Disclosures
September 14, 2015

Dr. Keith Duncan has disclosed that he/his group received a consultation fee from Abbvie (Redwood City) and Oxford Biotherapeutics (San Jose) for review of immunohistochemical stains. The activity planners have determined that these financial relationships are not relevant to the cases being presented.

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

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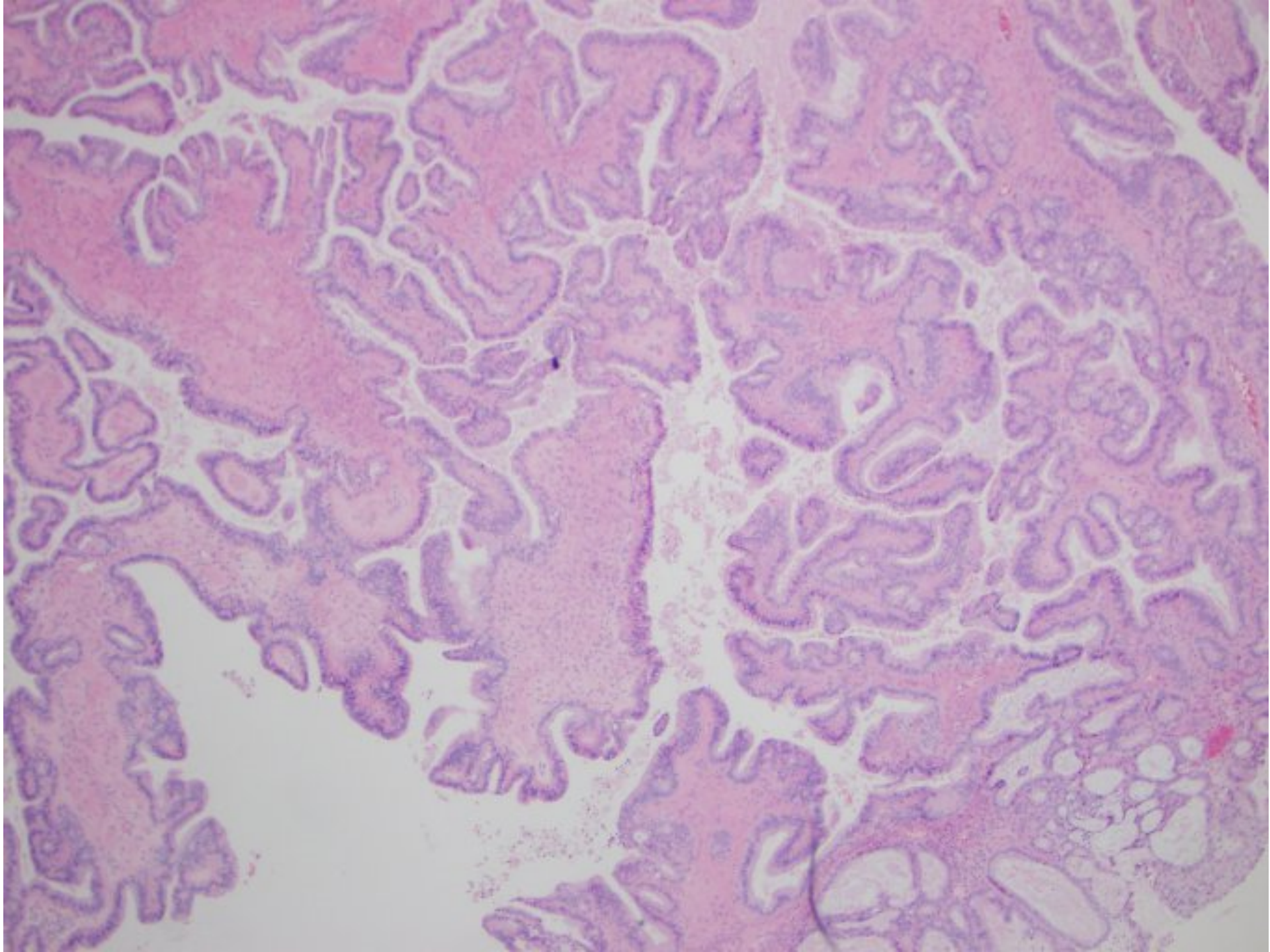
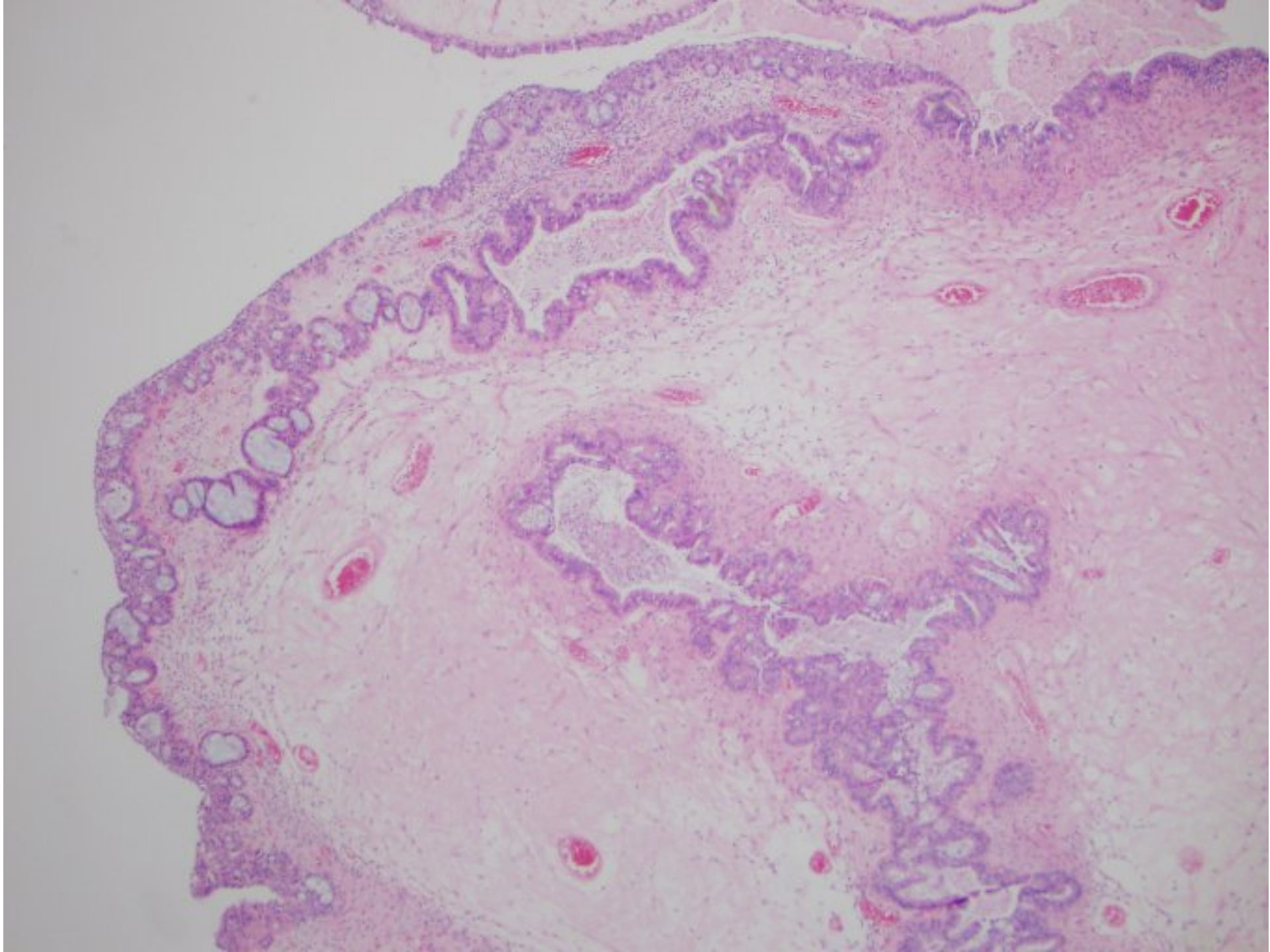
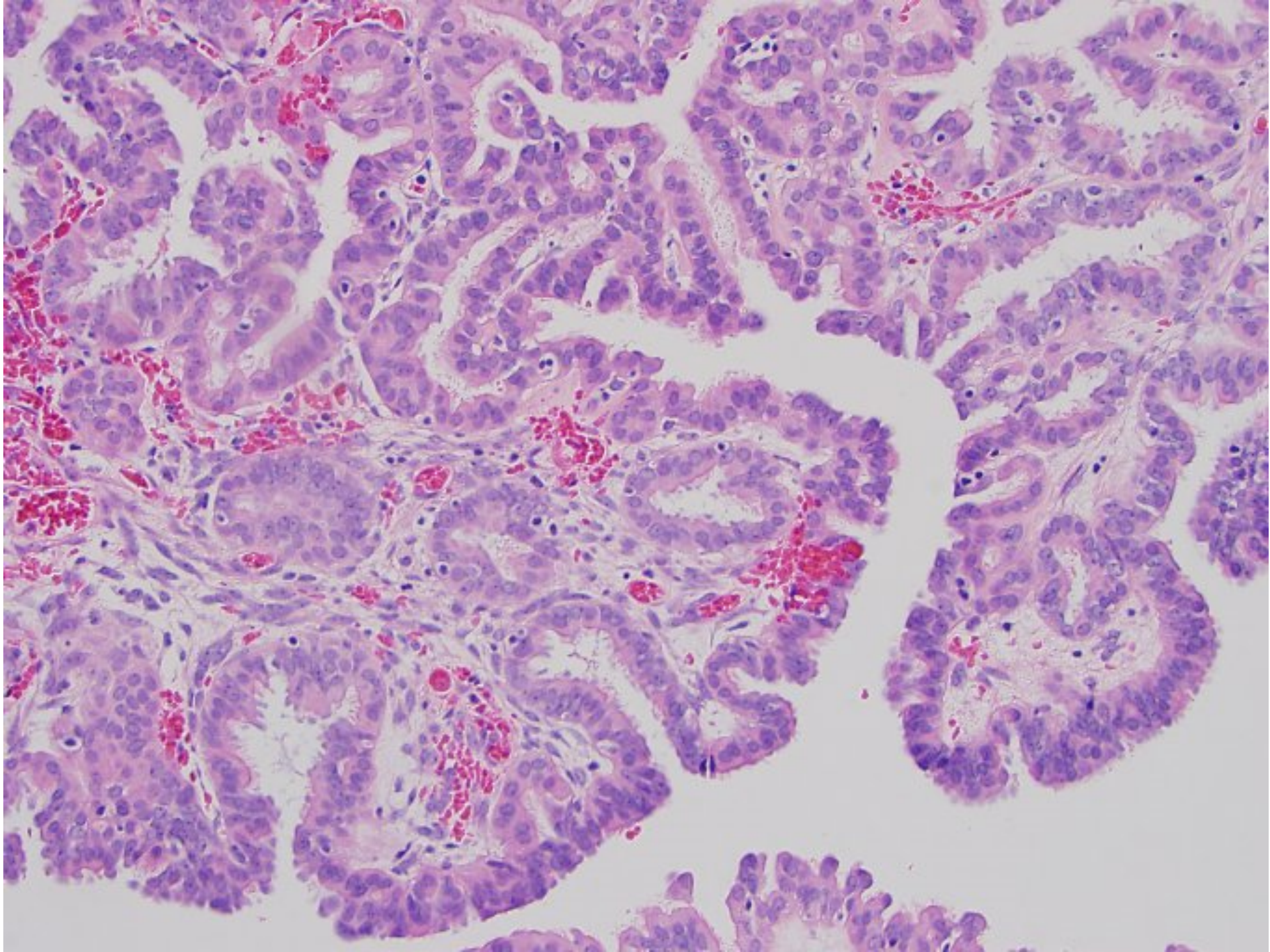
SB 5971

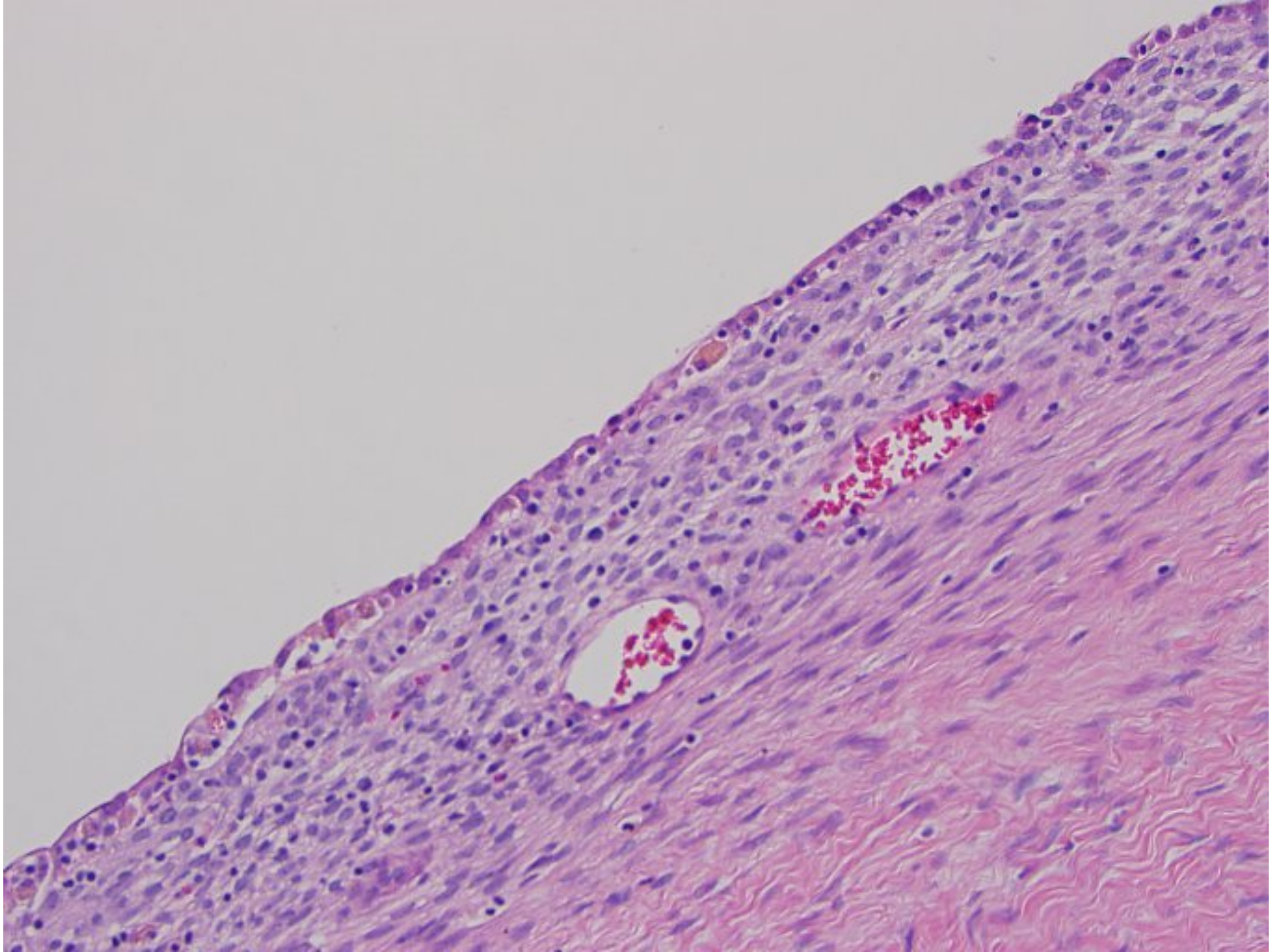
- 42-year-old woman with bilateral 8cm ovarian cystic lesions (both lesions had similar appearance)

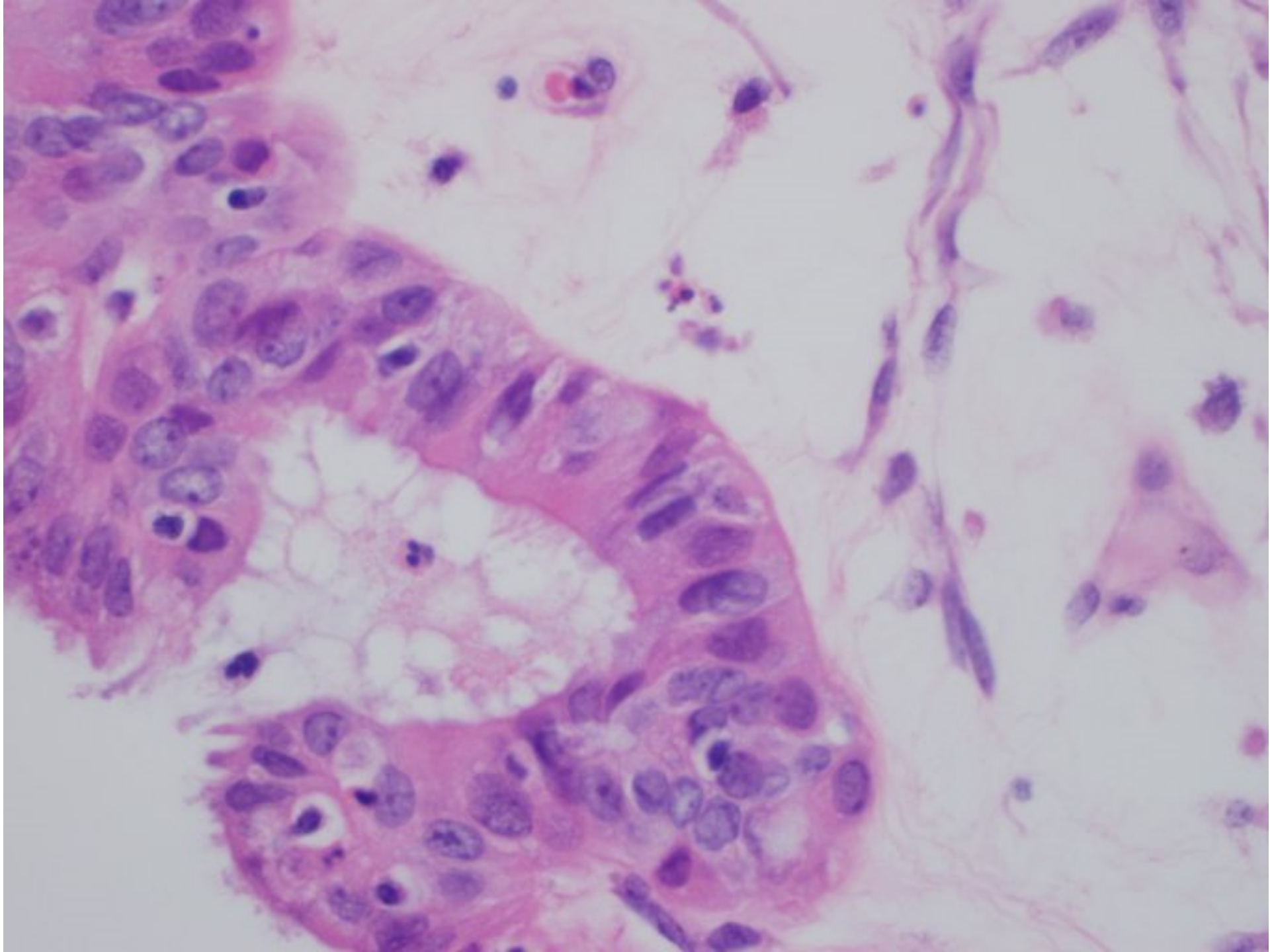
- **Greg Rumore; Kaiser Walnut Creek**

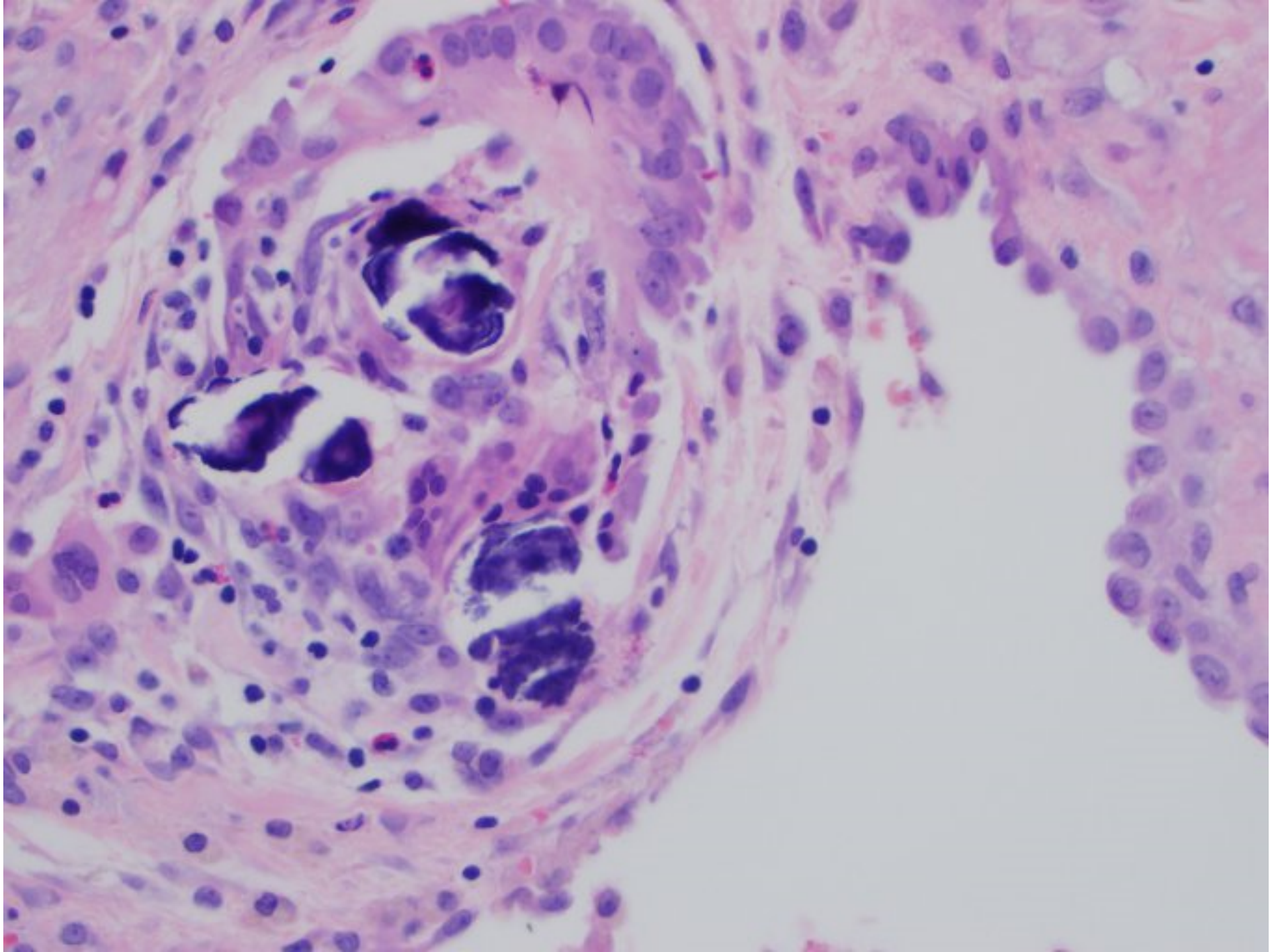


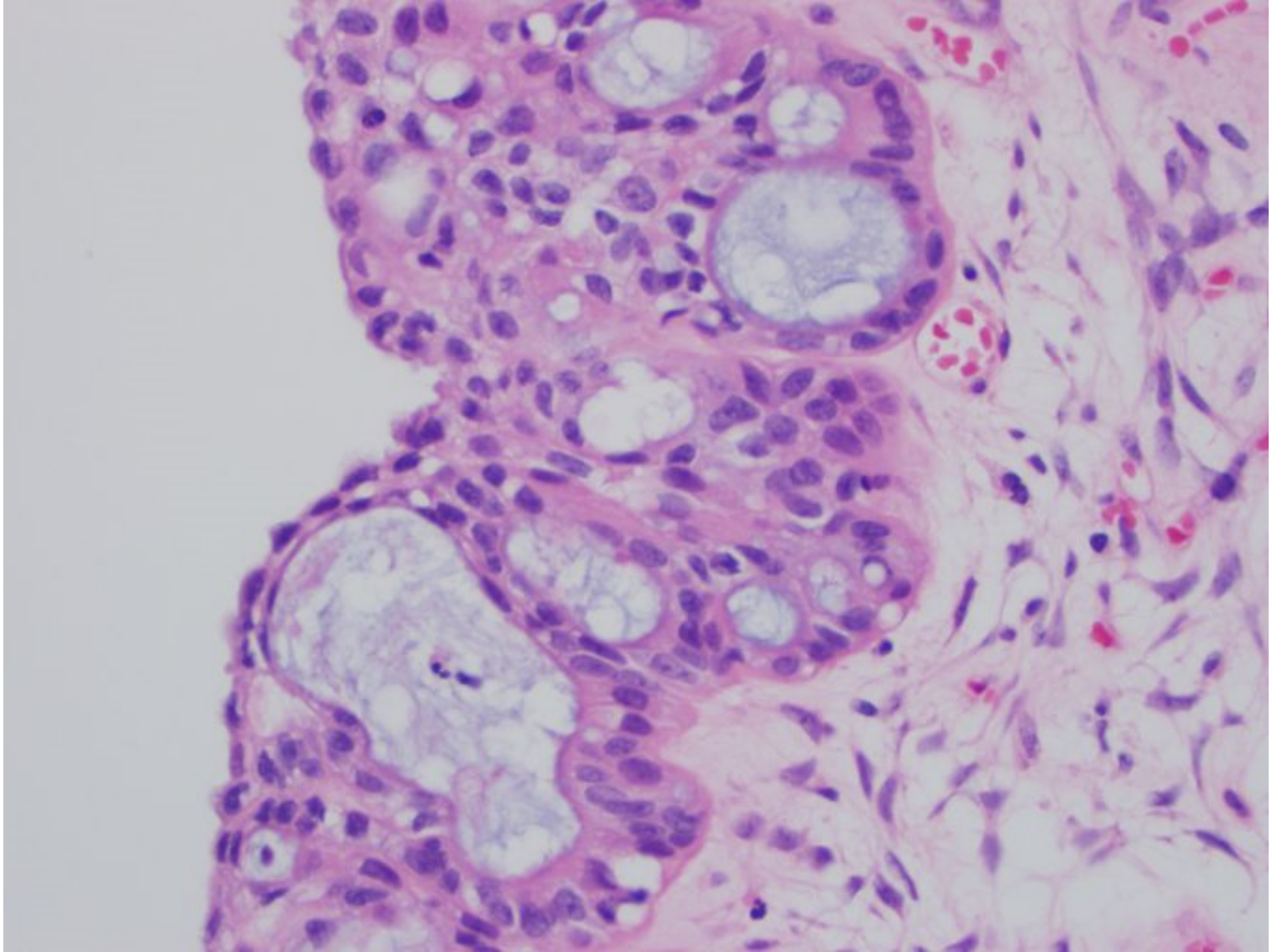


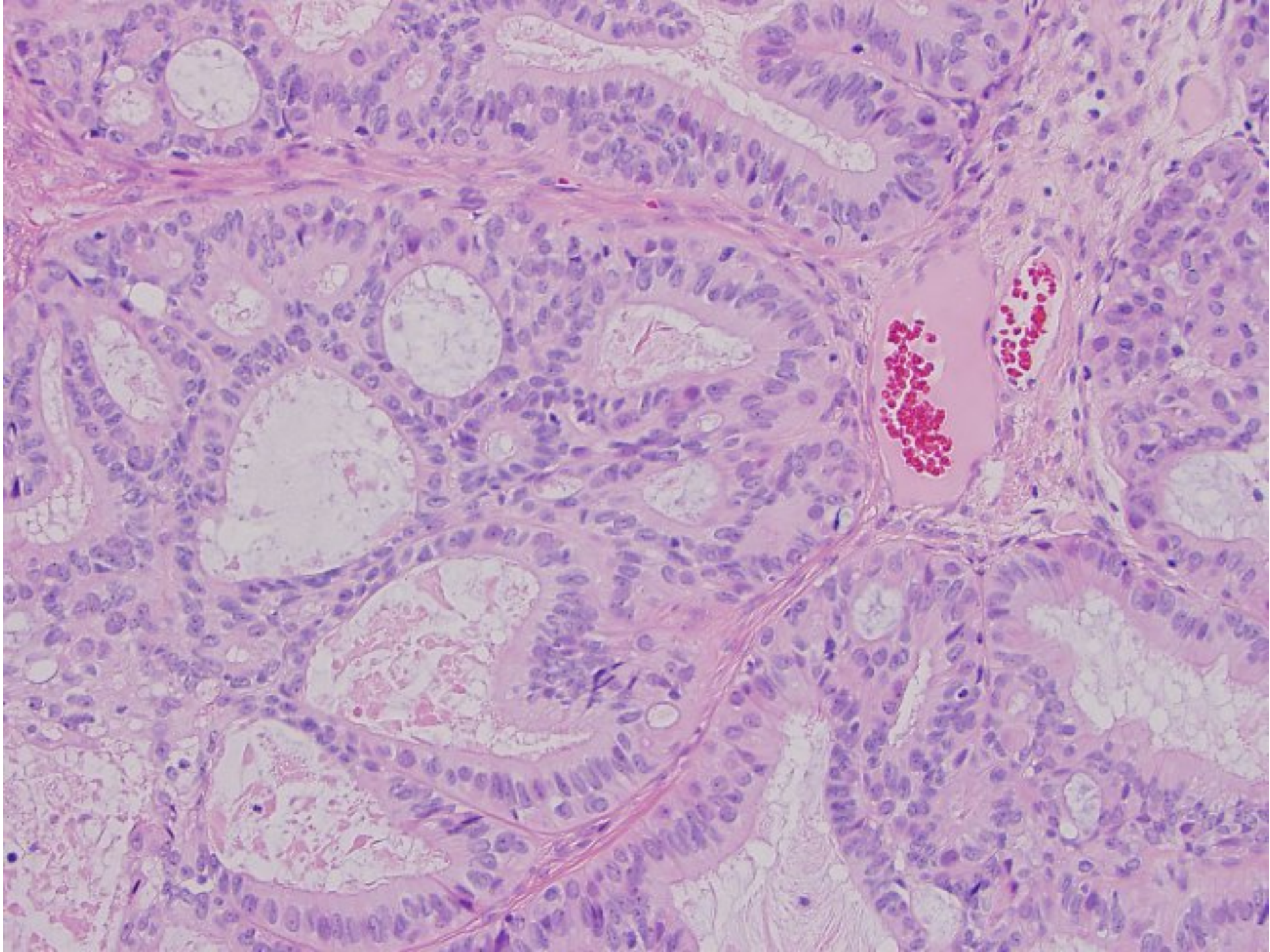


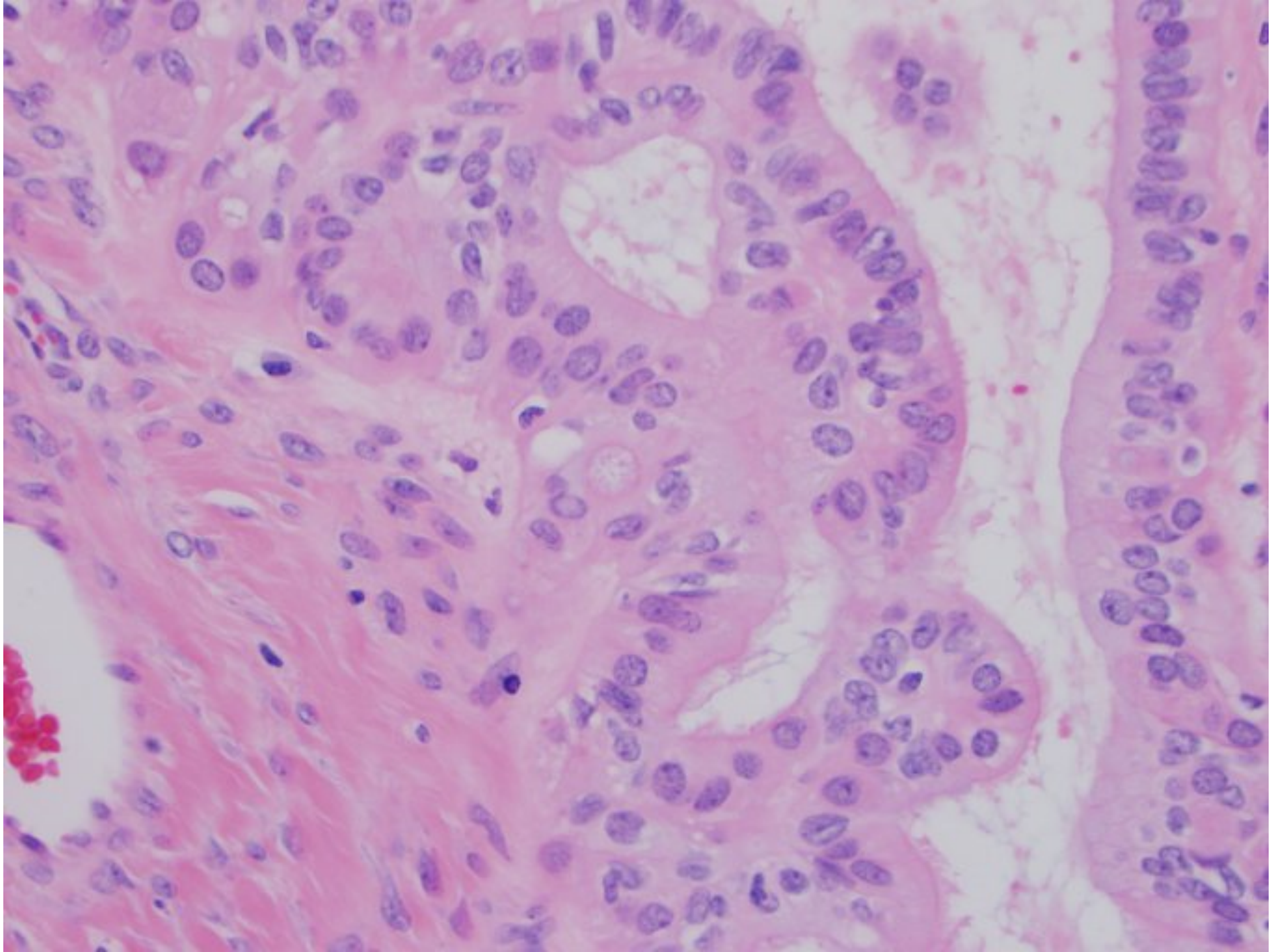












Diagnosis……??

Diagnosis: Seromucinous Borderline Tumors (Endocervical-like Mucinous Borderline Tumors)

Seromucinous Borderline Tumor

- AKA Endocervical-like MBT, “Mullerian-type” MBT,
- 1.5% of all Mucinous BTs
- Mean age is younger
- 80-95% Stage I
- Smaller (8cm) and more often unilocular/paucilocular than IMBTs
- Up to 40% bilateral
- 30-50% associated with endometriosis

Histologic Features

- Architecturally resemble SBTs
- Mixture of cell types-mucinous, eosinophilic, ciliated, occ. clear
- Papillary stroma may be edematous and infiltrated by PMNs
- Microinvasion in 10-20%

Prognosis

- Peritoneal implants/LN mets-no significance
- Tumor-related deaths rare

Differential Diagnosis

- Mixed Cell type EMBTs
- Typical Serous Borderline Tumors
- Endometrioid Borderline Tumors

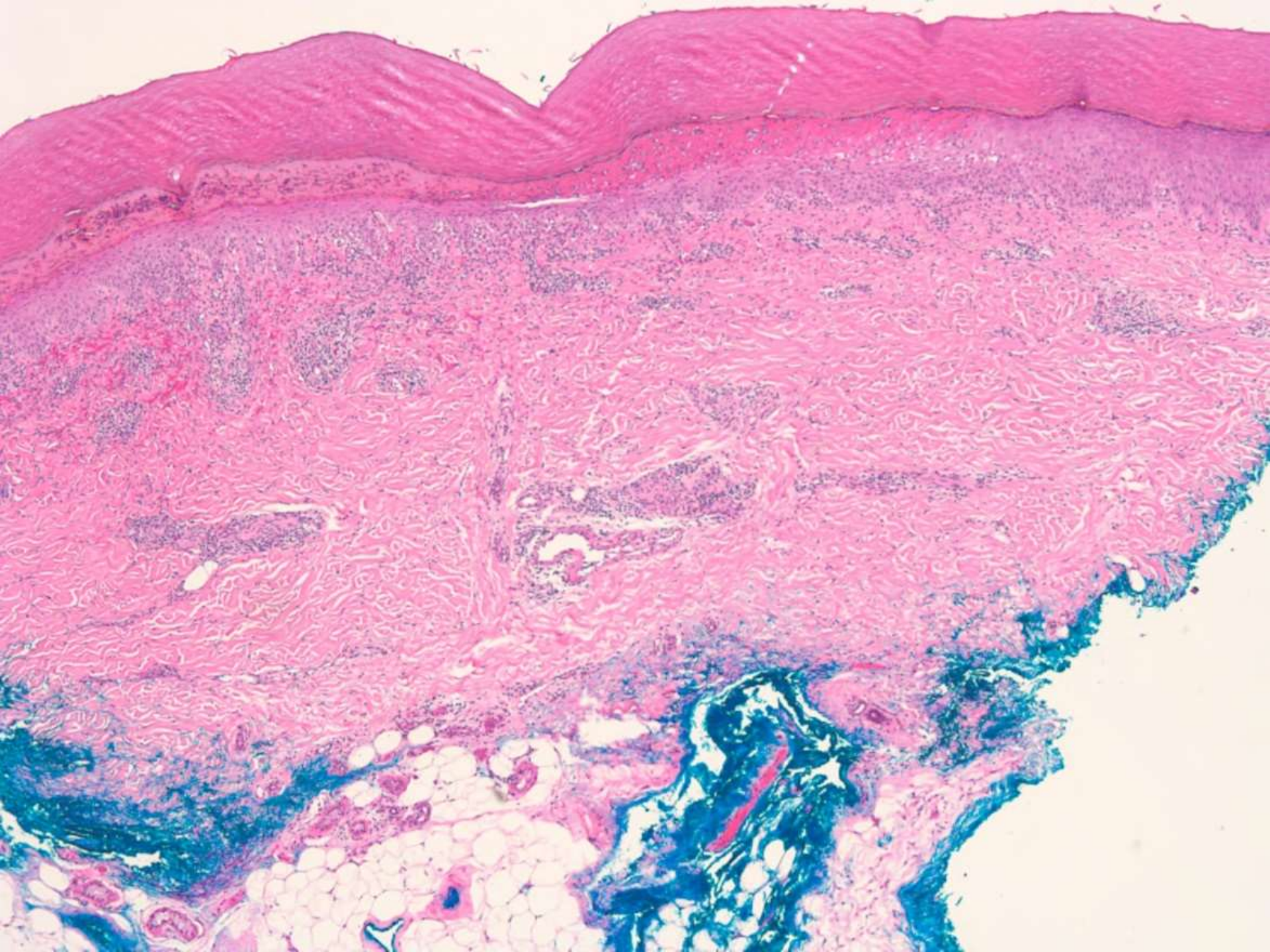
Endometriosis-Associated Tumors

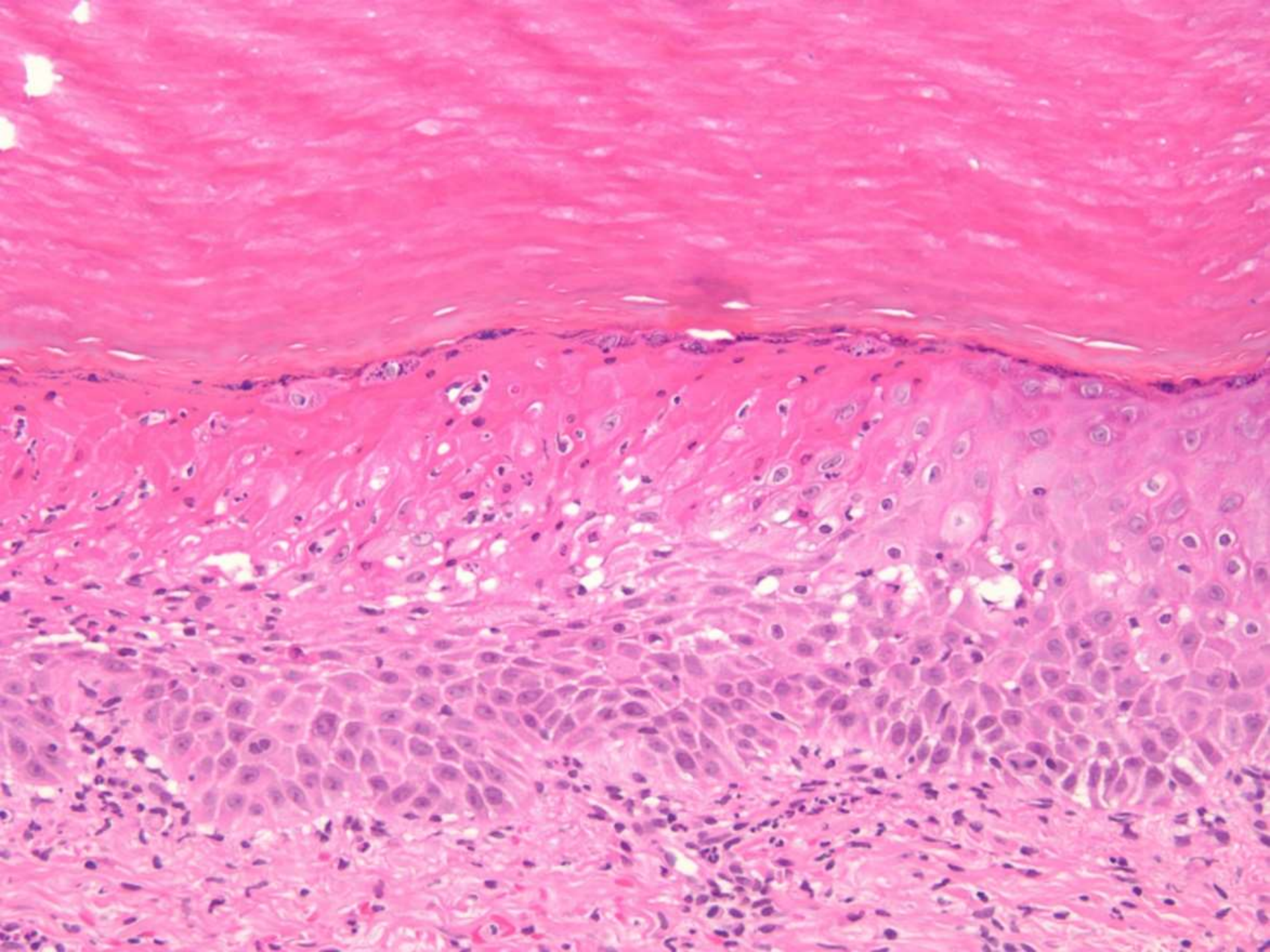
- Endometrioid Carcinomas-75%
- Clear Cell Carcinomas- 15% (larger proportion arise in endometriosis)
- EMBTs
- Endometrioid Adenofibroma
- ESS, Adenosarcoma, MMMT

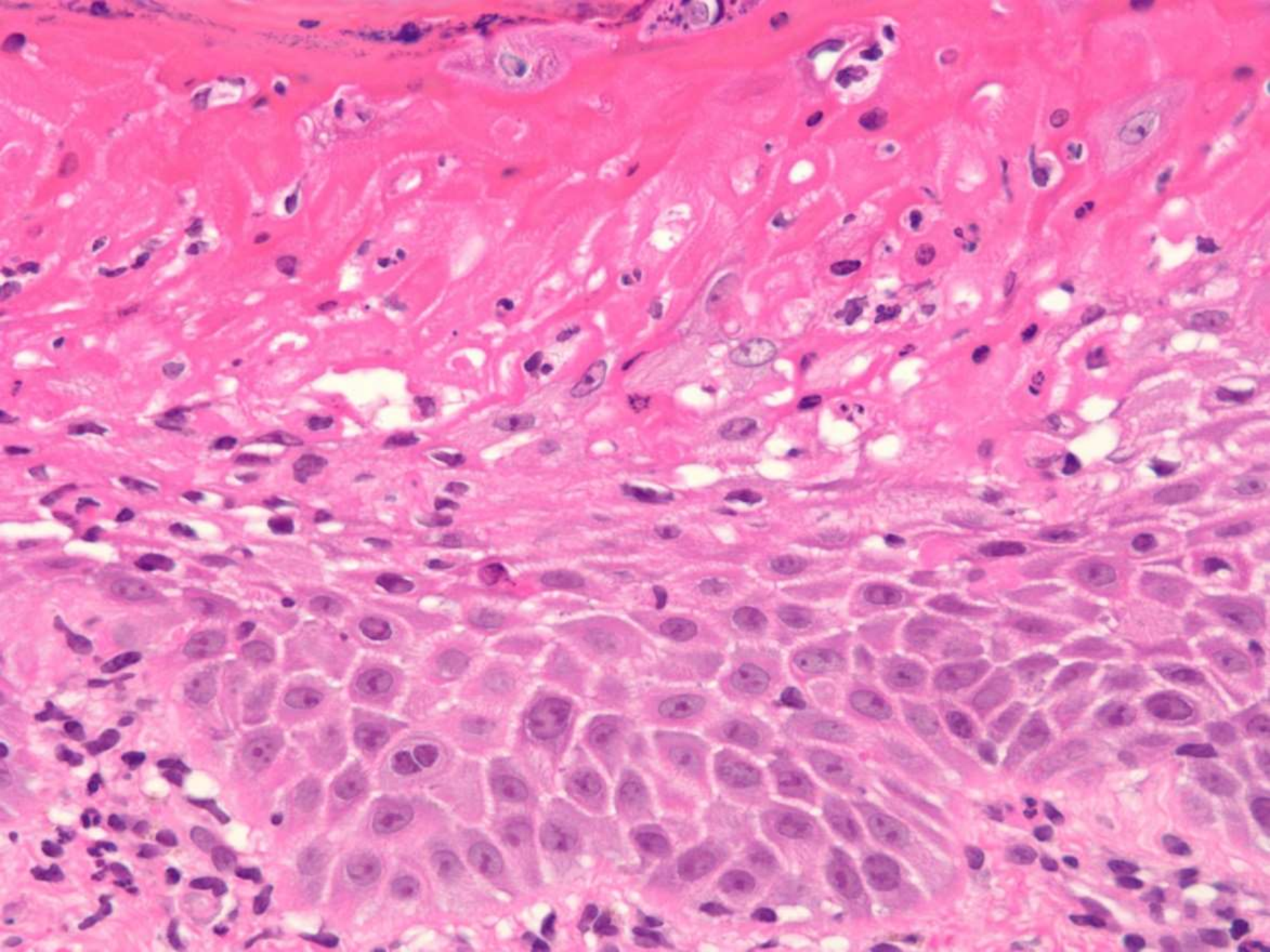
SB 5972

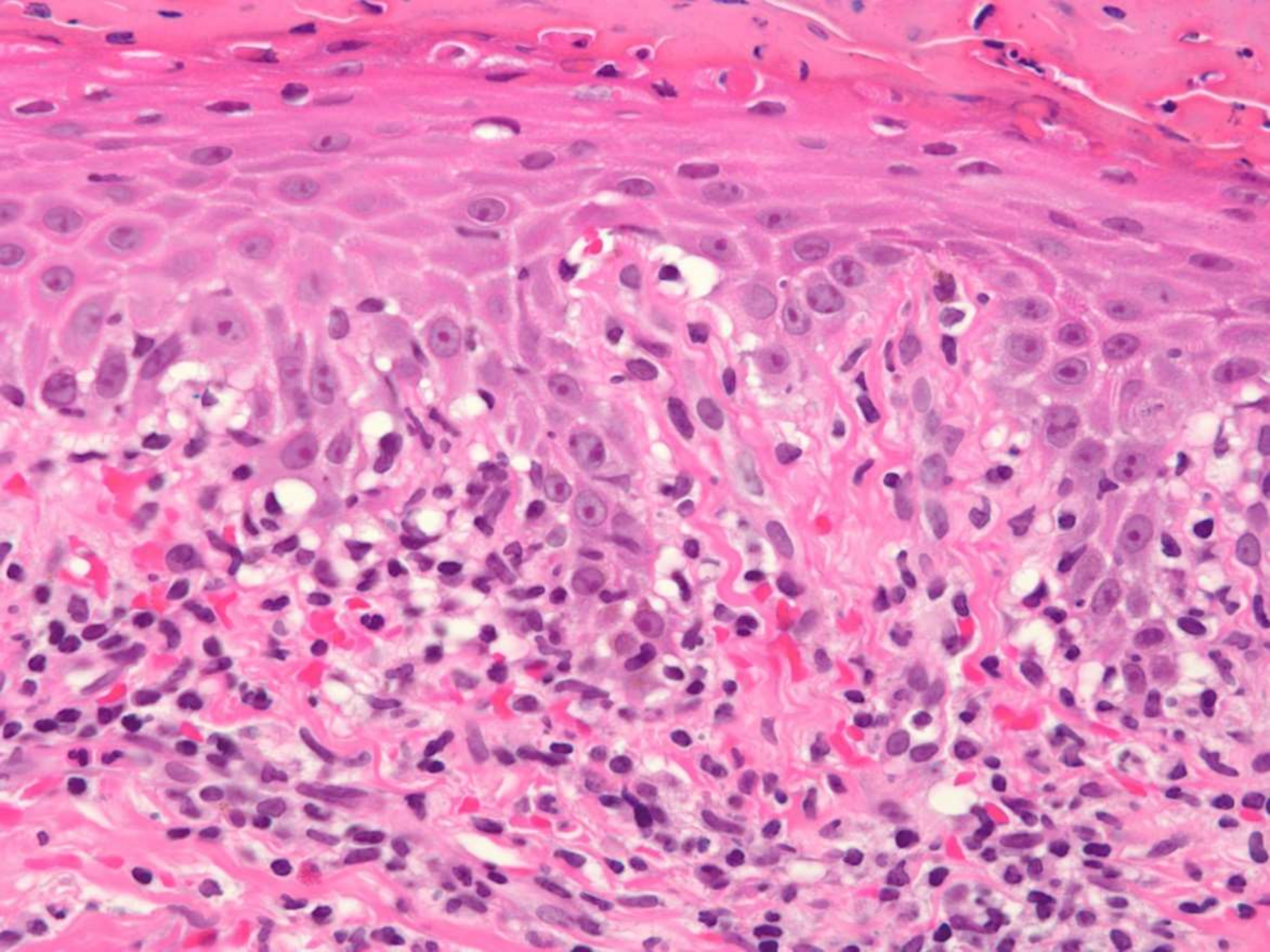
- 50-year-old woman presenting with acute onset of painful erythematous macules/papules on the palmar/plantar surfaces of the hands and feet. Clinical DDx: erythema multiforme, acral erythema, viral infection, bacterial infection. Biopsy of palmar lesion performed.

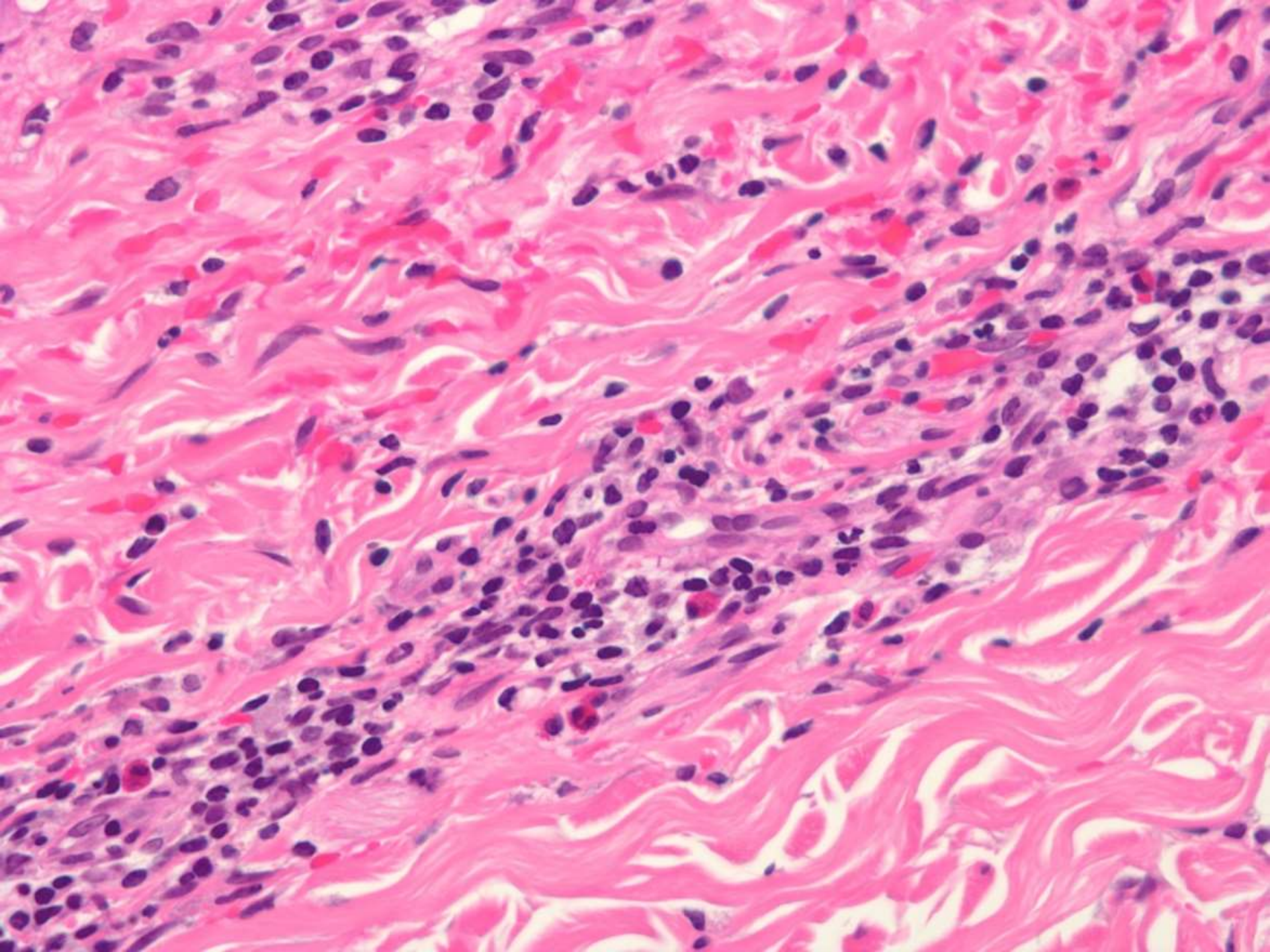
- **Charles Lombard; El Camino Hospital**

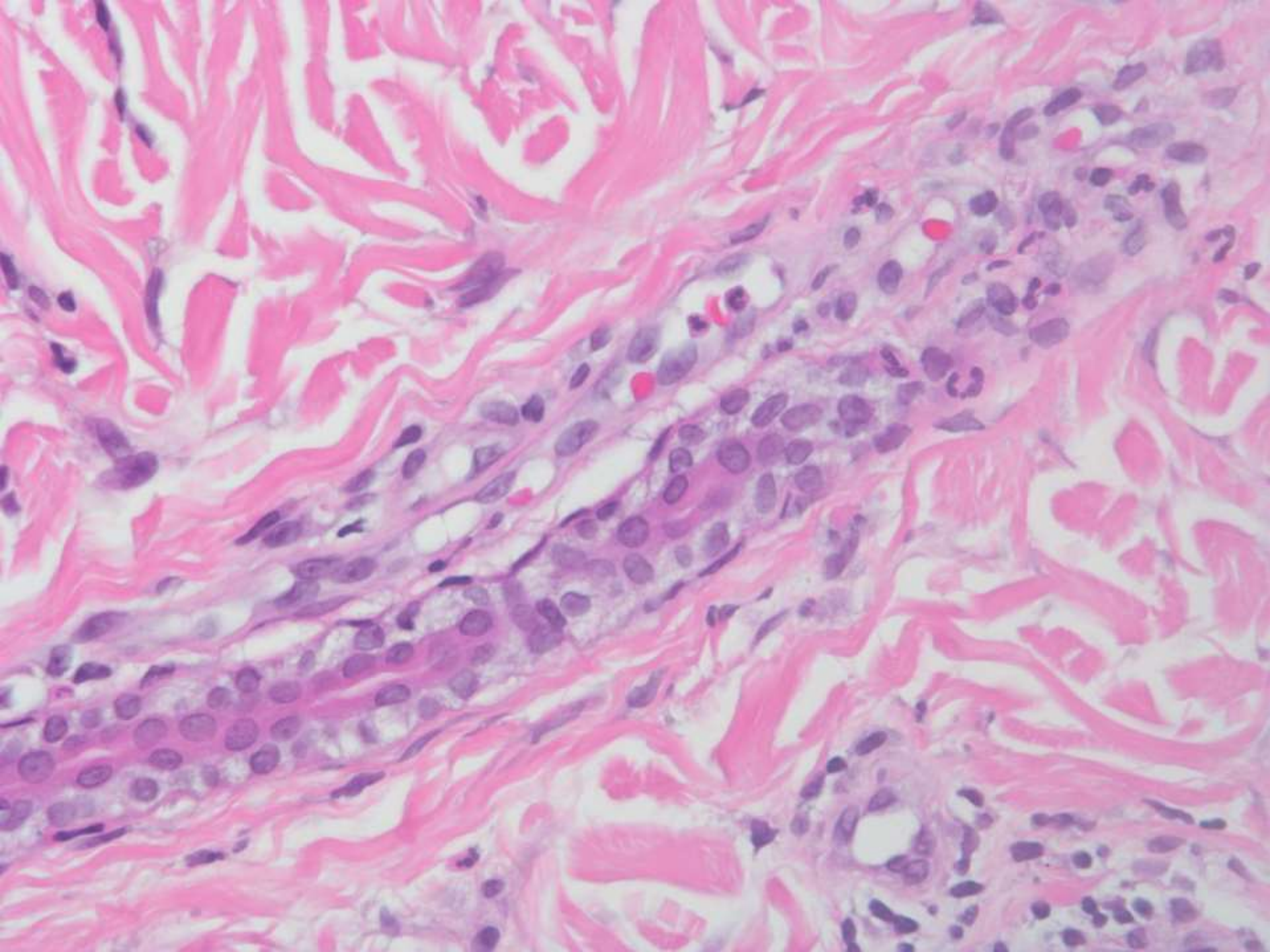












Diagnosis……??

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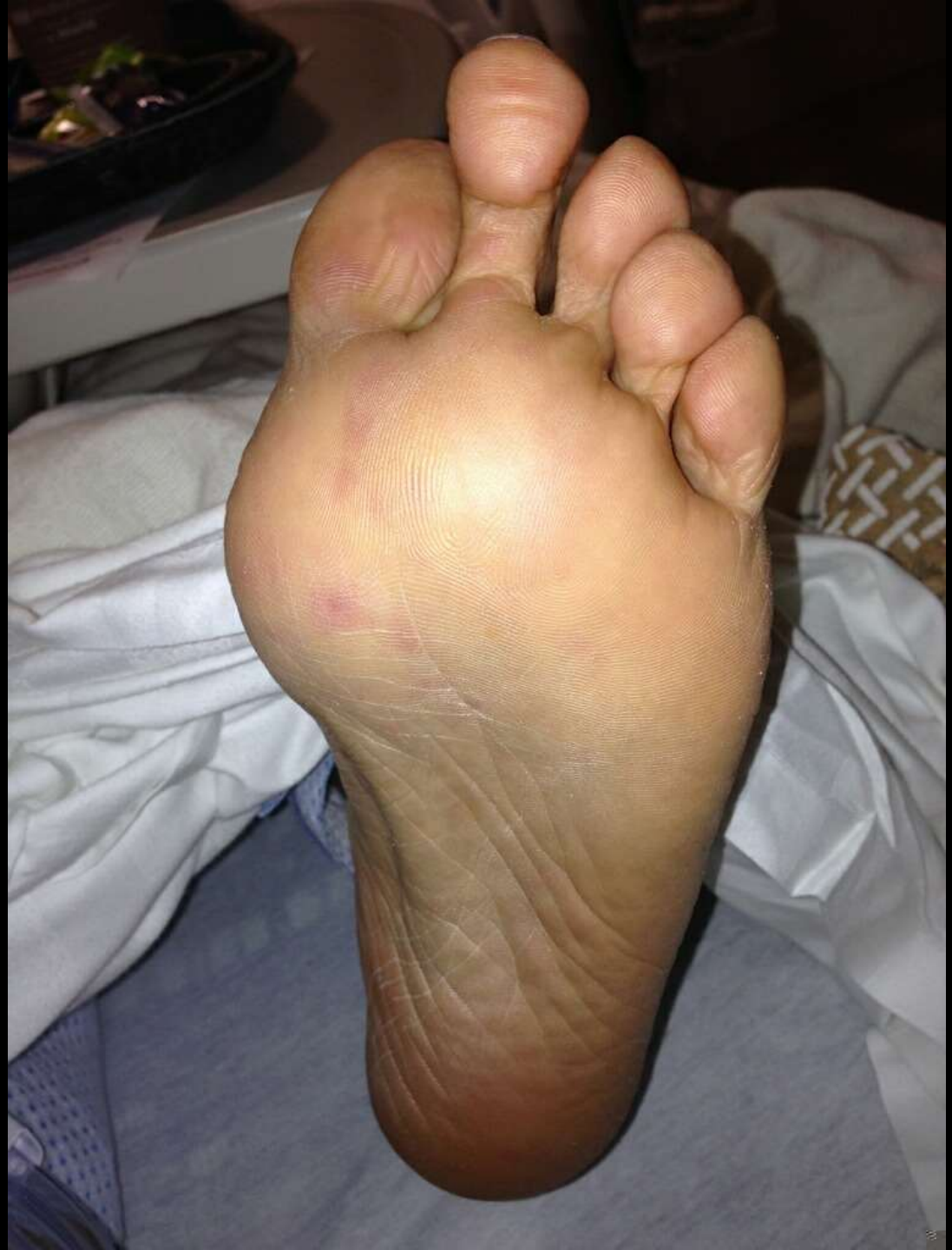

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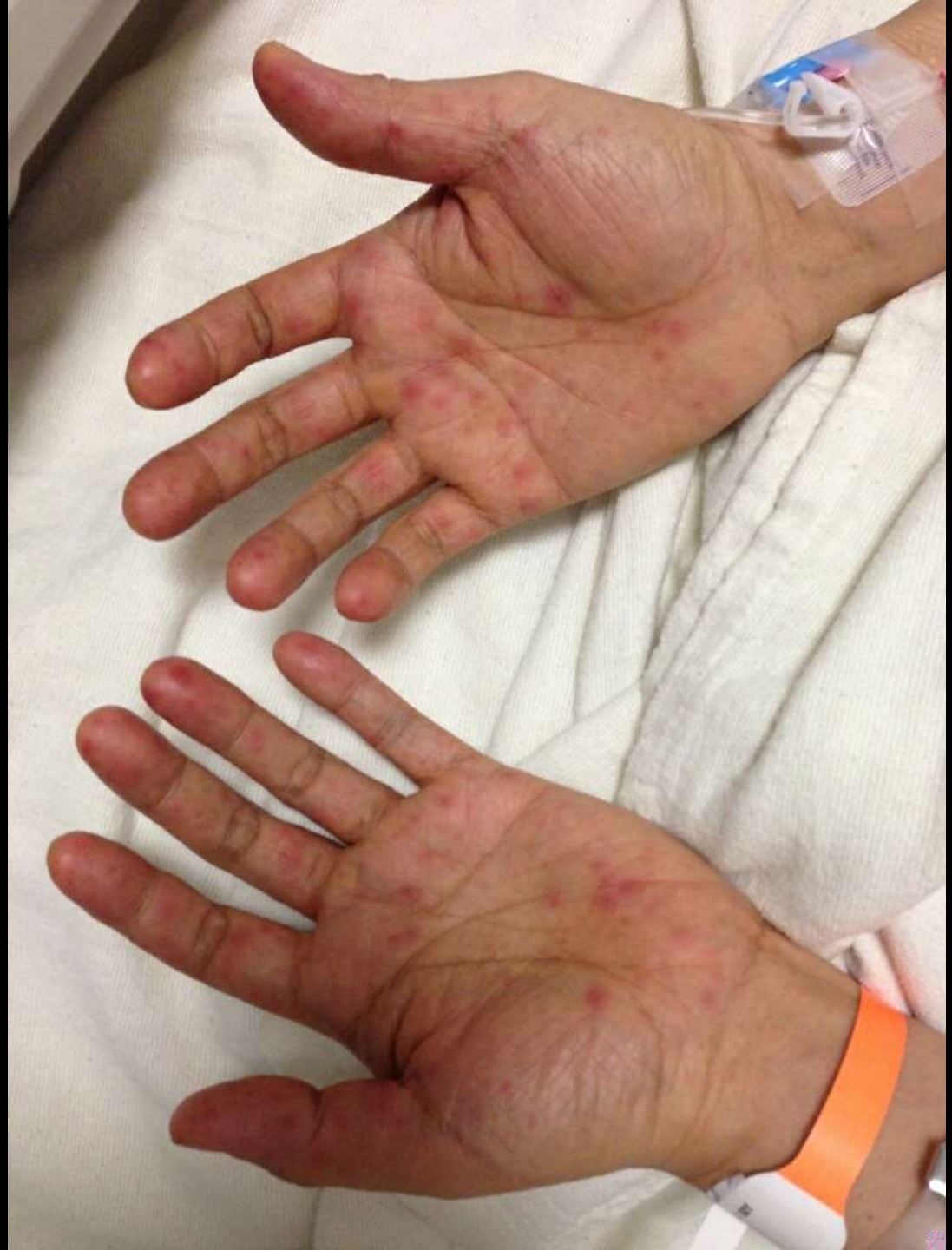

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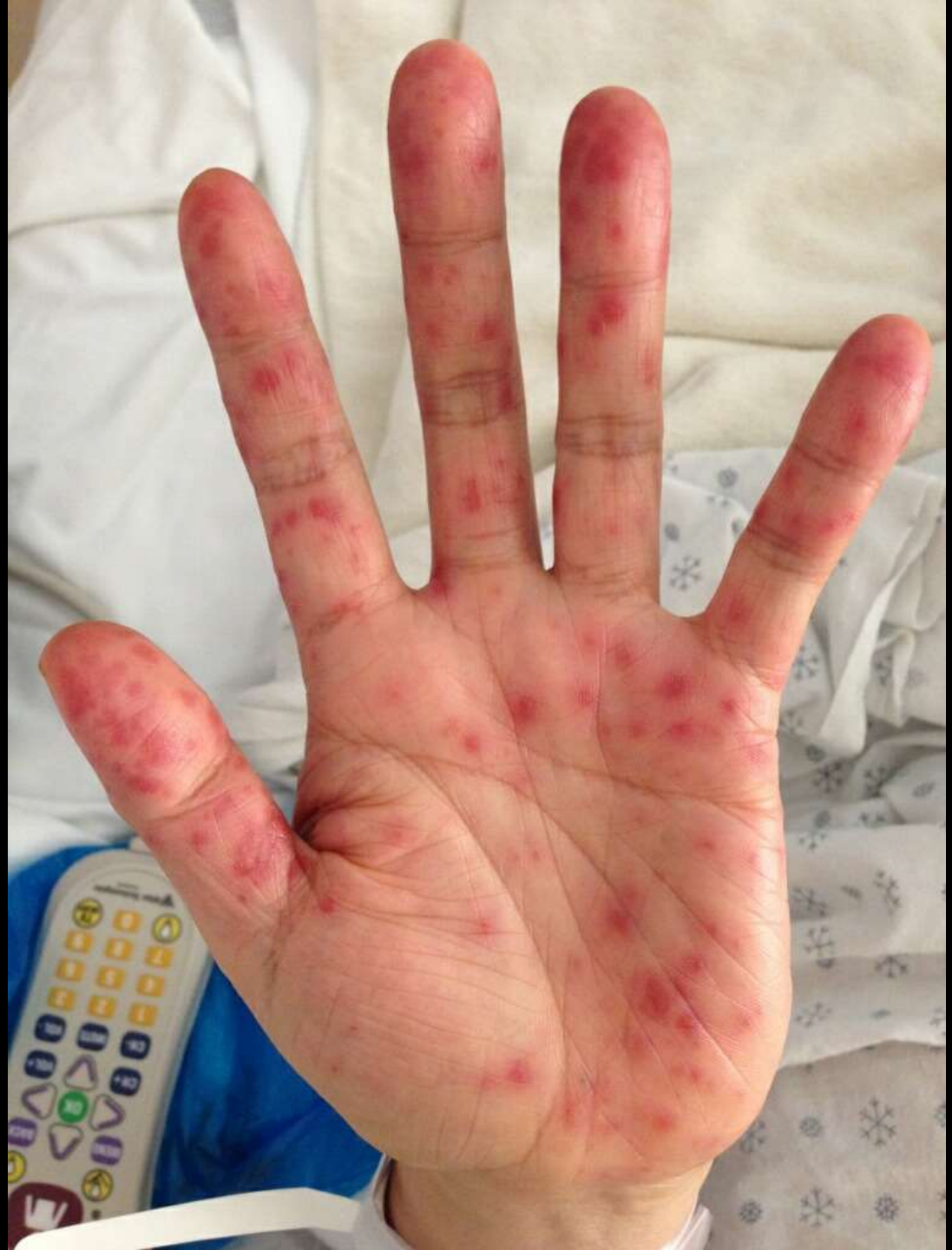
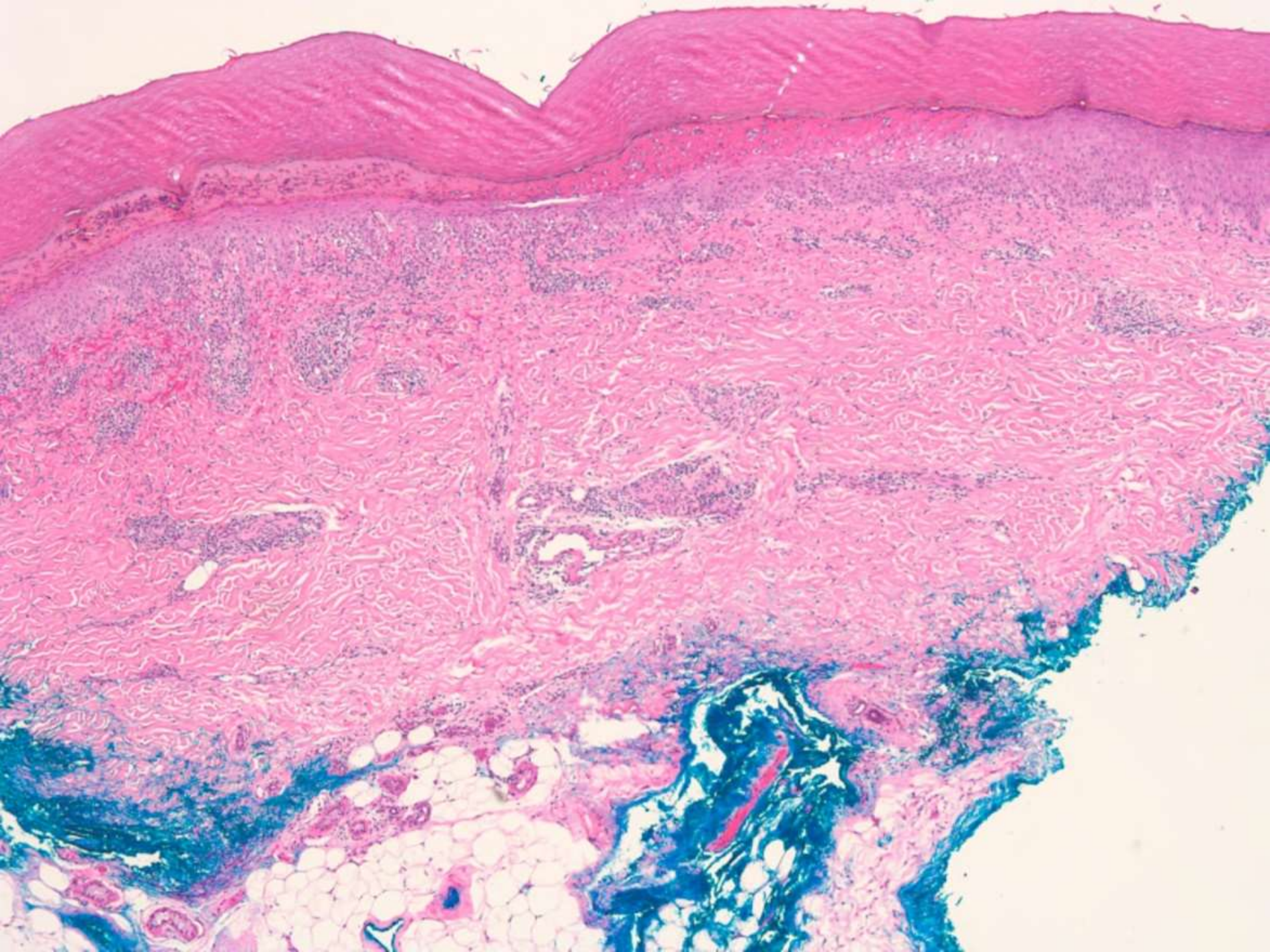
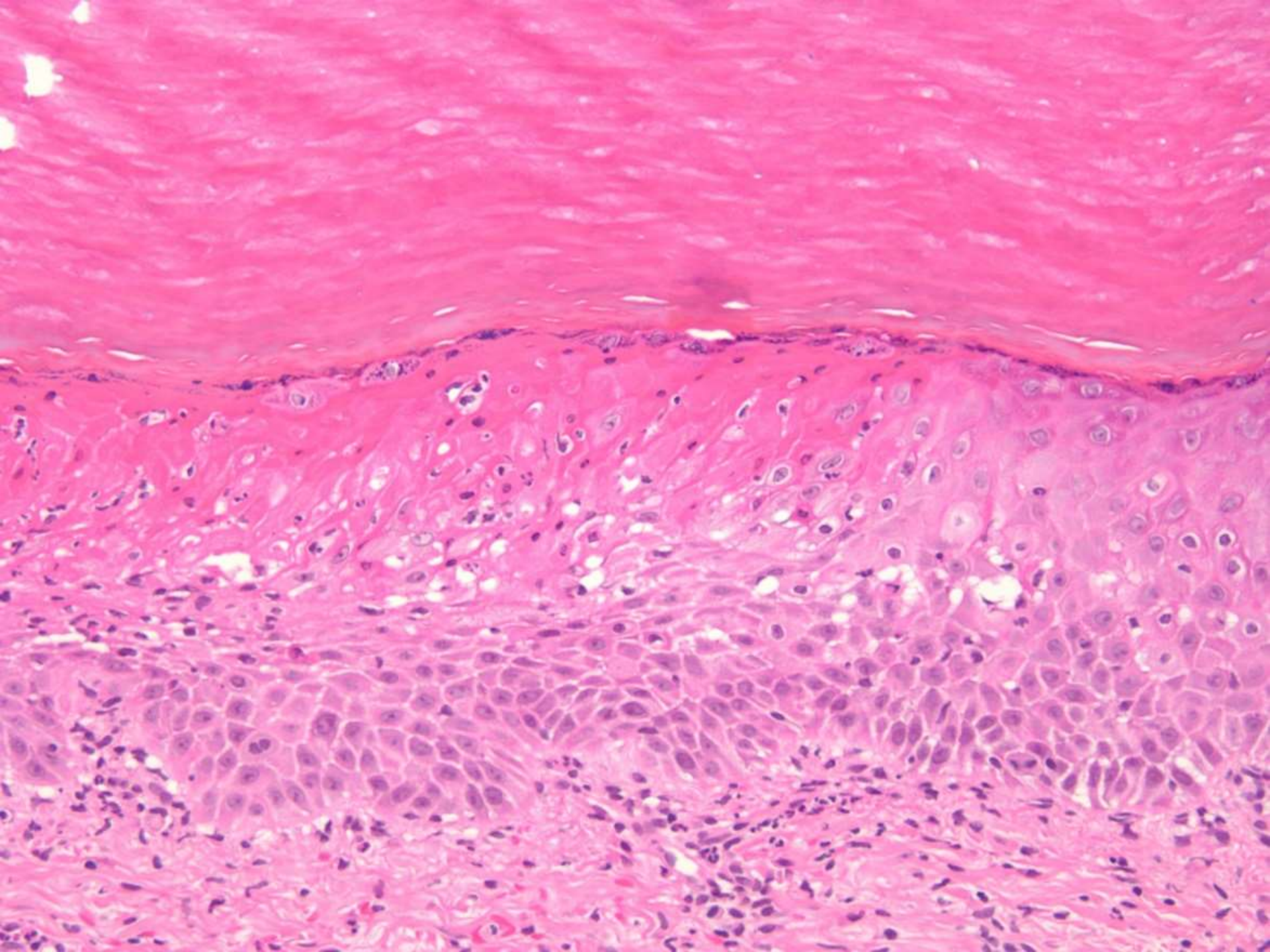
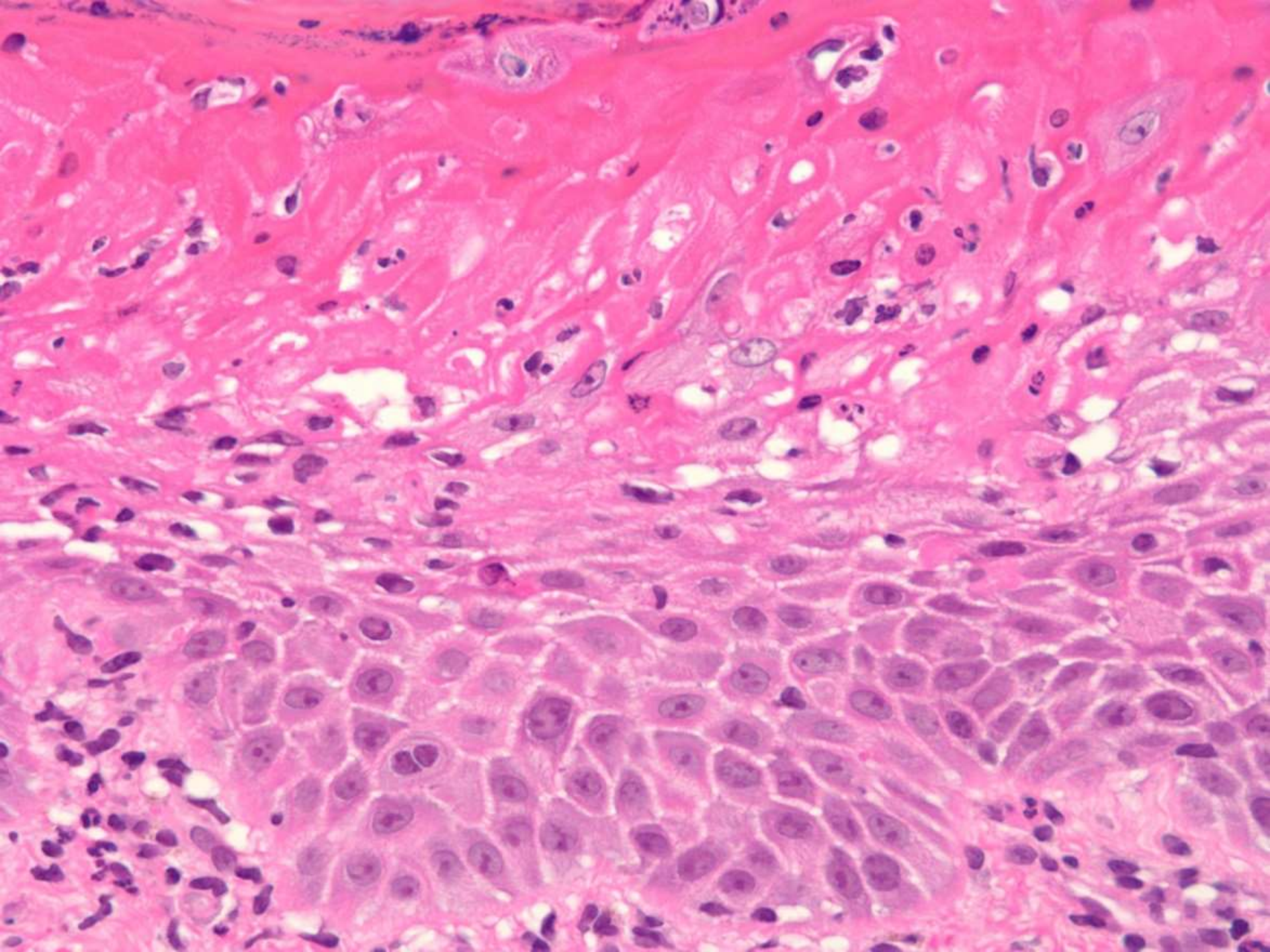
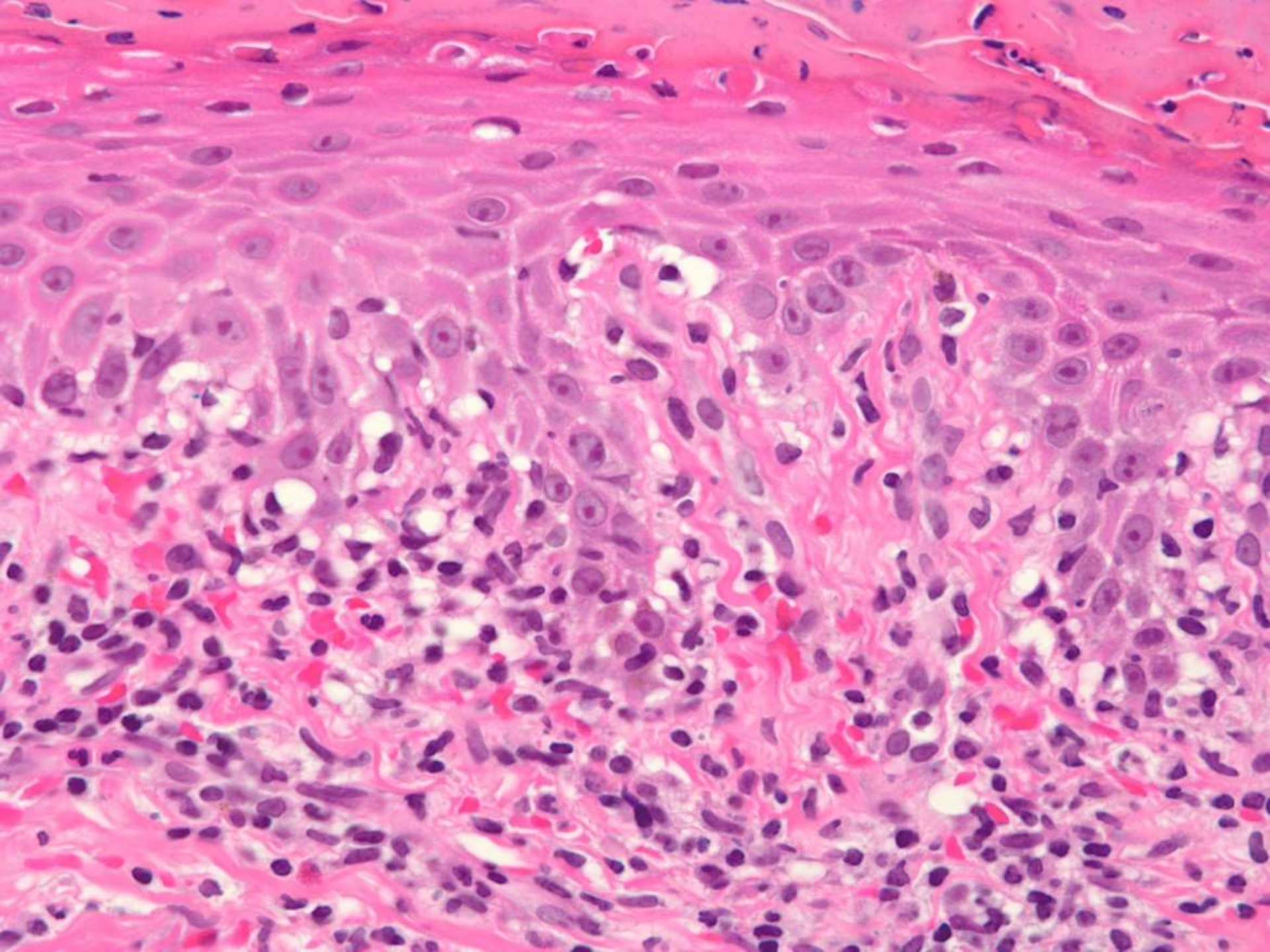
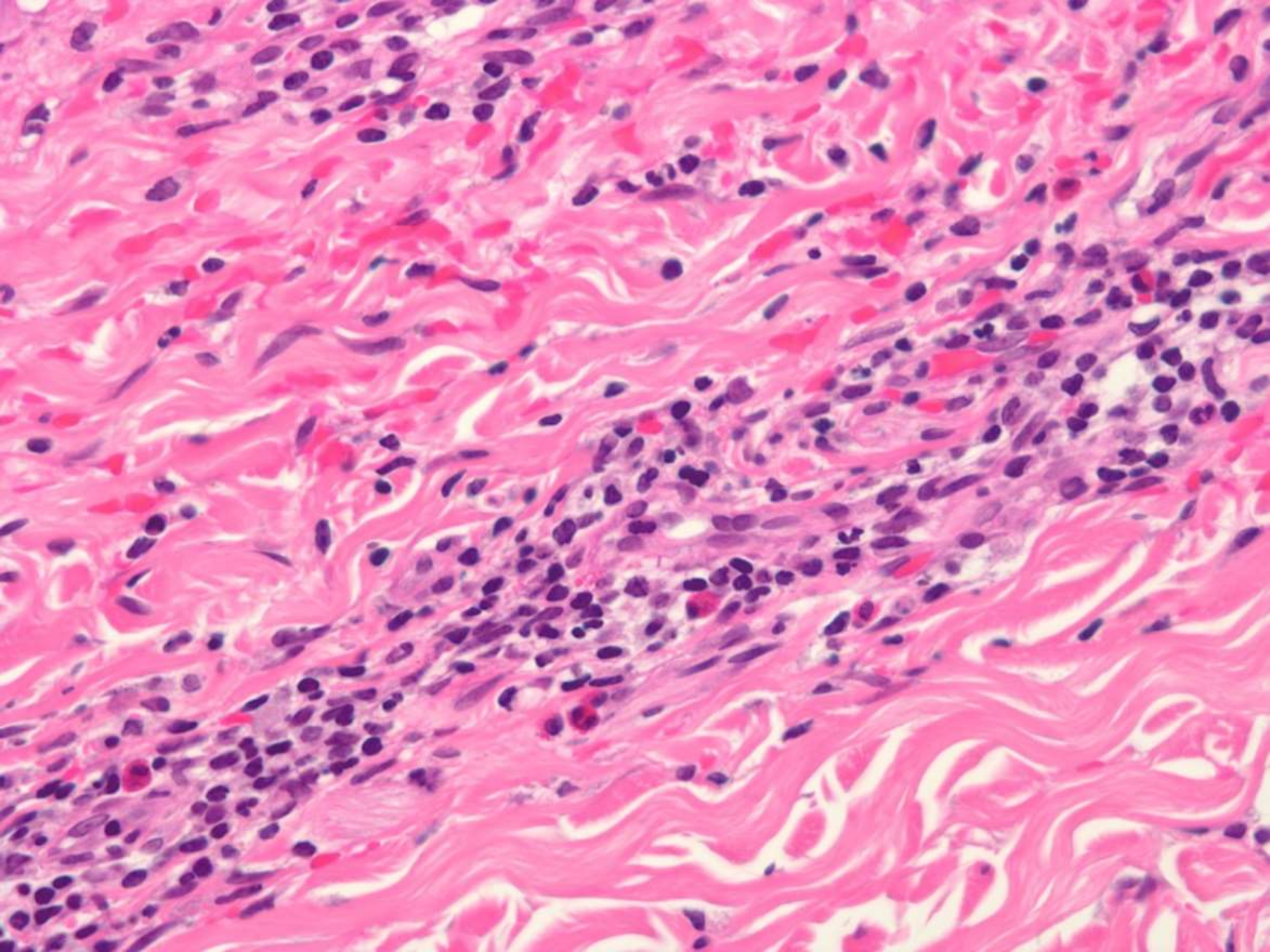


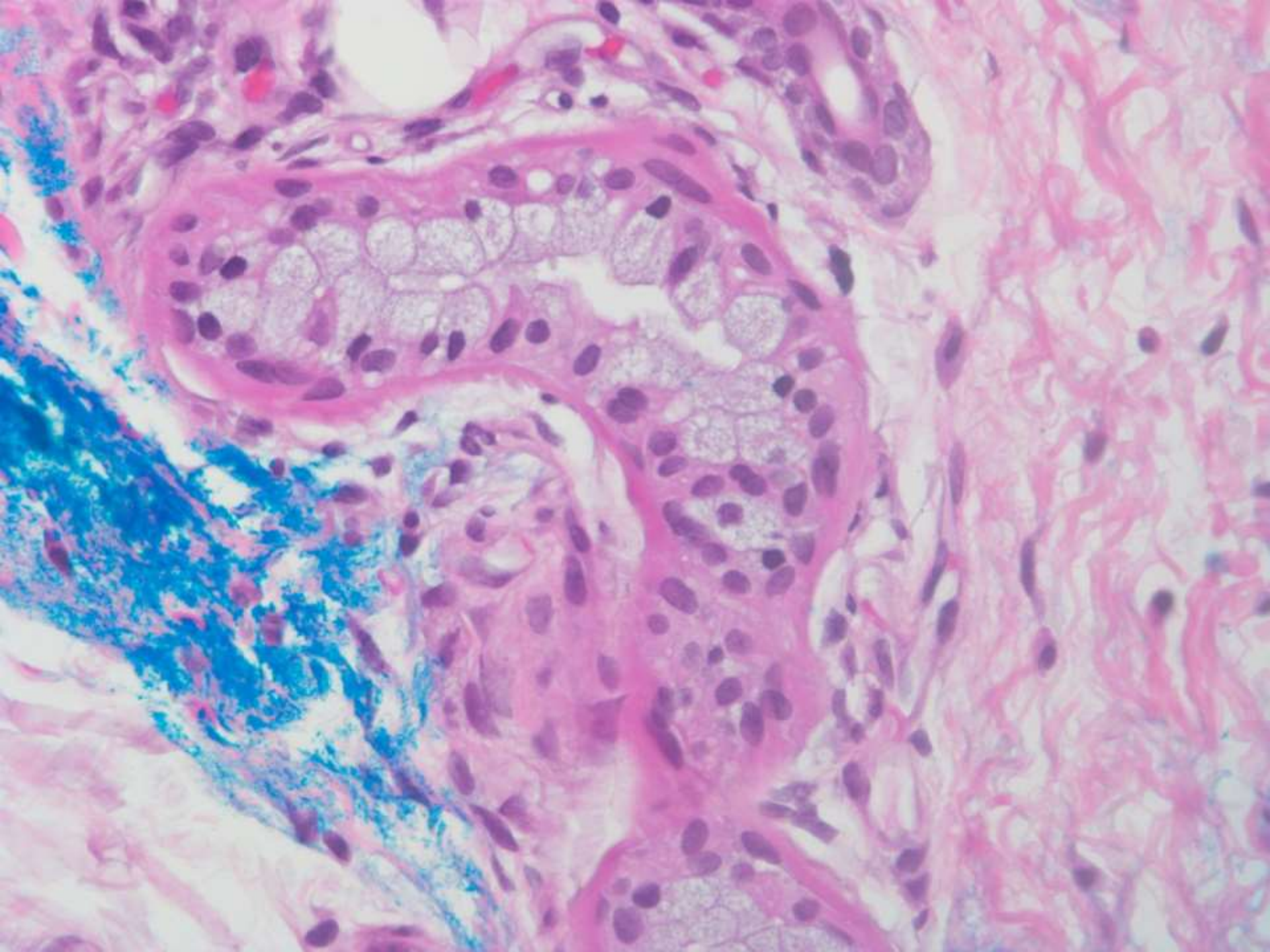


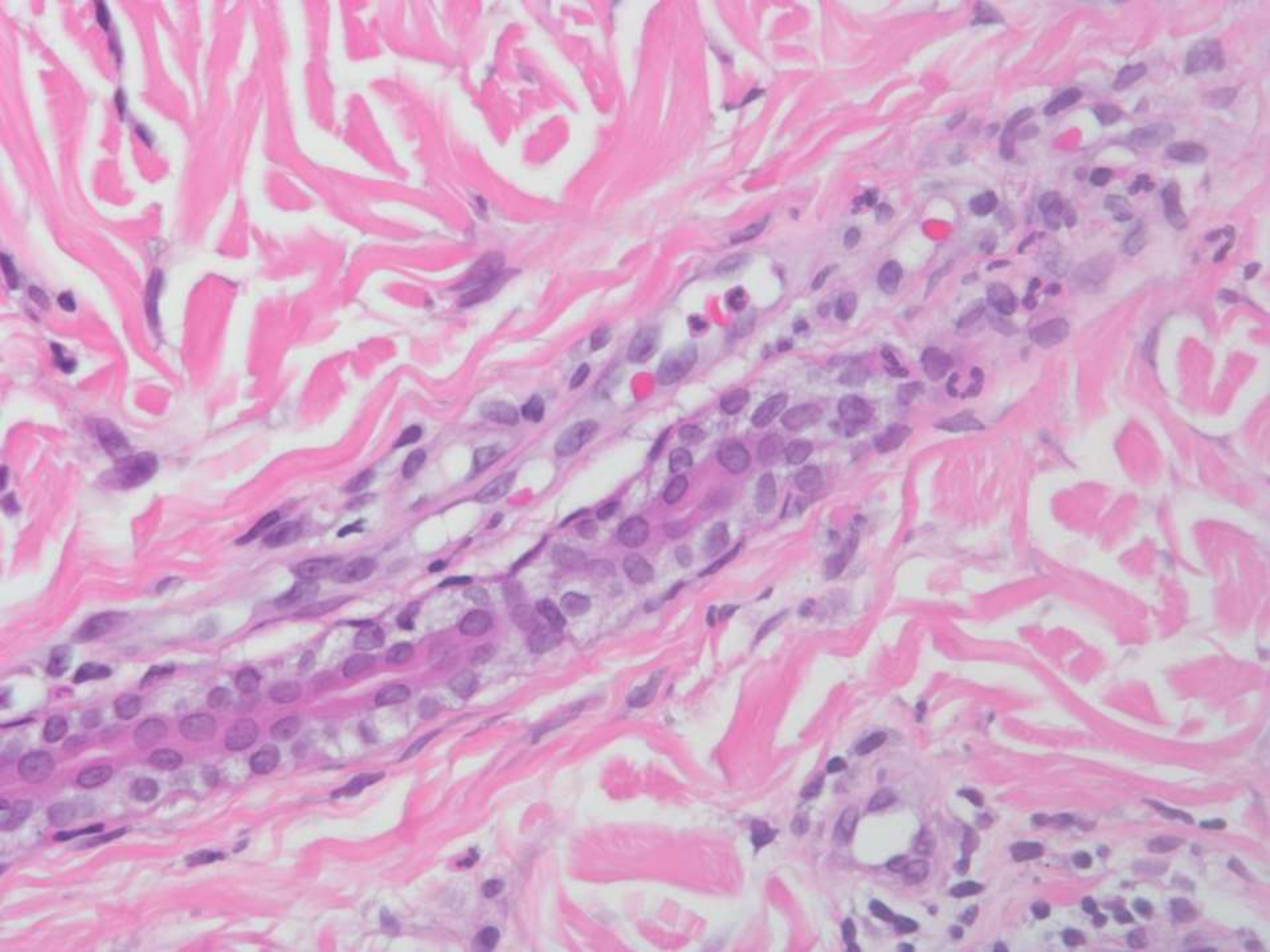












Diagnosis???

Further Clinical information

- Review of patient's pathology records revealed history of colonic adenocarcinoma metastatic to liver.
- Call to clinician revealed patient was being treated with Xeloda.

Toxic Erythema of Chemotherapy

Xeloda-associated

Consultant: Dr. Kerri Rieger
Stanford University Dermatopathology

Reference: Bolognia et al: "Toxic erythema of chemotherapy: A useful clinical term". J Am Acad Dermatol 2008;59:524-9.

Toxic Erythema of Chemotherapy Clinical

- Erythematous patches involving hands and feet
  - Arise 2-3 weeks following chemotherapy
- Pain, burning, pruritus, paresthesias
- “Dusty” petechiae and bullae may arise
- Desquamation
- Resolves spontaneously
- May recurr with further chemotherapy

Toxic Erythema of Chemotherapy Pathology

- Confluent necrosis of upper epidermis
- Vacuolar degeneration of basilar epithelium
- Variable nuclear atypia, mitosis arrest, and loss of peidermal polarity with crowding
- Inflammatory infiltrates are usually minimal
- Eccrine Syringometaplasia

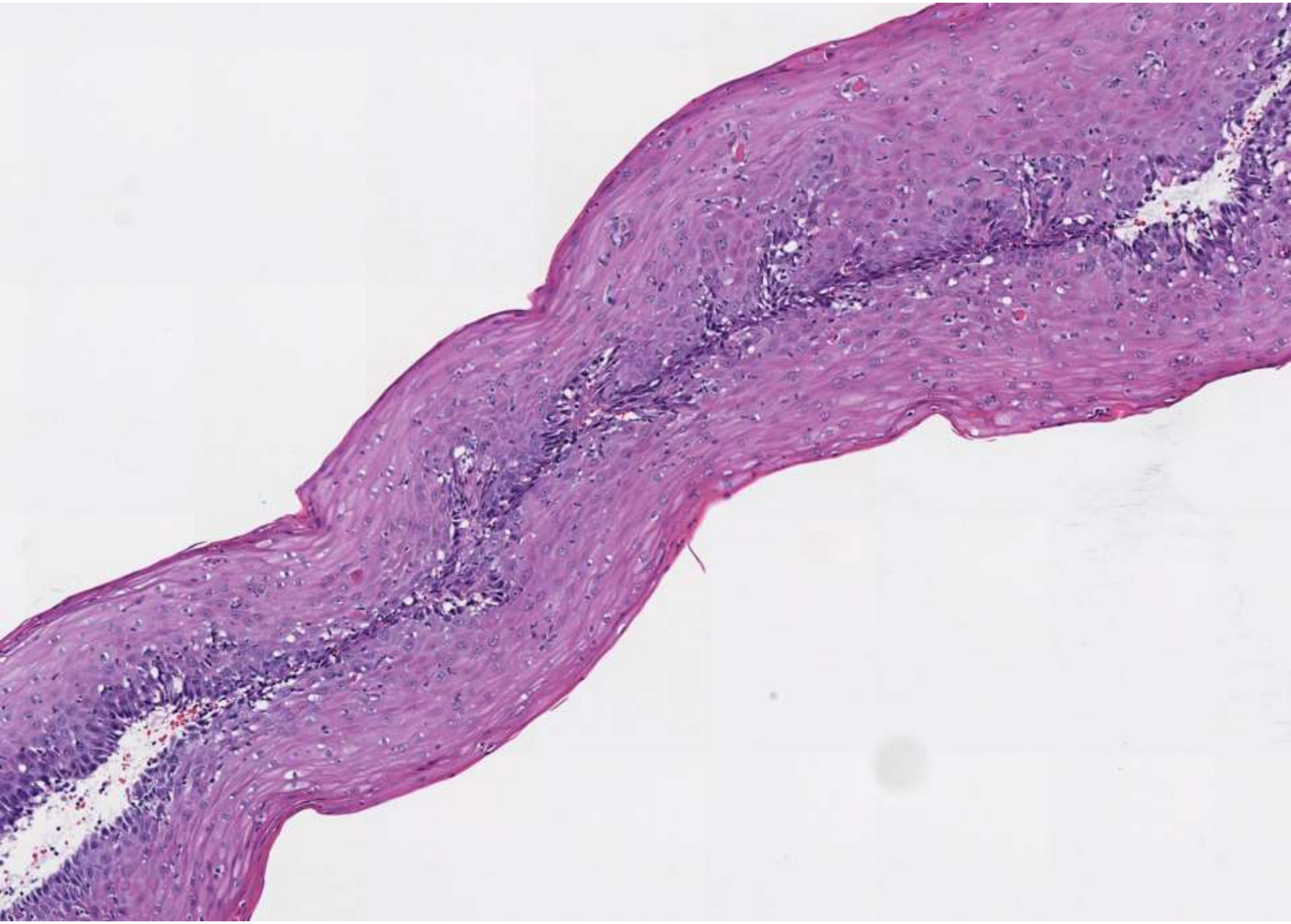
Toxic Erythema of Chemotherapy

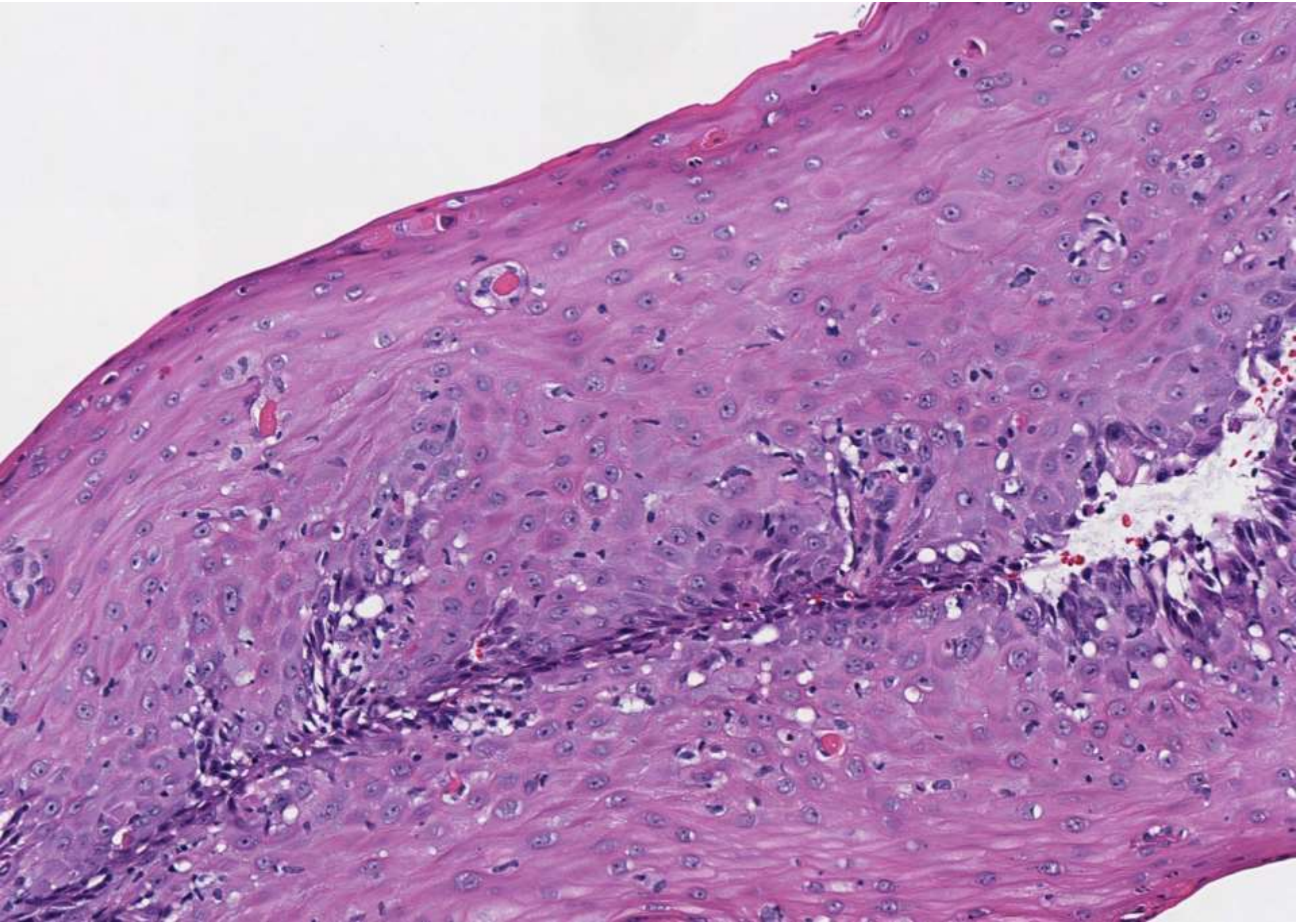
- Spectrum of diseases including:
  - palmar-plantar erythrodyaesthesia/erythroderma
  - Eccrine squamous syringometaplasia
  - Neutrophilic eccrine hidradenitis
- Thought to be a toxic reaction not an immunologic reaction
  - Excretion of drugs via eccrine sweat
    - Sweaty hands and feet
  - Do not treat with immunosuppressive agents

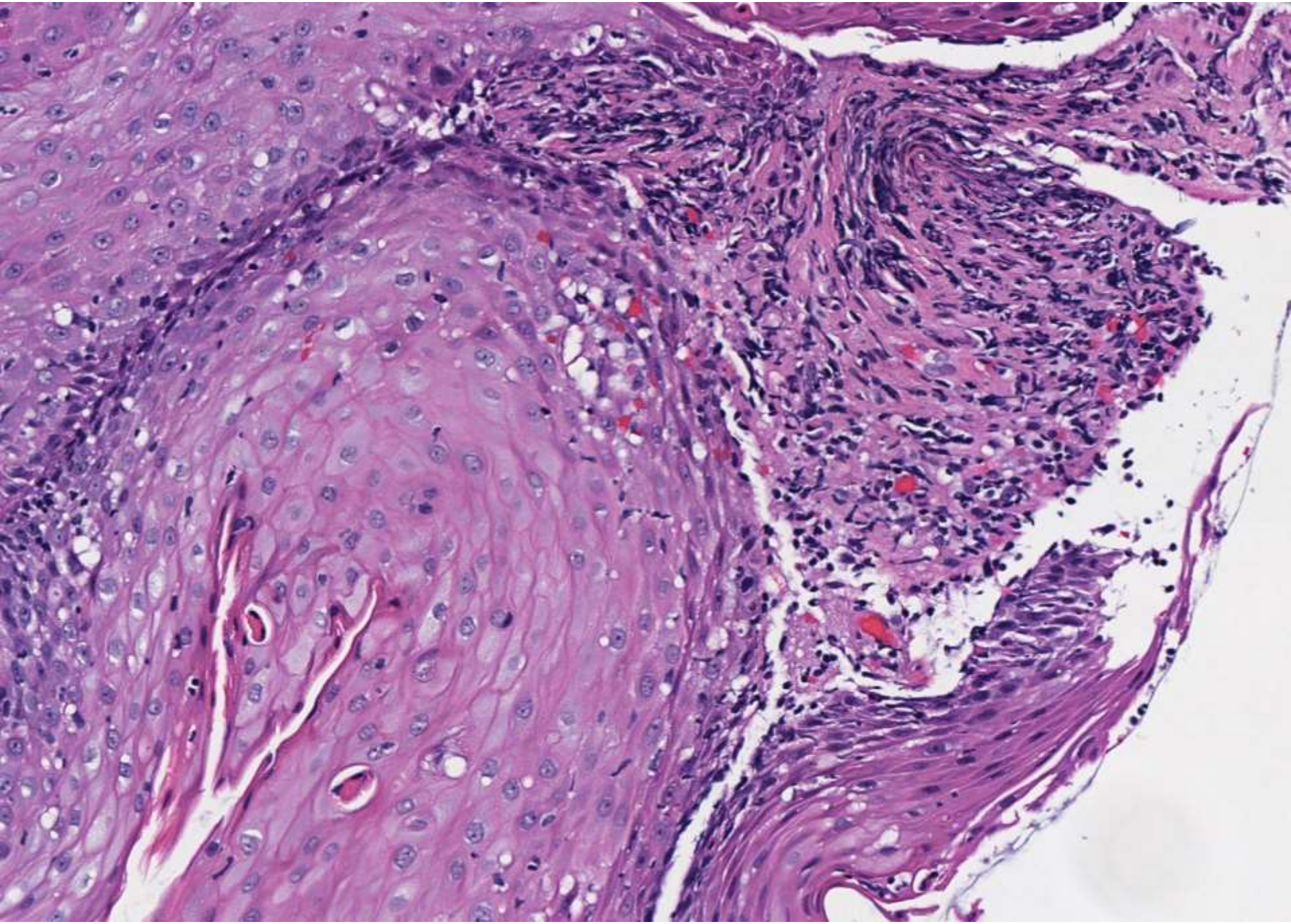
SB 5973

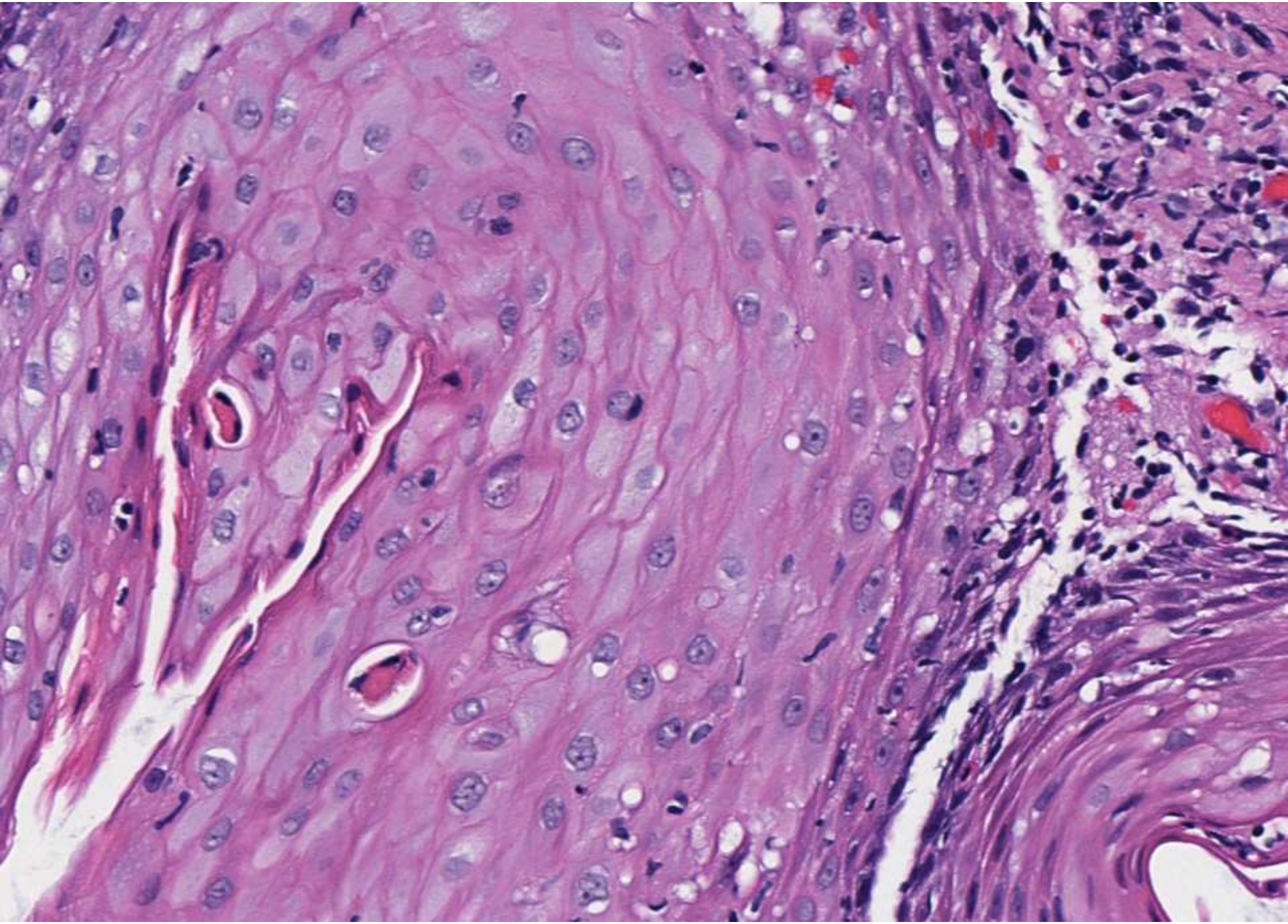
- 70-year-old female with dysphagia. Mid esophagus biopsy performed.

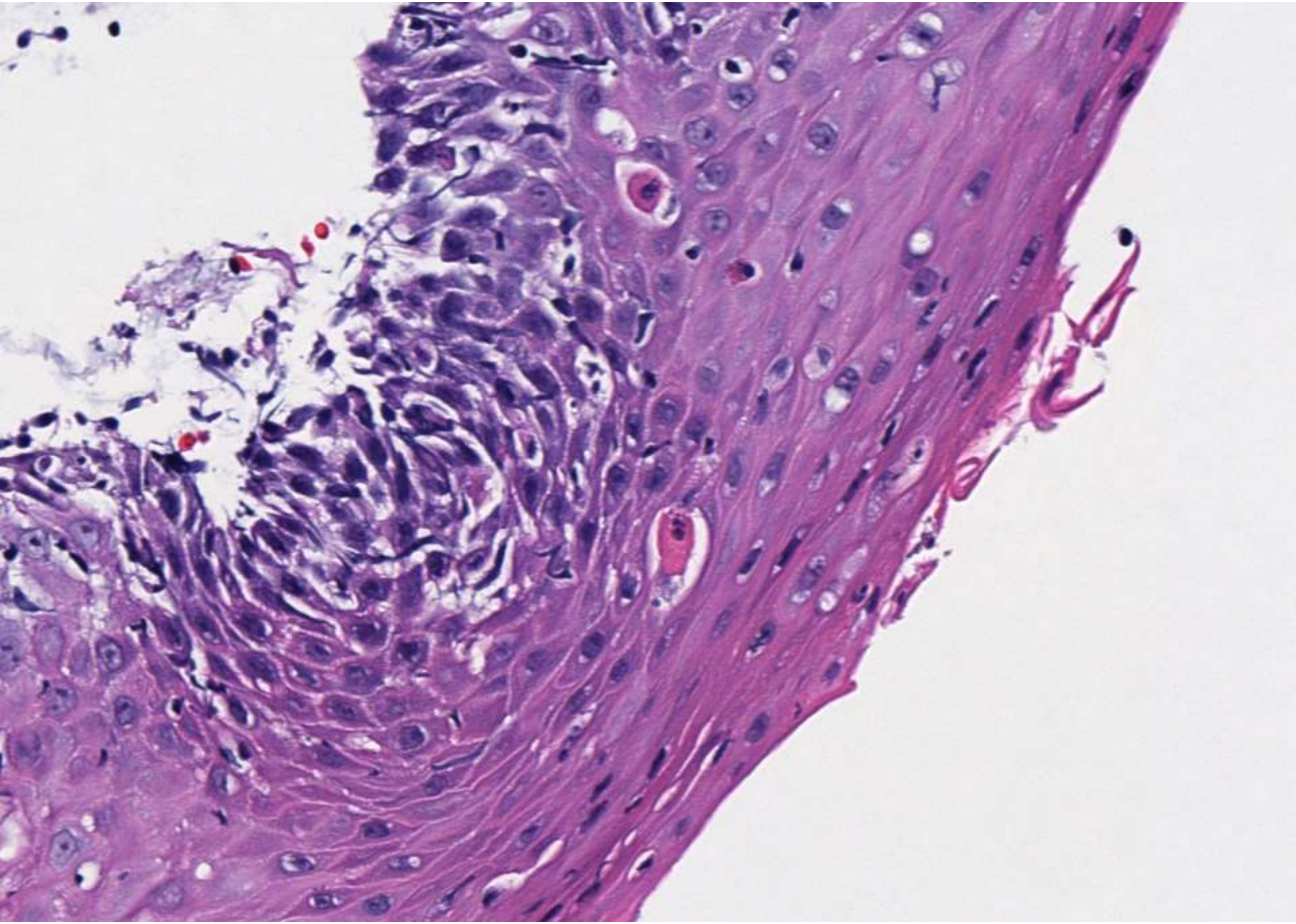
- **Will Rogers; El Camino Hospital**



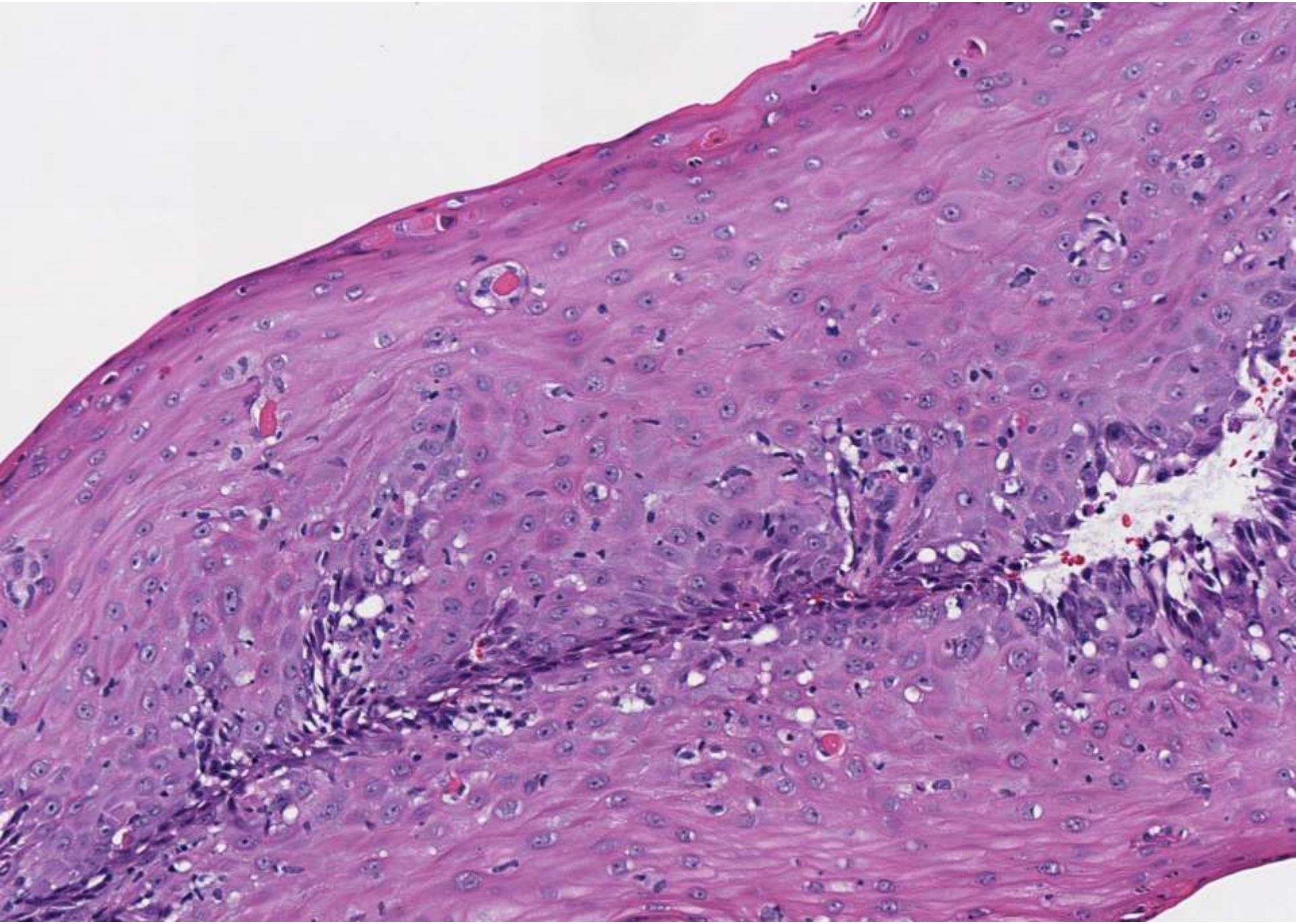


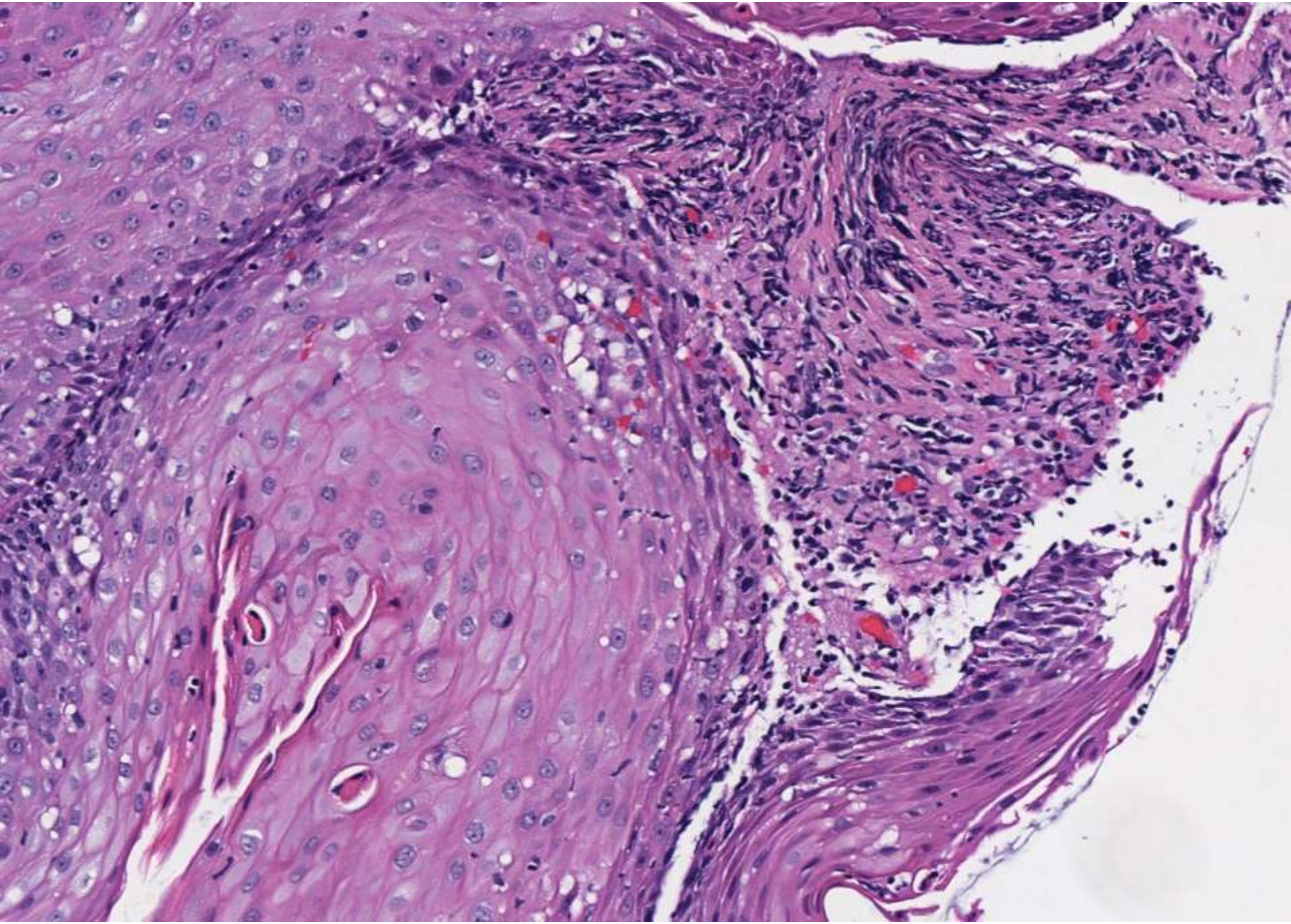






Diagnosis……??





Mucosal Lichen Planus

- Band-like inflammatory infiltrate
- Intraepithelial lymphocytes in basal layer
- Basal layer degeneration
- Prominent Civatte bodies

- Hyperkeratosis
- Wedge shaped hypergranulosis
- Saw-toothed rete ridges

Lichenoid Infiltrate

- Lichenoid drug reaction (especially monoclonal antibody preparations)
- Viral infections
- Mucosal lichen planus

Lichen Planus – Sites

- Flexor surface of the wrists
- Trunk
- Thighs and Genitalia
- Oral lesions (30-70% of cases)
  - Esophagus more rare (~50 reported cases)
    - 1%-26% of patients with oral LP

Esophageal Lichen Planus

- Rare cause of esophagitis and esophageal stricture
- Almost always associated with oral mucosal involvement
- Lesions
  - Peeling of friable mucosa, white plaques
  - Ulcers, erosions
  - Strictures

Treatment and Prognosis

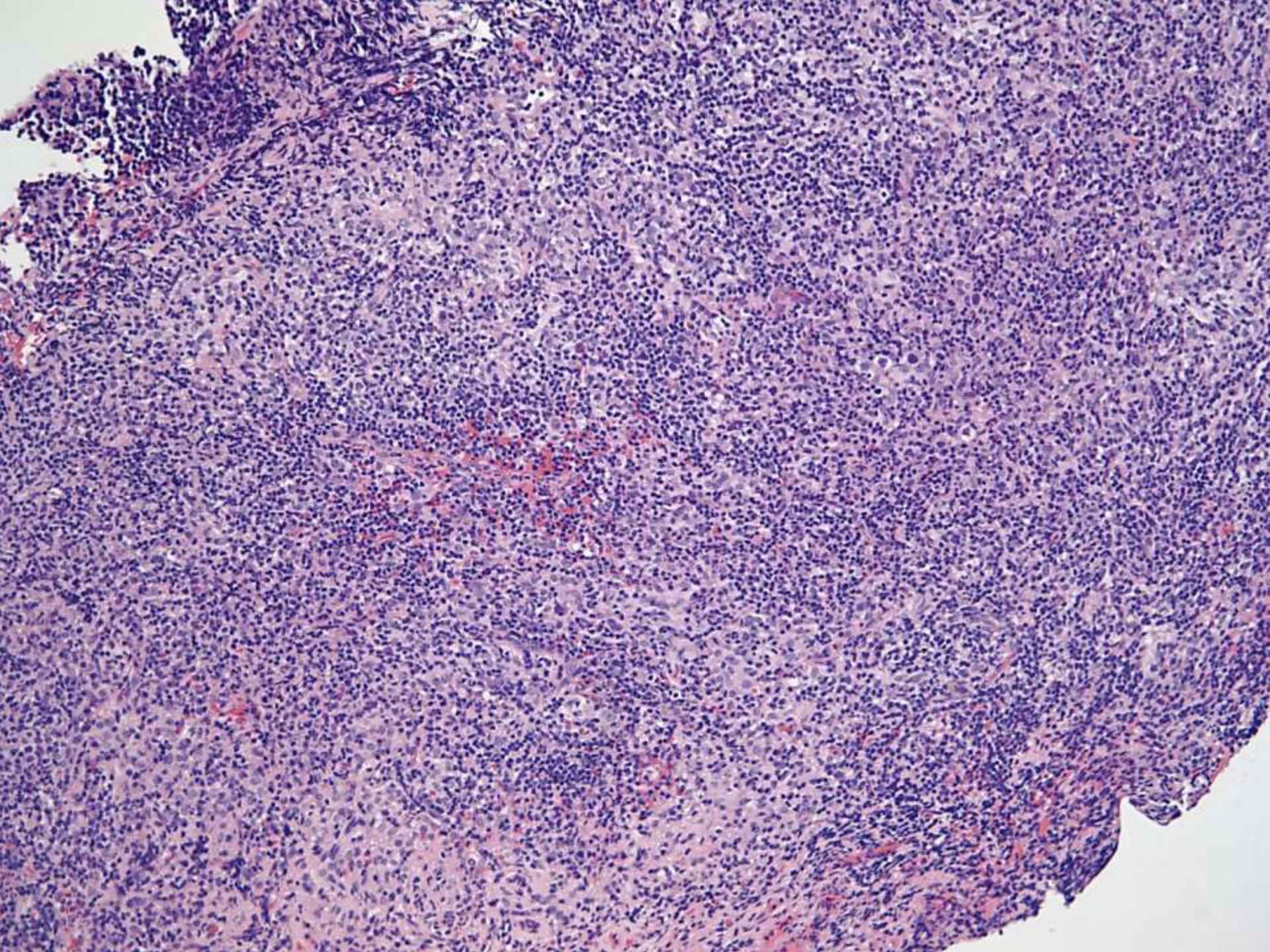
- Systemic and/or local therapy with corticosteroids
- May require dilations of strictures

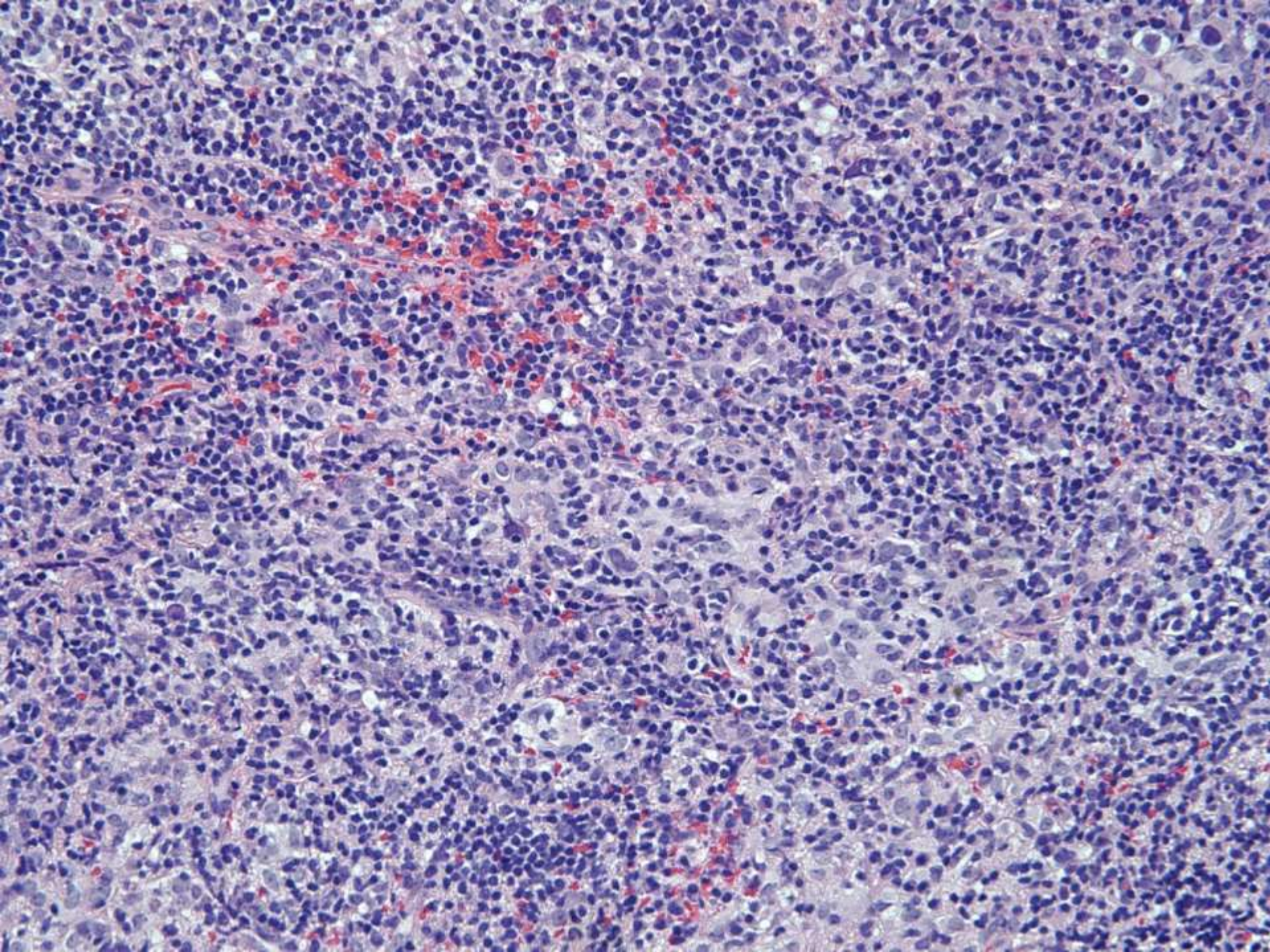
- Lesions may have long duration and may not self resolve
- 1-3% risk of malignancy with Oral LP patients
- 3 patients with longstanding esophageal LP developed squamous cell carcinoma

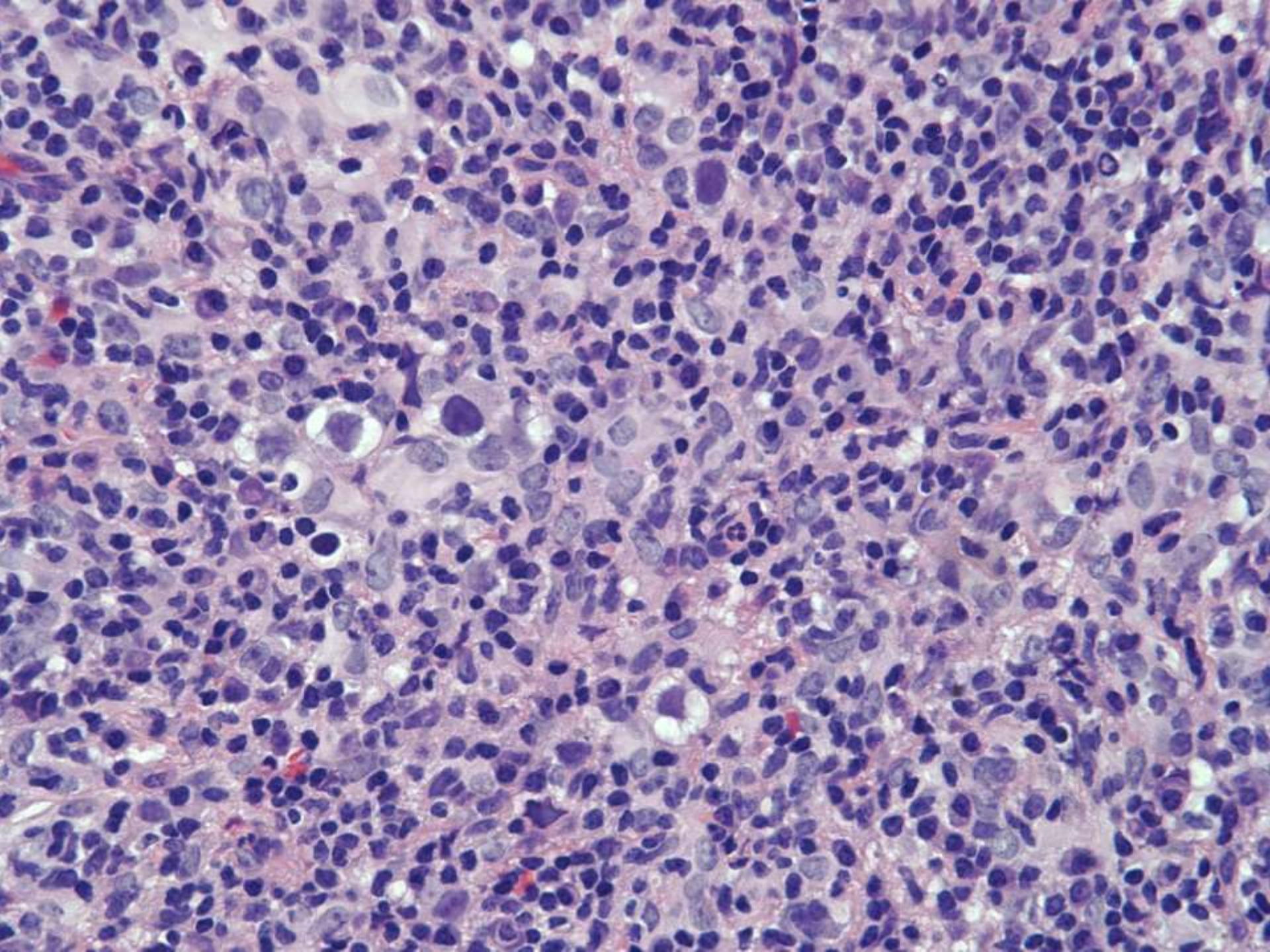
SB 5974

- 11-year-old girl with new onset diabetes insipidus, with MRI showing abnormal contrast enhancement of infundibulum, optic chiasm, and ependyma of 3rd and lateral ventricles.

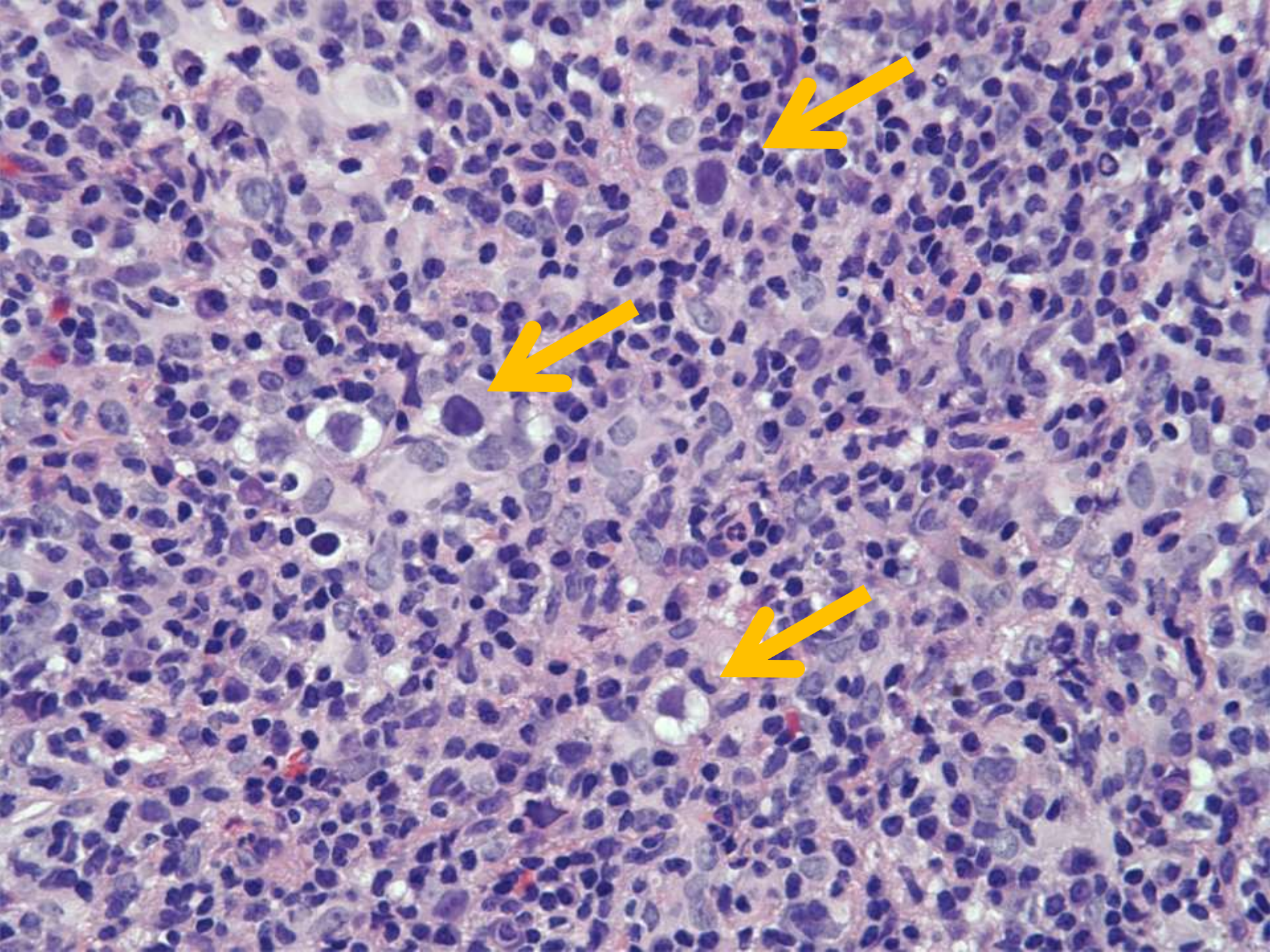
- **Allison Zemek/Hannes Vogel; Stanford**

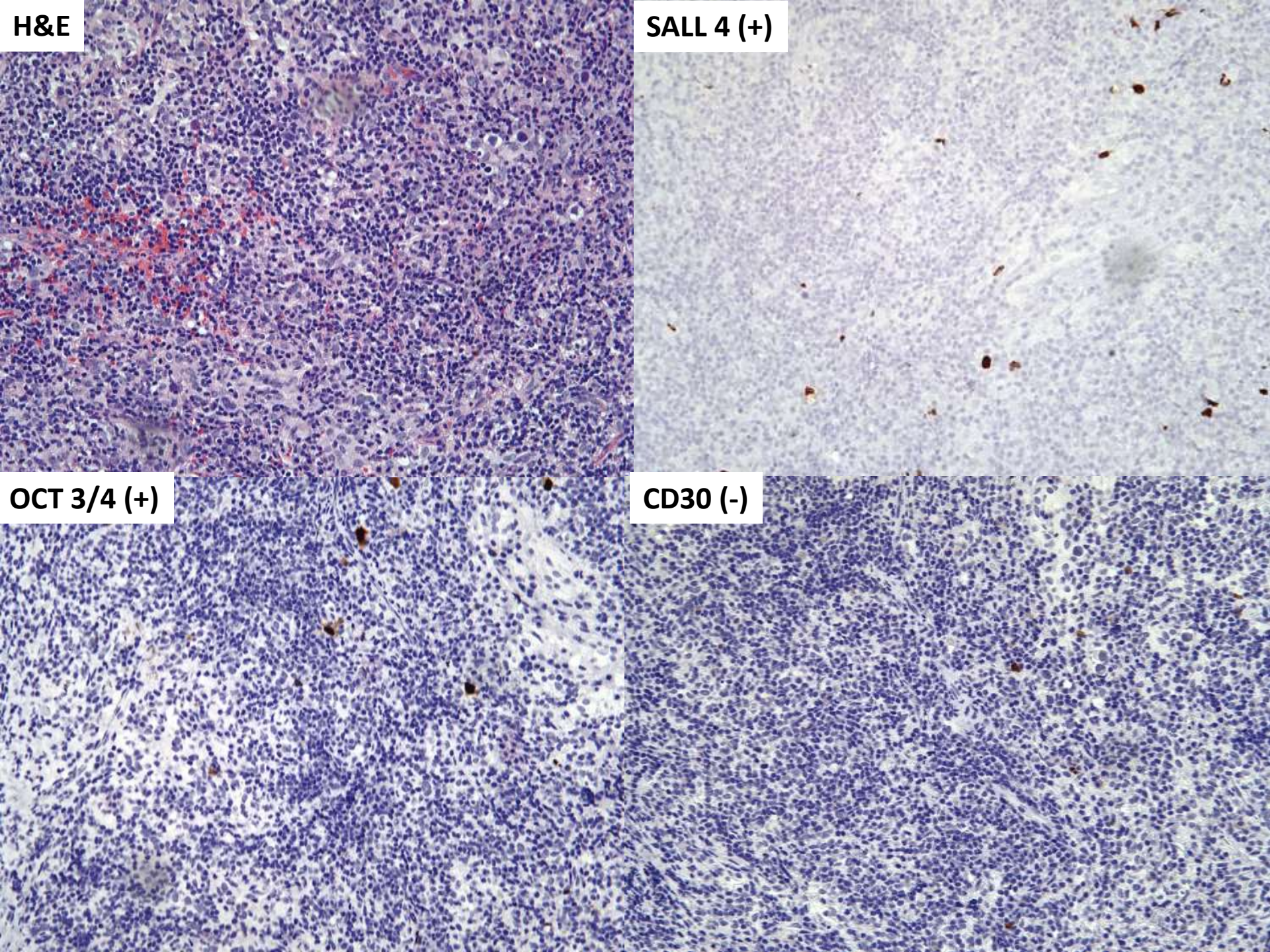






Diagnosis……??




H&E
SALL 4 (+)
OCT 3/4 (+)
CD30 (-)

Germinoma

Clinical features:

- 95% midline, pineal and suprasellar
- 3-5% of all brain tumors in children
- Predominance in adolescence/puberty
- Predominance in males

Cytogenetics:

- Loss of 13q and 18q

Germinoma

Histopathologic features:

- Biphasic
- Large, epithelioid cells
- Round vesicular nuclei
- Nests of polyclonal lymphocytes
- *Granulomatous inflammation*

Immunohistochemical features:

SALL4+ OCT3/4+ CD117+ CD30-

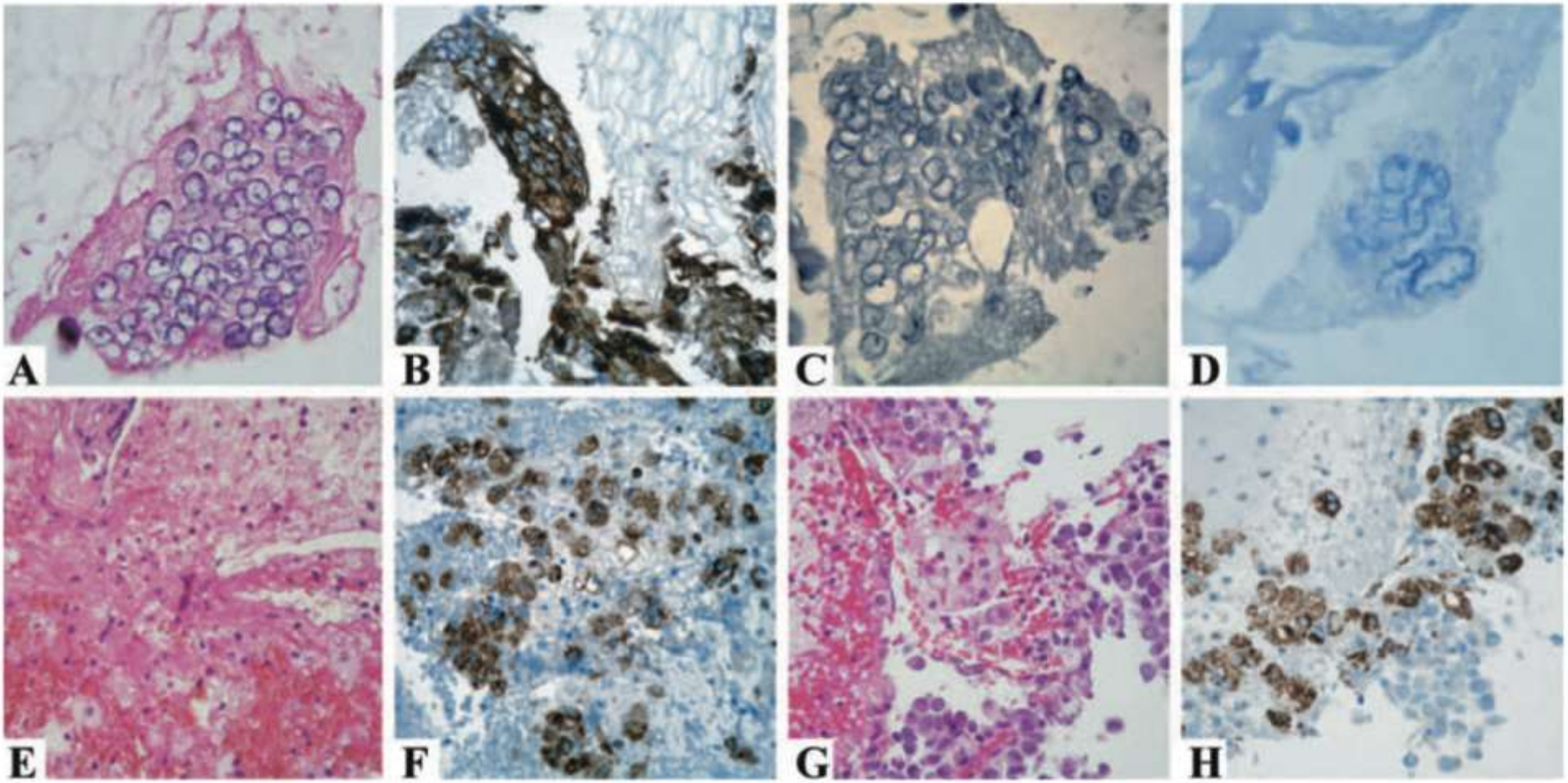
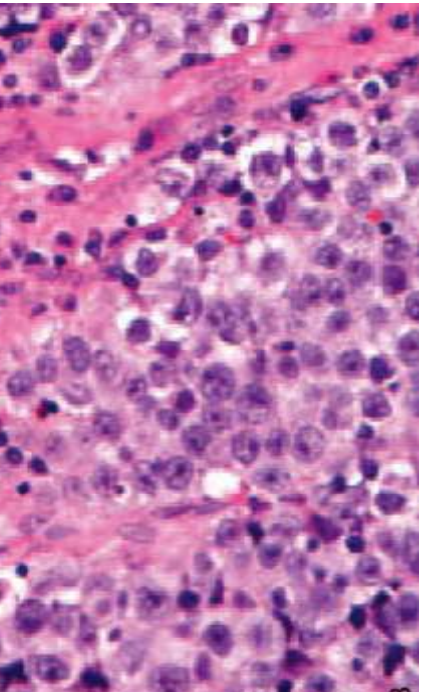
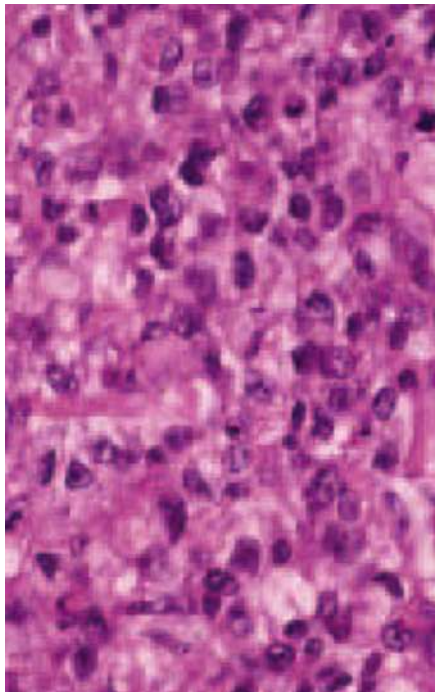
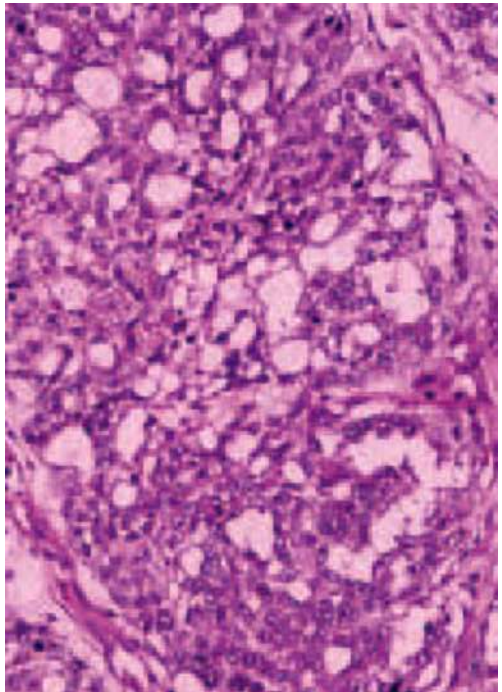
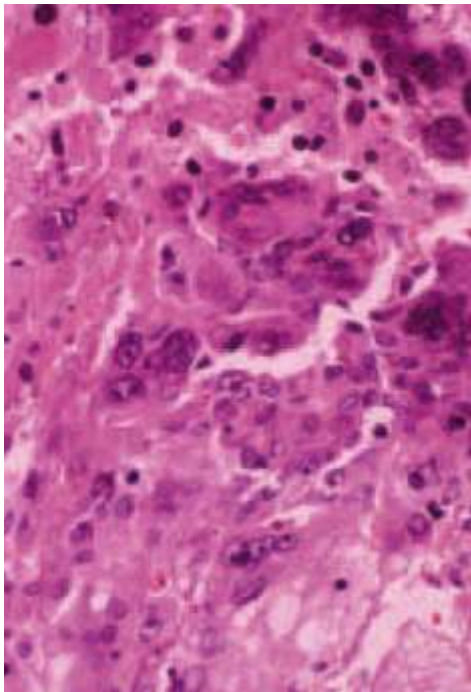


Fig. 2 Upper panel (A–D). Granulomatous tissue response seen in endoscopically navigated fine-needle biopsy. Foreign-body giant cells were the predominant feature of the specimen (A, HE ×1000). CD68 identifies these multinucleated and adjacent mononuclear cells as macrophages (B, CD68 ×1000). None of the multinucleated cells stained for beta-HCG or c-kit (C, beta-HCG ×1000; D, c-kit ×1000). Lower panel (E–H). Lesion-edge in open biopsy. Necrotic tissue, fresh hemorrhage and scattered macrophages obscure tumor on edge of lesion (E, HE ×400; F, CD68 ×400). Lesion edge with transition from granulomatous tissue response to vital tumor (G, HE ×400; H, CD68 ×400).

IPOX	Sem/Dys/Germinoma	Embroynal	Yolk Sac	Chorio
SALL4	+	+	+	+
OCT3/4	+	+	-	-
CD117	+	-	-	-
CD30	-	+	+/-	-
Glypican	-	-	+	+/-

Germinoma

Treatment:

- Very radiosensitive
- Whole brain irradiation vs. focal irradiation

Prognosis:

- 5-year progression-free survival 86.4%
- 5-year overall survival 93%

Take home point:

Germinomas can be associated with obscuring inflammation

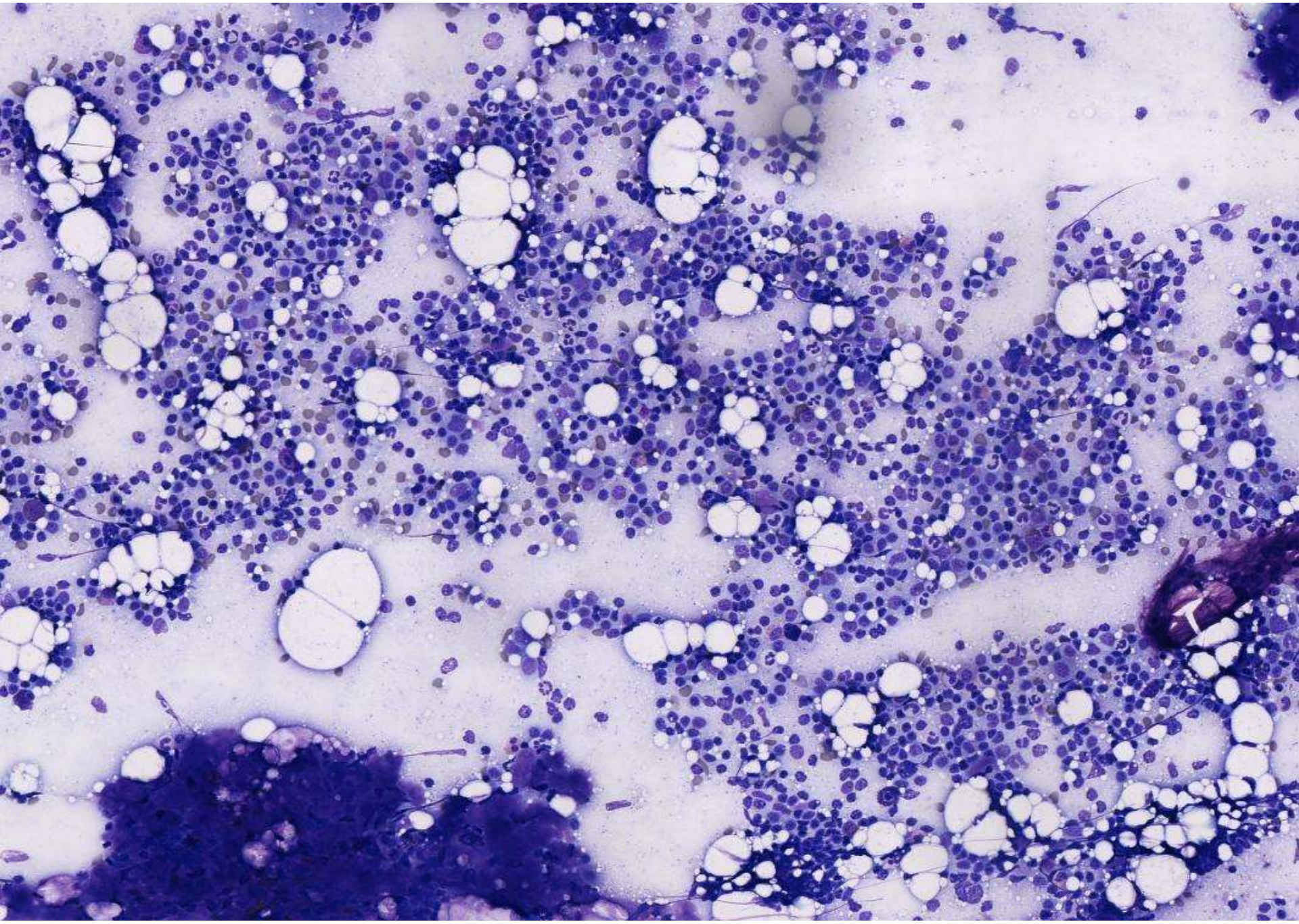
SB 5975

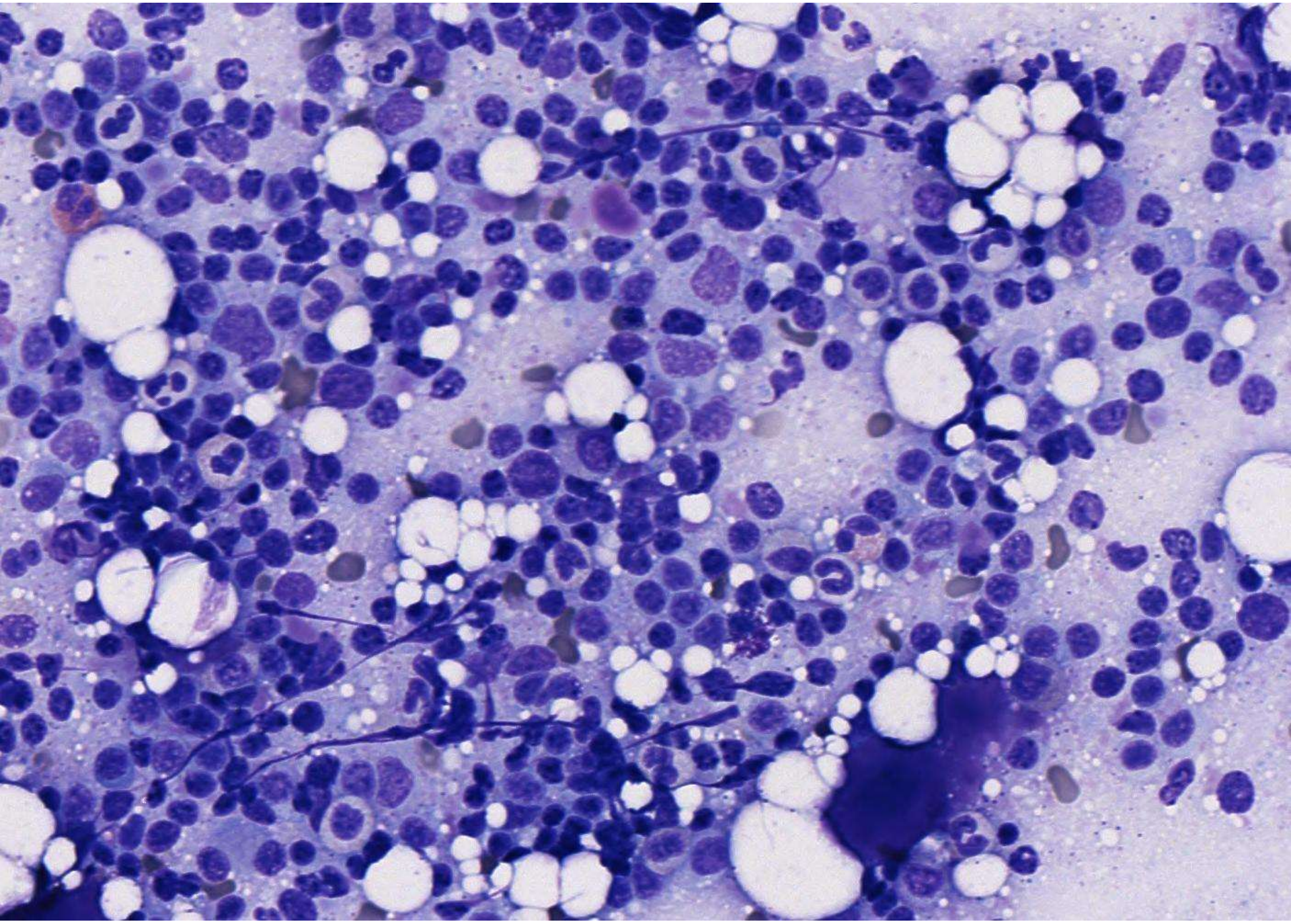
- POSTPONED

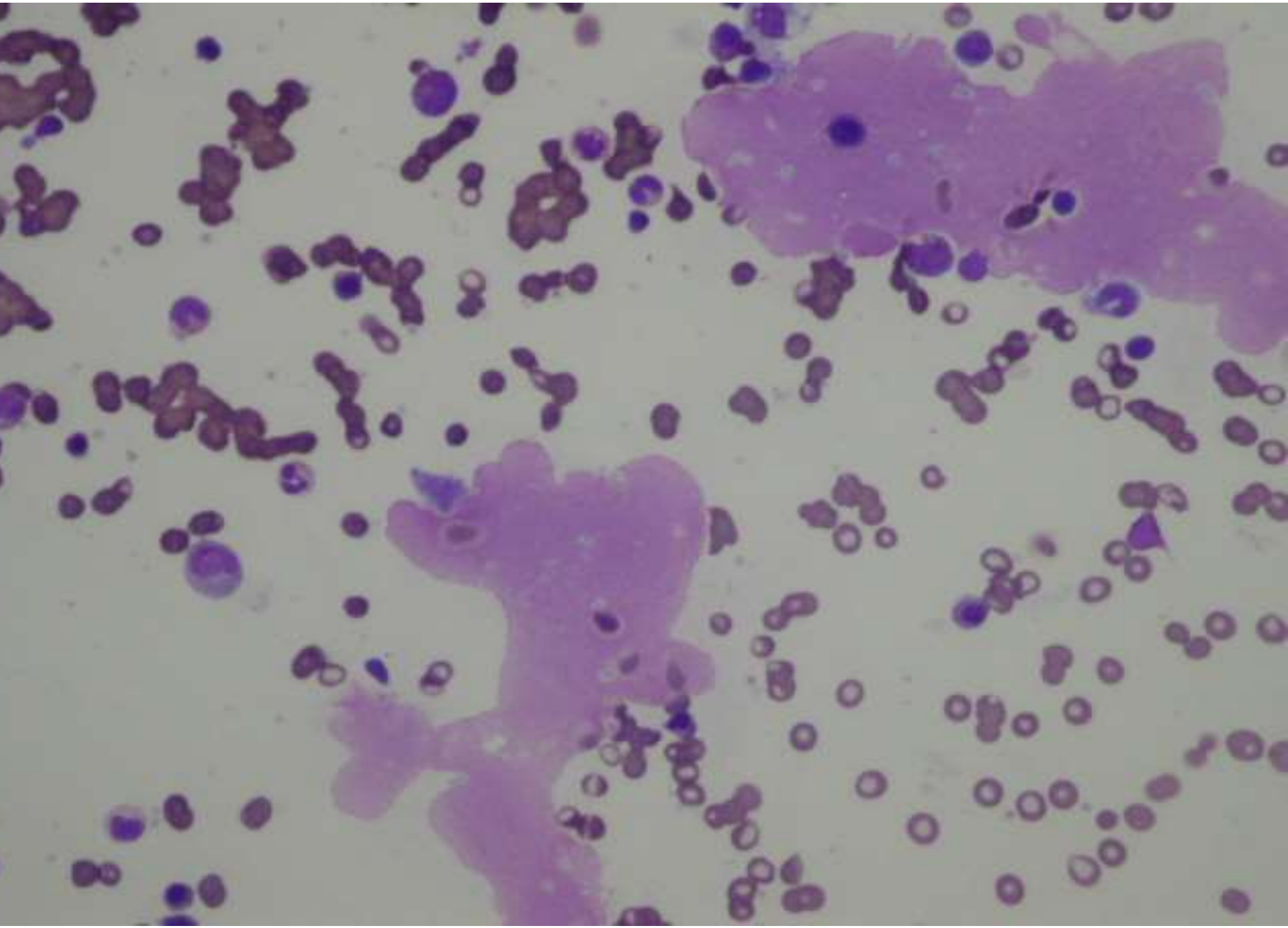
SB 5976

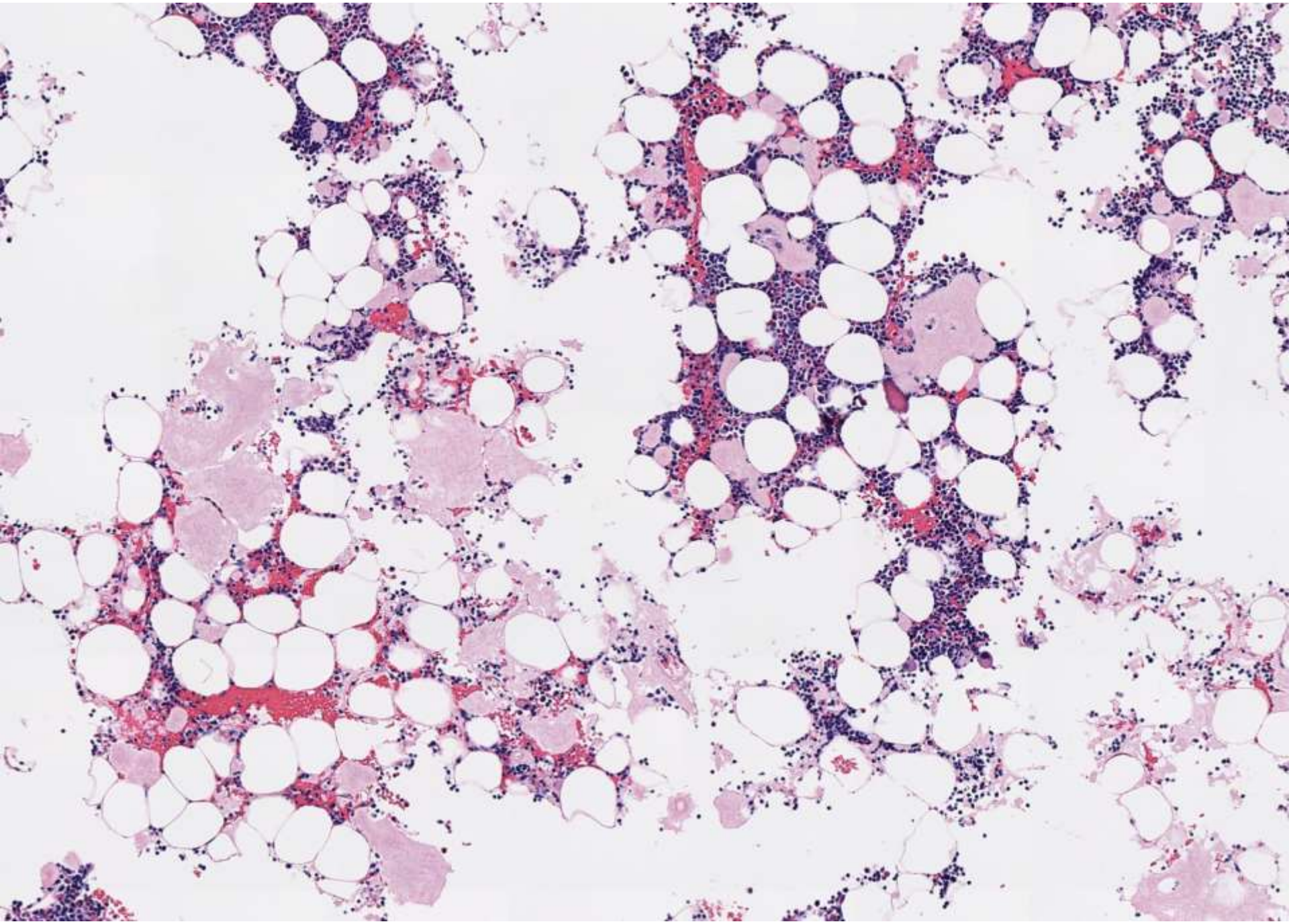
- 93-year-old woman with IgM lambda gammopathy and acute kidney failure. Rule out myeloma. Bone marrow performed.

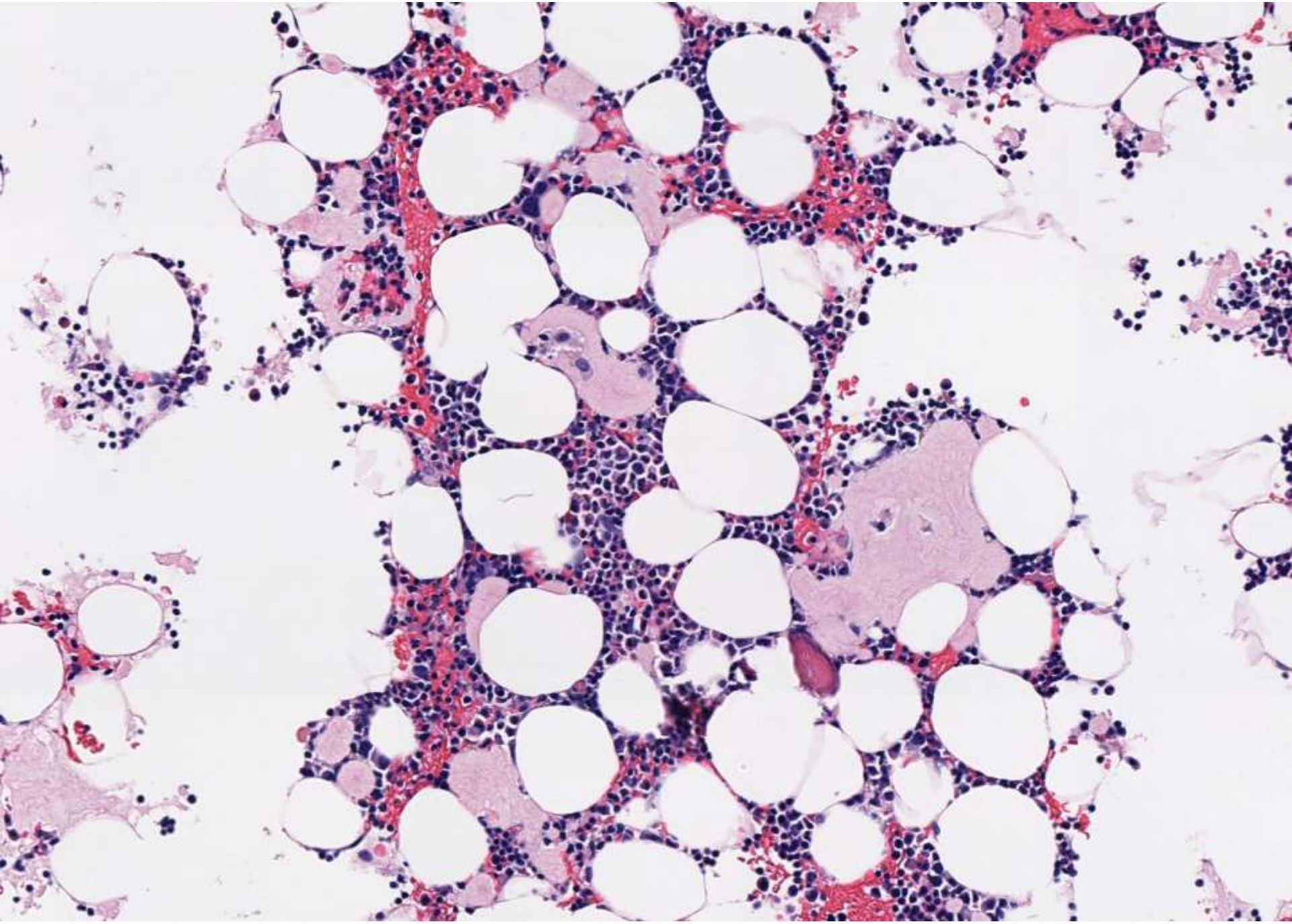
- **Keith Duncan; Mills-Peninsula Hospital**

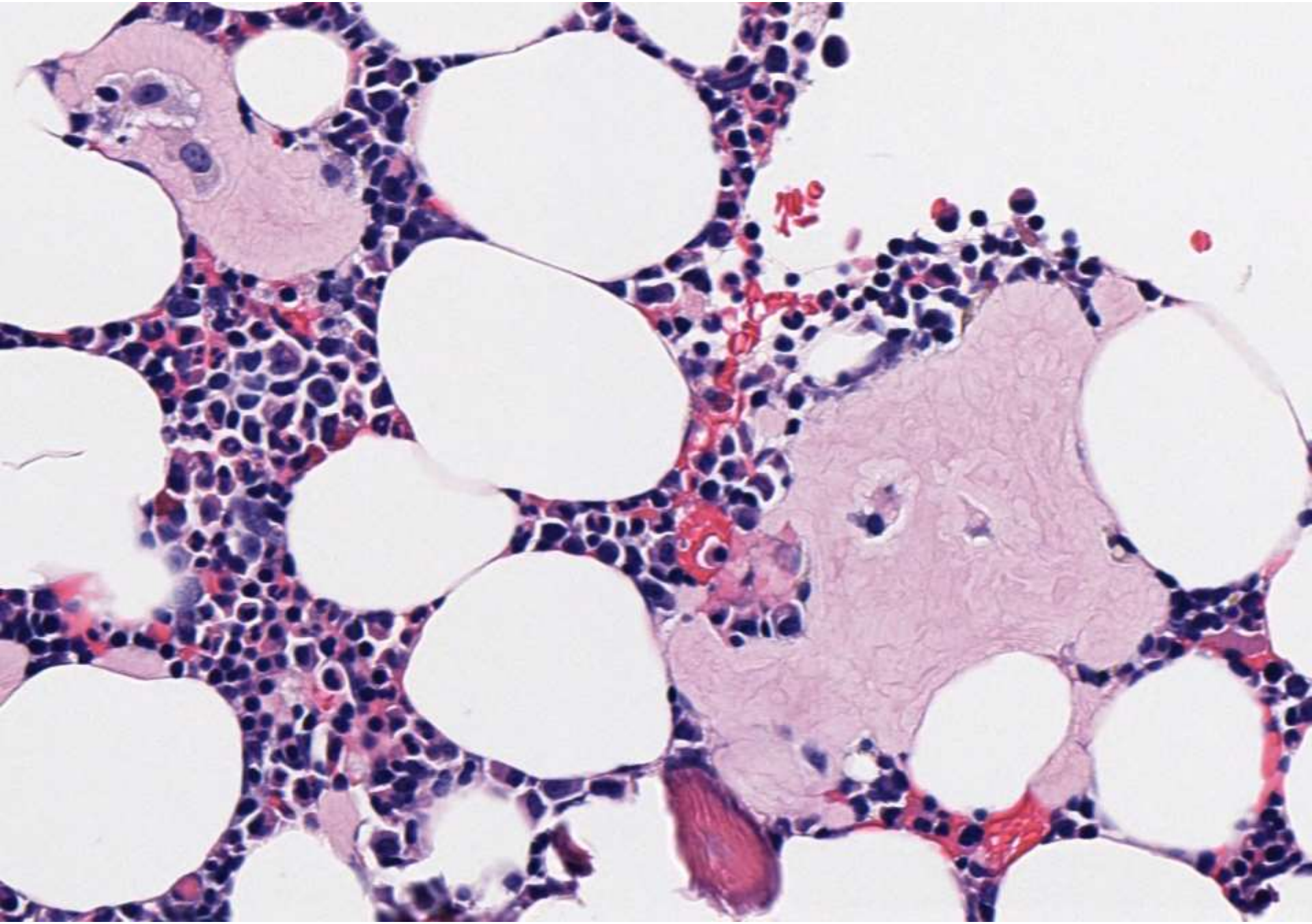






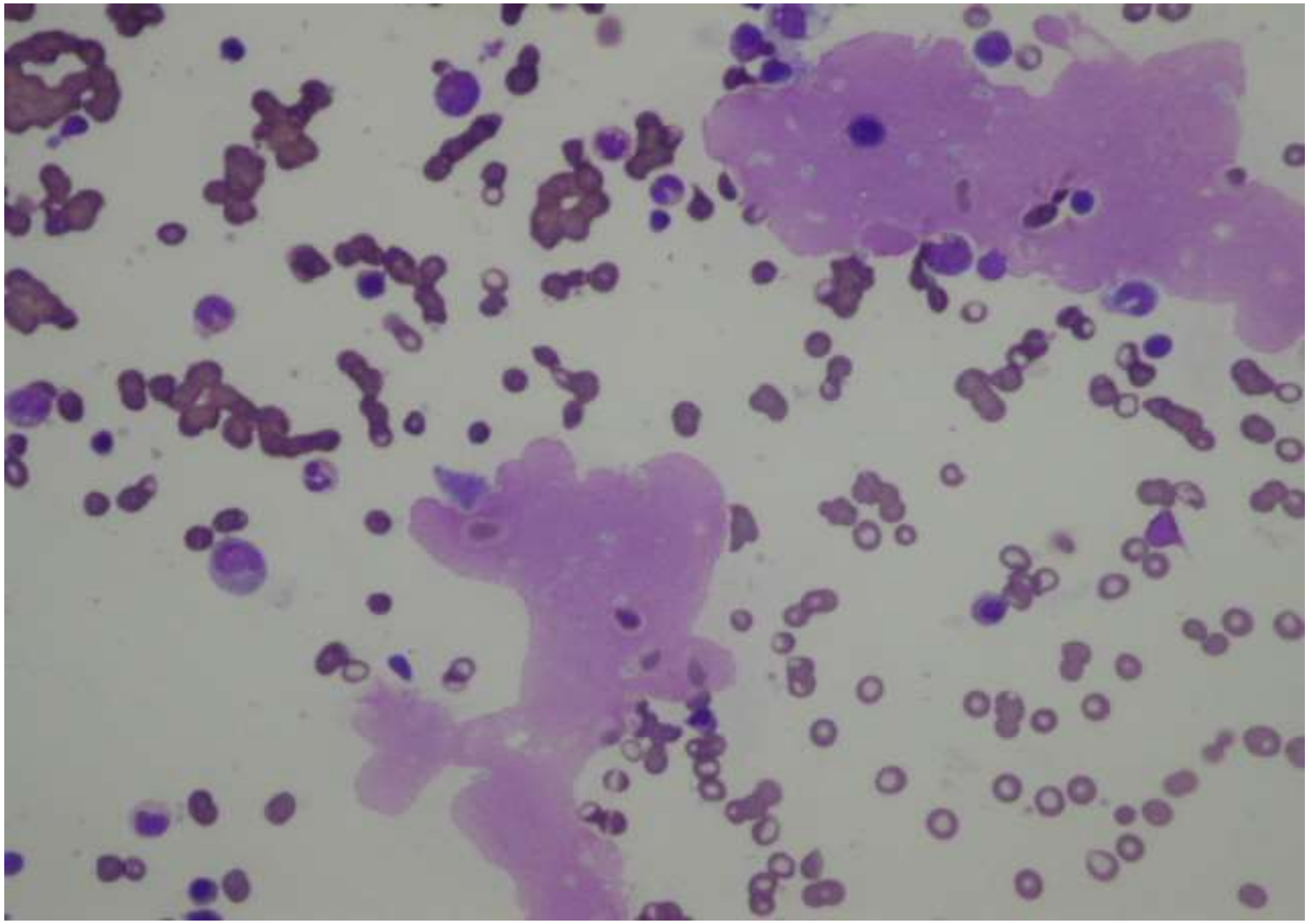




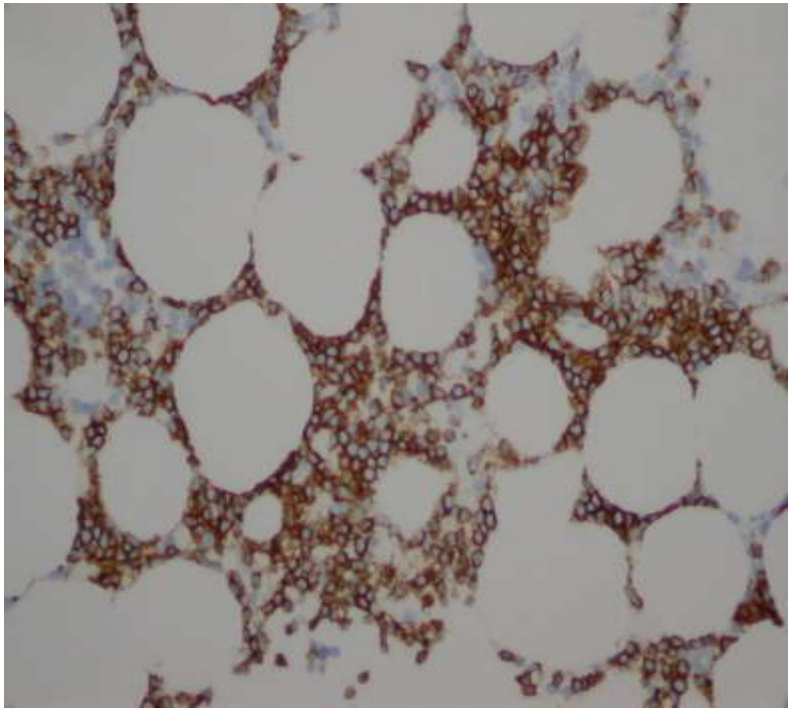


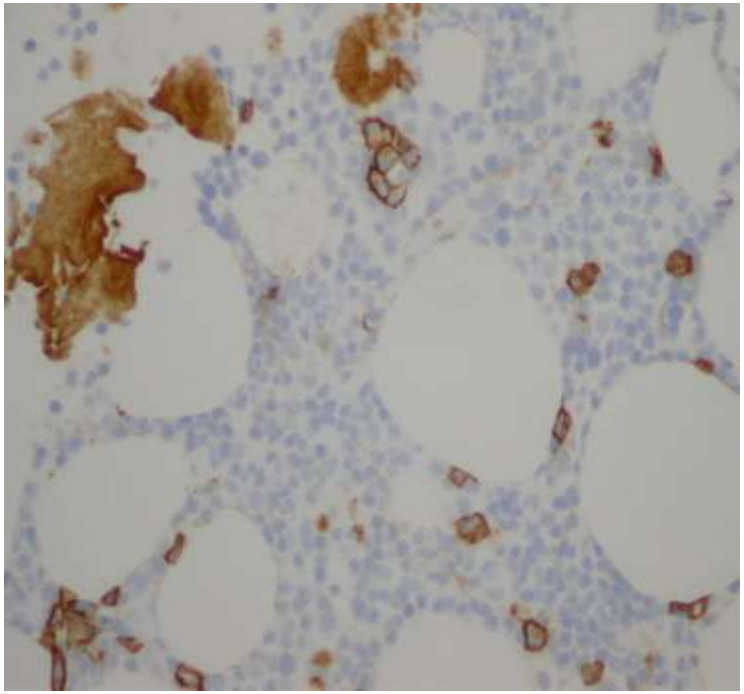
Diagnosis……??

ASPIRATE SMEARS

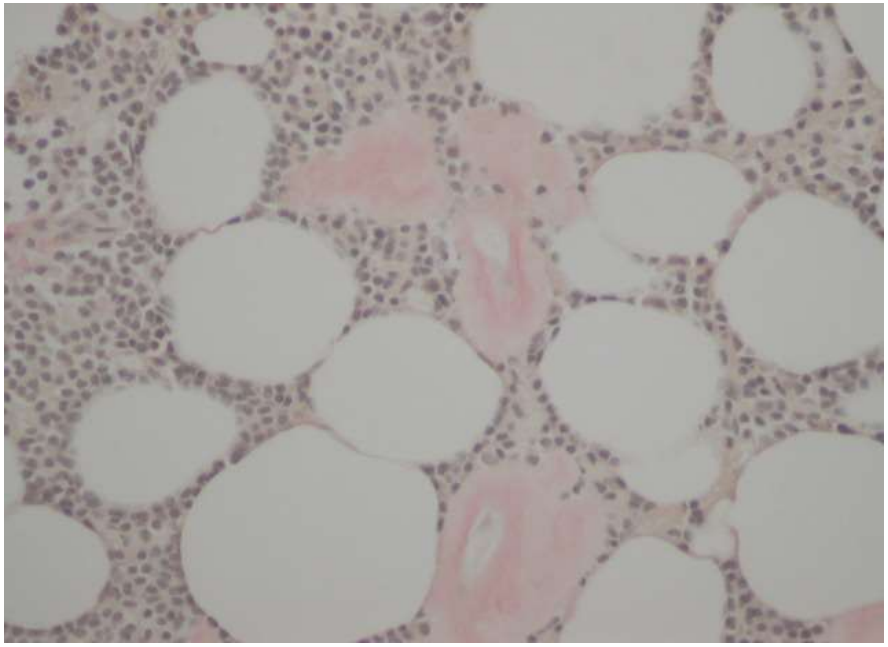


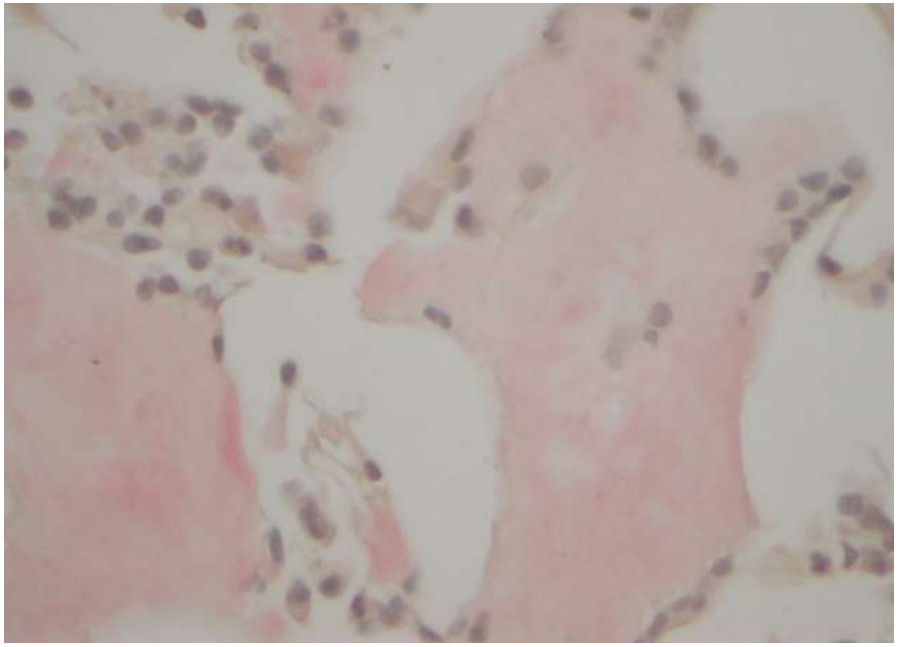
CD20/ CD138



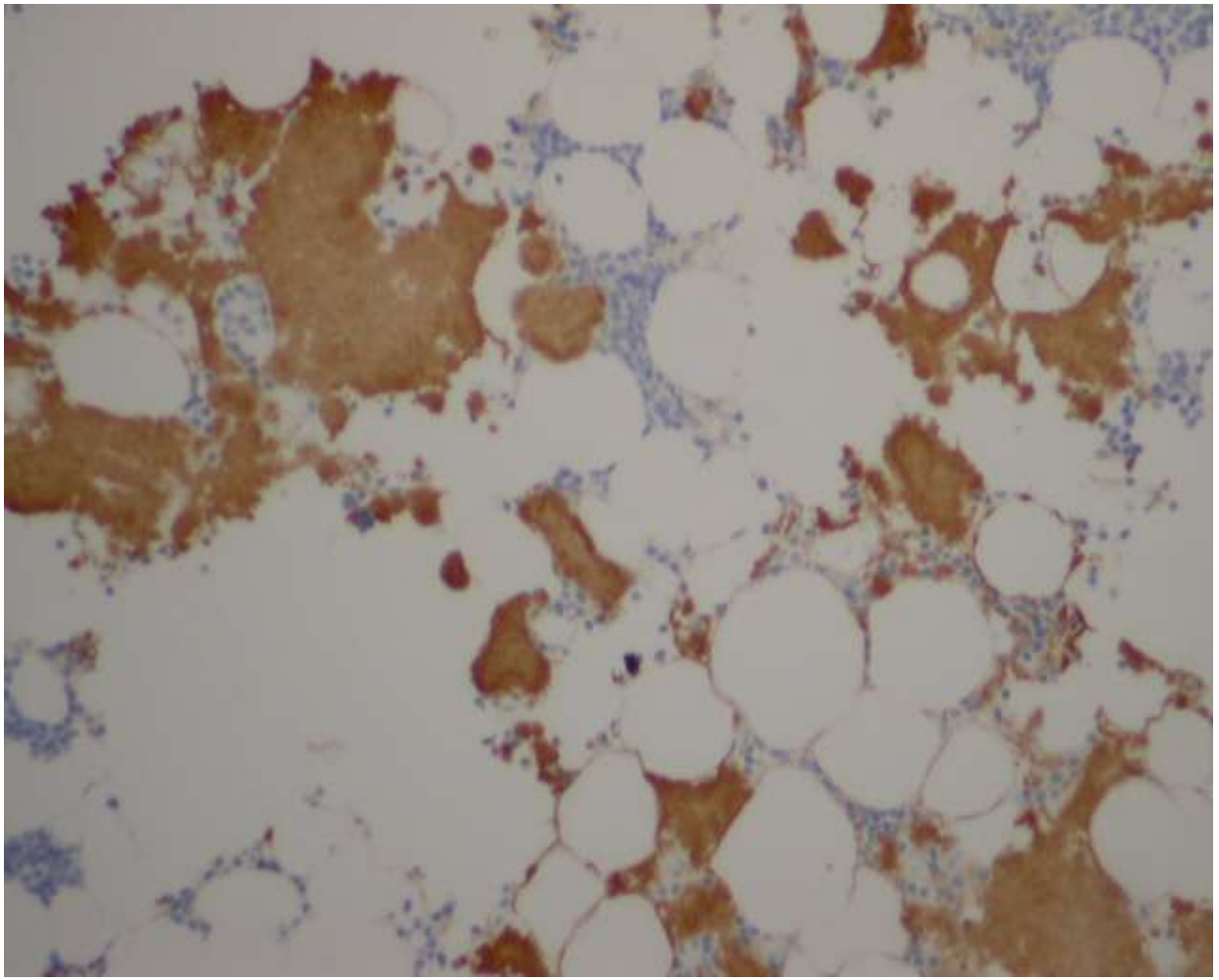


CONGO RED STAIN





AMYLOID P



Lymphoplasmic lymphoma

● Rare (2% of hematopoietic neoplasms) malignancy of older patients (50-69 years) with involvement of bone marrow, lymph node, spleen/liver

● No masses causing bony erosions as in myeloma

● Does not fulfill the criteria for any other B-cell lymphoma with plasmacytic differentiation

Monoclonal IgM and Waldenstrom's macroglobulinemia

Waldenstrom's macroglobulinemia

Diagnostic criteria:

- IgM monoclonal gammopathy
- Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation
- Intertrabecular pattern of bone marrow infiltration
- Immunophenotype is surface IgM+, CD19+, CD20+, CD22+, CD25+, CD27+, FMC7+, CD5 variable, CD10-, CD23-, CD103-, CD108-

Moderate to severe normochromic anemia with marked rouleaux formation

AMYLOID

● Monoclonal proliferation of plasma cells secreting free light chains (usually lambda), which are deposited as amyloid

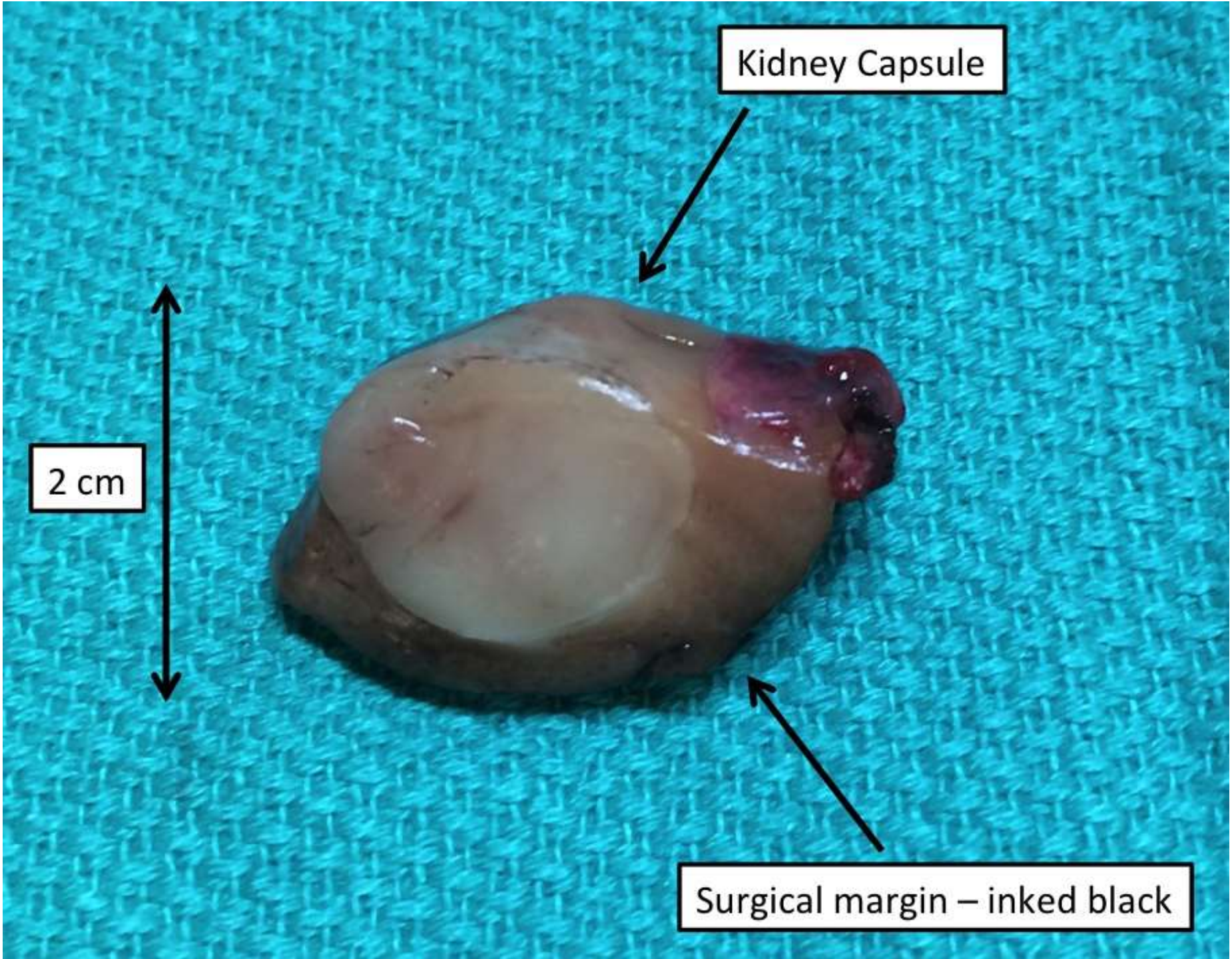
● **Amyloid:** fibrillary protein, 95% composed of non-branching fibrils 7.5 to 10 nm thick with variable length in a beta-pleated sheet conformation; 5% is serum amyloid P component, made of proteoglycans & glycosaminoglycans

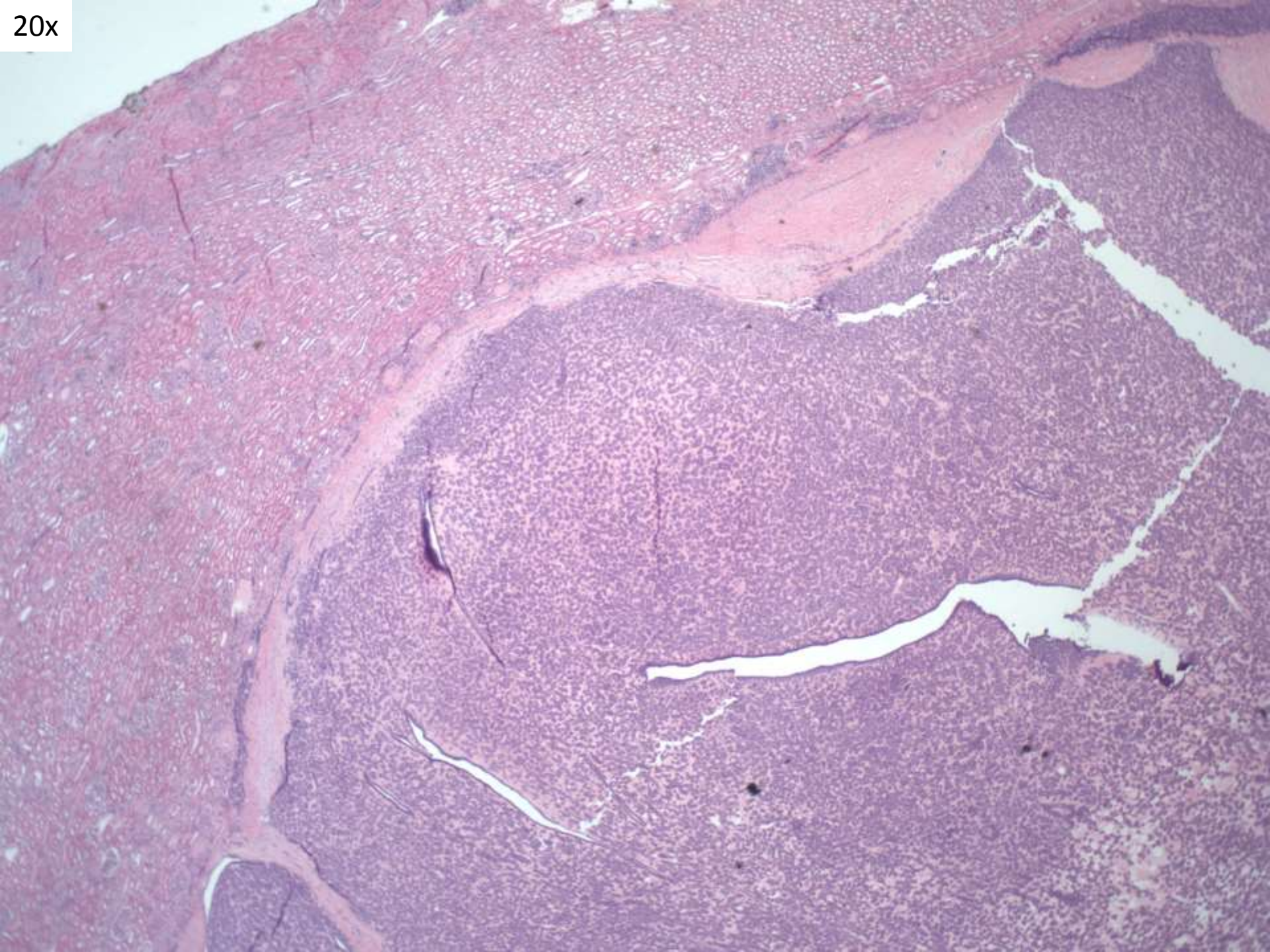
● **Symptoms:** weight loss, heart failure, peripheral neuropathy, nephrotic syndrome

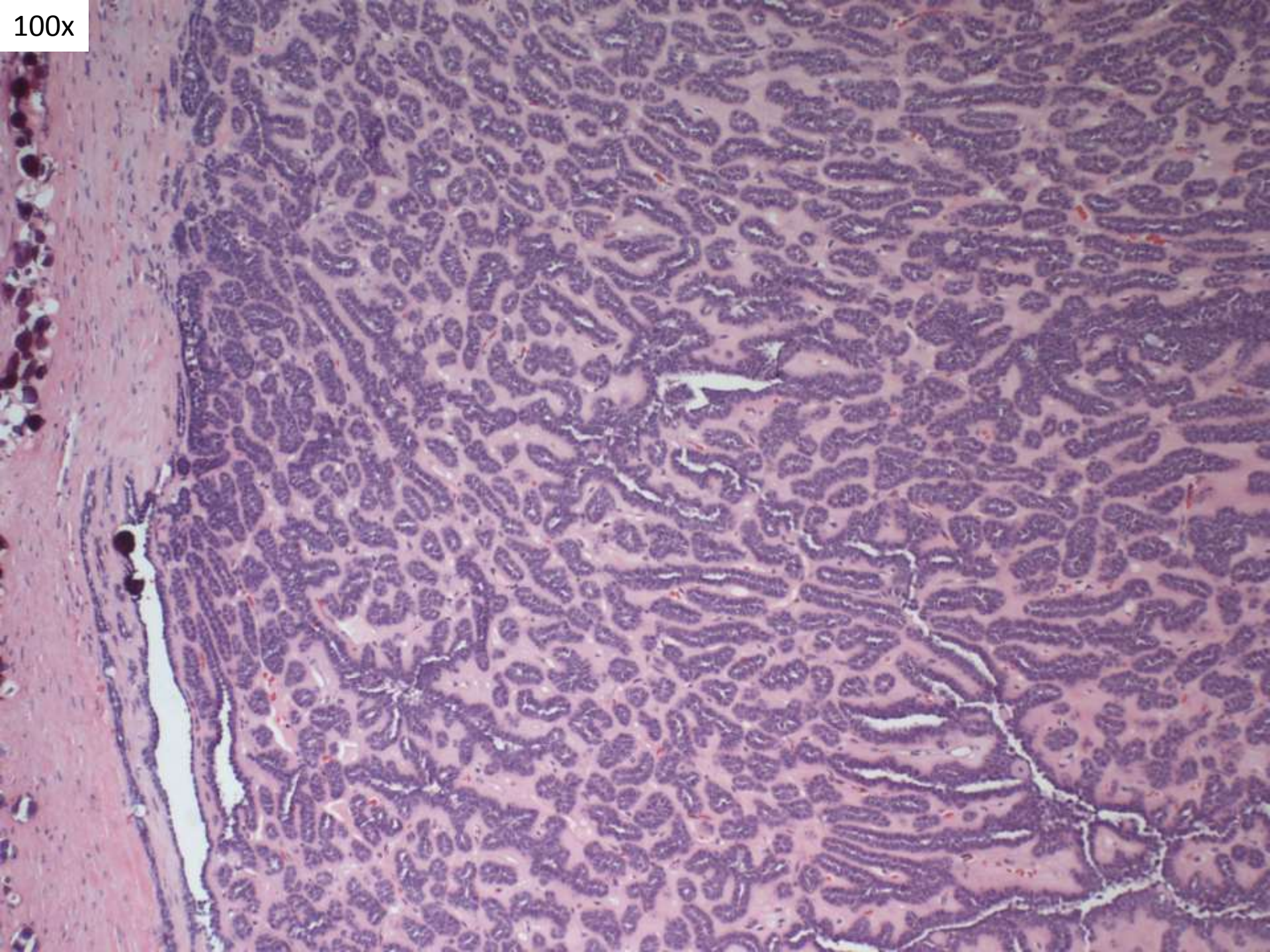
SB 5977

- 52-year-old woman with left renal mass. Sent for frozen section for gross examination of margin. Thought to be renal cell carcinoma but no prior biopsies performed.

- Sebastian Fernandez-Pol/Natalia Isaza/Neeraja Kambham/Erich Schwartz; Stanford


Kidney Capsule
2 cm
Surgical margin – inked black


20x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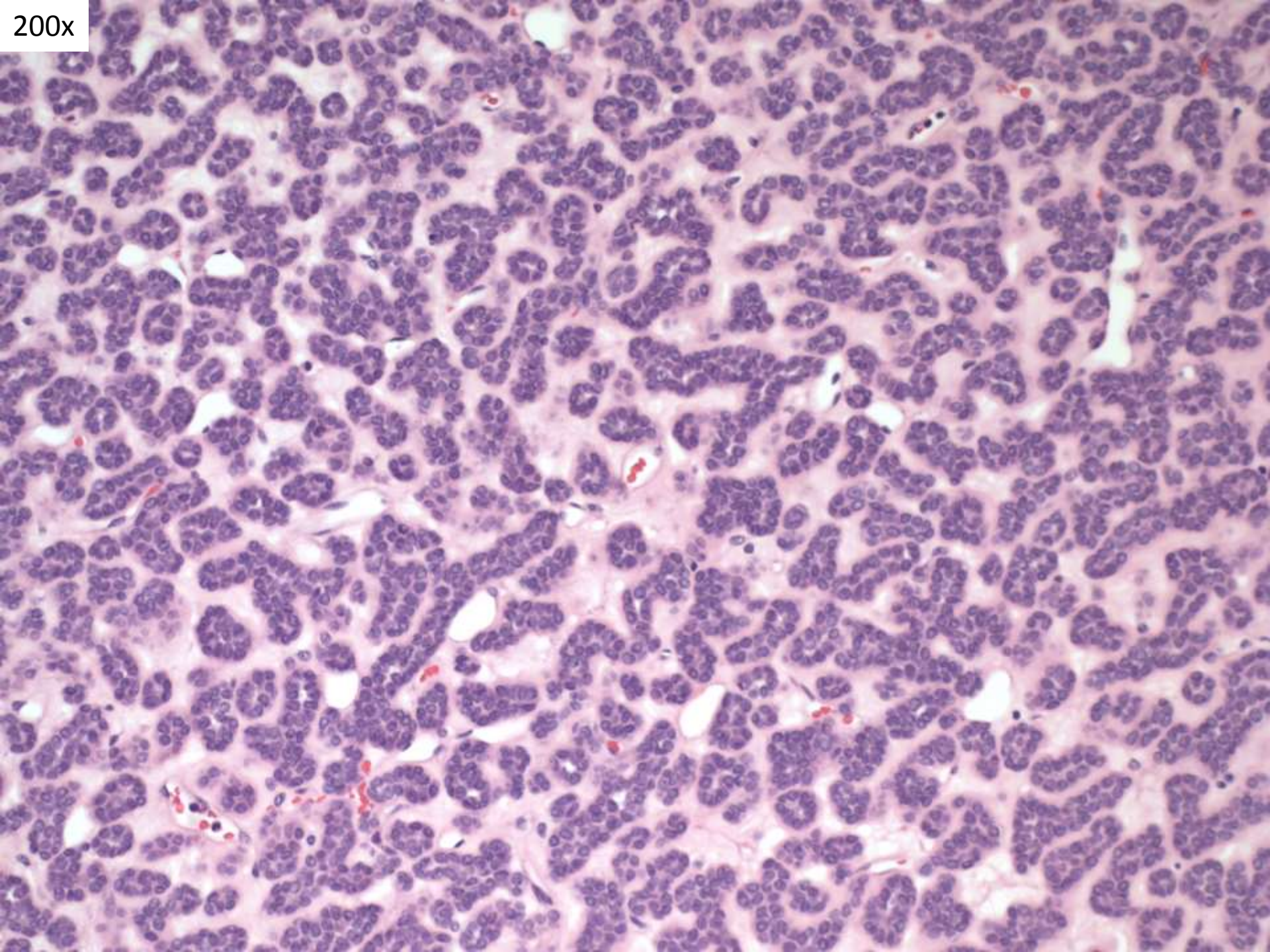
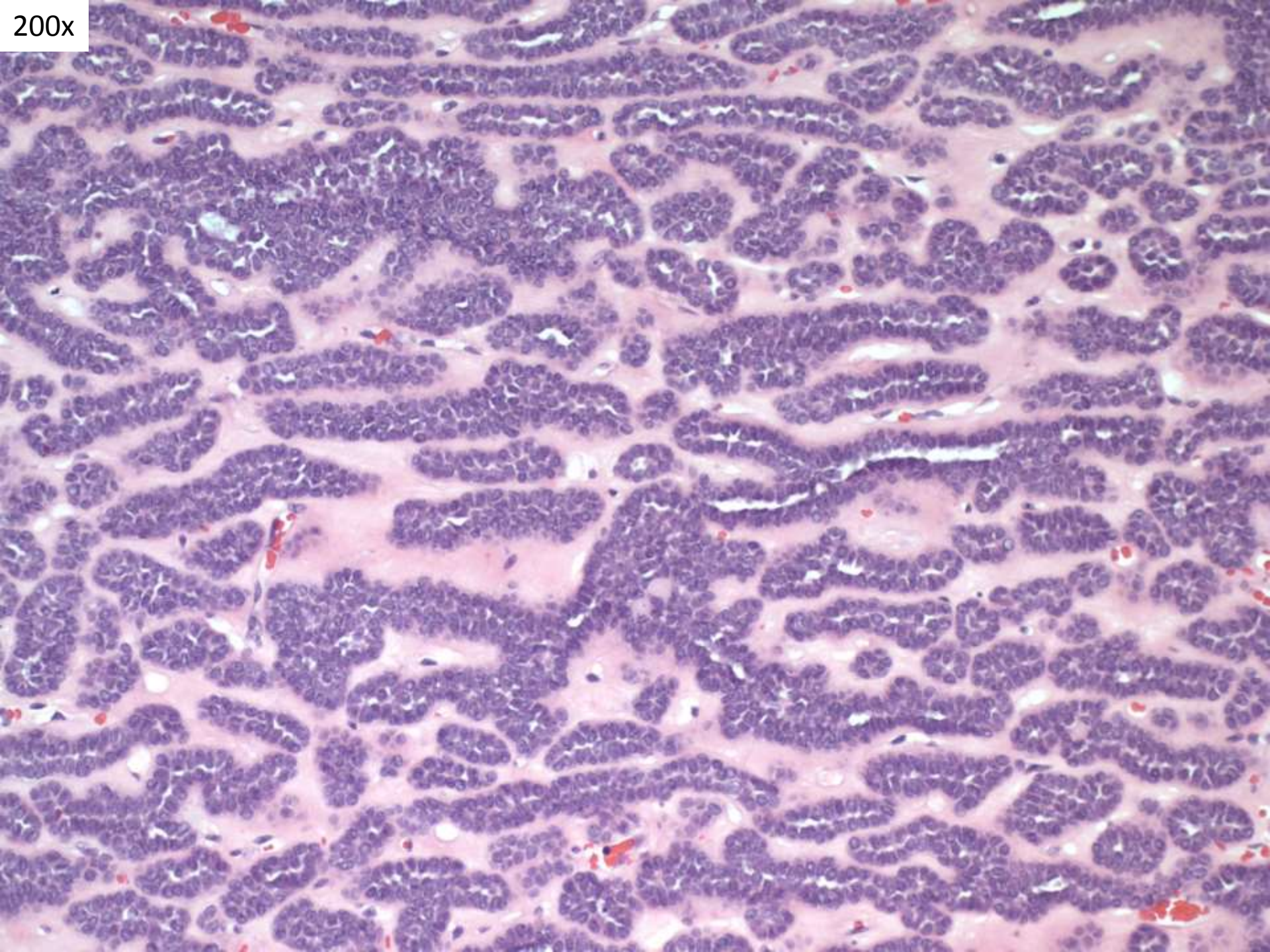

200x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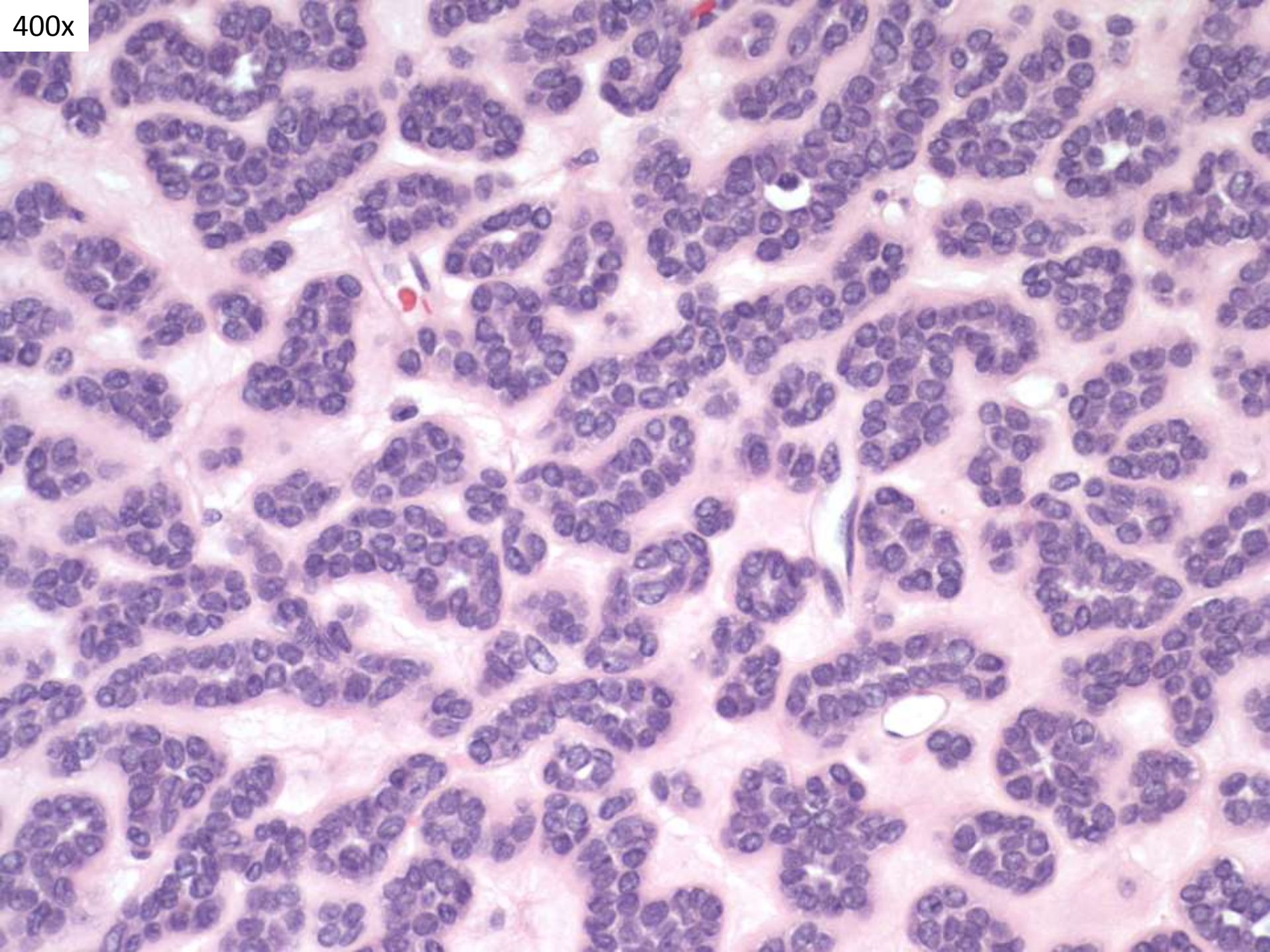

400x

Diagnosis……??

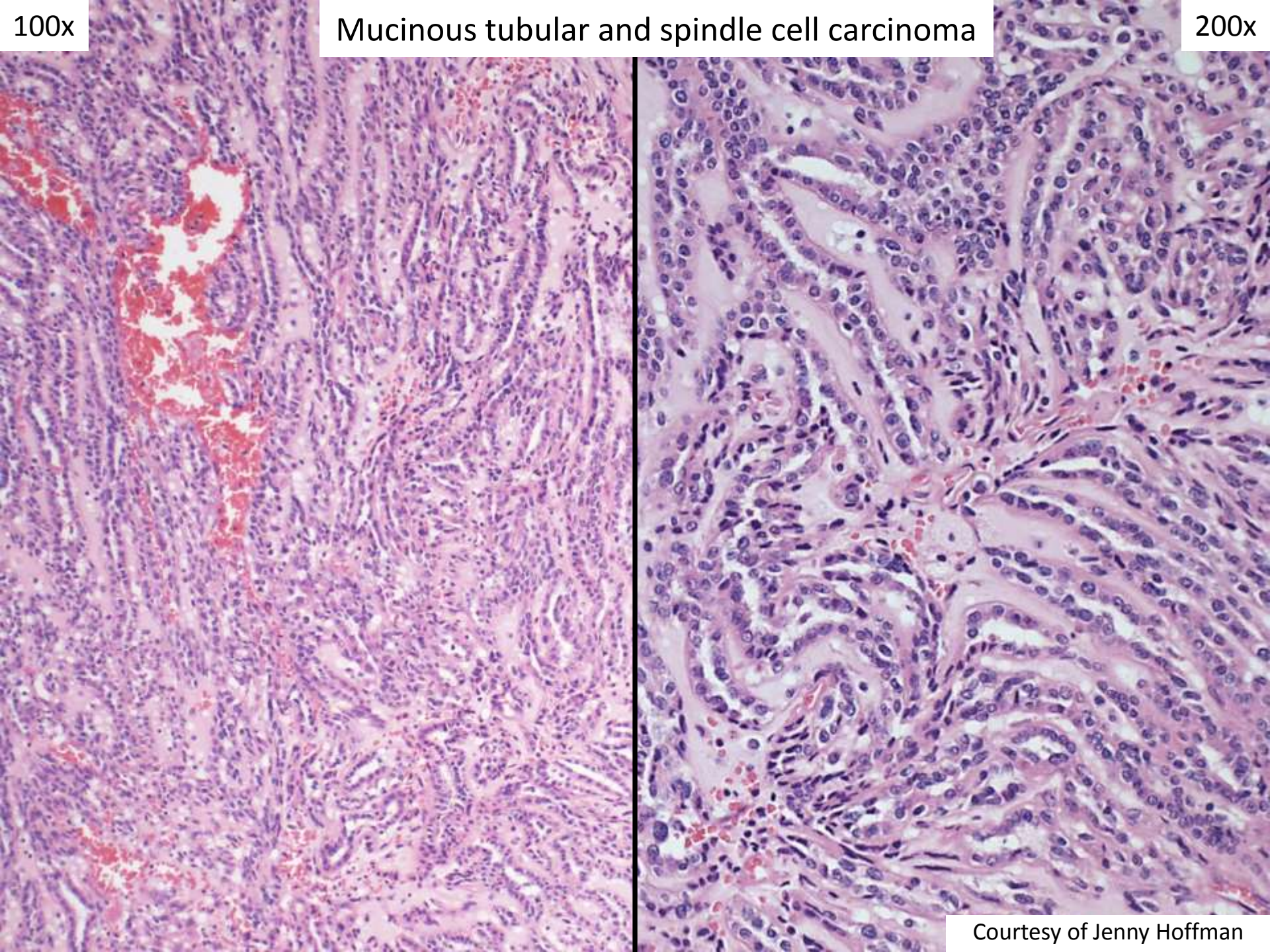
Metanephric adenoma

- Most common in 5^{th}-6^{th} decades
  - 0.2–0.7% of adult renal epithelial neoplasms
- Most common **purely epithelial** kidney tumor found in children
- About 50% are found incidentally
- 10 to 15% of patients have polycythemia
- Benign

Differential diagnosis of metanephric adenoma

- Papillary renal cell carcinoma
- Epithelial predominant Wilms tumor
- Mucinous tubular and spindle cell carcinoma

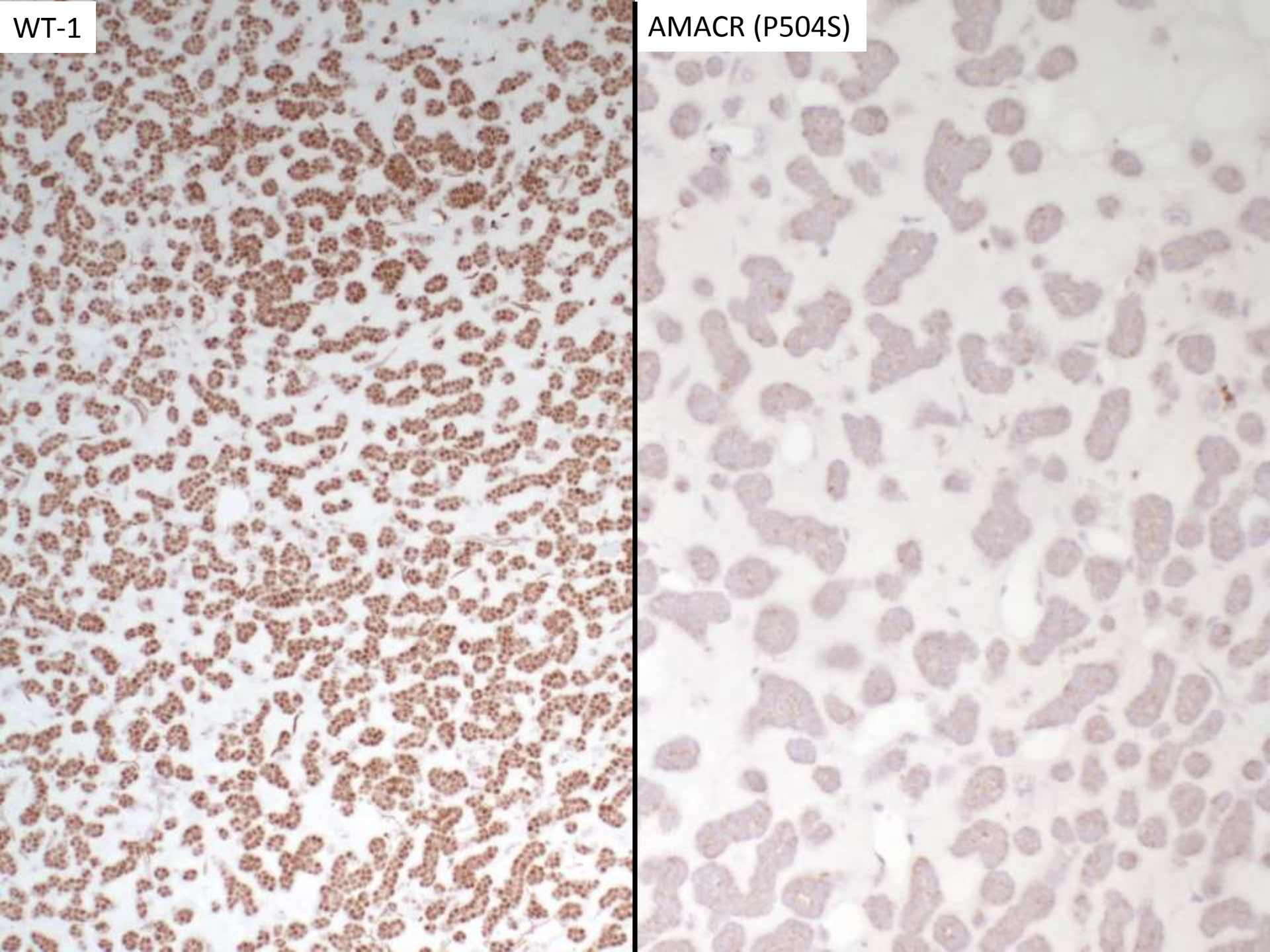
Mucinous tubular and spindle cell carcinoma



Courtesy of Jenny Hoffman

Differential diagnosis

	Metanephric adenoma	Papillary RCC	Wilms tumor	Mucinous tubular and spindle cell carcinoma
AMACR	**Negative**	Positive	Negative	Positive
WT-1	**Positive**	Negative	Positive	
CK7	Negative	Positive	Negative	Positive
CD57	Positive	Negative	Negative	
Additional studies	BRAF V600E	Trisomy 7 and 17		


WT-1
AMACR (P504S)

European Association of Urology

Eur Urol 2012

Kidney Cancer

BRAF Mutations in Metanephric Adenoma of the Kidney

Am J Surg Pathol 2015

Molecular and Immunohistochemical Characterization Reveals Novel *BRAF* Mutations in Metanephric Adenoma

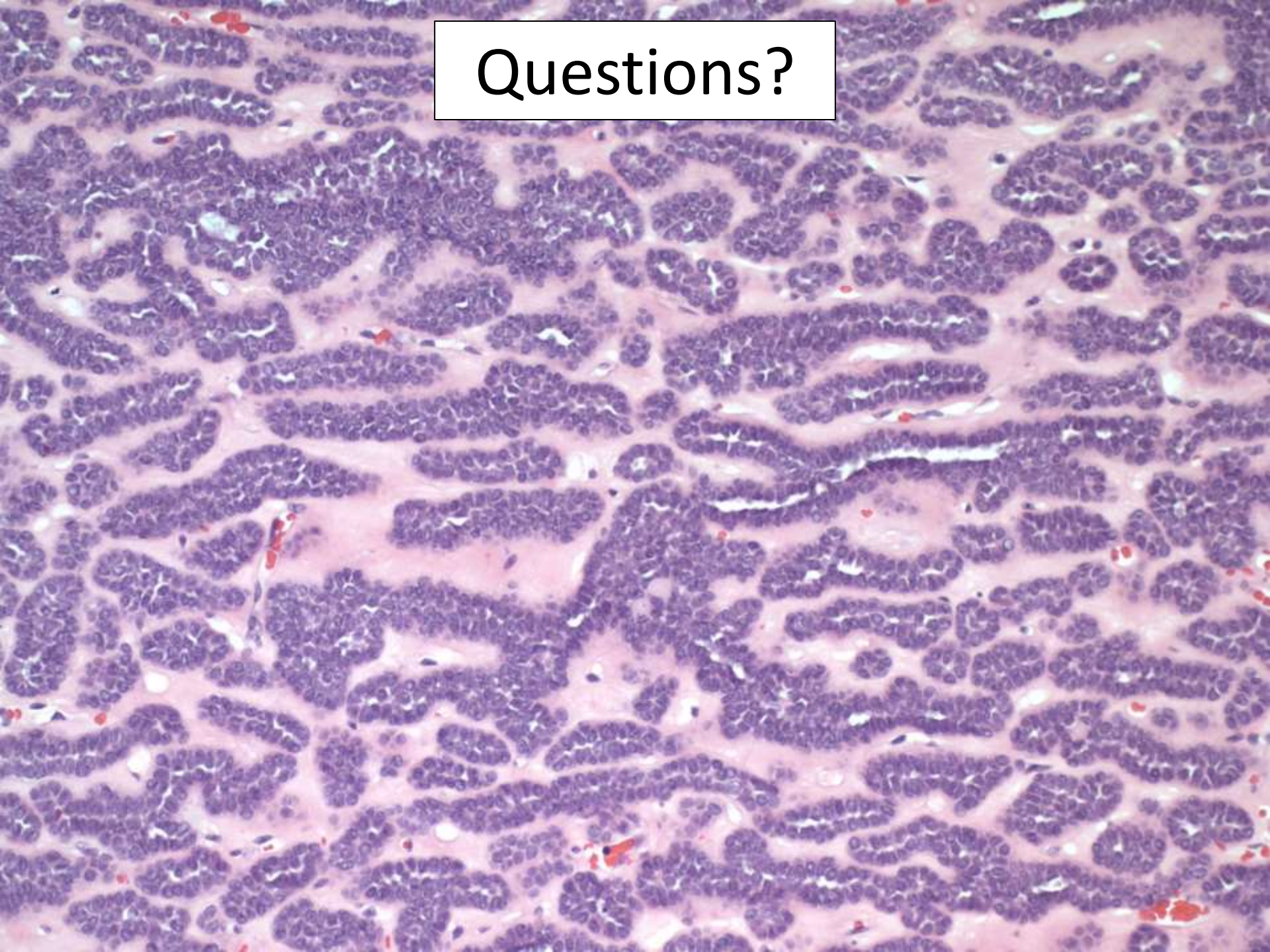
- BRAF V600E is present in 90% of metanephric adenomas
- 76% of metanephric adenomas are positive for V600E by immunohistochemistry
- Other BRAF mutations are also seen (eg V600D)
- BRAF mutations in other renal tumors are very infrequent (<1%)

Take home points

- Gross appearance may be characteristic
  - Solitary, well-circumscribed but in most instances not encapsulated
  - Fray to tan to yellow
- Differential diagnosis
  - Rule out papillary RCC
  - Also consider Wilms' tumor, mucinous tubular and spindle cell carcinoma
- BRAF V600E mutations are found in metanephric adenomas

References

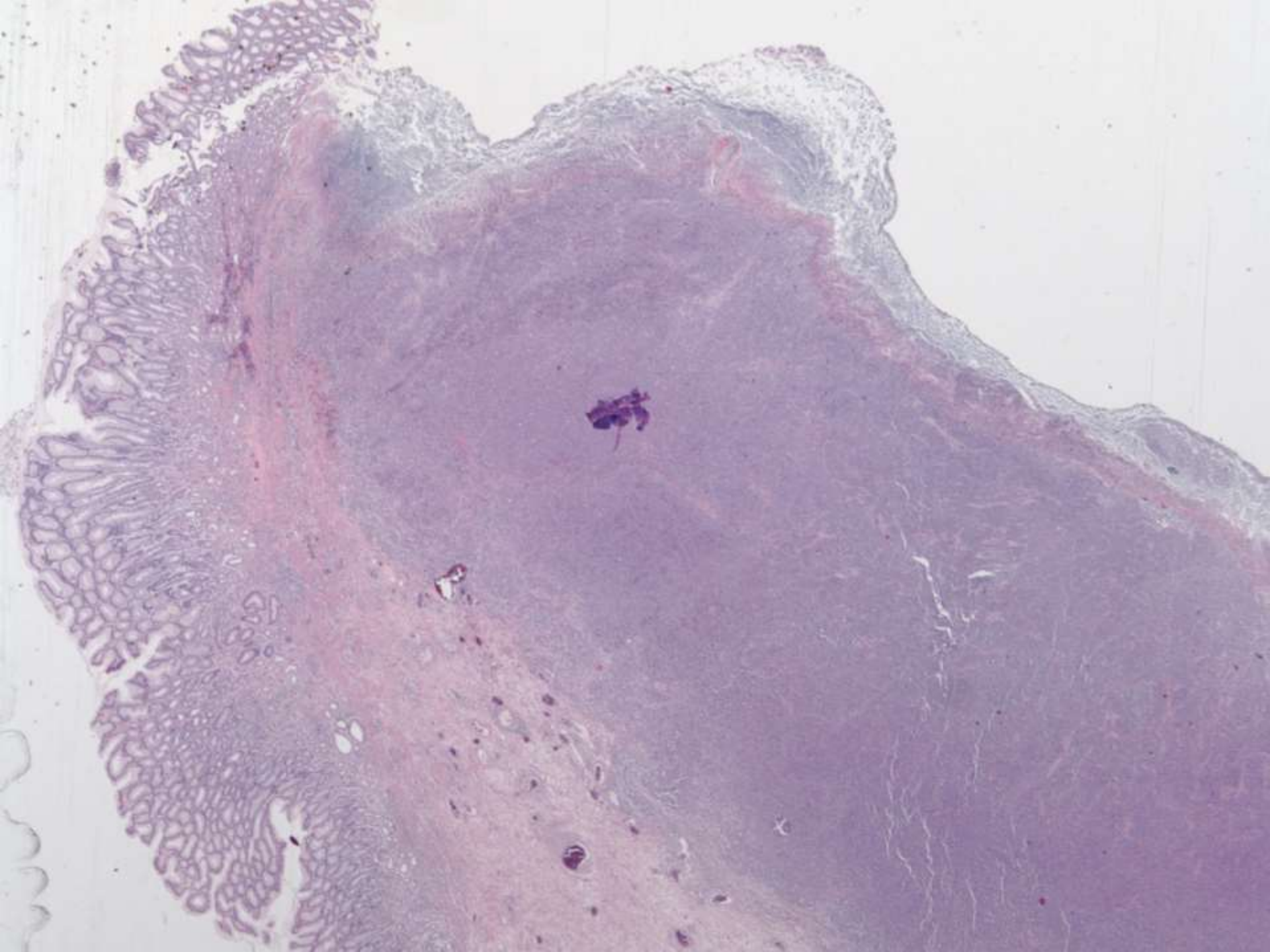
1. Choueiri TK, Cheville J, Palescandolo E, et al. BRAF mutations in metanephric adenoma of the kidney. Eur Urol. 2012;62:917–922.
2. Udager AM, Pan J, Magers MJ, et al. Molecular and immunohistochemical characterization reveals novel BRAF mutations in metanephric adenoma. Am J Surg Pathol. 2015;39:549-57.

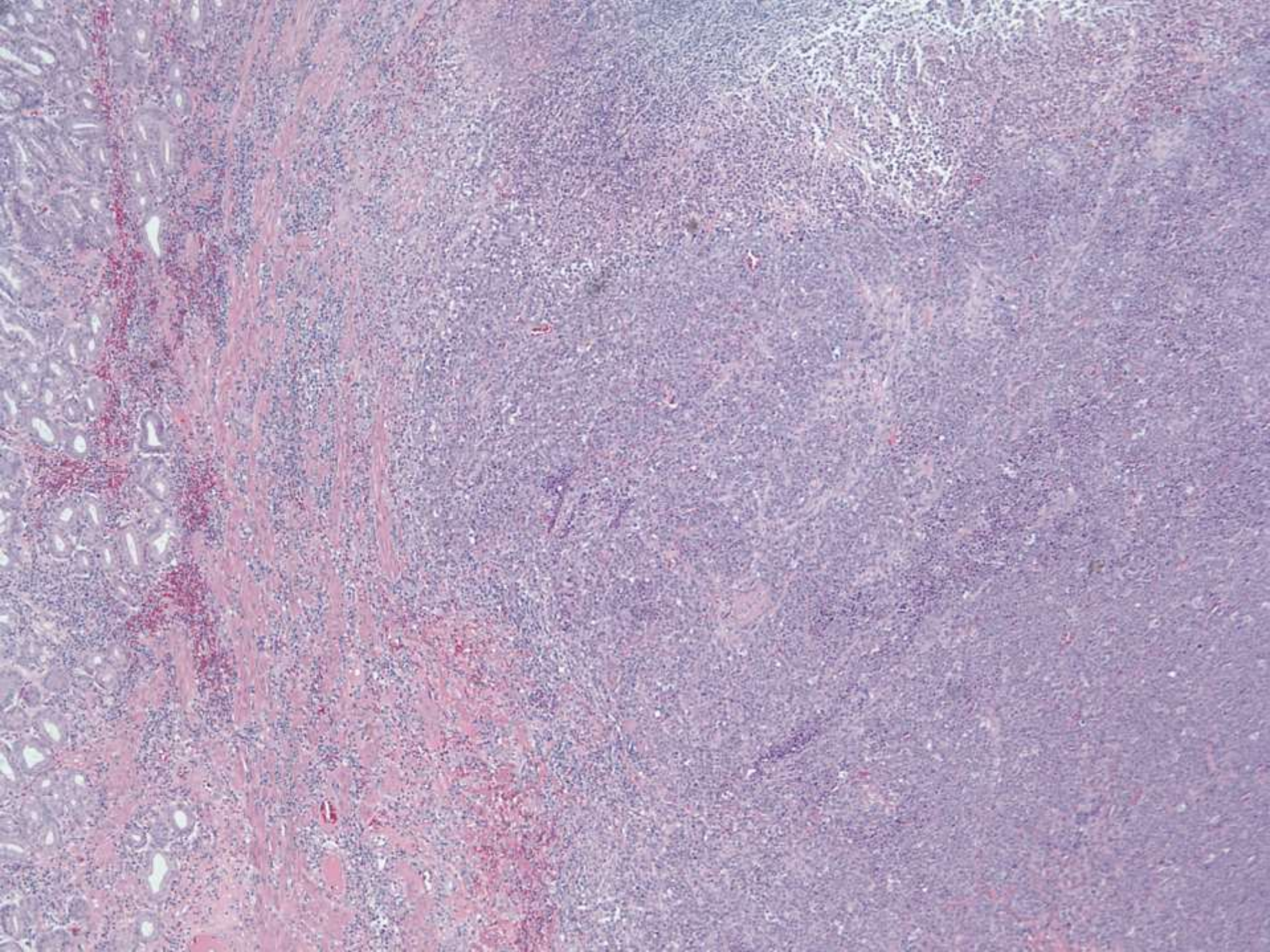

Questions?

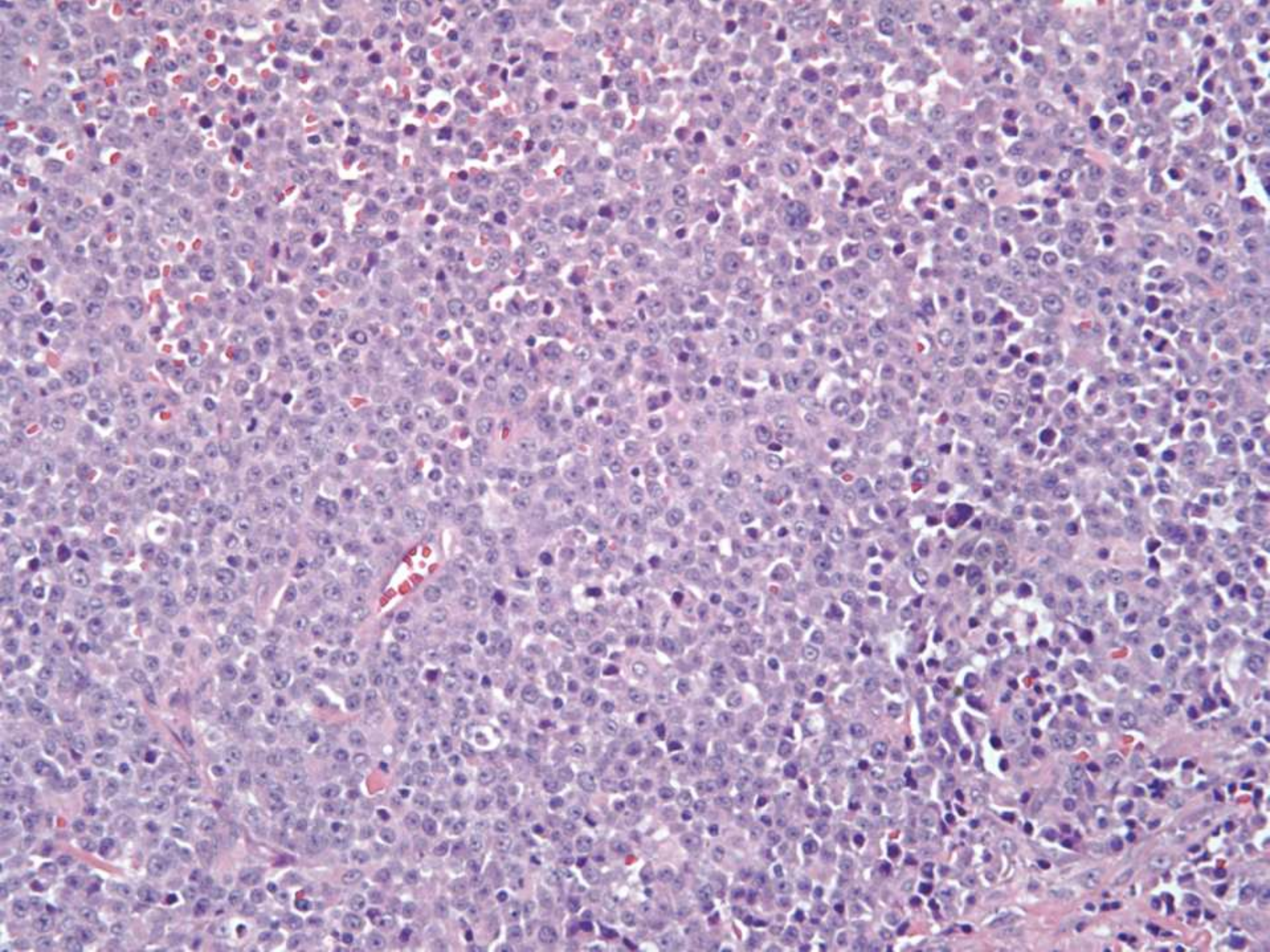
SB 5978

- 76-year-old man with a 9cm stomach mass.

- **Adam Gomez/Teri Longacre; Stanford**







Diagnosis……??

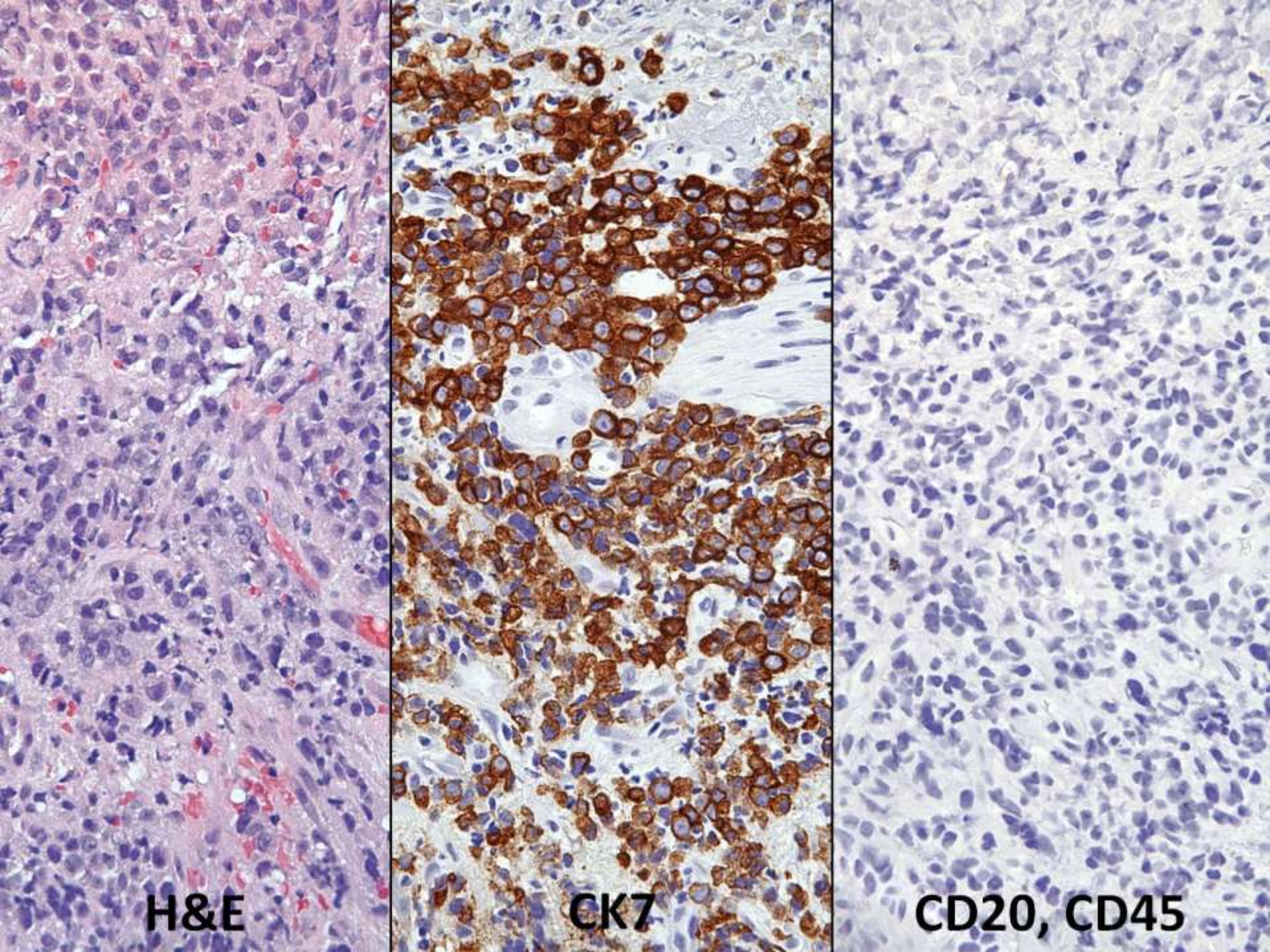
SB 5978

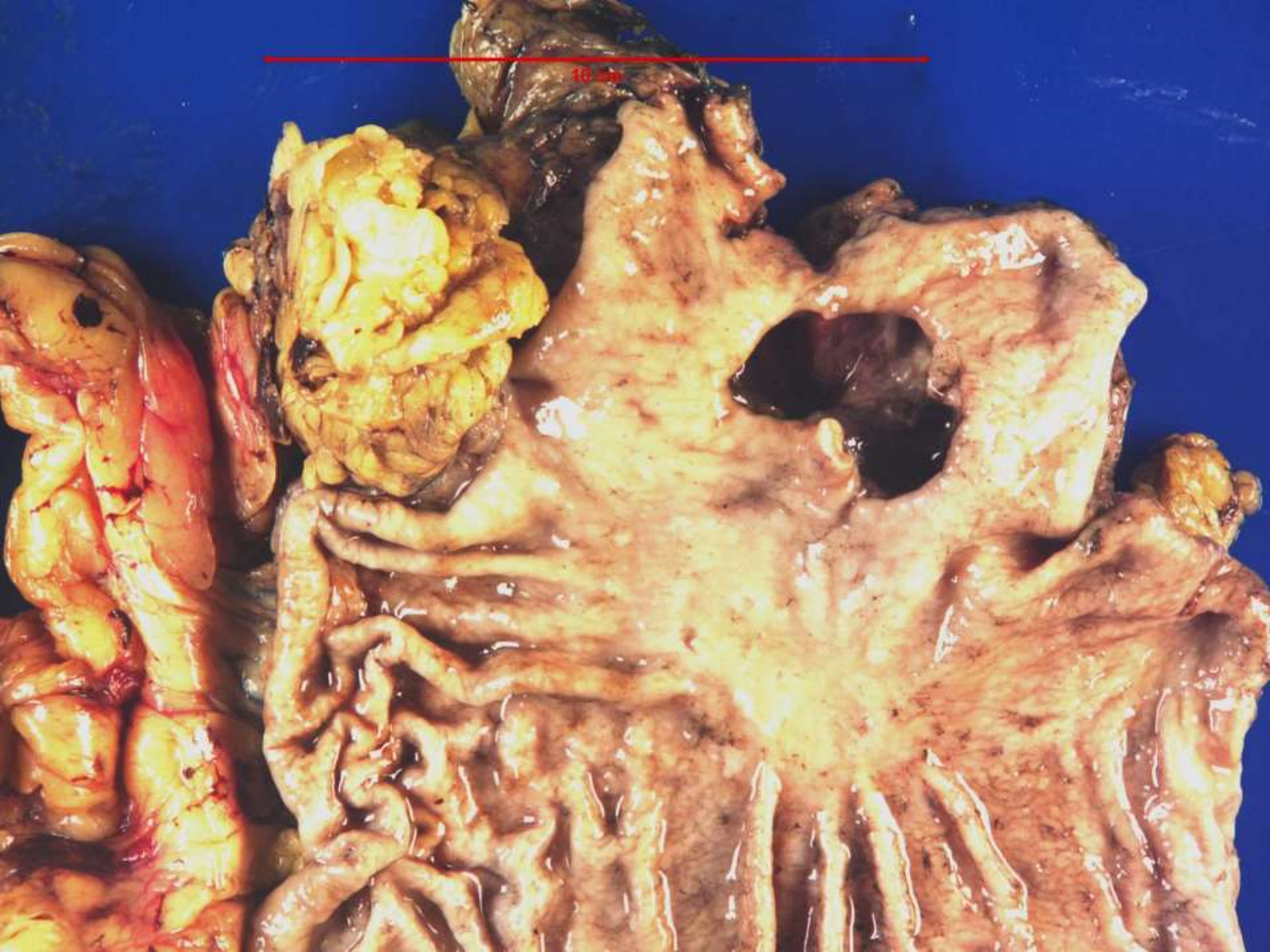
- Differential diagnosis:
  - Poorly differentiated carcinoma
  - Lymphoma
  - Melanoma

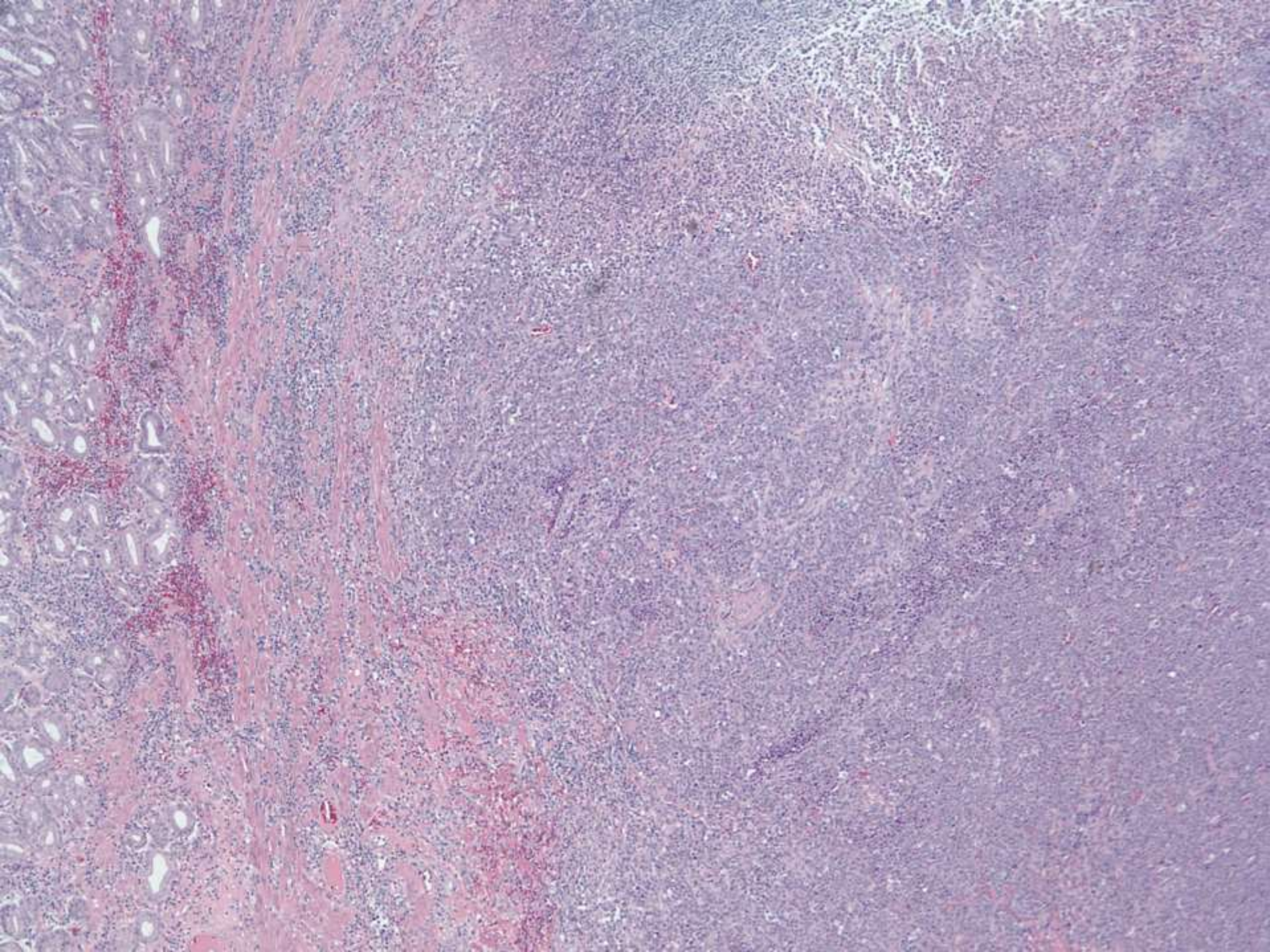
SB 5978

- 76-year-old man with a 9cm stomach mass.

- Additional history…
  - OSH (3 years prior): colonic moderate-to-poorly differentiated carcinoma, s/p APR
  - EGD & CT (3 months prior): gastric mass with ulcer
  - Biopsy (1 month prior)


H&E
CK7
CD20, CD45





SB 5978

WHO classification of Gastric Adenocarcinoma

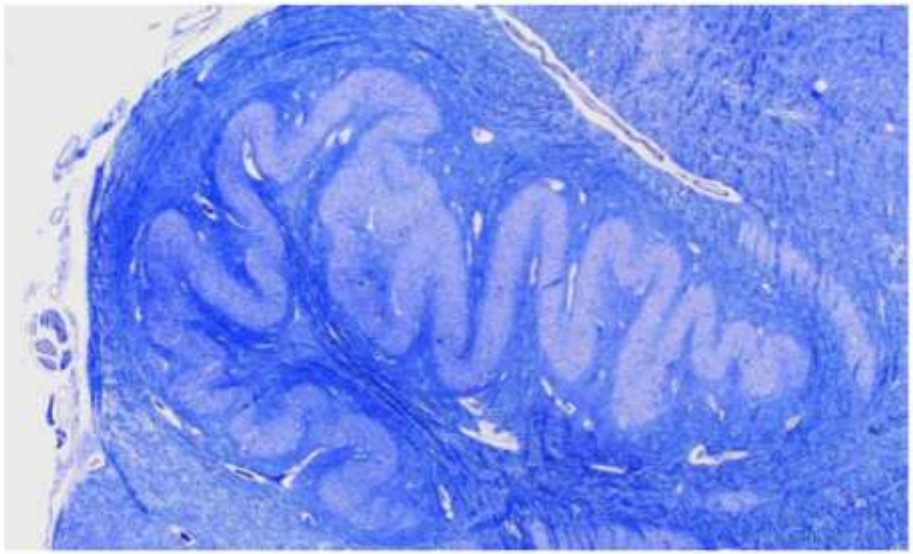
- Tubular
  - Tubules and acini
  - Becomes solid if poorly differentiated
- Papillary
  - Fibrovascular stalks
- Mucinous
  - >50% of tumor is mucin
- Poorly cohesive
  - Includes signet ring
    - >50% of carcinoma is composed of signet ring cells
- Mixed
- Other types
  - Adenosquamous
  - **Carcinoma with lymphoid stroma (medullary carcinoma)**
  - Hepatoid carcinoma
  - Squamous carcinoma
  - Undifferentiated carcinoma

http://surgpathcriteria.stanford.edu/gitumors/gastric-adenocarcinoma/

SB 5978

Gastric carcinoma with lymphoid stroma (GCLS)

- "Medullary carcinoma"
- "Lymphoepithelioma-like carcinoma"
- 1-4% of all gastric carcinomas



Chetty J Clin Pathol 2012

SB 5978

Gastric carcinoma with lymphoid stroma (GCLS)

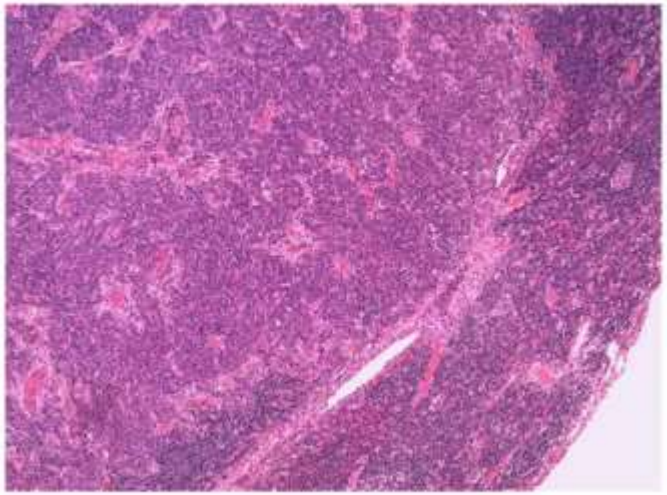
- **>80% associated with EBV**
  - Frequent loss of 4p, 11p, 18q
  - CpG island methlyator phenotype

**In contrast to Burkitt's lymphoma and nasopharyngeal carcinoma, which are endemic in equatorial Africa and Southeast Asia, respectively, EBV positive gastric carcinoma is a non-endemic disease distributed throughout the world.*

Takada Mol Pathol 2000

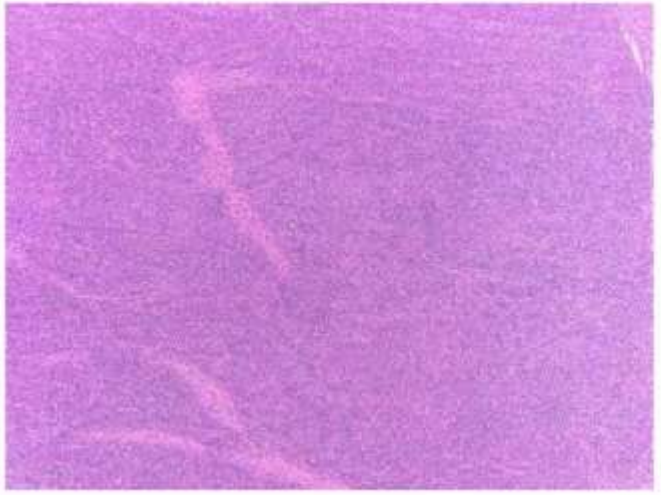
Park et al J Surg Res 2015

Gastric carcinoma with lymphoid stroma (GCLS)



MSI-High Medullary Gastric Carcinoma

- Large cells arranged in a diffuse syncytial sheet
- Edge of the tumor is well defined and regular
- Lymphocytes at the periphery of the tumor
- Scattered intra-tumoral lymphocytes
- Cardia, mid-stomach

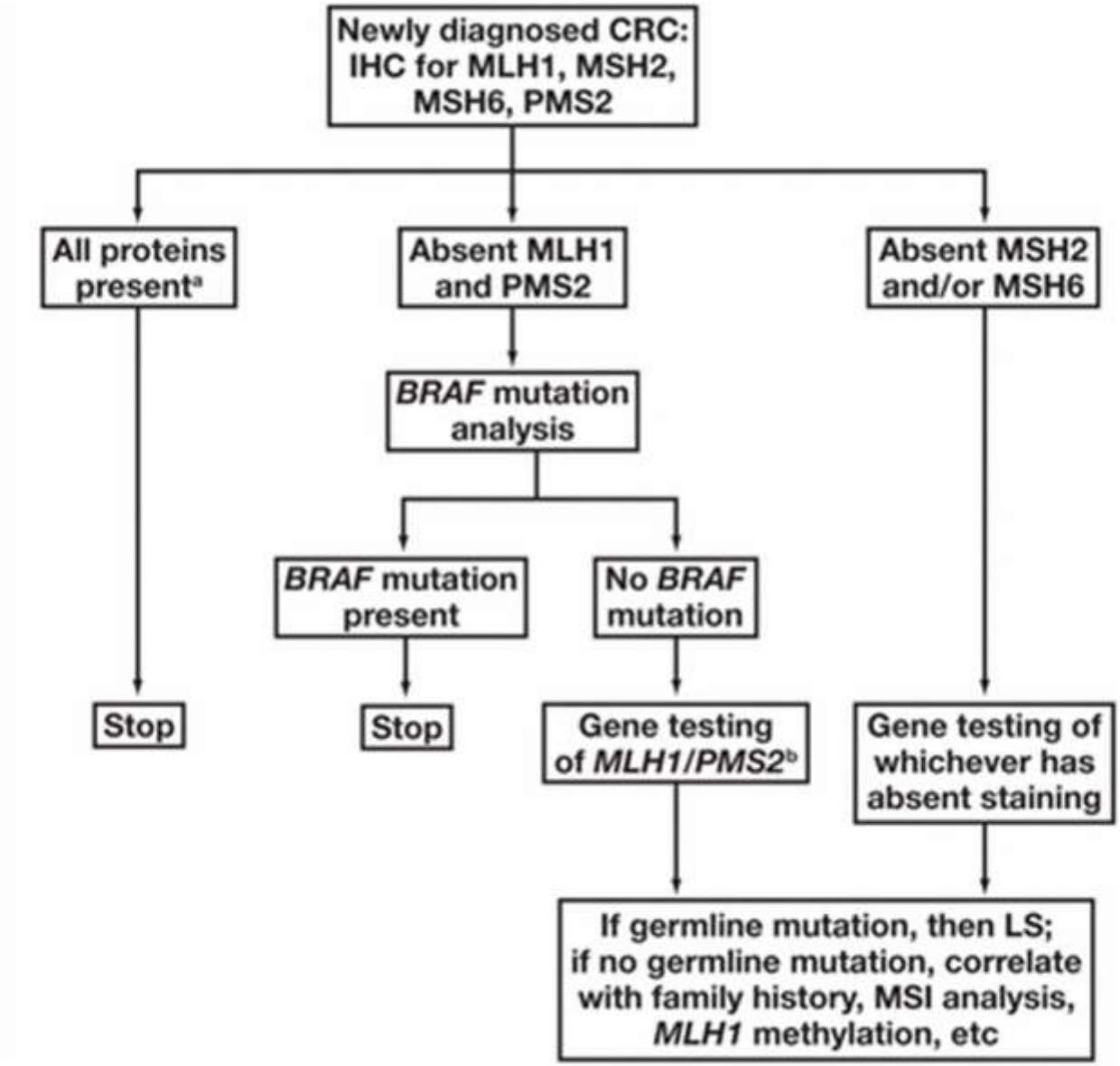


EBV+ Lymphoepithelioma-like Gastric Carcinoma

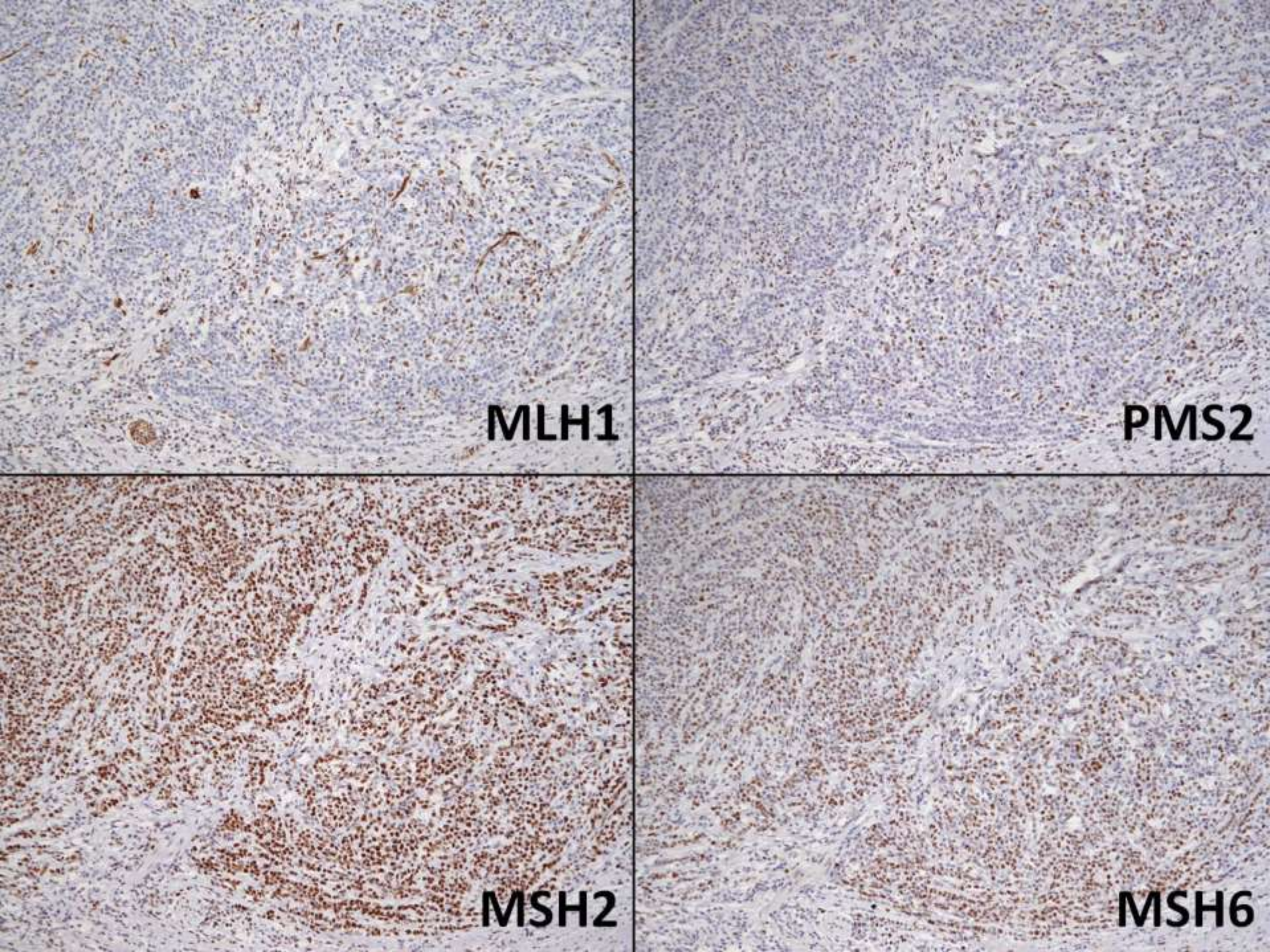
- Single cells, small clusters or nests of tumor
- Edge of the tumor is infiltrative and irregular
- Pervasive intra-tumoral lymphoid response
- Antrum

Chetty J Clin Pathol 2012

Bittar et al Diagn Pathol 2013



Jin et al Am J Clin Pathol 2013


MLH1
PMS2
MSH2
MSH6

SB 5978

IHC:

- CK7+, CD20-
- Loss of MLH1 and PMS2 (MSH2, MSH6 intact)

EBV ISH: negative

Allele-specific PCR:

- Negative for BRAF 1799T>A(V600E) mutation

SB 5978

Diagnosis:

INVASIVE HIGH GRADE CARCINOMA, MEDULLARY TYPE

- Loss of expression for MLH1 and PMS2 with intact expression for MSH2 and MSH6.
- Negative for the BRAF 1799T>A (V600E) mutation.

Comment:

- The absence of a BRAF mutation provides no support for sporadic hypermethylation of the MLH1 promoter.
- Genetic counseling for possible Lynch syndrome is strongly recommended.

SB 5978

- Follow-up (1 year later):
  - Referral for genetic counseling
  - Repeat CT normal
  - Endoscopy normal

SB 5978

Gastric carcinoma with lymphoid stroma (GCLS)

1. May be associated with EBV (80%) or MSI-high (mutually exclusive)

2. Clinical/pathologic features indicative of EBV or MSI-high

3. EBV+ gastric carcinoma is non-endemic

References

- Takada K. Epstein-Barr virus and gastric carcinoma. Mol Pathol. 2000 October; 53(5): 255–261.

- Park S, Choi MG, Kim KM, Kim HS, Jung SH, Lee JH, Noh JH, Sohn TS, Bae JM, Kim S. Lymphoepithelioma-like carcinoma: a distinct type of gastric cancer. J Surg Res. 2015 Apr;194(2):458-63. doi: 10.1016/j.jss.2014.12.005. Epub 2014 Dec 8.

- Jin M, MD, PhD, et al. BRAF V600E Mutation Analysis Simplifies the Testing Algorithm for Lynch Syndrome. 2013 American Journal of Clinical Pathology, 140, 177-183.

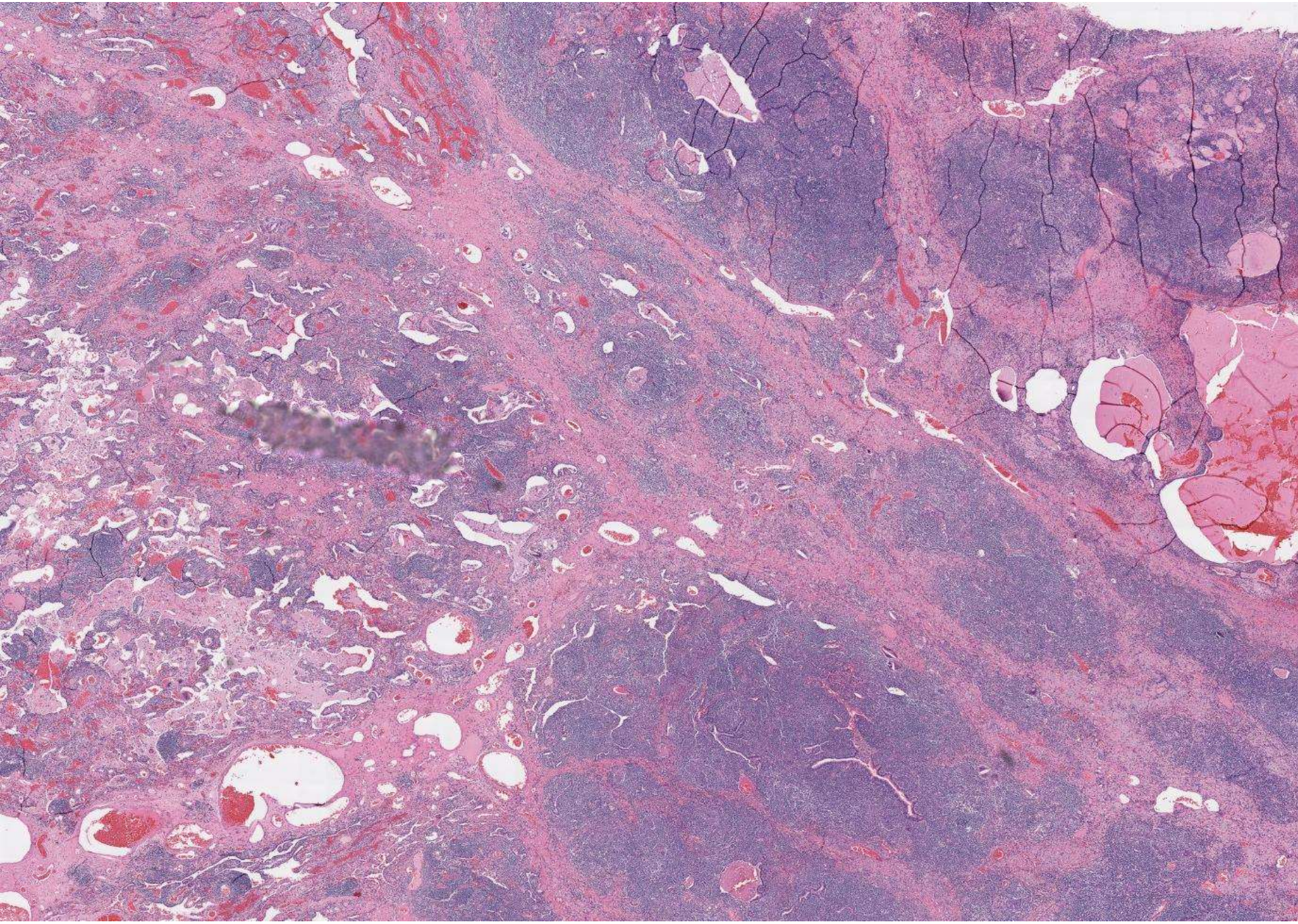
- Chetty R. Gastrointestinal cancers accompanied by a dense lymphoid component: an overview with special reference to gastric and colonic medullary and lymphoepithelioma-like carcinomas. J Clin Pathol. 2012 Dec;65(12):1062-5. doi: 10.1136/jclinpath-2012-201067. Epub 2012 Aug 22. Review.

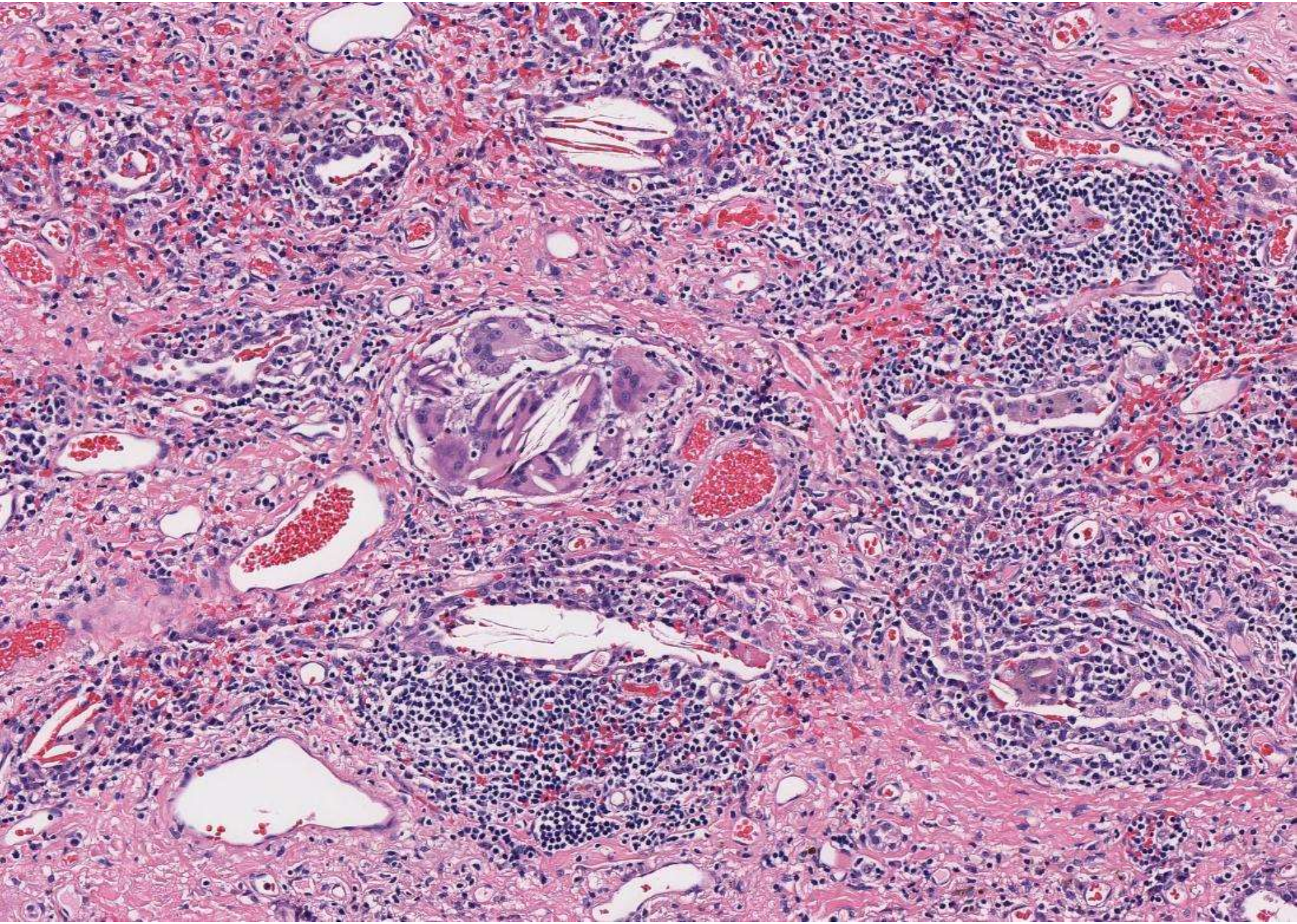
- Bittar Z, Fend F, Quintanilla-Martinez L. Lymphoepithelioma-like carcinoma of the stomach: a case report and review of the literature. Diagn Pathol. 2013 Nov 4;8:184. doi: 10.1186/1746-1596-8-184.

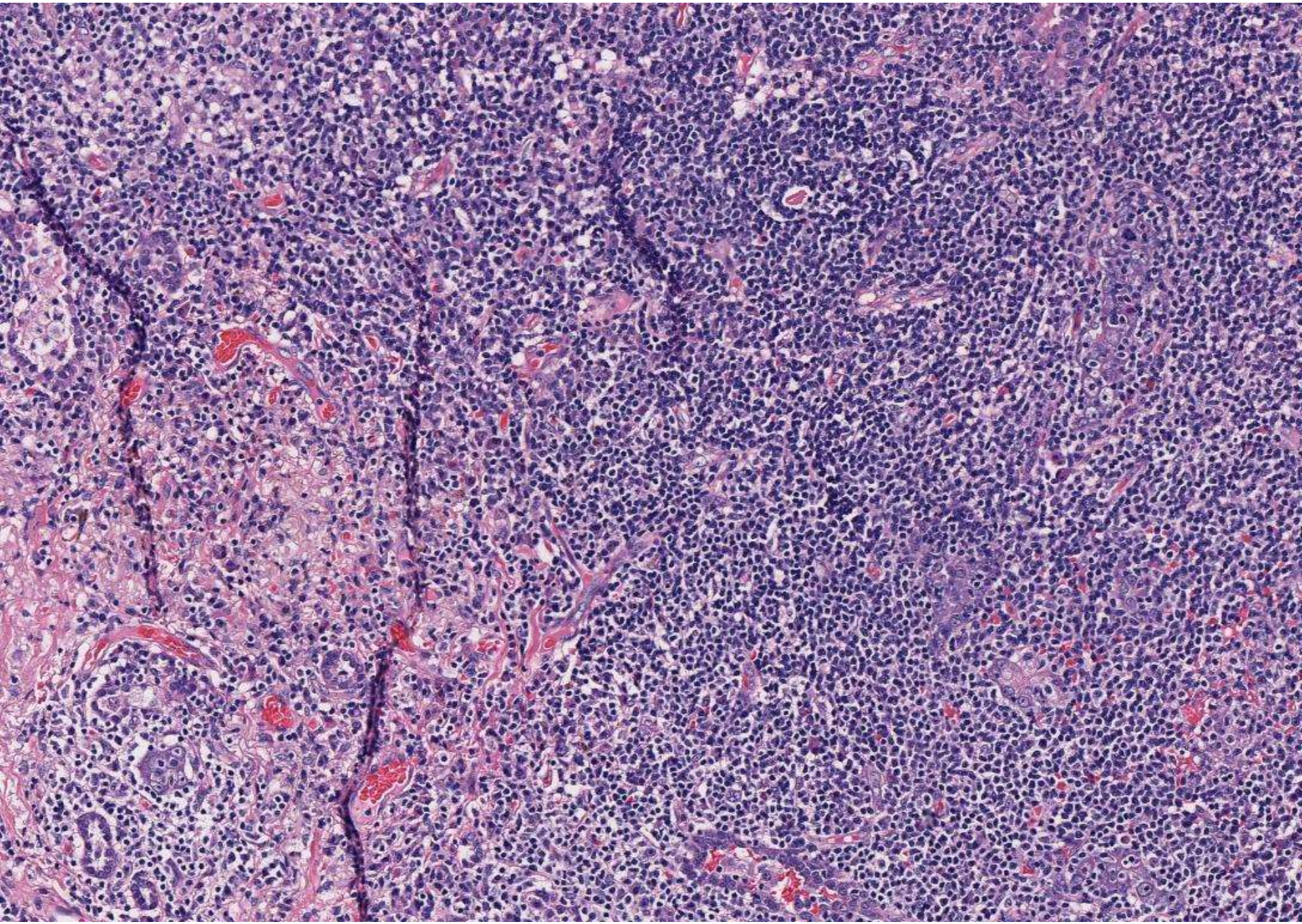
SB 5979

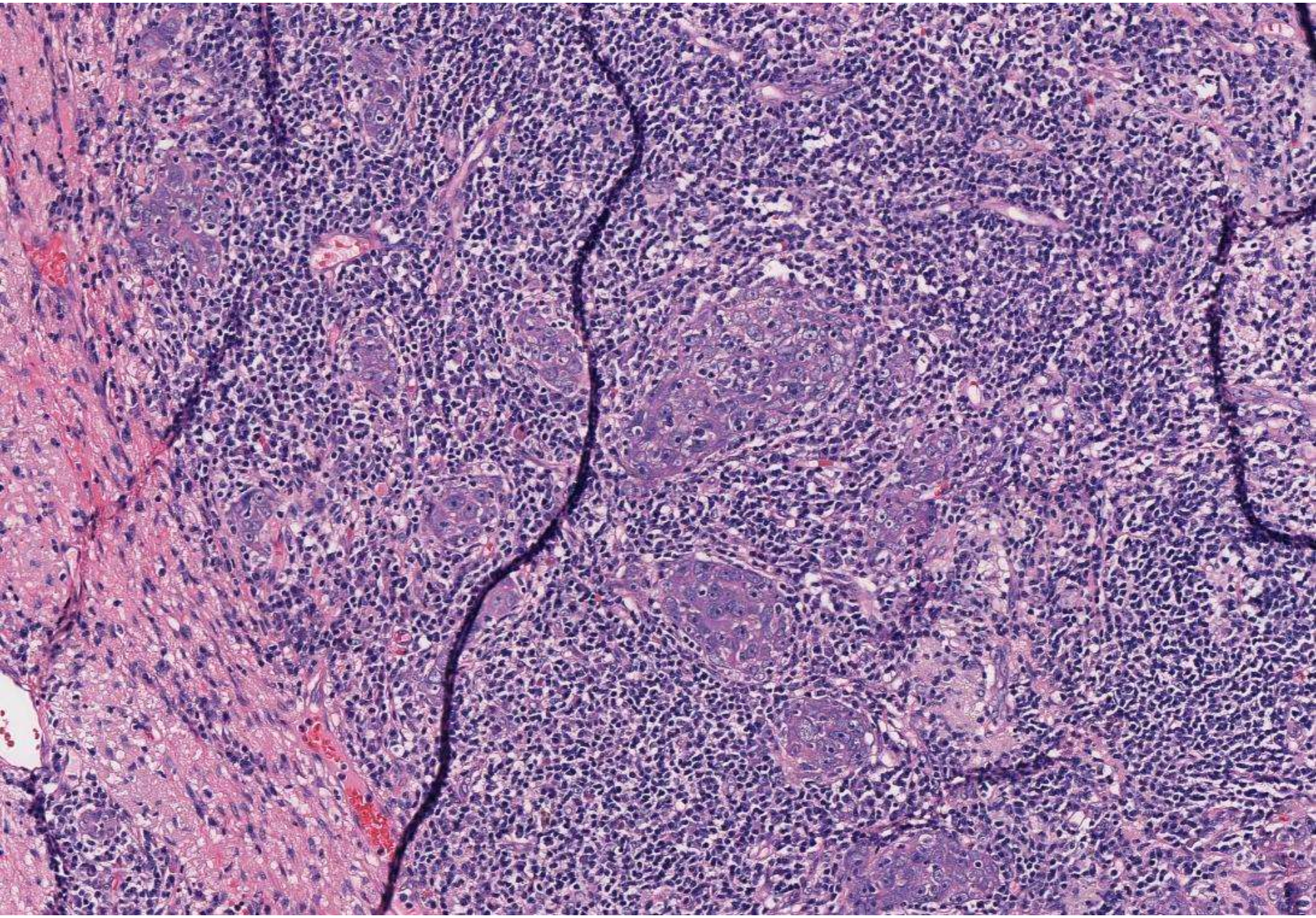
- 60-year-old Asian man, nonsmoker, with history of non-small cell carcinoma on a core biopsy. Status post chemotherapy. Left pneumonectomy performed.

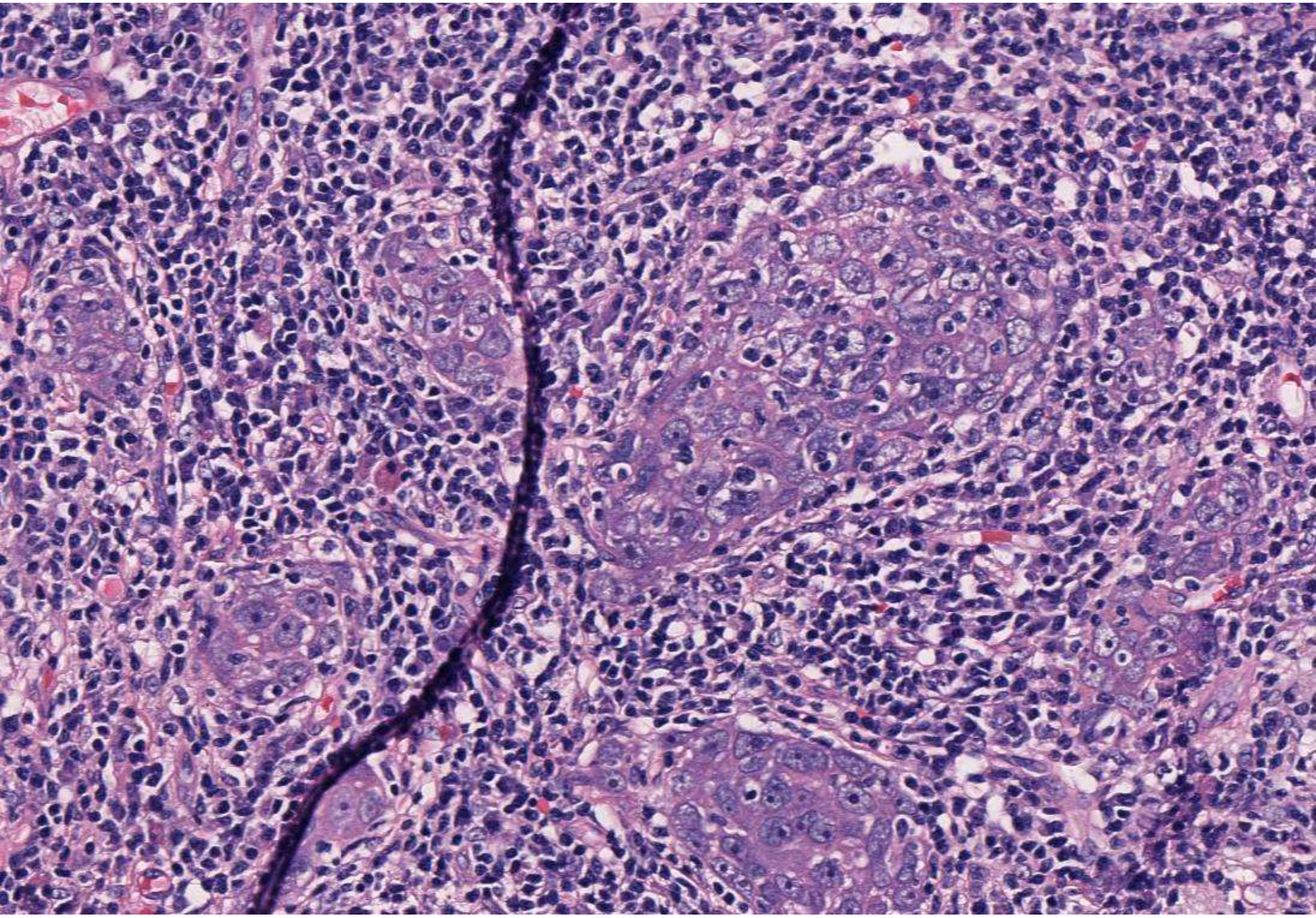
- **Mala Adhikari; Kaiser Santa Clara**



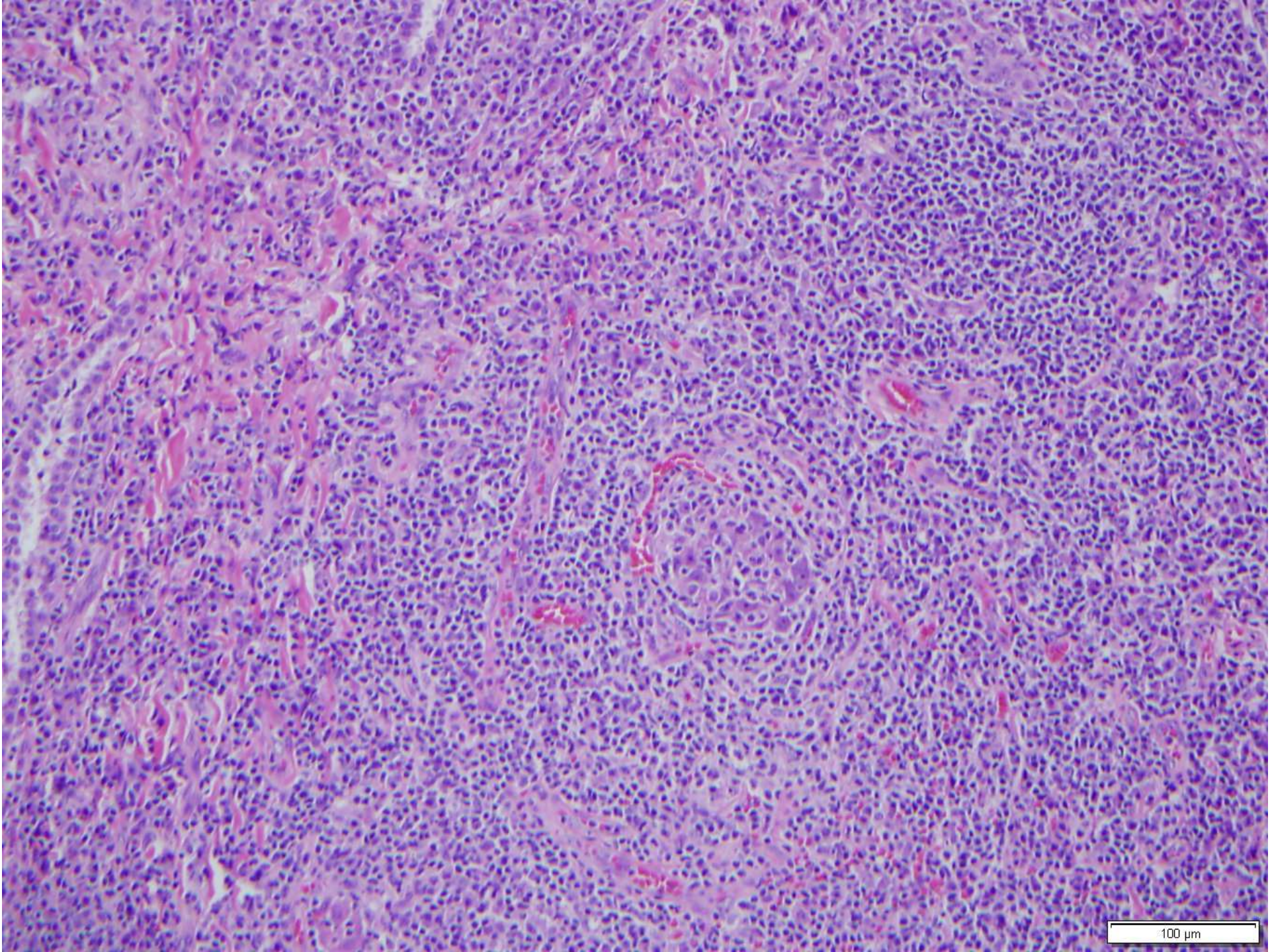


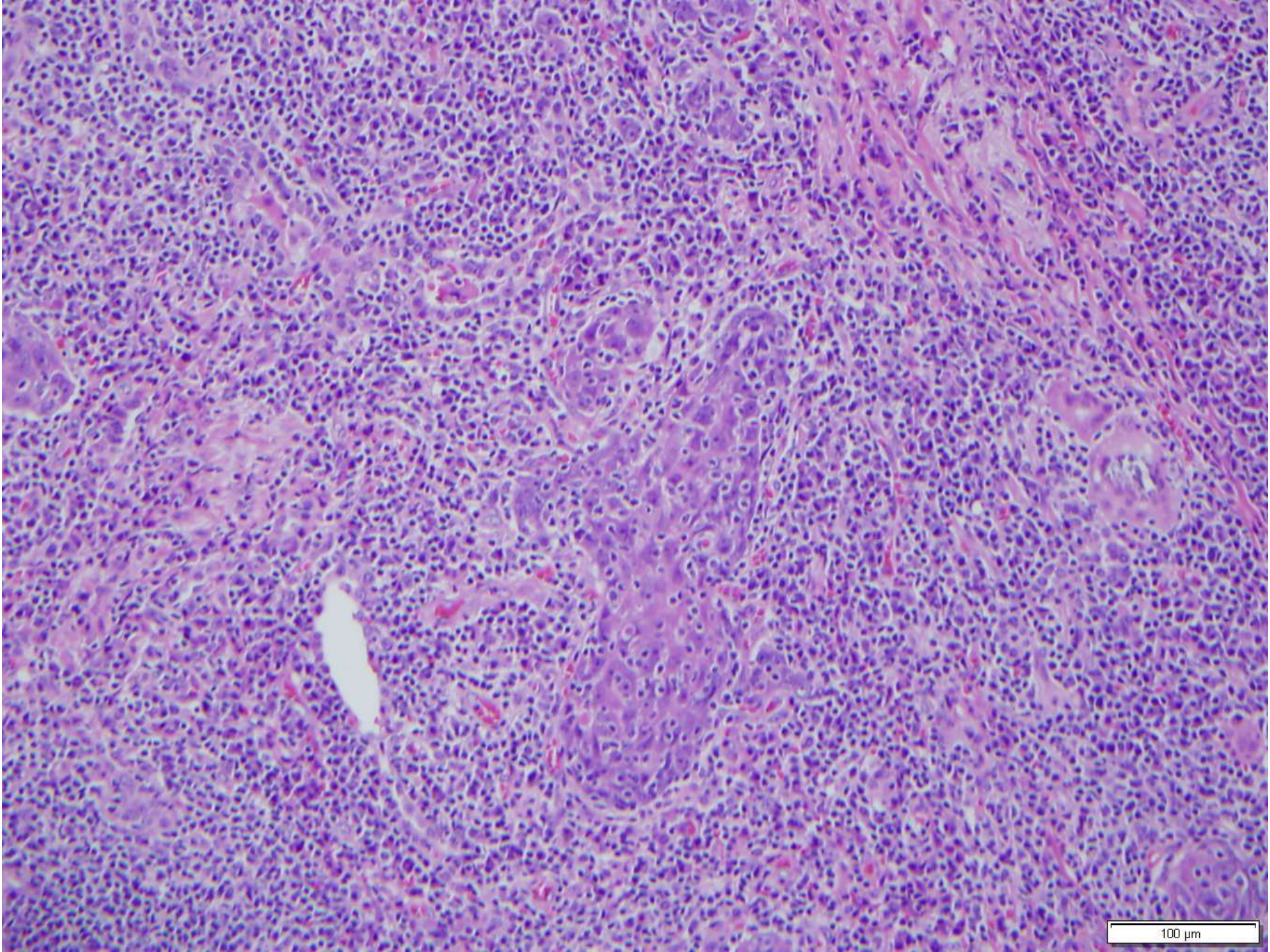


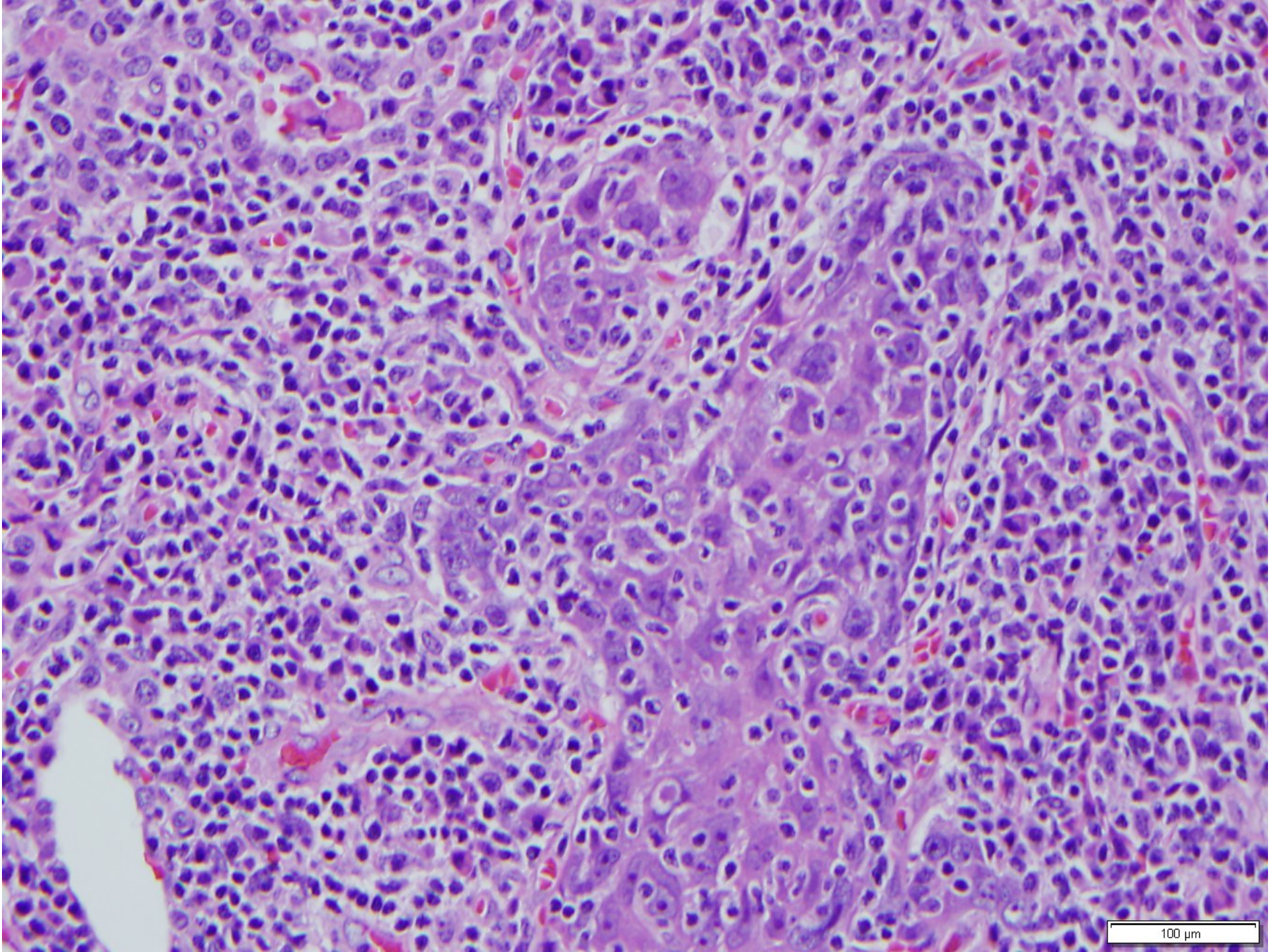


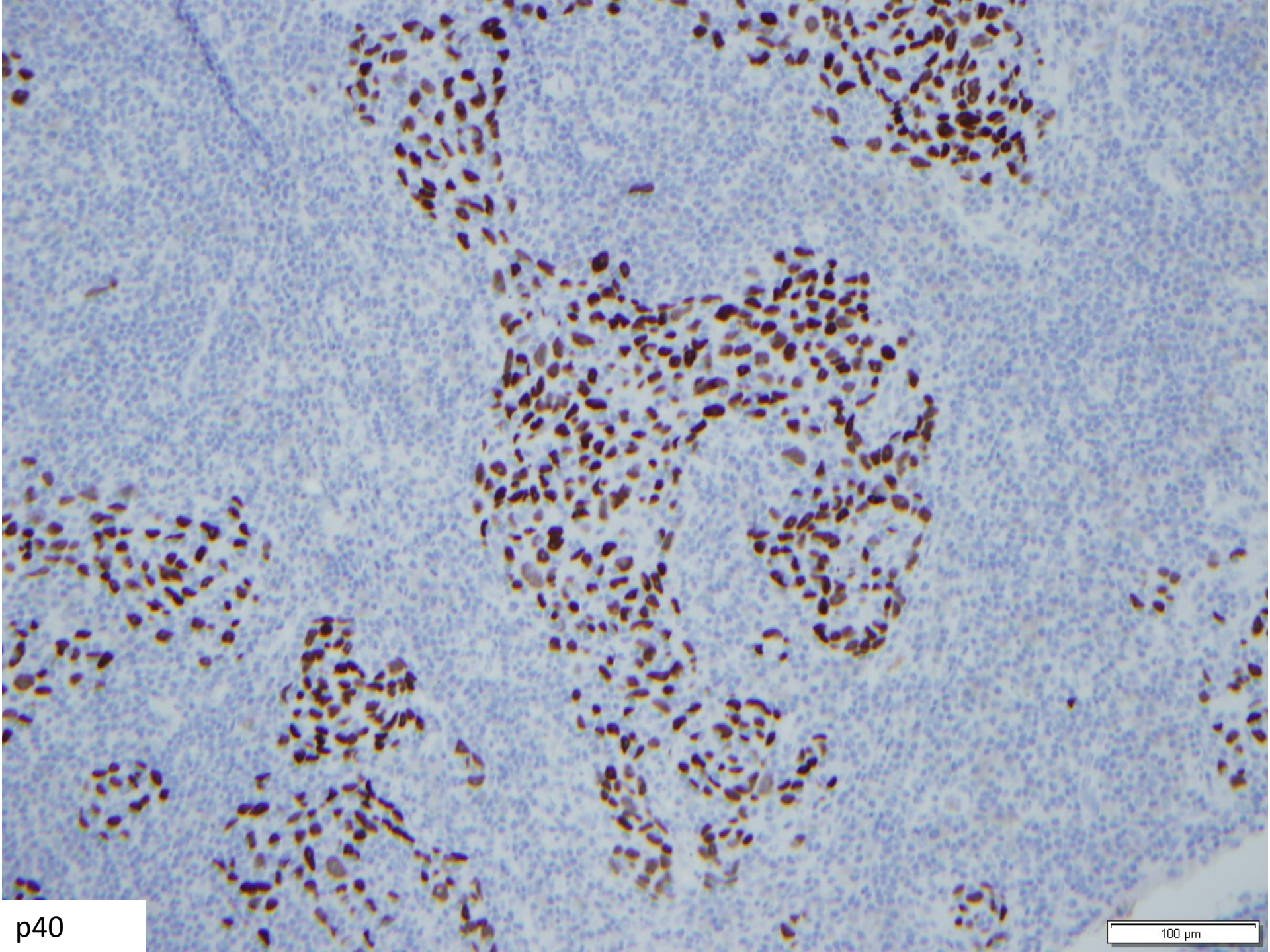


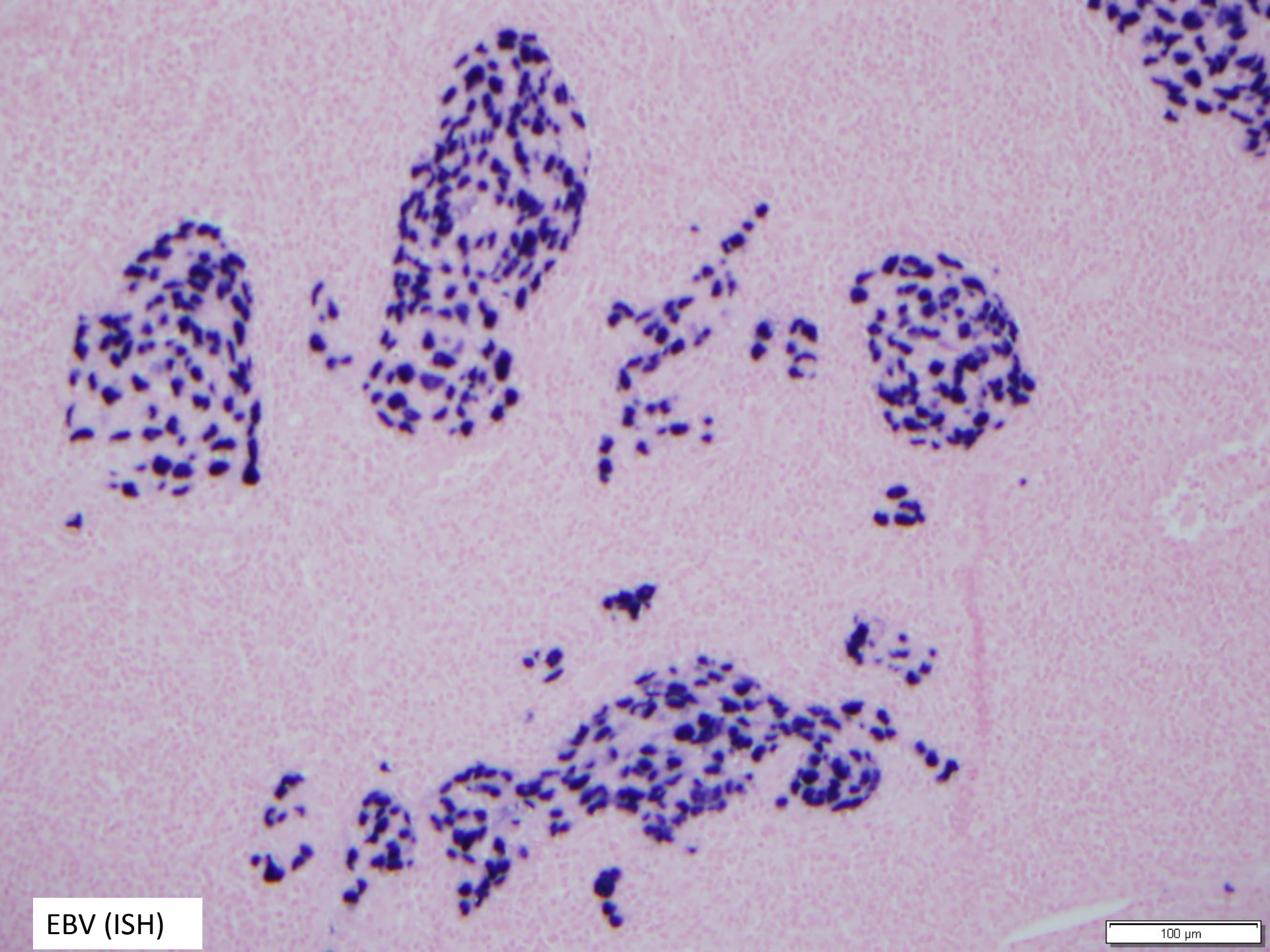
Diagnosis……??


100 µm


100 µm


100 µm


p40
100 µm


EBV (ISH)
100 µm

Primary Pulmonary Lymphoepithelioma-like carcinoma.

- Rare tumor with morphology similar to undifferentiated nasopharyngeal carcinoma, first reported in 1987 by Begin et al.
- Classified as a form of large cell carcinoma according to WHO classification.
- Mostly seen in Asians, younger, lower rate of cigarette smoking
- Highly variable behavior, some studies better prognosis compared to other types of NSCLC
- LELC reported in pharyngeal and foregut derivatives oral cavity, salivary glands, thymus, lungs, stomach, as also skin, liver, cervix, bladder, breast.

Pathology

- Solid nests of tumor cells with prominent nucleoli in syncytial arrangement surrounded by lymphocytic infiltrates.
- CK, CK5/6, p63, p40 expression.
- EBV (EBER by ISH) may or may not be positive (Western population)
- Differential diagnosis: metastatic nasopharyngeal carcinoma, inflammatory pseudotumor and non-Hodgkin Lymphoma.
- Frozen section: cells may be crushed, examine carefully for neoplastic cells.

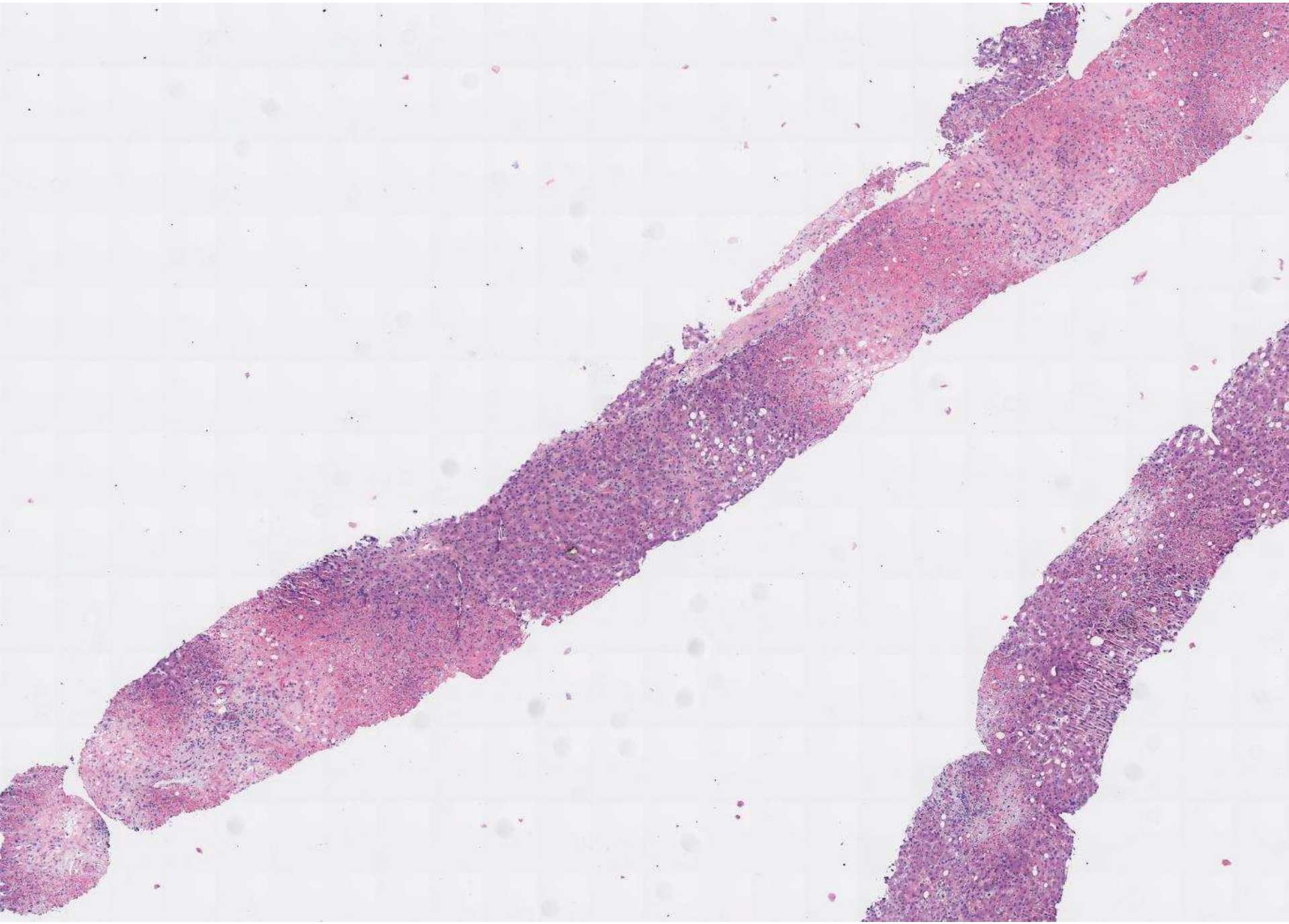
Treatment

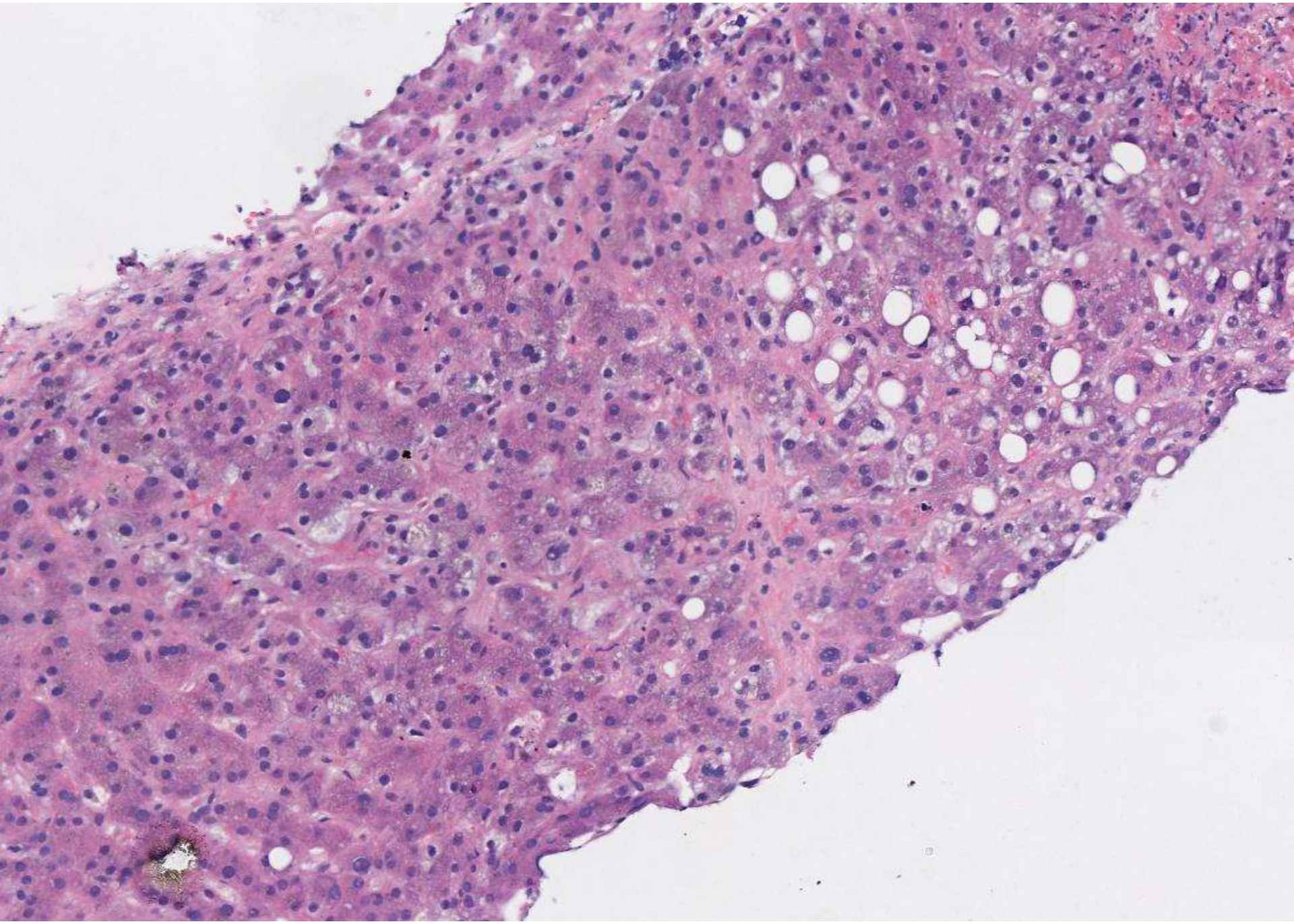
- Early stages: complete resection, locally advanced: multimodality treatment and metastatic disease; palliative chemotherapy.
- Biologic behavior similar to NPC.

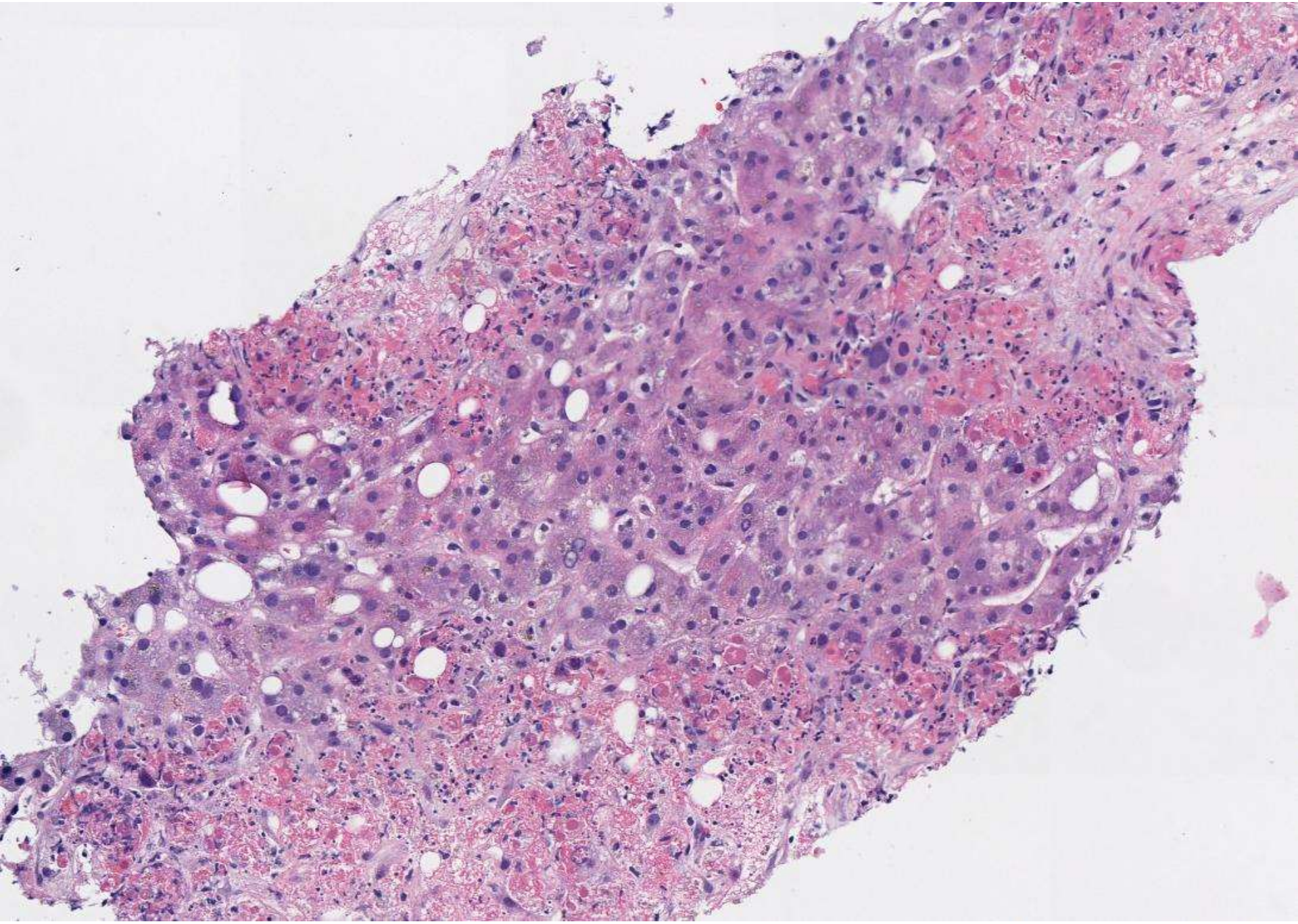
SB 5980

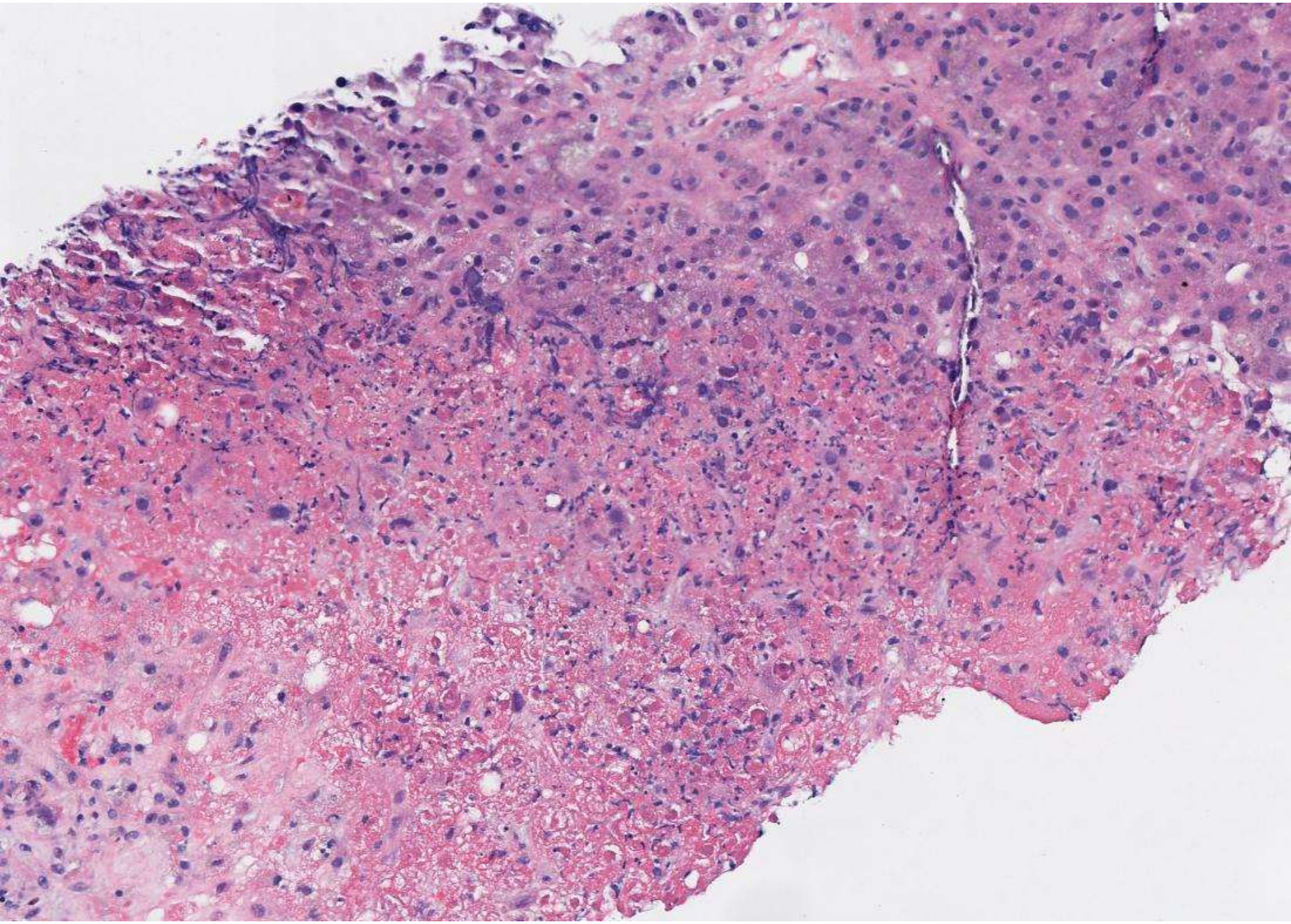
- 22-year-old man status post BMT for diffuse large B-cell lymphoma with liver biopsy.

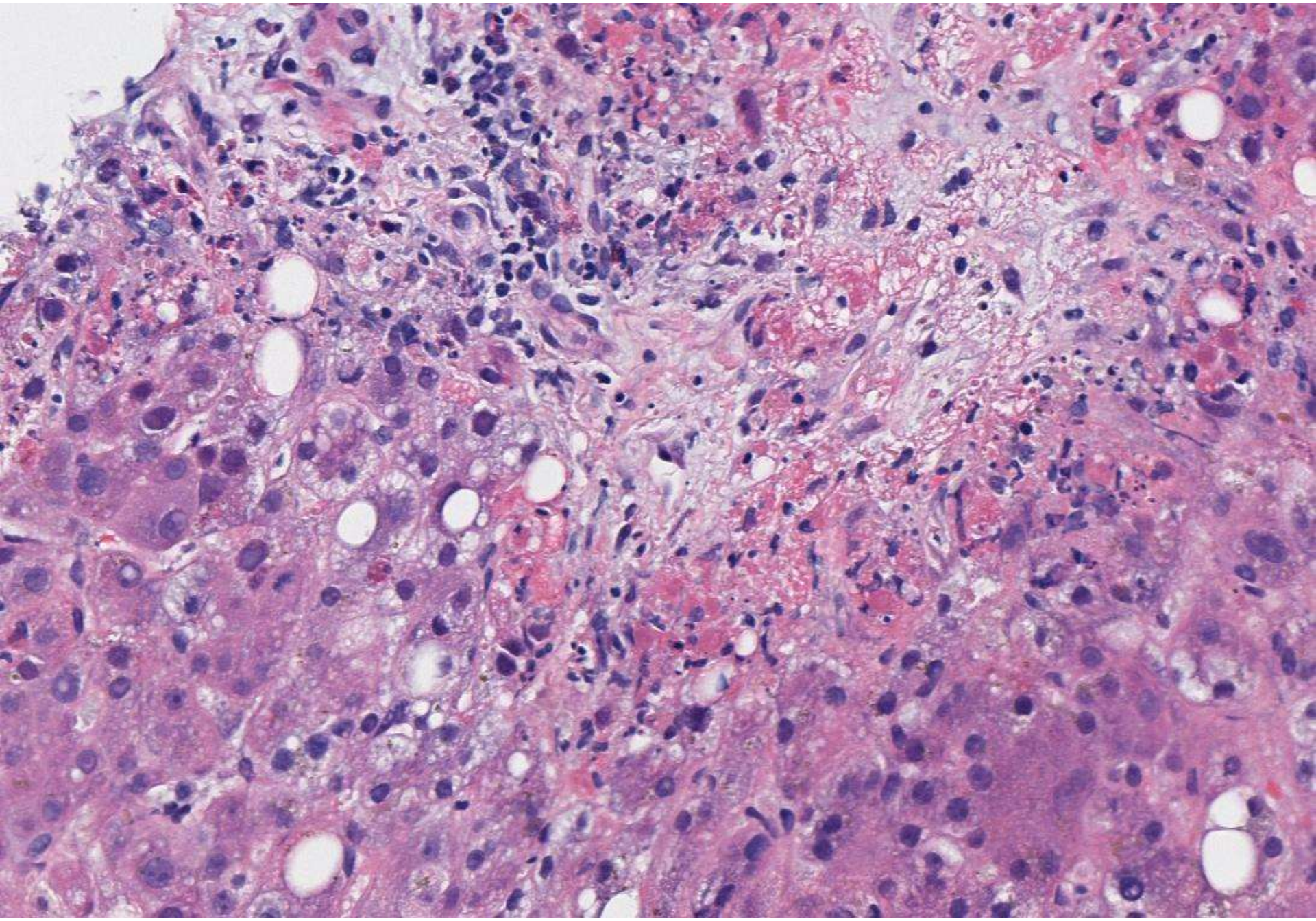
- **John Higgins; Stanford**

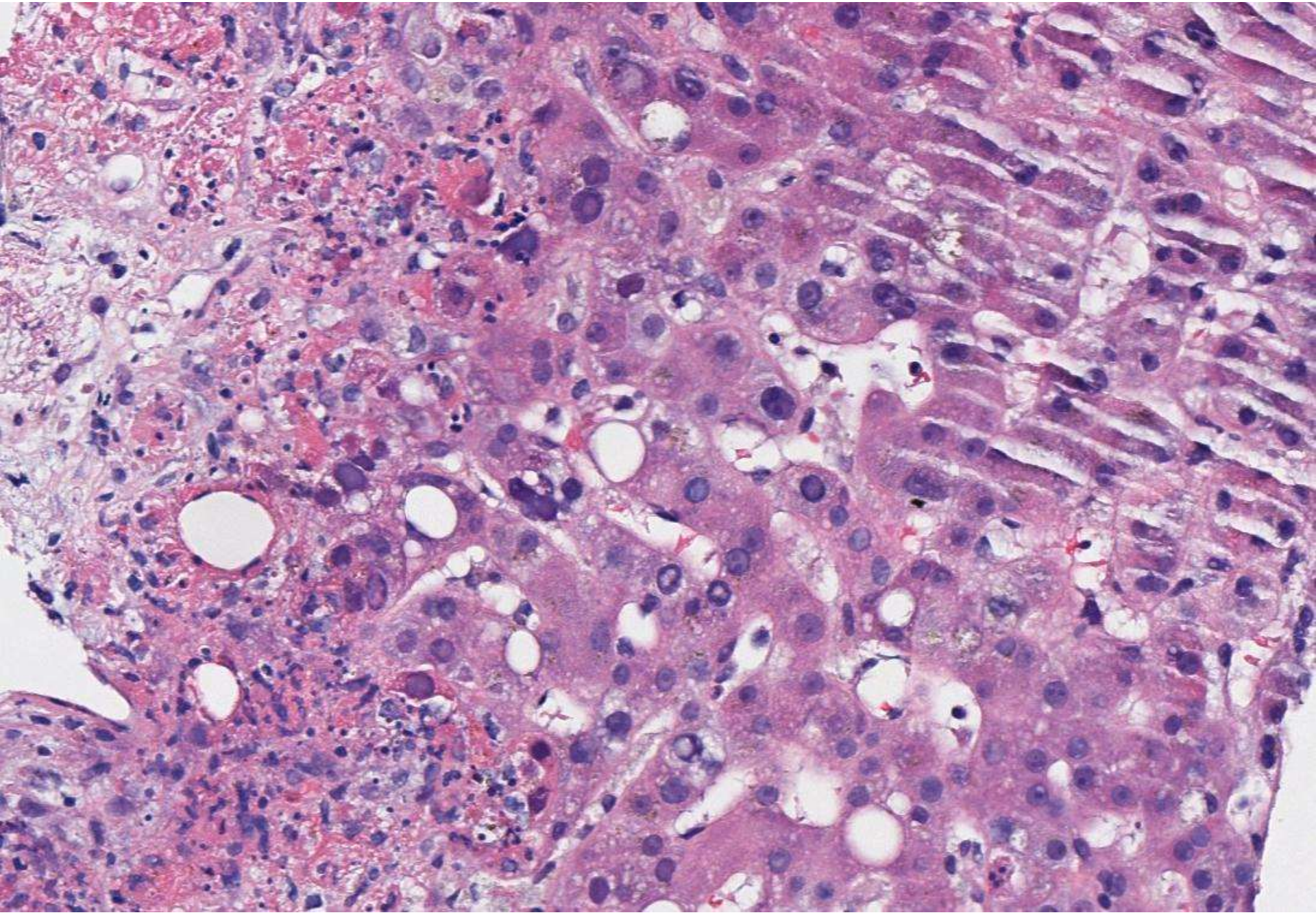


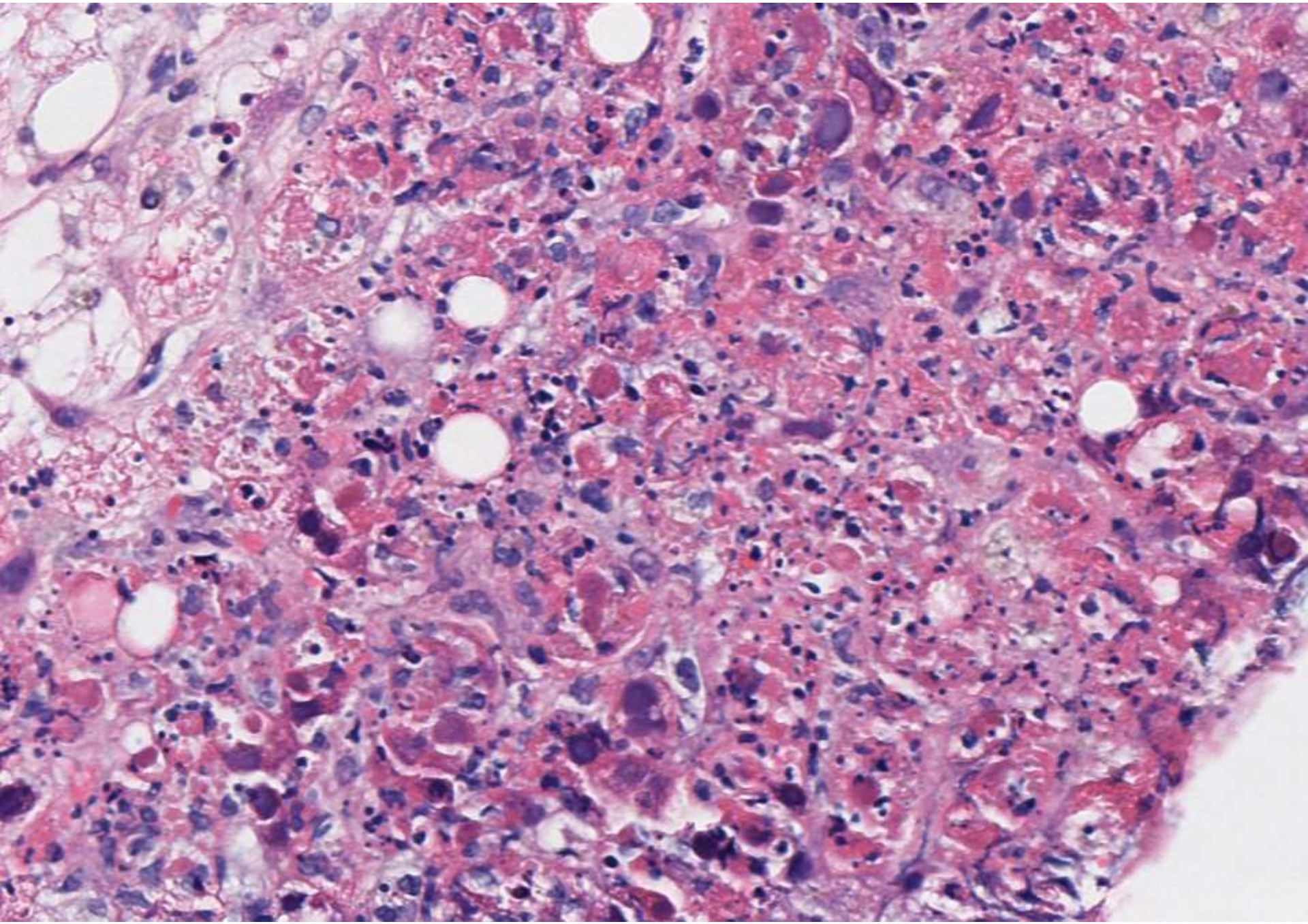








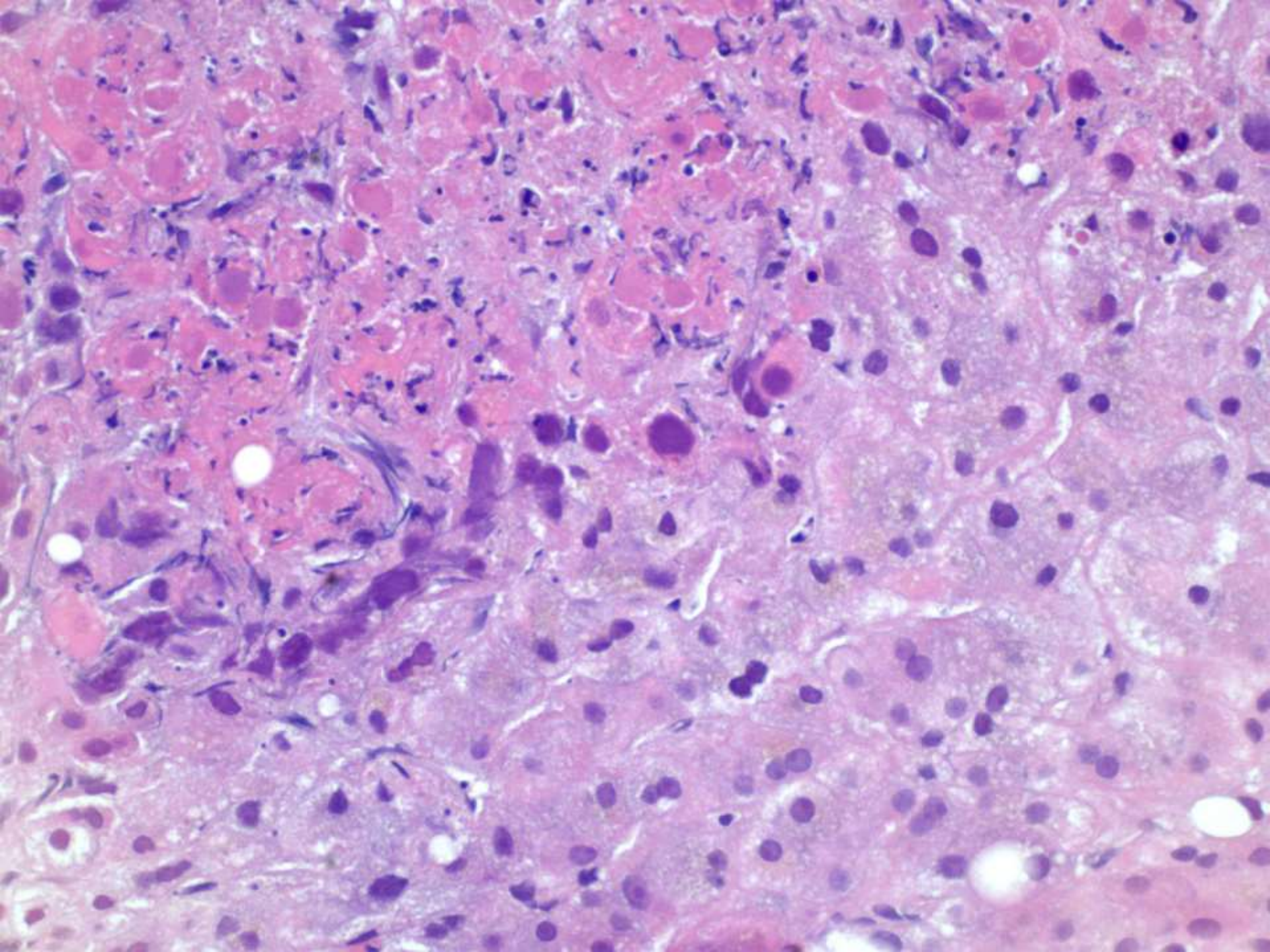


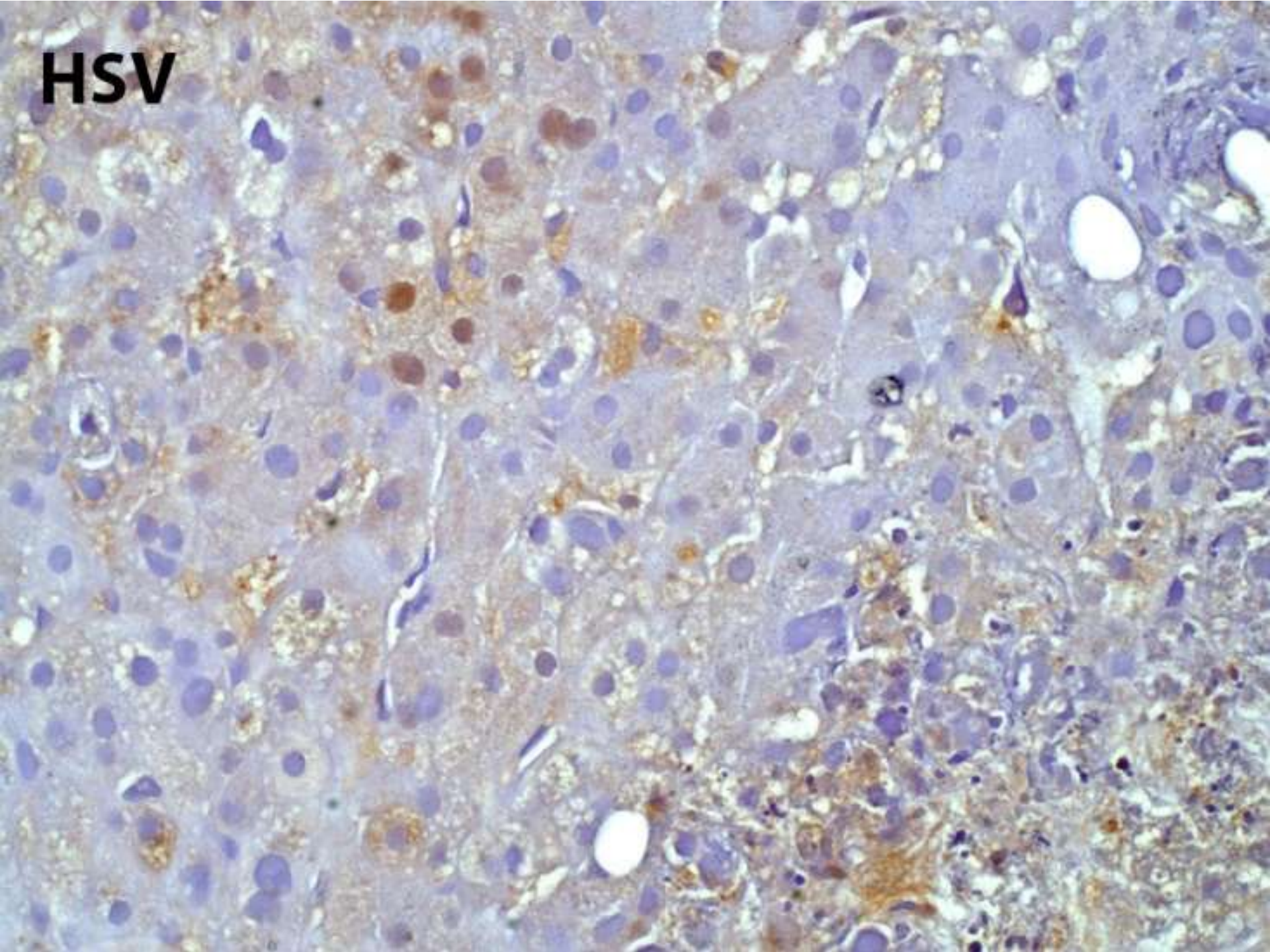


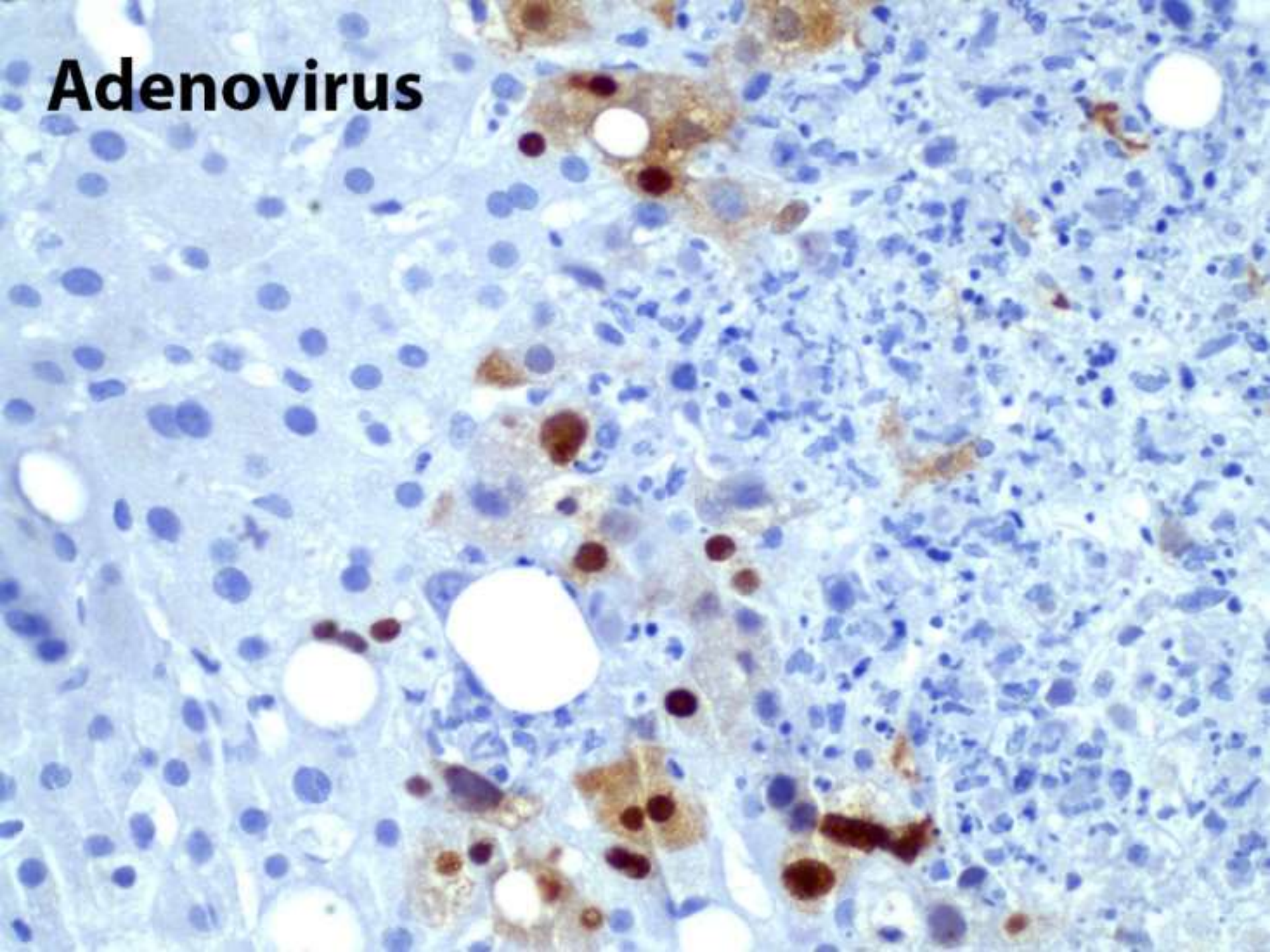
Diagnosis……??

Additional clinical history

- Recurrent High grade B cell lymphoma first diagnosed 18 months ago
- Recurred 11 months ago
- HSC 3 months ago
- Presented with hepatitis




HSV


Adenovirus

Follow-up

- Dead within 5 days