South Bay Pathology Society

October Meeting

10/5/15

Disclosures
October 5, 2015

The following planners and faculty had no financial relationships with commercial interests to disclose:

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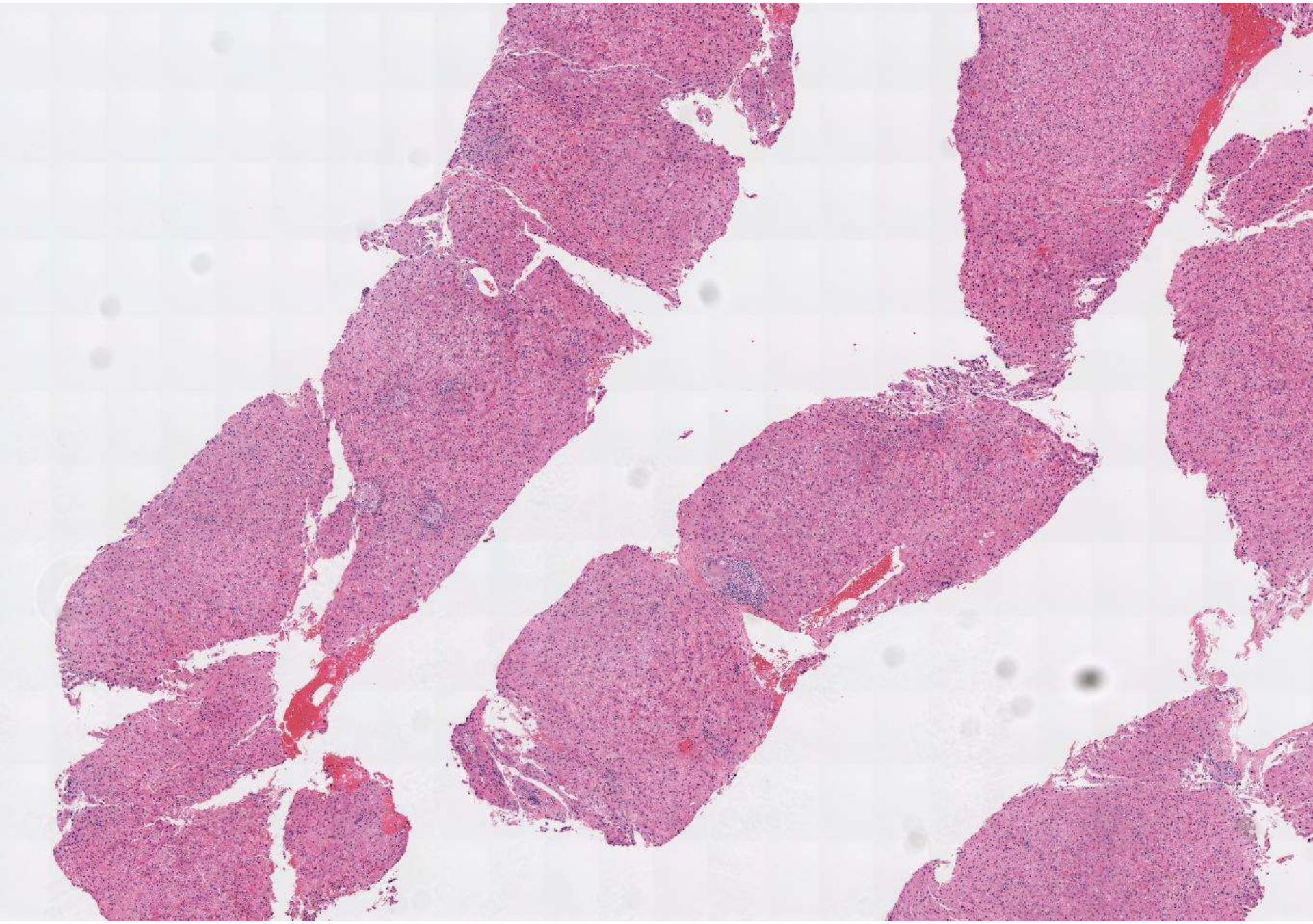
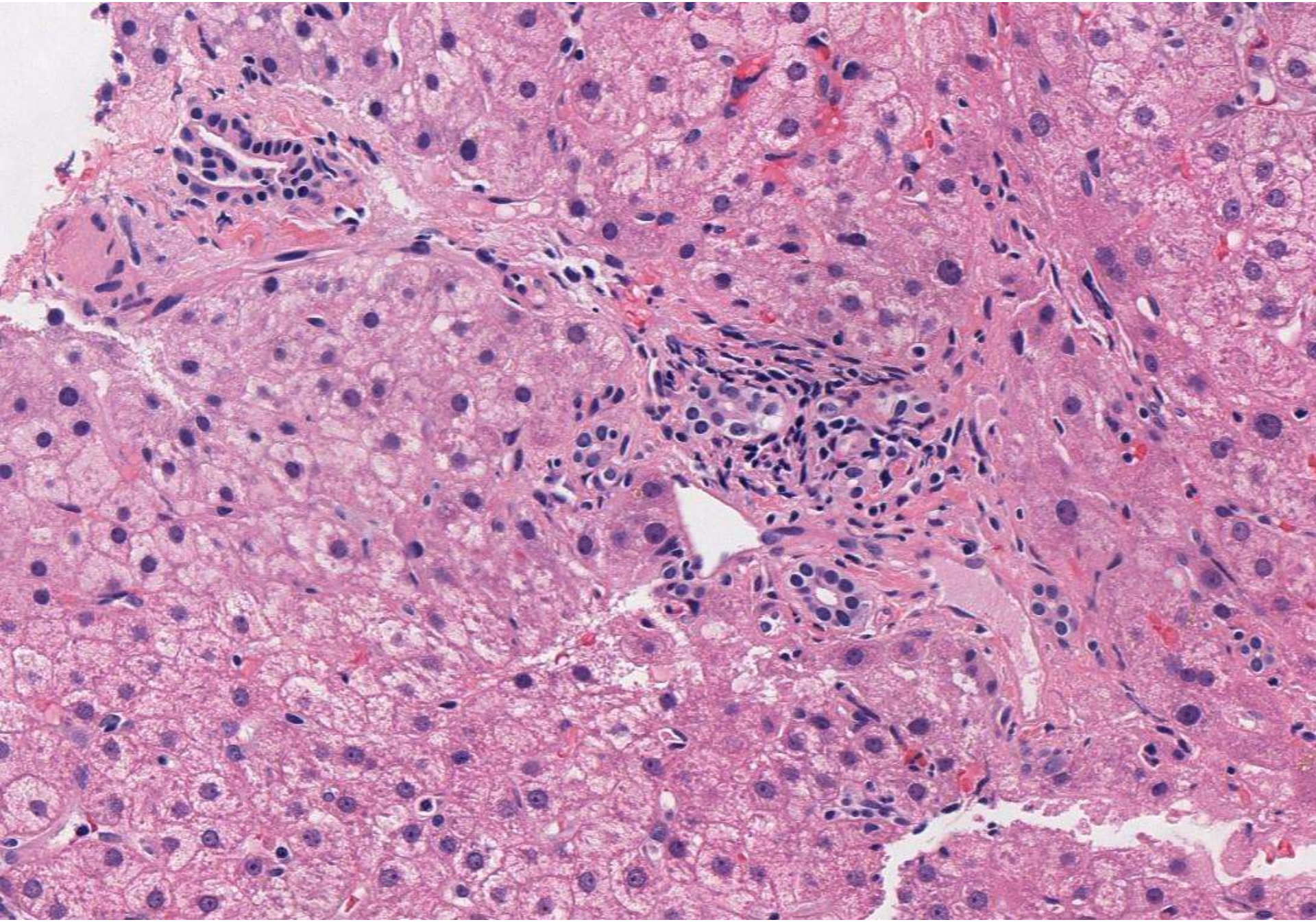
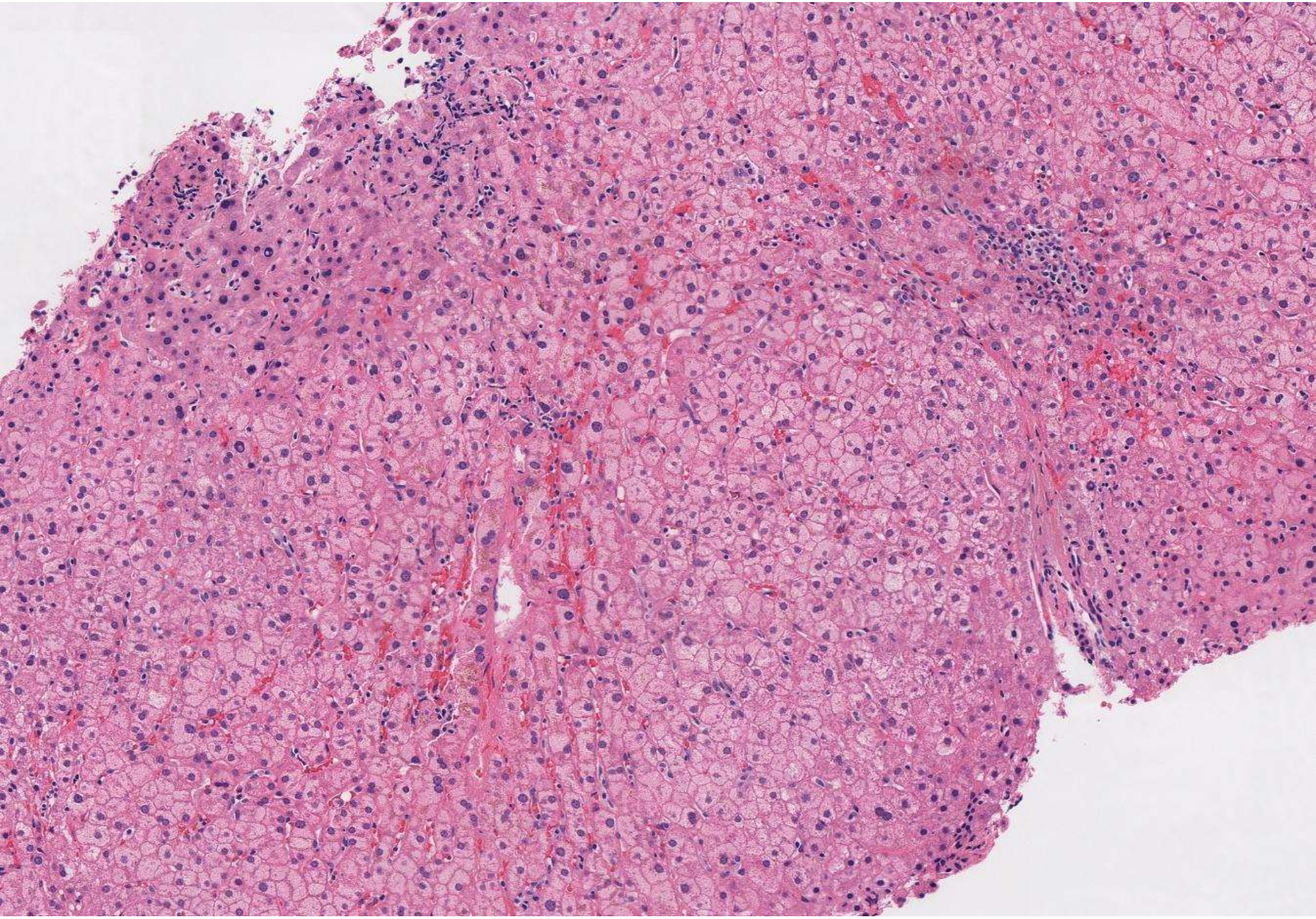
SB 5981

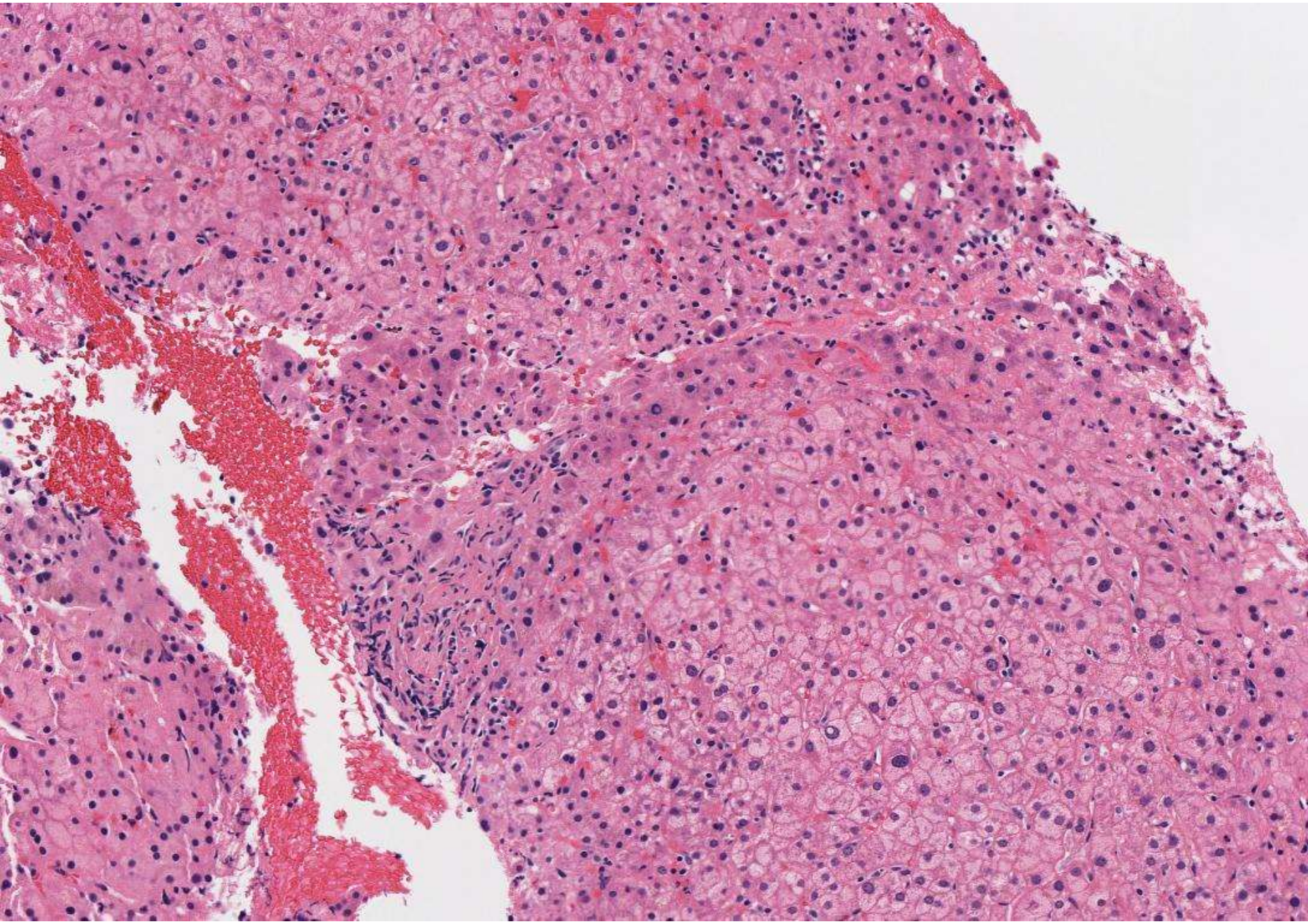
- 69-year-old male presents with abnormal LFTs (ALT 60-90 U/L, AST 60-80s U/L, alk phos 200s U/L, normal bilirubin). Liver biopsy performed.

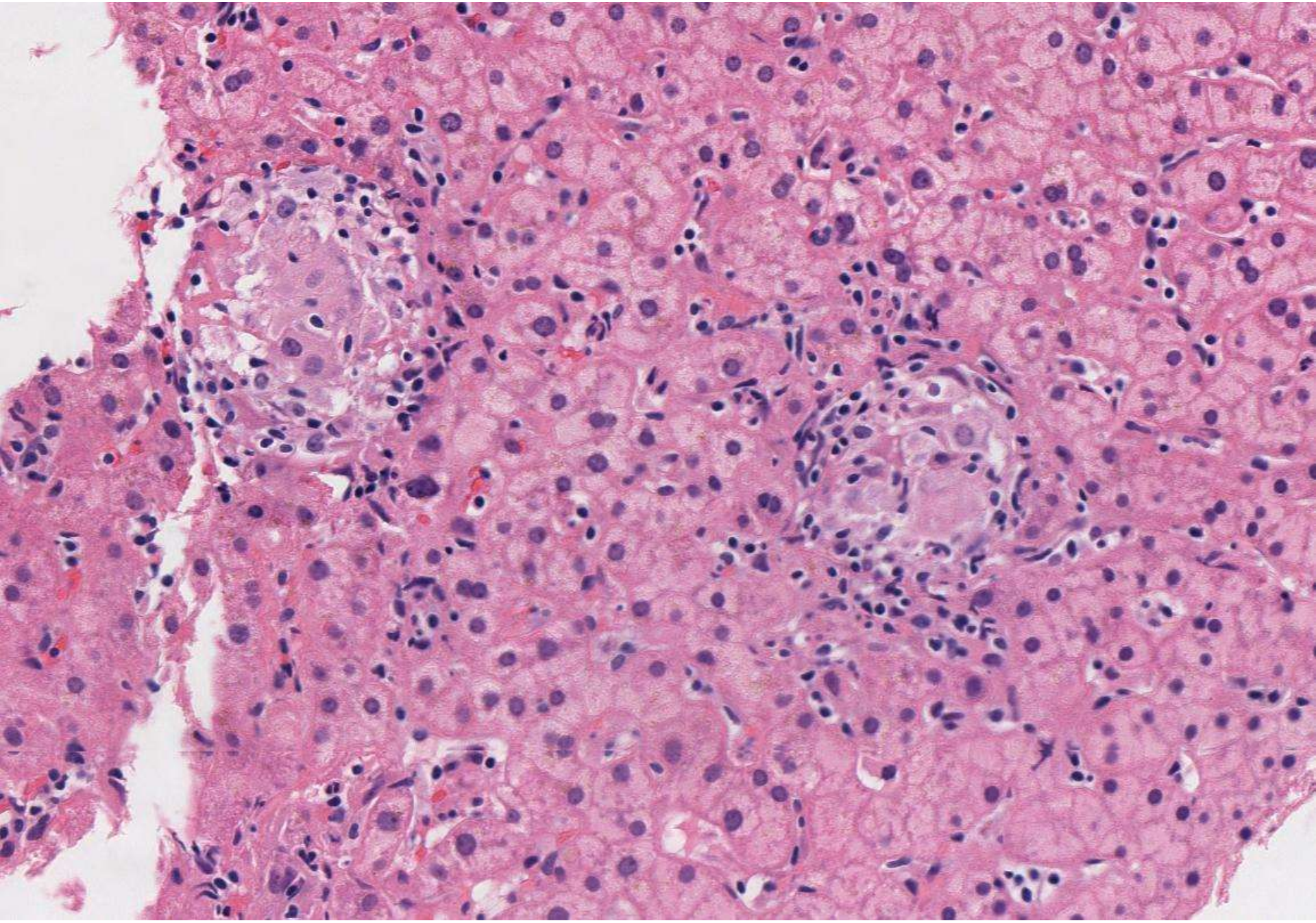
- **Thuy Nguyen; Mills-Peninsula**





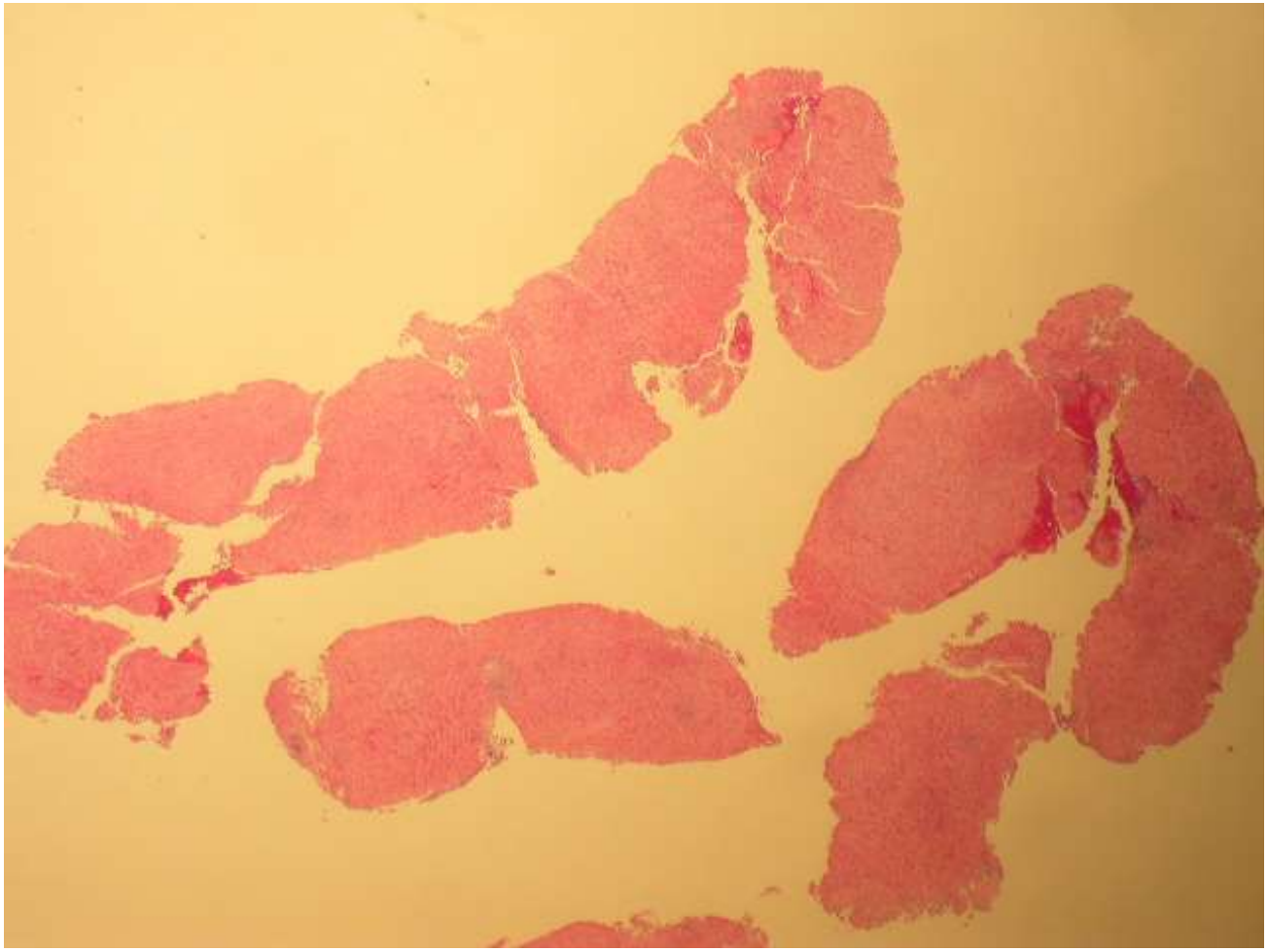


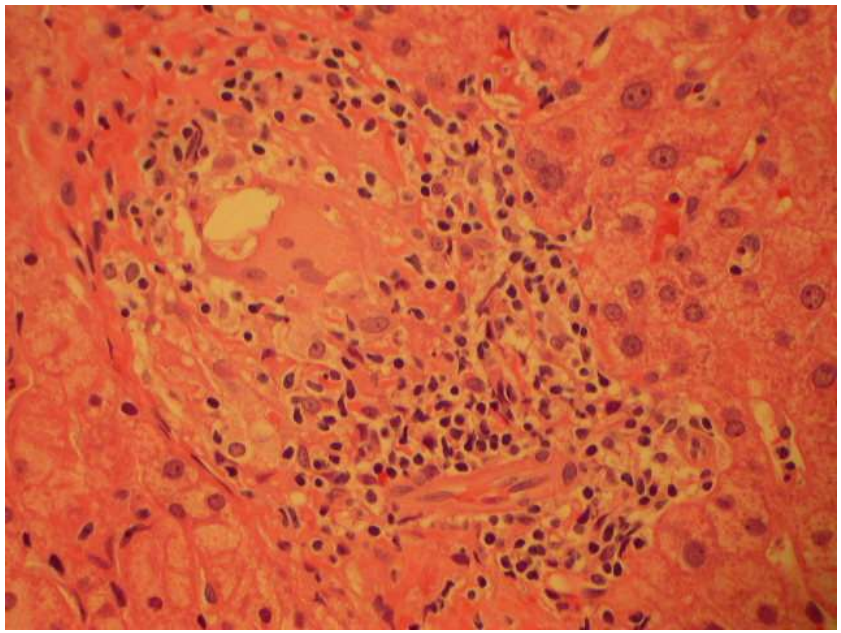
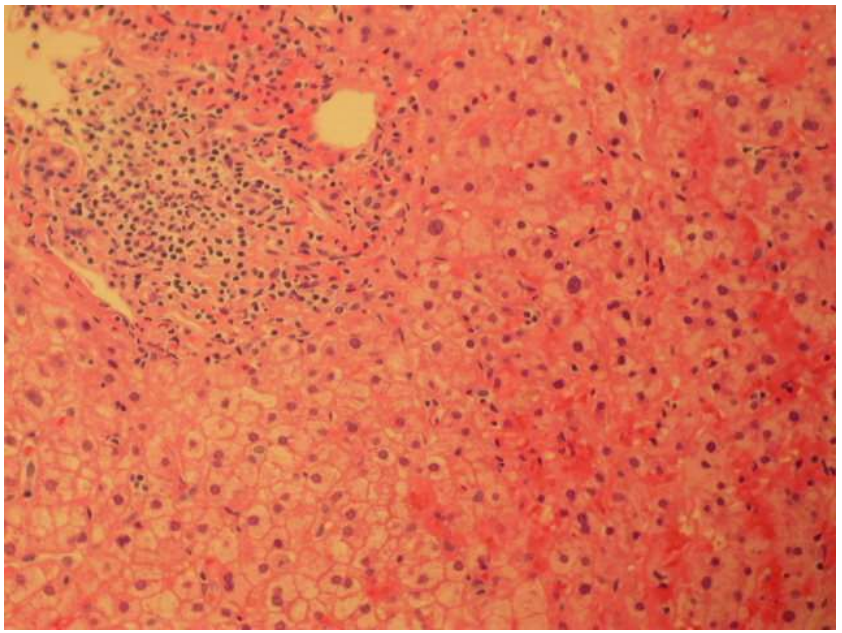




Diagnosis….?

Liver Biopsy



Non-necrotizing granulomas with mild portal and lobular chronic inflammation

Differential for Non-Necrotizing Granulomas in Liver Biopsy

- Infectious etiologies
  - Fungal, bacterial, parasitic
- Hypersensitivity
  - Drugs
  - Metals
- Immunological diseases
  - Common variable immunodeficiency
  - Chronic granulomatous disease
  - Polymyalgia rheumatica
  - Primary biliary cirrhosis
  - Systemic lupus erythematosus
  - Vascular disease
- Foreign material
- Neoplasm
  - Extrahepatic malignancy
  - Hodgkin disease
  - Non-Hodgkin lymphoma
- Scaroidosis

Common Variable Immunodeficency (CVID)

- Genetic immunodeficiency disorder
  - 1:25,000
  - ~ 90% of CVID resulted from a sporadic mutation
  - ~ 10% percent of patients have at least one family member with either CVID or selective immunoglobulin A (IgA) deficiency and demonstrate a familial pattern of inheritance (both autosomal dominant and autosomal recessive)
- Immunological features:
  - Impaired B cell function
  - Hypogammaglobulinemia
  - T cell or antigen presenting cell abnormalities
- Defined by:
  - Markedly reduced serum concentrations of immunoglobulin G (IgG), in combination with low levels of immunoglobulin A (IgA) and/or immunoglobulin M (IgM)
  - Poor or absent response to immunizations
  - An absence of any other defined immunodeficiency state
- Diagnosed in childhood but more typically after puberty
  - CVID data from the European Society for Immunodeficiencies registry between 2004-2012, 34% of patients were diagnosed before 10 years of age.
  - In studies from United States centers, approximately 20% of patients are diagnosed before the age of 20 years
  - The majority of patients are diagnosed between the ages of 20 and 45

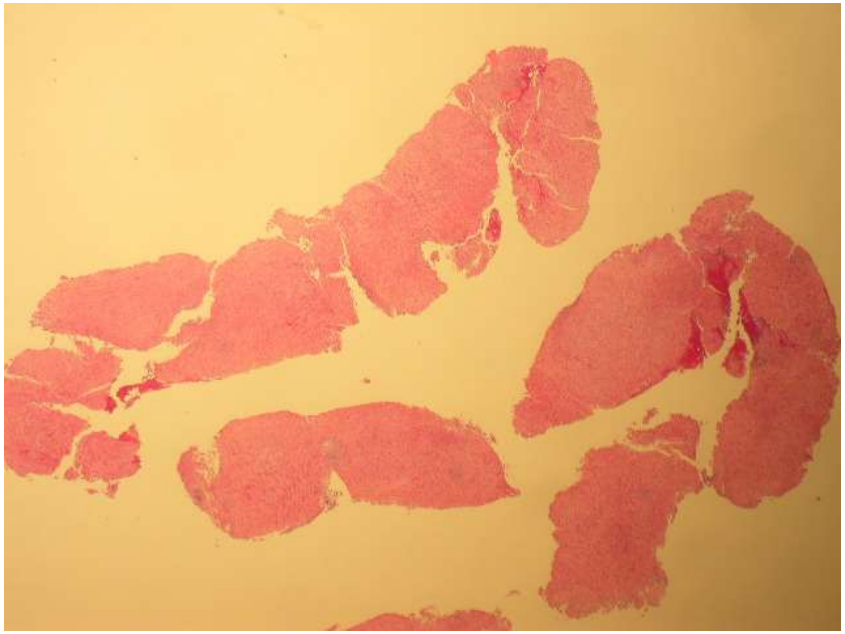
CVID Clinical Manifesations

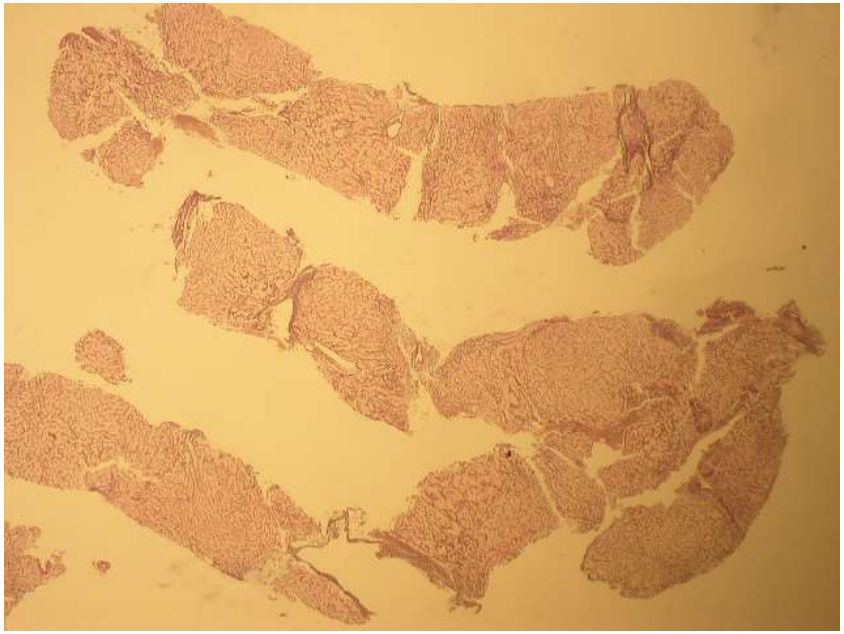
- In a series of 473 patients from one center, the following disorders were diagnosed over the course of 40 years:
  - Infections (94%)
  - Hematologic or organ-specific autoimmunity (29%)
  - Chronic lung disease (29%)
  - Bronchiectasis (11%)
  - Gastrointestinal inflammatory disease (15%)
  - Malabsorption (6%)
  - Granulomatous disease (10%)
  - Liver disease/hepatitis (9%)
  - Lymphoma (8%)
  - Other cancers (7%)
- Some exhibit autoimmune manifestations
  - Autoimmune conditions are diagnosed in almost one-quarter of CVID patients and can be the presenting disorder
    - Less likely to have a history of repeated infections and more likely to have
    - This group have become more prominent (possibly because of treatment lowering chronic infection)

Liver in CVID

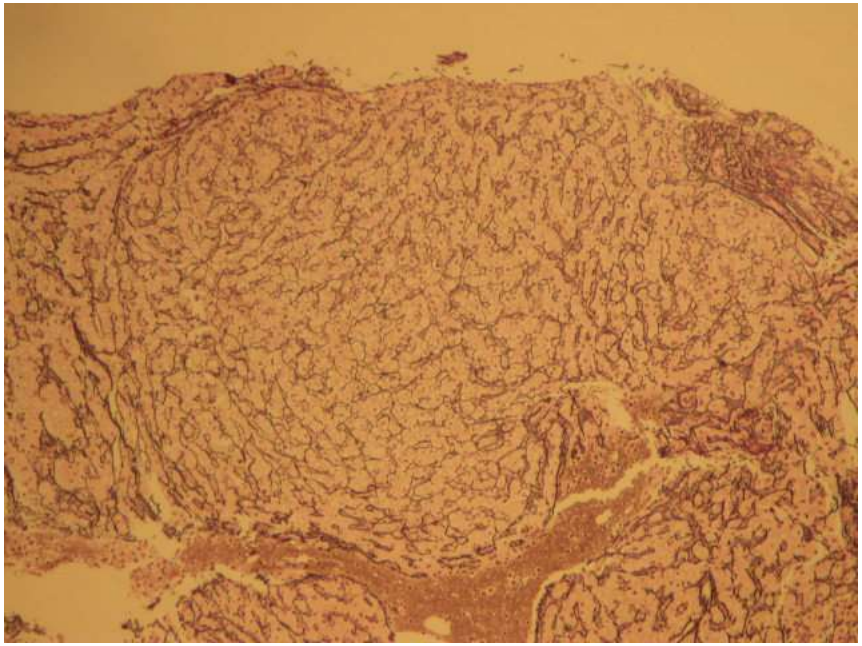
- Elevated alkaline phosphatase (ALP)
  - Progressive elevation
  - Fluctuating increases
  - Transient increase
- Mild elevation in AST and ALT
- Hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous liver disease have been reported
- Nodular regenerative hyperplasia

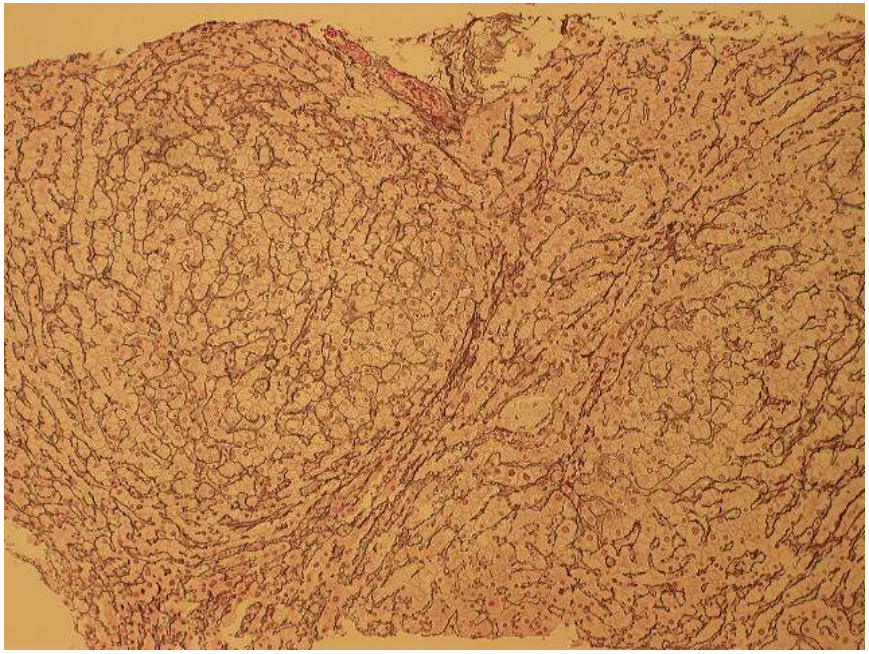
Nodular Architecture



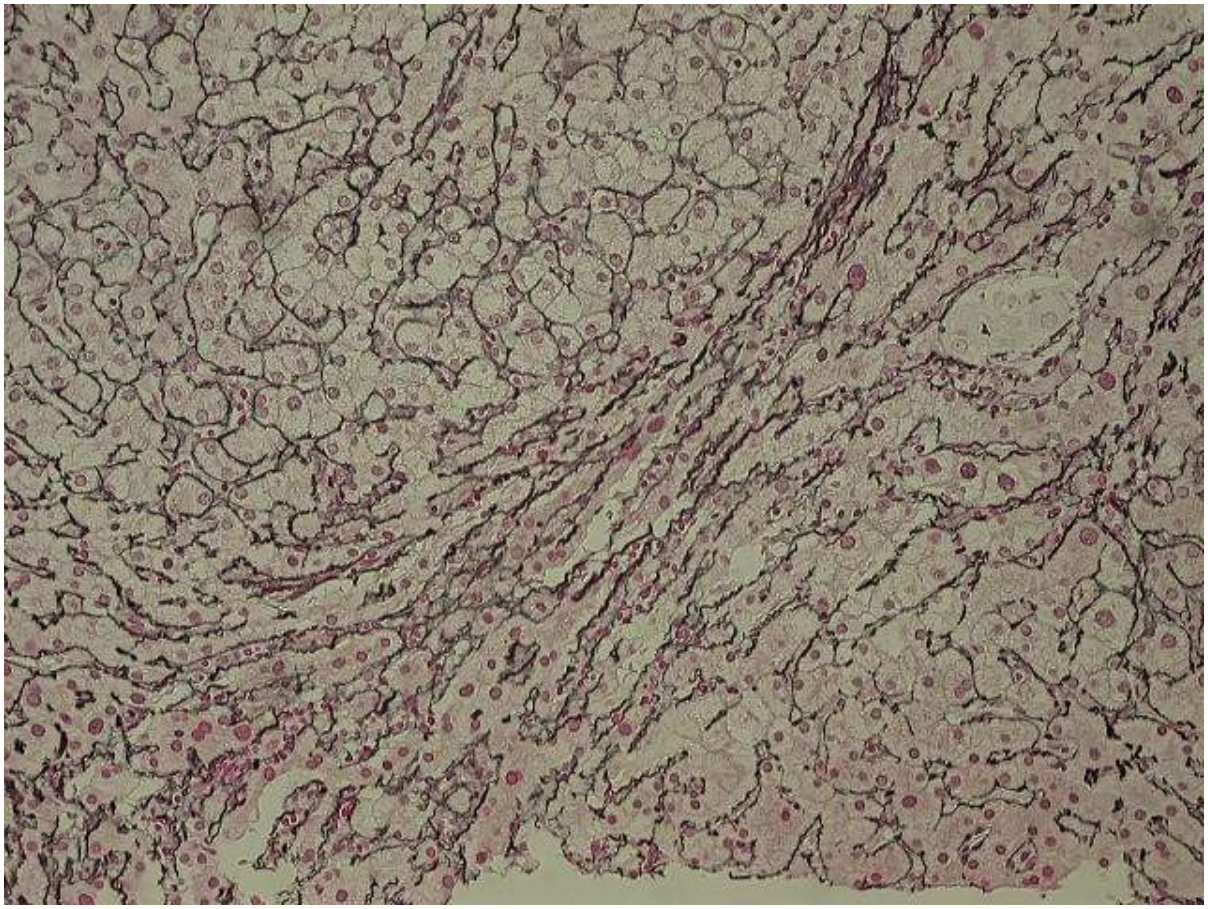


Nodular Architecture

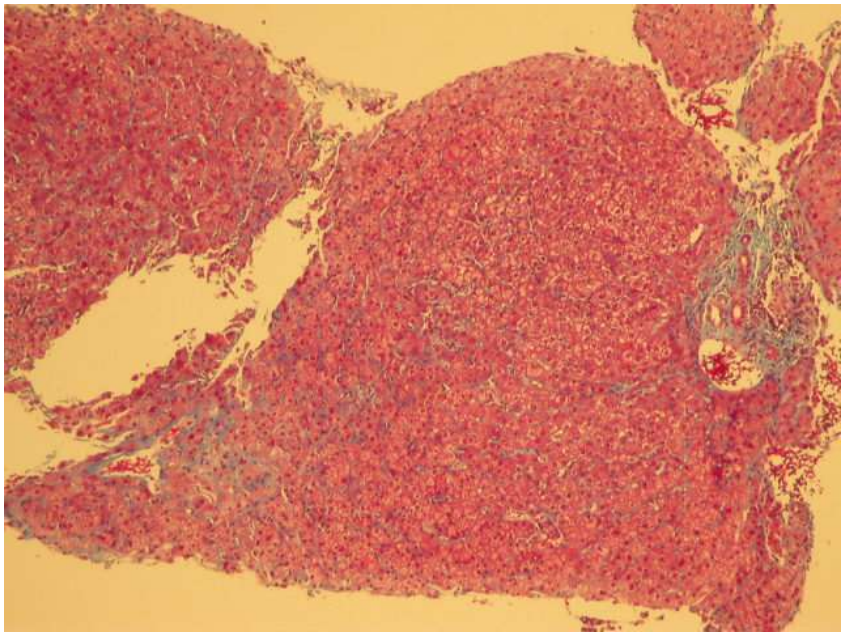


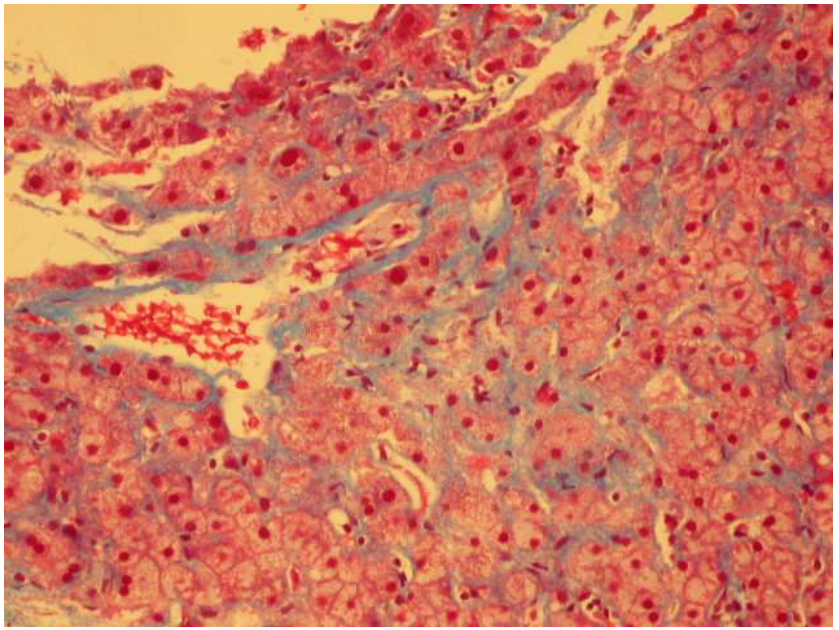


Hepatocyte Atrophy and Regenerative Changes



Patchy Sinusoidal Fibrosis





Nodular Regenerative Hyperplasia (NRH)

- Wanless defined NRH as hepatocellular nodules of less than 3 mm diameter, not surrounded by marked fibrosis
- Areas of hepatocyte atrophy and regeneration
- No inflammatory component
- Easy to miss unless sought deliberately
- Reticulin staining is essential to detect NRH
- Clinically may be associated with elevated ALP

CVID and NRH

- CVID patients often develop
  - Non-cirrhotic portal hypertension with granulomas
  - Abscesses
  - Small portal vein lesions
  - Nodular regenerative hyperplasia
- Study of 261 patients with CVID showed ~5% have NRH
- These patients appeared to have higher rates of autoimmune disease and nonceliac enteropathy, compared with CVID patients without liver disease

NRH

- Also associated with
  - Azathioprine
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Felty's syndrome
  - Celiac disease
  - Hematologic malignancies
  - Increased cellular production in bone marrow
- Elevated ALP (typically less than 3 times of upper normal limit)
  - Only 25% of patients exhibit elevated ALP
- Thought to be a result from intrahepatic vasculopathy common to these diseases

CVID and NRH

- NRH can be non-progressive or progress
- Cases with progression shows
  - Portal hypertension
  - Splenomegaly
  - Decreased WBC and platelets
  - Ascites, clinical symptoms of cirrhosis
- Subset with autoimmune-like syndrome which has a more rapid progression to liver dysfunction
  - Biopsy showed interface hepatitis, bridging necrosis and fibrosis in the portal areas
  - Study showed the majority of the inflammatory cells are CD3+ T-cells with co-expression of CD8 and RT-PCR showed increased production of IFN-ɣ mRNA
  - Recent studies of NRH showed increased CD8+ T-cells in liver sinusoids adjacent to areas of hepatocyte atrophy
    - suggesting that NRH may be initiated by destructive autoimmune process mediated by CD8+ cells that leads to hepatocyte loss and then a regenerative process that result in vascular abnormalities

NRH Mananagement

- Control underlying condition
- Management of complications should they arise
- Screening to detect evidence of portal hypertension with endoscopy to identify varices
- Ultrasound less useful as splenomegaly is seen in CVID in the absence of portal hypertension

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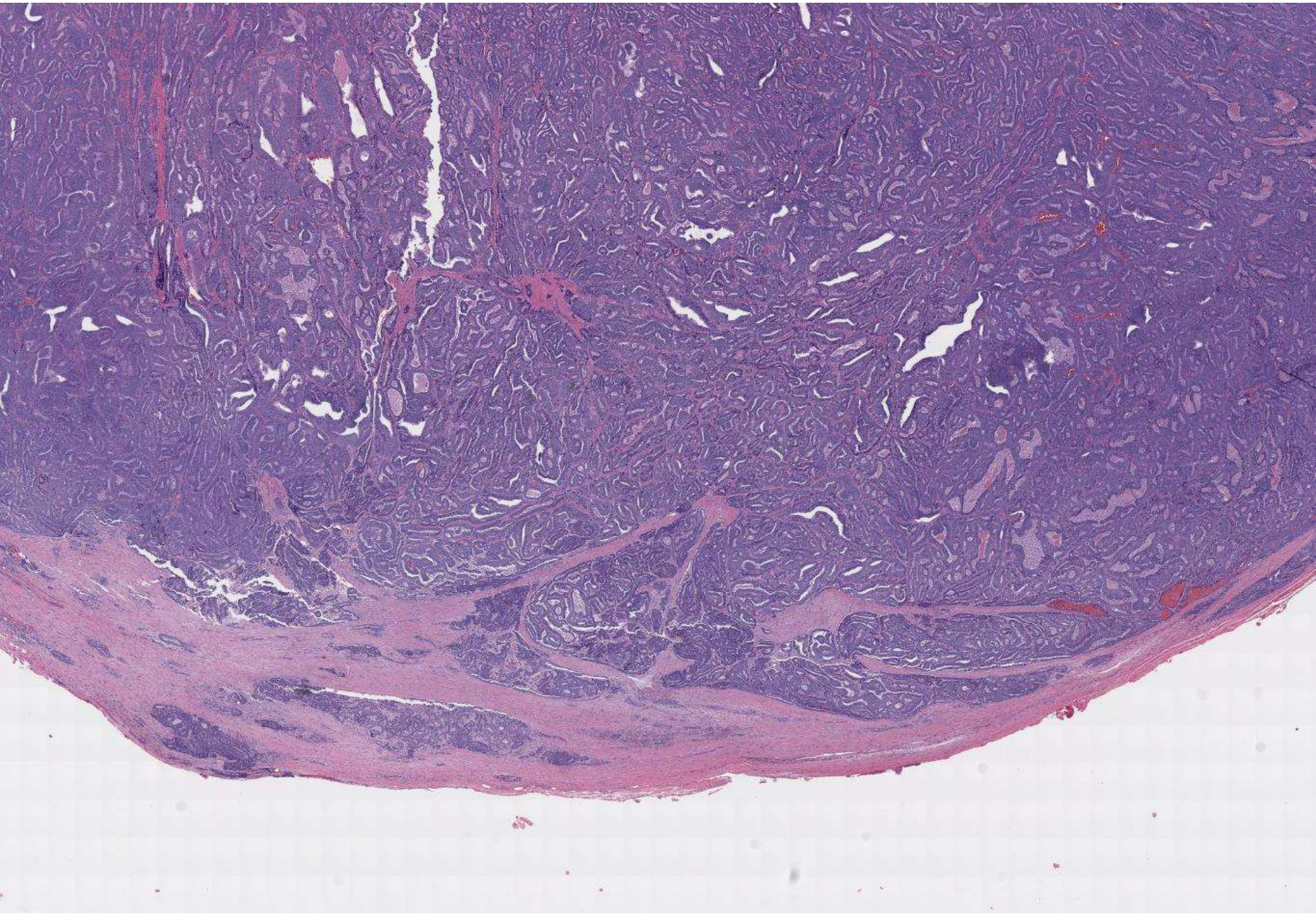
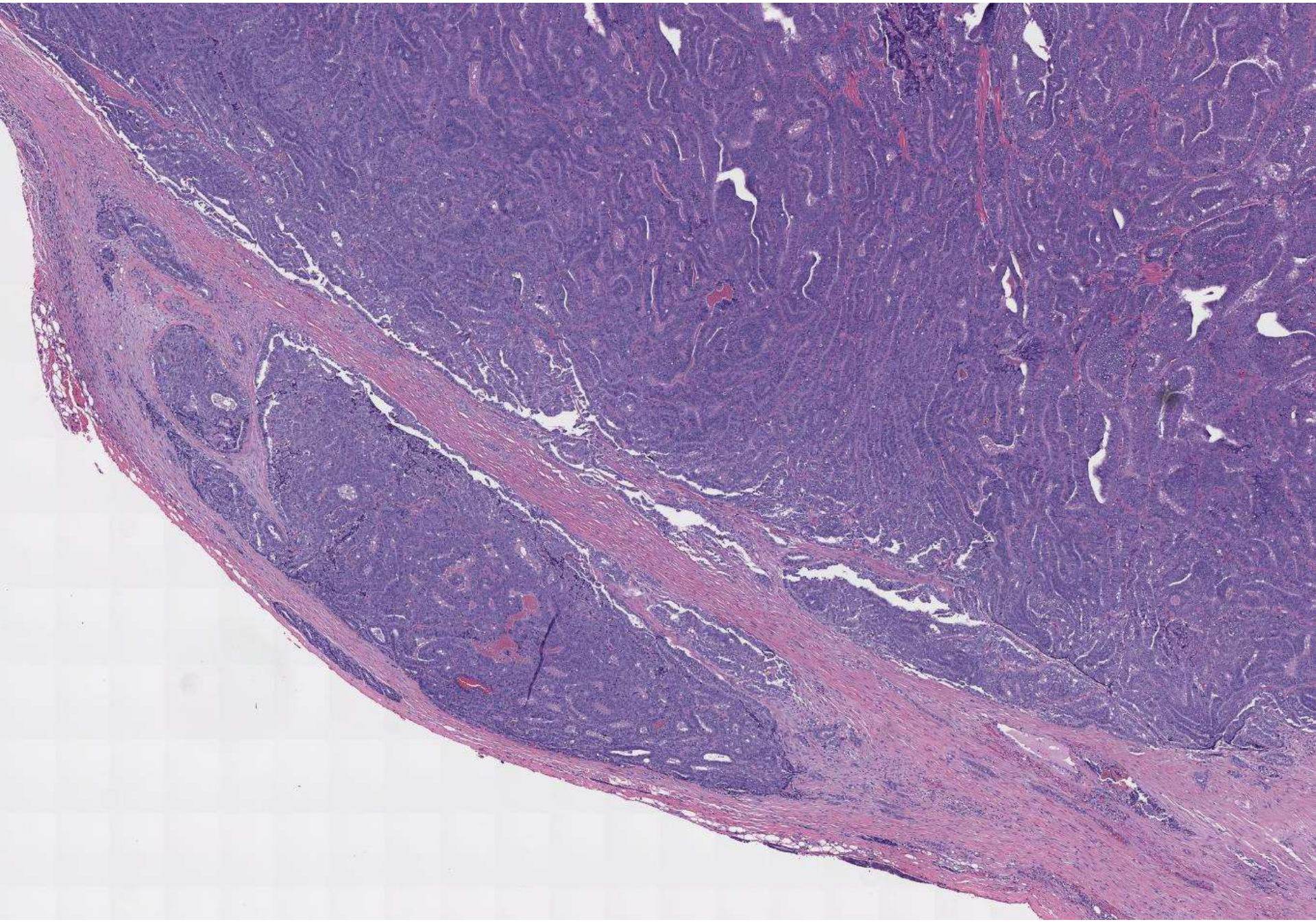
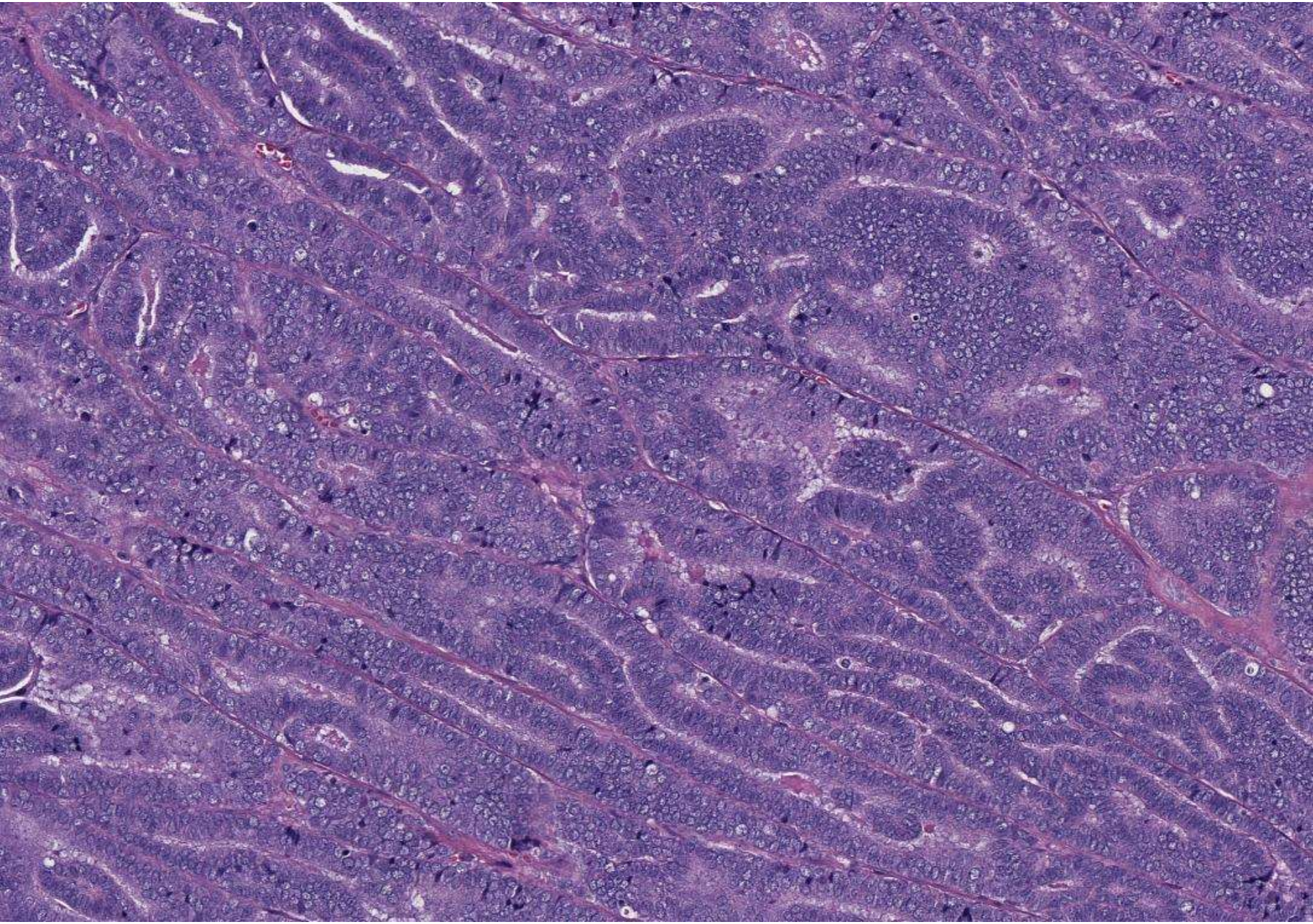
SB 5982

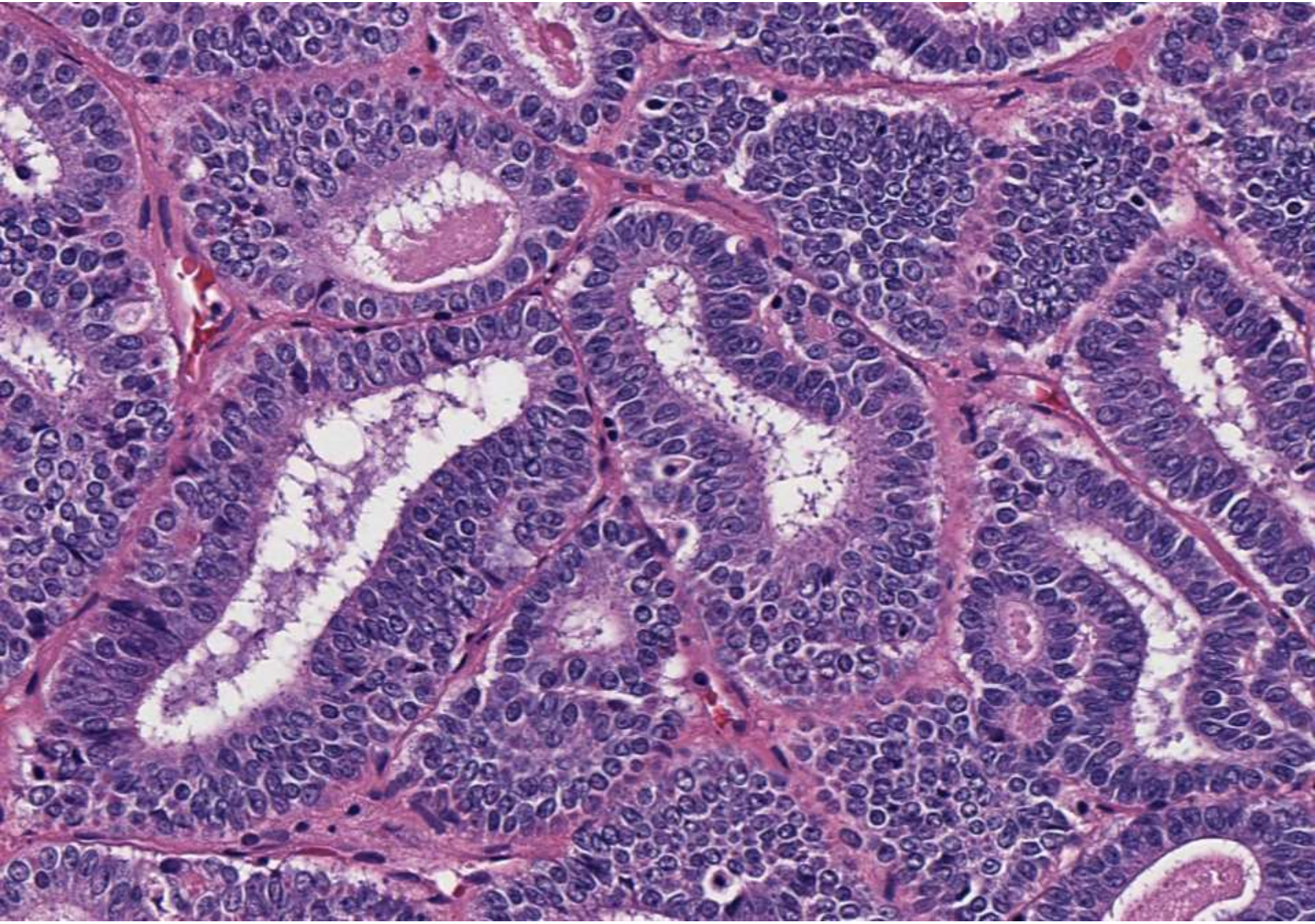
- 71-year-old male with enlarged thyroid gland and multiple enlarged cervical nodes.

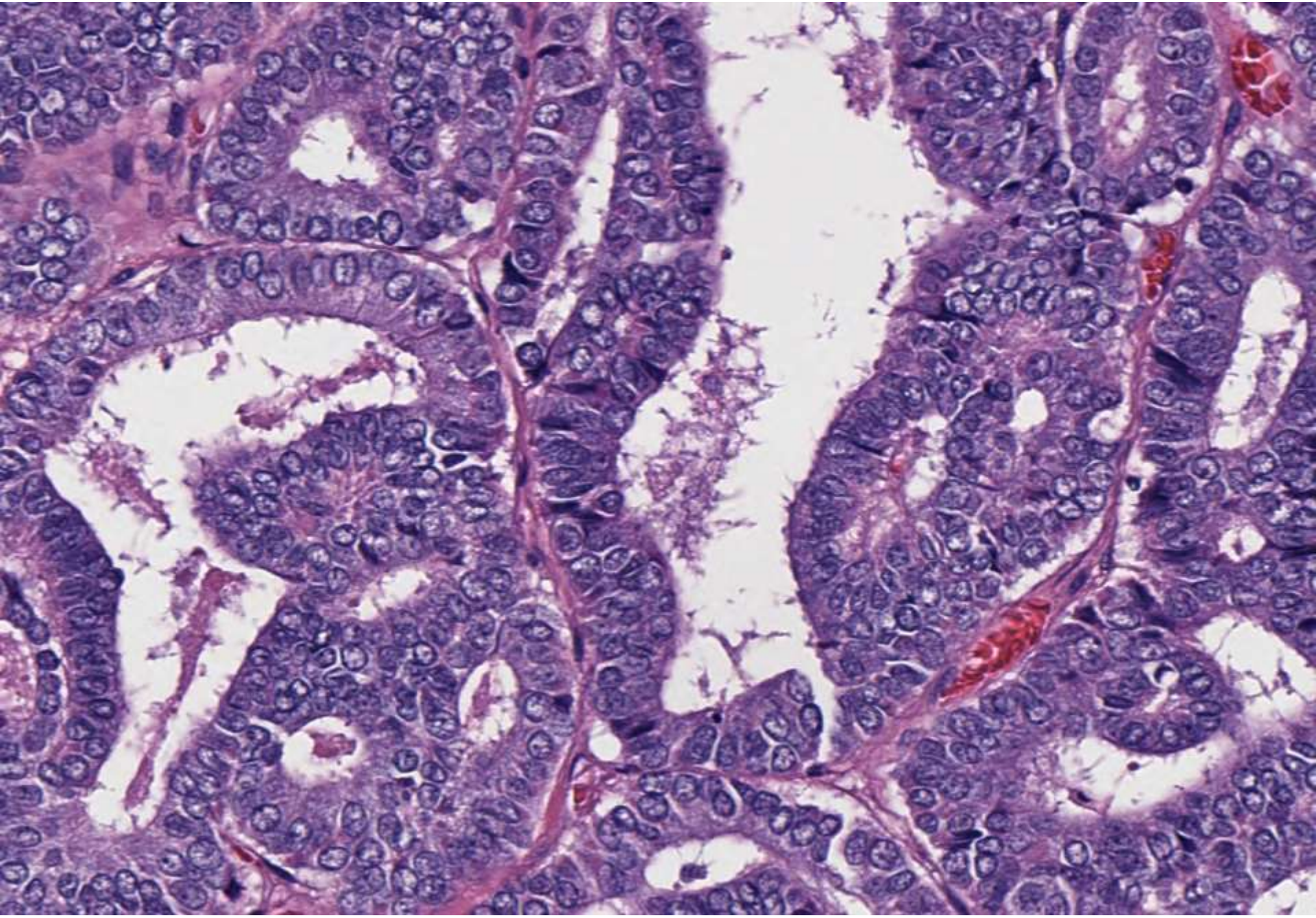
- **Mahendra Ranchod; Good Samaritan Hospital**



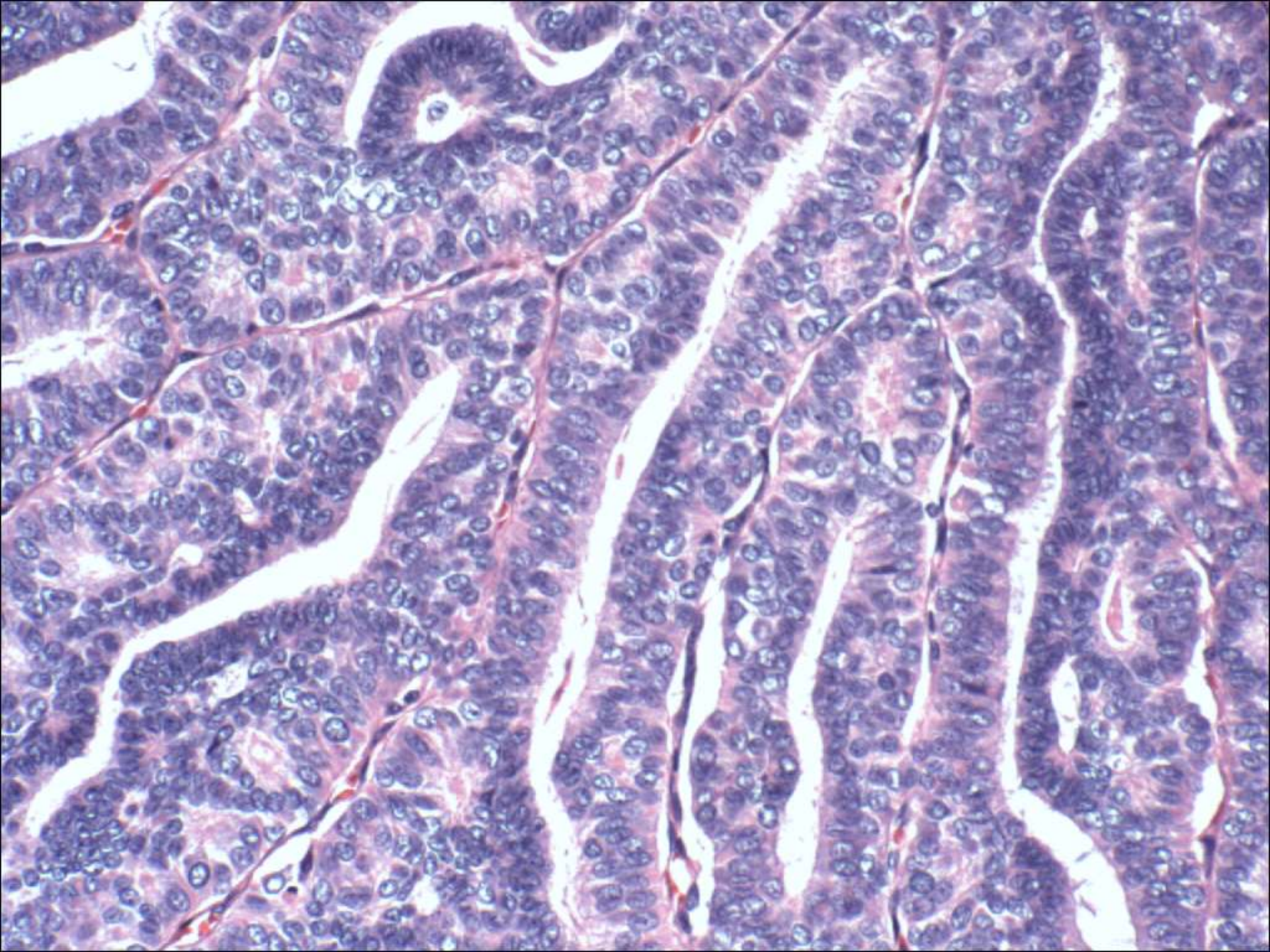


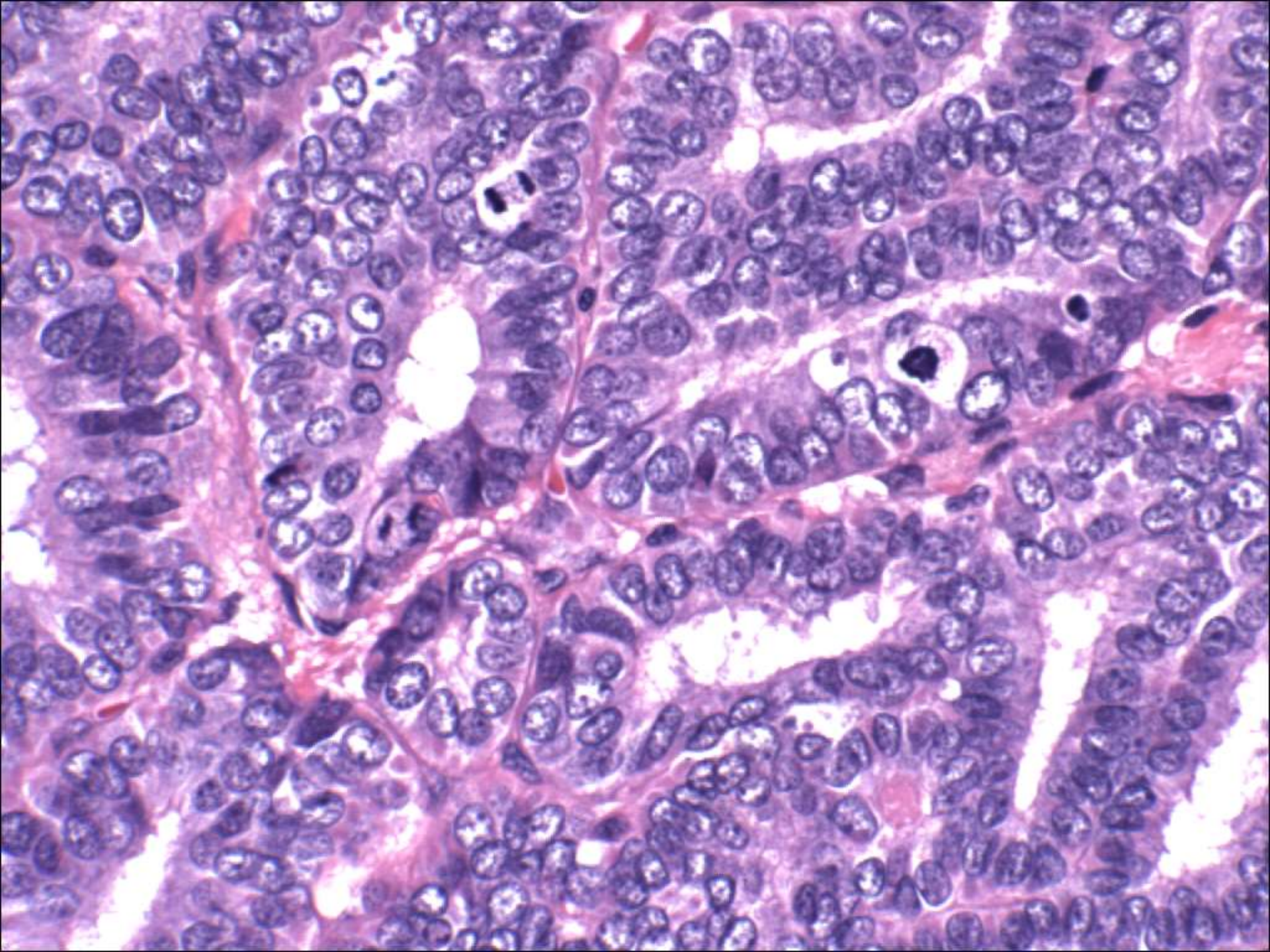


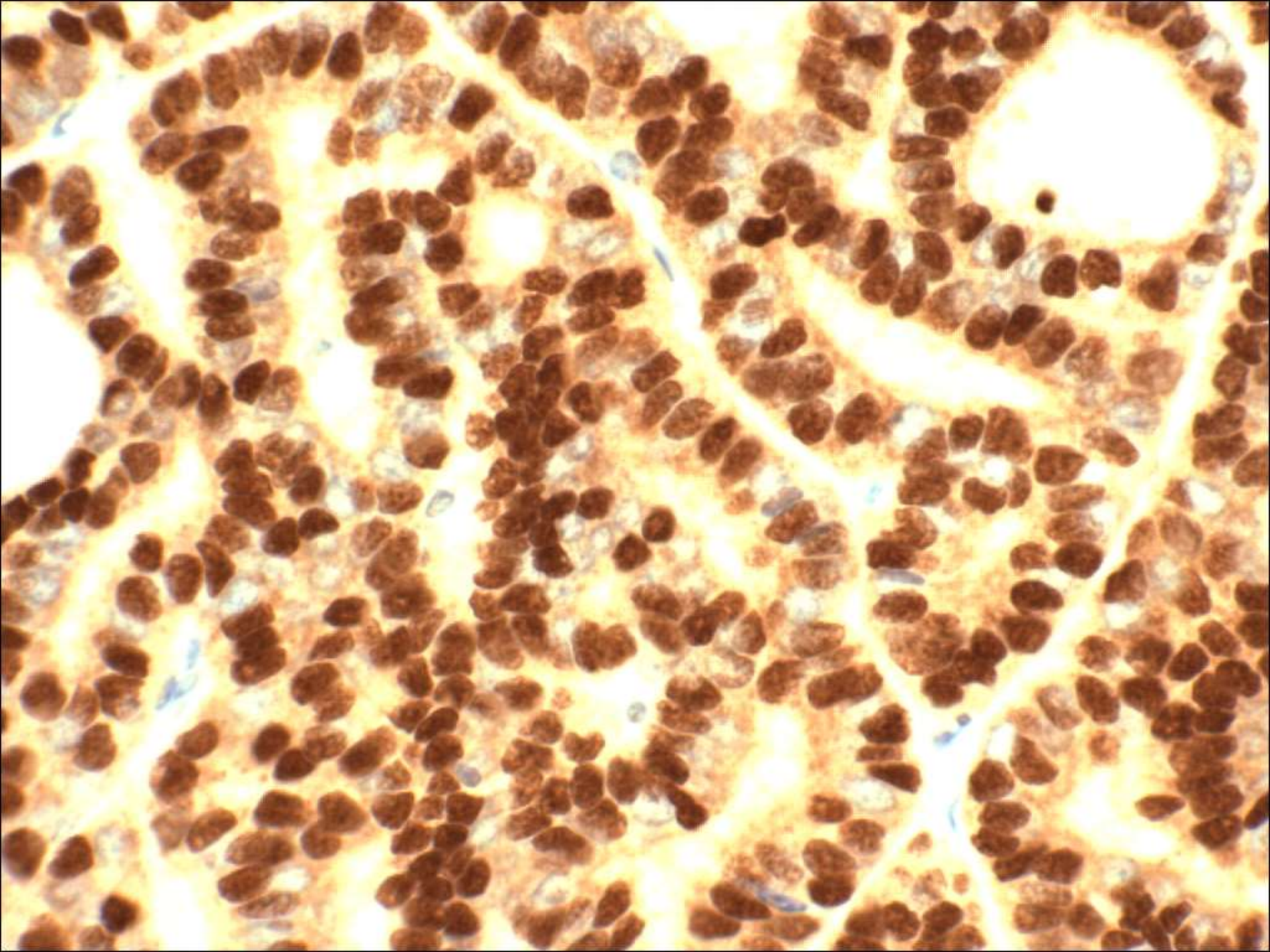


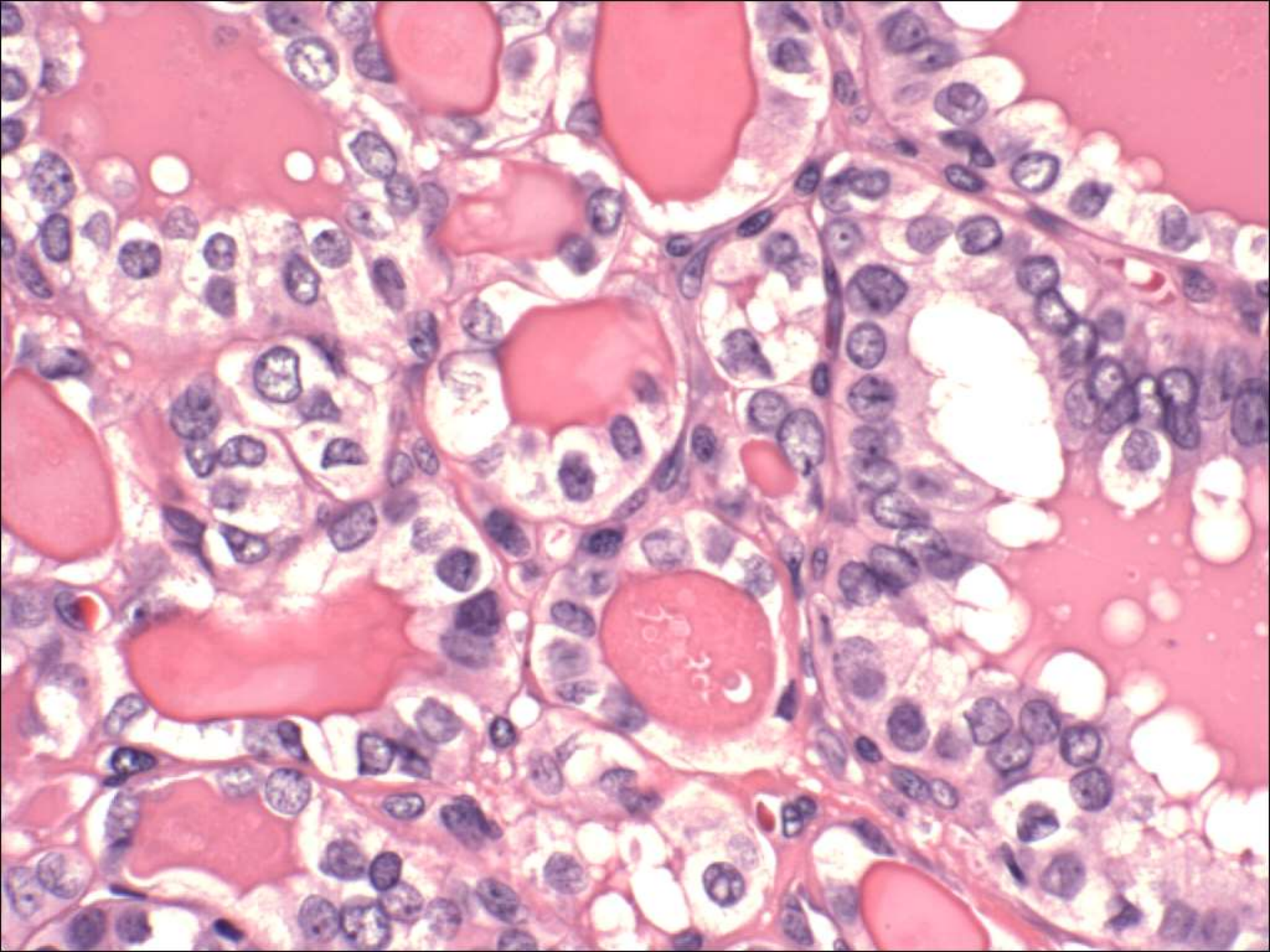


Diagnosis….?









Columnar cell variant of PTC

Uncommon variant of PTC

- **0.2% of PTC in Mayo series of 1500 cases, using cut off of 50%**
- **More aggressive than conventional PTC**
- **? Non-responsive to I_{131}**
- **May be confused with colon or endometrial CA in metastatic sites**

Columnar cell variant of PTC

- Reminiscent of TA of colon or atypical endometrium – with stratified nuclei
- Psammoma bodies rare
- Intranuclear inclusions rare
- Mitoses readily found
- Ki-67 up to 50%
- +ve for TTF-1
- 10-55% +ve for CDX2 (all other thyroid carcinomas negative)

Columnar cell variant of PTC

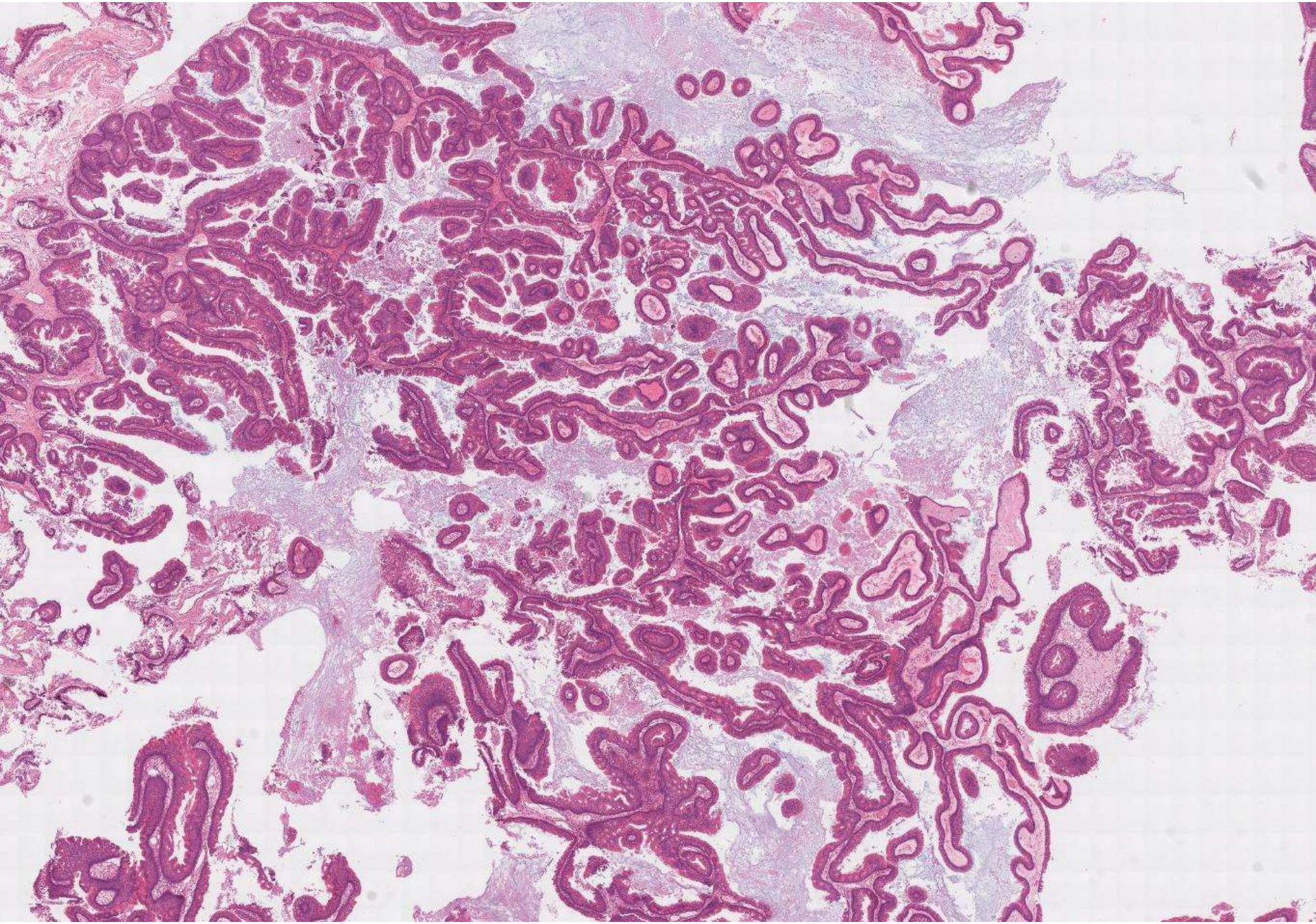
Clues to diagnosis

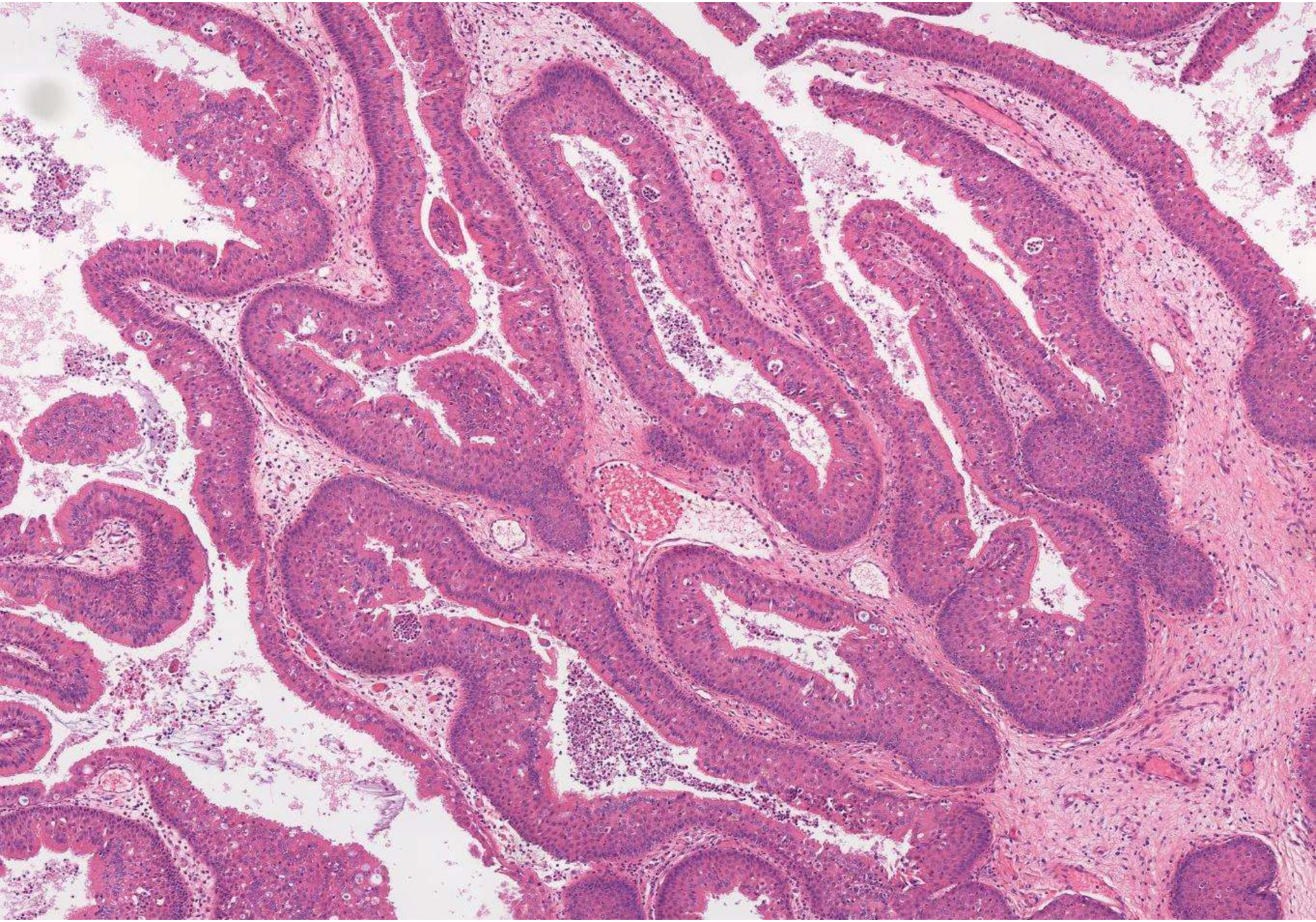
- Familiarity with this variant
- Search for areas of conventional PTC
- Confirm with TTF-1 and thyroglobulin stains
- Do not be misled by +ve CDX2

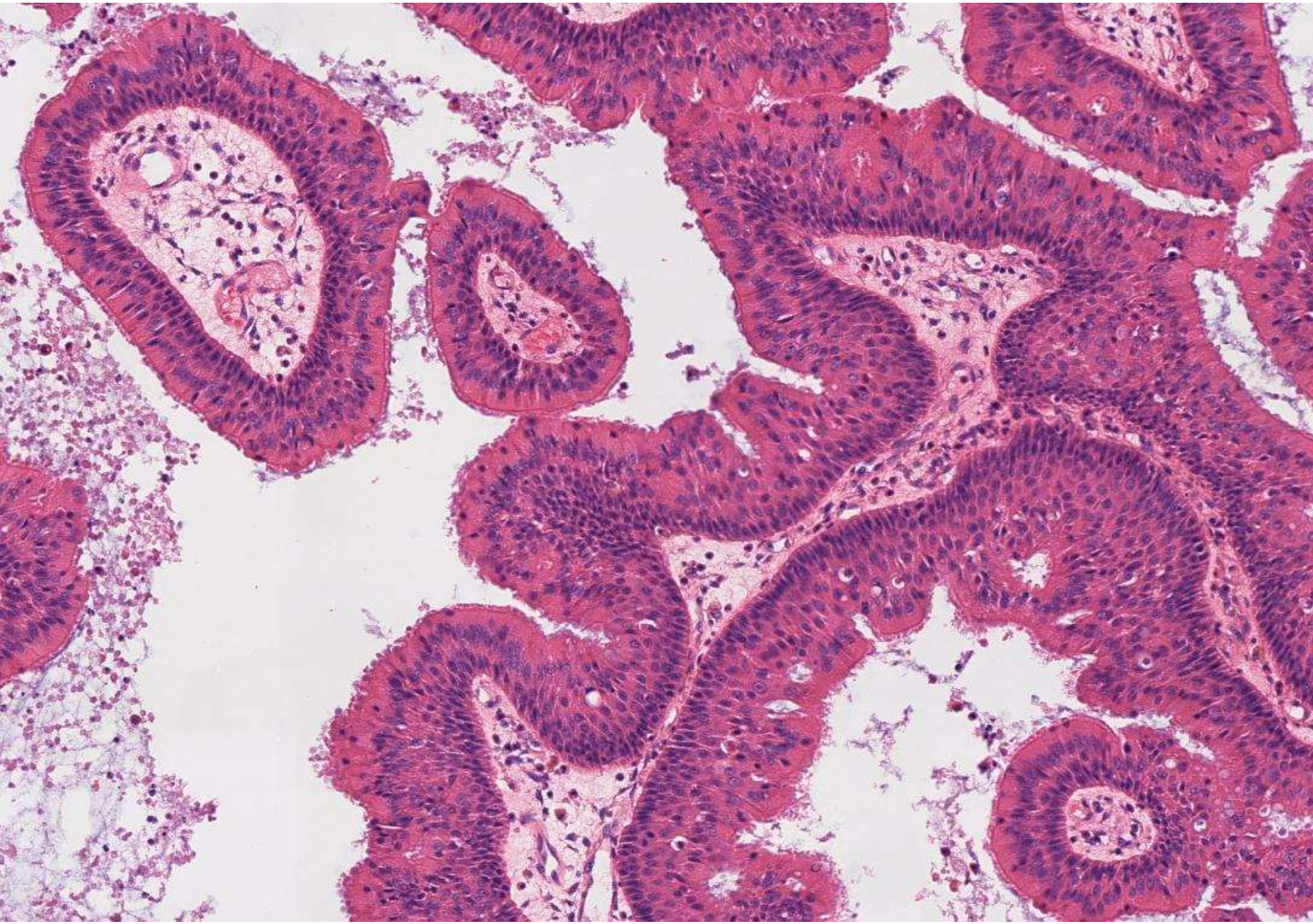
SB 5983

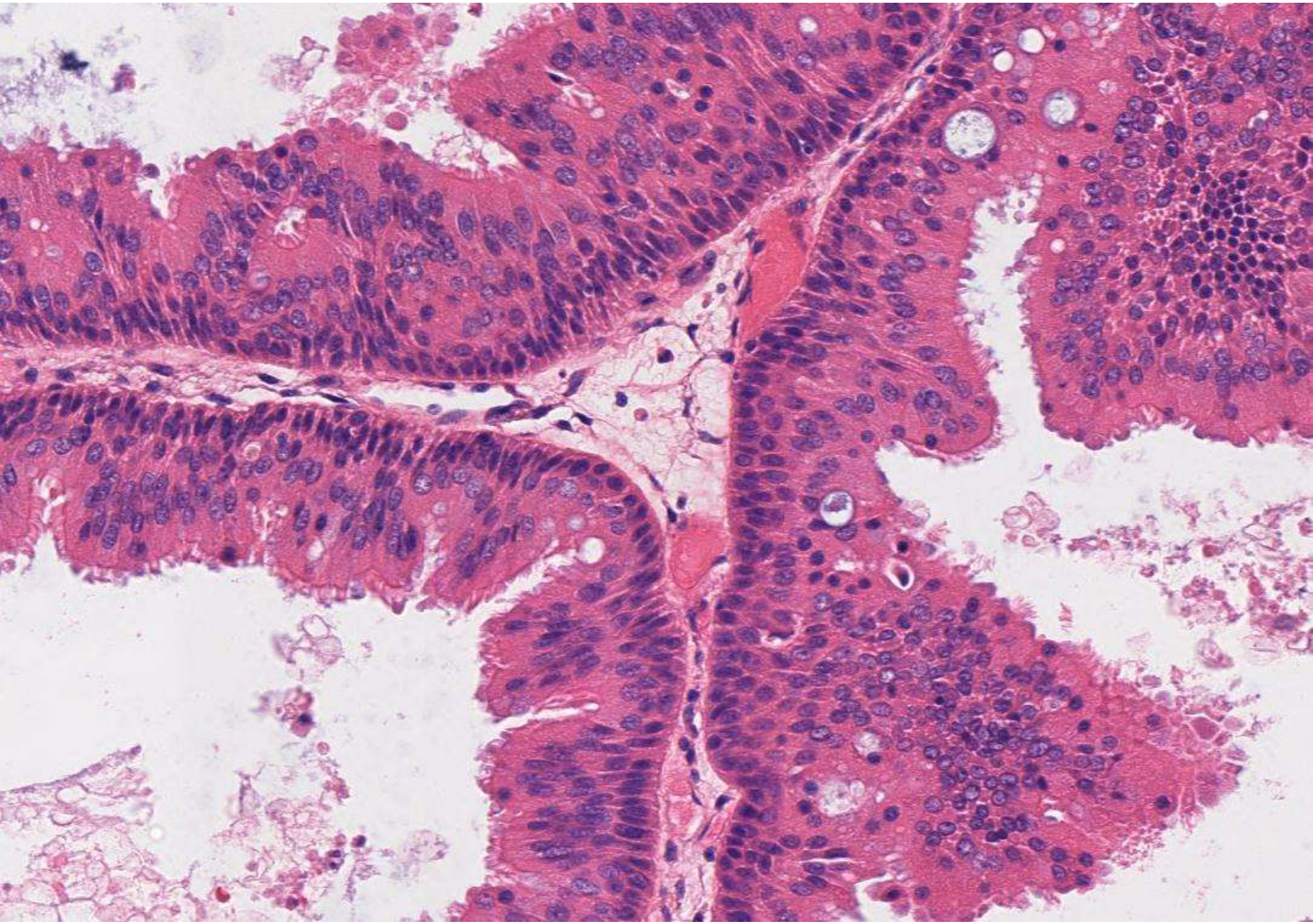
- 73-year-old male with right maxillary sinus mass.

- **Ben Buelow/Charles Zaloudek; UCSF**

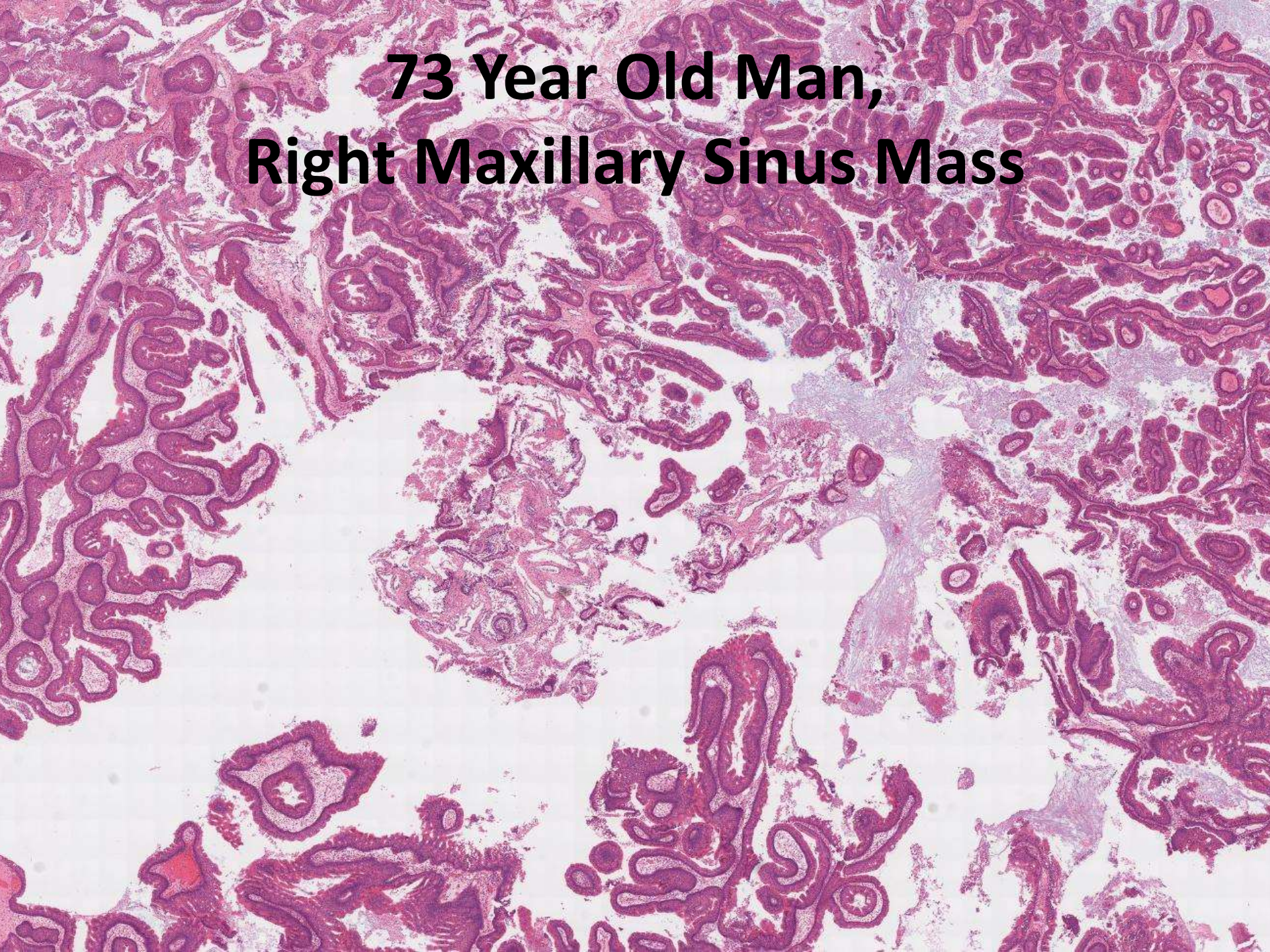


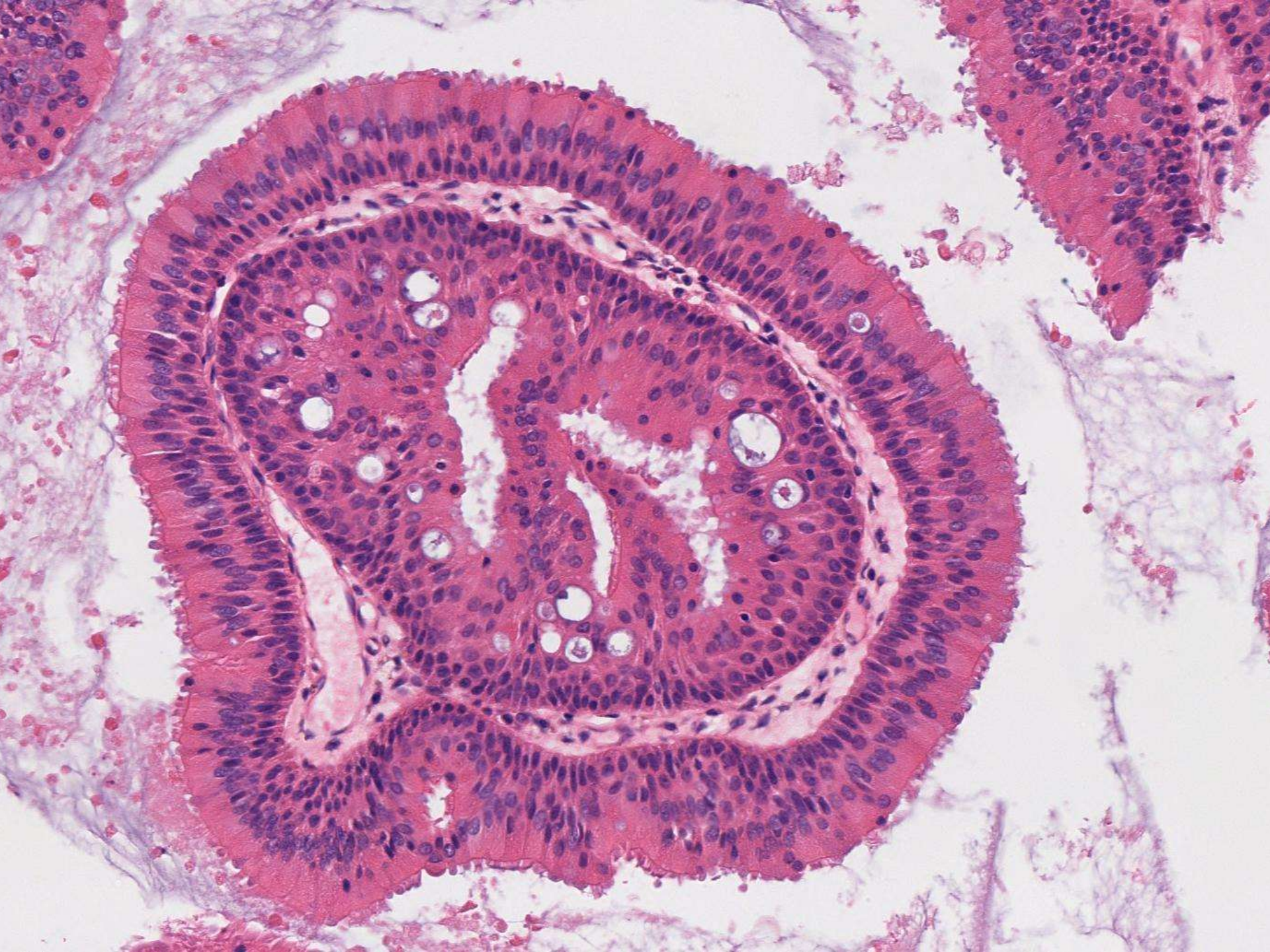






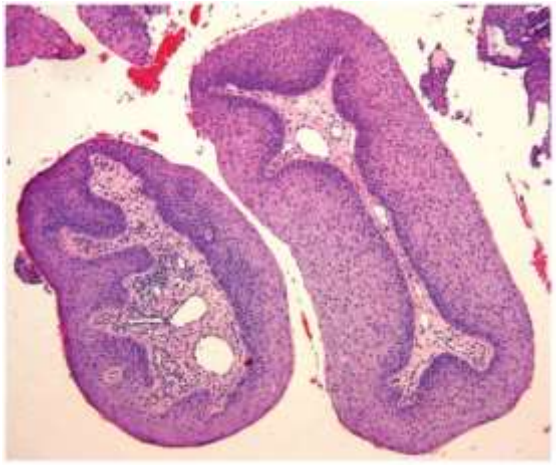
Diagnosis….?


73 Year Old Man,
Right Maxillary Sinus Mass

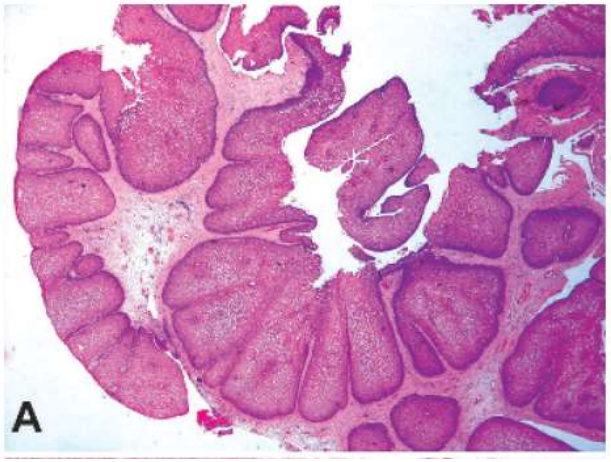


Schneiderian Papillomas

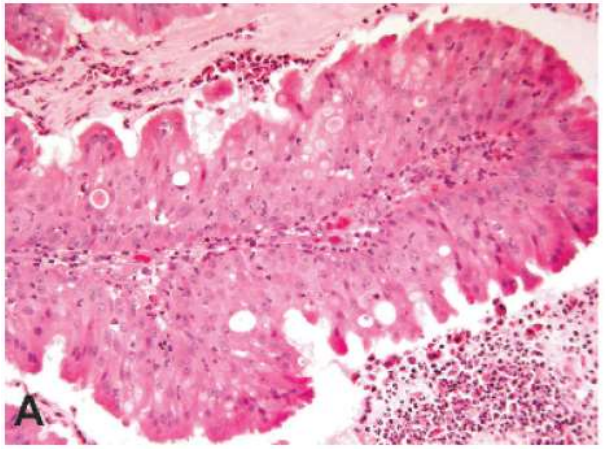
Exophytic

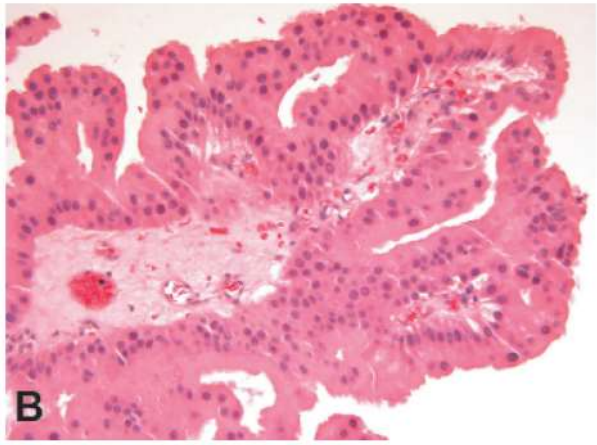


Inverted



Oncocytic

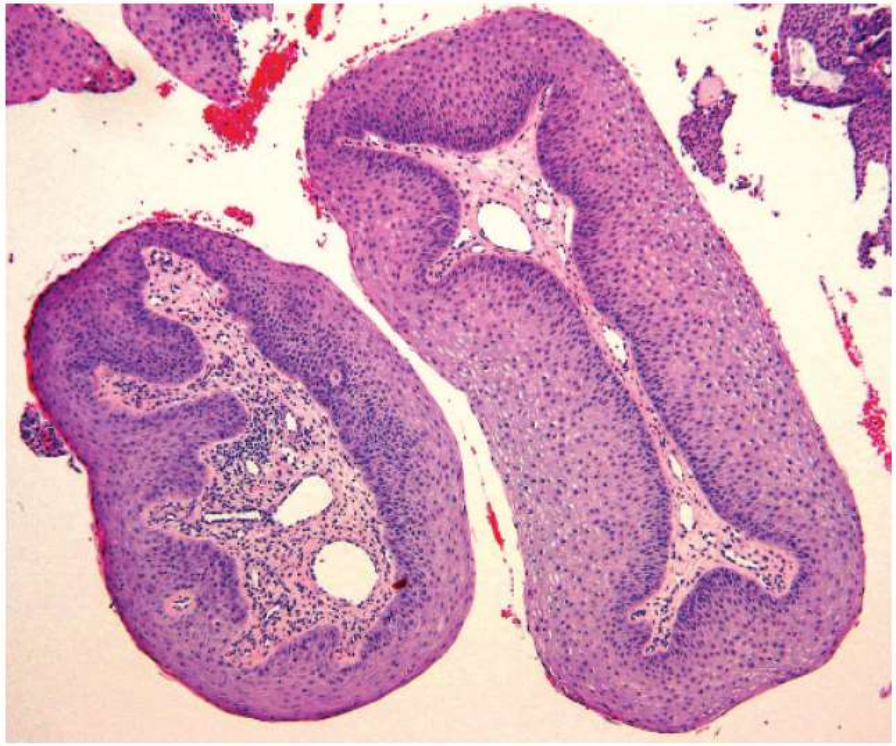




Perez-Ordonez, J Clin Pathol, 2009

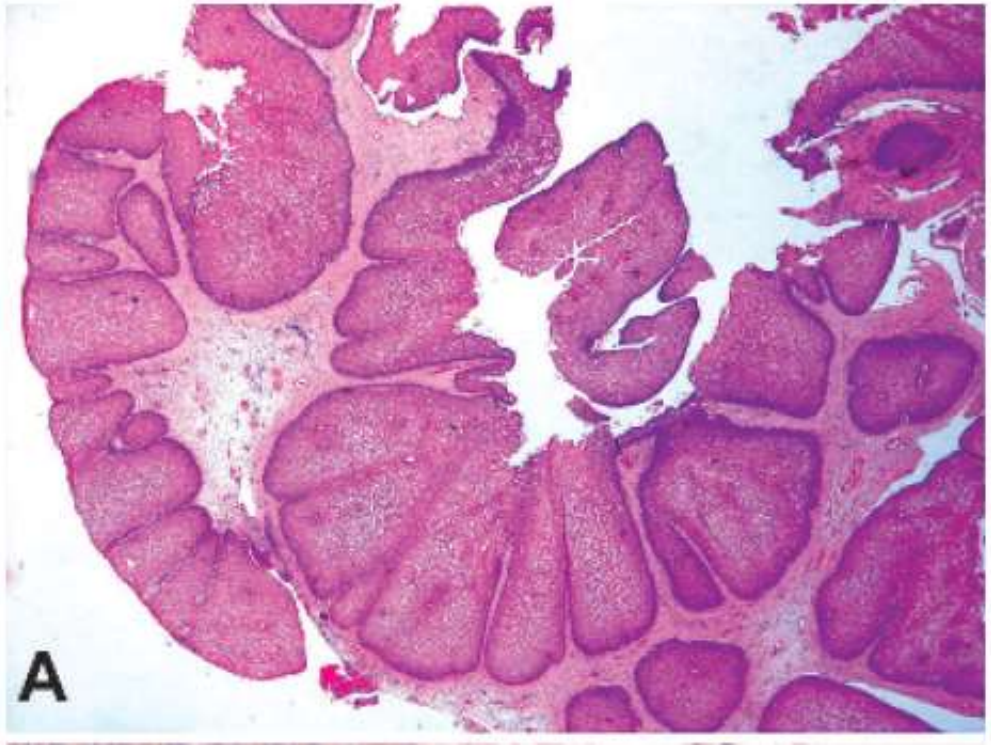
Exophytic Papilloma

- Benign
- Stratified squamous epithelium
- Seromucous glands in stroma
- IHC not well defined



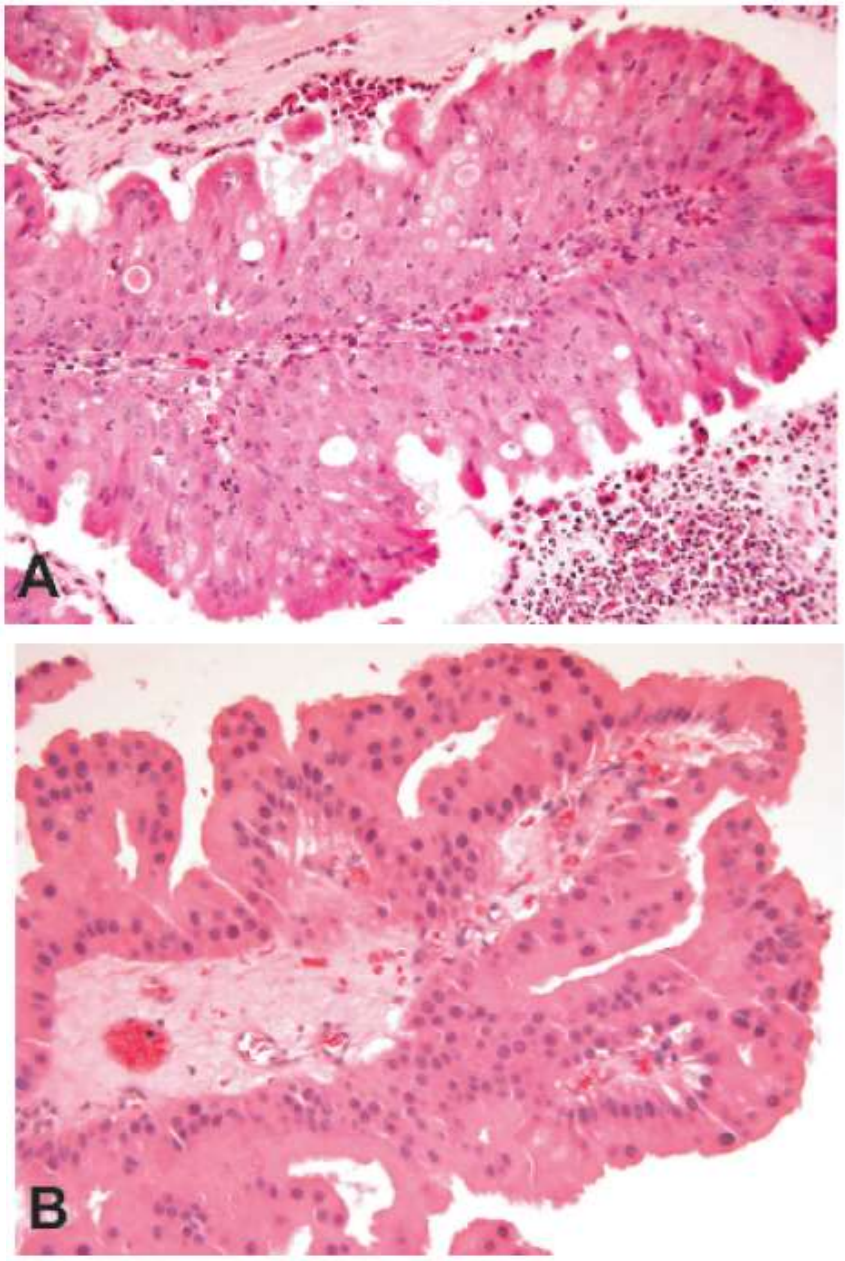
Inverted Papilloma

- Borderline
  - ~10% chance of malignant transformation
- Epithelium mixed
  - **(Nonkeratinizing) squamous**
  - Transitional
  - Mucous
- No seromucous glands in stroma
- IHC: coexpress CK7, CK8, CK19, p63, HMWK



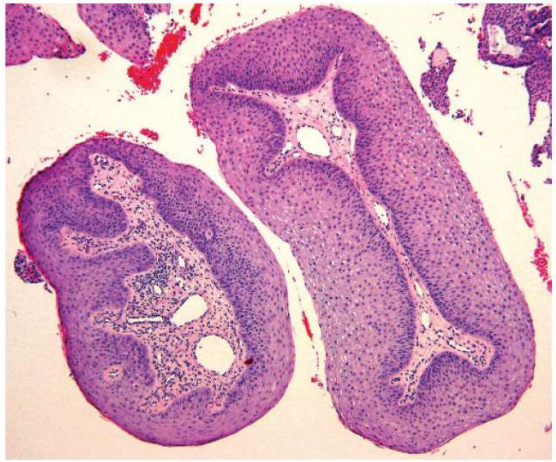
Oncocytic Papilloma

- Benign vs. Borderline?
  - 0-17% malignant transformation
- Multilayered columnar/ oncocytic epithelium
- Seromucous glands in stroma
- IHC not well defined



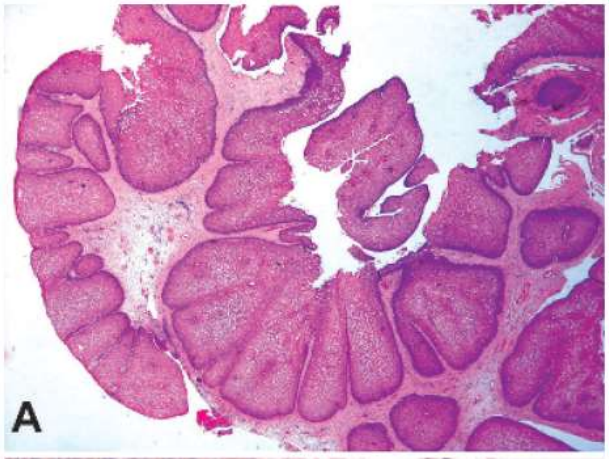
Schneiderian Papillomas

Exophytic



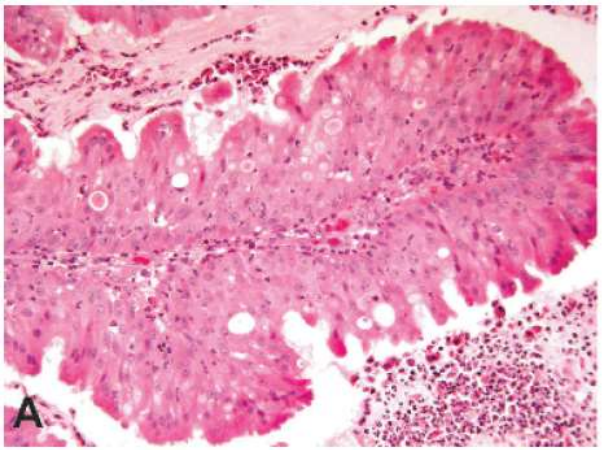
- **Benign**
- **Seromucous glands in stroma**
- **Stratified squamous**

Inverted



- **Risk of malignant transformation**
- **No glands**
- **Mixed epithelium**

Oncocytic



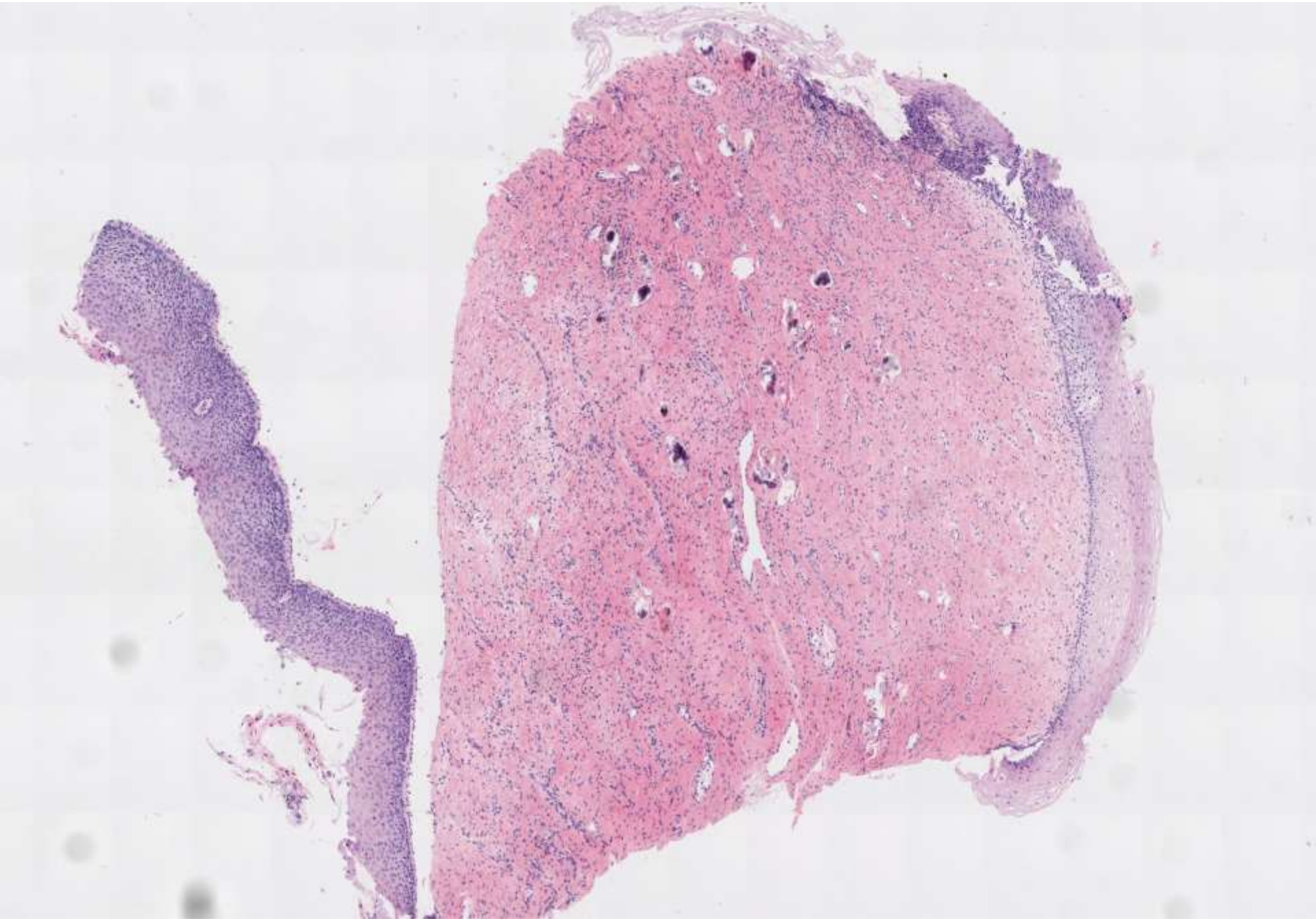
- **Risk of malignant transformation**
- **Seromucous glands in stroma**
- **Oncocytic epithelium**

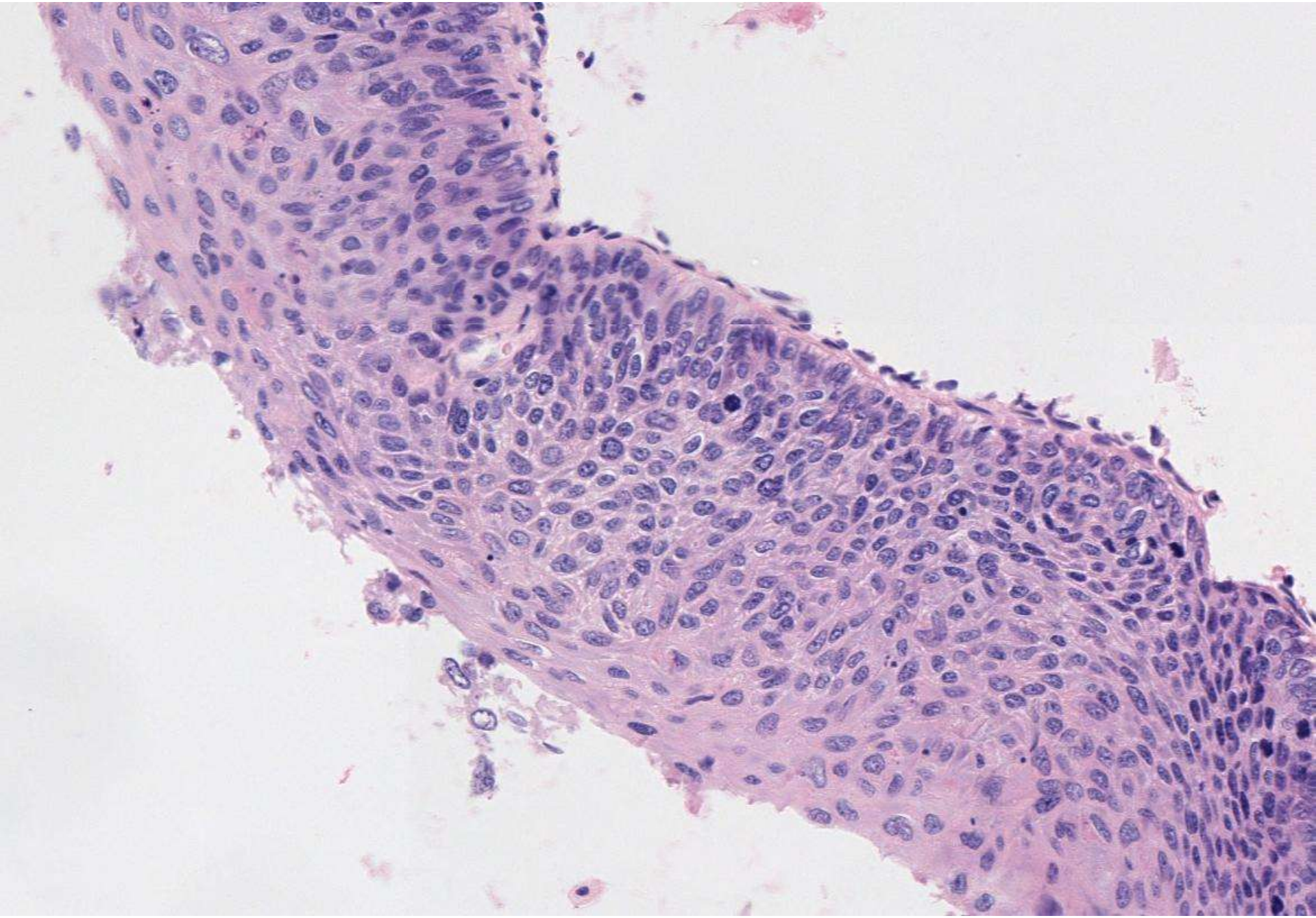
Perez-Ordonez, J Clin Pathol, 2009

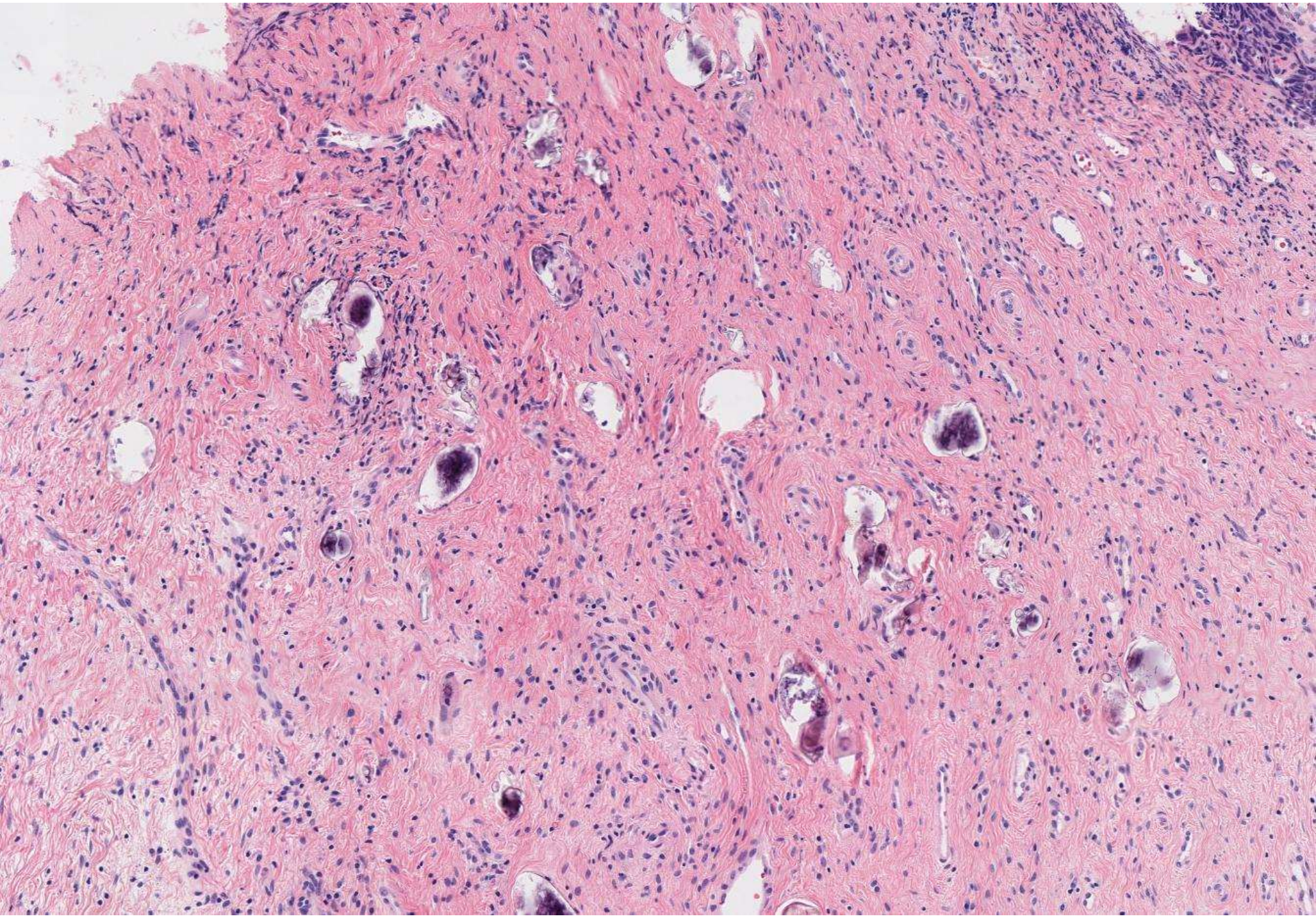
SB 5984

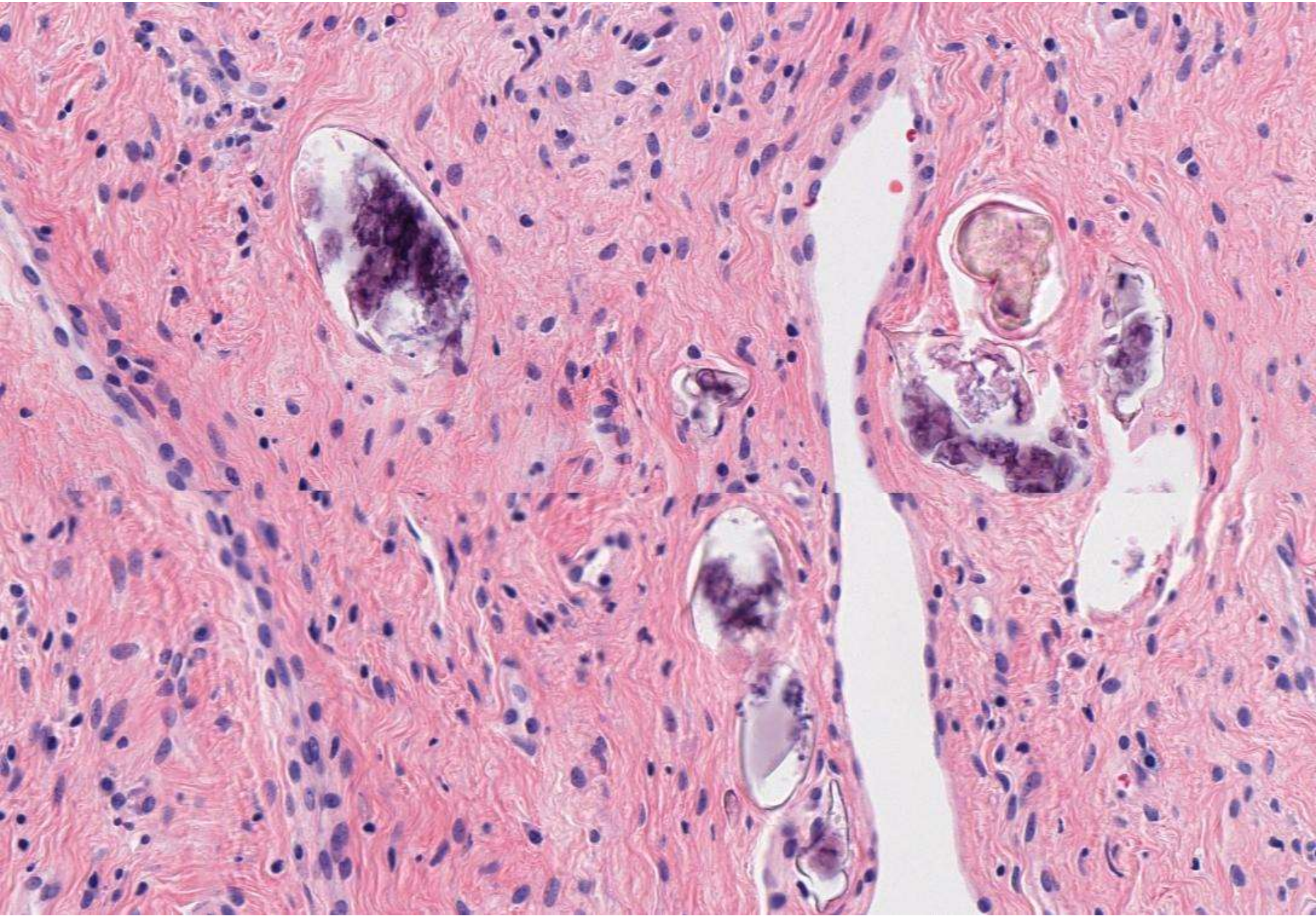
- 40-year-old female with history of micro-invasive cervical cancer. Cervical biopsy performed.

- **Ben Buelow/Charles Zaloudek; UCSF**



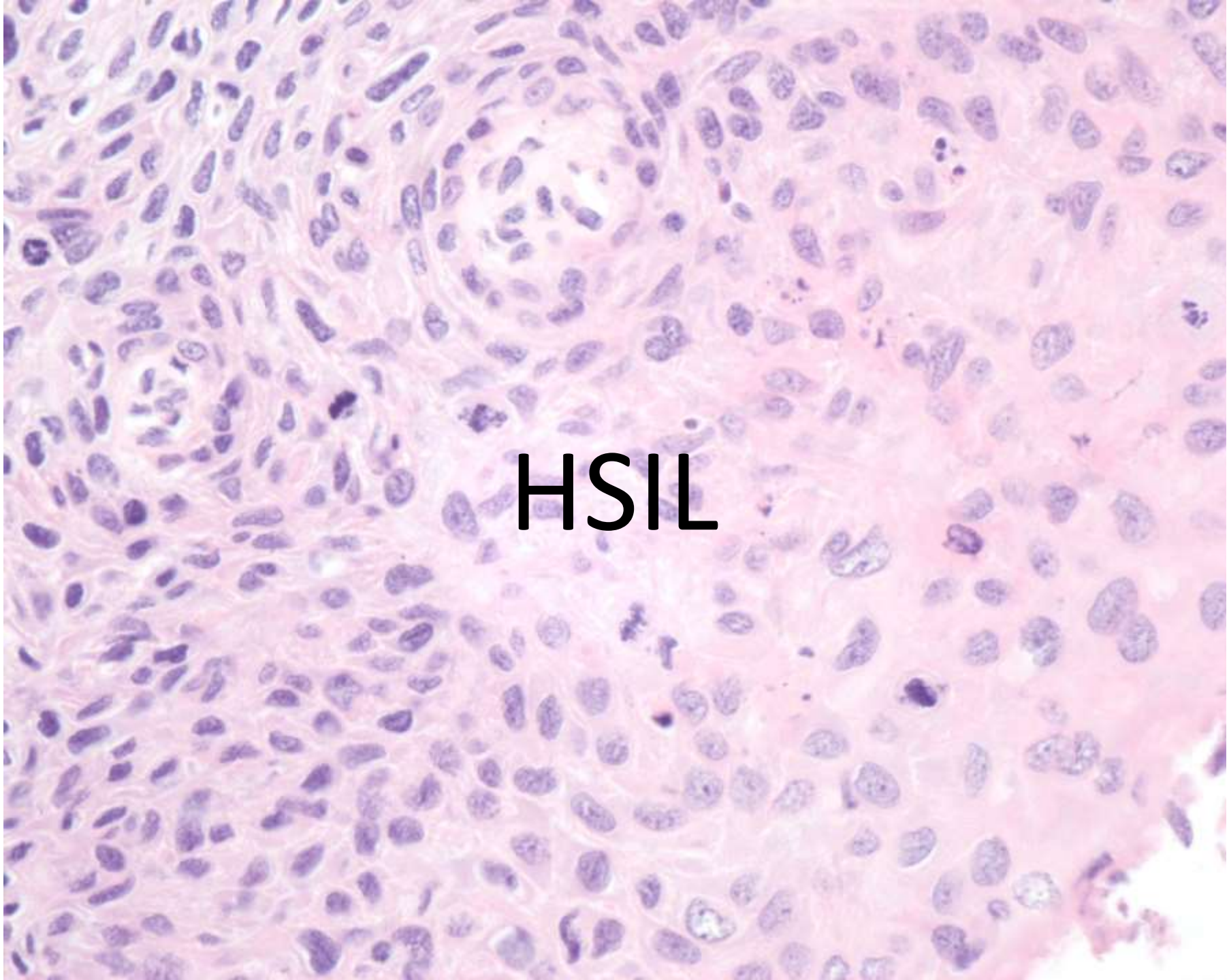


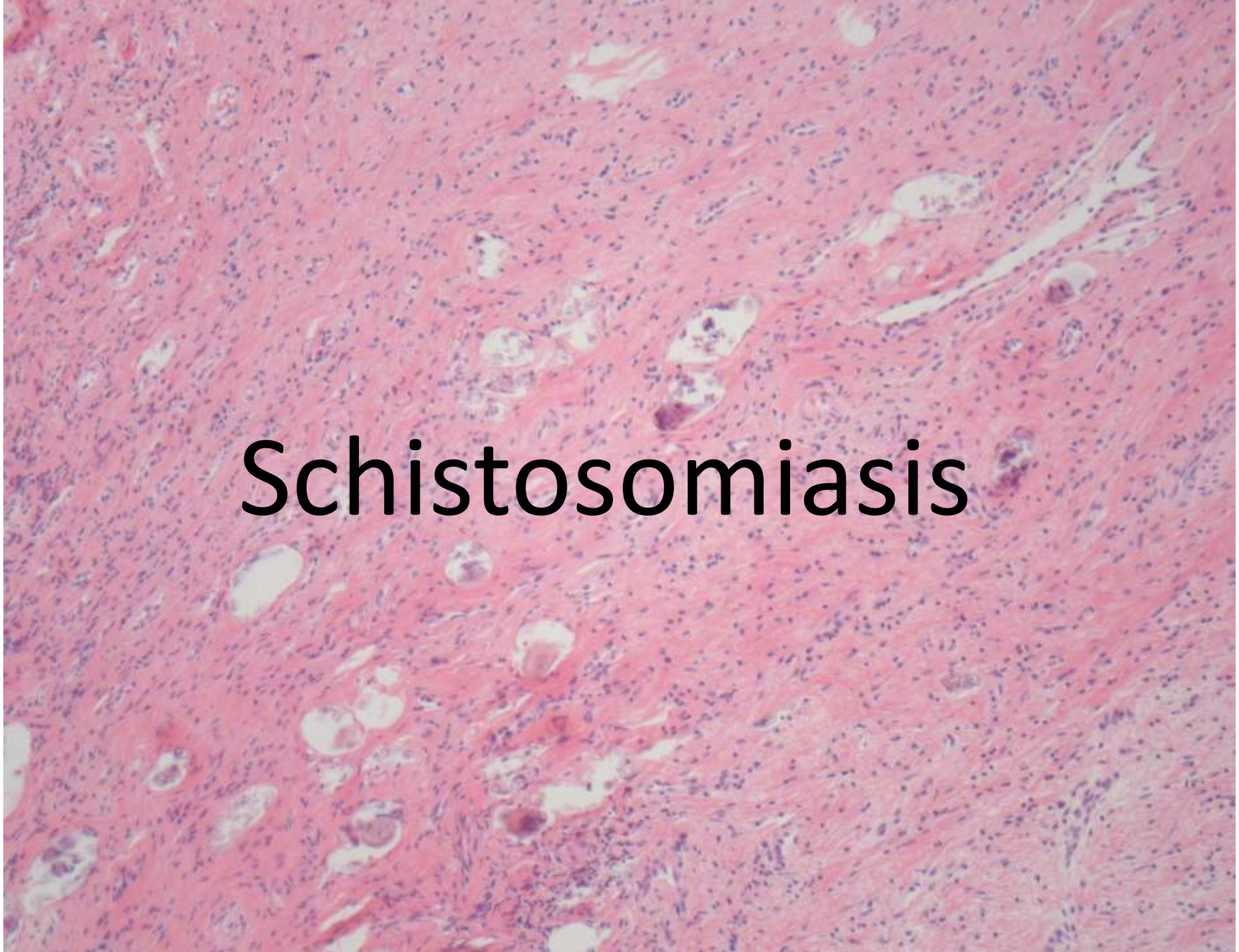


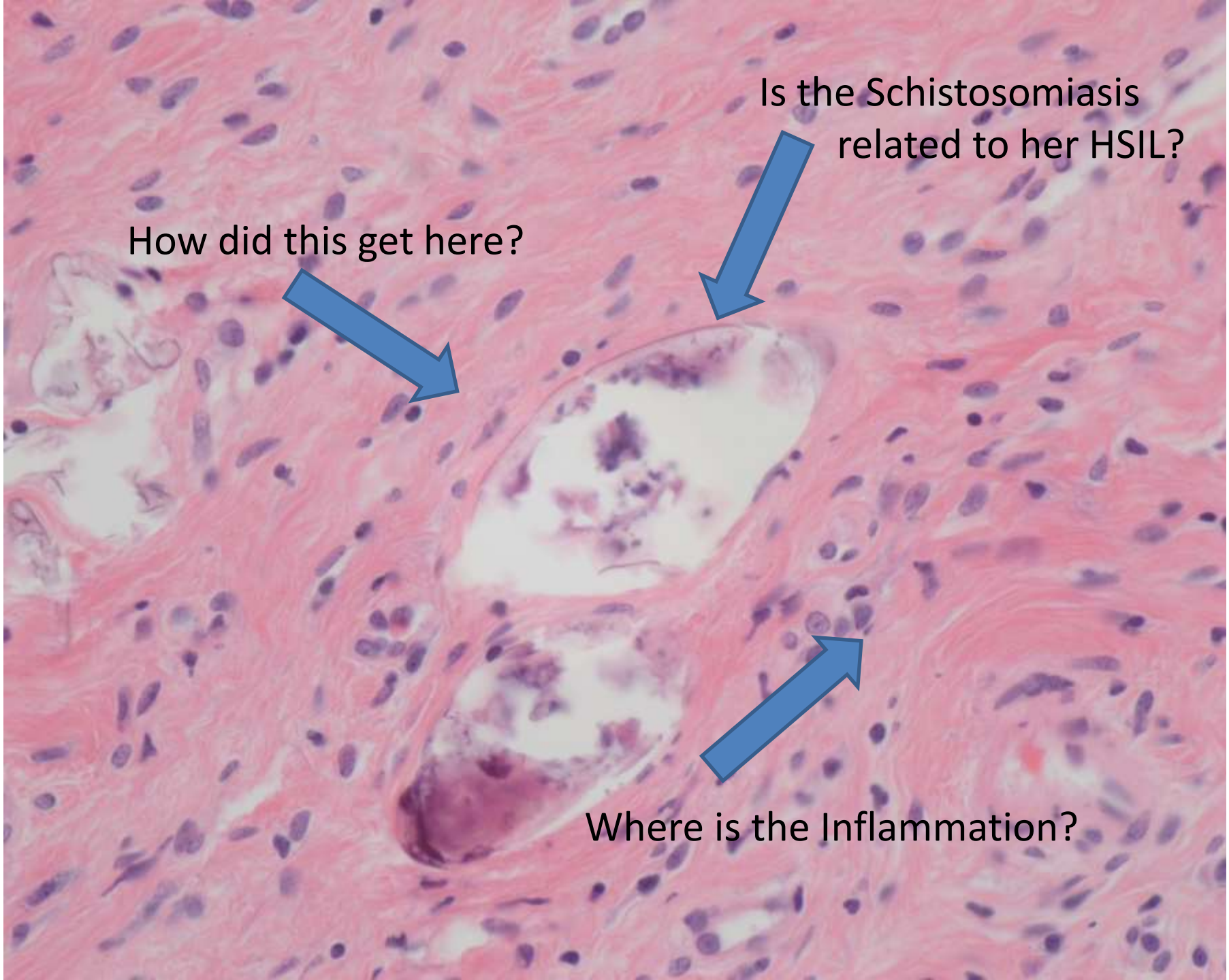


Diagnosis….?

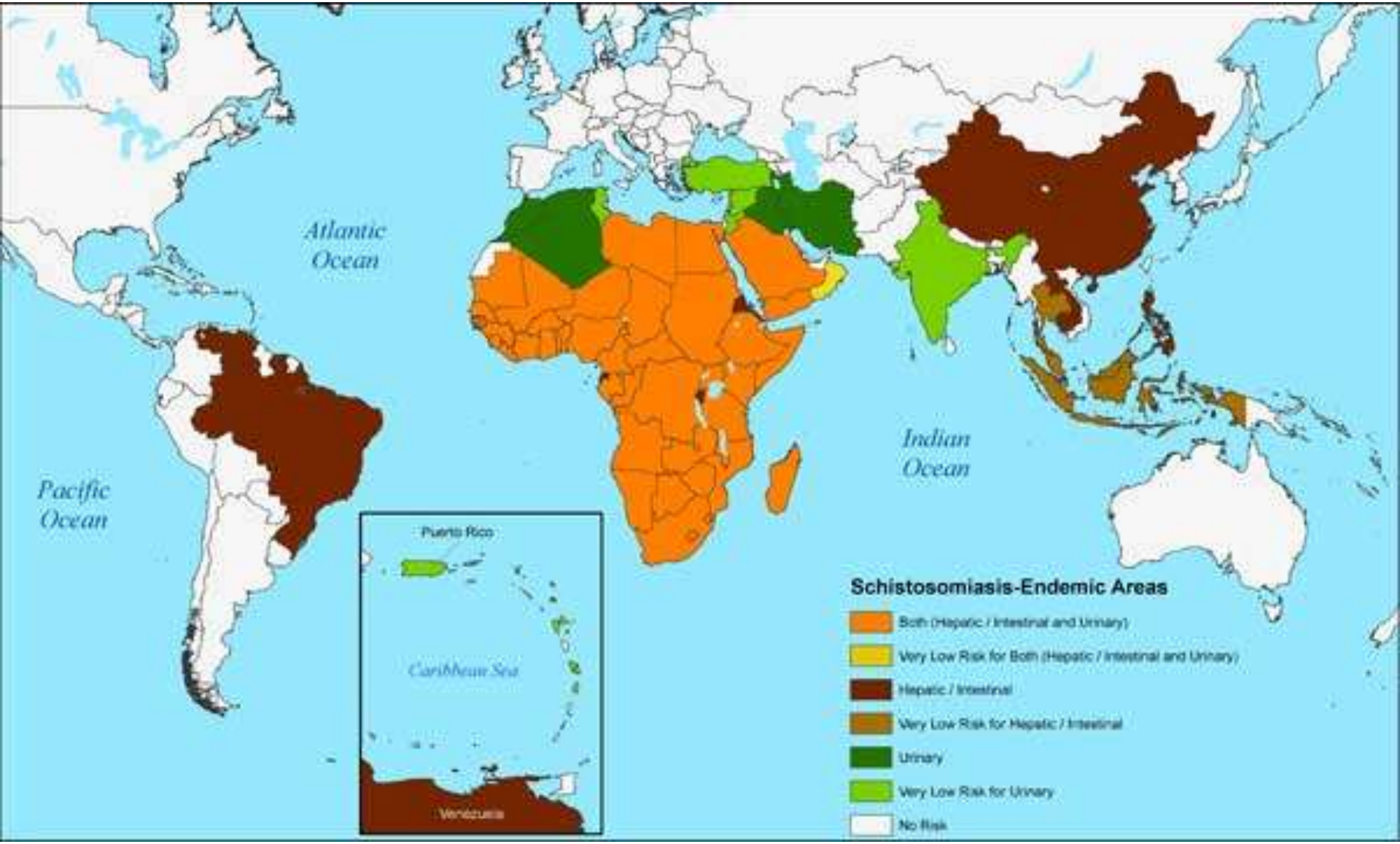
40 year old woman with a cervical lesion


HSIL


Schistosomiasis

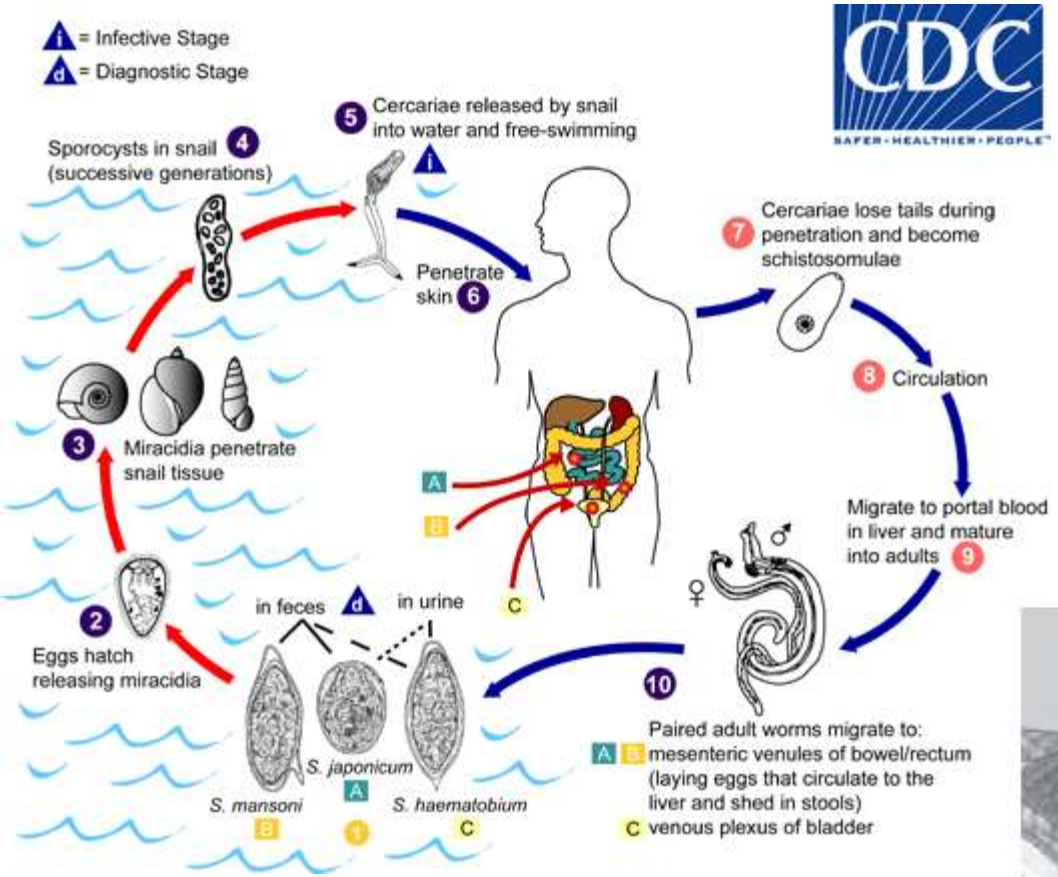

Is the Schistosomiasis related to her HSIL?
How did this get here?
Where is the Inflammation?

Schistosomiasis: Epidemiology

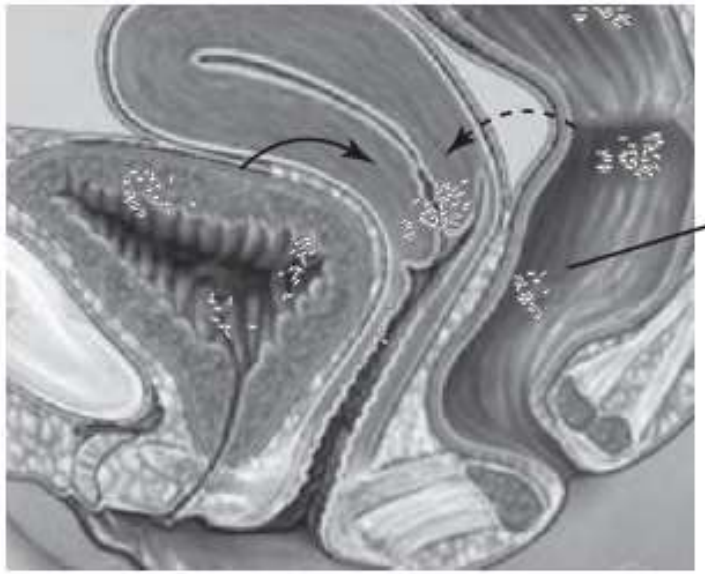


http://www.ucdmc.ucdavis.edu/pathology/education/residency_program/caseofthemonth/201103/final.html

Schistosomiasis: Pathogenesis

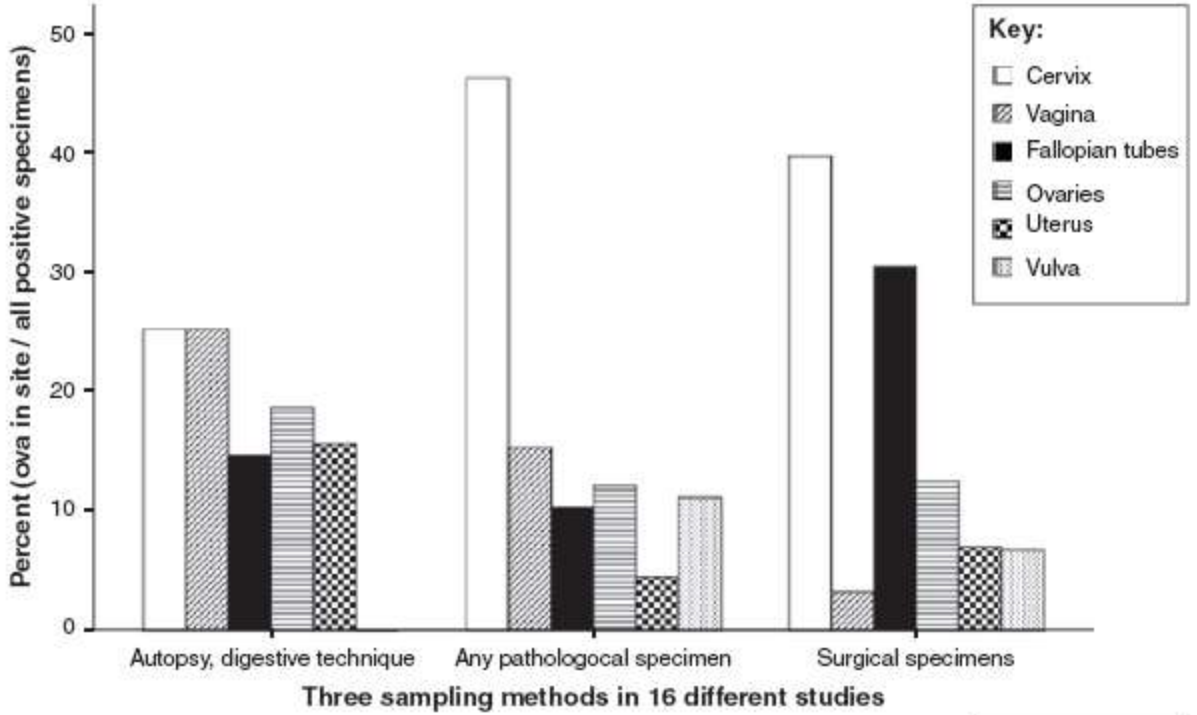


http://www.cdc.gov/dpdx/schistosomiasis/index.html

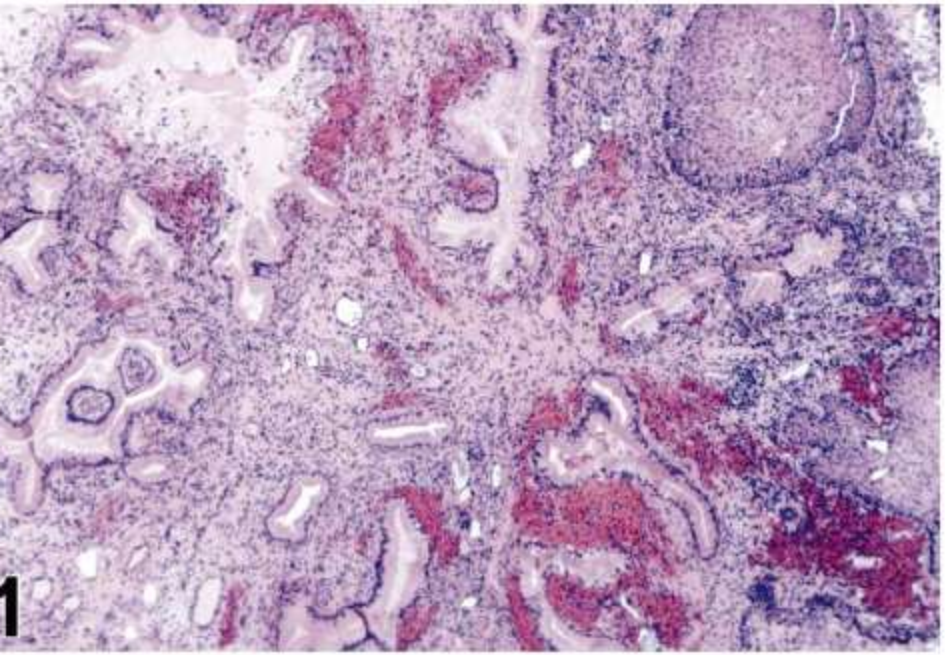


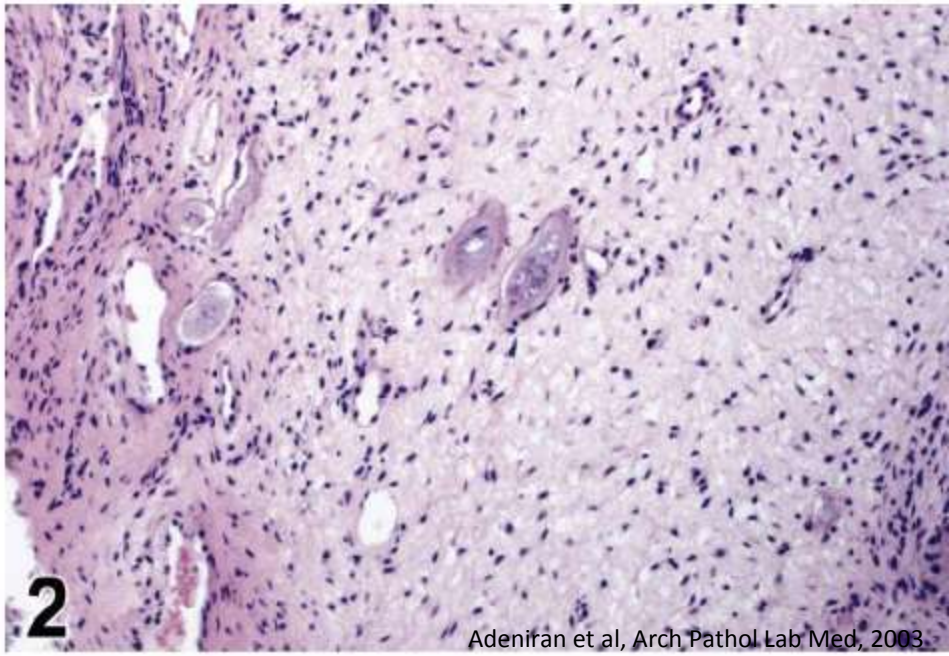
Kjetland et al, Trends Parasitol, 2012

TRENDS in Parasitology



Kjetland et al, Trends Parasitol, 2012 *TRENDS in Parasitology*

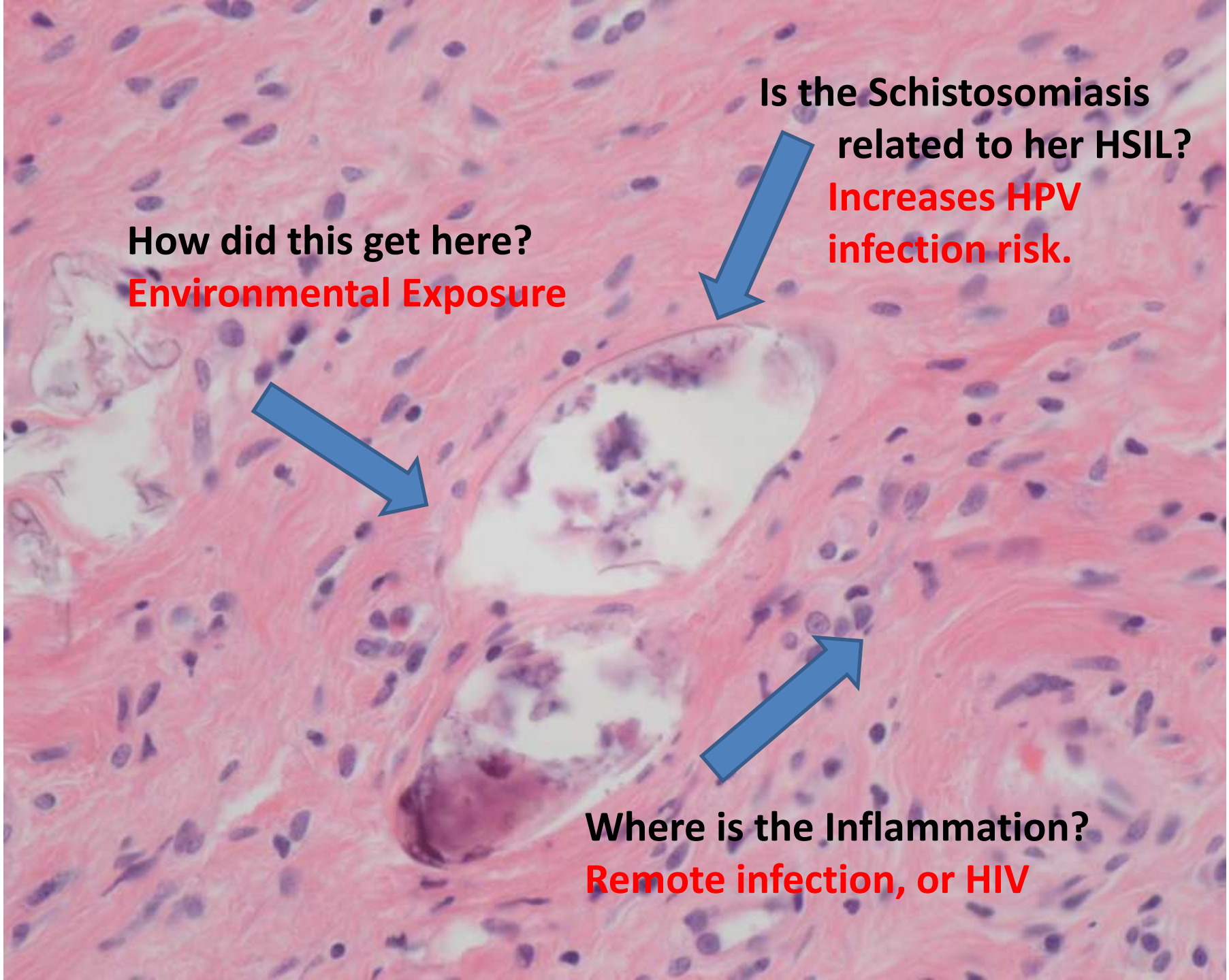




Adeniran et al, Arch Pathol Lab Med, 2003

Prabhakaran, V. C. and L. J. Brown (2004). Cervical schistosomiasis and neoplasia in HIV-infected patients. Int.J.Gynecol.Pathol **23**(4): 403-404.

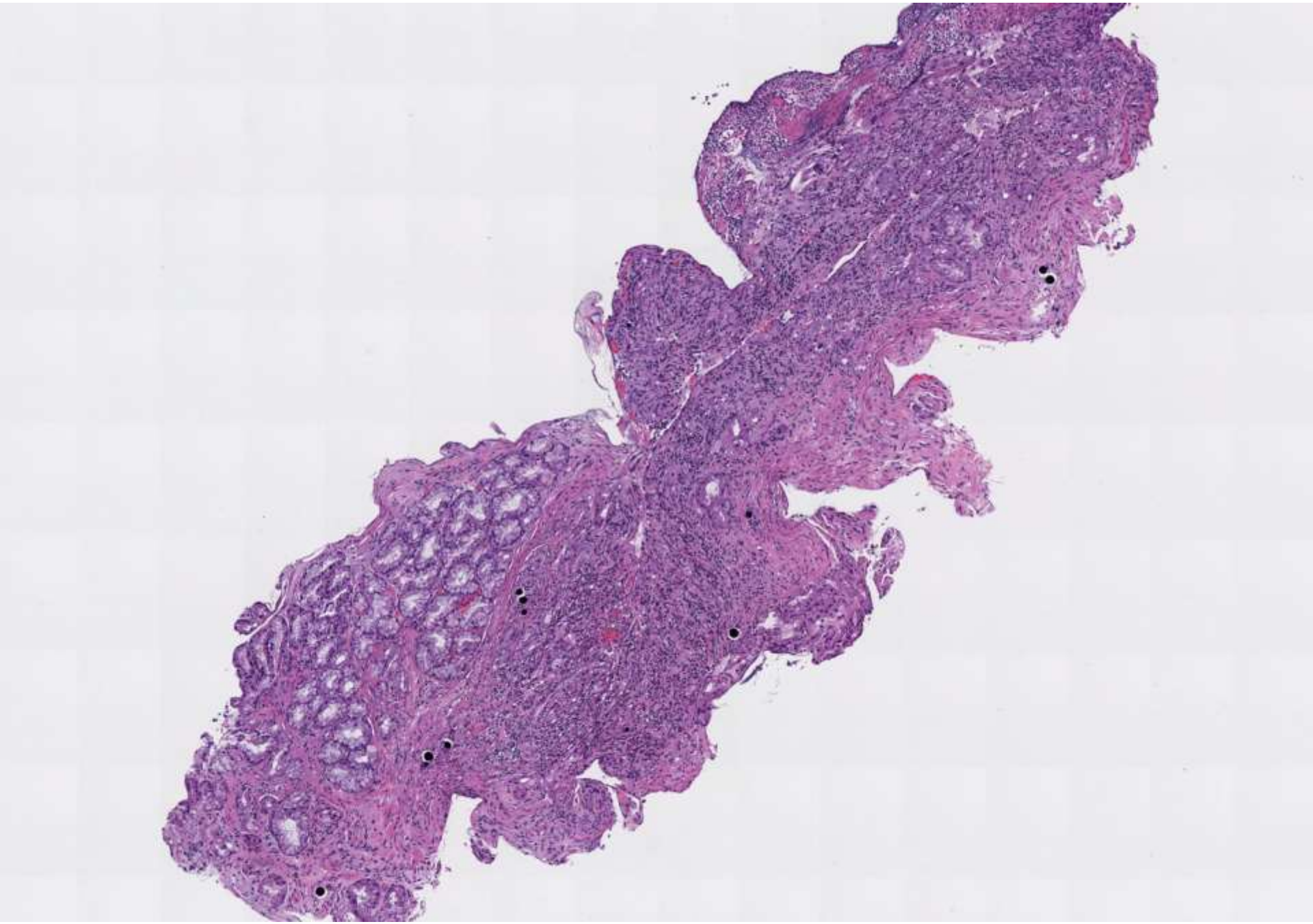
"We report two HIV-positive women with schistosomiasis of the uterine cervix, a disease that is being increasingly seen in developed countries. In both cases, there were no schistosoma ova in the cervical Papanicolaou smears. Both patients underwent LLETZ procedures that revealed **an absence of a granulomatous response to the schistosoma ova, a finding that should alert the pathologist to the possibility of HIV infection.** The absence of ova on cervical smears of HIV-infected women with schistosomiasis is probably related to the absence of granulomatous inflammation in these patients. A diligent search should be made for schistosoma ova in the cervical biopsy of patients from endemic areas. Treatment of schistosomiasis in HIV-infected patients should be prompt and complete to prevent recurrent high-risk HPV infection."

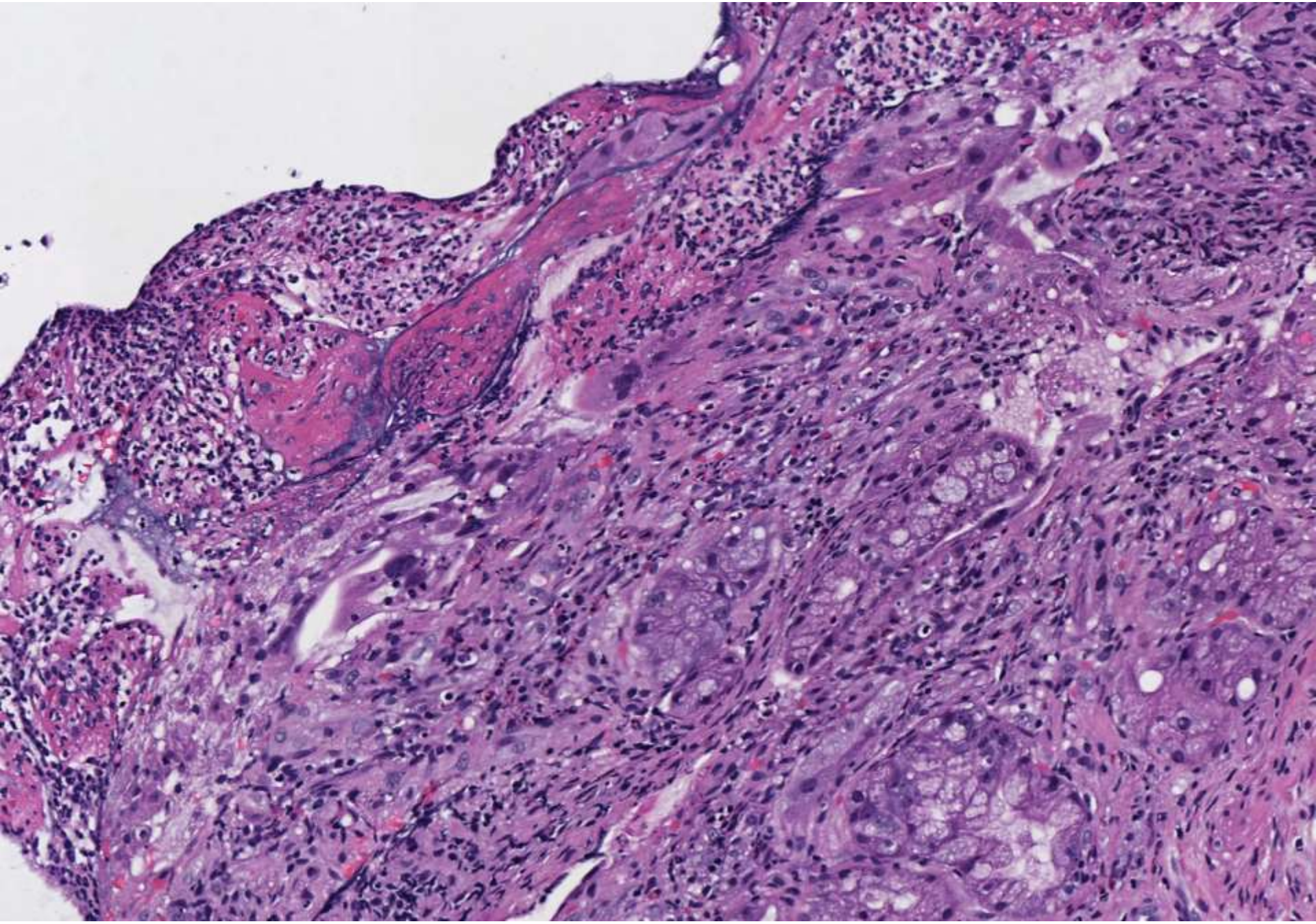

Is the Schistosomiasis related to her HSIL?
Increases HPV infection risk.
How did this get here?
Environmental Exposure
Where is the Inflammation?
Remote infection, or HIV

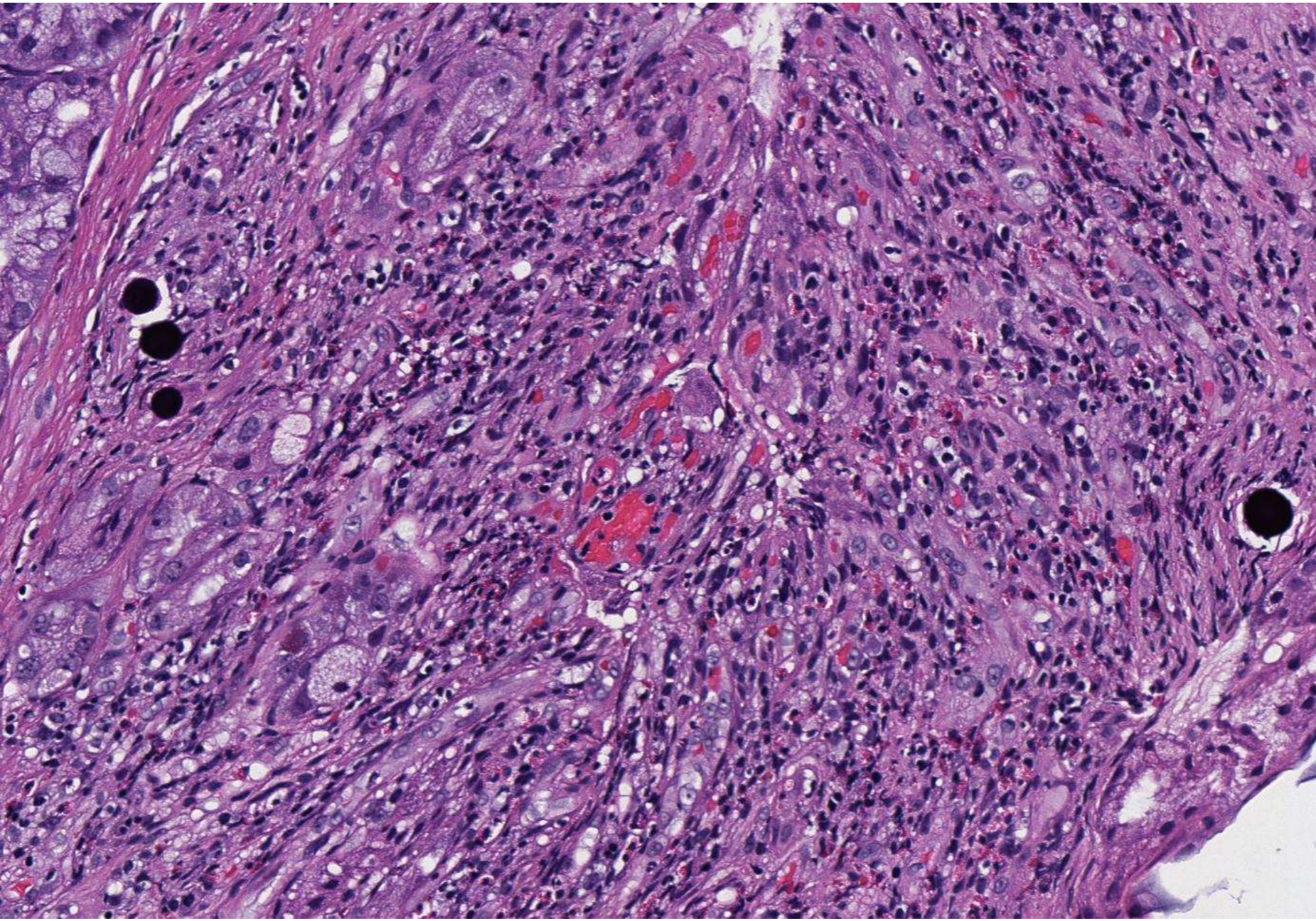
SB 5985

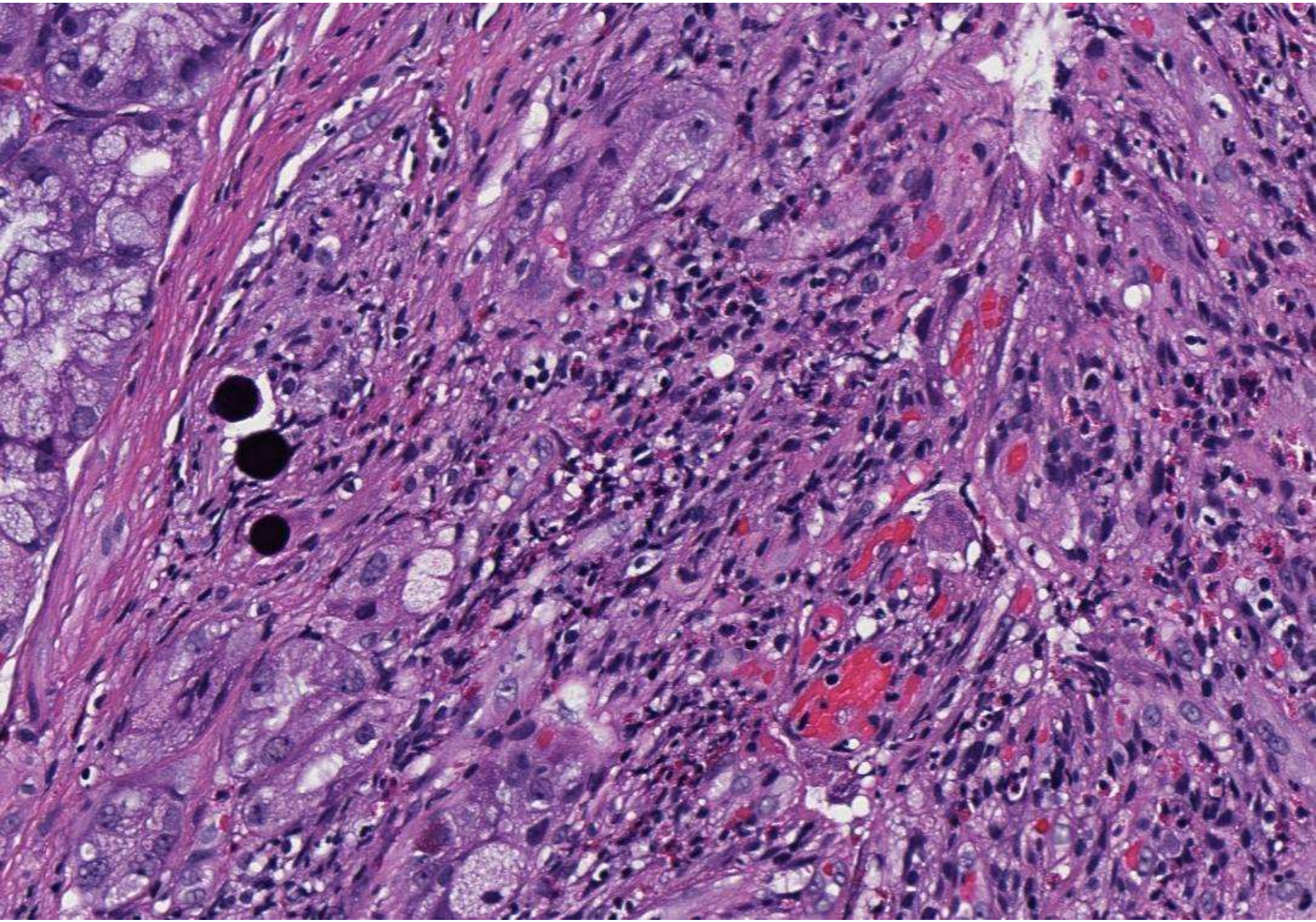
- 59-year-old female underwent upper endoscopy for unspecified etiology. Duodenal biopsy performed.

- **Will Rogers; El Camino Hospital**









Diagnosis….?

Yttrium induced duodenitis

- Additional History:
  - GI Neuroendocrine tumor with multiple liver metastases
  - The patient had Yttrium SIRT (selective internal radiation therapy) with Yttrium 90 microspheres 1 month prior to duodenal biopsy

Pathophysiology

- Yttrium microspheres delivered to liver tumor (usually CRC metastasis) via hepatic artery branches
- Retrograde migration of microspheres into the gastric and/or duodenal circulation
- Effects:
  - Gastric and duodenal ulceration, bleeding, perforation
  - Pancreatitis, hepatitis, cholecystitis

Histologic Features

- Purple particles measuring about 40 um in diameter
- Mucosal ulceration
- Fibrinopurulent exudate with granulation tissue and reactive stromal cells.
- Epithelial reactive changes:
  - Apoptosis and mucin depletion.
  - Glandular cystic dilatation, epithelial flattening
  - Foveolar hyperplasia
- Stromal reactive changes
  - Capillary ectasia and prominent plump endothelial cells.

Incidence

- 0-13%, generally within first 2 months after procedure (10 days to 5 months).
- One case series documented gastric ulceration in 29% of patients.

- Biopsies of this finding may increase as use of this treatment modality increases.

SB 5986

- 66-year-old male with elevated WBC count on peripheral blood (28K/uL). Bone marrow biopsy also subsequently performed.

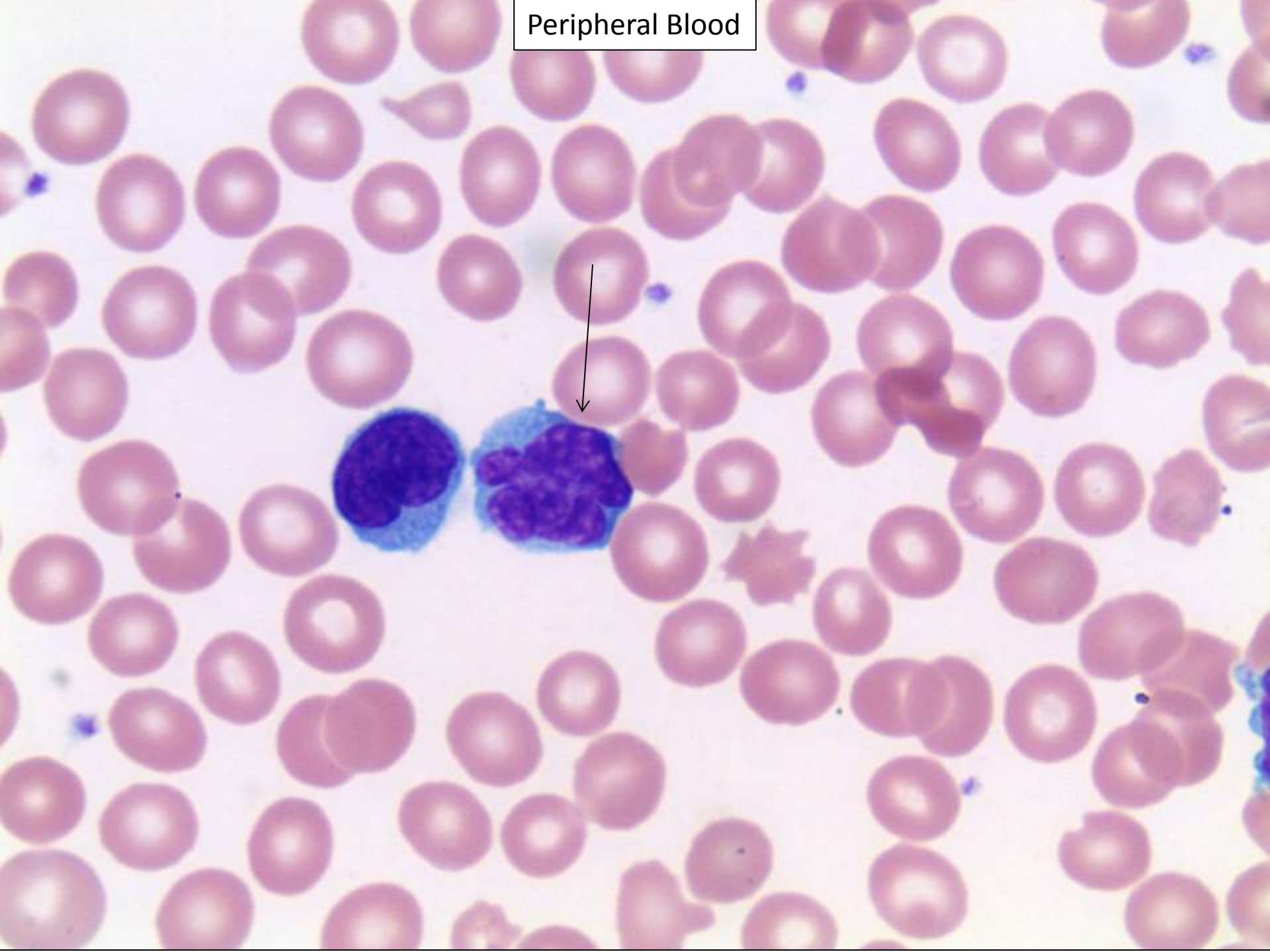
- **Bijayee Shrestha; El Camino Hospital**

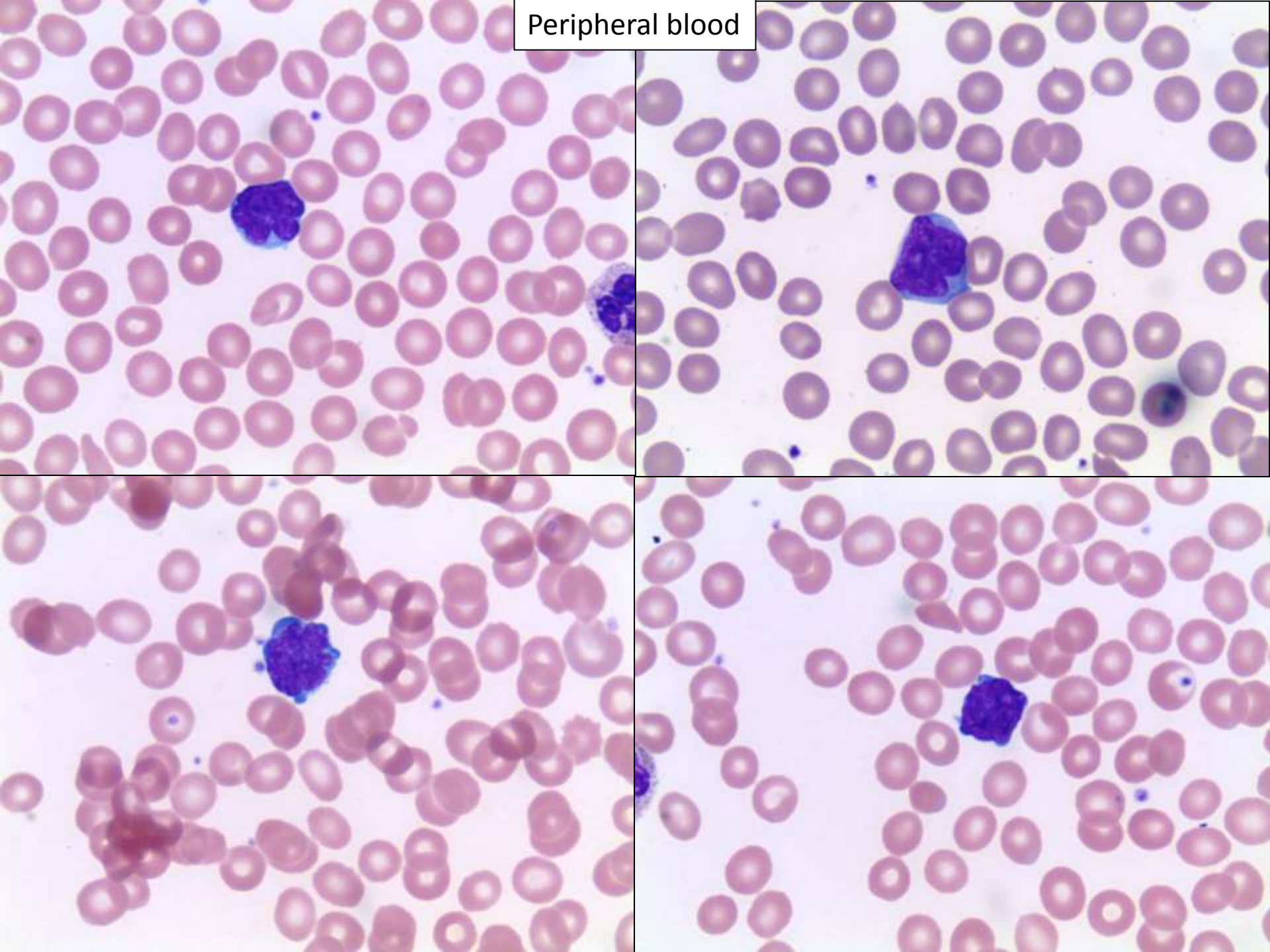
WBC:	28.7 K/uL
RBC:	4. 06 M/uL
Hgb:	12.6 g/dL
HCT:	37.6 %
MCV:	92.5 fL
MCHC:	30.9 g/dL
RDW:	13.6 %
Plt:	177 K/uL

Atypical lymph: 36%

Eosinophils: 14%

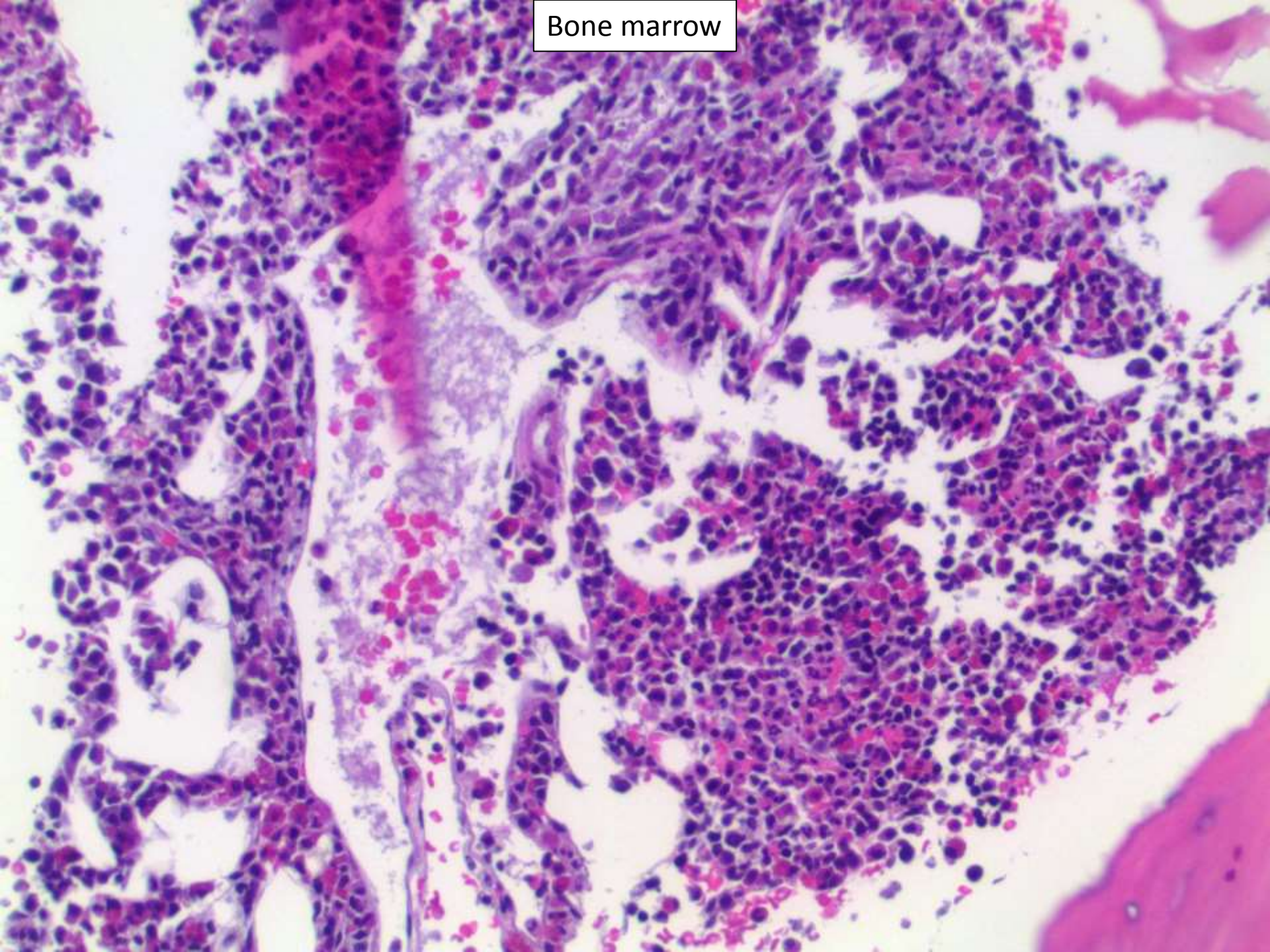
Monocytes: 6%

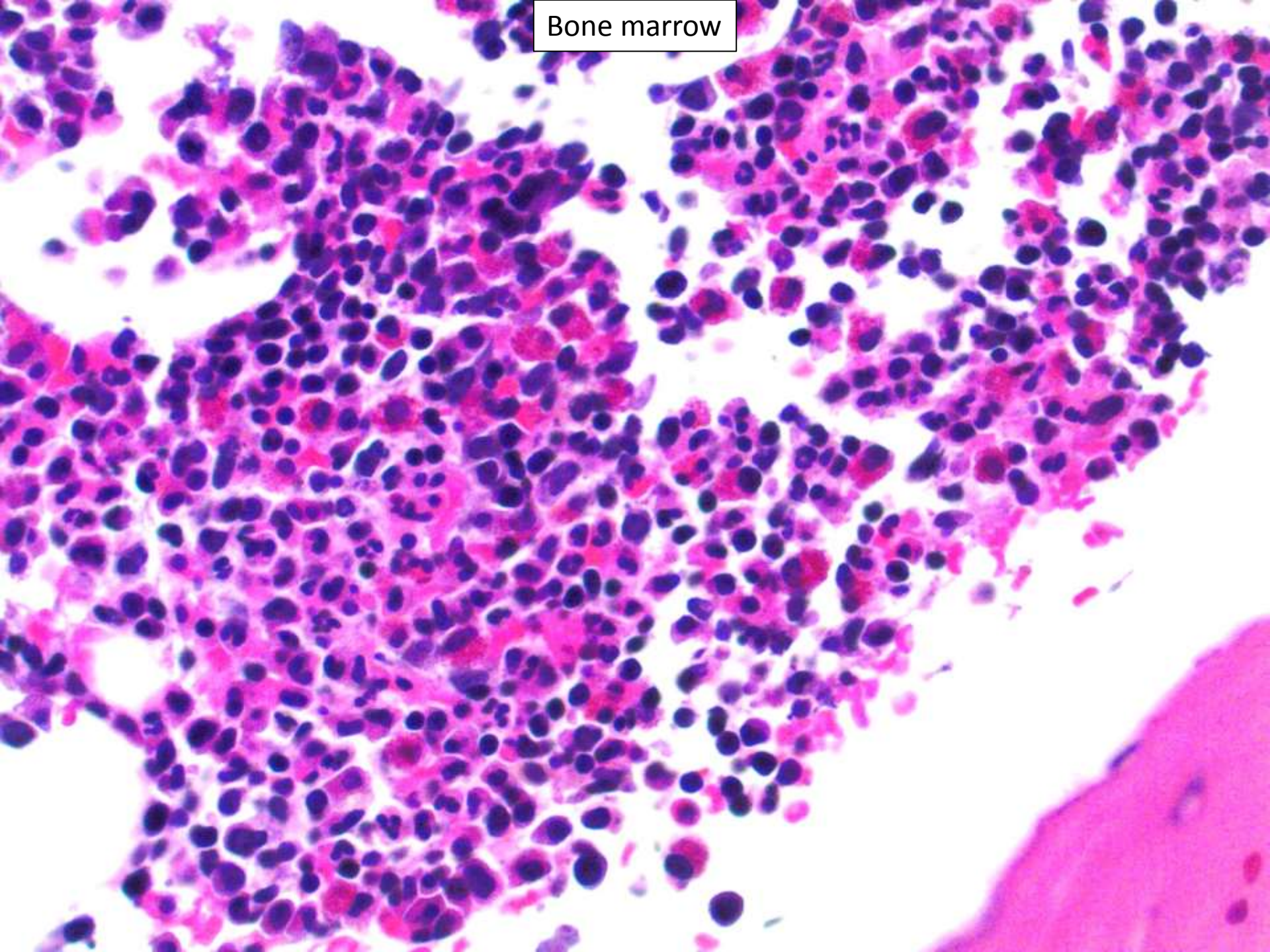

Peripheral Blood

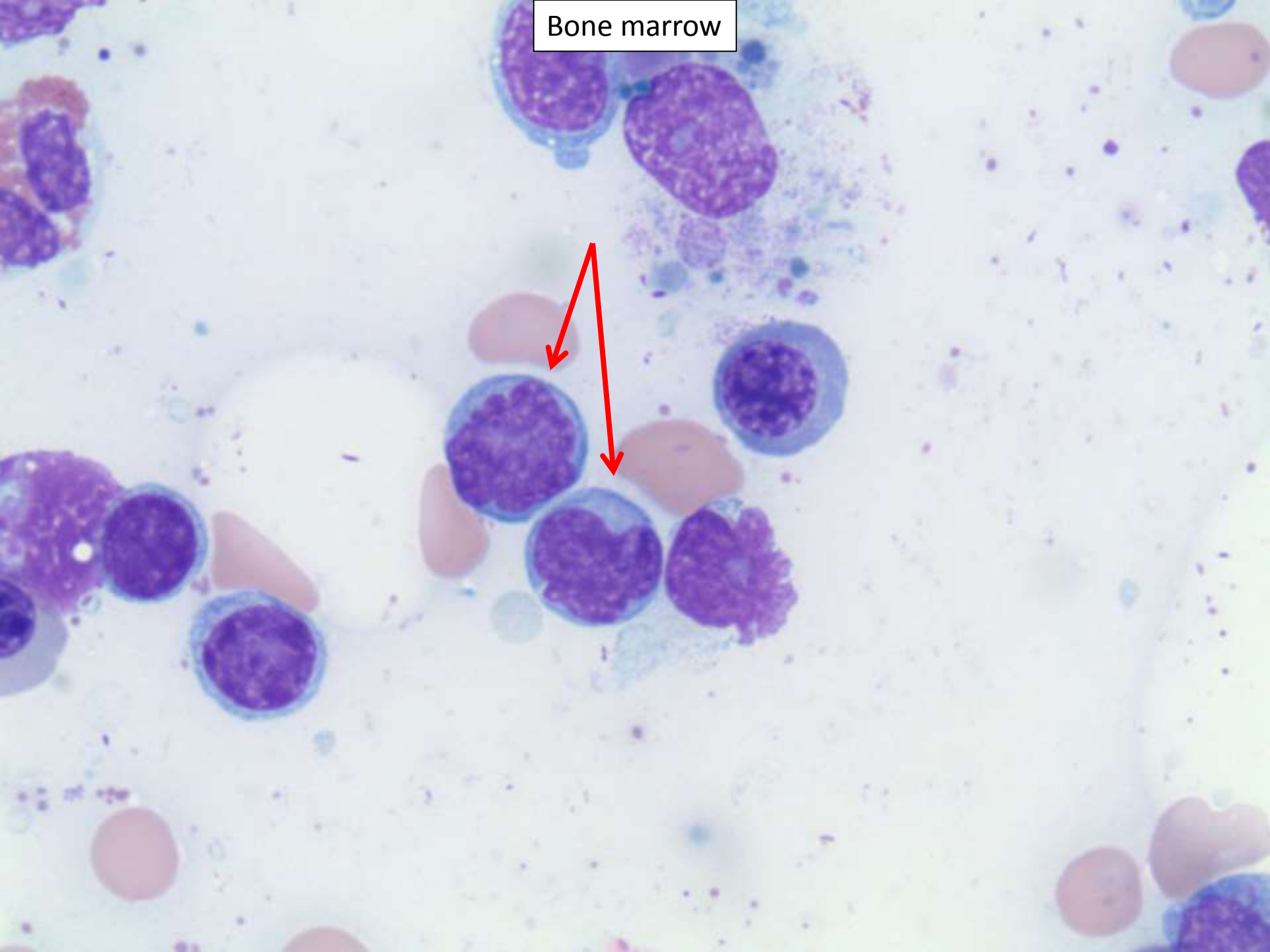

Peripheral blood

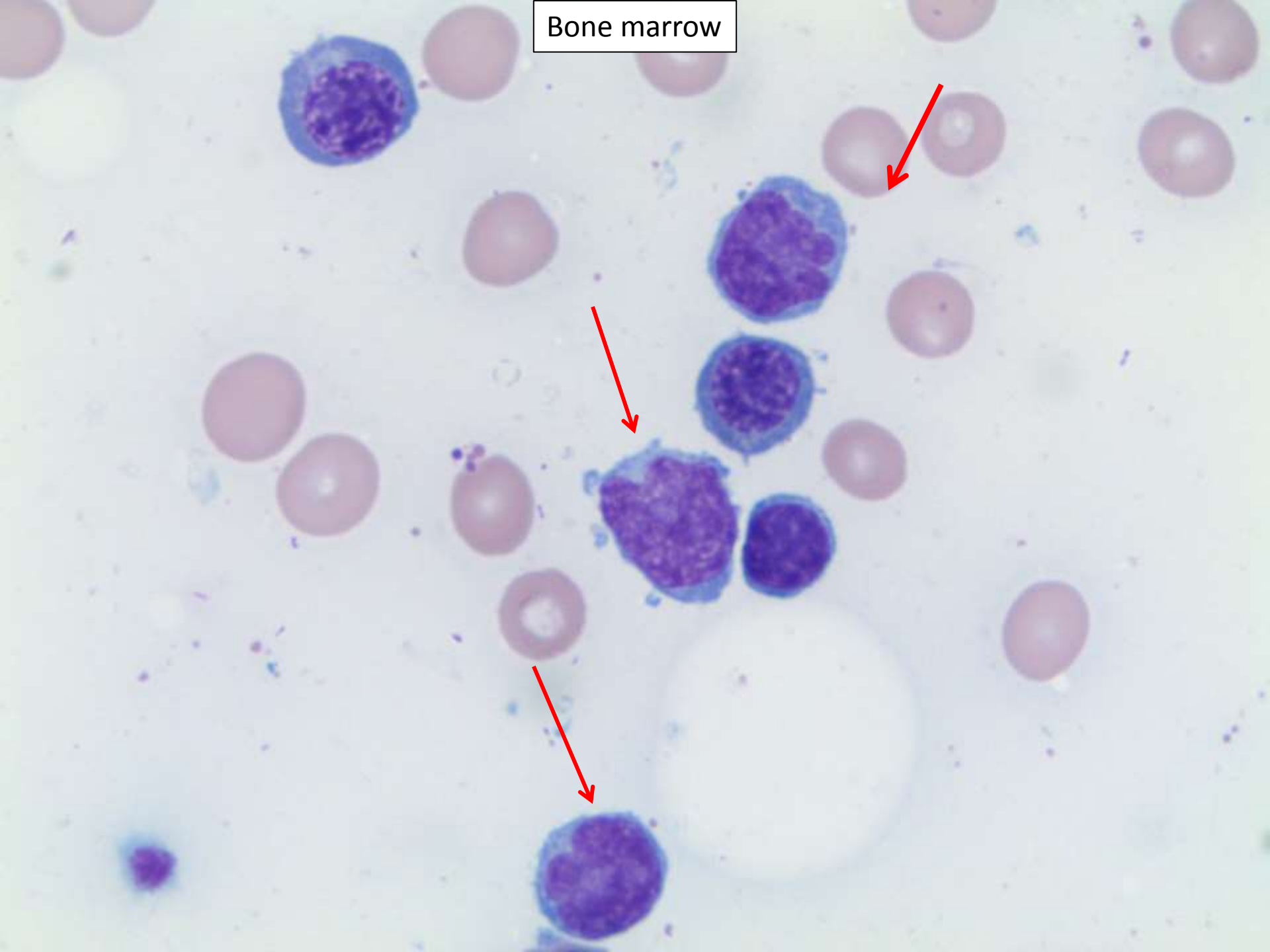
Flow cytometry

- Peripheral blood:
  - CD3+, CD4+, CD7-,CD8-, CD25-


Bone marrow


Bone marrow

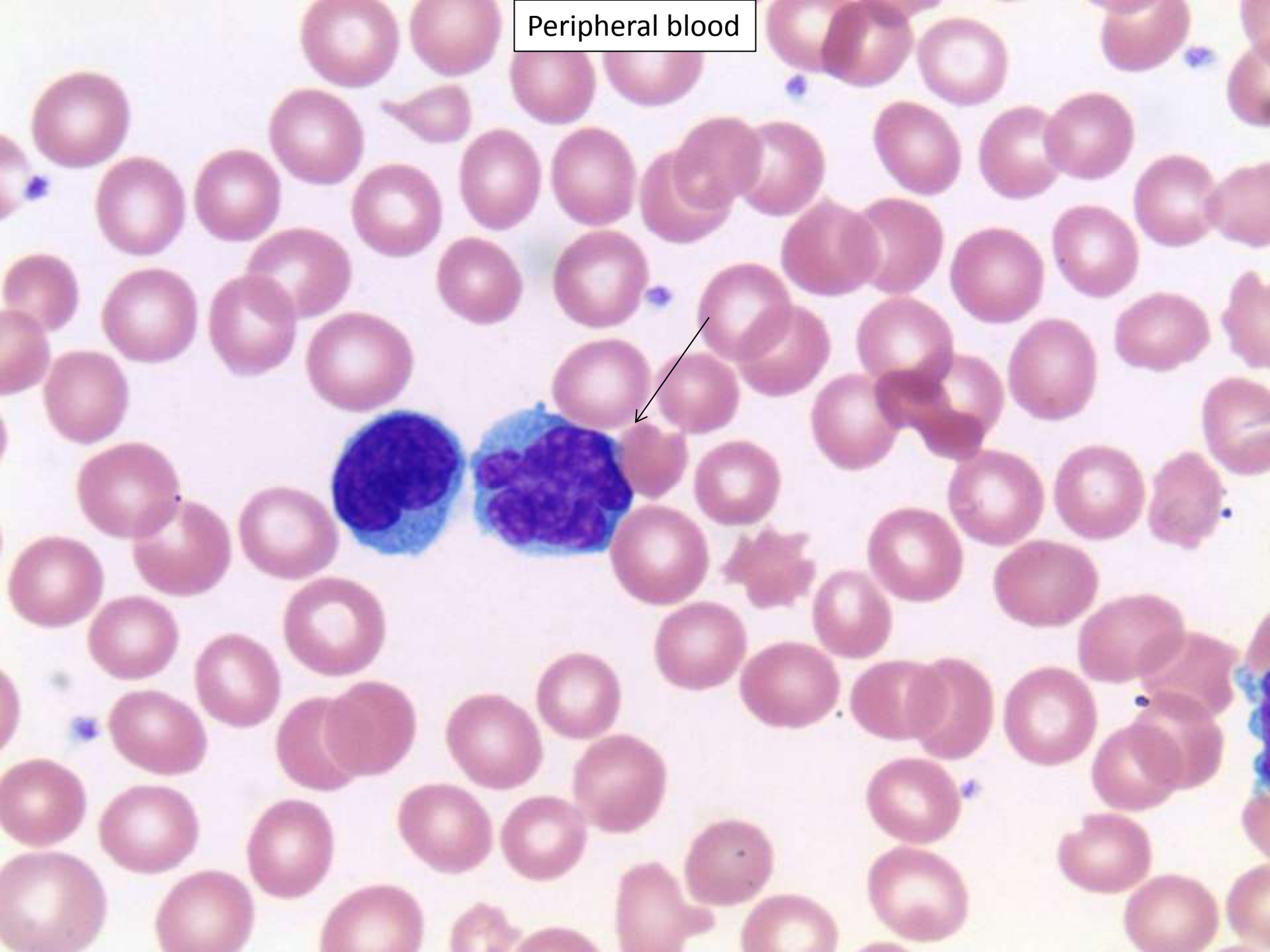

Bone marrow

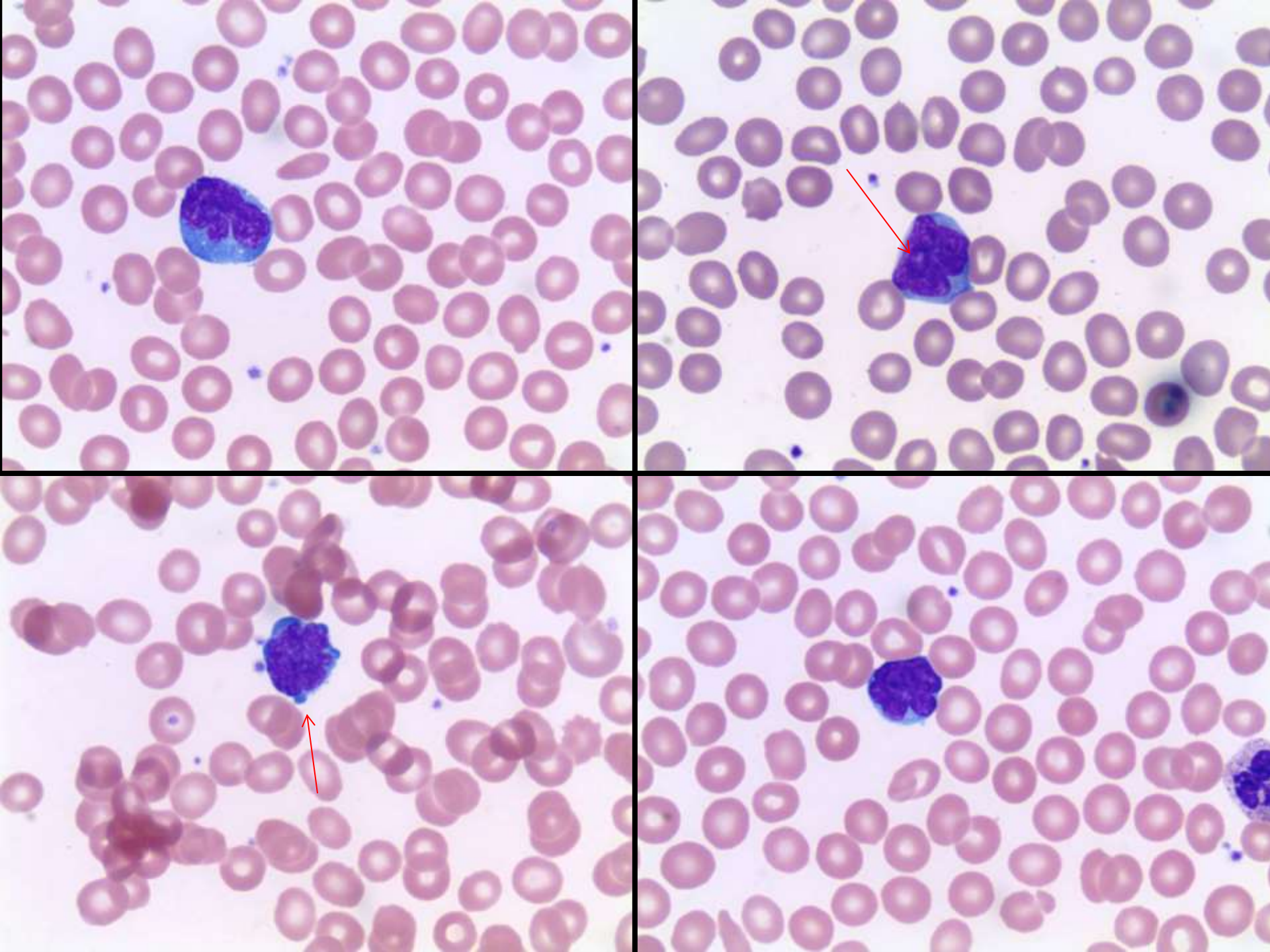

Bone marrow

Diagnosis….?

Clinical history:

- 66 M, Asian
- Generalized fatigue, nausea, constipation and dizziness
- No skin rashes, lymphadenopathy or organomegaly
- Serum Calcium: 13.3 mg/dL (8.9-10.1 mg/dL)
- LHD: 452 IU/L (98 -192 IU/L)
- CBC:
  - WBC: 28.7 K/μL
  - Absolute lymphocytosis, monocytosis and eosinophilia
  - 36% atypical circulating lymphocytes


Peripheral blood



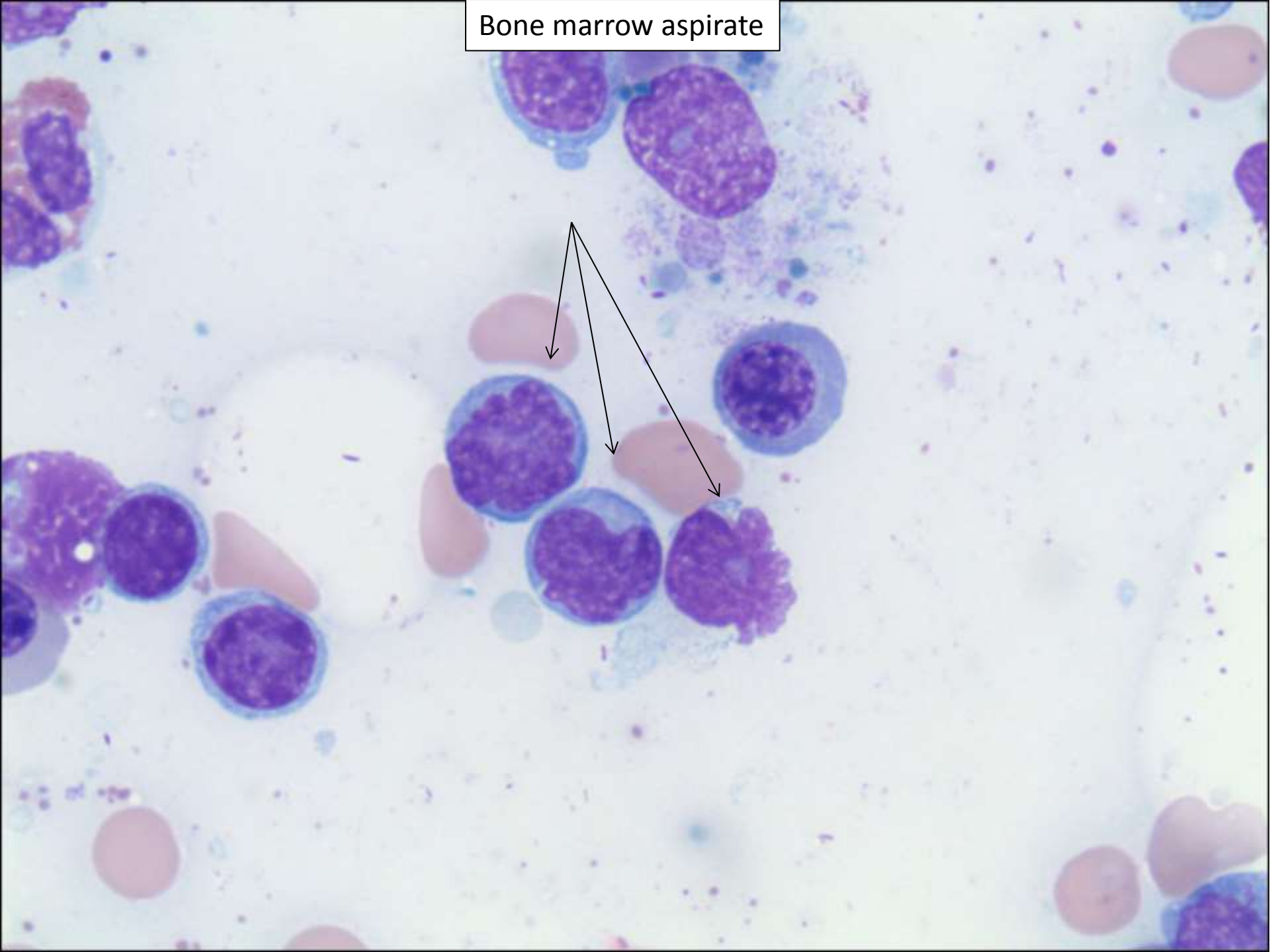
Peripheral blood flow cytometry:

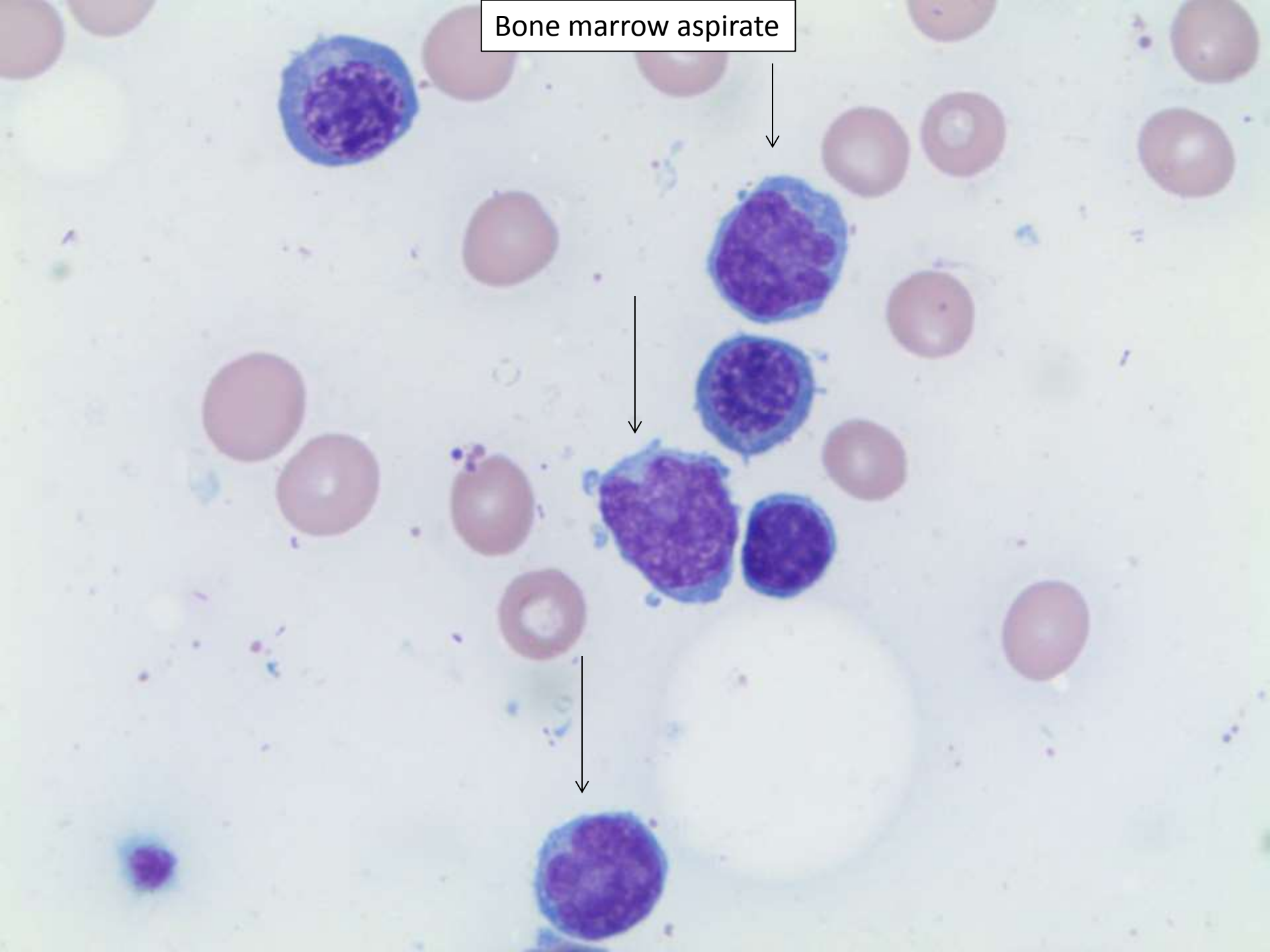
Positive

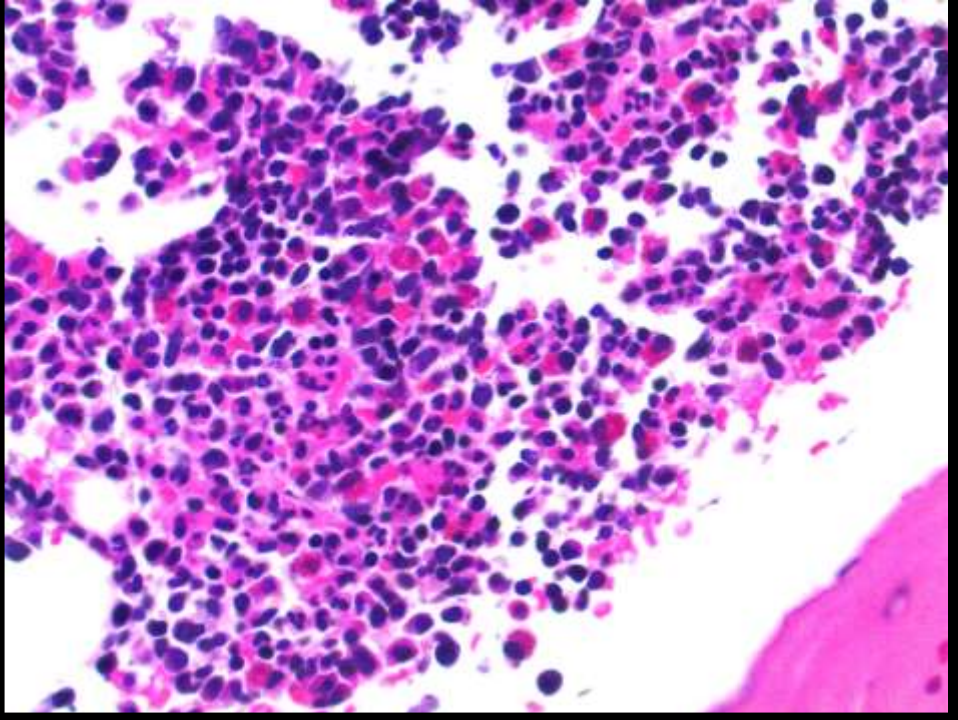
- CD2
- Dim CD3
- Dim CD4
- CD5
- CD38

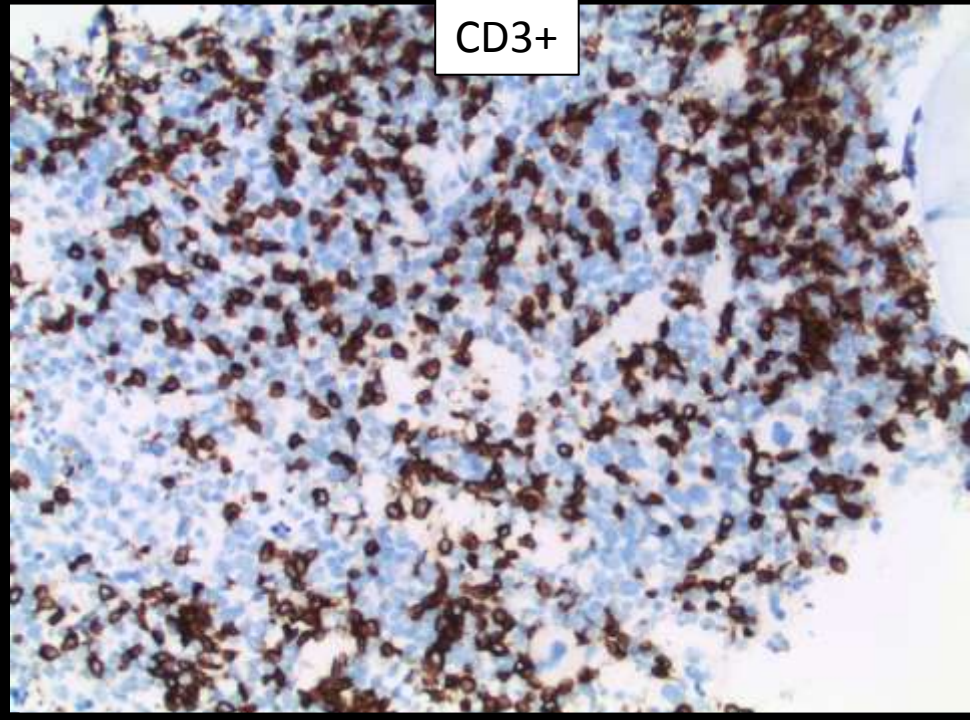
Negative

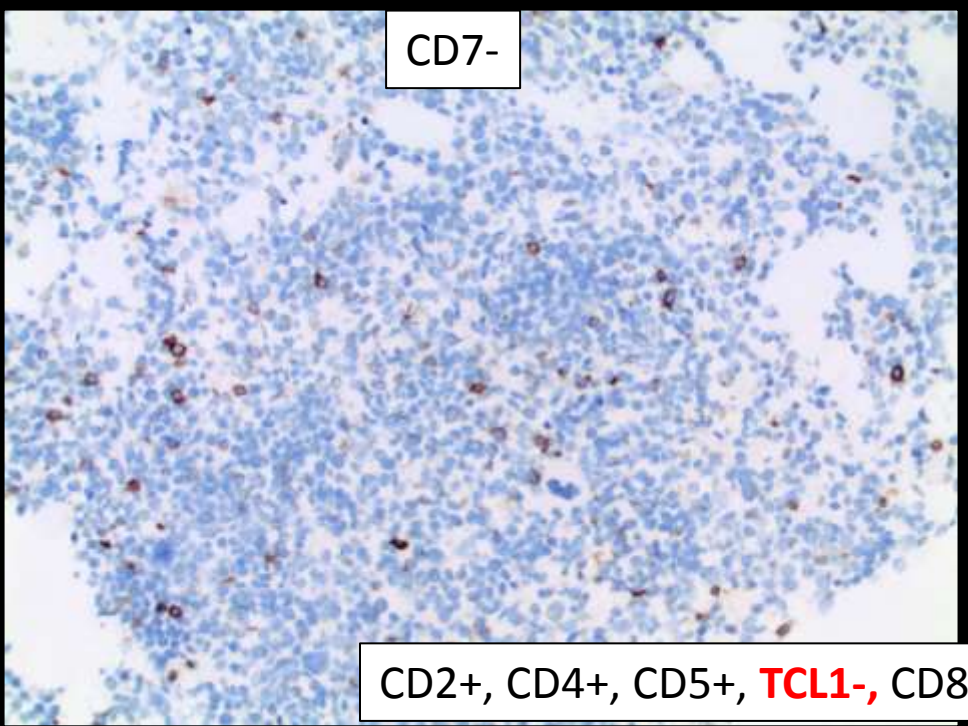
- CD7
- CD8
- CD10
- CD16
- CD25
- CD26
- CD30
- CD34
- CD56
- CD57

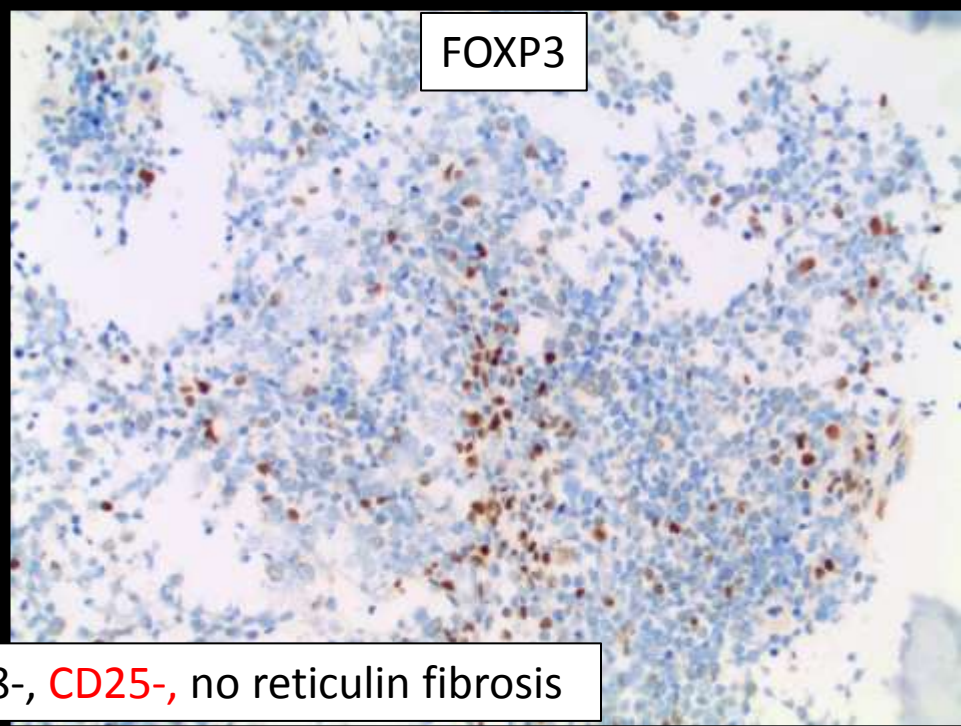

Bone marrow aspirate


Bone marrow aspirate









CD2+, CD4+, CD5+, **TCL1-,** CD8-, CD25-, no reticulin fibrosis

- TCR gene rearrangement: Positive
- Cytogenetics: 46, XY[20]

- HTLV-1 serology: Positive
- CT scan: 0.7 mm nodule in lung

- Peripheral blood for HTLV I/II DNA, Qualitative Real-Time PCR: pending results

	TPLL	ATLL
CBC	WBC >100 K/dL	WBC not as high
Hypercalcemia	Negative	Positive
HTLV-1 serology	Negative	Positive
Periorbital/conjunctival edema	Present	Absent
CD7	+ (strong)	Negative
TCL-1	Positive	Negative
FOXP3	Negative	Positive
CD25	Negative	Positive (our case negative)
Reticulin fibrosis	Present	Absent
Cytogenetics	Inv(14); t(14;14); chromosome 8 abnormalities	Nonspecific, usually complex

Final diagnosis:

T-cell malignancy with features of Adult T-cell lymphoma/leukemia

ATL

- Adult T-cell leukemia/lymphoma (ATL) caused by Human T-cell lymphtropic virus type (HTLV-1)
- Poor prognosis (median survival <1 yr) because of intrinsic chemoresistance and severe immunosuppression
- Associated with T-cell immunodeficiency: Pneumocystis carinii, malignant strongyloidiasis, CMV, disseminated Cryptococcus
- CD3/CD4/CD25/CCR4/FoxP3

Box 1 Clinical forms of adult T-cell leukaemia/lymphoma (ATLL)[3]

Acute (60% of cases)

- Leukaemic picture, organomegaly, high lactate dehydrogenase (LDH) and often hypercalcaemia

Chronic

- Lymphocytosis >4×10⁹/l with ATLL cells, skin, lung, liver or node involvement
- Calcium levels normal, LDH normal or less that twice the upper normal limit

Smouldering

- Skin and/or lung infiltrates
- No other organ involvement
- Normal lymphocyte count (1–5% ATLL cells), normal calcium and LDH

Lymphoma (20% of cases)

- Organomegaly
- Less than 1% circulating leukaemic cells
- High LDH and possible hypercalcaemia

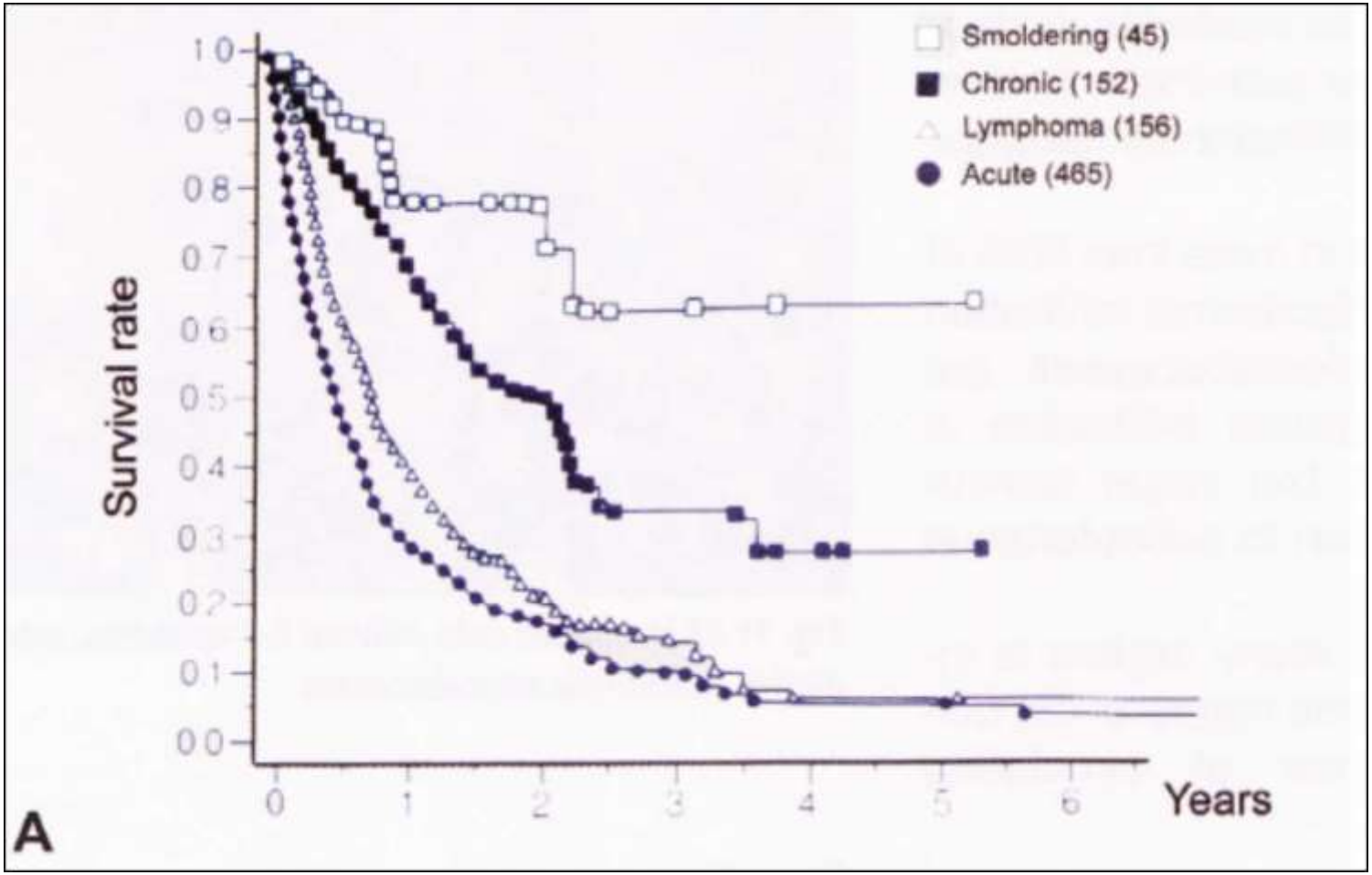
Of leukemic variants, only one with hypercalcemia and bone marrow involvement

Aggressive ATL

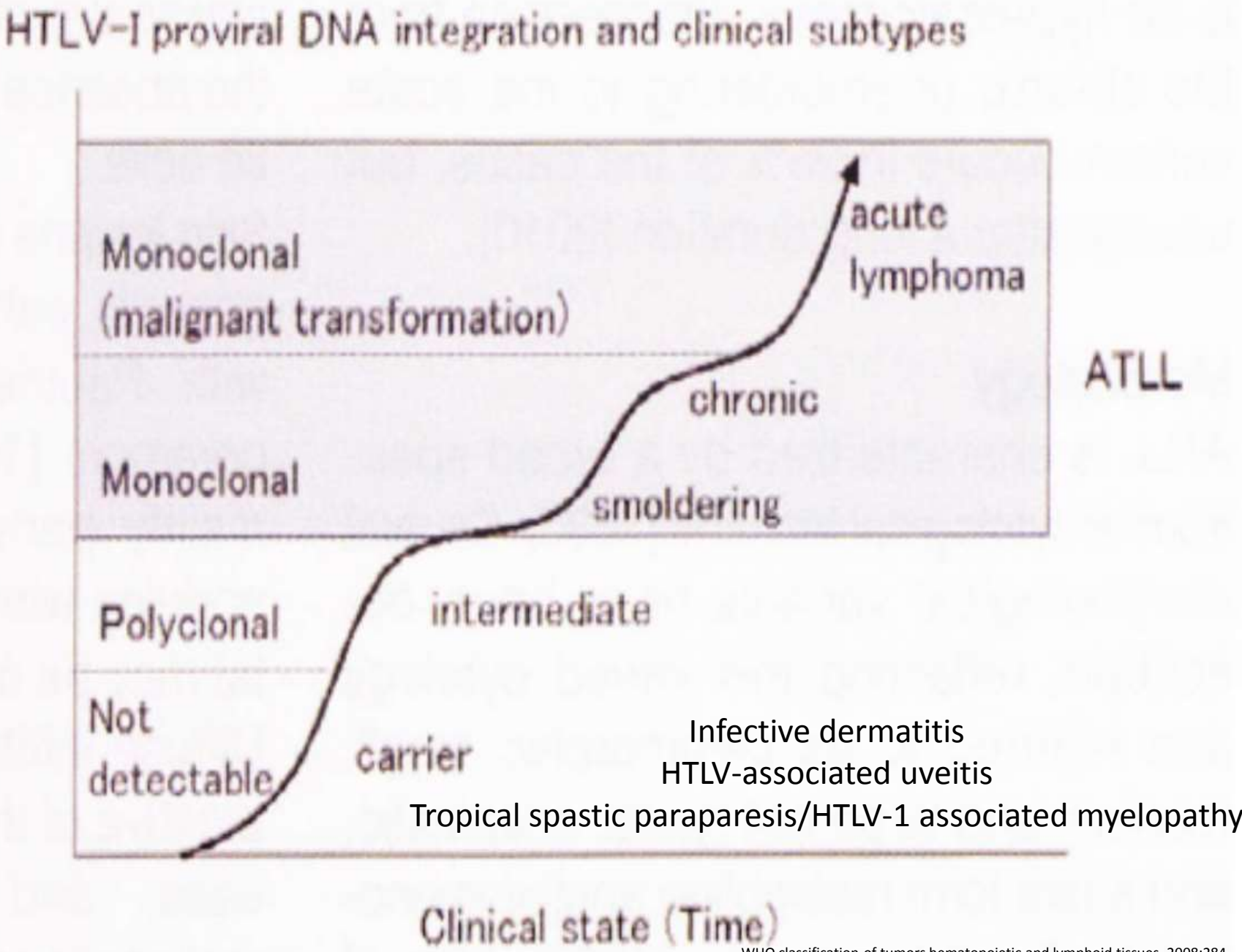
Indolent ATL

Only one without blood involvement

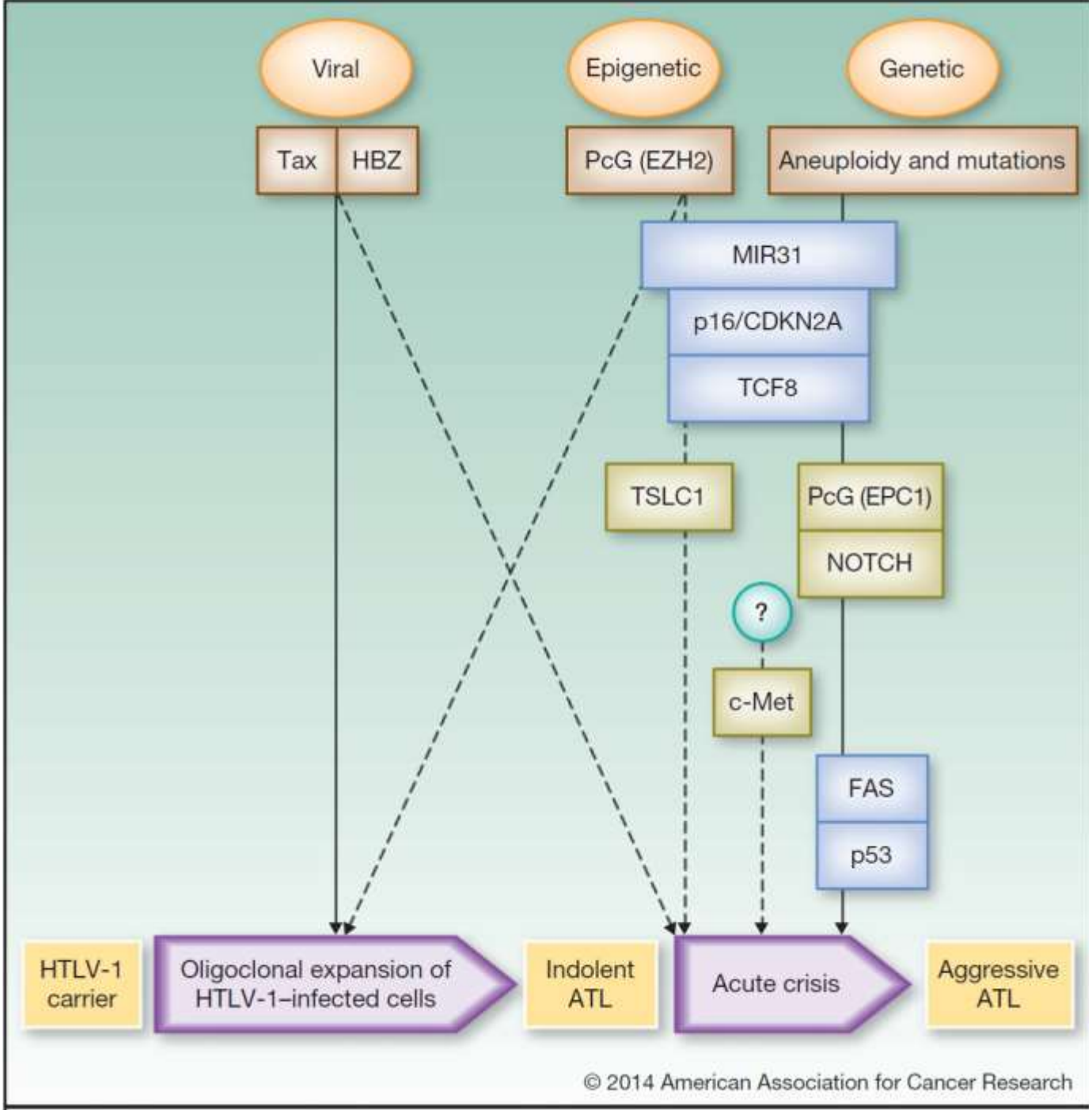
J Clin Pathol 2007;60:1371-1377
Br J Haematol. 1991 Nov;79(3):428-37

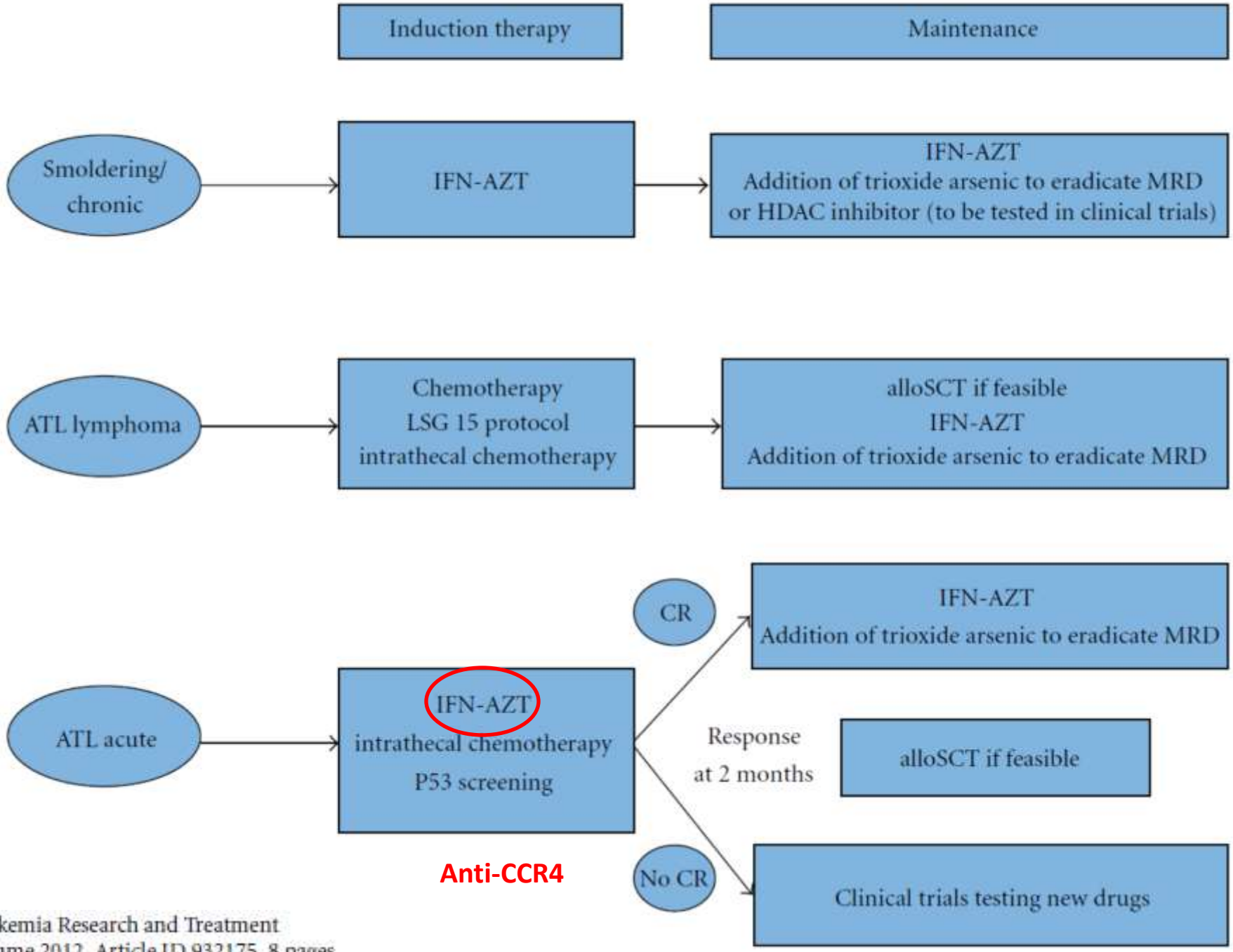


WHO classification of tumors hematopoietic and lymphoid tissues. 2008:284



WHO classification of tumors hematopoietic and lymphoid tissues. 2008:284



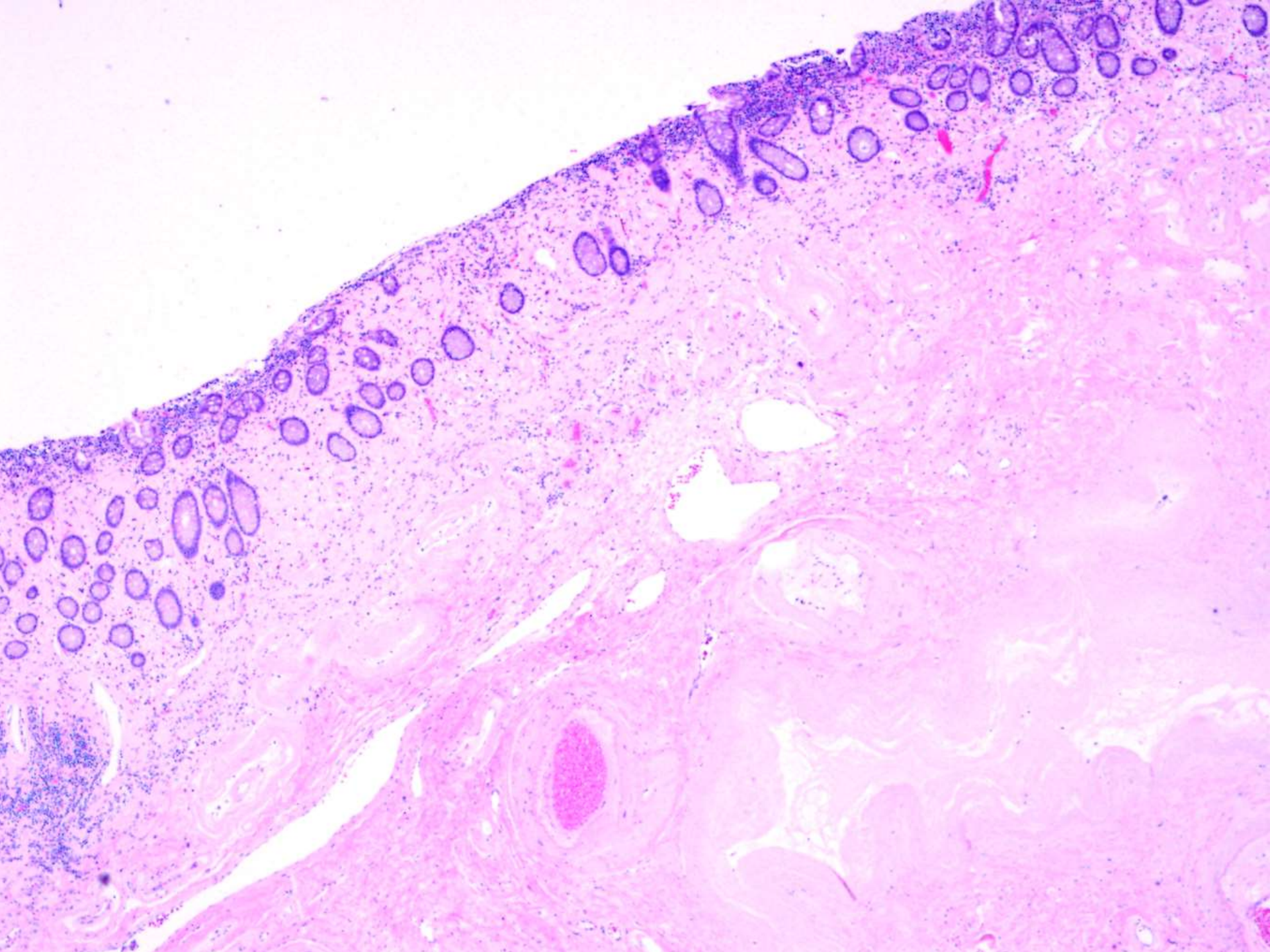


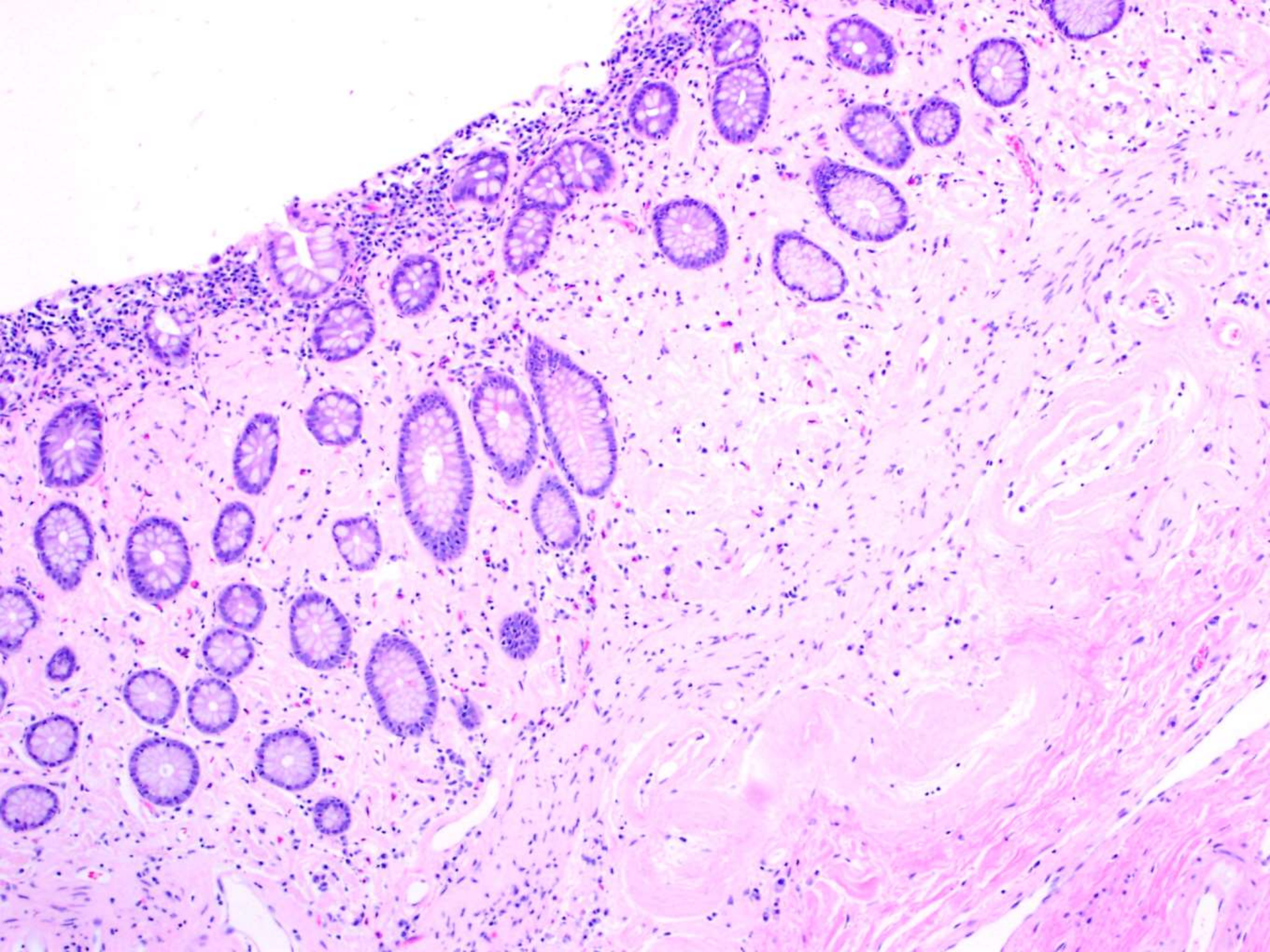
Leukemia Research and Treatment
Volume 2012, Article ID 932175, 8 pages

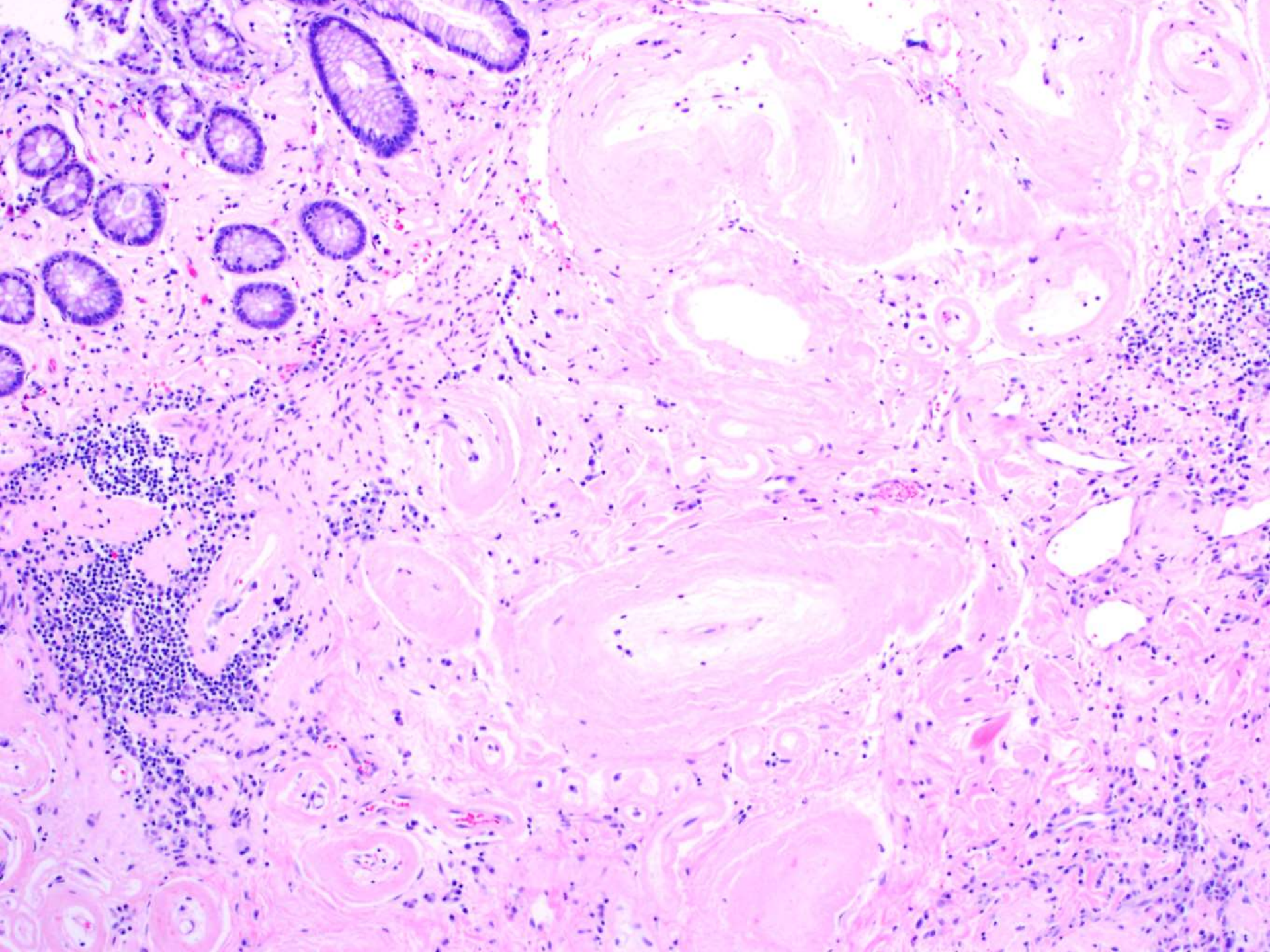
SB 5987

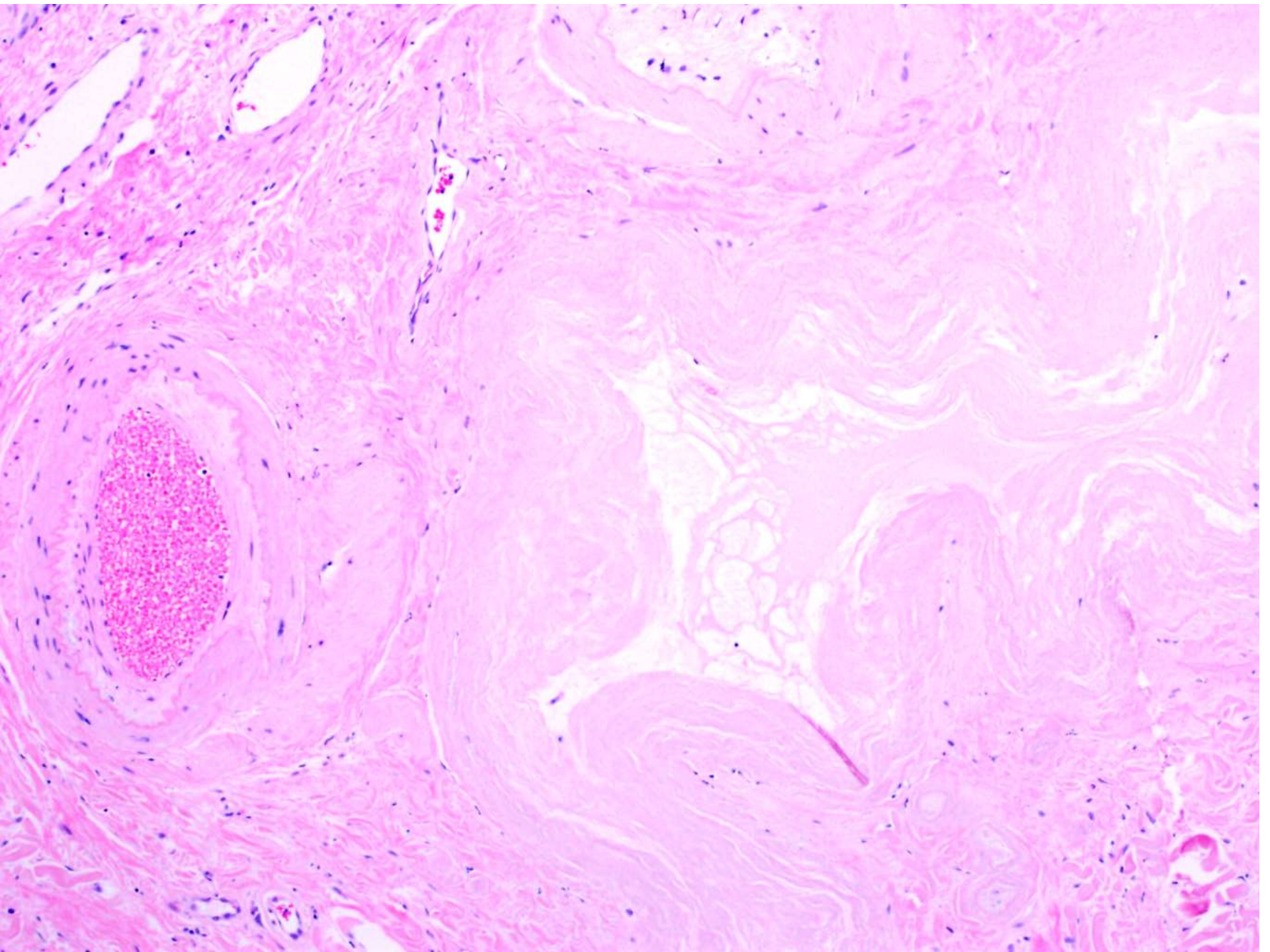
- 67-year-old Asian female with a history of abdominal pain and 15-pound weight loss over last 6 months. CT from two months ago showed thickening in the proximal ascending colon, with terminal distal ileal inflammation and dilation. Colonoscopy revealed a firm, smooth-appearing circumferential mass in the ascending colon. She undergoes a right hemicolectomy.

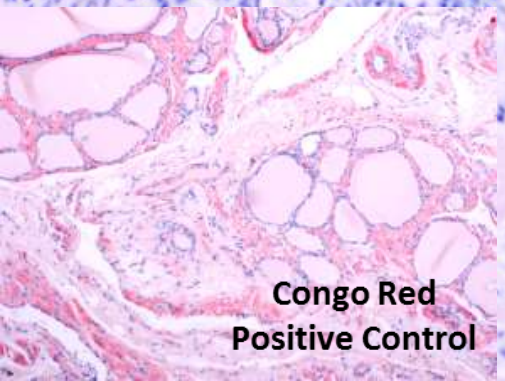
- **Linlin Wang; UCSF**





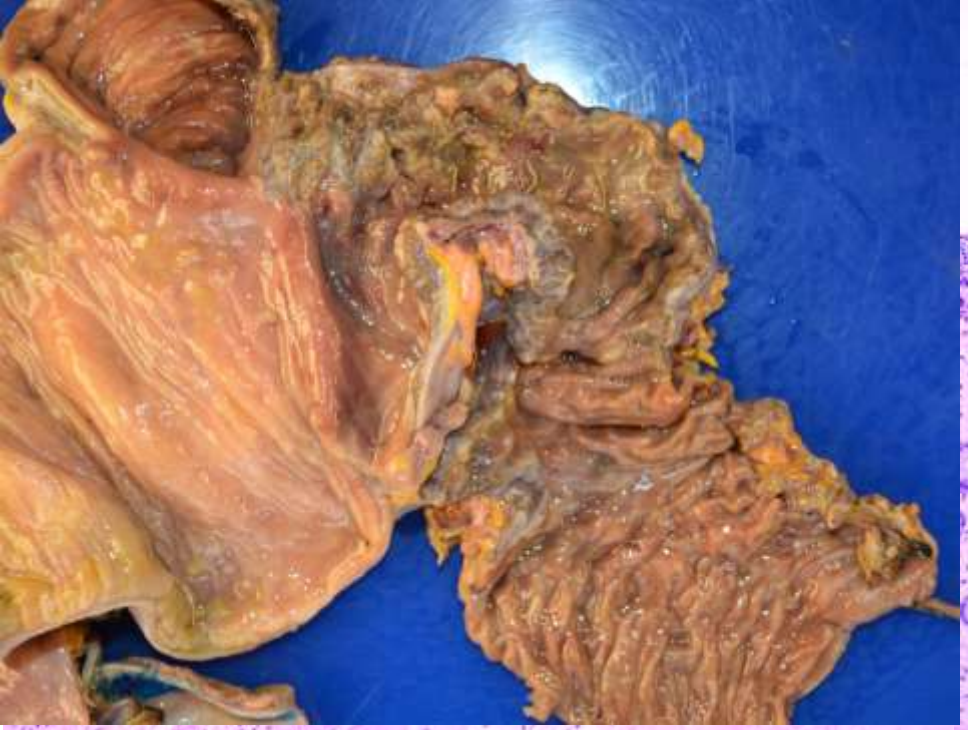


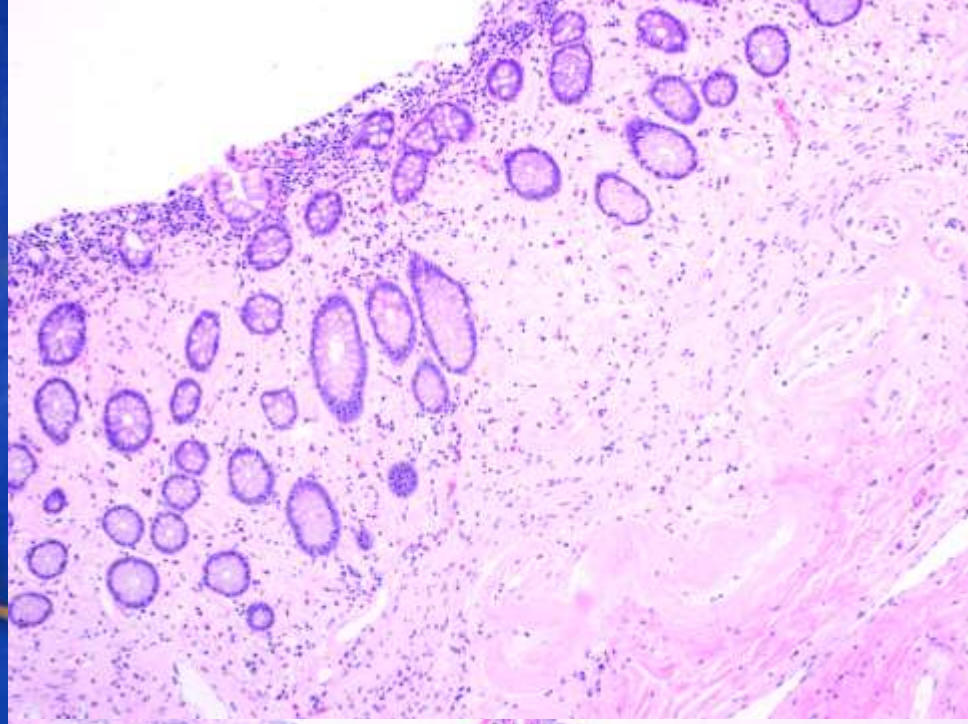


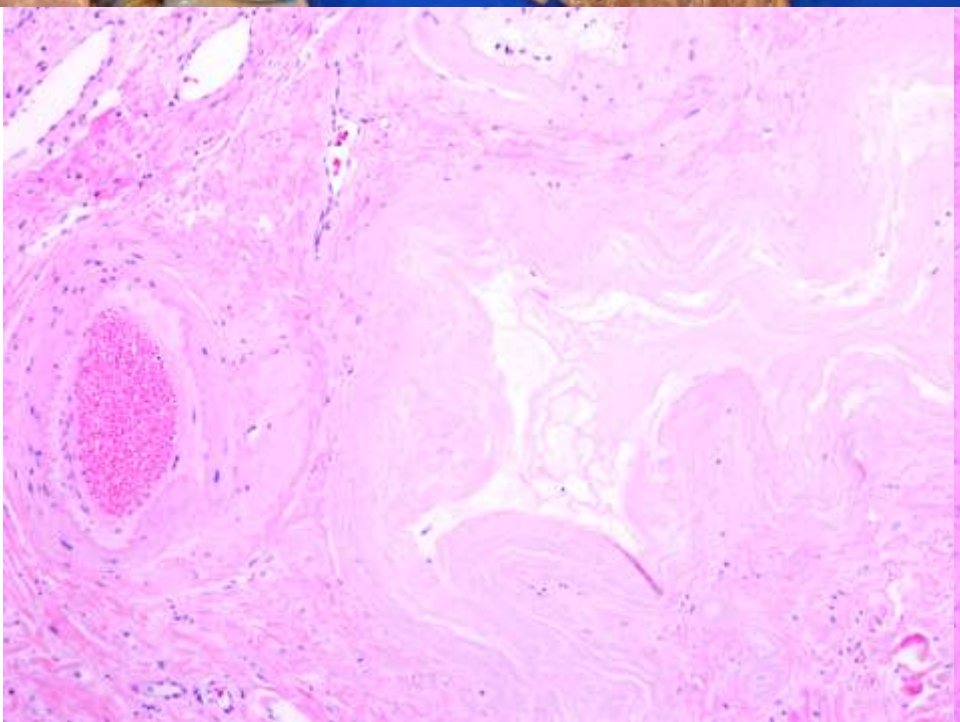


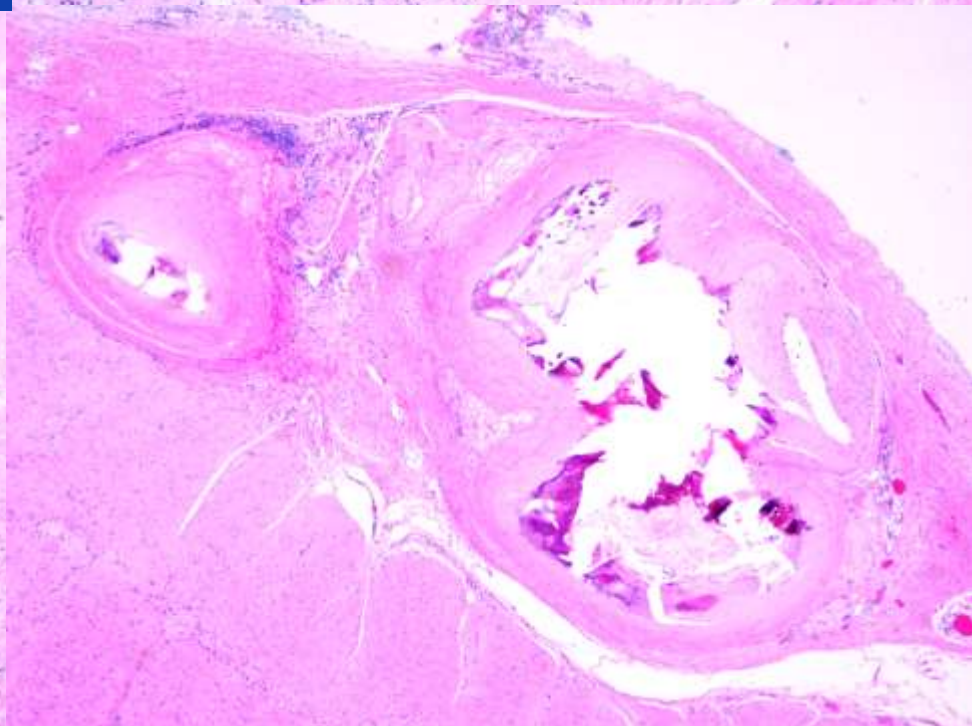
Congo Red

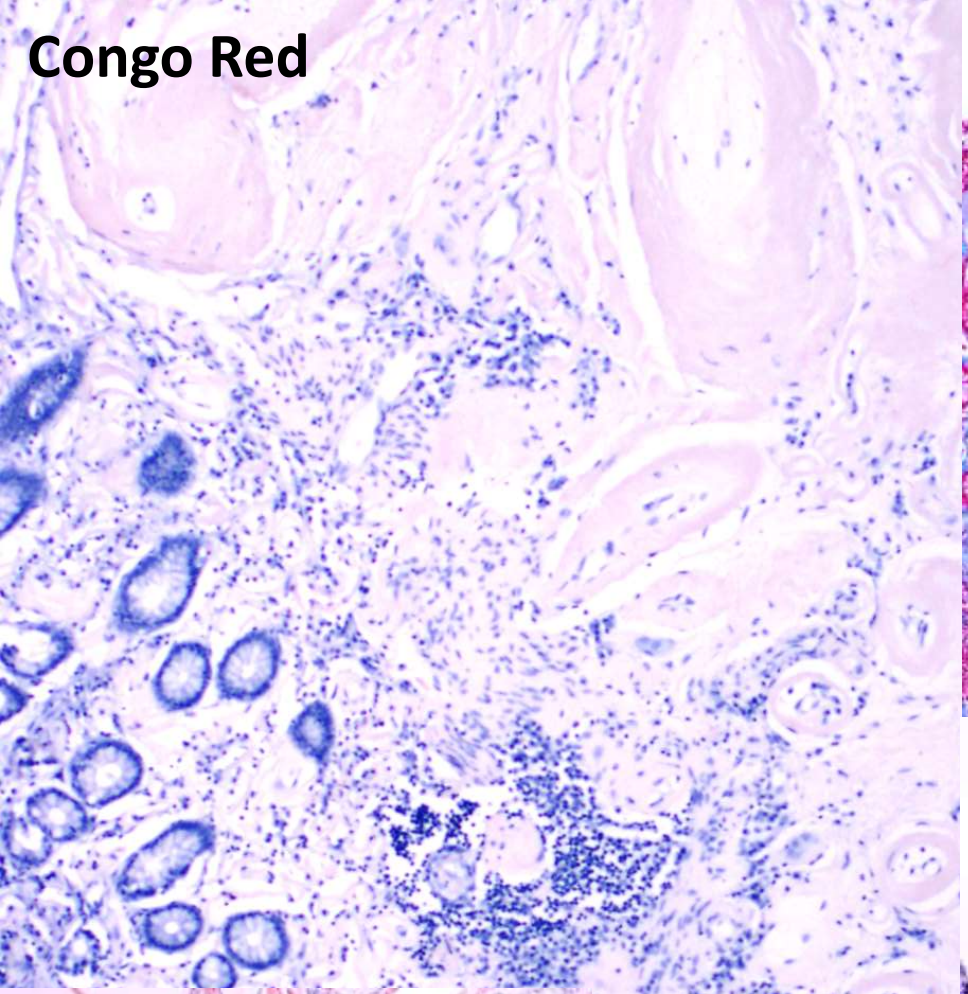
Diagnosis….?

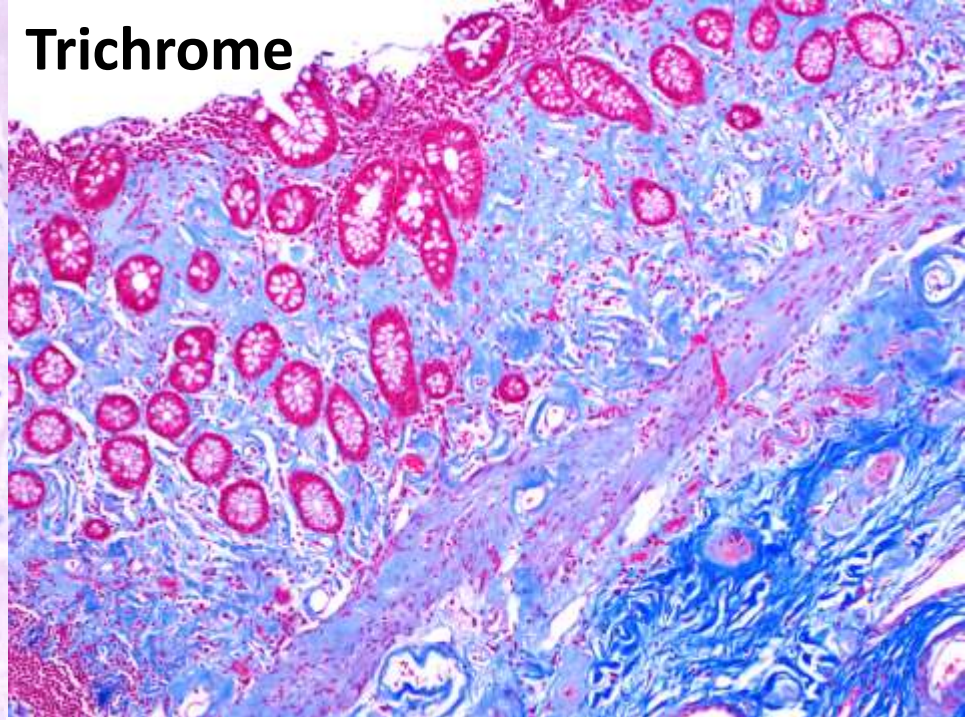


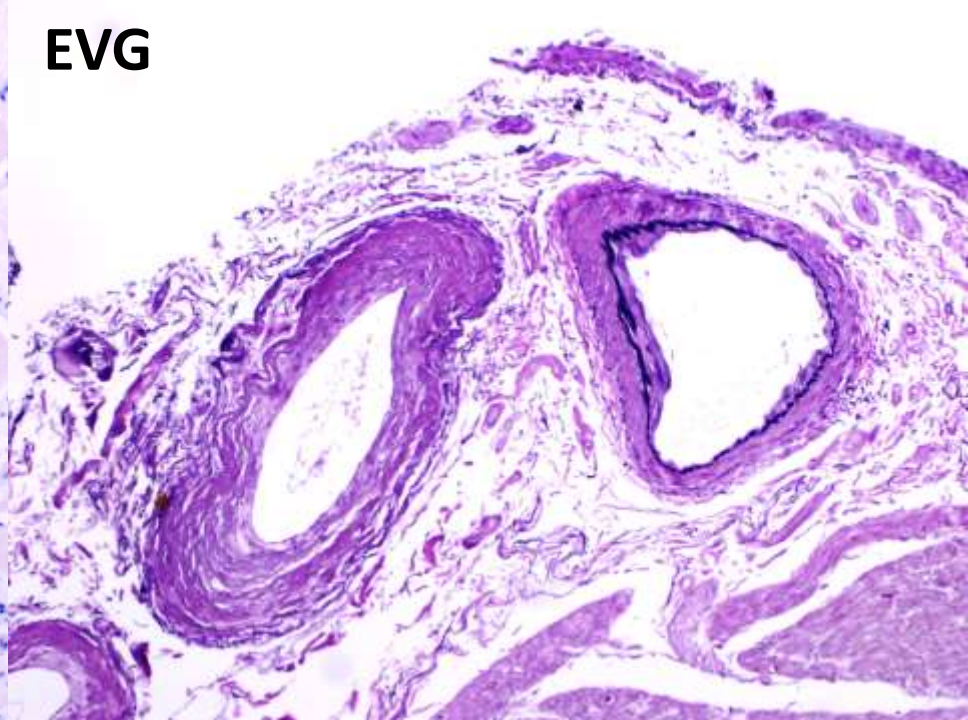


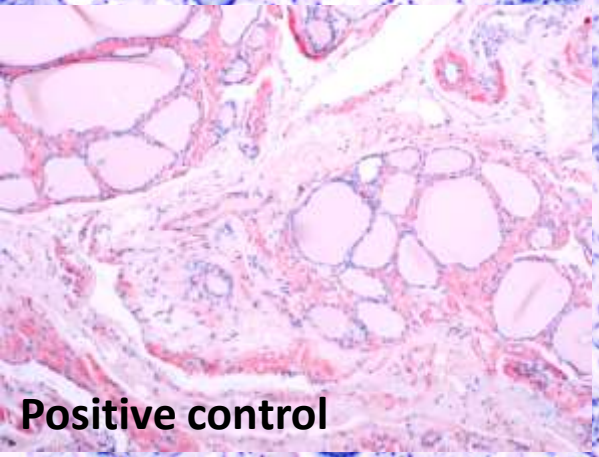





Congo Red


Trichrome


EVG


Positive control

Differential Diagnosis

- Light chain or heavy chain deposition diseases

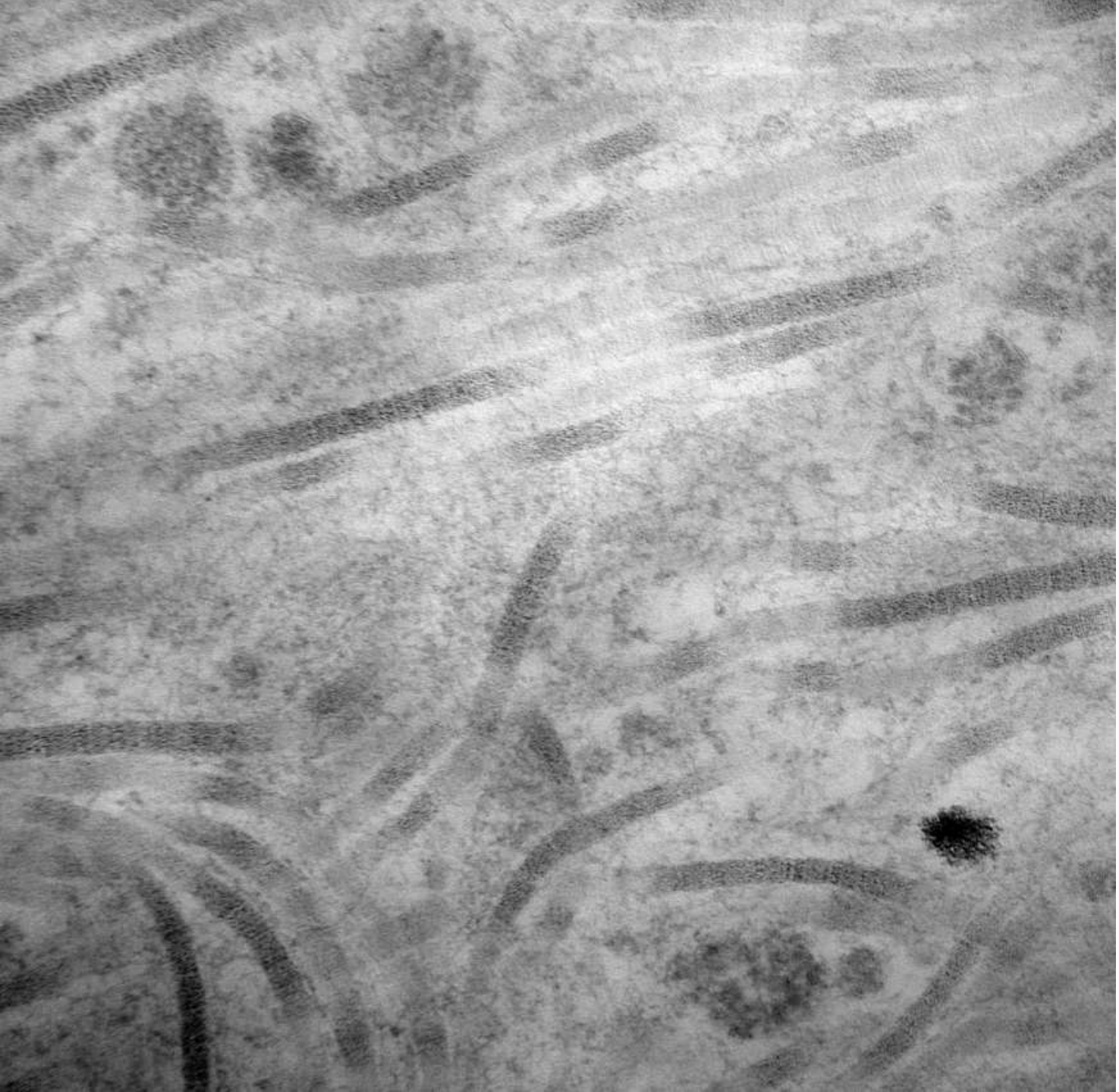
  Immunotactoid deposition

Ultrastruct Pathol. 2015 Feb;39(1):62-8. doi: 10.3109/01913123.2014.939796. Epub 2014 Sep 5.

Monoclonal light chain deposits within the stomach manifesting as immunotactoid gastropathy.

Jen KY[1], Fix OK, Foster EN, Laszik ZG, Ferrell LD.

- Hyalinization/fibrosis of the colon

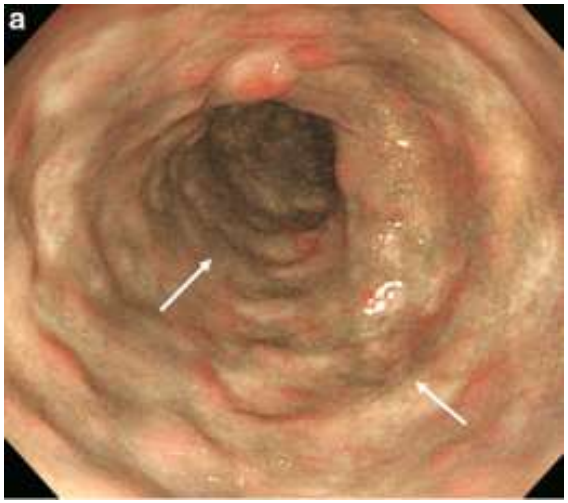


EM:
Collagen Fibers

Diagnosis:
Phlebosclerotic Colitis

Phlebosclerotic Colitis

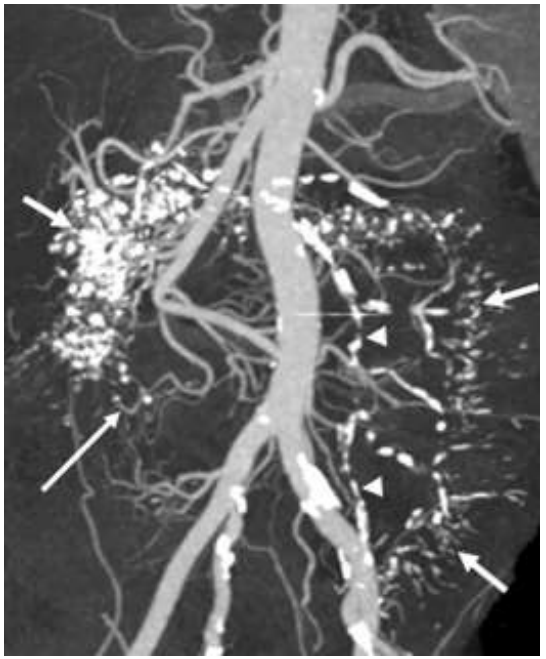
- A rare form of ischemic colitis resulting from phlebosclerosis of the colon.
- Primarily affects the right colon.
- Fibrosis/sclerosis and calcification of the colonic and mesenteric veins.
- Dark blue to bronze discoloration of the intestinal mucosa.



Fang YL et al. Exp Ther Med. 2014 Mar;7(3):583-586.
Lee SM, Seo JW. Jpn J Radiol. 2015 Aug 5.

Clinical Features

- Abdominal pain and diarrhea.
- Calcification of mesenteric veins on imaging.
- Occurs in Asian population.
- Strong association with using Chinese herbal medication.
- Hemicolectomy is considered curative.

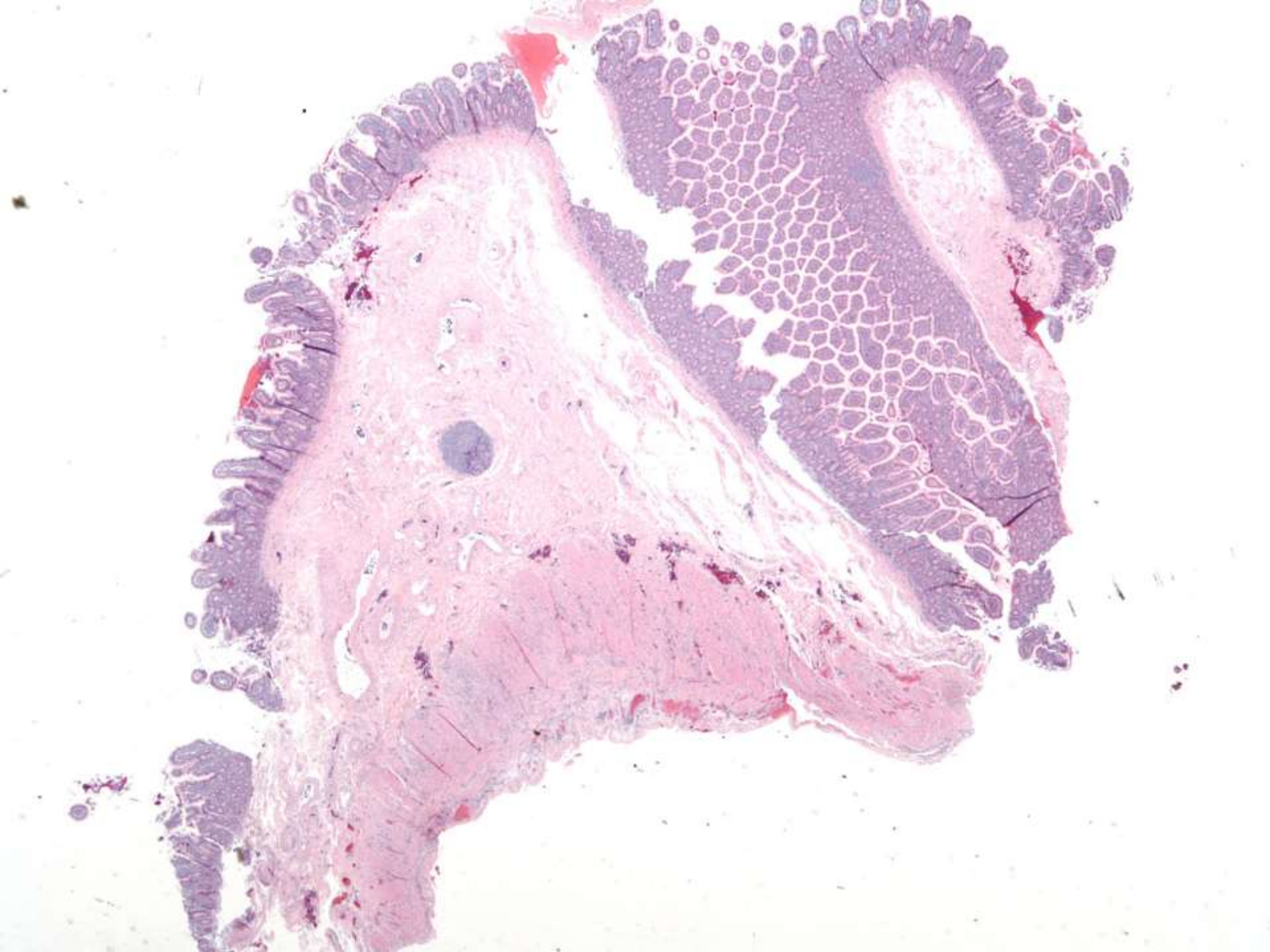


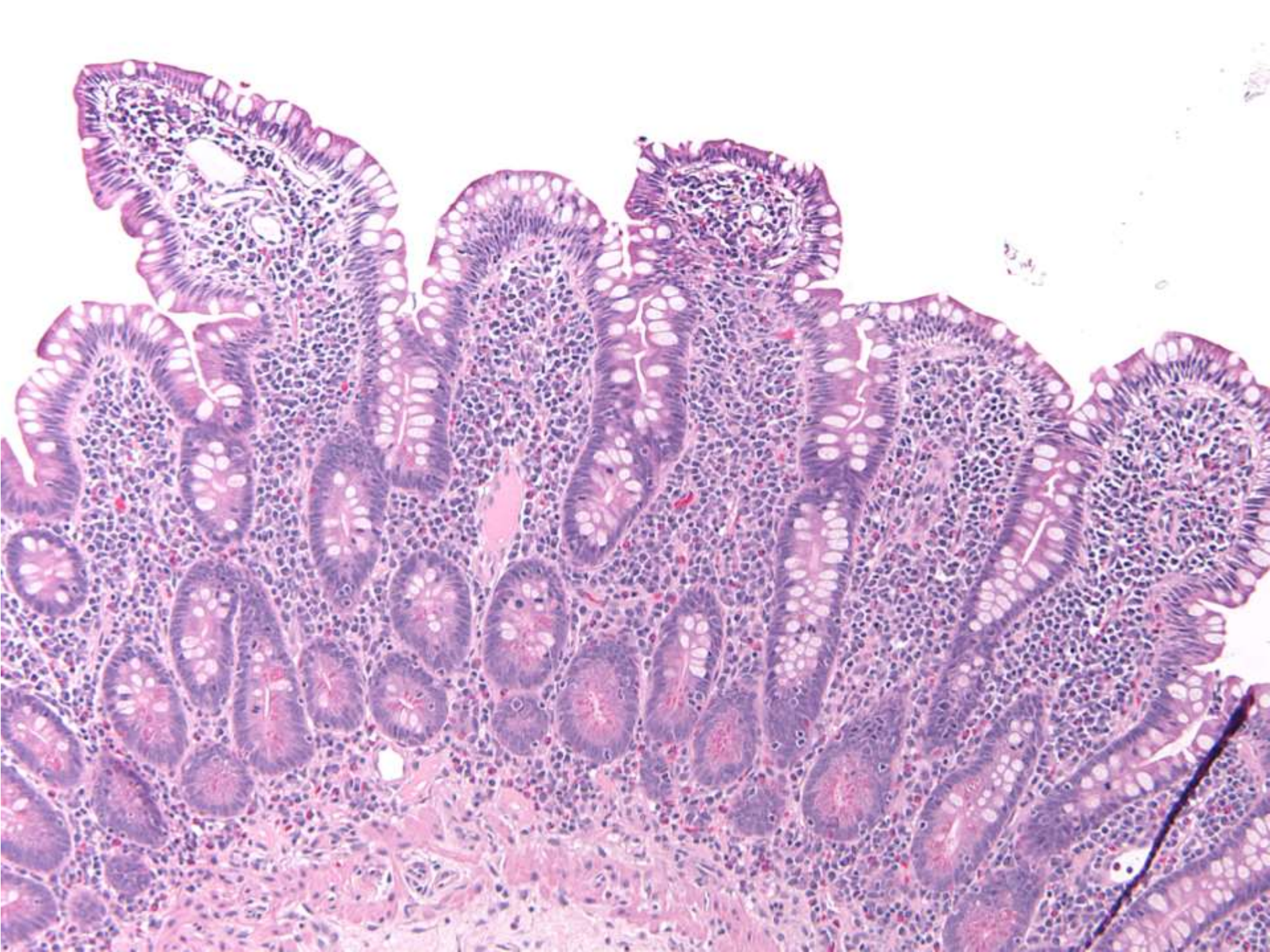
Fang YL et al. Exp Ther Med. 2014 Mar;7(3):583-586.
Lee SM, Seo JW. Jpn J Radiol. 2015 Aug 5.

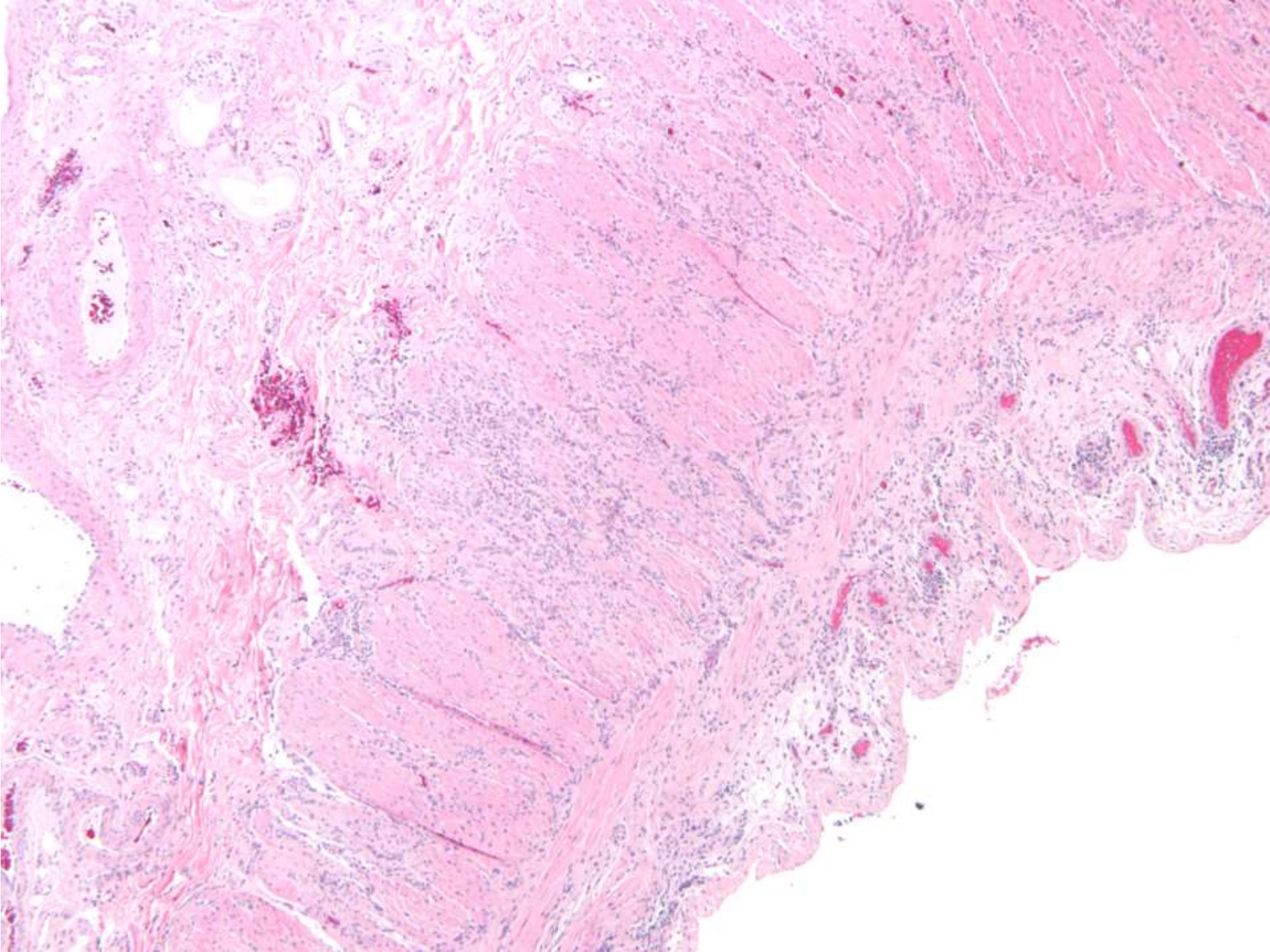
SB 5988

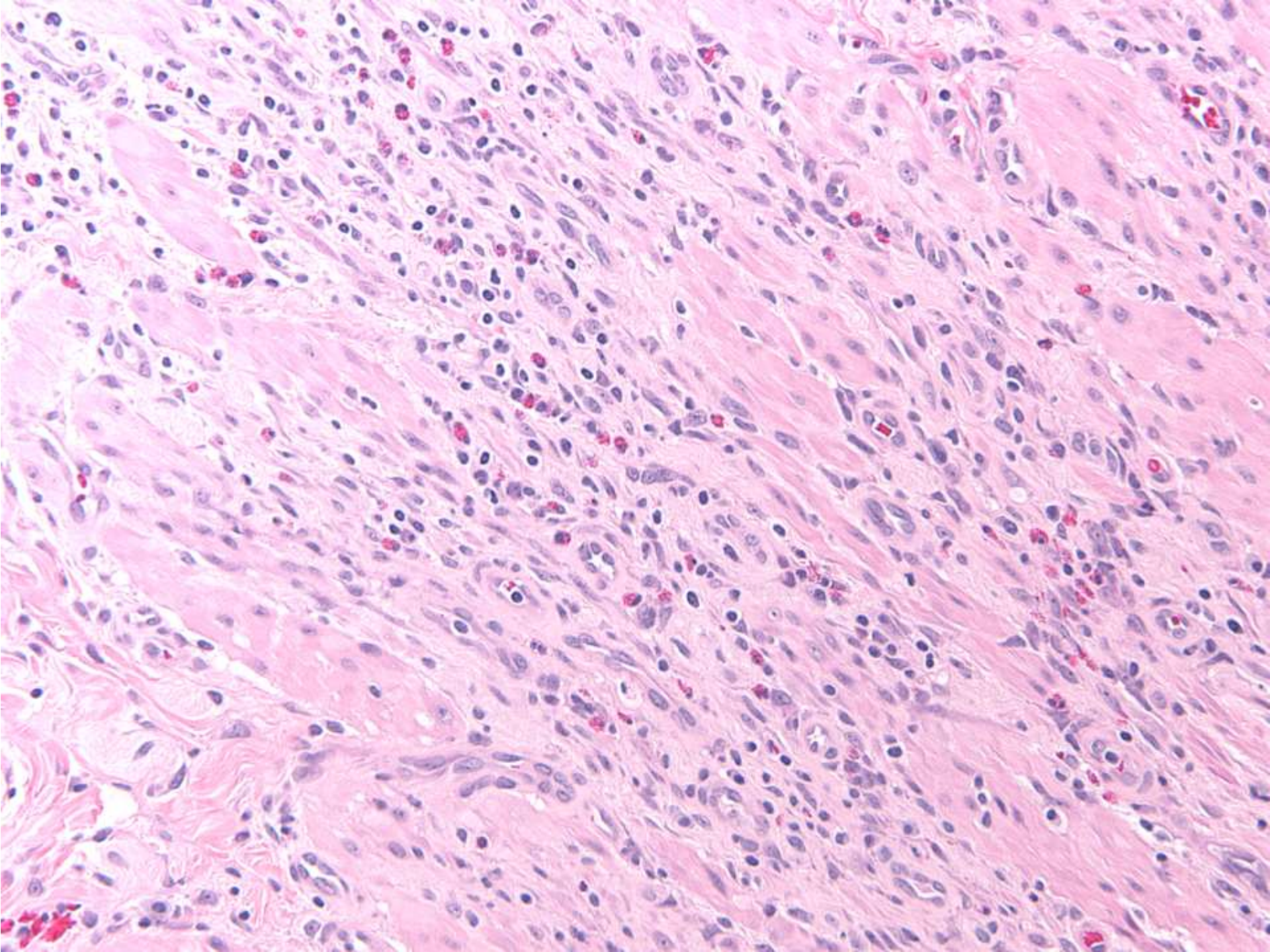
- 31-year-old male with ileus of unknown etiology. Small intestine resection submitted.

- **Kurt Schaberg/David Bingham; Stanford**





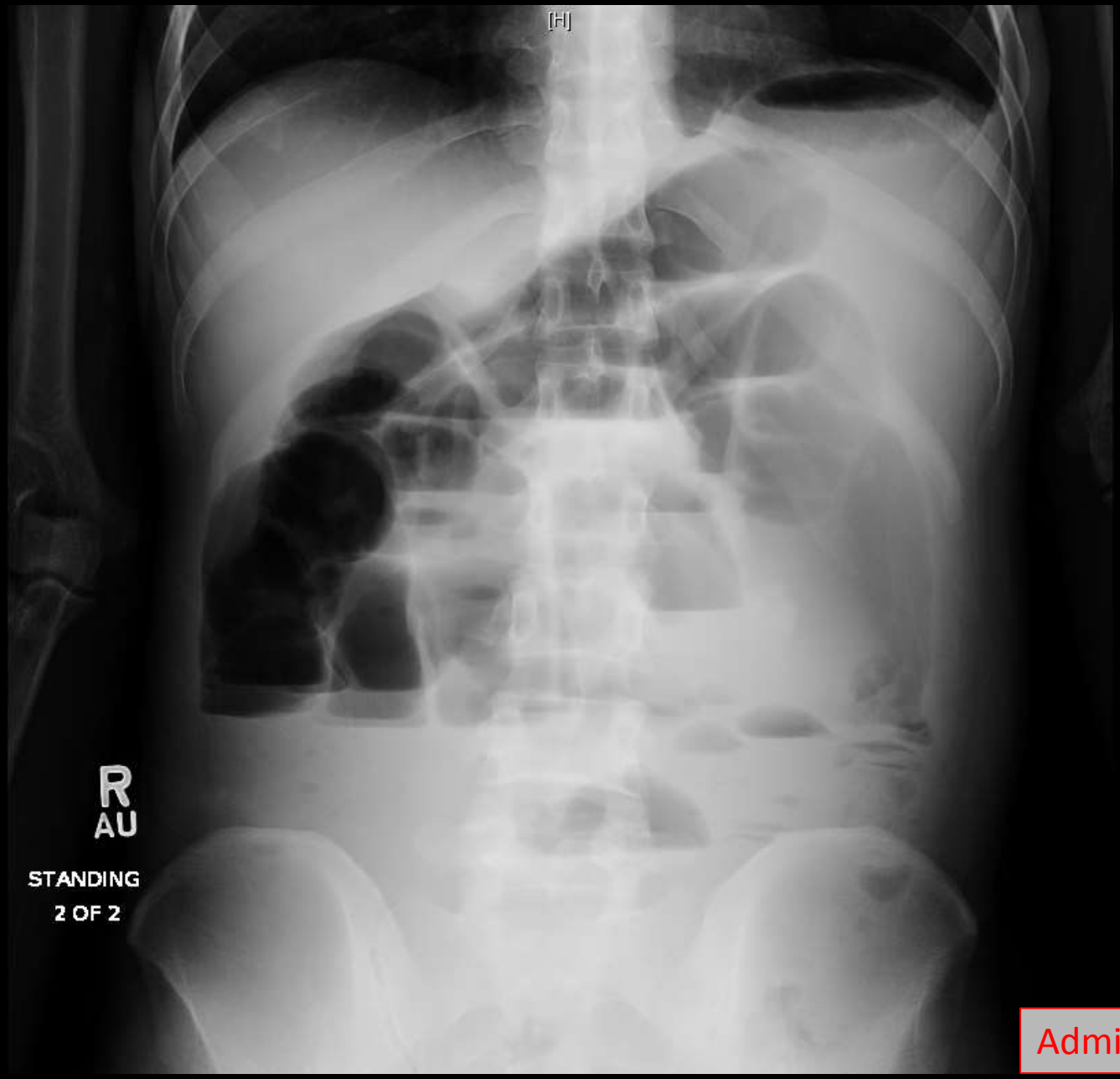




Diagnosis….?

Patient Presentation

- He was healthy and in usual state until about two months prior to presentation.
- Symptoms: nausea, vomiting, non-bloody diarrhea.
- Subsequent weight loss followed down to 95 lbs.



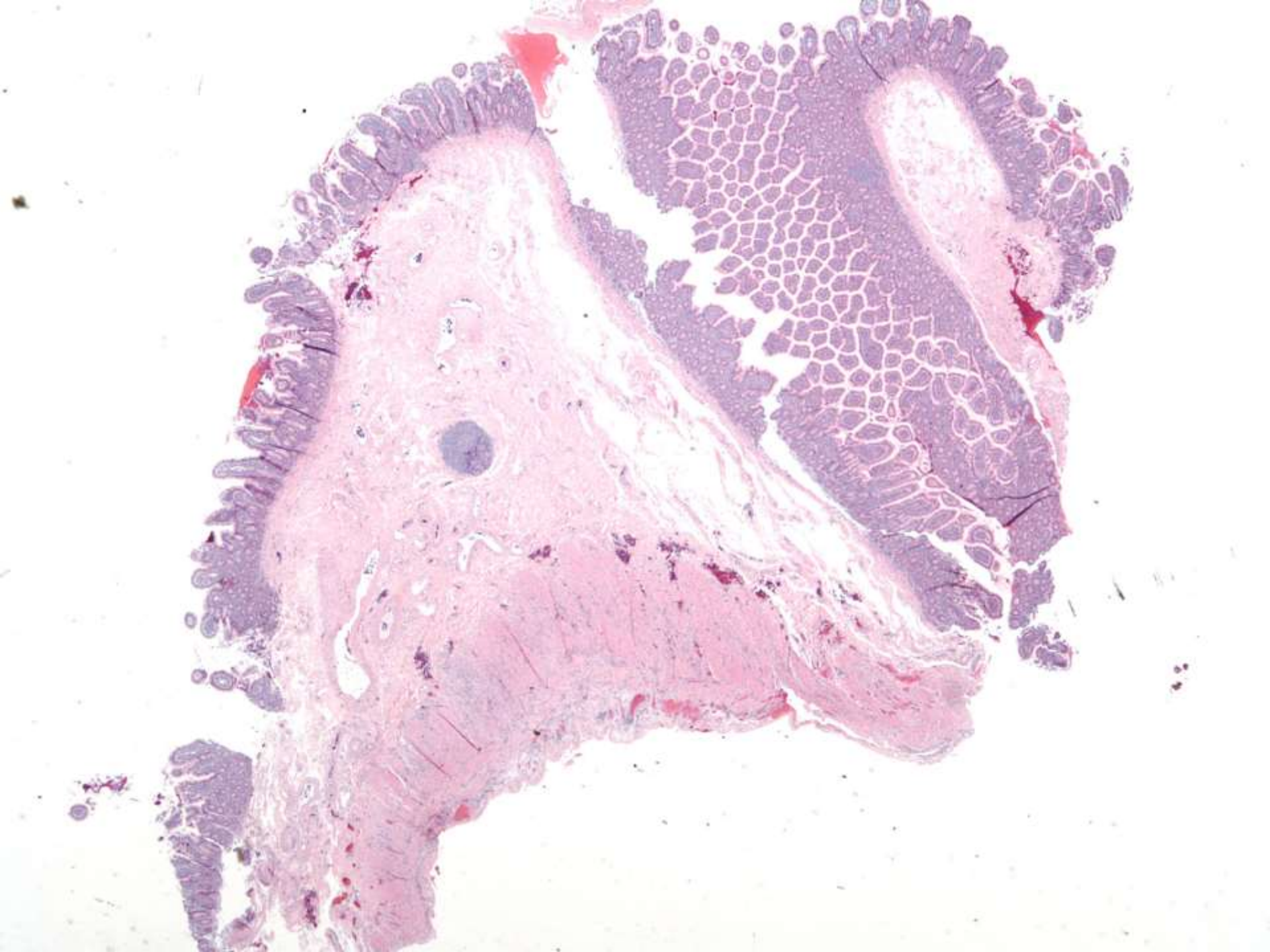
Admission X-ray

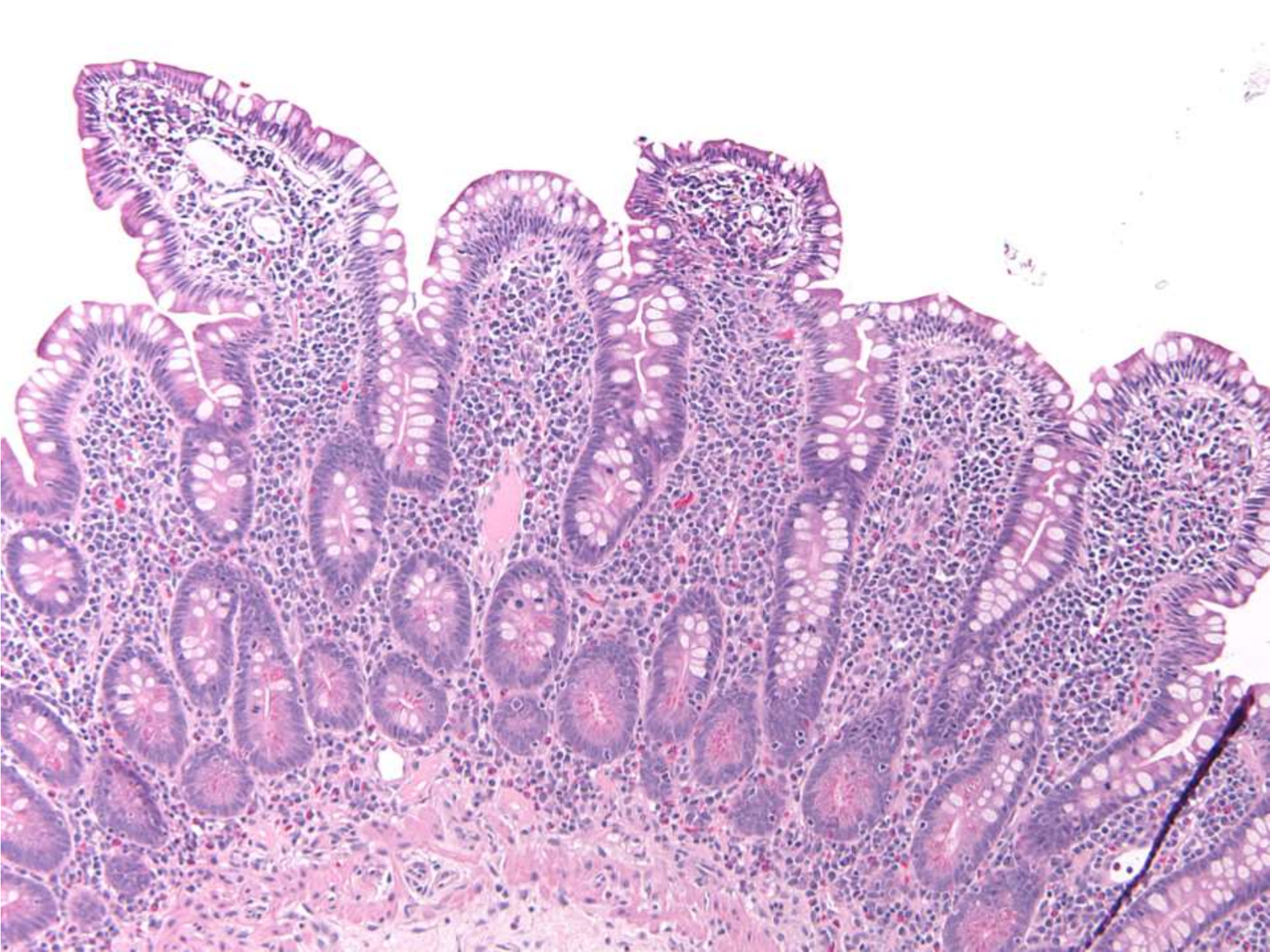
Initial Work-up

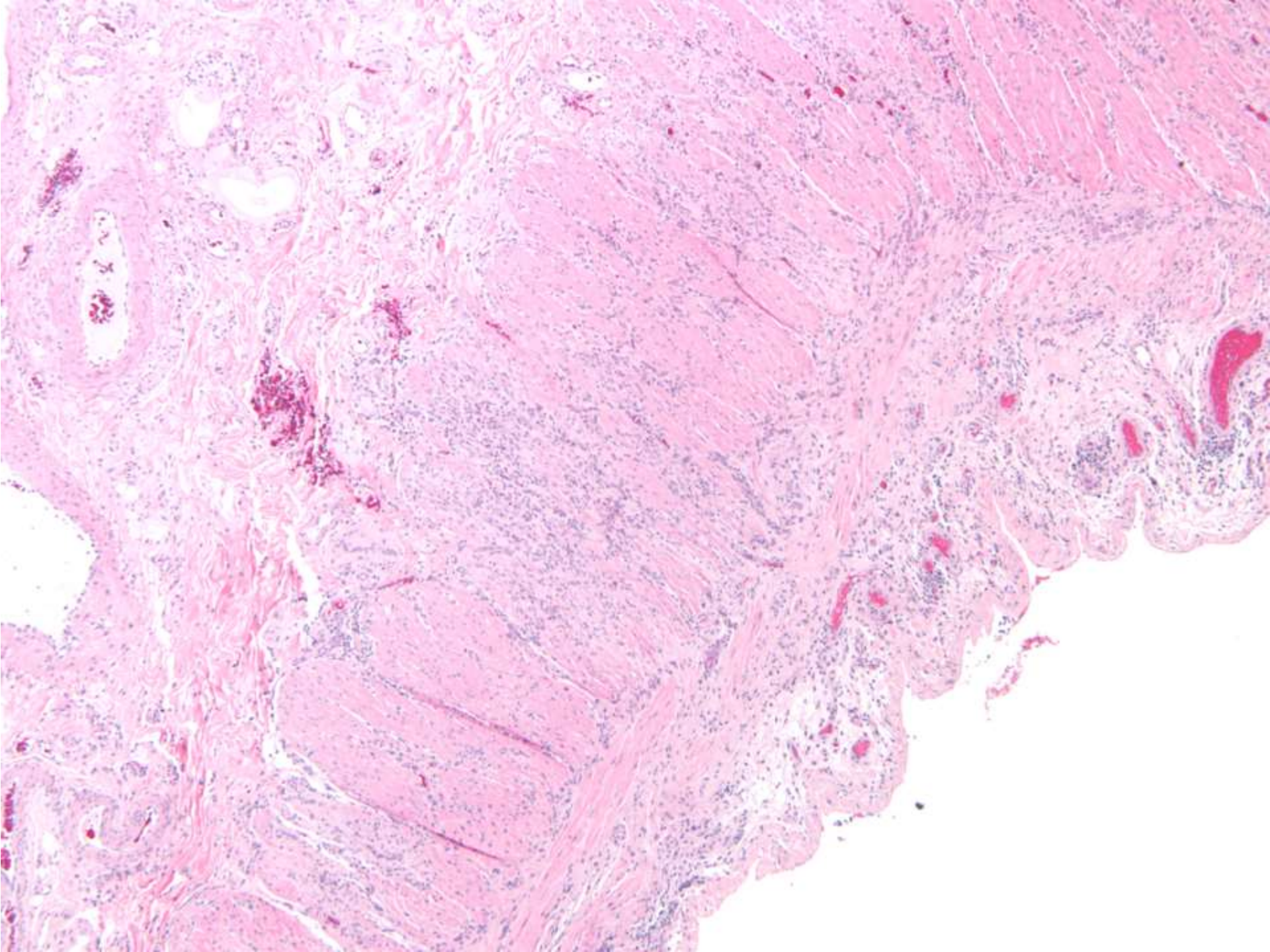
- EGD with biopsies: Normal
- Esophageal manometry: Aperistalsis
- Infectious disease work-up: Negative
- Lab work-up: Positive ANA and anti-RNP, markedly elevated IgE

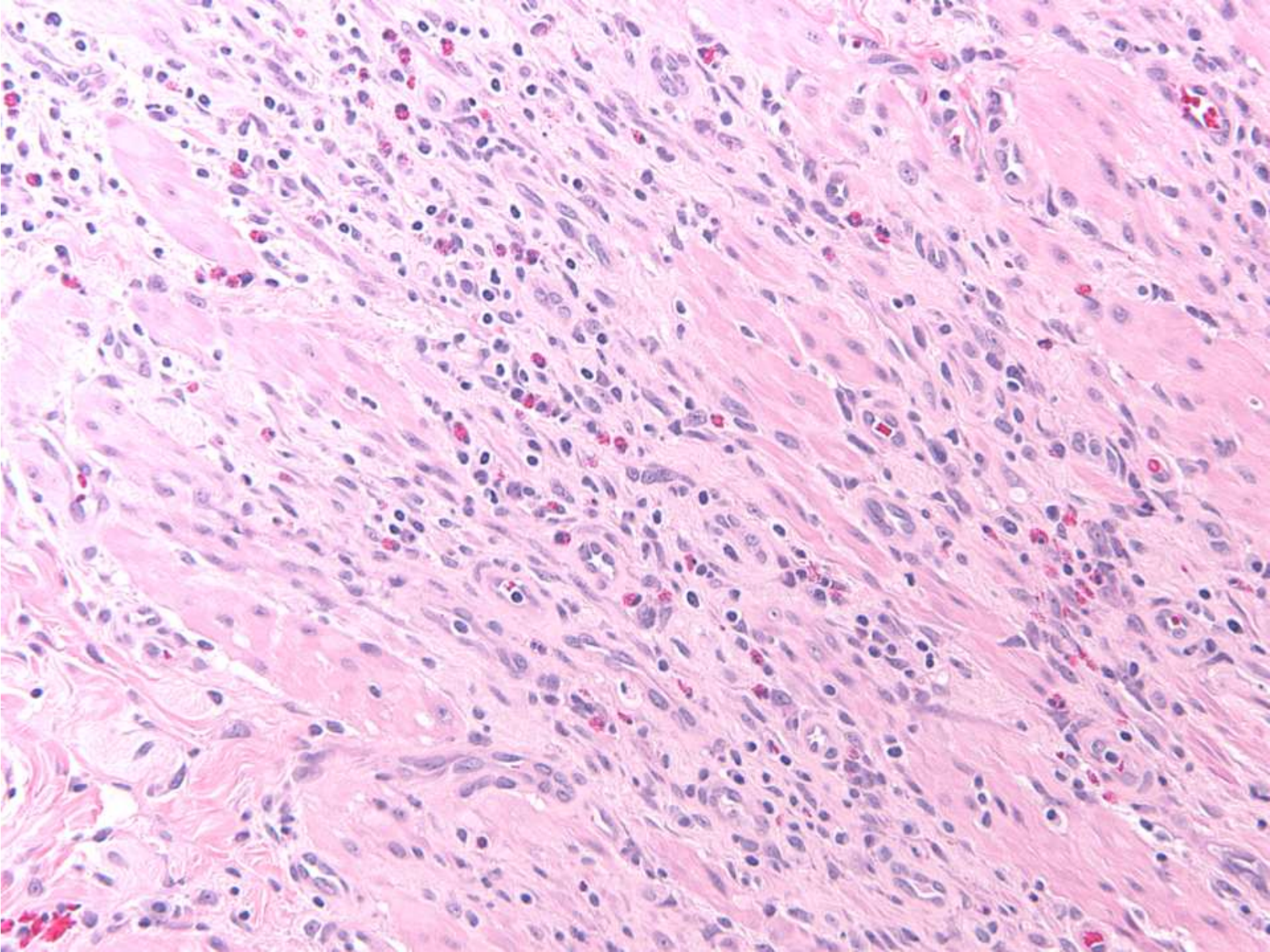
Recommendation:

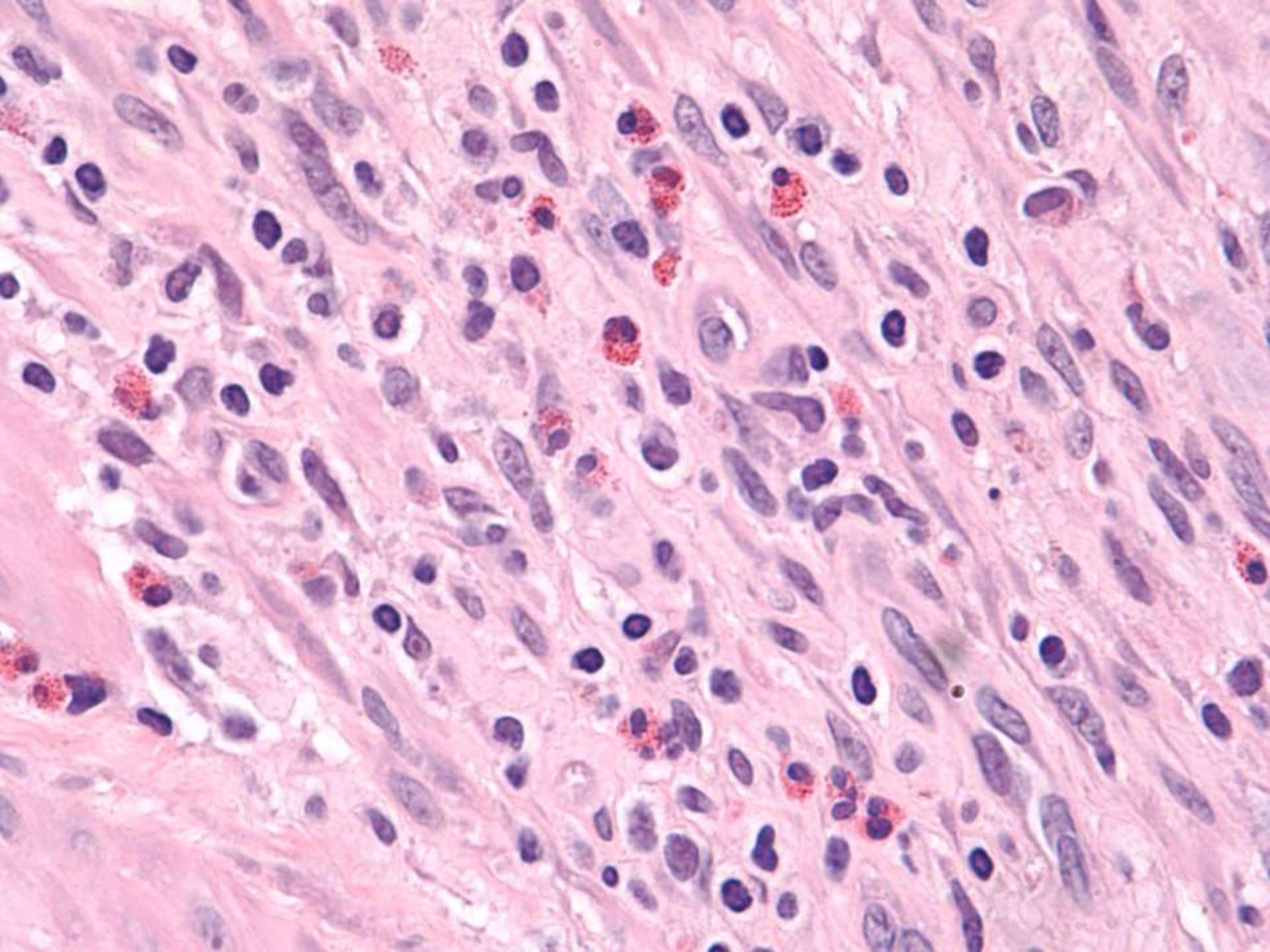
- Full-thickness gut biopsy











Diagnosis: Eosinophilic Gastroenteritis

- Relatively rare spectrum of diseases characterized by eosinophilic infiltration of one or more segments of the GI tract
- Most common in children and young adults
- Symptoms relate to the segment of bowel and layer of the bowel involved

Diagnosis: Eosinophilic Gastroenteritis

TABLE 13-6 Eosinophilic Gastroenteritis

Type	Clinical Characteristics	Pathology
Mucosal	Diarrhea, hemorrhage, protein-losing enteropathy	Mucosal eosinophils with degranulation, crypt abscesses, variable villous blunting
Mural	Abdominal pain, obstruction, nausea and vomiting	Thickened wall, mural and subserosal eosinophilic infiltrates, edema; mucosa may be normal
Serosal	Abdominal pain, obstruction, ascites, nausea and vomiting	Eosinophils and edema limited to serosa and subserosa, ascitic fluid with abundant eosinophils

Adapted from Klein NC, Hargrove RL, Sleisenger MH, et al: Eosinophilic gastroenteritis. Medicine 49:299-319, 1970.

From: Odze and Goldblum. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas. Saunders, 2 edition, 2009

Diagnosis: Eosinophilic Gastroenteritis

- Mucosal biopsies are frequently normal in mural and serosal disease.
- No strict criteria for diagnosis, but characterized by a “marked eosinophilic infiltrate”
- Differential diagnosis: parasitic infections, vasculitis, Crohn’s disease

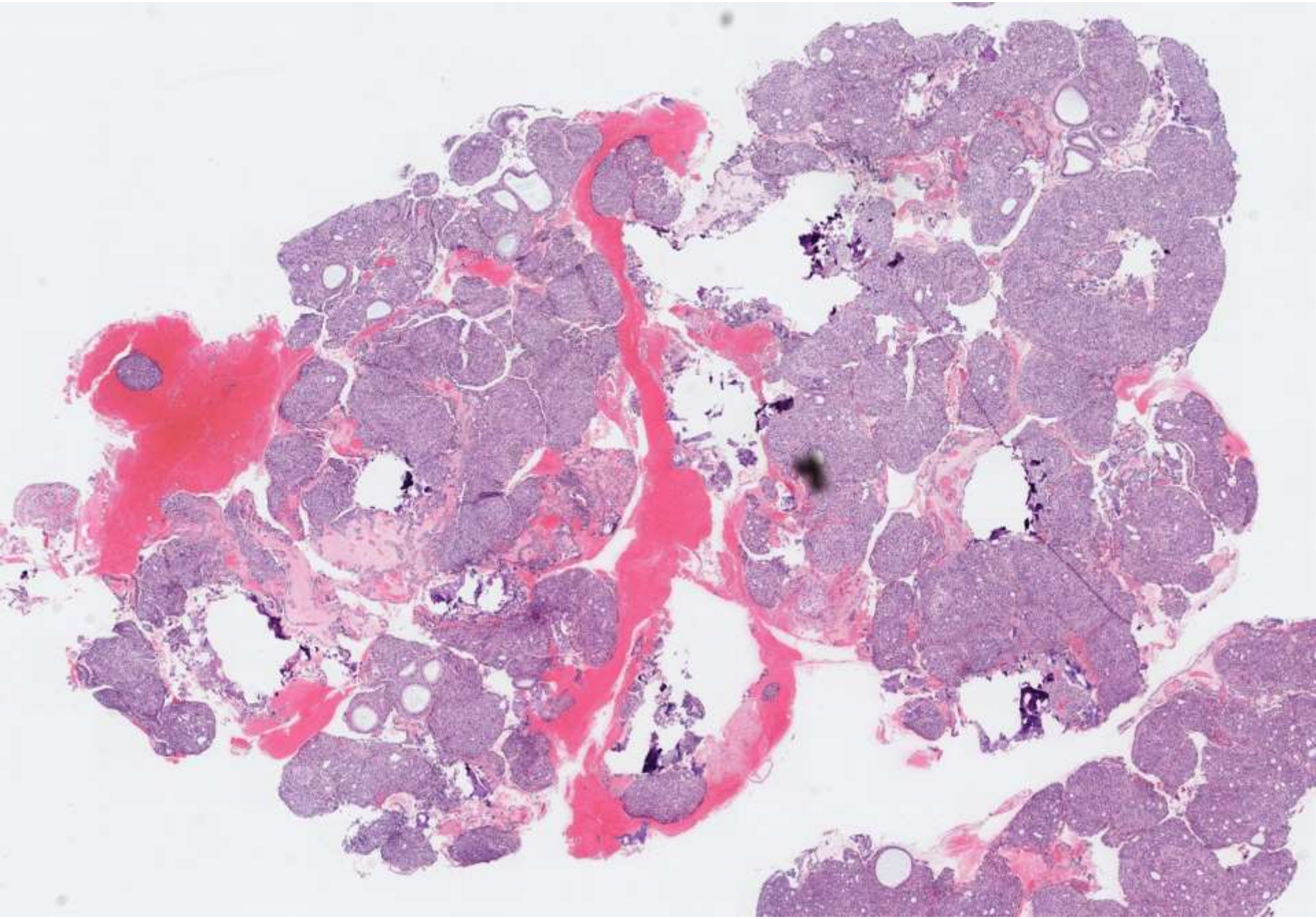
Diagnosis: Eosinophilic Gastroenteritis

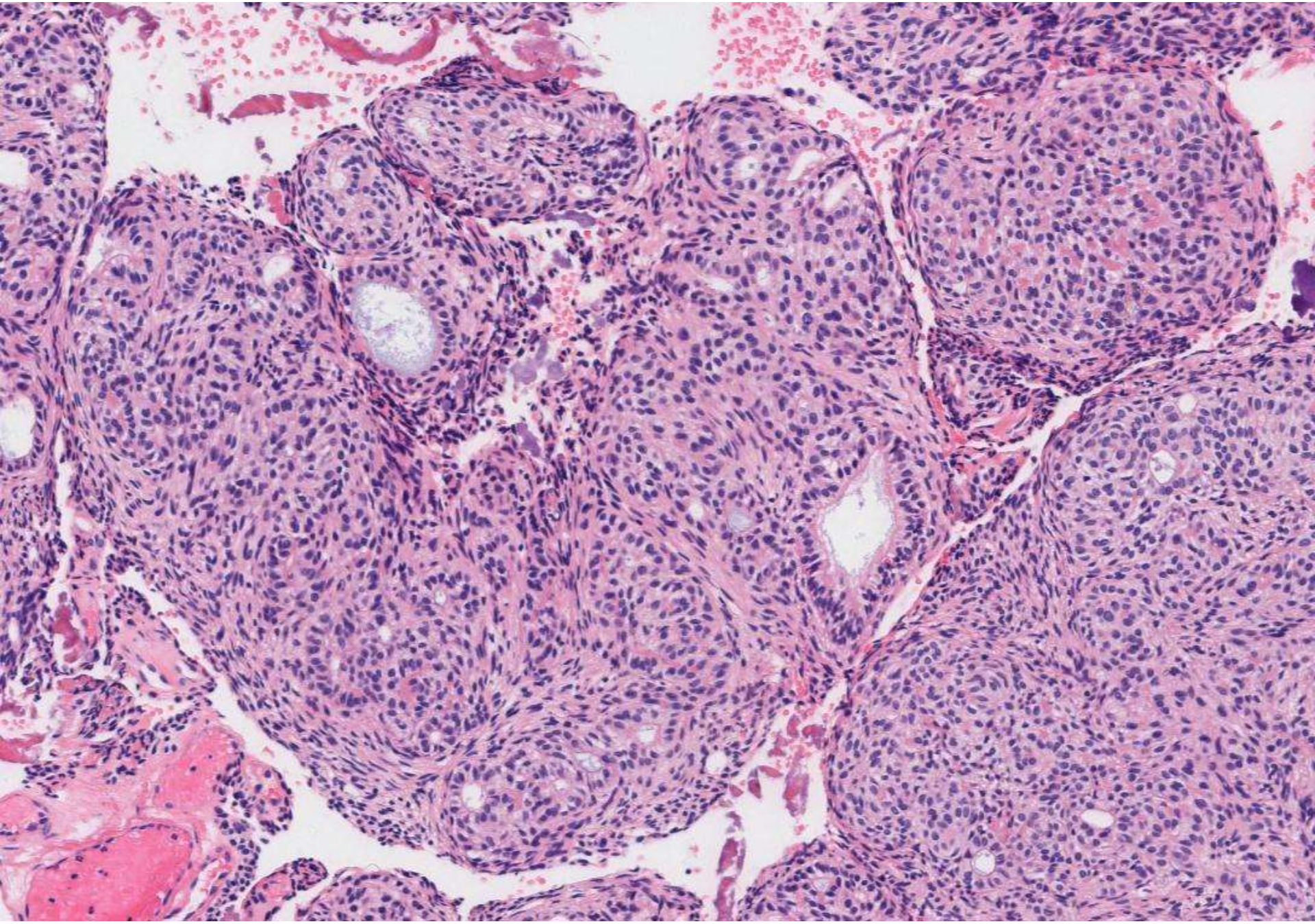
- Once accurately diagnosed, there is a greater than 95% response to steroids.
- Up to 40% of patients demonstrate spontaneous remission

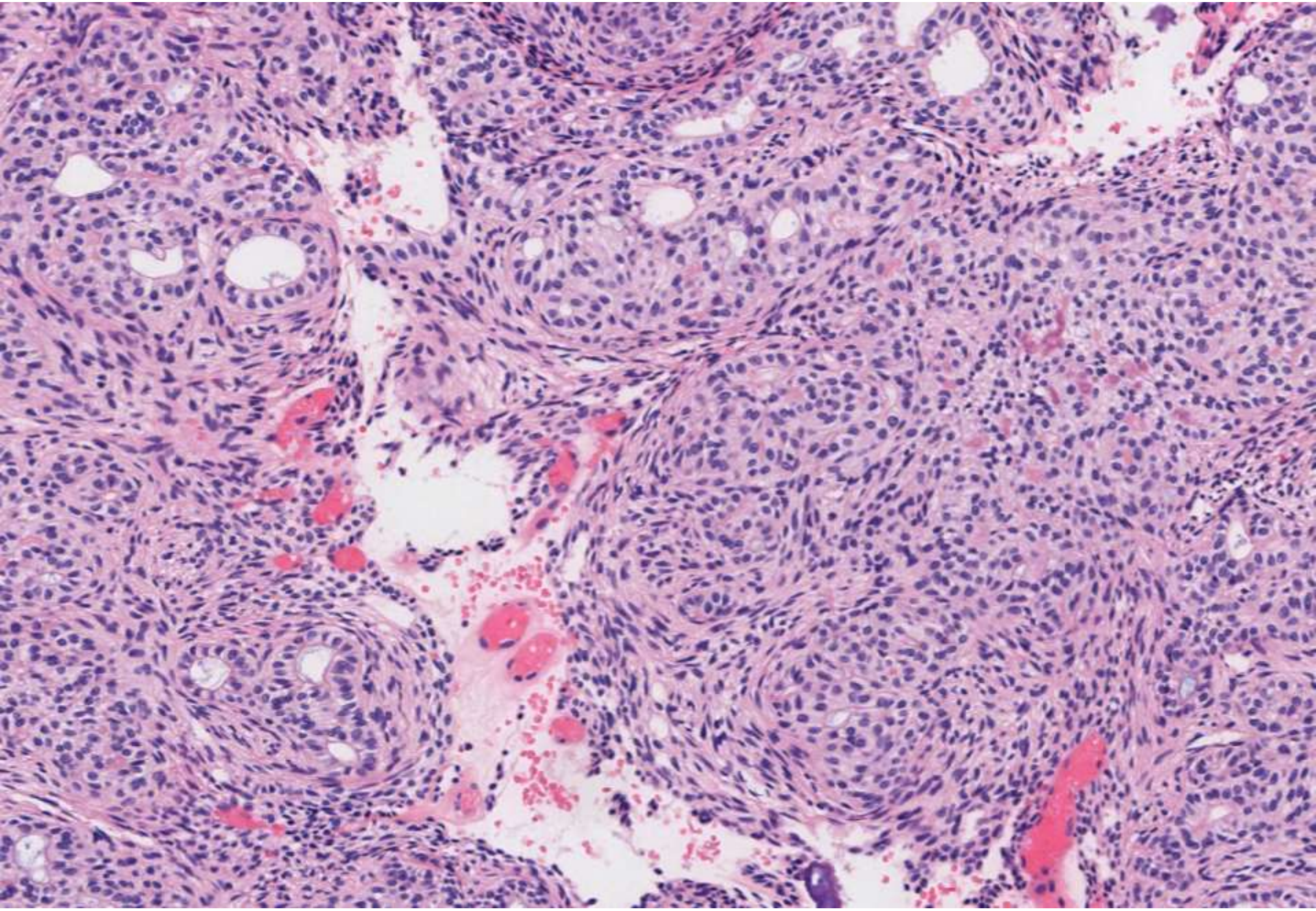
SB 5975

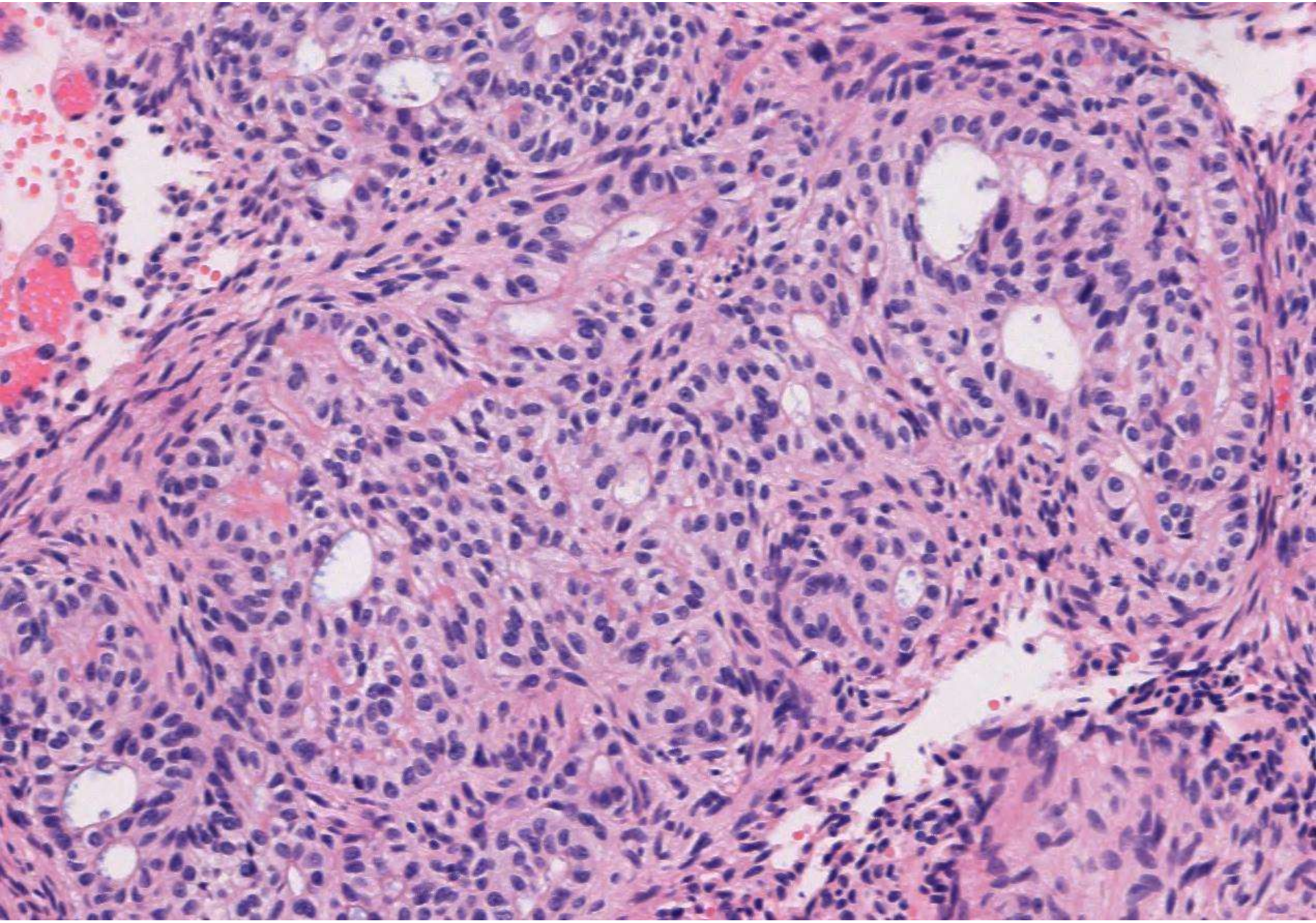
- 11-year-old boy found by his orthodontist to have a large unilocular cyst of left anterior mandible associated with impacted tooth #22.

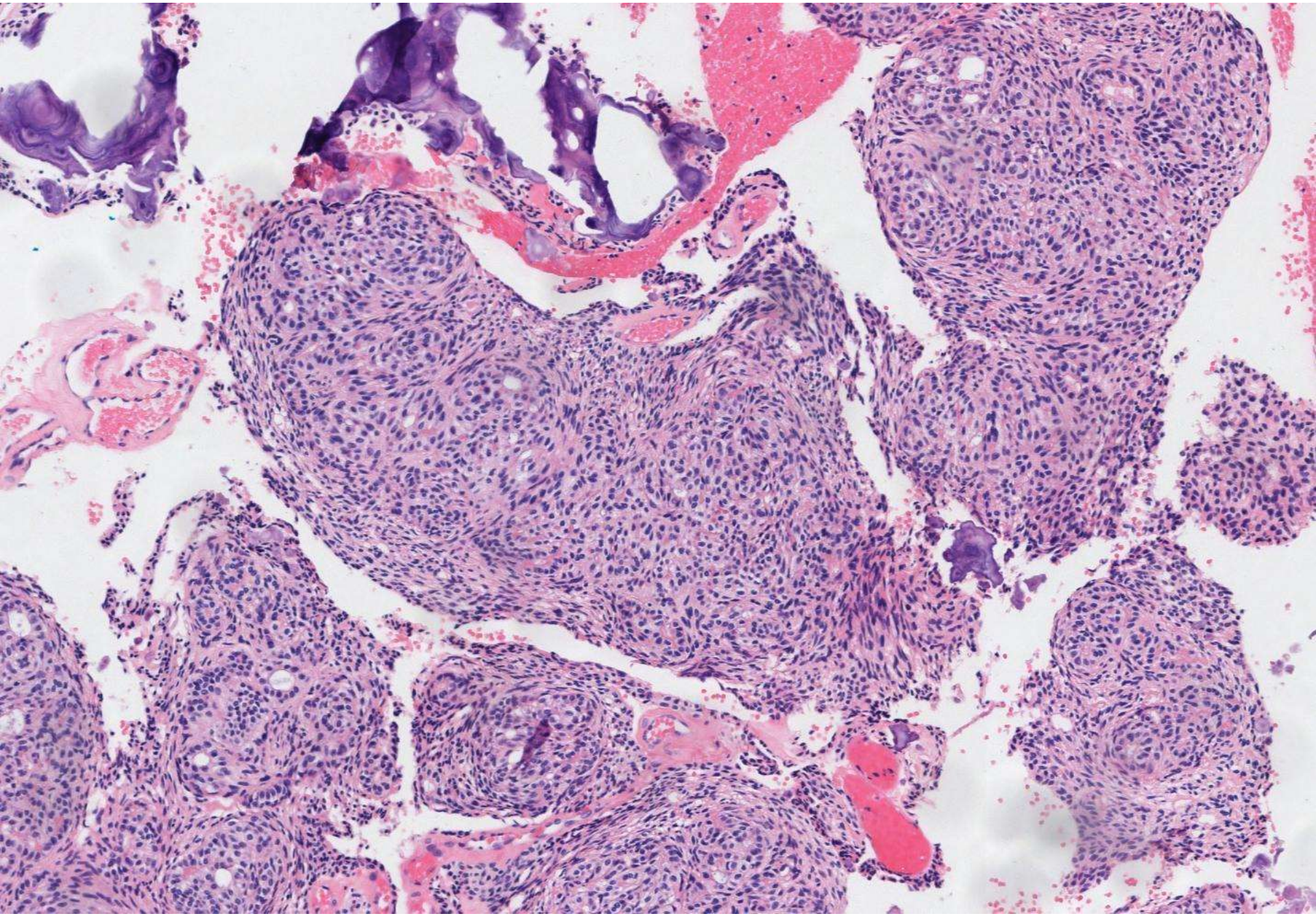
- **Balaram Puligandla; Kaiser Oakland**











Diagnosis….?

Adenomatoid Odontogenic Tumor (AOT)

AOT

- Third most common odontogenic tumor after ameloblastoma and myxoma.
- 2-7% of all odontogenic tumors.
- 5-30 Years age range, most in 2nd decade.

- J Oral Maxillofac Surg 2006; 64:1343-1352.

AOT

- The “ Two -Thirds Tumor”
- 2/3 in females.
- 2/3 in teenagers.
- 2/3 in maxilla.
- 2/3 associated with impacted teeth.

AOT

- Whorls of spindled cells forming rosettes associated with ductal structures.
- Psammoma like calcifications.
- Amyloid (Congo Red Positive)

AOT

- Main DDx is Calcifying Epithelial Odontogenic Tumor (CEOT) or Pindborg Tumor.
- CEOT occurs more often in the mandible and in an older age group (3^{rd}- 5^{th} Decades).
- Both are benign & treated conservatively.
- 2% recurrence rate for AOT and 10-15% for CEOT.

AOT

- Two other cases in the SBPS Files:
- SB 3263 Dec 1990 Dr. Bob Archibald
- SB 3352 Oct 1991 Dr. John Compagno

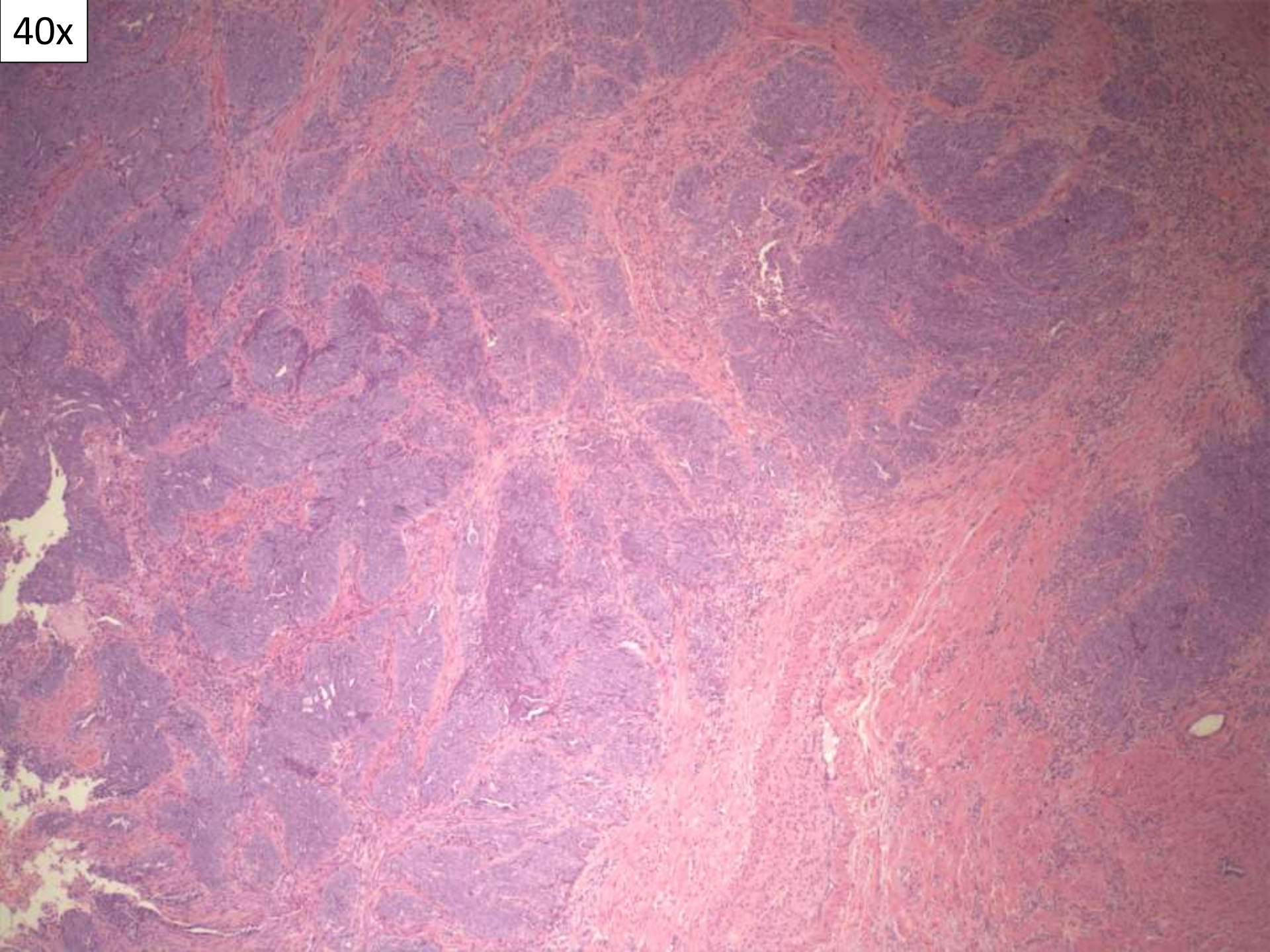
Take Home Message

- A cystic lesion associated with impacted teeth in a teenager think AOT.

SB 5990

- 57-year-old female with left ovarian cyst underwent bilateral salpingo-oophorectomy. Section of 1.5cm firm area of tube/ovary submitted.

- **Sebastian Fernandez-Pol/Teri Longare; Stanford**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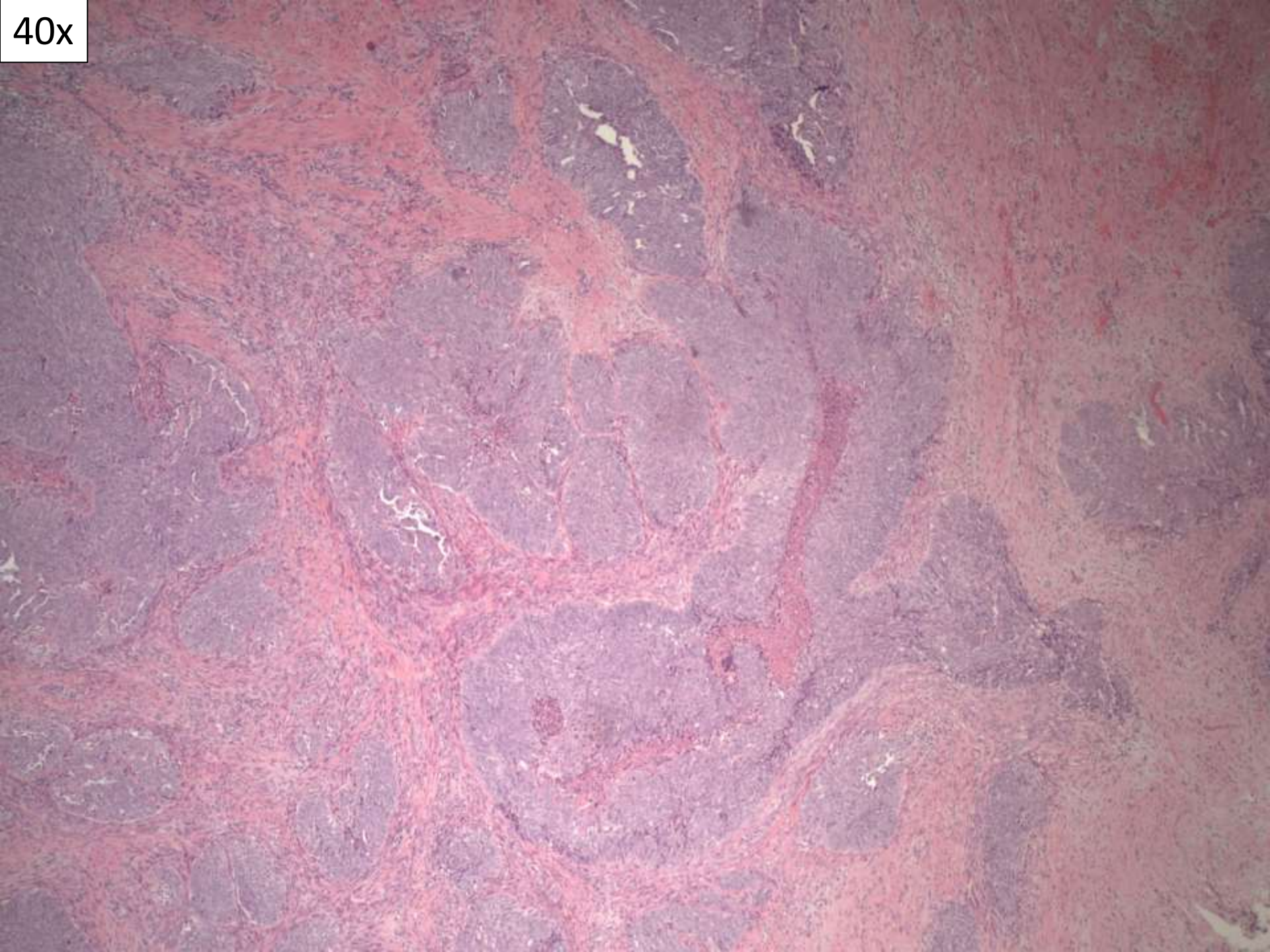
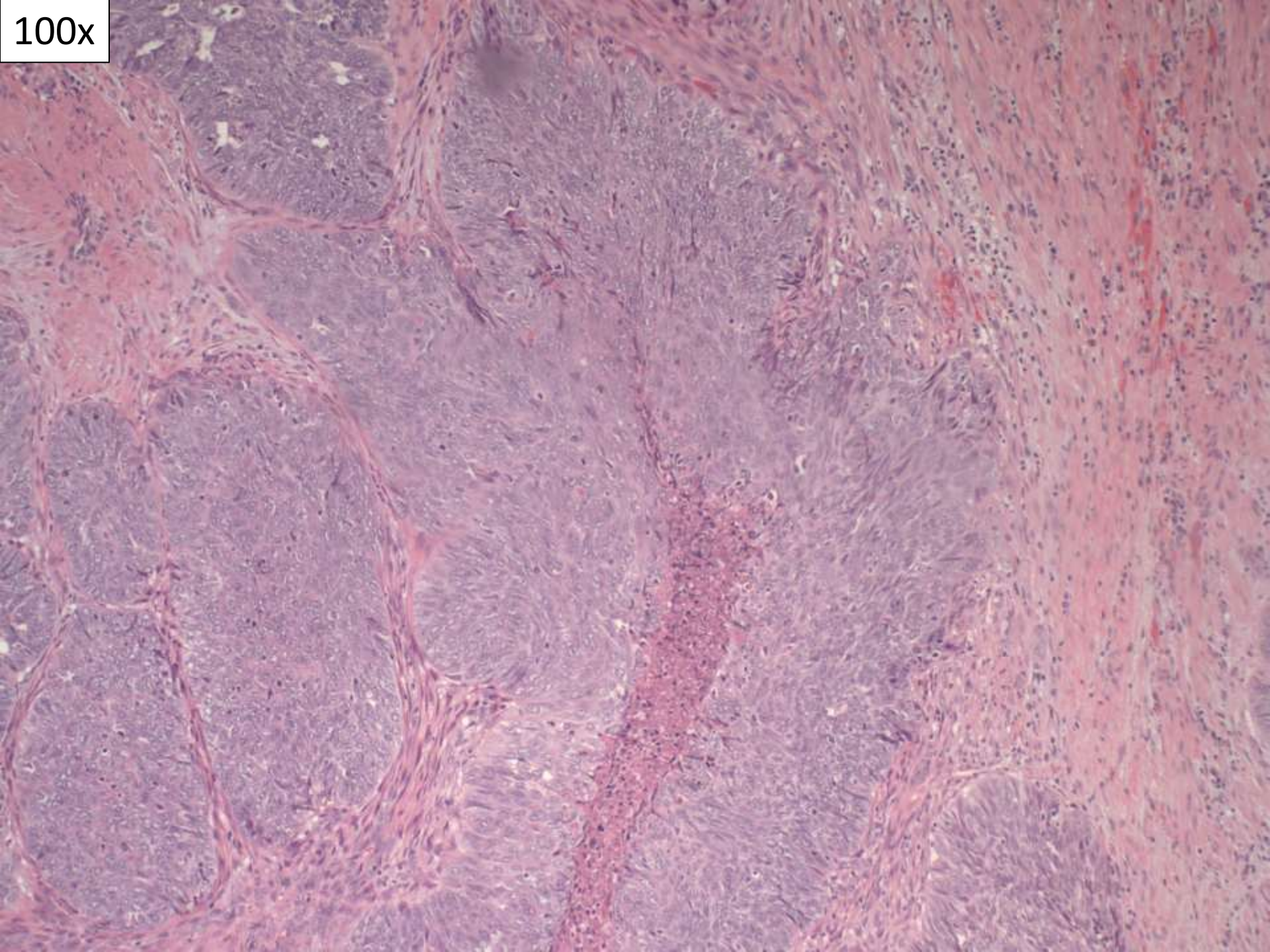
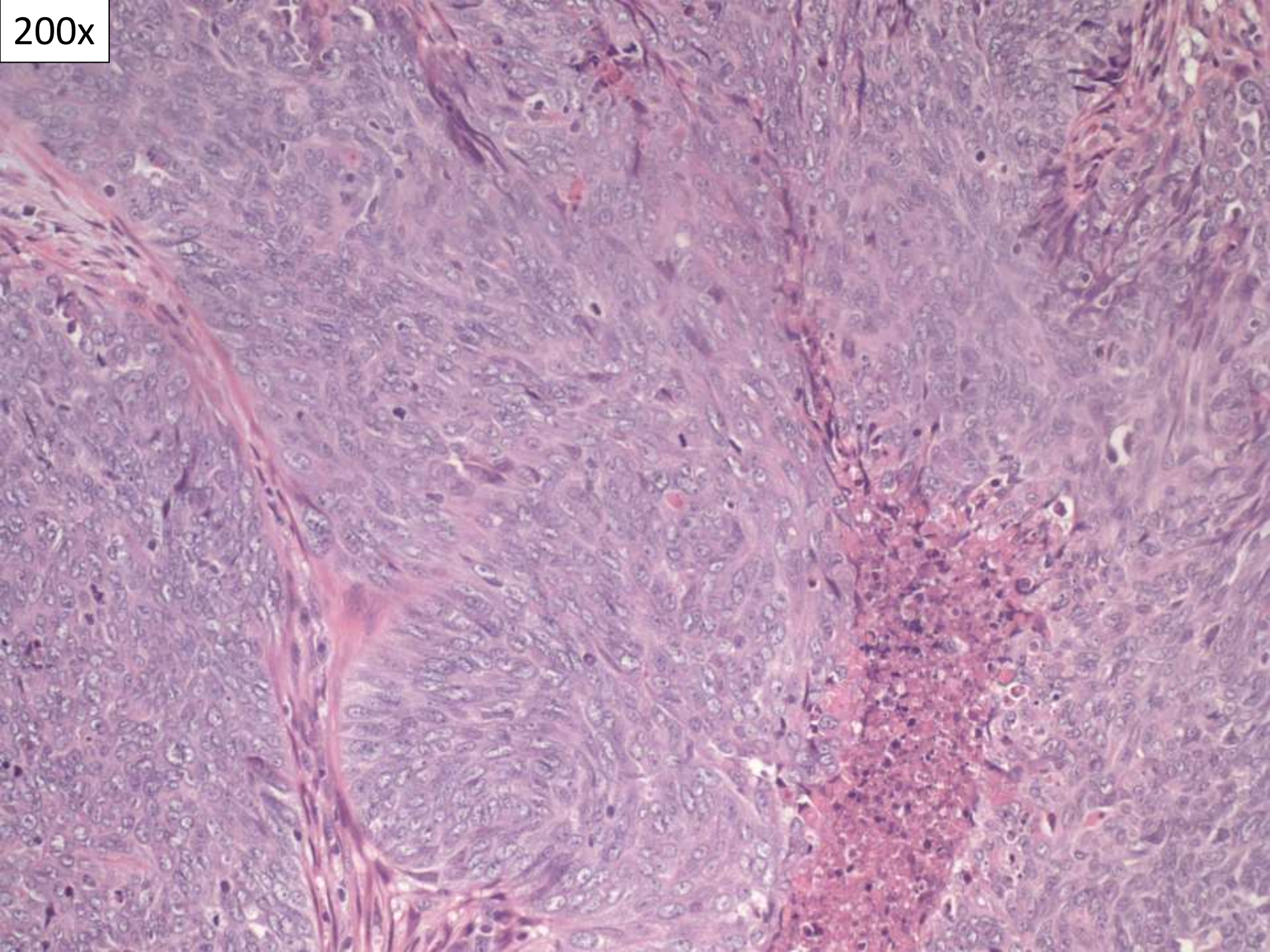
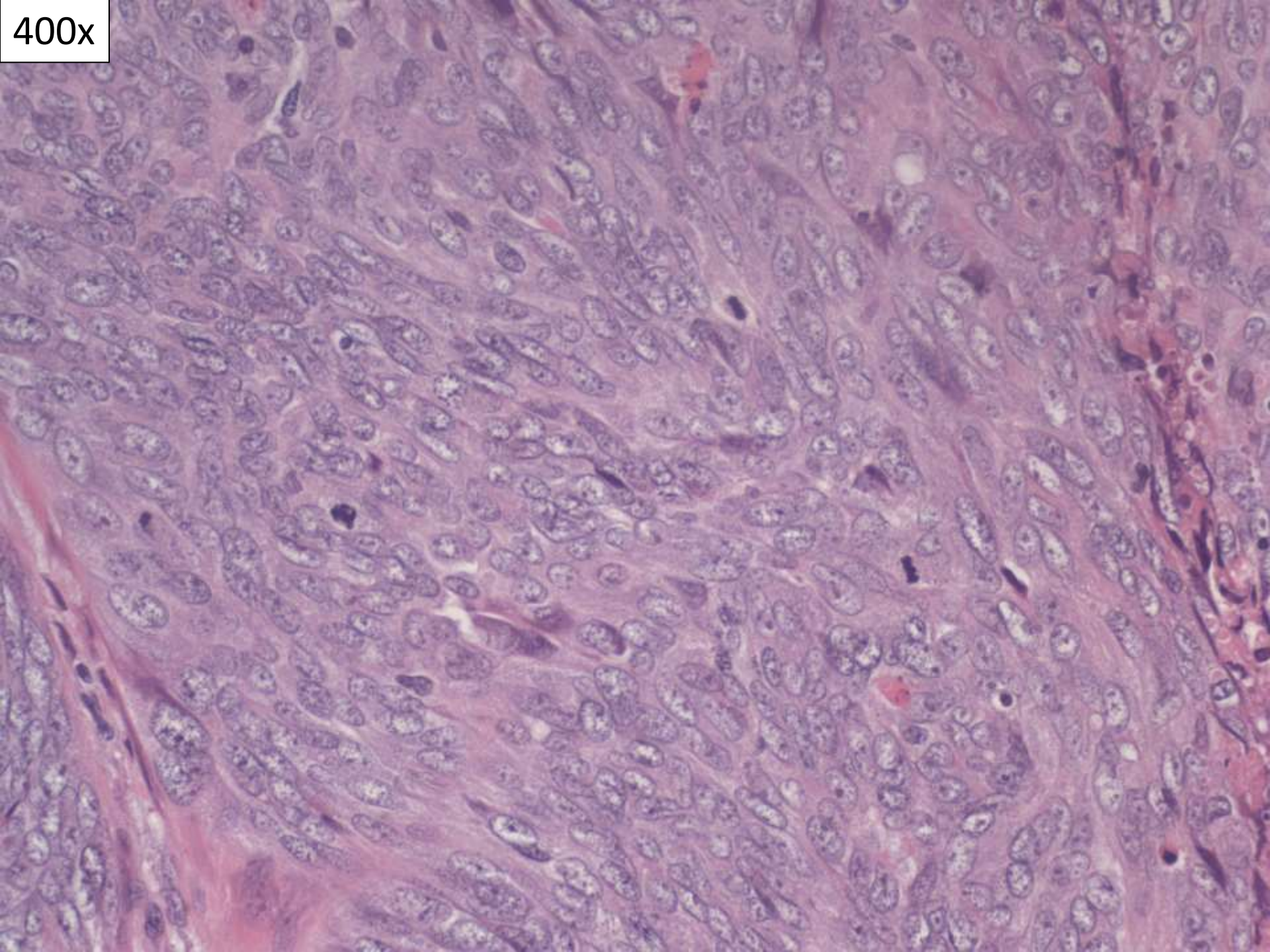

40x


100x


200x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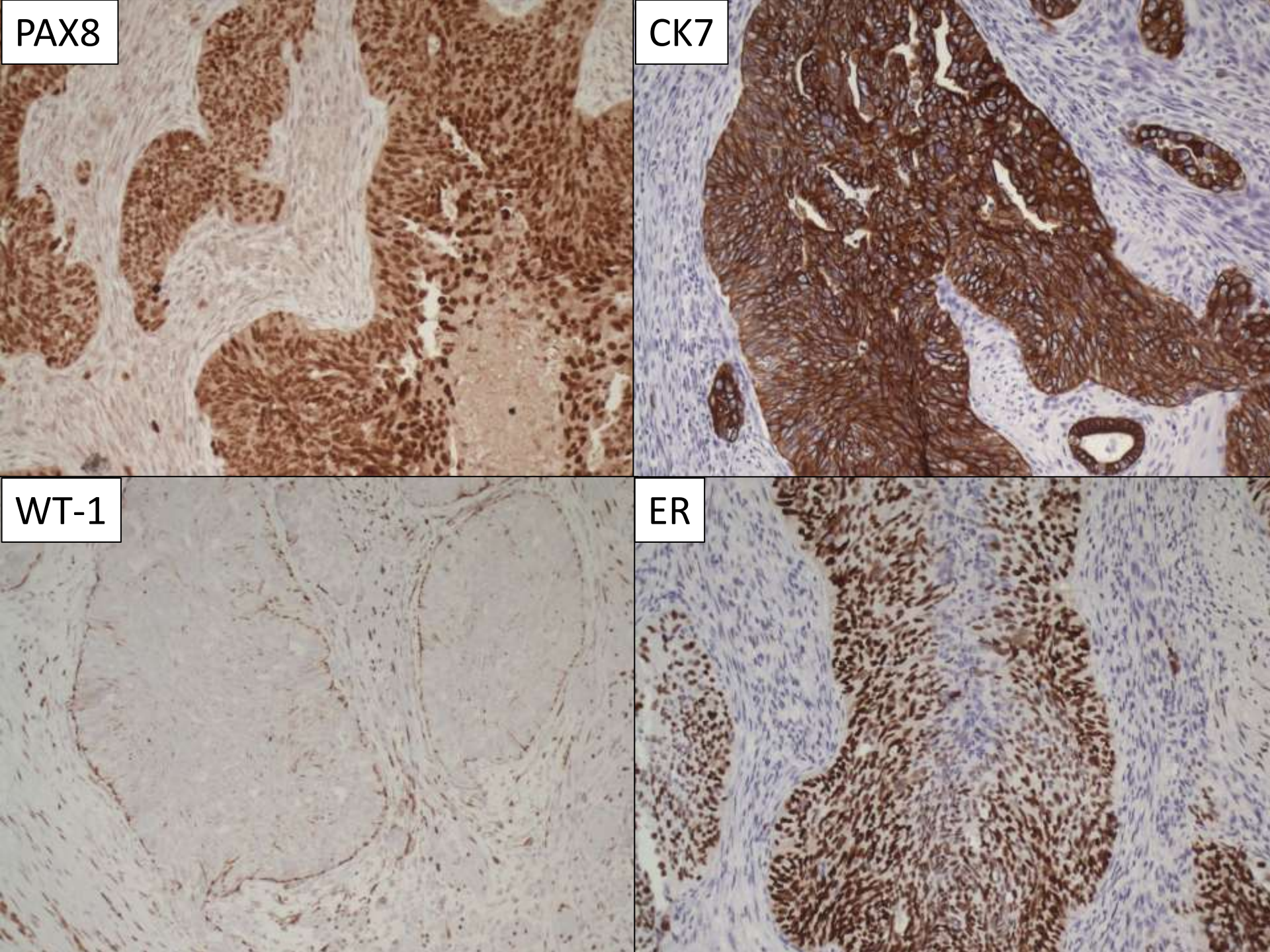
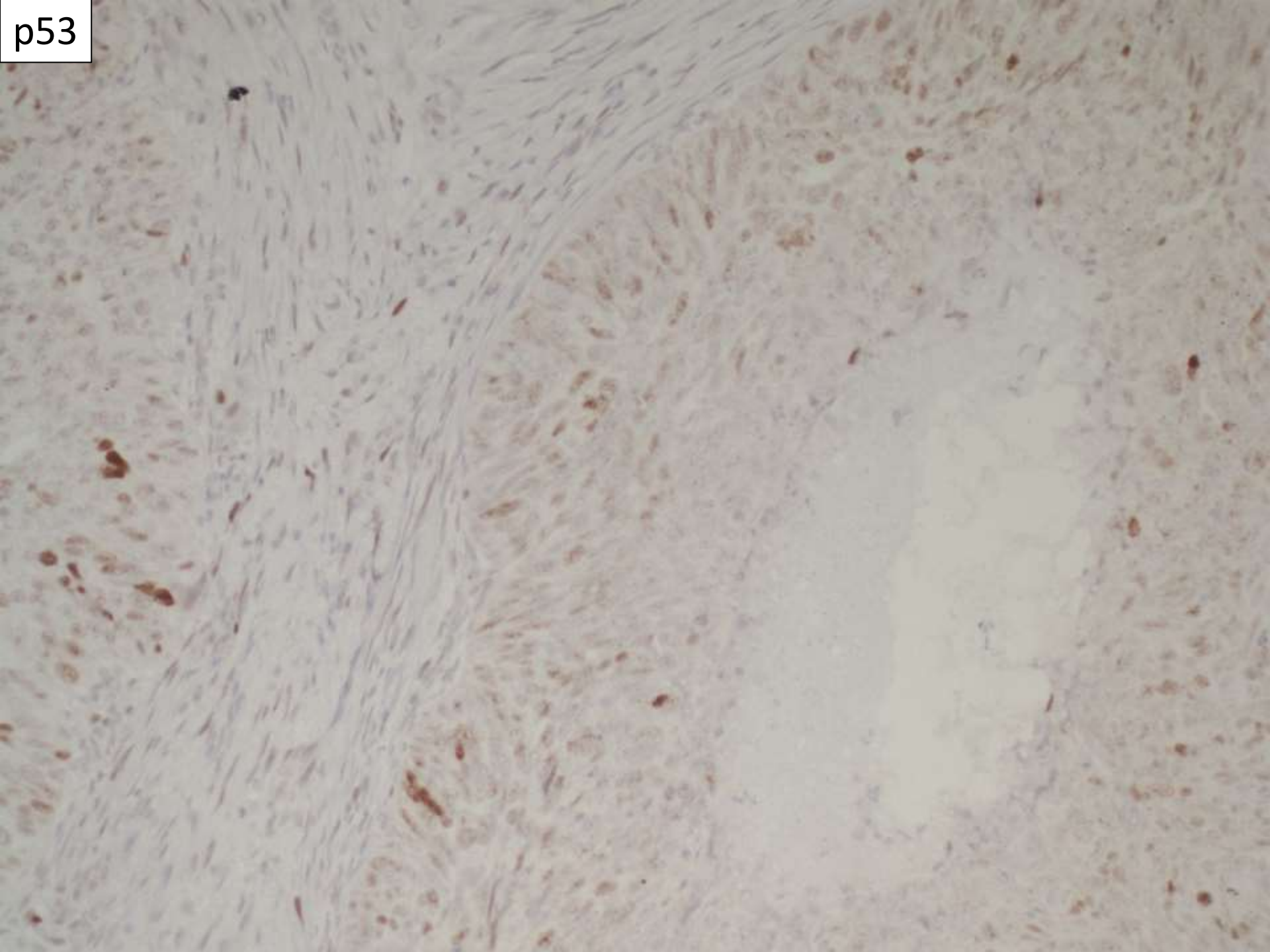
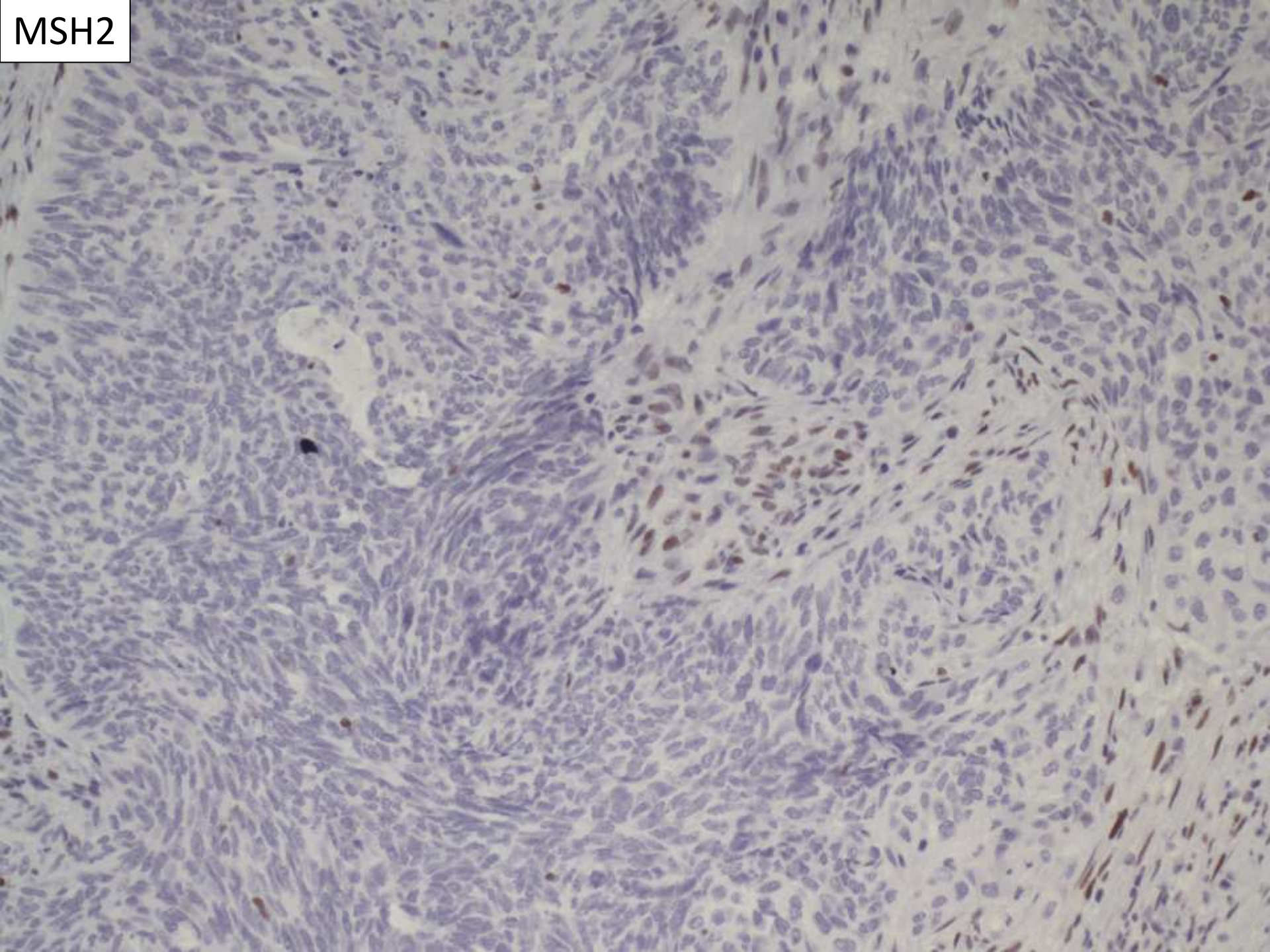
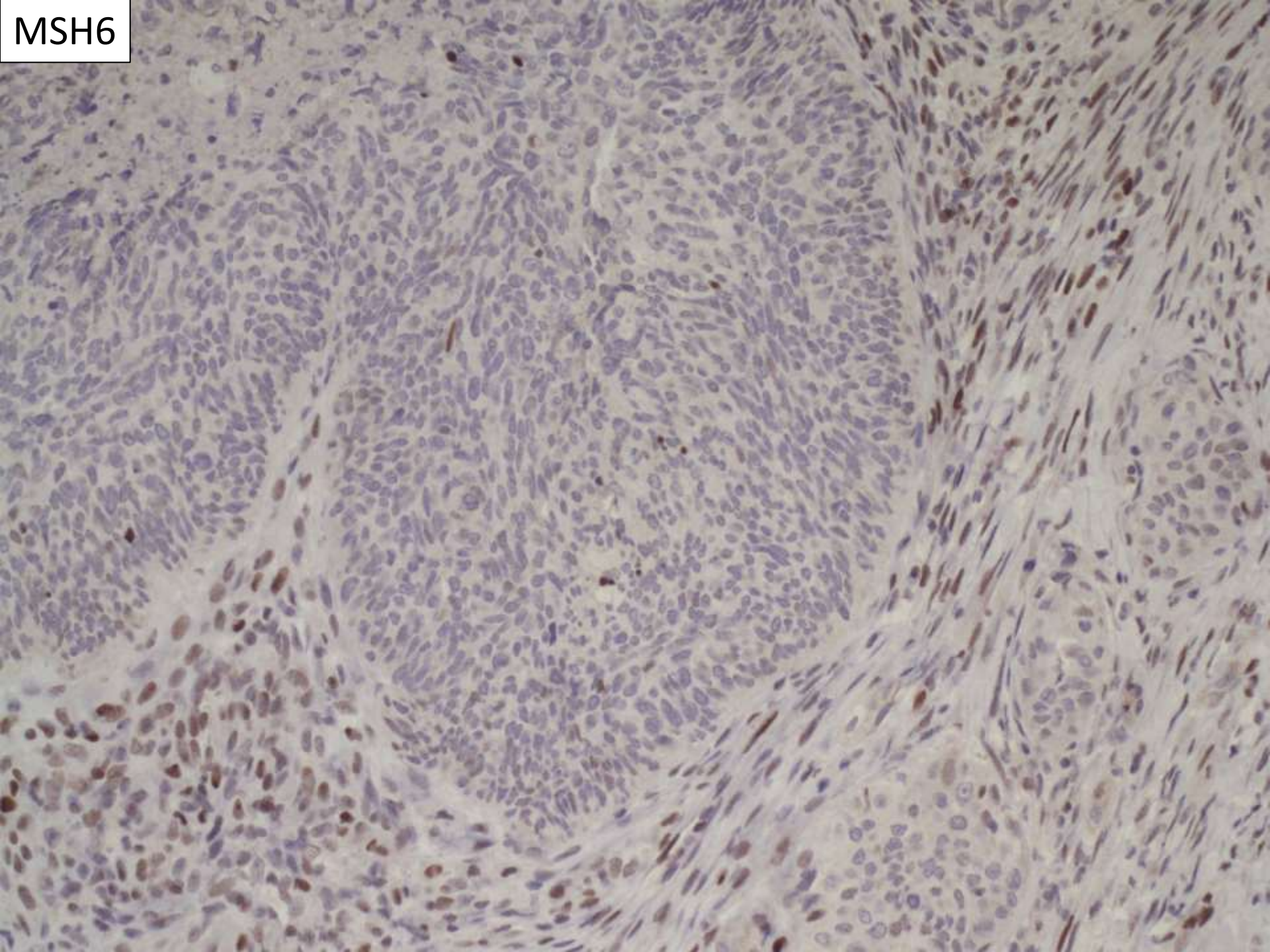

PAX8
CK7
WT-1
ER


p53

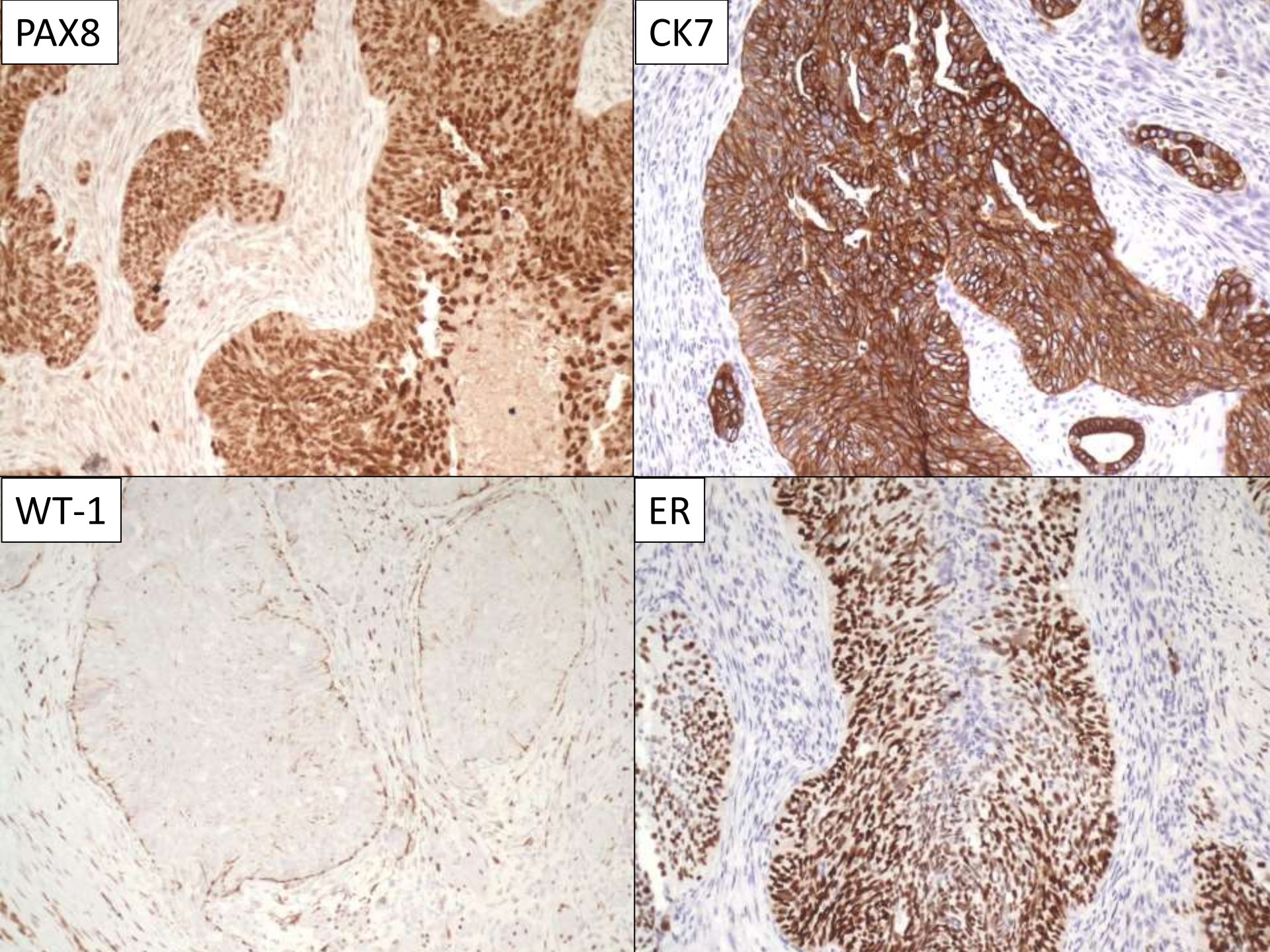

MSH2


MSH6

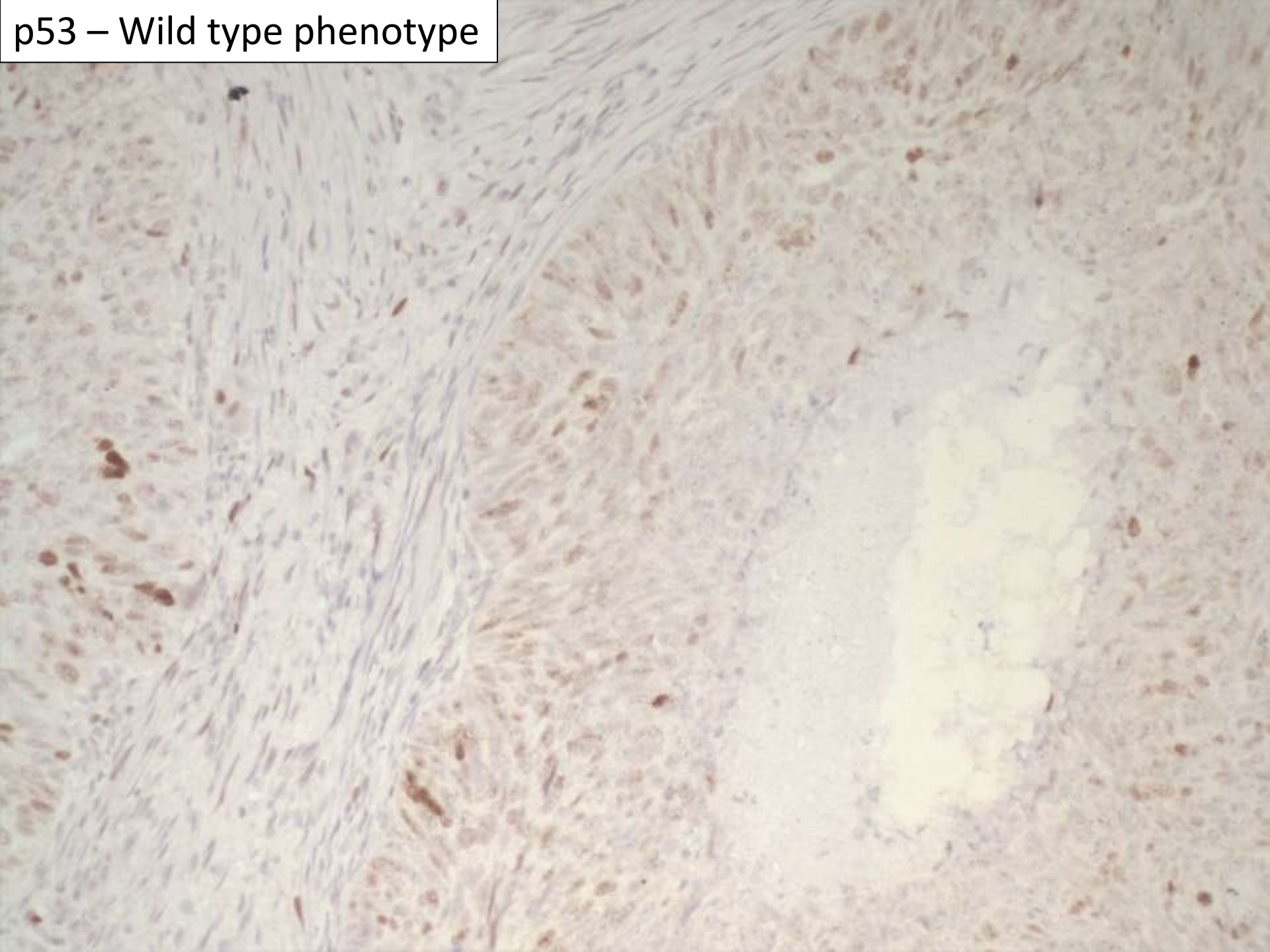
Diagnosis….?

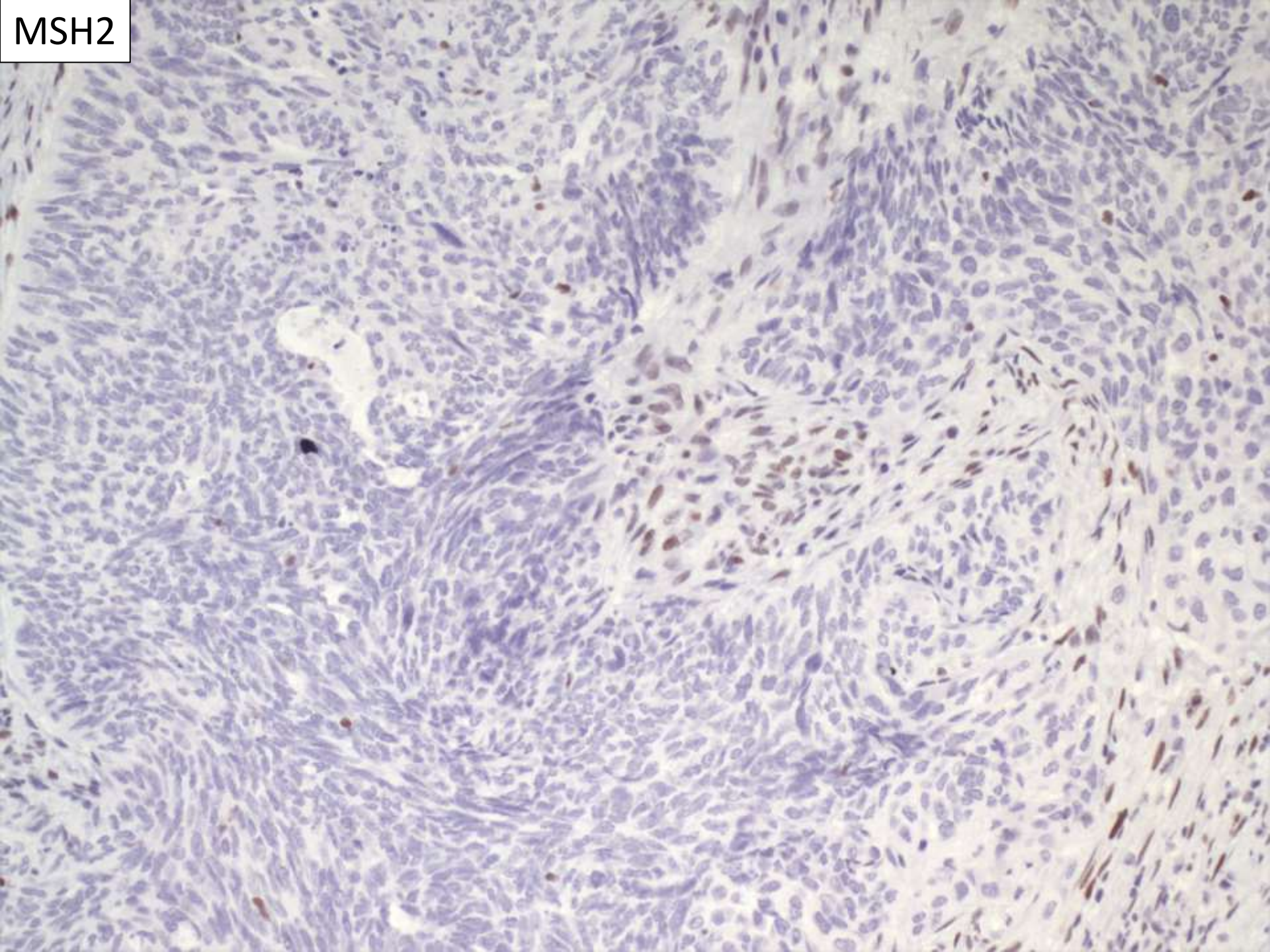
Differential Diagnosis

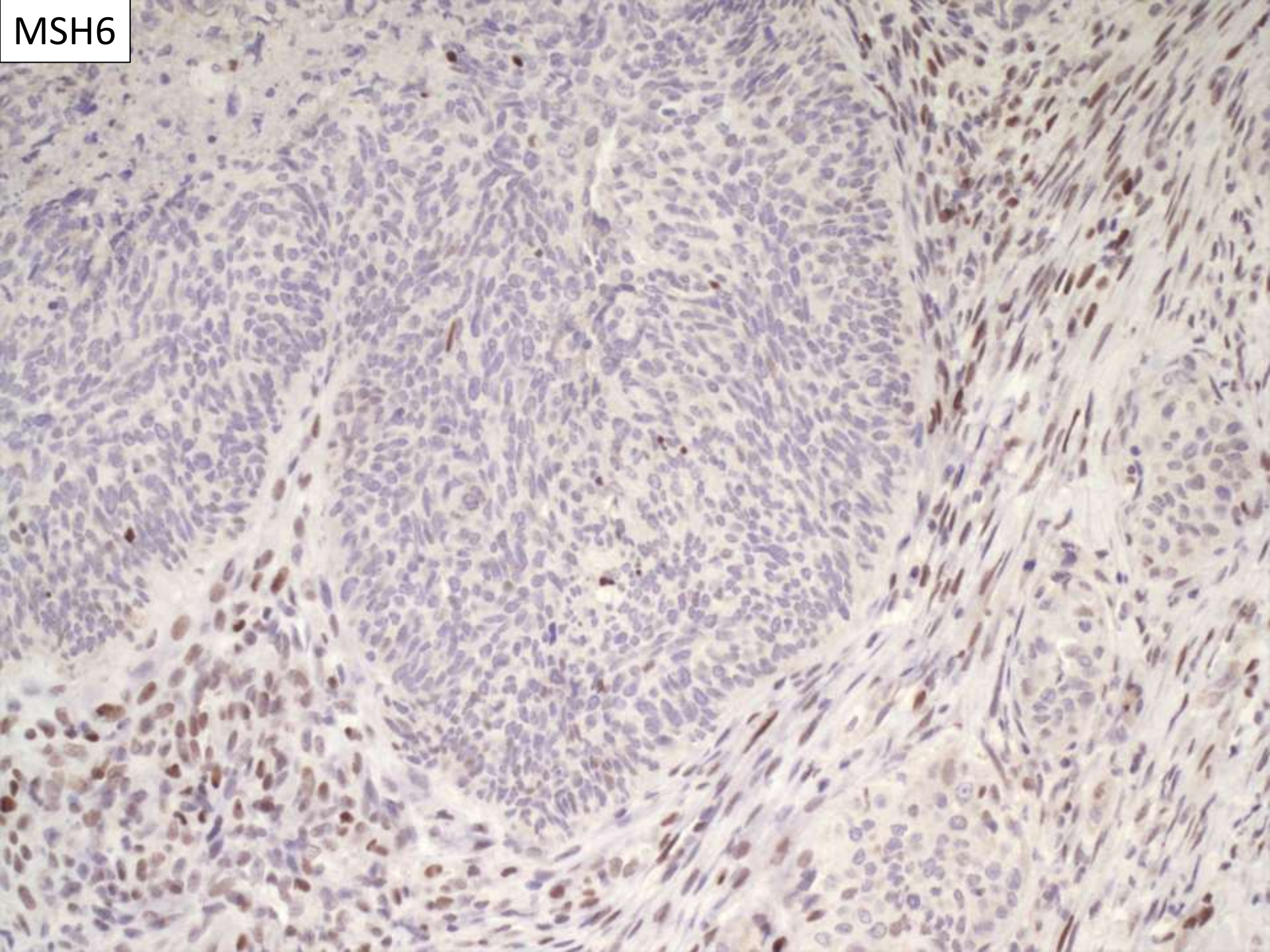
- Endometrioid adenocarcinoma
- High grade serous carcinoma
- Metastasis


PAX8
CK7
WT-1
ER

p53 – Wild type phenotype




MSH2


MSH6

Right ovary

Diagnosis:

Endometrioid adenocarcinoma, FIGO Grade 3, with loss of MSH2 and MSH6 expression

Comment:

Recommend genetic counseling for possible Lynch Syndrome (LS)

Lynch Syndrome

- Characterized by an increased risk of a variety of cancers including colon, rectum, small bowel, endometrium, ovary, stomach, pancreas, renal pelvis and ureter, and brain

- Germline defects in DNA mismatch repair (MMR) genes
  - *MLH1, PMS2, MSH2, MSH6*
  - Mutations in *EPCAM* causing hypermethylation and inactivation of the *MSH2* promoter

Hereditary Ovarian Cancer

- About 23% of ovarian tumors are associated with hereditary susceptibility
  - Most (65-85%) associated with germline BRCA1/2 mutations
  - 10-15% associated with mutations in MMR genes (Lynch syndrome)

- Colorectal cancer
  - ~3% of colorectal carcinomas associated with germline mutations in MMR genes
  - ~12% sporadic, acquired hypermethylation of the promoter of MLH1

Toss A, et al. Hereditary Ovarian Cancer: Not Only BRCA 1 and 2 Genes. Biomed Res Int. 2015;2015:341723. Epub 2015 May 17.

Ovarian carcinomas in Lynch Syndrome

Histologic type:

- Usually endometrioid (pure > mixed)
- Less commonly clear cell
- In contrast to BRCA1/2-associated tumors, which are usually high grade serous

Stage:

- Tumors are less advanced at the time of diagnosis

Survival:

- Show high stage-specific survival rate

Toss A, et al. Hereditary Ovarian Cancer: Not Only BRCA 1 and 2 Genes. Biomed Res Int. 2015;2015:341723. Epub 2015 May 17.

MMR screening for ovarian carcinomas

Jensen et al, 2008

- 5 of 52 (10%) ovarian tumors showed evidence of MMR defect

Vierkoetter et al, 2014

- 90 patients with endometrioid and clear cell carcinomas evaluated for MMR expression by IHC
- 7 of the 90 (7.8%) had loss of MMR expression

1. Jensen K. C., Mariappan M. R., Putcha G. V., et al. Microsatellite instability and mismatch repair protein defects in ovarian epithelial neoplasms in patients 50 years of age and younger. *American Journal of Surgical Pathology*. 2008;32(7):1029–1037.
2. Vierkoetter, et al. Lynch Syndrome in patients with clear cell and endometrioid cancers of the ovary. Gynecol Oncol. 2014 Oct; 135(1): 81–84.

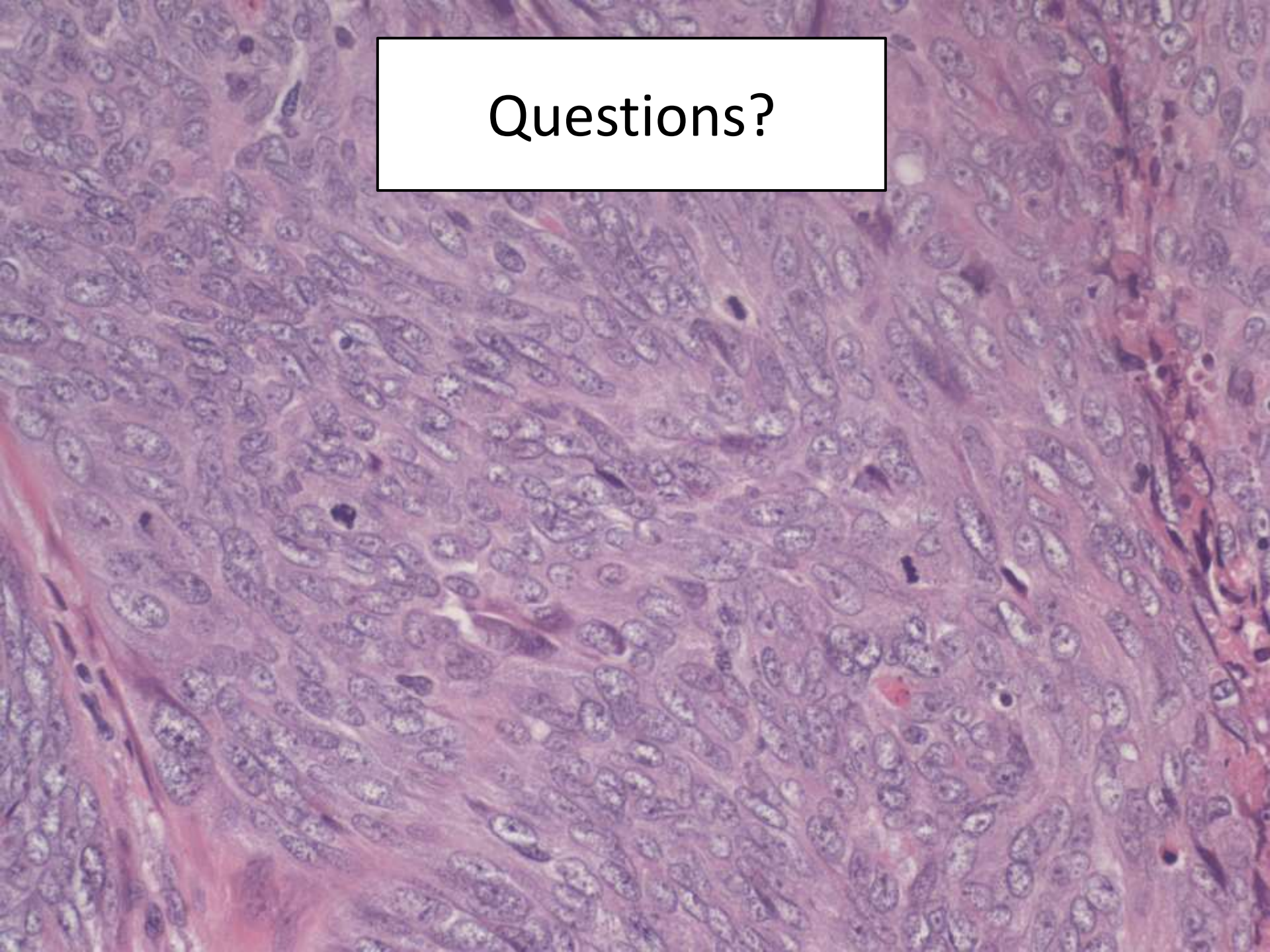
Summary and take home points

- Endometrioid and clear cell adenocarcinoma are the typical histologic types associated with germline mutations in MMR genes

- Test endometrioid and clear cell adenocarcinomas of the ovary for MMR defects

References

1. Friedberg E. (2001) How nucleotide excision repair protects against cancer. Nature Rev Cancer 1: 22–33. pmid:11900249
2. Toss A, et al. Hereditary Ovarian Cancer: Not Only BRCA 1 and 2 Genes. Biomed Res Int. 2015;2015:341723. Epub 2015 May 17.
3. Mills AM, Liou S, Ford JM, et al. Lynch syndrome screening should be considered for all patients with newly diagnosed endometrial cancer. Am J Surg Pathol.2014;38:1501–1509.
4. Karen H. Lu and Kari L. Ring. One size may not fit all: The debate of universal tumor testing for Lynch syndrome. Gynecologic Oncology. Volume 137, Issue 1, April 2015, Pages 2–3
5. Jensen K. C., Mariappan M. R., Putcha G. V., et al. Microsatellite instability and mismatch repair protein defects in ovarian epithelial neoplasms in patients 50 years of age and younger. *American Journal of Surgical Pathology*. 2008;32(7):1029–1037.
6. Vierkoetter, et al. Lynch Syndrome in patients with clear cell and endometrioid cancers of the ovary. Gynecol Oncol. 2014 Oct; 135(1): 81–84.


Questions?