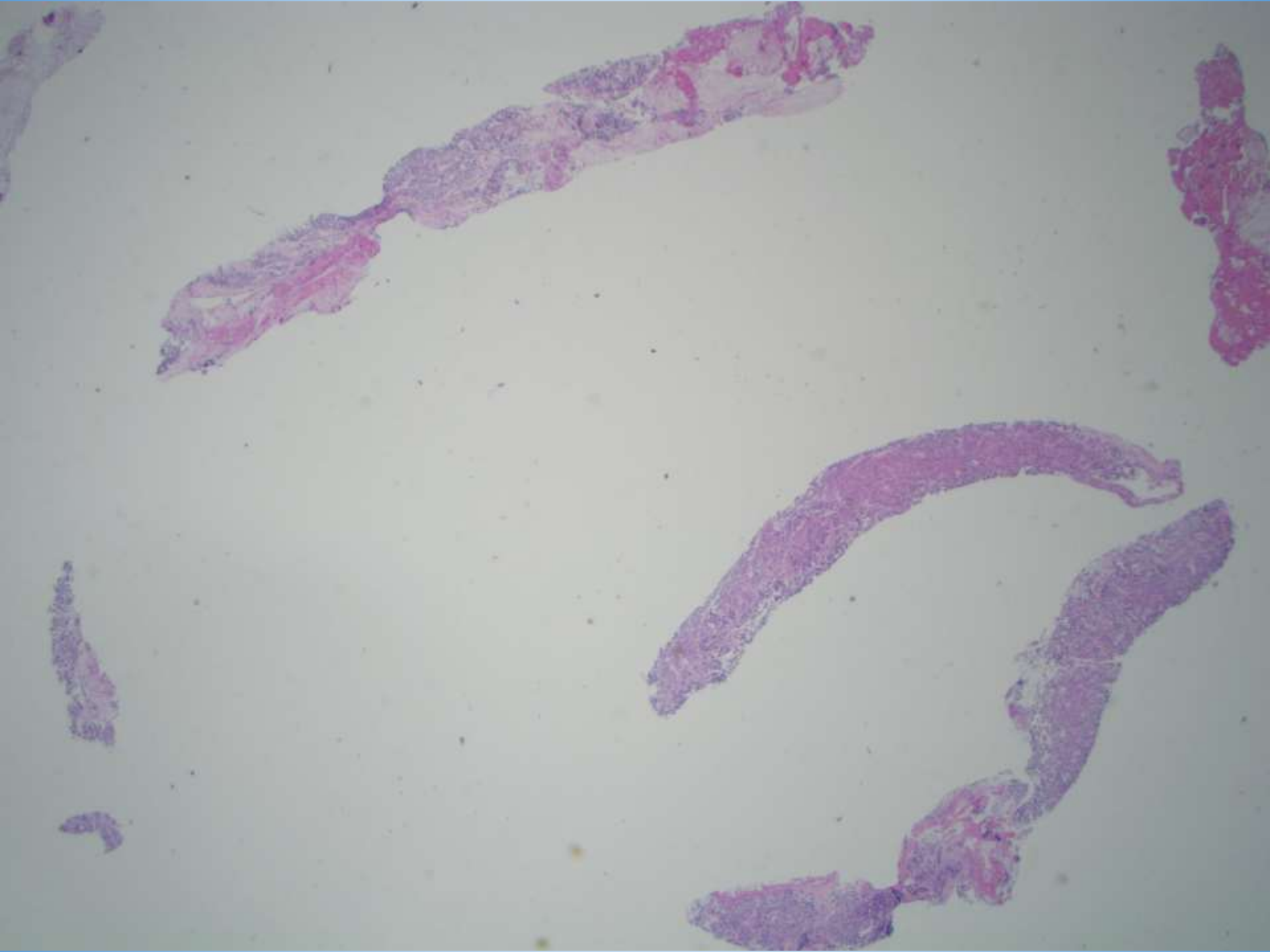
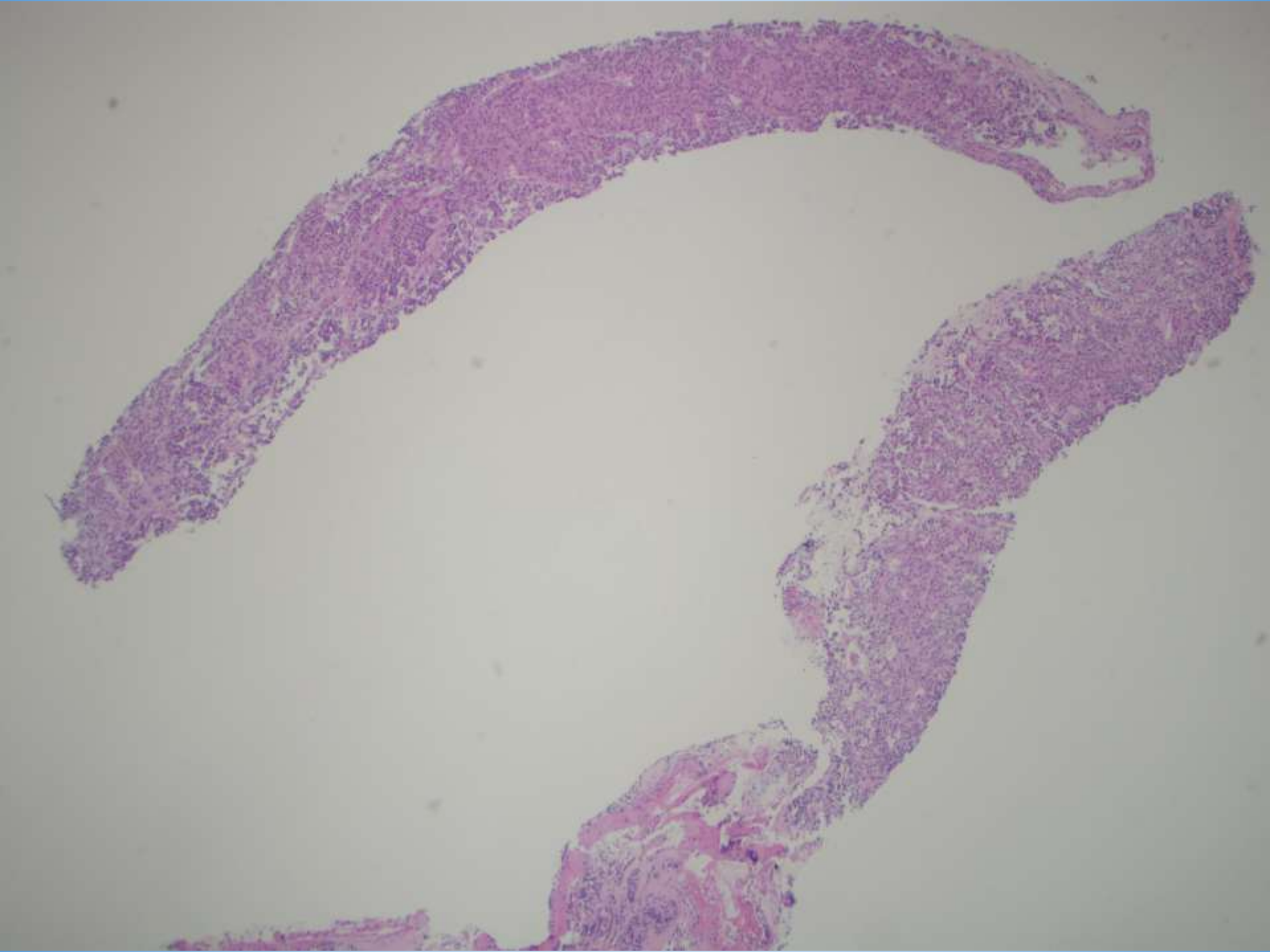
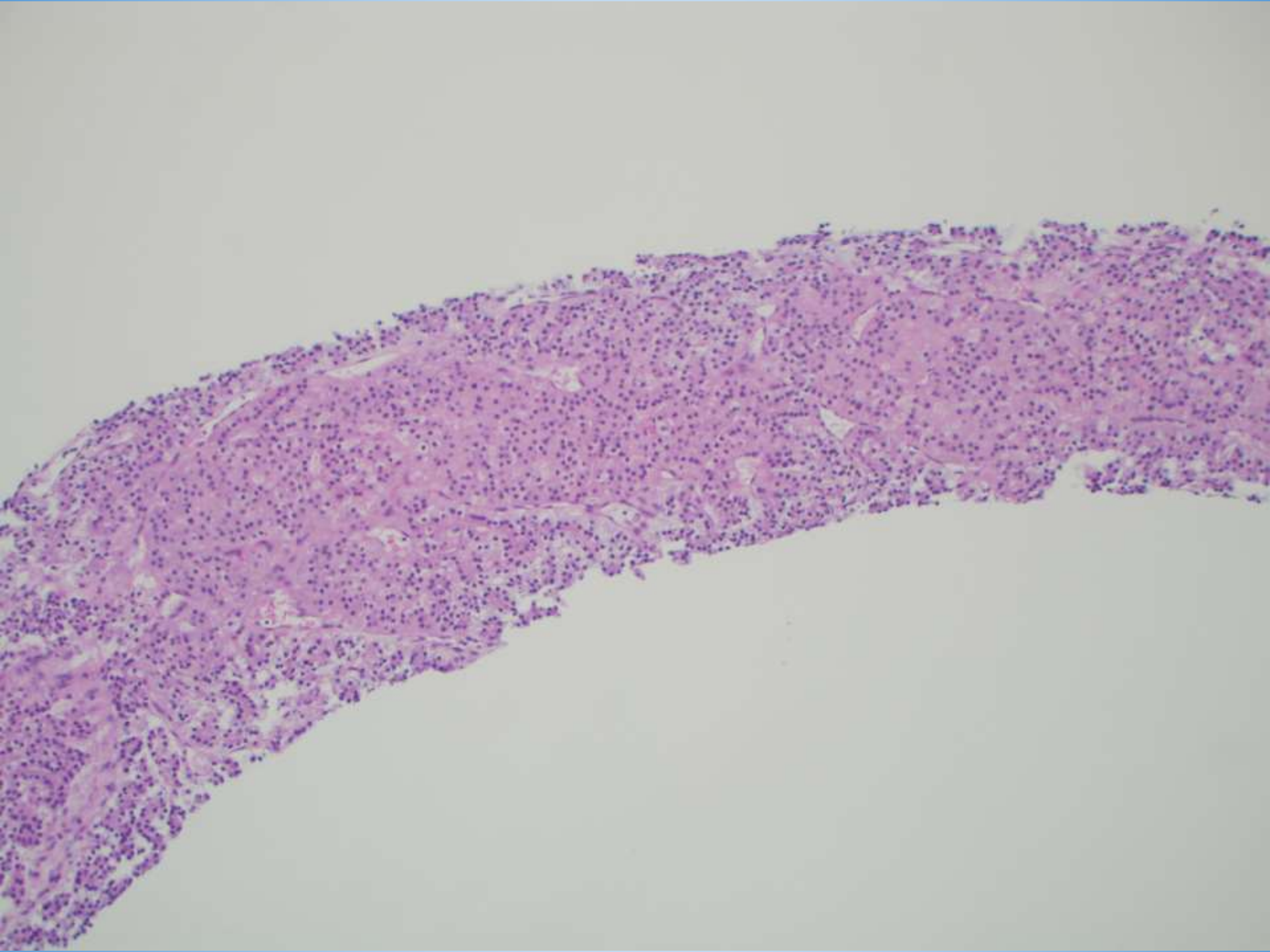
SB 6261

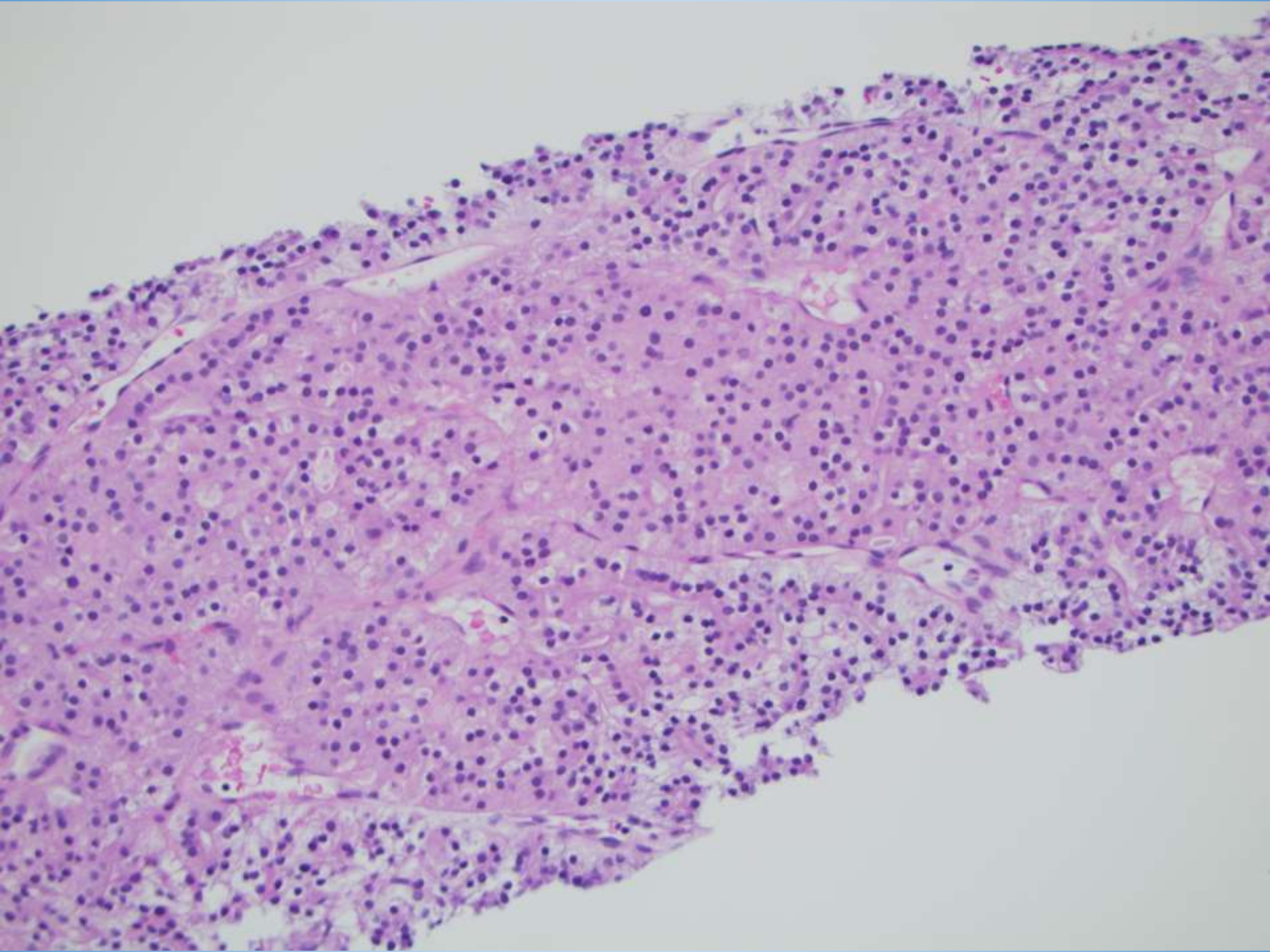
Shweta Agarwal/Poonam Vohra; UCSF

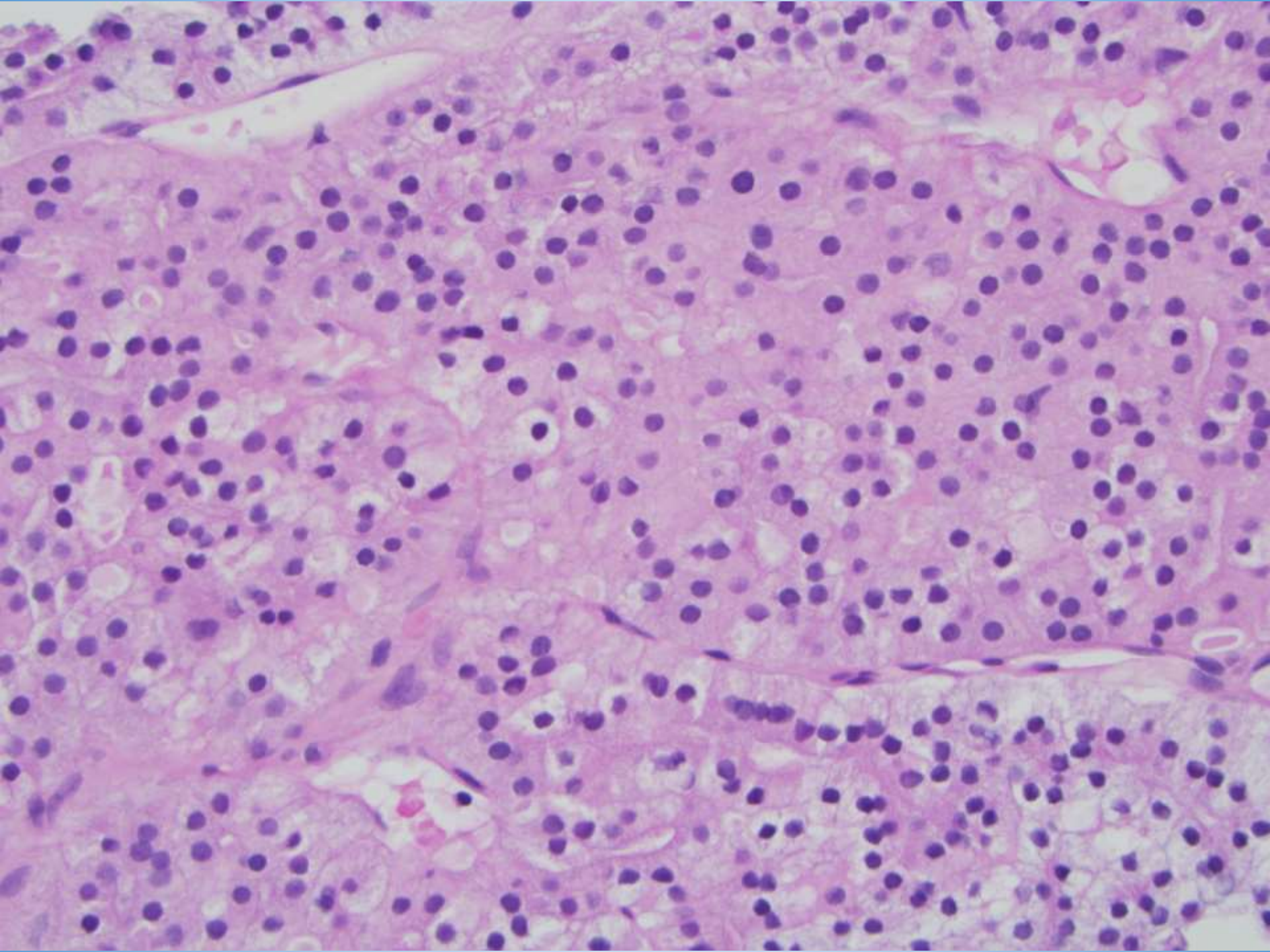
History of HIV/AIDS, multinodular goiter, bilateral hydronephrosis, and protruding mass along right iliac wing since 2016 which was concerning for soft tissue mass. MRI showed erosive masses in right iliac bone and left sacrum, larger one measuring 6.8cm on right. Right iliac wing biopsied.

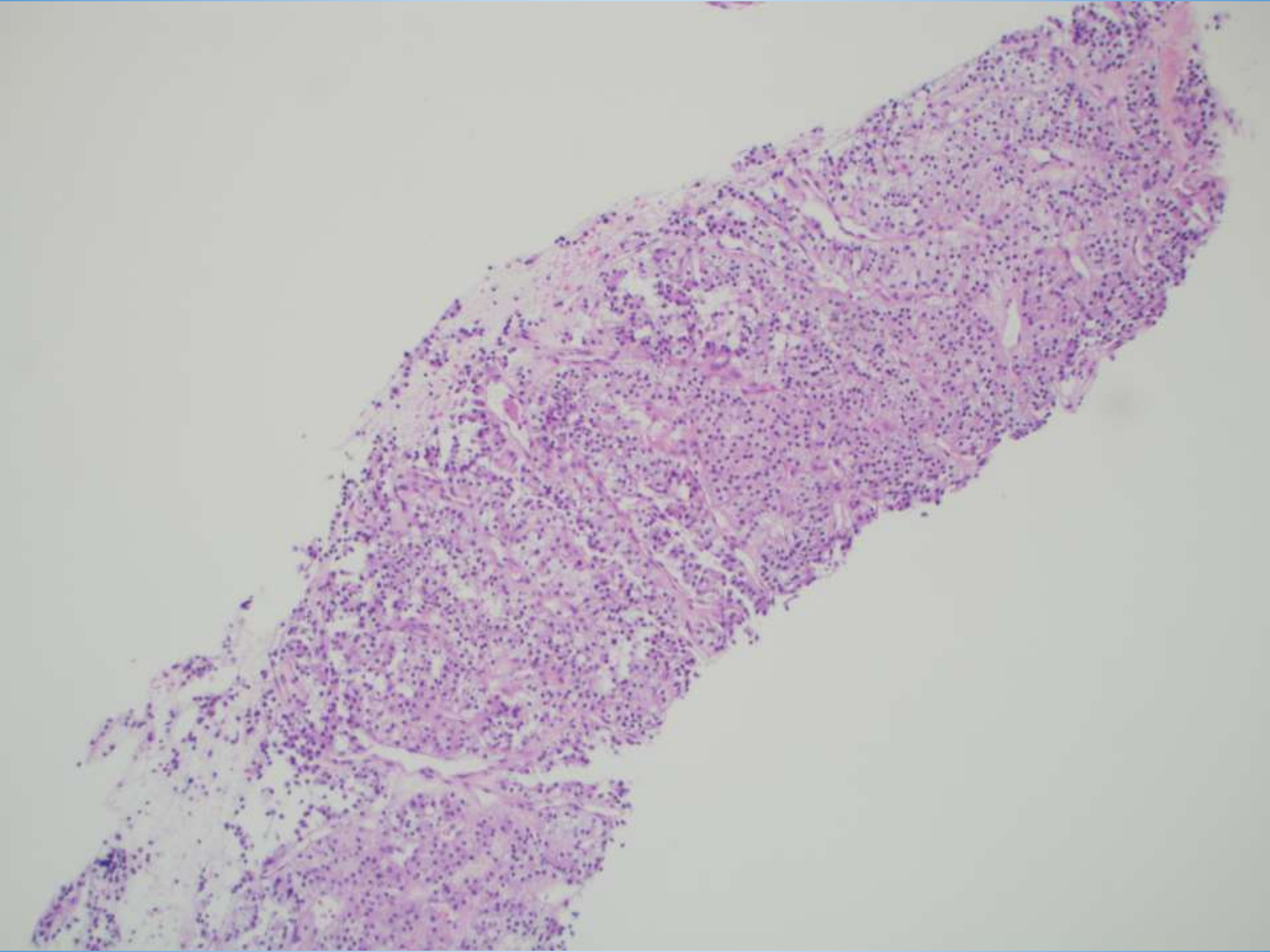


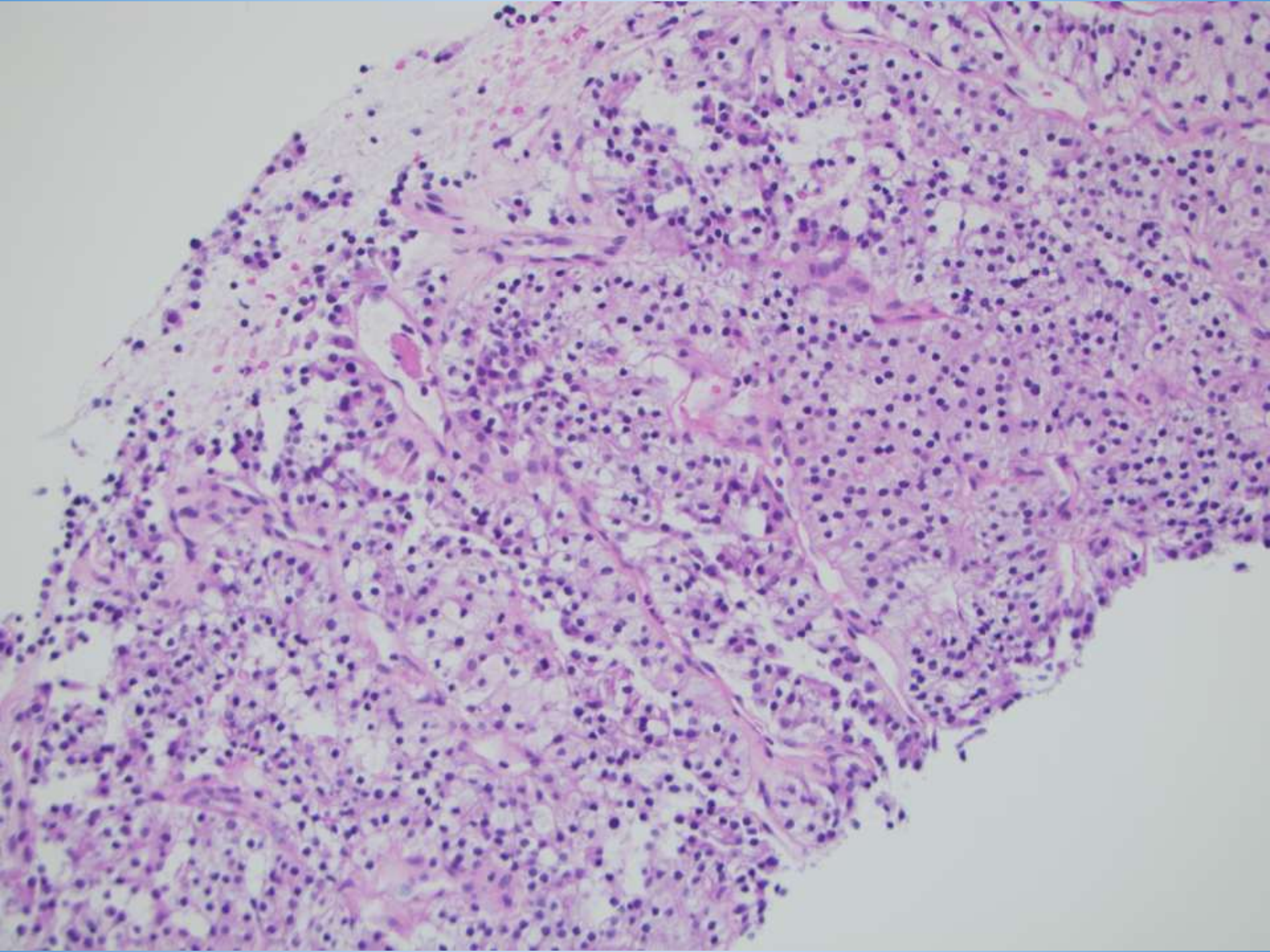


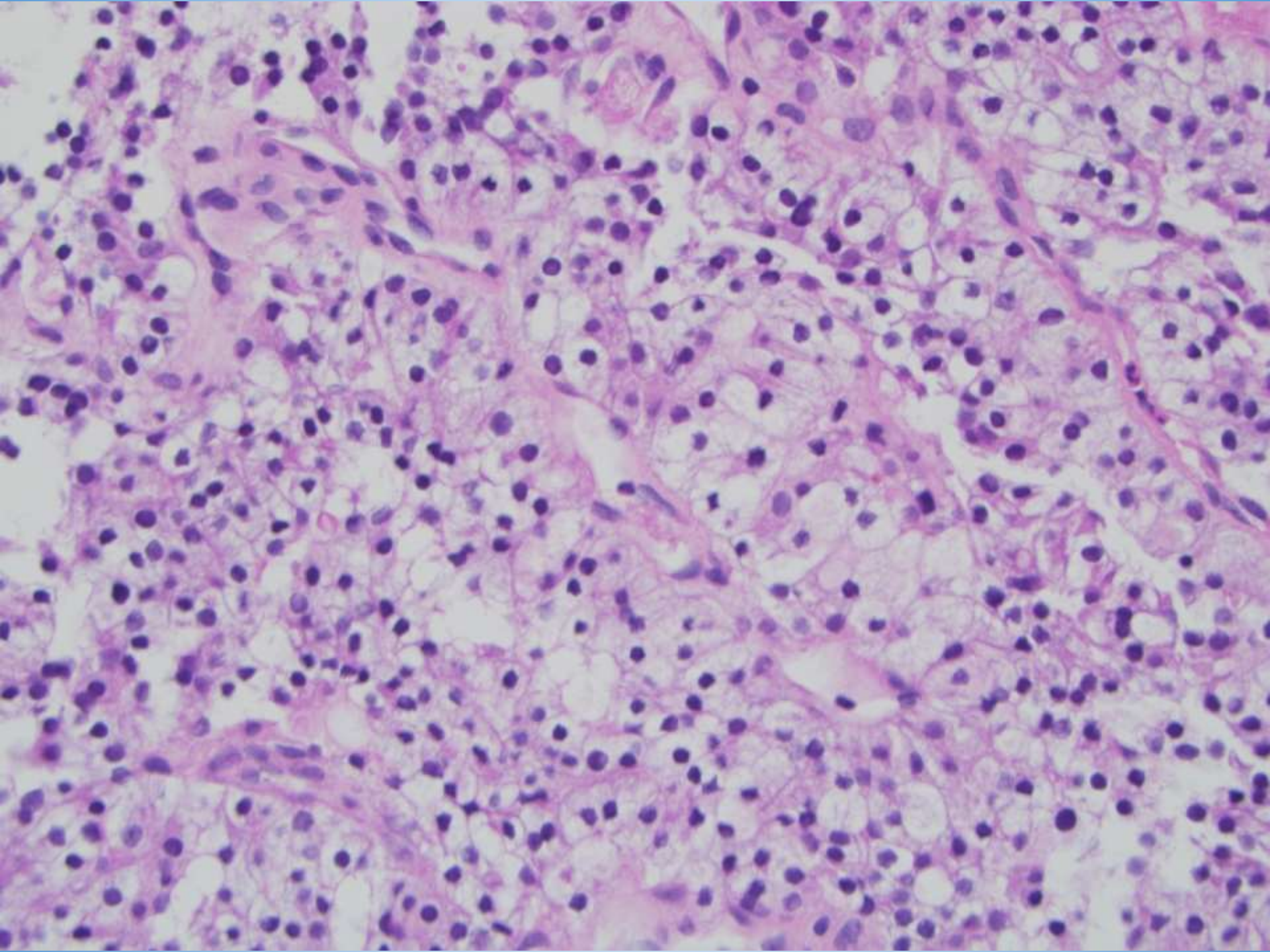






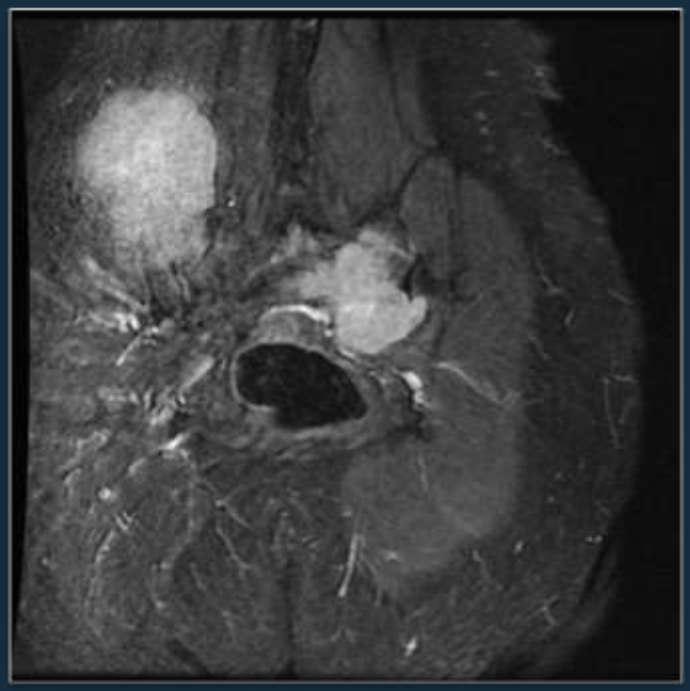






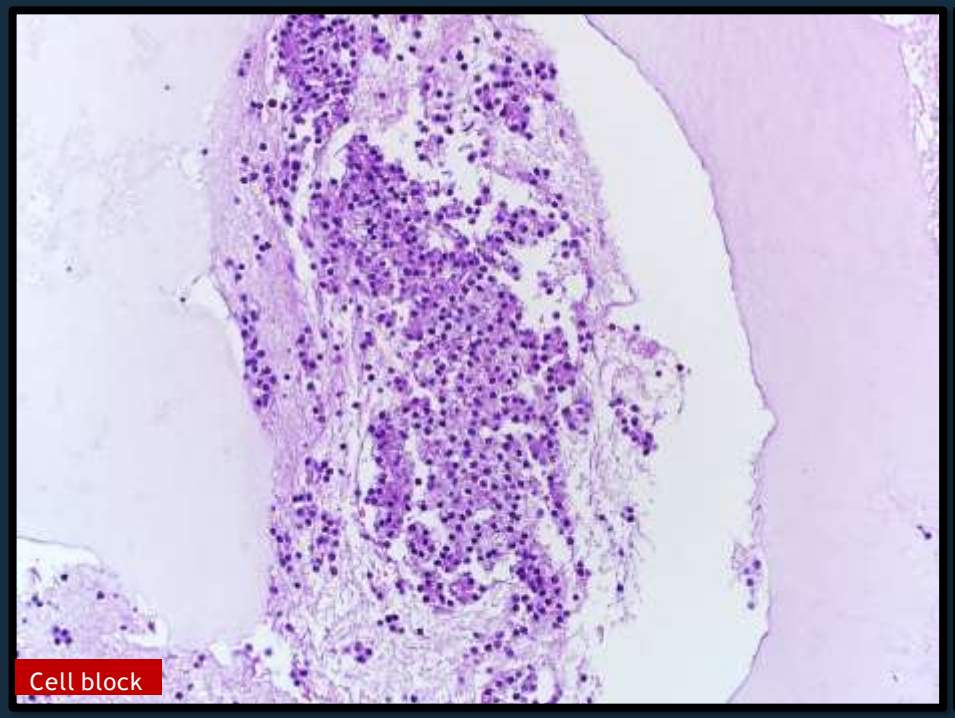
Case: Clinical (contd.)

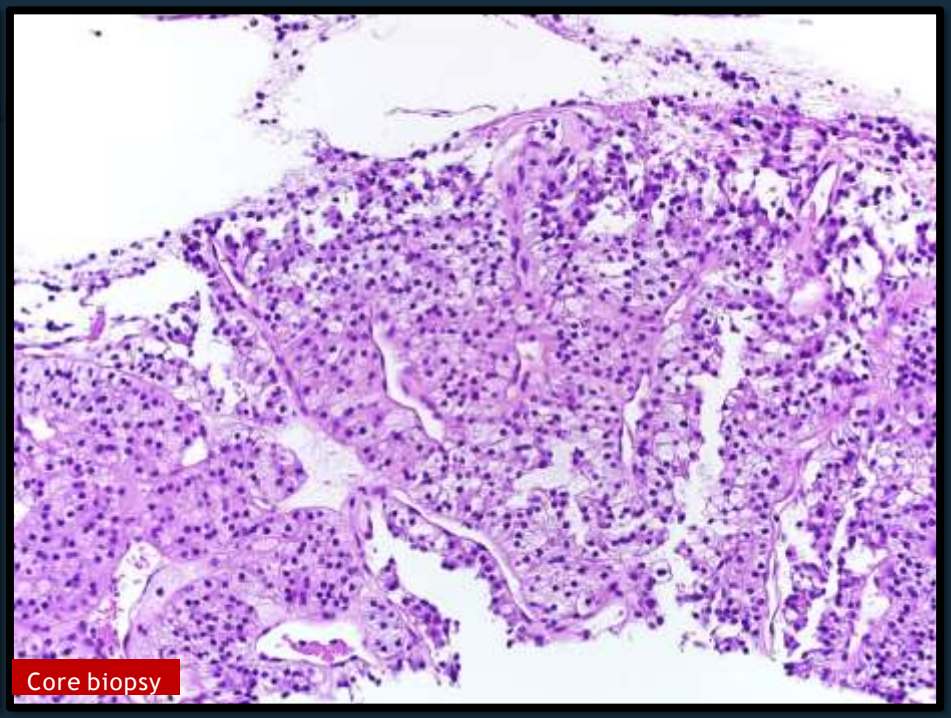
- Imaging findings:
  - MRI showed two, T1 hypointense and T2 hyperintense erosive masses
  - Right iliac bone (6.8 cm in maximum dimension)
  - Left sacrum (4.5 cm in maximum dimension)



Case: Biopsy

An ultrasound guided fine needle aspiration and a core biopsy were performed





Groups of tumor cells with eosinophilic, granular to clear cytoplasm

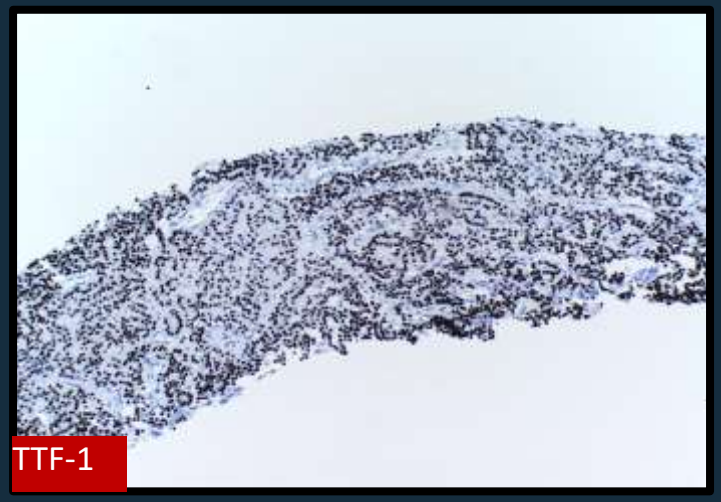
Differential diagnosis

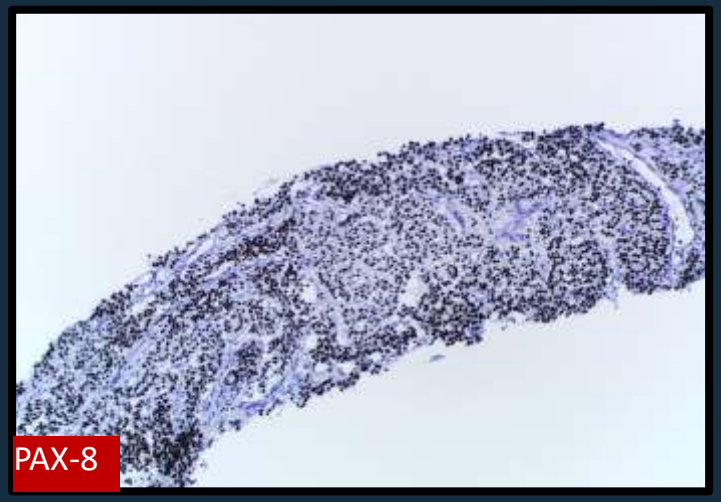
- Metastatic renal cell carcinoma
- Metastatic parathyroid carcinoma
- Metastatic thyroid carcinoma, follicular cell type with clear cell features
- Metastatic medullary thyroid carcinoma with clear cell features
- Clear cell sarcoma of soft parts

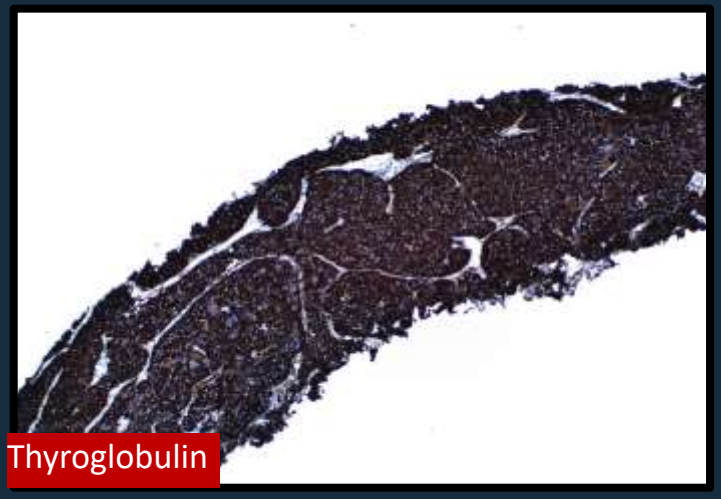
Work up

Negative stains

RCC, CD10, CAIX, PTH, Calcitonin, CK20







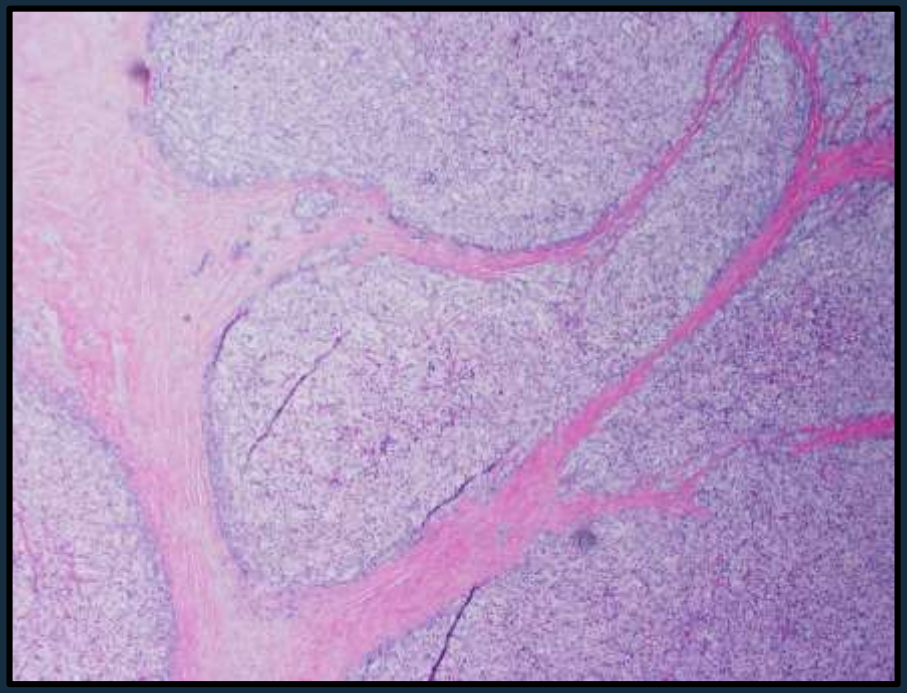
Other positive stain: CK7

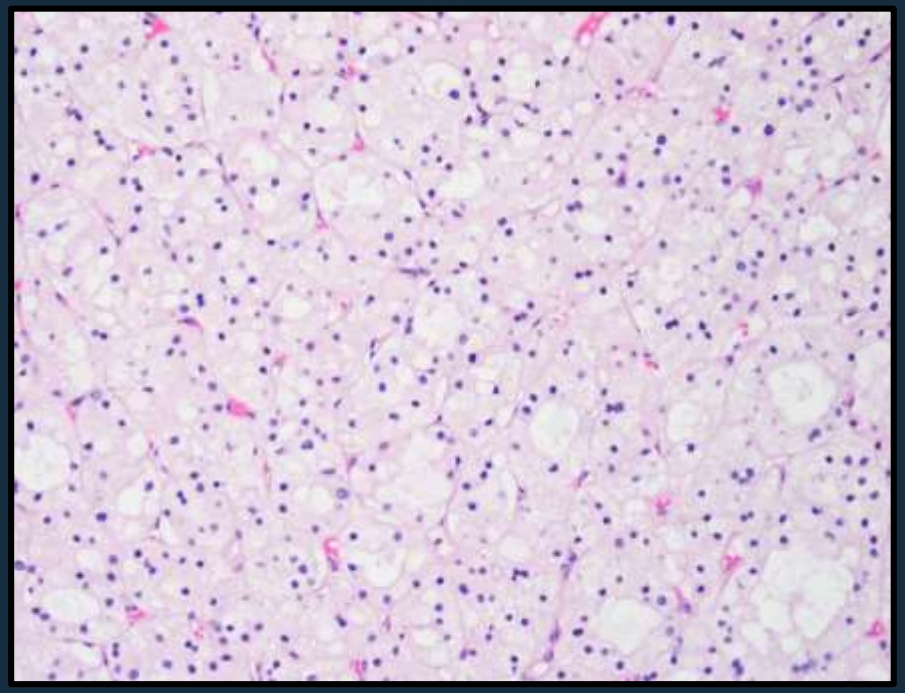
Diagnosis

Metastatic thyroid carcinoma, follicular cell type with clear cell features

Case (Surgical pathology)

- A total thyroidectomy was performed 2 months later:

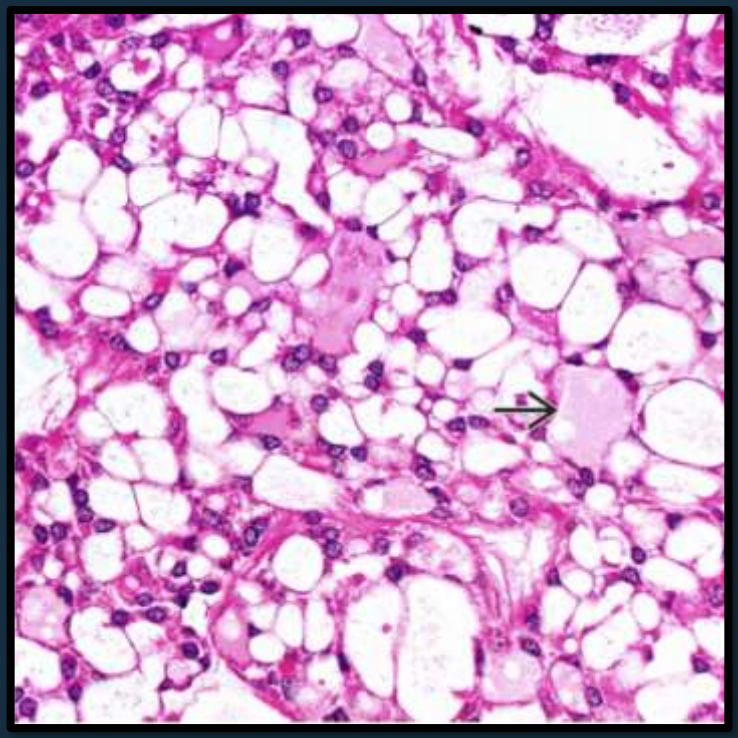




Follicular thyroid carcinoma, clear cell variant (7 cm), widely invasive, Angioinvasion +

Clear cell variant, FTC

- First described in 1985
- More common finding compared to PTC
- Defined as > 50% clear cells in tumor
- Histology:
  - Round to oval nuclei
  - Vesicles to signet ring type morphology
  - No PTC like features
  - No significant pleomorphism
  - Coexistent oncocytic cells



Diagnostic Pathology: Head and Neck, 2e by Lester D. R. Thompson, MD and Bruce Wenig, MD M

Clinical and Prognostic significance

- Conflicting data about clinical and prognostic significance of these tumors:
  - Rarity of tumor
  - Inconsistent morphologic diagnosis
  - Paucity of molecular studies
- Segal et al (1985) reported three cases of pure clear cell thyroid carcinoma with very aggressive behavior
- Carcangiu et al, 1985 concluded that natural history of thyroid tumors containing clear cells depends on their basic cytoarchitectural features

Clinical and Prognostic significance (contd.)

- Other studies supporting an aggressive nature of the these tumors:

Authors and no. of cases	Patients/ sex age	Duration of goiter	Clear cell component	Local invasion & regional metastases	Distant metastases	Follow-up
Kniseley & Andrews[1] 1956 2 cases	1/F/10	1 yr	Mixed	+	–	No information
	2/F/8	2 yrs	Mixed	+	Lung	
Chesky et al.[2] 1957 6 cases	1/F/31	Noticed on admission	Pure	+	–	Died from disease after 15 yrs
	2/F/67	7 yrs	Mixed	+	–	Died from disease after 6 yrs
	3/F/24	10 mo	Mixed		–	Alive with local disease 11 years
	4/F/38	20 yrs	Mixed	–	–	Alive and well 9 years
	5/F/53	8 yrs	Pure	+	–	Alive and well 6 years
	6/F/46	Unknown	Mixed	–	–	Alive and well 1 year
Civantos et al.[8] 1984 3 cases	1/F/72	10 yrs	Mixed	–	Bone	Alive and well
	2/F/62	1 yr	Mixed	+	Bone	Alive with disease
	3/F/60	5 yrs				Intraoperative death

Molecular Evidence

- Study by Tong et al in 2015
  - First molecular study on clear cell variant of follicular thyroid carcinoma
  - Aggressive tumor behavior
    - Patient died 6 months after thyroidectomy
  - Molecular analysis results
    - Gain of function mutation of **TSHR (L272V)**
    - Increased expression of **Na/I symporter (NIS)** and **Thyroglobulin (TG) gene** expression
    - Loss of function mutation of **TP53 (R248Q)**
    - BRAF, RAS, RET/PTC, PPARG/PAX8 not detected

New

Routinely decreased in thyroid cancers

Poorly differentiated & anaplastic thyroid cancers

THYROID
Volume 27, Number 6, 2017

DOI: 10.1089/thy.2016.0631

Clear Cell Change in Thyroid Carcinoma: A Clinicopathologic and Molecular Study with Identification of Variable Genetic Anomalies

Nicole A. Cipriani,[1] Shweta Agarwal,[2,3] Dora Dias-Santagata,[2,3] William C. Faquin,[2,3] and Peter M. Sadow[2,3]

Background: Clear-cell carcinoma of the thyroid has been regarded as a variant of follicular (FTC) or papillary (PTC) thyroid carcinoma. Twenty-one primary thyroid carcinomas with clear-cell features, diagnosed in 20 patients (12 female) were identified between 1992 and 2012 (0.5% of in-house thyroid carcinomas).
Methods: Hematoxylin and eosin slides were reviewed. SNaPshot multigene mutational analysis and a translocation panel were successfully performed on 15 of these cases.
Results: Twelve (57%) were FTC, five were conventional PTC, two were follicular variant of PTC, and two were poorly differentiated thyroid carcinomas. Five cases had *RAS* mutation (four FTC and one PTC); two had *PAX8-PPARgamma* translocations (both FTC, one with concurrent p53 mutation); one had an *EML4-ALK* translocation (PTC); and one had a *TFG-MET* translocation (follicular variant of PTC). Five carcinomas were metastatic to regional lymph nodes (three FTC and two PTC), and two were metastatic to bone (both FTC). Disease confined to the thyroid (67%) and rates of regional lymph node metastasis (24%) and distant metastasis (10%) were near the national averages (68%, 25%, and 5%, respectively). One patient with a poorly differentiated thyroid carcinoma died one year after diagnosis, and a patient with metastatic FTC died two years after diagnosis. Overall mortality was 10%.
Conclusions: Clear-cell change in thyroid carcinoma is rare, is more common in FTC than it is in PTC, is found focally or multifocally within a given lesion, and is frequently associated with *RAS* mutations (33%). Clear-cell change in thyroid neoplasia should raise the possibility of follicular carcinoma, and should not be treated differently from other carcinomas of similar grade and stage.

TABLE 1. CLINICAL, PATHOLOGIC, AND MOLECULAR FEATURES OF THYROID CARCINOMAS WITH CLEAR-CELL CHANGE

Case	Year of diagnosis	Age	Sex	Primary location	Type	Size in cm	Metastatic location	Other thyroid pathology	Other clinical	Molecular findings
1	2012	61	M	RL	FTC	4.2	Bone (ischium)		Metastatic to ischium 2012	NRAS 181C>A, 39%
2	2011	62	F	RL	FTC	2.3			No known complications 2012	Not tested
3	2011	80	M	RL	FTC	4.2		PTC microcarcinoma	No known complications 2012	HRAS 182A>G, 27%
4	2011	46	F	RL	FTC	1.6		PTC-FV, LL	No known complications 2012	NRAS 182A>G, 45%
5	2005	64	F	RL	FTC	7.5	LN (pretracheal)		Died 2007 due to disease	No aberrations detected
6	2010	66	F	UNK	FTC	UNK	Bone		Metastatic to bone, alive 2012	Not tested
7	2012	62	F	UNK	FTC	1.5	LN (supraclavicular)		No known complications 2012	No aberrations detected
8	2012	26	F	LL	FTC	4.0			No known complications 2012	PAX8-PPARgamma (exon 10-exon 2) TP53 818G>A, 72%;
9*	2012	31	M	RL	FTC	4.2		PTC-microcarcinoma	No known complications 2012	PAX8-PPARgamma (exon 10-exon 2)
10	2011	59	F	UNK	FTC	2.5		FA	No known complications 2012	No aberrations detected
11	2011	78	F	UNK	FTC	UNK	LN (paratracheal)		No known complications 2012	HRAS 181C>A, 70%
12	2002	71	M	UNK	FTC	UNK		Metastatic colon carcinoma in thyroid carcinoma	UNK	Not tested
13	2011	74	M	LL	PTC	5.5		Adenomatous nodule	Refractory to iodine, alive 2012	Not tested
14	2007	61	M	LL	PTC	0.6			No known complications 2012	No aberrations detected
15	1992	26	F	RL	PTC	0.2	LN (paratracheal)		No known complications 2008	NRAS 182A>G, 69%
16*	2012	31	M	LL	PTC	0.7		CLT adenomatous nodules	No known complications 2012	EML4-ALK (exon 6-exon20)
17	1996	48	M	UNK	PTC	UNK	LN (right cervical)		UNK	Technical failure
18	2012	51	F	RL	PTC, FV	2.8		PTC, LL adenomatous nodule	No known complications 2012	No aberrations detected
19	2011	43	F	RL	PTC, FV	1.8		PTC, LL CLT	UNK	TFG-MET (exon5-exon15)
20	1997	72	M	UNK	PDTC	UNK			Died 1998 due to disease	Not tested
21	2002	50	F	RL	PDTC	2.0		CLT	UNK	No aberrations detected

Conclusion regarding behavior and prognosis: Independent of clear cell morphology

Take Home Points

- Tumors of unknown origin with clear cells
  - Entity should be kept in mind: Thyroglobulin with TTF-1 helpful
- Metastasis as presenting symptom
- Differential diagnosis
  - Renal cell carcinoma
  - Parathyroid carcinoma
  - Clear cell medullary thyroid carcinoma
- Molecular mechanisms underlying clear cell morphology are unclear
- Scattered evidence regarding clinical behavior of tumor
  - Current belief: Behavior dependent on underlying histologic type

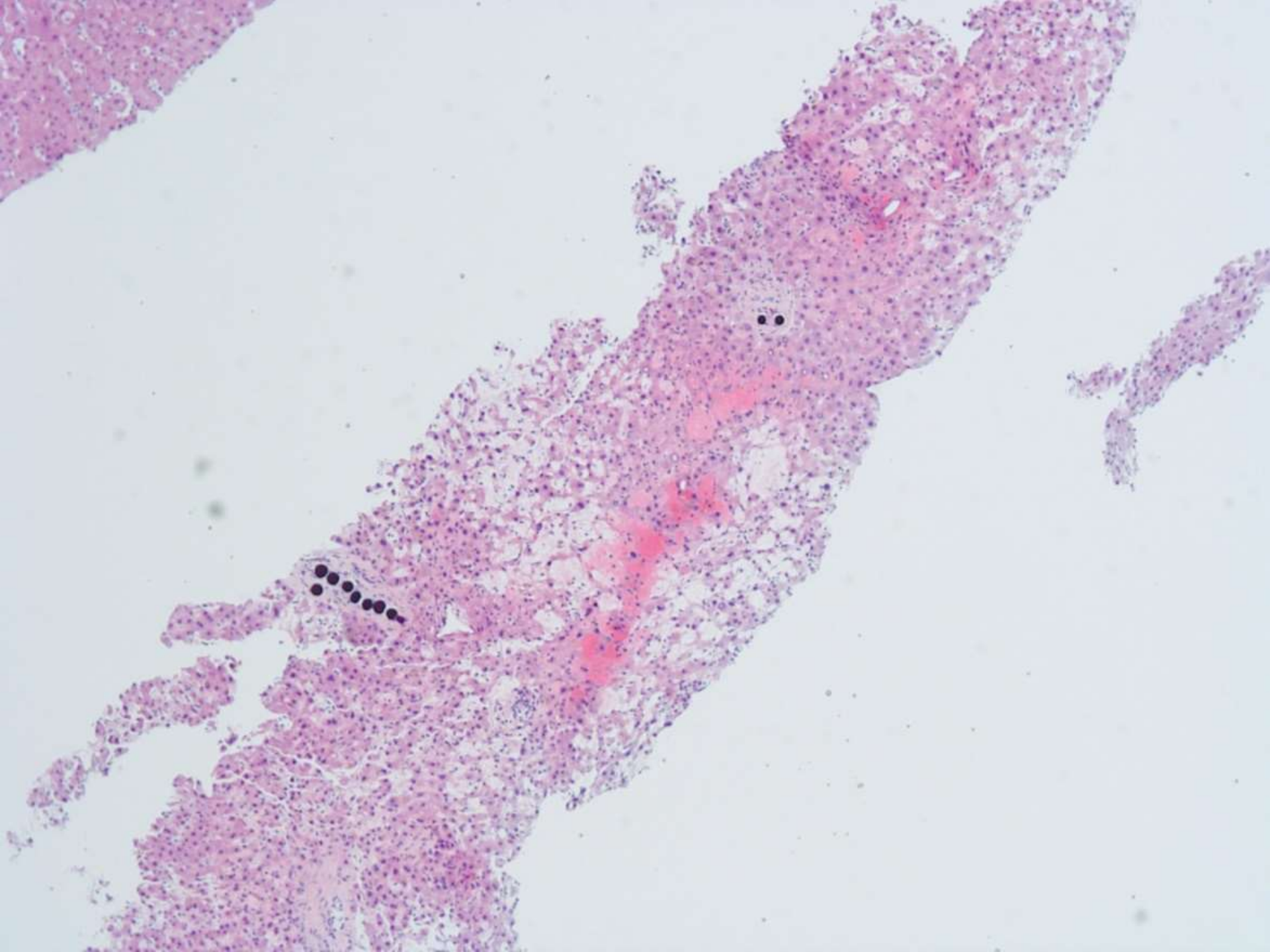
References

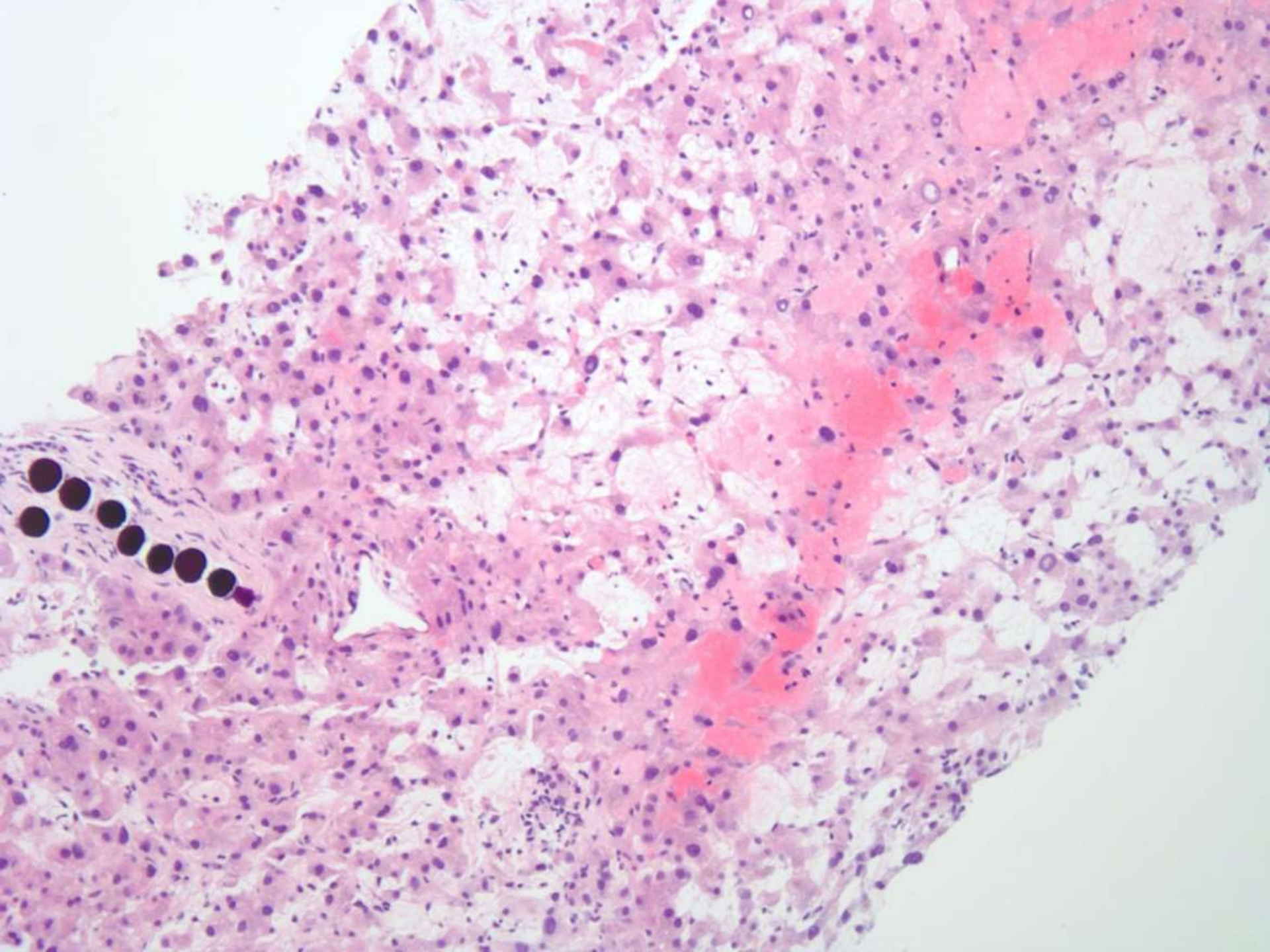
- *Ropp BG, Solomides C, Palazzo J,Bibbo M. Follicular carcinoma of the thyroid with extensive clear-cell differentiation: a potential diagnostic pitfall. Diagn Cytopathol. 2000 Sep;23(3):222-3.*
- *Cipriani NA, Agarwal S, Dias-Santagata D, Faquin WC, Sadow PM. Clear Cell Change in Thyroid Carcinoma: A Clinicopathologic and Molecular Study with Identification of Variable Genetic Anomalies. Thyroid. 2017 Jun;27(6):819-824.*
- *Tong GX, Mody K,Wang Z, Hamele-Bena D, Nikiforova MN, Nikiforov YE. Mutations of TSHR and TP53 Genes in an Aggressive Clear Cell Follicular Carcinoma of the Thyroid. Endocr Pathol. 2015 Dec;26(4):315-9.*
- *Sayar I, Peker K, Gelincik I, Demirtas L, Isik A. Clear cell variant of follicular thyroid carcinoma with normal thyroid-stimulating hormone value: a case report. J Med Case Rep. 2014 May 22;8:160.*
- *Segal K, Har-El G, Avidor I, Shvero J,Lubin E, Sidi J. Clear cell carcinoma of the thyroid gland. Head Neck Surg. 1986 Mar-Apr;8(4):313-9.*
- *Landon G, Ordóñez NG. Clear cell variant of medullary carcinoma of the thyroid. Hum Pathol. 1985 Aug;16(8):844-7.*
- *http://slideplayer.com/slide/7476675/24/images/60/Hydrophilic+Hormones:+Mode+of+Action+cAMP+as+Second+Messenger.jpg*

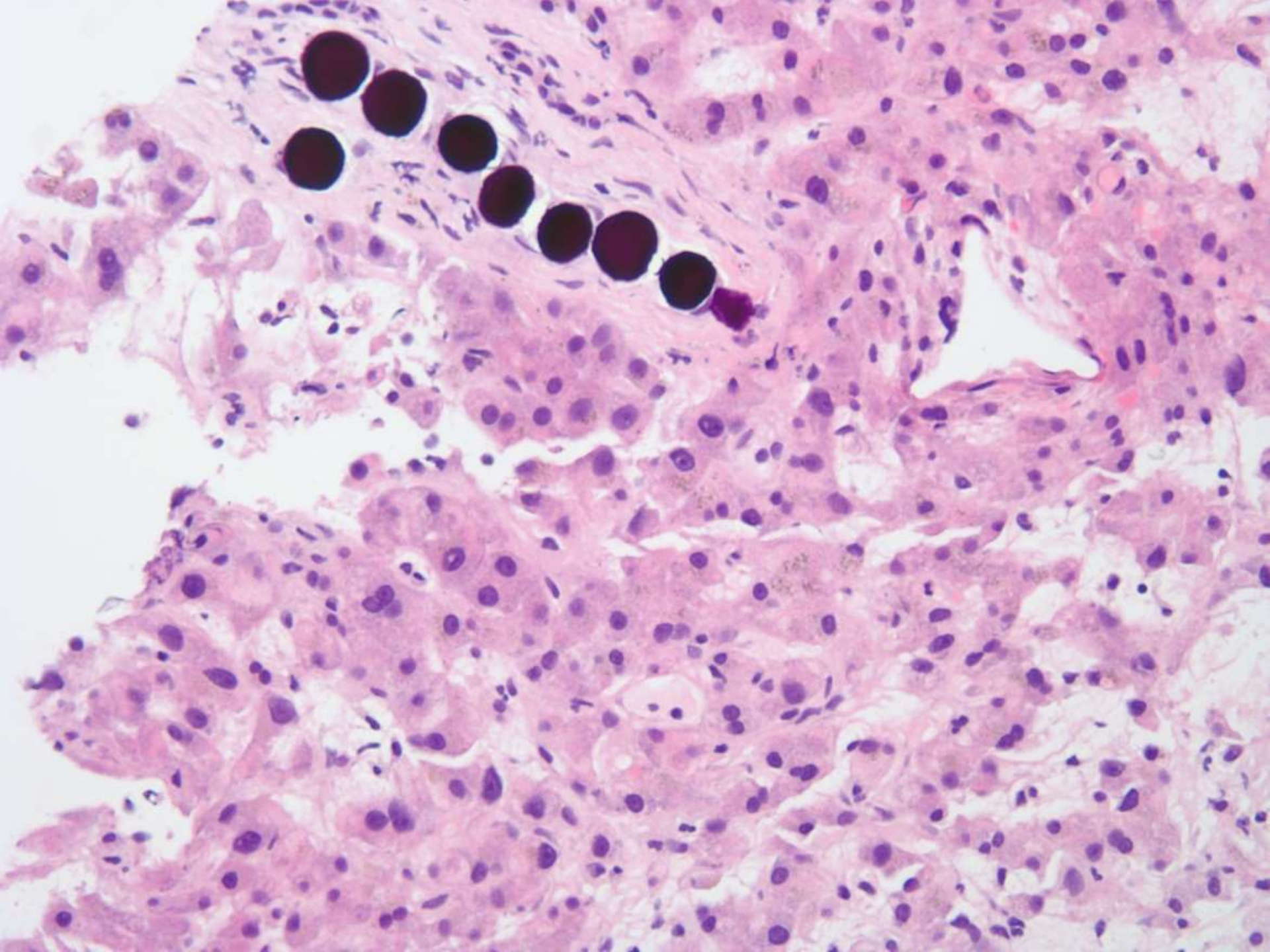
SB 6262

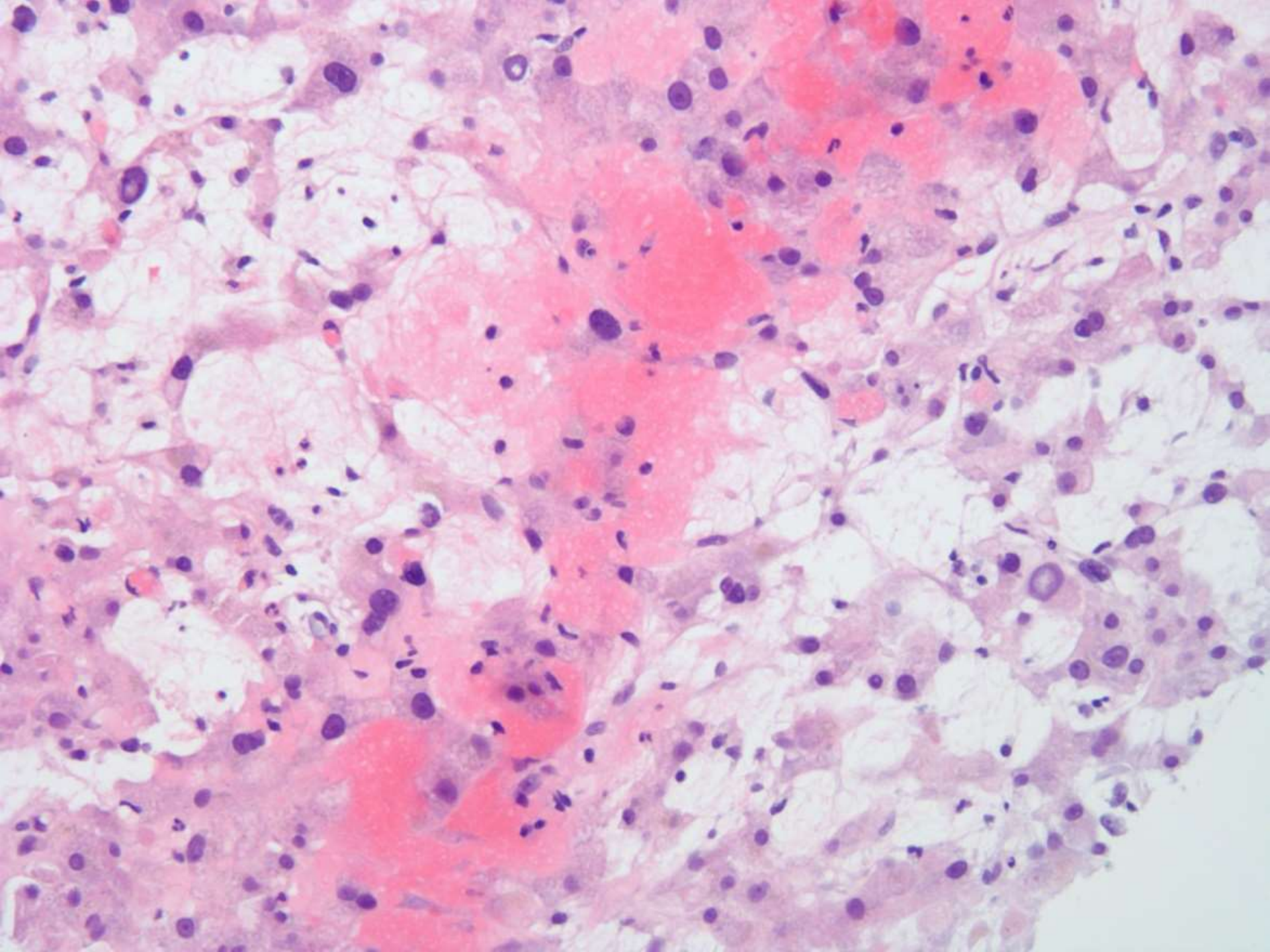
Charles Lombard; El Camino Hospital

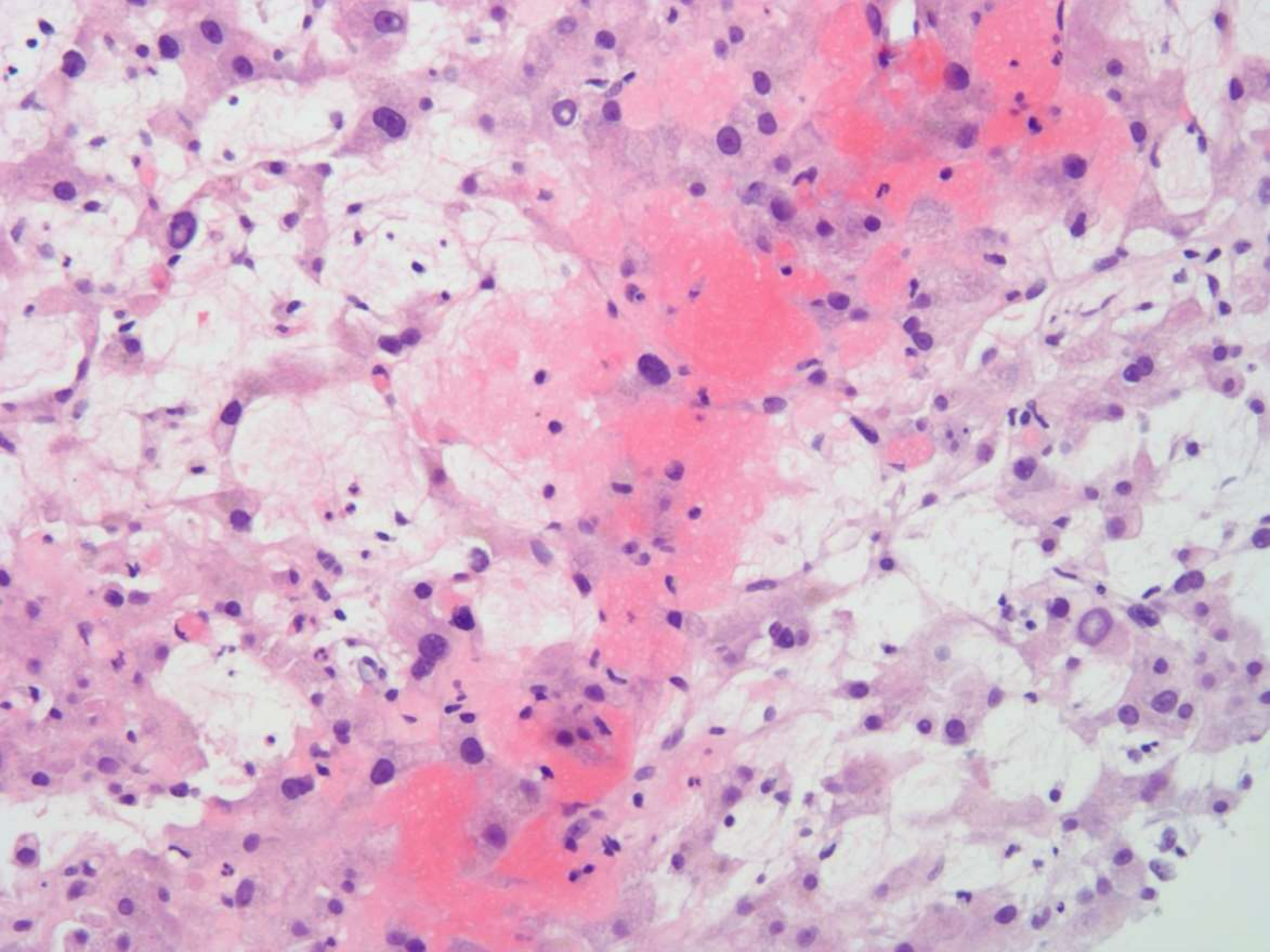
60-year-old male with h/o pancreatic acinar adenocarcinoma metastatic to liver. Has developed ascites and portal HTN of uncertain etiology. Transjugular liver biopsy performed.

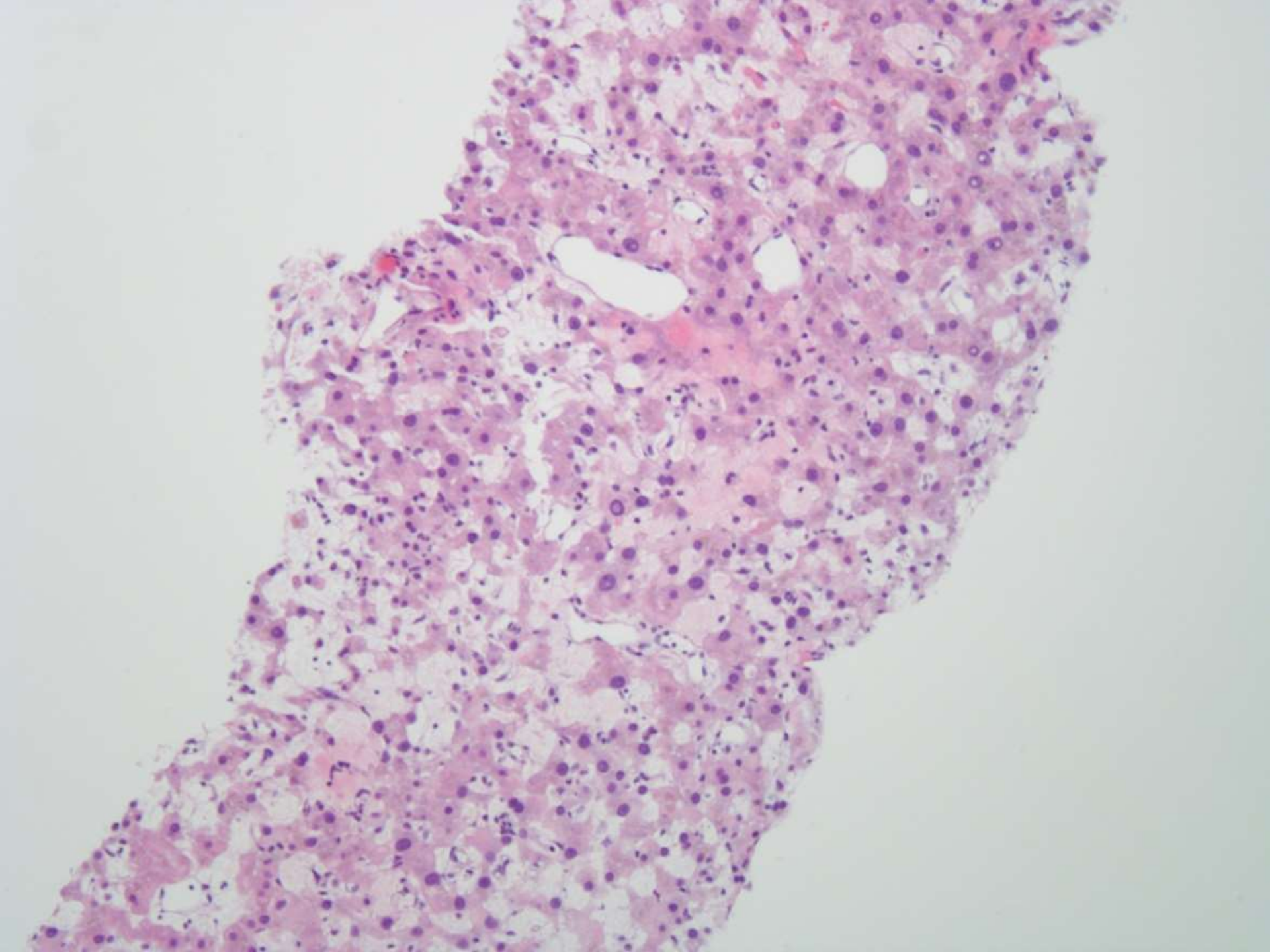


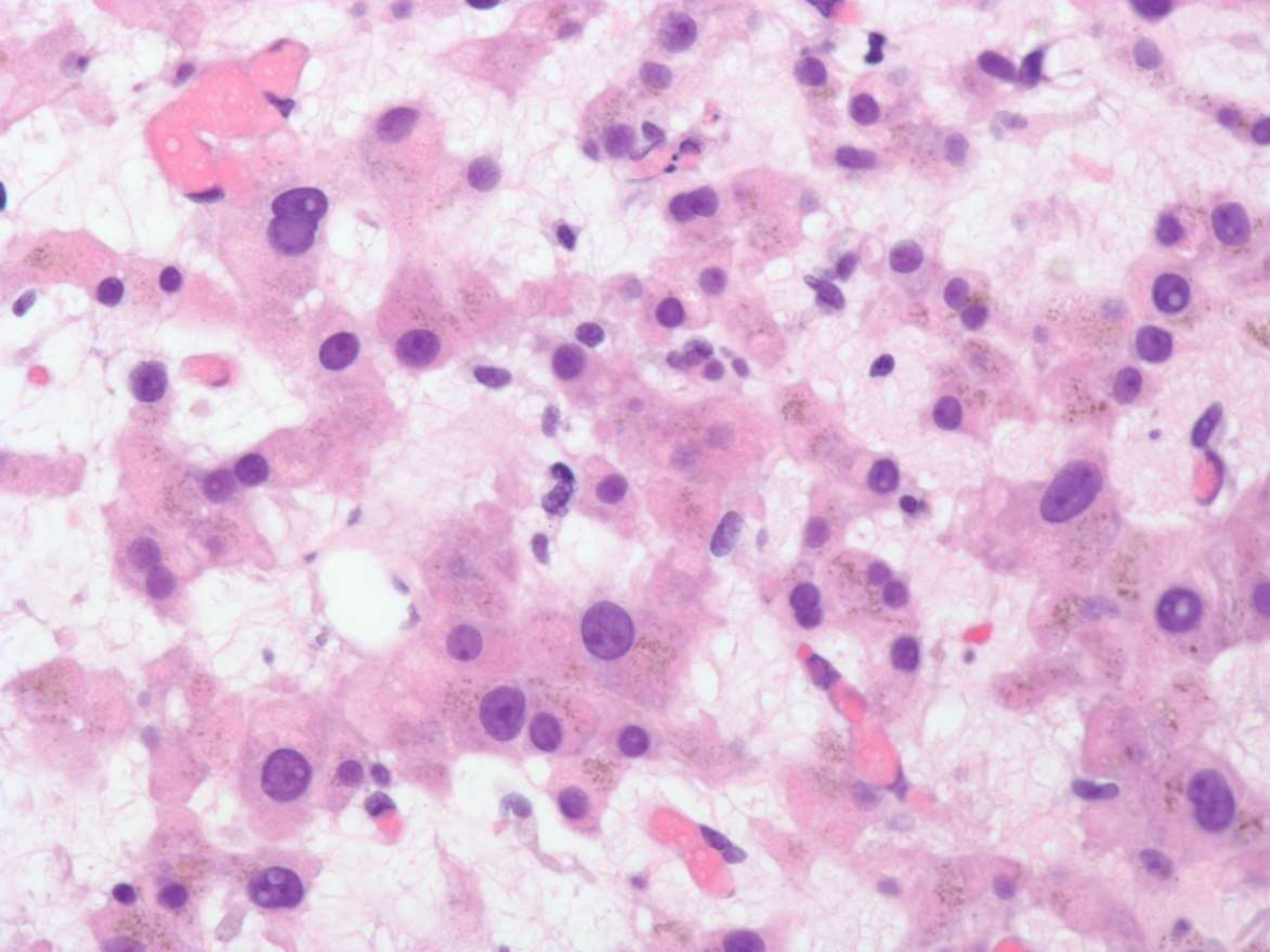


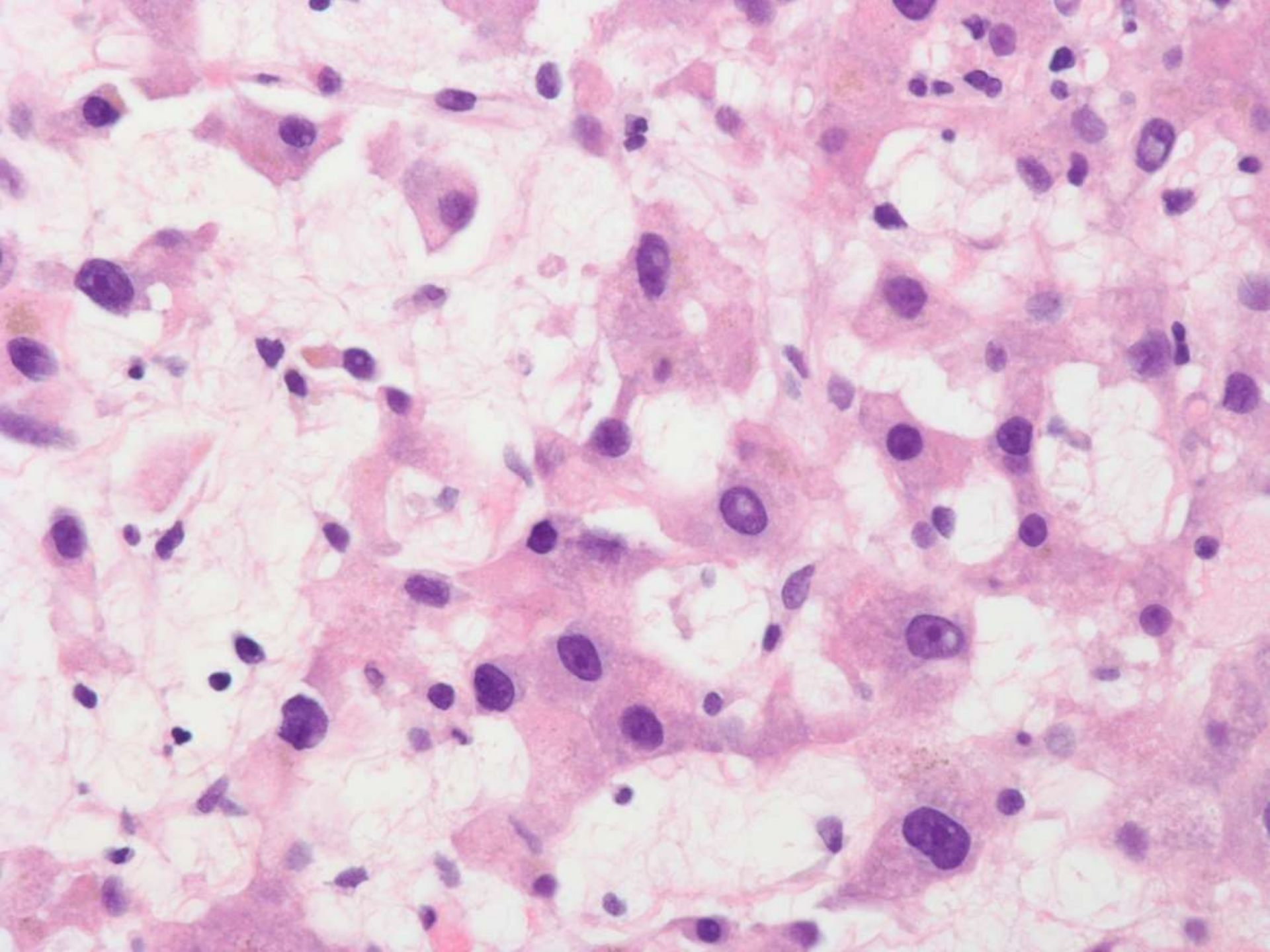






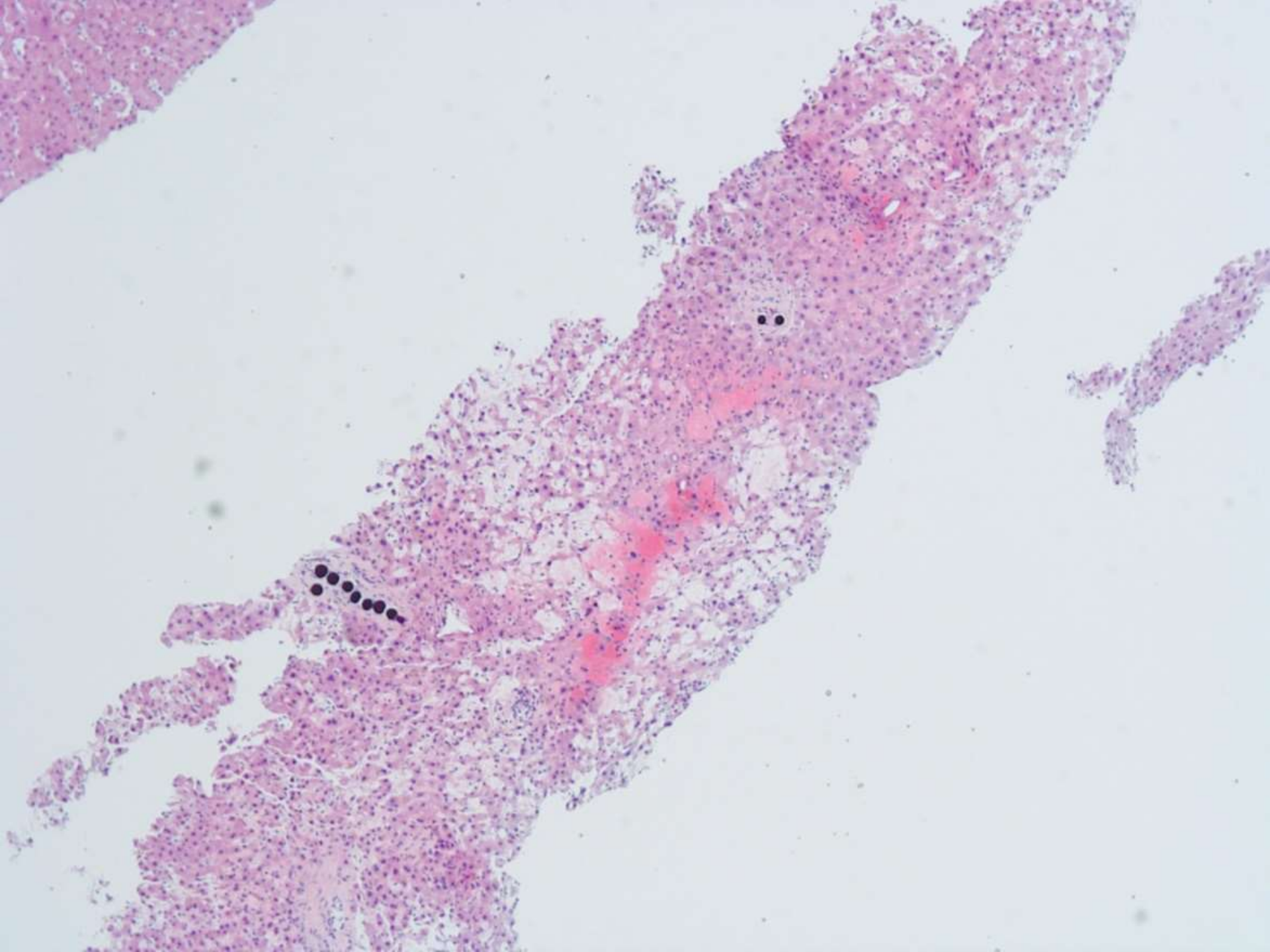


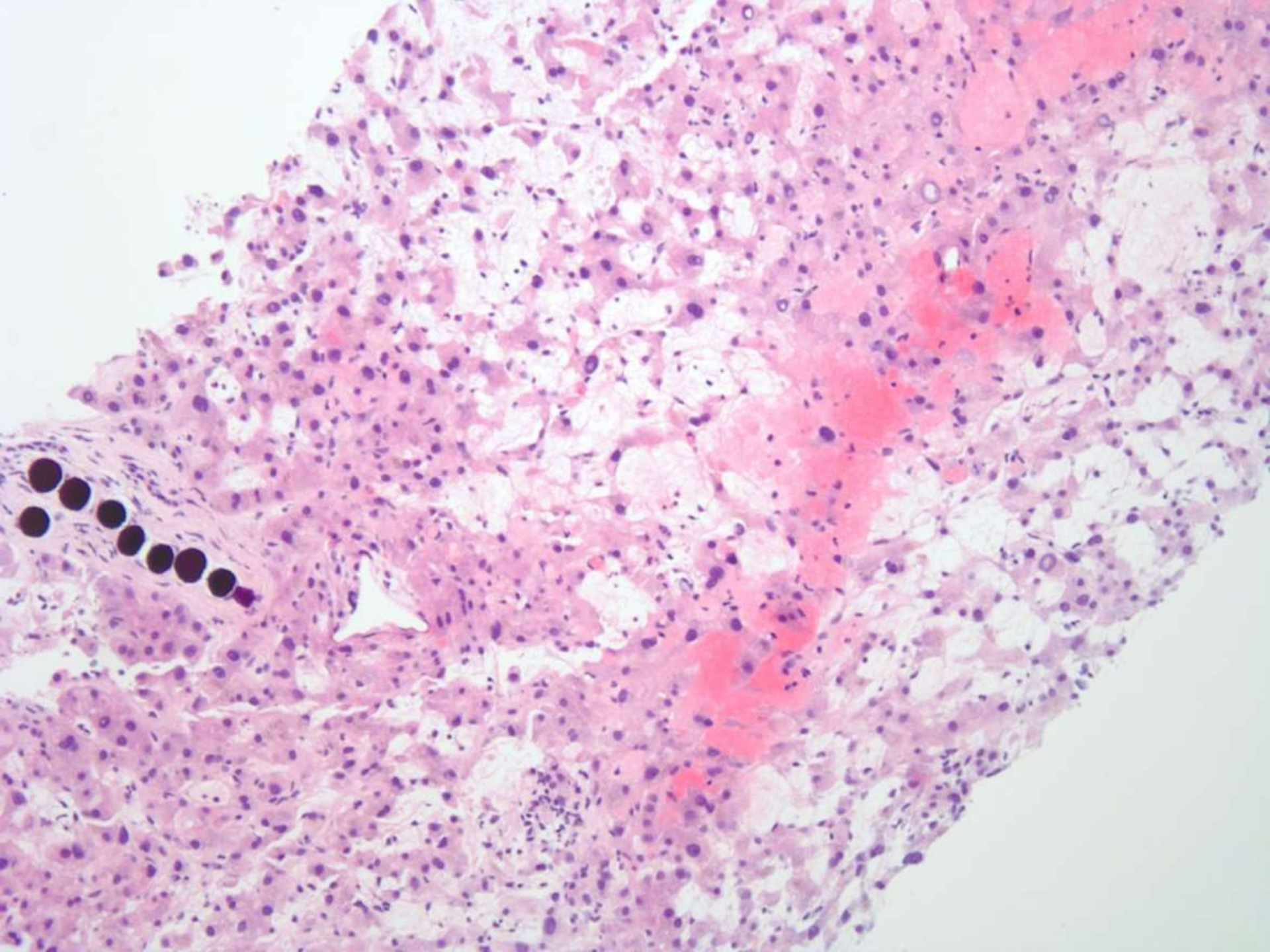


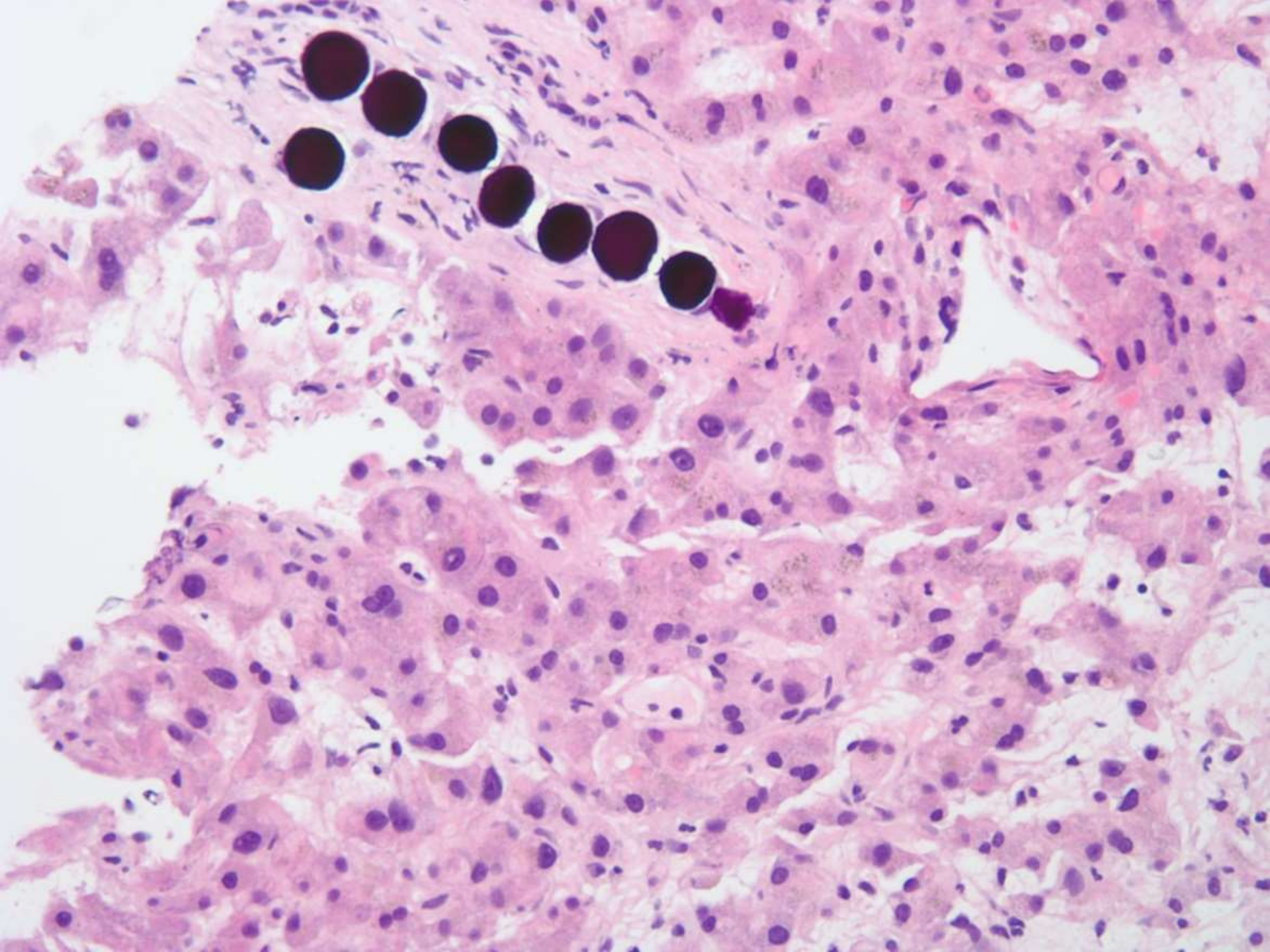


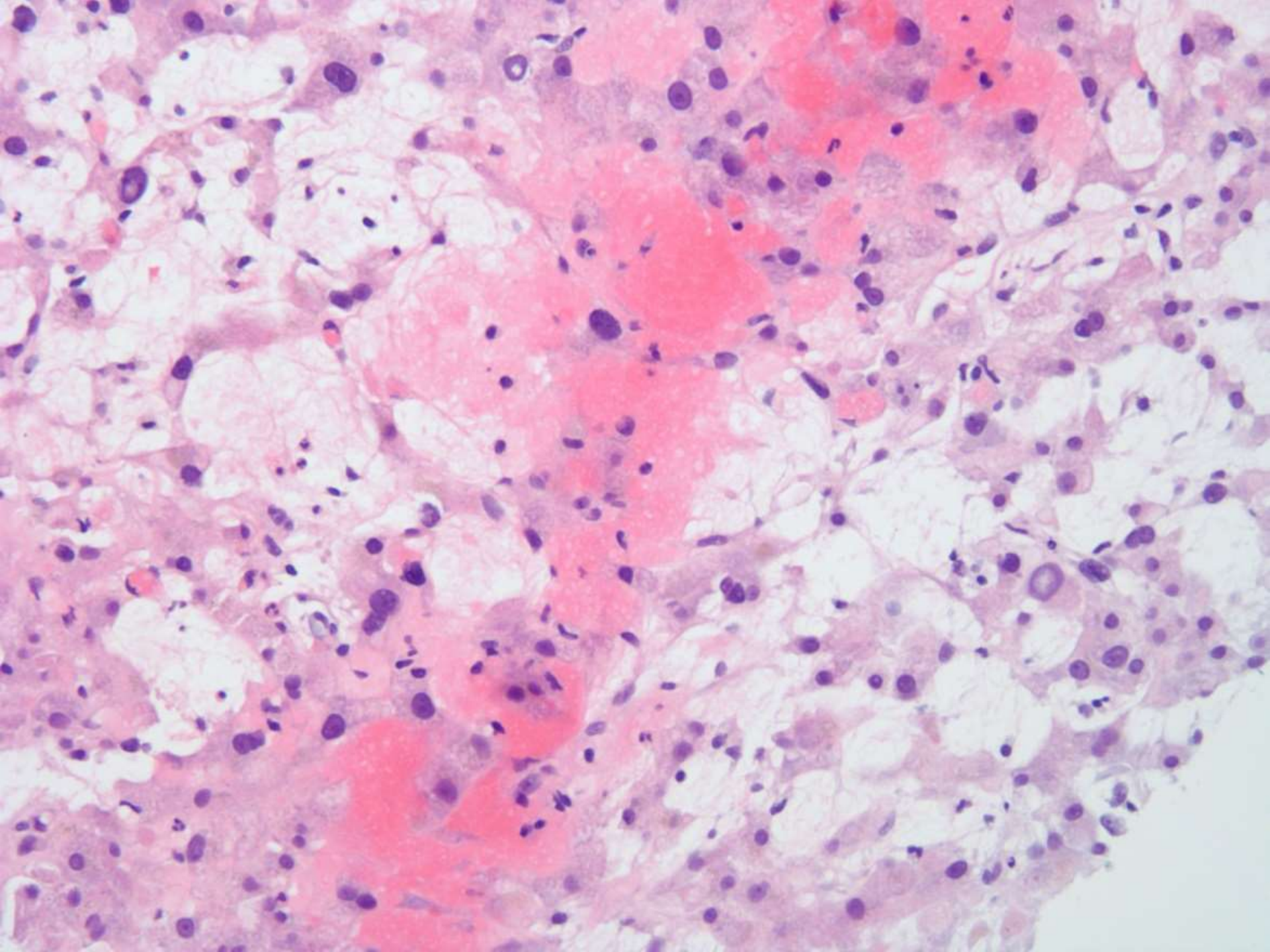
60 yo M
TJ needle bx liver

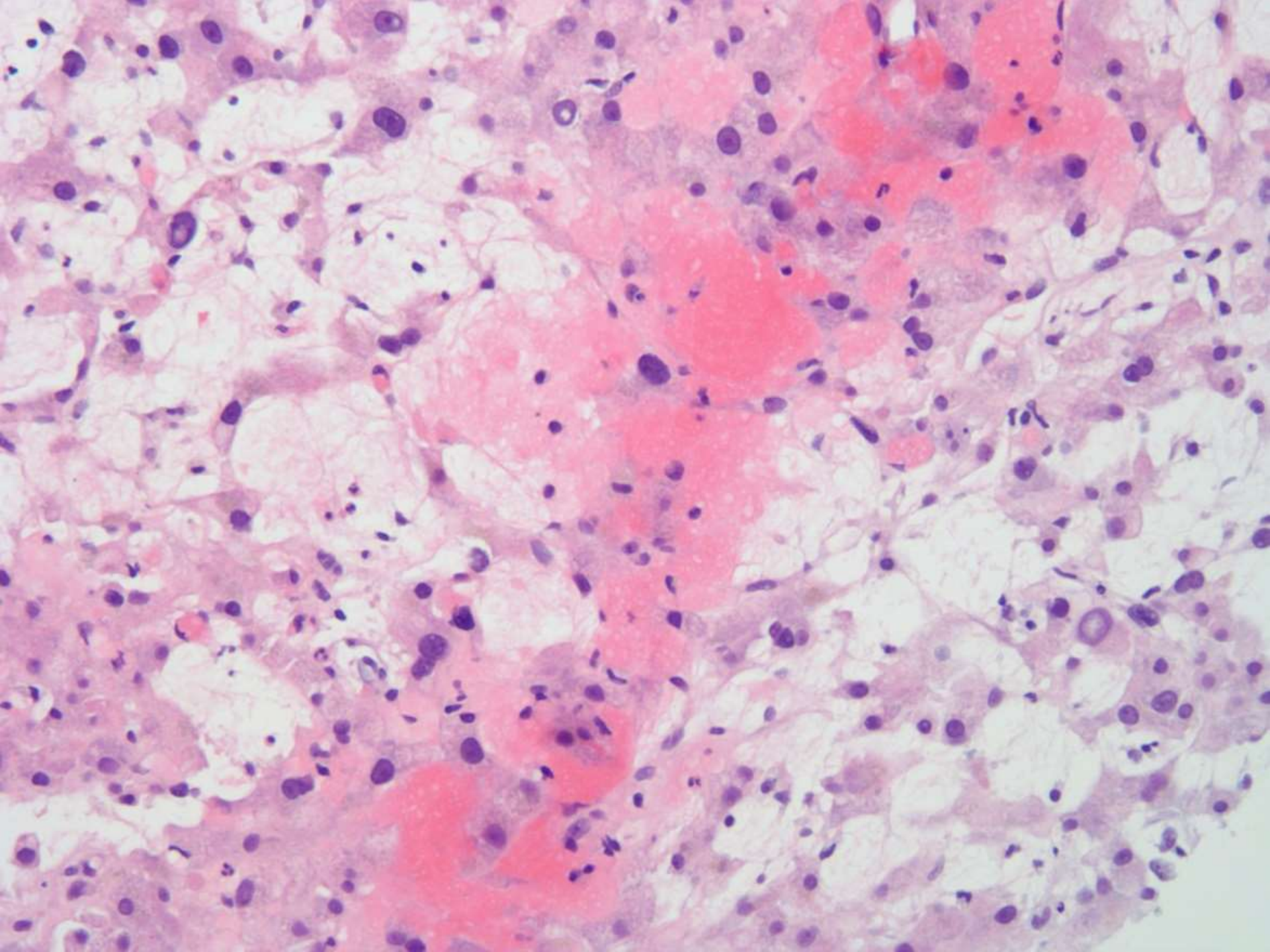
History of pancreatic acinar adenocarcinoma metastatic to the liver. Has developed ascites and portal hypertension of uncertain etiology

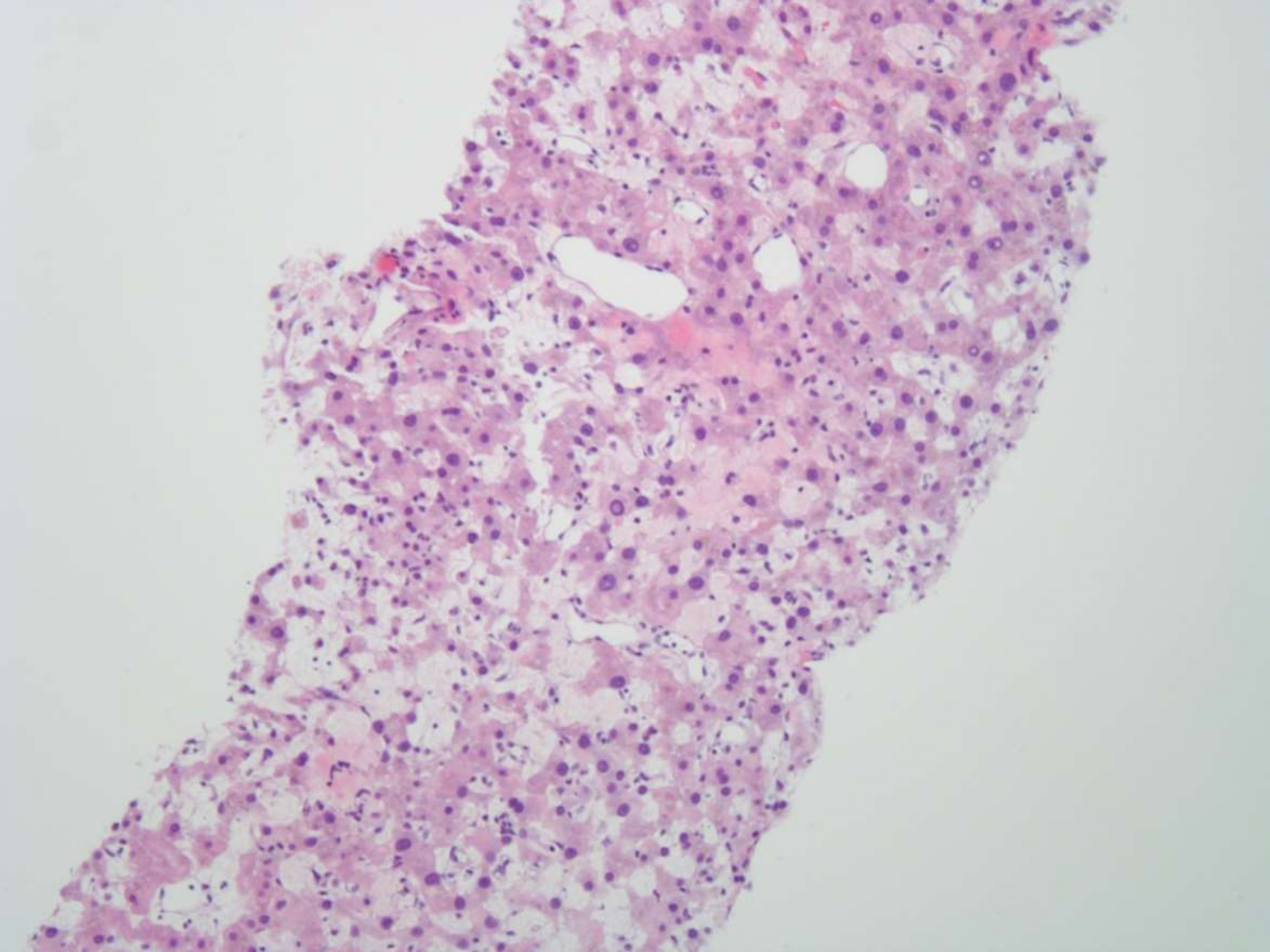


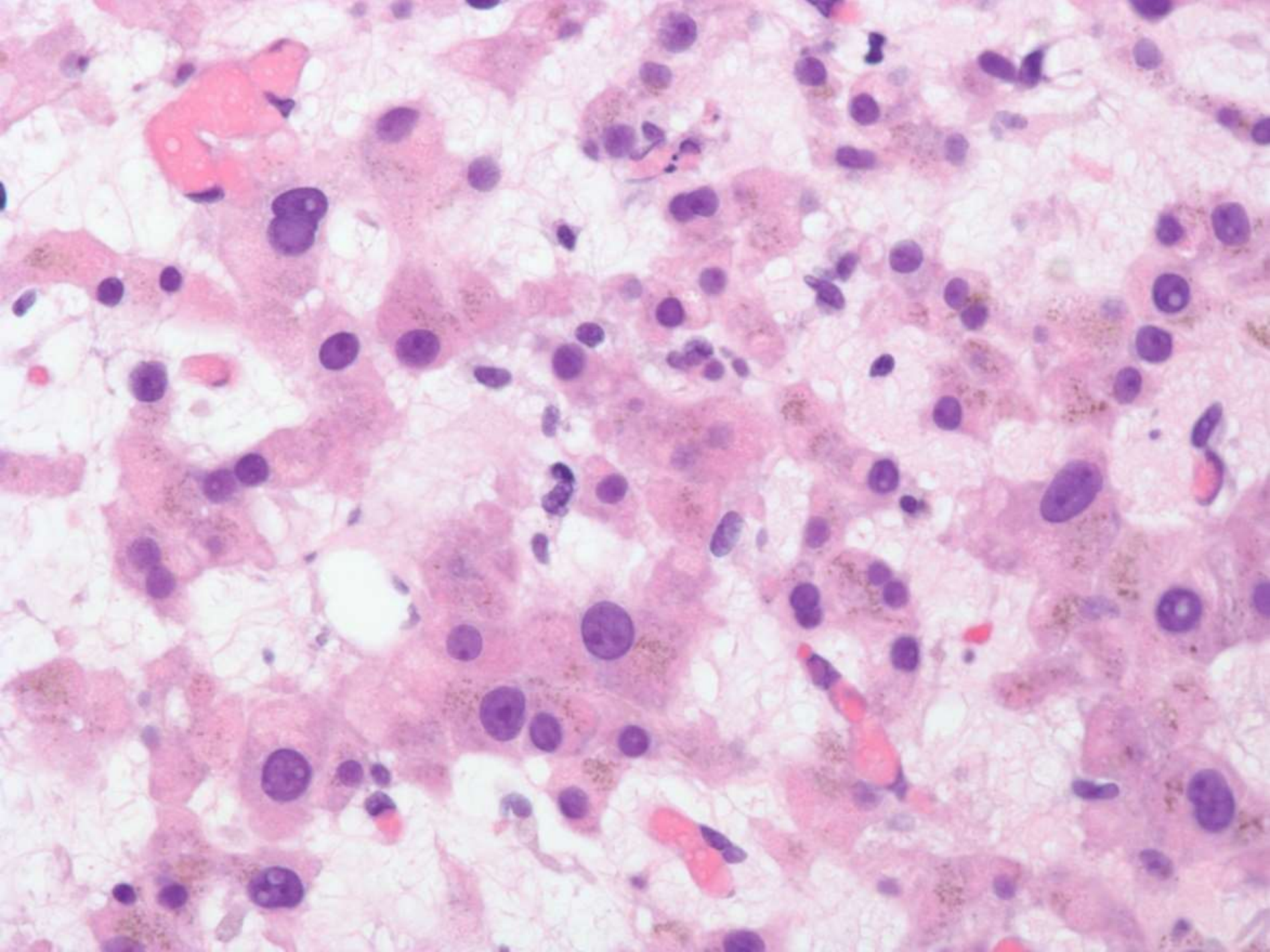


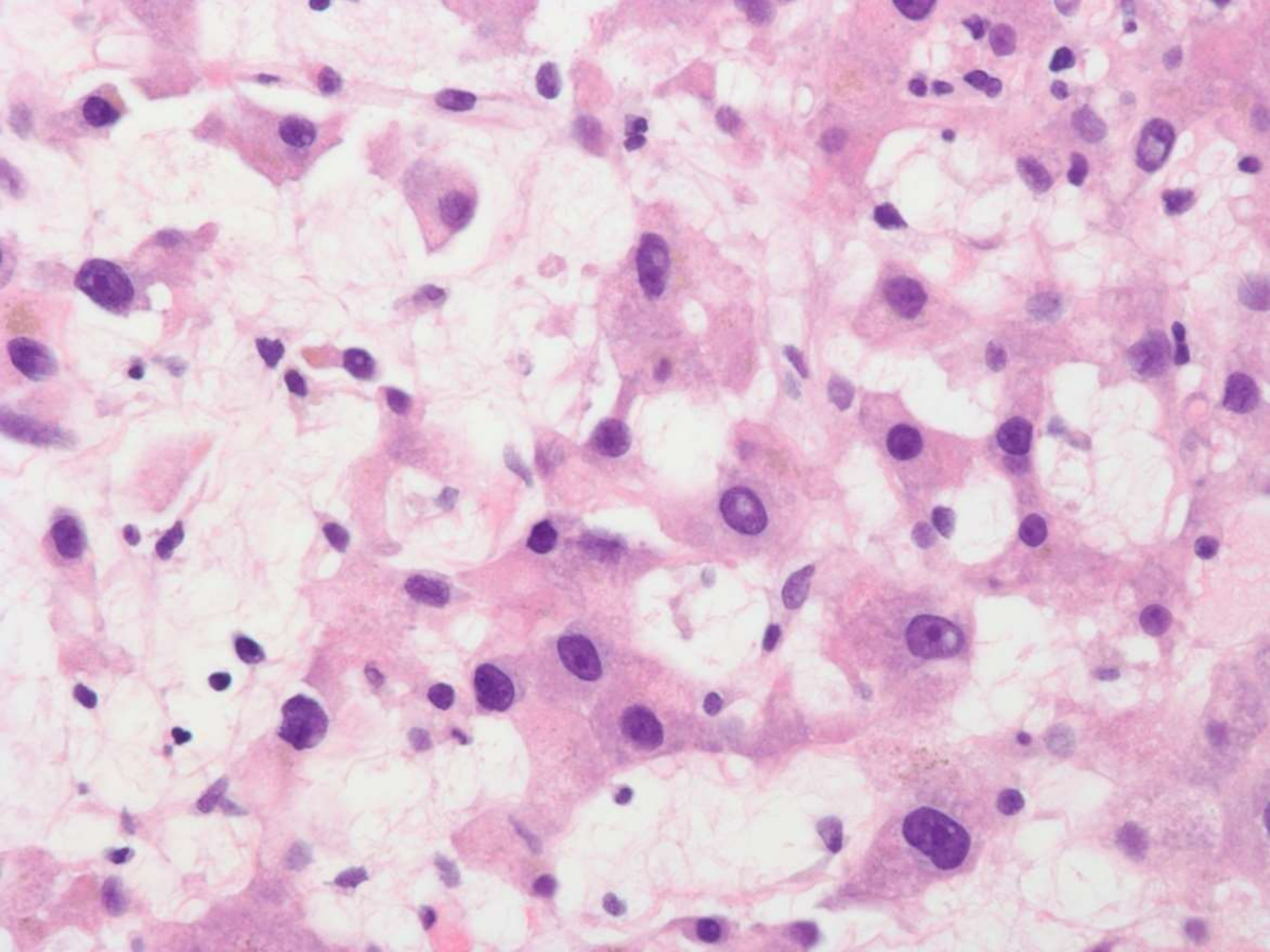












Hepatic veno-occlusive disease/SOS secondary to Yttrium radioembolization

Veno-occlusive disease/Sinusoidal Obstruction Syndrome

- Centrilobular changes of congestion, fibrinoid thrombosis, and atrophy of central hepatocytes c/w venous outflow obstruction
- Differential diagnosis would include cardiac disease, Budd-Chiari syndrome
- Syndrome results from injury to sinusoidal and venular endothelial cells with primary injury being 2 sinusoidal lining cells and in some cases involvement hepatic venules is not present, hence the term sinusoidal obstruction syndrome

HPVD/SOS
Differential diagnosis

- Chemotherapeutic agents
  - Primarily related to treatment of leukemia/lymphoma
- Transplant related
  - Stem cell transplantation
  - Liver transplantation
- Radiation therapy
  - Abdominal radiation for Wilms tumor
  - Radioembolization therapy
- Toxins
  - African Bush tea/herbal medications

Radioembolization-induced liver disease/ SOS

- In a series of 45 pts without CLD
- 9/45 developed SOS
  - Occurred in first 60 d post RE
  - Jaundice, ascites, variable changes in AP/Transaminases
- 3 pts had rapidly progressive disease
  - 2 improved with TIPS
- 6 had disease controlled by diuretics
- All died of metastatic disease

Risk factors

- Younger age
- Lean body habitus
- Amount of activity related to liver volume targeted
- Prior chemotherapy
  - Particularly oxaliplatin and capecitabine
  - ?? A seed and soil combination?? SOS seen only when sufficient radiation is given to tissue primed by chemotherapy ?? Or additive/synergistic effect of these two toxic therapies

References

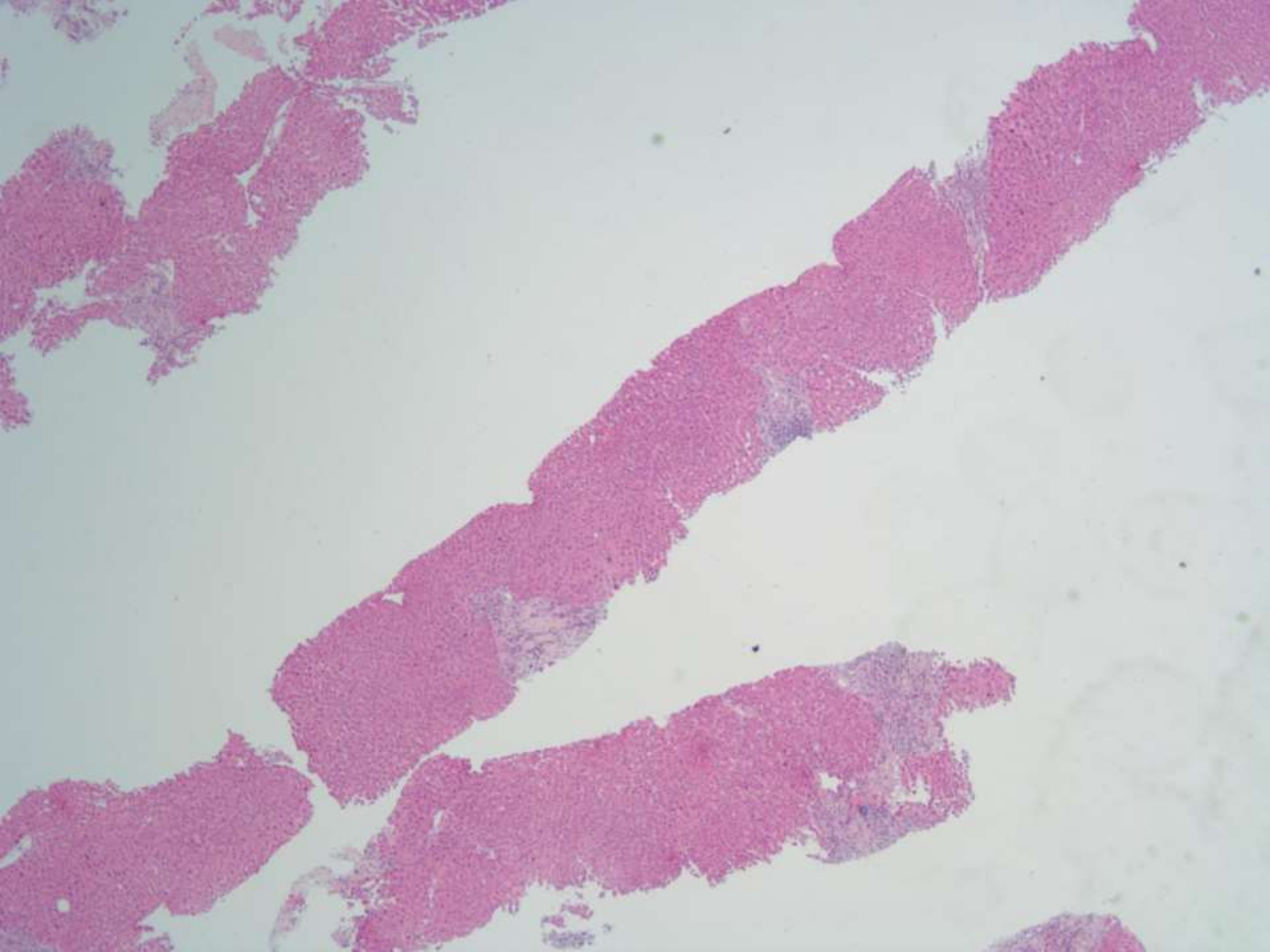
- Sangro et al: “liver disease induced by radio embolization of liver tumors: Description and possible risk factors”. Cancer 2008; 112: 1538-46.

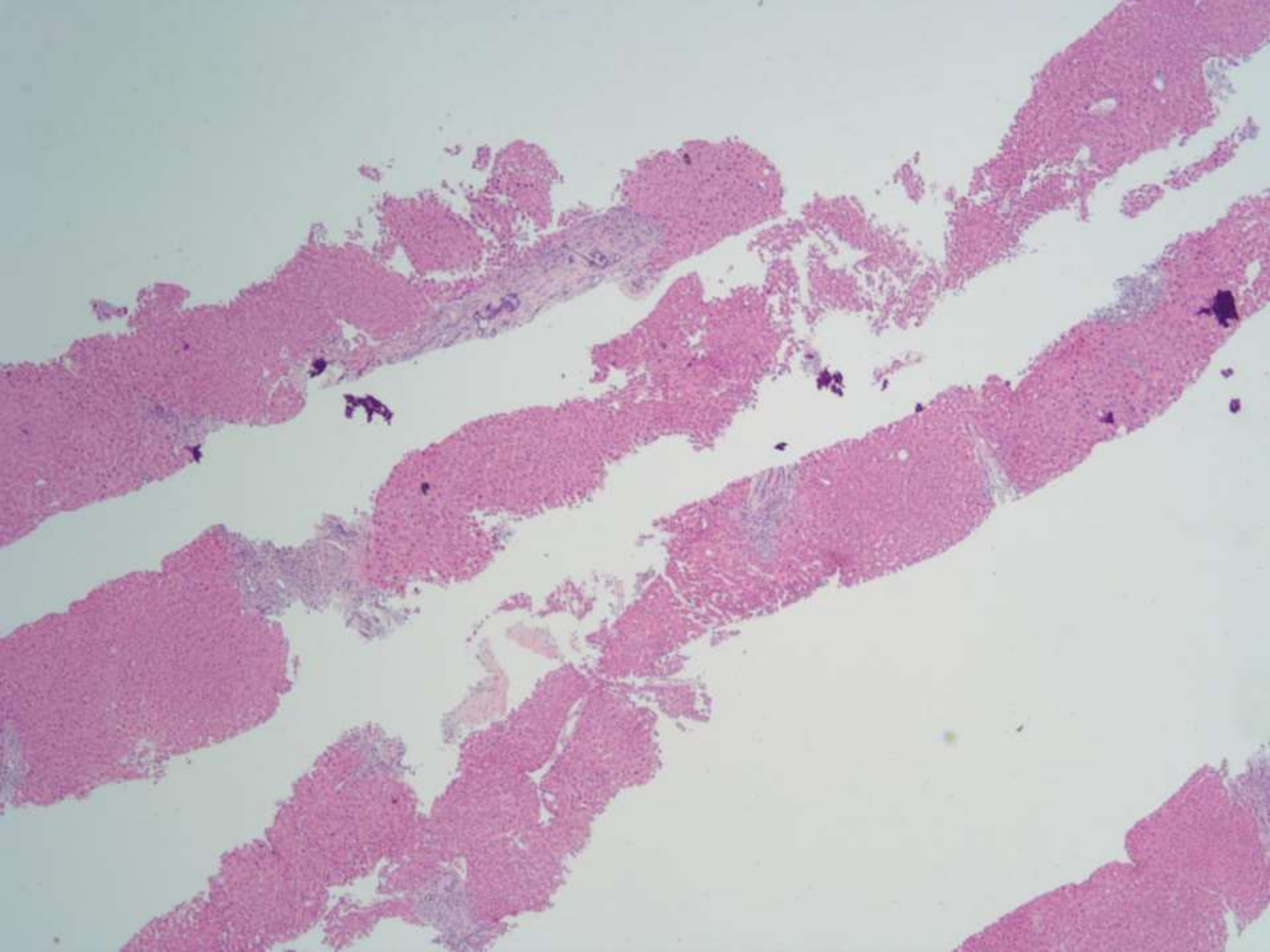
- Ferrell and Kakar: Case 11.3 pp182-3 in Liver Pathology. Demos Medical consultant pathology volume 4; 2011.

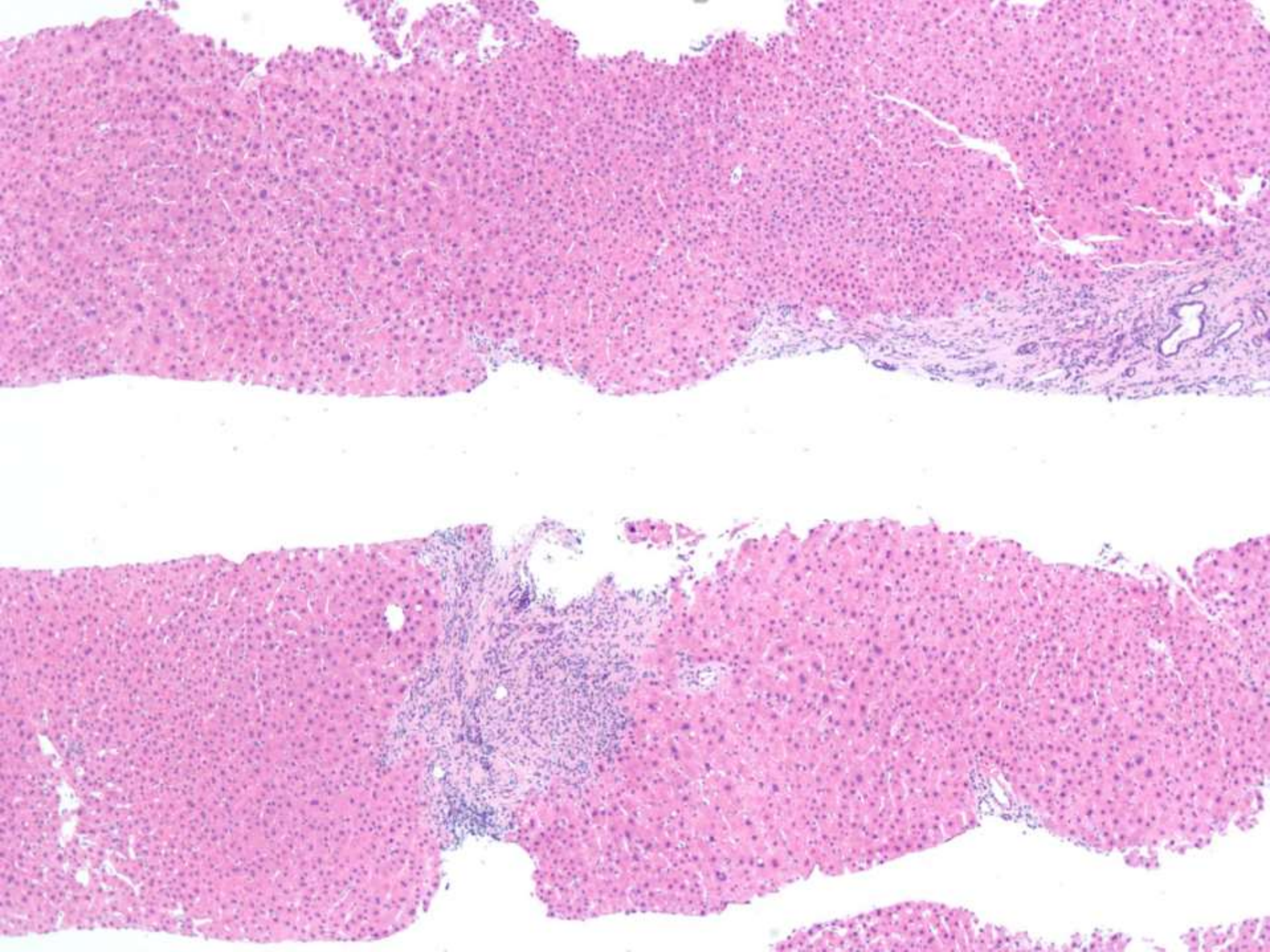
SB 6263

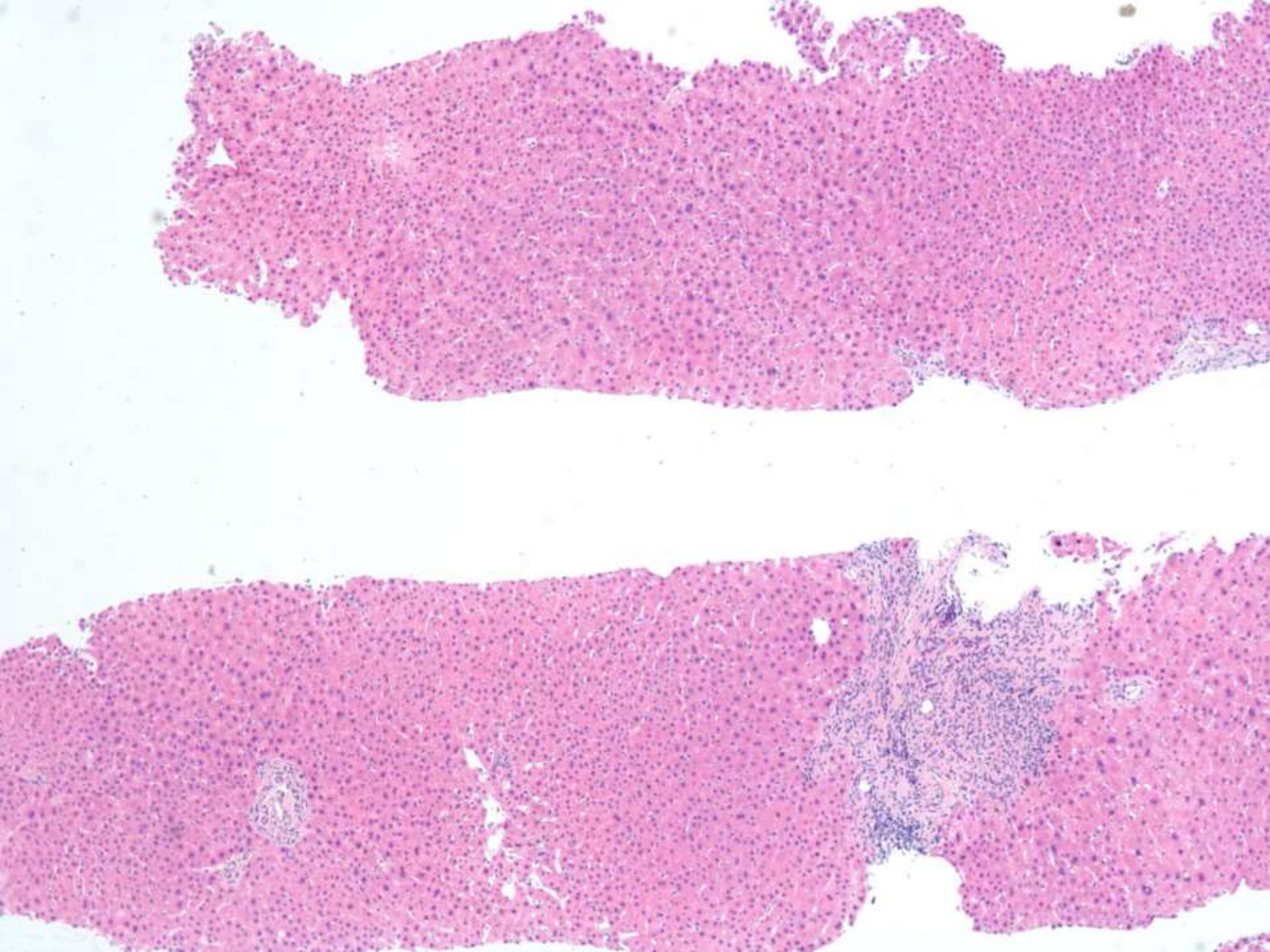
Charles Lombard; El Camino Hospital

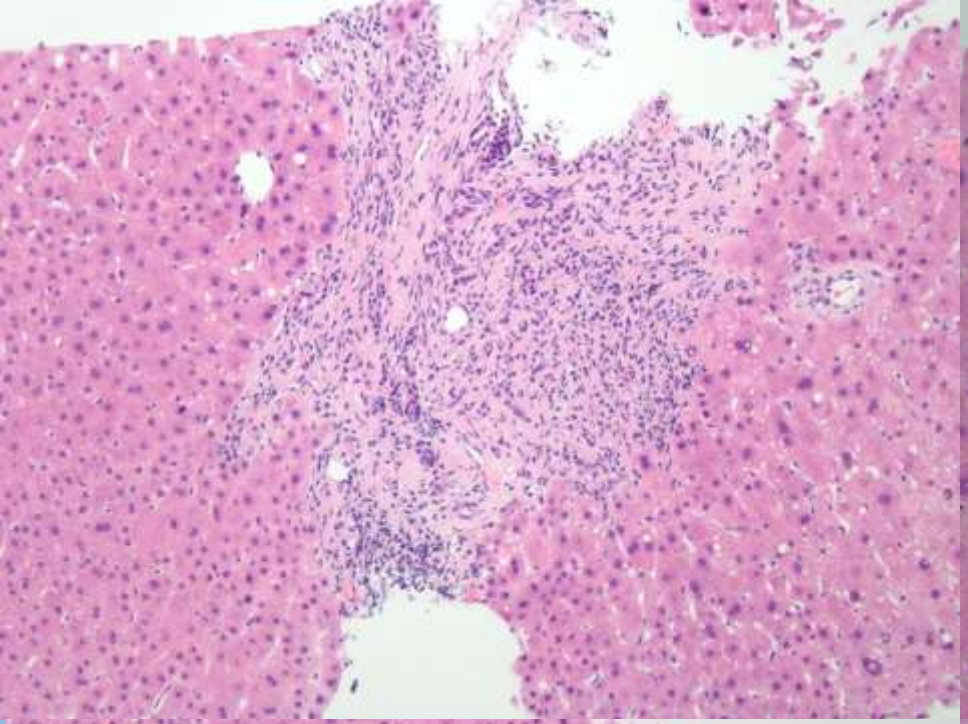
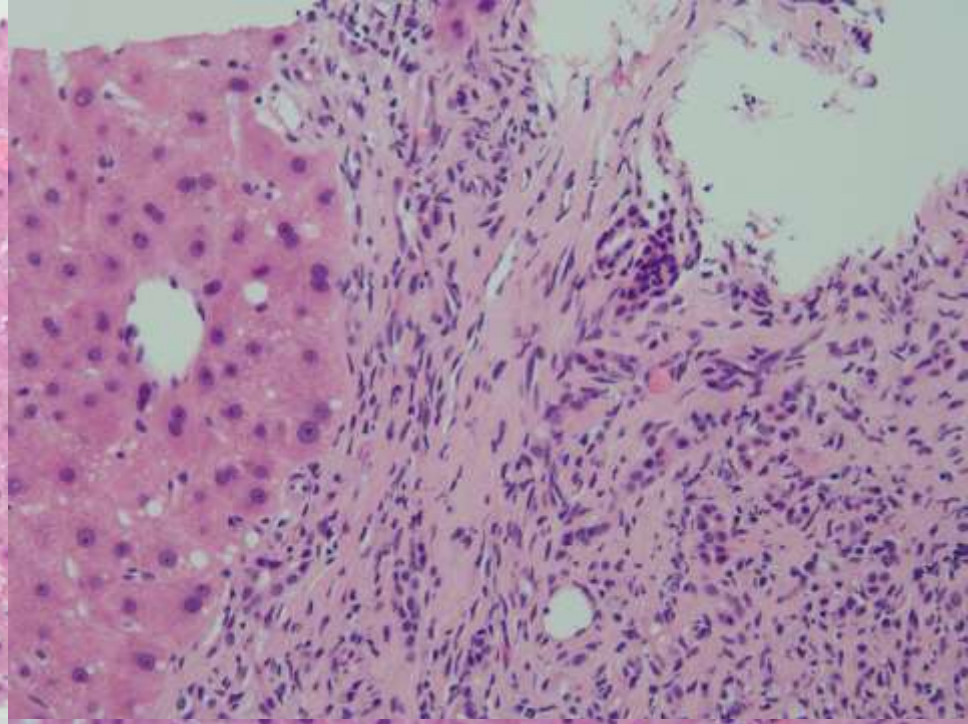
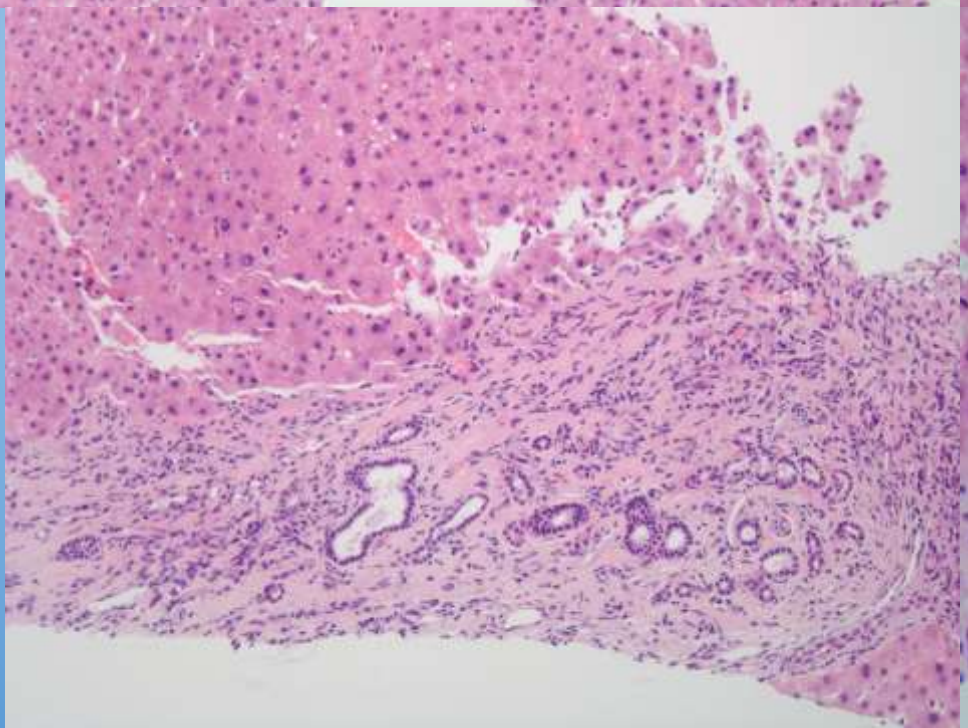
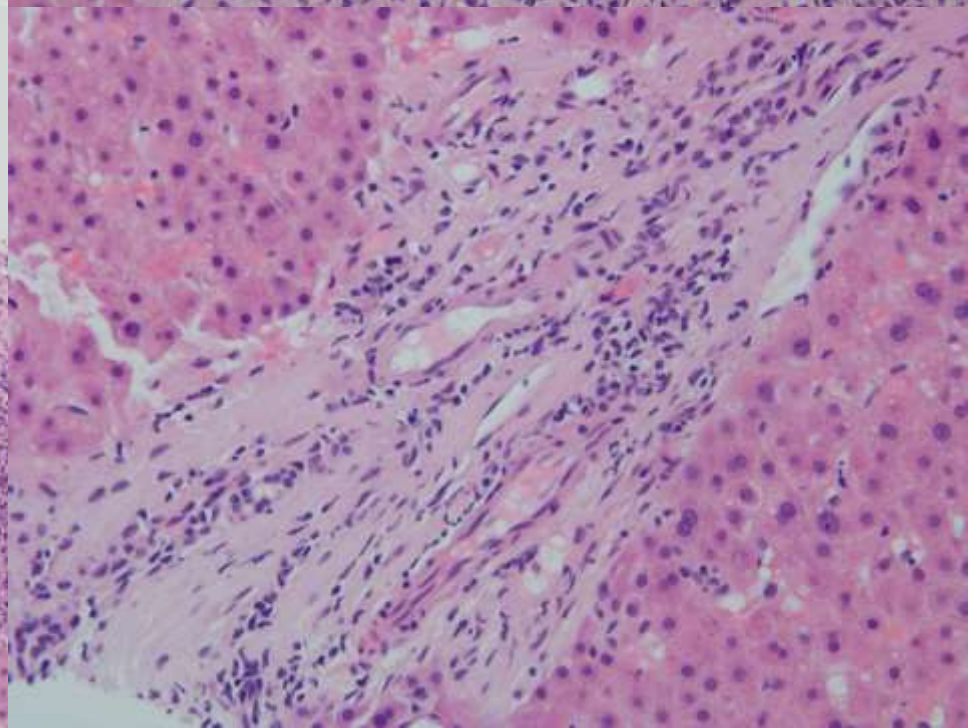
49-year-old male with portal HTN with pancytopenia (iron deficiency anemia), varices, and hepatic vein-portal vein gradient of 15-16mm Hg. Viral and auto-immune serology negative, AMA negative, ceruloplasmin/a1AT within normal limits. U/S: no evidence of intra/extra hepatic bile duct dilatation/obstruction/stones. U/S kidney: normal. U/S spleen: mild splenomegaly. Bili 1.1, AST/ALT 48/98, AP 267, GGT 155.

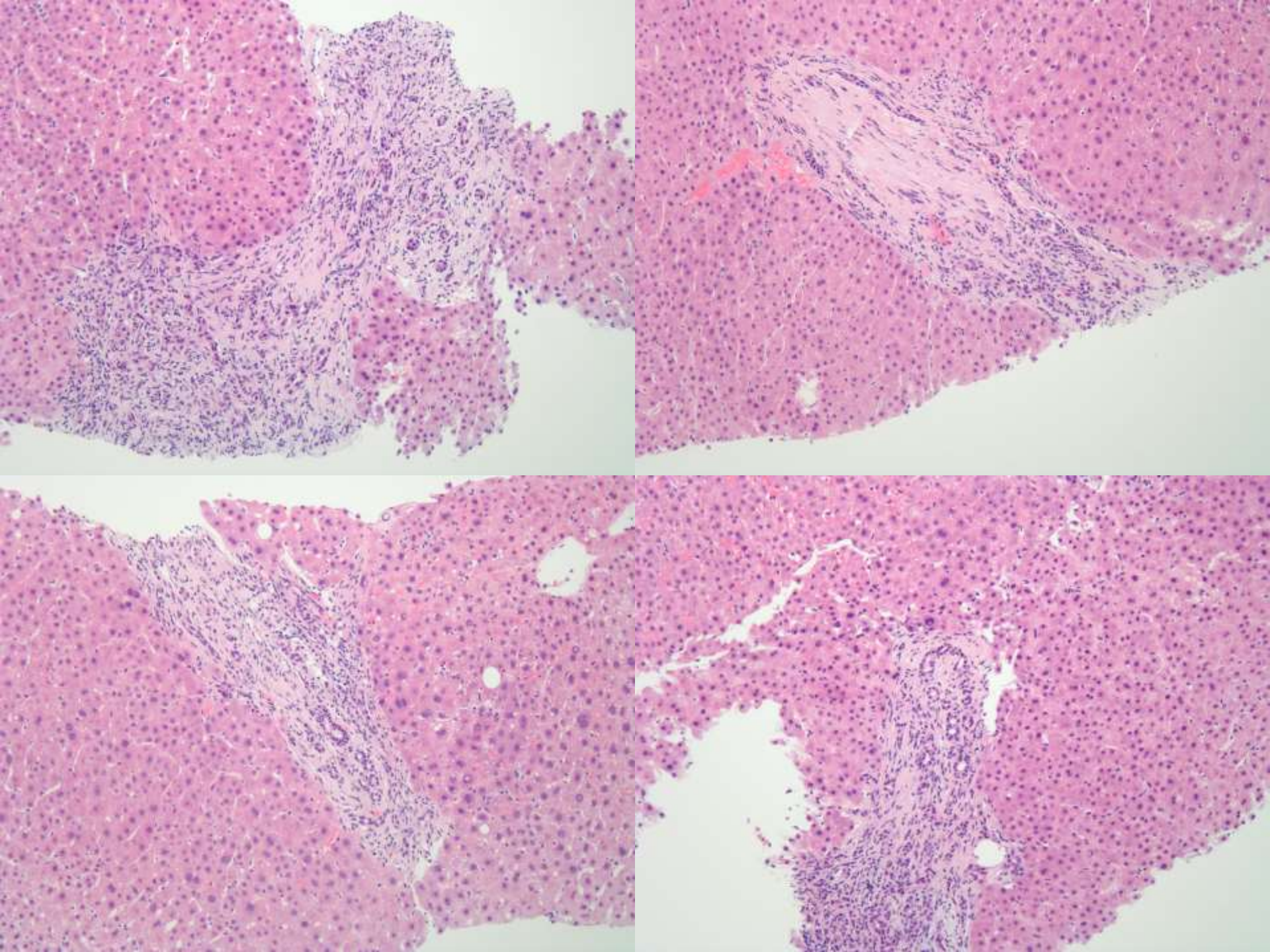


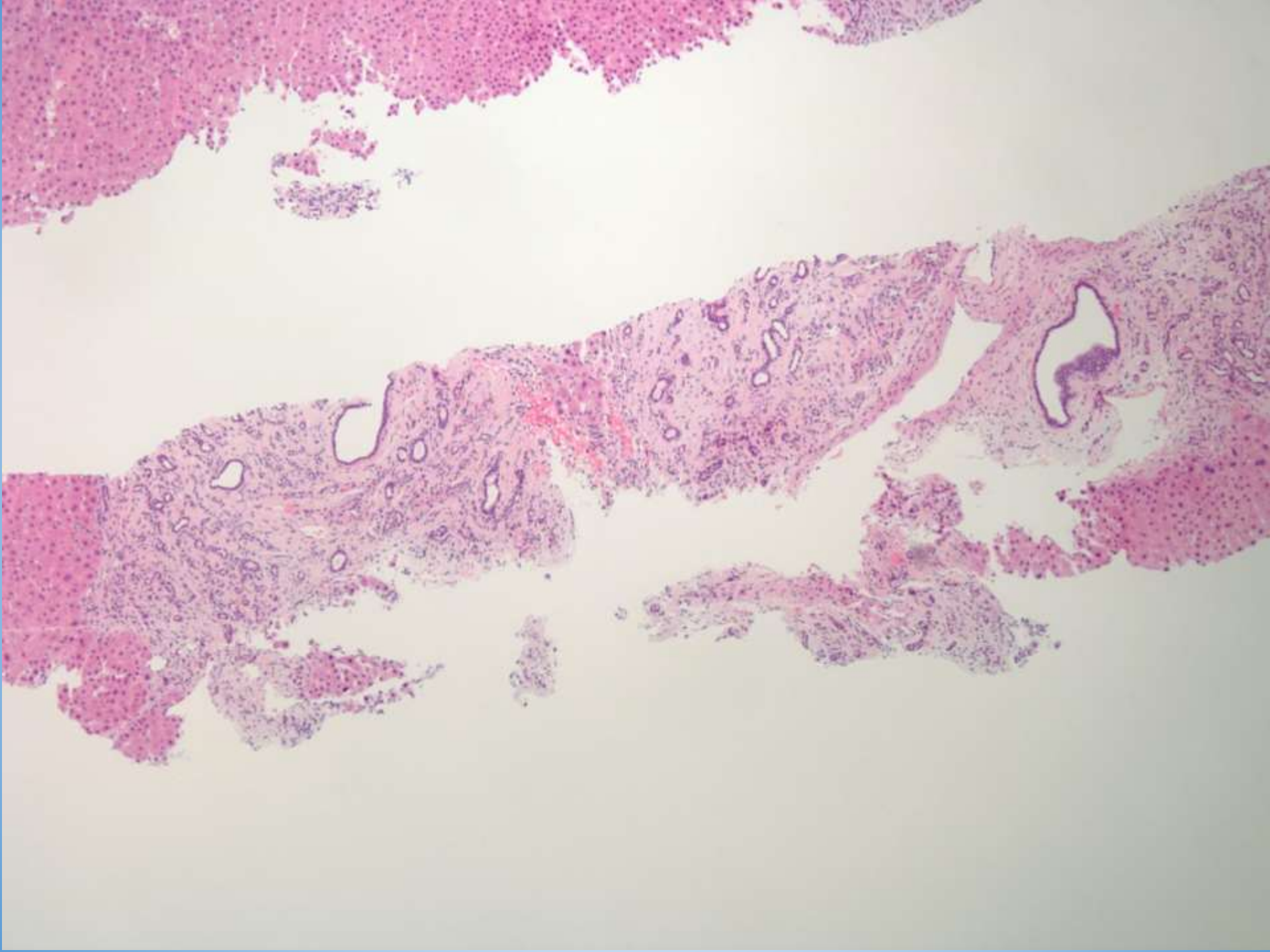


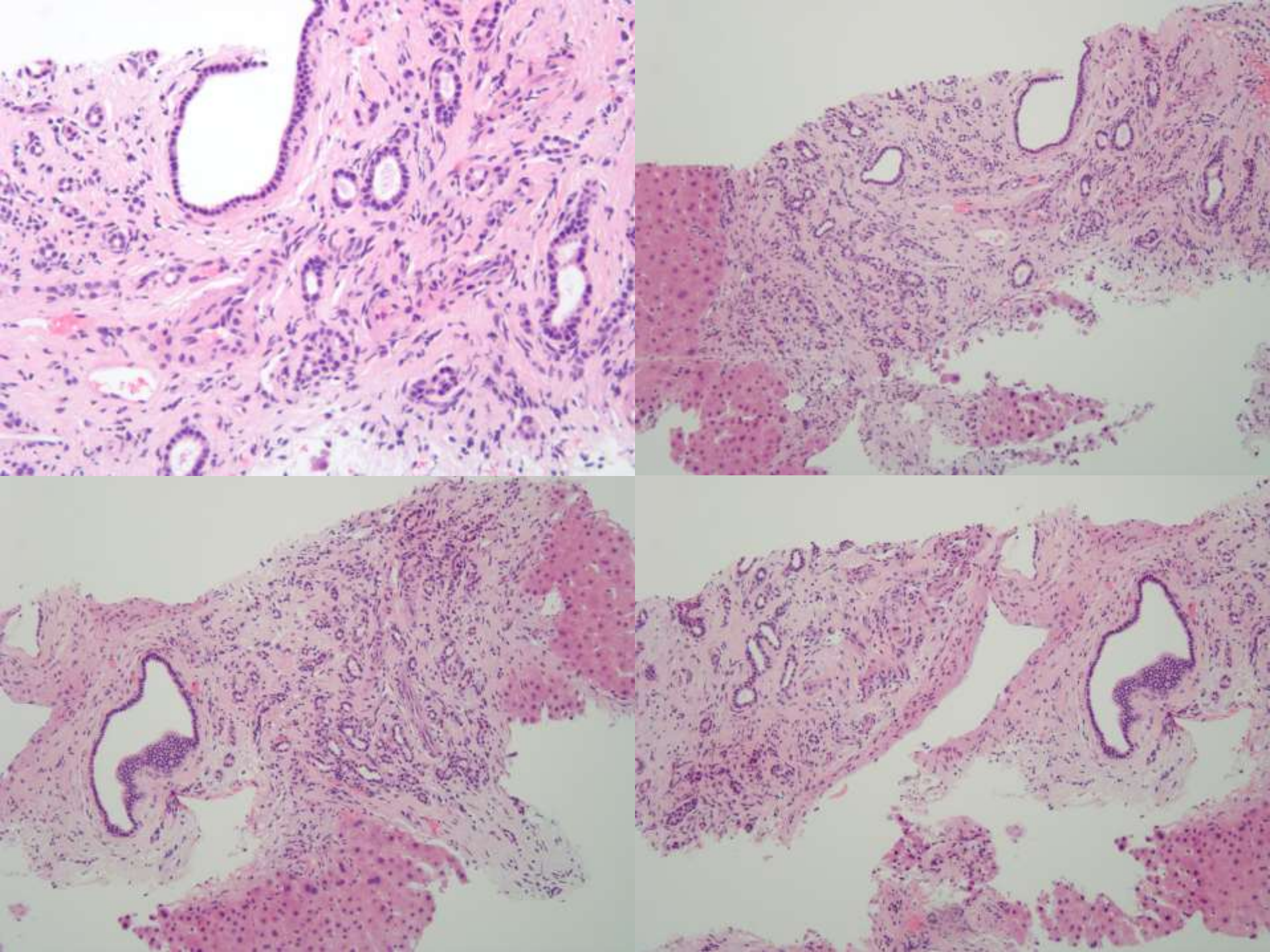




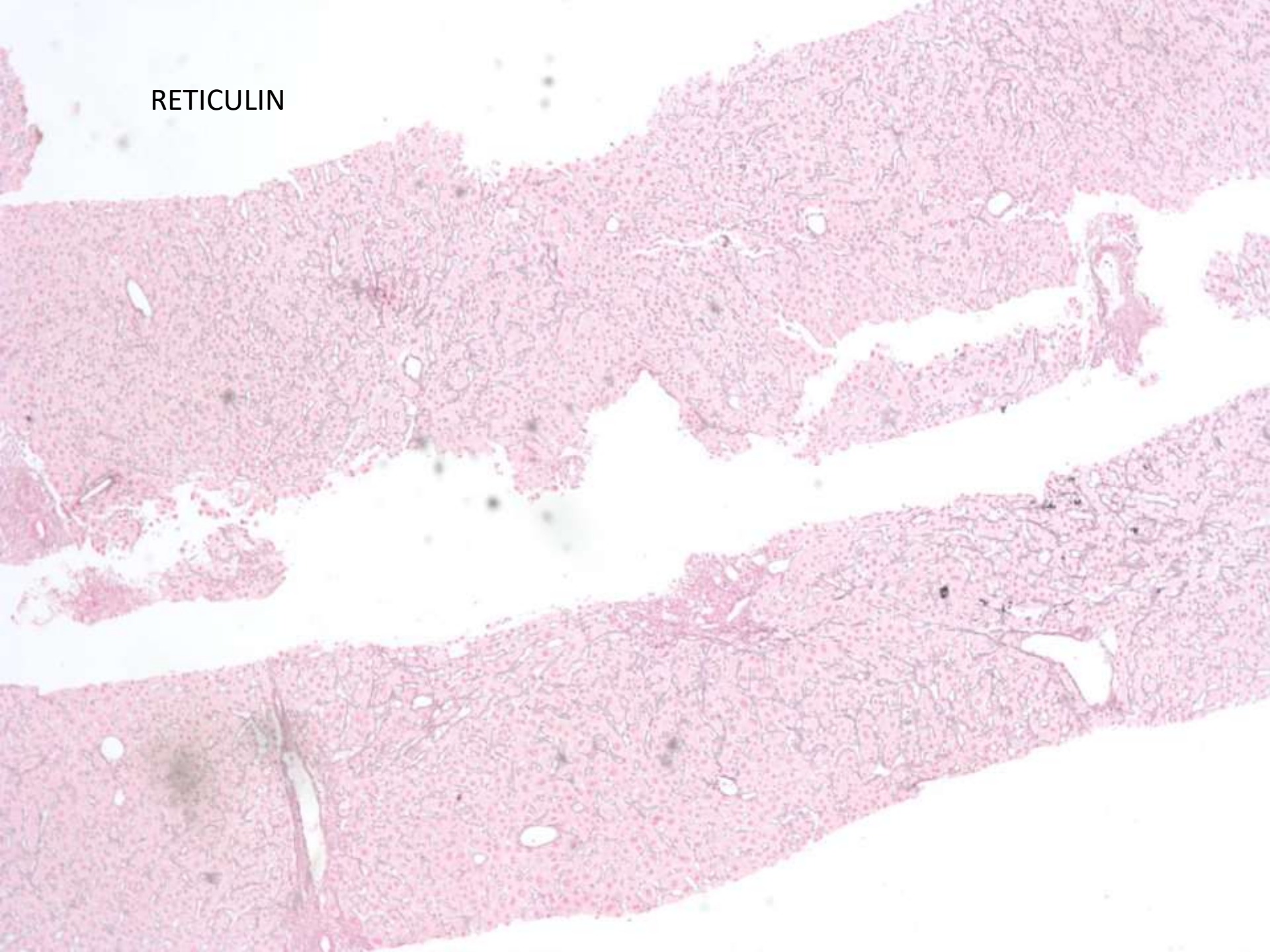







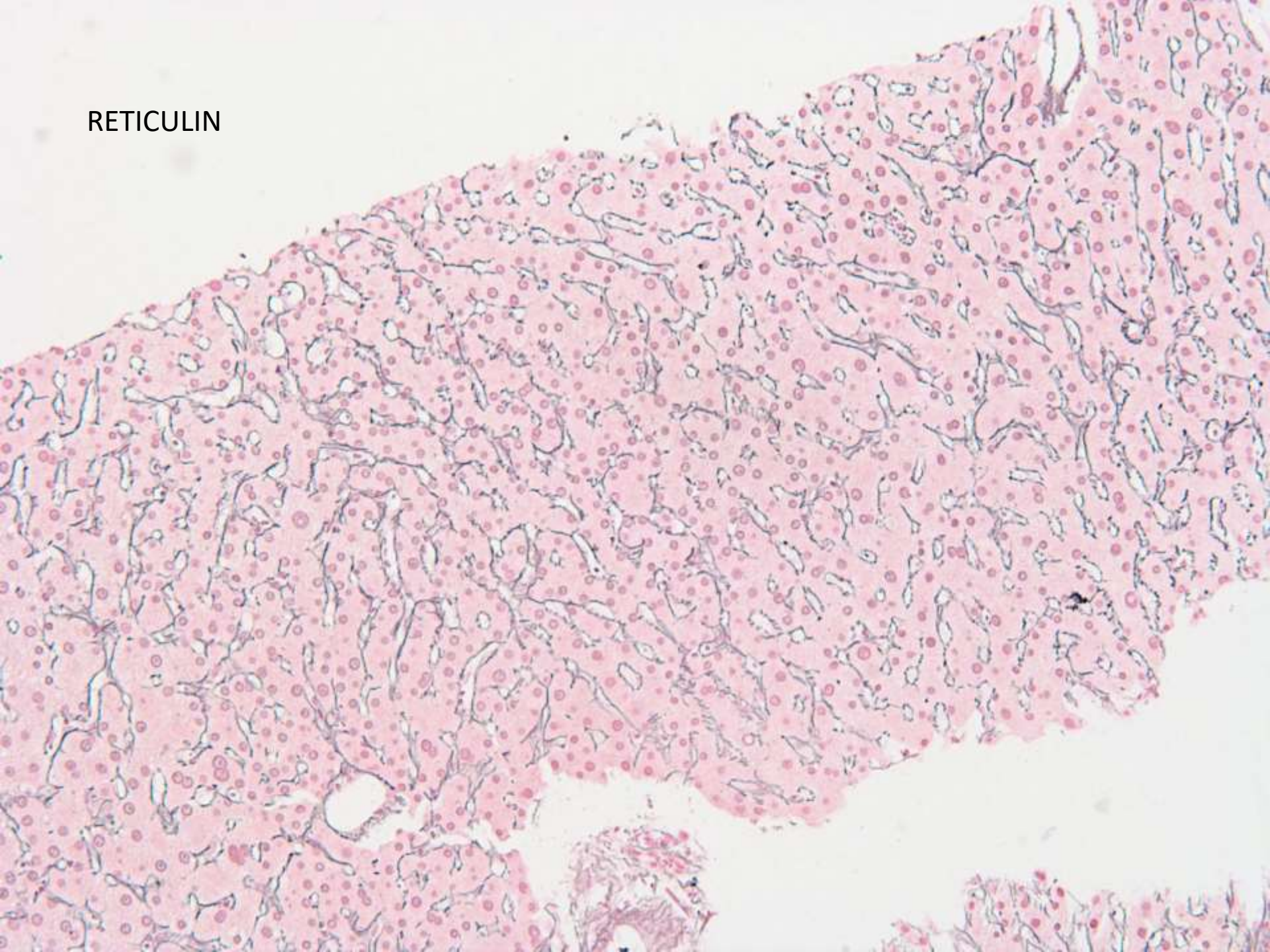


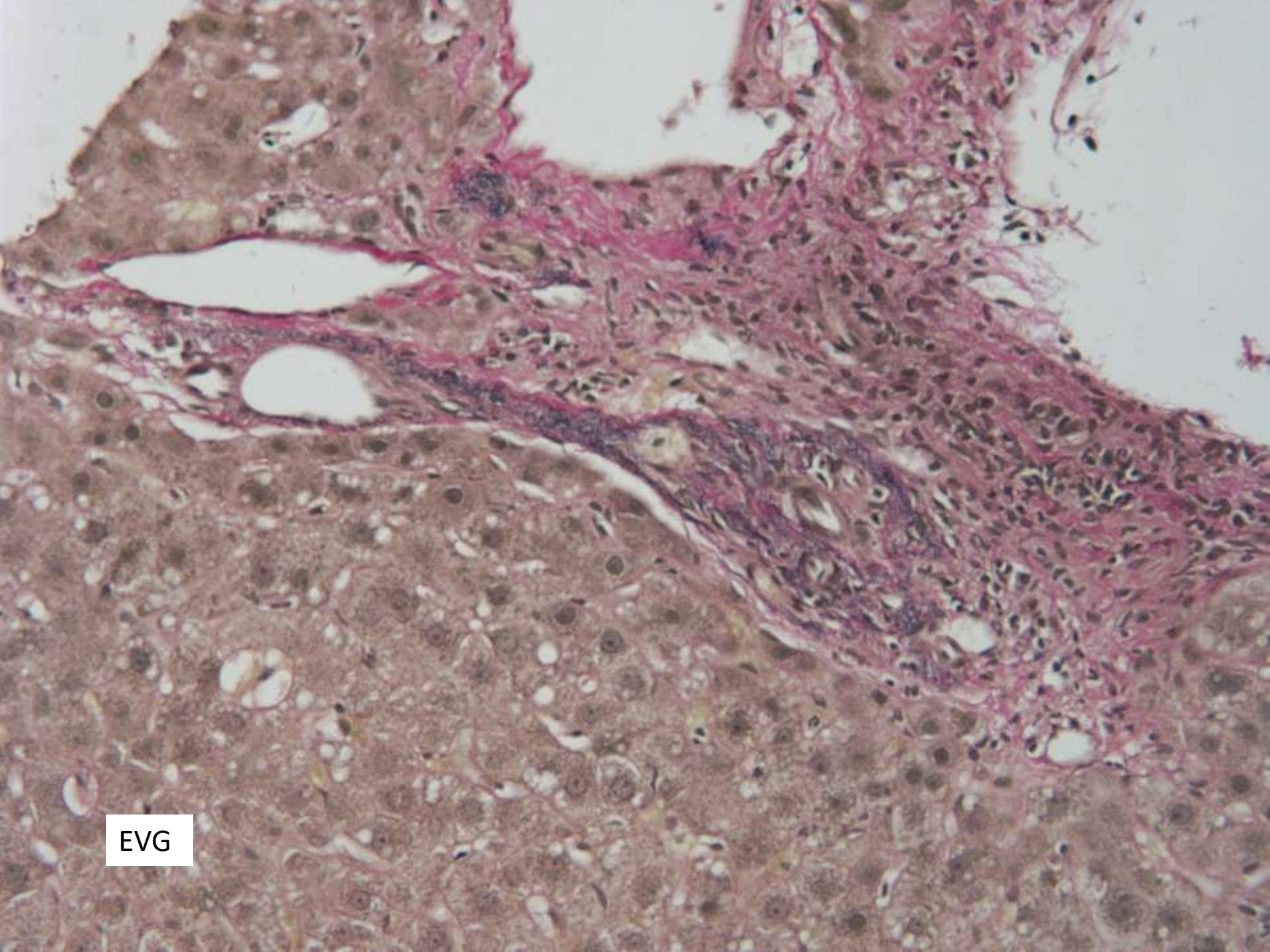


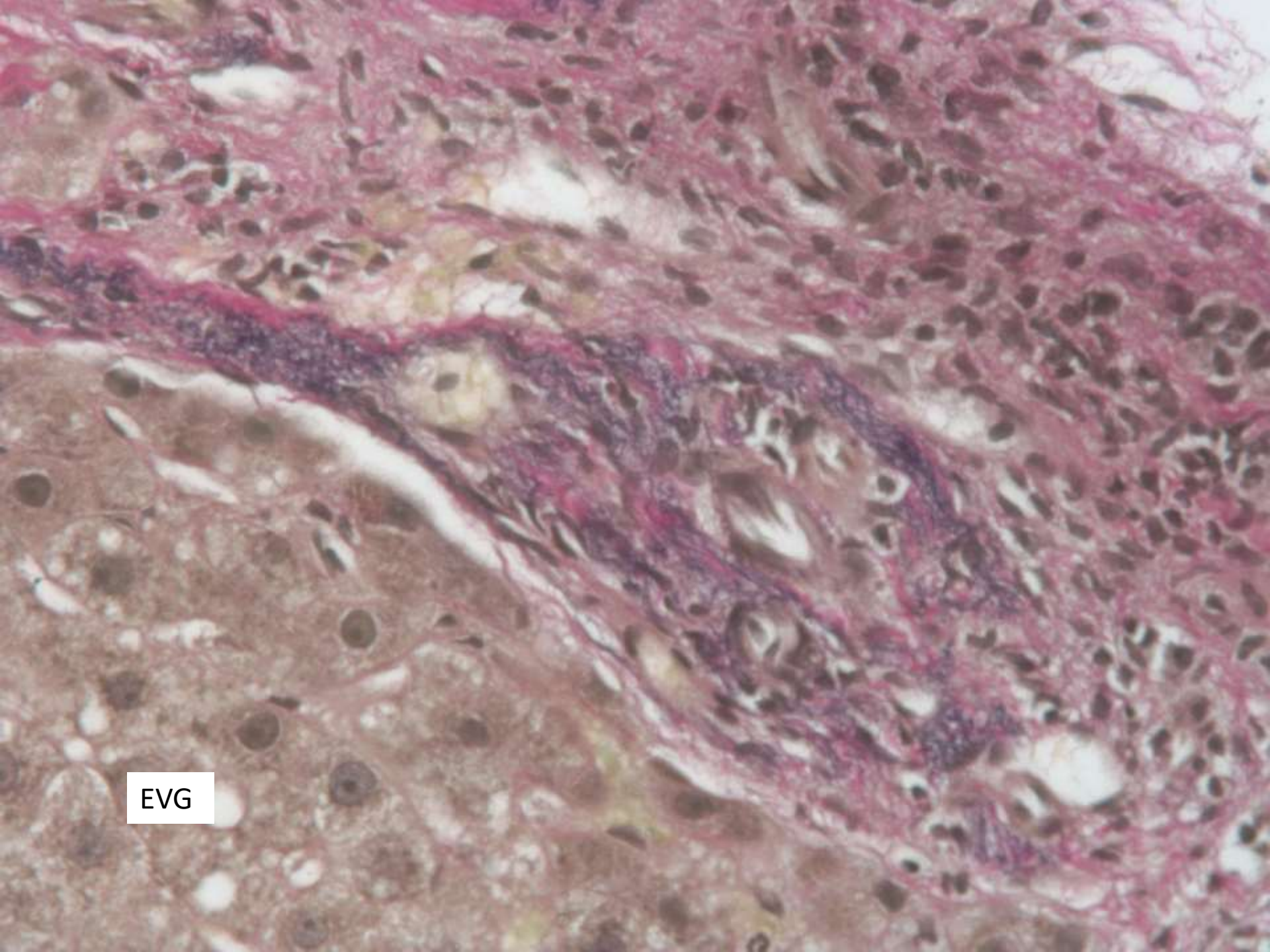
RETICULIN



RETICULIN

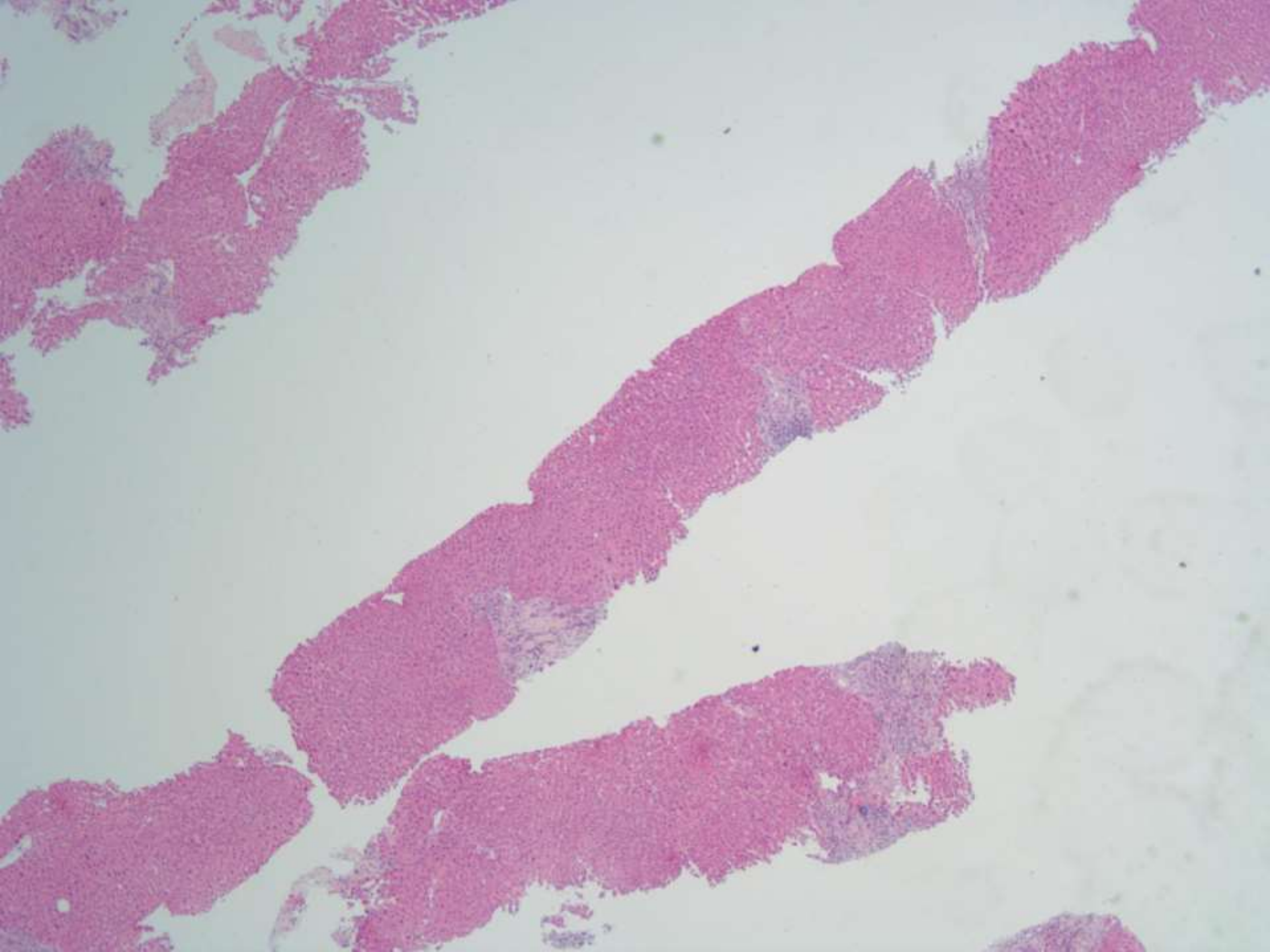


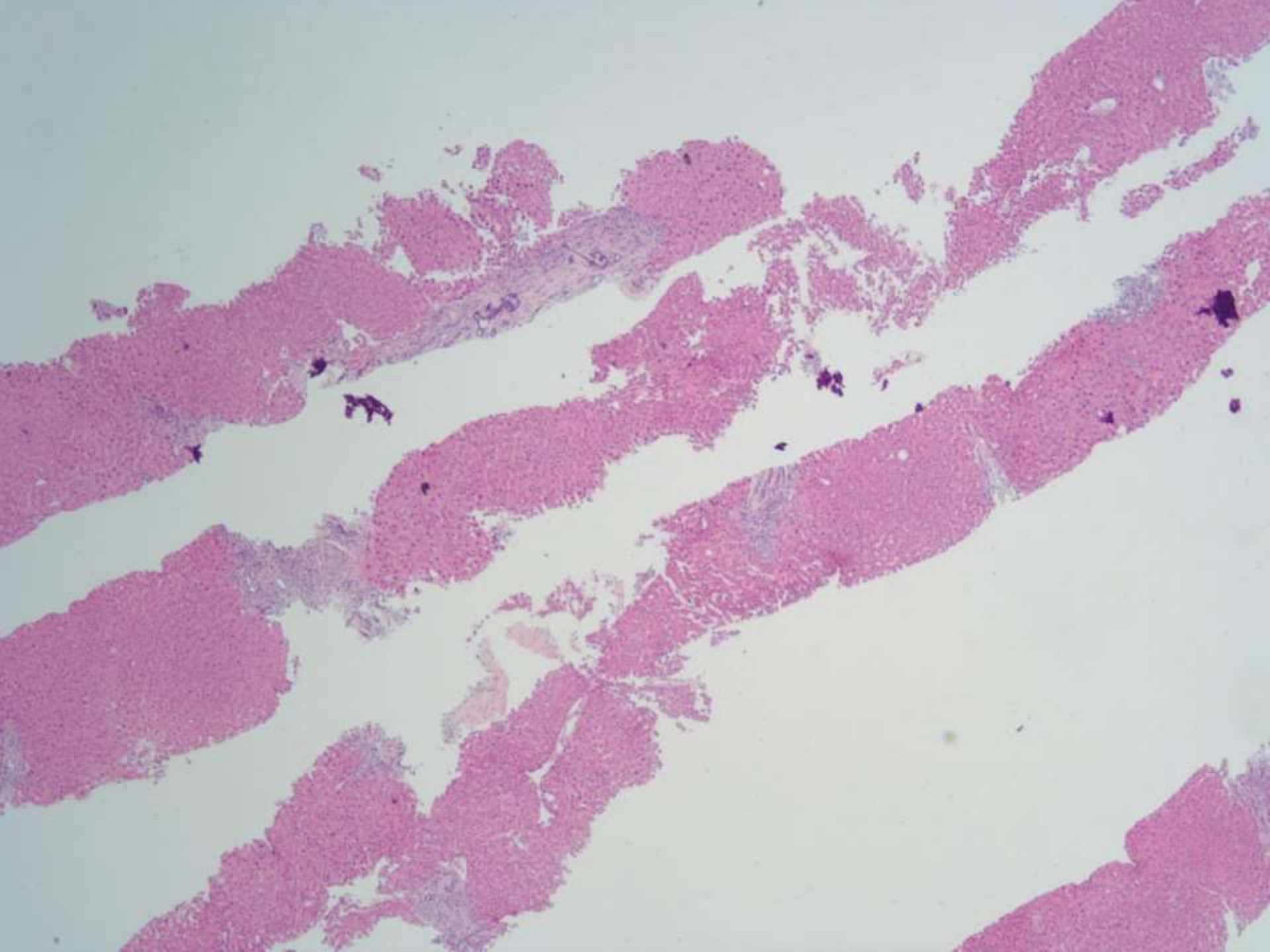

EVG

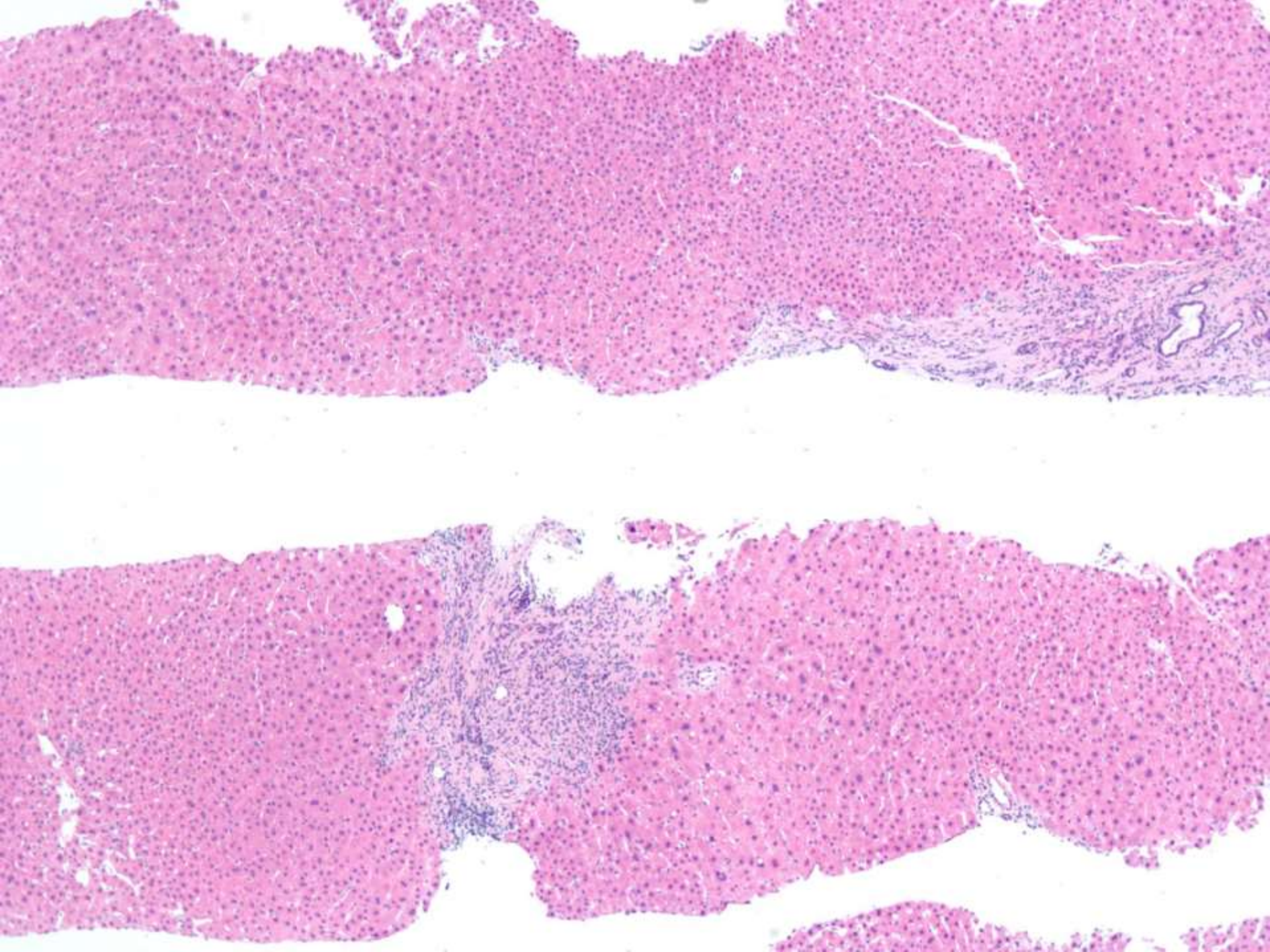

EVG

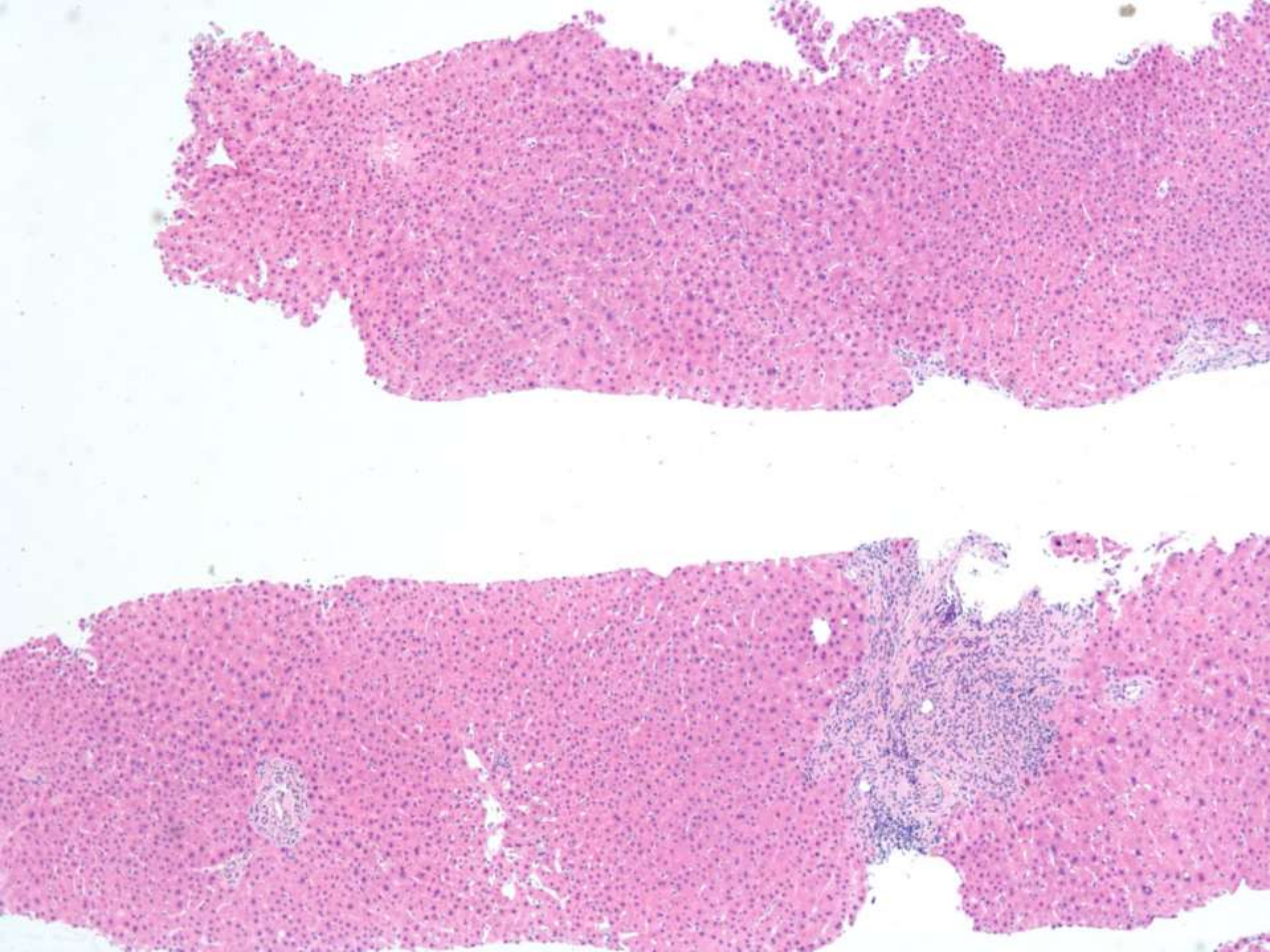
49 yo M TJ Needle bx liver

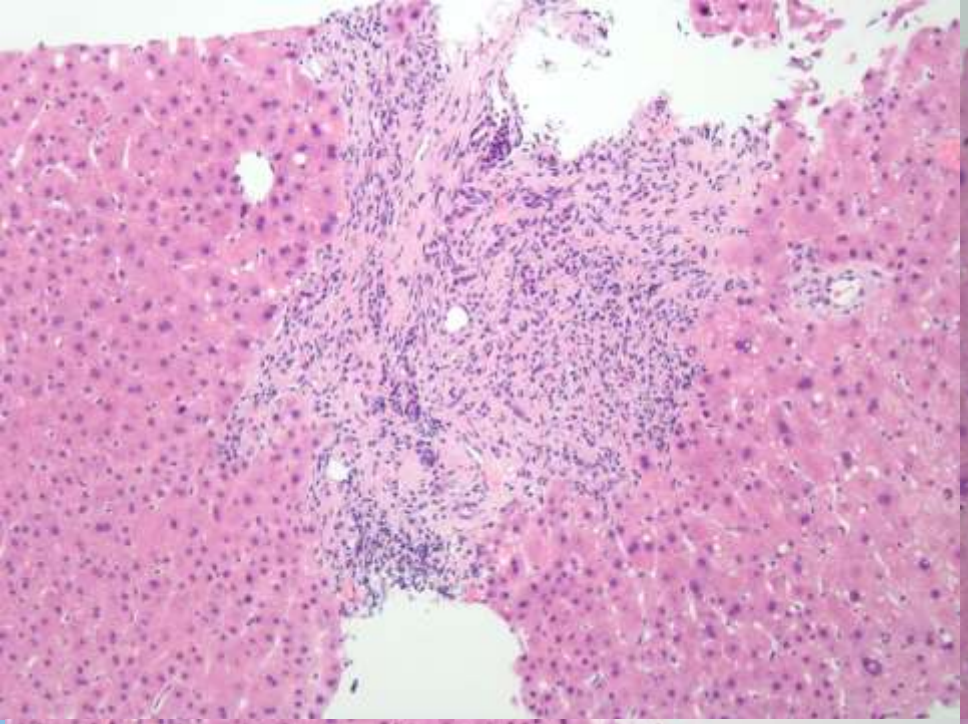
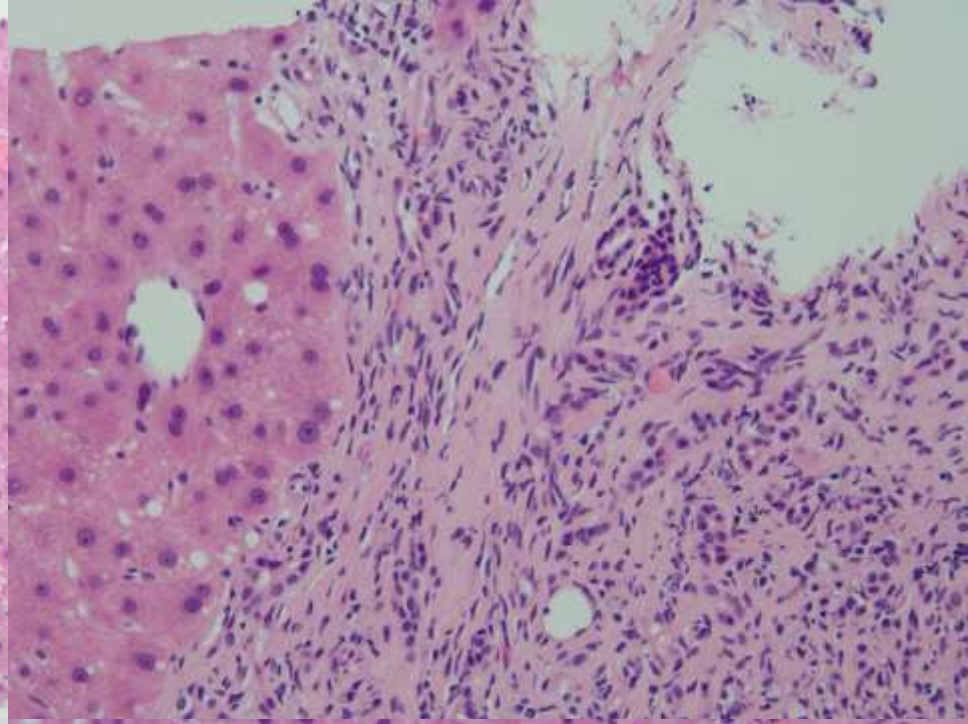
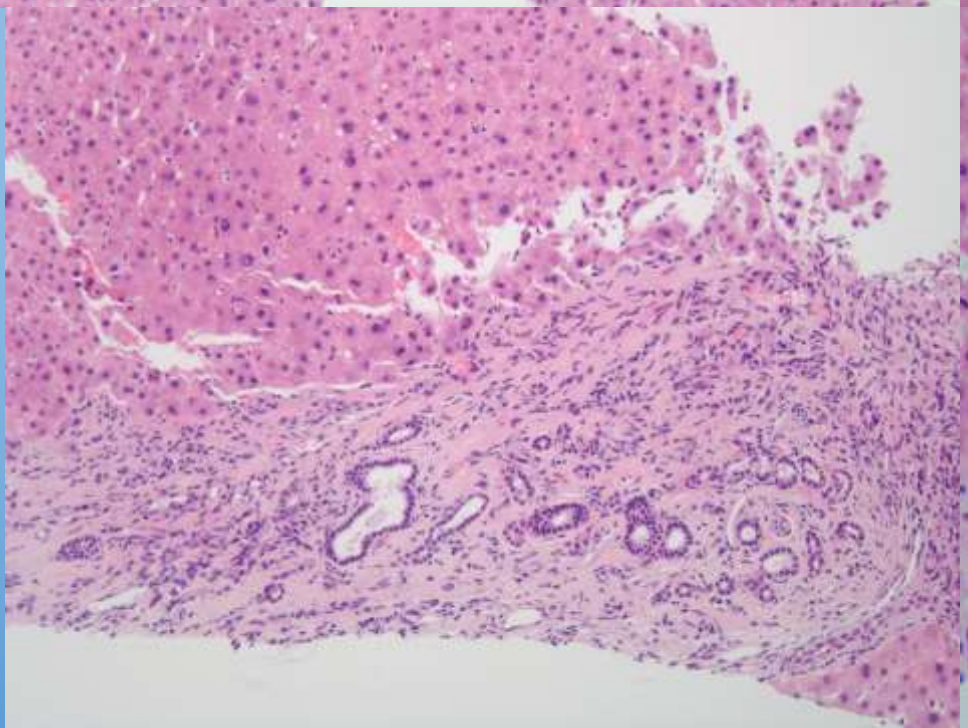
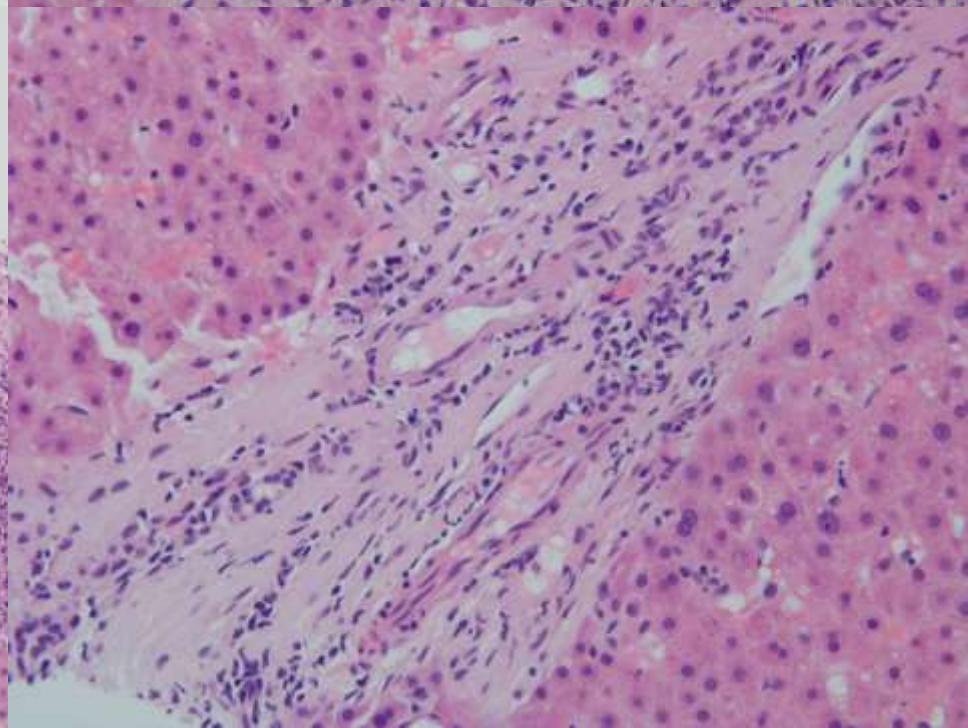
- Portal hypertension with pancytopenia (iron deficiency anemia), and varices.
  - Hepatic vein-Portal vein gradient : 15-16 mm Hg
- Viral and autoimmune serology negative
- AMA negative
- Ceruloplasmin/a-1-AT wnl
- U/S: No evidence of intra/extrahepatic bile duct dilatation/obstruction/stones
- U/S kidney: normal
- U/S spleen: mild splenomegaly
- Bili 1.1, AST/ALT 48/98, AP 267, GGT 155

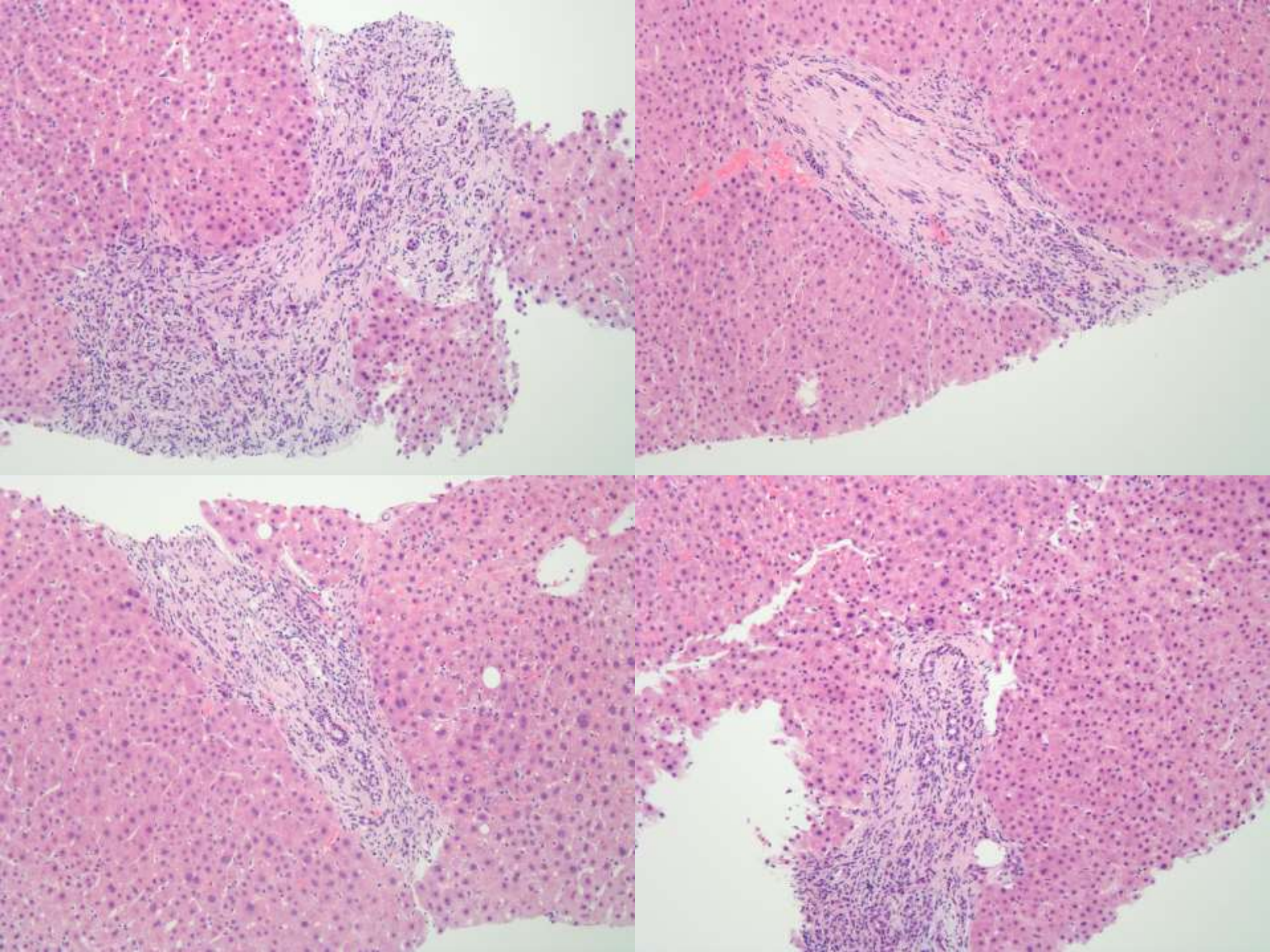


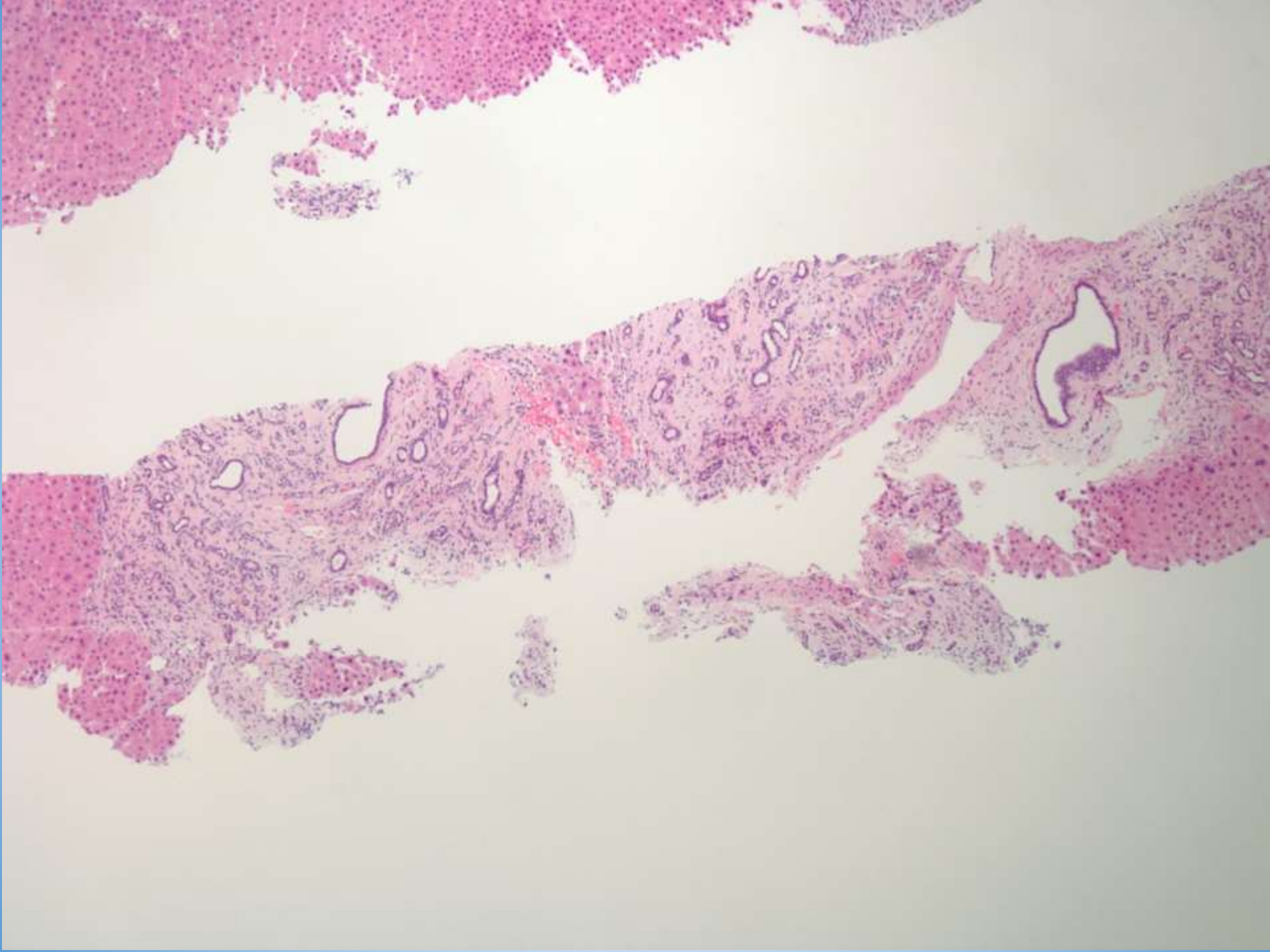


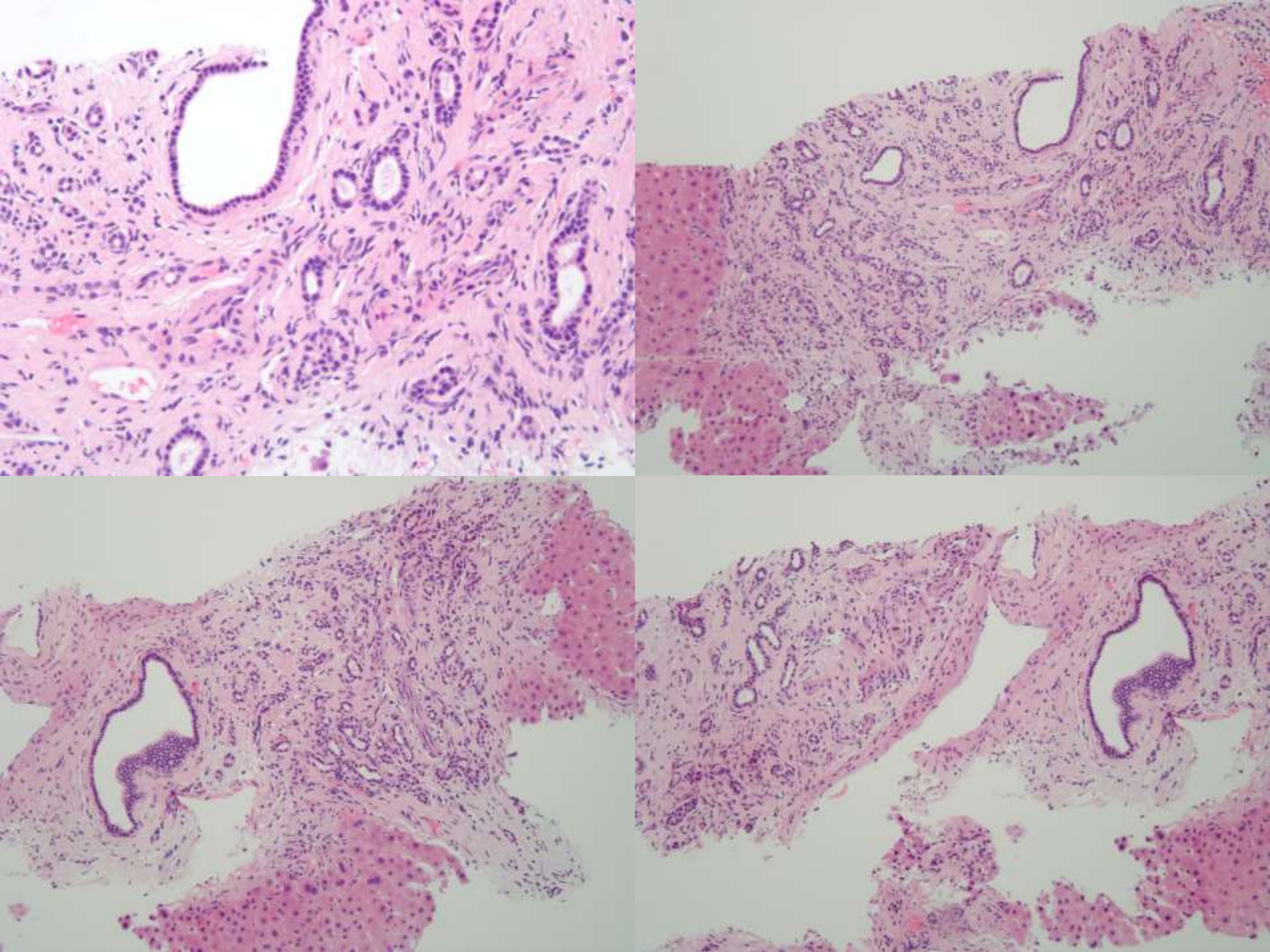




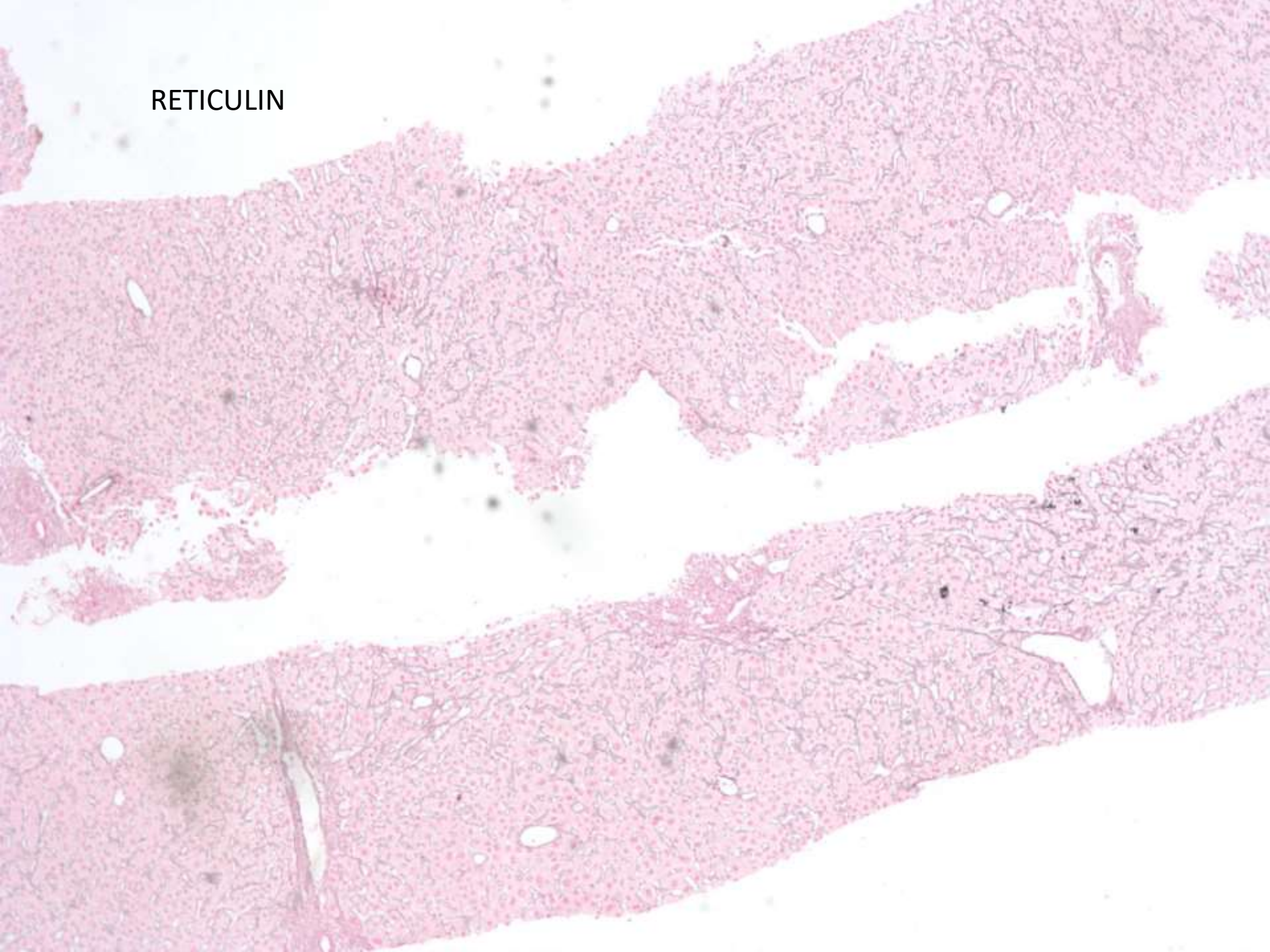







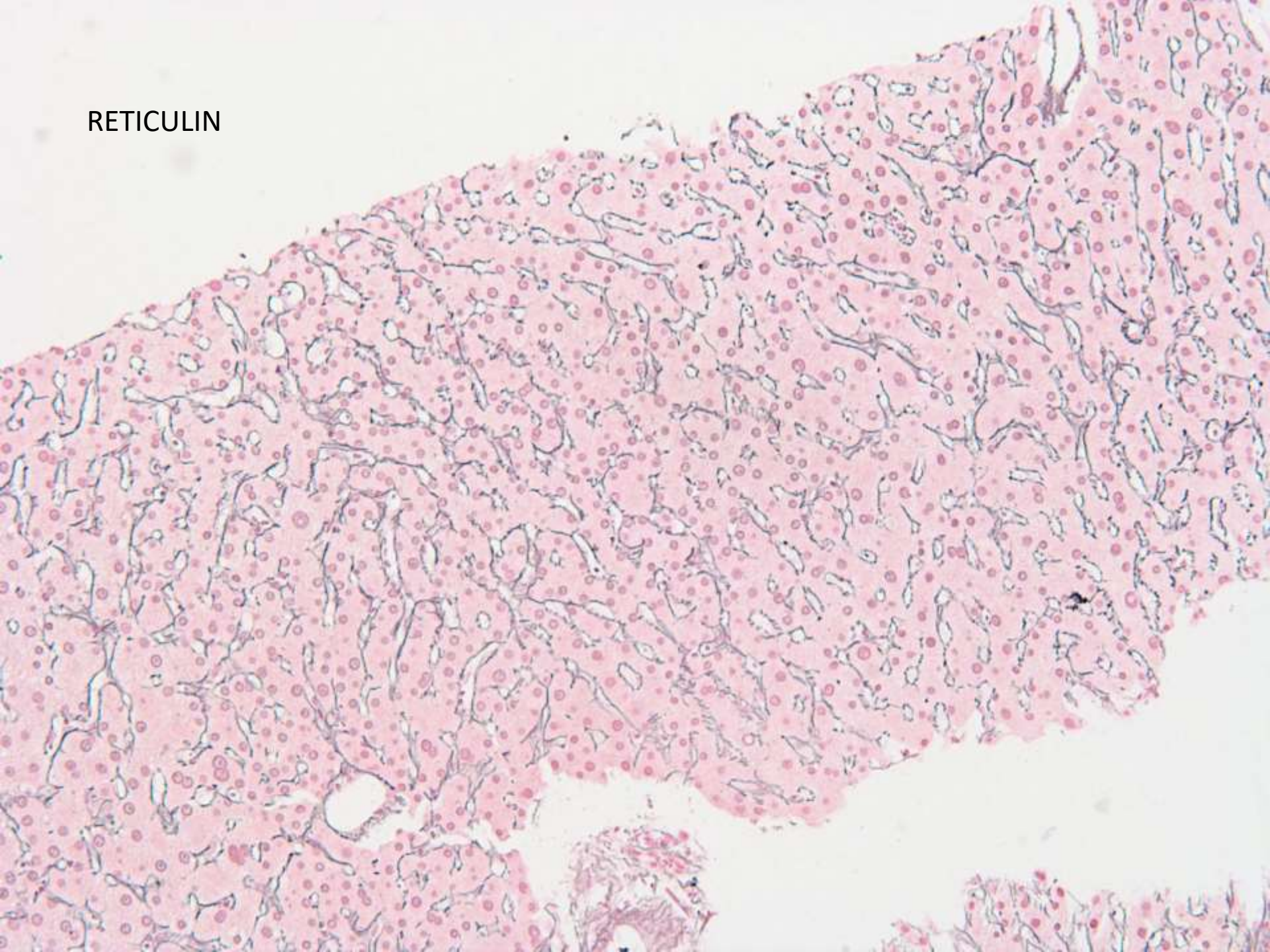


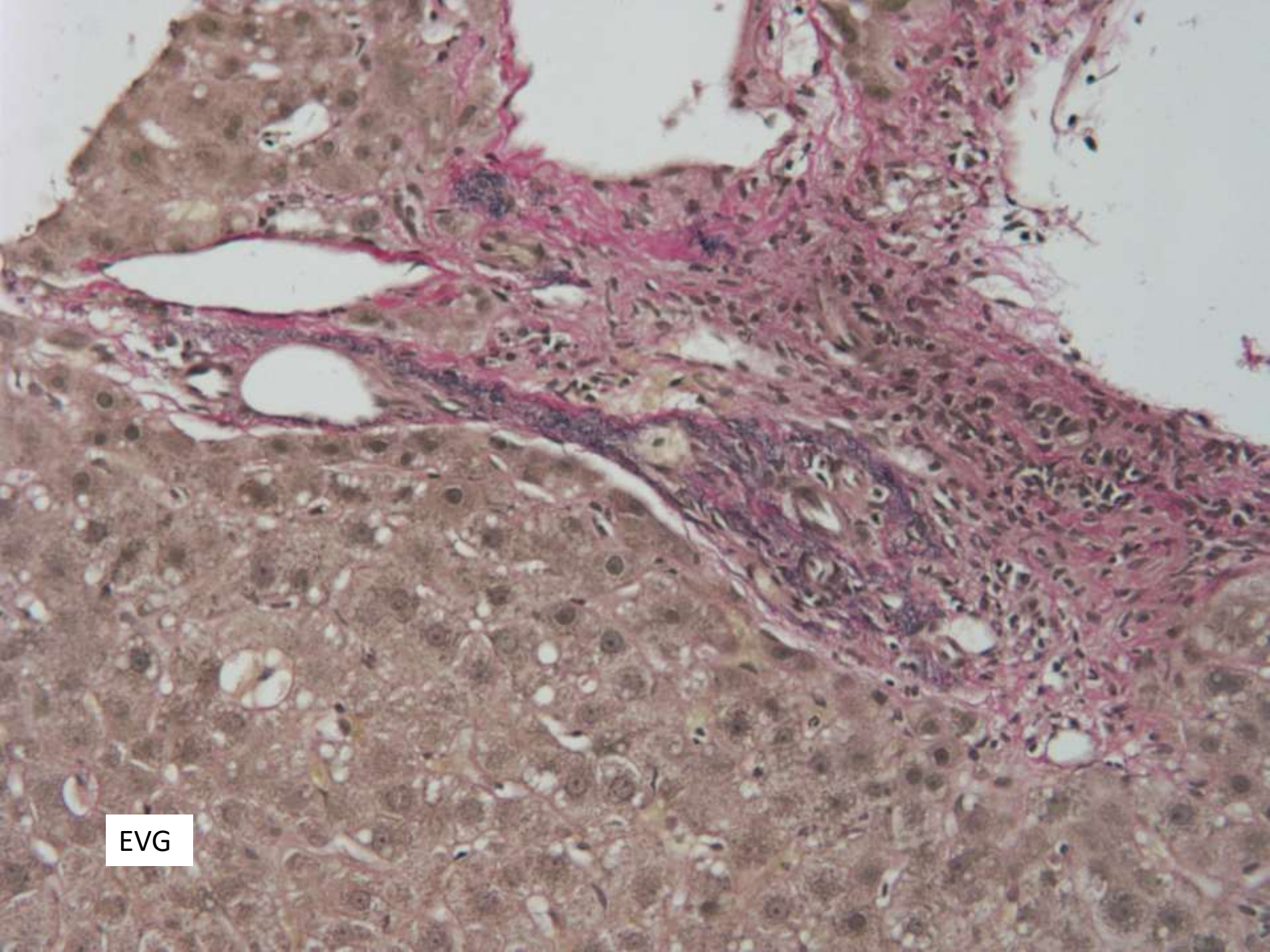


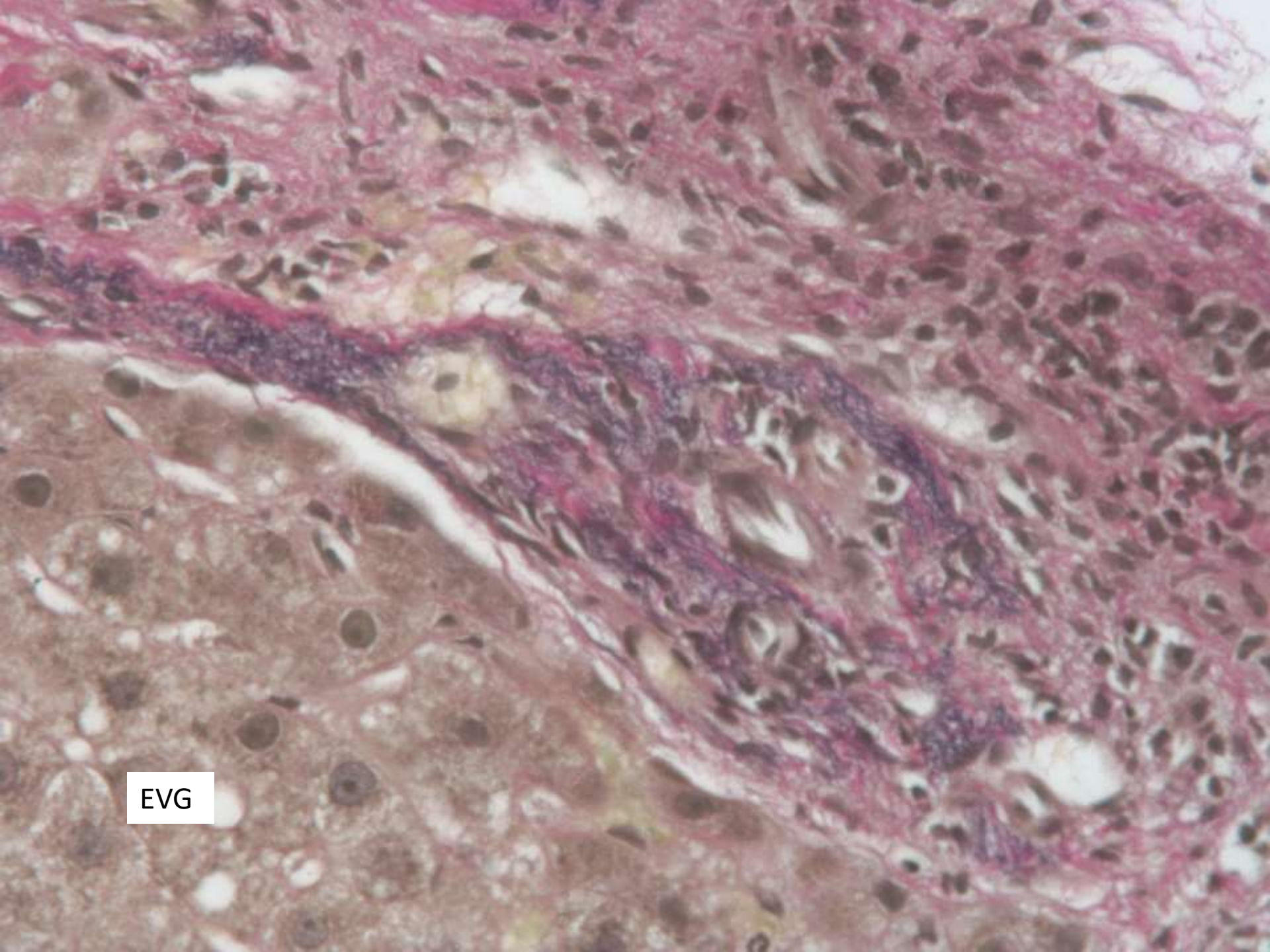
RETICULIN



RETICULIN




EVG


EVG

HV-PV gradient 15-16 mm Hg

Table 1

Different stage of liver fibrosis[17,18]

Classification	Stages				
METAVIR	F1-F3	F4	F4	F4	F4
HVPG (mmHg)		>6 mmHg	>10 mmHg	>12 mmHg	>16 mmHg
Clinical class		Stage 1	Stage 2	Stage 3	Stage 4
	No cirrhosis	Compensated	Compensated	Decompensated	Decompensated
			Varices	Variceal bleeding Ascites Encephalopathy	Variceal bleeding Ascites Encephalopathy Bacterial infection Hepatorenal syndrome
1-yr mortality		1%	3%	10-30%	60-100%

HVPG, hepatic venous pressure gradient.

Descriptive sign out

- Hepatic portal fibrosis and associated biliary hyperplasia (see description).

- ?? Noncirrhotic portal fibrosis/idiopathic portal hypertension
  - No active venous thrombosis but rare recanalized vein in portal area identified
  - Most portal areas appear to lack “normal” sized venous structures
  - Fibrosis is strictly portal without significant inflammation
  - Reticulin shows no evidence of NRH of liver
  - Degree of bile duct proliferation seems unusual as compared to most published cases

DDX:

- Biliary plate malformation group
  - Polycystic liver disease (no cysts in liver)
  - Caroli disease (no cysts/stones in liver)
  - Congen hepatic fibrosis (no cysts in liver/kidney)
    - Absence of typical curvilinear abnormal bile ductules
    - Atypically advanced age at presentation
- Common biliary diseases
  - Stone disease (no history in past; none seen now)
  - PSC
  - Occult biliary ca


@luishcruzc

Mayo Clinic Rochester Consult

- Agree with your impression. Although the bile ducts look funny, I do not think it is enough for CHF. As you have already noticed, there are portal vein loss and hypoplasia. We call these findings as hepatoportal fibrosis which could be idiopathic, drug/toxin induced, or secondary to portal vein thrombosis.
- UCSF: “The possibility of Idiopathic PHTN can be considered if diffuse involvement by ductal plate malformation is not supported by the clinical and radiographic findings”.

Noncirrhotic portal fibrosis/idiopathic portal hypertension

- Definition: The disease of uncertain etiology characterized by portal fibrosis and involvement of small and medium branches of the portal vein resulting in the development of portal hypertension.
  - Poorly characterized in western countries generally regarded as clinical entity of intrahepatic portal hypertension without evidence of cirrhosis or other diseases accountable for portal hypertension

IPF/NCPHTN

- 30-40% of PHTN cases in Japan/Indian subcontinent
- 3-5% of cases in Western countries
  - ?? Higher as some may be misdx as “cirrhosis”
- Male predominance in India/West; Female in Japan
- Age: 25-56 (cases tend to be younger in Japan)

IPF/NCPHTN
Clinical presentation

- Variceal bleeding
- Splenomegaly
- Pancytopenia
- HVPV gradient may be normal or increased
- Ascites, Jaundice, encephalopathy, HRS are infrequent
- LFT’s variable; hepatic synthetic function preserved

IPF/NCPHTN Etiology

- None identified > 50% of cases
- Multitude of immune disorders
  - RA,SLE,PSS,SS,MG,CD, thyroiditis, CVID…
- HIV ?? Treatment related (didanosine)
- Medication, chemicals, toxins
- Hypercoagulability
  - About 50% patients are thrombophilic
  - Secondary PV thrombosis is common

IPF/NCPHTN Pathology

- Depends on phase of disease but histologic components include:
  - Obliterative portal venopathy
  - Portal fibrosis
  - Other features
    - Absence of cirrhosis
    - May see NRH
    - May see bile duct hyperplasia (generally mild)
      - 12/32 in autopsy series
    - Inflammation absent to minimal
    - Abnormally dilated portal veins

IPF/NCPHTN Treatment/Outcomes

- Medical/endoscopic management of varices
- TIPS for refractory cases
- Consider anticoagulation for thrombophilic cases
- Liver transplantation for complicated PHTN
- Long term prognosis appears better than cirrhosis

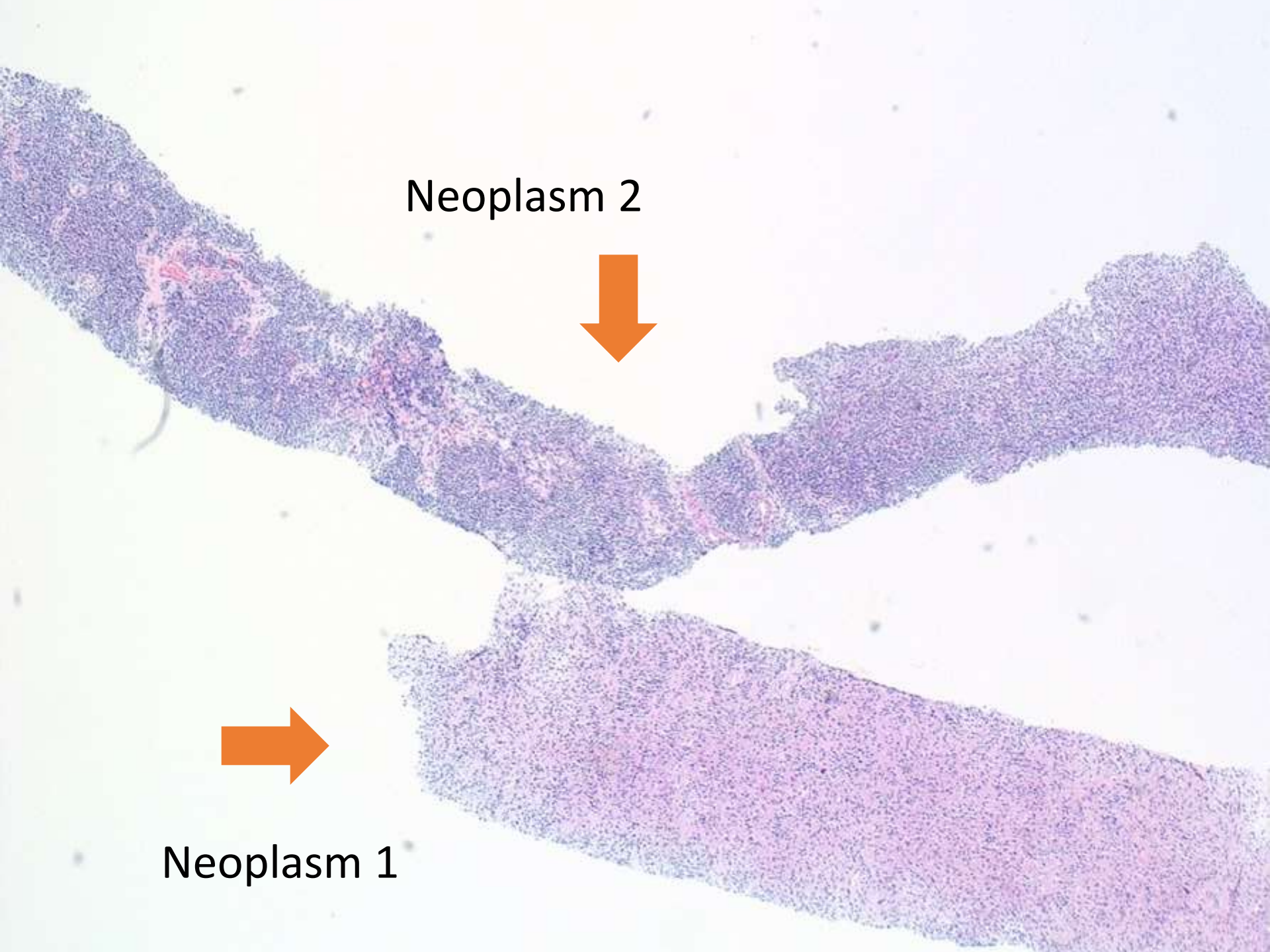
References

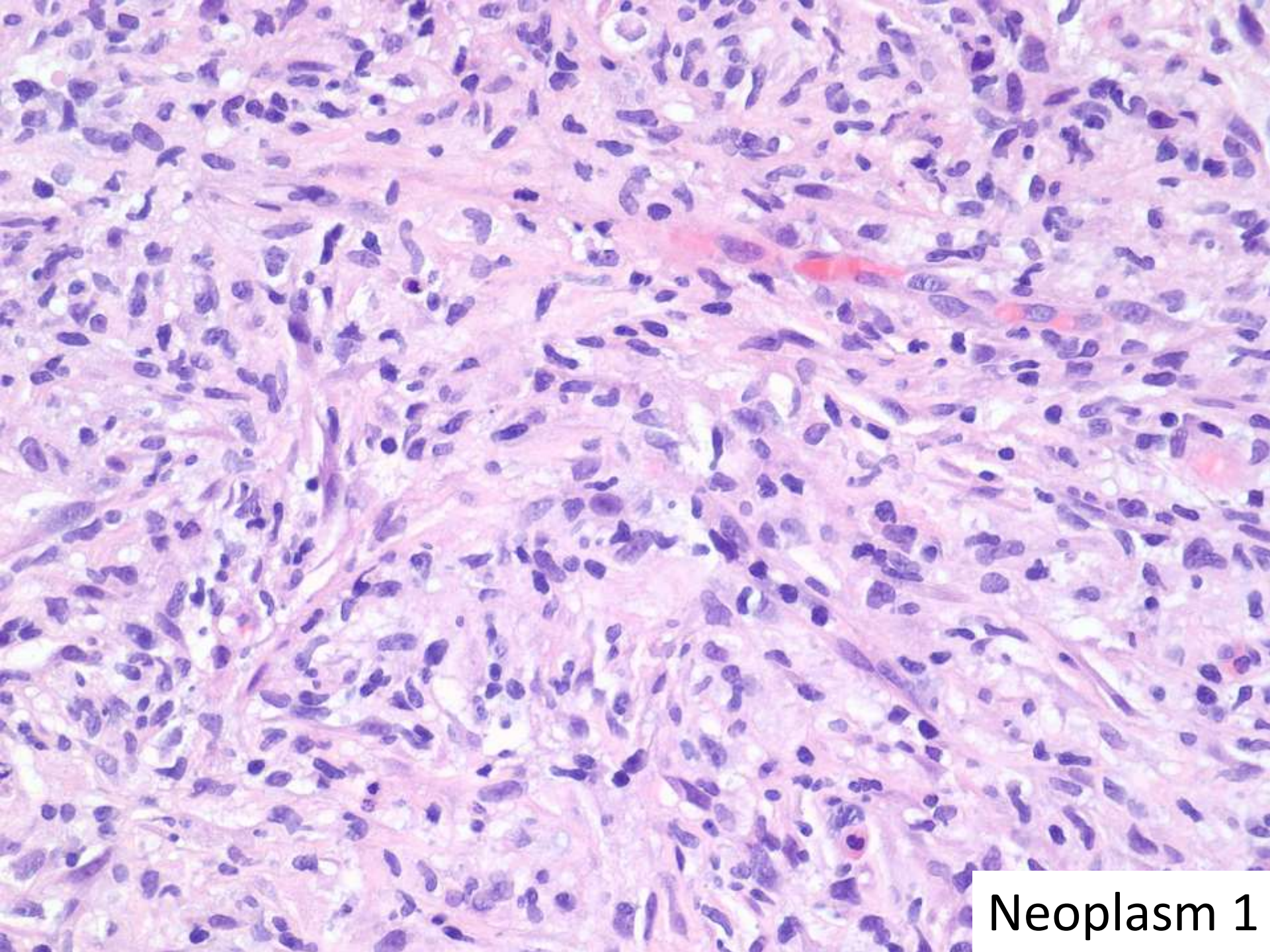
- Pathology of NC Portal HTN. Hum Path 1979;10:405-18
  - 12/32 showed biliary hyperplasia at autopsy
- Idiop NC PHTN. Hepatic Med 2016;6:81-88.
- Idiop NC PHTN: an appraisal. J Path and Trans Med 2016;50:17-25.
- NC PF/idiop PHT: APASL Recommendations. Hep Intl 2007;1:398-413.
- Liver failure and need for transplantation in advanced hepatoportal sclerosis. AJSP 2007;31:607-14.

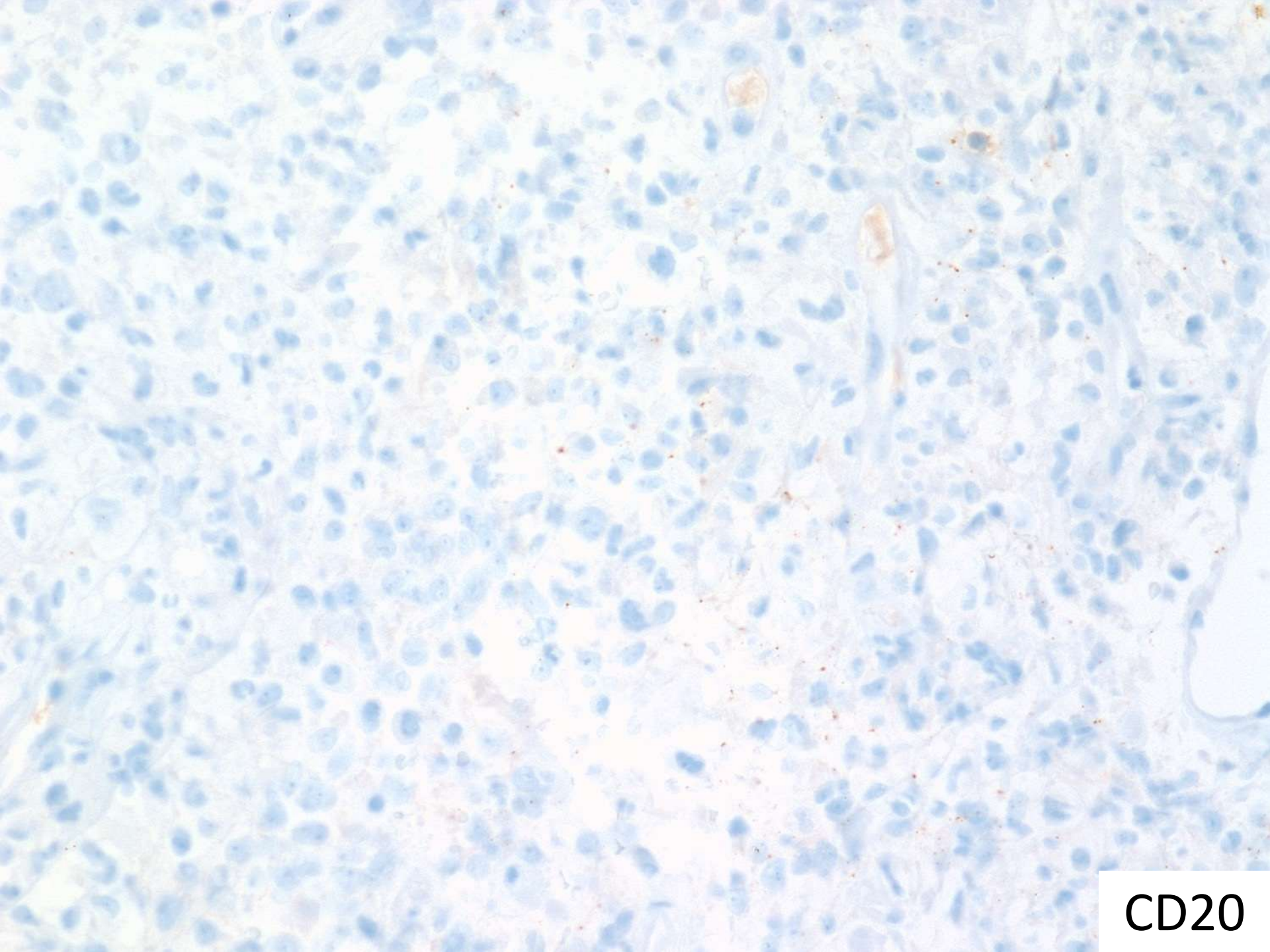
SB 6264

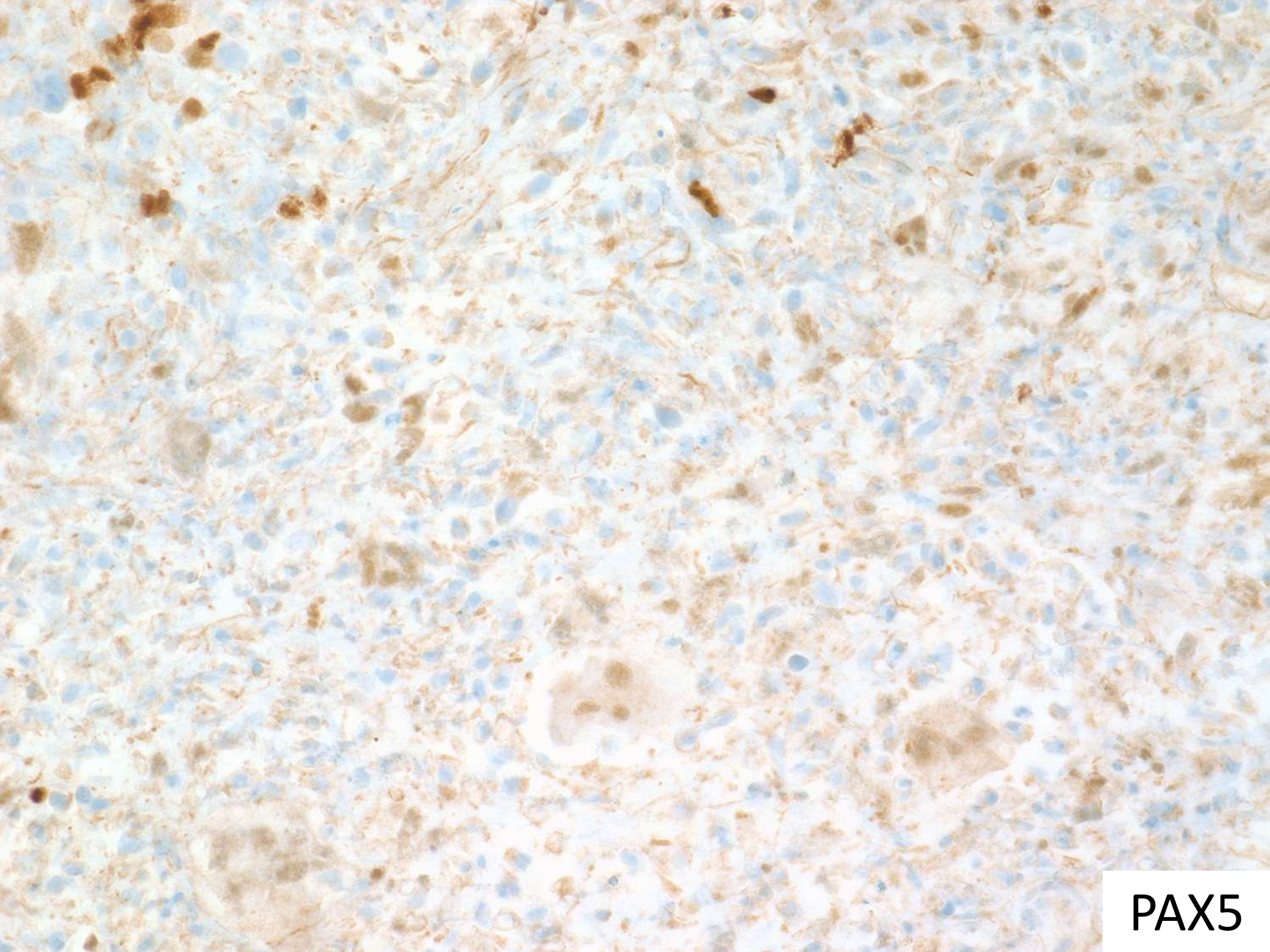
Joshua Menke/Sebastian Fernandez-Pol/Bob Ohgami; Stanford

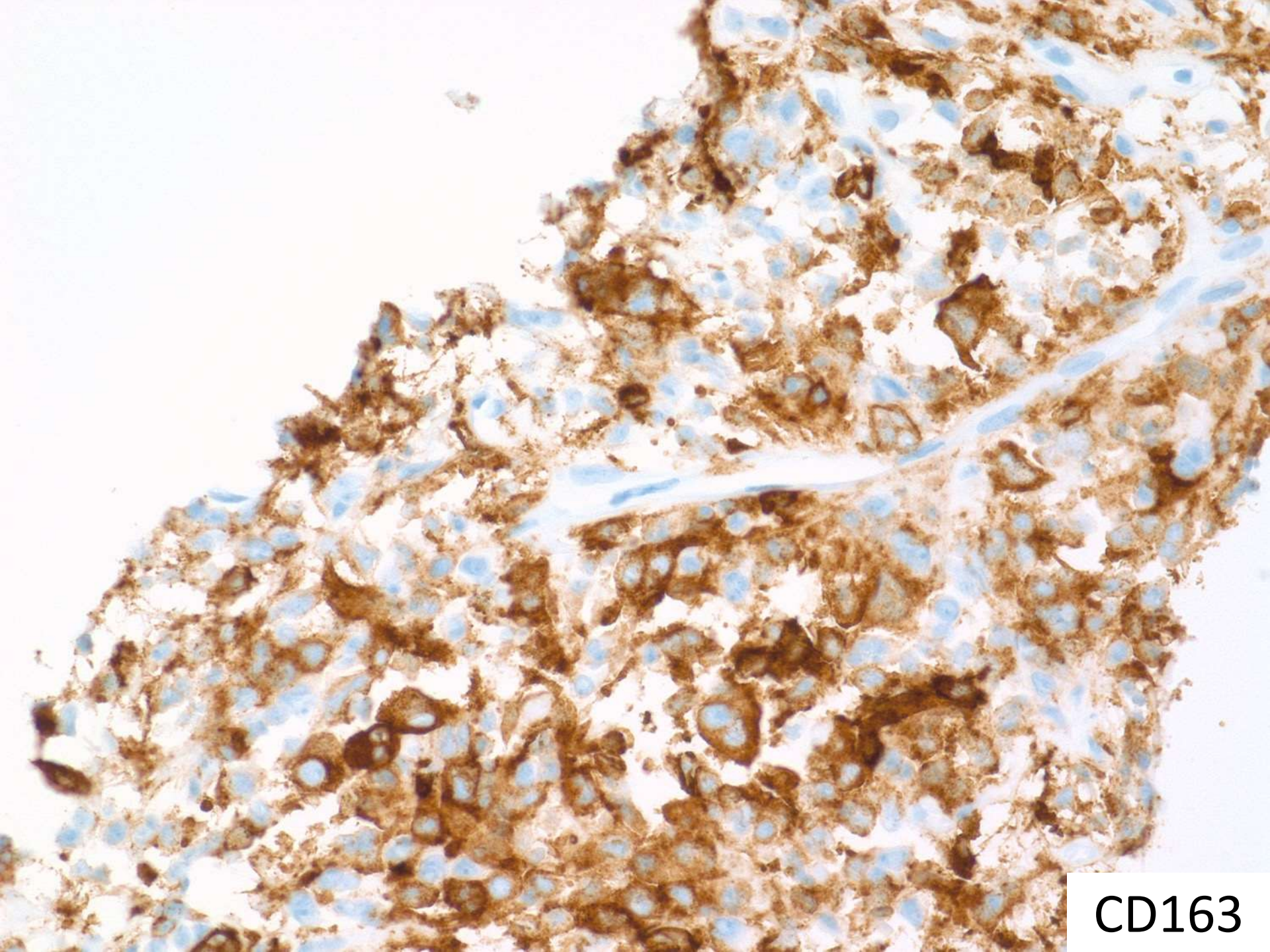
75-year-old male with mediastinal mass, clinical concern for lymphoma.

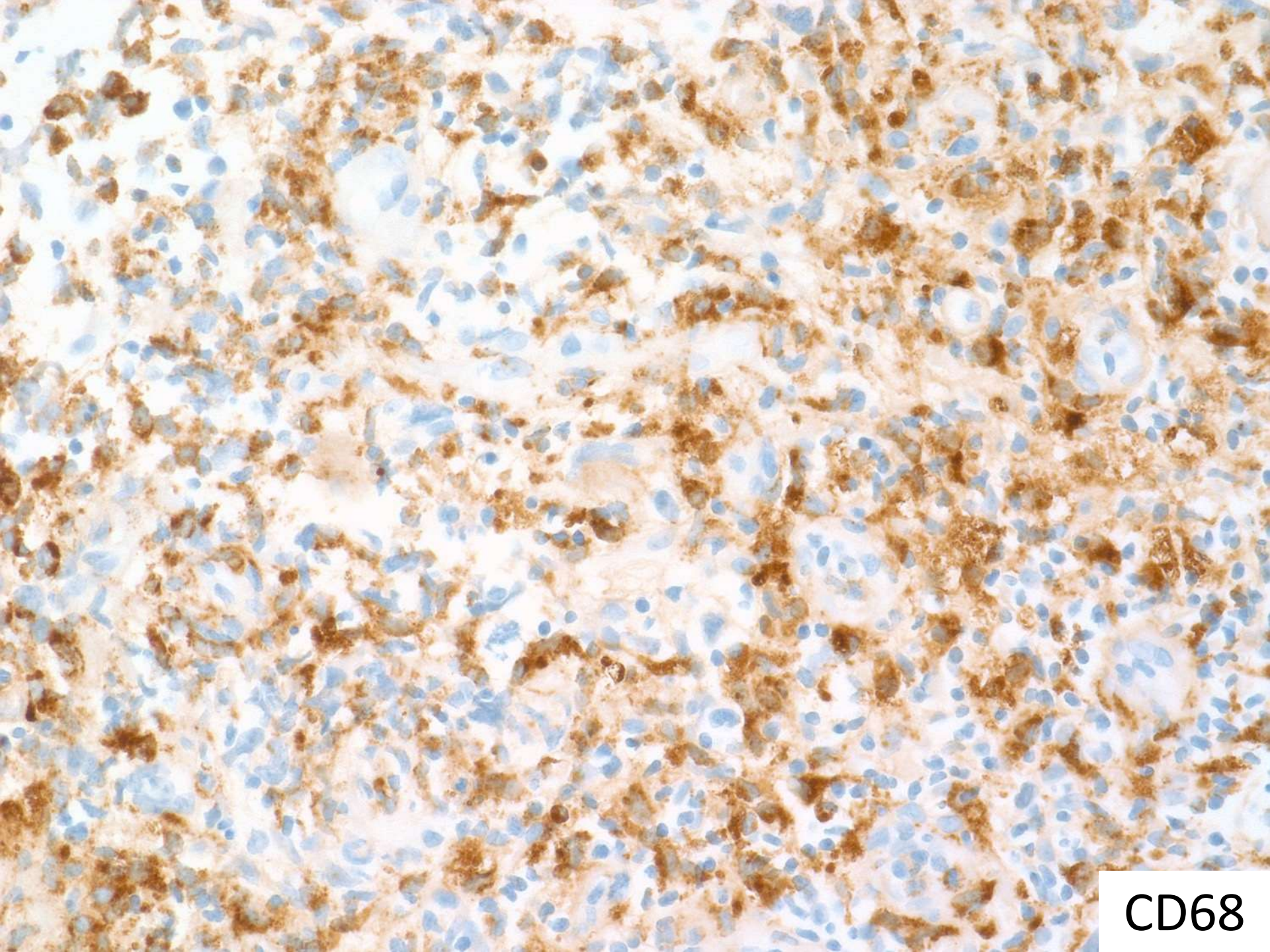

Neoplasm 2
Neoplasm 1

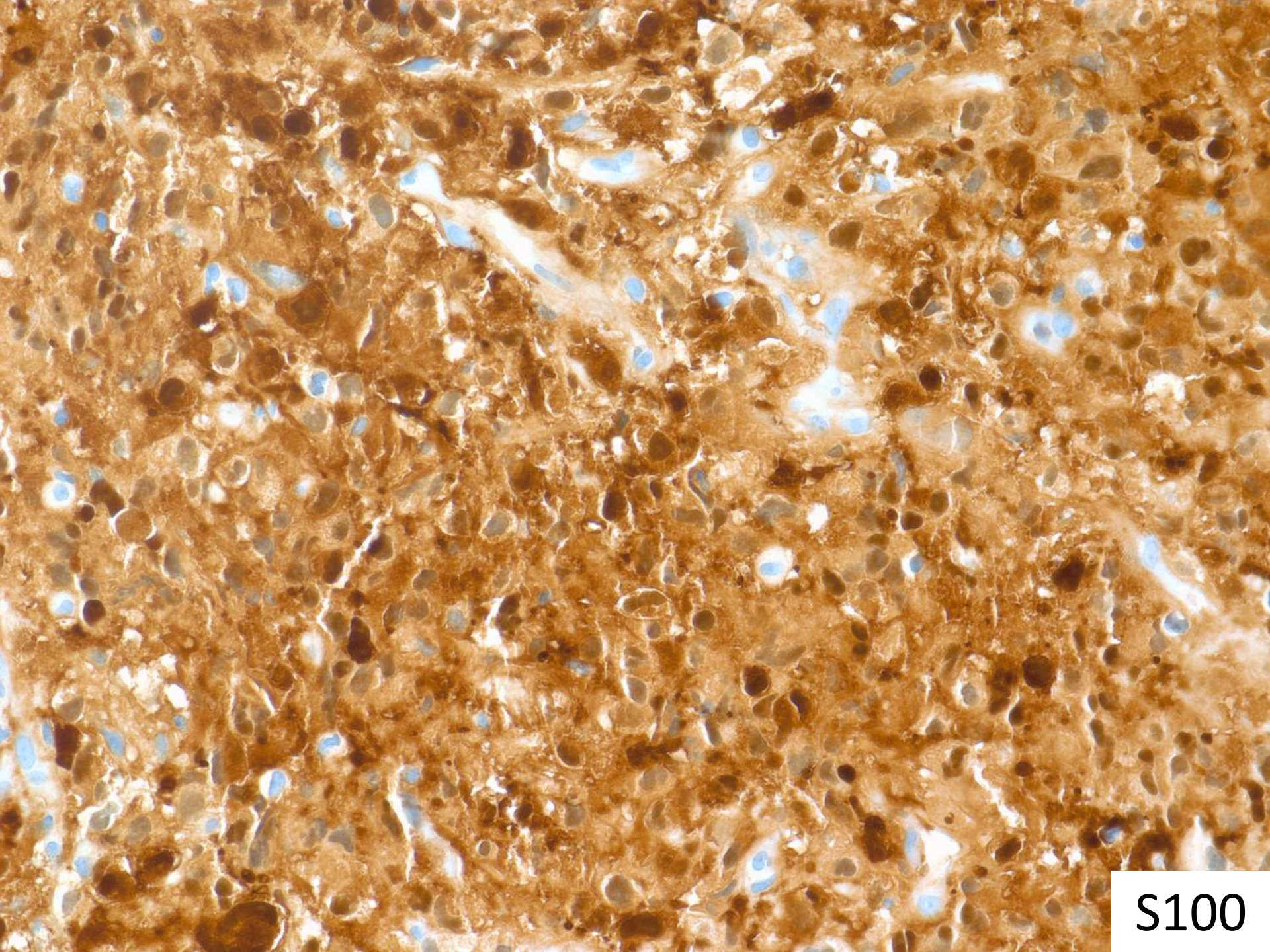

Neoplasm 1

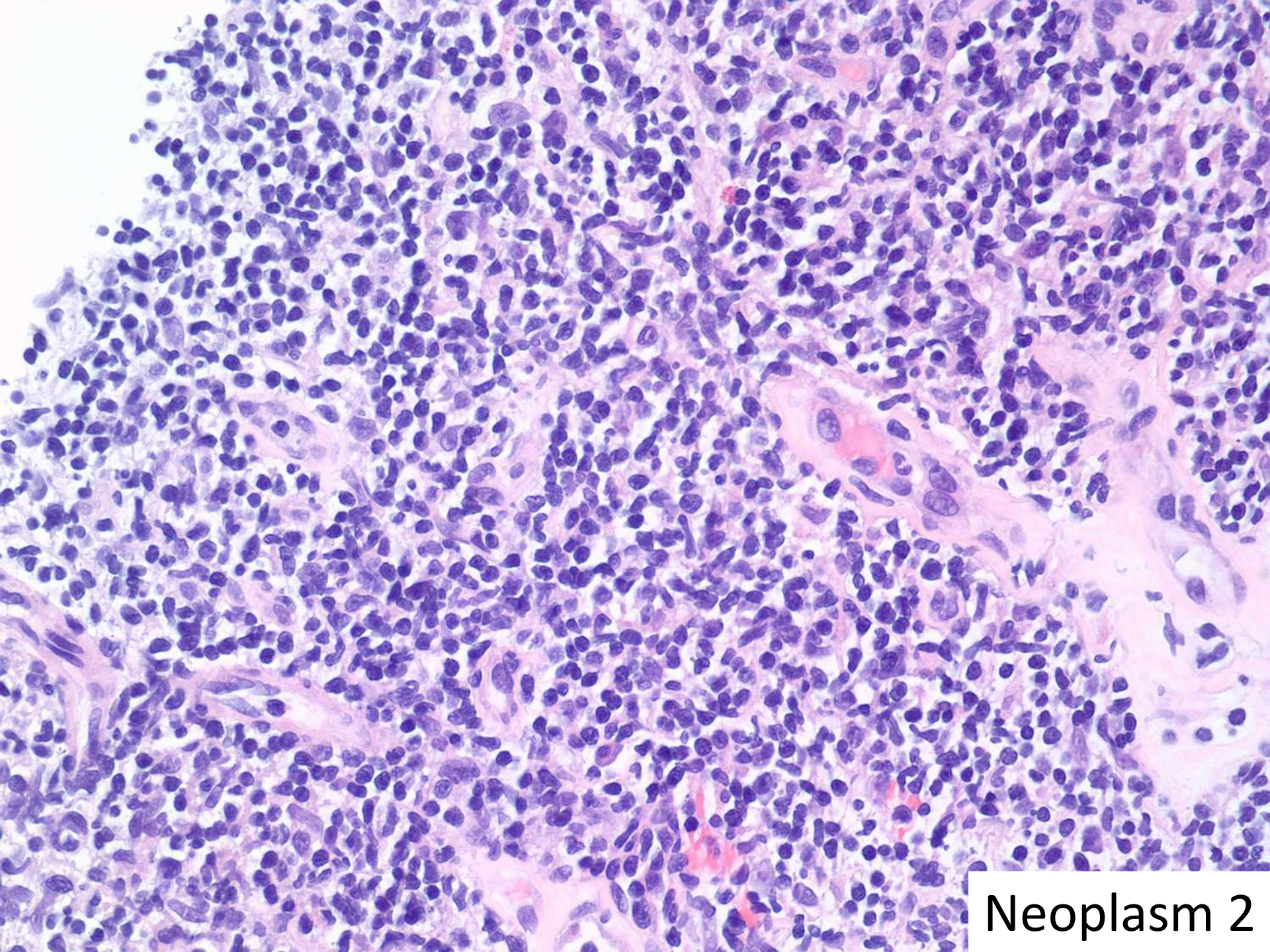

CD20

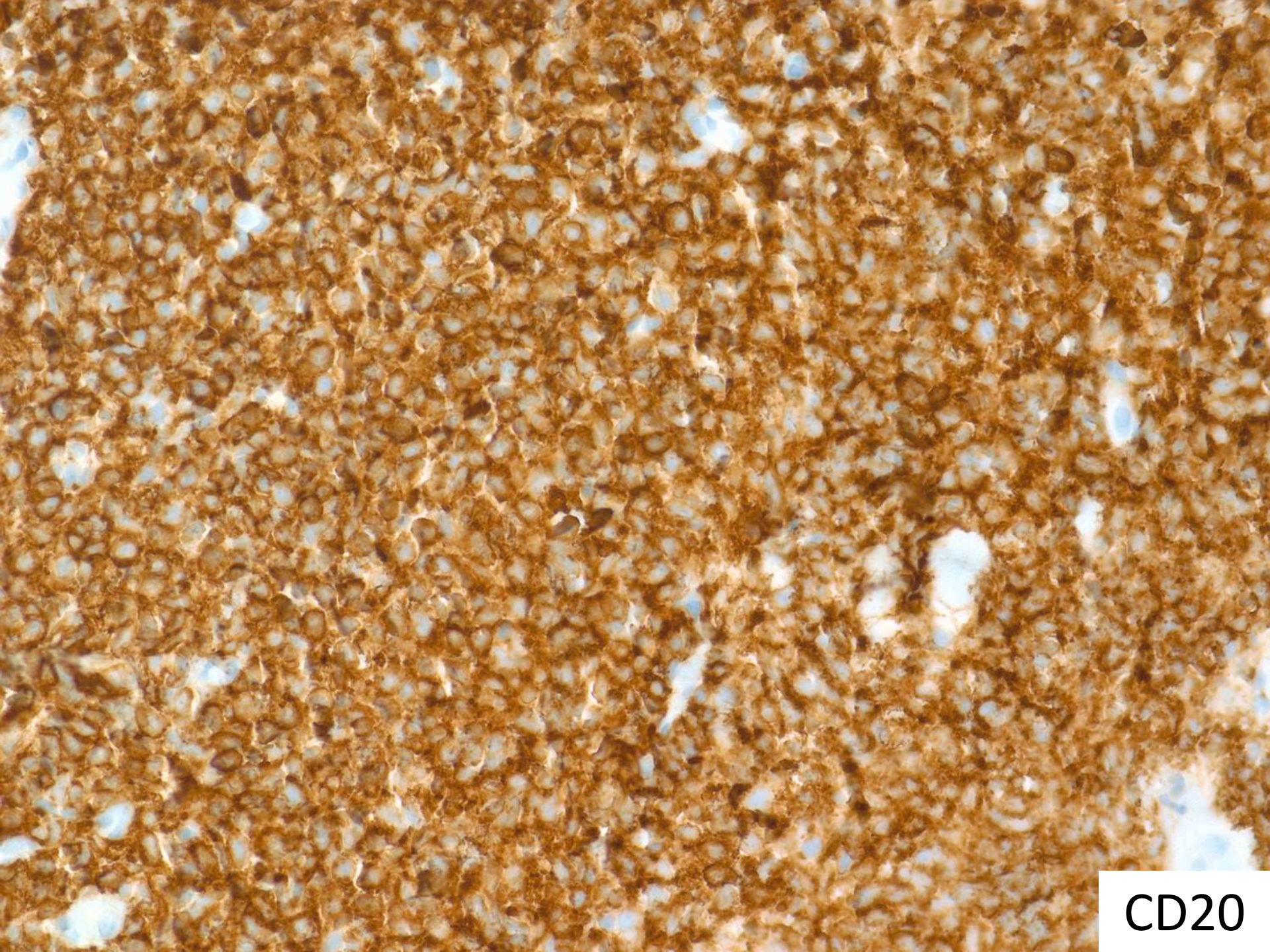

PAX5


CD163


CD68


S100


Neoplasm 2


CD20

Additional immunostains

- BCL2 is coexpressed on CD20 positive cells

Flow cytometry

- Per report, flow cytometry shows a monoclonal B-cell population (65% of total events) that expresses lambda light chains, CD10, CD19, CD20, CD22, and CD38.
- Abnormal cells have low forward scatter
- T cells (30% of total events) have a CD4:CD8 ratio of 4.6:1.

Diagnosis?

South Bay Case

Joshua Menke

Sebastian Fernandez-Pol

Bob Ohgami

Stanford University

Differential Diagnosis

Neoplasm 1

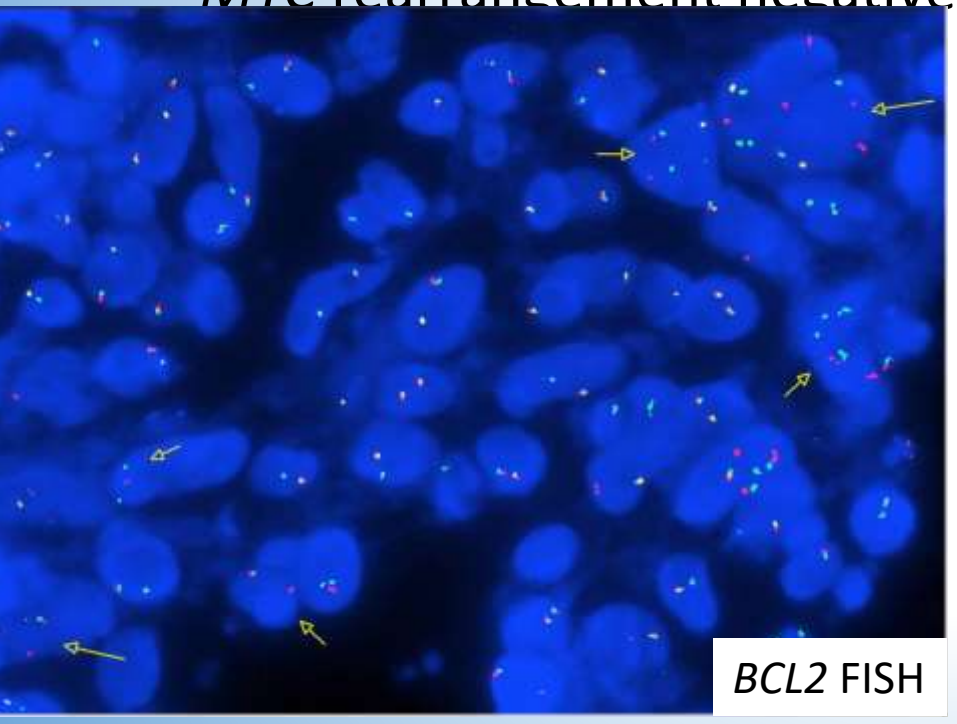
- Histiocytic sarcoma
- Myeloid sarcoma with monocytic differentiation

Neoplasm 2

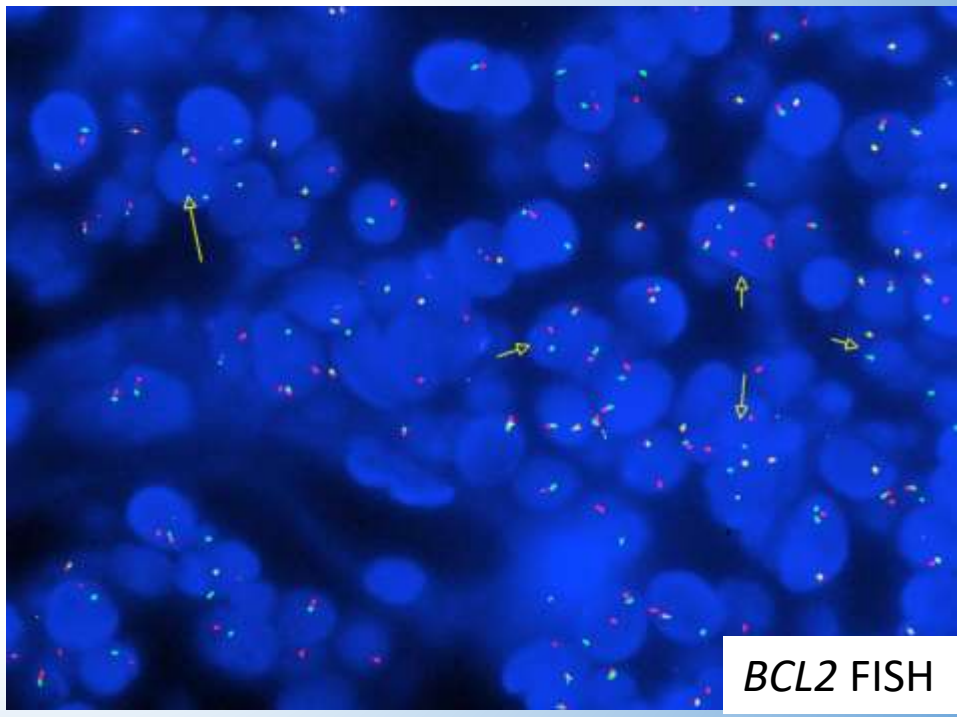
- Follicular lymphoma
- Other small B-cell lymphomas

FISH Results

- *BCL2* rearrangement ~80/200 cells in both neoplasms
- *MYC* rearrangement negative



Neoplasm 1



Neoplasm 2

Final diagnosis: Follicular lymphoma, grade 1-2 of 3 with associated histiocytic sarcoma

Association of follicular lymphoma and histiocytic sarcoma

- One study of 8 patients described clonally-related follicular lymphoma (FL) and histiocytic/dendritic cell (H/DC) neoplasms, either metachronous (n=5) or synchronous (n=3)
- In all metachronous cases, FL came first

Table 2. Immunophenotype and classification of histiocytic or dendritic cell tumors

Case	CD68	CD163	Lysozyme	S100	CD1a	CD20	PAX5	PU.1	CEBPβ	Classification
1	+	+	+	+	−	−	−	+	+	Histiocytic sarcoma with DC differentiation
2	+	−	−	+	−	−	−	+	+	Histiocytic sarcoma with DC differentiation
3	+	+	+	+	nd	−	nd	nd	nd	Histiocytic sarcoma with DC differentiation
4	F	+	−	+	F	−	−	+	+	Interdigitating DC sarcoma
5	+	+	+	−	−	−	−	+	+	Histiocytic sarcoma
6	+	nd	+	+	nd	−	−	+	+	Histiocytic sarcoma with DC differentiation
7	+	+	F	+	+	−	−	nd	nd	Histiocytic sarcoma with DC differentiation
8	+	+	+	−	−	−	−	+	+	Histiocytic sarcoma

DC indicates dendritic cell; F, focal; and nd, not done.

Feldman AL, et al. Blood. 2008.

Table 3. Genetic findings in follicular lymphoma and histiocytic or dendritic cell tumors

Case	t(14;18) by FISH	*BCL2/JH MBR* rearrangement by PCR	Clonal IGH rearrangement by PCR	Sequence similarity between FL and H/DC tumor
1-FL	+	+	+	+
1-HD/C	+	+	+	+
2-FL	+	+	+	+
2-HD/C	+	+	+	+
3-FL	+	+	+	unsat
3-HD/C	+	+	+	unsat
4-FL	+	−	+	+
4-HD/C	+	−	+	+
5-FL	+	+	+	+
5-HD/C	+	+	+	+
6-FL	unsat	+	+	unsat
6-HD/C	unsat	+	+	unsat
7-FL	unsat*	nd	+	nd
7-HD/C	+	nd	Not evaluable	nd
8-FL	unsat	+	−	+†
8-HD/C	unsat	+	−	+†

FL indicates follicular lymphoma; H/DC, histiocytic or dendritic cell; nd, not done; and unsat, unsatisfactory.

*Poor signal in the FL component of the specimen precluded interpretation.

†Clonal rearrangement not identified with Fr 2 or Fr3 primer sets. Sequencing performed on BCL2/JH product.

Murine models show B-cell plasticity

- Mature B-cells can “transdifferente” into macrophages in vitro induced by enforced expressed of the transcription factors C/EBP α and β, and associated with inhibition of the B-cell commitment transcription factor PAX5
- Conditional deletion of Pax5 causes mature B cells to dedifferentiate into uncommitted precursors in the bone marrow and Bcl2-mediated survival cooperates with PAX5 loss, leading to the development of “lymphomas” composed of progenitor cells.

Xie H, et al. Cell. 2004.

IGH rearrangements in histiocytic sarcoma are frequent

- 23 cases of histiocytic sarcoma without a preceding or concurrent history of B-cell lymphoma/leukemia i.e. de novo cases
- Nine of the 23 cases (39%) showed clonal *IGH* (±*IGK*) rearrangements, whereas 2 (9%) cases showed only clonal *IGK* rearrangement
- All negative for PAX5 and BOB.1, whereas 4 of 7 *IGH/IGK*-positive histiocytic sarcoma cases were positive for Oct2

Chen W, et al. Am J Surg Pathol. 2009

Conclusions

- Histiocytic sarcoma can share t(14;18) and/or *IGH* rearrangement with metachronous or synchronous follicular lymphoma
- Mouse models demonstrate mature B-cell to myeloid cell plasticity
- Histiocytic sarcomas show frequent *IGH* and/or *IGK* rearrangements - up to 50%!
- Consider *BCL2* FISH and *IGH/IGK* PCR in cases with histiocytic differentiation

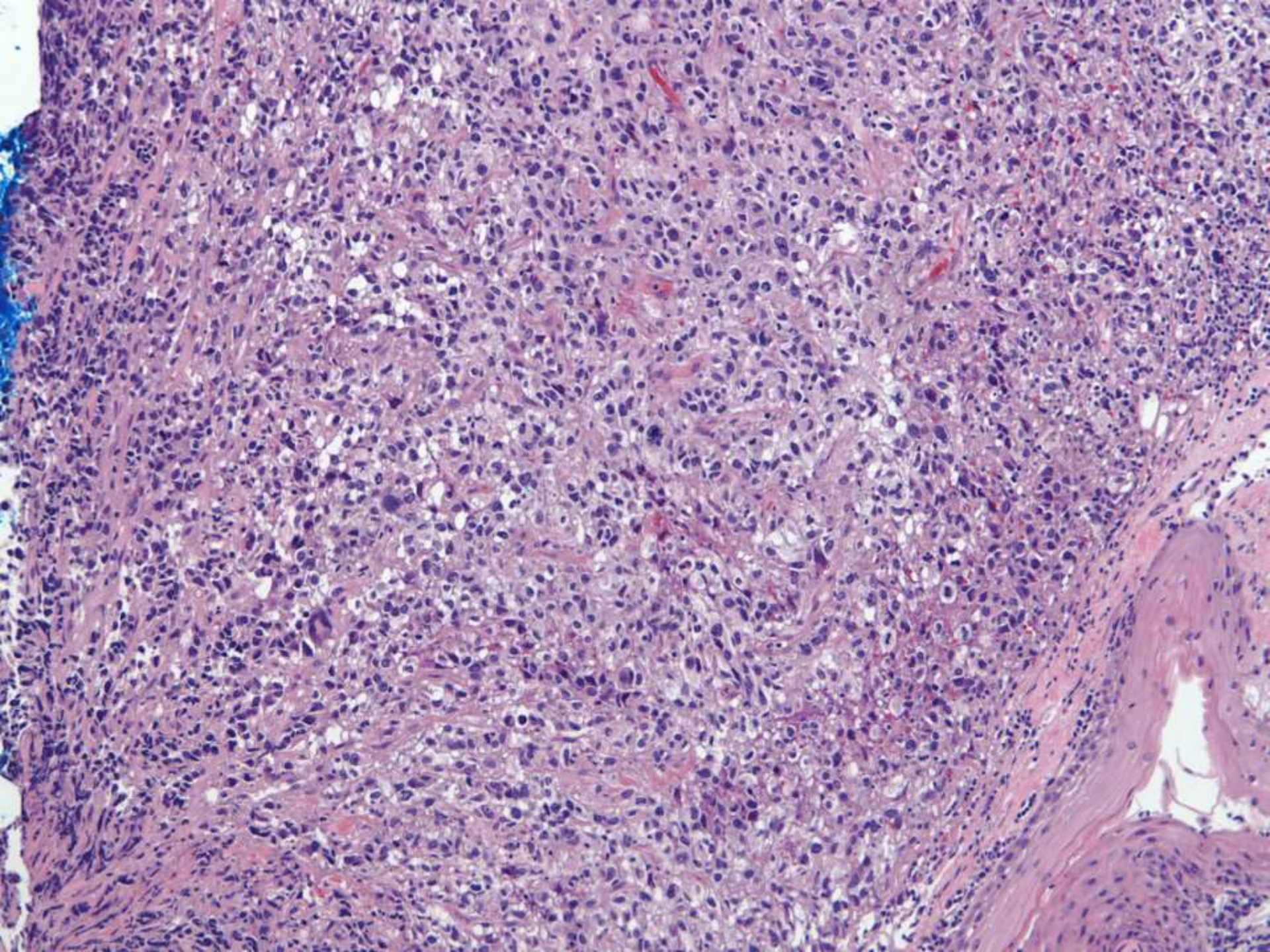
References

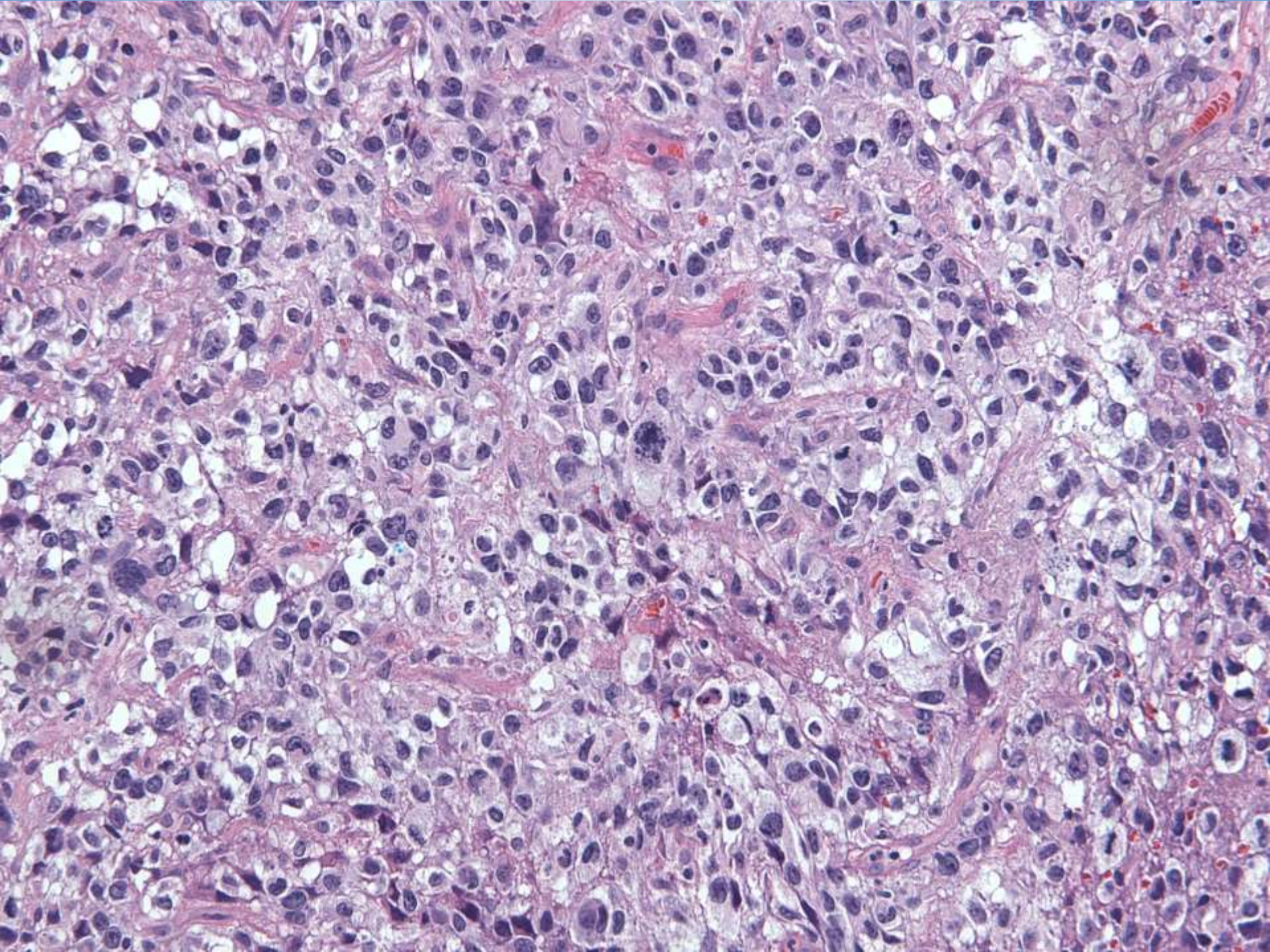
1. Feldman AL, Arber DA, Pittaluga S, Martinez A, Burke JS, Raffeld M, Camos M, Warnke R, Jaffe ES. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. Blood. 2008;111:5433-9. PMID: 18272816.
2. Xie H, Ye M, Feng R, Graf T. Stepwise reprogramming of B cells into macrophages. Cell. 2004 May 28;117(5):663-76. PubMed PMID: 15163413.
3. Chen W, Lau SK, Fong D, Wang J, Wang E, Arber DA, Weiss LM, Huang Q. High frequency of clonal immunoglobulin receptor gene rearrangements in sporadic histiocytic/dendritic cell sarcomas. Am J Surg Pathol. 2009 Jun;33(6):863-73. PMID: 19145200.

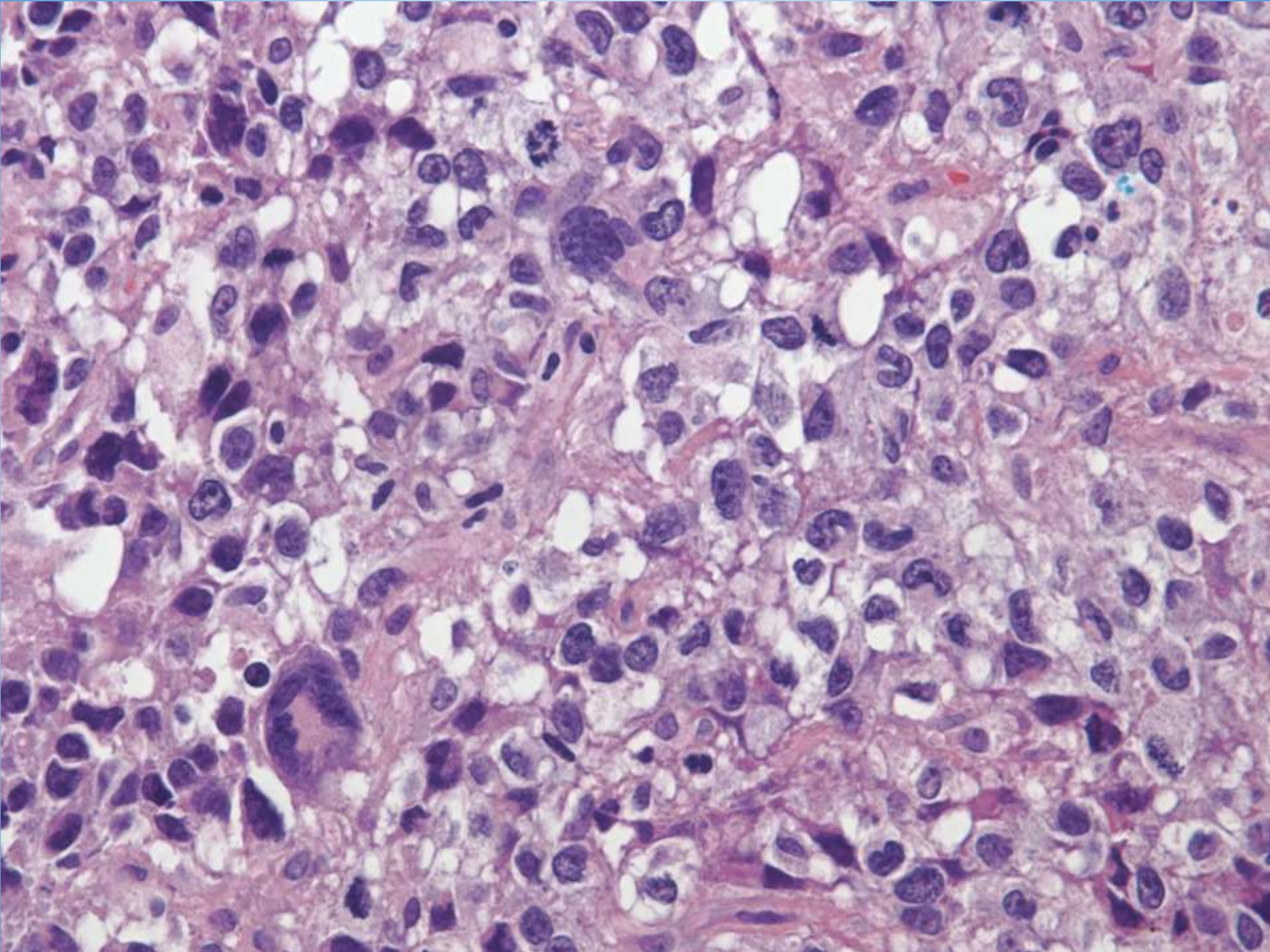
SB 6265

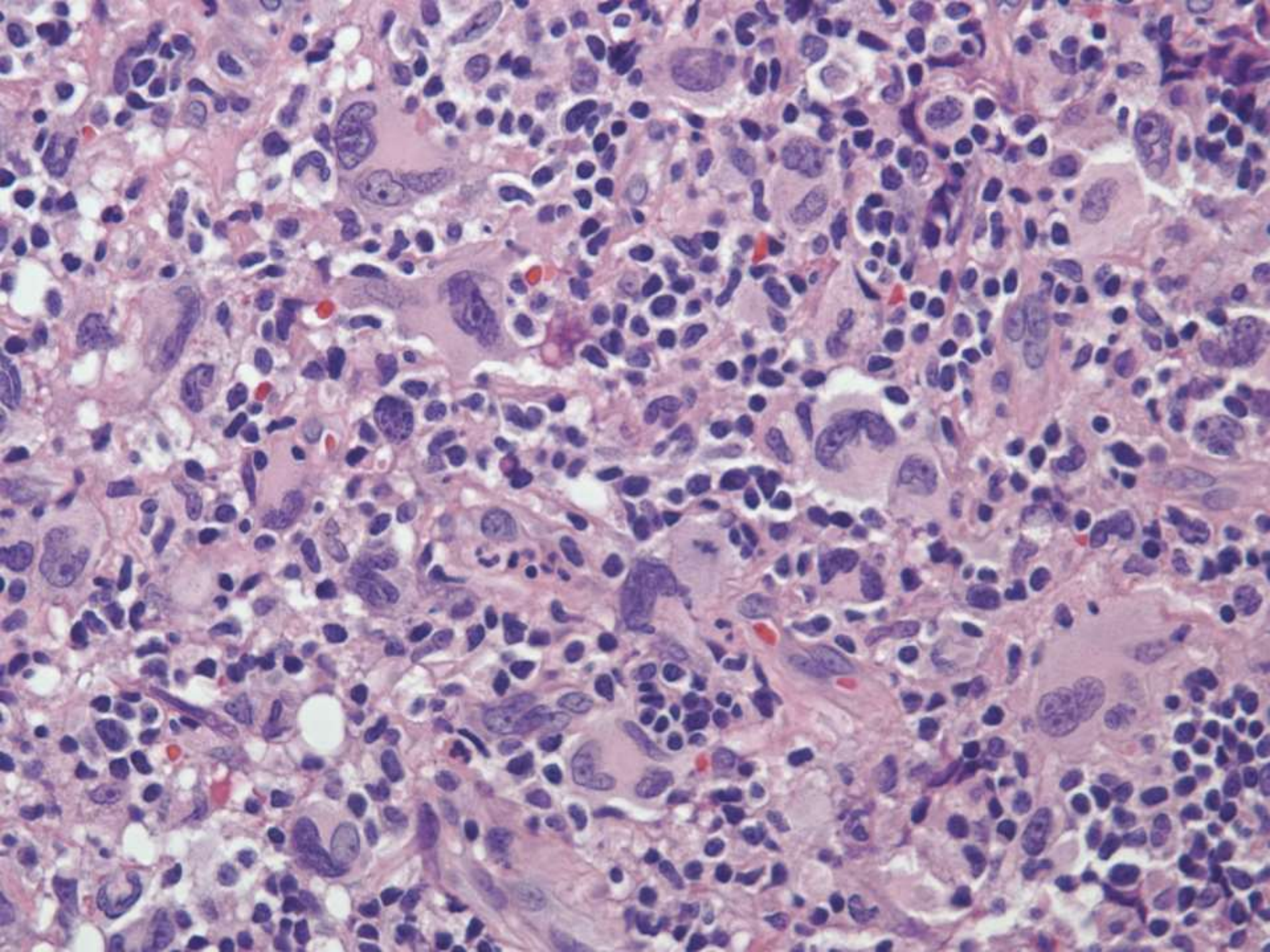
Sebastian Fernandez-Pol/ Joshua Menke/Bob Ohgami; Stanford

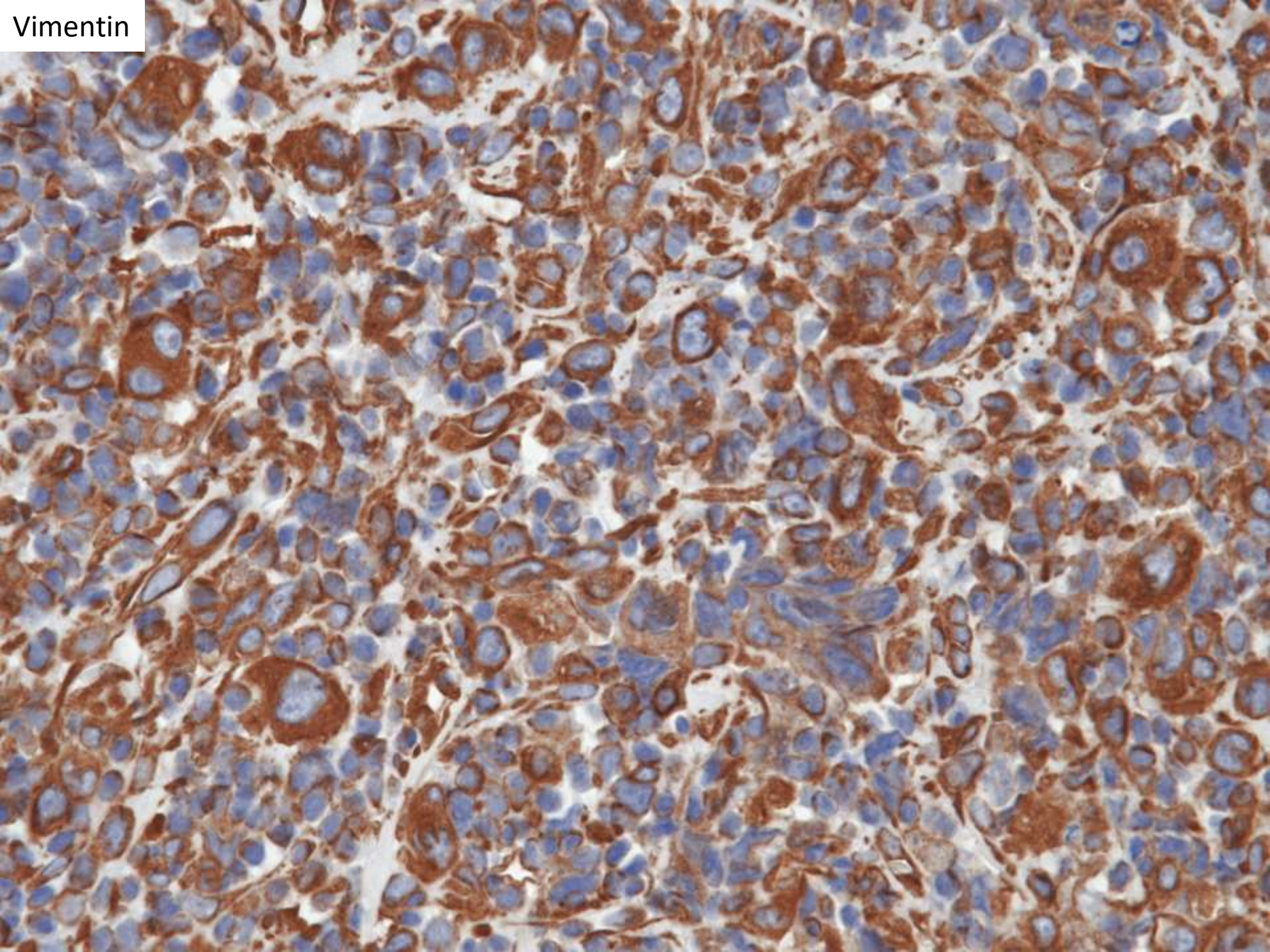
70-year-old female with h/o lymphoma (subtype unknown) and currently with right-sided sore throat for at least 6 weeks and mediastinal lymphadenopathy. No skin lesions are noted. Right tonsil biopsy performed.

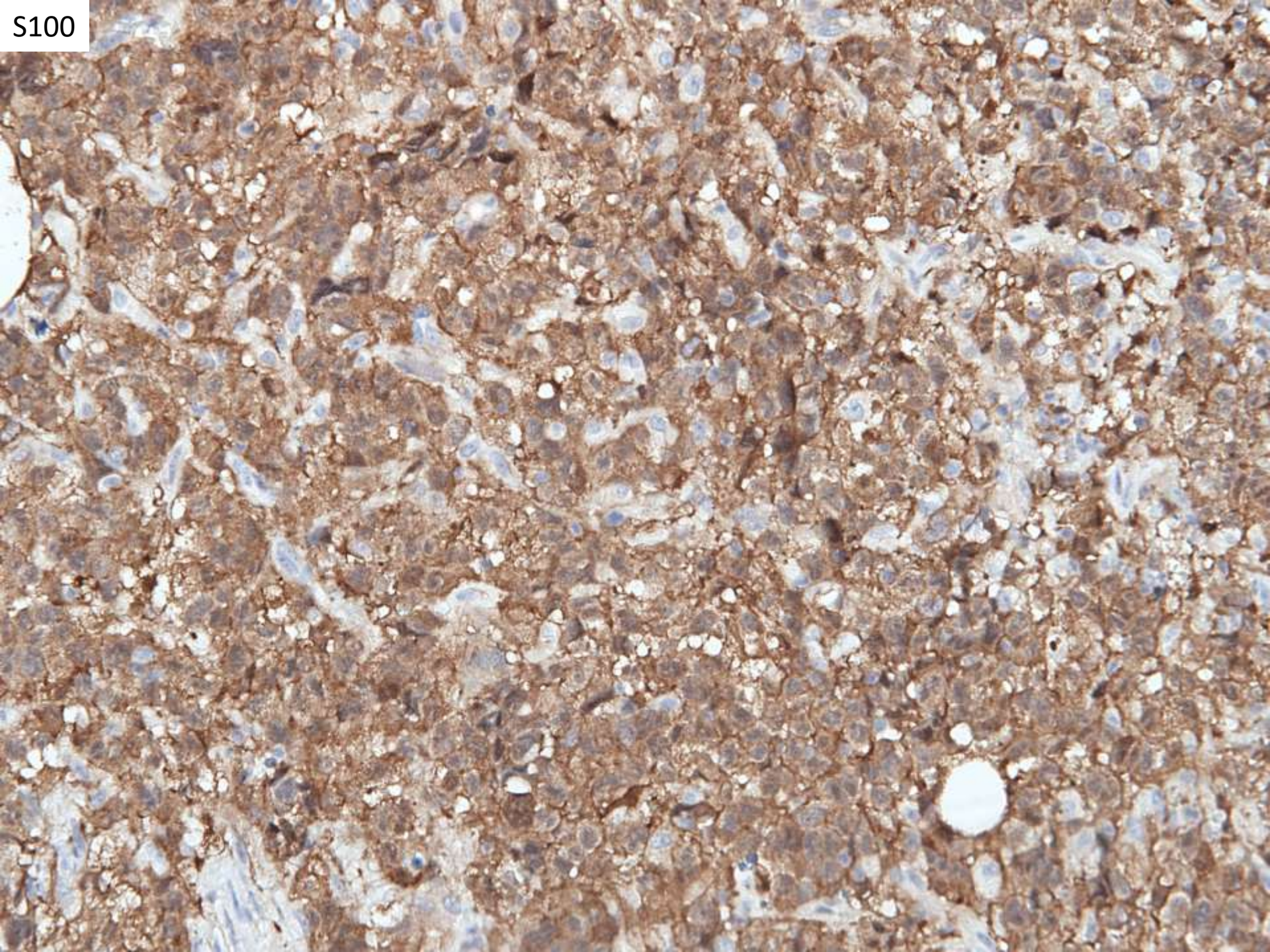


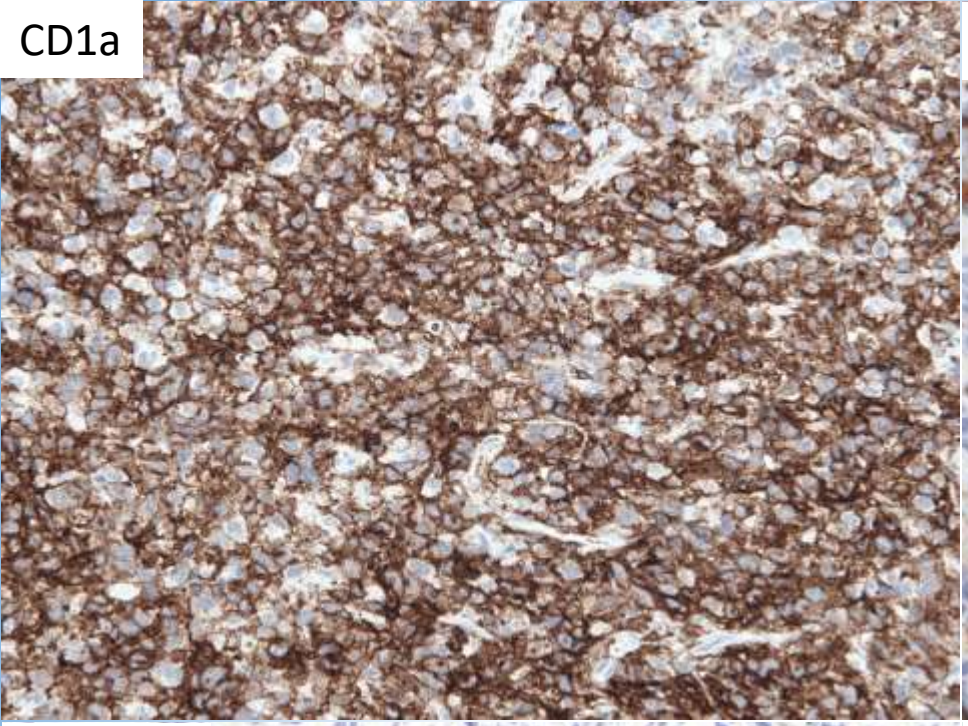


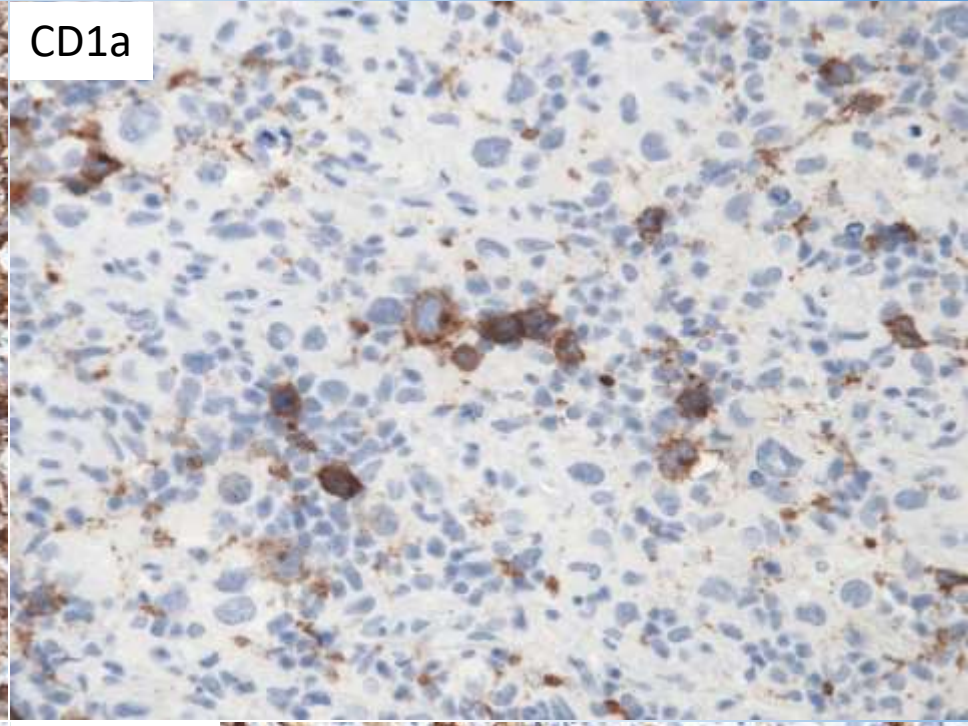


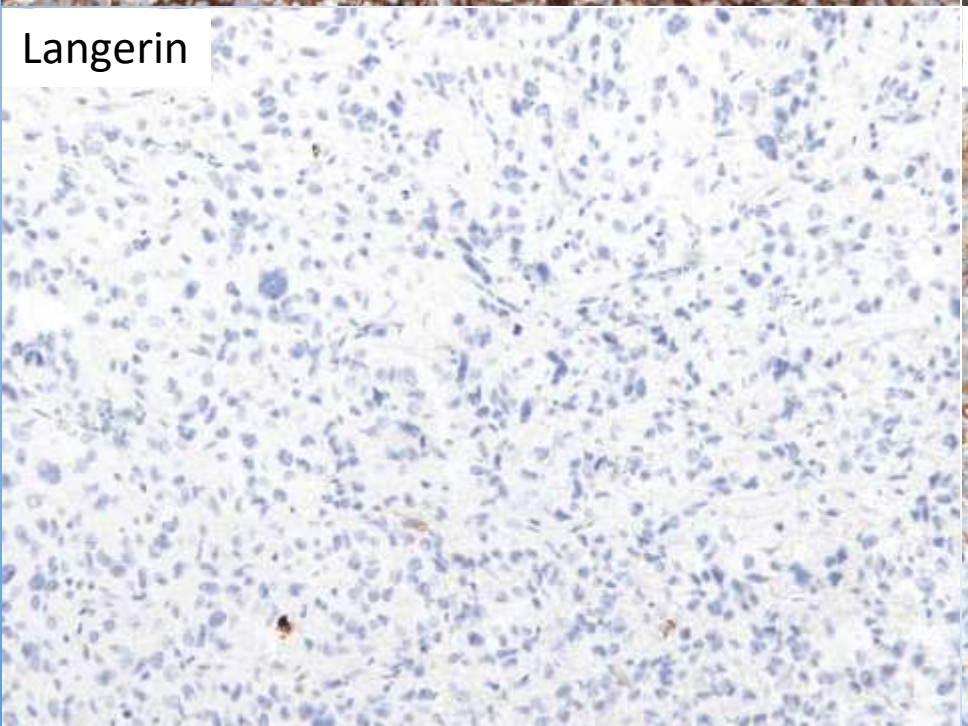


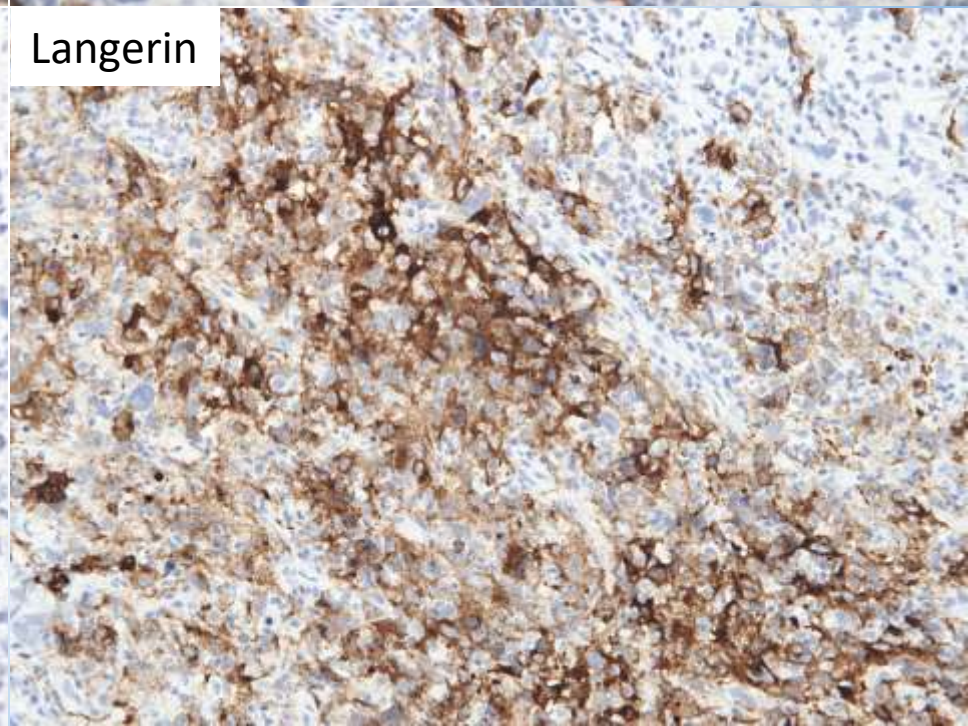

Vimentin

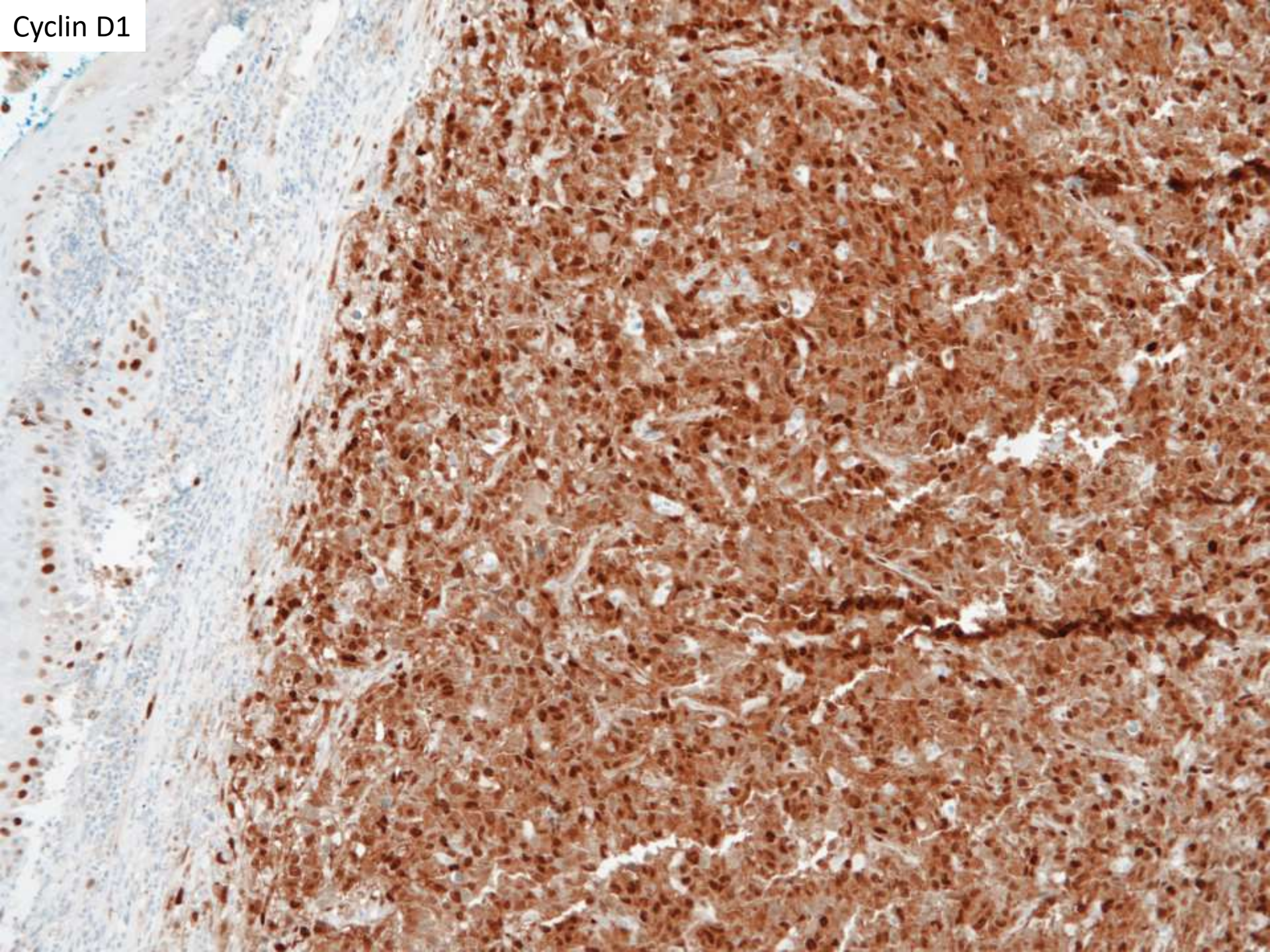

S100


CD1a


CD1a


Langerin


Langerin


Cyclin D1

Histiocytic and dendritic cell neoplasms

S100-positive

- Langerhans cell histiocytosis/sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma

S100-negative

- Follicular dendritic cell sarcoma
- Histiocytic sarcoma
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease

S100-positive histiocytic/dendritic cell lesions

	Langerhans cell histiocytosis or sarcoma	Indeterminate cell histiocytosis	Interdigitating dendritic cell sarcoma
S100	+	+	+
CD1a	+	+	
Langerin (CD207)	+		

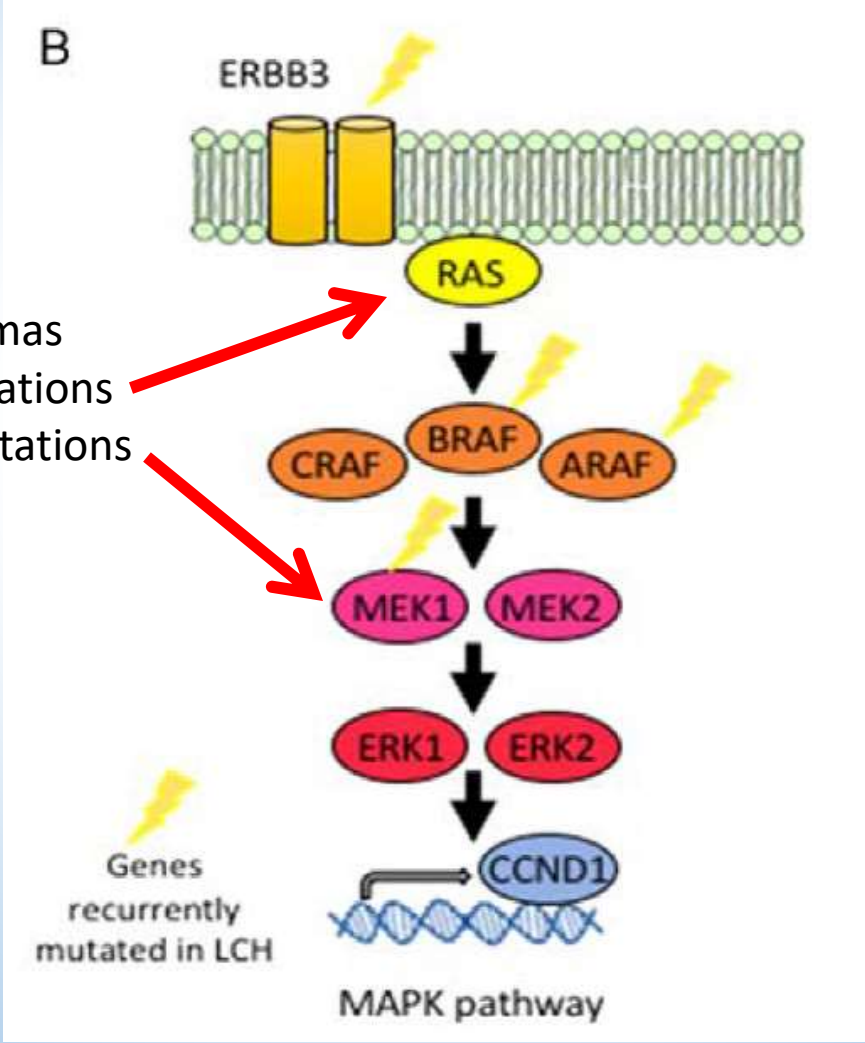
Langerhans cell sarcoma

- Pleomorphic
- Cytologic atypia
- Increased mitotic index
- Retains an at least partial Langerhans cell phenotype

Cyclin D1

Mutations identified in Langherhans cell sarcomas

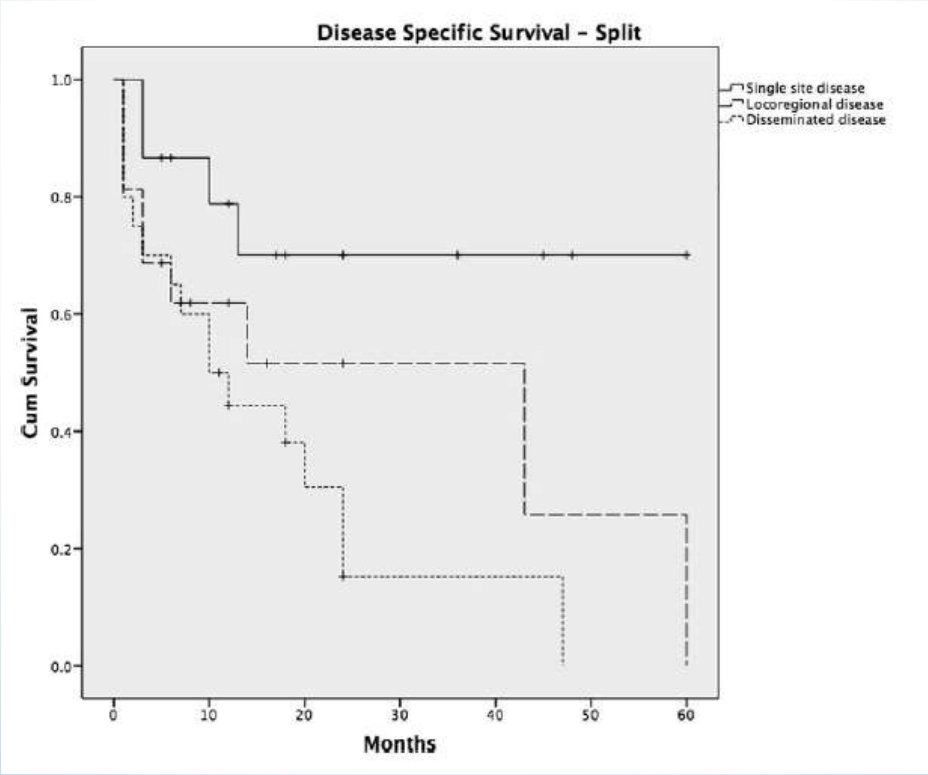
- *NRAS* and *KRAS* mutations
- *MAP2K1* (MEK1) mutations



Shanmugam V, Craig JW, Hornick JL, et al. Cyclin D1 Is Expressed in Neoplastic Cells of Langerhans Cell Histiocytosis but Not Reactive Langerhans Cell Proliferations. Am J Surg Pathol. 2017 Oct;41(10):1390-1396.

Clinical

- Overall mean disease specific survival is 27.2 months



Howard JE, Dwivedi RC, Masterson L, Jani P. Langerhans cell sarcoma: a systematic review. Cancer Treat Rev. 2015;41:320–31.

Summary of Langerhans cell sarcoma

- S100+, CD1a+, Langerin+ (may be focal)
- Expression of markers may be focal
- Pleomorphic, cytologically atypical, mitotically active
- Consider the possibility of a concurrent lymphoma
- Targetable mutations in

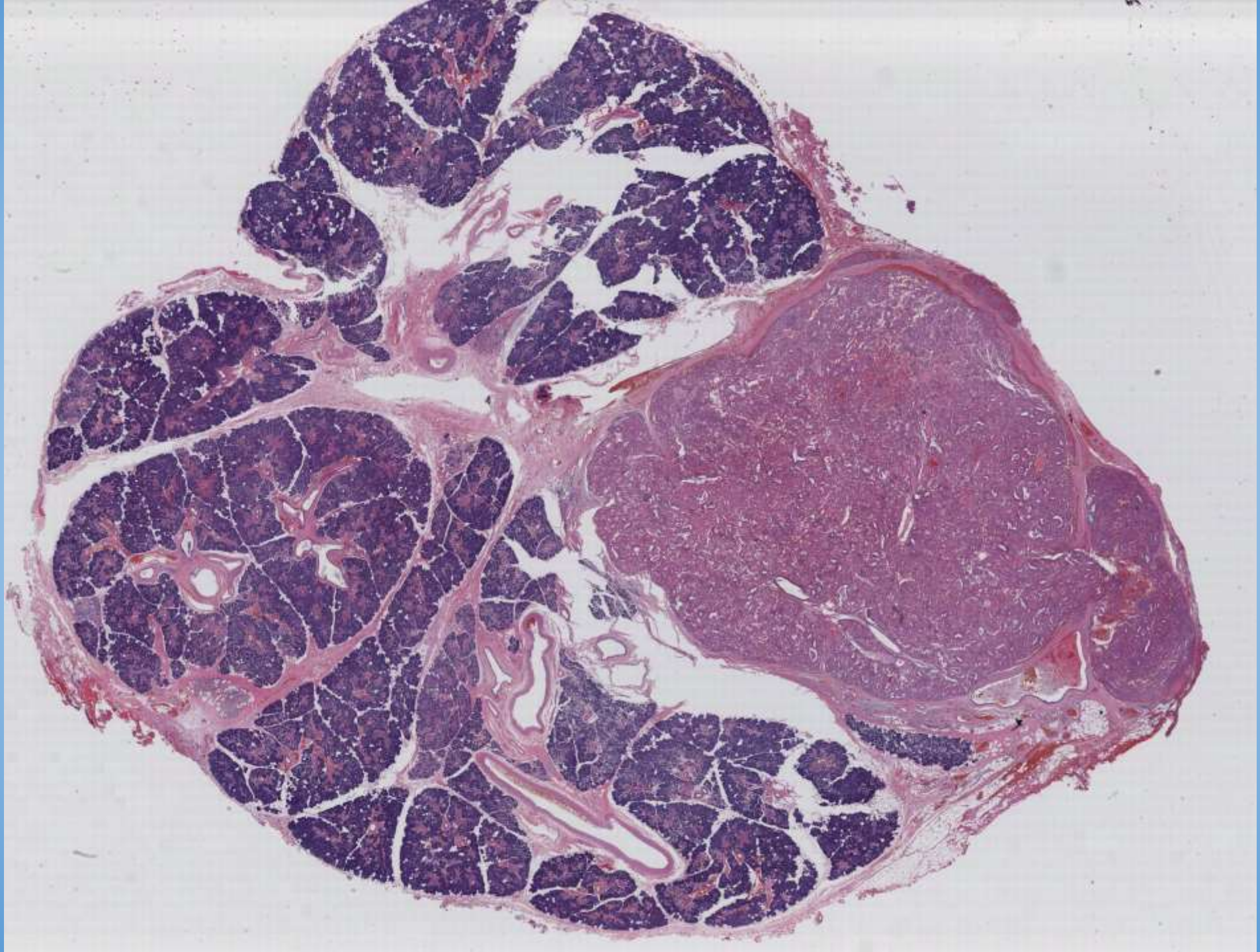
References

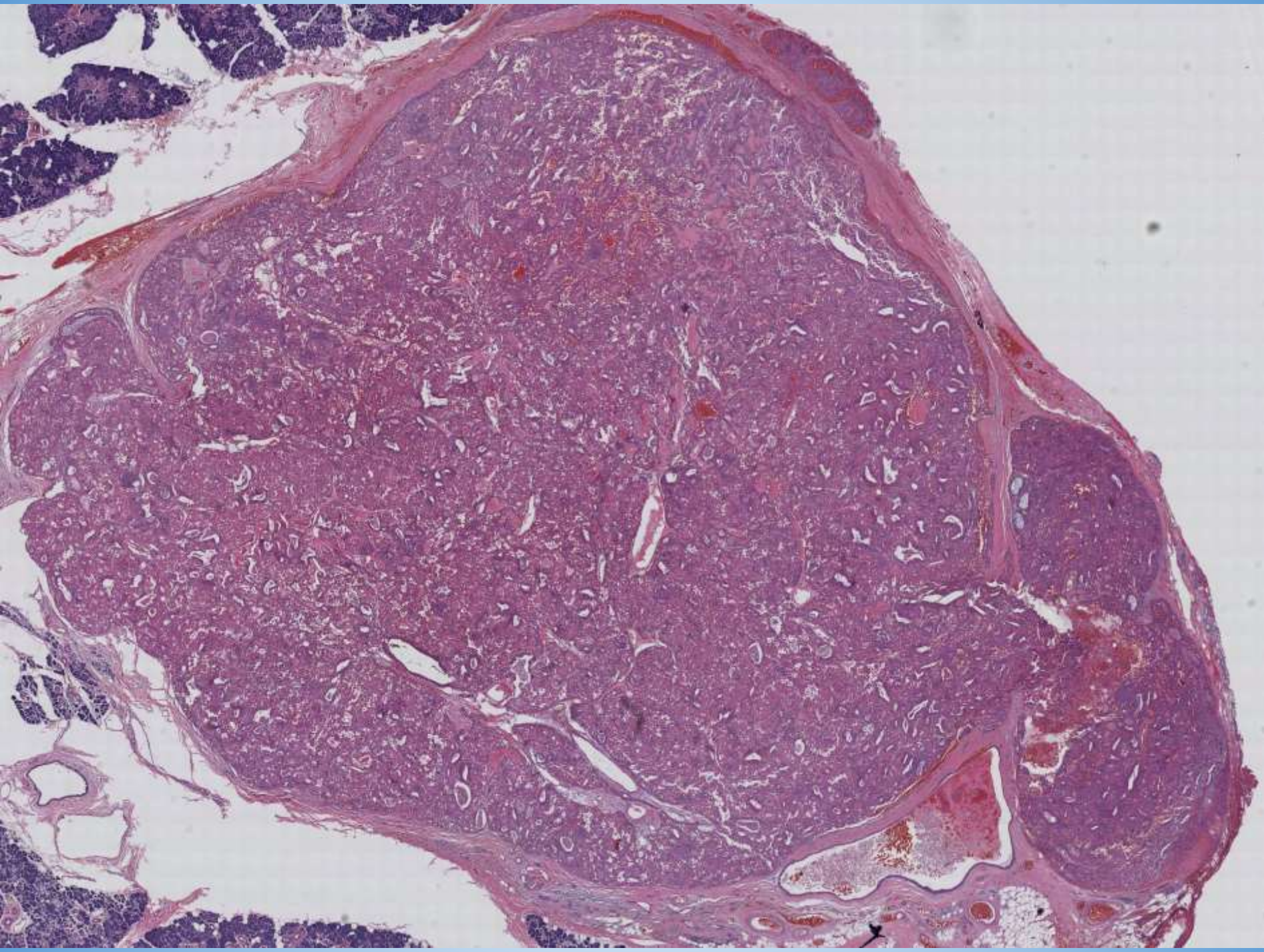
- Emile, J., Abla, O., Fraitag, S., et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016, 127(22), 2672-2681.

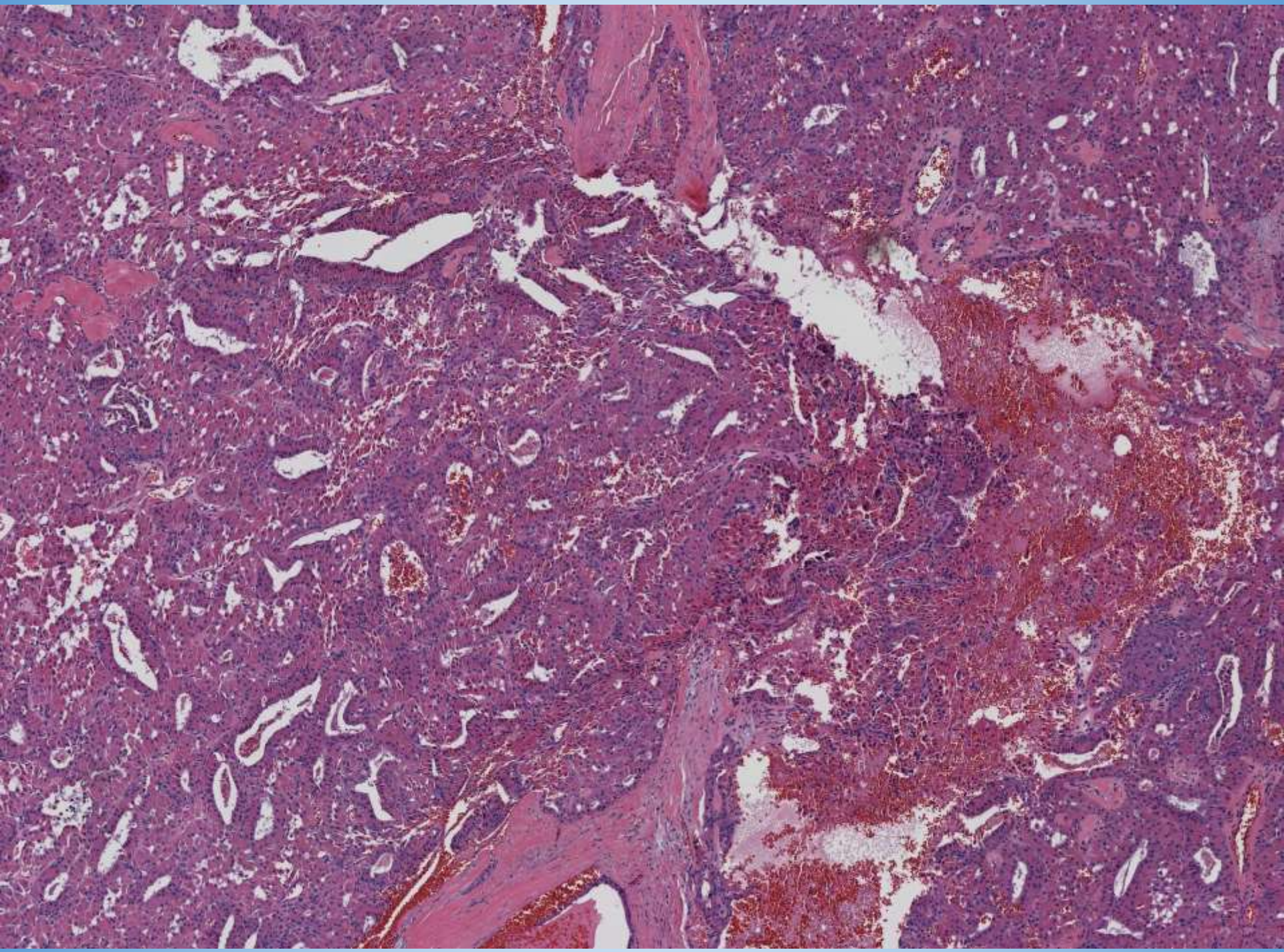
SB 6266
(scanned slide available)

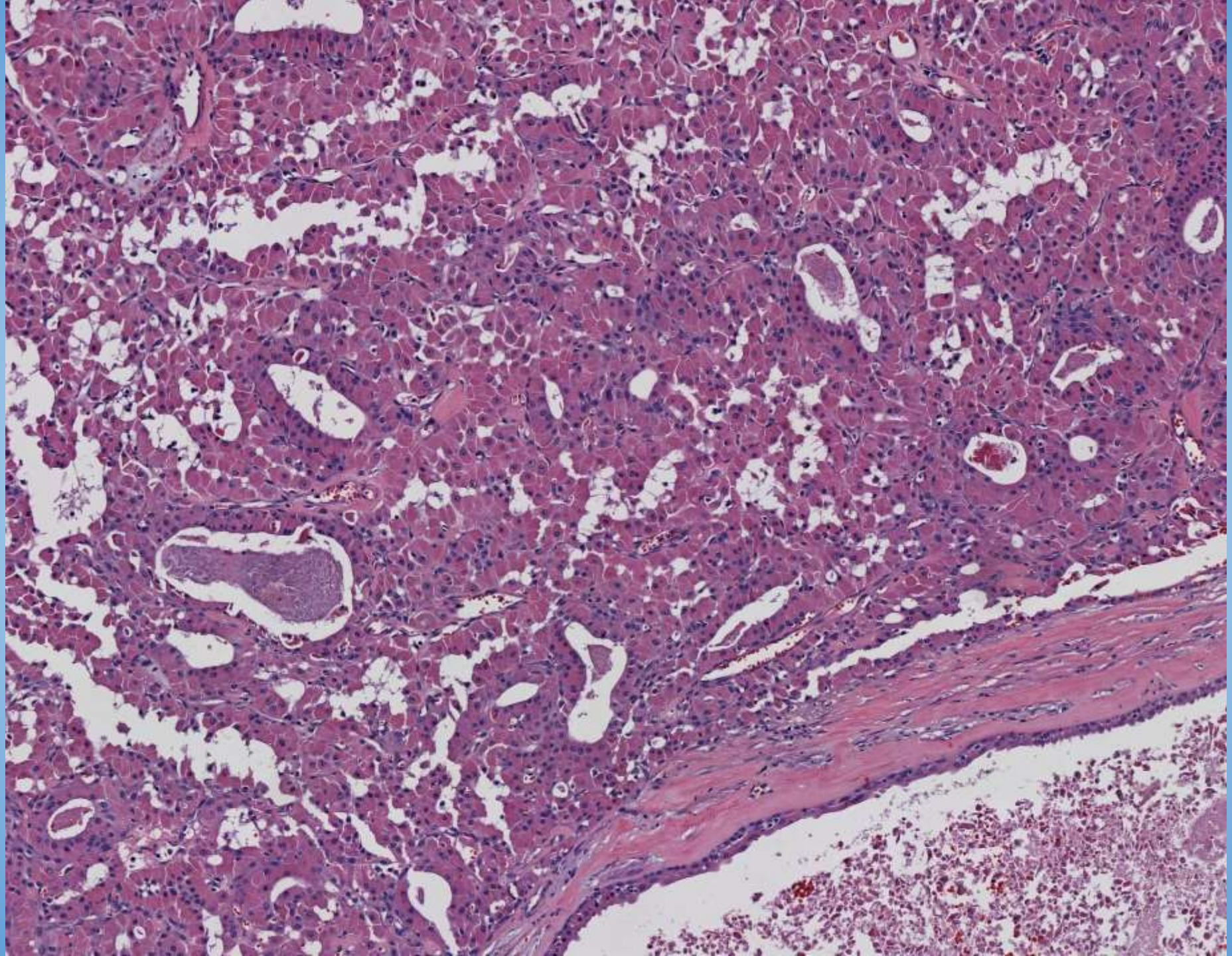
Mahendra Ranchod; Good Samaritan Hospital

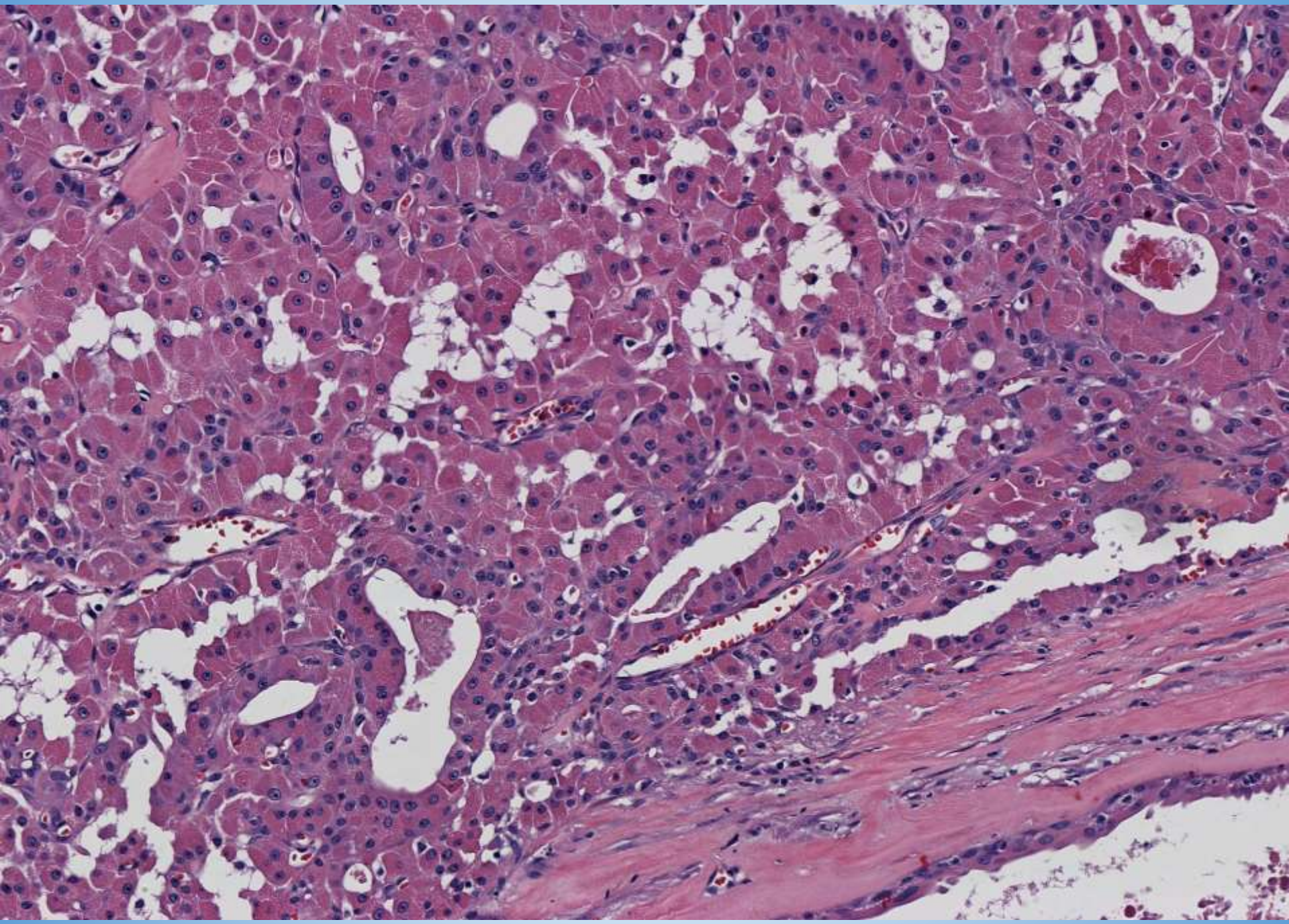
77-year-old male with mass in left submandibular salivary gland.

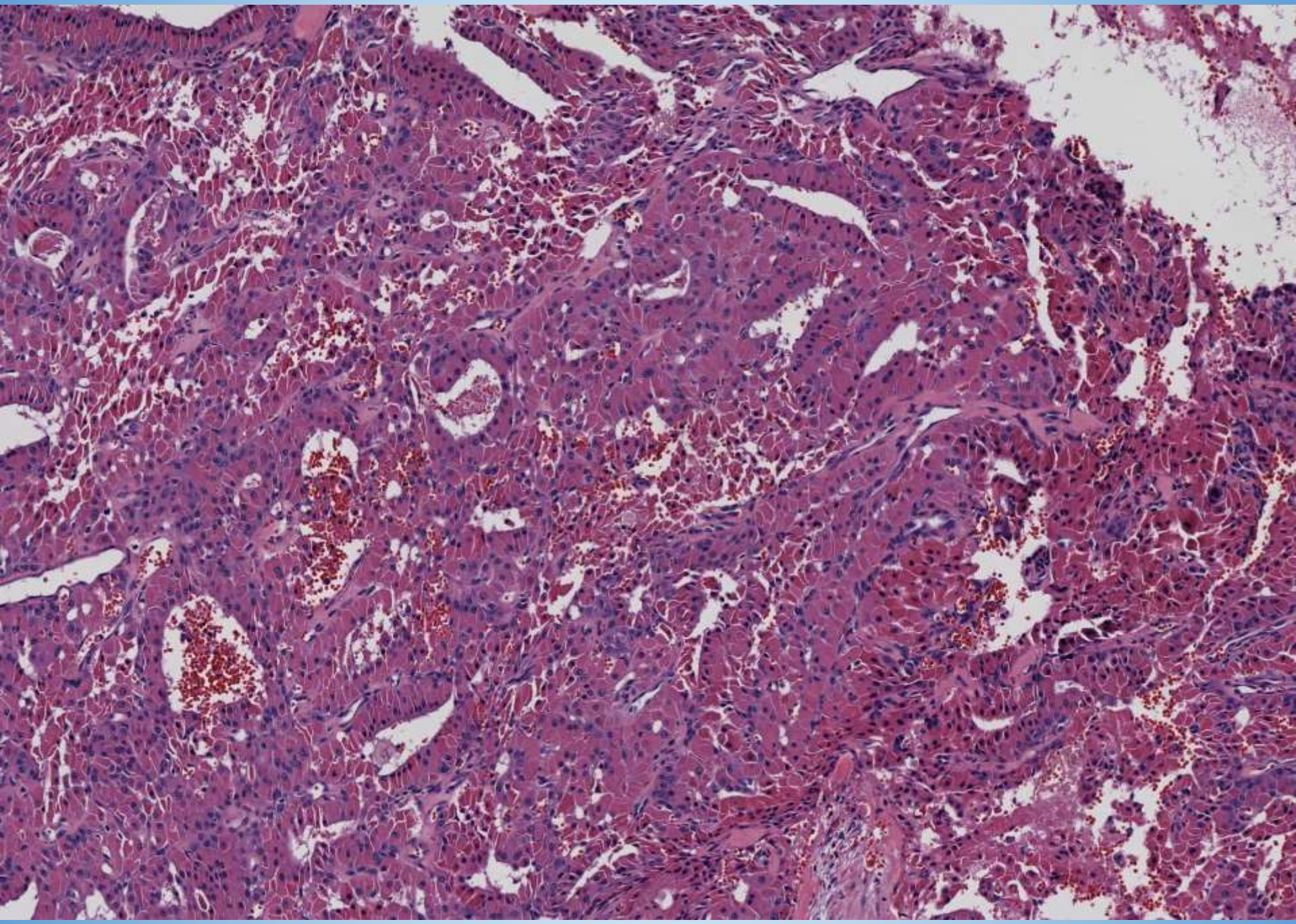


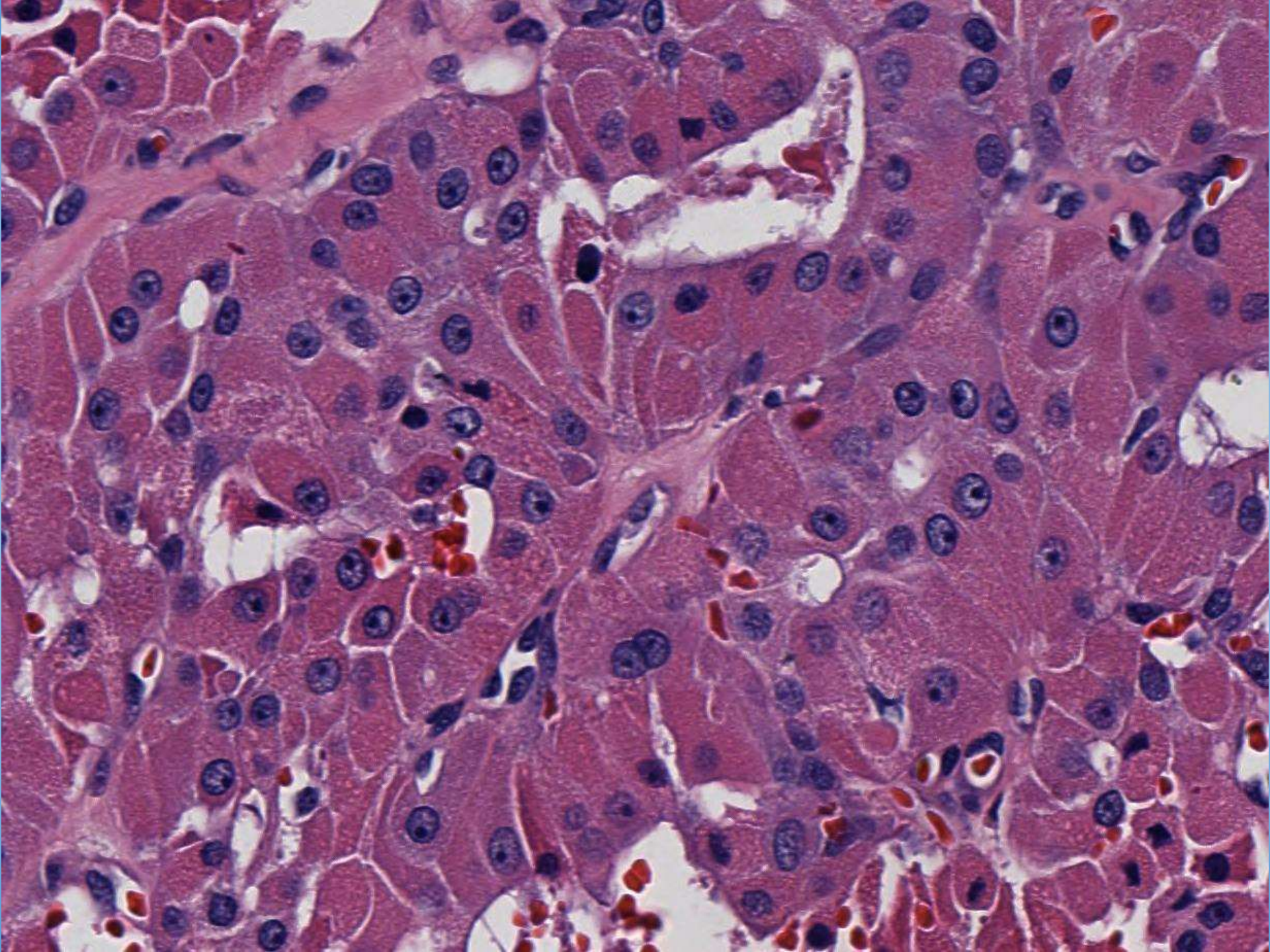












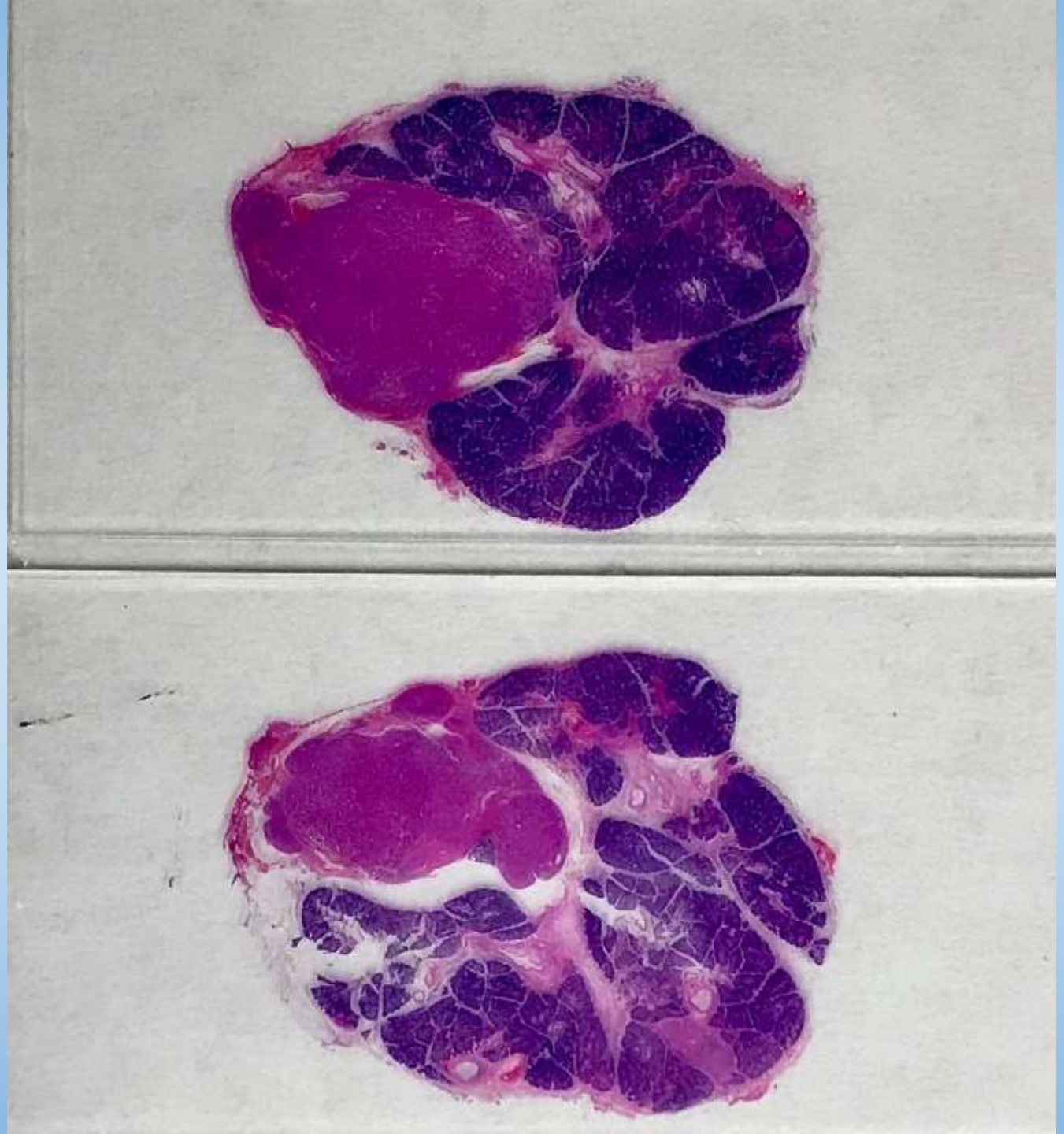
Oncocytoma

85-90% in parotid

7% bilateral

Solitary nodule or with nod. hyperplasia

Recurrence rate 10%

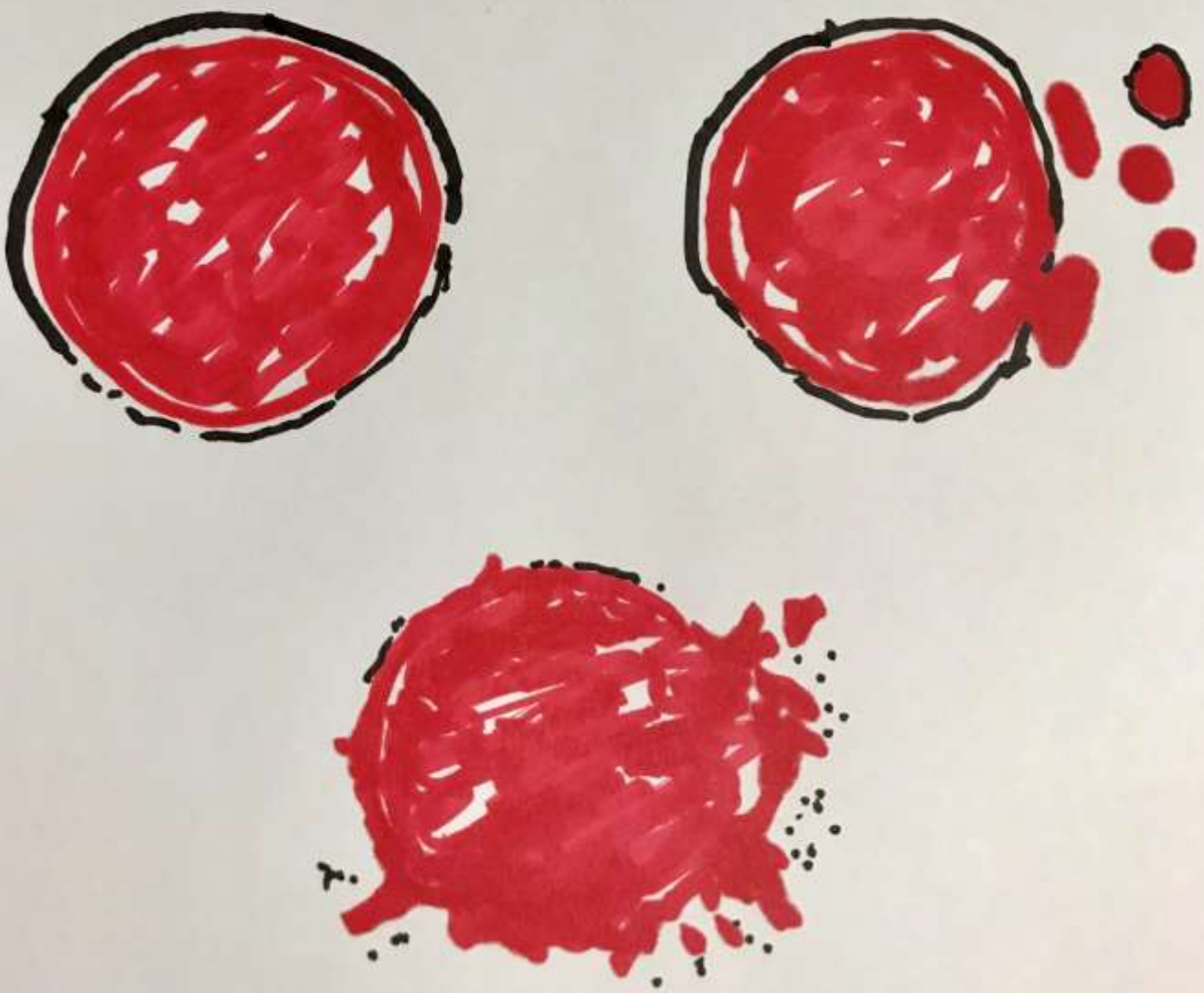


3

TOP

4

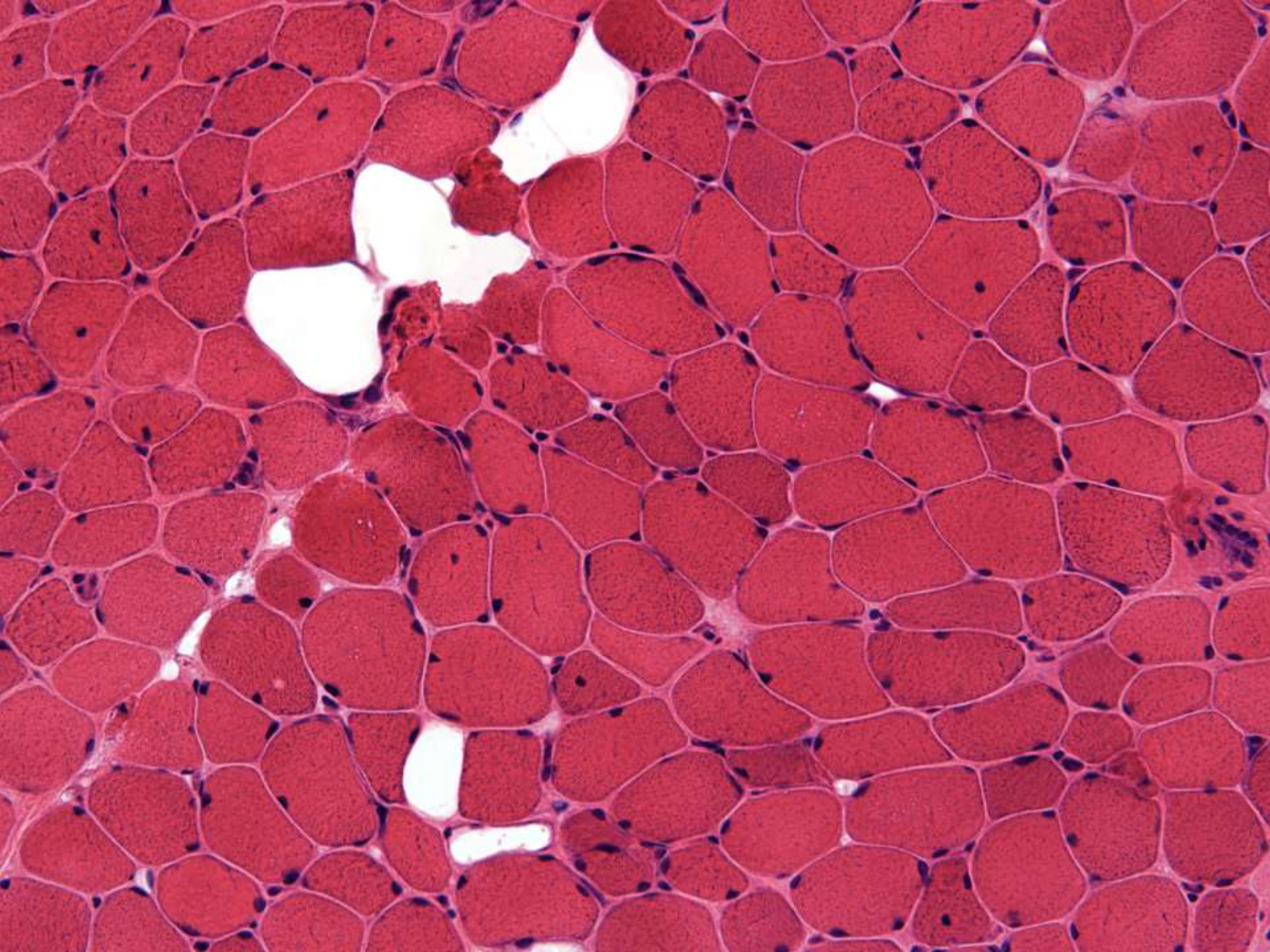
Top

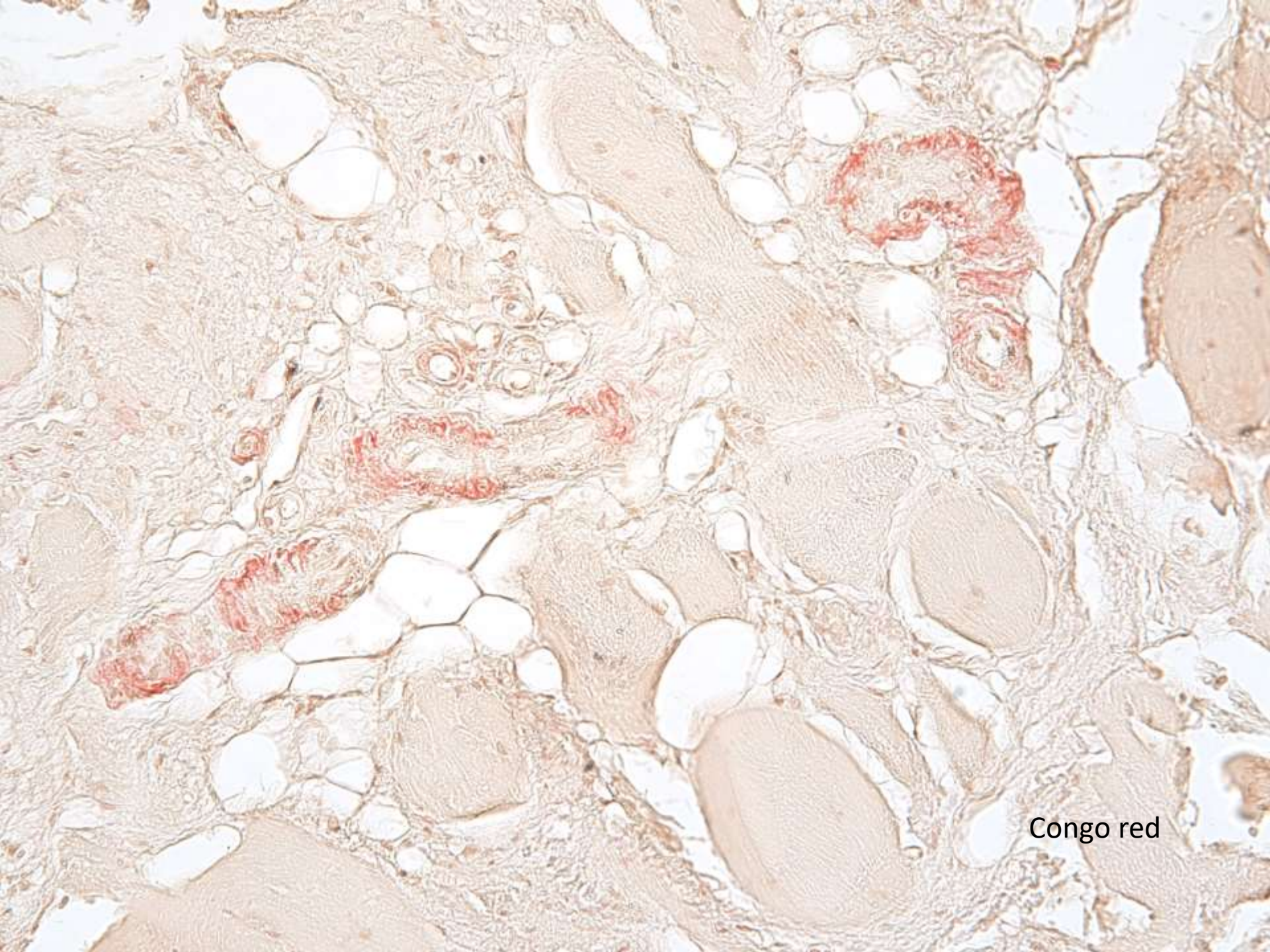


SB 6267

Hannes Vogel; Stanford

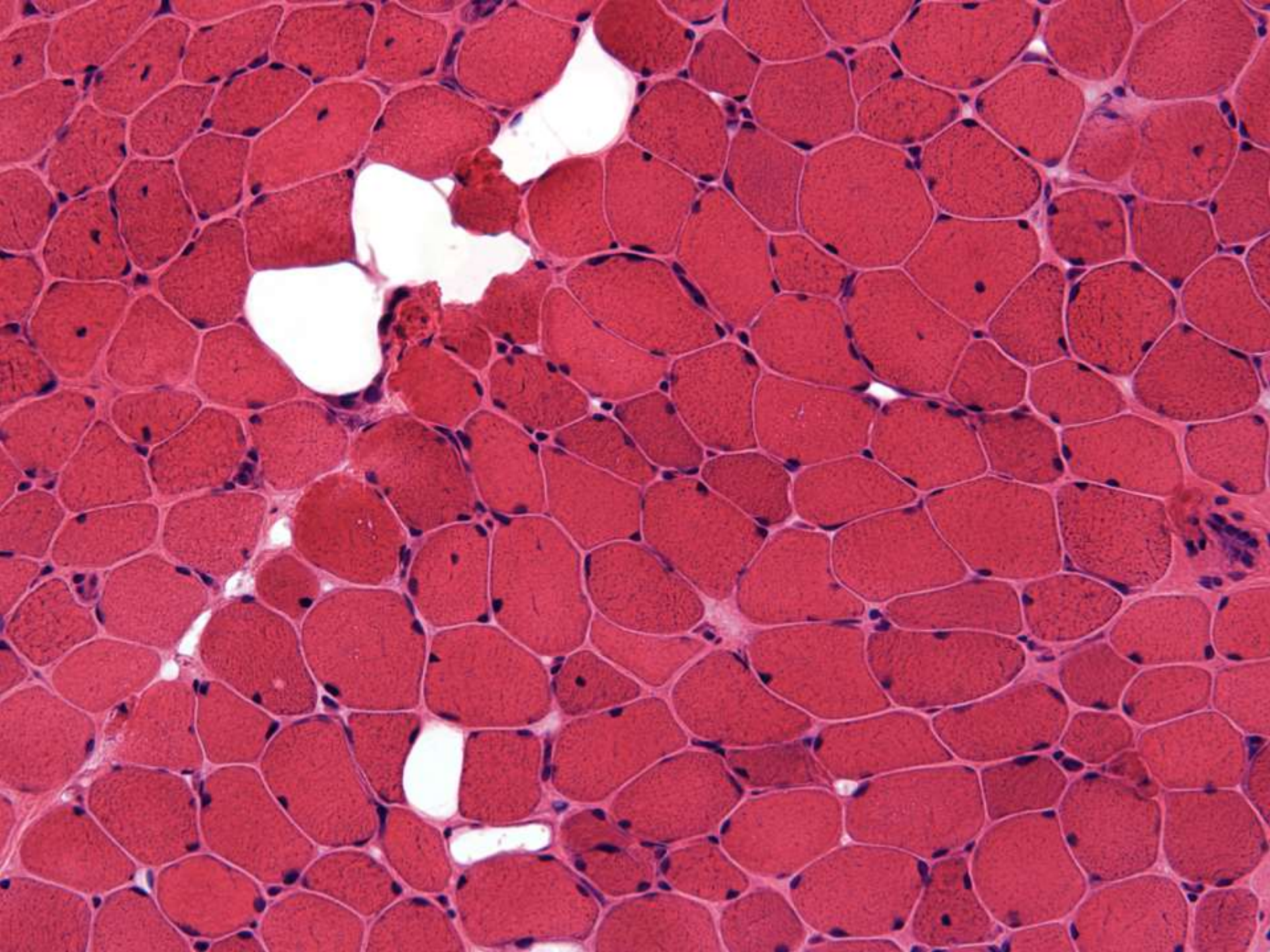
25-year-old female with leg and shoulder weakness for months. CK 6193. Muscle MRI shows diffuse fatty replacement. Right thigh biopsy performed.

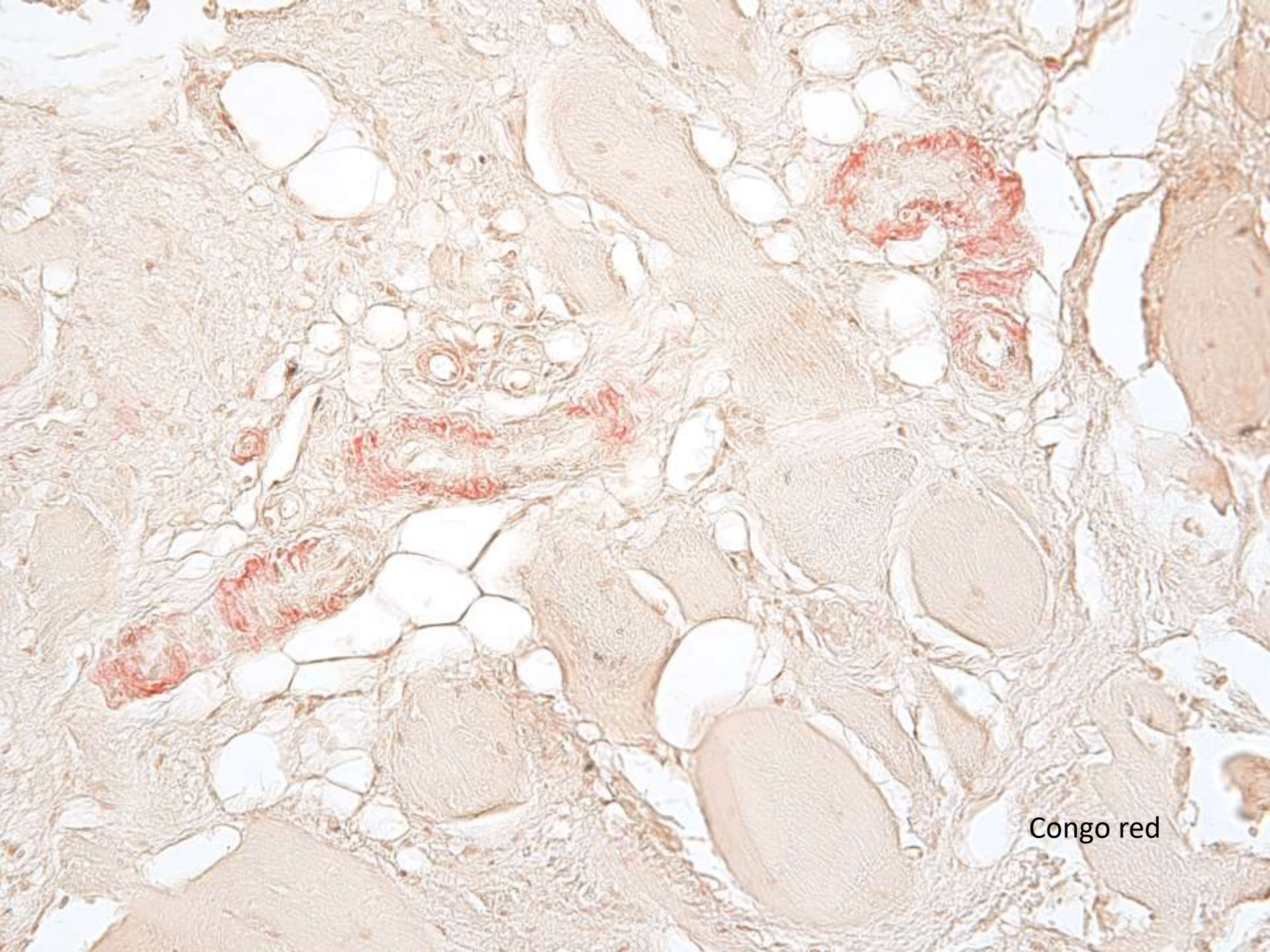


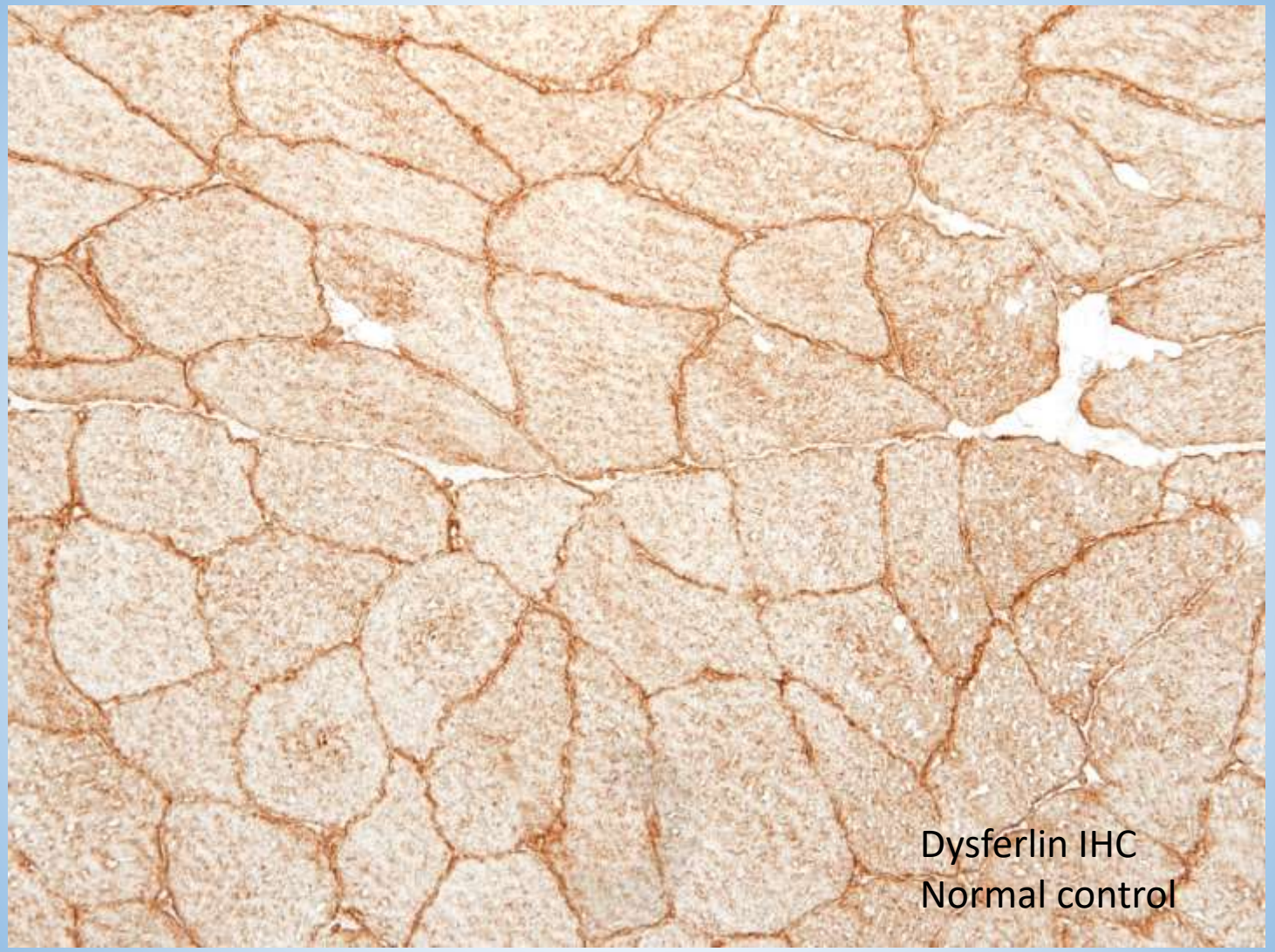

Congo red

South Bay Pathology Case Presentation
April 2018
H. Vogel

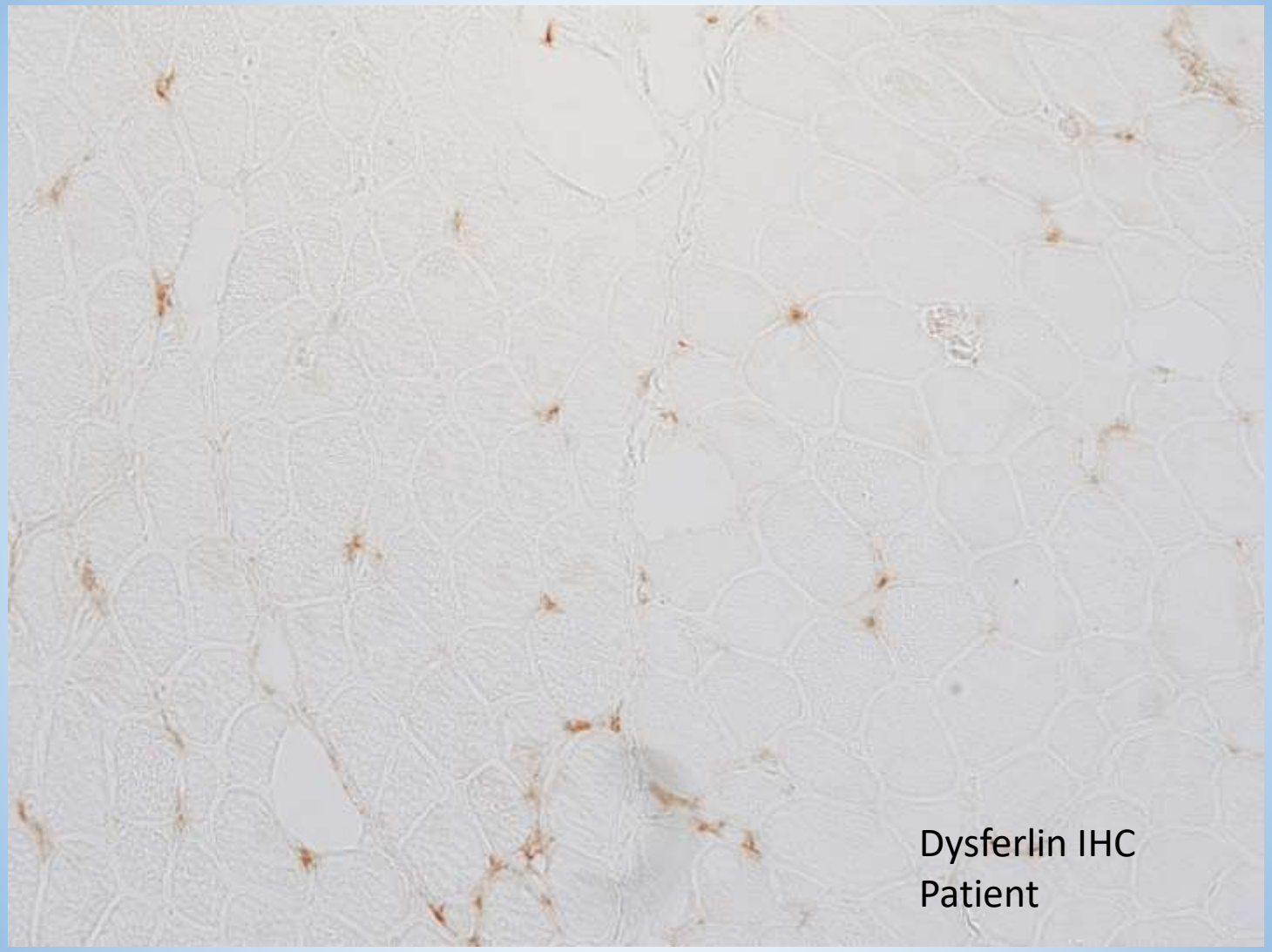
History: 25 year old female with leg and shoulder weakness X months. CK 6193. Muscle MRI shows diffuse fatty replacement. R thigh biopsy.

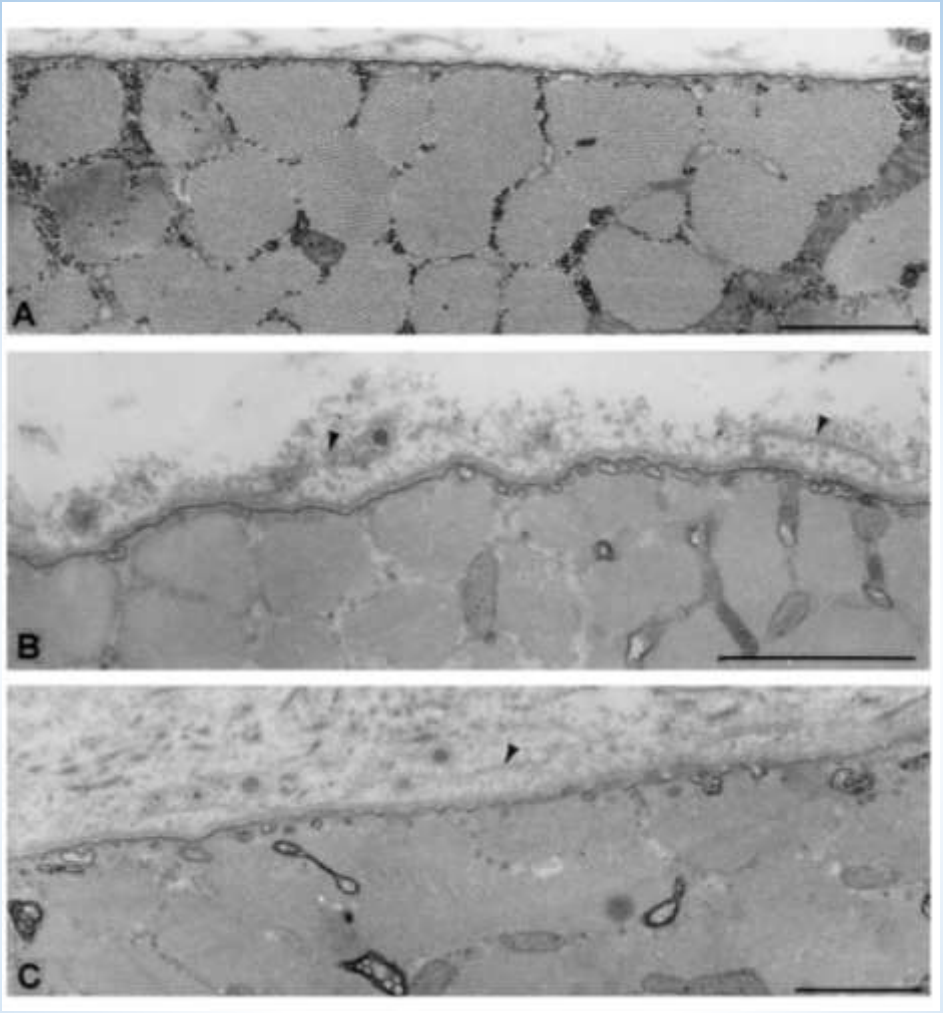



Congo red

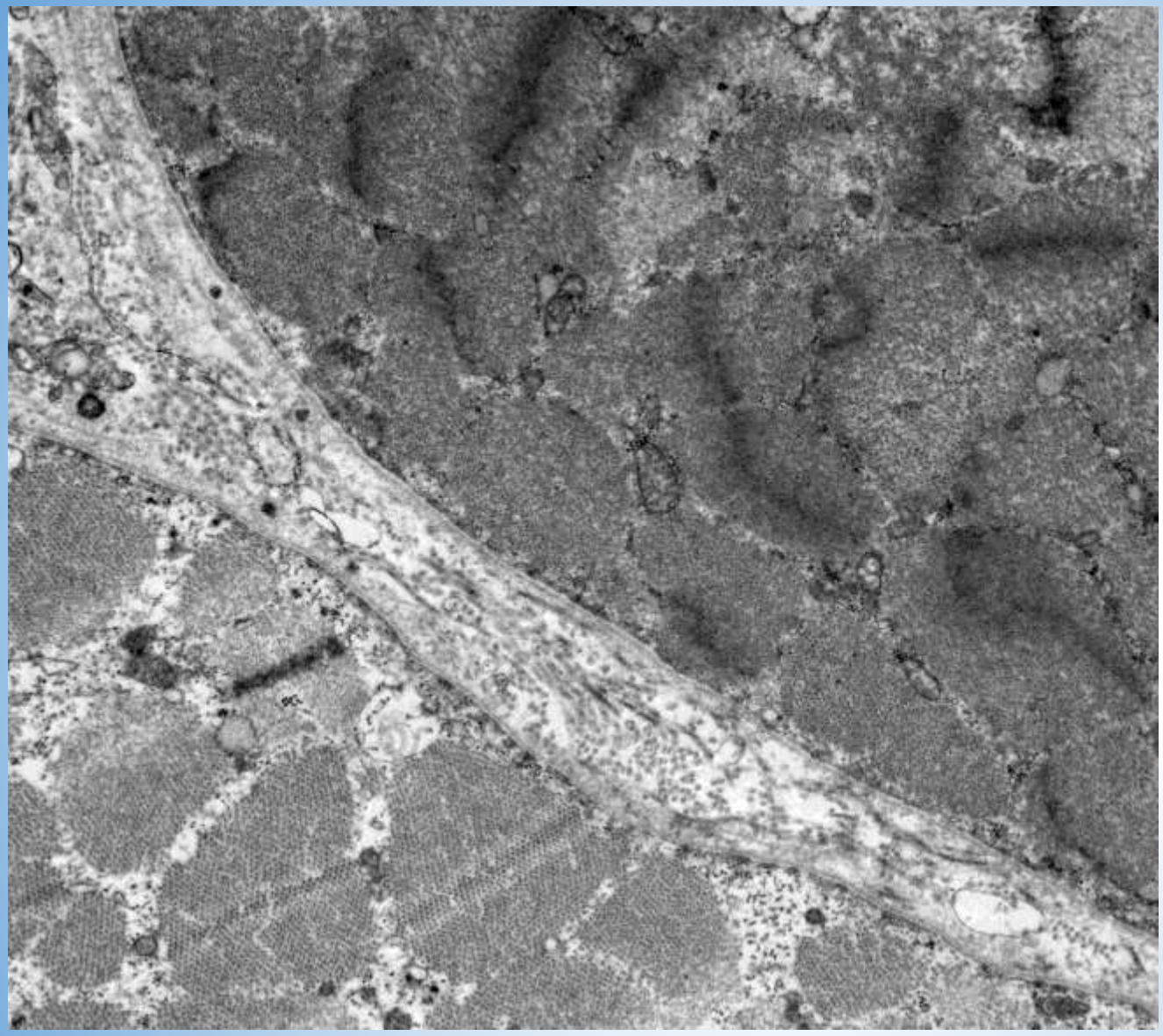

Dysferlin IHC
Normal control

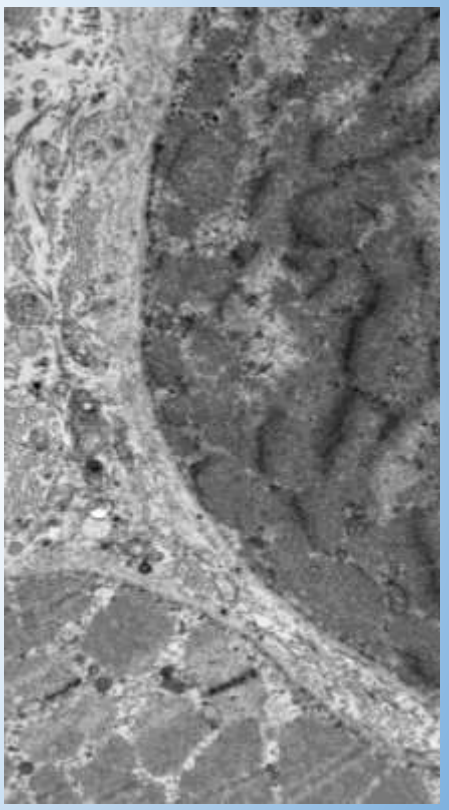
Diagnosis: Dystrophic myopathy with dysferlin deficiency





The earliest pathologic alterations in dysferlinopathy
NEUROLOGY 2001;56:1472–1481





INVITED REVIEW

PROGRESS AND CHALLENGES IN DIAGNOSIS OF DYSFERLINOPATHY

MARINA FANIN, PhD,[1] and CORRADO ANGELINI, MD[2]

[1] Department of Neurosciences, University of Padova, Biomedical Campus "Pietro d'Abano", via Giuseppe Orus 2B, 35129, Padova, Italy
[2] Fondazione San Camillo Hospital IRCCS, Venice, Italy

MUSCLE & NERVE November 2016

- In 1994, the genetic locus of autosomal recessive limb girdle muscular dystrophy type 2B (LGMD2B, MIM# 253601) and distal posterior-compartment Miyoshi myopathy (MM, MIM# 254130), was comapped to chromosome 2p13
- DYSF gene encodes a protein called "dysferlin," the muscle-specific member of a class of homologous proteins termed "ferlins."
- Dysferlin has been recognized to have a crucial role in the active process of repairing muscle membrane lesions where internal membranes are recruited to reseal
- Dysferlinopathies are characterized by a selective and progressive involvement of proximal and/or distal muscles of the limb girdles
- The age at onset of muscle weakness varies widely (from congenital to 73 years), but usually occurs in the teenage years or early adulthood (on average 15– 27 years)
- Serum creatine kinase (CK) levels are usually elevated (10–100 times normal values) from the early asymptomatic stage of the disease
- HyperCKemia characterizes all clinical phenotypes of dysferlinopathy and is a hallmark of the disease

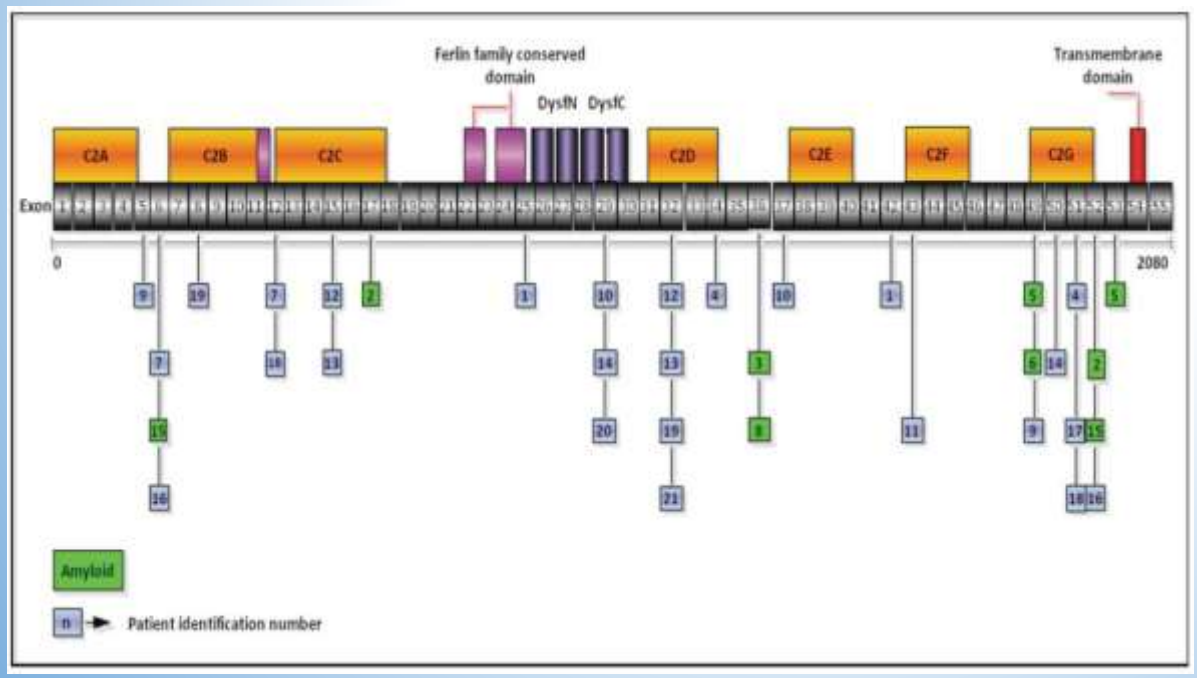
NOVEL DIAGNOSTIC FEATURES OF DYSFERLINOPATHIES

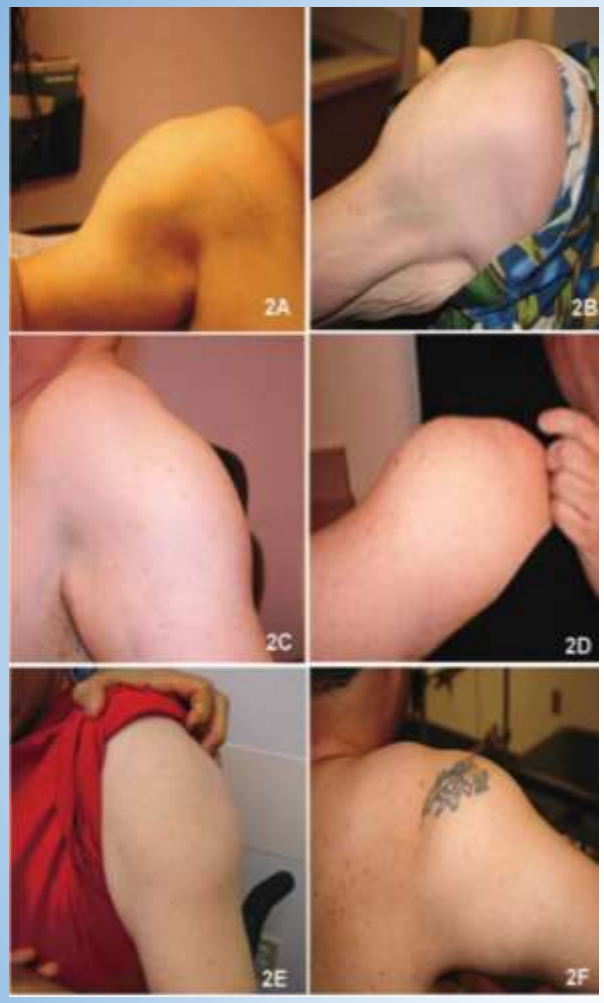
XIOMARA Q. ROSALES, MD,[1,2,4,5] JULIE M. GASTIER-FOSTER, PhD,[3,4] SARAH LEWIS, HT, ASCP,[1,2] MALIK VINOD, PhD,[1,2] DEVON L. THRUSH, MS,[3,4] CAROLINE ASTBURY, PhD,[3,4] ROBERT PYATT, PhD,[3,4] SHALINI RESHMI, PhD,[3,4] ZARIFE SAHENK, MD, PhD,[1,2,4,5] and JERRY R. MENDELL, MD[1,2,4,5]

[1] Department of Pediatrics, Neuromuscular Division, Nationwide Children's Hospital, Columbus, Ohio, USA
[2] Center for Gene Therapy, Research Institute at Nationwide Children's Hospital, Columbus, Ohio, USA
[3] Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA
[4] Department of Pediatrics, Ohio State University, Columbus, Ohio, USA
[5] Department of Neurology, Neuromuscular Division, Ohio State University, Columbus, Ohio, USA

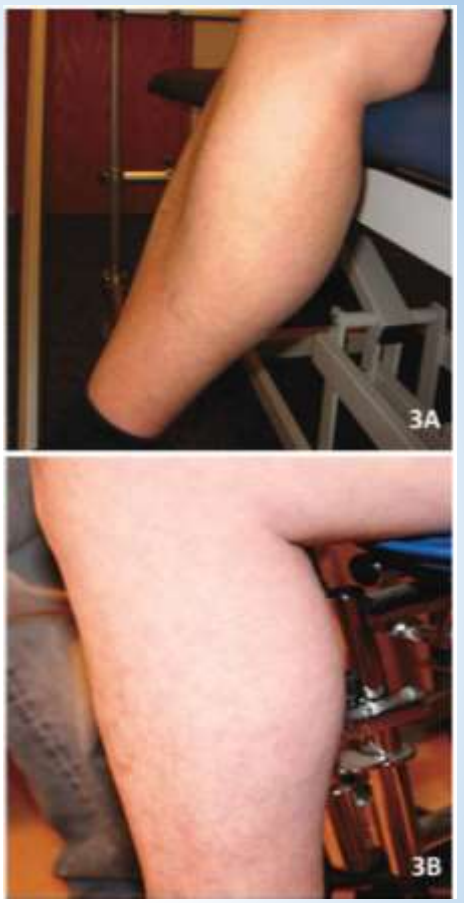
MUSCLE & NERVE July 2010

- A distinct 'bulge' of the deltoid muscle was a striking feature in all patients
- 6 subjects had atypical calf enlargement, and 3 of these exhibited a paradoxical pattern of dysferlin expression: severely reduced by direct immunofluorescence with overexpression on Western blots
- 6 patients showed amyloid deposits in muscle, distinct to LGMD2B
- Showed co-localization of amyloid with deposition of dysferlin



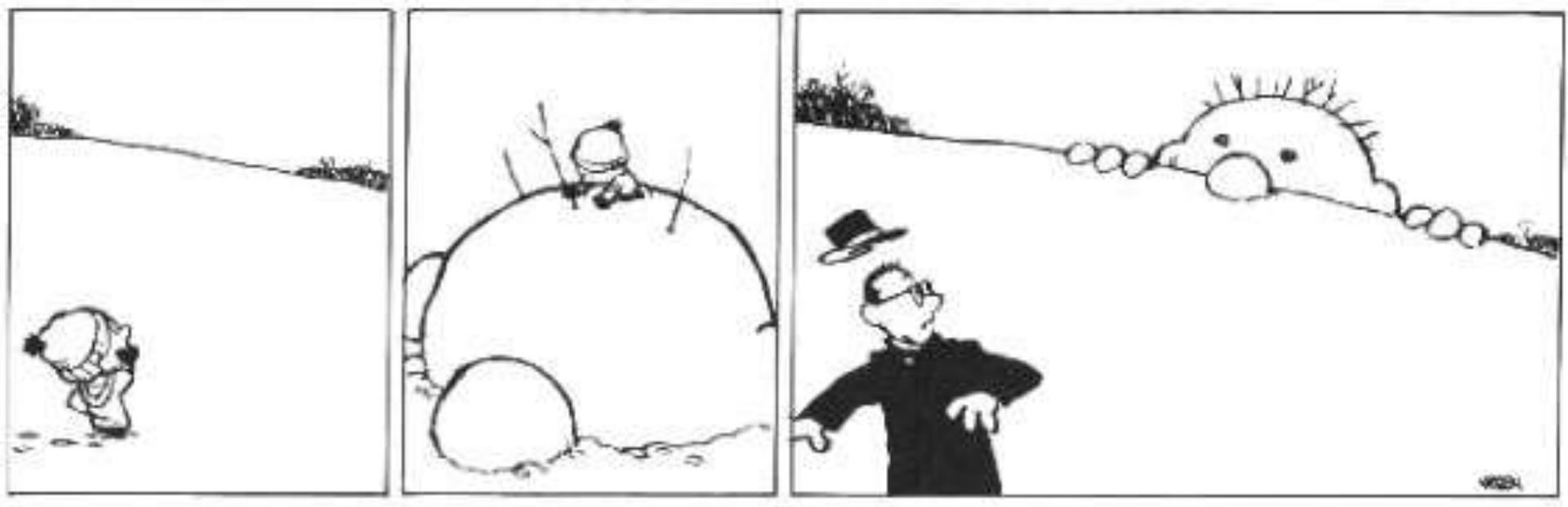


Deltoid hypertrophy in 6 cases of dysferlin deficiency. The surrounding muscles are atrophic



Calf muscle hypertrophy in patients with dysferlin gene mutations. These patients had been previously mislabeled with a diagnosis of Becker muscular dystrophy

MUSCLE & NERVE July 2010



SB 6268

Nabeen Nayak; Sir Ganga Ram Hospital, New Dehli

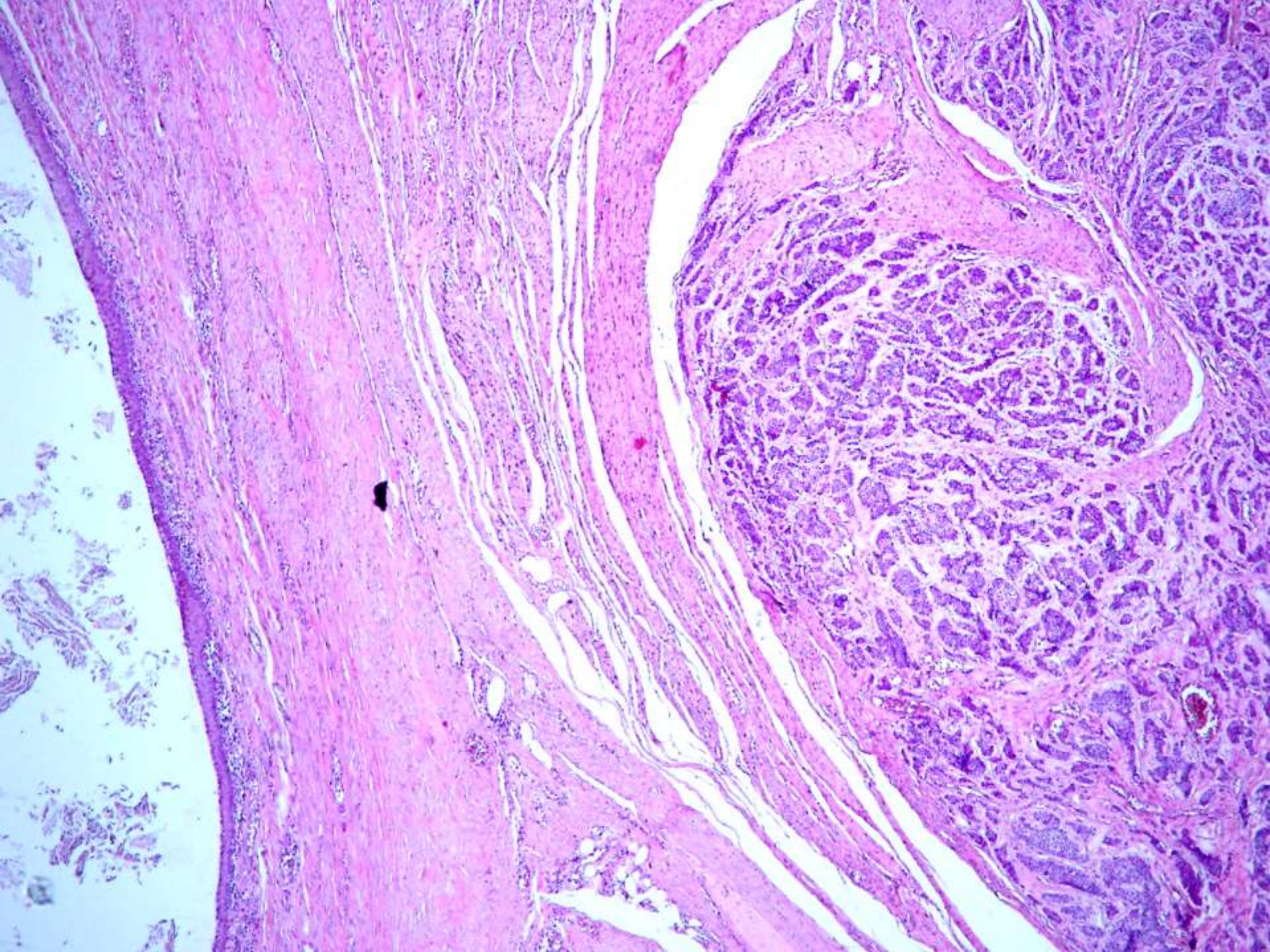
44-year-old male complained of upper abdominal pain for 6 months. PET-CT revealed 4cm partly cystic/solid soft tissue mass in lesser sac posterior/superior to pancreas, as well as 9cm cystic lesion in liver. Serum chromogranin A level=188 ng/L. Both lesser sac and liver lesions surgically resected.

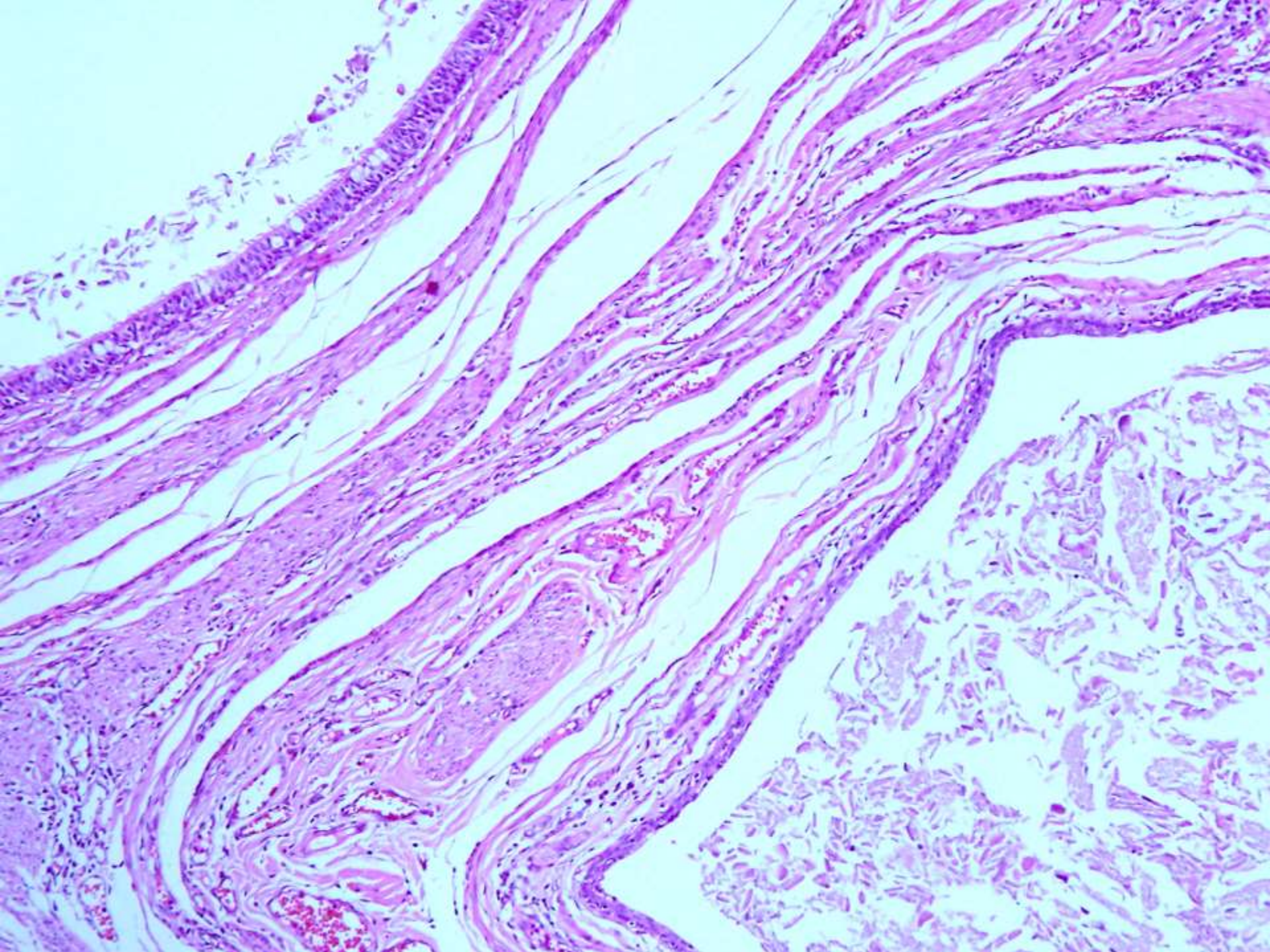
A 44-yr-old man complained of upper abdominal pain for 6 months.

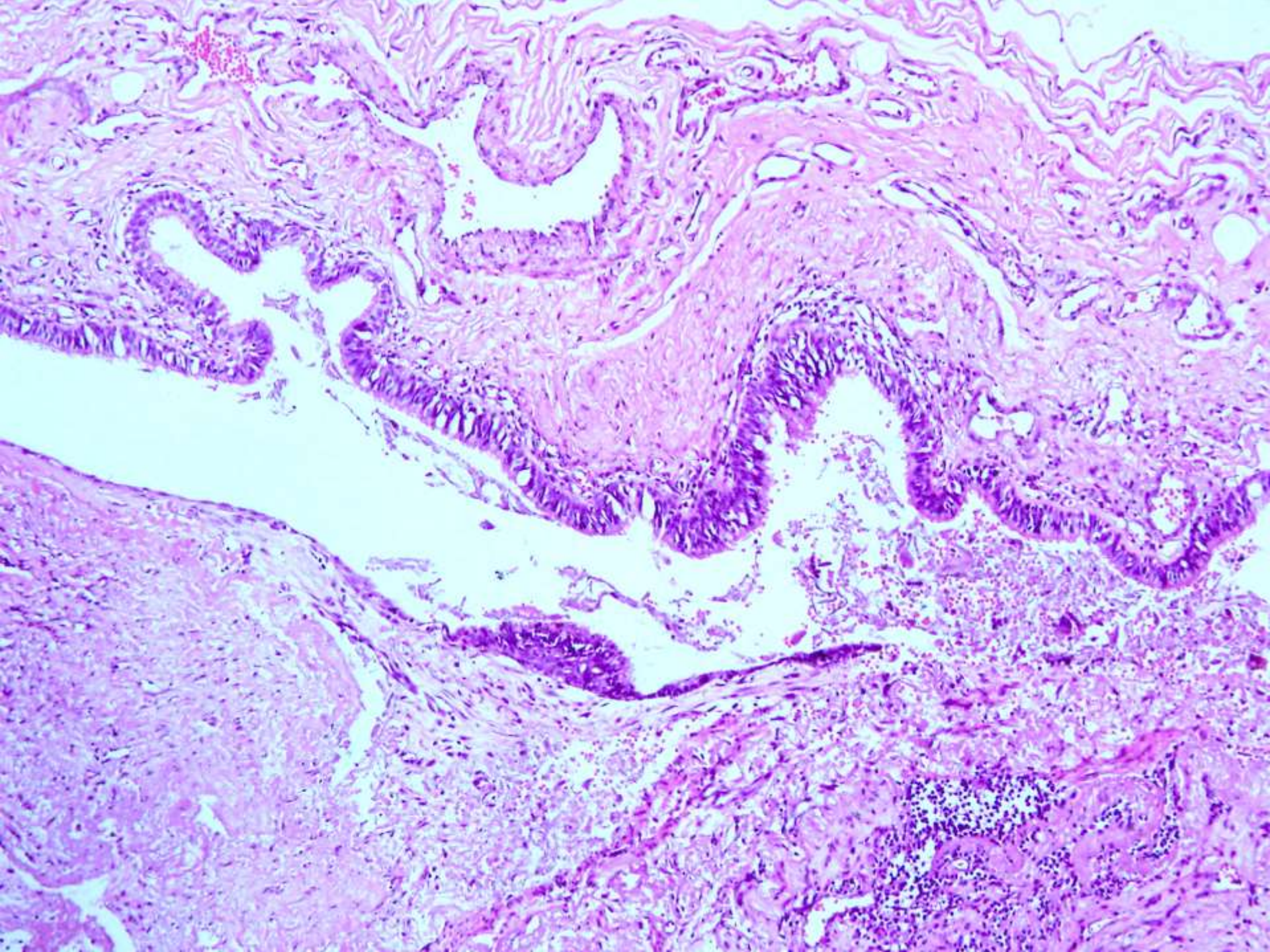
A PET-CT (DOTA Scan) revealed a 4x3x3 cm. partly cystic and partly solid soft tissue mass in the lesser sac, placed postero-superior to the pancreas, as well as a 9x8x6 cm. cystic lesion in the liver. His serum Chromogranin A level was 188 ng/L. Both the lesser sac and liver lesions were surgically resected.

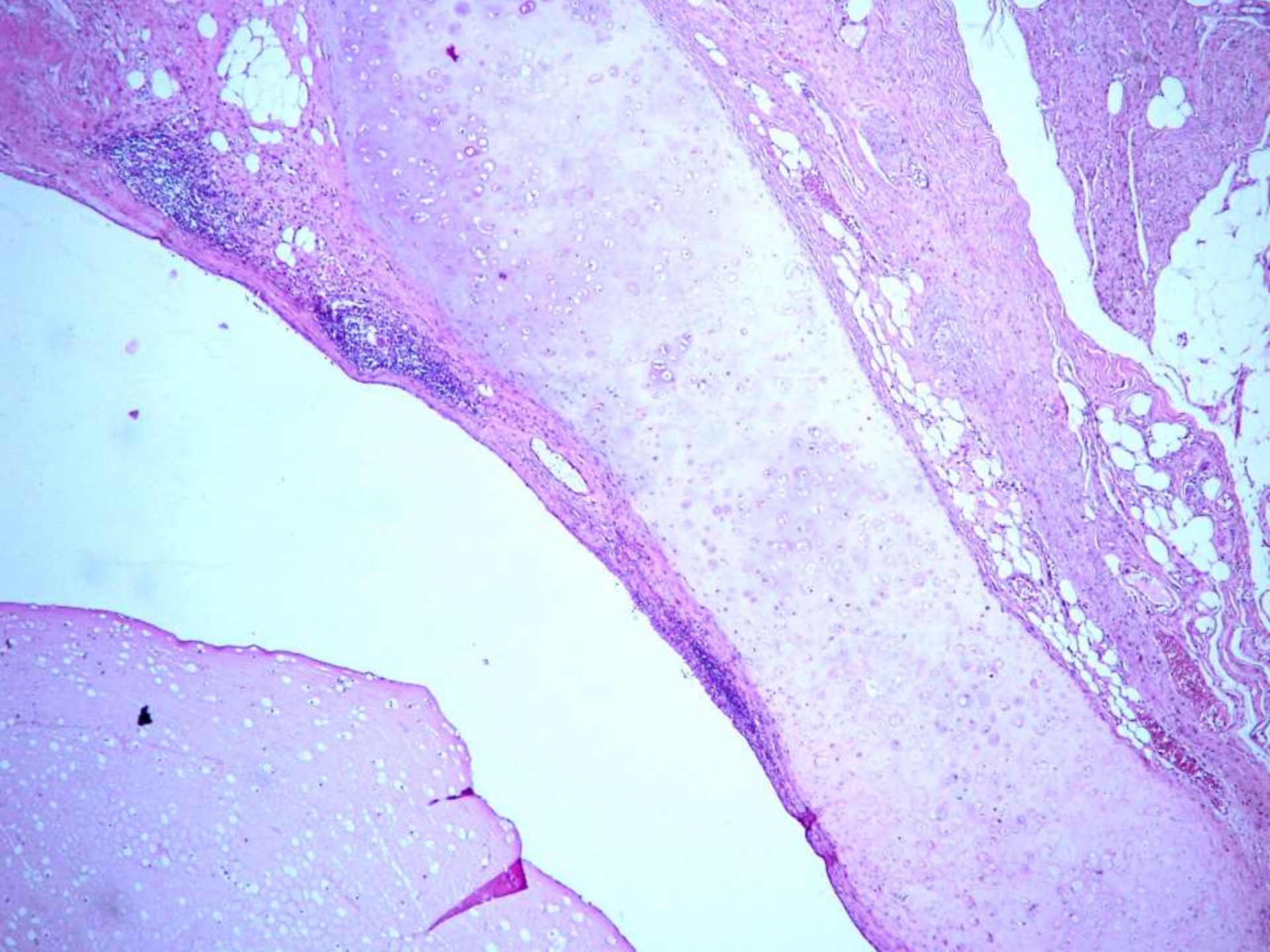
The first 8 histology pictures are from the lesser sac mass.

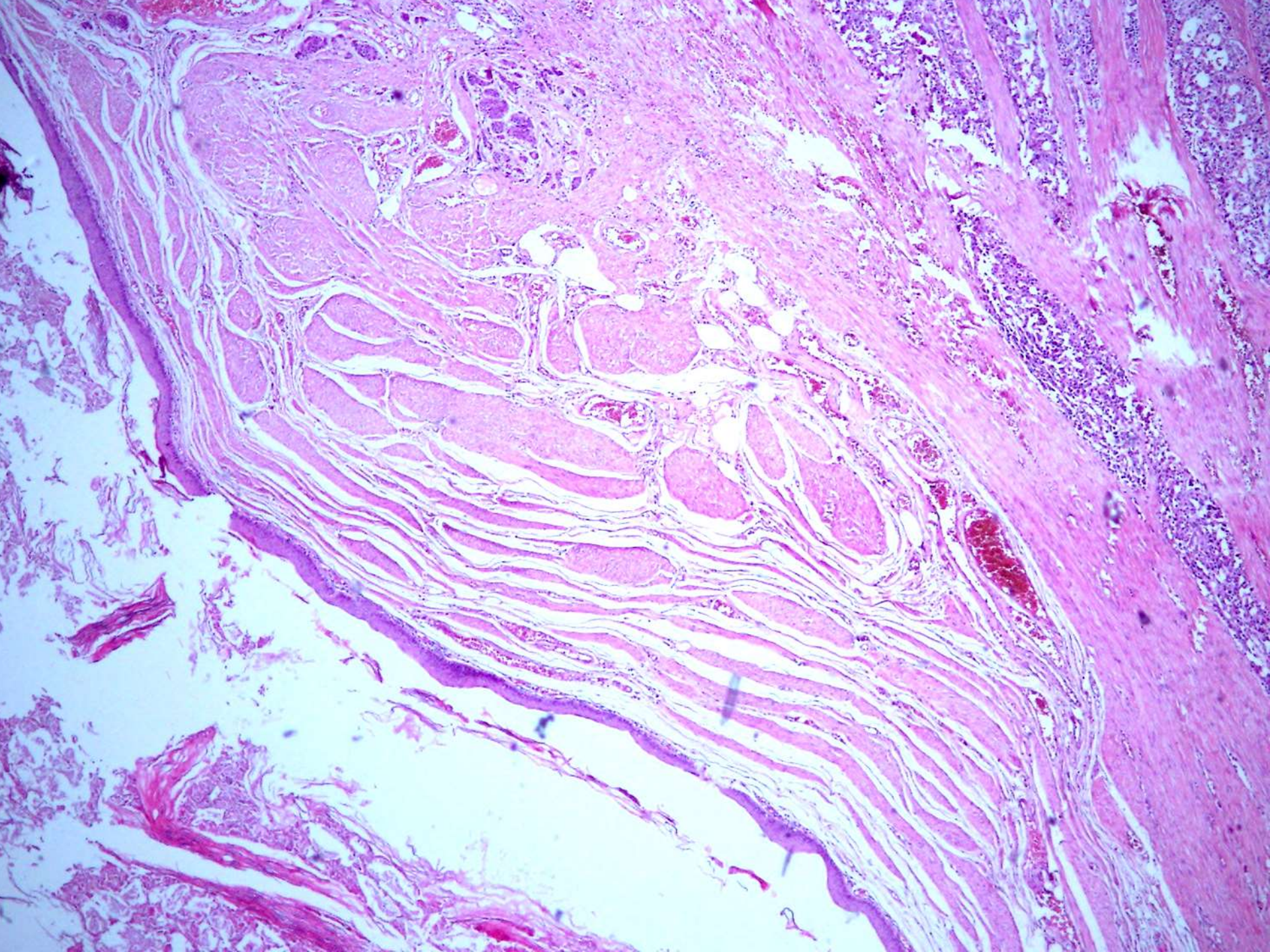
The last 2 are from the liver lesion.

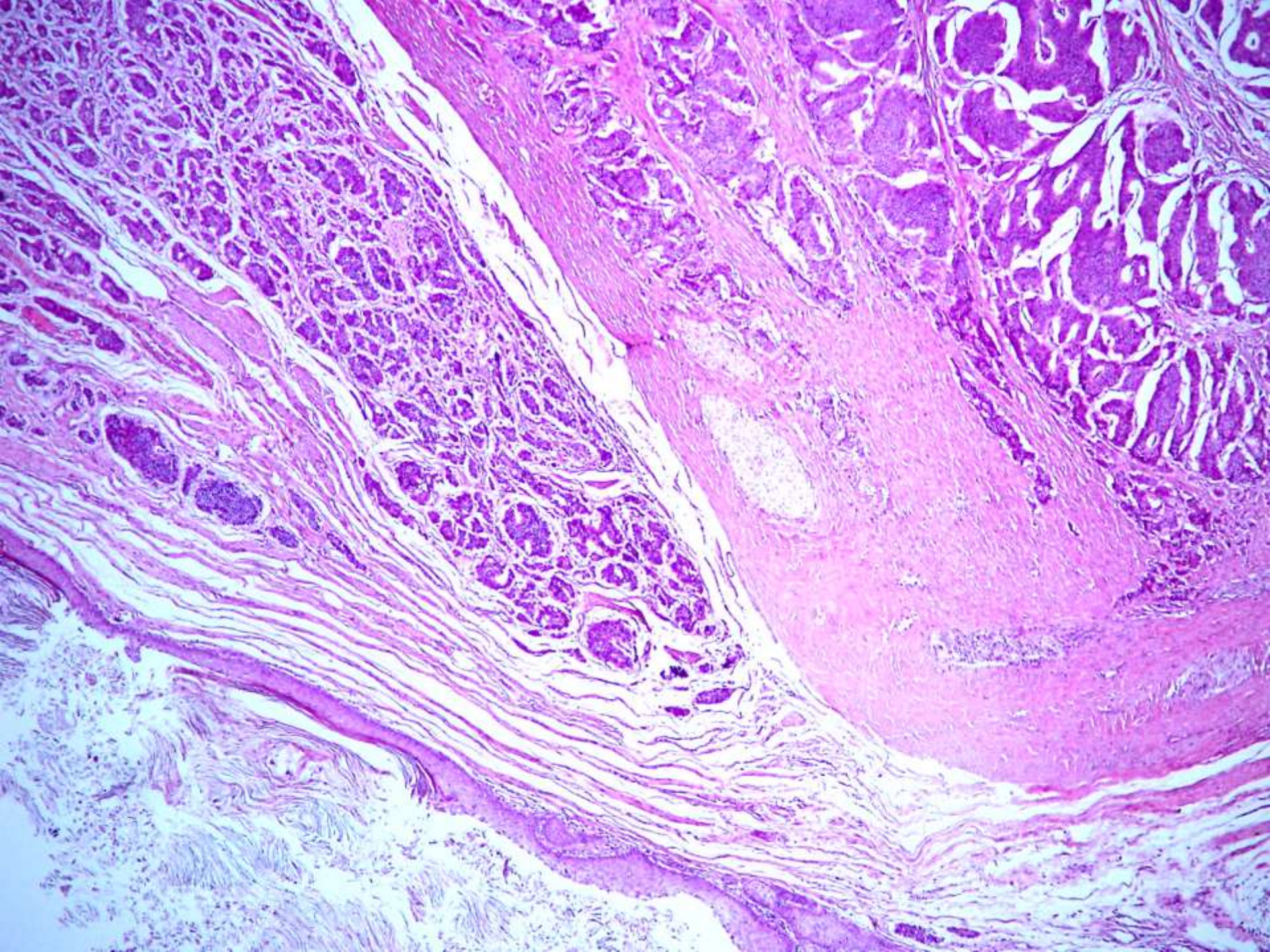


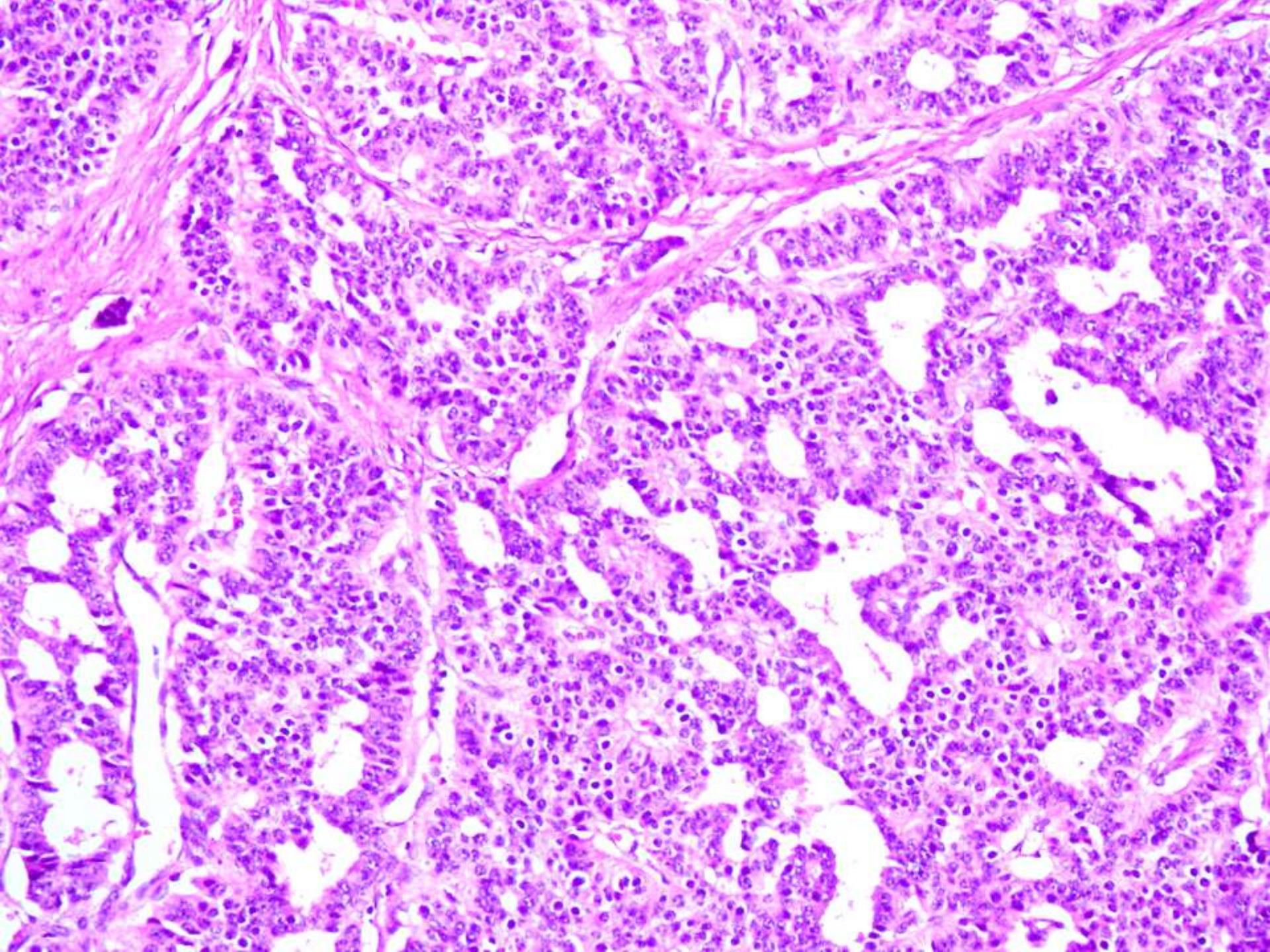


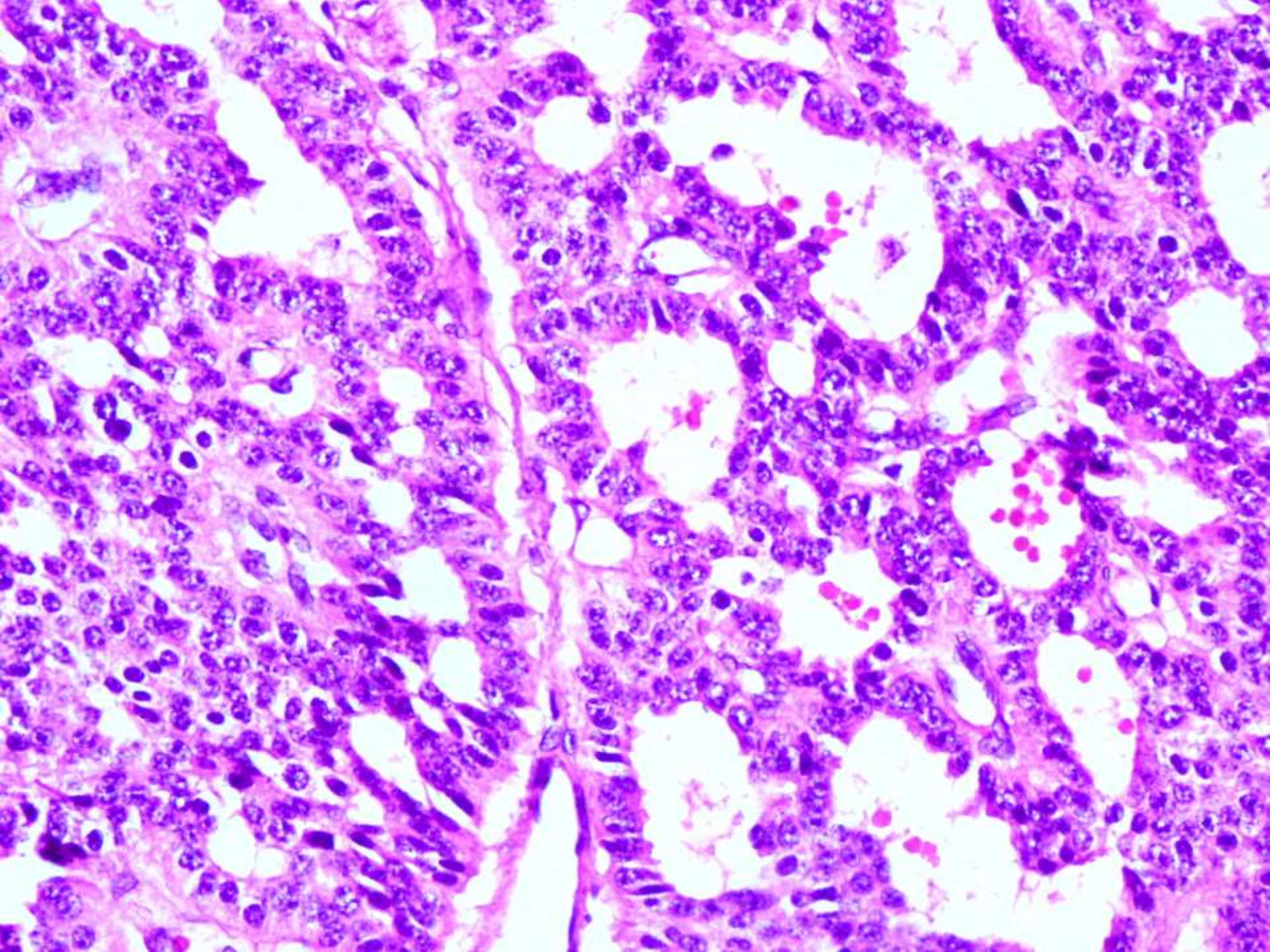




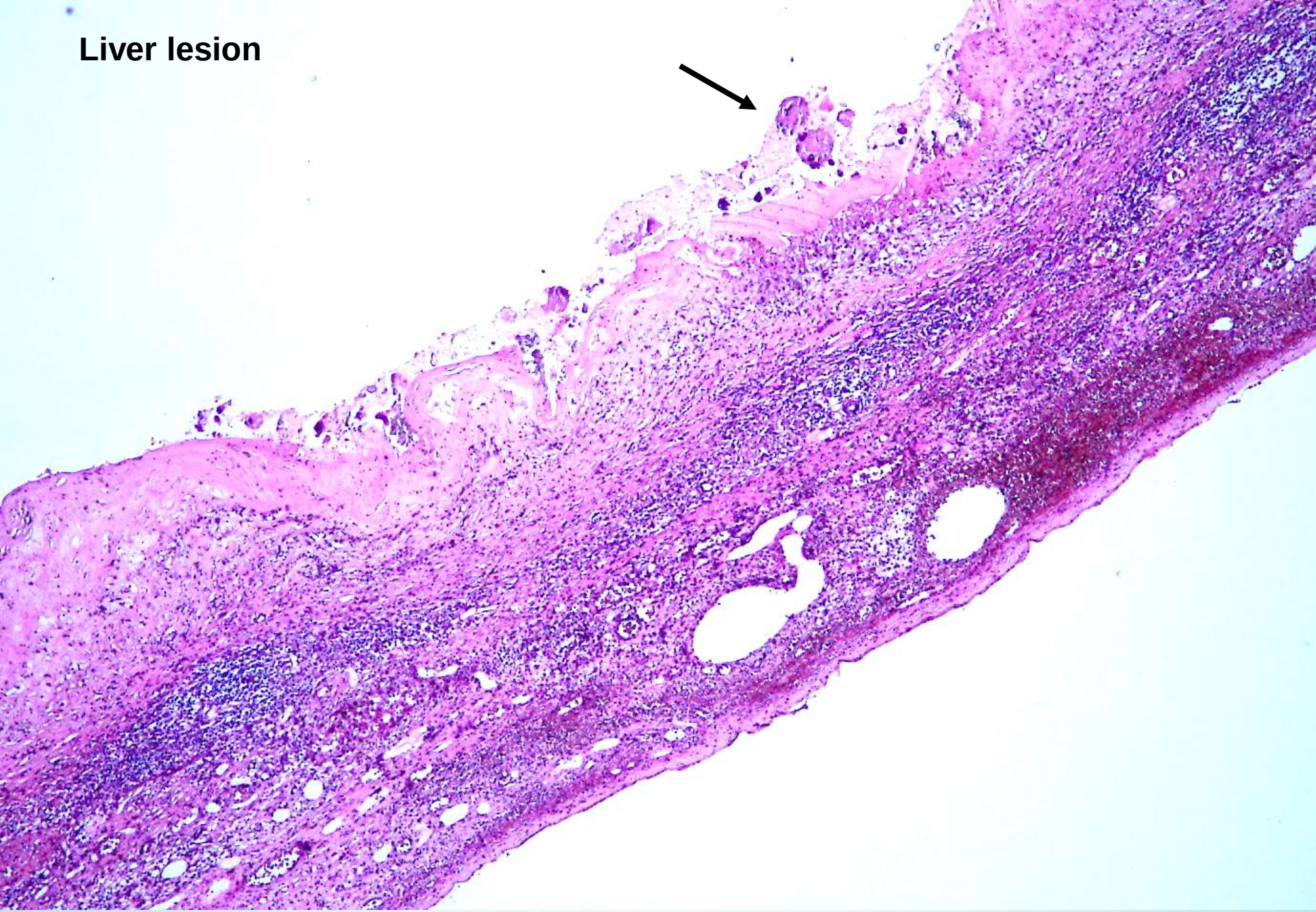


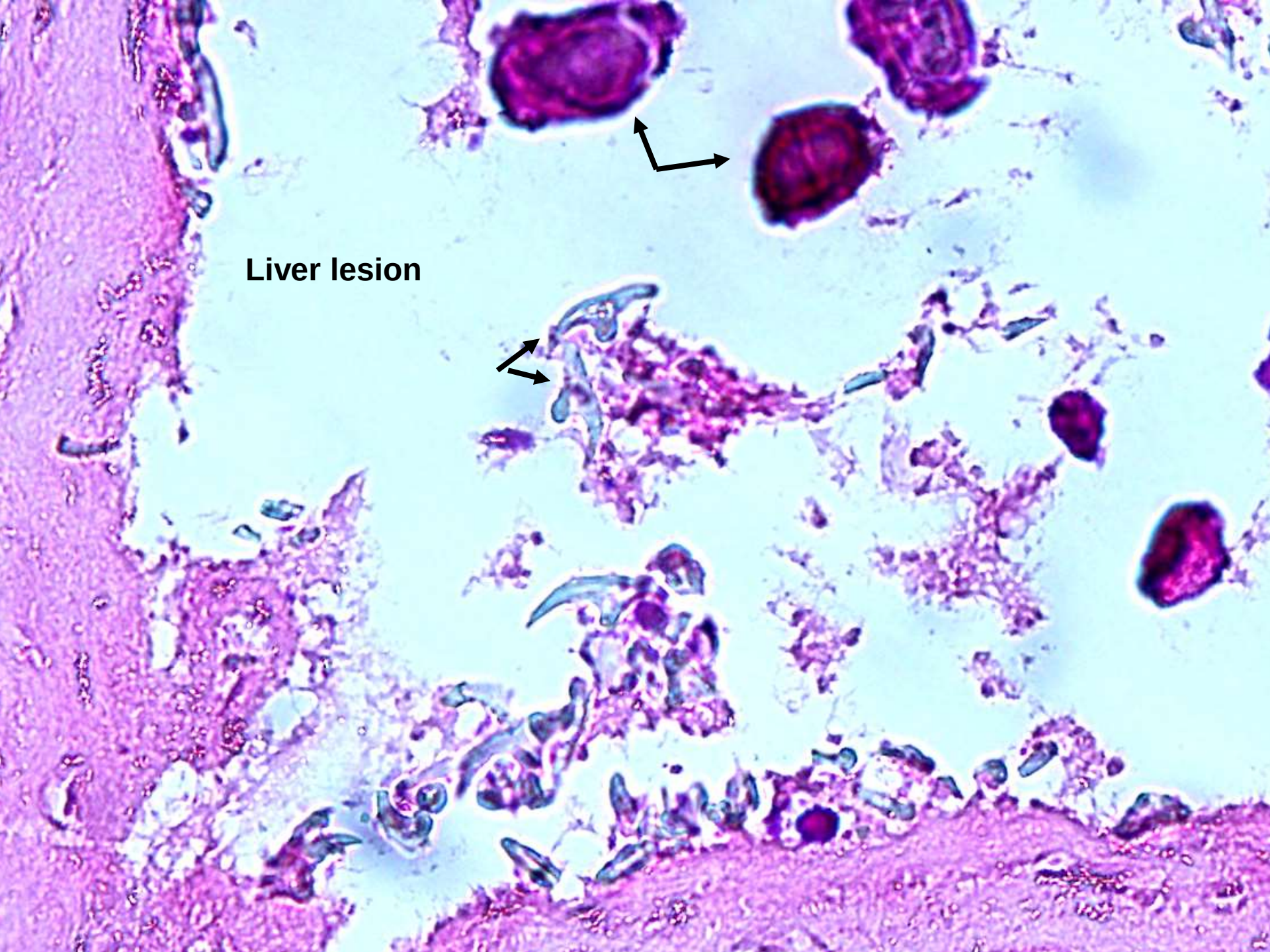




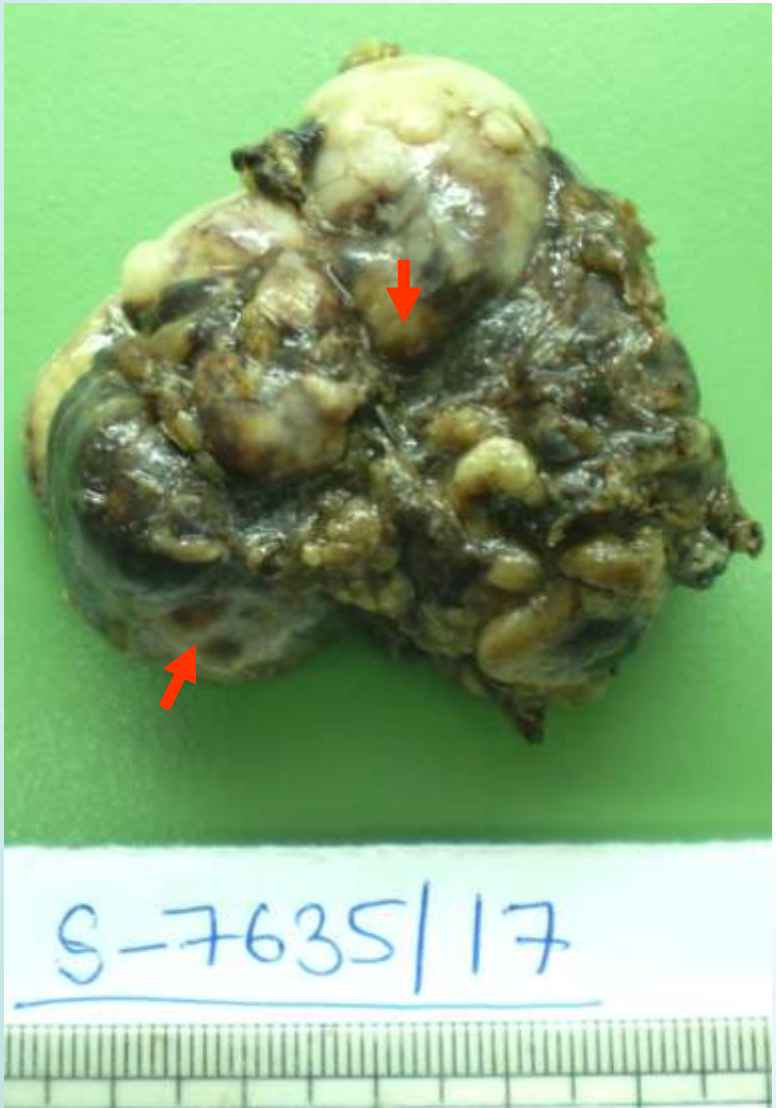


Liver lesion



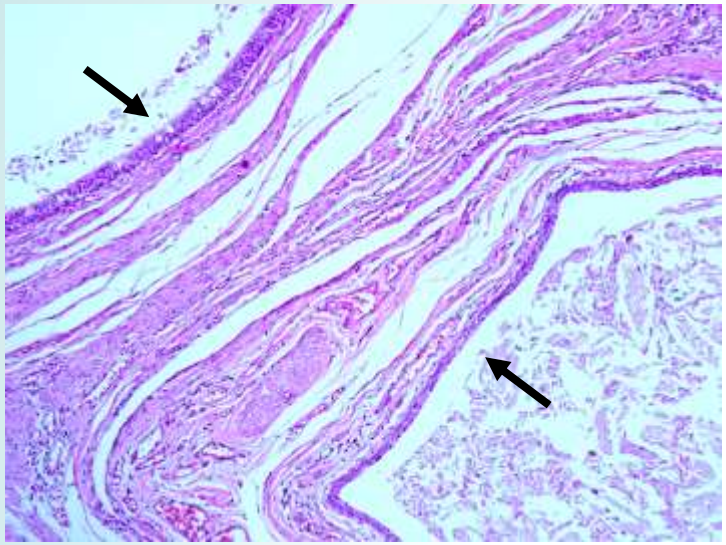

Liver lesion

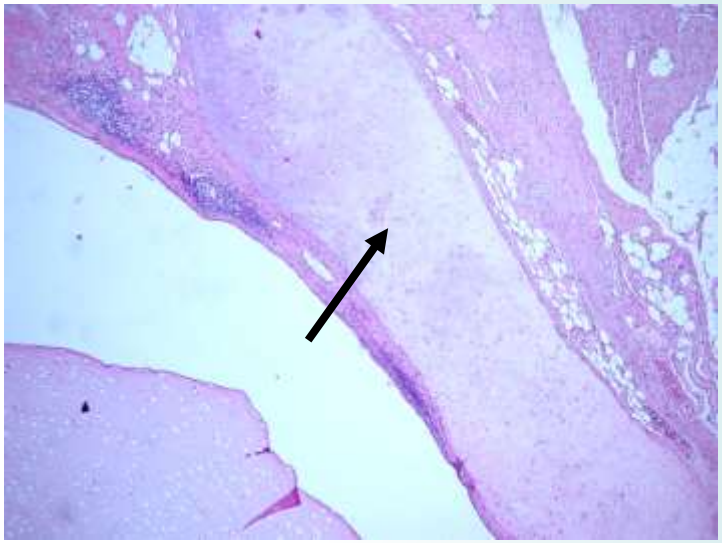
At open abdominal surgery the **M<u>ass in the Lesser Sac</u>** was unattached to any of the neighboring organs and was totally excised. Few somewhat enlarged but otherwise normal appearing lymph nodes were removed

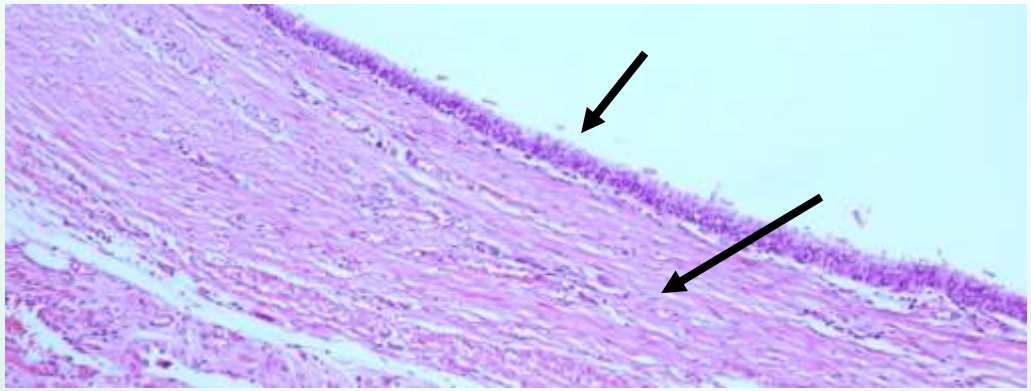


Cysts in the Lesser Sac mass have lining and wall of Bronchial constituents. No Adnexal structure or disorganized/different germ cell lineage component seen.

No other neighboring organ component present.

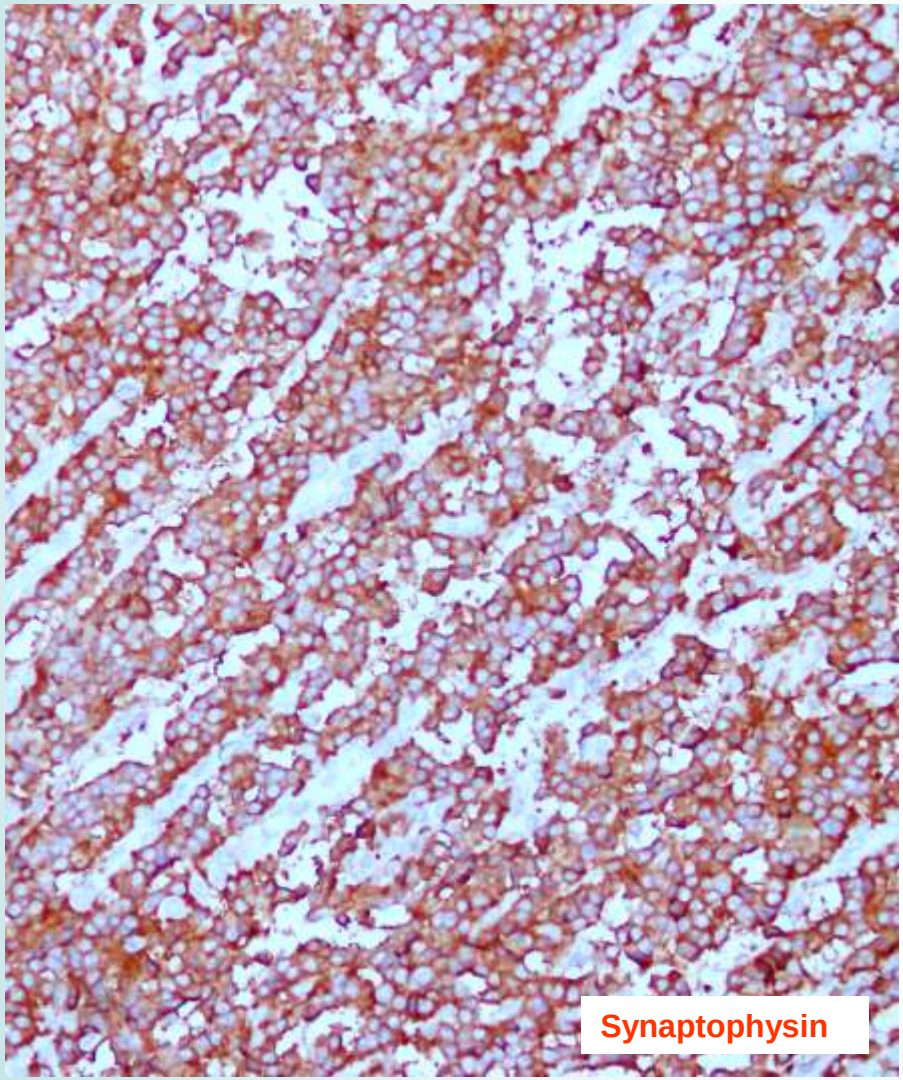




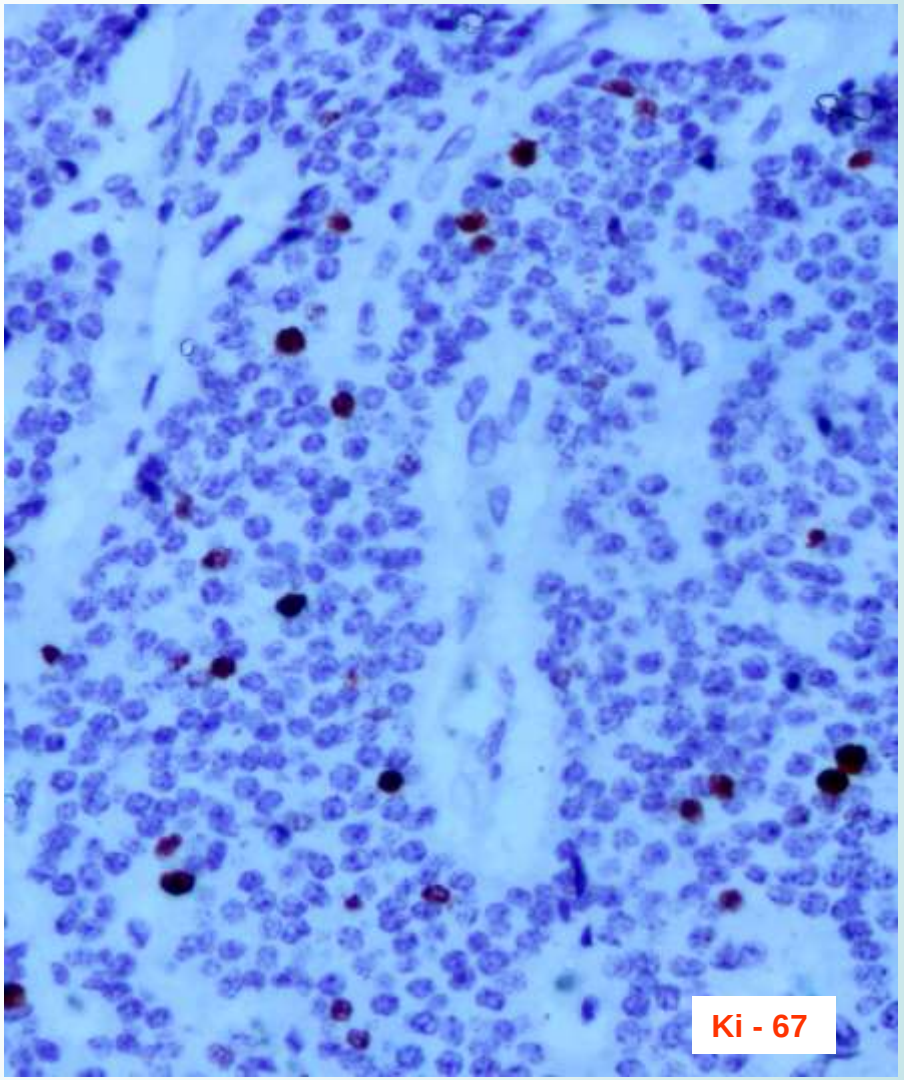


Histology suggestive of Foregut Duplication Cyst (Bronchogenic cyst)

Dominant solid part of Lesser Sac mass consists of a cellular tumor arising from cyst wall with features of an Intermediate Grade Neuro Endocrine Tumor.

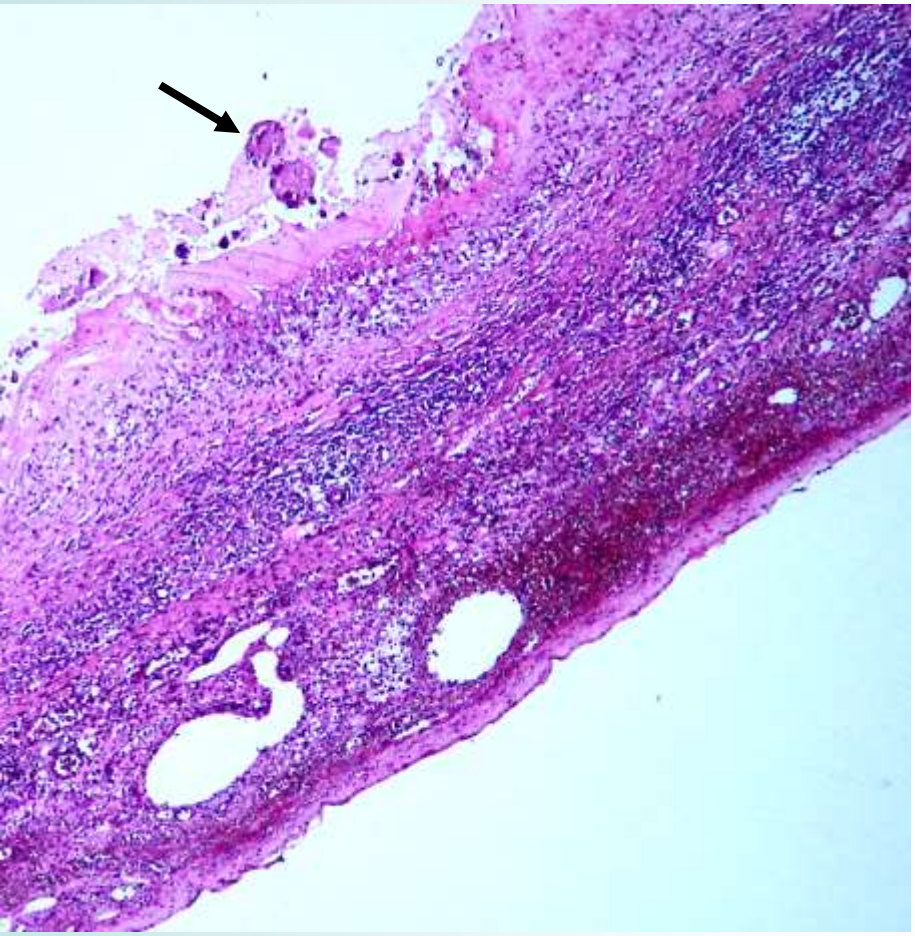


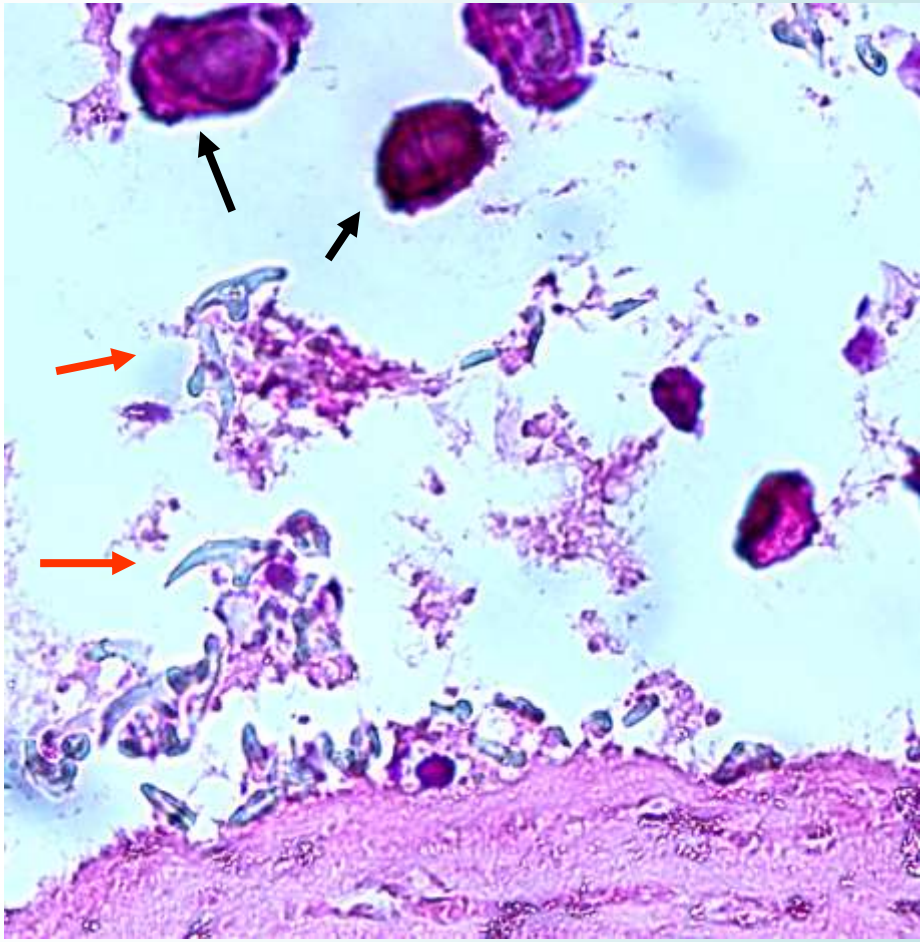
Mitosis 4/10 HPF



Ki-67 Index = 3%

The **Lesion in the Liver** was in the lateral aspect of the right lobe, almost entirely cystic, showing advanced degeneration of the wall and lining and some necrotic debris in the lumen.





Protoscolices and disrupted hooklets in the **Echinococcal cyst** (Hydatid cyst)

DIAGNOSIS :

LESSER SAC MASS – Neuroendocrine tumor, intermediate grade arising in Foregut Duplication Bronchogenic Cyst.

LIVER LESION – Echinococcal Cyst

Foregut Bronchogenic cysts typically arise as an abnormal budding of the Tracheobronchial analog of Primitive Gut early in gestation between the 3rd and 7th week.

They are predominantly found in the thoracic cavity while retroperitoneal location is extremely rare (0.03%) .
Dislodgement into the peritoneal cavity is possibly due to the wide pericardioperitoneal canal at this early stage of gestation.

The commonest site of such retroperitoneal Bronchogenic cyst (n=44), is the Adrenal glands (45%) and the next in order are the peripancreatic region (28%) and the crus of Diaphragm (27%) [Wang SE et al., J Chinese Med Assn. 2006].

So far only 2 cases of Foregut Duplication Bronchogenic cyst presenting as lesser sac mass have been reported (Fernandez JL et al., J Soc Laparo Surg. 2011)

Malignant Neoplasms occurring in Bronchogenic cysts is very rare (almost exclusively in those in the mediastinum and chest). They range from Adenocarcinoma to Sq. Cell Ca, Fibrosarcoma, Leiomyosarcoma, Undifferentiated Ca, Embryonal Rhabdomyosarcoma and Anaplastic Ca.

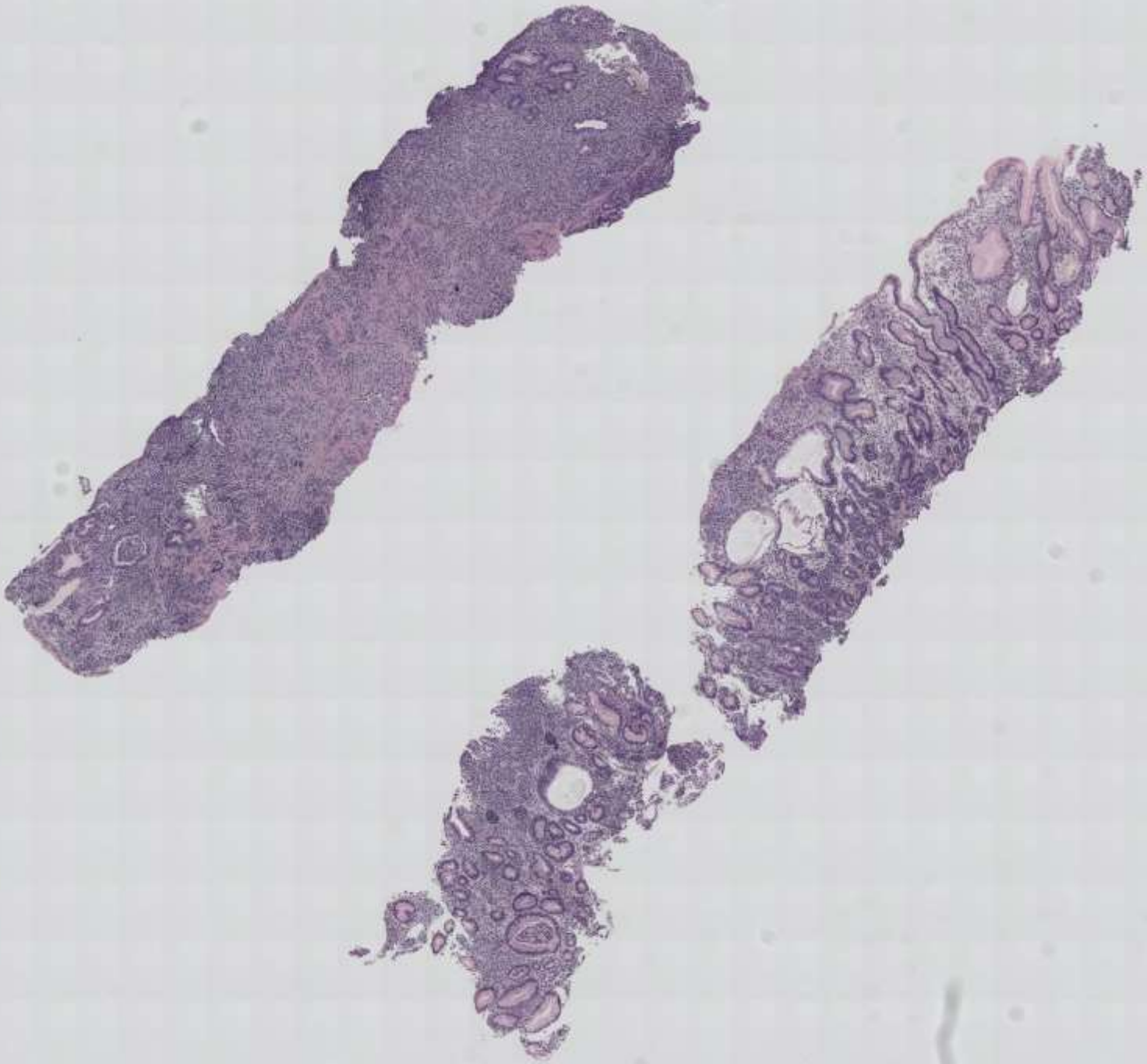
There is **only 1 report** available of Adenocarcinoma arising in a Retroperitoneal Bronchogenic cyst (Sullivan SM et al., Pathol Intnl.1999)

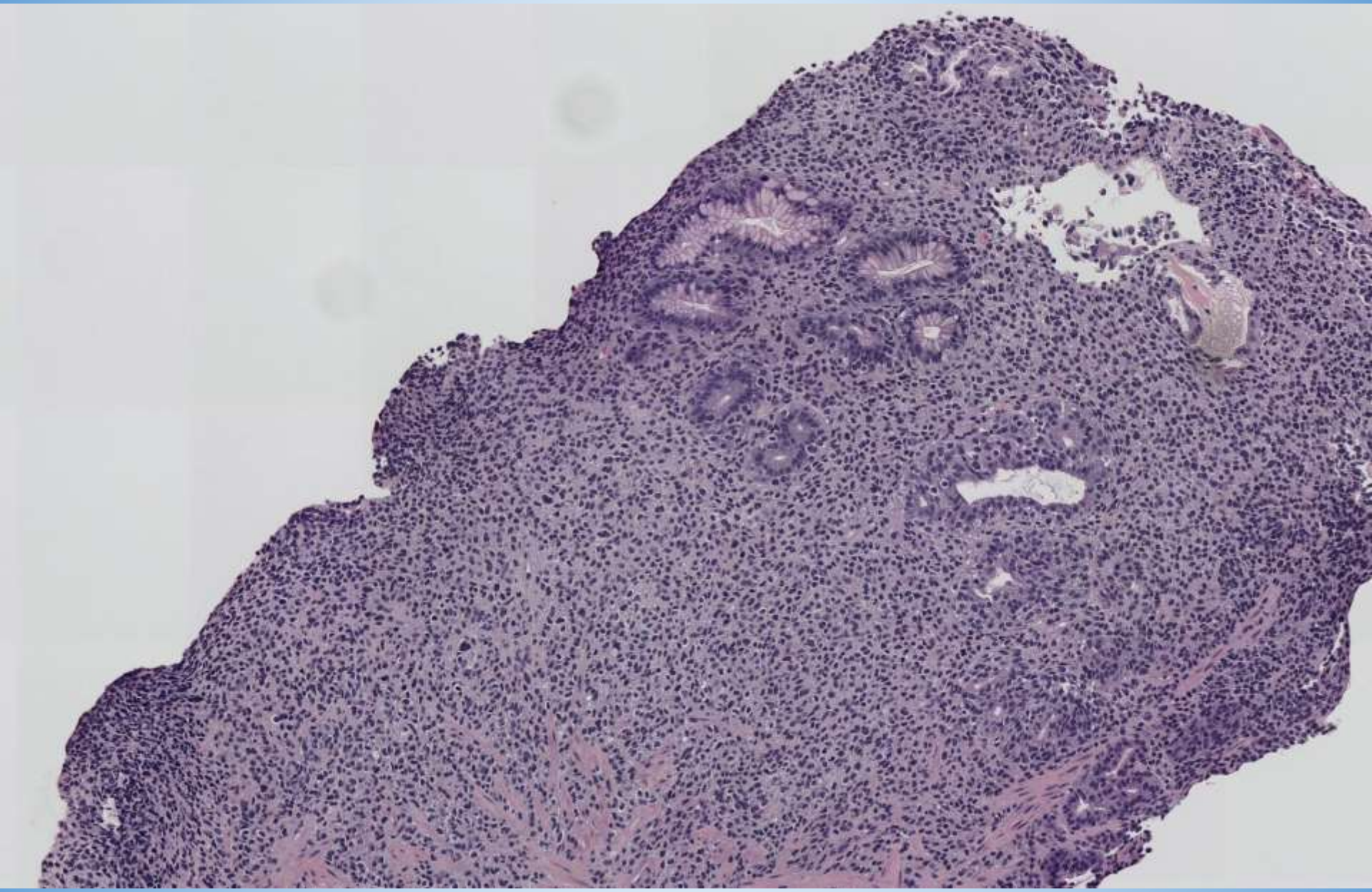
Neuroendocrine tumor arising in a Foregut duplication Bronchogenic cyst has not been reported

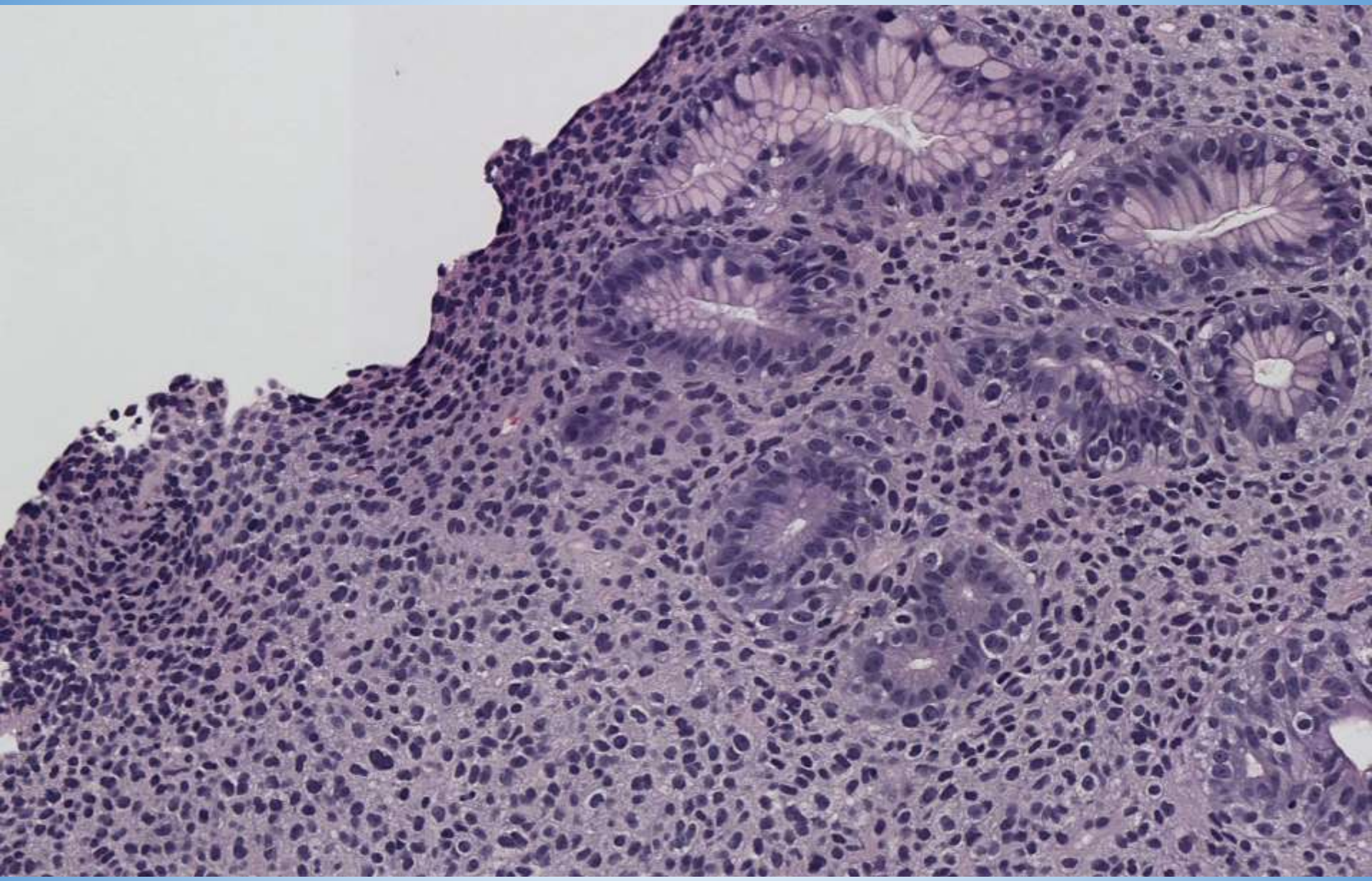
SB 6269
(scanned slide available)

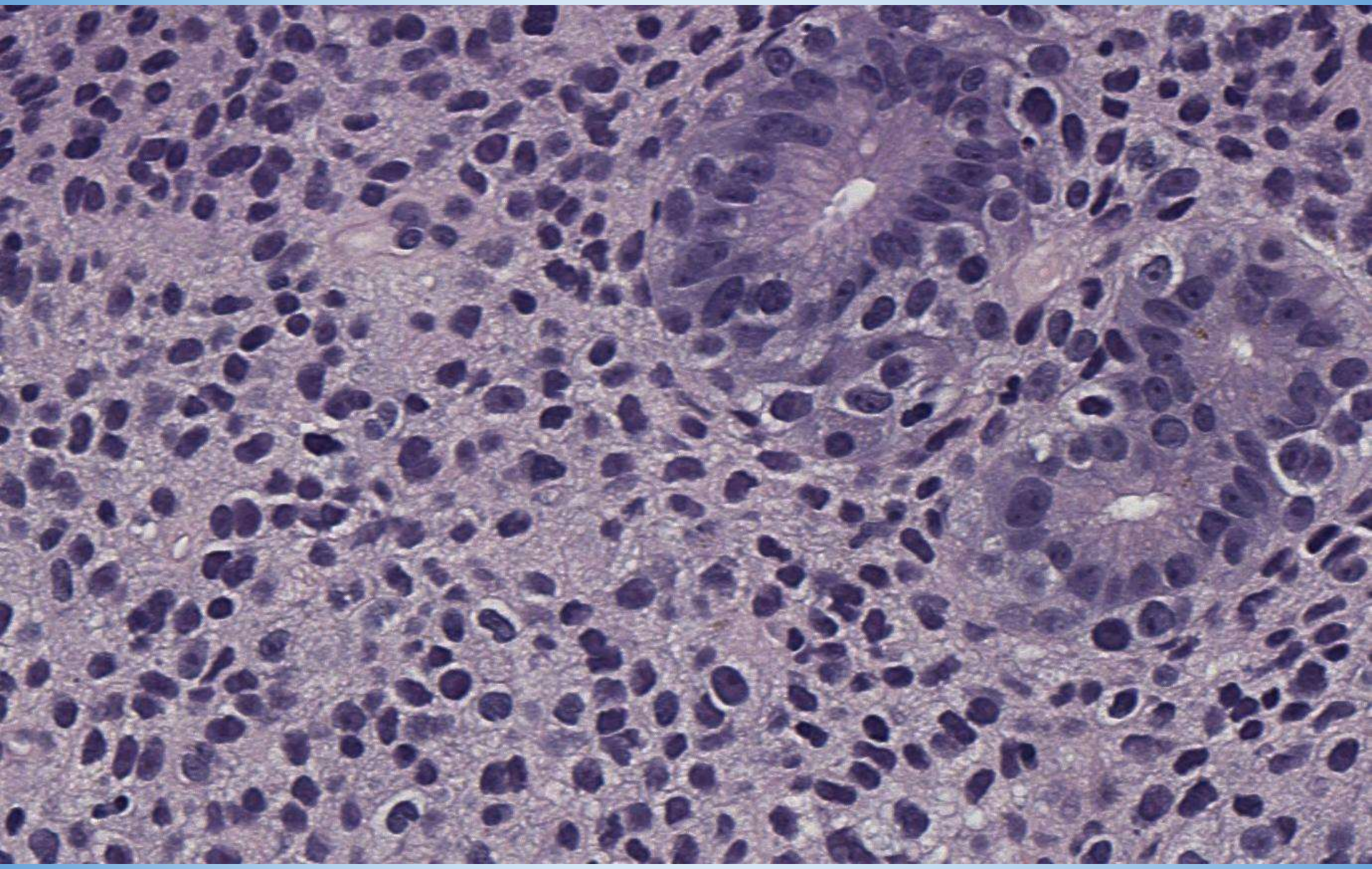
Keith Duncan; Mills-Peninsula Hospital

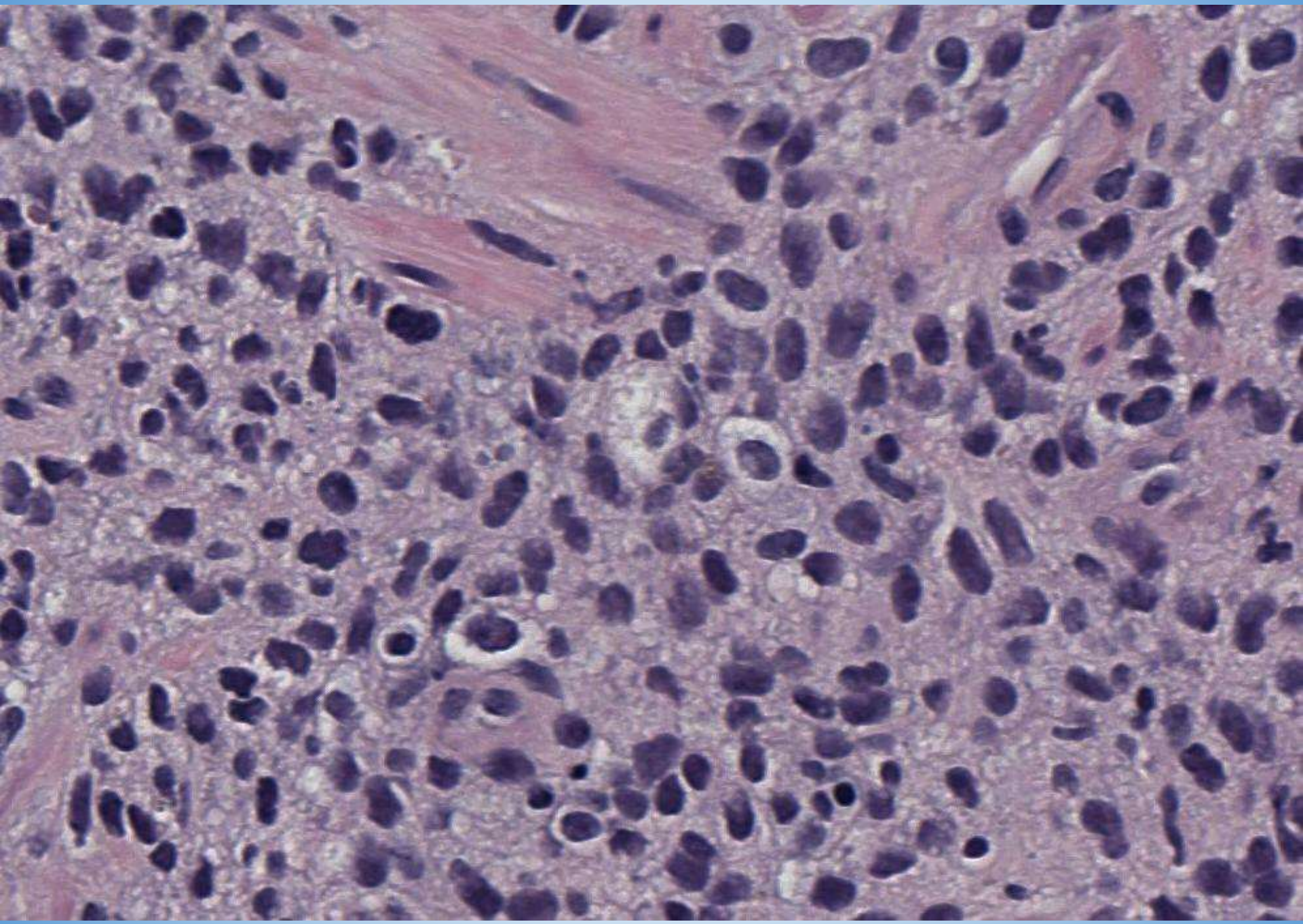
88-year-old female with gastric body/fundic polyp.

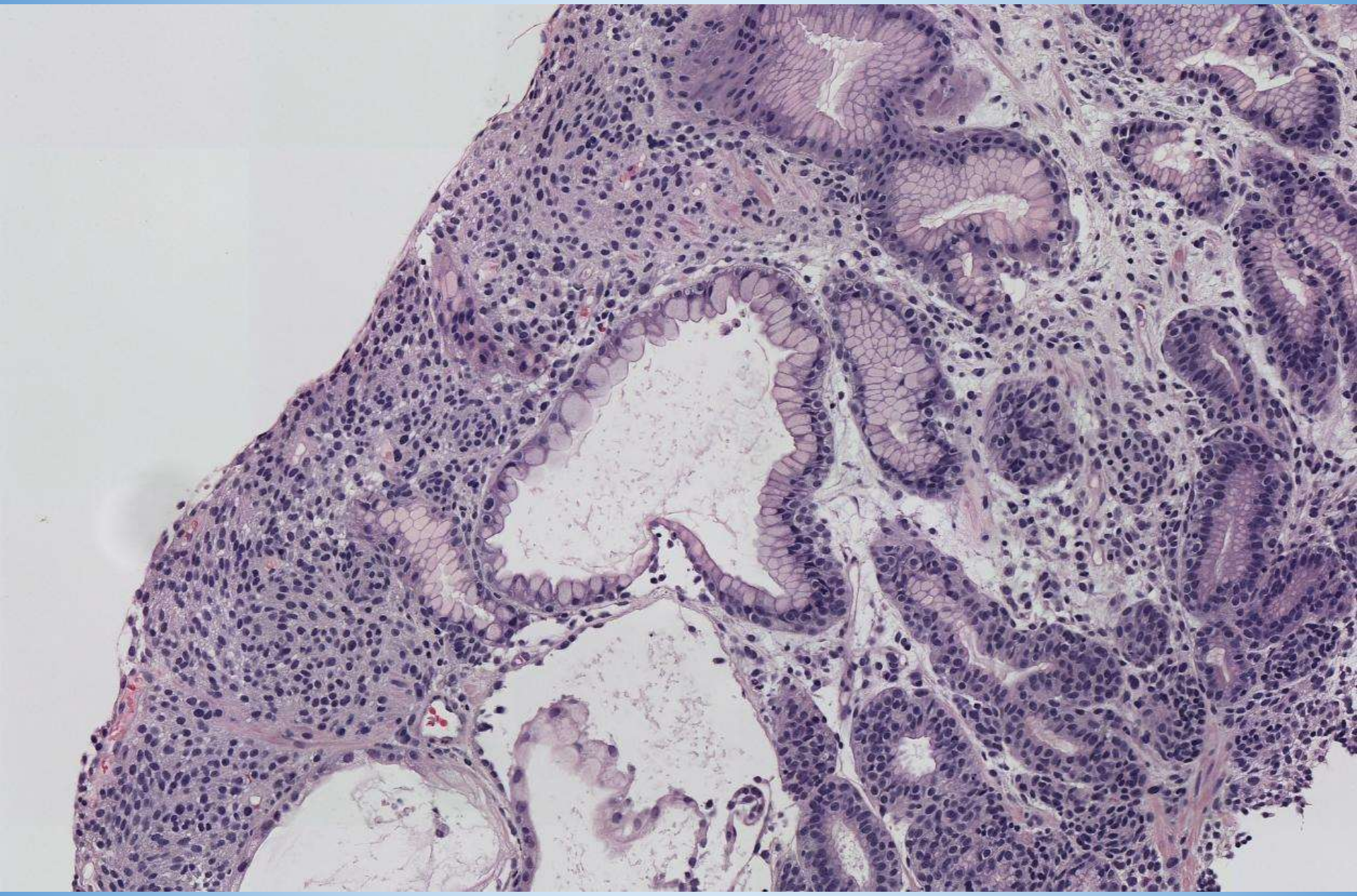


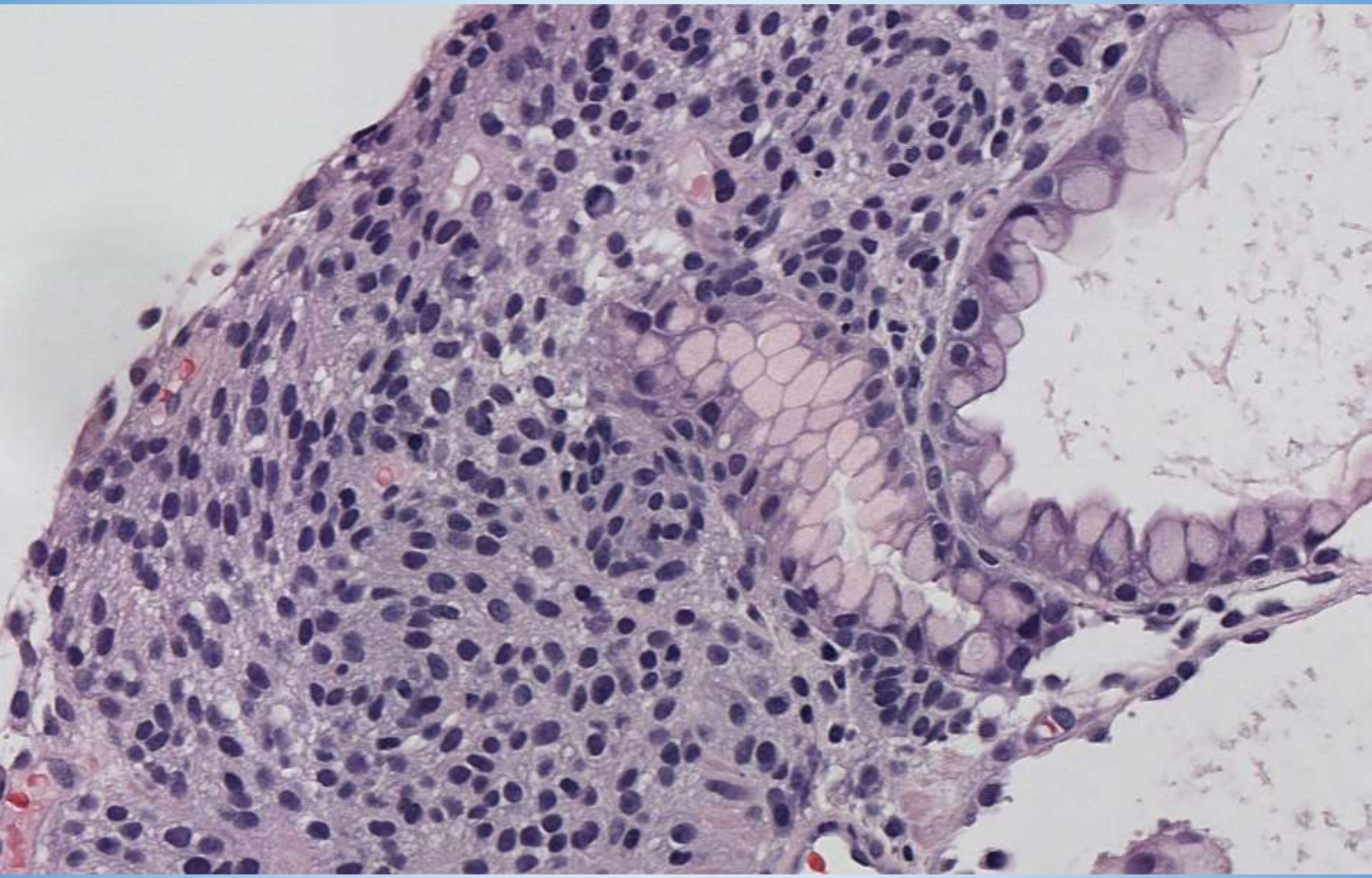


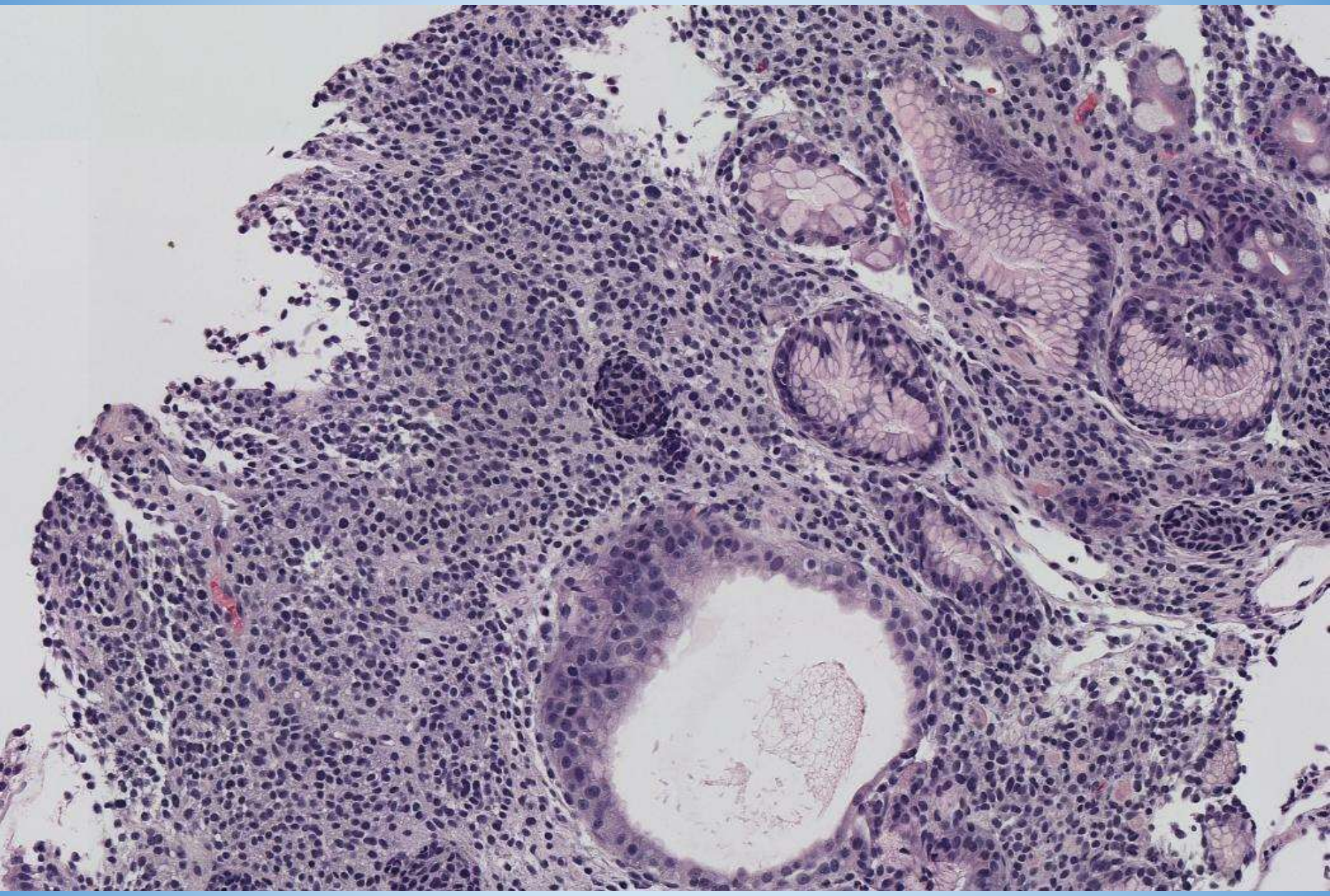


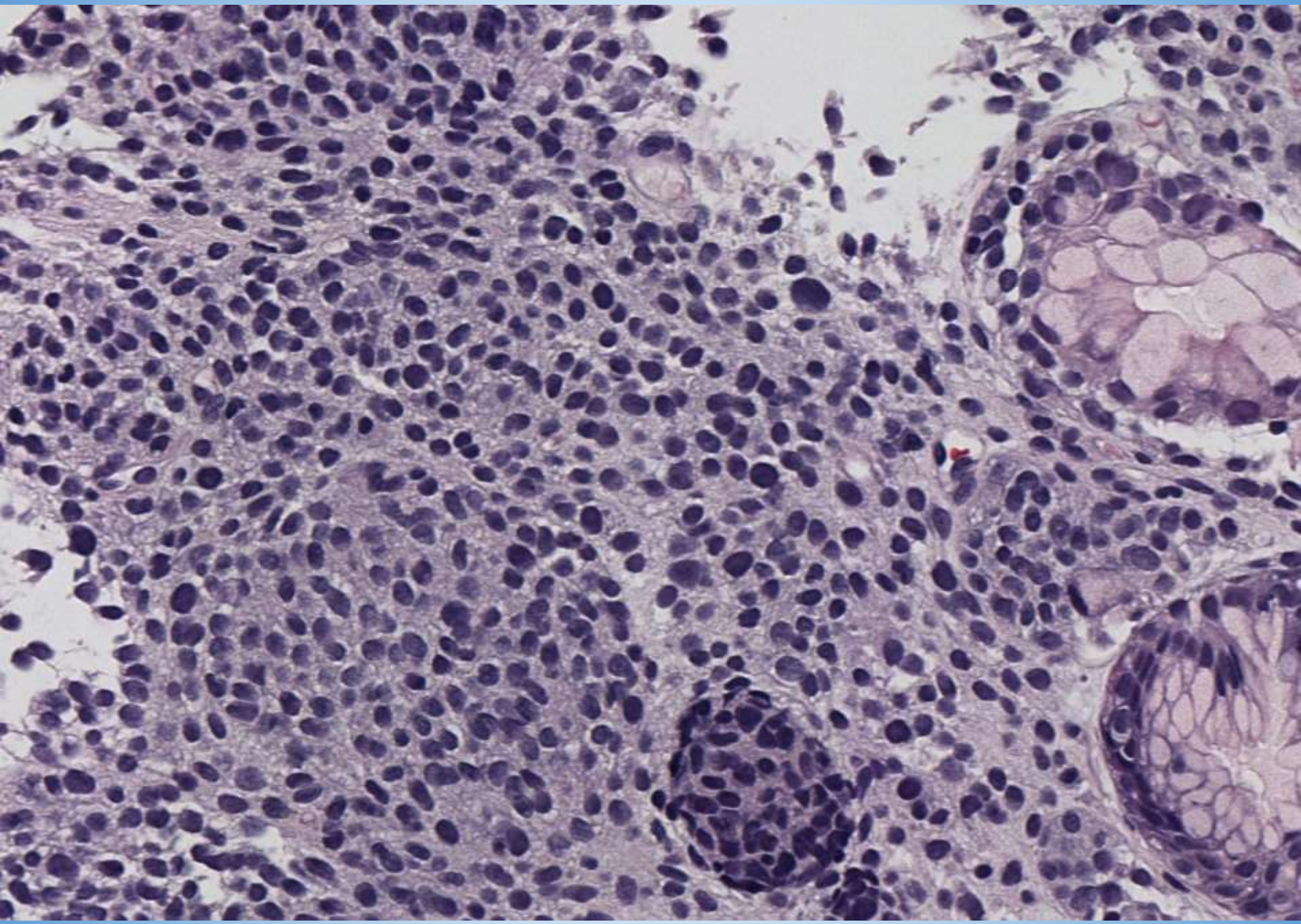








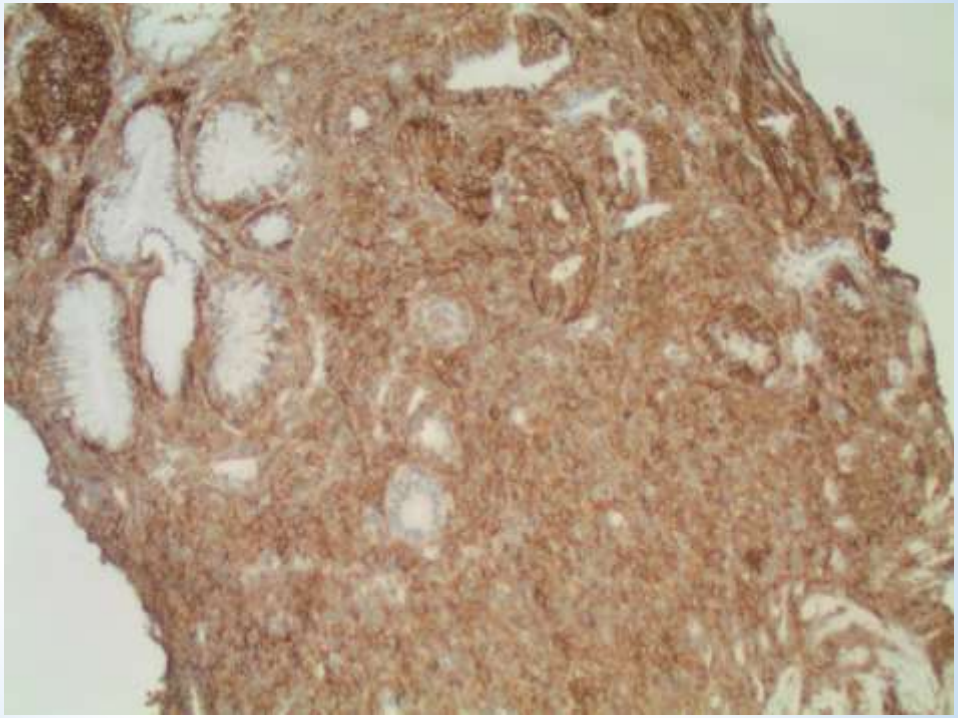




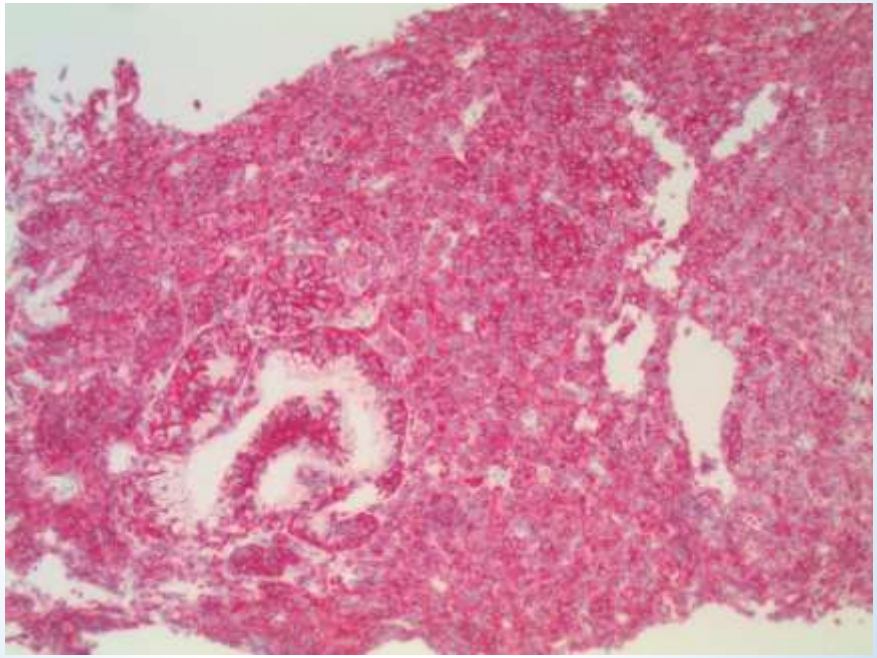
TUMOR DIFFERENTIAL DX

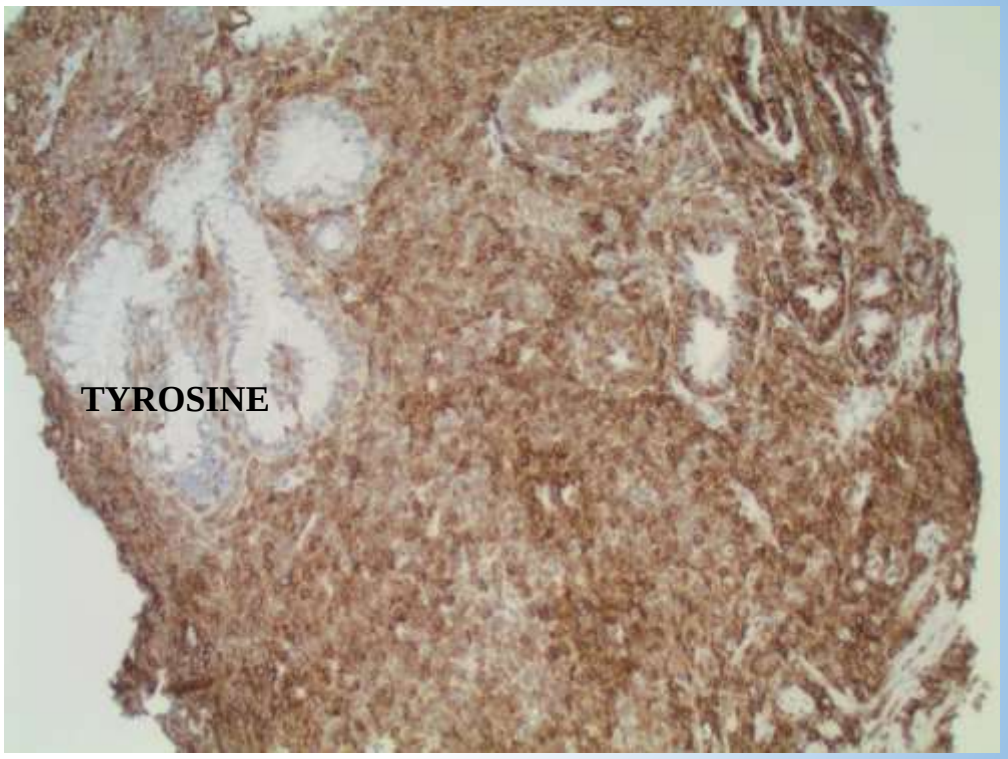
GIST
MAST CELL TUMOR
PECOMA
NEUROENDOCRINE TUMOR
LYMPHOMA
MELANOMA

CD117



MELANIN




TYROSINE

IPOX STAINS

POSITIVE STAINS:
S-100: SOME NESTS & UNDERMINING CELLS
POSITIVE:
(SHEET LIKE AREAS NEGATIVE)
MELAN-A, CD117, SOX10:

NEGATIVE STAINS:
CD163, CD138, CD3, CD20, CD25, CD1A
LANGERINM
PAN-CK, SYNAPTOPHYSIN, CHROMGRANIN, SMA

MELANOMA OF THE STOMACH

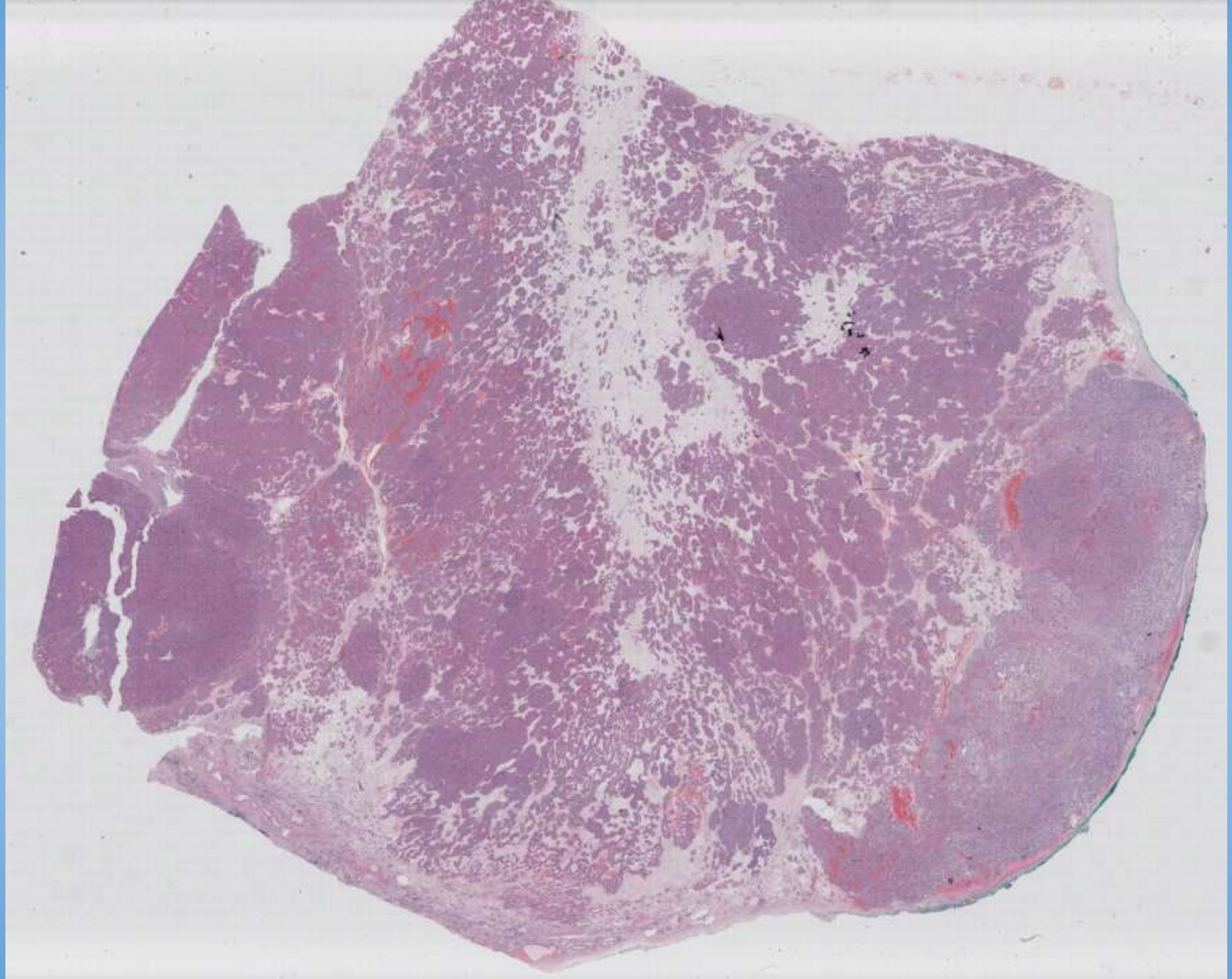
- Primary GI melanoma is unusual; Rarer still is primary gastric melanoma.
- Most melanomas Of stomach are metastases from cutaneous sources.
- Fewer than 15 cases of primary gastric melanoma have been documented.

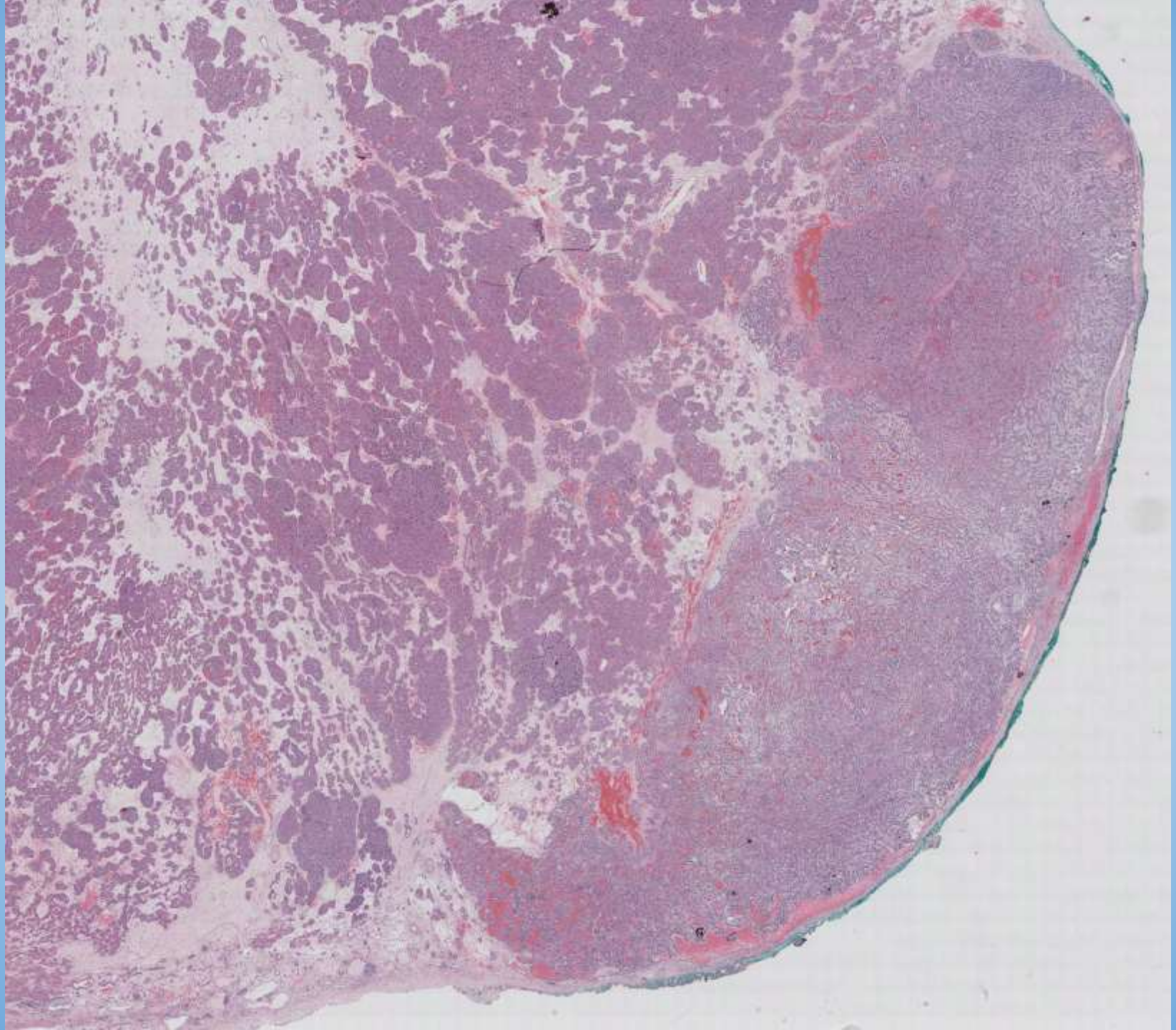
- Criteria for the dx of primary gastric melanoma include the absence of concurrent lesions & the lack of a history of melanoma or atypical melanocytic lesion removal from the skin or other organs.
- Dz-free survival of 12 months after curative surgical excision of the involved organ has been proposed for the distinction of a primary lesion from a metastatic lesion, since 50% of patients with stage IV melanoma of the skin or visceral disease from an unknown primary lesion die 12 mo after dx.

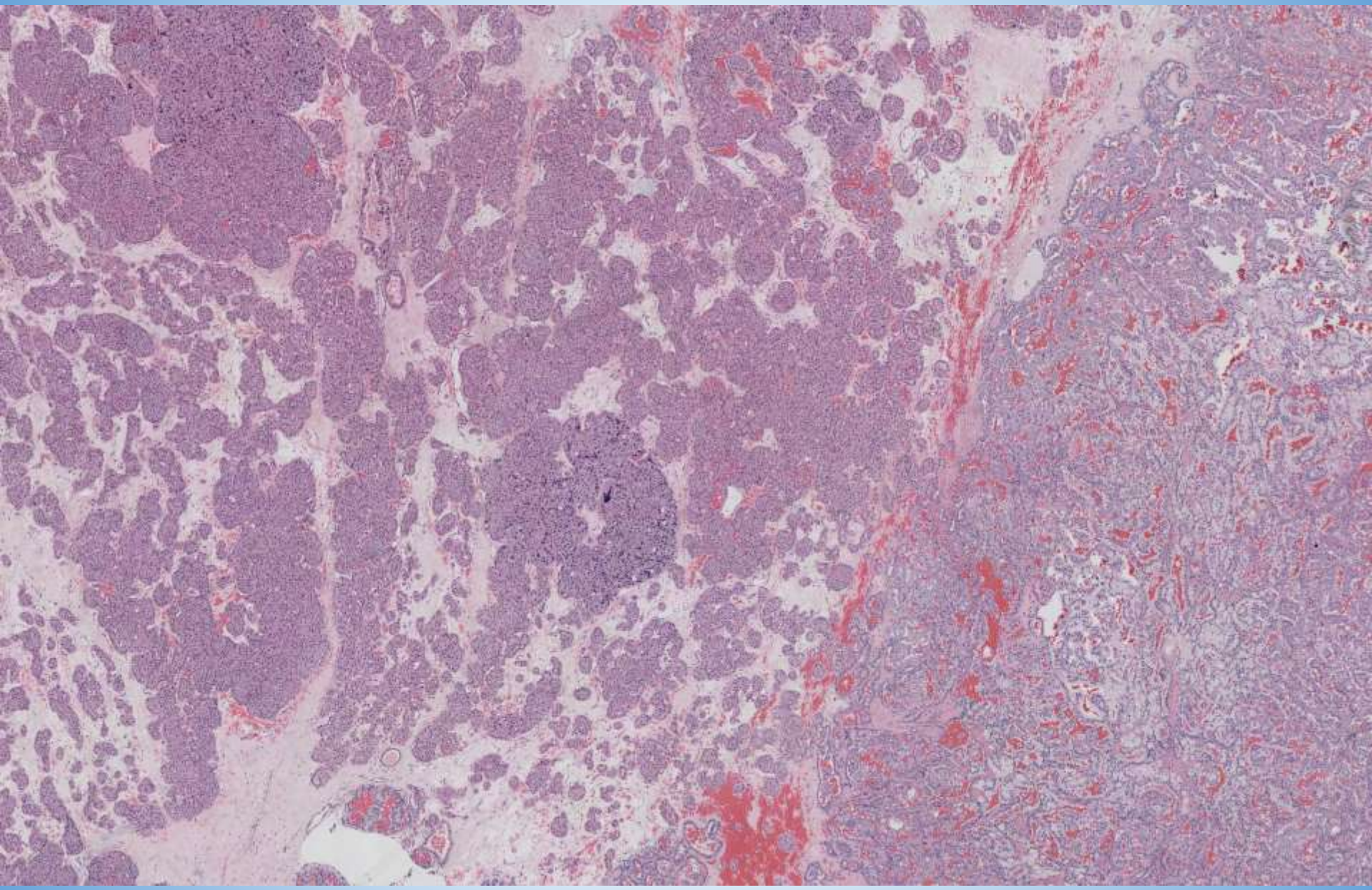
SB 6270
(scanned slide available)

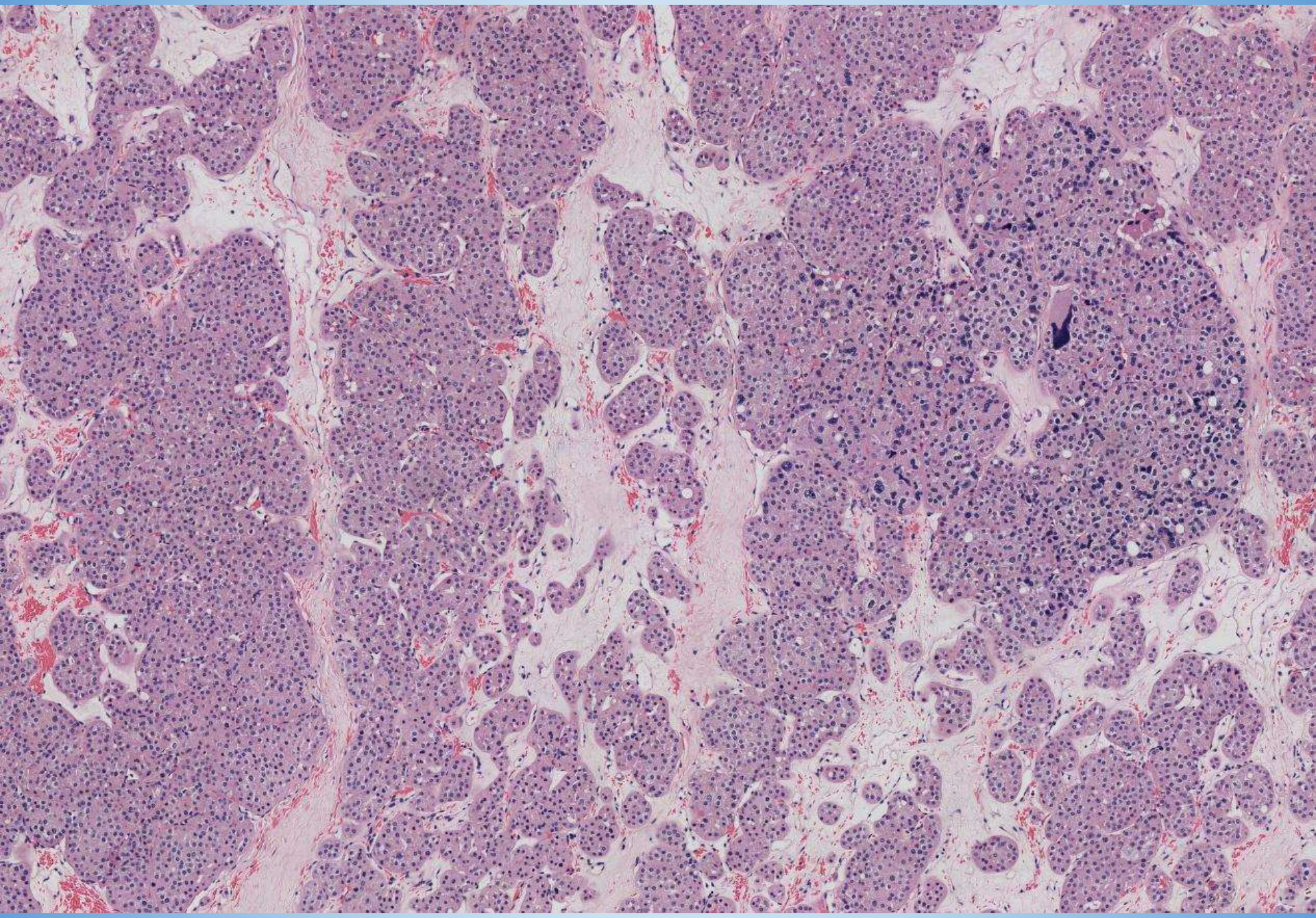
Libby Allard/Dean Fong; Stanford/Palo Alto VA

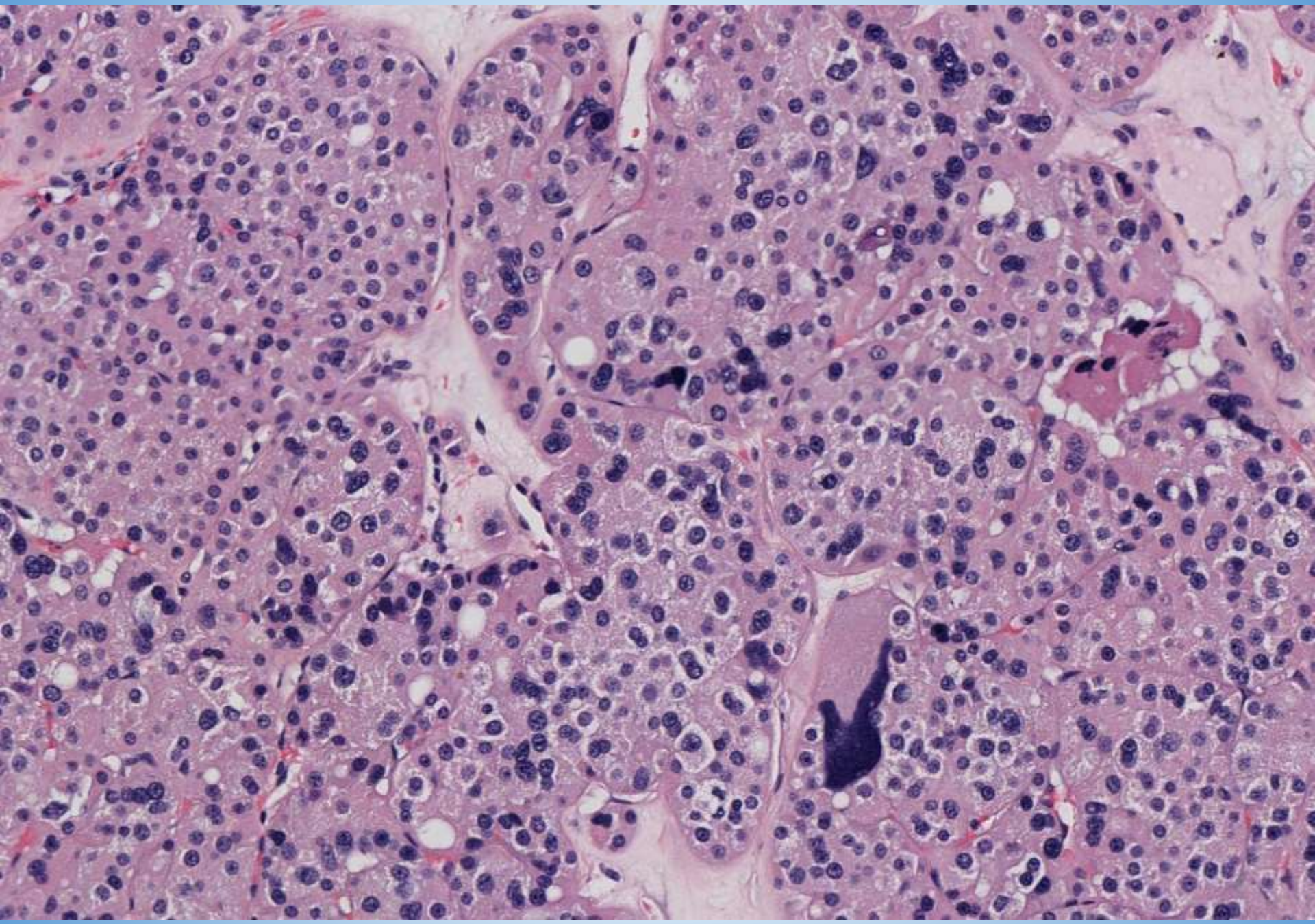
62-year-old male with right renal mass.

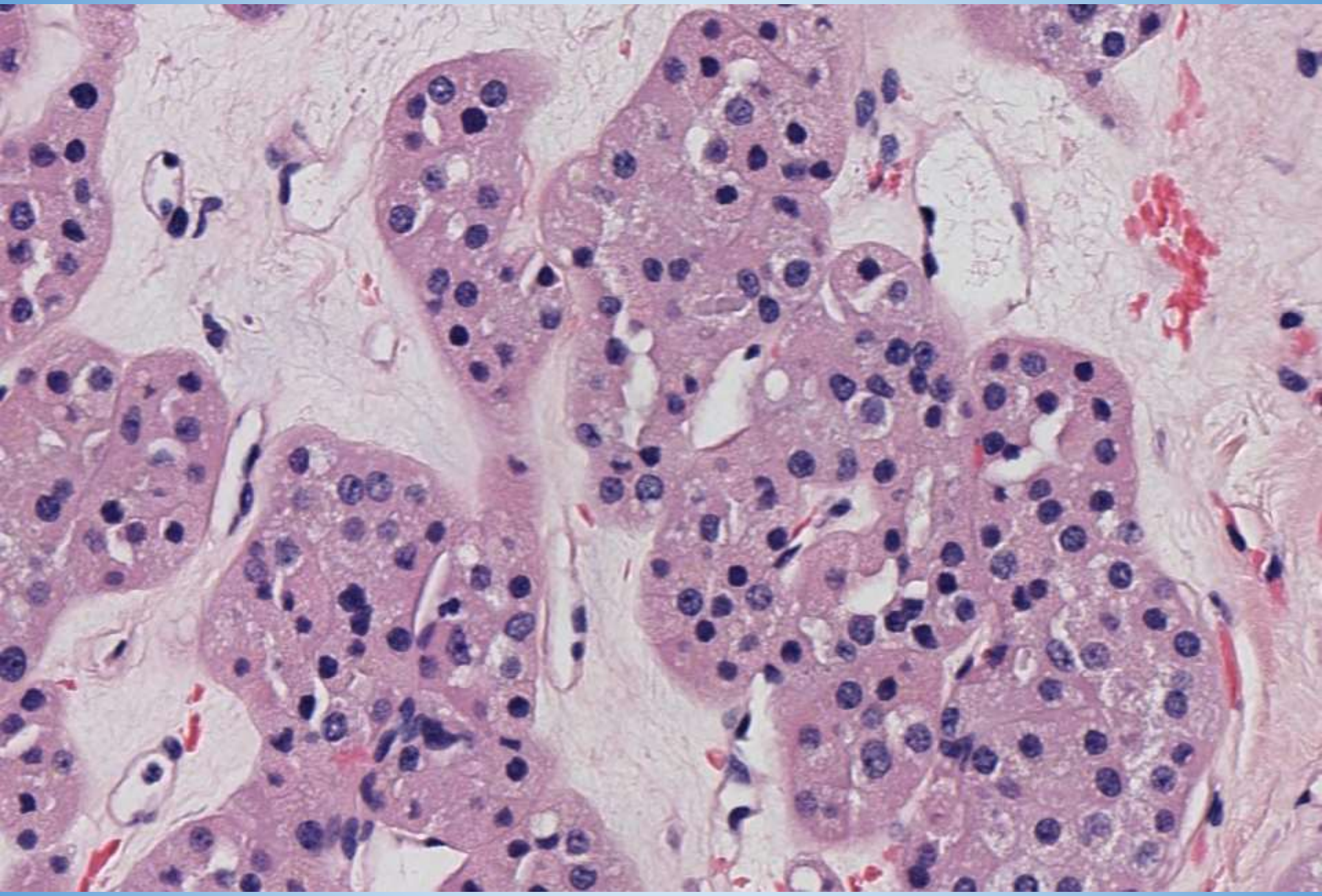


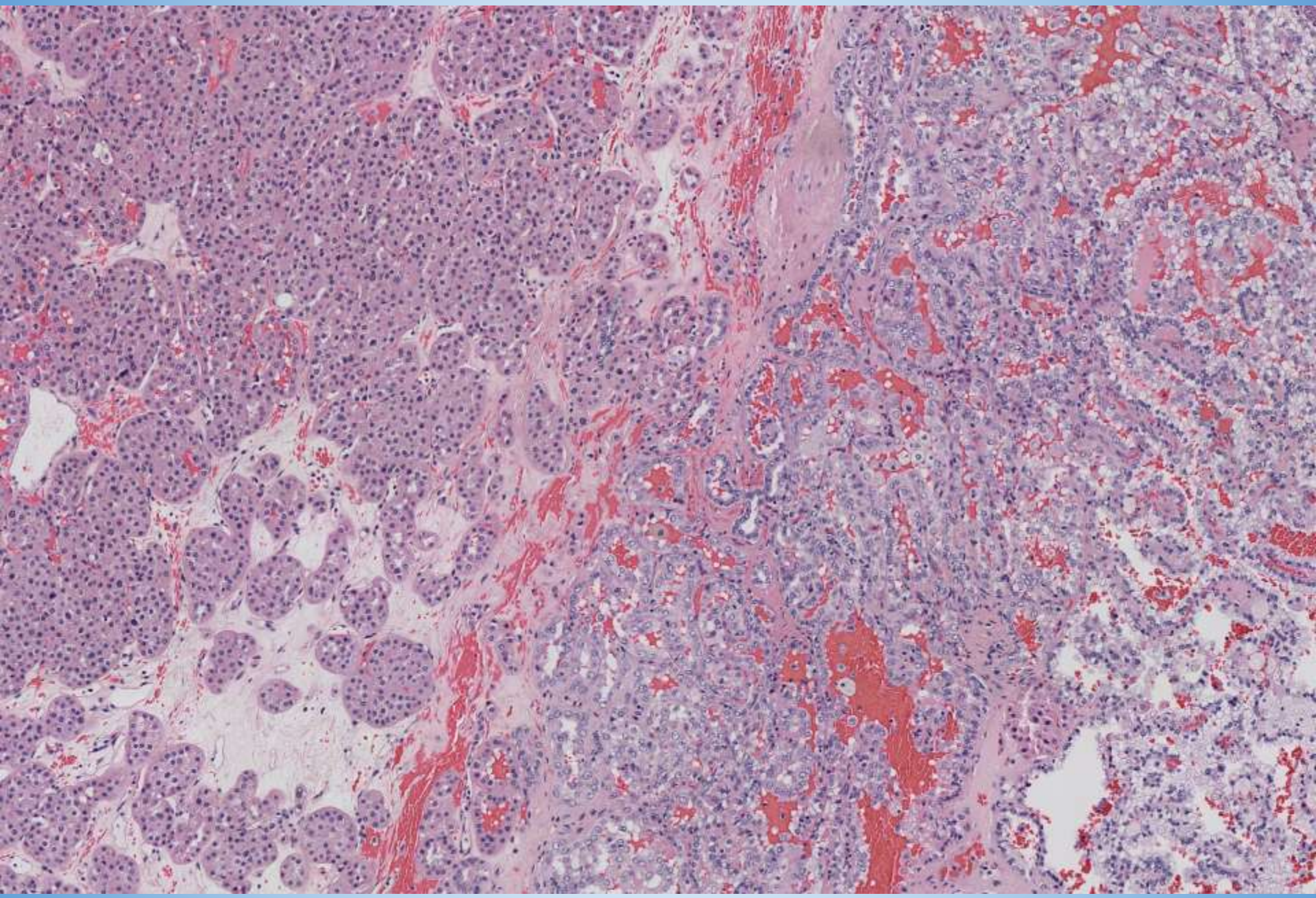


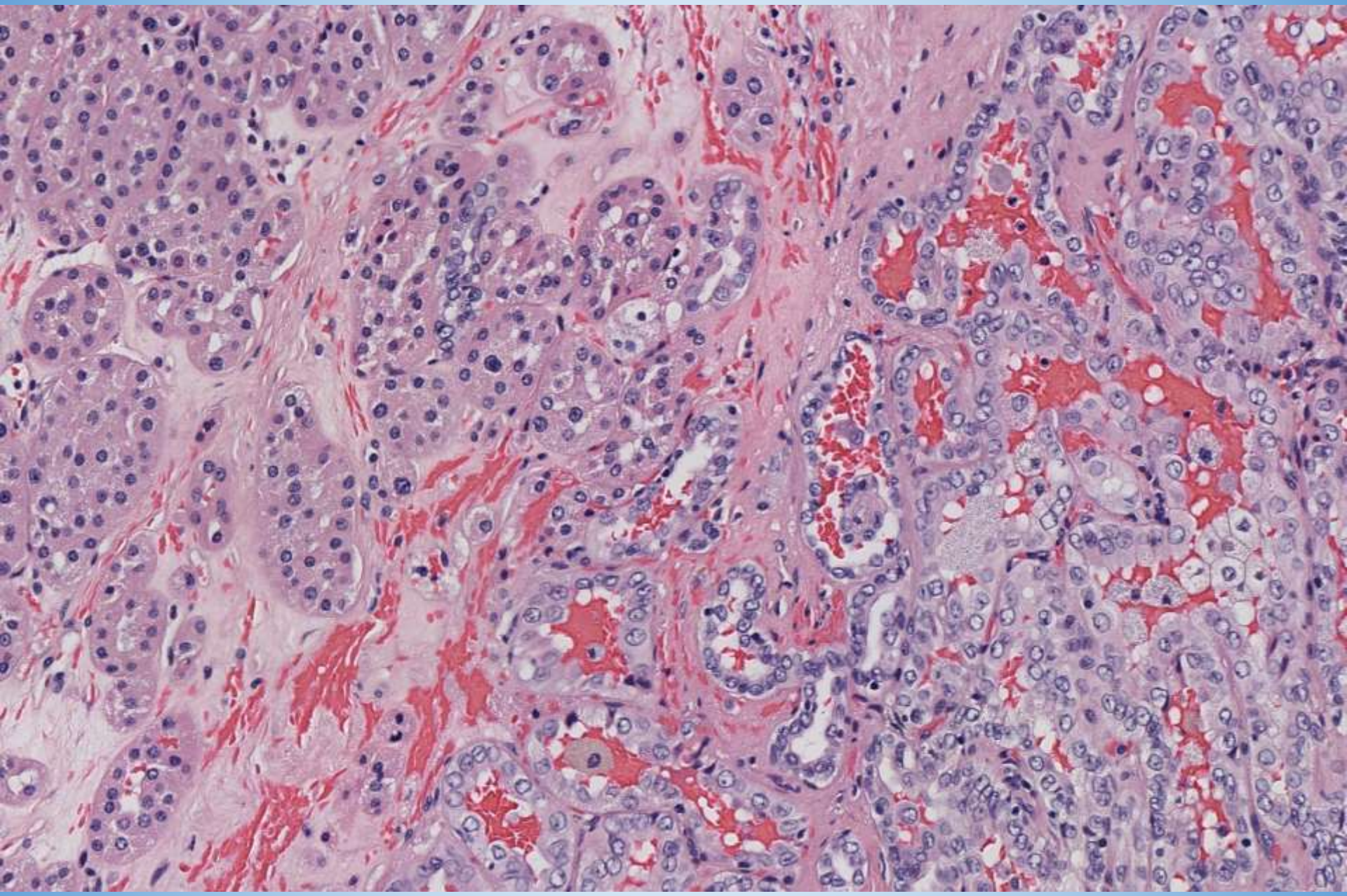


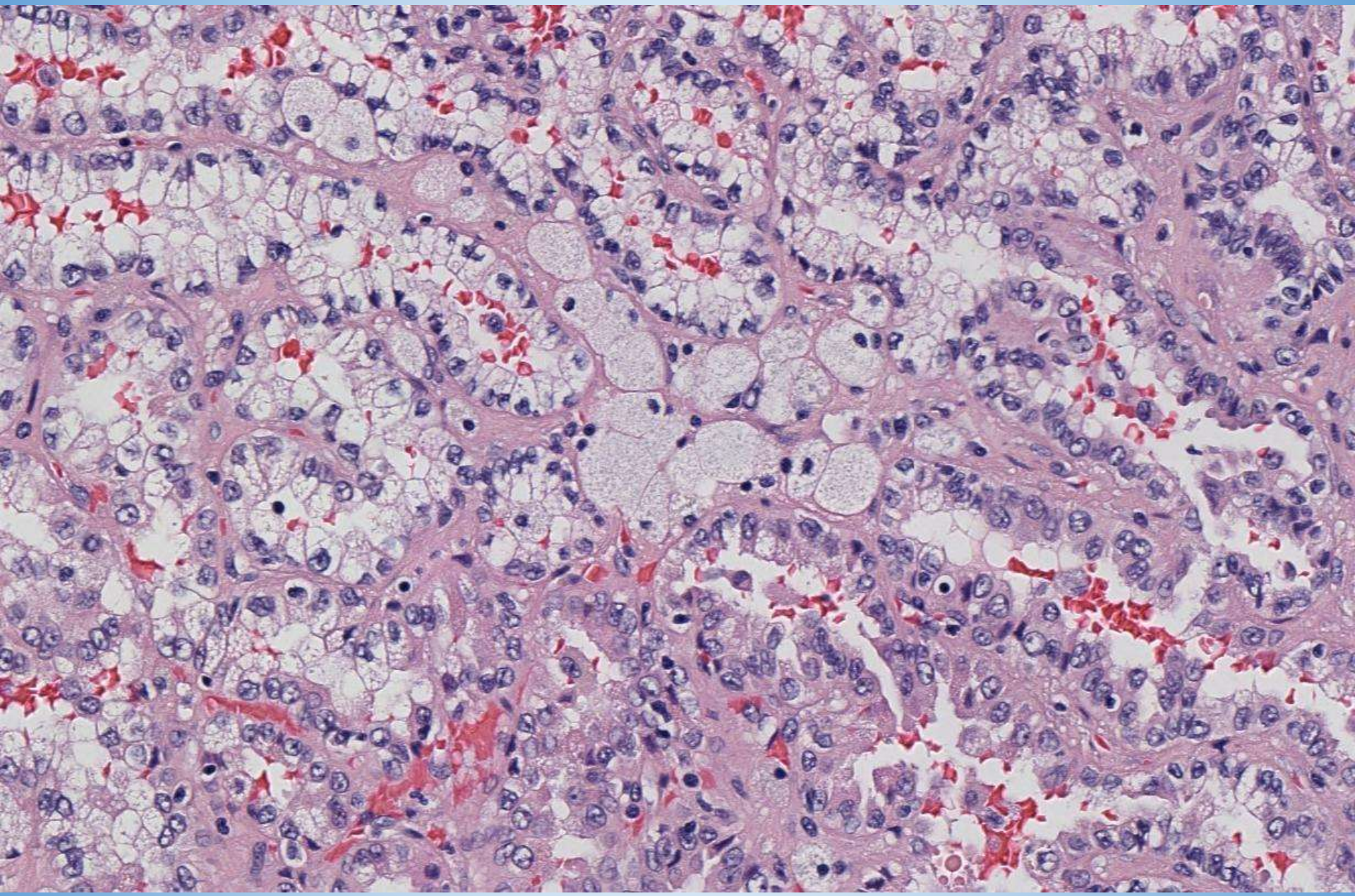


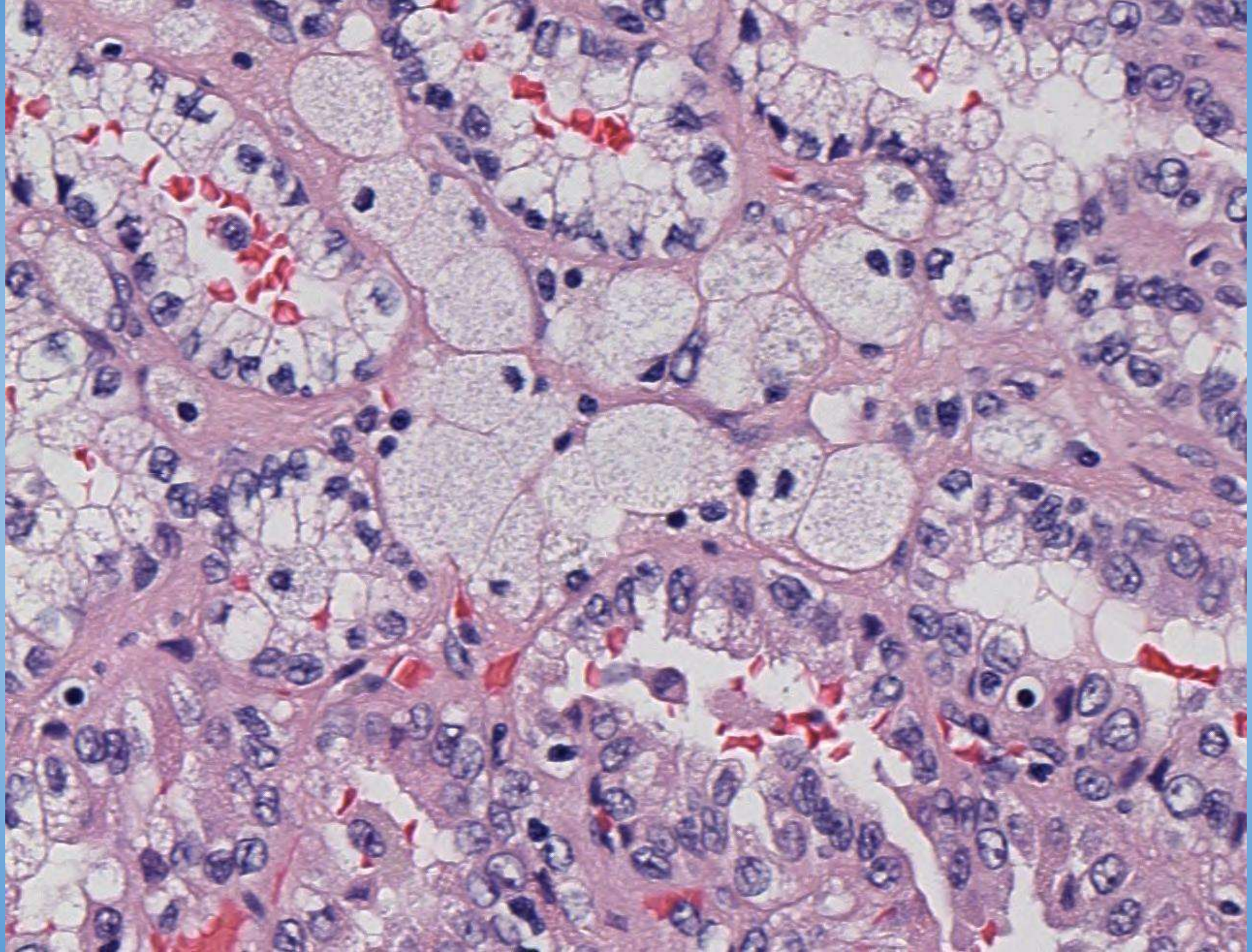


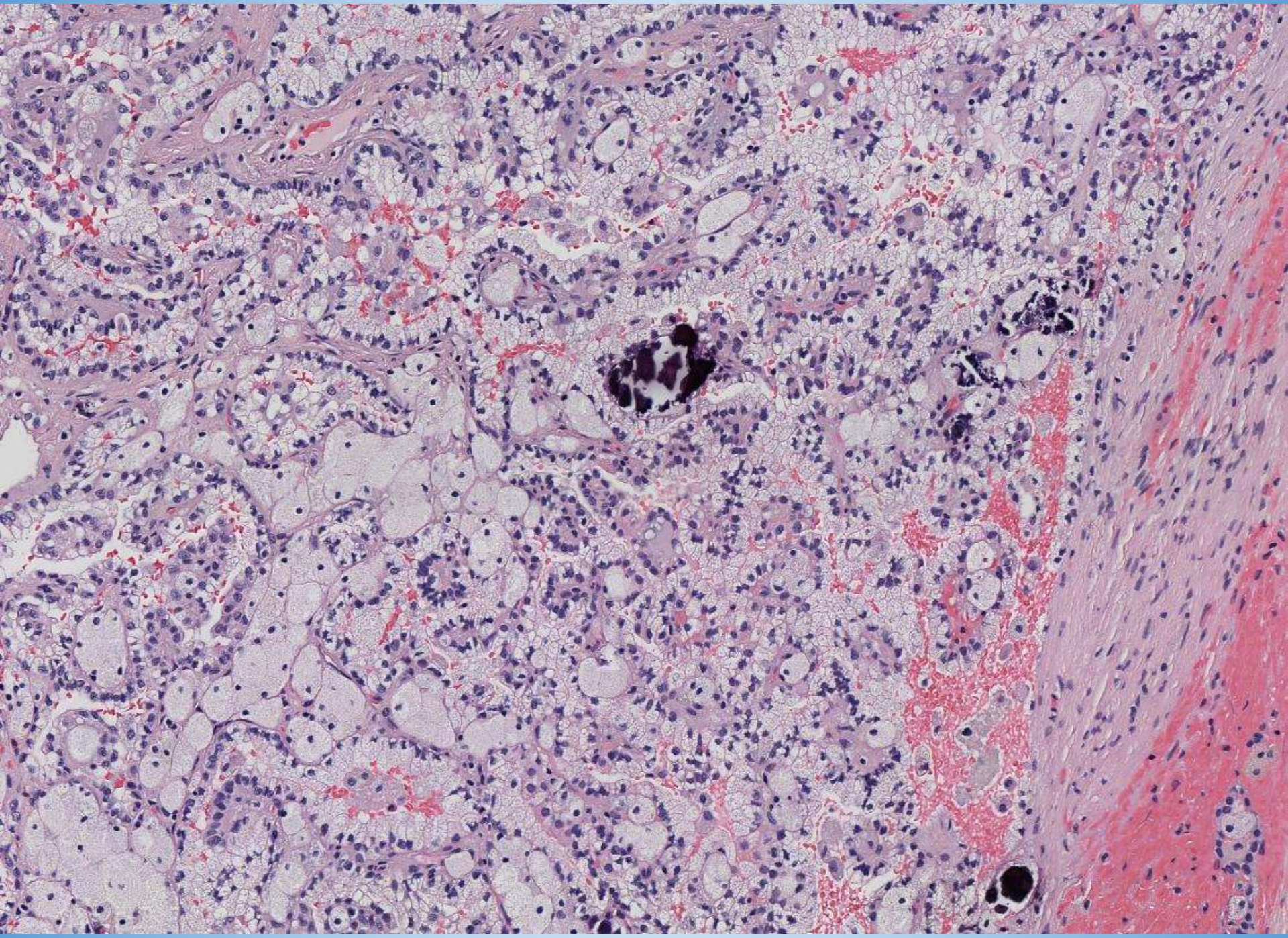


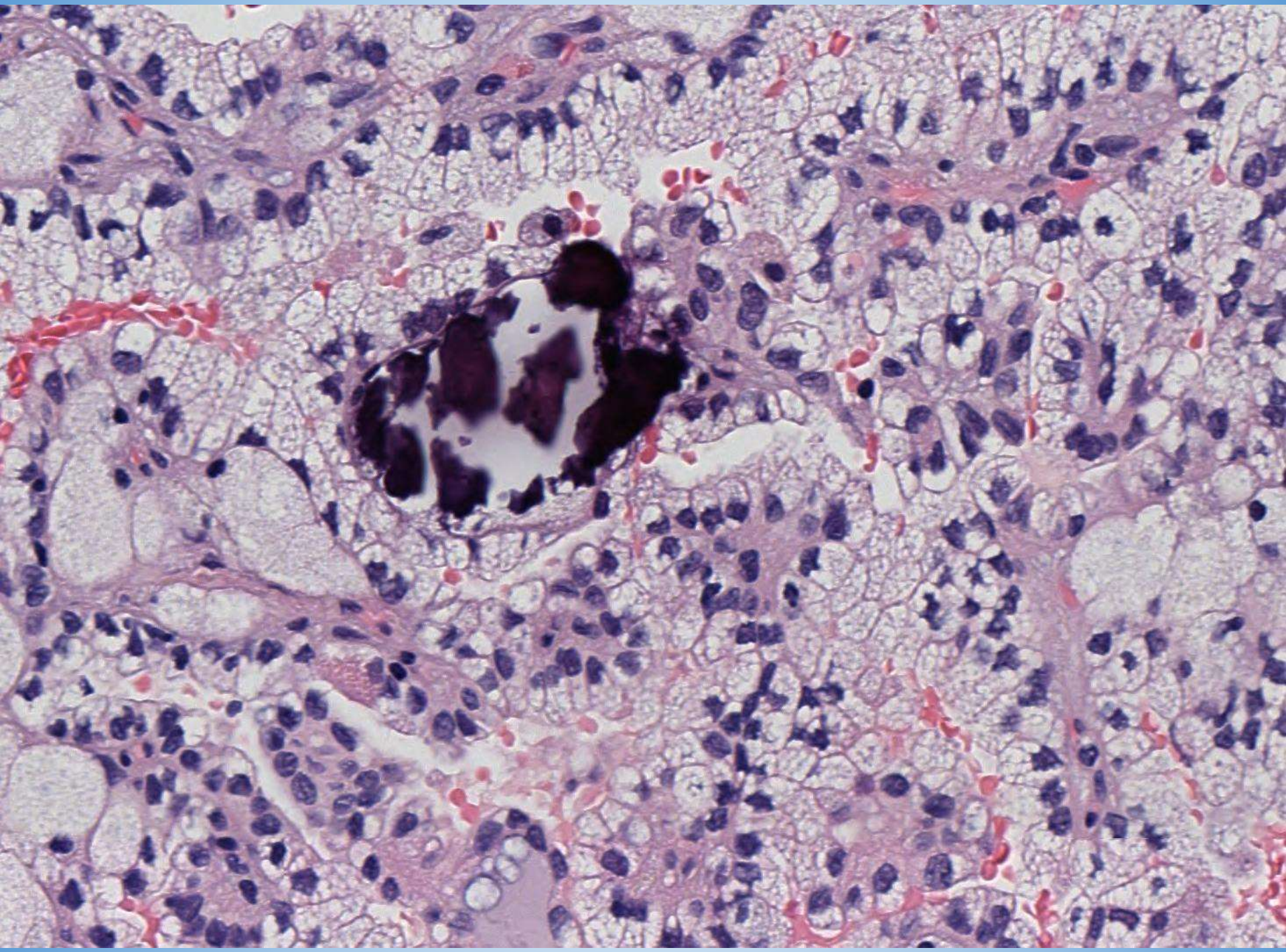










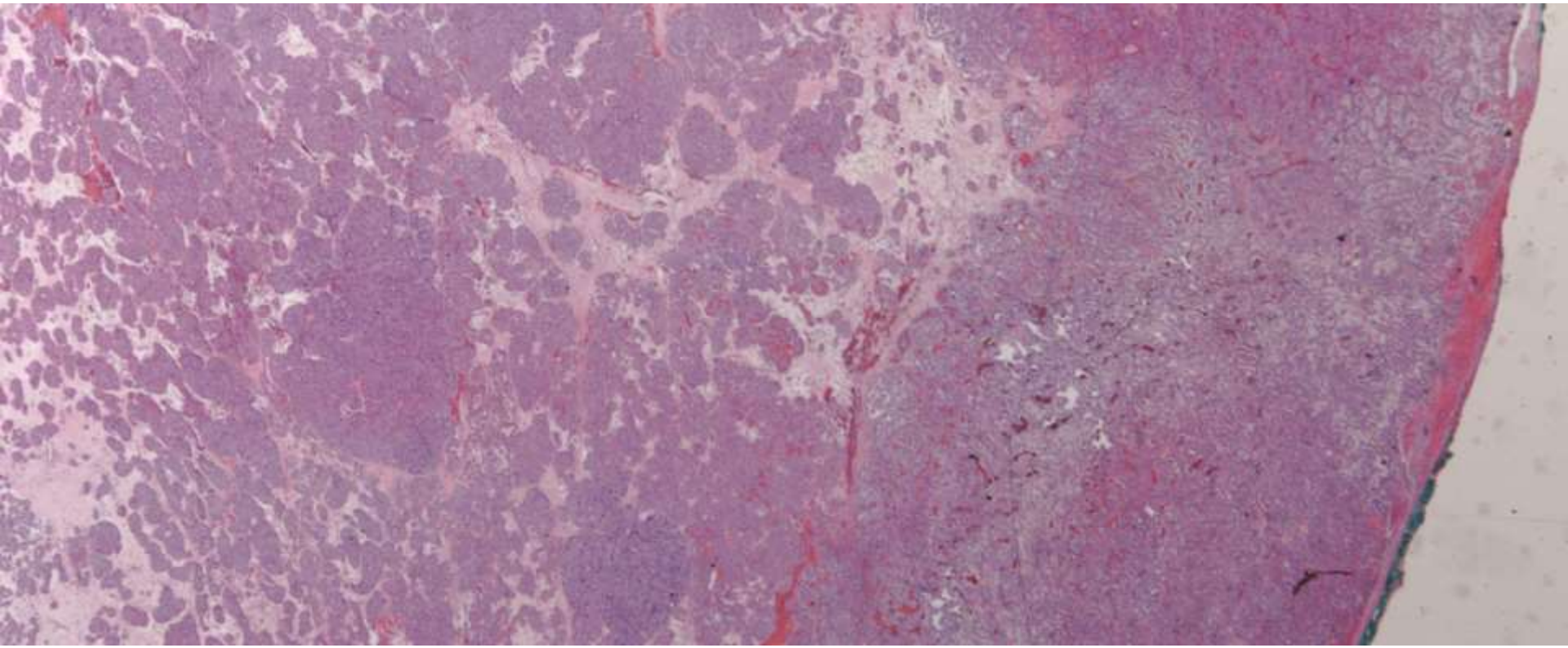


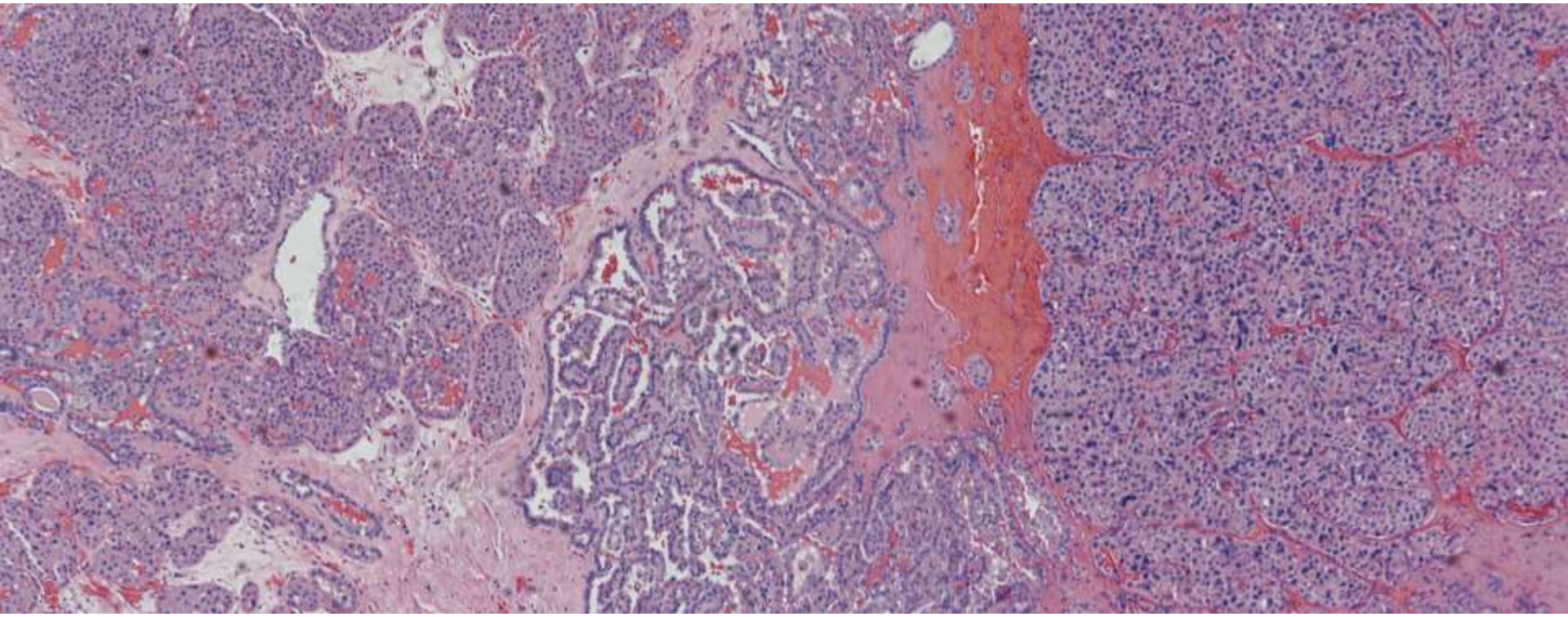
Renal Mass in a 62yM

LIBBY ALLARD, PGY-1

Past Medical History

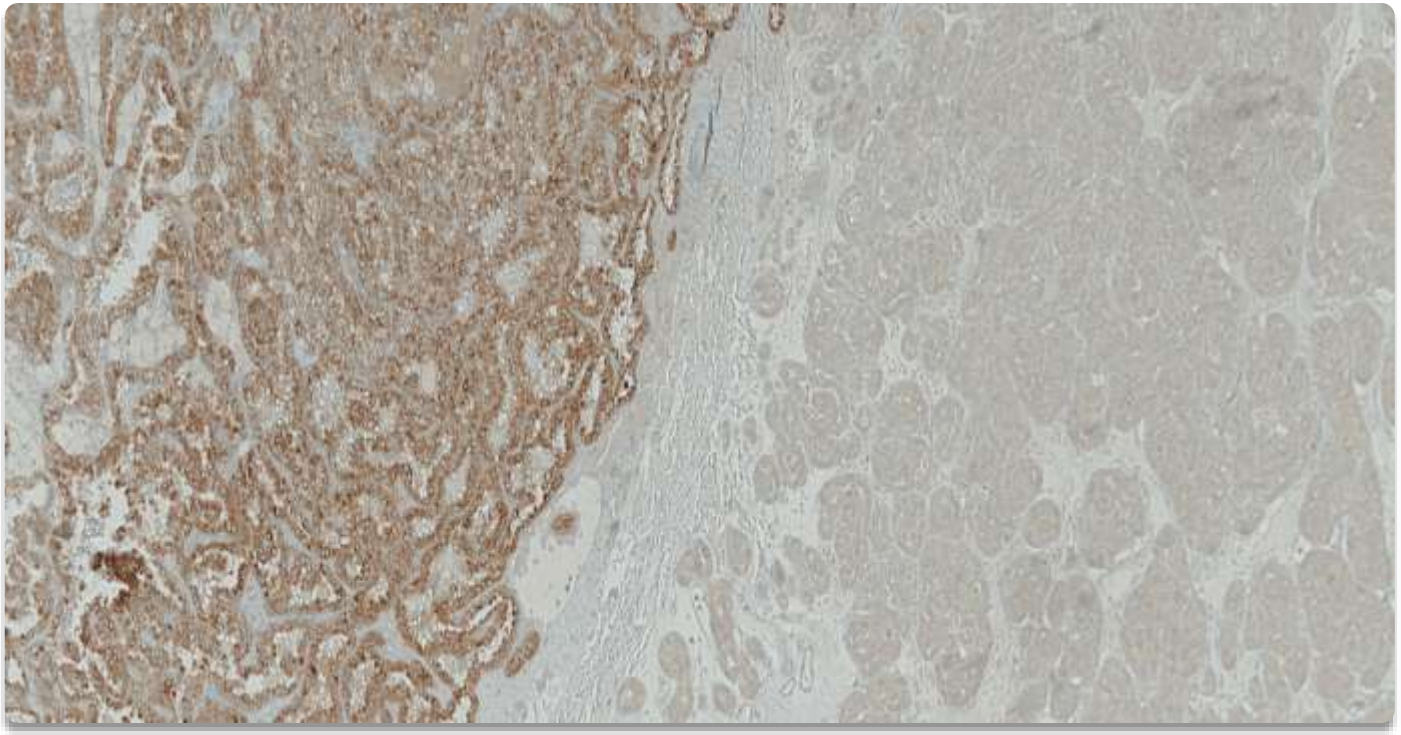
- 62yM with pmh DM2, HTN, HLD and urolithiasis
- On CT surveillance for his urolithiasis (6/2017), found incidentally to have a 5.6 x 6.3cm right renal mass s/p right open partial nephrectomy (9/28/2017)





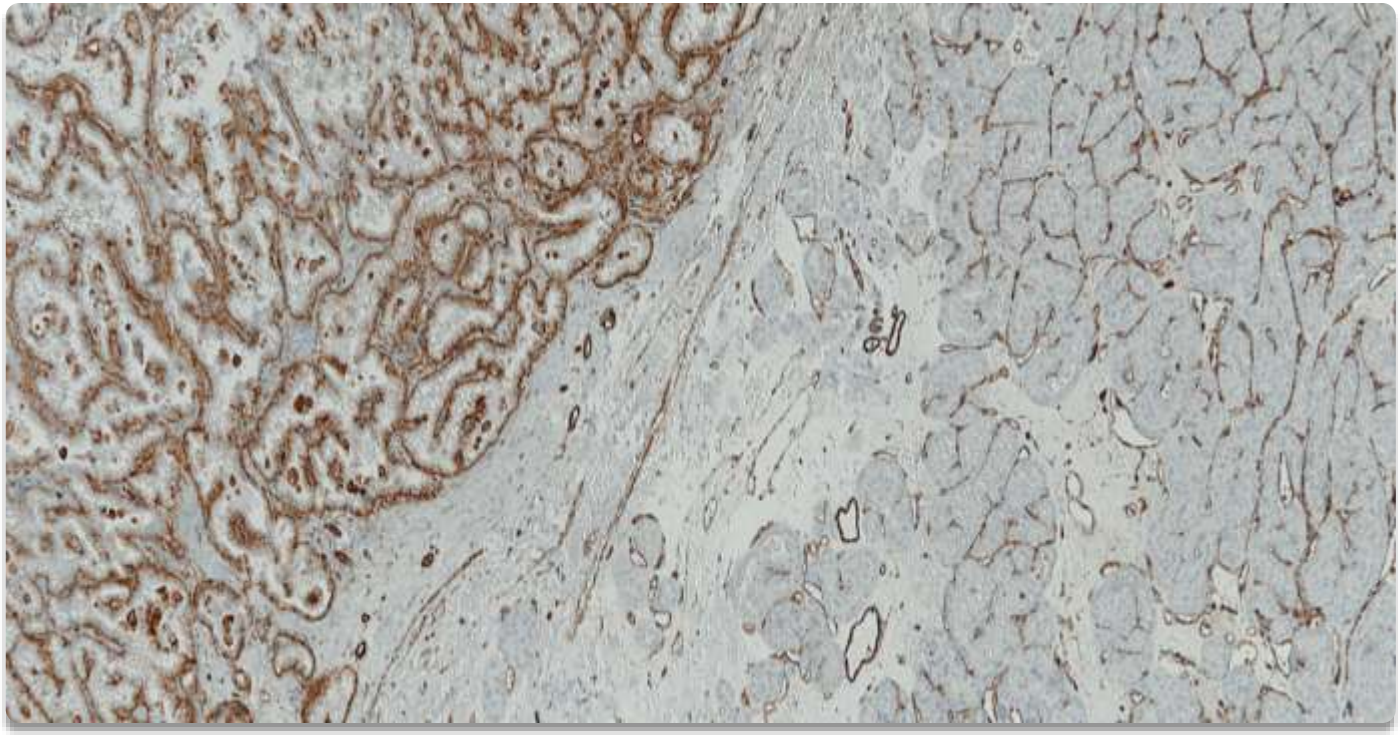
CK7 staining

IHC stains were performed which differentiated the two tumors. The papillary area is positive for CK7 with negative staining on the oncocytoma



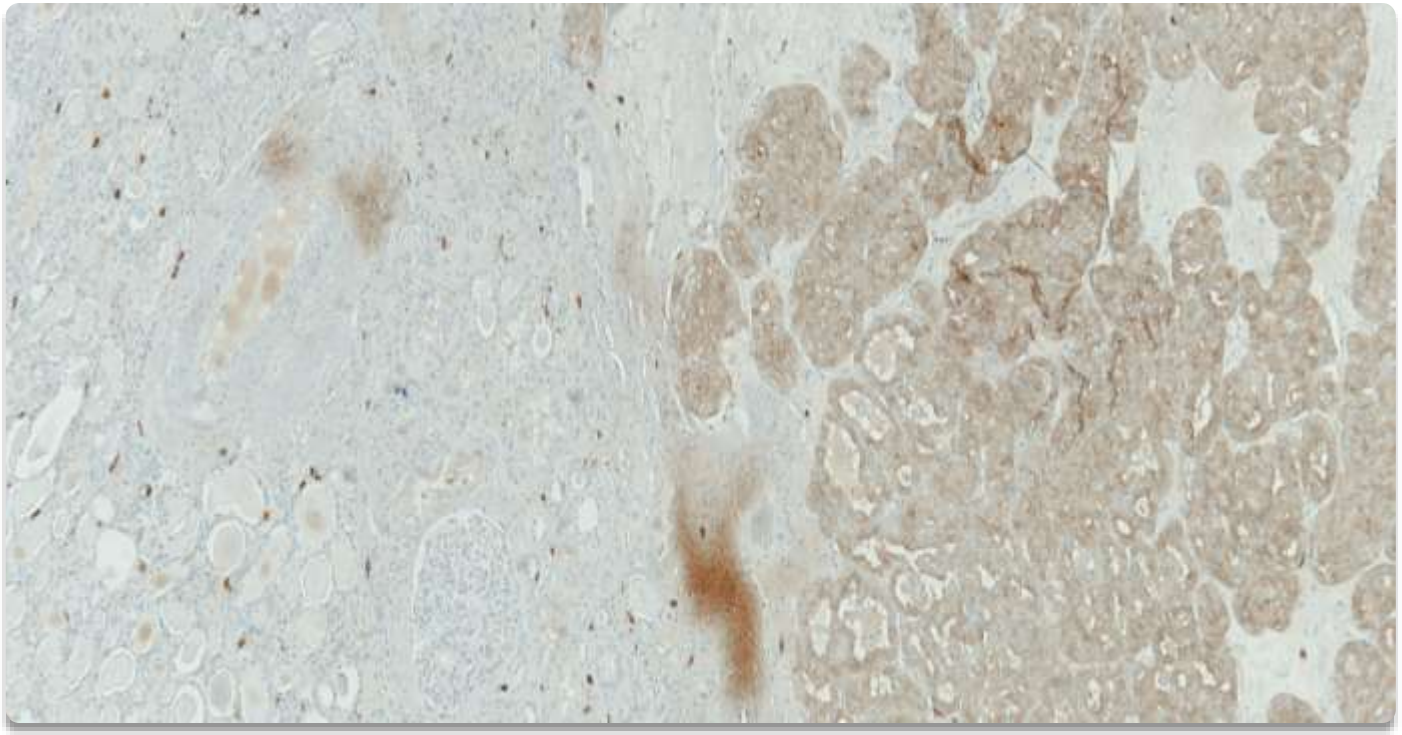
Racemase

IHC stains were performed which differentiated the two tumors. The papillary area is positive for racemase with negative staining on the oncocytoma



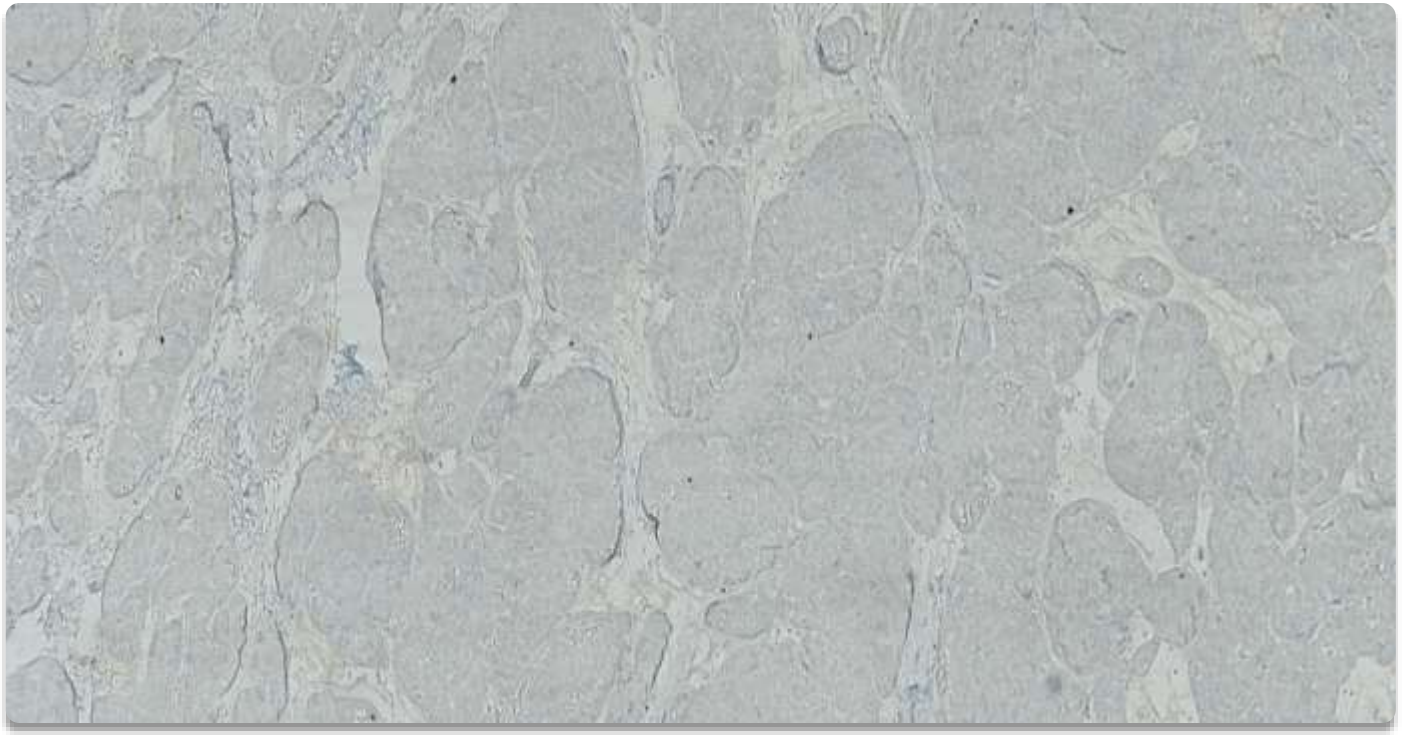
Vimentin

IHC stains were performed which differentiated the two tumors. The papillary area is positive for vimentin with negative staining on the oncocytoma



IHC stains were performed which differentiated the two tumors. The Image above shows CD117 negative papillary area with positive staining on the oncocytoma

CD117



The proliferation index (Ki67) for the oncocytoma component is <1%

Ki67

Summary

- Combined morphologic and immunohistochemical findings support the diagnosis of a collision tumor, composed of papillary renal cell carcinoma, 1.3cm, and an oncocytoma, 4.5 cm
- Collision tumor – coexistent but independent tumors that are histologically distinct, believed to result from two separate neoplasms
- PRCC is the second most common subtype of RCC, (11-18.5% of all RCCs), and is thought to originate from proximal renal tubular epithelial cells. PRCC commonly shows trisomy or gains of chromosomes 7 and 17
- Oncocytomas are also not uncommon (3-7% of renal tumors) and are thought to originate from collecting duct intercalated cells. Oncocytomas commonly show loss of chromosomes 1 and Y, and may have translocations between chromosomes 6 and 9
- Concurrent RCC within the same kidney has been described and most commonly involves clear cell RCC and chromophobe RCC. The occurrence of PRCC and oncocytoma within the same tumor mass is extremely rare (only eight cases previously described in the literature)

Extremely Rare Incidence of PRCC/Oncocytoma Collision Tumor

- Only nine cases reported in the literature (all as individual case reports)
- **PRCC represented the smaller component**
- In all reported cases, there was no progression on follow-up (4-28 month range) or recurrence
- Recent recommendation (McCroskey, et. Al, 2017) for generous sampling of the periphery of otherwise classic oncocytomas or papillary growth areas to unveil this association

Authors (Ref. #)	Year	Size of oncocytoma (cm)	Size of p-RCC (cm)	p-RCC type, grade	Chromosomal alterations
1. Al-Saleem et al. [5]	2005	6	Small nests	No type or grade	Both components with trisomy 7
2. Rowsell et al. [6]	2007	1.5	0.7	Type 1, F2	Trisomy 7 in p-RCC
3. Vasuri and Fellegara [7]	2009	3.5	N/A	N/A	N/A
4. Floyd et al. [8]	2011	3.6	0.15	Type 2, F2	N/A
5. Sejben et al. [9]	2013	3.5	1.0	Type 2, F2	No abnormality in both components
6. Özer et al. [10]	2013	5.0	1.7	Type 2, no grade	N/A
7. Goyal et al. [11]	2015	6.4	1.0	Type 1, F2	Trisomy 17 in p-RCC
8. Baydar et al. [12]	2016	4.5	blended	Type 1, no grade	N/A
9. Current case	2016	3.7	Adjacent (25% of tumor)	Type 1, F1	N/A

p-RCC, papillary renal cell carcinoma; F - Fuhrman nuclear grade; N/A, not available.

References

- Goyal R, Parwani AV, Gellert L, Hameed O, Giannico GA. A Collision Tumor of Papillary Renal Cell Carcinoma and Oncocytoma: Case Report and Literature Review. *American Journal of Clinical Pathology*. 2015;144(5):811-816. doi:10.1309/ajcpq0p1yhdbzufl.
- Mccroskey Z, Sim SJ, Selzman AA, Ayala AG, Ro JY. Primary collision tumors of the kidney composed of oncocytoma and papillary renal cell carcinoma: A review. *Annals of Diagnostic Pathology*. 2017;29:32-36. doi:10.1016/j.anndiagpath.2017.04.011.