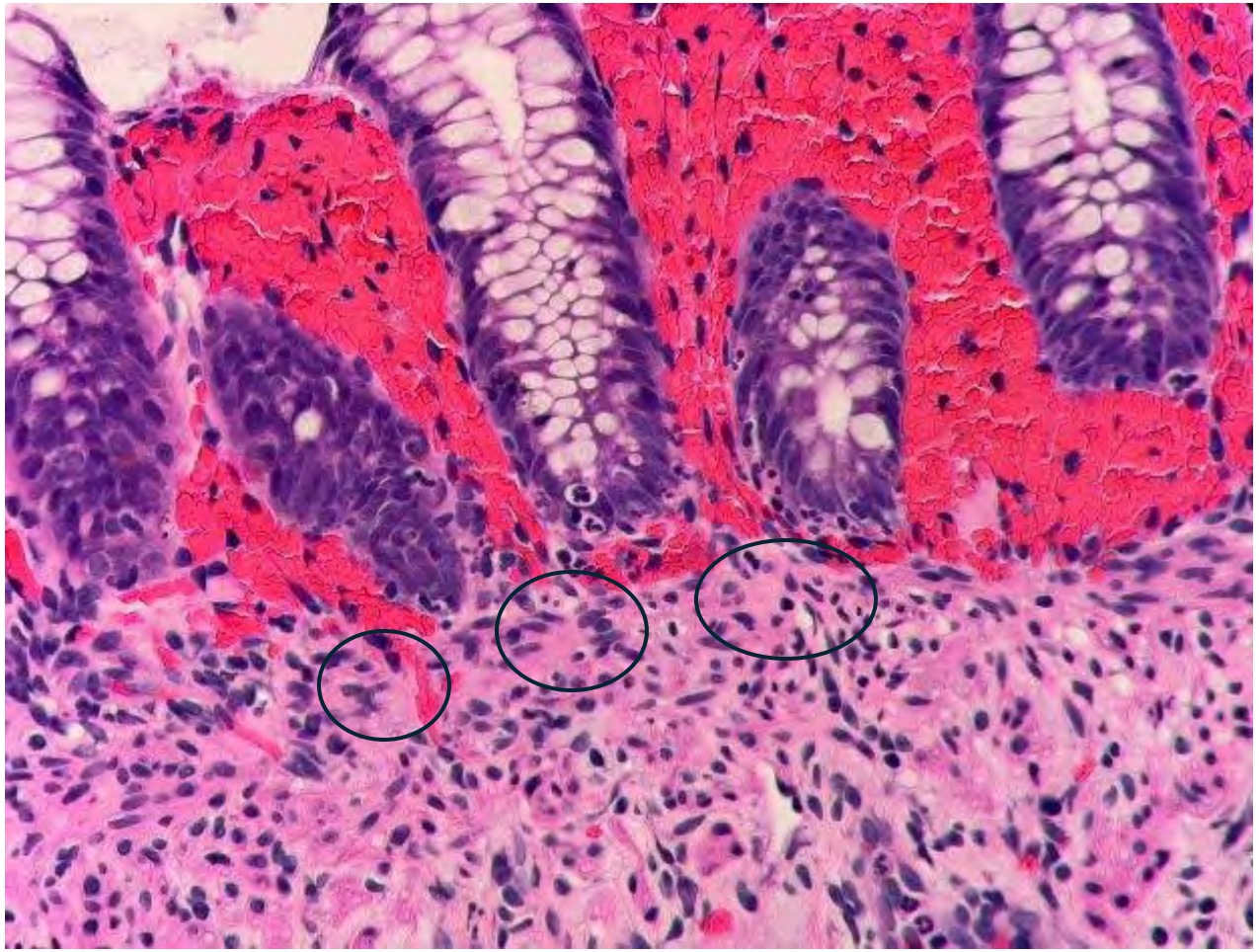


Calretinin: mucosal neurites present within lamina propria; no ganglion cells identified within the submucosal tissue (representative of transition zone)



Abnormal Calretinin immunostain with complete absence of submucosal Ganglion cells and mucosal neurites.

Hirschsprung-associated enterocolitis (HAEC)



Intraepithelial neutrophils within the colonic crypts (acute colitis)

Etiology/Pathogenesis

- Hirschsprung disease (HD) is defined as incomplete colonization of the gut by neural progenitor cells which leads to complex multigenetic disease characterized by absence of intrinsic ganglion cells (aganglionosis) in the submucosal (Meissner) and myenteric (Auerbach) plexuses in the rectum, and extending variable lengths proximally
- Complex multigenetic disease, can be associated with congenital abnormalities: Trisomy 21 (most common), cardiac defects, CNS anomalies, MEN2a, GI/GU/limb defects

Definition/presentation

Remove this slide – let us focus on "diagnosis" only.

- Aganglionic segment: starts at internal anal sphincter (IAS), extends proximally, leading to distal narrow aperistaltic and proximal dilated GI segments
  - Short-segment classic HD (75-80%): Rectosigmoid colon
  - Long-segment HD (10-15%): Proximal to splenic flexure
  - Total colonic aganglionosis/HD (5-10%): Entire colon
  - Zonal ("segmental") and "skip segment" variants (rare)
- Clinical presentation:
  - Neonates:
    - delayed passage of meconium (>48 hours), feeding intolerance, abdominal distention, bilious emesis (concern for intestinal obstruction)
    - Can rarely have bowel perforation of cecum, ascending colon, appendix
    - Longer segment of aganglionosis: commonly present as neonates with symptoms of intestinal obstruction
  - Infants/children:
    - long standing mild to severe constipation, refractory to oral laxatives, a/w vomiting, abdominal distention, growth failure
    - Complications: acute intestinal obstruction, recurrent fecal impactions, and acute life-threatening or chronic enterocolitis

o Hirschsprung-associated enterocolitis (HAEC): explosive (usually bloody) diarrhea, fever, abdominal distention
  - Milder forms may be treated with antibiotics; however, severe forms require surgical interventions

Diagnostic procedures

- Screening tests
  - Contrast enema (CE)
    - Water-soluble contrast is instilled into the colon using a catheter that is placed inside the anus followed by live fluoroscopic imaging
    - Suggestive of HD: presence of a radiographical transition zone with proximal dilated bowel, microcolon, retention of contrast on post-evacuation film, irregular colonic contractions, mucosal irregularity, and abnormal rectosigmoid ratio (n=>1; HD= <1)
    - Less accurate in patients <30 days old, recommend rectal suction biopsy even if normal CE if there is high index of suspicion for HD
  - Anorectal manometry (ARM)
    - Motility test used to evaluate the voluntary and involuntary properties of the anorectum
    - Measures intraanal pressures=manometric assessment of the anorectal function
      - Measures resting pressures, RAIR (rectoanal inhibitory reflux), rectal sensation, ability to squeeze and simulate defecation
- Concern for HD:
  - Rectal suction biopsy (RSB)
    - Initial/primary modality for obtaining tissue to R/O HD in infants <6 months of age
  - If results equivocal--> full thickness biopsy (FTB)

Adequacy and Diagnostic Features of HD

1) Unequivocal identification of a ganglion cell
2) Appropriate location (mucosa): surface of the biopsy should be lined entirely by colonic mucosa
   - Sections from TZ or squamous mucosa can be physiologically aganglionic, hence these biopsies are inadequate unless a ganglion cell is identified (excluding HSCR)
   - Most places take biopsies at 2, 3, and 4 cm above the anal verge
3) Adequate submucosa: suction biopsy should be at least 2-3 mm in greatest dimension and have 50% or more of submucosa
   - 50-75 H&E-stained sections at 4 to 5 um thickness (TCH: 40 sections (5 slides with 8 sections on each slide); some institutions will exhaust the block as their protocol
     - No ganglion cells; overt submucosal nerve hypertrophy (>40um), then diagnosis can be established without further ancillary testing
     - Submucosal nerve hypertrophy may be absent in patients with total colonic aganglionosis
4) Ancillary tests:
   - Acetylcholinesterase (AChE) histochemistry
   - Cholin transporter (ChT) histochemistry
   - Calretinin IHC

- AChE:
  - Highlights abnormally coarse and dense cholinergic mucosal innervation
  - Performed on frozen sections, typically on unfixed tissue, not compatible for FFPE tissue
- Calretinin:
  - Highlights enteric neurons and cell bodies/neurites
  - Normal: calretinin (+) nerves in muscularis mucosae and lamina propria
  - Aganglionic rectal tissue: complete absence of calretinin (+) mucosal nerves
- Cholin transporter:
  - Expressed in the abnormal cholinergic nerves found in aganglionic rectal mucosa
  - Can be performed on FFPE tissue sections
  - Highlights larger/more numerous nerves in the mucosa of aganlionic bowel, helpful in patients with very short segment HD (vssHD), where calretinin may be misleading

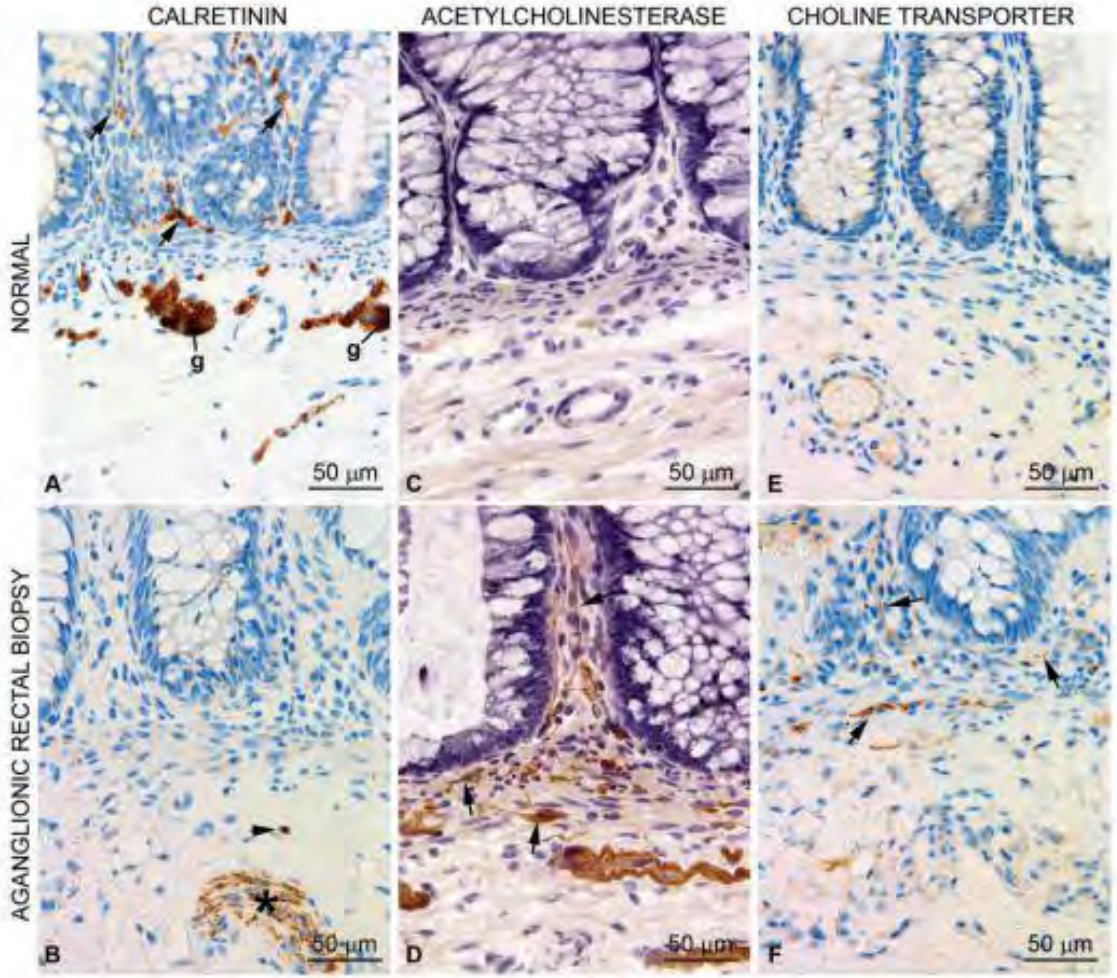


Figure 7. Ancillary diagnostic techniques. A, Calretinin immunohistochemistry highlights mucosal nerves (arrows) and a subset of superficial submucosal ganglion cells (g) in normal rectal tissue. B, Immunoreactive mucosal nerves and ganglion cells are completely absent in a biopsy from aganglionic rectum, although expression is present in enlarged submucosal nerves (asterisk) and mast cells (arrowhead). Acetylcholinesterase histochemistry (C and D) or choline transporter immunohistochemistry (E and F) demonstrate sparse or absent cholinergic mucosal nerves in biopsies from normal ganglionic rectum (C and E), as opposed to numerous coarse mucosal nerves (arrows in D and F) in aganglionic rectum.

Pediatr Dev Pathol. 2020 Jan-Feb;23(1):8-22.

Pathology report

- At minimal should include:
  - Location and type of biopsy
  - Presence/absence of ganglion cells
  - Presence/absence of submucosal nerve hypertrophy
  - Results of ancillary testing (AChE, ChT, and/or calretinin)

Remove this slide.

Surgery

- 1-stage (primary pull-through) vs 2-stage (initial fecal diversion, with pull-through procedure performed later) surgical intervention based on clinical stability (enterocolitis), bowel dilation, location of TZ
- Resect greater than or equal to 5 cm proximal to where ganglion cells were identified
- Frozen section: makes sure margin does not include TZ so euganglionic proximal margin is used for anastomosis
- Enterocolitis:
  - Can be life-threatening; presence of acute enterocolitis on biopsy requires a call to the clinician
  - Can be managed with rectal irrigations, antibiotics, and supportive care
  - Fecal diversion with ostomy in severe cases
- If bowel is dilated, need to do fecal diversion to allow decompression of GI tract and ensure proximal and distal ends of the anastomosis fit together

Intraoperative pathology

1) Seromucosal biopsy:
   - 3-10mm in thickness of Seromucosal biopsy, include both layers of muscularis propria, and ensure proper orientation, get sections perpendicular to serosal surface
   - Start with 2 slides each with 2-3 sections, 4-5 um in thickness, stain with H&E or Romanowsky stain (Diff Quik).
   - Cut more if no ganglion cells are identified (usually up to 10 sections)

2)Proximal margin of the pull-through specimen (the "donut"):
   - Take full-circumferential 5 mm thick transverse section from the proximal margin
   - Orient tissue well, and cut tissue deeply if necessary to obtain full-thickness representation of the entire circumference of proximal margin (see picture)
   - Exam for unequivocal ganglion cells and features of transition zone (TZ)
     - TZ defined by partial circumferential aganglionosis, myenteric hypoganglionosis, and submucosal nerve hypertrophy— any one of these features are considered diagnostic of TZ, and are an indication to position enterostomy/anastomosis in a more proximal position

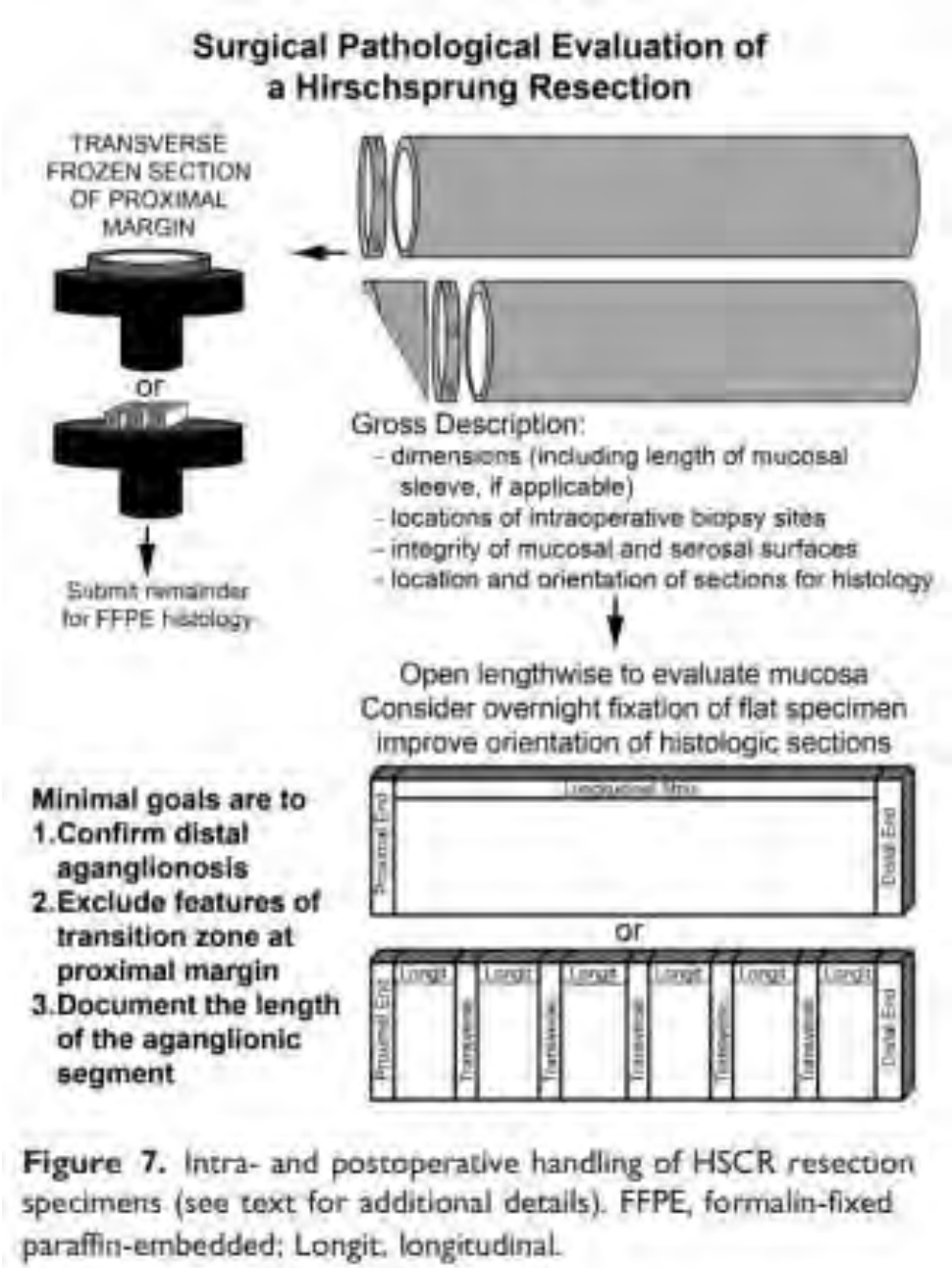


Figure 7. Intra- and postoperative handling of HSCR resection specimens (see text for additional details). FFPE, formalin-fixed paraffin-embedded; Longit. longitudinal.

Smith C, Ambartsumyan L, Kapur RP. Surgery, Surgical Pathology, and Postoperative Management of Patients With Hirschsprung Di sease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):23-39. doi: 10.1177/1093526619889436. Epub 2019 Nov 20. PMID: 31747833.

References:

- Ambartsumyan L, Smith C, Kapur RP. Diagnosis of Hirschsprung Disease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):8-22. doi: 10.1177/1093526619892351. Epub 2019 Dec 2. PMID: 31791203.
- Gershon EM, Rodriguez L, Arbizu RA. Hirschsprung's disease associated enterocolitis: A comprehensive review. World J Clin Pediatr. 2023 Jun 9;12(3):68-76. doi: 10.5409/wjcp.v12.i3.68. PMID: 37342453; PMCID: PMC10278080.
- Kapur RP, Ambartsumyan L, Smith C. Are We Underdiagnosing Hirschsprung Disease? Pediatr Dev Pathol. 2020 Jan-Feb;23(1):60-71. doi: 10.1177/1093526619889434. Epub 2019 Nov 20. PMID: 31747832.
- Kapur RP, Smith C, Ambartsumyan L. Postoperative Pullthrough Obstruction in Hirschsprung Disease: Etiologies and Diagnosis. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):40-59. doi: 10.1177/1093526619890735. Epub 2019 Nov 21. PMID: 31752599.
- Karim A, Tang CS, Tam PK. The Emerging Genetic Landscape of Hirschsprung Disease and Its Potential Clinical Applications. Front Pediatr. 2021 Aug 5;9:638093. doi: 10.3389/fped.2021.638093. PMID: 34422713; PMCID: PMC8374333.
- Smith C, Ambartsumyan L, Kapur RP. Surgery, Surgical Pathology, and Postoperative Management of Patients With Hirschsprung Disease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):23-39. doi: 10.1177/1093526619889436. Epub 2019 Nov 20. PMID: 31747833.
- Veras LV, Arnold M, Avansino JR, Bove K, Cowles RA, Durham MM, Goldstein AM, Krishnan C, Langer JC, Levitt M, Monforte-Munoz H, Rabah R, Reyes-Mugica M, Rollins MD 2nd, Kapur RP, Gosain A; American Pediatric Surgical Association Hirschsprung Disease Interest Group. Guidelines for synoptic reporting of surgery and pathology in Hirschsprung disease. J Pediatr Surg. 2019 Oct;54(10):2017-2023. doi: 10.1016/j.jpedsurg.2019.03.010. Epub 2019 Mar 21. PMID: 30935730; PMCID: PMC6754813.
- Yoshimaru K, Yanagi Y, Obata S, Takahashi Y, Irie K, Omori A, Matsuura T, Taguchi T. Acetylcholinesterase staining for the pathological diagnosis of Hirschsprung's disease. Surg Today. 2021 Feb;51(2):181-186. doi: 10.1007/s00595-020-02055-x. Epub 2020 Jun 23. PMID: 32577882.

- Q1: 10-day old female presented with abdominal distention, bilious emesis with concern for bowel obstruction, and lack of stools for six days, previously normal, ultrasound negative for pyloric stenosis, underwent rectal suction biopsy.

  Which of the following is an adequate biopsy specimen for the diagnosis of this condition?
  A) 2 cm above the anal verge, showing transitional mucosa, and all biopsy specimen showing at least 50% submucosal tissue, 20 sections are given for microscopic review?
  B) 2, 3, and 4 cm above the anal verge, all biopsy exhaustively sectioned, most biopsy sections include at least 50% submucosal tissue, showing colonic mucosa
  C) 2, 3, and 4 cm above the anal verge, maximum up to 40 sections, showing minimal sub-mucosal tissue with overlaying colonic epithelium
  D) 5 cm proximal to the transition zone, with presence of ganglion cells and does not show submucosal nerve hypertrophy or myenteric hypoganglionosis

- Q2: Which of the following features define the transition zone (TZ)?

  A) Partial circumferential aganglionosis

  B) Myenteric hypoganglionosis

  C) Submucosal nerve hypertrophy (defined as > 40 um)

  D) A, B, and C (all 3 necessary)

  E) A, B, or C (any one of these features)

- Explanations
- Q1: Answer B
  - Adequate biopsies are at 2, 3, and 4 cm above the anal verge, all biopsy exhaustively sectioned, most biopsy sections include at least 50% submucosal tissue, showing colonic mucosa
  - In suspected HD, the biopsy must be adequate ot diagnose or rule out HD. An adequate biopsy must have tissue from multiple areas (conventionally taken at 2, 3, and 4 cm above the anal verge), and each biopsy must show at least 50% submucosal tissue in most of the sections. Biopsies from 2.0 cm can sometimes show transitional mucosa, however, colonic mucosa is typically considered reassuring for adequacy. Finally, adequate sections must be examined to confidently rule out HD, ranging from 40 to >100 section
- Q2:
  - Answer: E) A, B, or C, if any of these features are present, this is considered diagnostic of TZ.
  - TZ is the intestinal segment immediately proximal to the aganglionic bowel, leading to more proximal euganglionic tissue. The presence of any of these features is diagnostic of TZ. Intraoperative recognition of the TZ at the proximal margin of the pull-through specimen is necessary to ensure that the anastomosis does not contain aganglionic or TZ tissue.

- Hirschsprung disease (HD) is defined as incomplete colonization of the gut by neural progenitor cells which leads to complex multigenetic disease characterized by absence of intrinsic ganglion cells

(aganglionosis) in the submucosal (Meissner) and myenteric (Auerbach) plexuses in the rectum, and extending variable lengths proximally

- Multiple variants of HD exists, based on the length of the aganglionic intestinal tract, including 1. Short-segment classic HD (75-80%): Rectosigmoid colon, 2. Long-segment HD (10-15%): Proximal to splenic flexure, 3. Total colonic aganglionosis/HD (5-10%): Entire colon, 4. Zonal ("segmental") and "skip segment" variants (rare).
- Patients usually present with abdominal distension and symptoms of intestinal obstruction, and neonates may also have delayed passage of meconium. Hirschsprung-associated enterocolitis (HAEC) is an explosive (usually bloody) diarrhea, fever, abdominal distention, which can be life-threatening. While milder forms may be treated with antibiotics, severe forms require surgical interventions.
- Screening for HD can be done with contrast enema or anorectal manometry; when there is clinical concern for HD, a rectal suction biopsy (RSB) may be performed, especially in infants <6 months of age. If results of the RSB are equivocal, a full-thickness biopsy (FTB) is recommended.
- Biopsies for HD should be from the appropriate location, normally taken at 2, 3, and 4 cm above the anal verge. They should be at least 2-3 mm in thickness and have greater than or equal to 50% of submucosa. There should be adequate sections cut to examine for ganglion cells (TCH does at least 40 sections; some papers recommend 50-75 H&E sections at 4 to 5 um thickness; some institutions may choose to exhaust the block). Submucosal nerve hypertrophy (nerves > 40 um) without the presence of ganglion cells is considered diagnostic of HD.

- Ancillary tests (acetylcholinesterase, cholin, or calretinin immunostains) may be helpful in diagnosis.

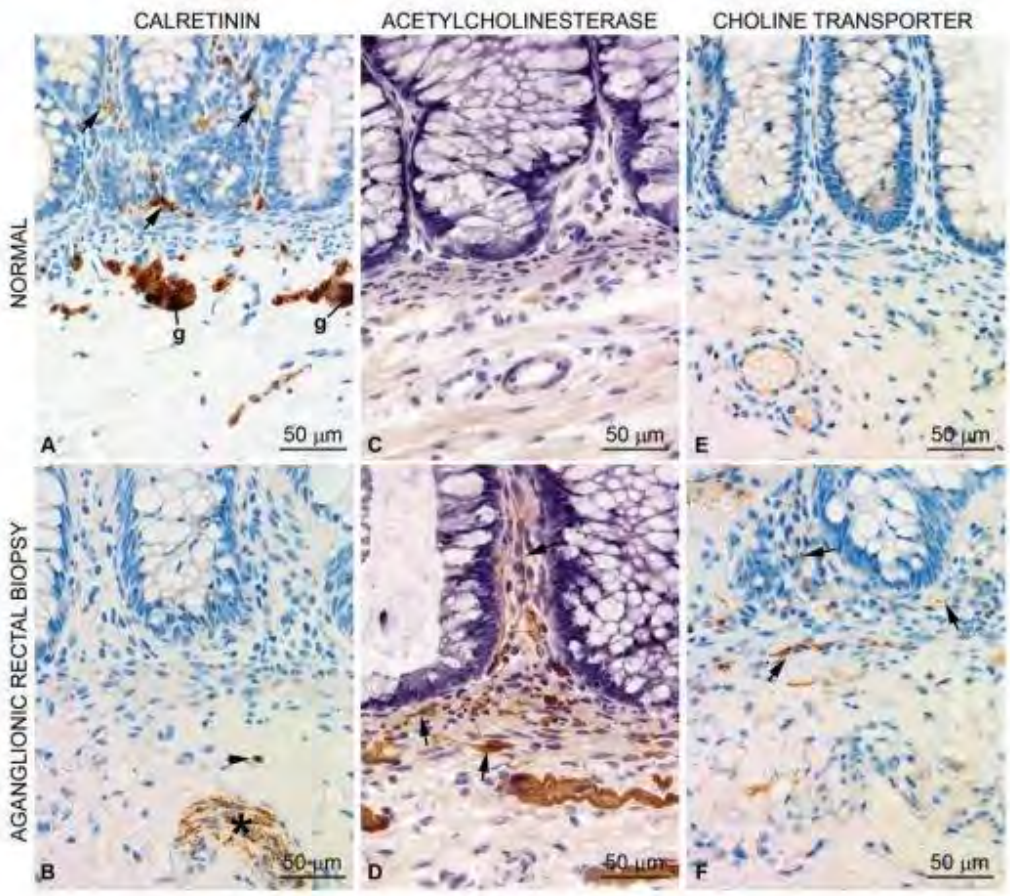


Figure 7. Ancillary diagnostic techniques. A, Calretinin immunohistochemistry highlights mucosal nerves (arrows) and a subset of superficial submucosal ganglion cells (g) in normal rectal tissue. B, Immunoreactive mucosal nerves and ganglion cells are completely absent in a biopsy from aganglionic rectum, although expression is present in enlarged submucosal nerves (asterisk) and mast cells (arrowhead). Acetylcholinesterase histochemistry (C and D) or choline transporter immunohistochemistry (E and F) demonstrate sparse or absent cholinergic mucosal nerves in biopsies from normal ganglionic rectum (C and E), as opposed to numerous coarse mucosal nerves (arrows in D and F) in aganglionic rectum.

Citation: Ambartsumyan L, Smith C, Kapur RP. Diagnosis of Hirschsprung Disease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):8-22. doi: 10.1177/1093526619892351. Epub 2019 Dec 2. PMID: 31791203

- Pathology reports should include at minimum:
    - Location and type of biopsy
    - Presence/absence of ganglion cells
    - Presence/absence of submucosal nerve hypertrophy
    - Results of ancillary testing (AChE, ChT, and/or calretinin)
- Surgery is the mainstay of treatment. Initial 1-stage (primary pull-through) versus 2-stage (initial fecal diversion, with pull-through procedure performed at a later time) is determined patients' clinical stability, bowel dilation, and location of the transition zone (TZ). Pull-through specimen
- Intraoperative Pathology (frozen section analysis) is an integral part of the surgical procedure in a HD case. Seromucosal biopsies and proximal margins of pull-through specimen can both be sent for interoperative analysis for presence or absence of ganglion cells and to exclude the presence of TZ. Proper orientation of the specimen is imperative to accurate analysis of the frozen section.

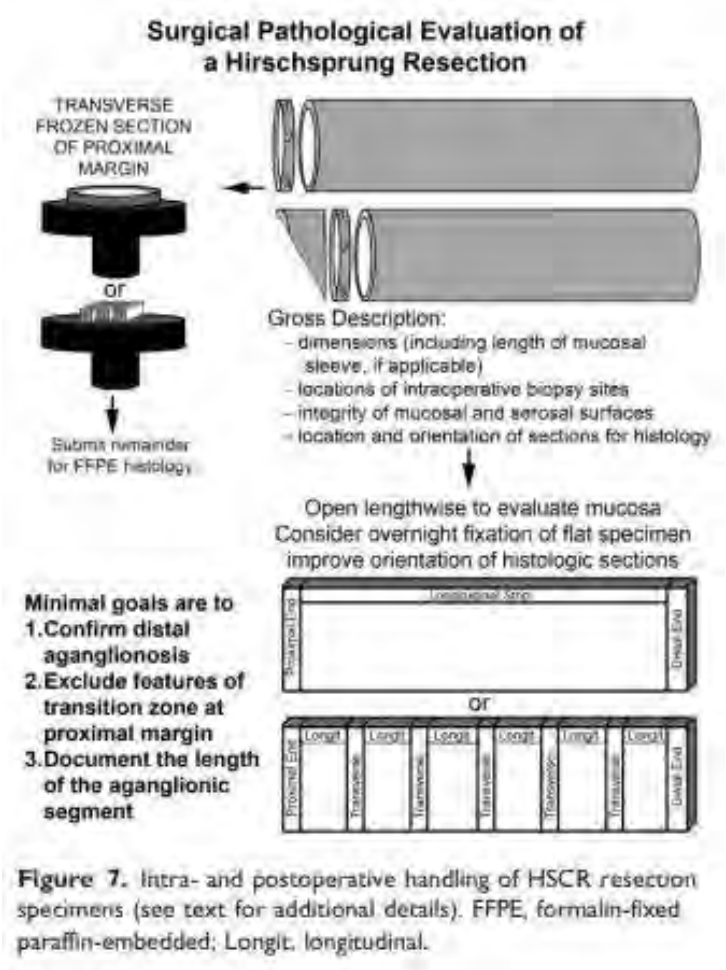


Figure 7. Intra- and postoperative handling of HSCR resection specimens (see text for additional details). FFPE, formalin-fixed paraffin-embedded; Longit, longitudinal.

Citation: Smith C, Ambartsumyan L, Kapur RP. Surgery, Surgical Pathology, and Postoperative Management of Patients With Hirschsprung Disease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):23-39. doi: 10.1177/1093526619889436. Epub 2019 Nov 20. PMID: 31747833.

- References

  - Ambartsumyan L, Smith C, Kapur RP. Diagnosis of Hirschsprung Disease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):8-22. doi: 10.1177/1093526619892351. Epub 2019 Dec 2. PMID: 31791203.
  - Gershon EM, Rodriguez L, Arbizu RA. Hirschsprung's disease associated enterocolitis: A comprehensive review. World J Clin Pediatr. 2023 Jun 9;12(3):68-76. doi: 10.5409/wjcp.v12.i3.68. PMID: 37342453; PMCID: PMC10278080.
  - Kapur RP, Ambartsumyan L, Smith C. Are We Underdiagnosing Hirschsprung Disease? Pediatr Dev Pathol. 2020 Jan-Feb;23(1):60-71. doi: 10.1177/1093526619889434. Epub 2019 Nov 20. PMID: 31747832.
  - Kapur RP, Smith C, Ambartsumyan L. Postoperative Pullthrough Obstruction in Hirschsprung Disease: Etiologies and Diagnosis. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):40-59. doi: 10.1177/1093526619890735. Epub 2019 Nov 21. PMID: 31752599.
  - Karim A, Tang CS, Tam PK. The Emerging Genetic Landscape of Hirschsprung Disease and Its Potential Clinical Applications. Front Pediatr. 2021 Aug 5;9:638093. doi: 10.3389/fped.2021.638093. PMID: 34422713; PMCID: PMC8374333.

- Smith C, Ambartsumyan L, Kapur RP. Surgery, Surgical Pathology, and Postoperative Management of Patients With Hirschsprung Disease. Pediatr Dev Pathol. 2020 Jan-Feb;23(1):23-39. doi: 10.1177/1093526619889436. Epub 2019 Nov 20. PMID: 31747833.
- Veras LV, Arnold M, Avansino JR, Bove K, Cowles RA, Durham MM, Goldstein AM, Krishnan C, Langer JC, Levitt M, Monforte-Munoz H, Rabah R, Reyes-Mugica M, Rollins MD 2nd, Kapur RP, Gosain A; American Pediatric Surgical Association Hirschsprung Disease Interest Group. Guidelines for synoptic reporting of surgery and pathology in Hirschsprung disease. J Pediatr Surg. 2019 Oct;54(10):2017-2023. doi: 10.1016/j.jpedsurg.2019.03.010. Epub 2019 Mar 21. PMID: 30935730; PMCID: PMC6754813.
- Yoshimaru K, Yanagi Y, Obata S, Takahashi Y, Irie K, Omori A, Matsuura T, Taguchi T. Acetylcholinesterase staining for the pathological diagnosis of Hirschsprung's disease. Surg Today. 2021 Feb;51(2):181-186. doi: 10.1007/s00595-020-02055-x. Epub 2020 Jun 23. PMID: 32577882.

Case of the month
April 2025

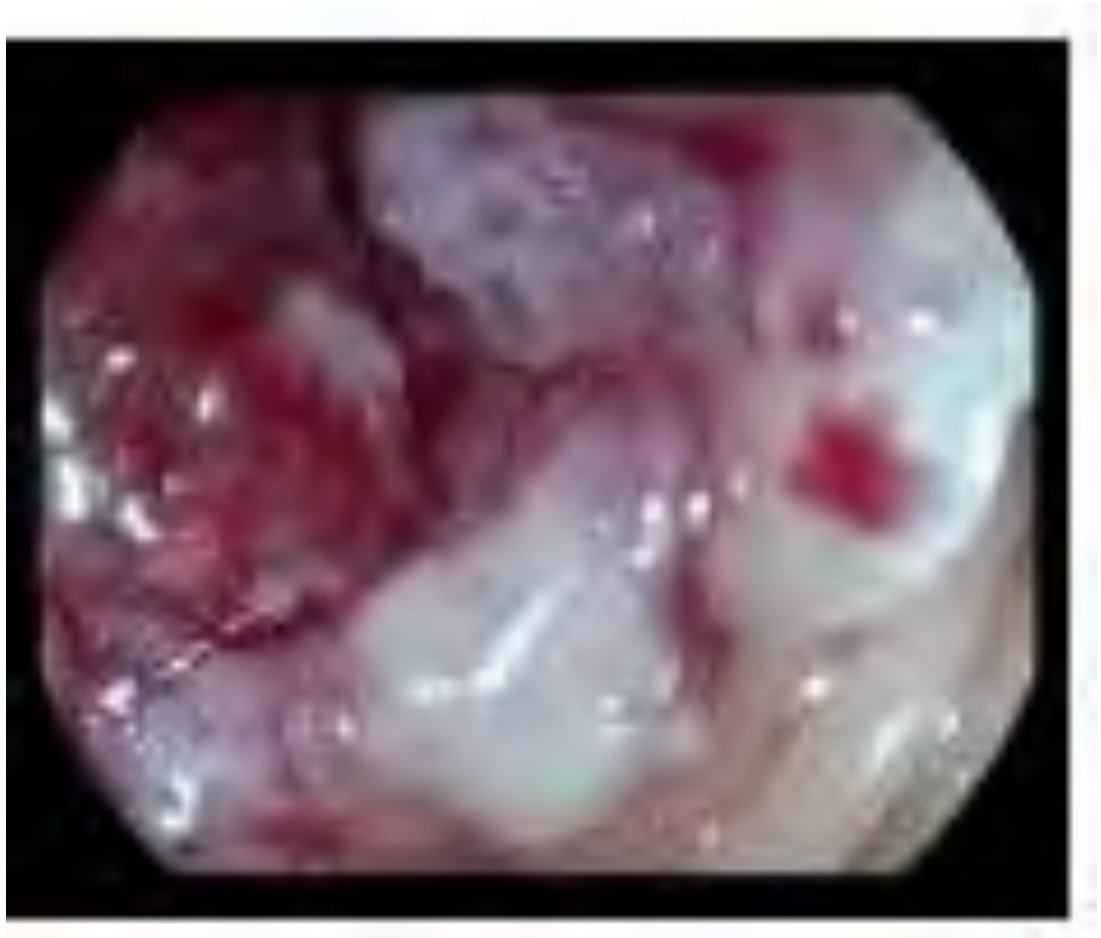
Sonal Italiya, MD, (Pathology Resident,PGY-2)

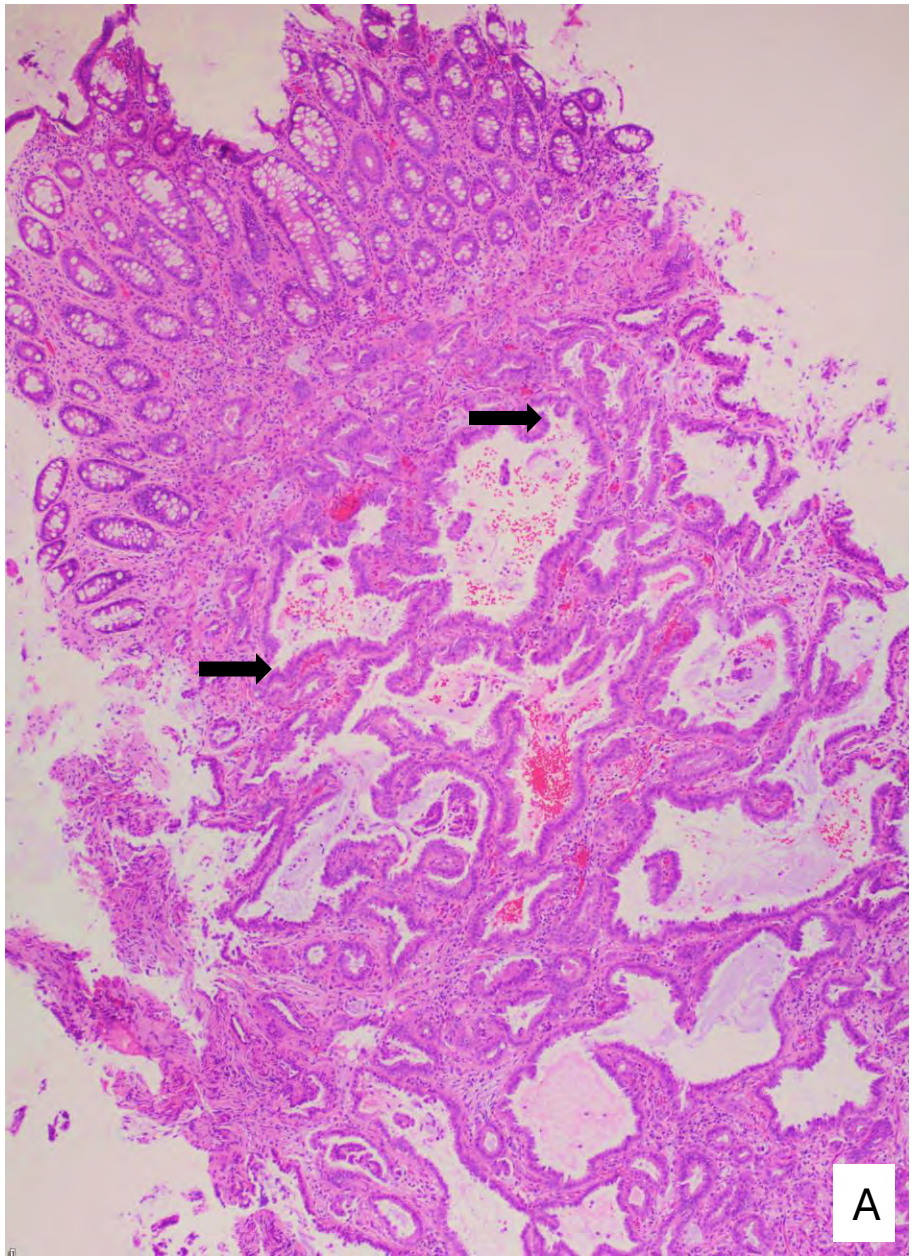
Yuriko Fujita, M.D., Ph. D. (Surgical Pathology Fellow)

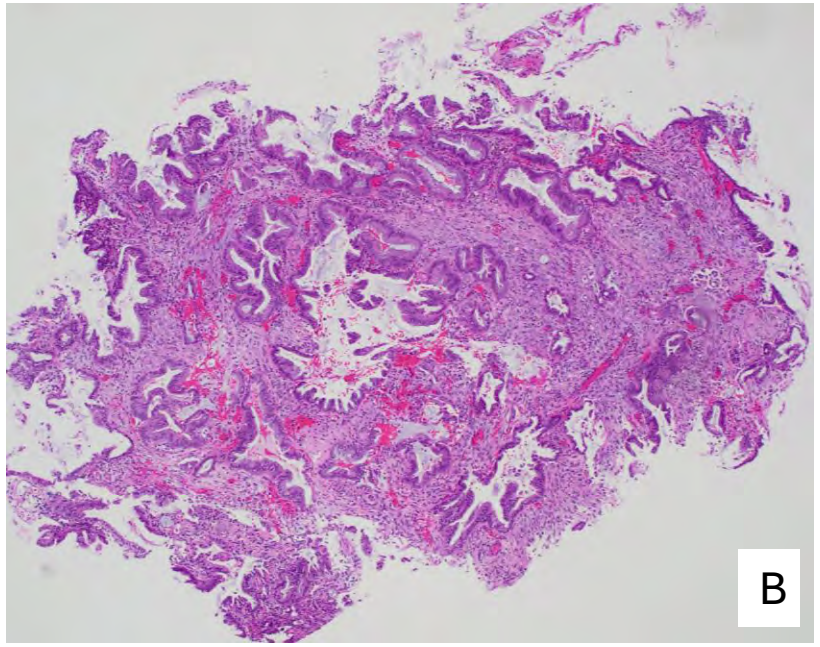
Shilpa Jain , M.D. (Associate Professor, Director of GI Pathology at Baylor St. Lukes Hospital)

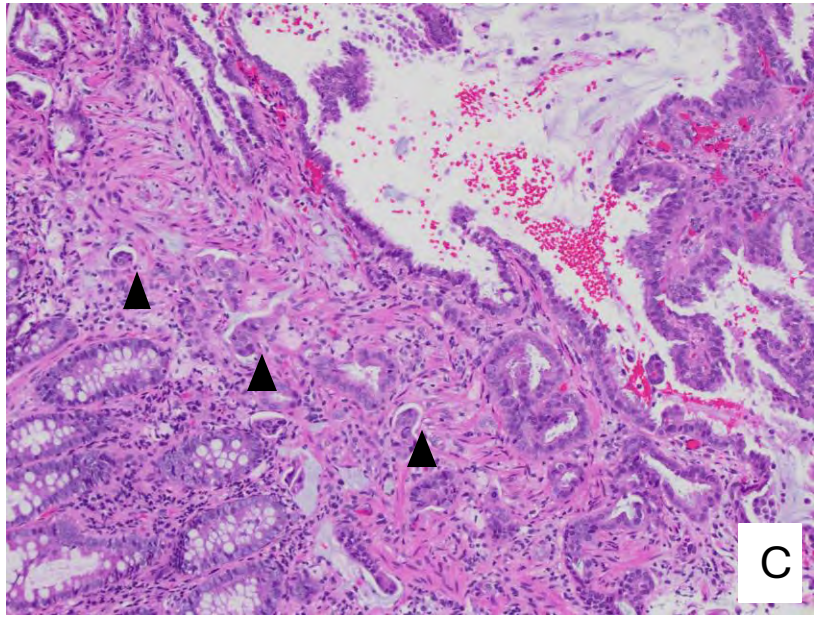
Clinical Presentation

- A 77-year-old female presented with nausea, vomiting, and abdominal pain.
- She recently underwent an ERCP, which revealed a severe fibrotic stricture with nodularity in the upper third of the main duct, and a stent was placed. However, her symptoms did not resolve.
- A subsequent abdominal CT scan showed signs of colitis, including distention and mural thickening of the descending colon, as well as irregularity of the sigmoid colon. She was treated empirically with Fidaxomicin for 10 days.
- A sigmoidoscopy later revealed a frond-like/villous partially obstructing large mass in the recto-sigmoid colon (see image), and a biopsy of the mass was performed.





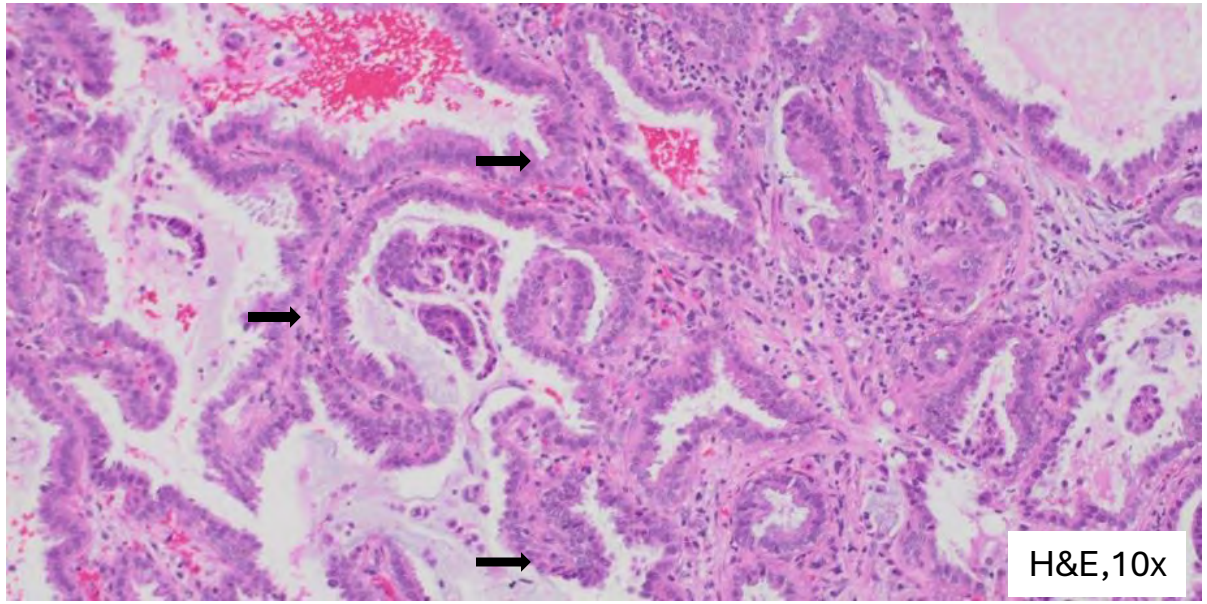


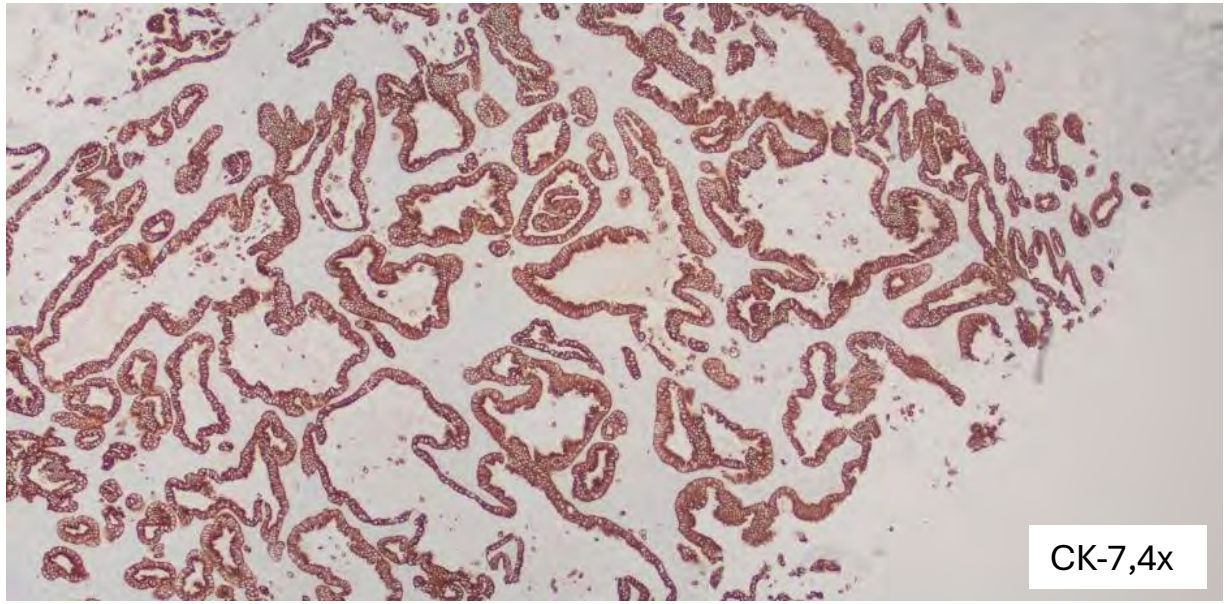


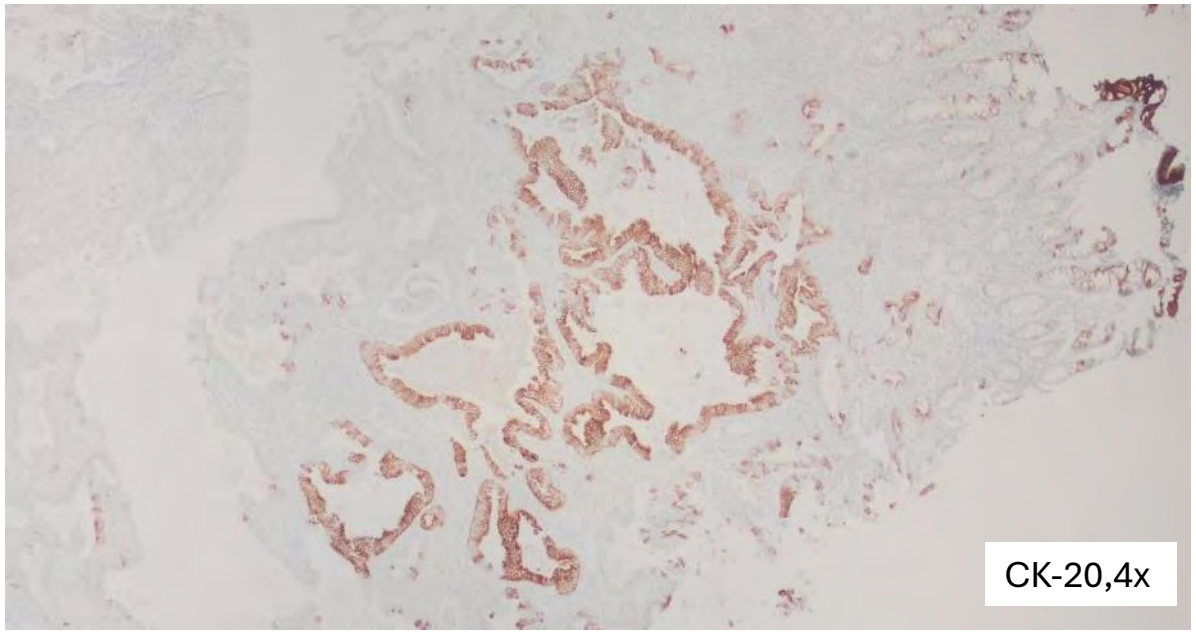
A. The biopsy shows a moderately differentiated adenocarcinoma involving predominantly the submucosa (indicated by the arrow) without any surface dysplasia (H&E,10x).

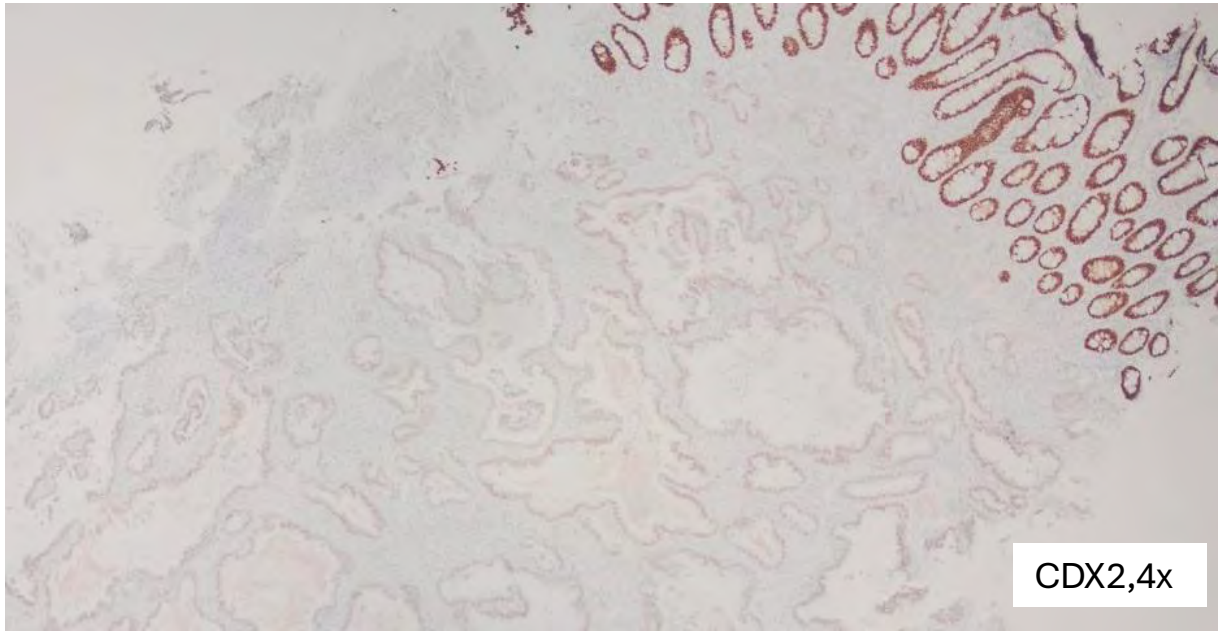
B. The tumor involves the surface, but no precursor lesions such as tubular adenoma are noted (H&E,4x).

C. There is extensive lymphovascular invasion present in the lamina propria and superficial submucosa (H&E,40x).





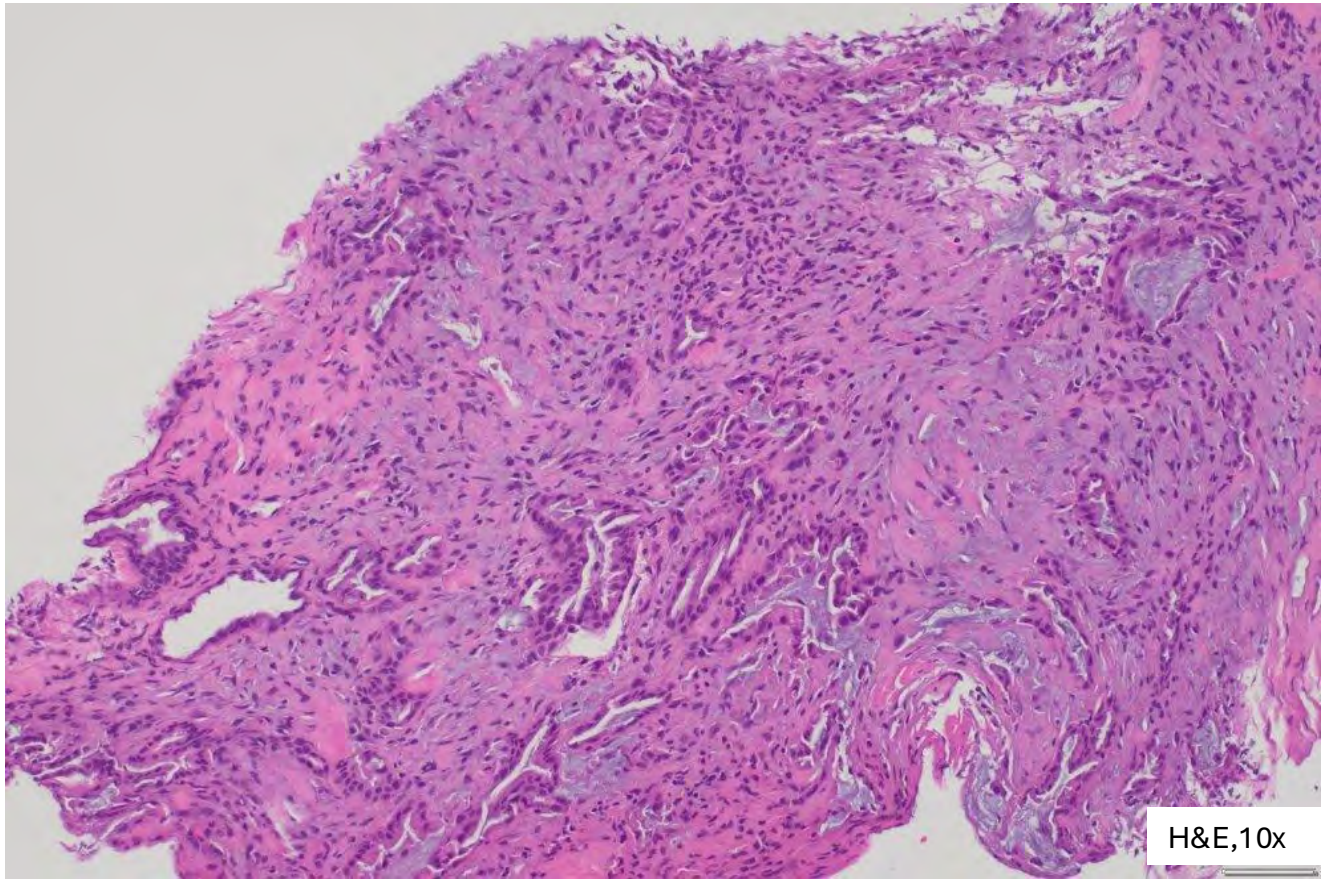


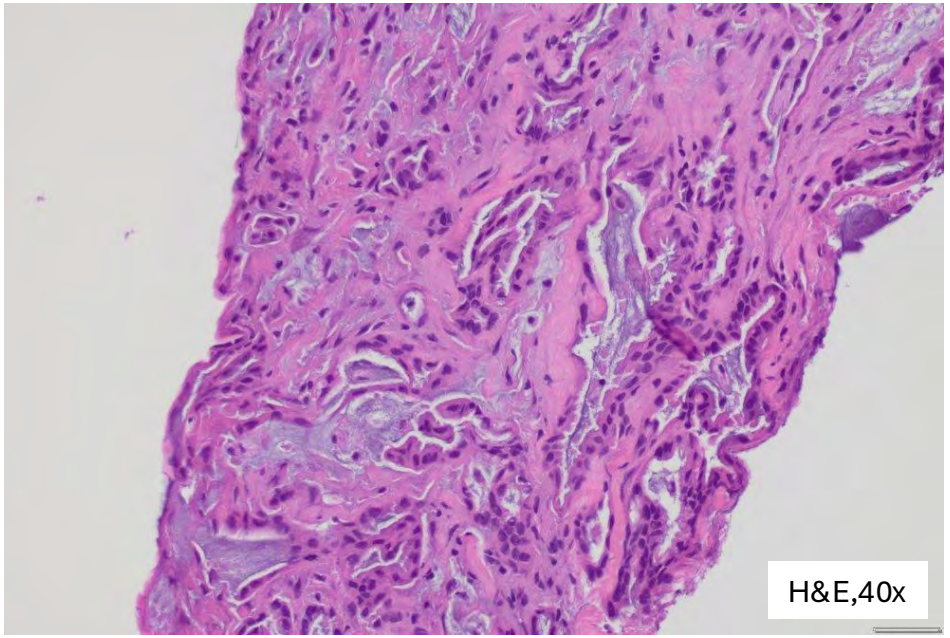


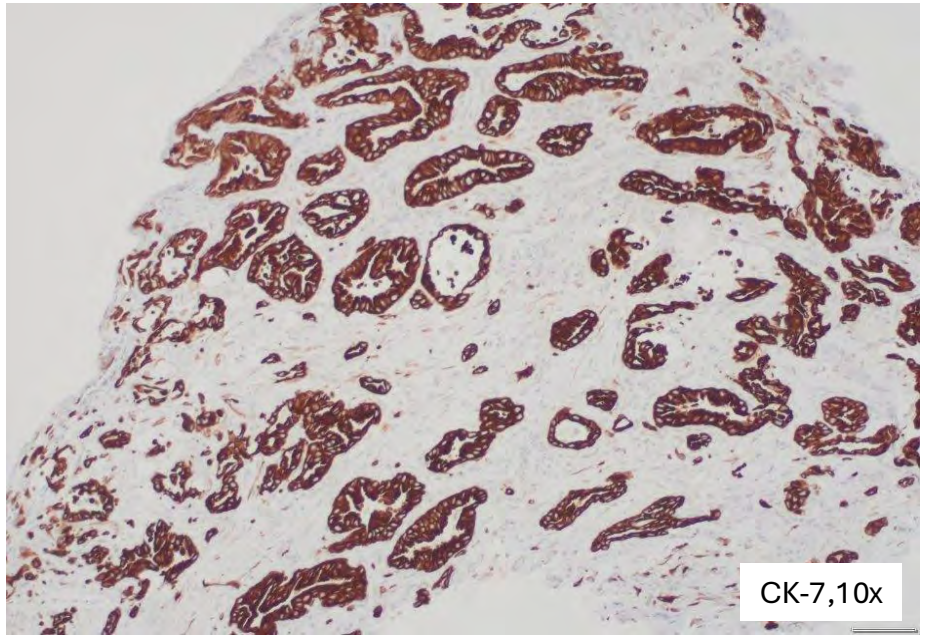
The high-power shows infiltrating glands lined by cuboidal cells with low N:C ratio, basally located round nucleus with mild pleomorphism(arrow). The cells are diffusely positive for CK7, patchy positive for CK20 and weakly nuclear positive for CDX2.

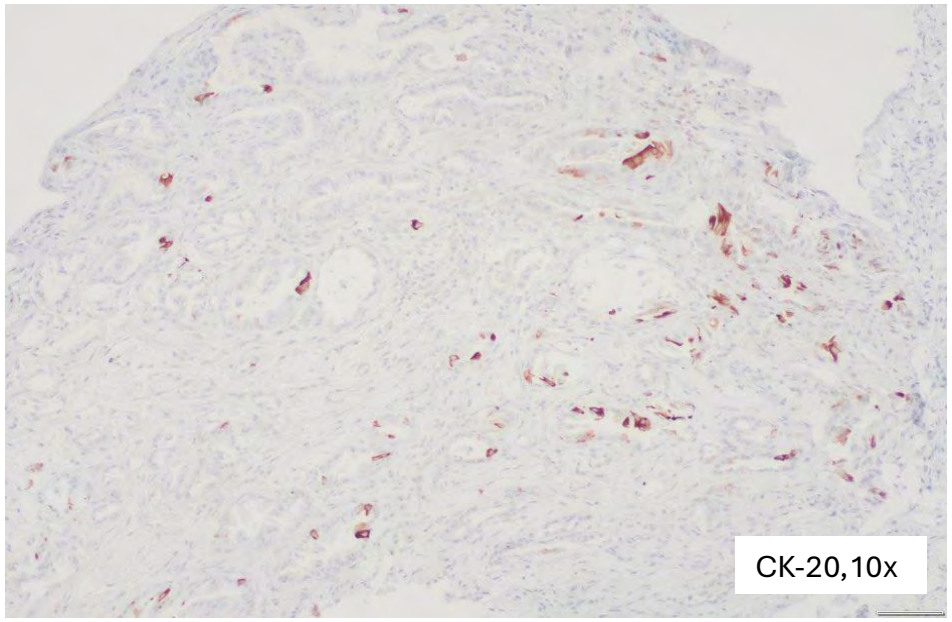
Clinical Course

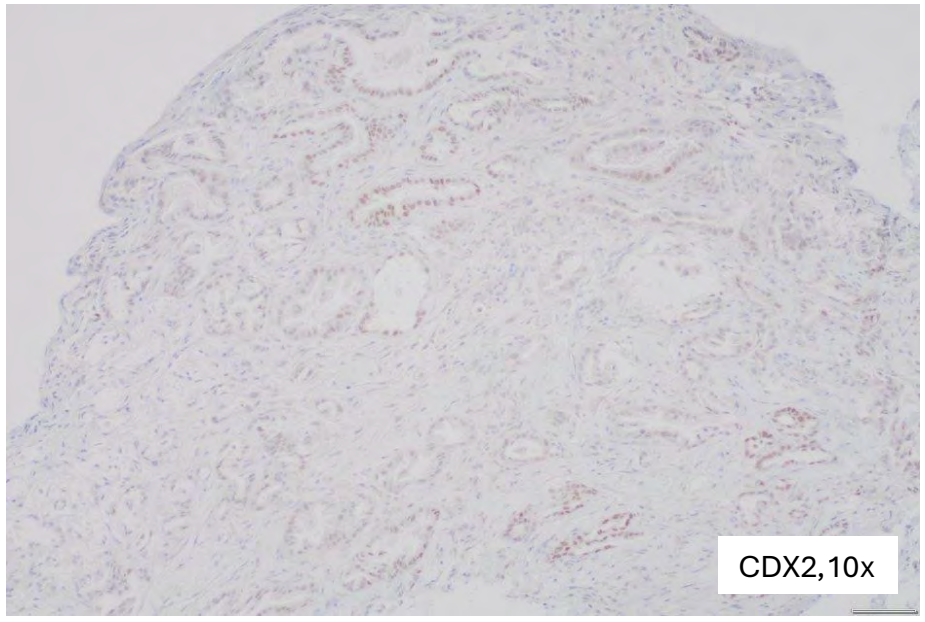
- The patient was planned for exploratory laparoscopy.
- Exploratory laparoscopy revealed firm mass in recto-sigmoid colon adherent to pelvis, diffuse peritoneal studding, and innumerable nodules on small bowel and mesentery.
- Also palpated nodules along right lobe of liver as well as firm mass at porta hepatis were identified.
- Intraoperative frozen section of the peritoneal lesion was positive for malignancy. Decision was made to abort resection or diversion.
- Permanent section of this peritoneal lesion was examined.







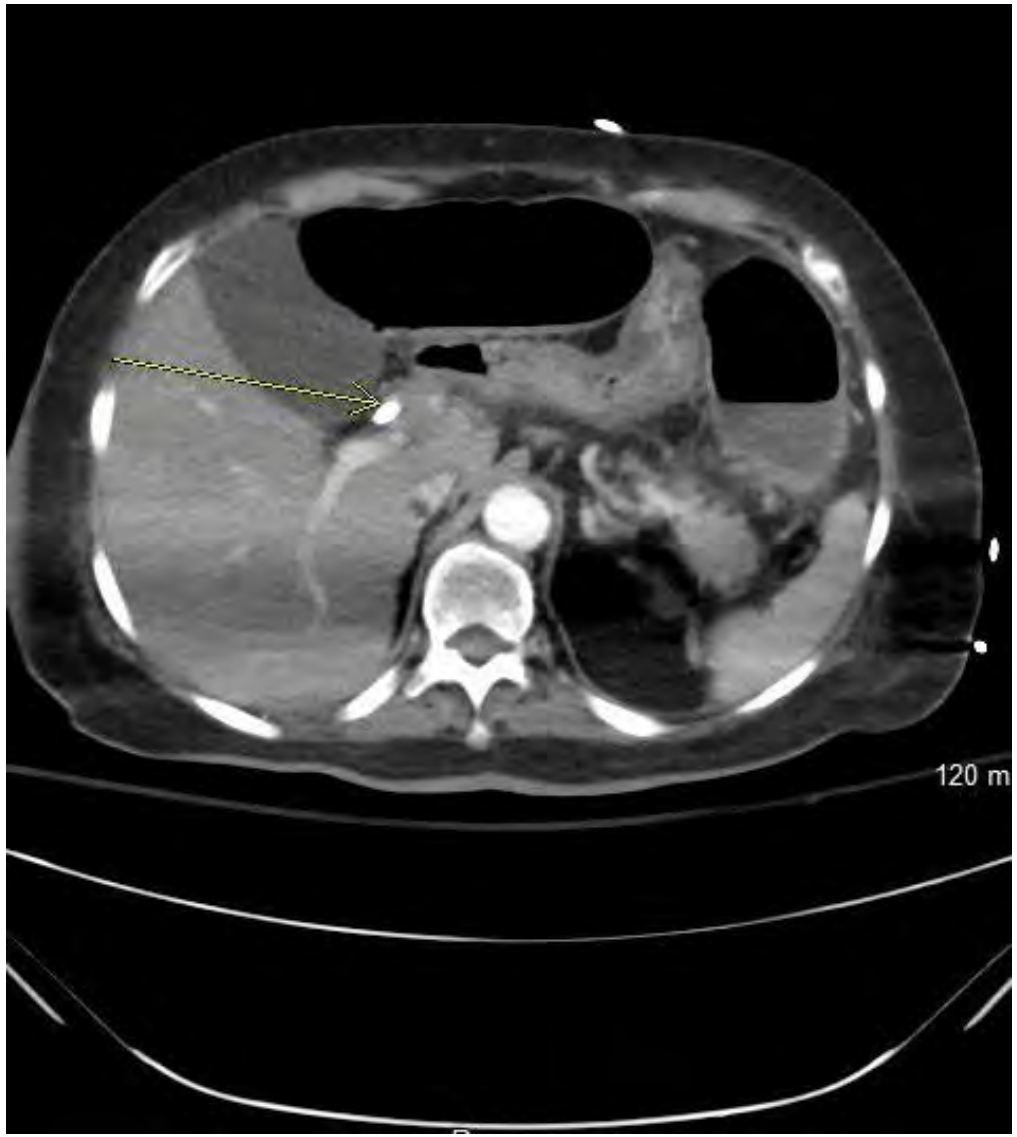


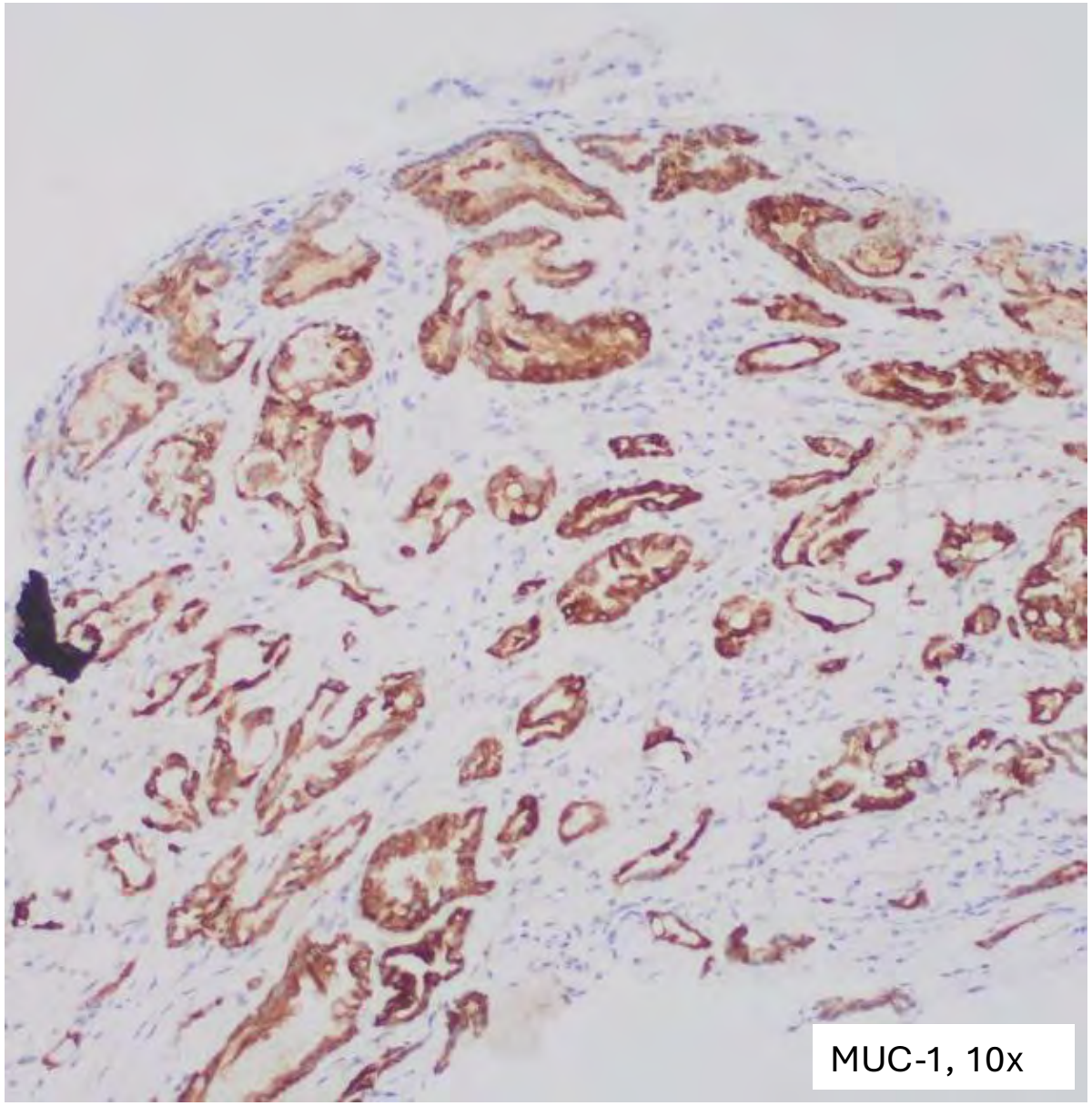


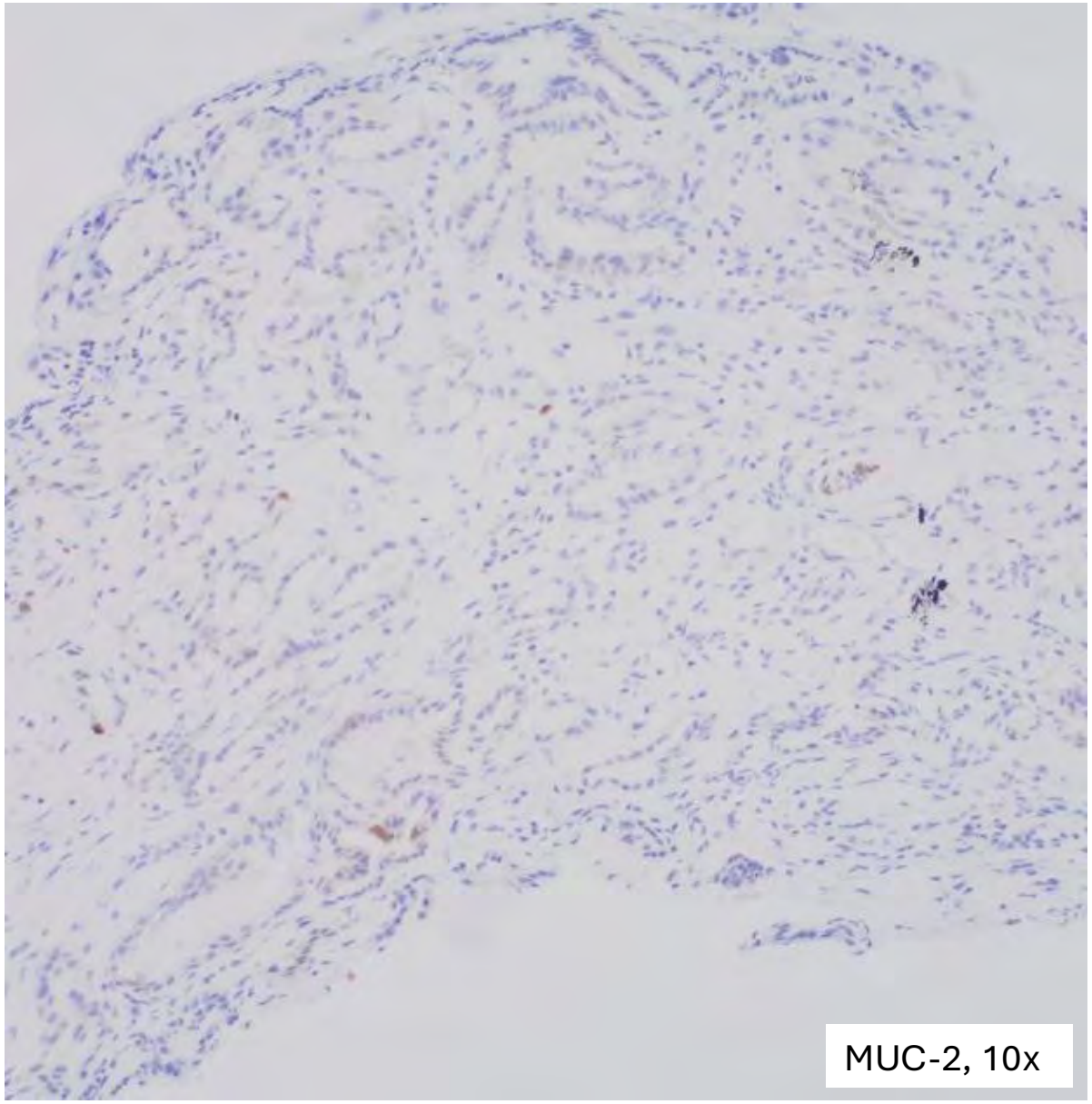
The biopsy shows a moderately differentiated adenocarcinoma which is diffusely positive for CK-7, patchy positive for CK-20, and weak positive for CDX2.

Chest CT revealed a mass along the CBD

- CT chest showed a 2x 2 cm mass along the common bile duct with moderate intrahepatic duct dilation.
- The leftportal vein was either occluded or infiltrated by a mass (see imaging)







Tumor cells are diffusely positive for MUC-1 and negative for MUC-2.

Q1: Which of the following morphological features most strongly suggest a metastatic tumor rather than a primary tumor origin?

A) Adenocarcinoma without any overlying precursor lesion
B) Extensive lymphovascular invasion in lamina propria or superficial submucosa
C) Endoscopic and radiological correlation
D) All of the above

Answer: D. All of the above.

Explanation for Q1:

- The biopsy of the rectal mass demonstrated infiltrating irregular glands within the submucosa. Importantly, the overlying epithelium was unremarkable, showing no evidence of dysplasia (refer to the PowerPoint image).
- While metastatic adenocarcinoma to the rectum may occasionally involve the surface epithelium through cancerization, this case lacked any precursor lesions such as tubular adenoma or high-grade dysplastic changes.
- The presence of extensive lymphovascular invasion in the lamina propria and superficial submucosa supports a metastatic origin rather than a primary rectal neoplasm. Correlation with endoscopic findings and imaging studies is crucial before finalizing the diagnosis.
- Histologically, the tumor exhibits glands lined by cuboidal cells with a low nuclear-to-cytoplasmic ratio, basally located round nucleus with mild pleomorphism, and infrequent mitoses unlike primary colorectal adenocarcinoma, which usually shows columnar epithelium with stratified oval nuclei, frequent mitosis/apoptosis or dirty necrosis, further supporting the likelihood of a metastatic process.
- Although metastatic carcinoma in the rectum is uncommon, differentiating between primary and metastatic cancer can be particularly challenging, especially when biopsies are conducted by a gastroenterologist.
- As per the literature, potential sources of metastasis include pancreaticobiliary adenocarcinoma (as in this case); endometrial

carcinoma, ductal carcinoma of the breast, ovarian serous carcinoma (in females); prostatic adenocarcinoma (in males), and others such as bladder, gastric carcinoma, and melanoma.

- Metastasis of pancreaticobiliary carcinoma to the rectum is exceptionally uncommon but can occur. Therefore, heightened clinical suspicion, thorough diagnostic workup, and close follow-up are essential.
- Pancreaticobiliary carcinomas are among the most aggressive malignancies, often carrying a poorer prognosis than primary intestinal tumors. When rectal metastasis occurs, it may mimic primary rectal cancer, complicating both diagnosis and management.

Q 2: Which of the following immunoprofile will support diagnosis of metastatic adenocarcinoma of pancreatobiliary origin over intestinal/colorectal type primary tumor?

A) CK7 patchy positive, CK20 diffuse positive, CDX2 strong positive, MUC1 Negative, MUC 2 positive
B) CK7 diffuse positive, CK20 patchy positive, CDX2 weak positive, MUC 1 positive, MUC 2 Negative
C) CK7 negative, CK20 diffuse positive, CDX2 weak positive, MUC 1 negative, MUC 2 positive
D) CK7 patchy positive, CK20 patchy positive, CDX2 weak positive, MUC 1 negative, MUC 2 positive

Answer: B. CK7 diffuse positive, CK20 patchy positive, CDX2 weak positive, MUC 1 positive, MUC 2 Negative

Explanation for Q2:

- Accurate identification of the primary site of a metastatic adenocarcinoma is essential for appropriate treatment planning and patient management. The expression patterns of CK7 and CK20 vary depending on the tissue of origin, making them valuable markers in determining the source of metastatic disease.

- Immunohistochemical profiling using CK7, CK20, and CDX2 offers critical diagnostic information in pinpointing the primary site. Additionally, mucin stains such as MUC1 and MUC2 further aid in differentiating between primary tumor origins, enhancing diagnostic accuracy.
- The pancreaticobiliary-type adenocarcinomas are more aggressive compared to the intestinal type. Since morphologic distinction can be challenging, immunohistochemistry has been advocated to make this distinction as the histologic subtype (intestinal vs pancreaticobiliary) can help in the choice of adjuvant therapy.

Tumor Type	Positive Markers	Negative/Weak Positive Markers
Intestinal type	CK20 or CDX2 or MUC2	MUC1
	CK20, CDX2, and MUC2 (irrespective of MUC1)	
Pancreatobiliary-type	MUC1	CDX2 and MUC2 (irrespective of CK20)

References

1- Olivier Janjic et al.Metastasis to the rectum: A systematic review of the literature,European Journal of Surgical Oncology,Volume 48, Issue 4,2022, Pages 822-833, https://doi.org/10.1016/j.ejso.2021.10.004.
2- Galanopoulos M, Gkeros F, Liatsos C, Pontas C, Papaefthymiou A, Viazis N, Mantzaris GJ, Tsoukalas N. Secondary metastatic lesions to colon and rectum. Ann Gastroenterol. 2018 May-Jun;31(3):282-287. doi: 10.20524/aog.2018.0244. Epub 2018 Mar 3. PMID: 29720853; PMCID: PMC5924850.

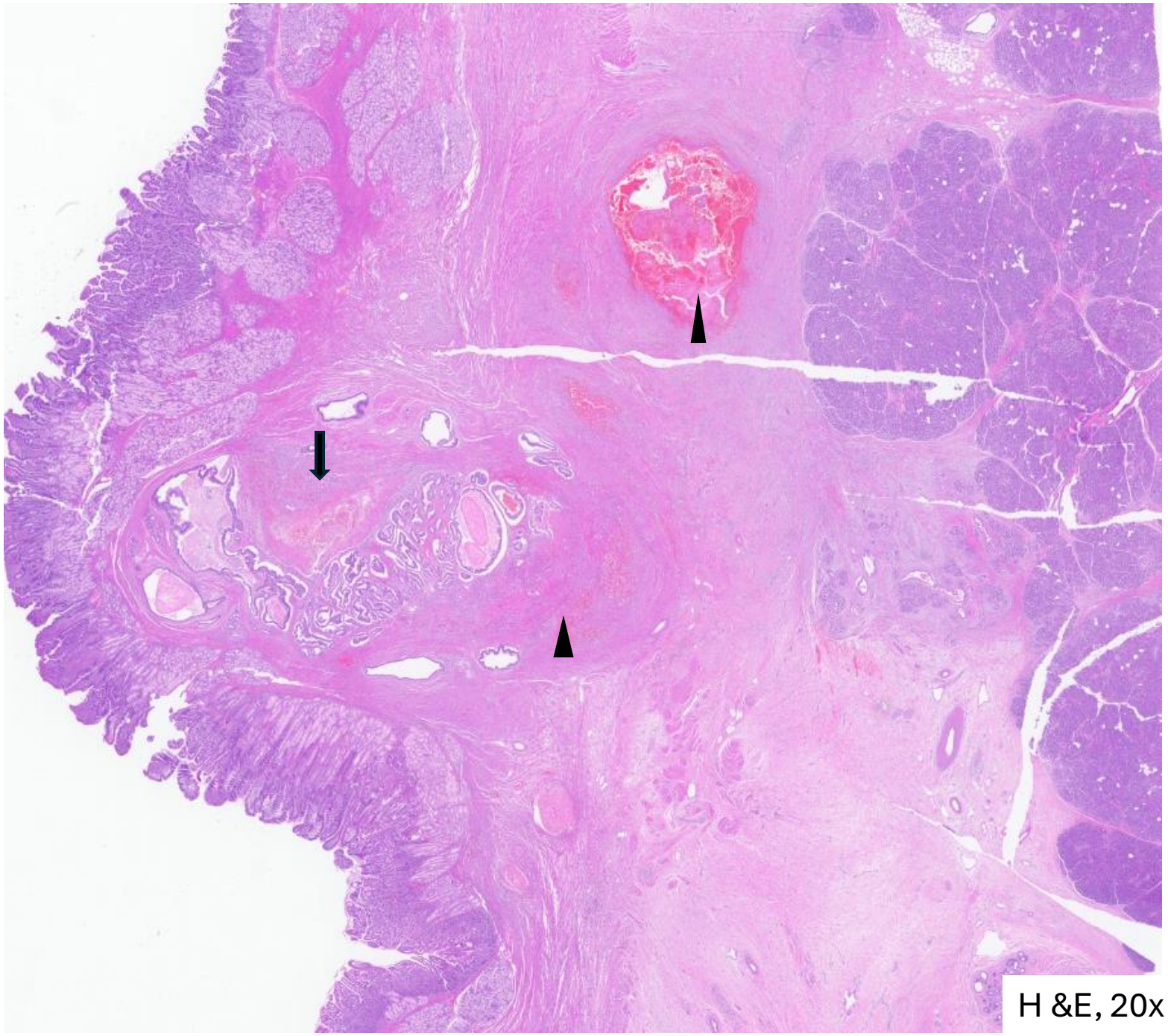
3- Sanjay Kakar, MD*; Chanjuan Shi, MD, PhD*; N. Volkan Adsay, MD; Patrick Fitzgibbons, MD; Mary K. Washington, MD, PhD: CAP Cancer and CAP Pathology Electronic Reporting Committees. Protocol for the Examination of Specimens from Patients with Carcinoma of the Ampulla of Vater
4- Tianzhu, Q., Xiaohan, W., Yang, L., Wen, P., Yirui, Z., Rui, Yanhong, G. (2022). Pancreatic metastases to the rectum: a case report and literature review. All Life, 15(1), 1325–1329. https://doi.org/10.1080/26895293.2022.2156624.
5- Digestive System Tumours, WHO Classification of Tumours, 5th Edition, Volume 1, WHO Classification of Tumors Editorial Board, 2019, ISBN-13.
6- Brian O'Sullivan, Thomas Burton, Ralph Van Dalen, Fraser Welsh, Archana Pandita, Jesse Fischer, Beware the pancreatic incidentaloma in colorectal tumours: pancreatic adenocarcinoma with metastases to the colon and rectum, Journal of Surgical Case Reports, Volume 2022, Issue 1, January 2022, rjab629, https://doi.org/10.1093/jscr/rjab629
7- Pernick N. MUC2-MUC6. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/stainsmuc2.html. Accessed April 17th, 2025.

Case of the month
May 2025

Sonal Italiya, MD, (Pathology Resident,PGY-2)

Oluwaseyi Olayinka, MD (Assistant Professor)

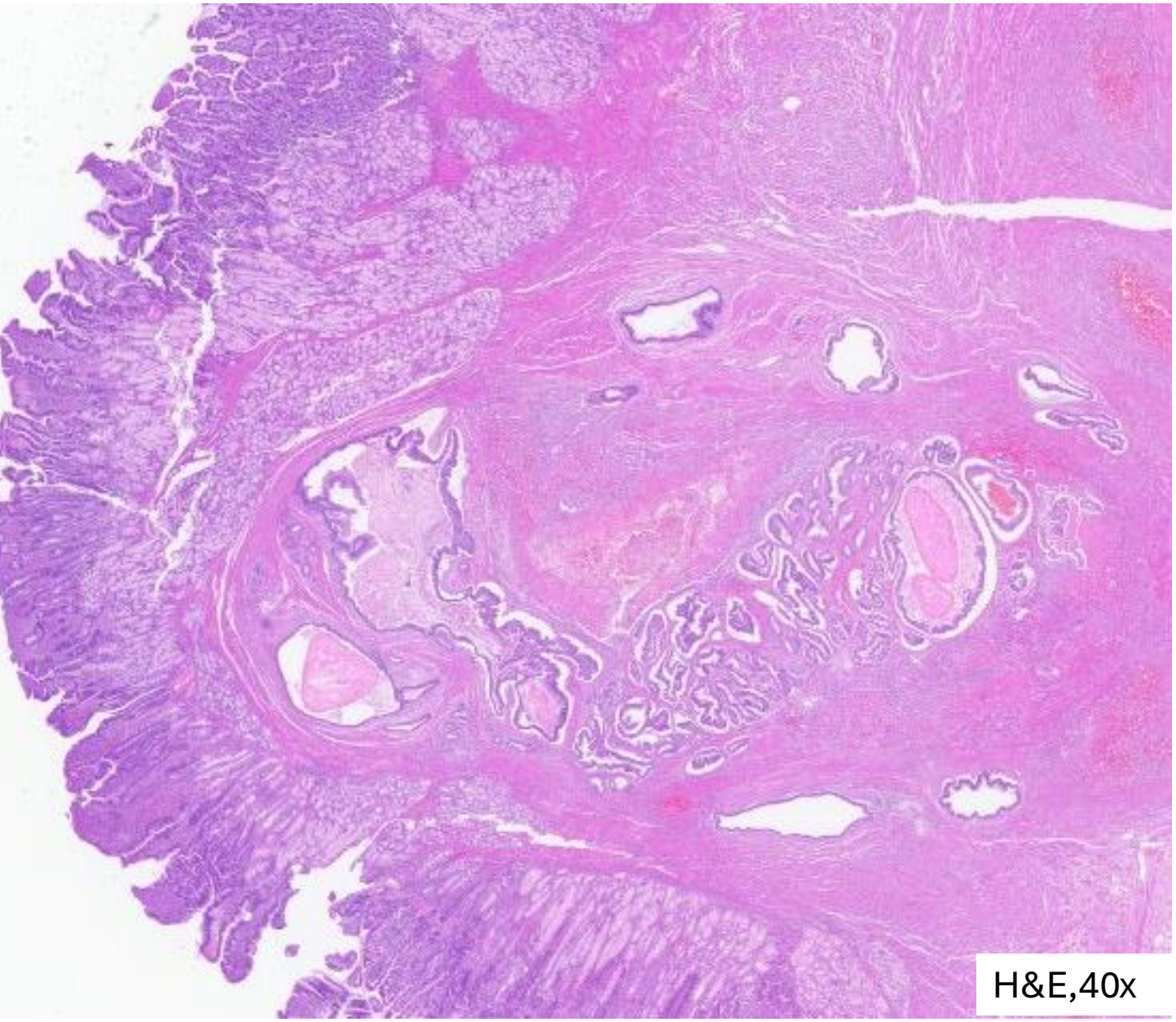
E. Celia Marginean, MD (Professor, Director of GI/Liver fellowship)



H &E, 20x

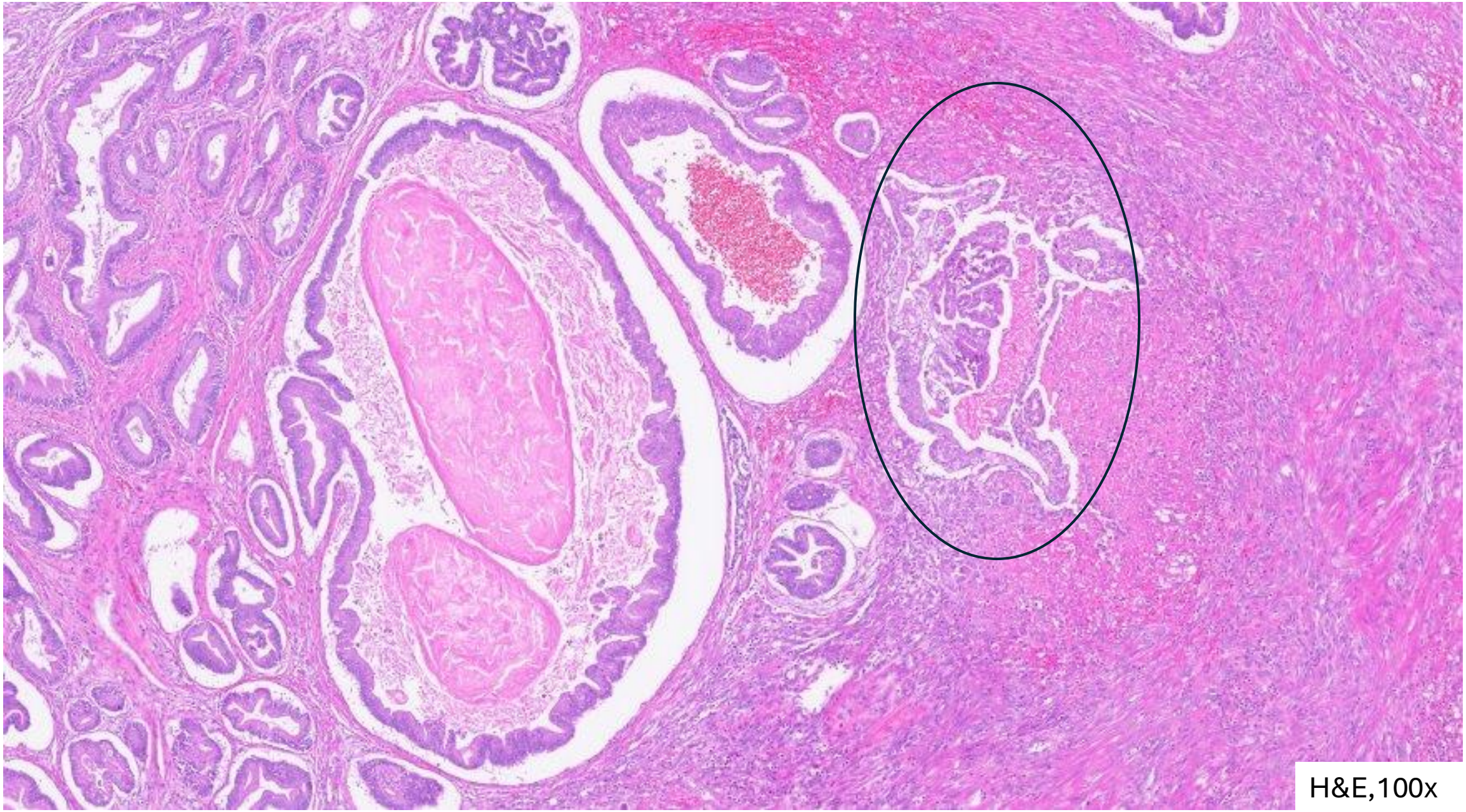
The duodenum shows Brunner gland hyperplasia

The ampulla (arrow) and pancreatoduodenal groove shows marked fibrosis, few abscess formation along with dilated and ruptured ducts containing proteinaceous material (arrow heads)

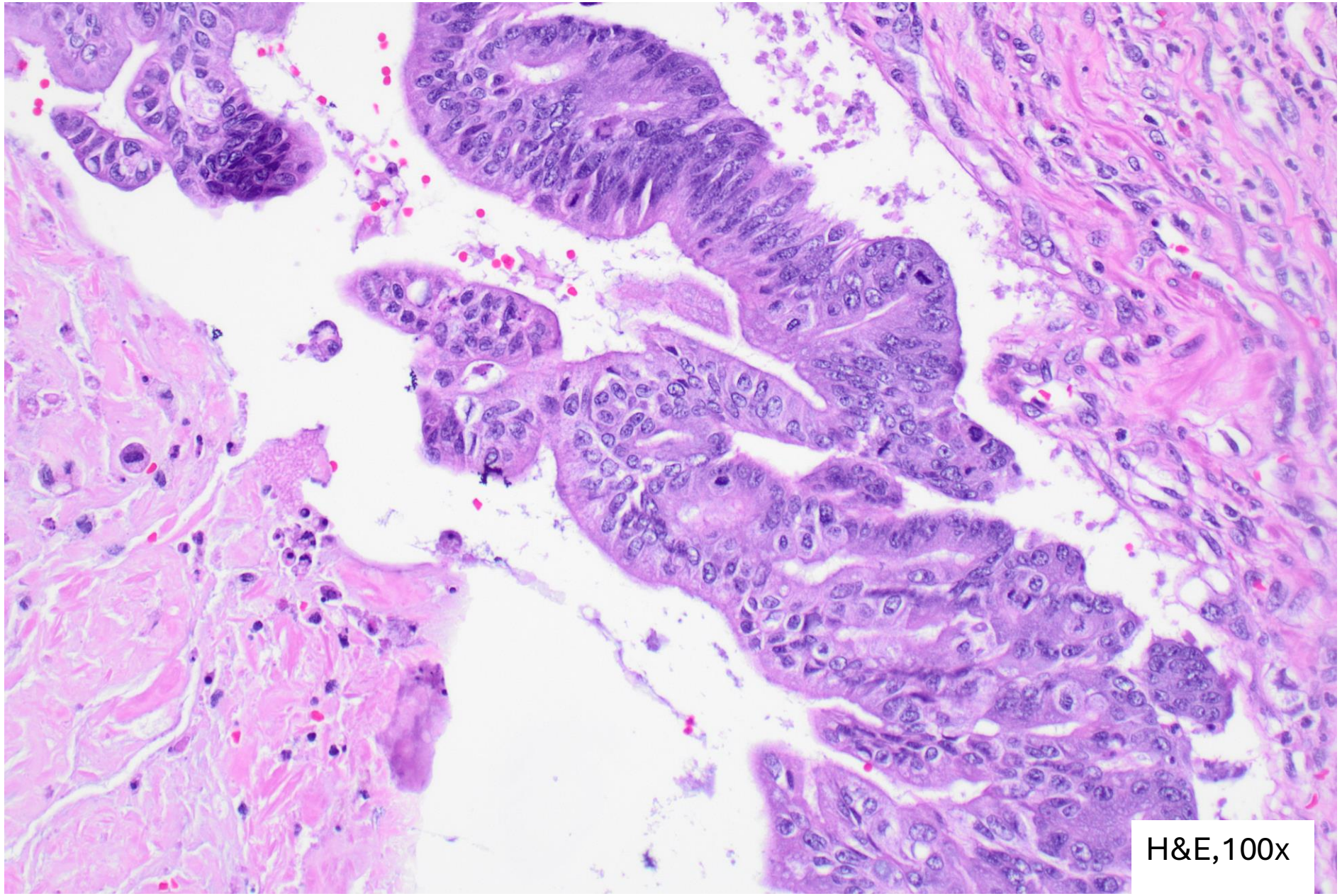


H&E,40x

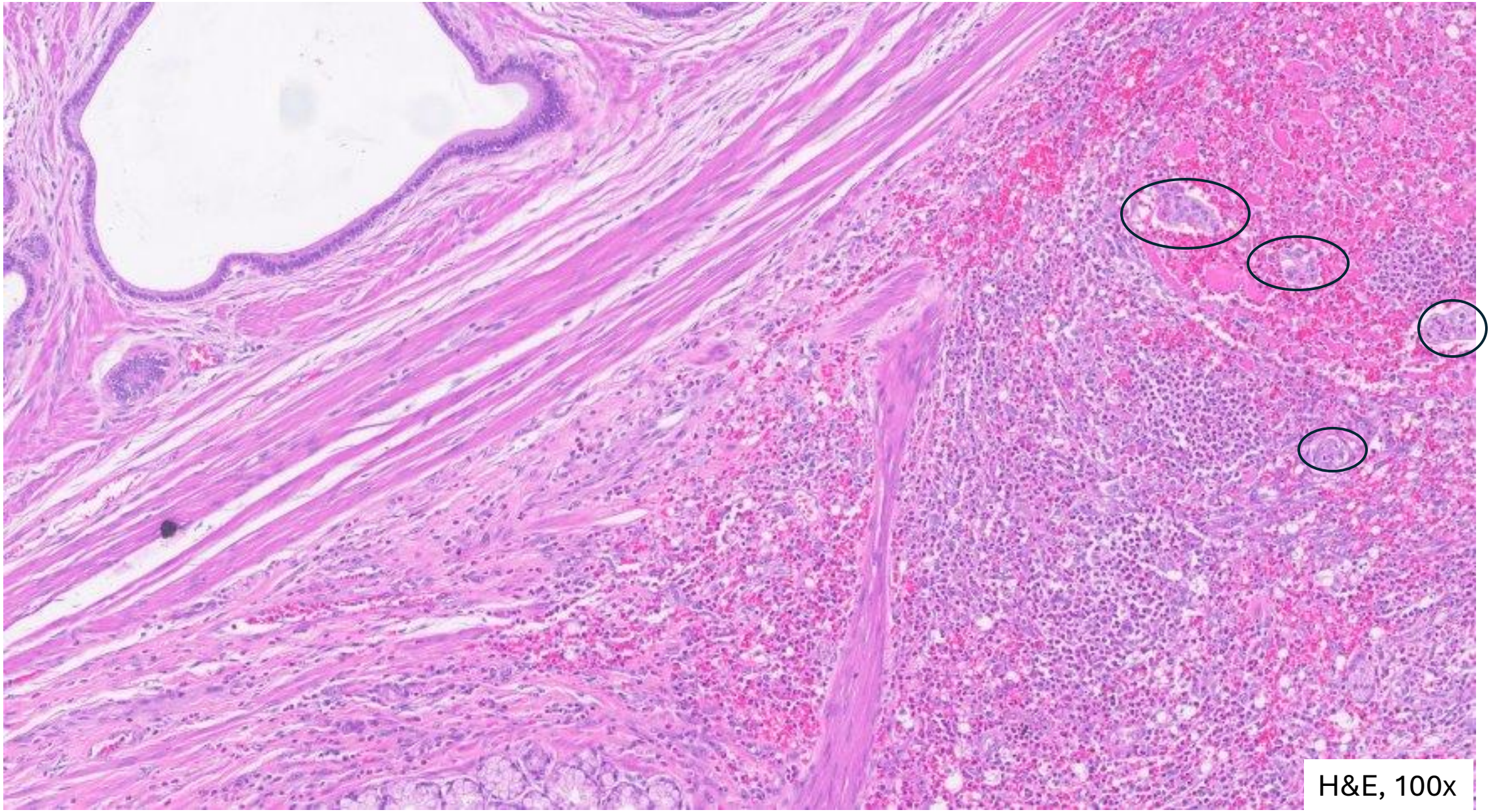
The high-power view shows ampulla and pancreatoduodenal groove with marked fibrosis and dilated ducts containing proteinaceous material (arrow heads)



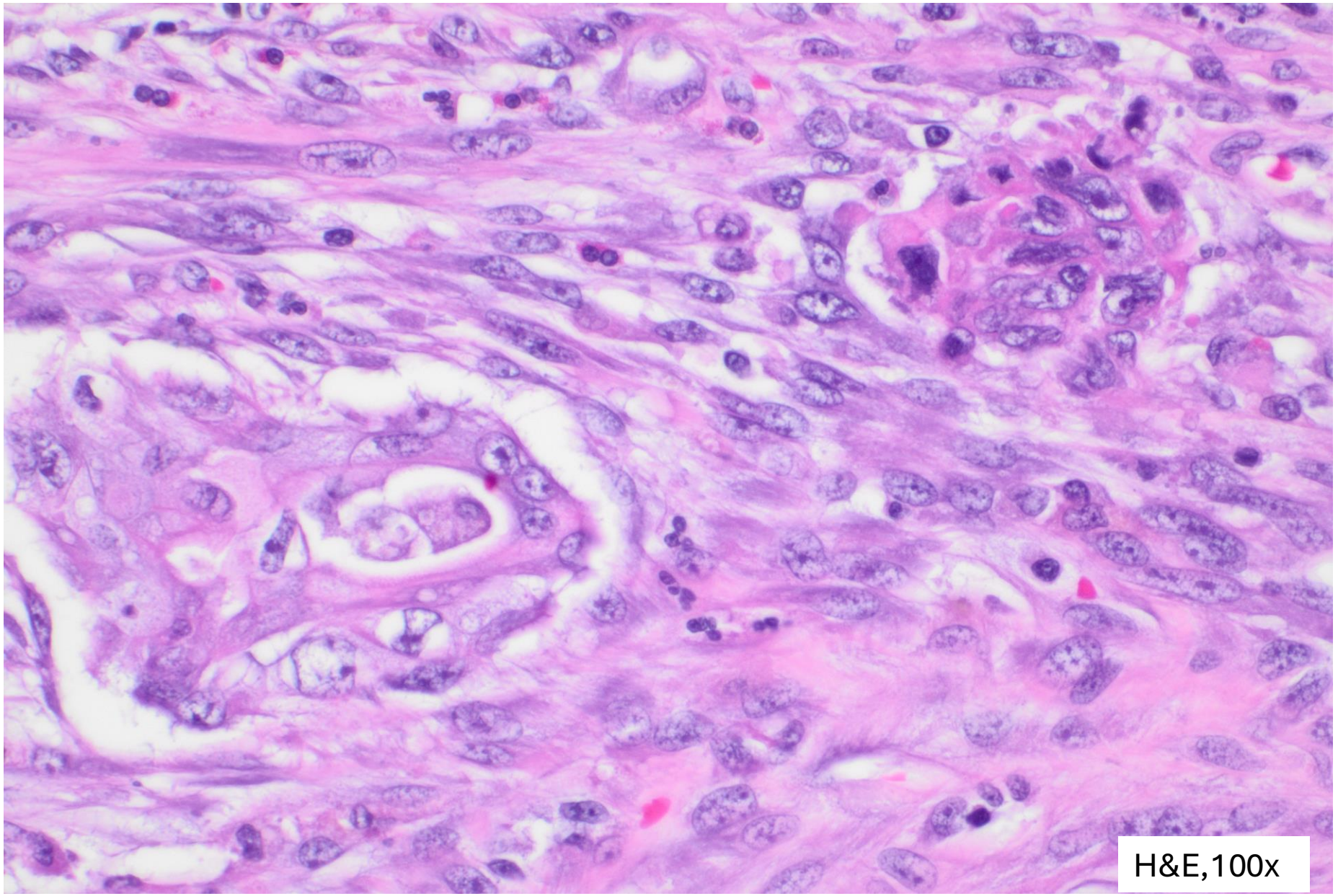
An 1mm focus of invasive adenocarcinoma next to ampulla (circled). Ampulla shows focal low and high-grade dysplasia



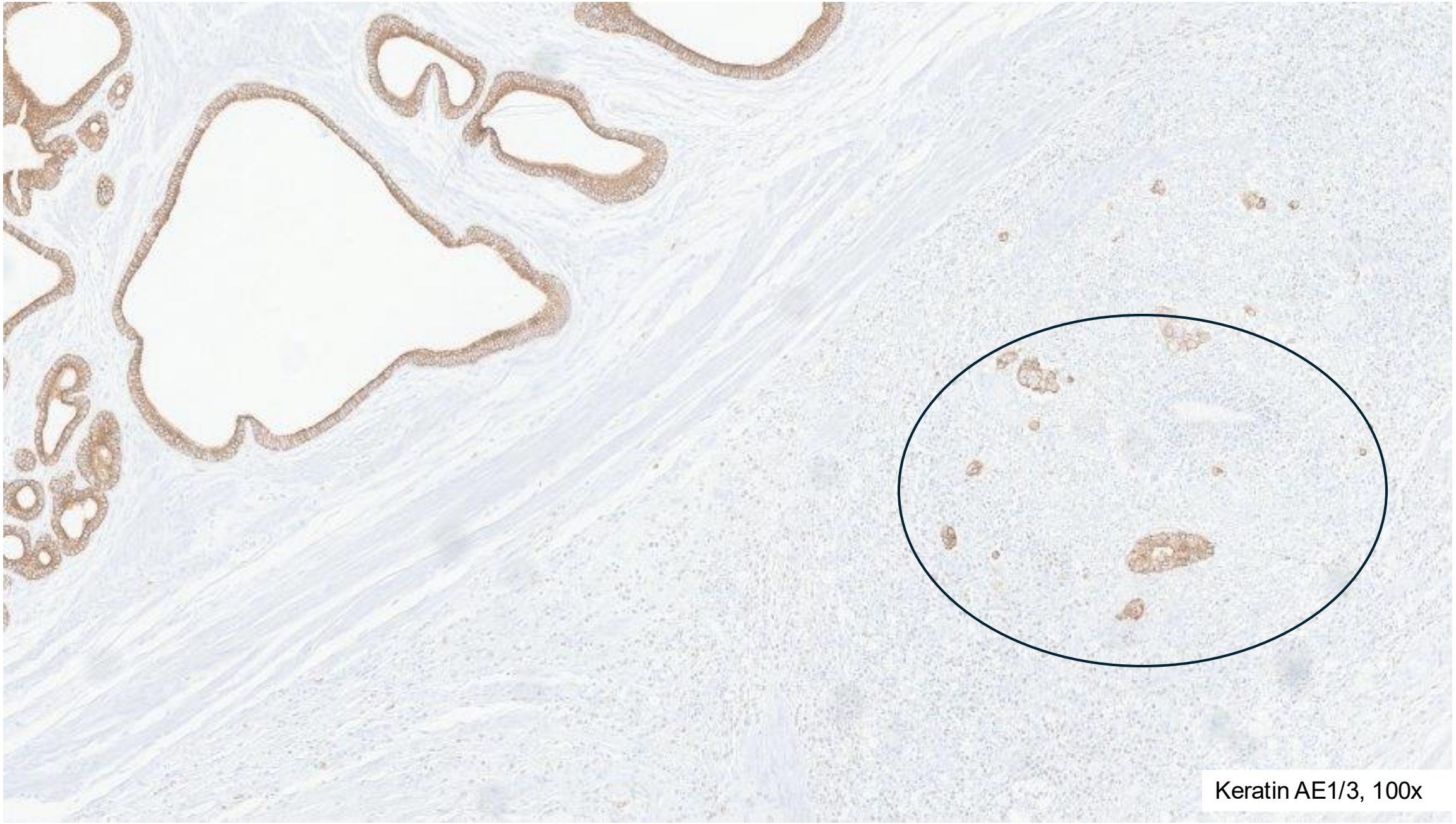
The high-power view shows dysplastic epithelium



Minute foci and single cells of invasive adenocarcinoma (circled) admixed with purulent exudate



The high-power view shows focus of invasive adenocarcinoma



Minute foci and single cells of invasive adenocarcinoma (circled) confirmed by pan cytokeratin

Q: A 57-year-old female with a resected pancreatic mass. All of the below sentences are true about this entity except?

A. On imaging, it may present as cystic lesions in the pancreatic groove.

B. It is often misdiagnosed clinically as cancer arising either in the duodenum, distal CBD, or pancreas.

C. Commonly associated with ductal adenocarcinoma.

D. More frequent in males with history of alcohol abuse and smoking.

Answer: C. Commonly associated with ductal adenocarcinoma

Explanation: Adenocarcinoma is very rarely associated with Groove Pancreatitis (GP). In this case, a 1mm focus of invasive adenocarcinoma was identified next to the ampulla. The ampulla also showed focal low and high-grade dysplasia. Please see images (circled).

- Groove pancreatitis (GP) is a unique form of chronic pancreatitis affecting the pancreatoduodenal groove, a potential space between the head of the pancreas, duodenum, and common bile duct (CBD).
- On imaging, it may present as either mass-like lesions or cystic lesions in the pancreatic groove, mimicking malignancy. Discerning between GP and pancreatic cancer is often challenging but clinically very important.

- Histology shows marked fibrosis of the pancreaticoduodenal groove, dilated and ruptured ducts containing proteinaceous material, acute and chronic inflammation, giant cell reaction, and Brunner gland hyperplasia.
- GP is rare and often misdiagnosed clinically as cancer arising either in the duodenum, distal CBD, or pancreas. GP is more frequent in males and is associated with alcohol abuse, smoking, and anatomical or functional obstruction of the minor papilla.
- Infrequently, adenocarcinoma may be present in the duodenal groove, making differential diagnosis with GP difficult. GP may be treated conservatively, but surgery is indicated when malignancy is suspected and/or symptoms get worse.
- Identifying typical features of GP in a Whipple specimen should not preclude the pathologist from a thorough examination for adenocarcinoma.

- **References:**

1. Kristjan Ukegjini, Thomas Steffen et al. Systematic review on groove pancreatitis: management of a rare disease, *BJS Open*, Volume 7, Issue 5, 2023, October;7(5):1-8.

2. E. Fagundo, E. Weisberg, E. Fishman, Pancreatic cancer in patient with groove pancreatitis: Potential pitfalls in diagnosis, Radiology Case Reports,2022, December;17 (12) :4632-4635.

3. T. Tarvainen, T. Nykänen et al. Diagnosis, natural course, and treatment outcomes of groove pancreatitis, Hepato-pancreato-biliary journal, 2021; August;23(8):1244-1252.

4. Koji Yamaguchi, Masao Tanaka, Groove pancreatitis masquerading as pancreatic carcinoma: The American Journal of Surgery, 1992, March; 163(3): 312-316.

5. Raman SP, Salaria SN, Hruban RH, Fishman EK. Groove pancreatitis: spectrum of imaging findings and radiology-pathology correlation. AJR Am J Roentgenol. 2013 Jul;201(1):W29-39. doi: 10.2214/AJR.12.9956. PMID: 23789694; PMCID: PMC4005339.

Case of the month
June 2025

Dorsay Sadeghian, MD (PGY2)

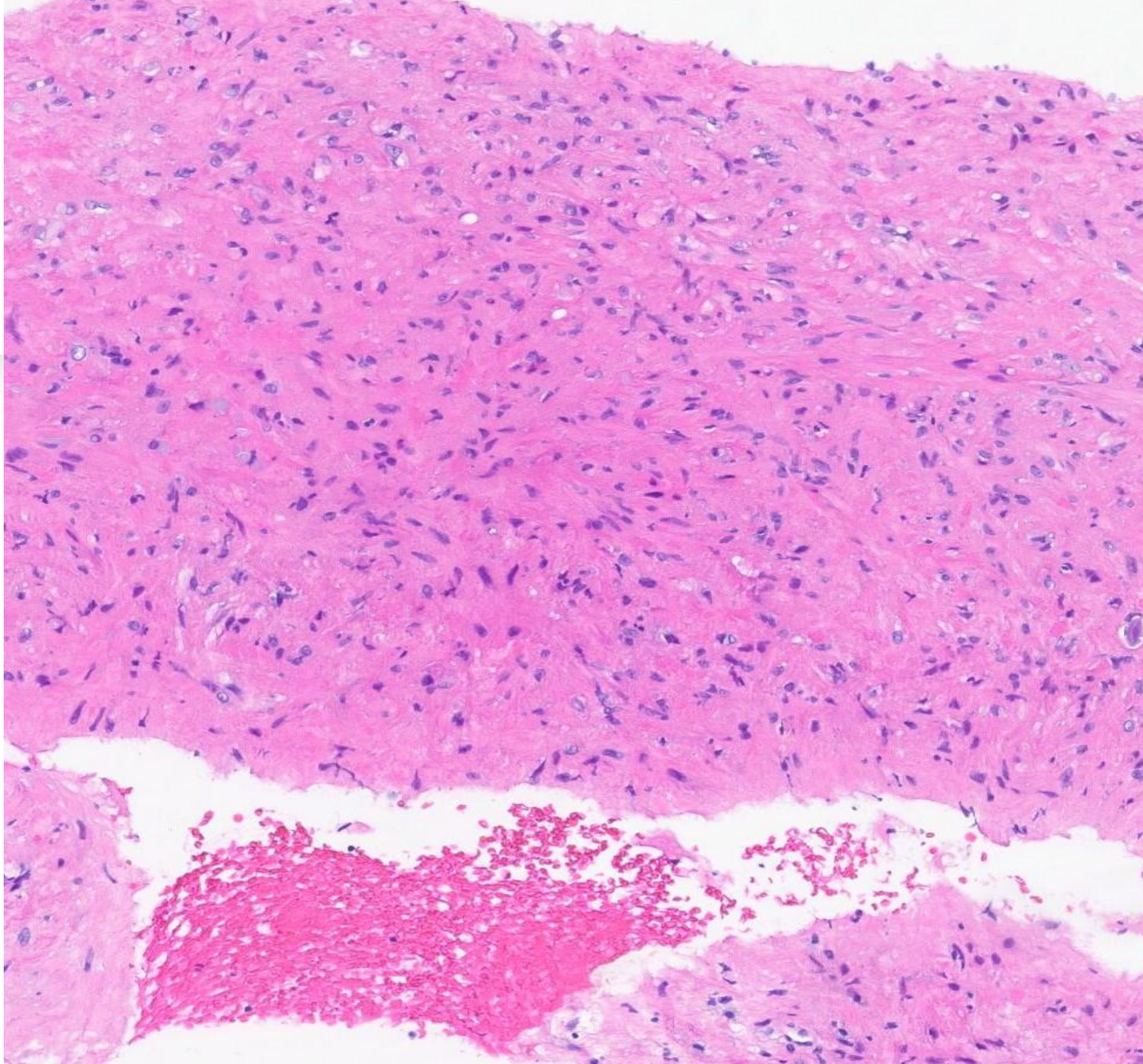
Roshan Raza, MD (Assistant professor)

Clinical History

- A 47-year-old male patient presented with occasional dysphagia.

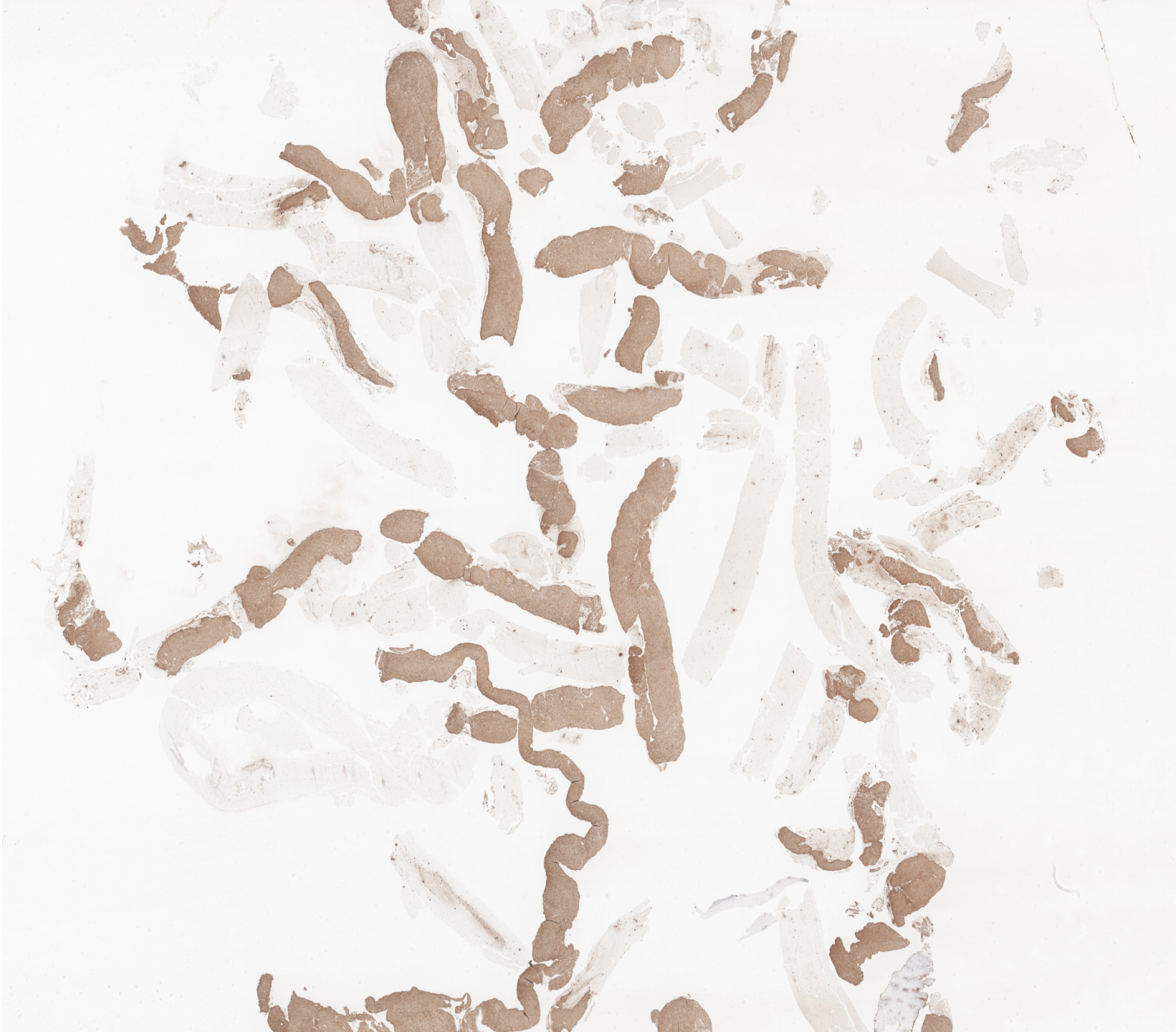
- An upper gastrointestinal endoscopy was performed, revealing a 2.8 cm esophageal nodule with intact overlying epithelium, showing no signs of erosion or ulceration. Biopsies were obtained from the lesion for further evaluation.

- Microscopic examination of the biopsy revealed a moderately cellular neoplasm, consists of short fascicles of spindle cells with bland cytologic features. No evident mitotic activity or necrosis was observed.

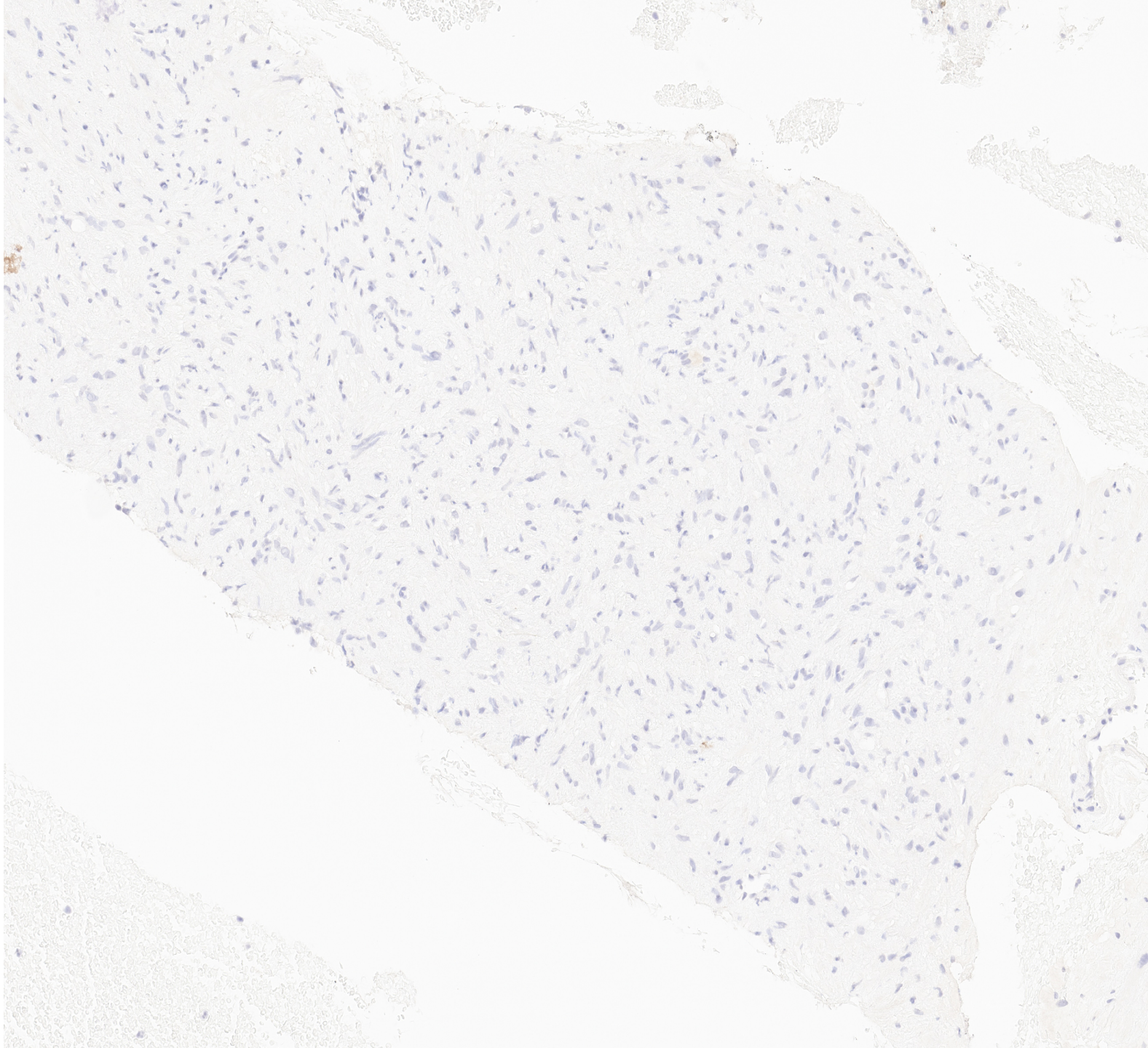


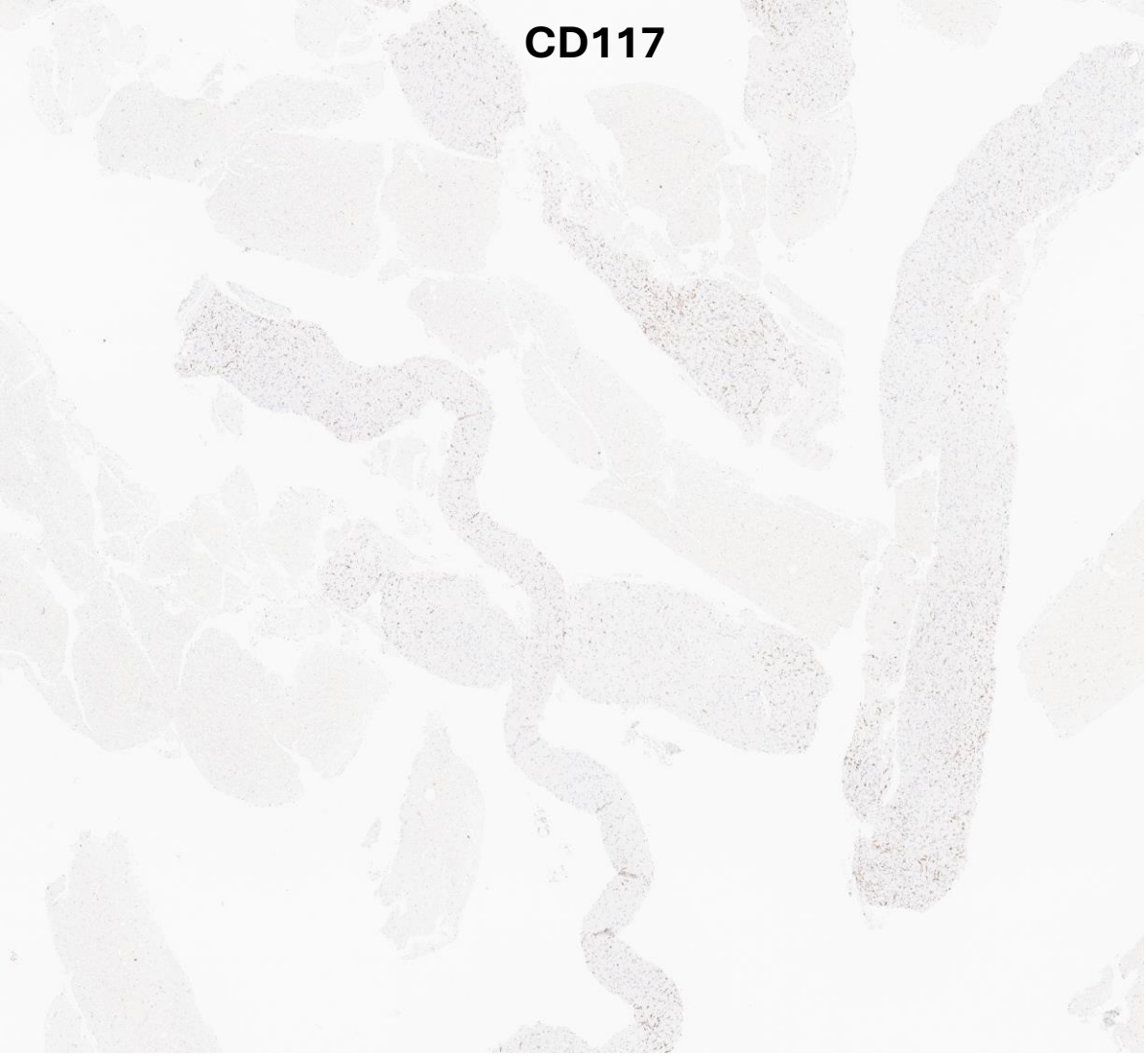
- Immunohistochemical staining for **Desmin** showed diffuse positive cytoplasmic expression.

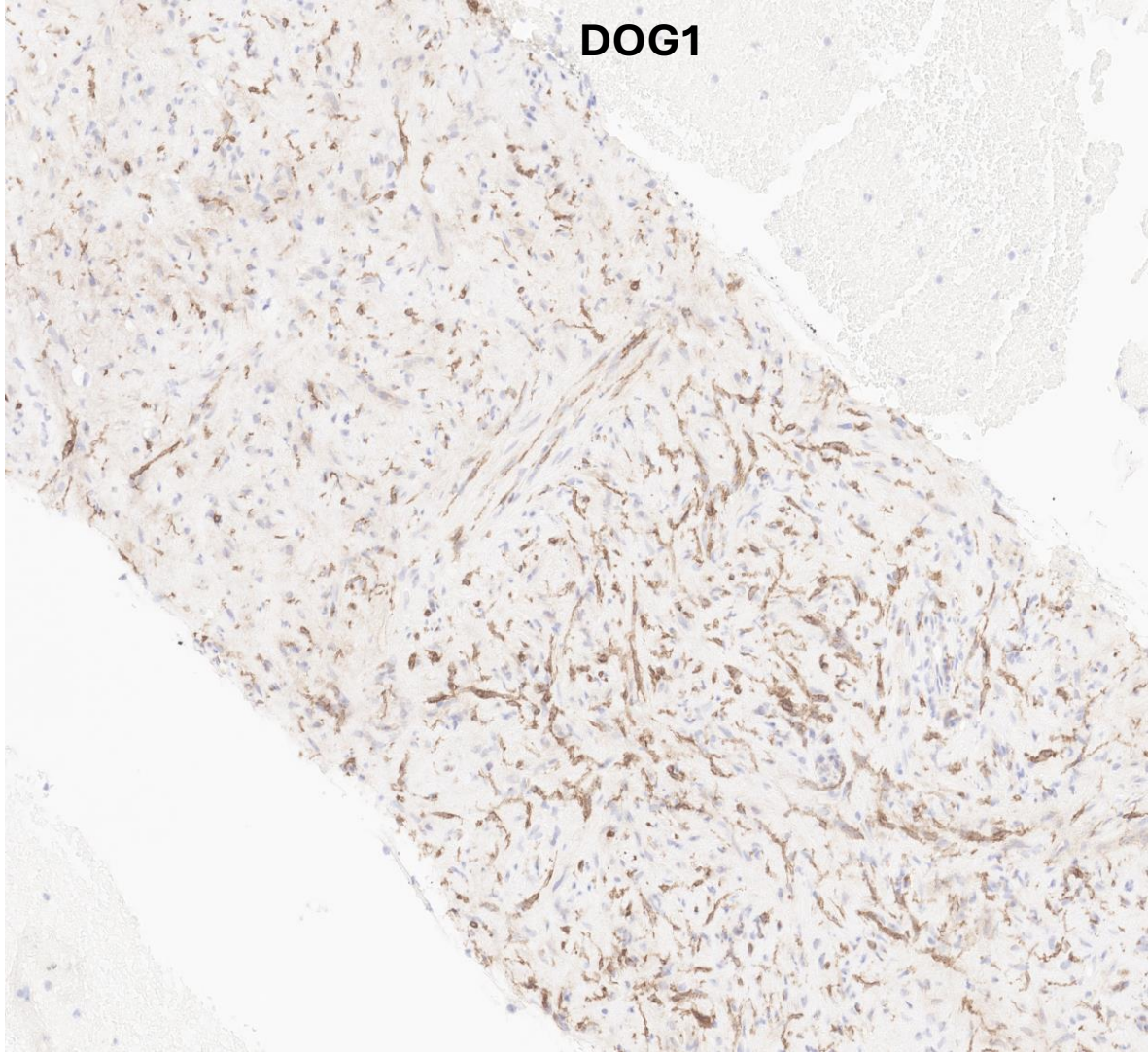
- Immunohistochemical staining for **Smooth Muscle Actin (SMA)** showed diffuse positive cytoplasmic expression.



- Immunohistochemical staining for **S100** showed negative results.







- **<u>DOG1 and CD117</u>** immunostaining demonstrated positive cytoplasmic and membranous expression in interspersed spindle cells, mimicking GIST.

Discussion

- Spindle cell neoplasms arising in the gastrointestinal tract encompass a spectrum of mesenchymal tumors. While gastrointestinal stromal tumors (GISTs) are the most frequently encountered, other possibilities include leiomyomas, leiomyosarcomas, and a variety of rare mesenchymal lesions.

- Preoperative differentiation between a GIST and a leiomyoma is crucial, as leiomyomas are typically managed with enucleation, whereas GISTs may need more extensive resections, especially in esophageal GIST which in some cases may require esophagectomy.

- Some leiomyomas have been found to contain a significant population of spindle-shaped cells that are positive for DOG1 and KIT, likely representing entrapped interstitial cells of Cajal (ICCs). These cells can be readily distinguished from mast cells by their spindled morphology, characterized by elongated dendritic processes that occasionally exhibit dichotomous branching.

- Mast cells can also cause KIT positivity; however, they are usually presented in limited number, mainly oval shaped and have a denser chromatin pattern, in comparison with ICCs.

- Interstitial cells of Cajal (ICCs) can be present in substantial number, distributing throughout the whole leiomyoma. Significant DOG1 and KIT positivity can raise suspicion for a gastrointestinal stromal tumor (GIST). This overlap can pose significant diagnostic challenges, particularly in small biopsy samples.

- A combination of histomorphology of KIT positive cells (presence of dendritic cytoplasmic extensions), as well the immunohistochemical findings (including presence of extensive smooth muscle cell markers positivity) can be helpful in better distinction and categorization of these tumors.

- Although this finding is predominantly seen in deep seated leiomyomas, there are some reports of superficial leiomyomas with entrapped DOG1 and CD117 positive ICCs.

References

- Deshpande A, Nelson D, Corless CL, Deshpande V, O'Brien MJ. Leiomyoma of the gastrointestinal tract with interstitial cells of Cajal: a mimic of gastrointestinal stromal tumor. Am J Surg Pathol. 2014 Jan;38(1):72-7. doi: 10.1097/PAS.0b013e3182a0d134. PMID: 24145645.

- Janevska V, Qerimi A, Basheska N, Stojkova E, Janevski V, Jovanovic R, Zhivadinovik J, Spasevska L. Superficial leiomyomas of the gastrointestinal tract with interstitial cells of Cajal. Int J Clin Exp Pathol. 2015 Dec 1;8(12):15977-84. PMID: 26884872; PMCID: PMC4730085.

Question 1. Which statement is true about gastrointestinal-originated spindle cell neoplasms? (More than one statement can be true)

A. Significant CD117 and DOG1 positivity in gastrointestinal spindle cell tumors rules out the diagnosis of leiomyoma.
B. Interstitial cells of Cajal can only exhibit focal DOG1 positivity.
C. The presence of cytoplasmic dendritic extensions is in favor of ICCs.
D. Entrapped ICC cells in leiomyomas can be only seen in deep leiomyomas.
E. The presence of ICCs in esophageal leiomyoma causes more significant clinical implications compared to gastric leiomyoma.
F. Mast cells usually mimic the same histological findings that can be observed in ICCs entrapped in leiomyoma.

Answer: C and E are true statements.

Explanation:

Interstitial cells of Cajal (ICCs) are specialized mesenchymal cells that serve as pacemakers for gastrointestinal motility and are thought to play a key role in neuromuscular transmission. Although all subtypes of ICCs share fundamental ultrastructural characteristics, their morphology can vary depending on species and anatomical location, ranging from fibroblast-like to smooth muscle cell-like appearances.

Distinguishing gastrointestinal stromal tumors (GISTs) from leiomyomas can pose a significant histopathological challenge, especially in fine-needle aspiration or core biopsy specimens. This distinction is particularly crucial in the esophagus, where therapeutic approaches differ markedly. Leiomyomas, even when large, are often amenable to conservative management such as enucleation, thereby avoiding more invasive procedures like esophagogastrectomy—an operation associated with considerable morbidity and a small but real mortality risk. In contrast, esophageal GISTs, the majority of which exhibit malignant potential, typically necessitate more radical surgical intervention, such as esophagectomy. In the stomach, however, the therapeutic distinction is less critical, as both GISTs and leiomyomas are generally treated with conservative resection.

The diagnostic complexity is further compounded by the observation that some gastrointestinal leiomyomas contain cells that resemble interstitial cells of Cajal. These ICC-like cells are morphologically similar to native ICCs, characterized by cytoplasmic dendritic processes and strong immunoreactivity for DOG1 and KIT. They are most identified in deep-seated leiomyomas, reflecting the anatomical distribution of ICCs within the muscularis propria. Nonetheless, rare reports have documented their presence in more superficial lesions as well, supporting the

hypothesis that smooth muscle cells and ICCs may originate from a common progenitor, possibly reflecting a spectrum of stromal tumors with mixed differentiation.

Mast cells—another population of KIT-positive cells—may also be present within smooth muscle tumors. However, they can be distinguished from ICCs by their oval shape, dense chromatin, and limited numbers. In contrast, ICCs are more diffusely distributed and possess elongated, branching processes.

Careful histological assessment of KIT-positive cells, with attention to their morphology, can aid in differentiating ICCs from mast cells. Immunohistochemical profiling also plays a critical role. Extensive and diffuse positivity for smooth muscle markers such as desmin and smooth muscle actin (SMA) supports a diagnosis of leiomyoma, even when patchy areas of reduced expression are present. This is reinforced by the fact that desmin positivity is rare in GISTs—reported in only about 5% of gastric and up to 15% of esophageal cases.

References:

1. Deshpande A, Nelson D, Corless CL, Deshpande V, O'Brien MJ. Leiomyoma of the gastrointestinal tract with interstitial cells of Cajal: a mimic of gastrointestinal stromal tumor. Am J Surg Pathol. 2014 Jan;38(1):72-7. doi: 10.1097/PAS.0b013e3182a0d134. PMID: 24145645.

2. Janevska V, Qerimi A, Basheska N, Stojkova E, Janevski V, Jovanovic R, Zhivadinovik J, Spasevska L. Superficial leiomyomas of the gastrointestinal tract with interstitial cells of Cajal. Int J Clin Exp Pathol. 2015 Dec 1;8(12):15977-84. PMID: 26884872; PMCID: PMC4730085.

Case of the month
July 2025

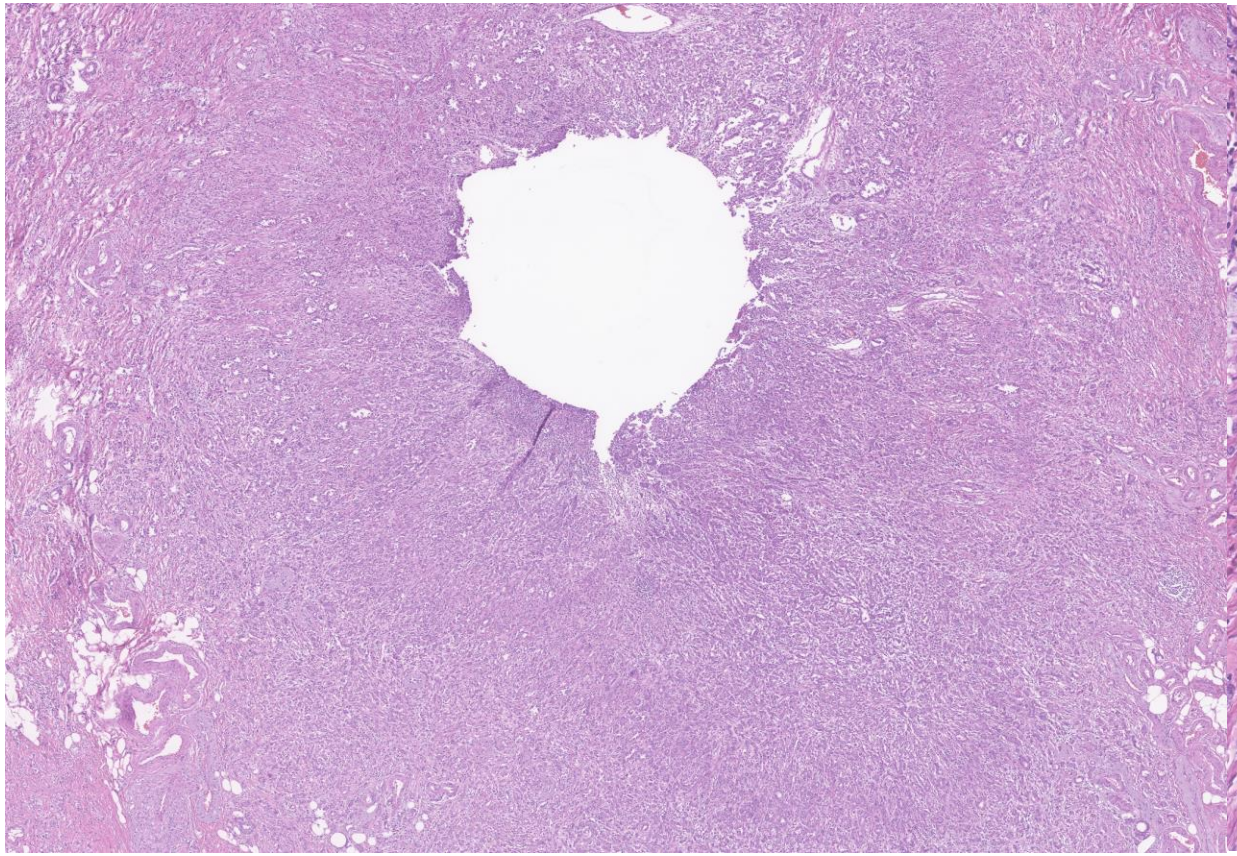
Hareem Hamza- PGY2, Dr. Celia Marginean

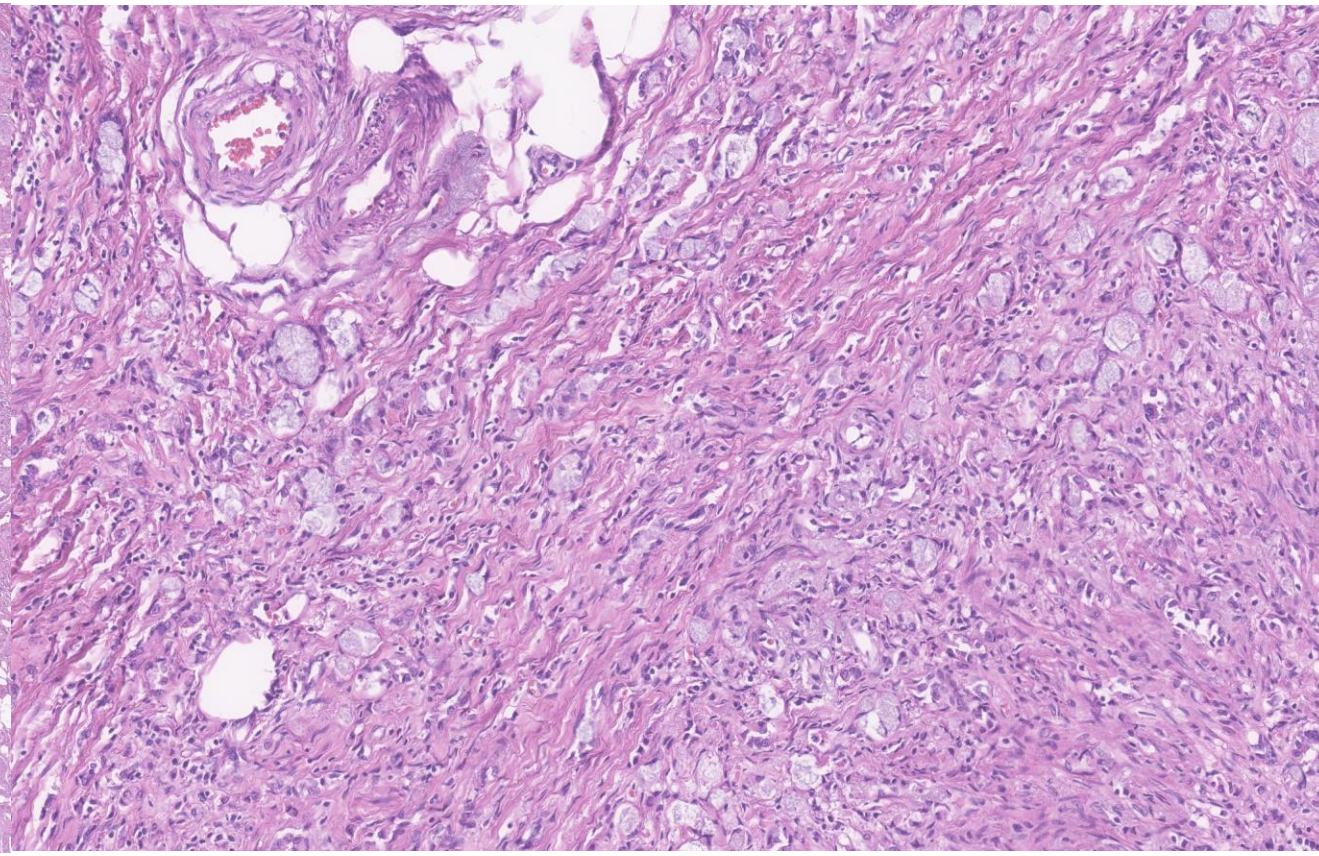
History

- A 60-year-old male with hematochezia and weight loss
- History of colon cancer in mother
- A colonoscopy revealed a friable, hard, infiltrative mass in the cecum, possibly involving the appendiceal orifice.
- Outside biopsy reported as signet ring cell carcinoma

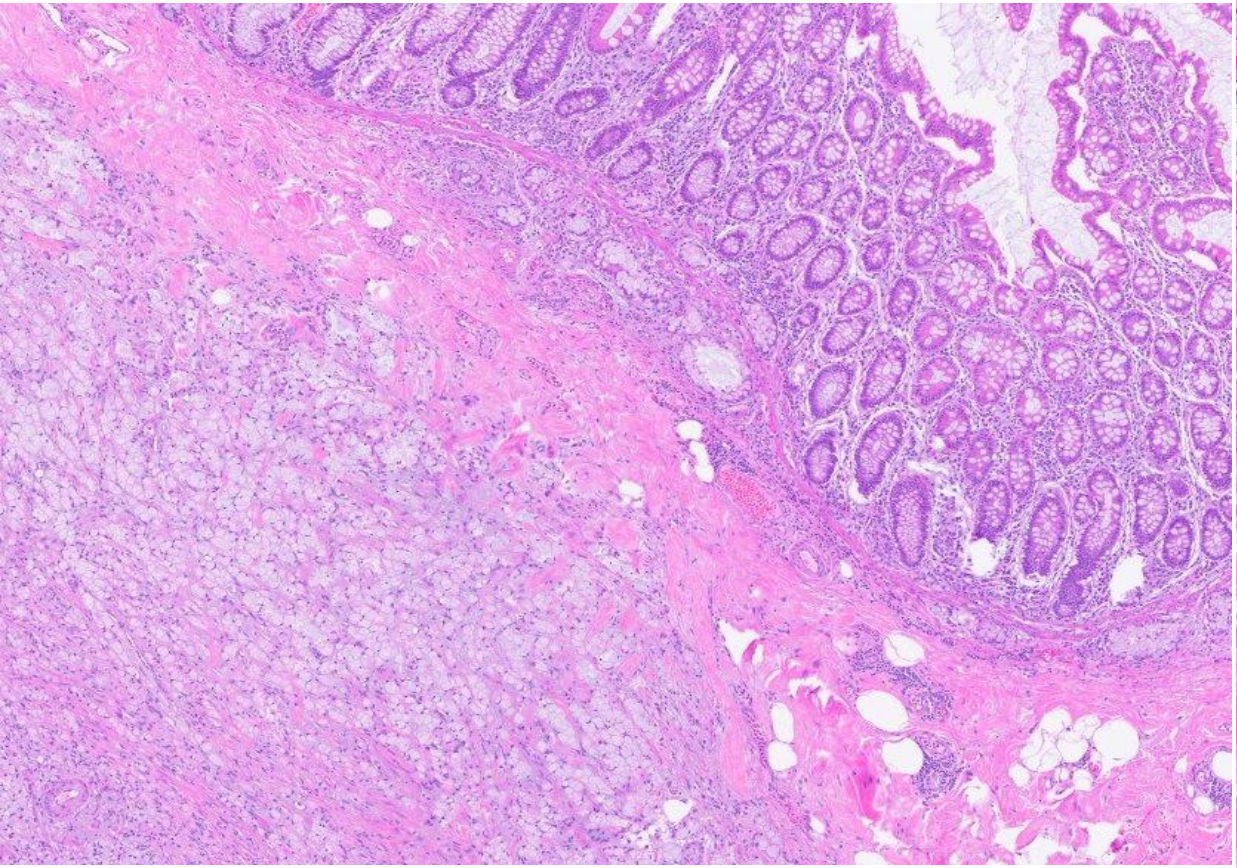
Gross

- A firm, tan-red, ulcerative lesion at the appendiceal orifice, with a depth of invasion of 1.1 cm.
- This lesion involves the serosal surface, pericolonic fat, and the appendix.

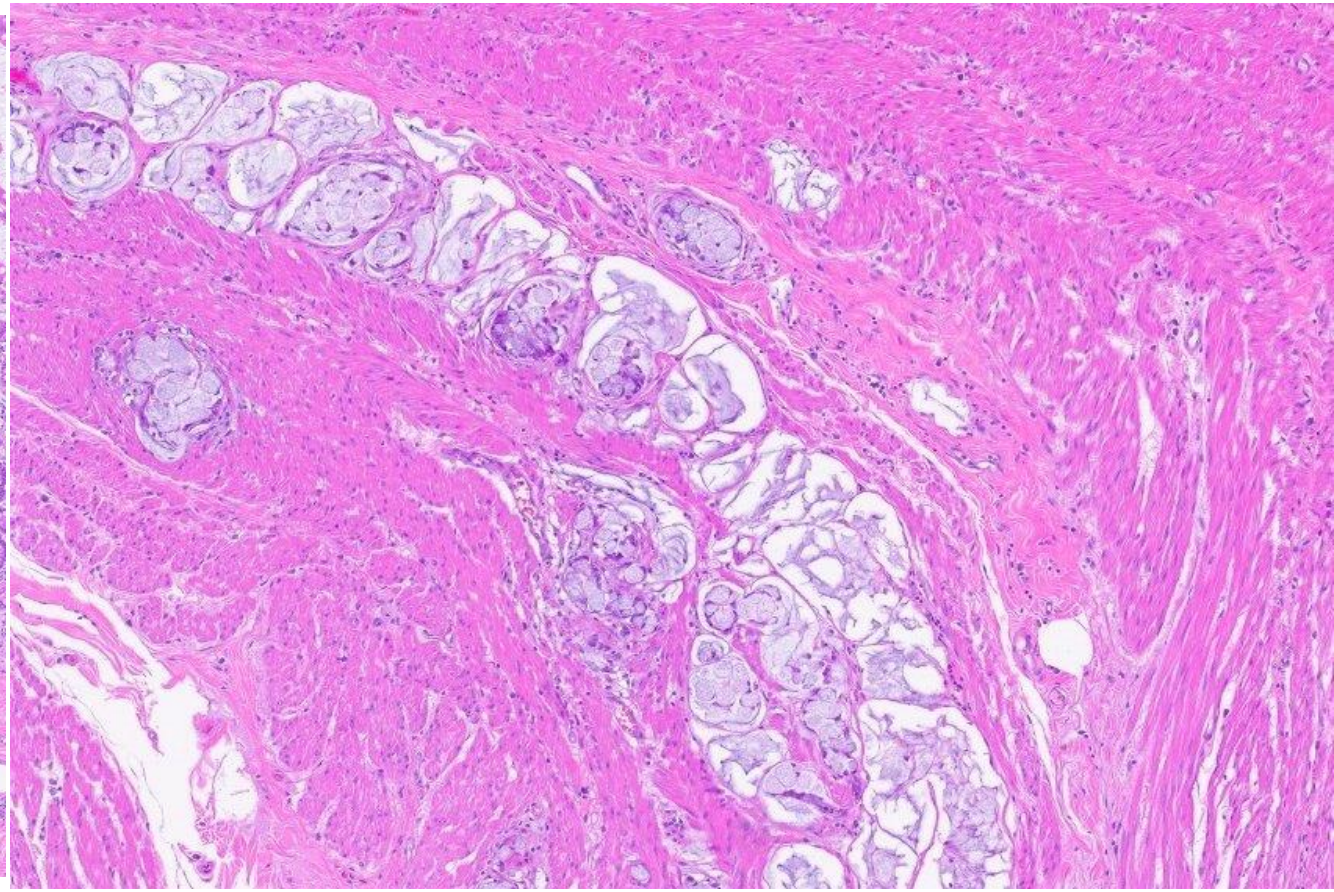




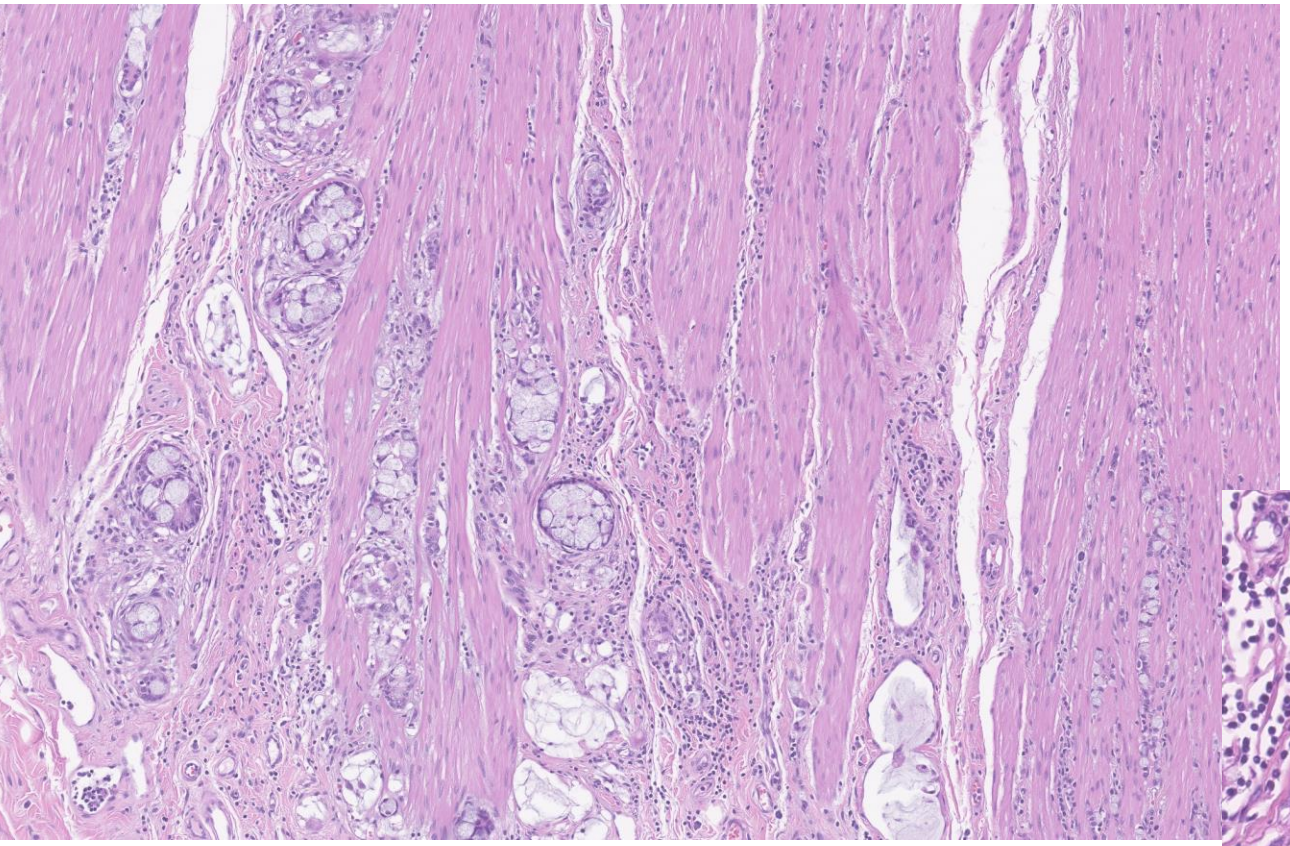
- The tumor infiltrates the appendiceal wall, circumferentially, and lacks a mass formation

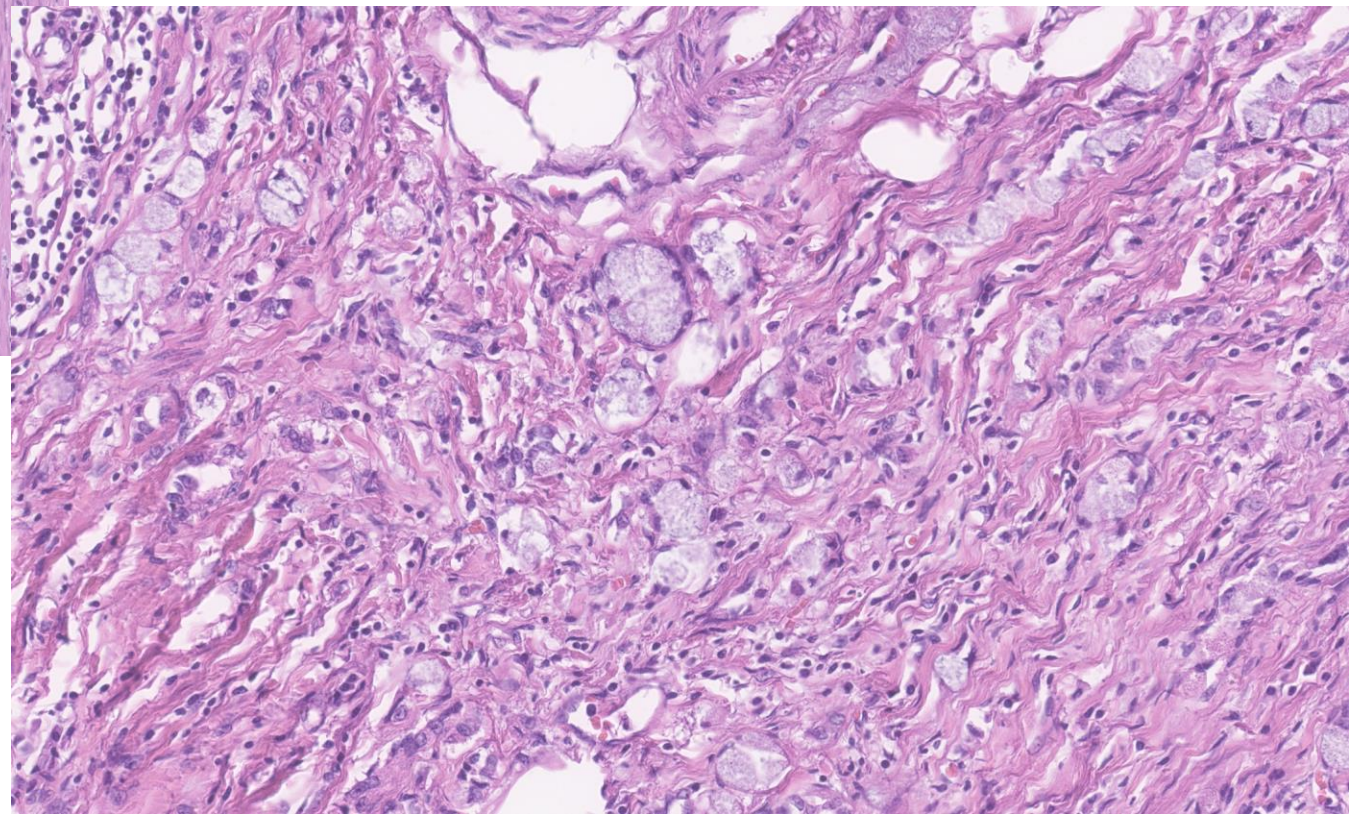


Appendiceal and cecal appendiceal orifice mucosa is unremarkable, with no evidence of dysplasia.

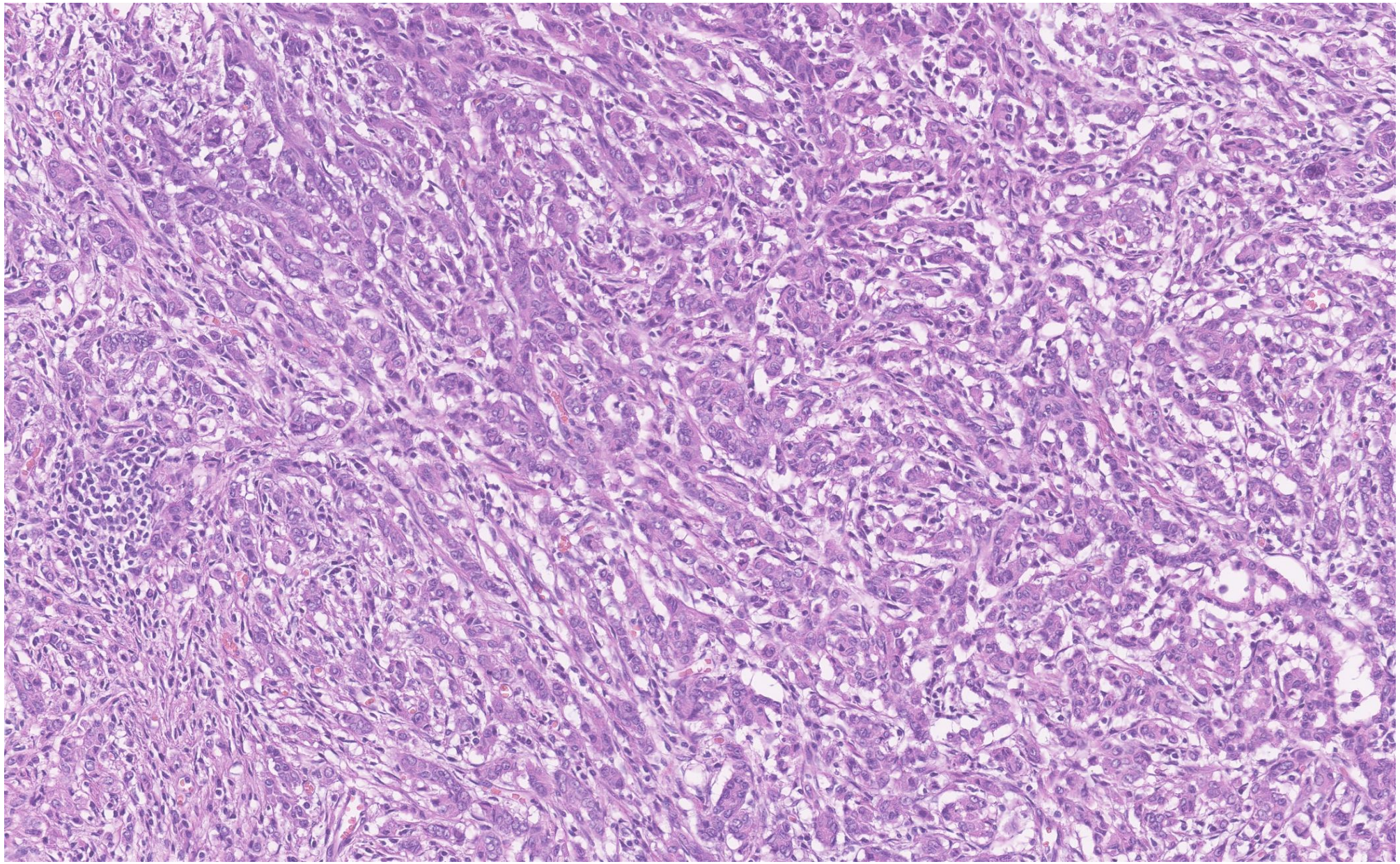


Abundant signet ring cells, some floating in mucin pools.



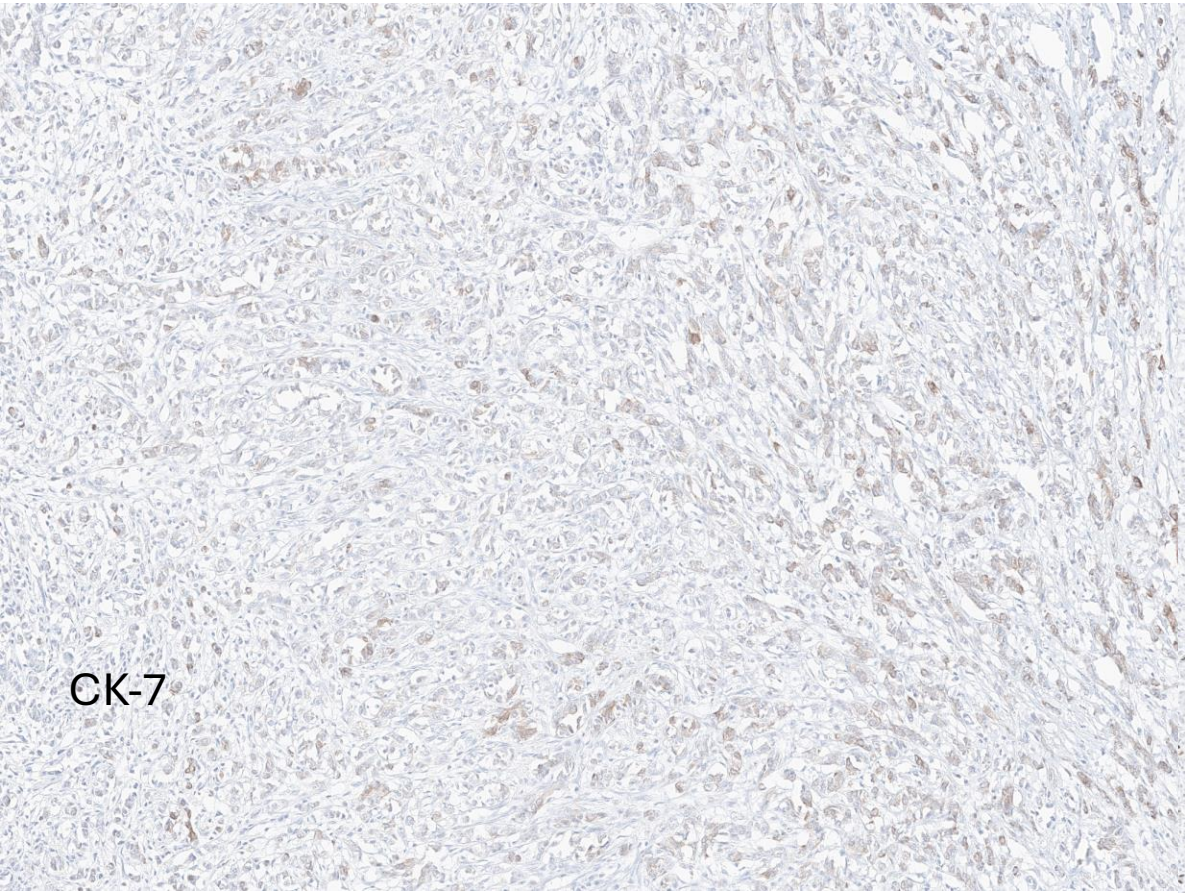


Typical areas of low-grade goblet cell adenocarcinoma, composed of small cluster of tubules, nests or cords of tumor cells with no lumen, minimum to no desmoplasia

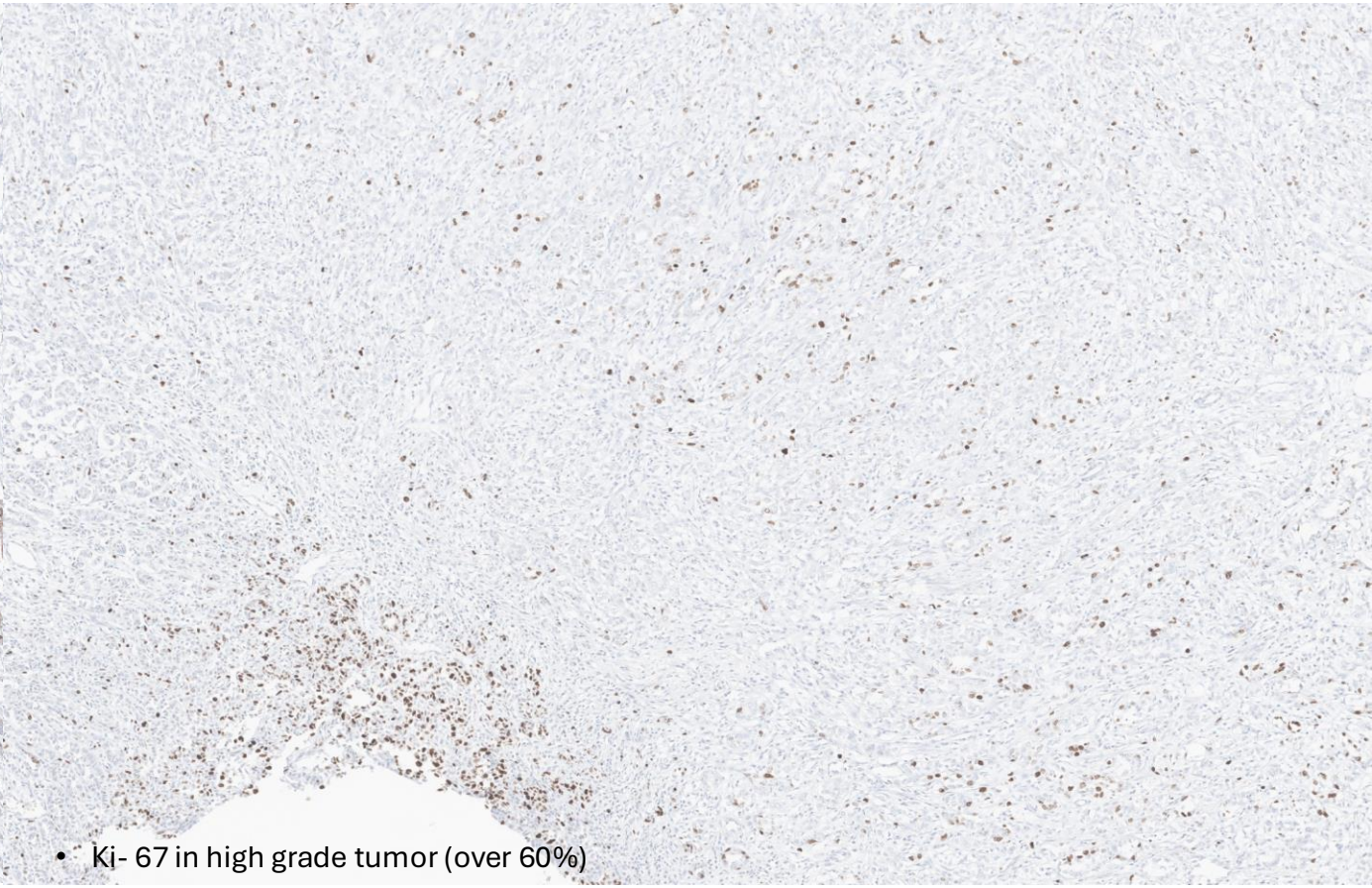


- High-grade growth pattern

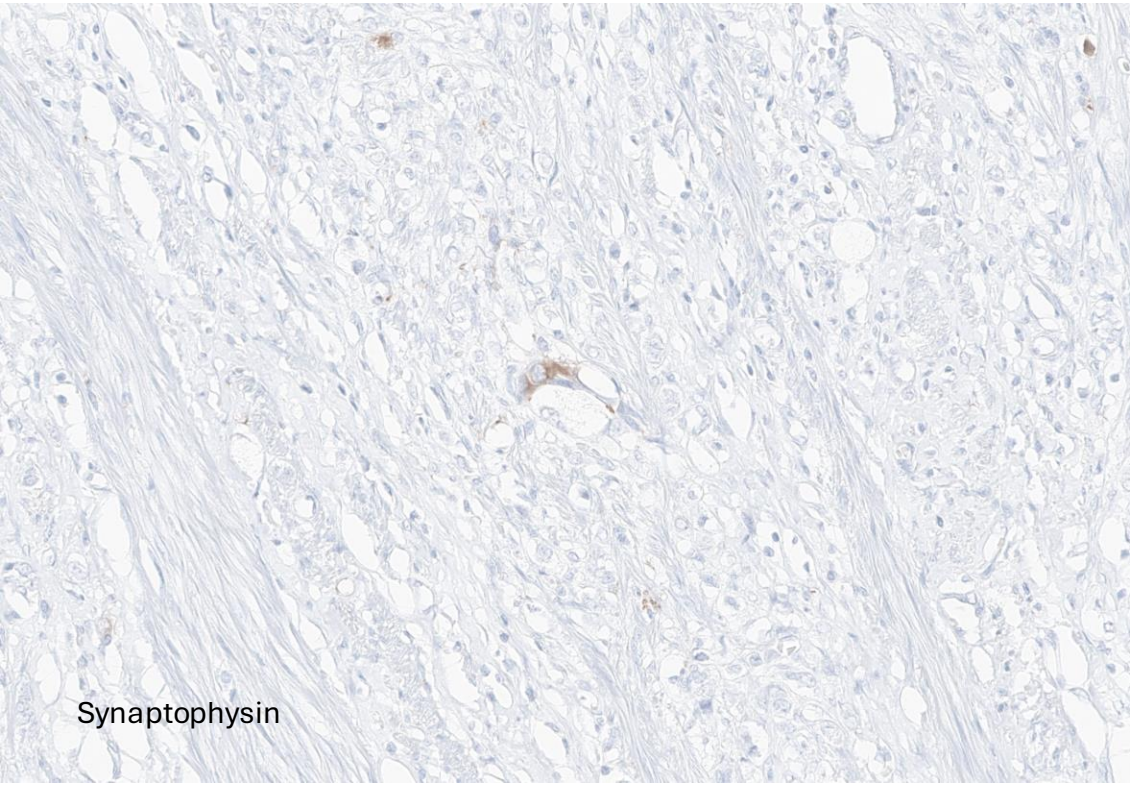
- Diffusely positive



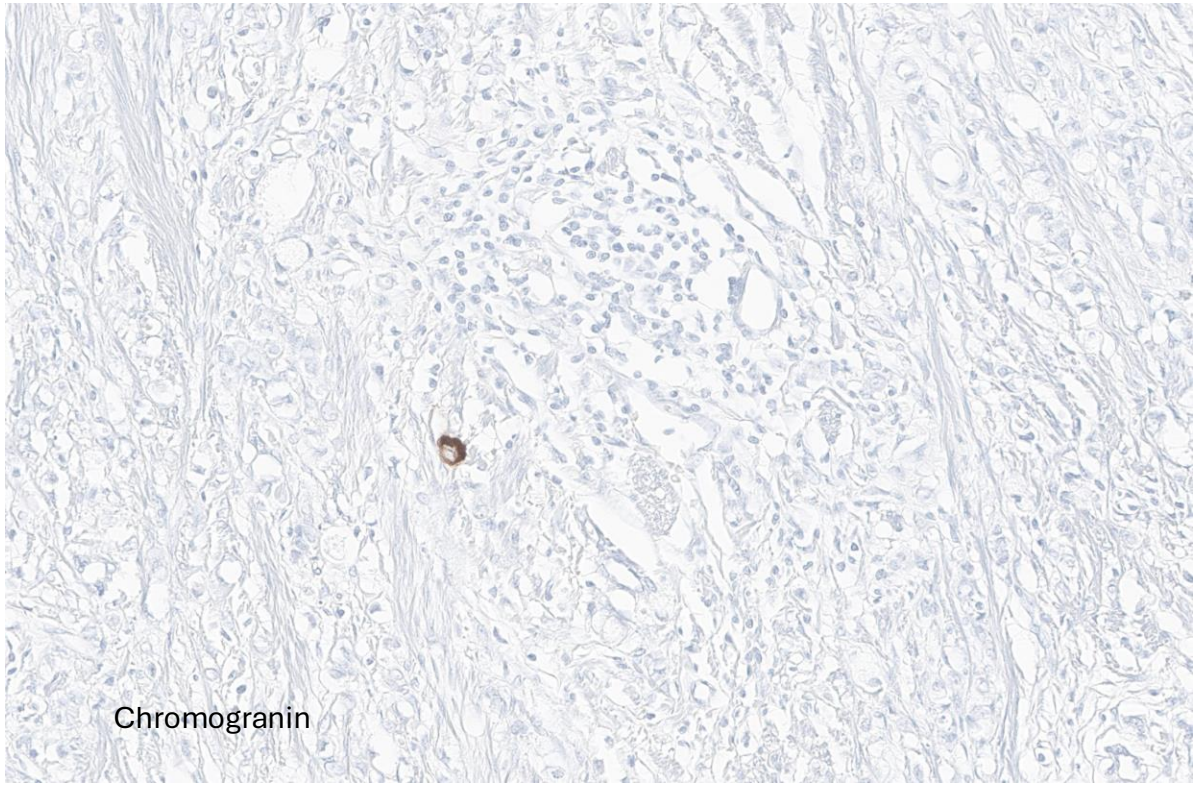
CK-7



- Ki- 67 in high grade tumor (over 60%)



Synaptophysin



Chromogranin

Questions:

1. A 55-year-old woman undergoes an appendectomy for a suspected appendiceal mass. Histopathologic examination reveals an infiltrative neoplasm composed of clusters and small nests of goblet cells with areas of extracellular mucin production. Immunohistochemistry shows focal positivity for synaptophysin and chromogranin in the goblet cells.

Which of the following is the most appropriate interpretation of the neuroendocrine marker expression? (Select one answer)

A. Indicates a high-grade neuroendocrine carcinoma (NEC), warranting chemotherapy
B. Suggests a mixed adenoneuroendocrine carcinoma (MANEC) requiring dual component quantification
C. Is a known feature of goblet cell adenocarcinoma
D. Confirms the diagnosis of well-differentiated neuroendocrine tumor (NET) of the appendix
E. Reflects non-specific staining and should be disregarded in diagnosis

Answer:
C(Correct)**.** Focal and weak positivity for synaptophysin and chromogranin is a known feature of goblet cell adenocarcinoma

Explanation:
Goblet cell adenocarcinoma (previously called goblet cell carcinoid) is a unique neoplasm of the appendix that exhibits features of both adenocarcinoma and neuroendocrine differentiation. However, the expression of neuroendocrine markers such as synaptophysin and chromogranin can be focal or weak and does not imply true neuroendocrine differentiation or behavior. Moreover, even when INSM1 (a sensitive neuroendocrine marker) is positive, staining is typically limited to a small minority of tumor cells (mean ~8%), underscoring that expression is focal and not diagnostic of a neuroendocrine neoplasm. Unlike classical neuroendocrine tumors, GCAs behave more aggressively and are treated like adenocarcinomas. Misinterpreting this marker positivity could lead to inappropriate treatment choices.

2.Which of the following features help differentiate goblet cell adenocarcinoma (GCA) from signet-ring cell adenocarcinoma (SRCA)?

(Select one answer)

A. Presence of a low-grade goblet cell component

B. Widespread (>50%) discohesive signet-ring cells

C. High mitotic activity and necrosis

D. Cribriform growth pattern with extracellular mucin

Answers:

A (Correct). The presence of a low-grade goblet cell component. Goblet cell adenocarcinoma is defined by the presence of a recognizable low-grade goblet cell adenocarcinoma component.

Explanation:

Signet-ring cell adenocarcinoma shows widespread (> 50%) discohesive and disorganized growth of signet-ring cells with high-grade cytological features and lacks a low-grade goblet cell component.

While high-grade areas of GCA can show numerous atypical mitotic figures and necrosis, these features are not exclusive to SRCA and can be seen in both high-grade GCA and SRCA. Therefore, they do not help differentiate between the two.

The cribriform pattern and extracellular mucin are features that can be present in high-grade GCA, but they are not specific enough to distinguish it from SRCA. SRCA is defined more by its discohesive signet-ring cells and lack of low-grade GCA component, not by architectural patterns like cribriform growth. Extracellular mucin is often present and sometimes abundant in SRCA.

Goblet cell adenocarcinoma diagnostic criteria and grading

Low grade features

1. Required: Classic round tubular growth pattern composed of predominantly of goblet-like mucinous cells and a fewer number of Paneth-like cells and endocrine-like cells
2. Common : Extracellular mucin pools containing round tubules or cohesive clusters, including ruptured tubules
3. Uncommon: Tubules with non mucinous glands, including oncocytic tubules

High grade features: 5 patterns

1. Signet ring-like/goblet-like cells diffusely infiltrating predominantly as single cells or abortive tubules.
2. Signet ring-like/goblet-like cells with fusion of clusters to form large complex anastomosing structures or very large aggregates.
3. Infiltrative single-file or anastomosing cords of tumor cells with high-grade nuclei. Intracytoplasmic mucin may be only very focally present.
4. Gland-forming adenocarcinoma, often with a microglandular growth pattern of tubules with high-grade nuclei. Intestinal-type adenocarcinoma is less common.
5. Solid sheet-like growth of tumor cells with high-grade nuclei and minimal intracytoplasmic mucin.

Grading: 3 tier grading system based on low grade versus high grade patterns:

Grade	Low grade pattern (tubular or clustered growth)	Any combination of high grade features (loss of tubular or clustered growth)
1	> 75%	< 25%
2	50 - 75%	25 - 50%
3	< 50%	> 50%

Reference:

1. **WHO Classification of Tumours Editorial Board.**
   Digestive System Tumours (5th edition). IARC, 2019.
   Appendix tumors are reclassified; GCA is considered distinct from NETs and NECs.

2. Roy P, Chetty R. Goblet cell carcinoid tumors of the appendix: An overview. World J Gastrointest Oncol. 2010 Jun 15;2(6):251-8. doi: 10.4251/wjgo.v2.i6.251. PMID: 21160637; PMCID: PMC2998842.

3. Lin DL, Wang LL, Zhao P, Ran WW, Wang W, Zhang LX, Han M, Bao H, Liu K, Wu X, Shao Y, Xing XM. Gastrointestinal Goblet Cell Adenocarcinomas Harbor Distinctive Clinicopathological, Immune, and Genomic Landscape. Front Oncol. 2021 Nov 5;11:758643. doi: 10.3389/fonc.2021.758643. PMID: 34804955; PMCID: PMC8603204

Case of the month
August 2025

Joumane El Zein, MD (Pathology Resident, PGY-2)

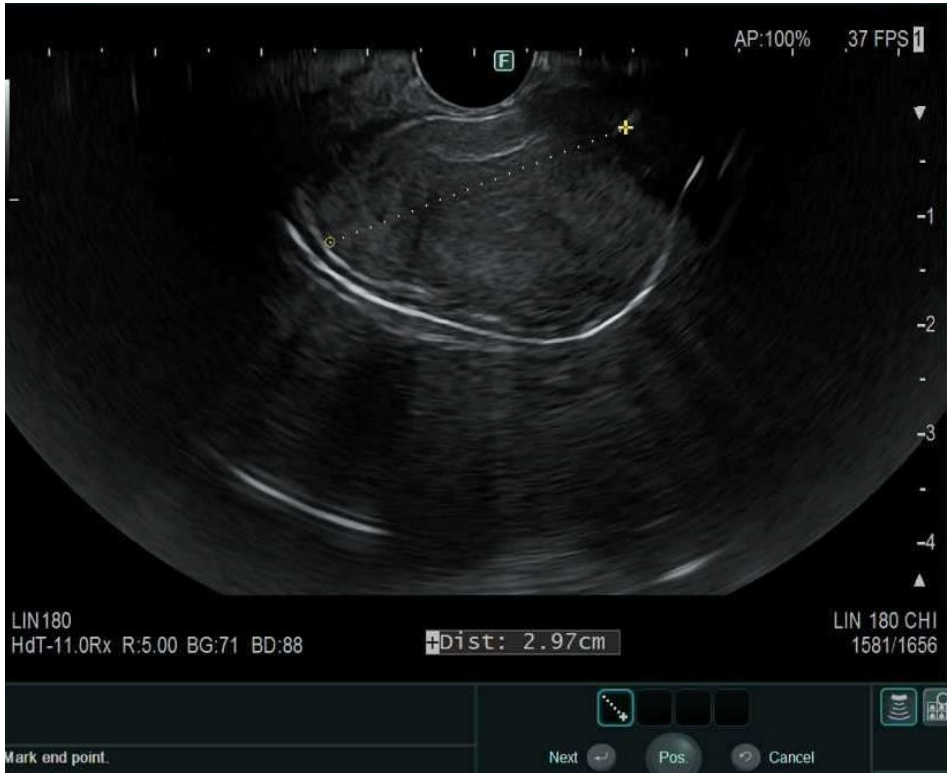
Shilpa Jain , MD (Associate Professor, Director of GI Pathology at Baylor St. Lukes Hospital)

Clinical Presentation

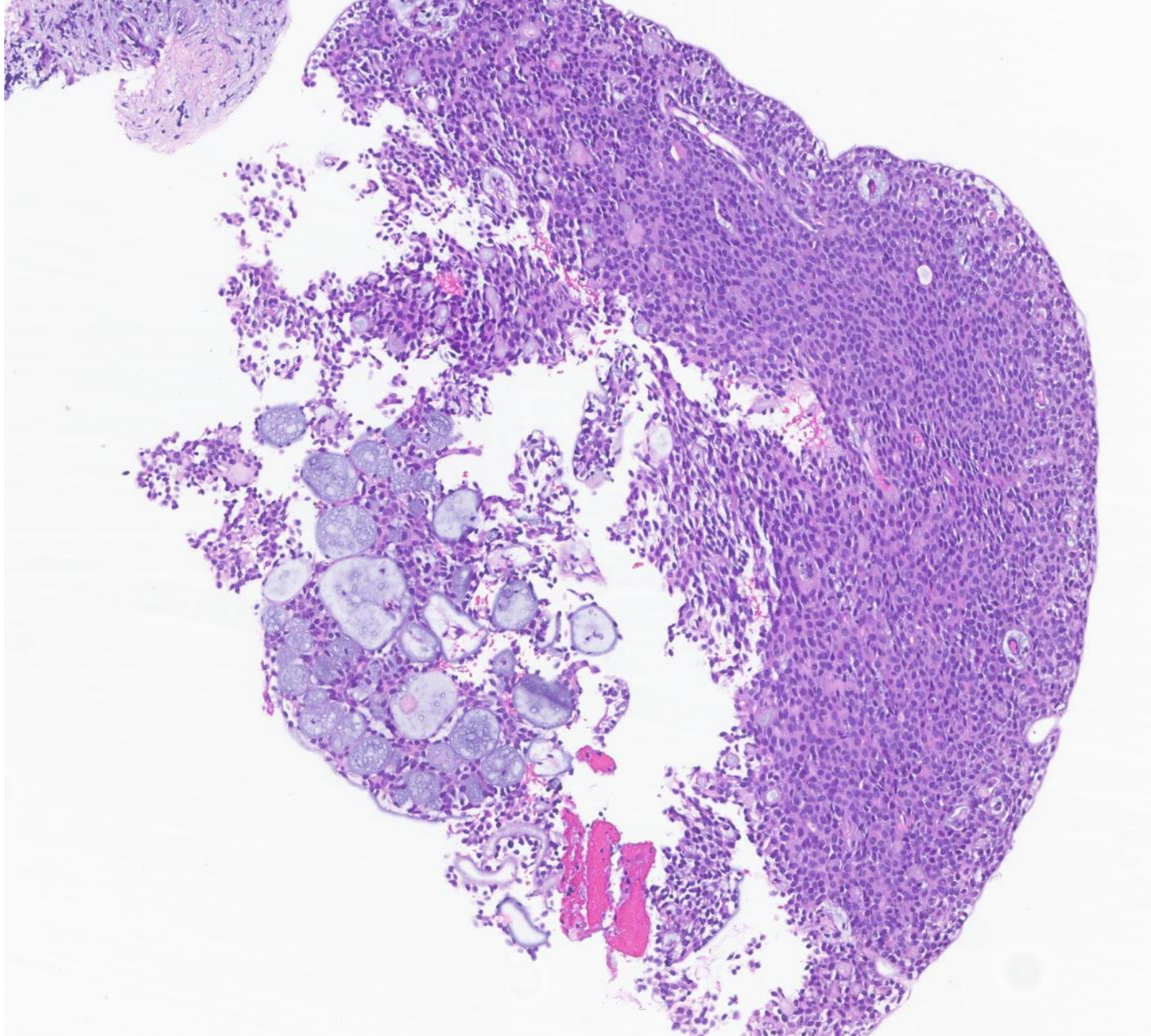
- A 63-year-old woman with incidental finding on CT chest of an esophageal or paraesophageal soft tissue prominence at the level of the clavicular heads.

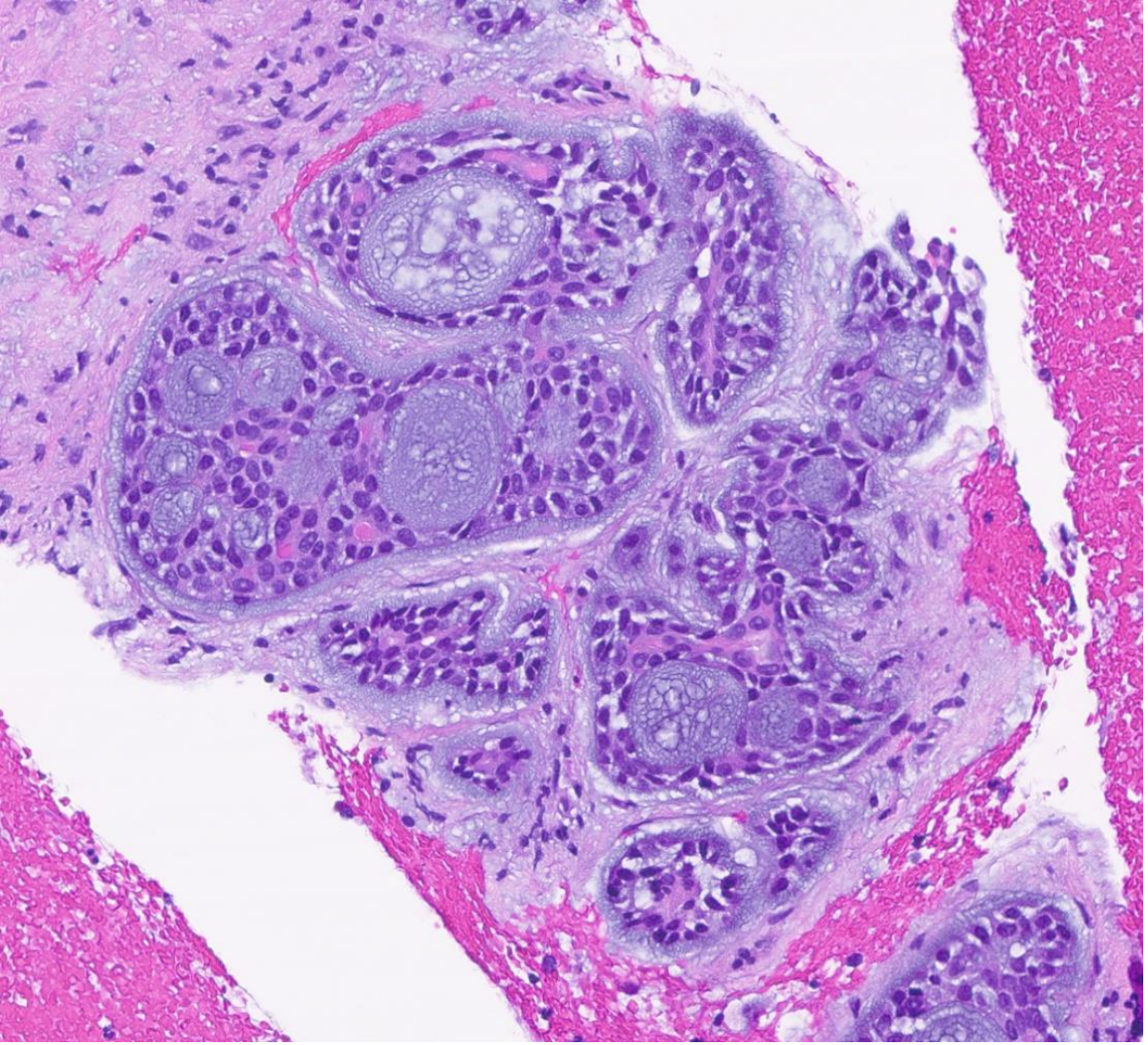
- CT neck showed a heterogeneously enhancing mass measuring approximately 2.6 x 2.7 x 2.8 cm which appears to be centered in the posterior tracheal wall and the anterior wall of the esophagus.

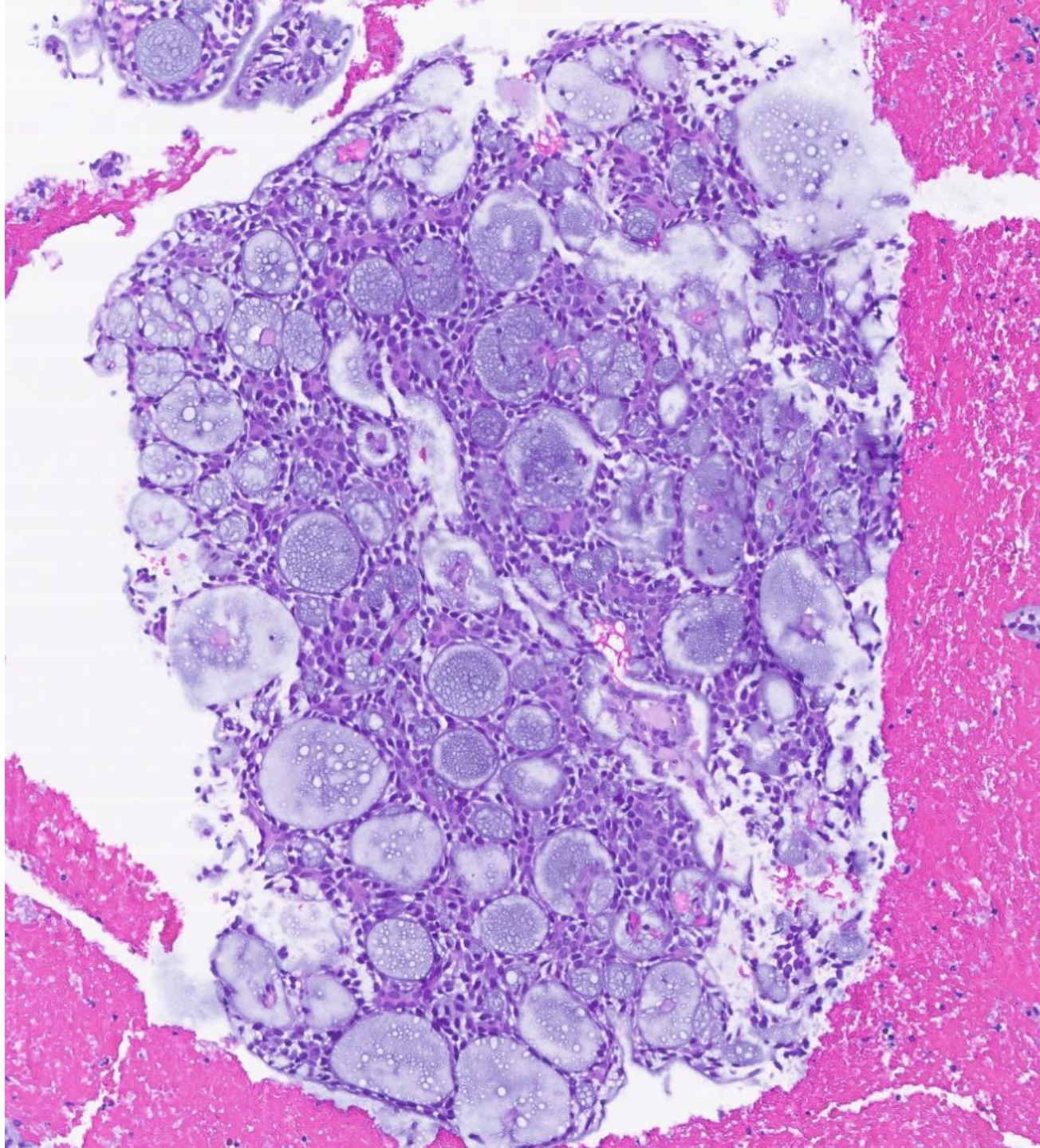
- On endoscopy, no mass was seen. **However, a peri-esophageal mass measuring 2.5cm, 19 cm from the incisors, was found on endoscopic ultrasound and was biopsied.**



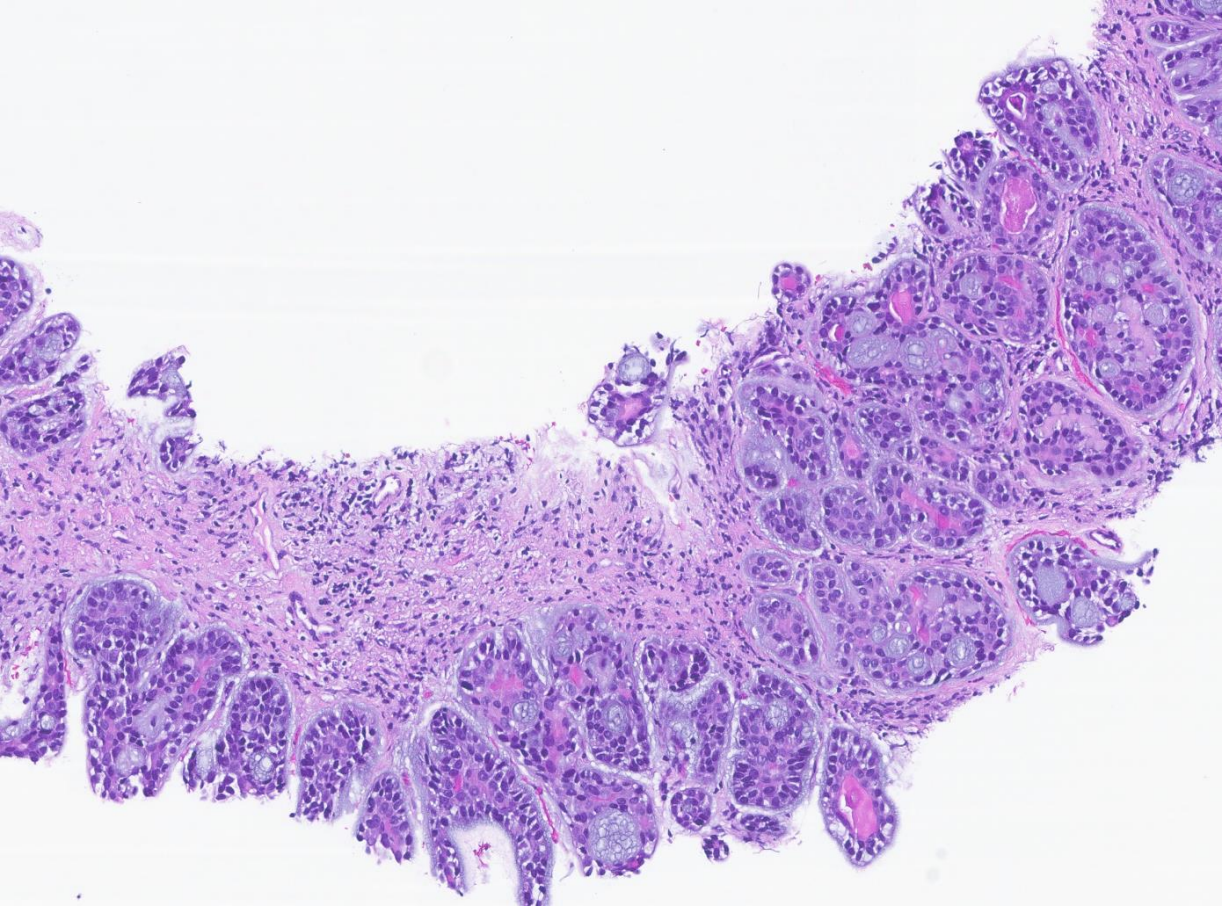
The Endoscopic ultrasound guided (EUS) deep core biopsy from the paraoesophageal mass showed some areas with a solid pattern.

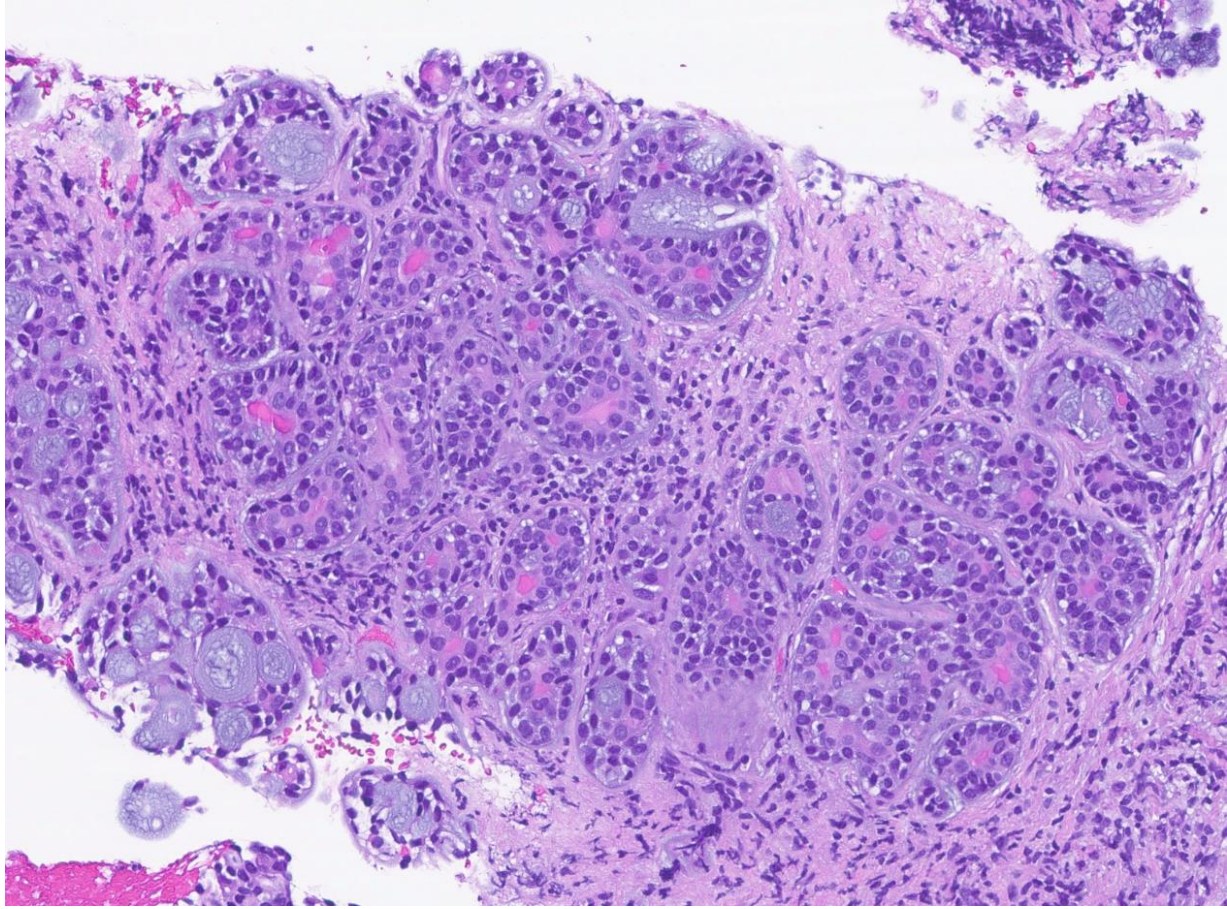






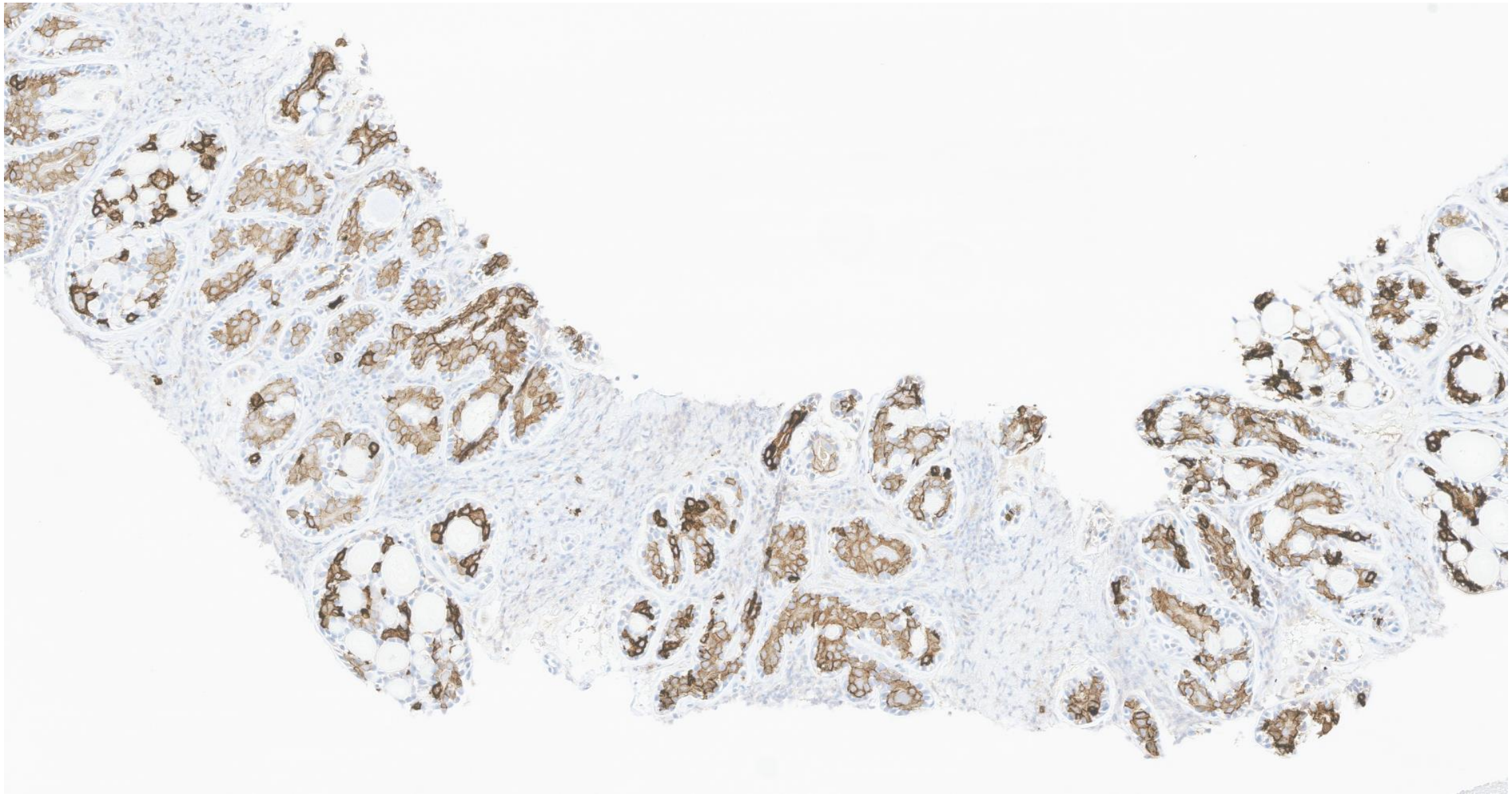
Other areas show a cribriform pattern with punched out spaces containing amorphous material.



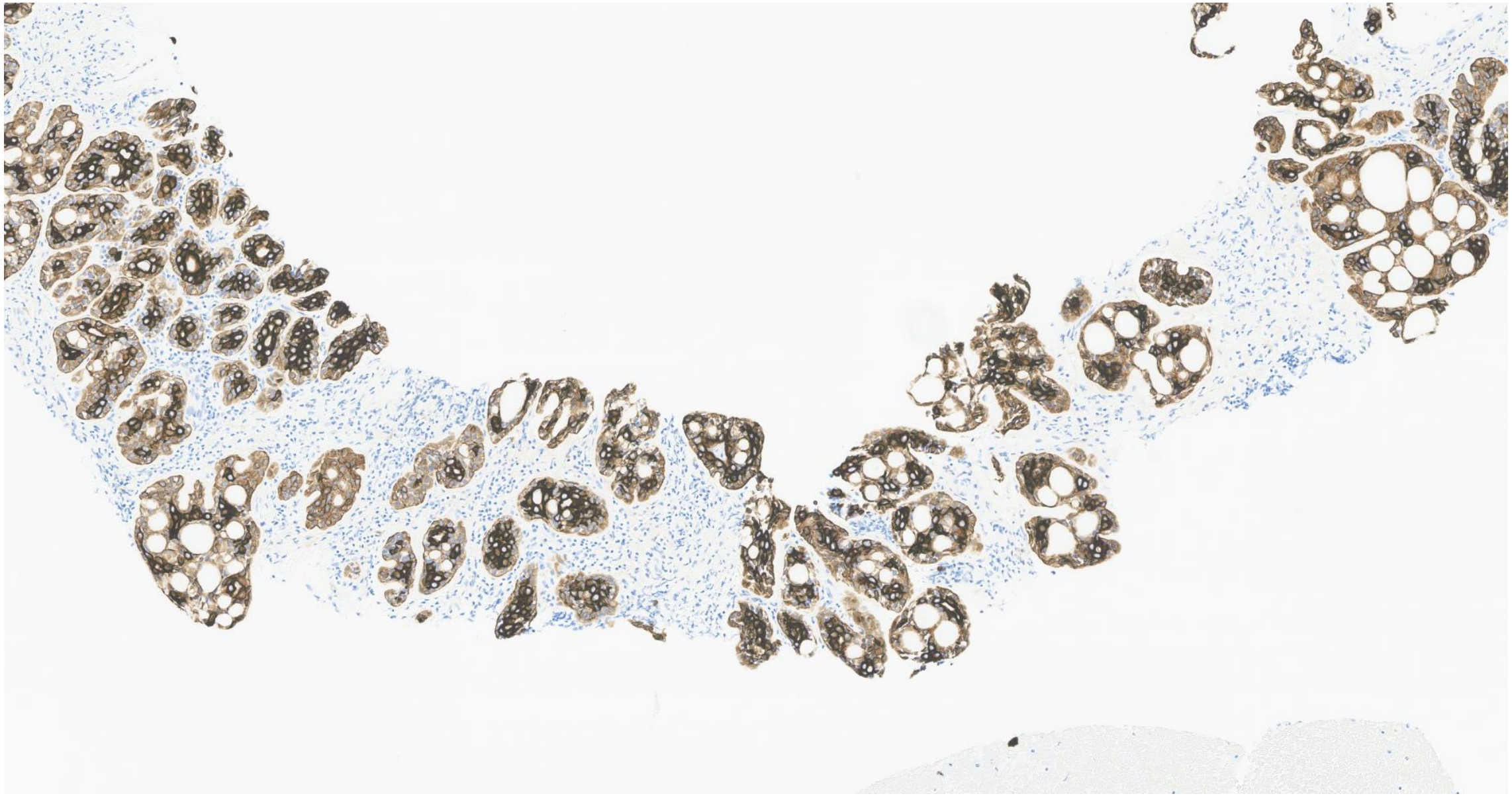


Other areas show a tubular pattern with a true lumen, filled with hyaline material. The tubules are lined by 2 types of cells, oval and angulated with scant eosinophilic cytoplasm.

CD117

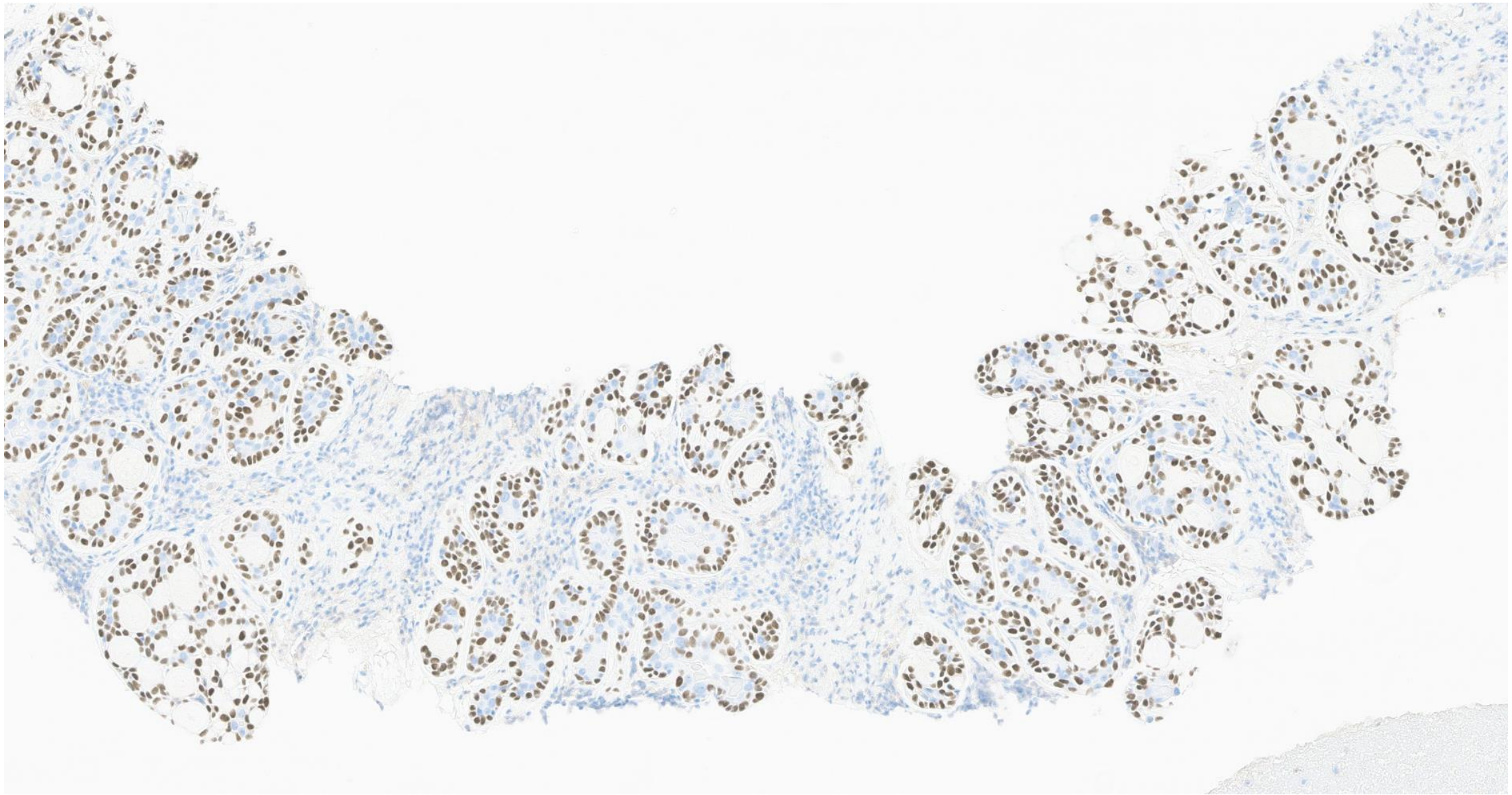


CAM 5.2

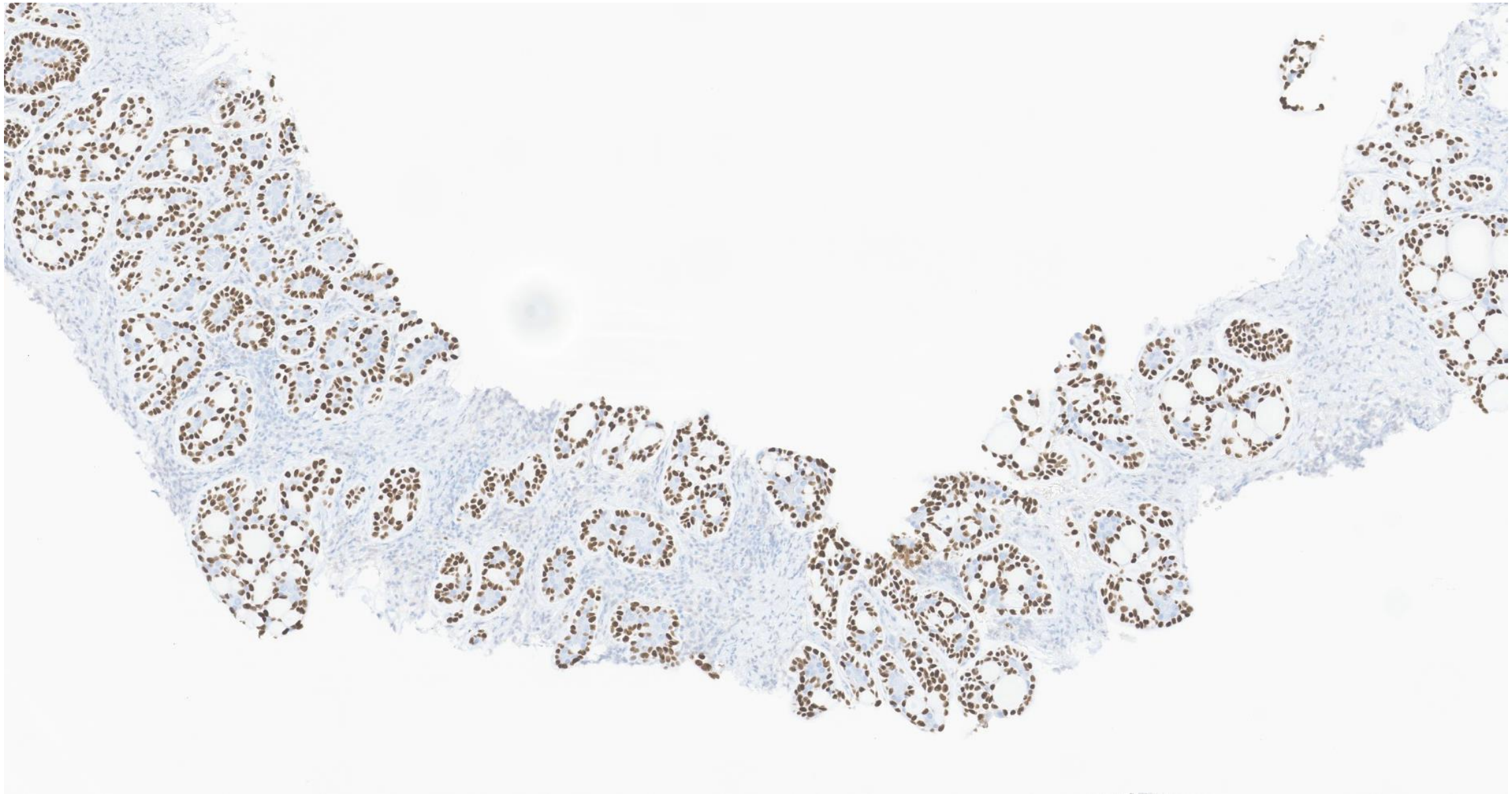


CK 5/6

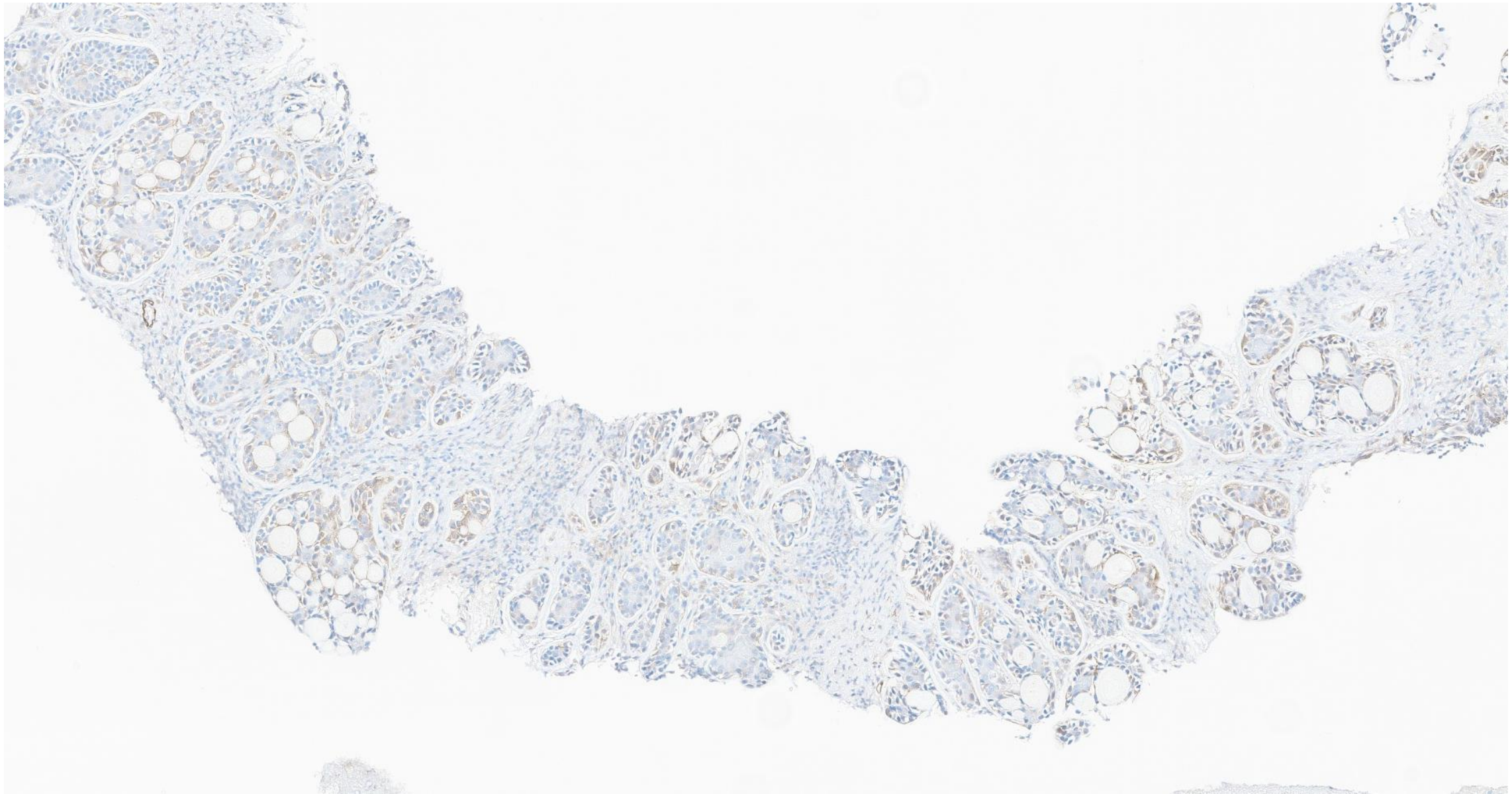
p40



p63



SMA



+

Q1: Which of the following histologic patterns is associated with a higher grade?

A. Cribriform
B. Tubular
C. Solid
D. This tumor is not graded based on histopathologic features

Answer: C (Solid).

Explanation for Q1:

Two main cell types are found in this tumor: ductal cells, with an eosinophilic cytoplasm and uniform round nuclei, and myoepithelial cells with a clear cytoplasm and hyperchromatic angular nuclei. In ACC, ductal cells are strongly positive for CK7 and CD117. Myoepithelial cells are positive for p63, p40, calponin, and α-SMA. Perineural invasions are commonly found.

Histologically, three architectural patterns are recognized, tubular, cribriform, and solid, and a combination of all three is common. The tubular pattern consists of ducts and tubules lined with luminal ductal and abluminal myoepithelial cells. The cribriform pattern is characterized by nests of tumor cells with microcystic-like spaces filled with hyaline or basophilic mucoid material. The solid pattern is characterized by tumor sheets of basaloid without a specific architecture.

Recent studies have shown that the presence of any solid tumor component indicates a higher grade. The clinical course is more aggressive when > 30% of the solid component is found. Other factors that affect survival include patient age, tumor site, TNM stage, surgical margins, and *NOTCH1* mutation status.

Q2: Which genetic alterations are most commonly found in adenoid cystic carcinoma?

A. CRTC1–MAML2 fusion
B. MYB::NFIB fusion
C. MYBL::NFIB fusion
D. PLAG1 rearrangements

Answer: B and C (MYB::NFIB and MYBL1::NFIB fusion).

Explanation for Q2:

Salivary ACC commonly harbors a t (6;9) chromosomal translocation, resulting in fusions involving the MYB or MYBL1 and NFIB genes (>90% of cases).

In our case, a universal solid tumor NGS fusion panel was performed, and no fusion was detected. This does not exclude the diagnosis of ACC. Since the mass was in the periesophageal space, centered in the posterior tracheal wall and the anterior wall of the esophagus, it is uncertain where it originates from. It could be arising from the trachea and extending towards the esophagus, or it could be arising from the esophageal submucosa.

Primary tracheobronchial adenoid cystic carcinoma is rare (<1% of all lung tumors) but still more common than primary esophageal ACC (0.1%). Previous studies have reported an MYB::NFIB fusion in 41-50% of tracheobronchial ACCs. Another case series (n=7) has shown the presence of fusions involving MYB or MYBL1 and NFIB in 100% of cases [4]. Given the higher incidence of ACC in the respiratory tract and the absence of detectable fusion, determining the exact origin of the tumor in this biopsy specimen remains challenging. Additionally, since the patient has no history of other tumors, metastasis is unlikely.

References

1. van Weert S, van der Waal I, Witte BI, Leemans CR, Bloemena E. Histopathological grading of adenoid cystic carcinoma of the head and neck: analysis of currently used grading systems and proposal for a simplified grading scheme. *Oral Oncol*. 2015;51(1):71-76. doi:10.1016/j.oraloncology.2014.10.007
2. Morita N, Murase T, Ueda K, et al. Pathological evaluation of tumor grade for salivary adenoid cystic carcinoma: A proposal of an objective grading system. *Cancer Sci*. 2021;112(3):1184-1195. doi:10.1111/cas.14790
3. Brayer KJ, Frerich CA, Kang H, Ness SA. Recurrent Fusions in MYB and MYBL1 Define a Common, Transcription Factor-Driven Oncogenic Pathway in Salivary Gland Adenoid Cystic Carcinoma. *Cancer Discov*. 2016;6(2):176-187. doi:10.1158/2159-8290.CD-15-0859
4. Pei J, Flieder DB, Patchefsky A, et al. Detecting MYB and MYBL1 fusion genes in tracheobronchial adenoid cystic carcinoma by targeted RNA-sequencing. *Mod Pathol*. 2019;32(10):1416-1420. doi:10.1038/s41379-019-0277-x
5. Yoshikawa K, Kinoshita A, Hirose Y, et al. Endoscopic submucosal dissection in a patient with esophageal adenoid cystic carcinoma. *World J Gastroenterol*. 2017;23(45):8097-8103. doi:10.3748/wjg.v23.i45.8097
6. Inagaki H, Faquin WC, Stenman G, Urano M. Adenoid cystic carcinoma. In: WHO Classification of Tumours Chapter 4: Salivary gland tumours. 5th ed. International Agency for Research on Cancer (IARC)

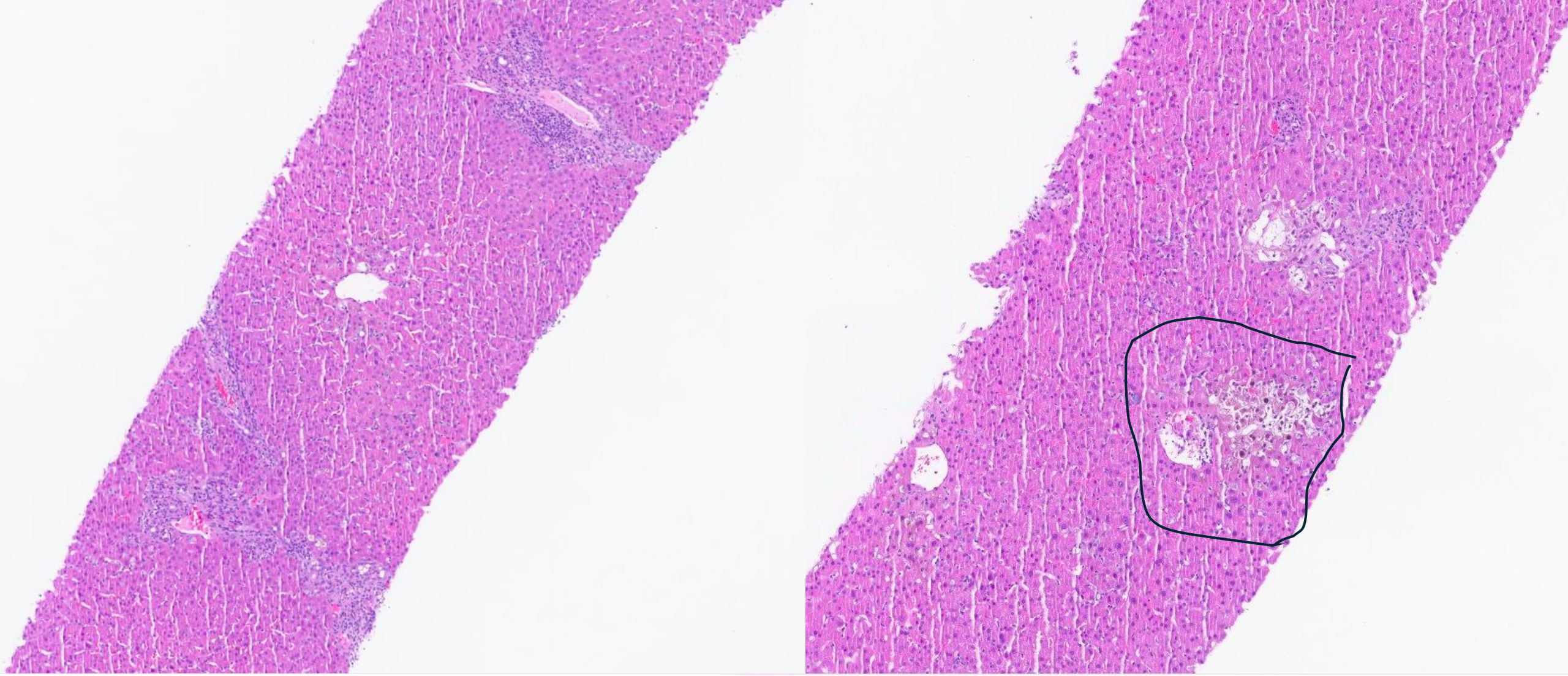
Case of the month September 2025

Laura Cuello, MD (Pathology Resident, PGY-2)

E. Celia Marginean, MD

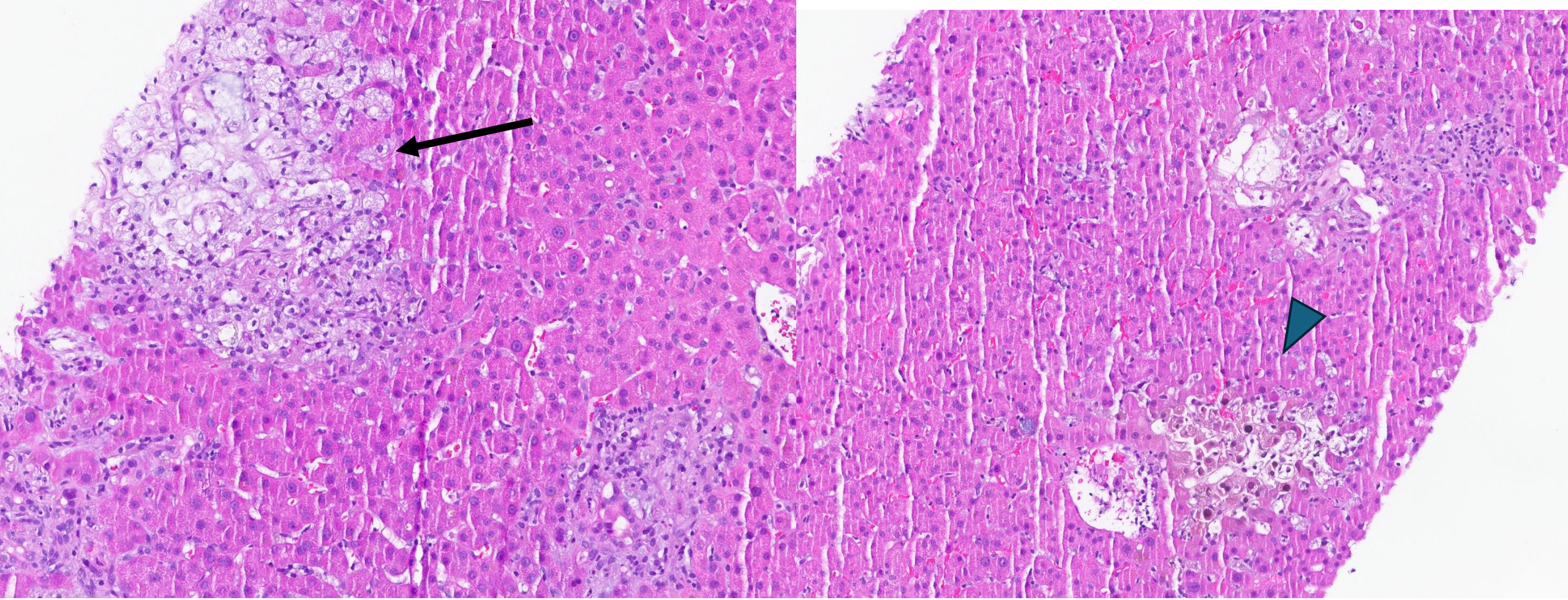
Clinical Presentation

- 48-year-old male with past medical history of metastatic esophageal adenocarcinoma, status post neoadjuvant chemotherapy and radiotherapy (2023) followed by esophagogastrectomy with no residual carcinoma (2024), on Xeloda-Nivo (capecitabine and nivolumab) presents with abdominal pain, worsening jaundice, and elevated liver function tests.
- Alkaline phosphatase: 758 U/L, Total Bilirubin: 11.9 mg/dL, Direct Bilirubin: 8.1 mg/dL, AST: 321 U/L, ALT: 272 U/L.
- Abdominal and pelvic CT showed mesenteric and retroperitoneal lymphadenopathy throughout the abdomen and pelvis. No focal liver masses or intra or extrahepatic biliary ductal dilation was seen.
- An ultrasound guided liver core biopsy was performed.

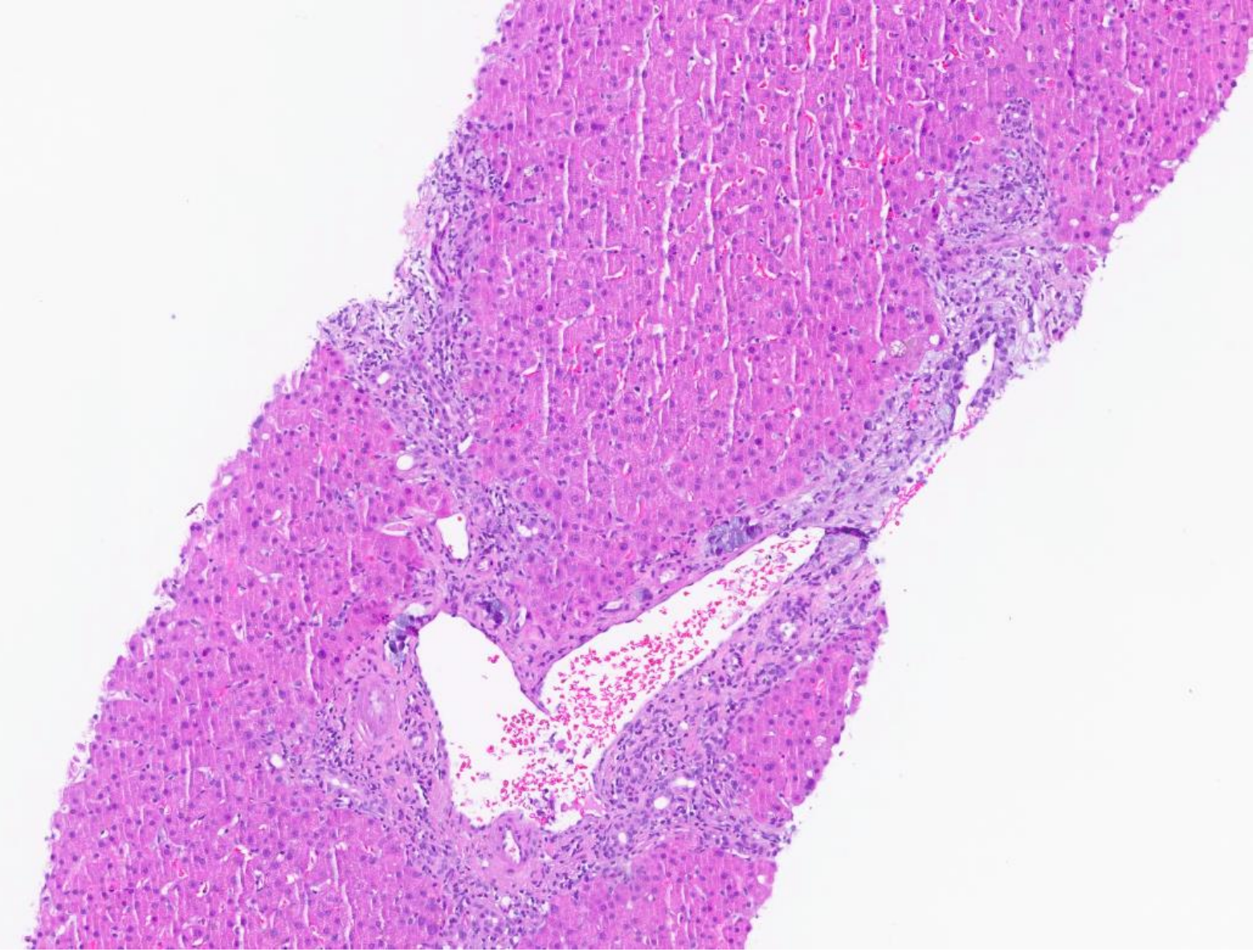


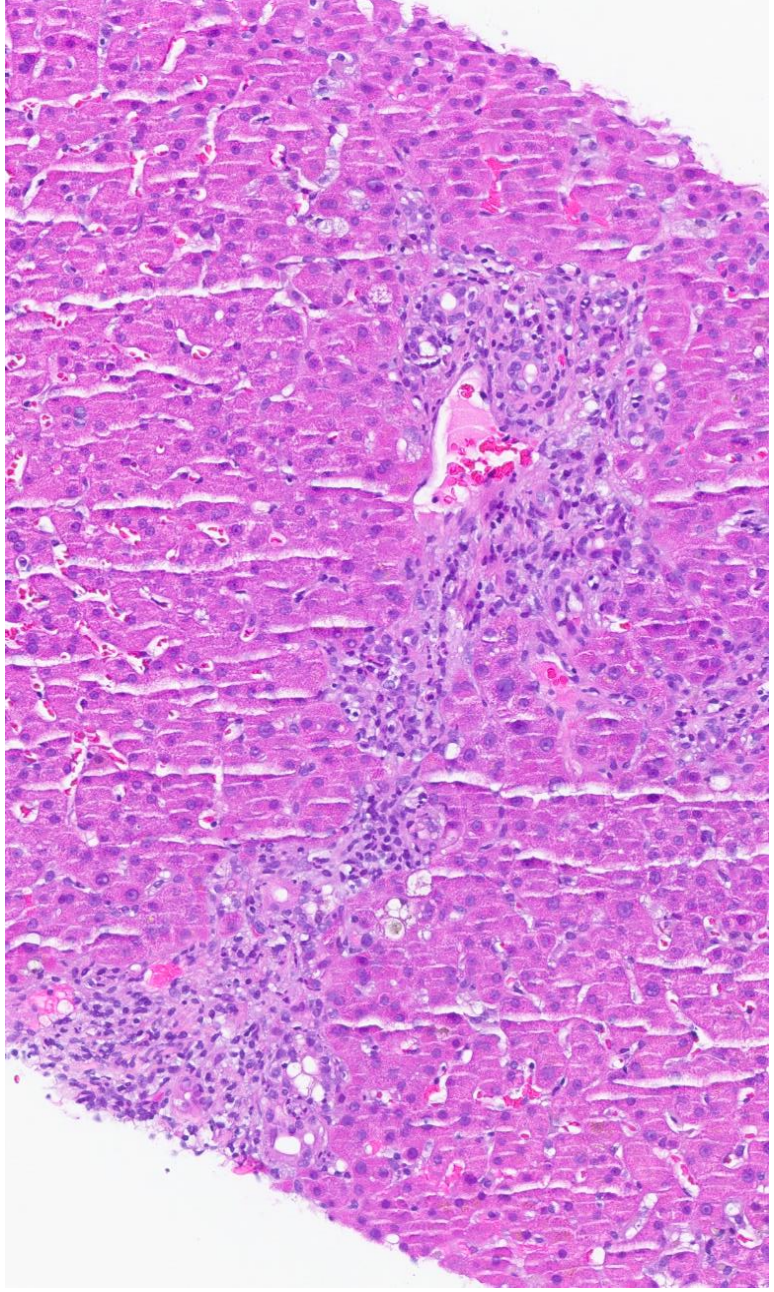
Features supporting a diagnosis of immune checkpoint inhibitor toxicity:

- Severe perivenular cholestasis and perivenular hepatocytic dropout with perivenulitis (circled);



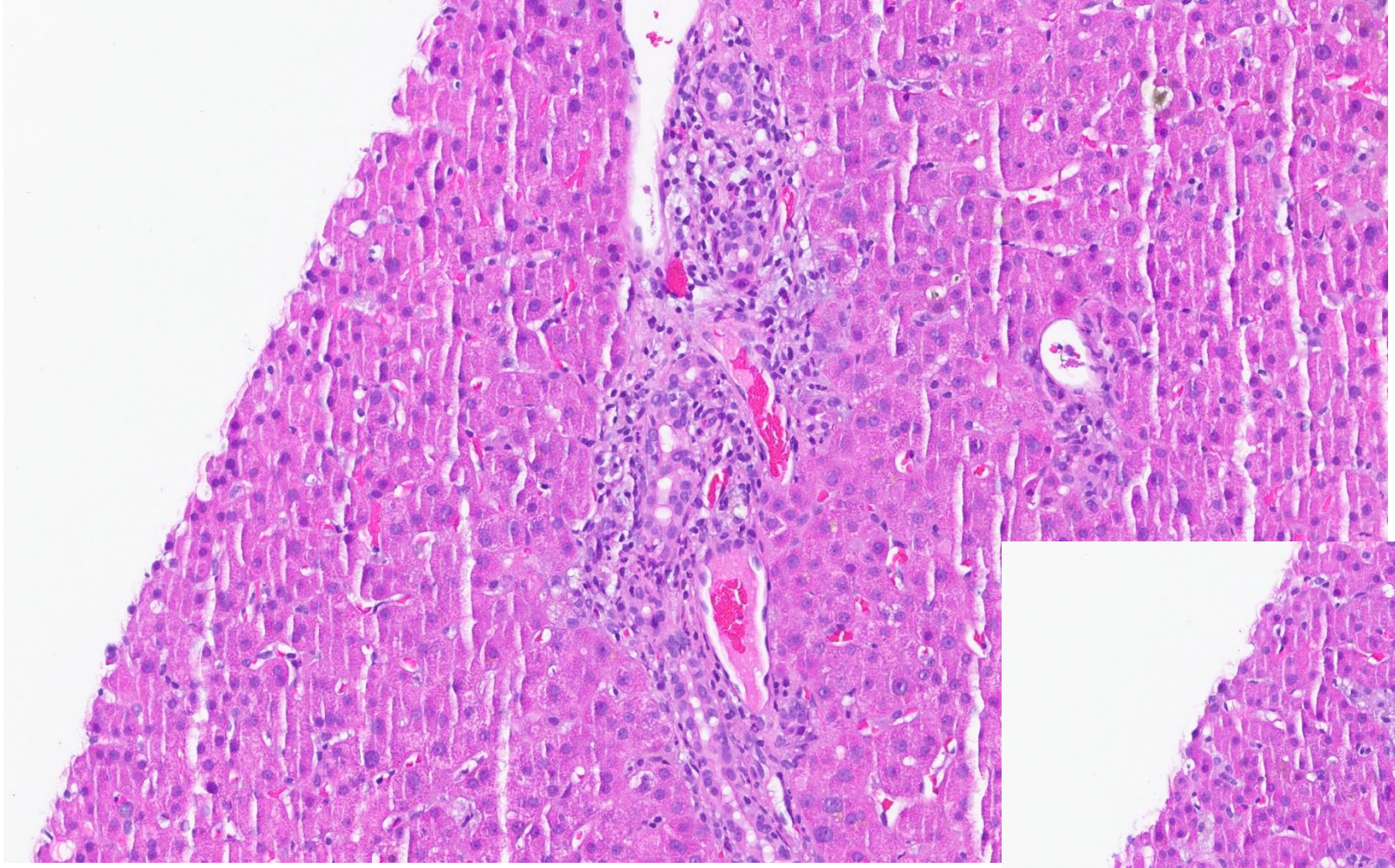
- Collections of foamy histiocytes within the lobules, some forming granulomata, arrow
- Perivenular cholestasis (arrow head)



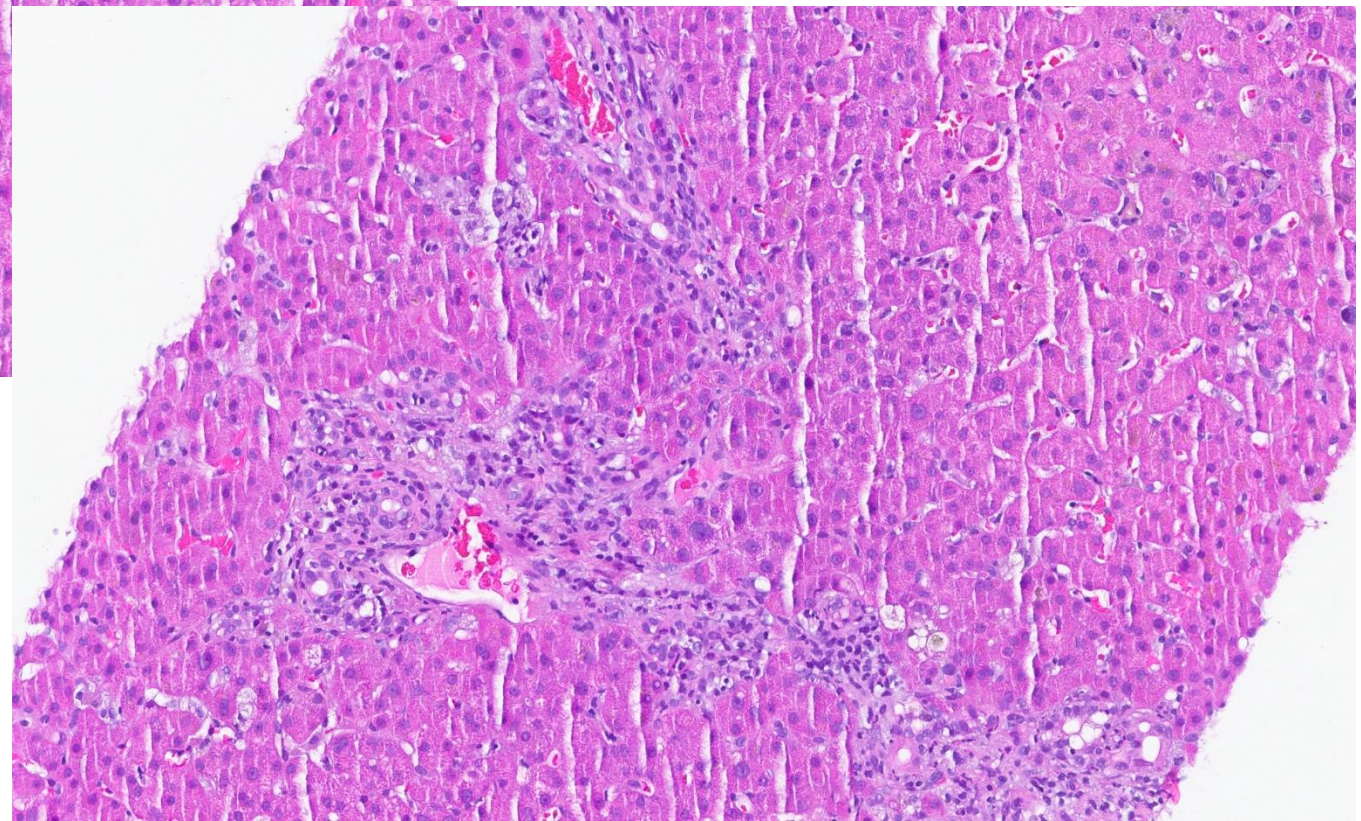


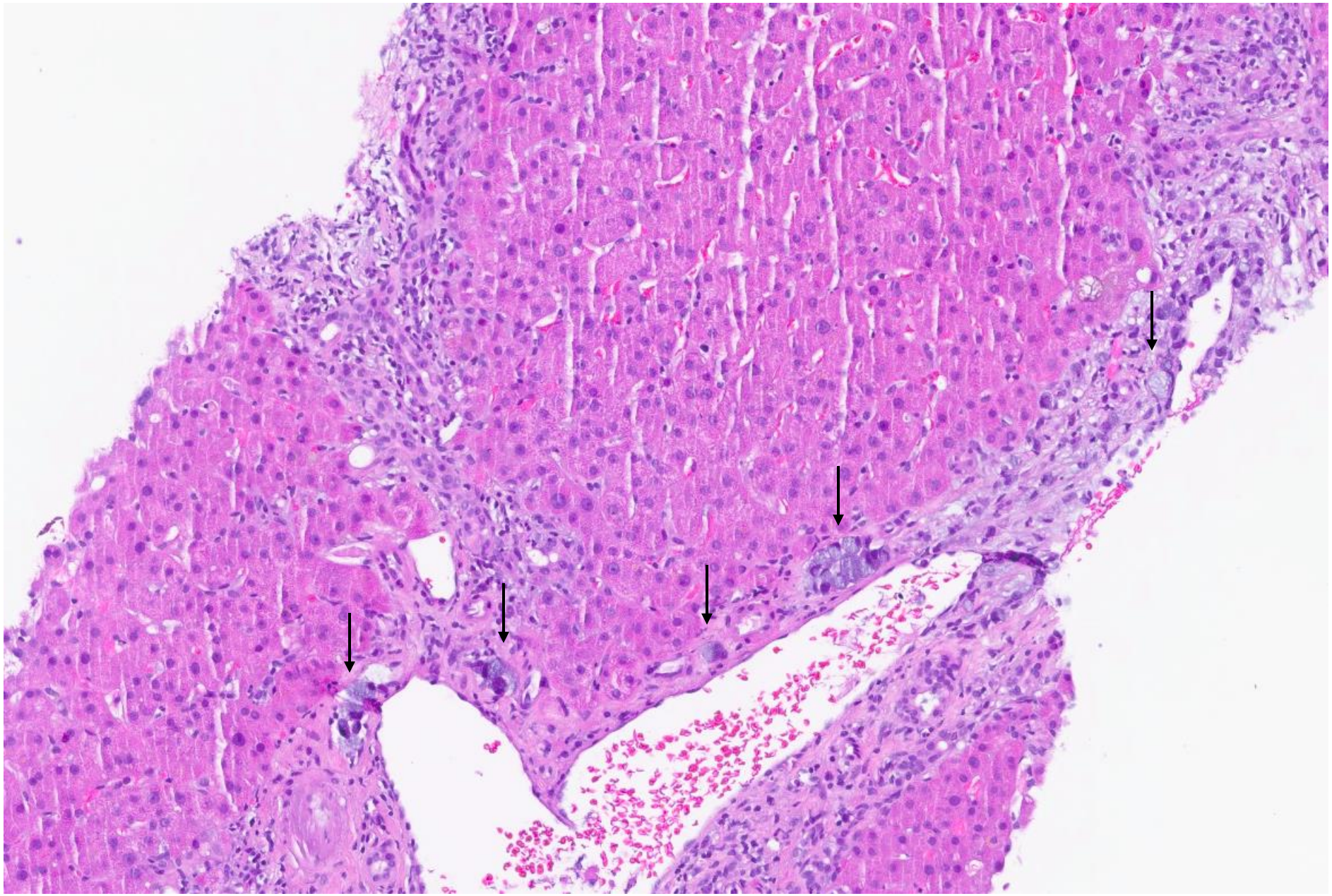
Features supporting a diagnosis of immune checkpoint inhibitor toxicity:

- Portal expansion by mixed lymphocytic and neutrophilic inflammatory infiltrate with rare eosinophils and extensive bile ductular proliferation

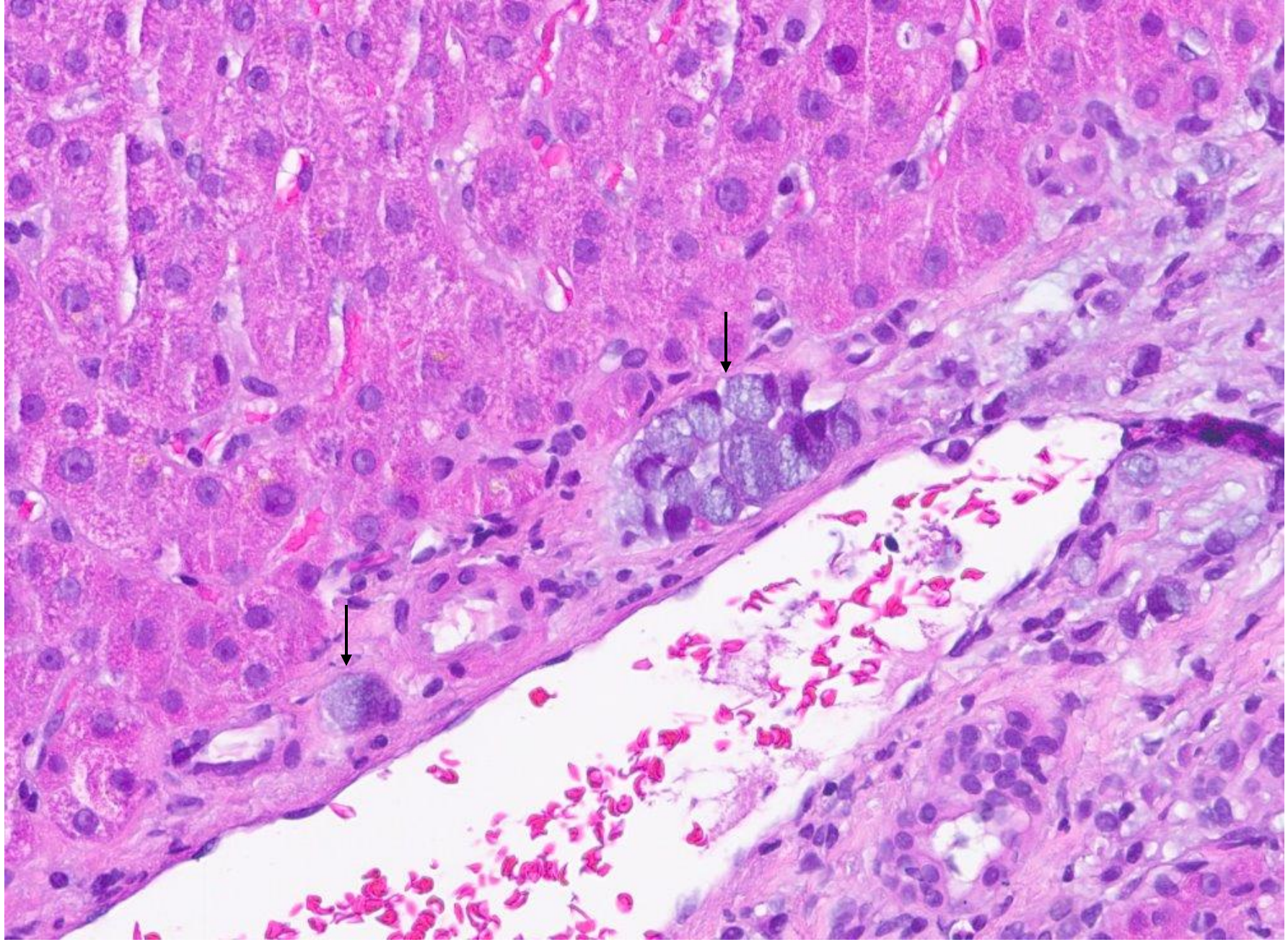


Mixed portal inflammation



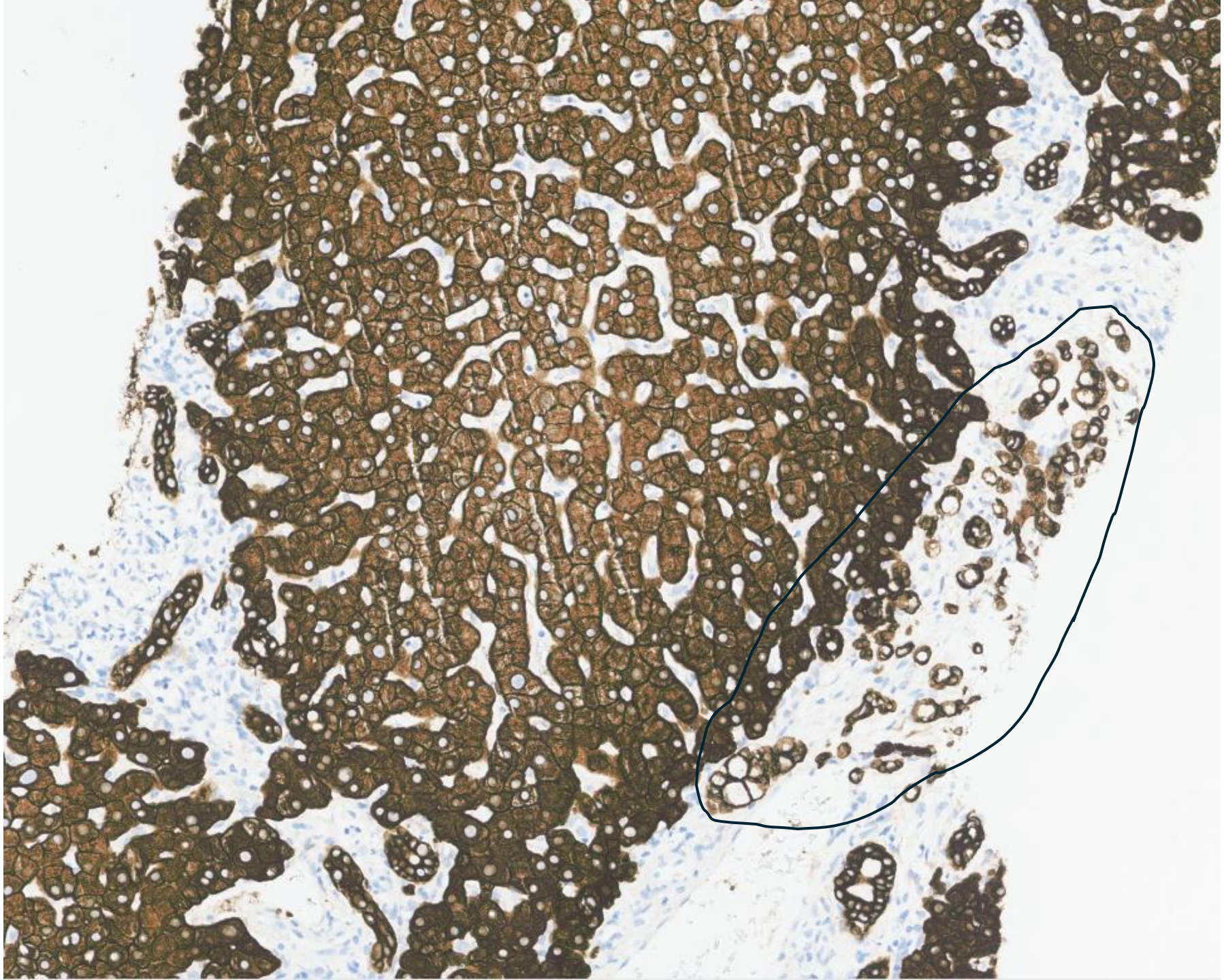


A single portal tract shows a few signet ring cells present within lymphatics and stroma (arrows).



These cells have abundant intracytoplasmic mucin that pushes the nucleus to the side, giving the classic signet ring appearance. They are positive for CK7 and keratin CAM 5.2.

CAM 5.2



Diagnosis:

- Liver with metastatic poorly differentiated carcinoma with signet ring cells, consistent with patients known esophageal primary

-Background liver with histologic features consistent with immune checkpoint inhibitor toxicity.

Q1. Which of the following statements about esophageal signet ring cell (SRC) adenocarcinoma is correct?

A. SCR adenocarcinoma is associated with better response to neoadjuvant therapy when compared to non-SCR adenocarcinoma
B. SRC adenocarcinoma represents less than 1% of histologic subtypes in esophageal adenocarcinoma and typically has inferior overall survival compared to non-SRC cases
C. SRC adenocarcinoma has a more aggressive behavior when compared to non-SRC adenocarcinoma, with poor response to neoadjuvant treatment, more positive margins after surgical resection, and worse overall survival.
D. Negative CK7 and CK20 immunohistochemistry support a diagnosis of SRC adenocarcinoma arising from the esophagus

Answer: C.
SRC adenocarcinoma has a more aggressive behavior when compared to non-SRC adenocarcinoma, with poor response to neoadjuvant treatment, more positive margins after surgical resection, and worse overall survival.

Explanation for Q1:

Esophageal adenocarcinoma represents about 80% of esophageal cancers in Western countries, with a poor 5-year survival of only 21.7% across all stages. Signet ring cell carcinoma is a histologic subtype of adenocarcinoma, characterized by abundant intracytoplasmic mucin that pushes the nucleus to the side, giving the classic signet ring appearance. While most cases arise in the stomach, signet ring cell (SRC) carcinoma is seen in up to 26% of patients with esophageal adenocarcinoma. Compared with non-SRC adenocarcinomas, tumors with SRC features behave more aggressively, showing poor response to neoadjuvant therapy, higher rates of positive surgical margins, and worse overall survival. Patients with SRC adenocarcinoma may benefit from combined neoadjuvant and adjuvant chemotherapy than neoadjuvant therapy alone.

A high index of suspicion has to be maintained when evaluating atypical cells in liver biopsies, especially in patients with a history of esophageal adenocarcinoma. In the context of background liver injury, special vigilance is required, as inflammation and cell injury can obscure SRC morphology, or benign mimickers such as signet-ring cell change may be encountered. Immunohistochemistry highlighting CK7, CK20, and pancytokeratin positive signet-ring cells can be helpful when diagnosing metastatic poorly differentiated carcinoma with SRC features from an esophageal primary.

Q2. What is the most common pattern of injury in checkpoint inhibitor (CPI) therapy–induced liver injury, and what histologic feature distinguishes it from autoimmune hepatitis?

E. Cholestatic pattern, presence of fibrin ring granulomas
F. Panlobular hepatitis; absence of significant plasma cell infiltrate
G. Cholestatic pattern; multiple lobular granulomata
H. Panlobular hepatitis; dense portal based plasma cell rich inflammatory infiltrates with interface activity

Answer: B.
Panlobular hepatitis; absence of significant plasma cell infiltrate

Explanation for Q2:

Checkpoint inhibitor (CPI) associated liver injury is an immune related adverse event secondary to immune checkpoint inhibitors such as anti-PD1 (nivolumab, pembrolizumab), anti-PDL1 (atezolizumab, avelumab, darvalumab) and anti-CTLA4 therapies (ipilimumab and tremelimumab). It is reported in 1-17% of patients on monotherapy and in up to 25% of patients receiving combination therapy.
The most frequent histologic pattern is panlobular hepatitis. This pattern is characterized by panlobular hepatitis with proportionately milder portal inflammation and perivenular infiltrate with endothelialitis. The lobular infiltrate is composed of lymphocytes and histiocytes, with few scattered plasma cells, neutrophils, and eosinophils. Sinusoidal histiocytic infiltrates can be present. There is no significant infiltrate of plasma cells, an important feature distinguishing it from autoimmune hepatitis.
A cholestatic pattern of injury can also be seen. This pattern of injury presents with portal inflammation predominantly composed of lymphocytes and occasional eosinophils, neutrophils, and plasma cells, with varying degree of bile duct injury (cholangitis, bile ductular proliferation, ductopenia, and rarely, vanishing bile duct system).

Granulomas can be seen in either pattern of injury, especially fibrin ring granulomas, which are more commonly seen in anti-CTLA-4 therapy.

Most patients' liver function tests are normalized after systemic corticosteroids and discontinuation of the offending medication. However, disease can still progress histologically even if liver function tests normalize. Infliximab can be considered as a rescue therapy.

References:

Solomon D, Abbas M, Feferman Y, et al. Signet Ring Cell Features are Associated with Poor Response to Neoadjuvant Treatment and Dismal Survival in Patients with High-Grade Esophageal Adenocarcinoma. *Ann Surg Oncol*. 2021;28(9):4929-4940. doi:10.1245/s10434-021-09644-1

Rompen IF, Billeter AT, Crnovrsanin N, et al. Definition and Predictors of Early Recurrence in Neoadjuvantly Treated Esophageal and Gastroesophageal Adenocarcinoma: a Dual-Center Retrospective Cohort Study. *Ann Surg Oncol*. 2025;32(3):1617-1627. doi:10.1245/s10434-024-16403-5

Tang A, Rappaport J, Raja S, et al. Signet Ring Cell Histology Confers Worse Overall Survival in Treated Esophageal Adenocarcinoma. *Ann Thorac Surg*. 2021;111(1):214-222. doi:10.1016/j.athoracsur.2020.04.134

Chornenkyy Y, Pezhouh MK. Checkpoint inhibitor associated hepatitis. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/livericpihep.html. Accessed September 3rd, 2025.

Patil PA, Zhang X. Pathologic Manifestations of Gastrointestinal and Hepatobiliary Injury in Immune Checkpoint Inhibitor Therapy. *Arch Pathol Lab Med*. 2021;145(5):571-582. doi:10.5858/arpa.2020-0070-RA

Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury. *Mod Pathol*. 2018;31(6):965-973. doi:10.1038/s41379-018-0013-y

Cohen JV, Dougan M, Zubiri L, Reynolds KL, Sullivan RJ, Misdraji J. Liver biopsy findings in patients on immune checkpoint inhibitors. *Mod Pathol*. 2021;34(2):426-437. doi:10.1038/s41379-020-00653-1

Kim KW, Ramaiya NH, Krajewski KM, et al. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. *Invest New Drugs*. 2013;31(4):1071-1077. doi:10.1007/s10637-013-9939-6

Case of the Month
October 2025

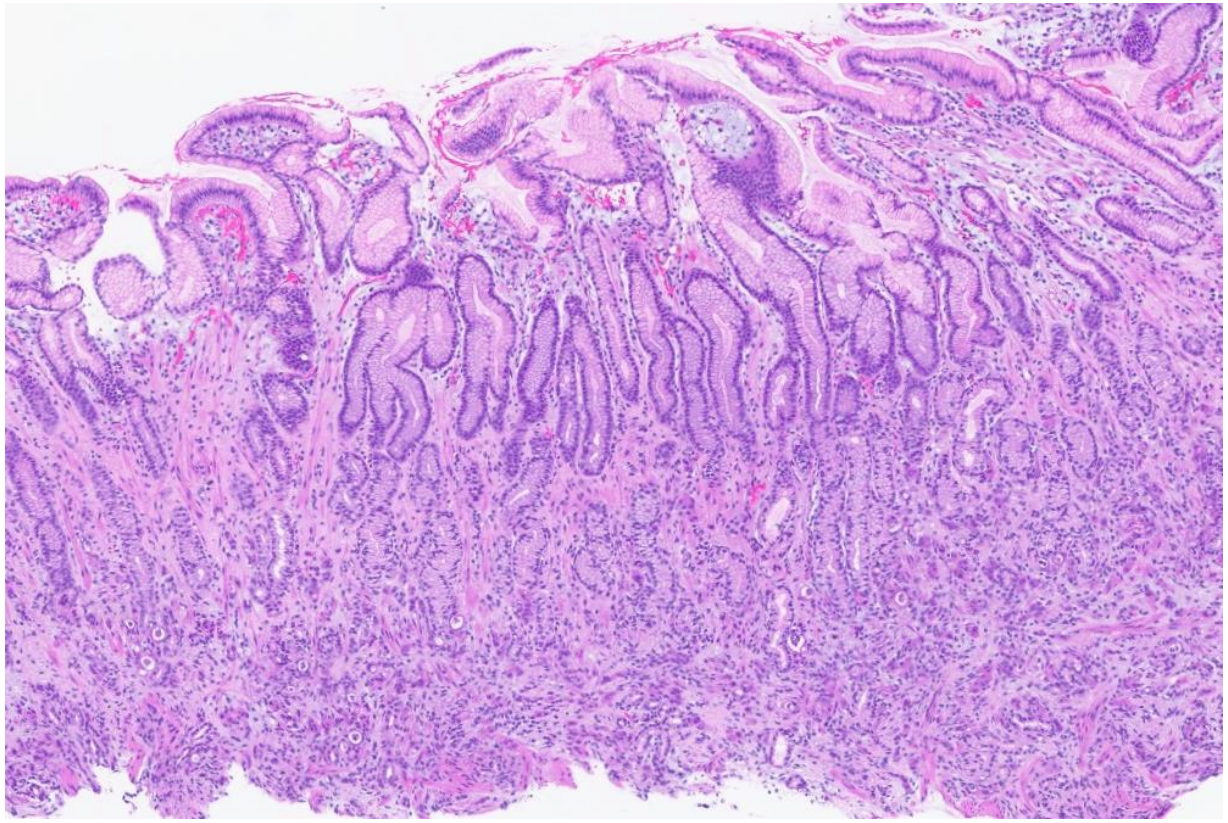
Gladson Scaria, MBBS (GI Pathology Fellow)

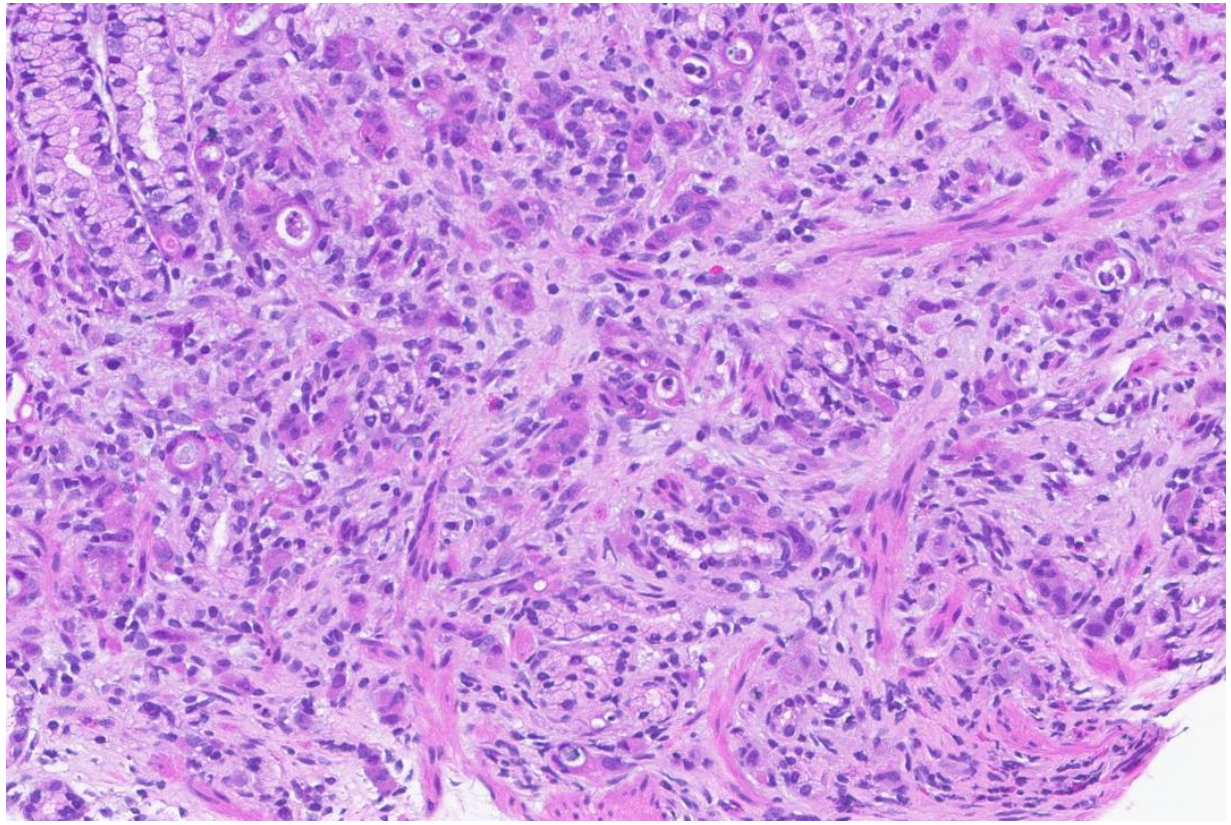
Celia Marginean, MD

Clinical Presentation

- 45-year-old male with past medical history of hypertension, hyperlipidemia, type 2 diabetes, prior H. pylori–associated peptic ulcer disease, and gastric outlet obstruction requiring dilation
- Symptoms
  - Progressive nausea/vomiting
  - Severe weight loss
- Prior interventions:
  - Prior hospitalization revealed substantial gastric stasis requiring endoscopic decompression
  - Previous H. pylori treatment
  - Pyloric stent placed with only short-lived symptom relief
- Current workup:
  - CT A/P: 4.1 × 4.8 cm pancreatic tail mass with upstream ductal dilation; abnormal pylorus with fat stranding; suspicious gastrohepatic nodes
  - Endoscopy/EUS: Severe pyloric stenosis (biopsied); heterogenous pancreatic tail mass; cystic lesion also noted

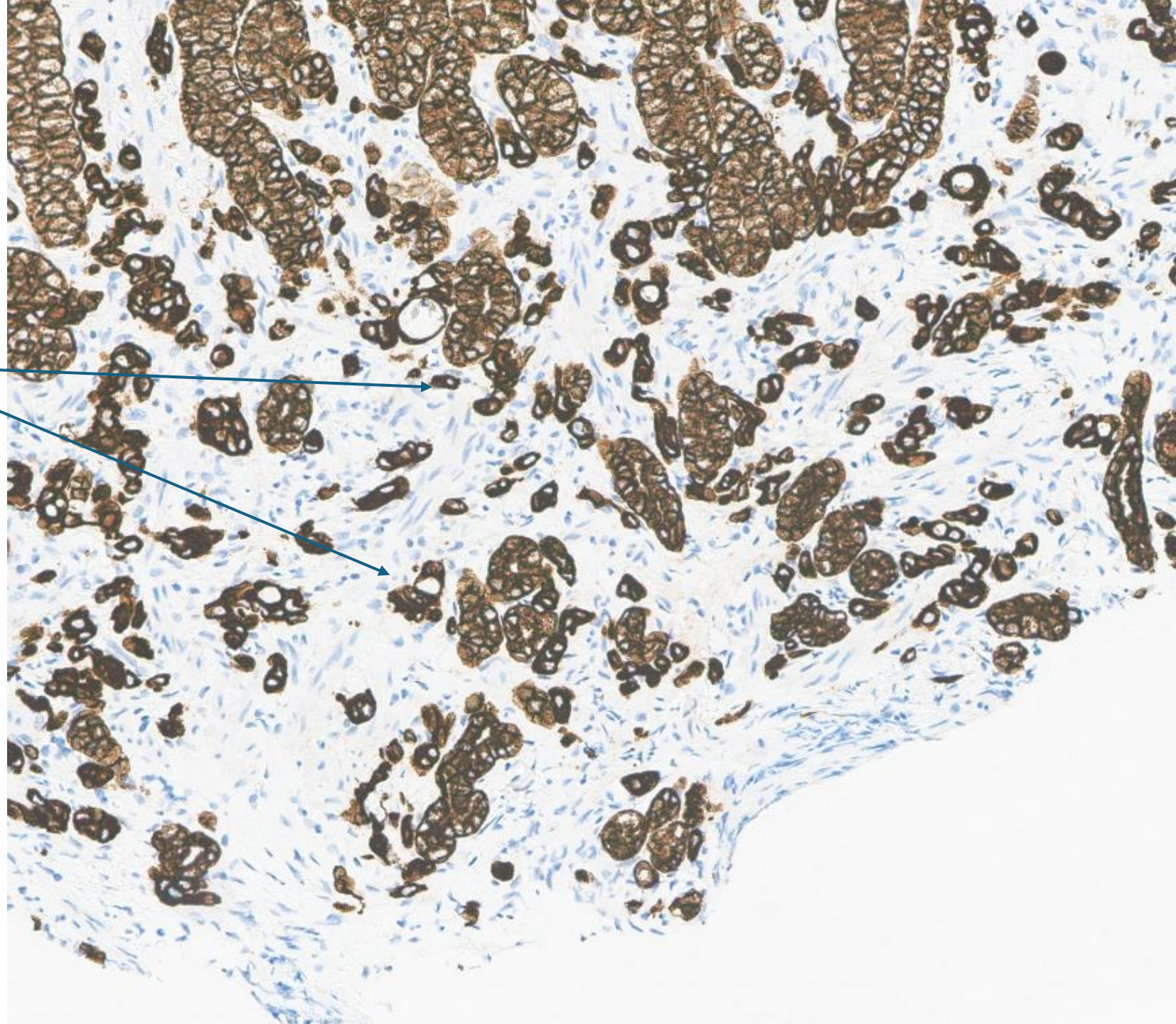
Part A: Gastric biopsy of the thickened pre-pyloric region





Keratin Cam 5.2

Highlights the normal gastric glands, and the poorly formed neoplastic glands and infiltrative single cells

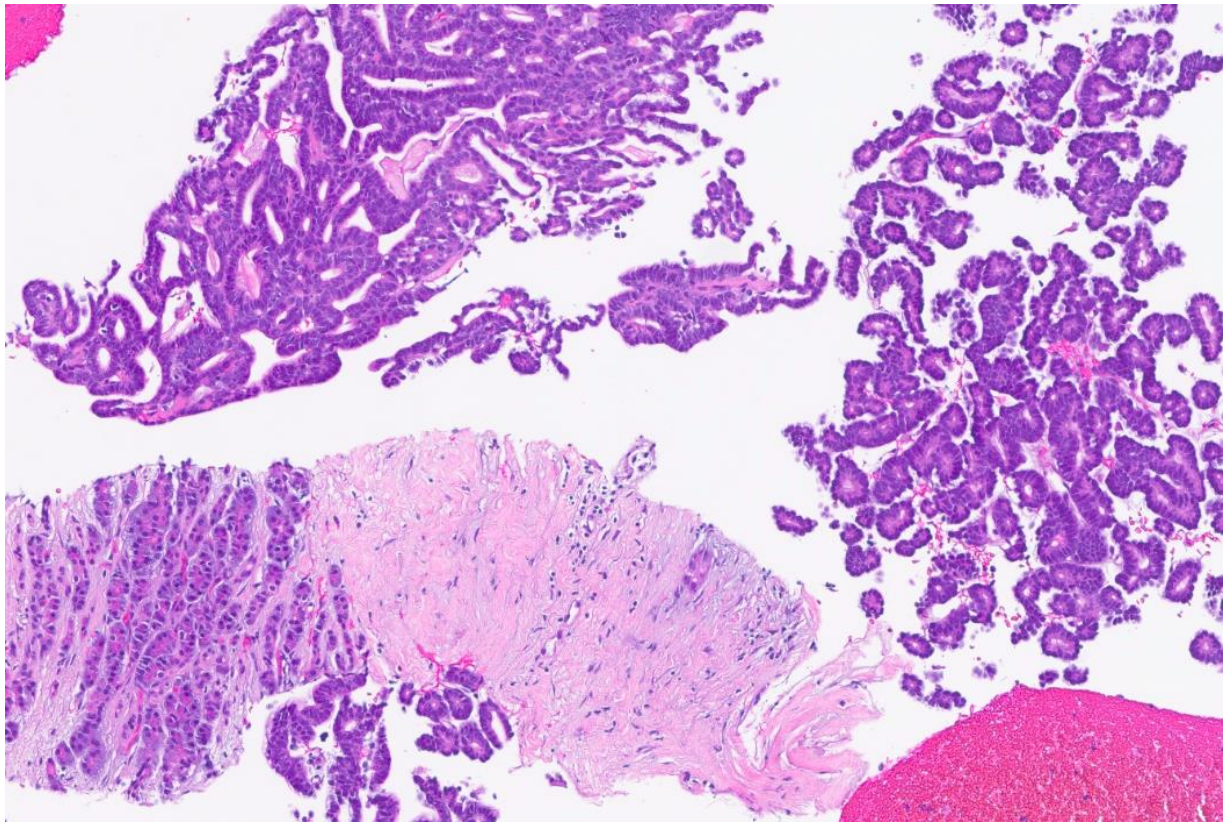


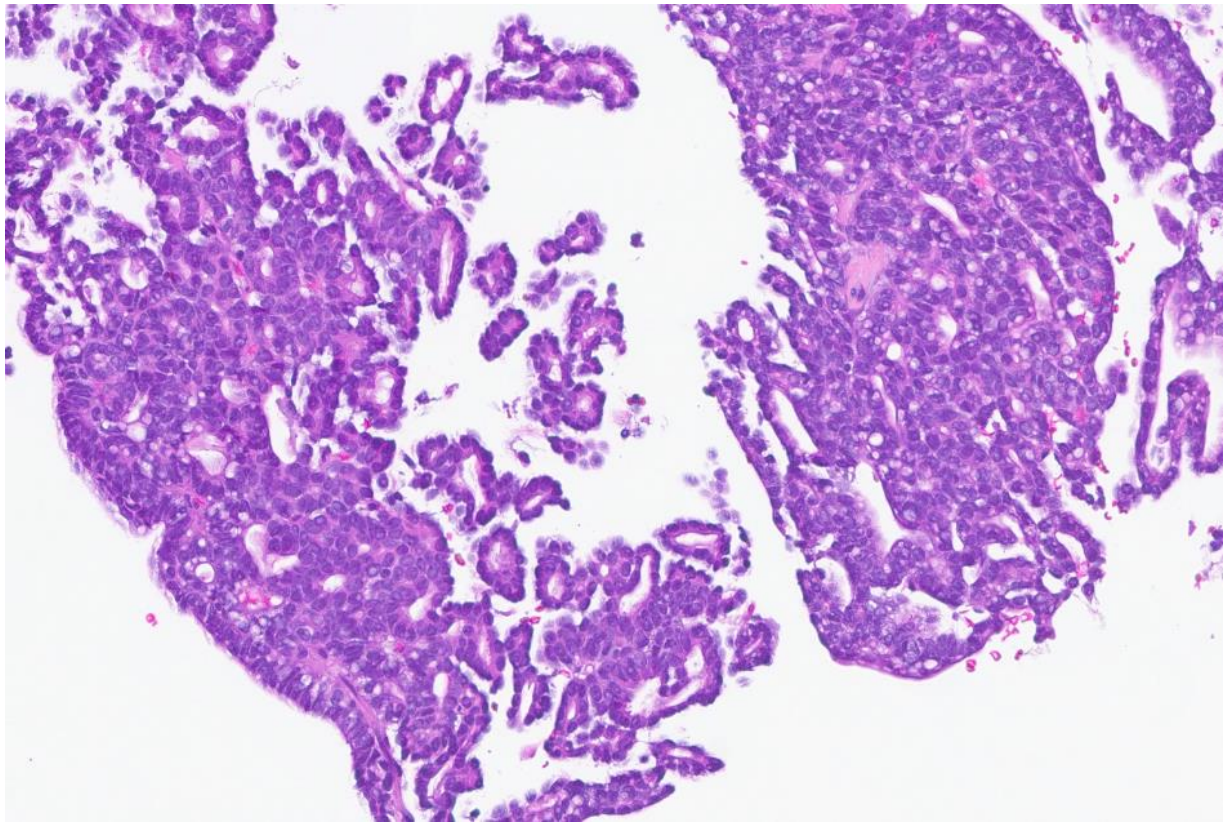
Dx

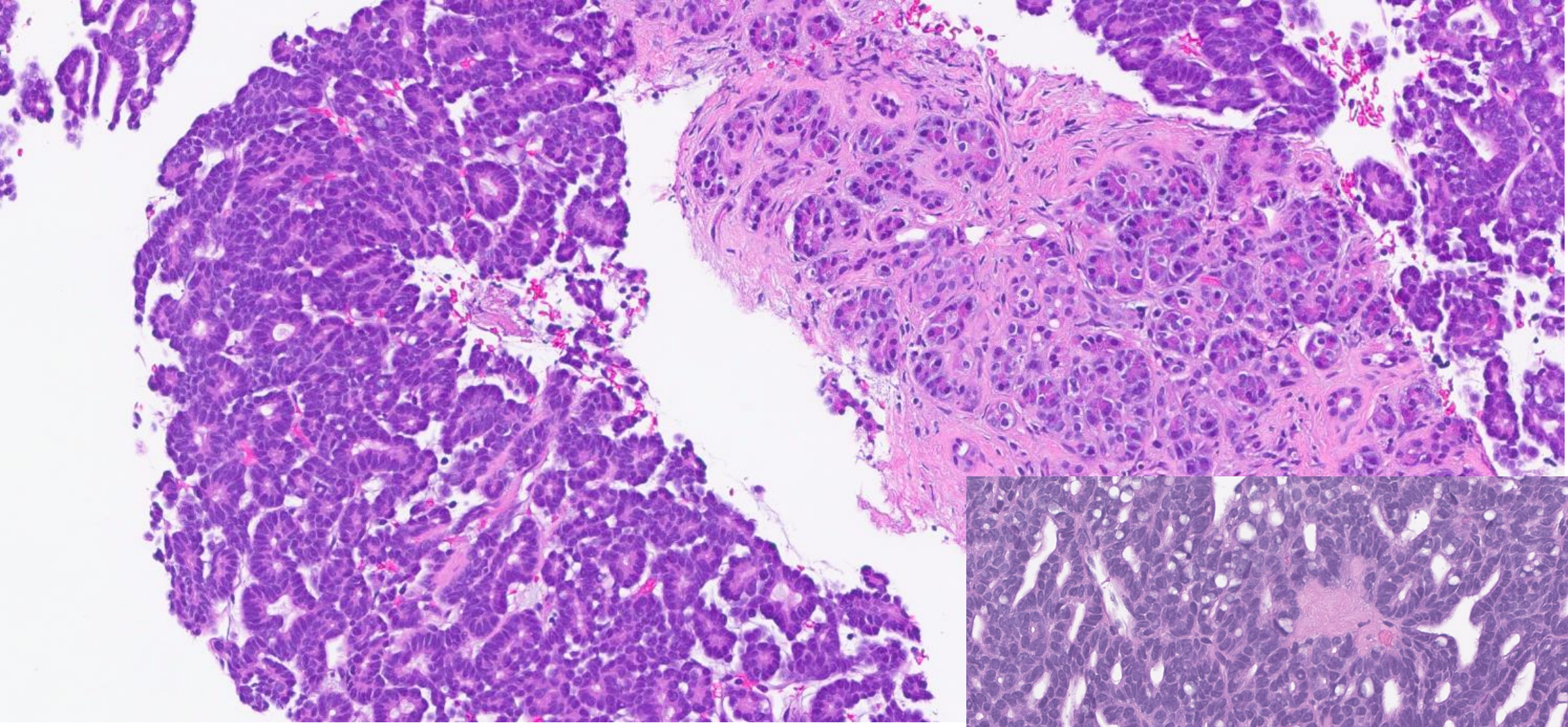
A. Stomach with poorly cohesive carcinoma with signet ring cells

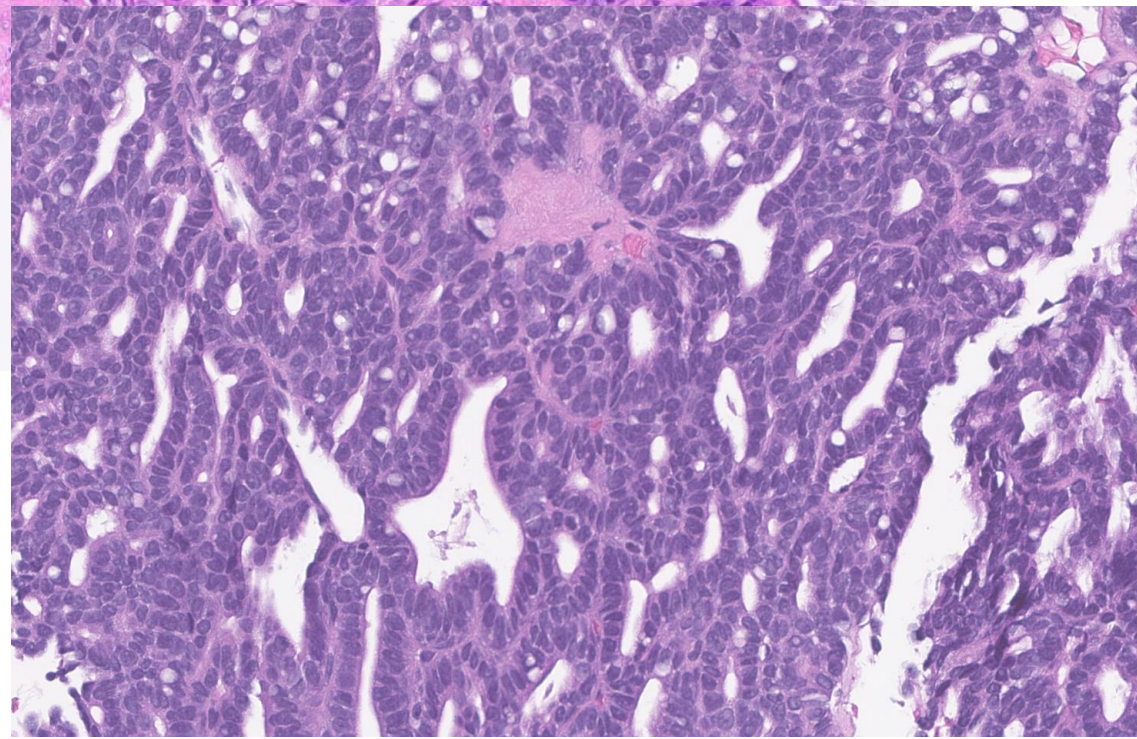
IHC Stain	Result	Interpretation / Comments
HER2 (IHC)	Negative (Score 0)	No HER2 protein overexpression
MLH1, MSH2, MSH6, PMS2	Intact nuclear expression	MMR proficient
Keratin (CAM 5.2)	Positive	Highlights infiltrating single tumor cells and abortive glands
Synaptophysin	Negative	No neuroendocrine differentiation
Chromogranin	Negative	No neuroendocrine differentiation

Part B: Biopsy of the pancreatic tail mass

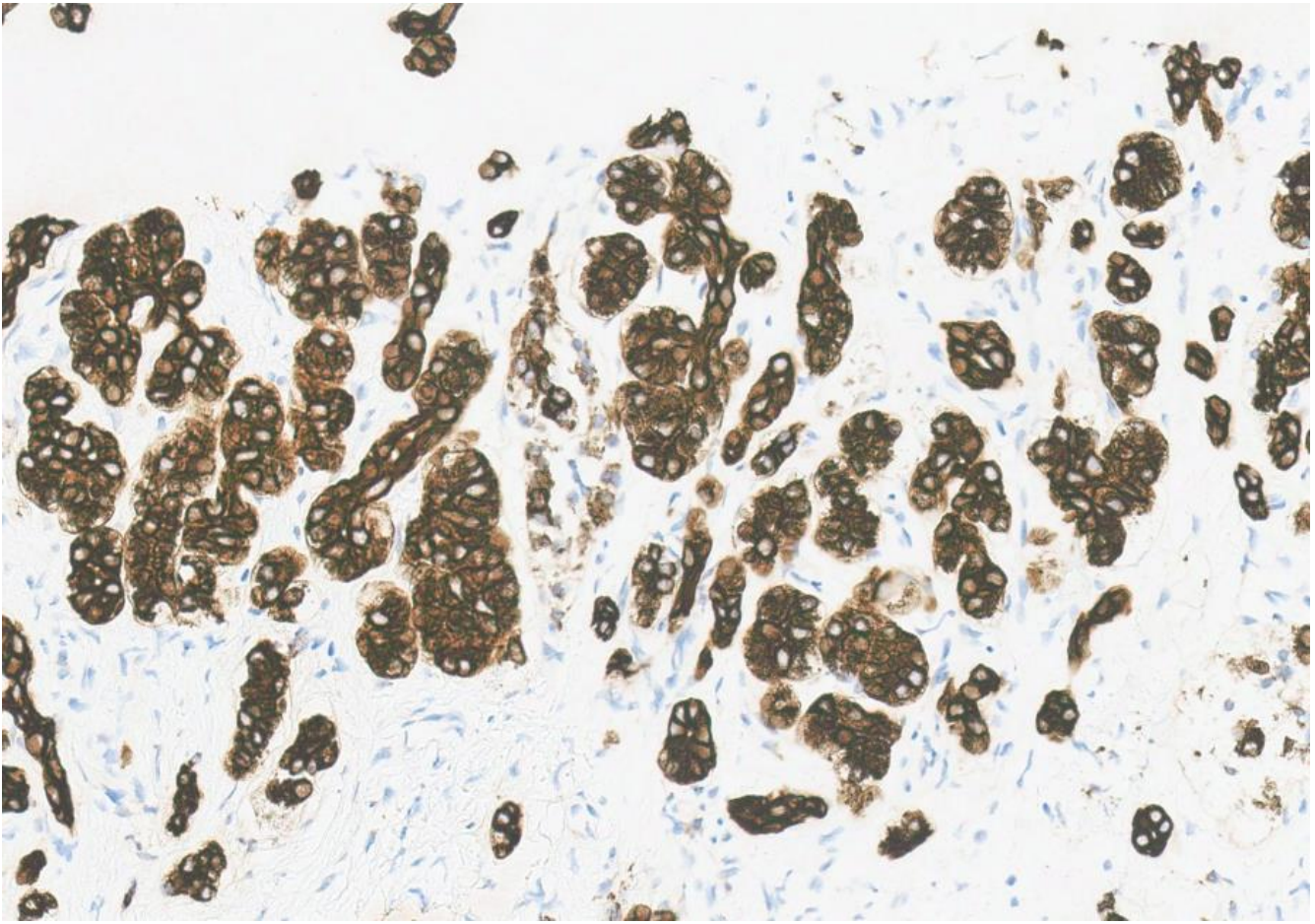




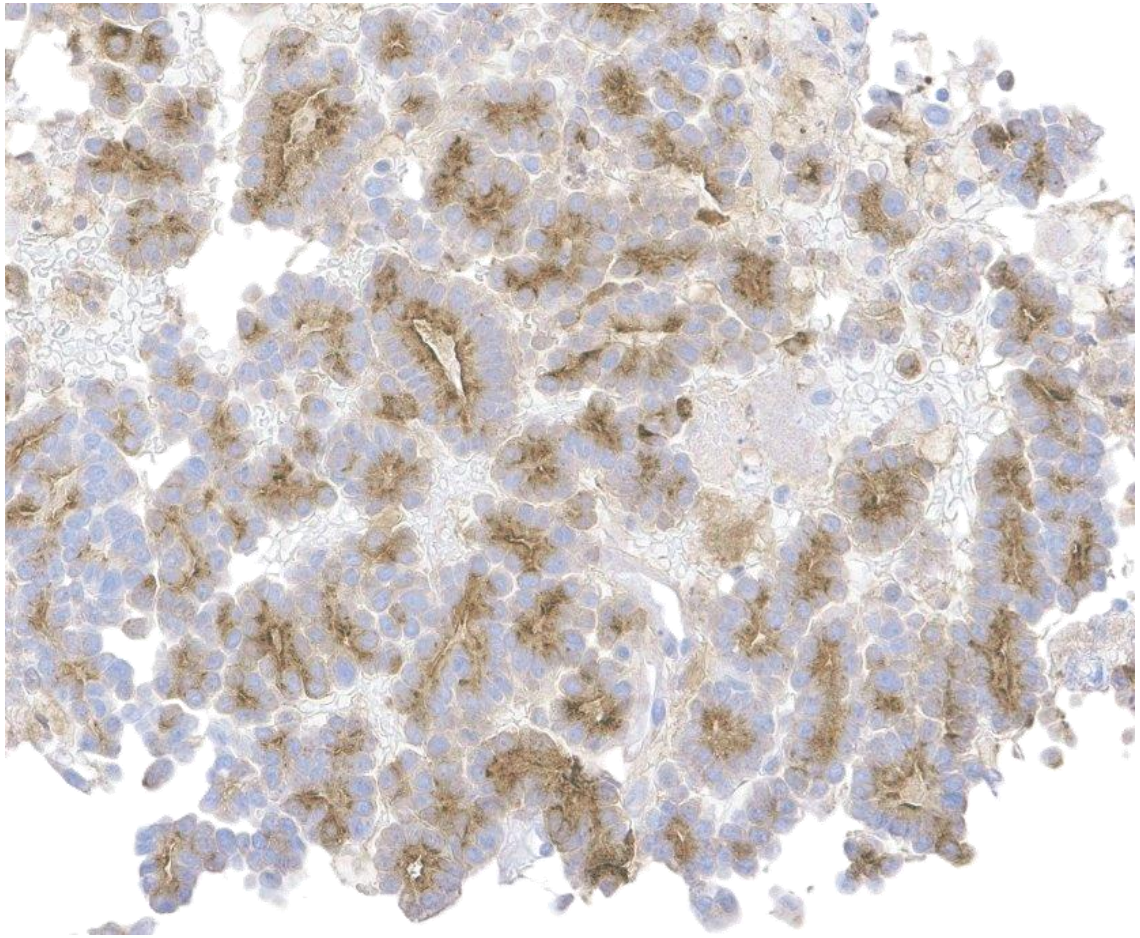




CAM 5.2



Trypsin



Dx

B. Pancreatic acinar cell carcinoma

IHC Panel	Result	Interpretation / Comment
HER2 (IHC)	Negative (Score 0)	No HER2 protein overexpression
MLH1, MSH2, MSH6, PMS2	Intact nuclear expression	Mismatch-repair (MMR) proficient
Trypsin	Positive	Supports pancreatic acinar differentiation
CK7	Positive	Favors pancreaticobiliary phenotype
CAM 5.2	Positive	Confirms epithelial nature of tumor
CDX2	Weak, focal positivity	
Synaptophysin	Negative	No neuroendocrine differentiation
Chromogranin	Negative	No neuroendocrine differentiation
Ki-67 (Proliferation Index)	~50% (in hotspots)	Indicates high proliferative activity

Clinical management

1. Treatment Plan

- Unresectable
- Current regimen: mFOLFIRINOX (targets both gastric carcinoma and pancreatic acinar cell carcinoma)

2. NGS / Molecular Testing

- Comprehensive molecular testing ordered
- Results pending to guide therapy and identify actionable mutations

3. Genetics Evaluation

- Genetic counseling recommended given dual primaries and age

A 45-year-old man with a past medical history of hypertension, hyperlipidemia, type 2 diabetes, and prior *H. pylori*–associated peptic ulcer disease presented with progressive nausea, vomiting, and severe weight loss. He had previously undergone dilation for gastric outlet obstruction and placement of a pyloric stent, which provided only transient symptom relief.

Imaging (CT Abdomen/Pelvis) revealed a 4.1 × 4.8 cm pancreatic tail mass with upstream ductal dilation, thickened pylorus with surrounding fat stranding, and suspicious gastrohepatic lymphadenopathy. Endoscopy/EUS showed severe pyloric stenosis (biopsied), a heterogeneous pancreatic tail mass, and an associated cystic lesion.

Pathology Findings:

- Gastric biopsy demonstrated poorly cohesive carcinoma with signet ring cells, confirmed by keratin CAM 5.2 highlighting infiltrative neoplastic single cells and poorly formed glands.
- Pancreatic tail biopsy showed acinar cell carcinoma, positive for CAM 5.2 and trypsin, supporting acinar differentiation.

Clinical Course & Management:
Given multifocal malignancy and evidence of metastatic disease on imaging, the patient was not a candidate for upfront resection. He underwent port placement and was initiated on mFOLFIRINOX to target both neoplasms.

Molecular and Genetic Workup:
Comprehensive NGS testing was ordered on both gastric and pancreatic specimens; results are pending to identify actionable mutations. The patient was also referred to genetic counseling due to his young age and synchronous dual primaries (gastric and pancreatic), and germline testing is currently pending.

Questions

A 39-year-old woman is diagnosed with poorly cohesive carcinoma (signet-ring cell type) on a stomach biopsy. Family history is significant for multiple relatives with early-onset gastric cancer. Which of the following molecular alterations is most implicated in hereditary forms of this tumor?

A) KRAS mutation
B) MLH1 promoter hypermethylation
C) CDH1 germline mutation
D) HER2 gene amplification

Answer: C

Explanation:

- Hereditary diffuse gastric cancer (HDGC) is strongly associated with germline mutations in CDH1 (E-cadherin gene).
- Loss of E-cadherin leads to discohesive, infiltrative growth of tumor cells and is a key feature of diffuse/PCC gastric carcinoma.

- KRAS mutations and HER2 amplification are characteristic of intestinal-type gastric adenocarcinoma, not PCC.
- MLH1 hypermethylation leads to MSI-high gastric cancers, which often have a medullary/lymphoid stroma phenotype and a better prognosis.
- Hereditary diffuse gastric cancer (HDGC) may warrant prophylactic total gastrectomy in affected families due to high penetrance and difficulty of early detection.

References:

1. WHO Classification of Digestive System Tumours, 5th Ed. (2019) – Gastric Adenocarcinoma.
2. Hansford S et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. *JAMA Oncol.* 2015;1(1):23–32.

A 58-year-old man presents with abdominal pain, 20-lb weight loss, and multiple tender subcutaneous nodules on his lower extremities. Imaging shows a 7 cm pancreatic mass. Biopsy shows a cellular neoplasm with granular eosinophilic cytoplasm and prominent nucleoli. What is the *most likely associated paraneoplastic finding* in this tumor type?

A) Severe hyperbilirubinemia with pruritus due to biliary obstruction
B) Marked hyperlipasemia with subcutaneous fat necrosis and polyarthritis
C) Elevated gastrin levels with multiple duodenal ulcers (Zollinger-Ellison)
D) Hyperglycemia due to pancreatic islet β-cell loss

Answer: B

Explanation:

- Lipase hypersecretion syndrome is a classic (though uncommon) paraneoplastic feature of acinar cell carcinoma (ACC).
- Presents with subcutaneous fat necrosis, polyarthritis, and eosinophilia — correlating with markedly elevated serum lipase.
- ACCs are typically large, well-circumscribed tumors with acinar differentiation (trypsin/chymotrypsin/BCL10 positive).
- Jaundice is uncommon because ACC more often arises in the body/tail than the head of pancreas.
- Gastrin elevation/Zollinger-Ellison is associated with gastrinomas (a type of PanNET), not ACC.

References:

- WHO Classification of Digestive System Tumours, 5th Edition (2019) – Pancreas, “Acinar Cell Carcinoma.”
- Nizam W, Shah AA, Rajack F, Ramdath A, Naab T, Williams M. Lipase hypersecretion syndrome: A rare cutaneous manifestation of advanced pancreatic acinar cell carcinoma. *Clin Case Rep*. 2020; 8: 905–910. **https://doi.org/10.1002/ccr3.2785**

Case of the month

November 2025

Hong Yu - PGY2, Dr. Roshan Raza, Dr. Celia Marginean

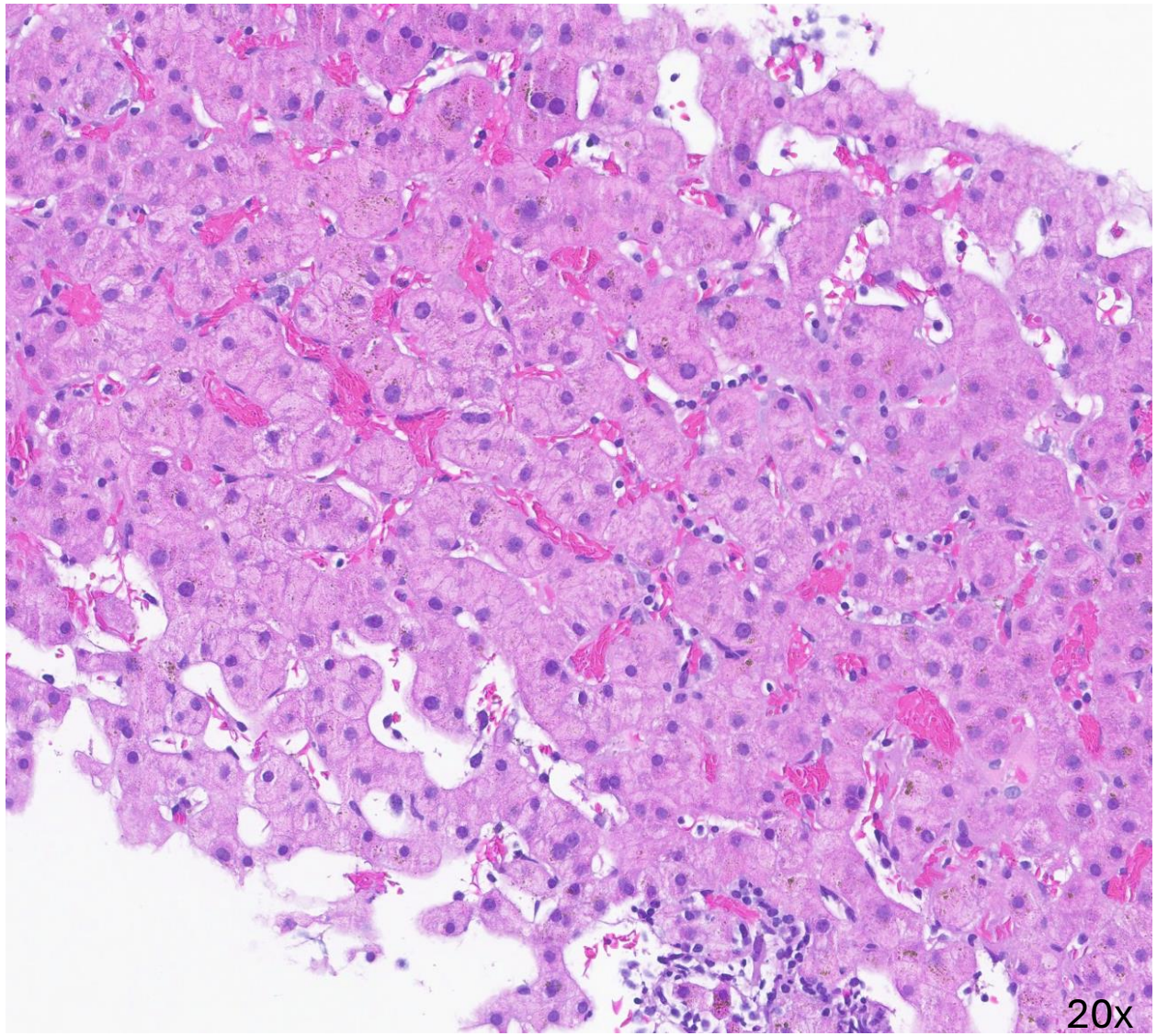
Case presentation

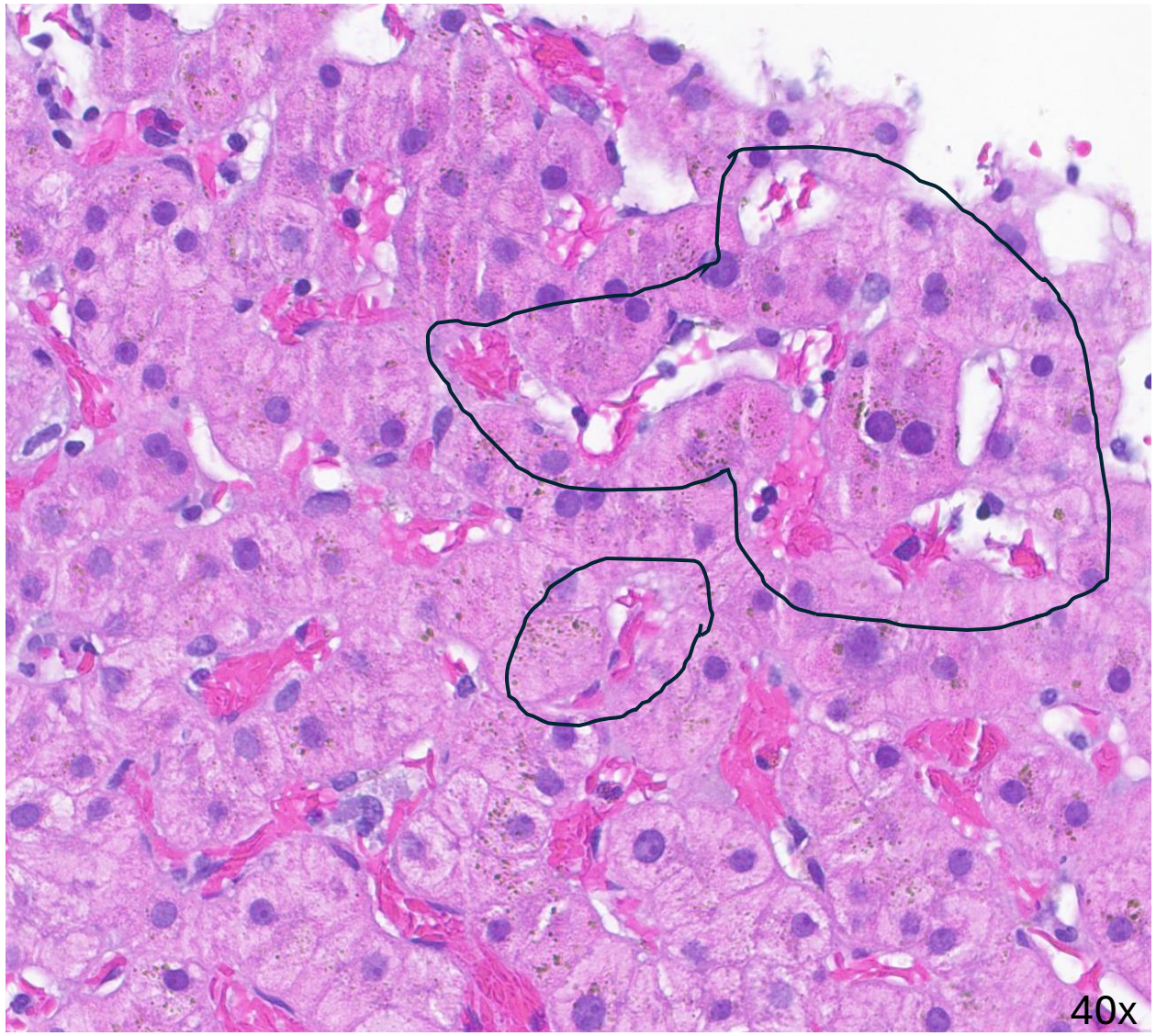
45-year-old male with sickle cell disease (frequent transfusions), ESRD on hemodialysis, and portopulmonary hypertension, evaluated for portal hypertension/cirrhosis. Alcohol: 4 tall beers daily ×7 years, quit 2001. Serologies: Hep A IgG reactive (07/2022); Hep B surface Ag: nonreactive.

MRI findings: significant hepatic iron overload, no cirrhotic morphology, no portal hypertension, and no focal hepatic lesions. Additional findings included an atrophic scarred spleen (consistent with sickle cell disease) and atrophic bilateral kidneys with acquired cystic changes.

Laboratory data: persistent elevation of liver function tests for several months, markedly high alkaline phosphatase (346-582 U/L), elevated total bilirubin (2.4-4.4 mg/dL, both direct and indirect fractions), mildly elevated AST (up to 78 U/L), normal ALT, and occasional hyperproteinemia.

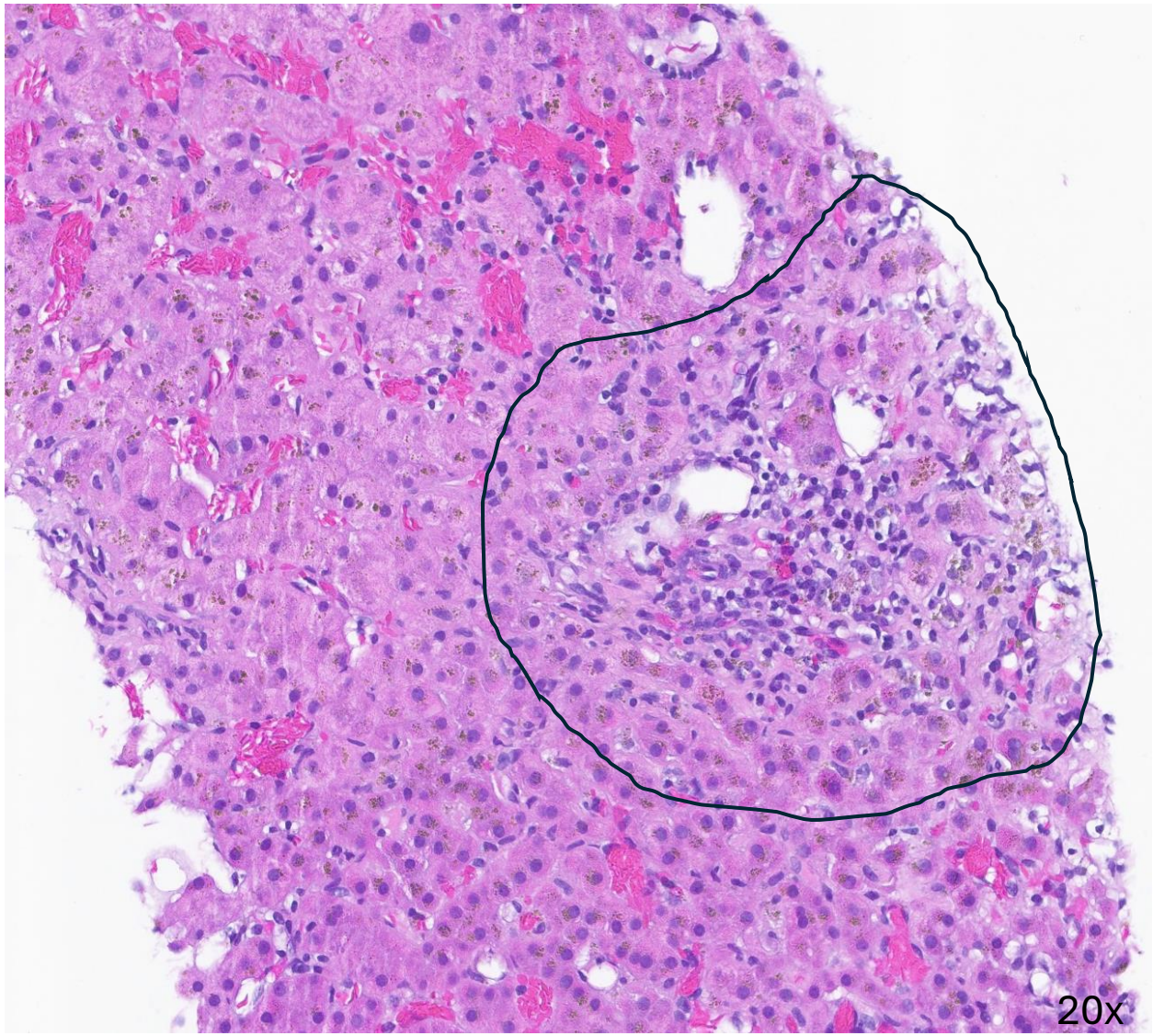
An ultrasound-guided transjugular liver core biopsy was performed.

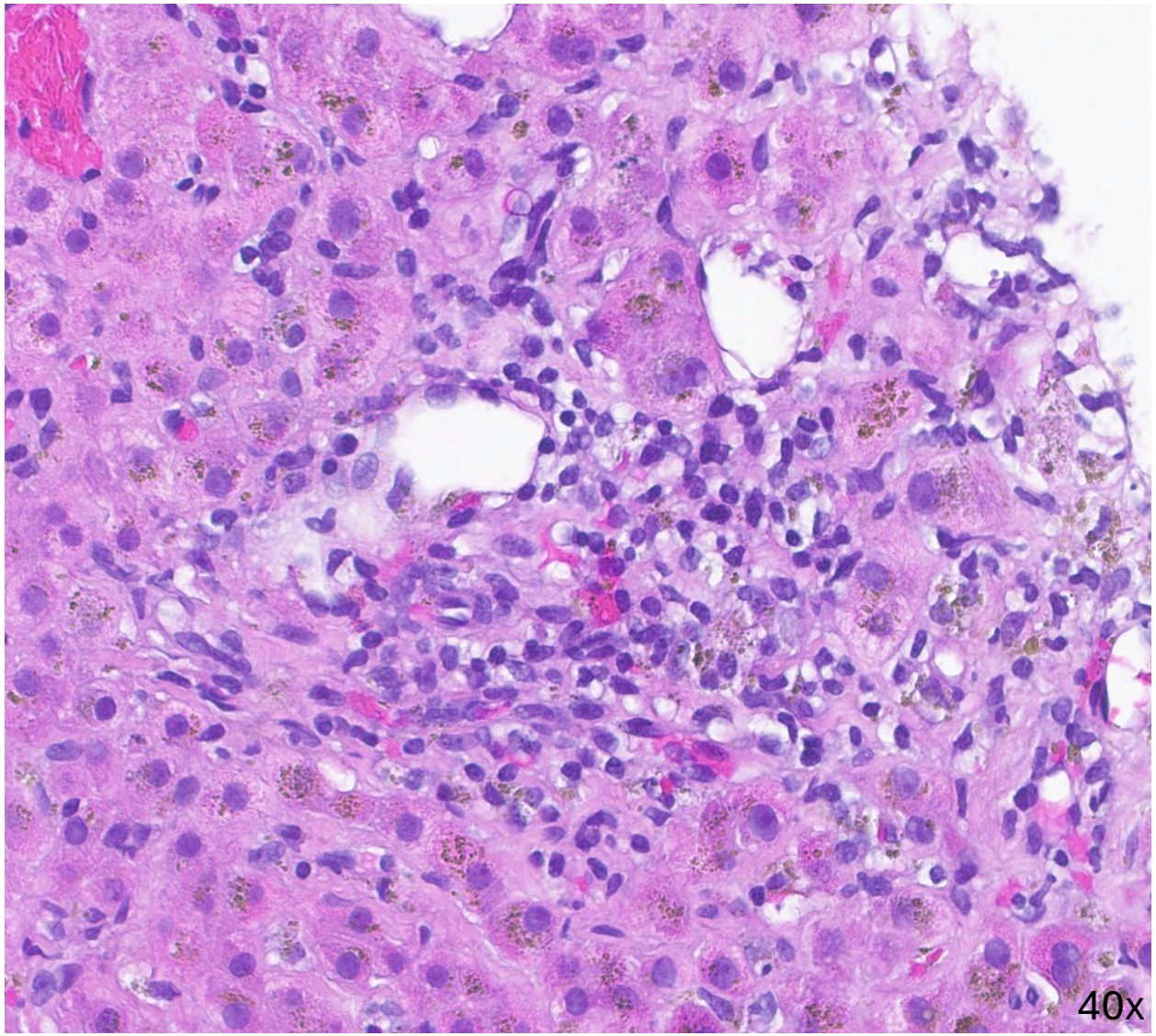




Histologic features:

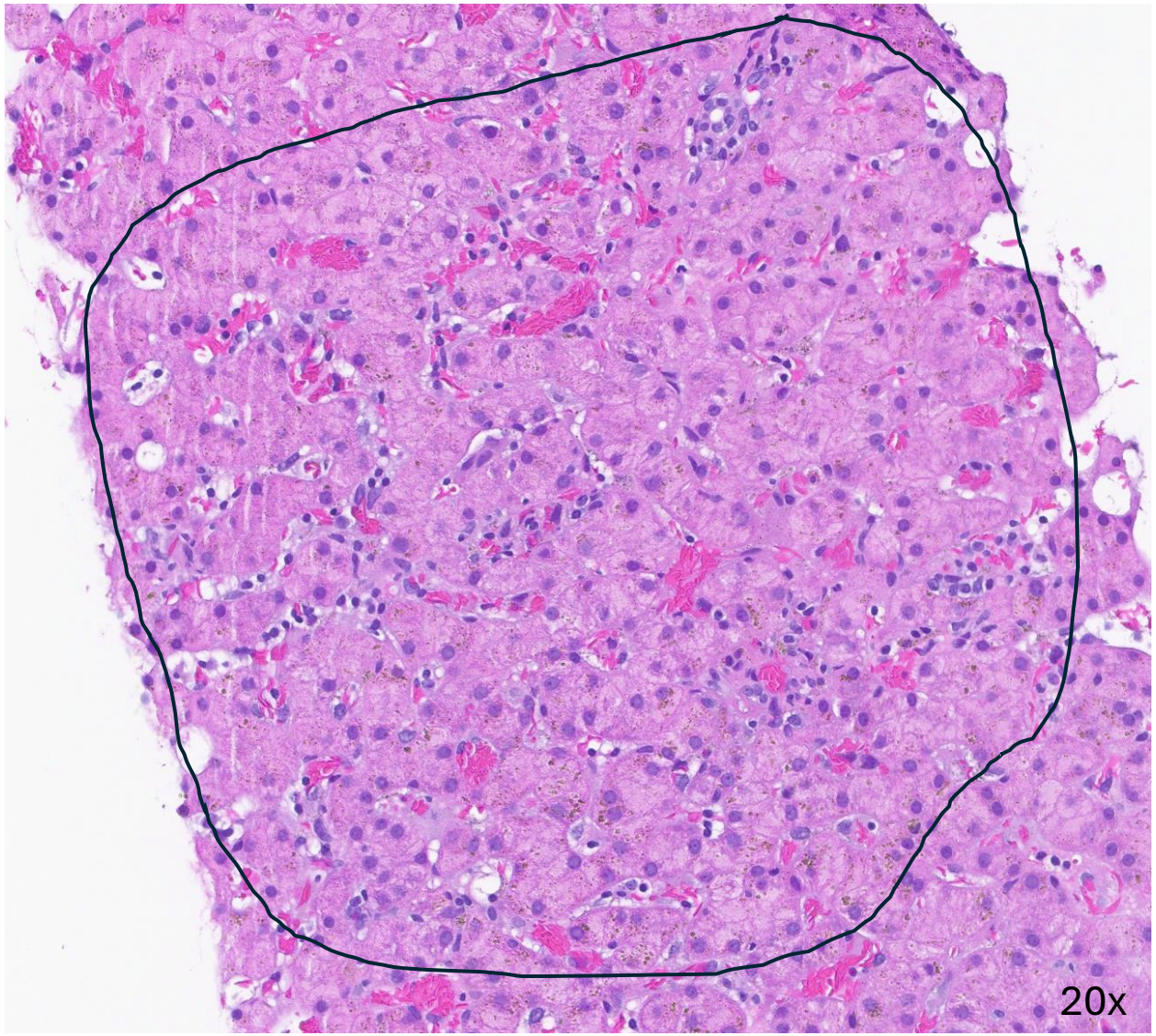
- Prominent sinusoidal dilation and congestion with sickled RBCs

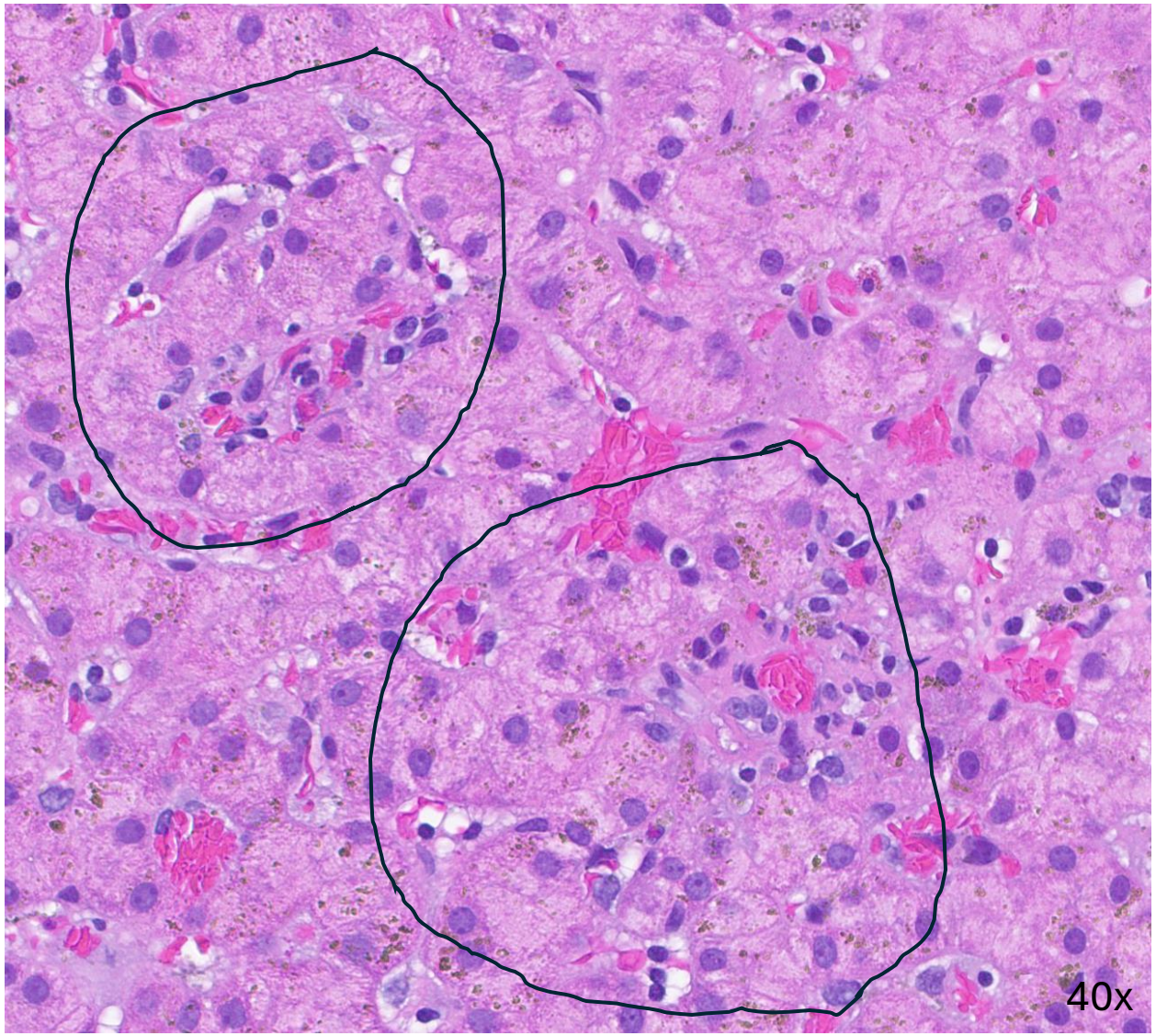




Histologic features:

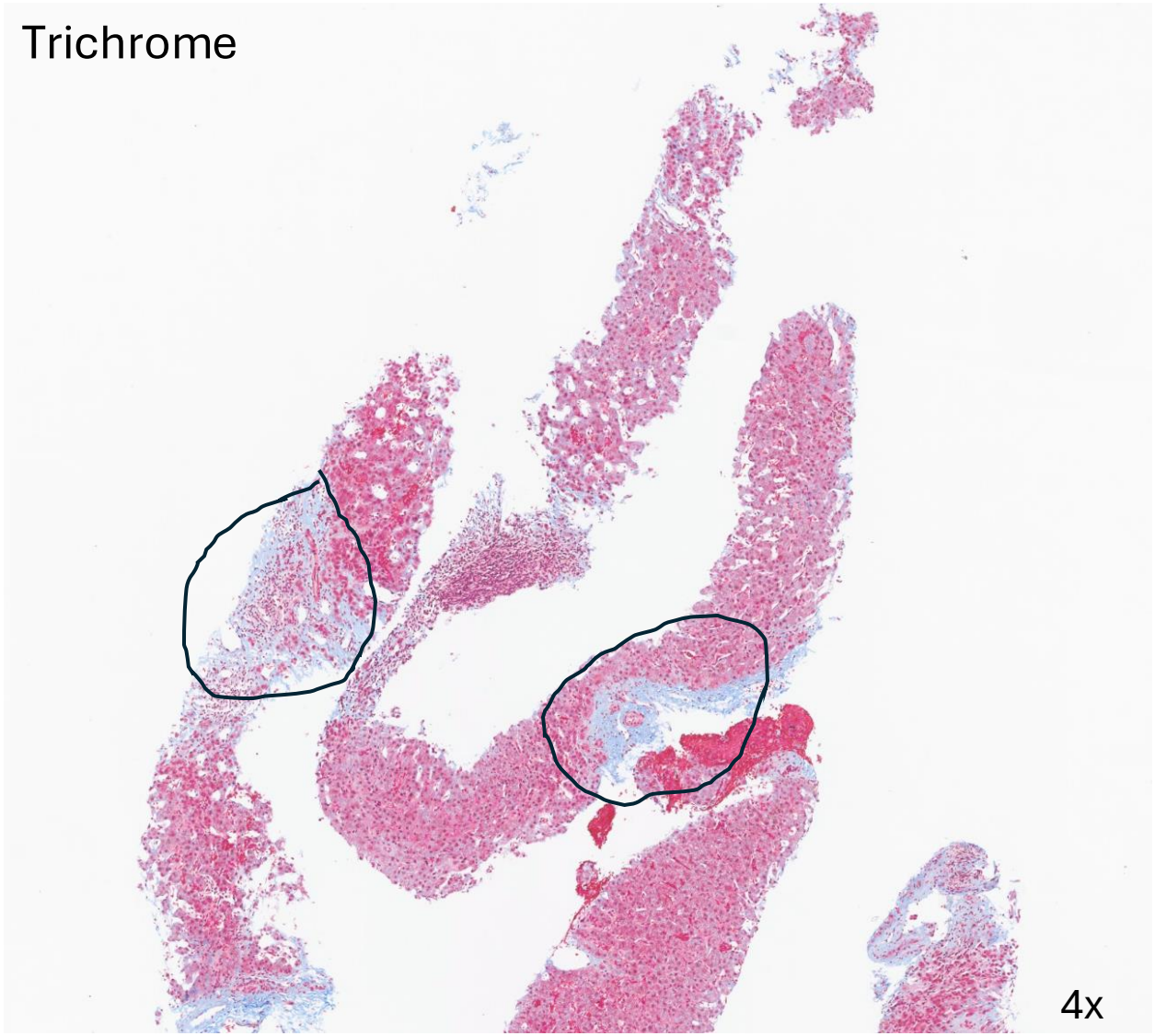
- Mild portal and lobular inflammation

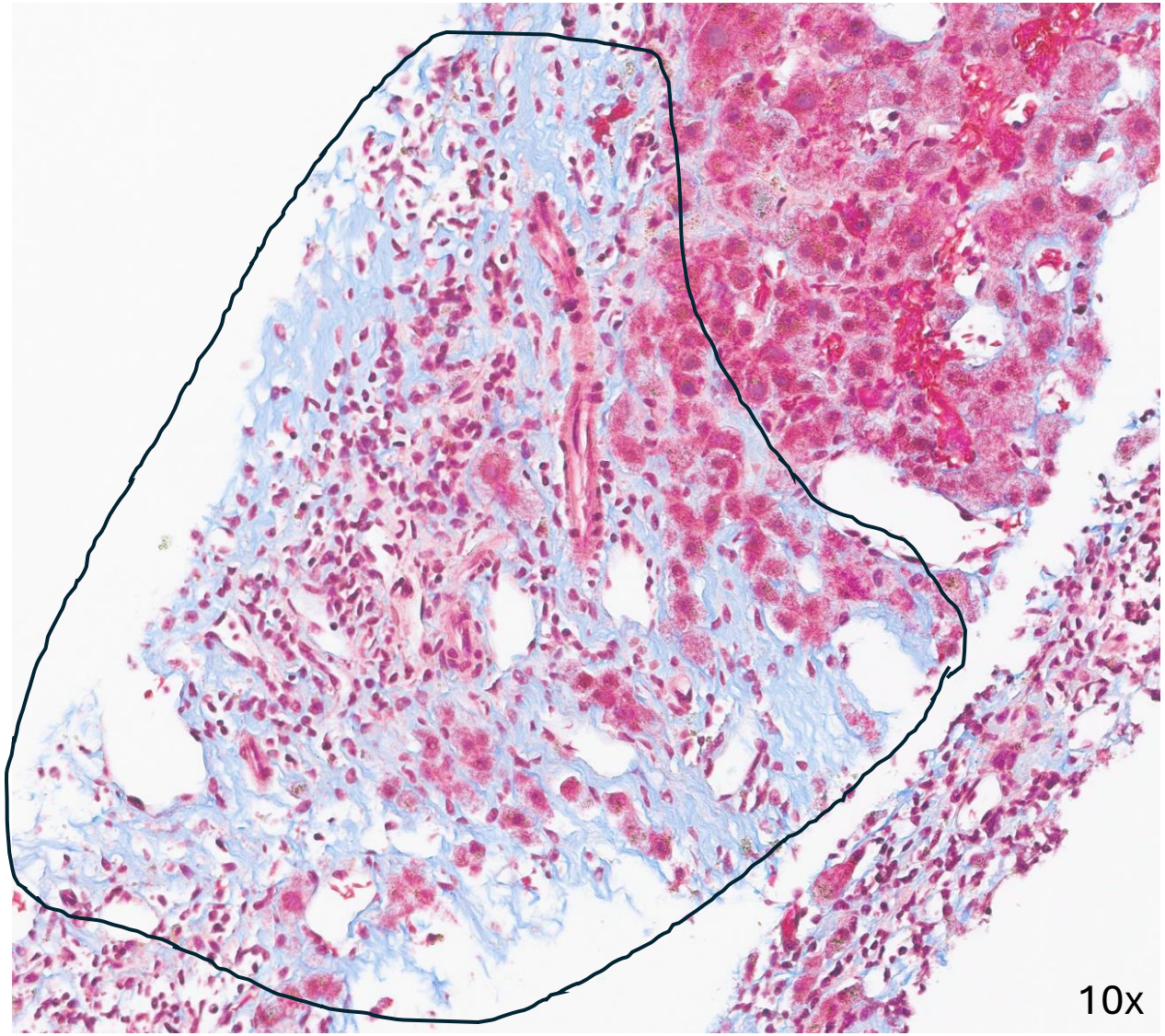




Histologic features:

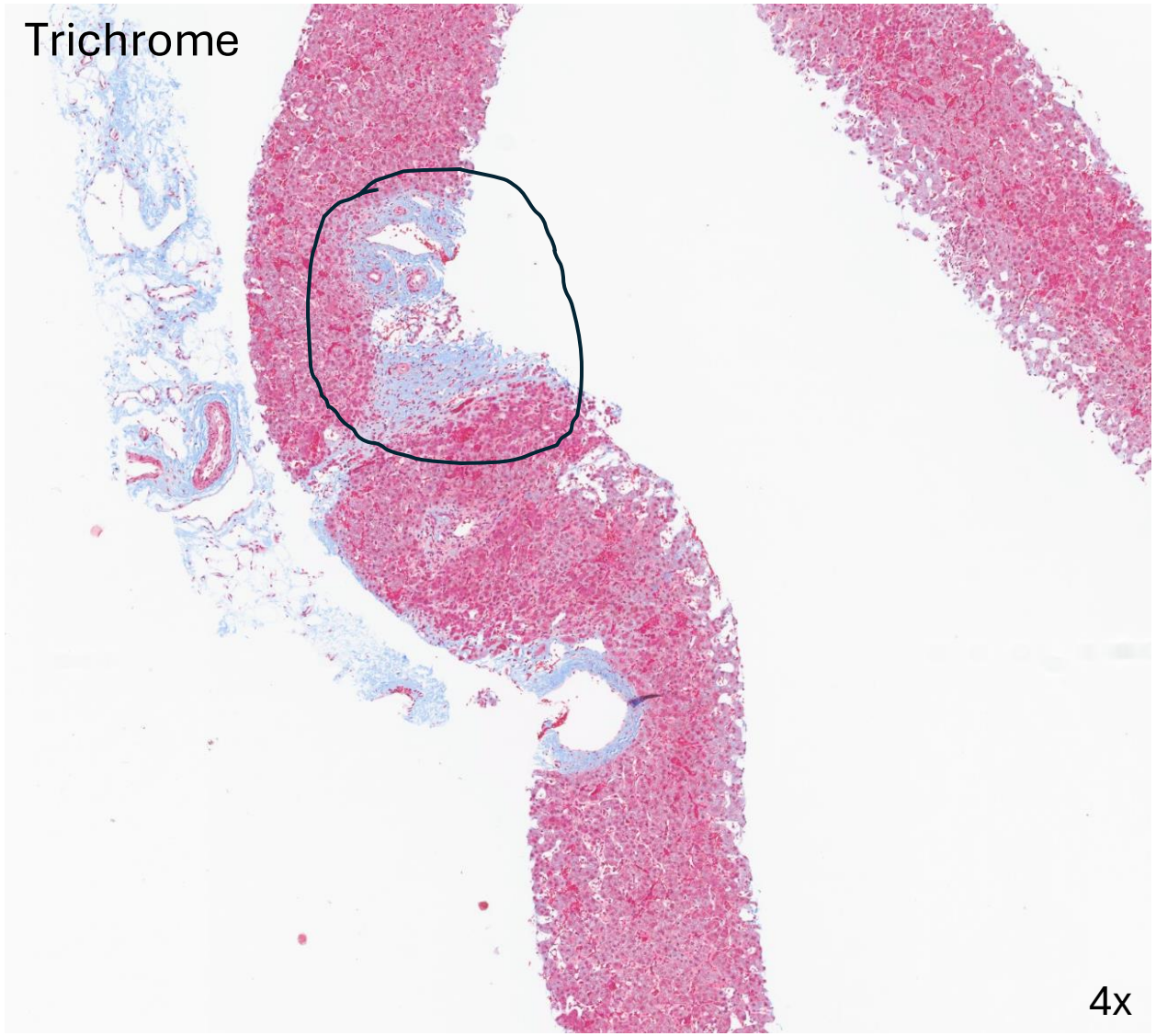
- Mild lobular inflammation

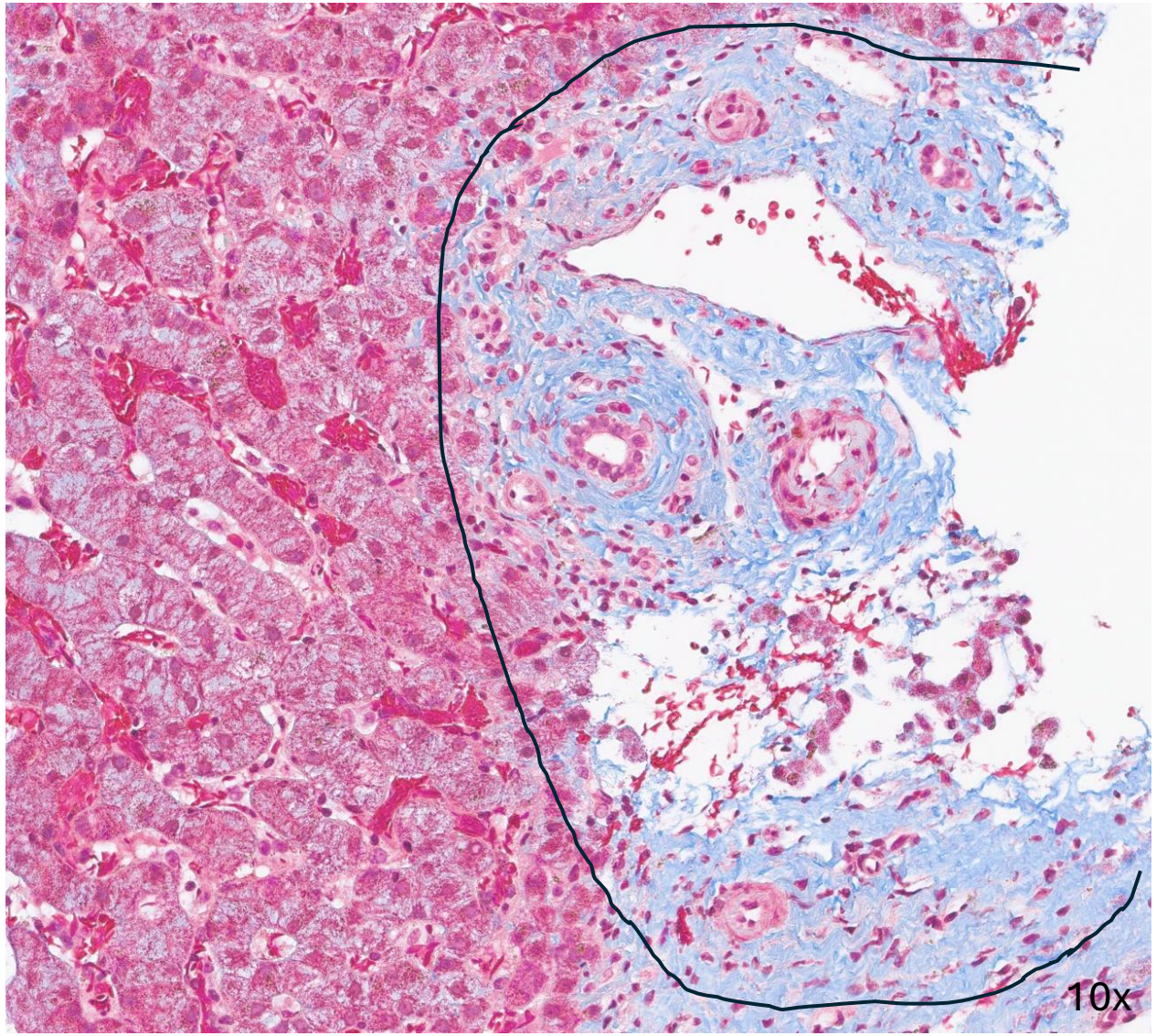




Special stains:

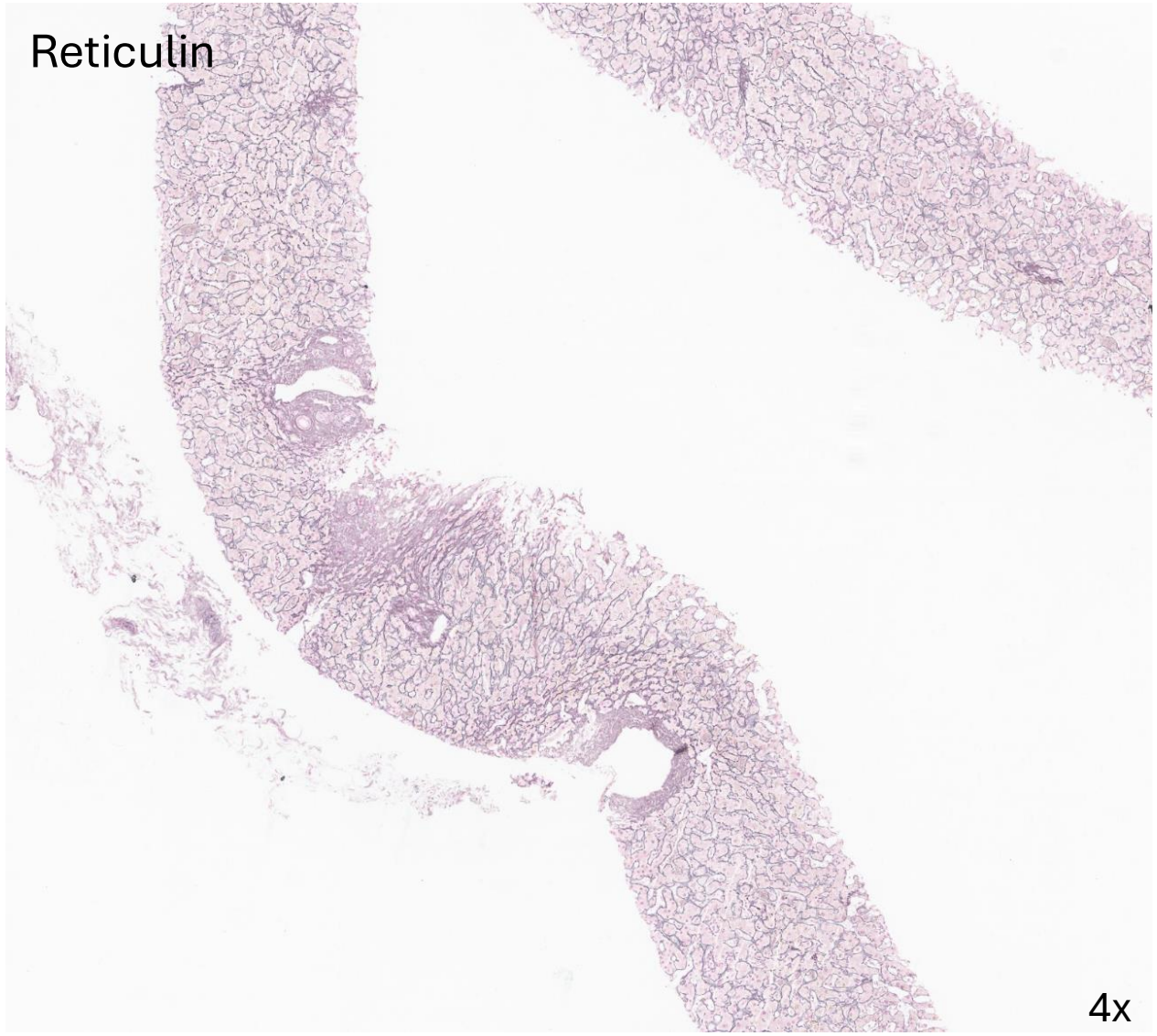
- Portal, periportal, and pericellular fibrosis (stage 2/4), no bridging fibrosis or cirrhosis

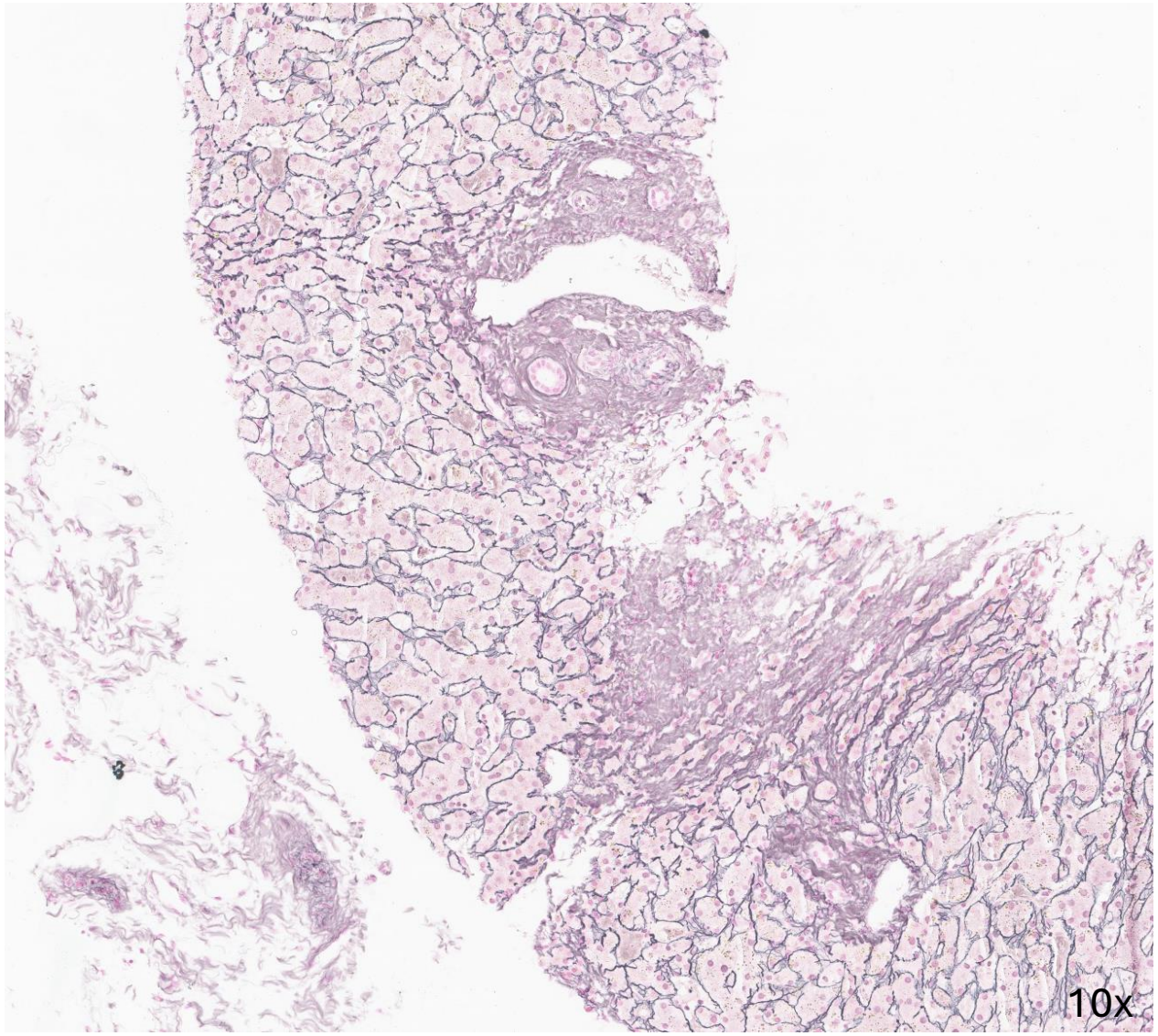




Special stains:

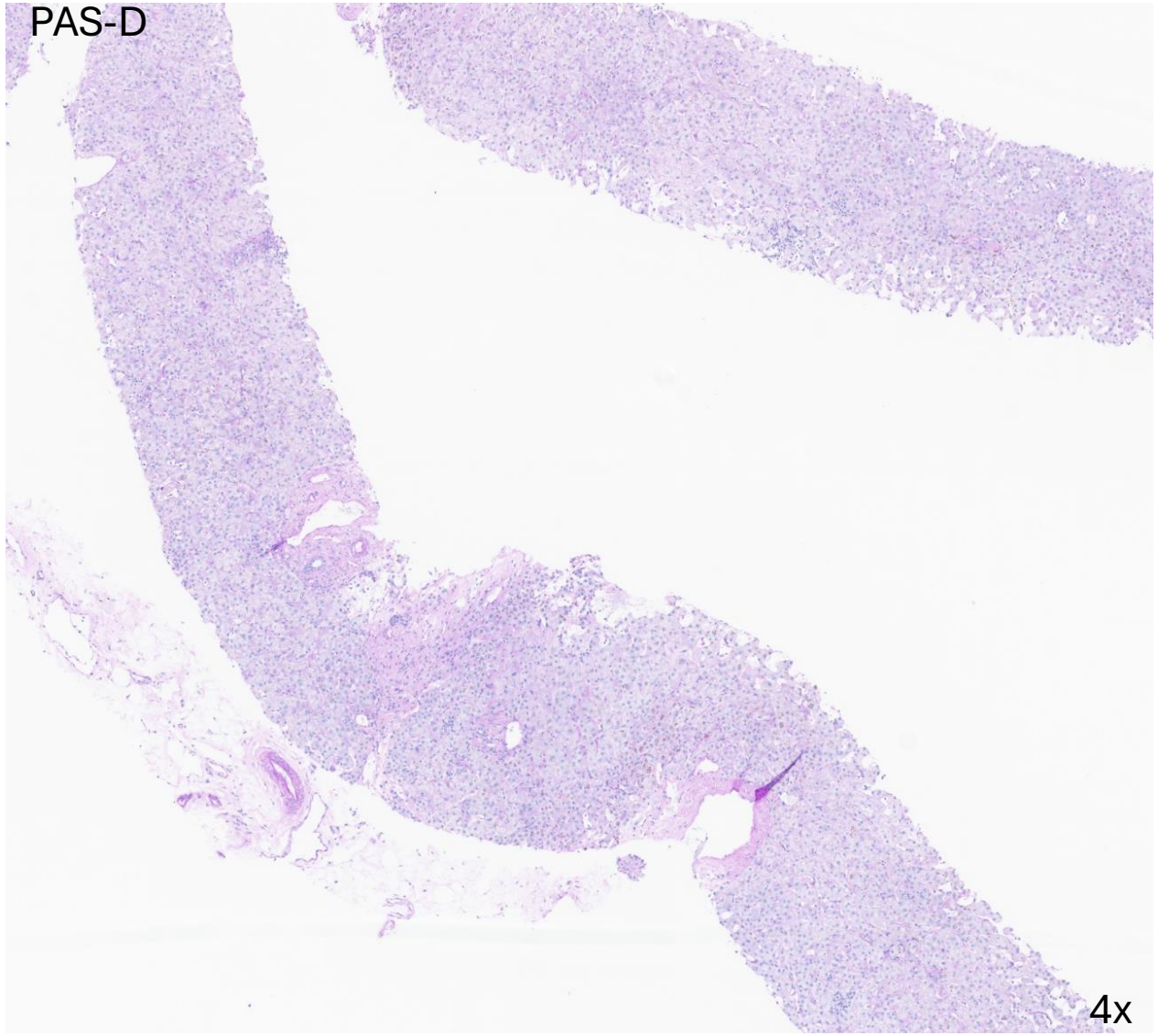
- Portal, periportal, and pericellular fibrosis (stage 2/4), no bridging fibrosis or cirrhosis

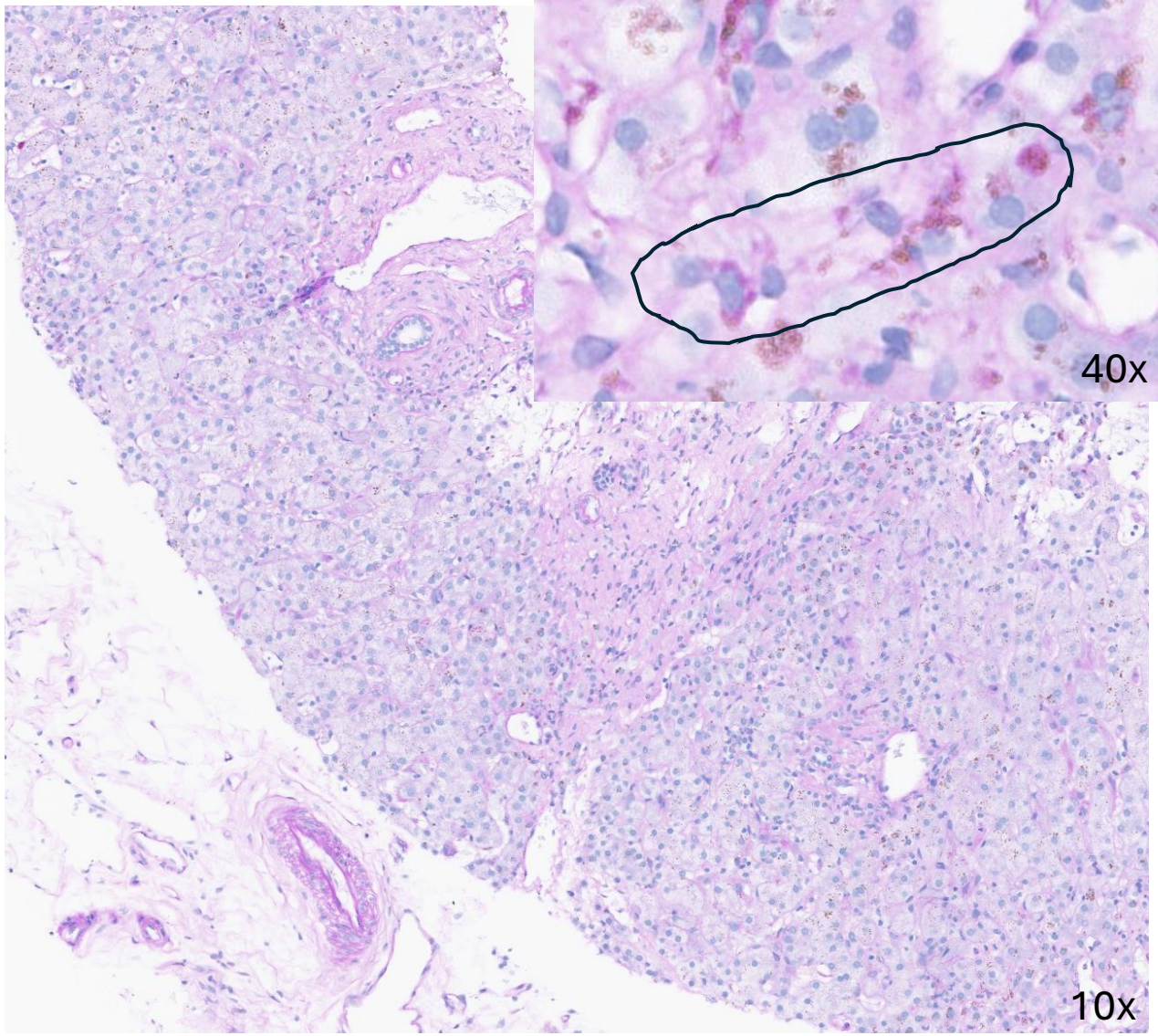




Special stains:

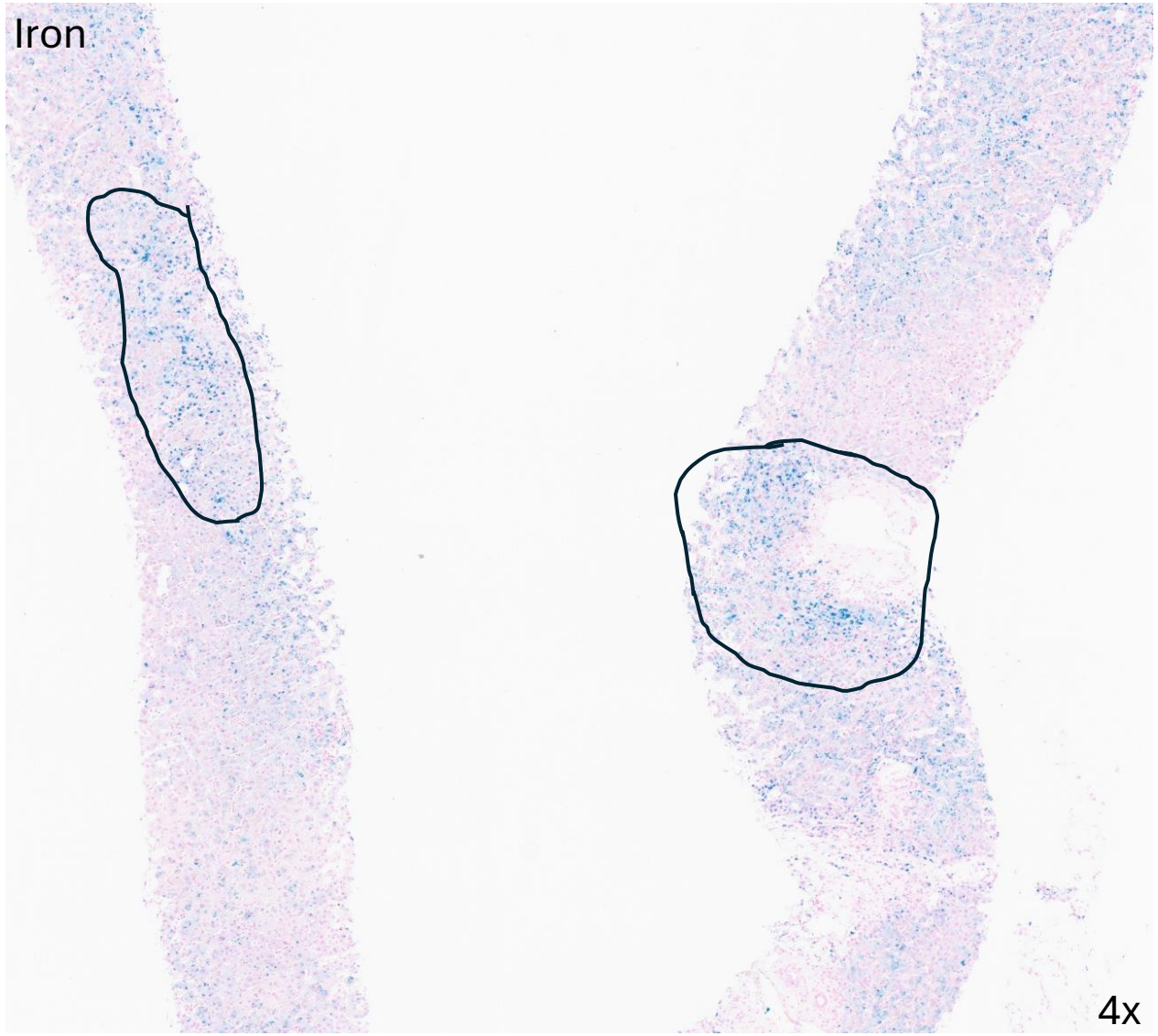
- Reticulin network remains intact, reflecting preserved tissue architecture

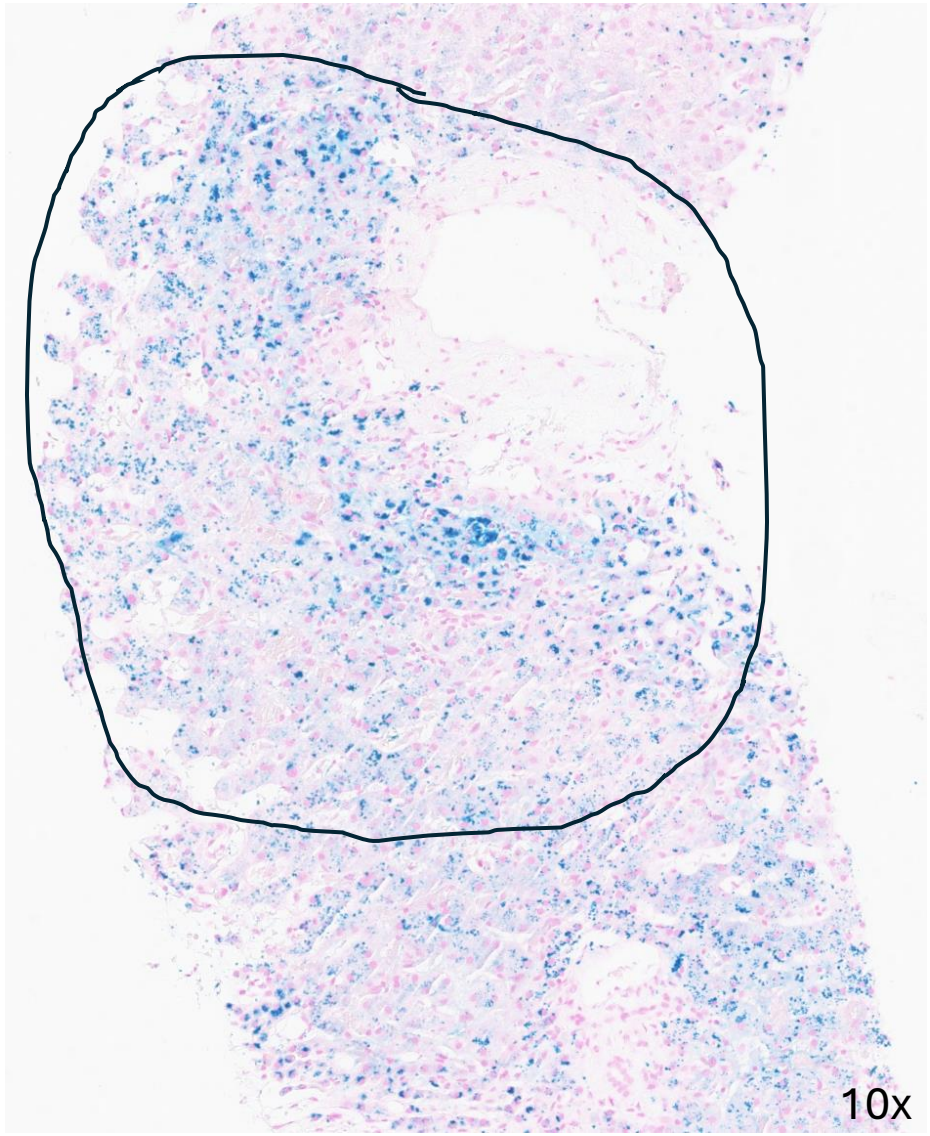




Special stains:

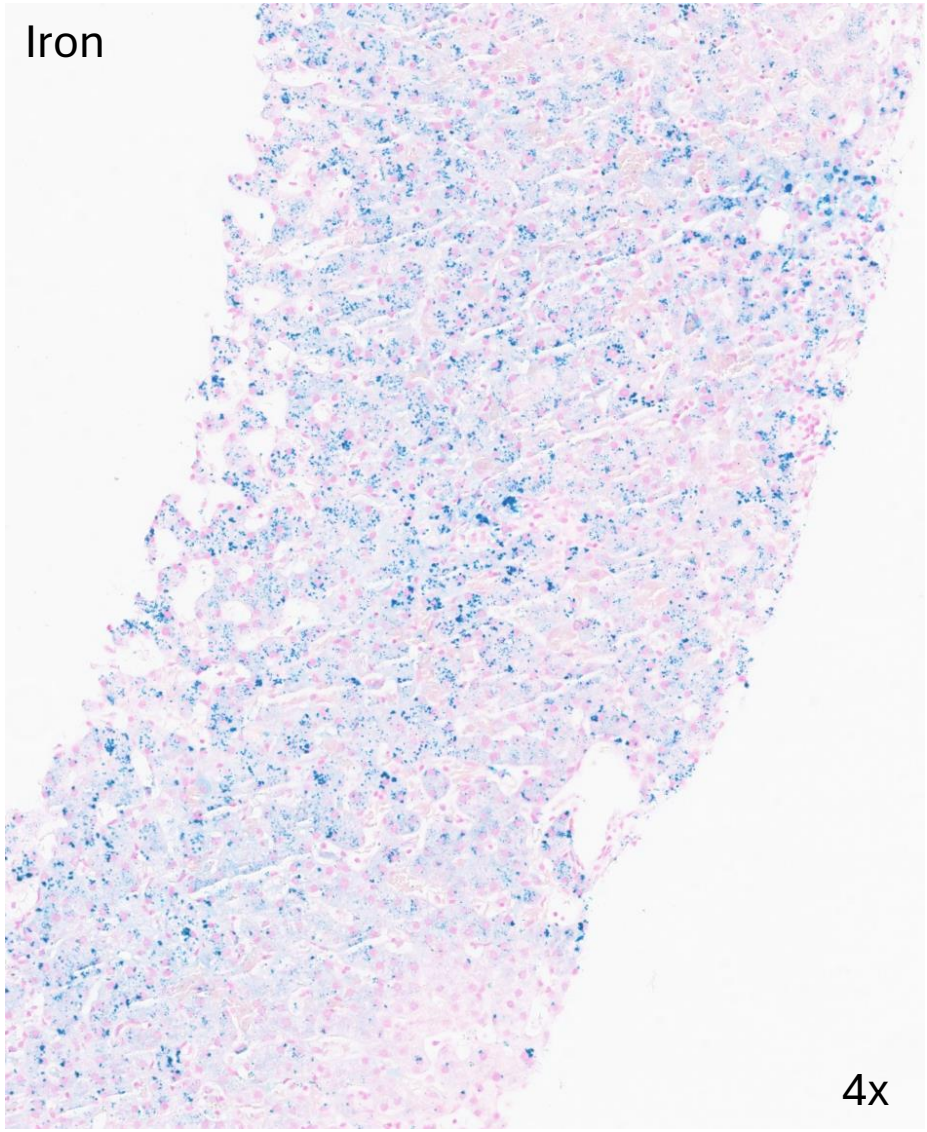
- PAS-D: highlights ceroid-laden macrophages

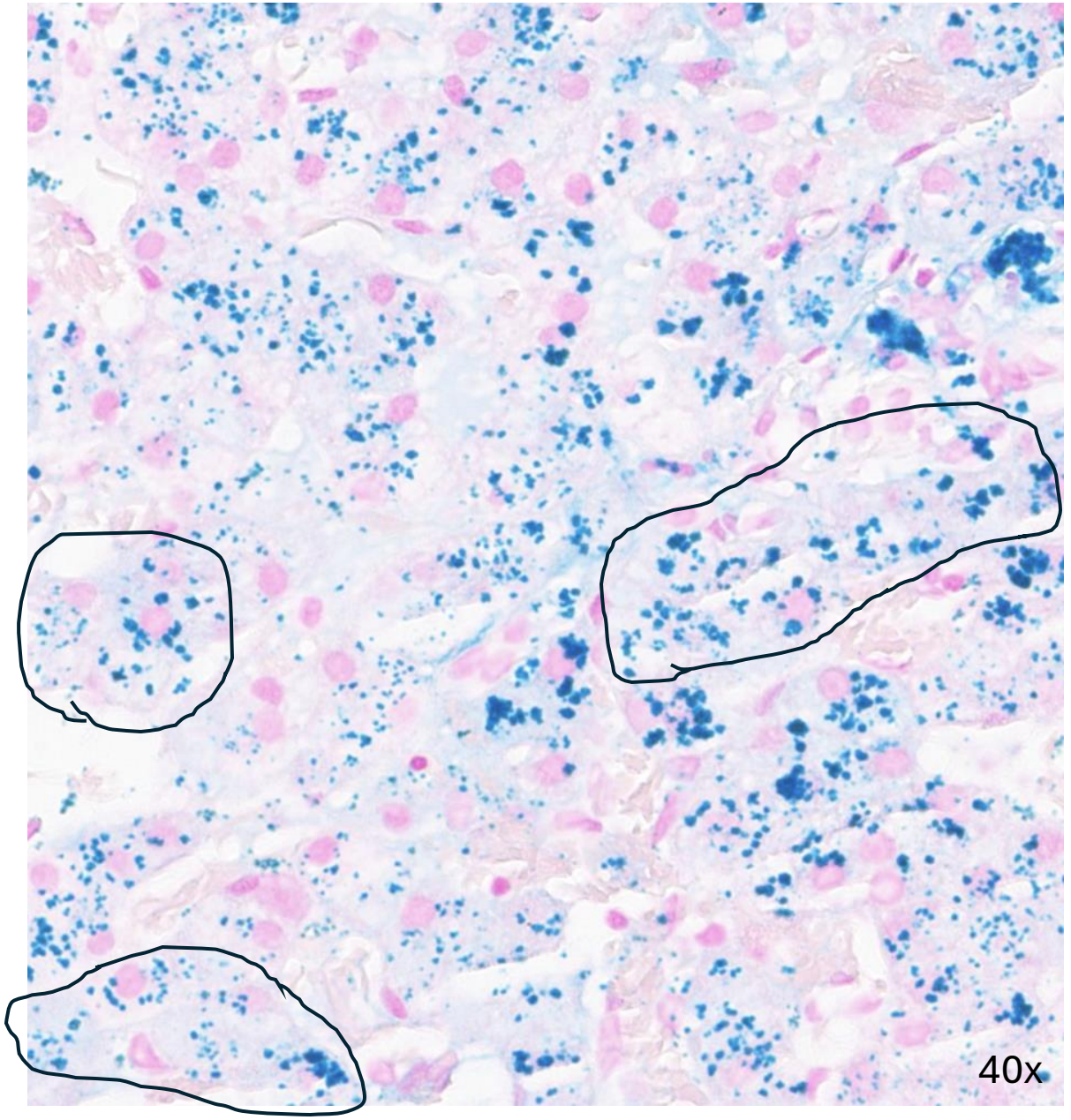




Special stains:

- Marked hepatocellular and reticuloendothelial iron deposition (3+)





Special stains:

- Marked hepatocellular and reticuloendothelial iron deposition (3+)

45-year-old male with sickle cell disease (frequent transfusions), ESRD on hemodialysis, and portopulmonary hypertension, evaluated for portal hypertension/cirrhosis. Alcohol: 4 tall beers daily ×7 years, quit 2001. Serologies: Hep A IgG reactive (07/2022); Hep B surface Ag: nonreactive.

MRI findings: significant hepatic iron overload, no cirrhotic morphology, no portal hypertension, and no focal hepatic lesions. Additional findings included an atrophic scarred spleen (consistent with sickle cell disease) and atrophic bilateral kidneys with acquired cystic changes.

Laboratory data: persistent elevation of liver function tests for several months, markedly high alkaline phosphatase (346-582 U/L), elevated total bilirubin (2.4-4.4 mg/dL, both direct and indirect fractions), mildly elevated AST (up to 78 U/L), normal ALT, and occasional hyperproteinemia.

An ultrasound-guided transjugular liver core biopsy was performed.

Q1. Which of the following is the most appropriate interpretation of the histology and special stains?

A. Significant iron overload likely secondary to transfusion therapy
B. Sickle cell hepatopathy with acute and chronic changes
C. Genetic hemochromatosis
D. Chronic viral hepatitis with superimposed iron deposition
E. Alcohol-associated or metabolic steatohepatitis with secondary siderosis

The best answer for Question 1 is B. Sickle cell hepatopathy with acute and chronic changes, because the histology demonstrates classic features of this condition: prominent sinusoidal dilation and congestion with sickled red blood cells, mild portal and lobular inflammation, and portal/pericellular fibrosis without bridging fibrosis or cirrhosis. These findings, combined with preserved architecture on reticulin stain, strongly indicate sickle cell hepatopathy rather than other chronic liver diseases. A (Significant iron overload likely secondary to transfusion therapy), while present, is a secondary process and not the primary interpretation of the biopsy. C (Genetic hemochromatosis) is incorrect because iron deposition involves both hepatocytes and reticuloendothelial cells, which is typical of transfusion-related overload, not genetic hemochromatosis. D (Chronic viral hepatitis) is excluded due to the absence of interface hepatitis, lymphoplasmacytic infiltrate, or bridging fibrosis. E (Alcohol-associated or metabolic steatohepatitis) is ruled out because there is no steatosis, ballooning degeneration, Mallory-Denk bodies, or neutrophilic infiltrate. Thus, the dominant process is sickle cell hepatopathy with chronic remodeling and acute vaso-occlusive changes.

Overview of sickle cell hepatopathy

Sickle cell hepatopathy refers to the spectrum of acute and chronic liver dysfunctions in patients with sickle cell disease (SCD), encompassing hepatobiliary complications directly related to SCD pathophysiology. These include acute hepatic crisis, hepatic sequestration, intrahepatic

cholestasis, chronic liver injury, and, in advanced cases, fibrosis or cirrhosis. The underlying mechanisms involve recurrent vaso-occlusion, hemolysis, and ischemia from sickled erythrocytes, causing hepatocellular injury, sinusoidal congestion, and impaired bile flow. Histologically, it is characterized by sinusoidal dilatation, intrasinusoidal sickled RBCs, Kupffer cell erythrophagocytosis, and hemosiderosis, usually with minimal inflammation. Clinically, presentations range from asymptomatic enzyme elevations to severe jaundice, right upper quadrant pain, and rarely acute liver failure. Chronic forms often progress to fibrosis or cirrhosis, exacerbated by repeated hepatic crises, transfusional iron overload, and ongoing hemolysis. Diagnosis requires exclusion of other liver diseases and consideration of SCD-specific complications such as gallstones and iron overload. In short, sickle cell hepatopathy encompasses any hepatobiliary dysfunction in SCD, driven by its unique vascular and hemolytic pathology.

Q2. It is important to recognize that patients with sickle cell disease frequently exhibit features of porto-sinusoidal vascular disease (PSVD). Which histologic finding is considered specific for PSVD?

A. Nonzonal sinusoidal dilatation
B. Portal vein stenosis
C. Mild perisinusoidal fibrosis
D. Increased number of arteries in portal tracts
E. Periportal abnormal vessels

The best answer is B. Portal vein stenosis, because this finding, defined as luminal narrowing or obliteration of portal vein branches, sometimes with fibrotic portal tracts, is considered a hallmark and specific histologic feature of PSVD. It reflects the underlying microvascular remodeling that characterizes this disease and helps distinguish PSVD from other vascular or sinusoidal disorders. A (Nonzonal sinusoidal dilatation) is nonspecific, as it can occur in congestive hepatopathy, sickle cell hepatopathy, or drug-induced injury. C (Mild perisinusoidal fibrosis) is also nonspecific and commonly seen in chronic liver diseases such as metabolic dysfunction-associated steatohepatitis or alcohol-related injury. D (Increased number of arteries in portal tracts) and E (periportal abnormal vessels) represent vascular abnormalities that may accompany PSVD but are not diagnostic on their own, as they can be seen in other conditions with portal tract remodeling.

Diagnostic criteria of PVSD

PSVD diagnosis requires either 1) specific histological features, such as nodular regenerative hyperplasia, obliterative portal venopathy, incomplete septal fibrosis/cirrhosis, or characteristic microvascular changes (e.g., sinusoidal dilatation, herniated portal veins, hypervascularized portal tracts), with or without clinical signs of portal hypertension, or 2) clinical signs of portal hypertension (e.g., varices, splenomegaly, ascites) in the absence of cirrhosis, supported by suggestive histology or imaging findings. In sickle cell disease, nearly all liver biopsies show at least one PSVD feature, and over 90% meet diagnostic criteria, with immunohistochemical markers (aberrant CD34, von Willebrand factor staining) supporting diagnosis.

Clinical significance and prognosis

PSVD in sickle cell hepatopathy is associated with an increased risk of portal hypertension and its complications (variceal bleeding, ascites, portal vein thrombosis), even in the absence of cirrhosis. Prognosis is determined by the severity of portal hypertension and underlying conditions; most patients have good transplant-free survival when managed at expert centers, but severe associated conditions, ascites, and abnormal liver/renal function predict worse outcomes. Management focuses on surveillance and treatment of portal hypertension complications, as disease-modifying therapies are lacking.

References

1. Banerjee S, Owen C, Chopra S. Sickle Cell Hepatopathy. *Hepatology*. 2001;33(5):1311-1318.
2. Saeed O, Panarelli N, Umrau K, et al. Histopathologic Features of Sickle Cell Hepatopathy: A Multi-Institutional Study. *Am J Clin Pathol*. 2022;157(1):73-81.
3. Suddle AR. Management of liver complications in sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):345-350.
4. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. *World J Gastrointest Pathophysiol*. 2017;8(3):108-116.
5. Lacaille F, Allali S, de Montalembert M. The Liver in Sickle Cell Disease. *J Pediatr Gastroenterol Nutr*. 2021;72(1):5-10
6. Schouten JN, et al. Porto-sinusoidal vascular disease: A clinical update. *J Hepatol*. 2022;77:1124-1136
7. International Liver Pathology Study Group. Consensus on histologic features of PSVD. *Histopathology*. 2019;74:219-229
8. De Gottardi A, et al. Porto-sinusoidal vascular disease: Pathogenesis and management. *Lancet Gastroenterol Hepatol*. 2019;4:399-411
9. Clinical implications of PSVD. *Liver Int*. 2025;45:e16196

GI Case of the Month

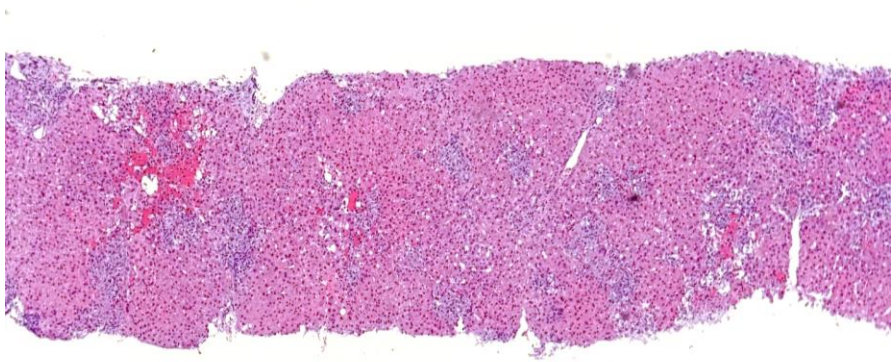
December 2025

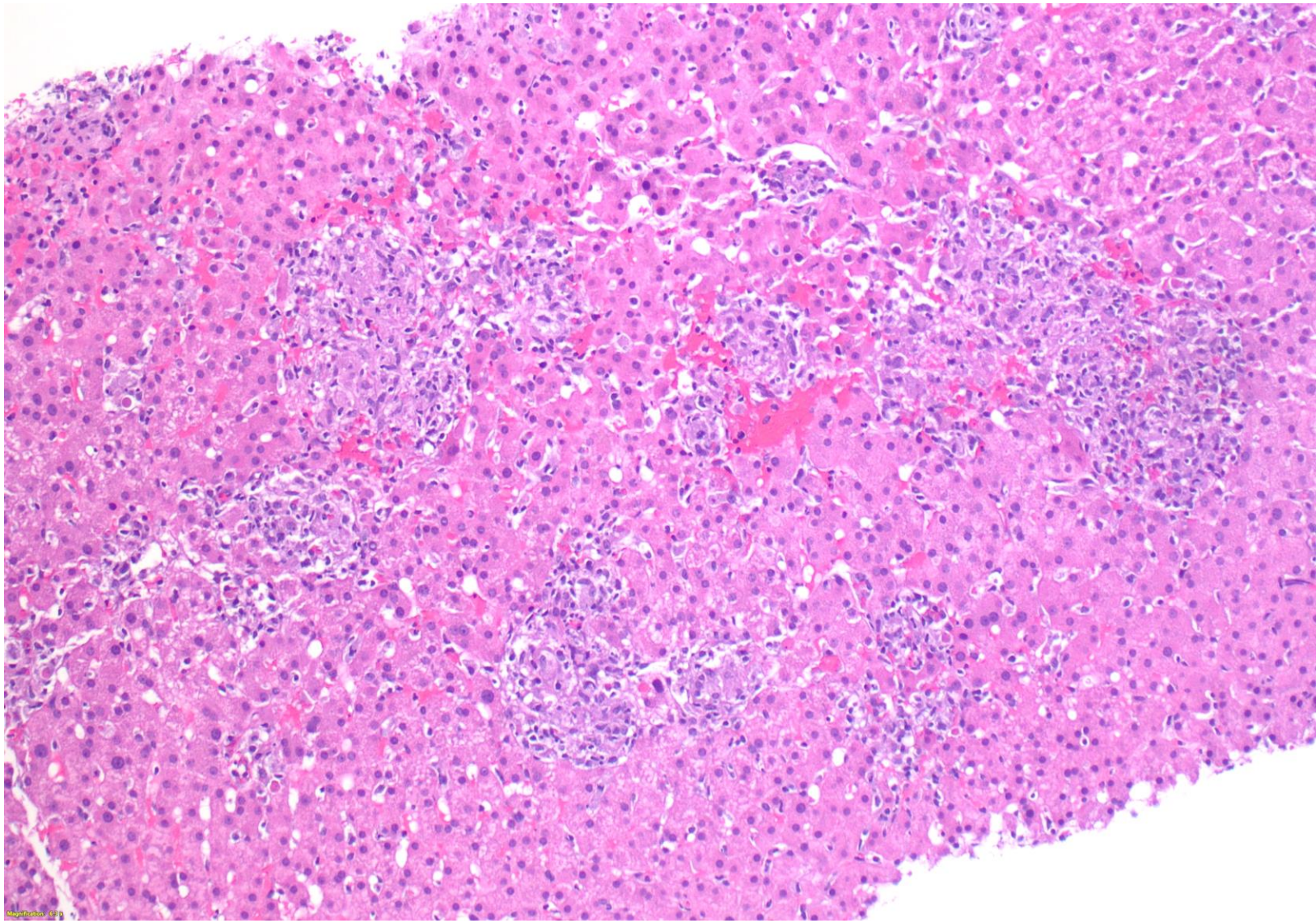
Dr. Celia Marginean, MD (Professor, Director of GI/Liver fellowship)

Dorsay Sadeghian, MD (Resident, PGY3)

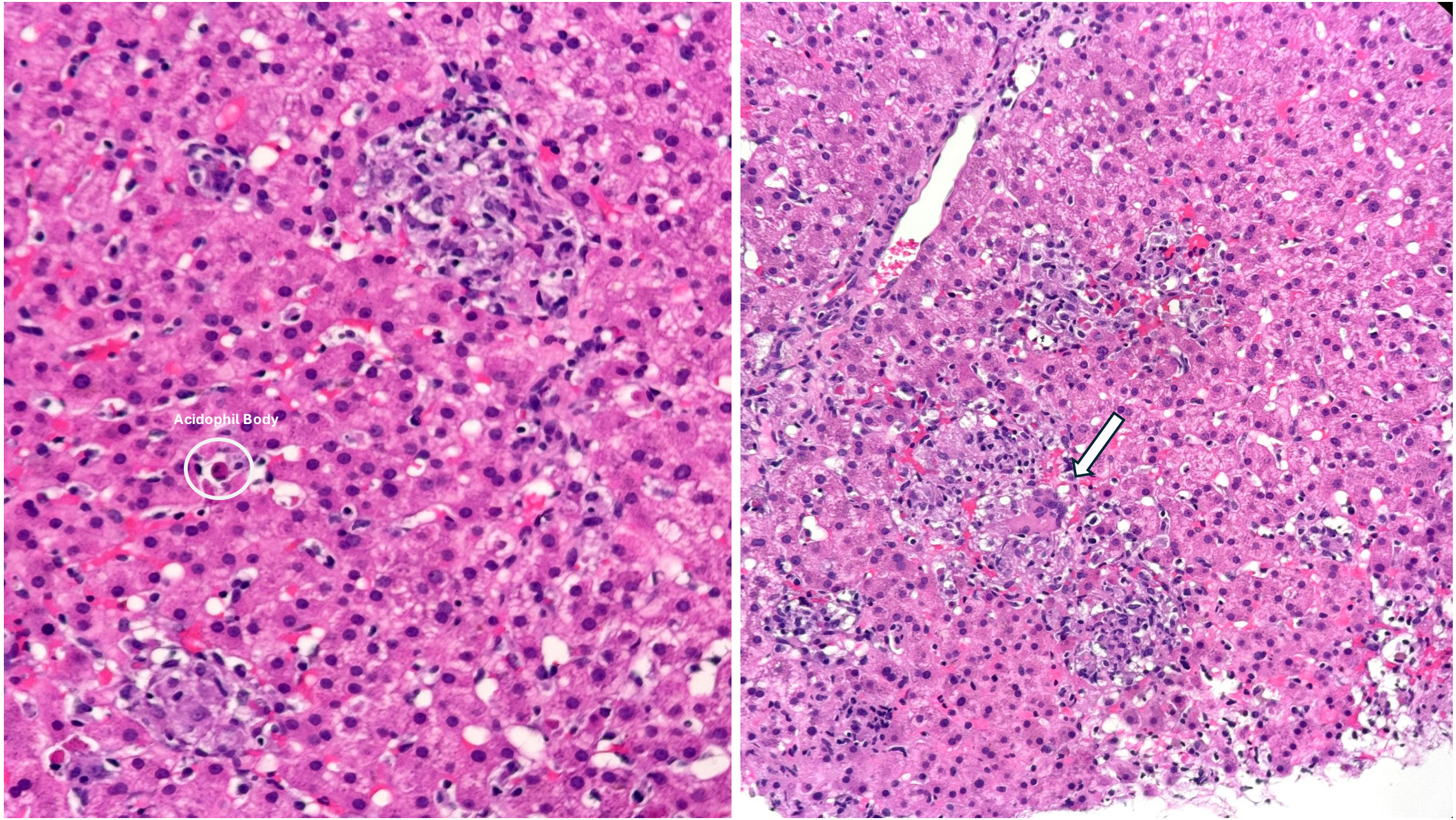
Clinical History:

- The patient is a 59 y.o. female with history of Metabolic Associated Liver Disease (MALD), progressed to liver cirrhosis, who underwent orthotopic liver transplant in May 2025.
- Four months after the transplantation, she presented with fatigue, weakness and altered mental status.
- Lab work up showed elevated AST: 650 U/L and ALT: 594 U/L, as well as leukopenia. ALP and bilirubin levels were unremarkable.
- Liver ultrasound revealed intrahepatic bile ducts and common bile duct dilatation.
- Chest CT scan revealed right pleural effusion with adjacent consolidation. Several nodules measuring up to 8 mm were noted in the right lung.
- Broad spectrum antibiotics was started for her, and she underwent liver percutaneous biopsy for further investigation.

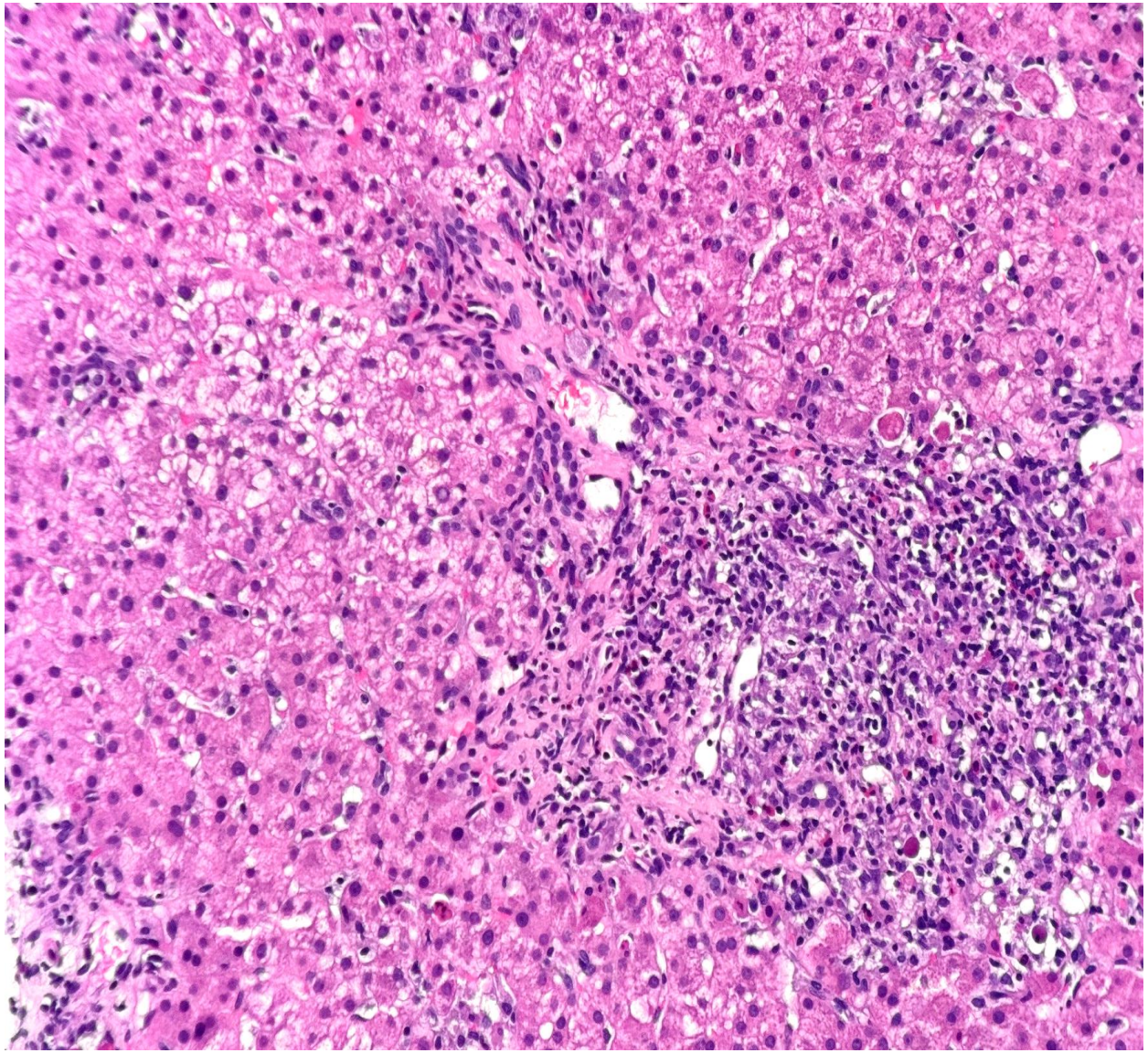


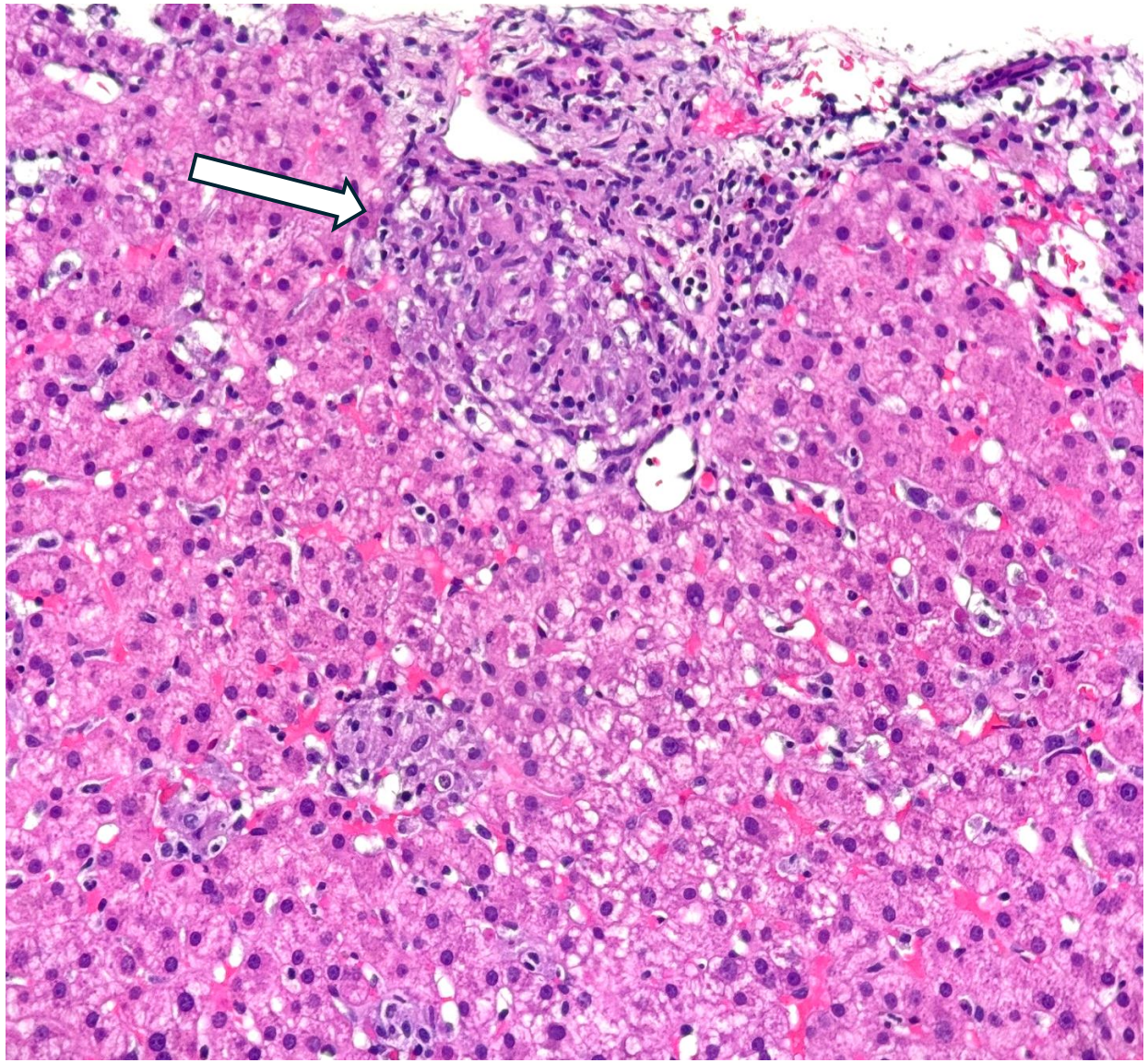


The liver biopsy shows numerous non-necrotizing lobular and portal granulomas in various sizes.



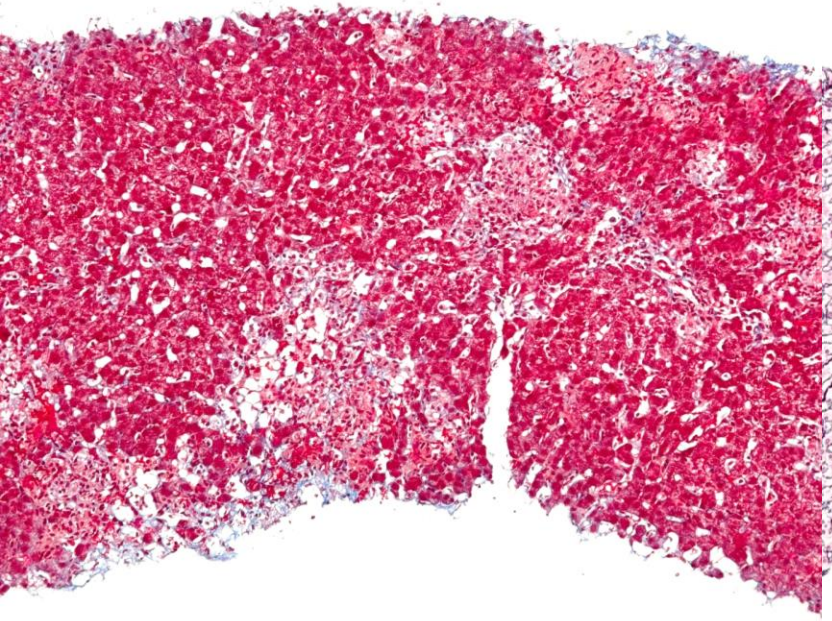
High power view shows variable size non-necrotizing granulomas, some coalescing, and a few are centered by multinucleated giant cells (arrow). Mild to moderate lobular inflammation, as well as acidophil bodies (necrotic hepatocytes) are present .



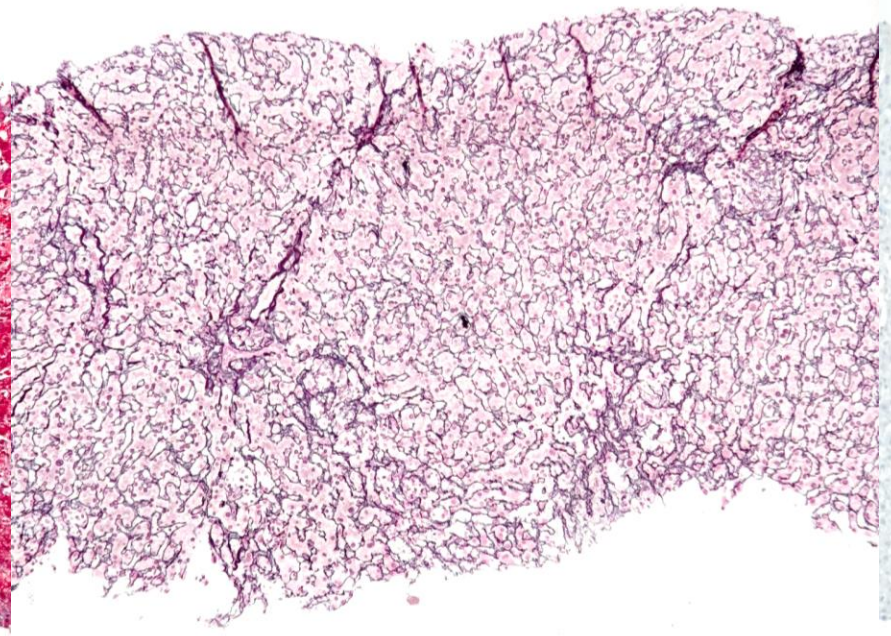


Two out of the 10 portal tracts show expansion by a mixed inflammatory infiltrate, composed of lymphocytes, numerous eosinophils and very scant plasma cells; one of them also includes a portal granuloma (arrow). The bile ducts in these 2 portal tracts show epithelial injury, with lymphocytic infiltration and cytoplasmic vacuolization.

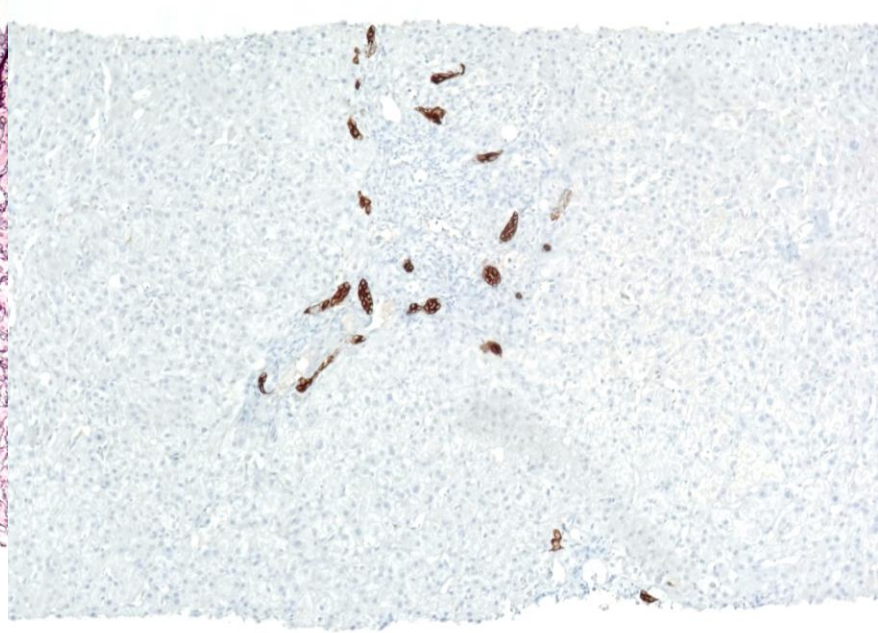
Trichrome



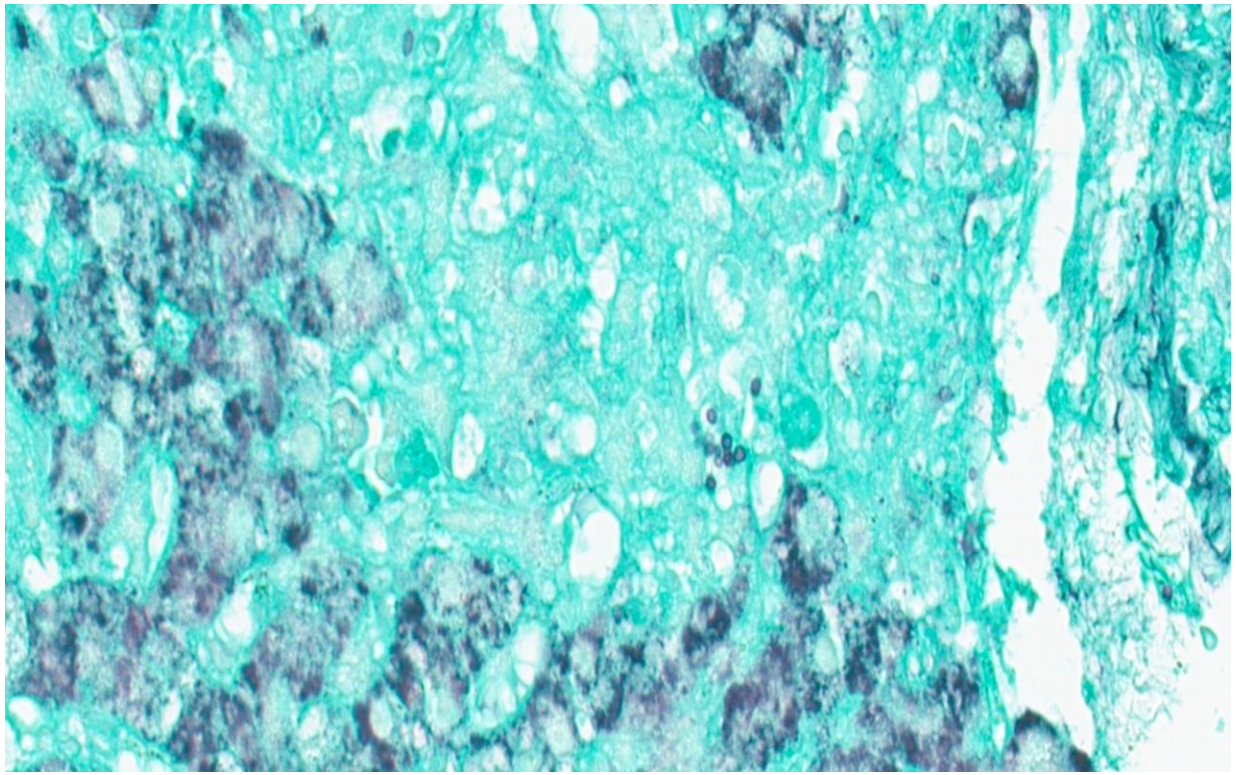
Reticulin

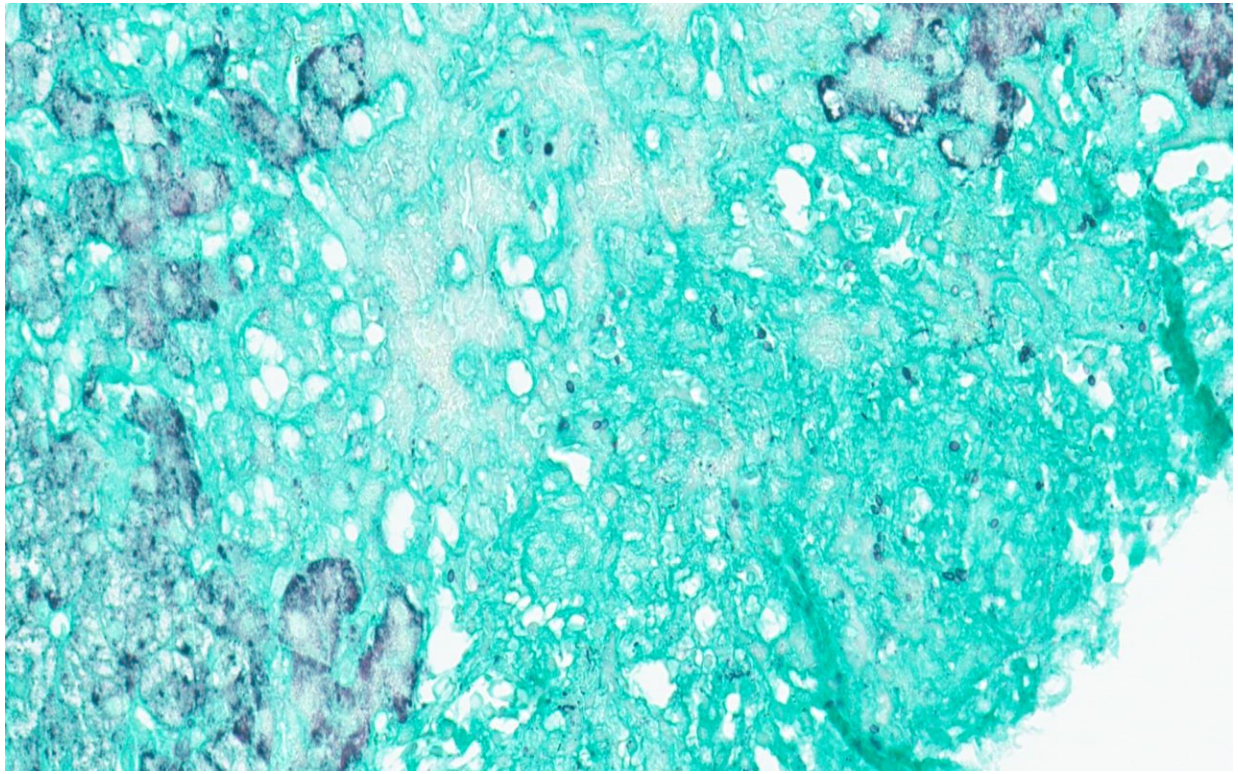


Cytokeratin 7

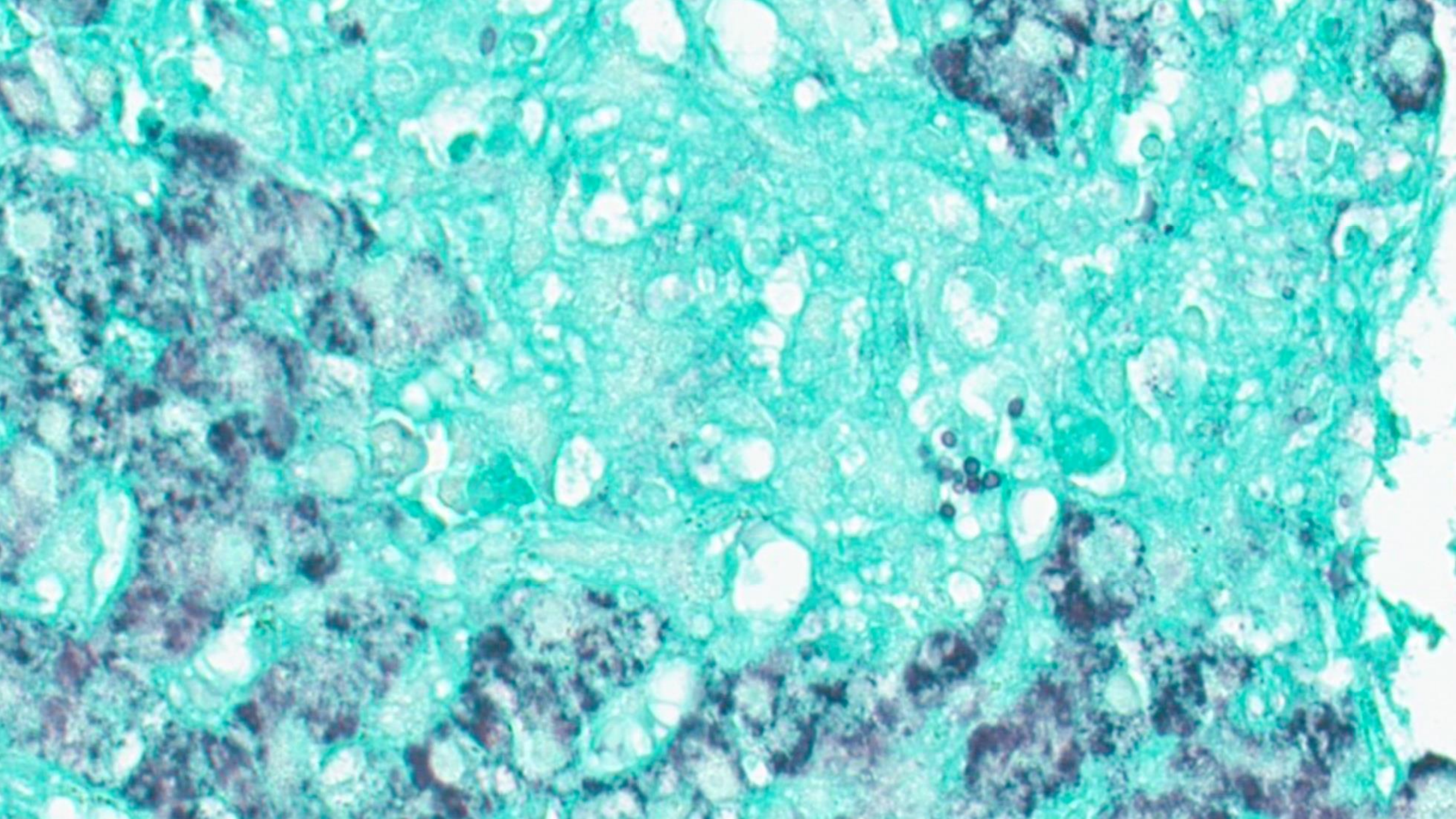


Trichrome and reticulin stains show preserved lobular architecture, with no evidence of fibrosis.
CK7 also highlights bile ductular proliferation in most of the portal tracts.





GMS special stains shows numerous fungal spores within the granulomata, some with narrow budding, consistent with histoplasmosis. AFB special stain shows no acid-fast bacteria.



Final Diagnosis:

Liver, post-transplant biopsy:

- Liver with granulomatous hepatitis
- GMS special stain highlights numerous fungal organisms, consistent with histoplasma species

Question 1. Which histologic finding most strongly favors histoplasmosis over tuberculous granulomatous hepatitis in a liver biopsy?

A. Presence of multinucleated giant cells
B. Portal-based granulomatous inflammation
C. Occasional caseation necrosis
D. Intracellular narrow budding yeasts highlighted by GMS stain
E. Cholestasis with elevated alkaline phosphatase

Answer: D

Portal granulomas and cholestasis can be seen in multiple conditions. Identification of small intracellular yeasts on fungal stains is diagnostic of histoplasmosis and distinguishes it from tuberculosis.

Question 2. A liver biopsy demonstrates granulomatous hepatitis with rare areas of caseation necrosis. Acid-fast stains are negative. Which interpretation is most appropriate?

A. Caseation excludes fungal infection
B. This finding rules out histoplasmosis
C. Caseation may rarely be seen in histoplasmosis
D. Sarcoidosis is the most likely diagnosis
E. The biopsy is nondiagnostic

Answer: C.

Caseation may rarely be seen in histoplasmosis. Although uncommon, caseation necrosis can occur in histoplasmosis, creating overlap with tuberculosis, and emphasizing the need for fungal stains.

Question 3. A pathologist notes small oval organisms surrounded by clear halos within Kupffer cells on liver biopsy. Which statement regarding this feature is most accurate?

A. The halo represents a true polysaccharide capsule
B. It indicates extracellular replication

C. It is a fixation-related retraction artifact
D. It is specific for cryptococcal infection
E. It corresponds to lipid accumulation within macrophages

Answer: C.

It is a fixation-related retraction artifact. In histoplasmosis, the apparent halo is not a capsule but an artifact, helping differentiate it from Cryptococcus, which has a true capsule.

Summary:

Histoplasma granulomatous hepatitis results from hematogenous dissemination of Histoplasma capsulatum, a dimorphic fungus acquired by inhalation of microconidia from soil contaminated with bird or bat droppings. In the lungs, the organism converts to its yeast form and survives within macrophages, allowing spread through the reticuloendothelial system. Hepatic involvement occurs when infected macrophages seed portal tracts and hepatic sinusoids.

Diagnosis is established by liver biopsy in the appropriate clinical context and is often supported by positive urine or serum Histoplasma antigen testing in disseminated disease.

Histologically, the liver shows both portal and lobular-based granulomatous hepatitis, with granulomas composed of epithelioid histiocytes, surrounded by lymphocytes, and variable multinucleated giant cells. In more chronic conditions, these granulomas may be surrounded by a rim of fibrosis and even calcification. In immunocompetent hosts, granulomas are usually well-formed, compact, and noncaseating. In contrast, immunocompromised patients frequently demonstrate poorly organized granulomas or absent granuloma formation, with expansion of portal tracts and sinusoids by macrophages densely packed with organisms, sometimes producing a pseudo–storage disease appearance. Caseation necrosis is uncommon but may occur, creating potential histologic overlap with tuberculosis. Other potential histologic features include portal lymphohistiocytic inflammation and Kupffer cell hyperplasia in sinusoids, leading to sinusoidal congestion.

The pathognomonic diagnostic feature is the identification of the organism within macrophages. These organisms are rarely visible on the H&E stain, and fungal special stains are required for better visualization. They appear small (2–4 μm), round-to-oval yeasts with narrow-based budding, which can be single or can form grape-like clusters. A surrounding

clear halo is often present and represents a fixation-related retraction artifact rather than a true capsule. Gomori methenamine silver (GMS) is the most sensitive stain, highlighting yeasts as black, round-to-oval structures, while PAS stains them magenta. Acid-fast stains are negative, helping distinguish histoplasmosis from mycobacterial causes of granulomatous hepatitis.

References:

1. Michael S. Torbenson, editors. Biopsy Interpretation of the Liver, 4th edition. Philadelphia (PA): Wolters Kluwer; 2022.

2. Tran J, Nguyen N, Elgouhari H, Tran T. S3786 Granulomatous Hepatitis Due to Histoplasma Capsulatum While on Treatment with Adalimumab. Official journal of the American College of Gastroenterology| ACG. 2023 Oct;118(10S): S2435.

3. Muhanna A, Nimri FM, Almomani ZA, Al Momani L, Likhitsup A, Nimri F, Al Momani Z. Granulomatous Hepatitis Secondary to Histoplasmosis in an Immunocompetent patient. Cureus. 2021 Sep 1;13(9).

4. Rihana NA, Kandula M, Velez A, Dahal K, O'Neill EB. Histoplasmosis presenting granulomatous hepatitis: case report and review of the literature. Case Reports in Medicine. 2014;2014(1):879535.