South Bay Pathology Society
April 2025

Disclosures
April 7, 2025

Dr. Yaso Natkunam has disclosed active financial relationships with Leica Biosystems and Roche Tissue Diagnostics (consultancy) and with Kite Pharma (research funding). Dr. Greg Bean has disclosed active financial relationships with Advanced Cell Diagnostics (speaking engagement). Dr. Sebastian Fernandez-Pol has disclosed active financial relationships with Leica Biosystems (advisory board) and Cartography Biosciences (consultant). South Bay Pathology Society has determined that none of these relationships are relevant to the clinical diagnostic cases being discussed. The activity planners and faculty listed below have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Dave Bingham, MD

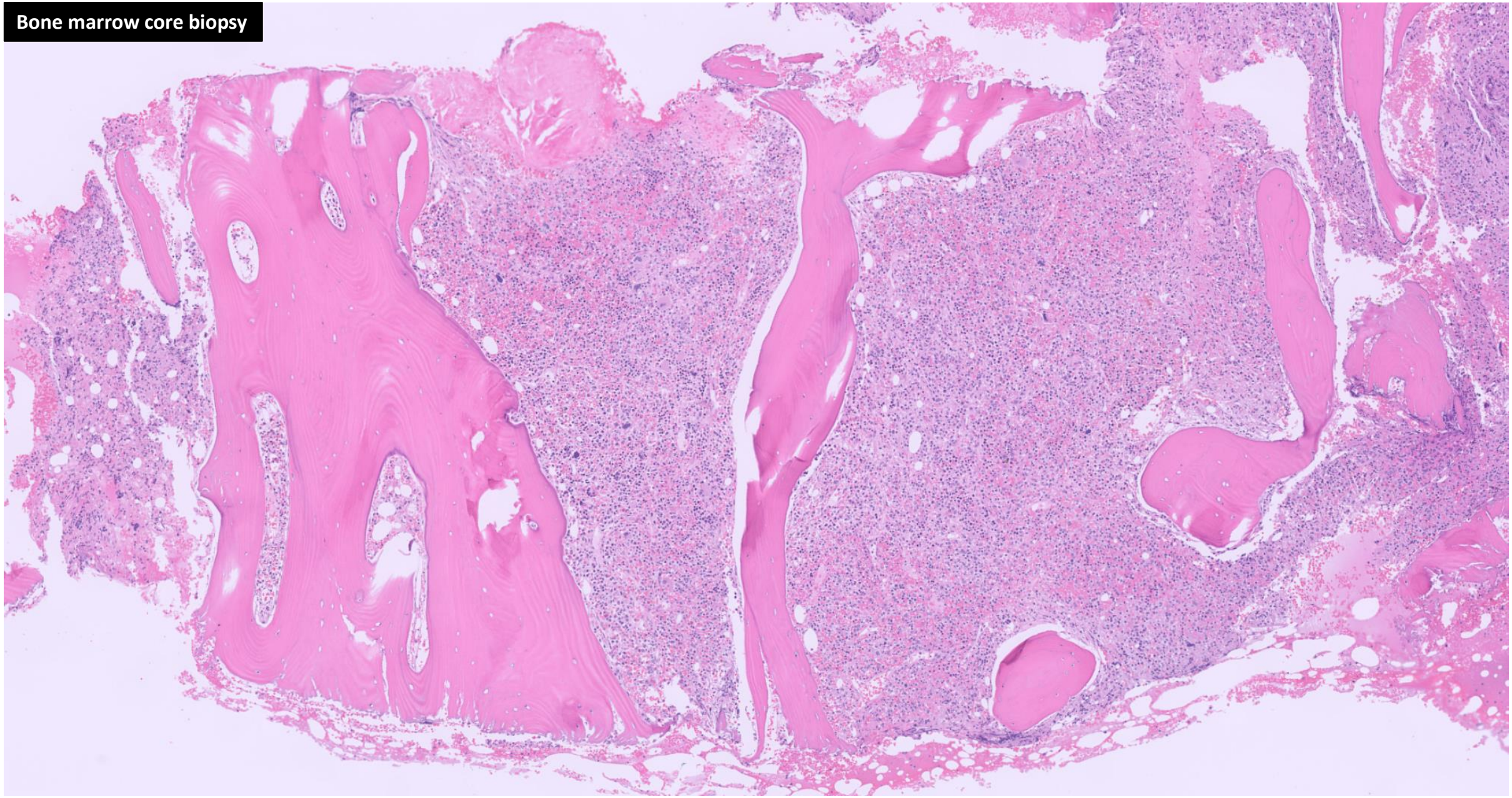
25-0401

Aaron Wilk, Oscar Silva; Stanford

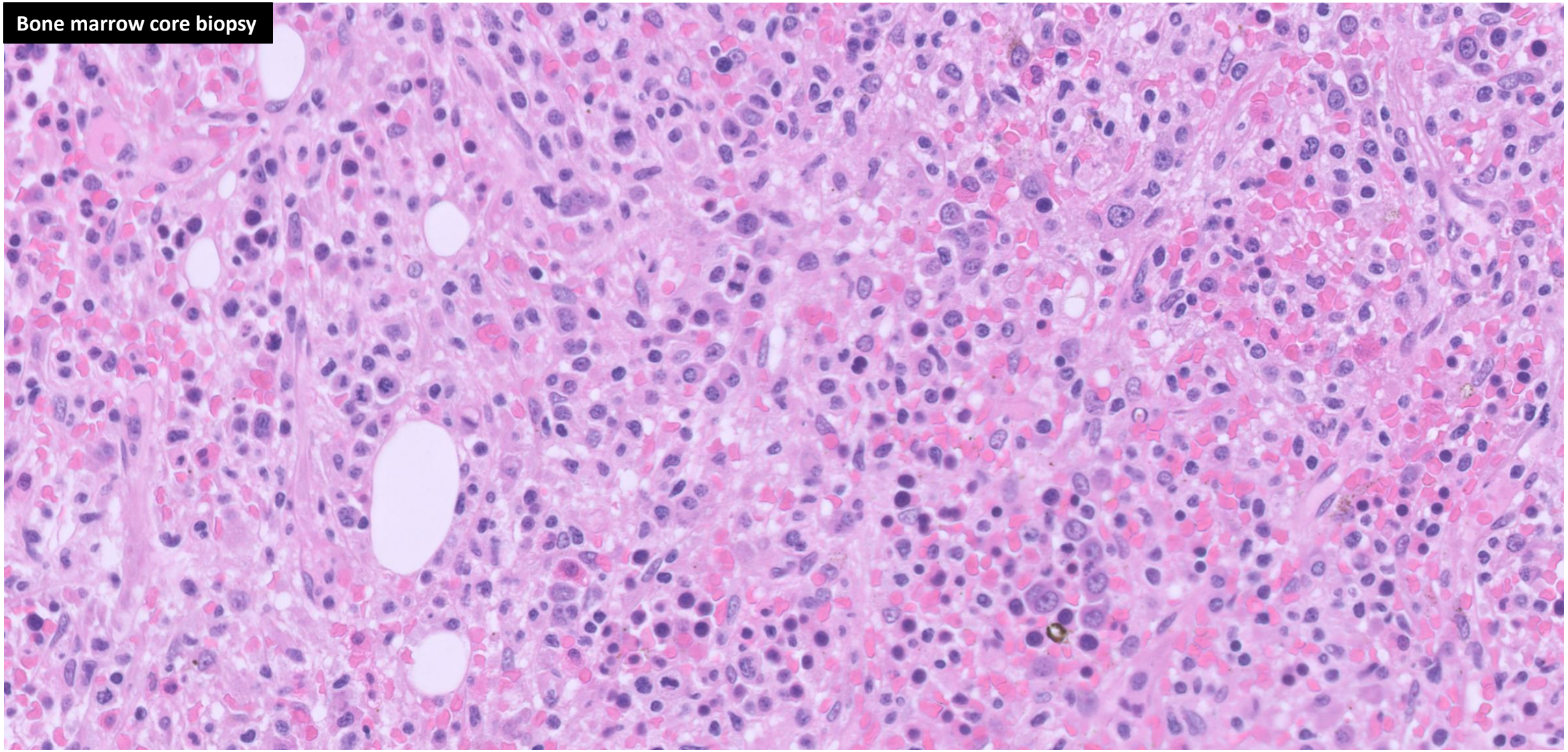
66 Y male with history of hyperlipidemia presents with 2 weeks of fevers, headaches, nausea/vomiting, found to be pancytopenic and have acute liver injury, concern for hemophagocytic lymphohistiocytosis

WBC: 2.0
Hgb: 12.2
Plt: 81
AST: 581
ALT: 1391
Ferritin: 17419
sCD25: 8612 [175-858]

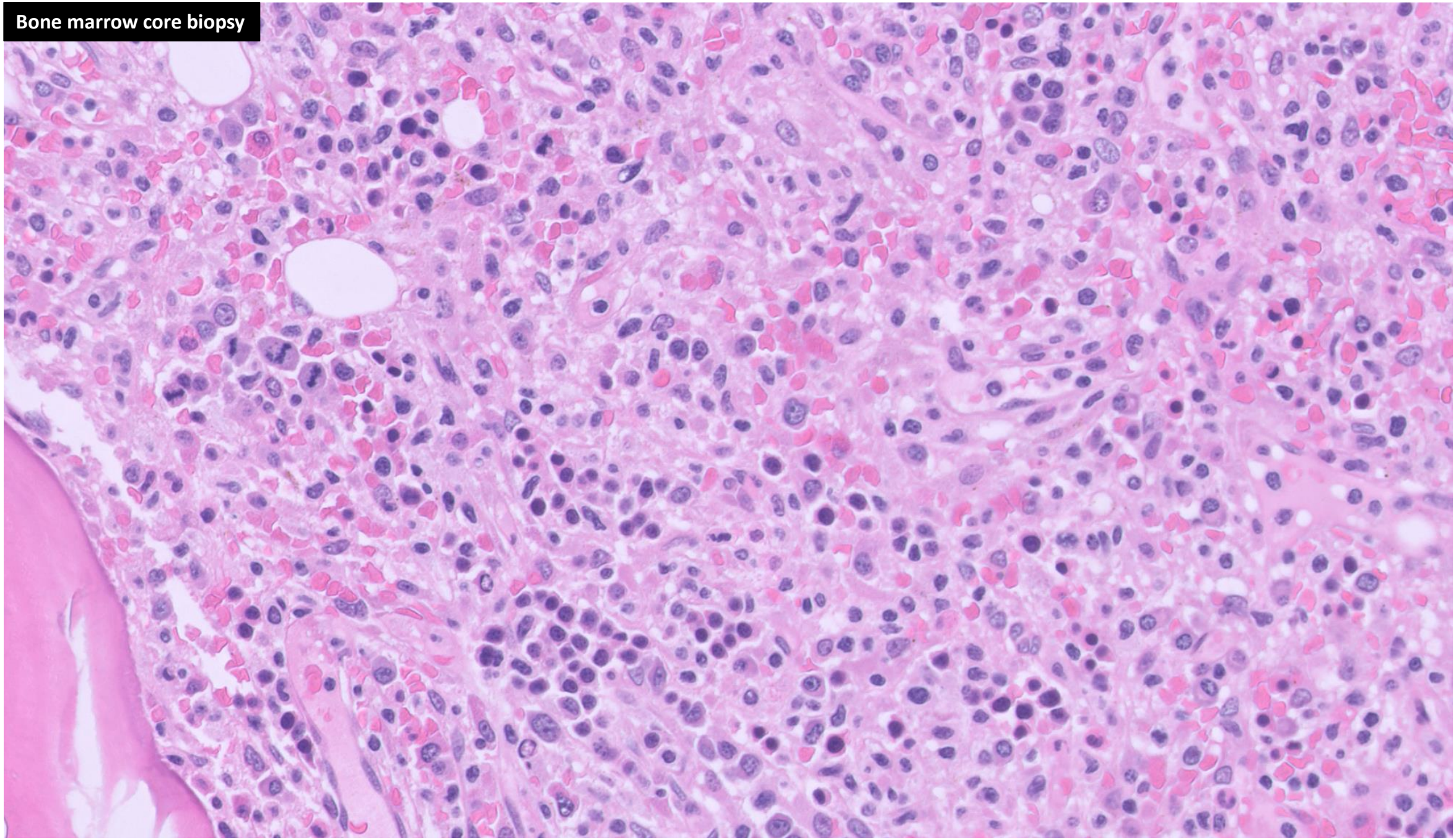
Bone marrow core biopsy



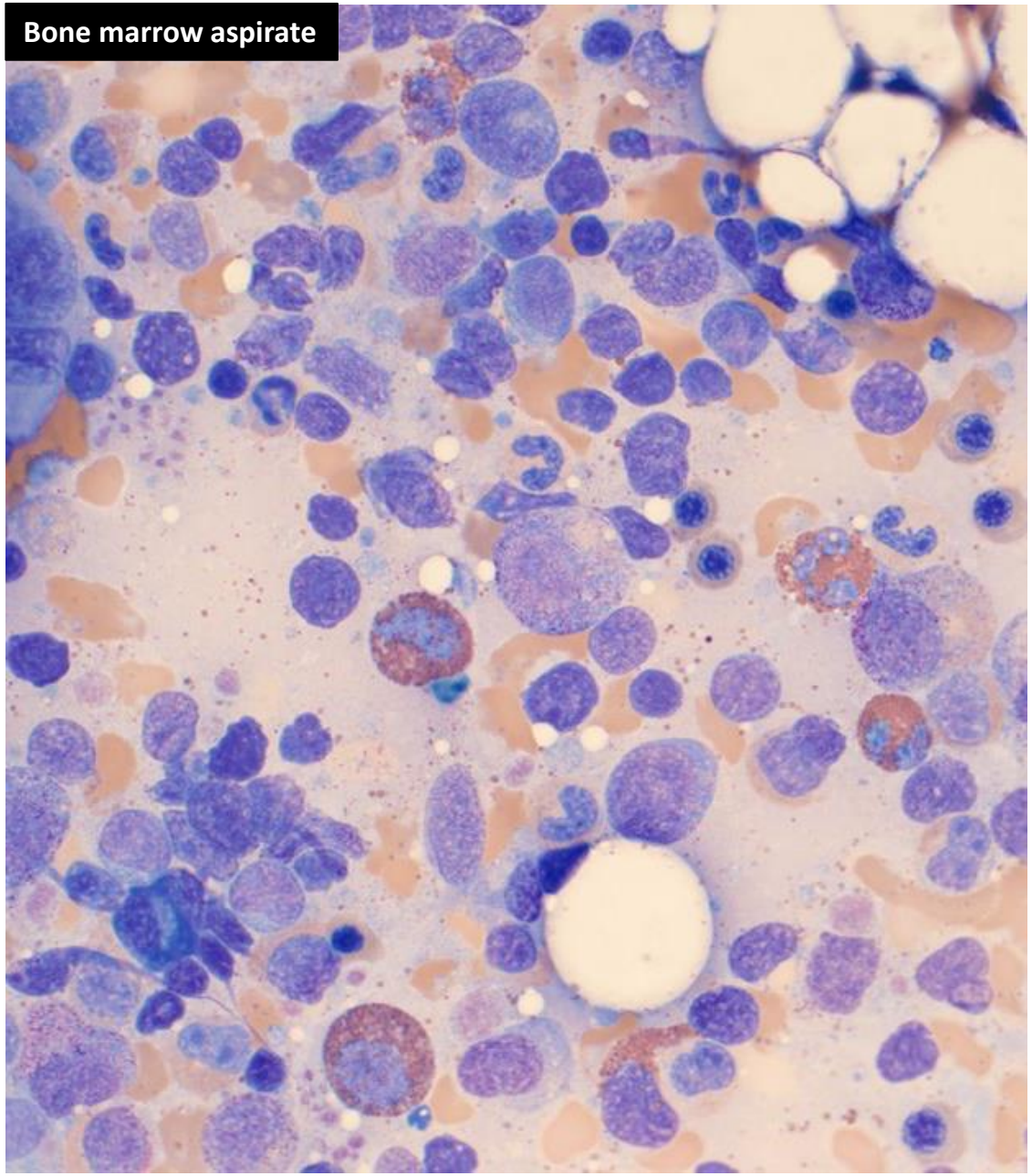
Bone marrow core biopsy

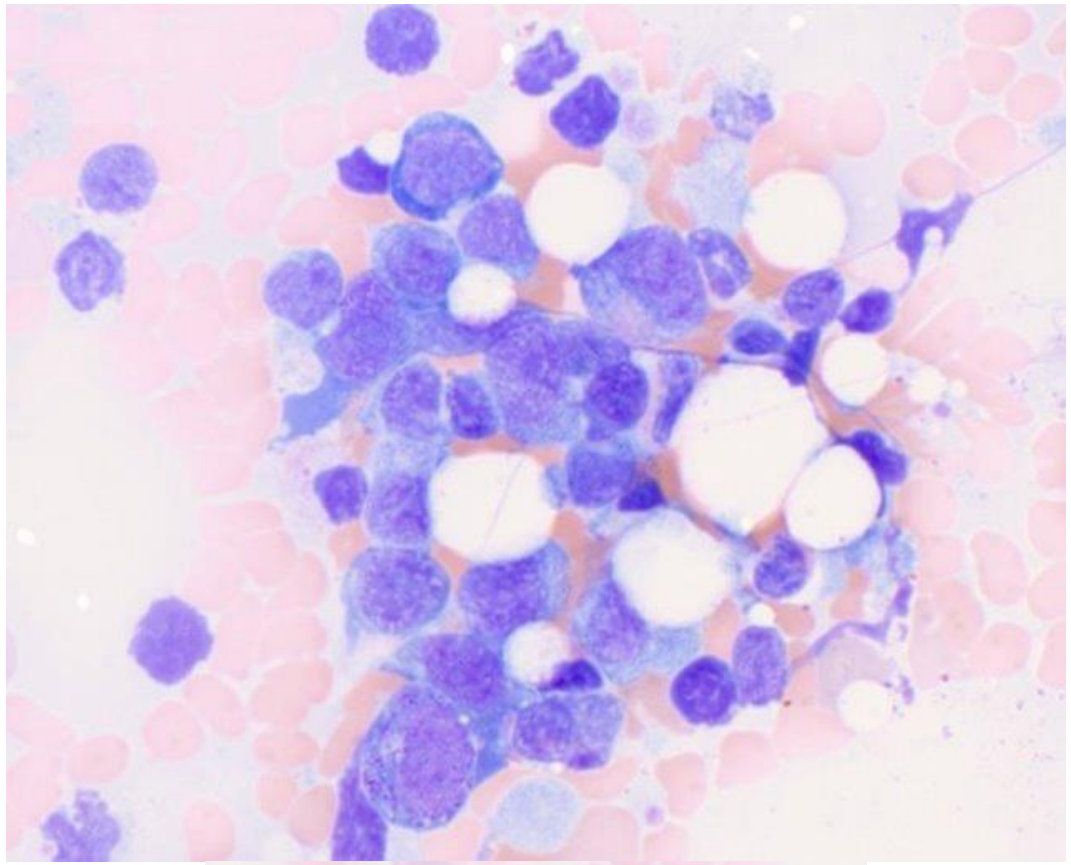


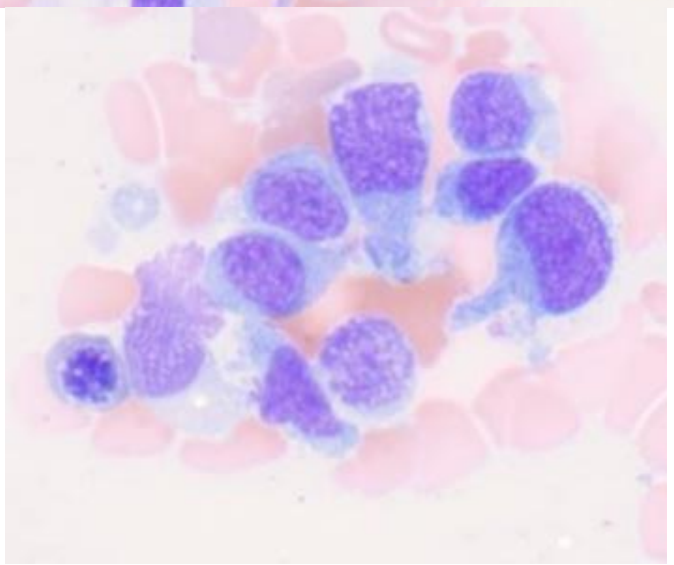
Bone marrow core biopsy

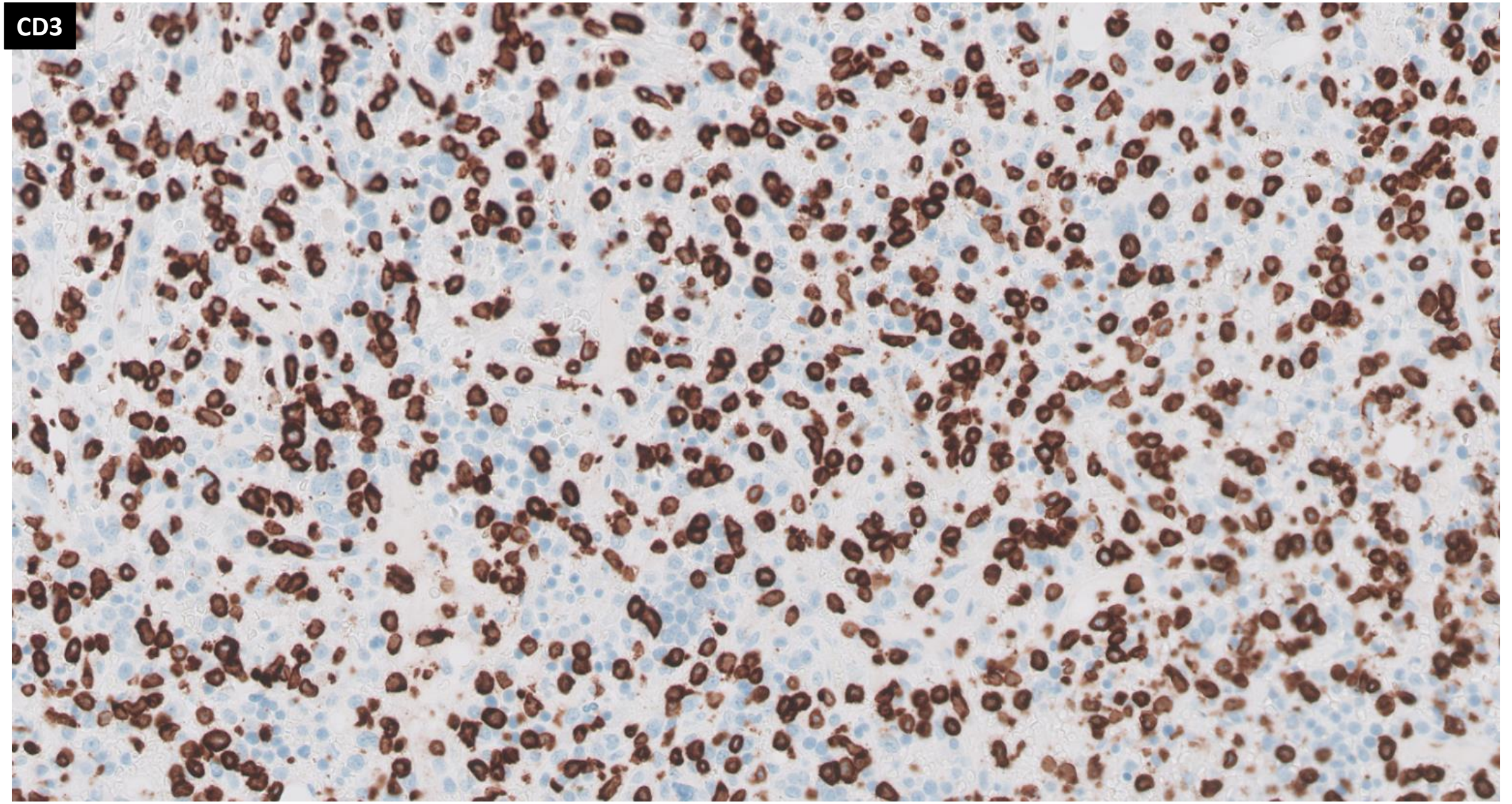


Bone marrow aspirate





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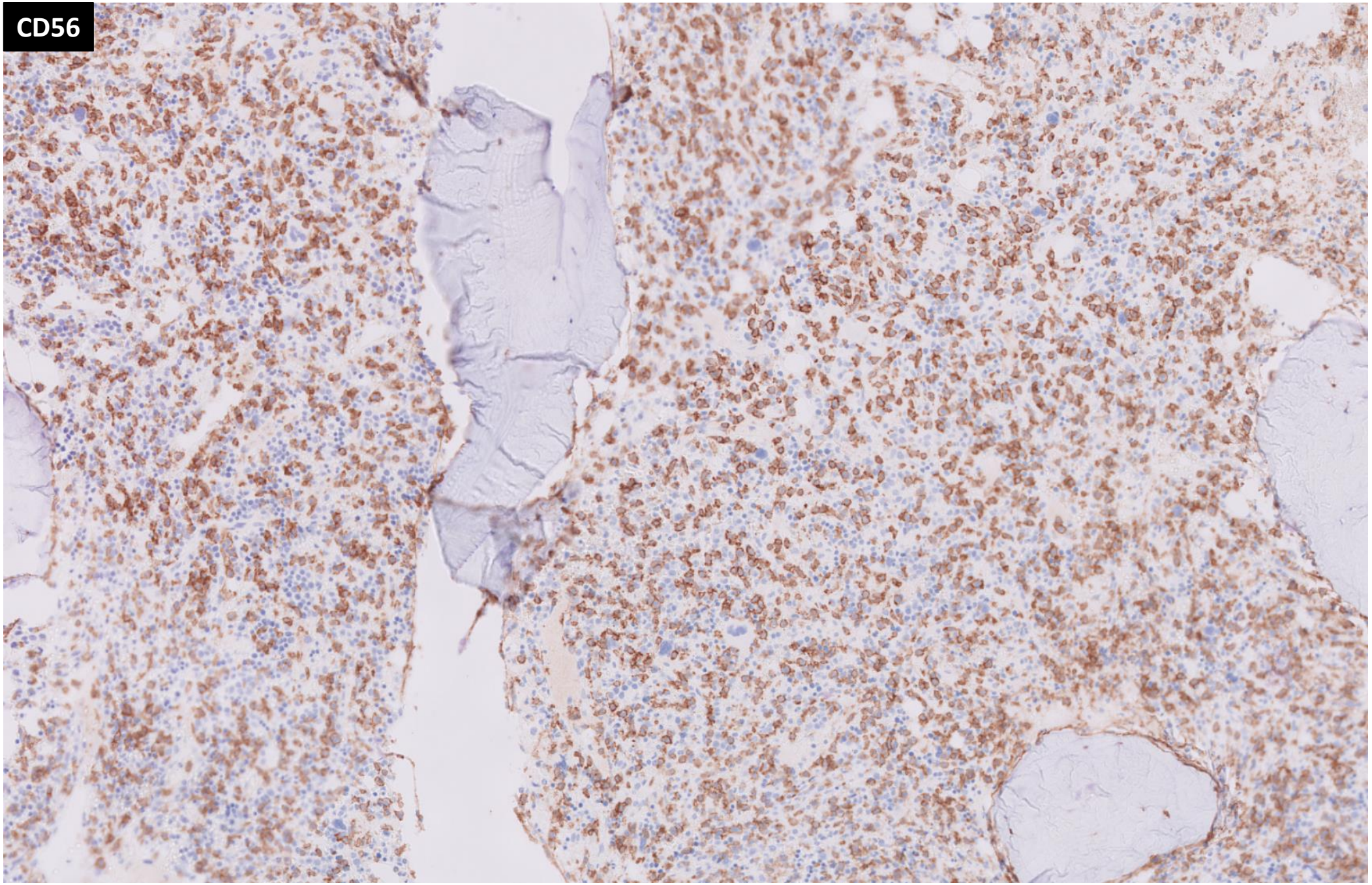
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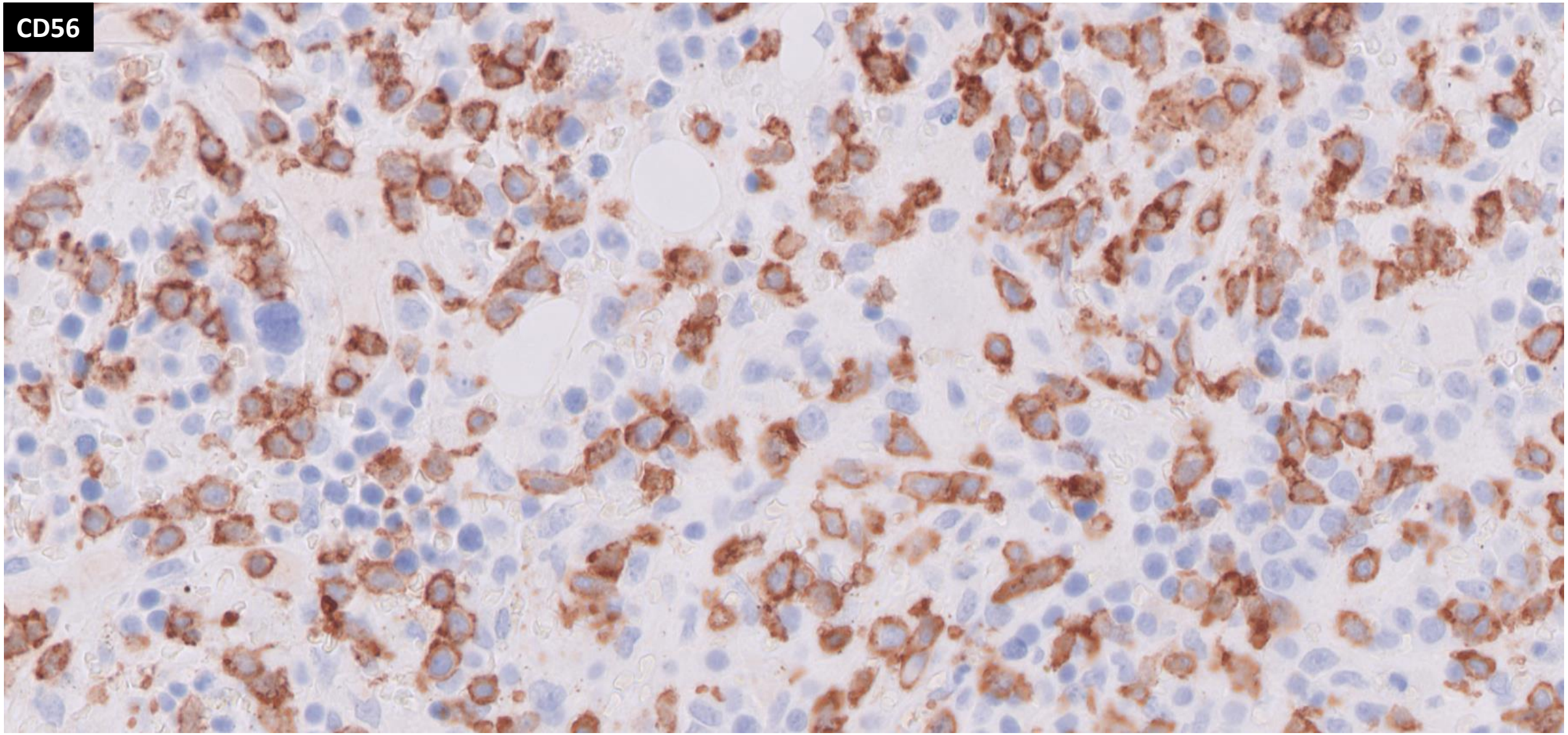
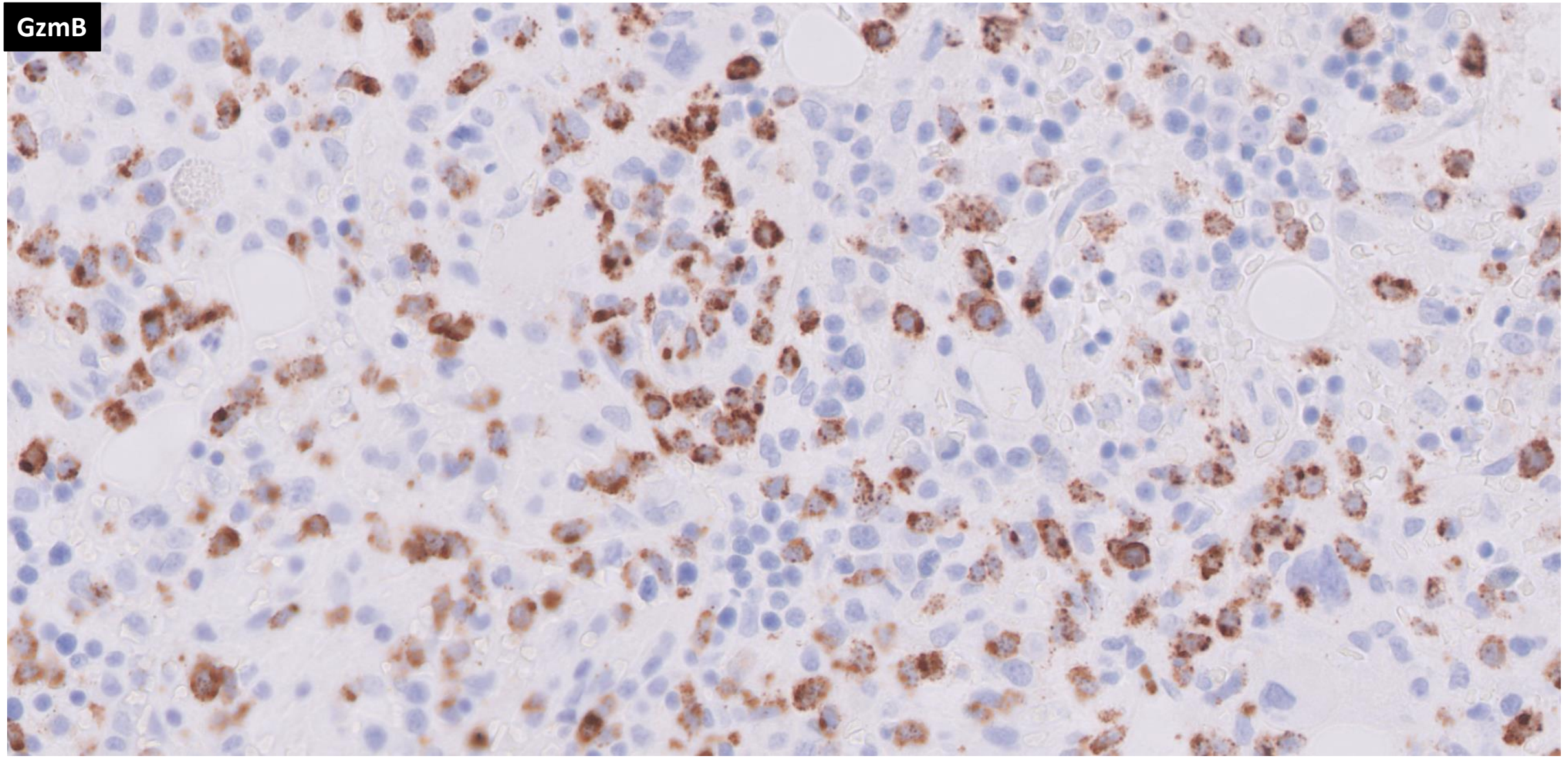
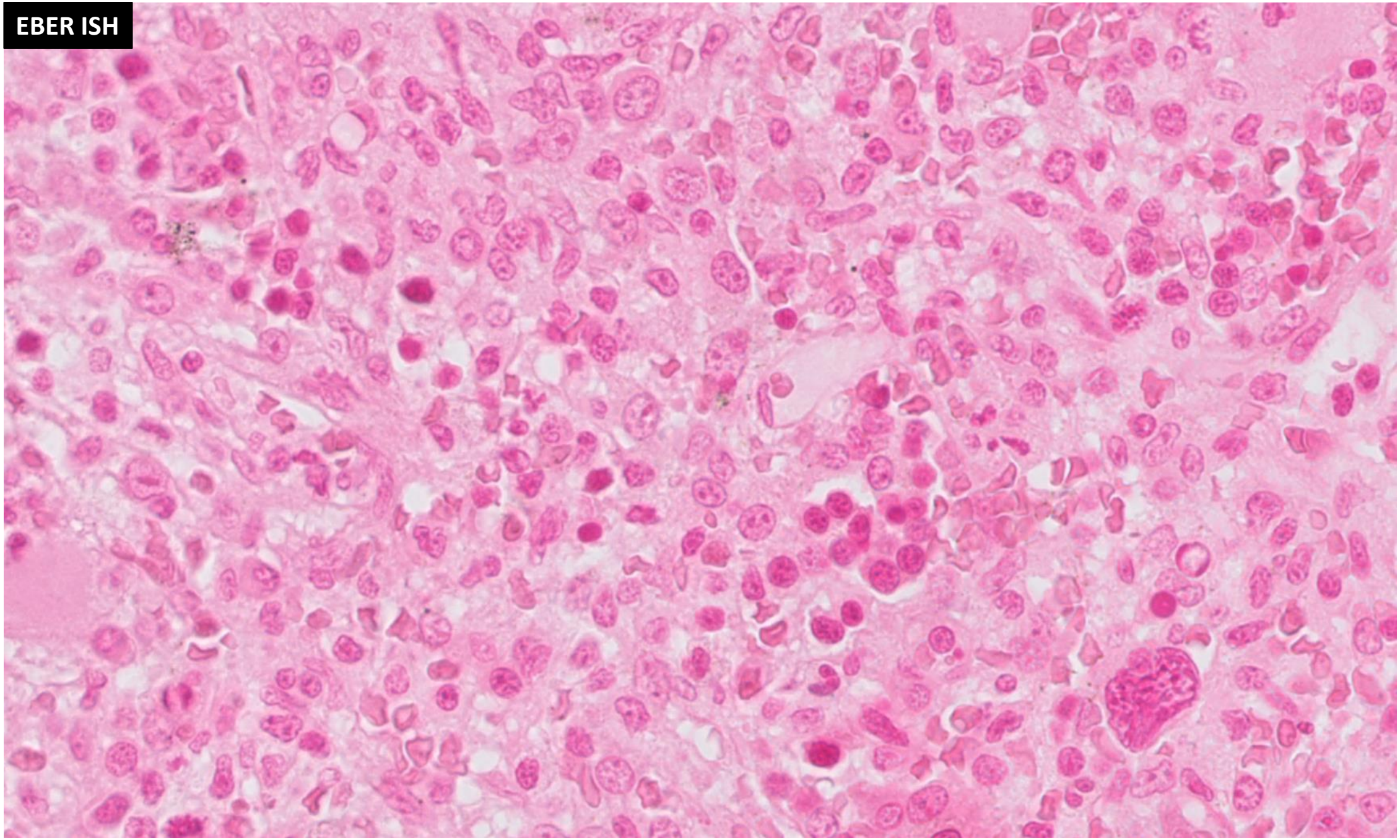
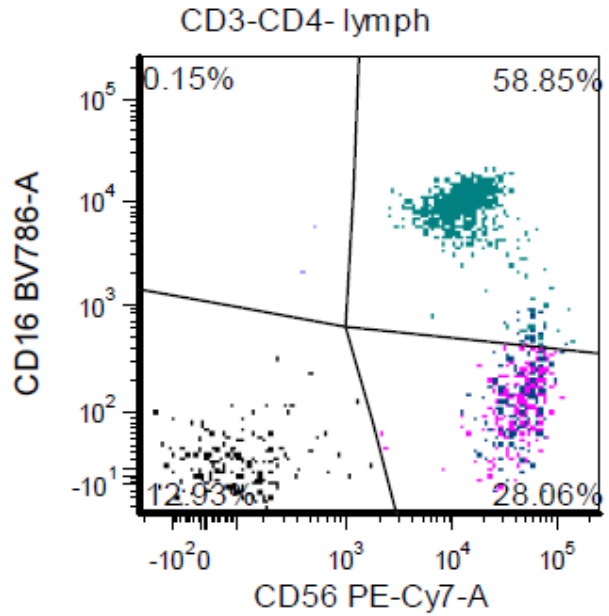
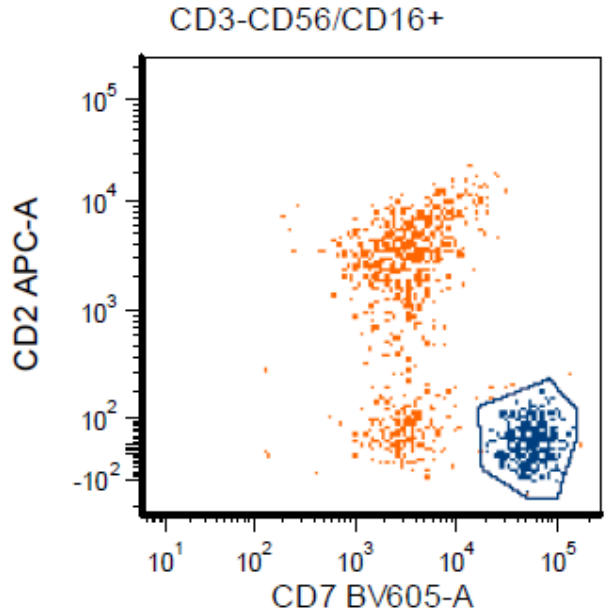

CD56

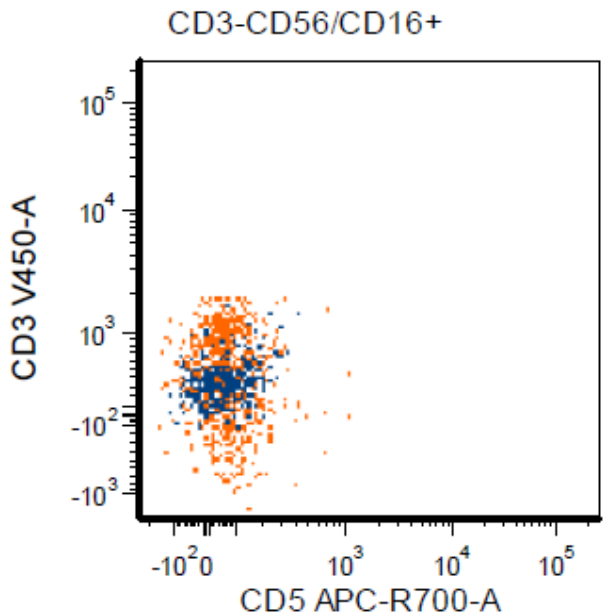

GzmB

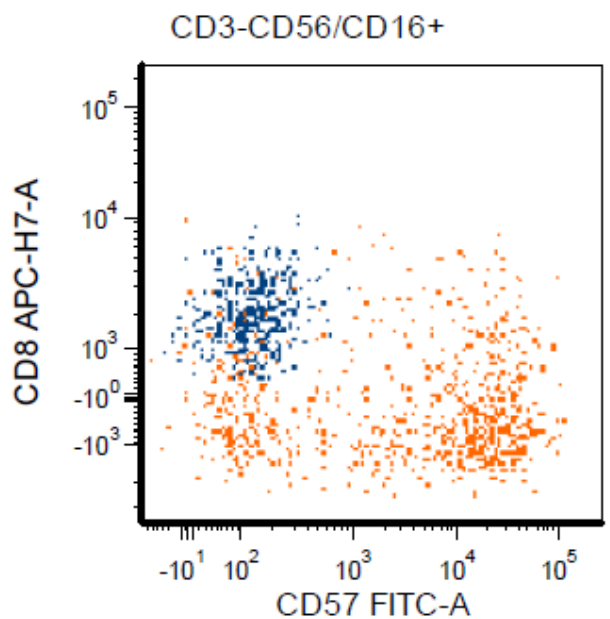

EBER ISH

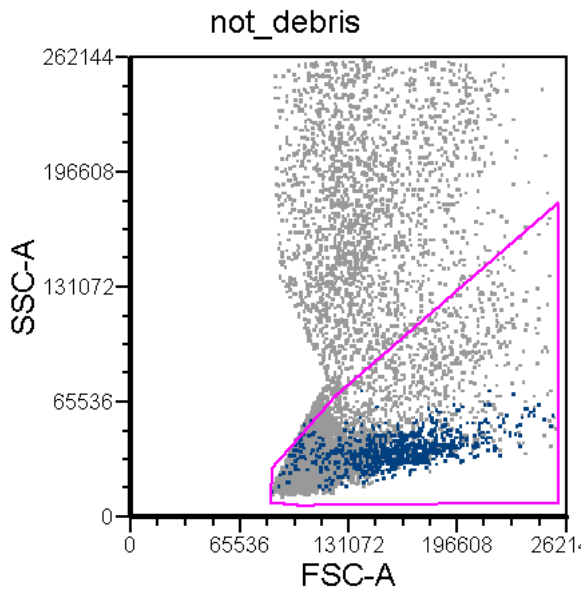
Bone marrow flow cytometry





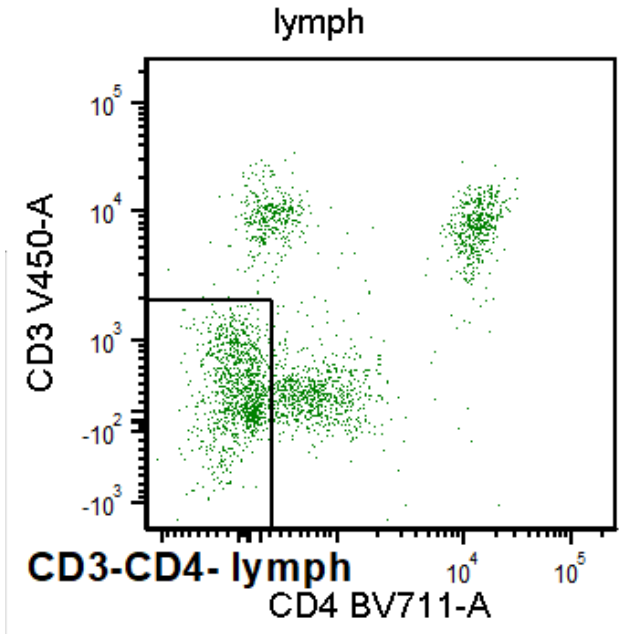


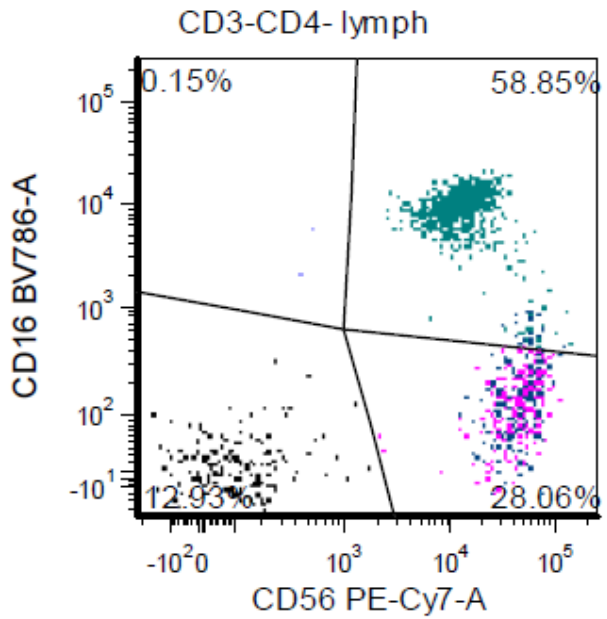


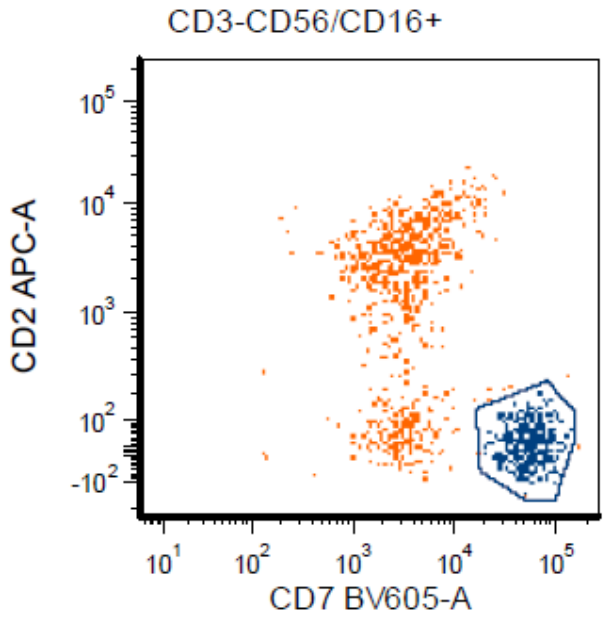


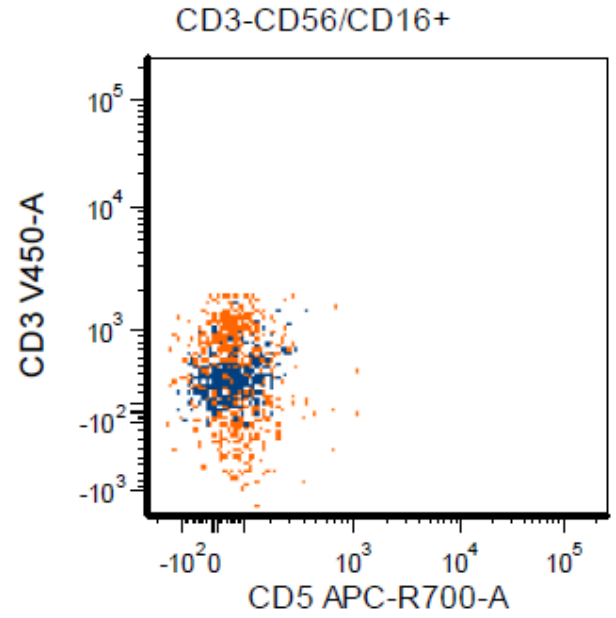
DIAGNOSIS?

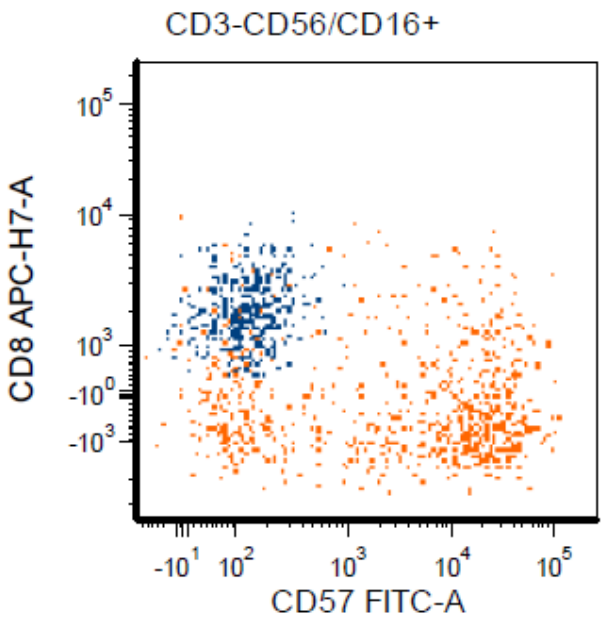
Bone marrow flow cytometry

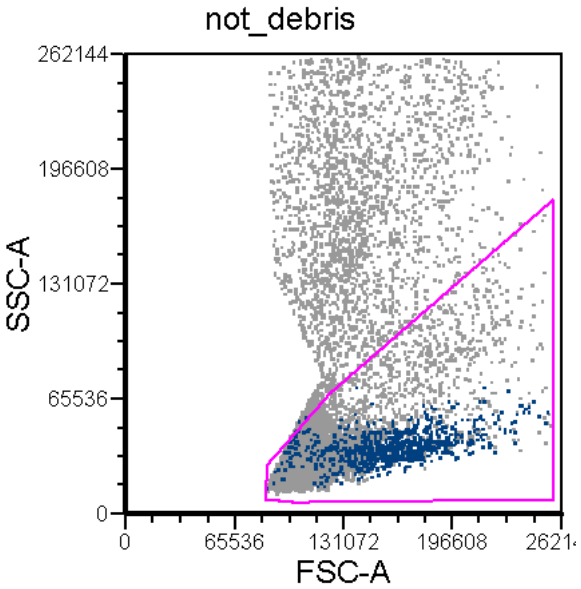




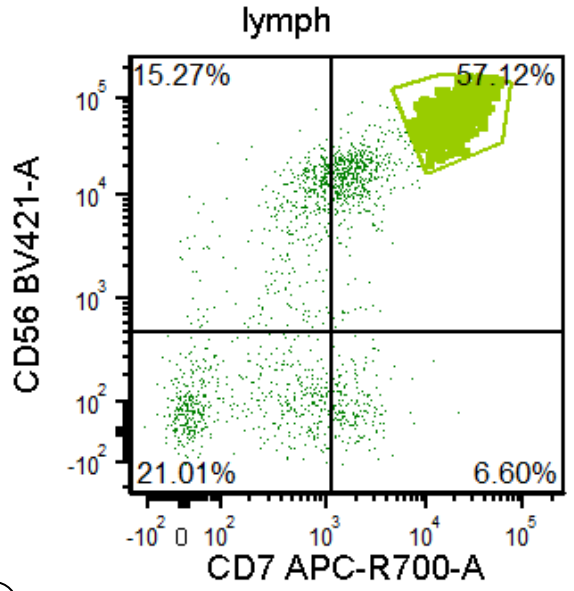


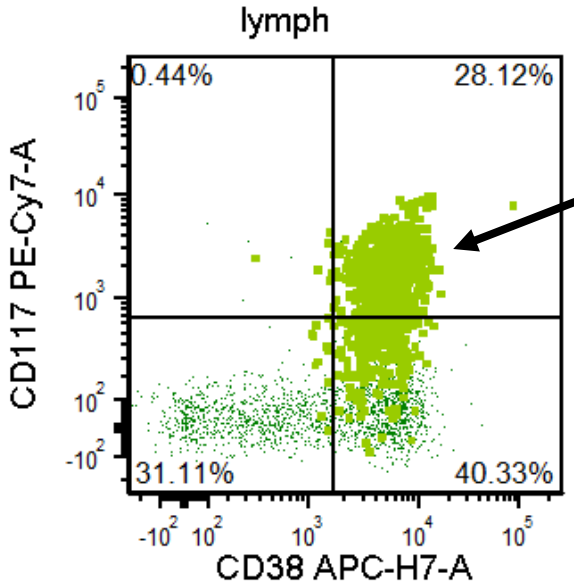






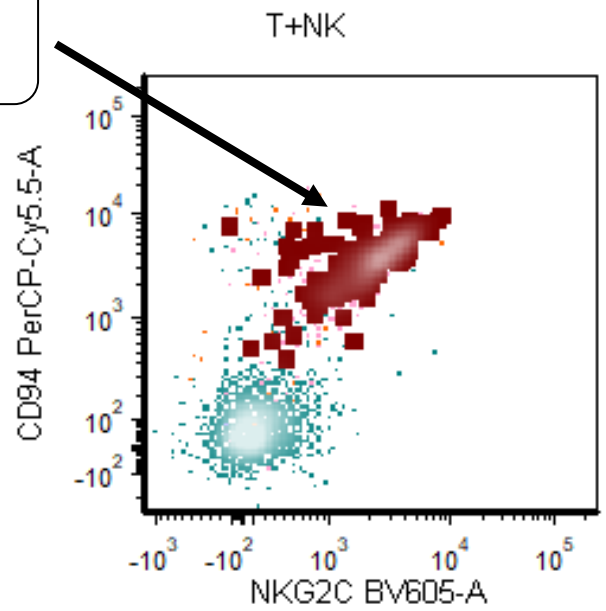
Bone marrow flow cytometry

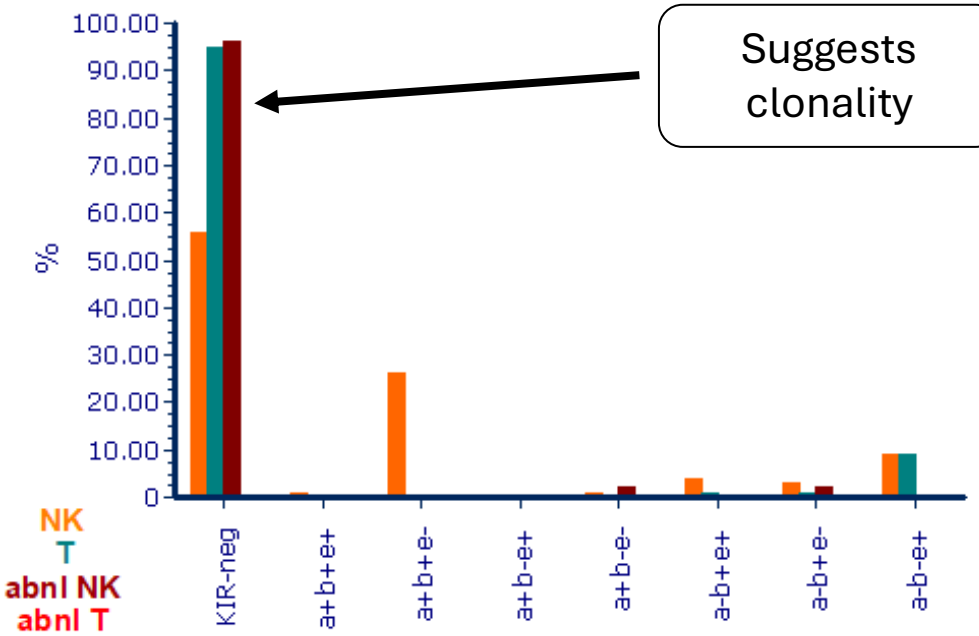




Suggests immaturity

Aberrant for CD16- NK cells





Suggests clonality

Cytogenetic and molecular studies

Chromosome analysis:

- ISCN Description:
  - 26~29,inc[cp8]/46,XY[13]
  - *"…grossly abnormal and characterized by a near haploid karytotype of 26 to 29 chromosomes with numerous aneuploidies, structural anomalies and marker chromosomes… an incomplete composite karyotype"*

HEME-STAMP:

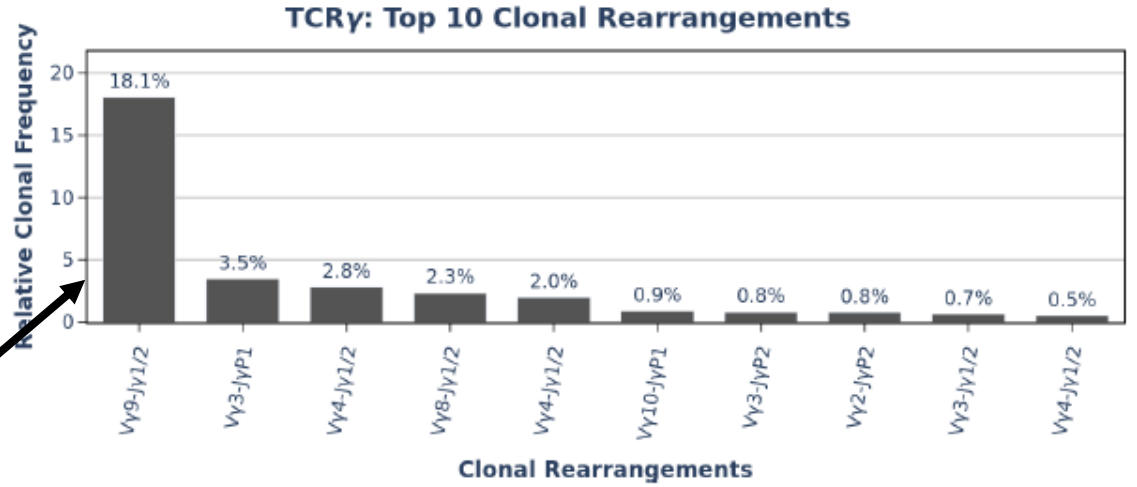
- TP53 R175H mutation identified, VAF 10%
- STAT5B N642H mutation identified, VAF 4%

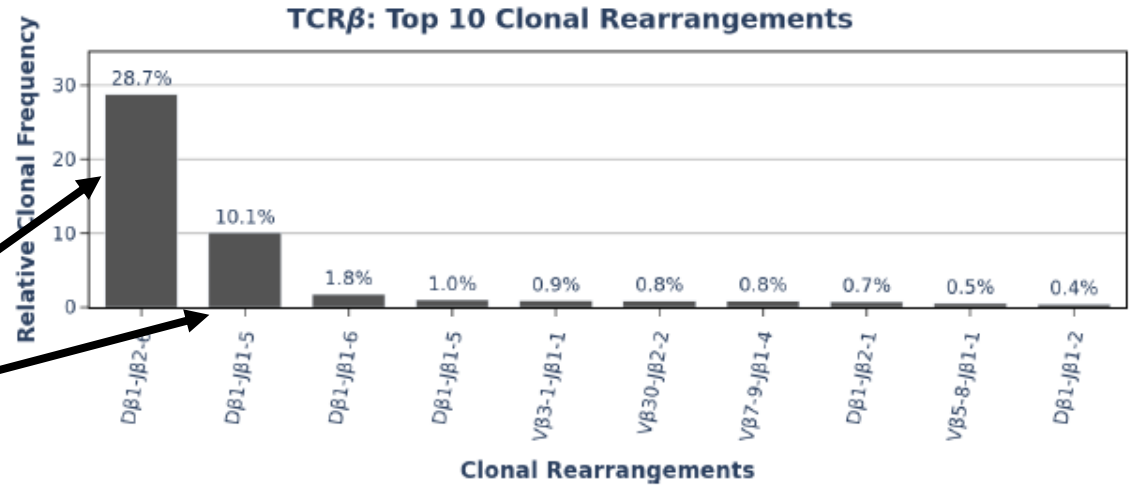
Cytogenetic and molecular studies

T cell clonality studies:

- Positive

Clonal T-cell receptor gene rearrangement(s) detected by next-generation sequencing.





Predicted to be functional

Predicted to be non-functional

Additional studies and follow-up

- MR abdomen: Imaging findings most consistent with **hepatitis (infectious or inflammatory etiology)**
- Underwent liver biopsy: **Involved by same process as described in bone marrow**

- Started on **Daratumumab, Cytoxan, Jakafi**

Discussion

- Proposed diagnosis: **Aggressive NK cell leukemia, EBV-negative**
- Differential may include Hepatosplenic T cell lymphoma

	HSTCL	ANKL
Cell type	Cytotoxic T cells (frequently γδ; ~75%)	NK cells: immature, mature, or transformed from NK-LGLL (rare)
Presentation	Marked hepatosplenomegaly and B symptoms, presents with advanced disease	B symptoms, HLH, liver/spleen involvement common
Circulating disease	Uncommon	Common
EBV	Negative	Positive (~90%)
Immuno-phenotype	CD2+CD3+CD8+ CD56 (70%); CD16 (60%) PRF, GzmB +	CD2+CD3-CD8+ CD56+; CD16+ PRF, GzmB +
Molecular features	JAK/Stat mutations	Mutated *TP53* (~1/3) JAK/Stat mutations
Cytogenetics	iso(7q); +8 (50-60%)	del(6q); del(7p); del(11q); del(17p)
T cell clonality	Positive	Negative*

Discussion

- Proposed diagnosis: **Aggressive NK cell leukemia, EBV-negative**
- Differential may include Hepatosplenic T cell lymphoma

	HSTCL	ANKL
Cell type	Cytotoxic T cells (frequently γδ; ~75%)	NK cells: immature, mature, or transformed from NK-LGLL (rare)
Presentation	Marked hepatosplenomegaly and B symptoms, presents with advanced disease	B symptoms, **HLH**, liver/spleen involvement common
Circulating disease	Uncommon	**Common**
EBV	**Negative**	Positive (~90%)
Immuno-phenotype	CD2+CD3+CD8+ CD56 (70%); CD16 (60%) PRF, GzmB +	CD2+**CD3-**CD8+ CD56+; CD16+ PRF, GzmB +
Molecular features	JAK/Stat mutations	**Mutated *TP53* (~1/3)** JAK/Stat mutations
Cytogenetics	iso(7q); +8 (50-60%)	del(6q); del(7p); del(11q); del(17p)
T cell clonality	**Positive**	Negative*

Discussion

- EBV-negative ANKL:
  - Represent ~5-10% of ANKL cases
  - Similar histopathologic and immunophenotypic features
  - No consistent distinguishing molecular or cytogenetic features from EBV+ ANKL
  - EBV-negative ANKL may have better prognosis
- NK cells and TCR rearrangement:
  - Expression of sCD3 or s/cTCR protein excludes NK lineage
  - NK precursors express TCR recombination machinery
- Future directions:
  - Flow cytometric staining of cytoplasmic TCR components
  - T cell clonality on sorted T/NK subsets

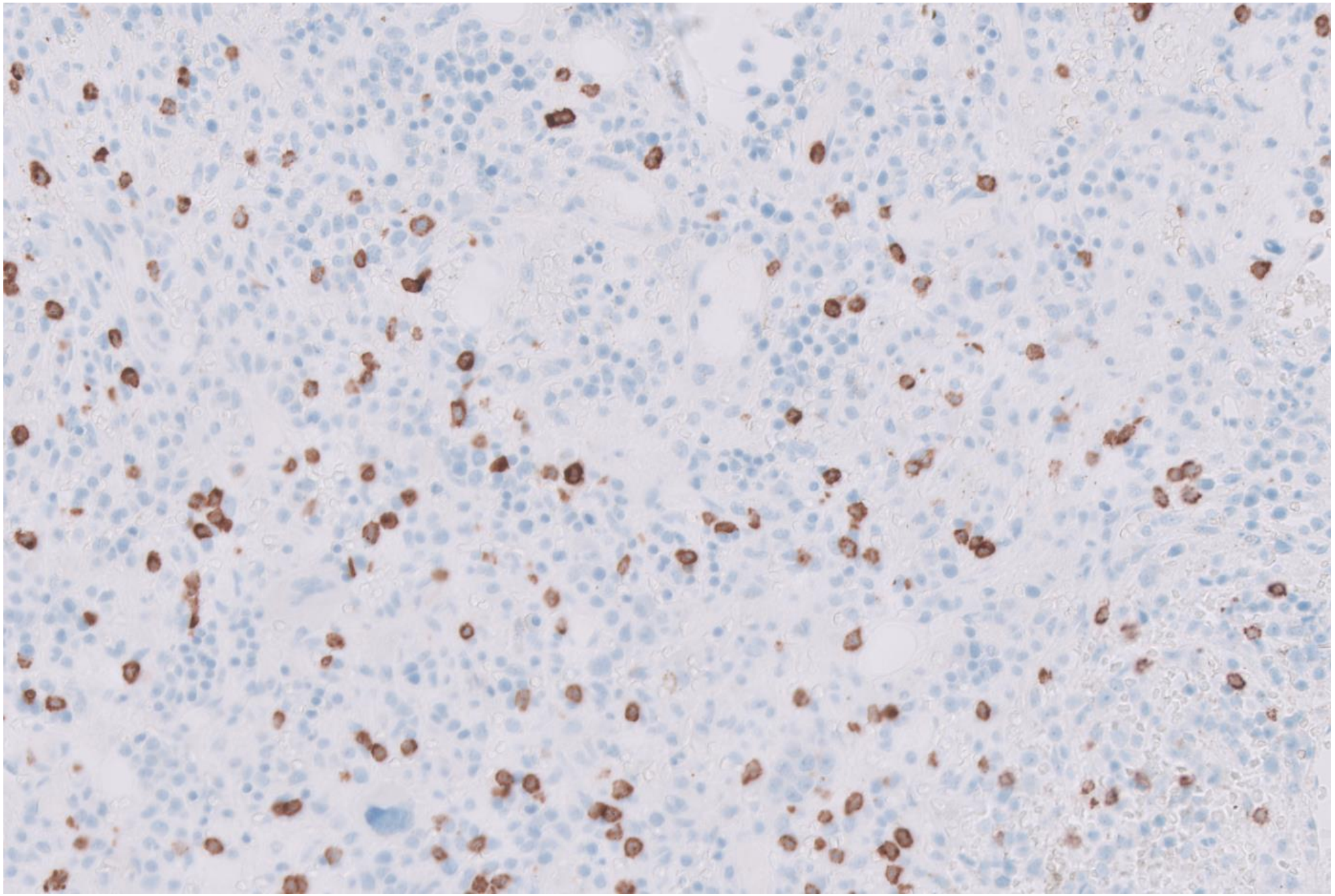
	7/2024	11/2024	1/2025
Atypical NK population on flow	+	+	-
CD8 TCUS by flow	+	-	-
TCR clonality	+	+	-

Ohno, et al. *Cancer* (1988); (1989)
Suzuki, et al. *Leukemia* (2004)
Ko, et al., *Acta Haematol* (2009)
Iqbal, et al. *Leukemia* (2011)
Nicolae, et al. *Am J Surg Pathol* (2017)
Gao, et al. *Mod Pathol* (2017)
McKinney, et al. *Cancer Discov* (2018)
Calderon, et al. *Exp Hem* (2019)
Calderon, et al. *Unpublished* (2021)

Acknowledgements

- Oscar Silva
- Sebastian Fernandez-Pol
- Miguel Gonzalez-Mancera
- Extended flow immunophenotyping:
  - Jean Oak
  - Gary Gitana
  - Michael Khodadoust

Appendix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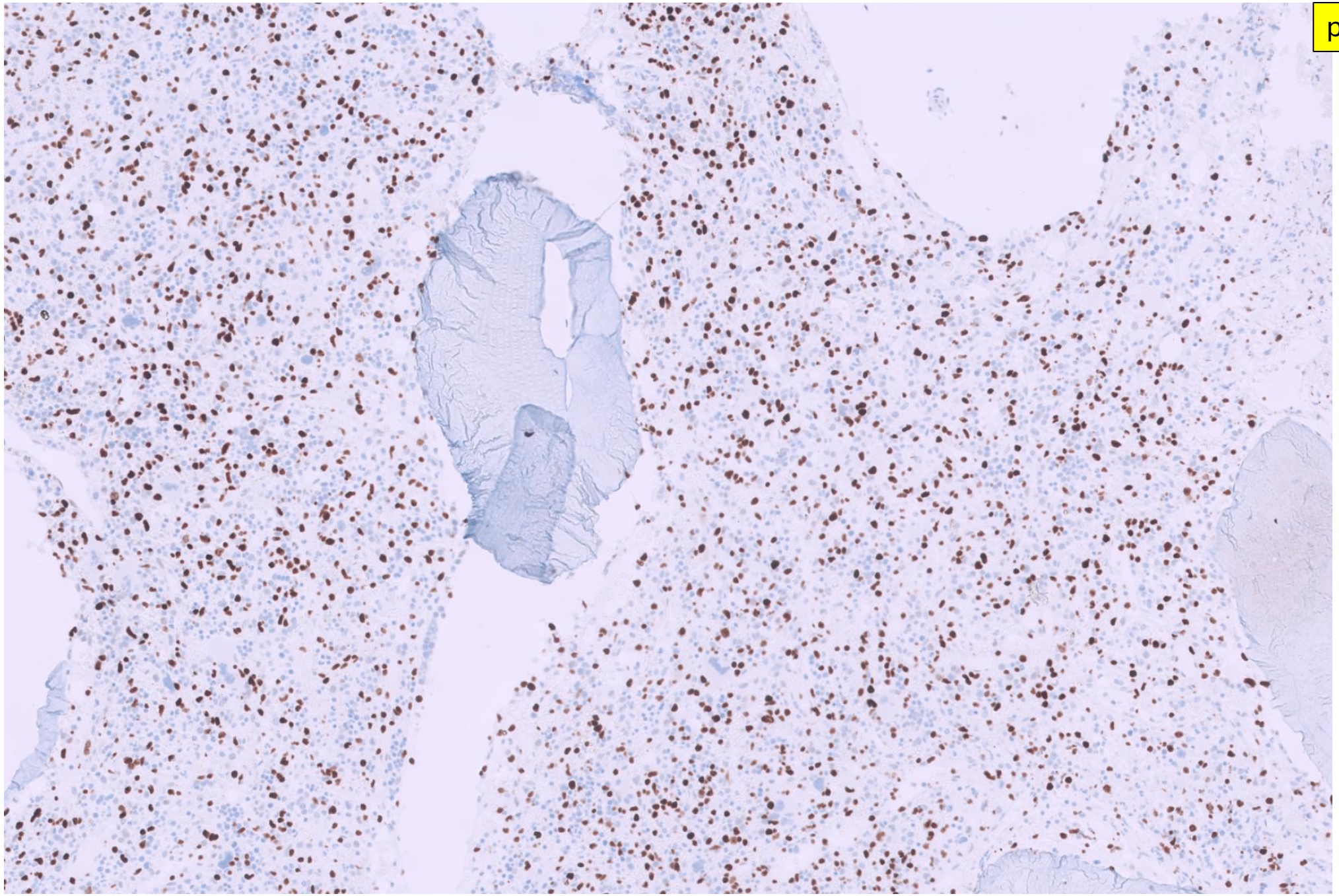
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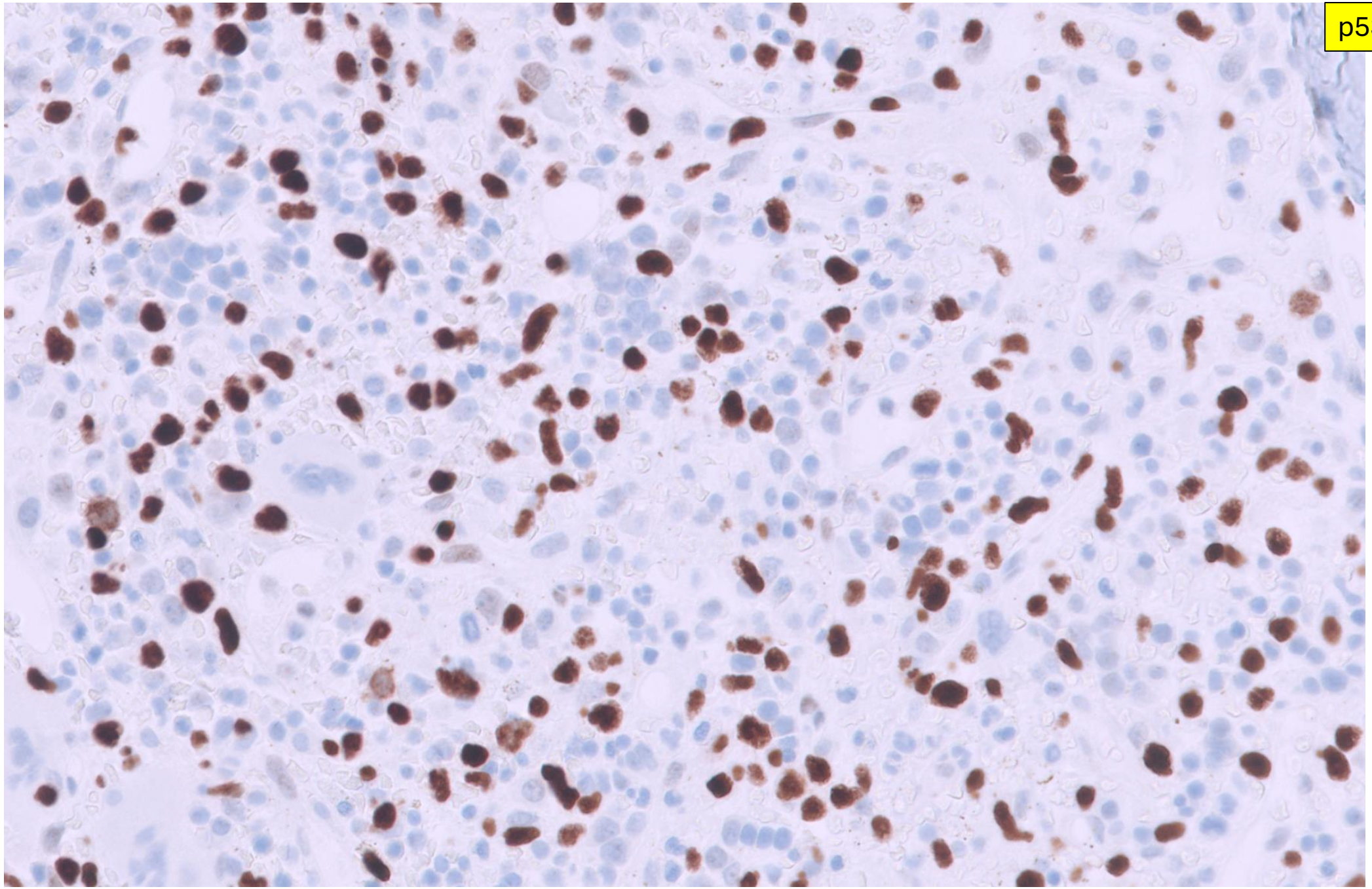
p53

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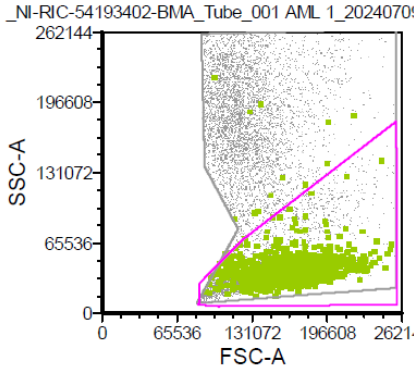
SHC BD Lyric B

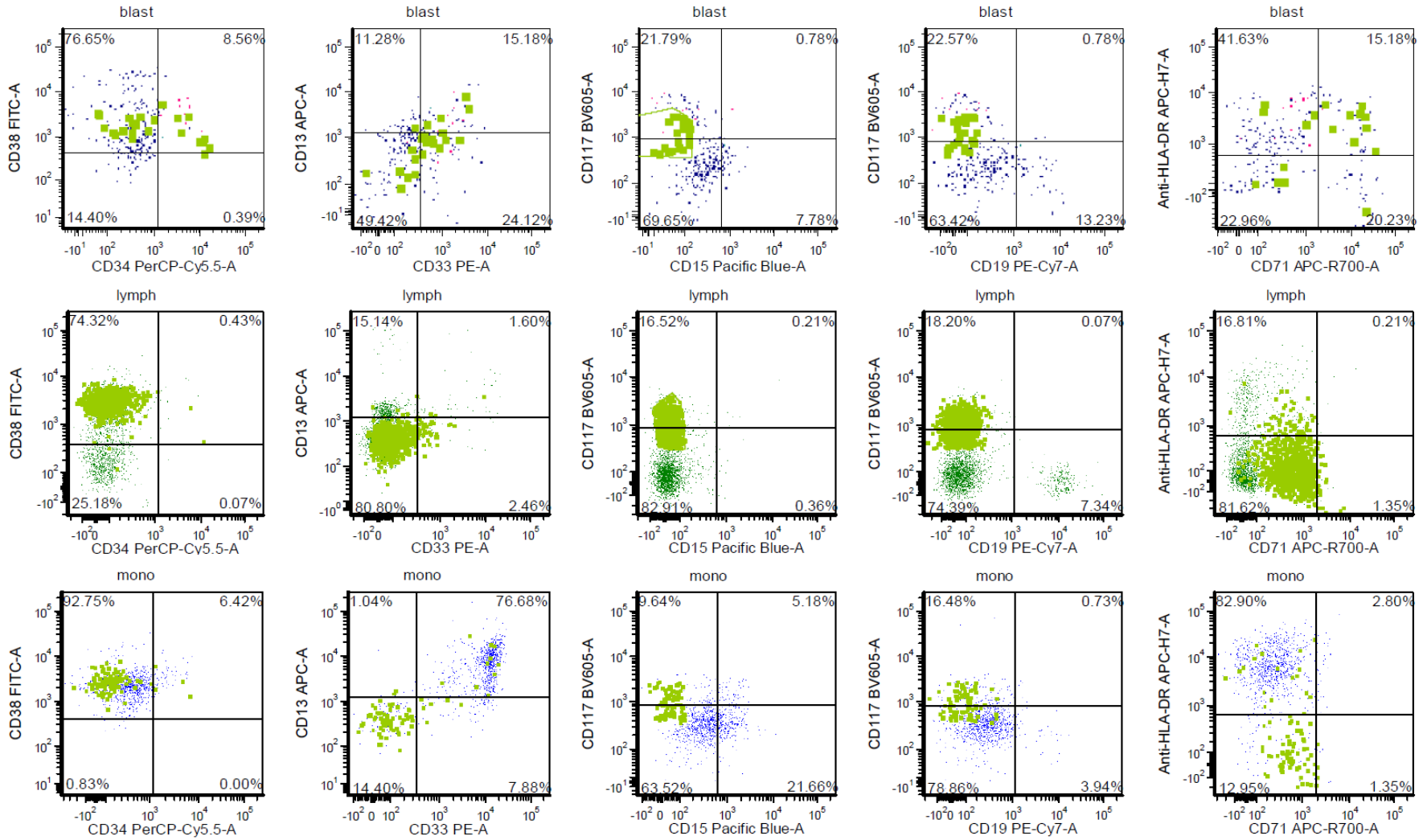
09-JUL-2024 10:41:19

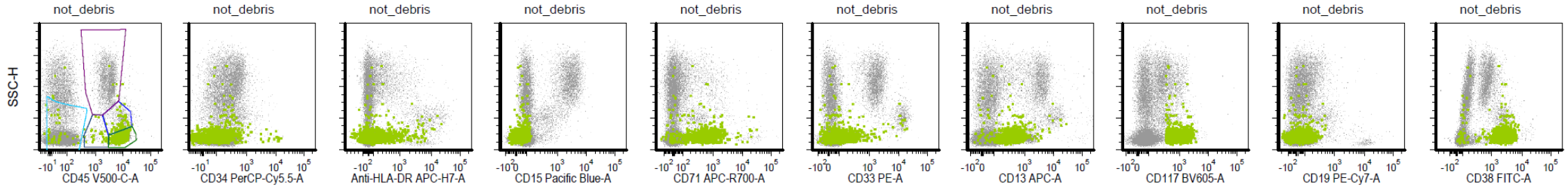
AML1

Gate color	Gate	# of Events	% of gated cells (from plot)	% of gated - parent (from plot)
n/a	No Gate	7999	100.0	26.5
	blast	257	3.2	0.9
	117+34+_AML1	14	0.2	0.0
	19+34+_AML1	1	0.0	0.0
	Other_AML1	875	10.9	2.9
	lymph	2808	35.1	9.3
	mono	965	12.1	3.2

%of gated cells = % of CD45+
% of gated-parent = %of not_debris







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SHC BD Lyric B

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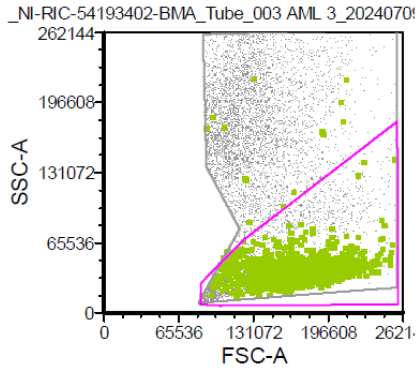
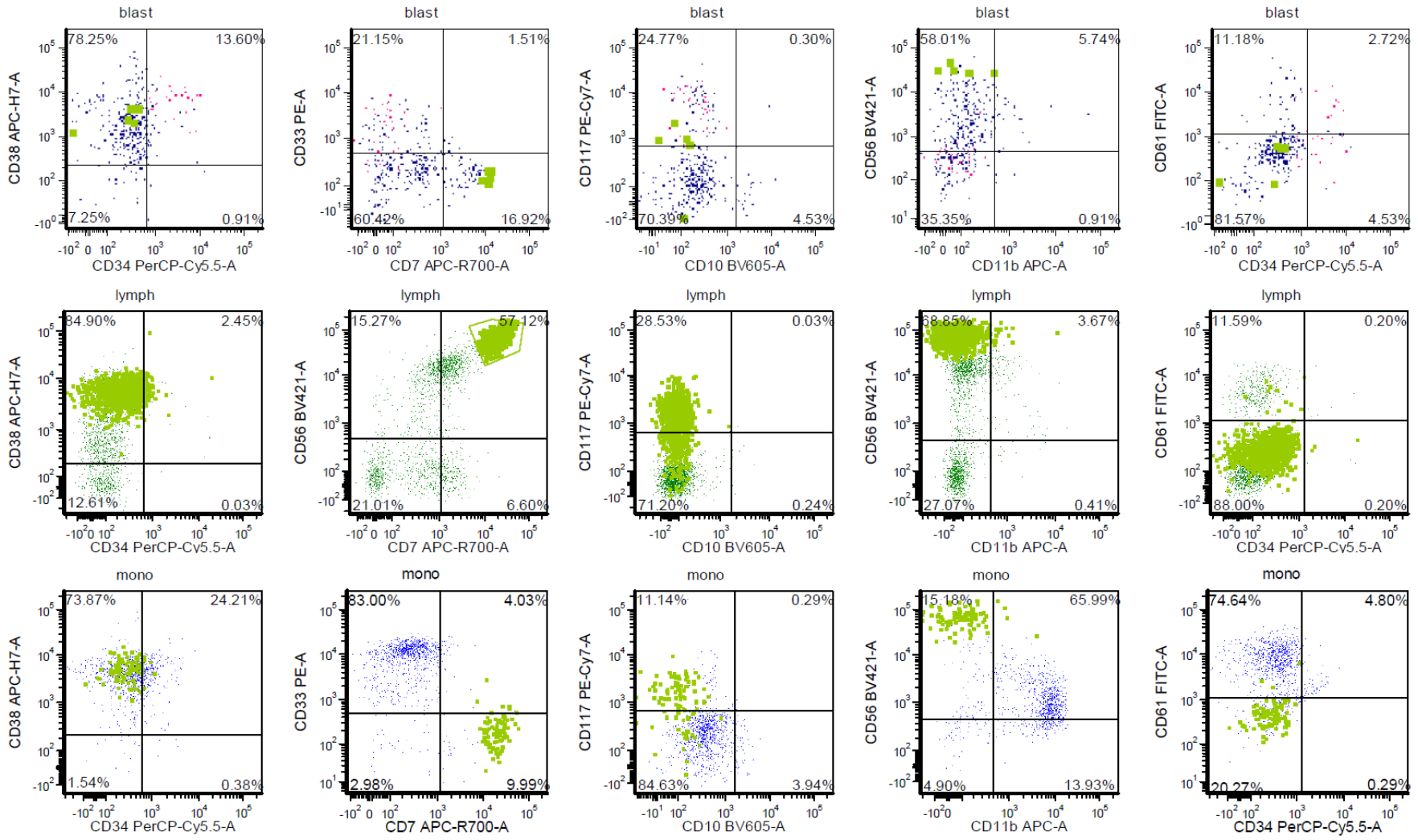
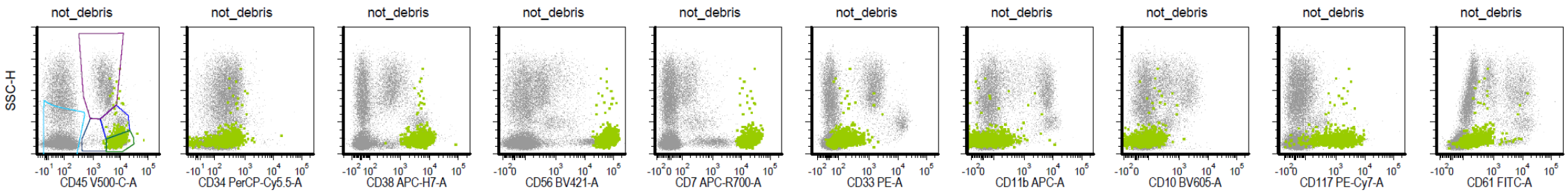
AML3

Gate color	Gate	# of Events	% of gated cells (from plot)	% of gated - parent (from plot)
n/a	No Gate	8206	100.0	26.6
	blast	331	4.0	1.1
	117+34+_AML3	27	0.3	0.1
	10+34+_AML3	0	0.0	0.0
	Other_AML3	1174	14.3	3.8
	lymph	2941	35.8	9.5
	mono	1041	12.7	3.4

%of gated cells = % of CD45+
% of gated-parent = %of not_debris







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SHC BD Lyric B

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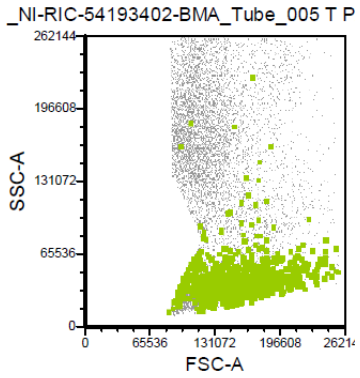
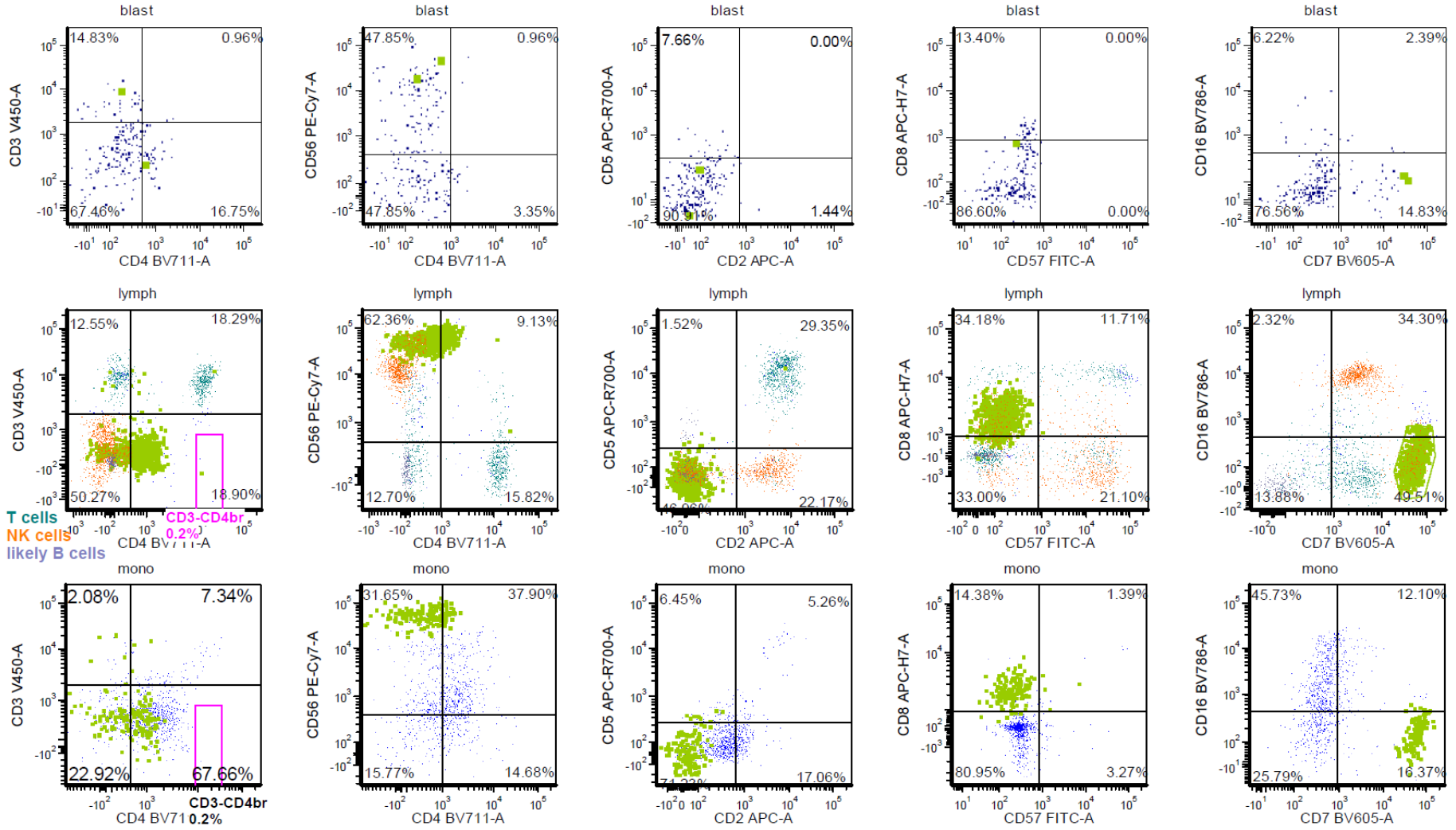
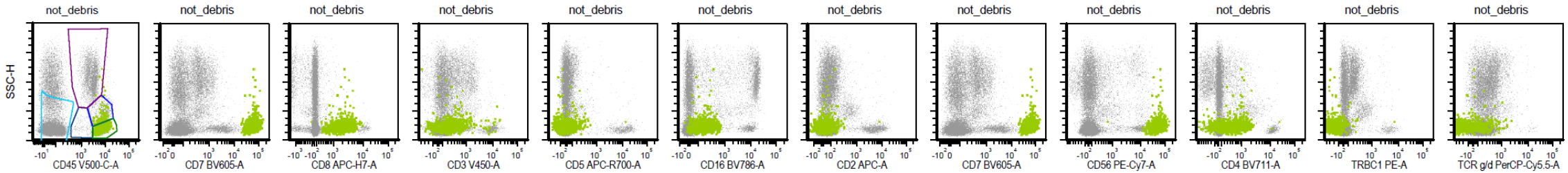
T cell

Gate color	Gate	# of Events	% of gated cells (from plot)	% of gated - parent (from plot)
n/a	No Gate	8146	100.0	28.3
	blast	209	2.6	0.7
	Other_T	955	11.7	3.3
	lymph	2630	32.3	9.1
	mono	1008	12.4	3.5

%of gated cells = % of CD45+
% of gated-parent = %of not_debris







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SHC BD Lyric B

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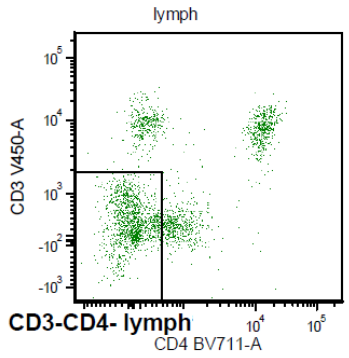
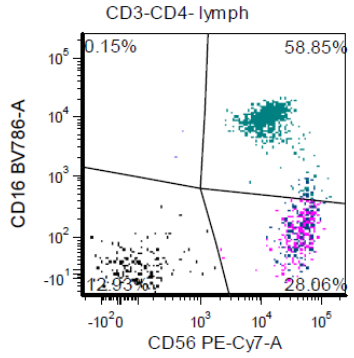
NK cell analysis

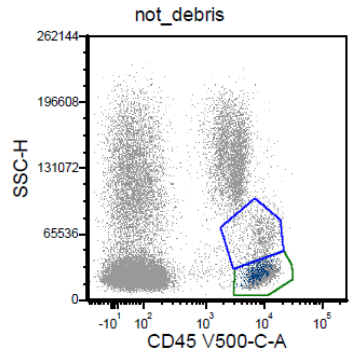
Gate color	Gate	# of Events	% of gated cells (from plot)	% of all cells	% of gated - parent (from plot)
n/a	No Gate	2630	100.0	2.6	32.3
	CD3-CD56/CD16+	1151	43.8	1.2	14.1
	CD3-CD56-CD16+	2	0.1	0.0	0.0
	CD3-CD56+CD16+	778	29.6	0.8	9.6
	CD3-CD56+CD16-	371	14.1	0.4	4.6

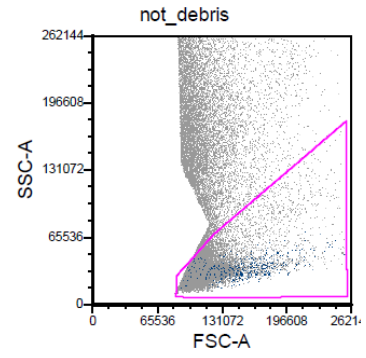
%of gate = % of lymph
%of gated-parent=% of CD45+

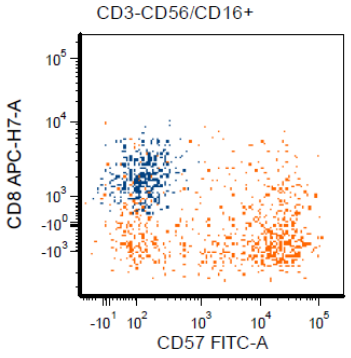
Abnl_NK	**4.6% of CD45+ (374 events)**

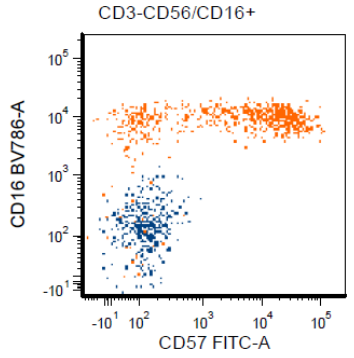


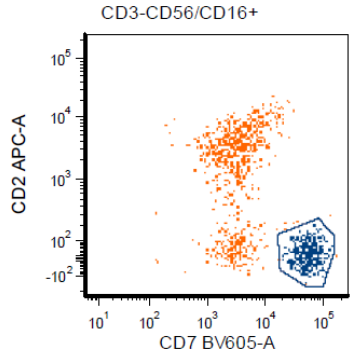


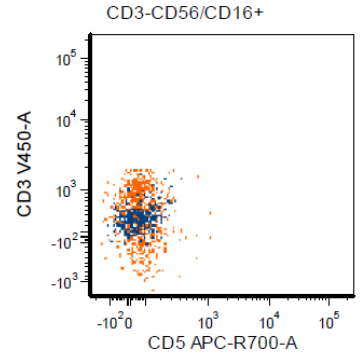












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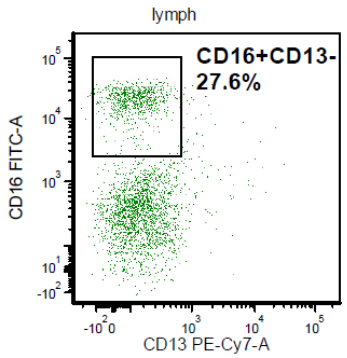

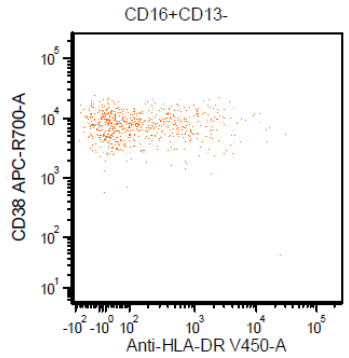

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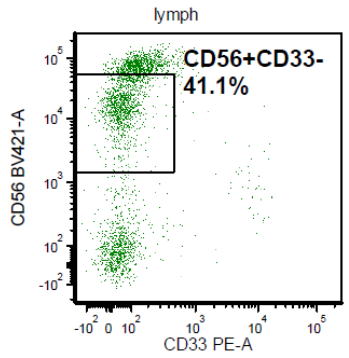
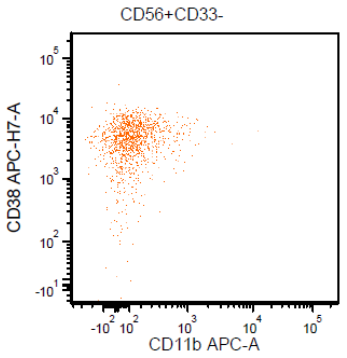
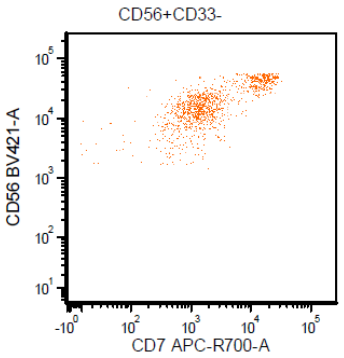






- **Bone Marrow Aspirate, Flow Cytometry Immunophenotyping**
- **Abnormal NK cell population (14% of CD45+ events) expressing CD56 (bright), CD8 (moderate), CD7 (bright), CD38 (100%), CD117 (dim), CD127 (dim), CD45; negative for CD16, CD2, CD5, surface CD3, CD57, CD11b, HLA-DR, TCRgd, TCRab, TRBC1, CD25, and CD34**
- **Polytypic B cells without immunophenotypic abnormality**
- **T lymphocytes without immunophenotypic abnormality**
- **No increased CD34+ blasts**

- 66m, with history of HLD presents with fever and headache found to have elevatred LFTs with concern for HLH vs progressive liver disease.

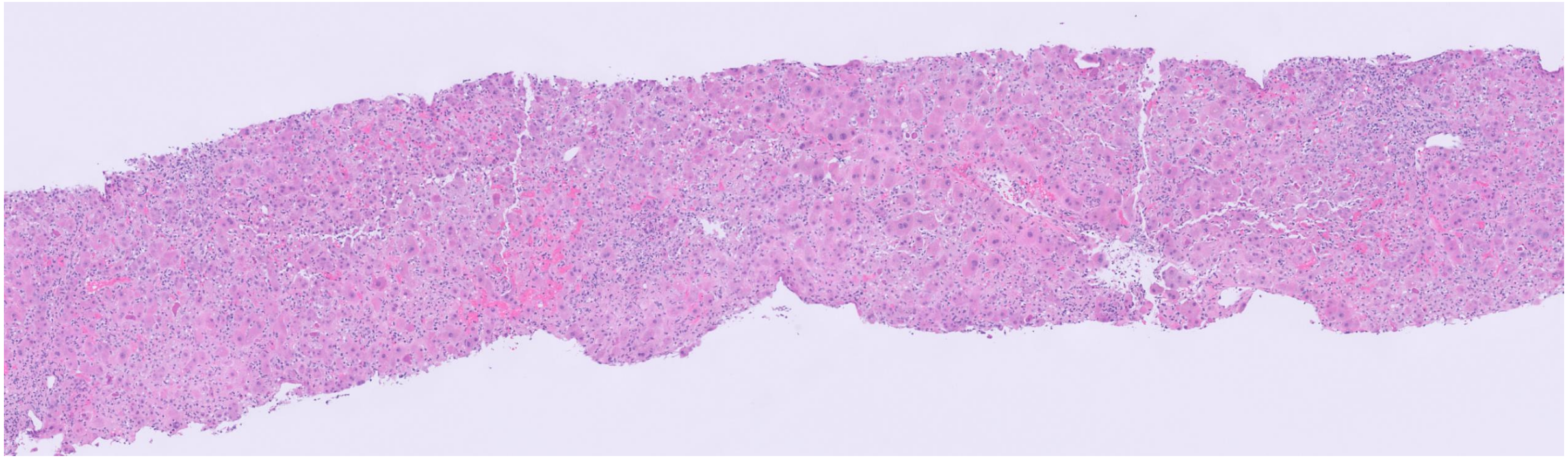
- CT (7/4/2024):
- 1. Stranding within the porta hepatis surrounding the cystic duct, common hepatic duct, and extending inferior around the second portion of the duodenum. Mild hyperemia of the decompressed gallbladder and cystic duct. Findings could reflect cholangitis or possibly duodenitis, with groove pancreatitis considered less likely.
- 2. No biliary obstruction or radiopaque cholelithiasis. No gallbladder dilation to suggest cholecystitis.
- 3. Mild prostatomegaly with trace bilateral hydronephrosis.

- MRI (7/5/2024):
- 1. **Imaging findings most consistent with hepatitis (infectious or inflammatory etiology)** with reactive changes of the biliary ducts and duodenum. Cholangitis is also possible, however, considered less likely given the pattern of hepatic parenchymal changes.
- 2. No evidence of malignancy in the abdomen.
- 3. Hyperenhancing pelvic bones and vertebral bodies, likely reactive marrow related to hematologic abnormalities.

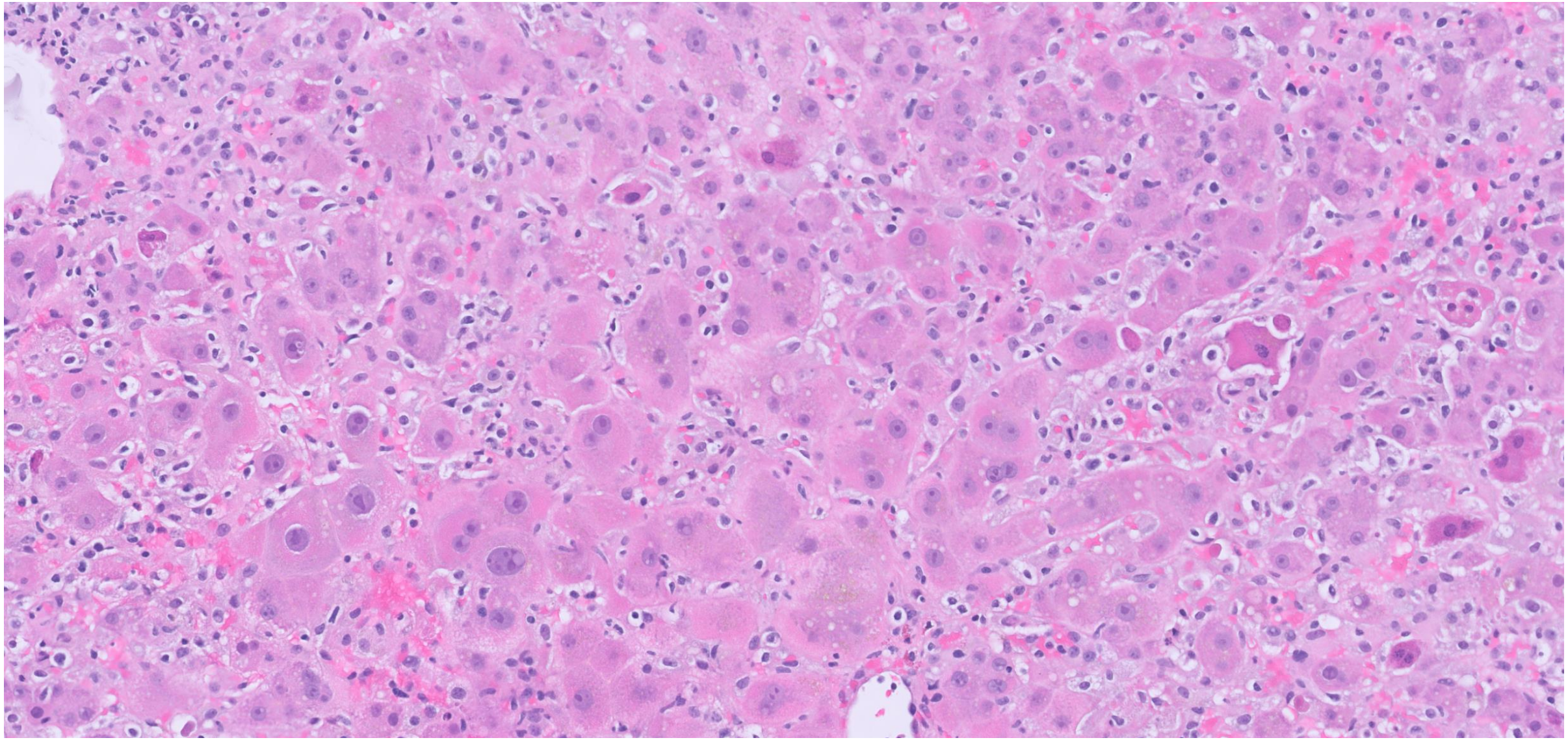
- Infectious labs all negative except for EBV IgG and CMV IgG.

- Interpretation:
- Abnormal clonal karyotype, consistent with a neoplastic process
- Comments:
- These findings are clonal in nature and, as such, consistent with a neoplastic process. The complex nature and poor morphology of this clone renders more specific diagnostic correlation impossible.
- Chromosome Analysis:
- Bone marrow aspirate was cultured, and chromosomes were analyzed using the GTW banding method. Twenty-one metaphase cells were analyzed, eight of which were grossly abnormal and characterized by a near haploid karytotype of 26 to 29 chromosomes with numerous aneuploidies, structural anomalies and marker chromosomes. Due to the considerable heterogeneity of these cells, they have been described above as an incomplete composite karyotype.
- ISCN Description:
- **26~29,inc[cp8]/46,XY[13]**

Liver, native, biopsy



Liver, native, biopsy



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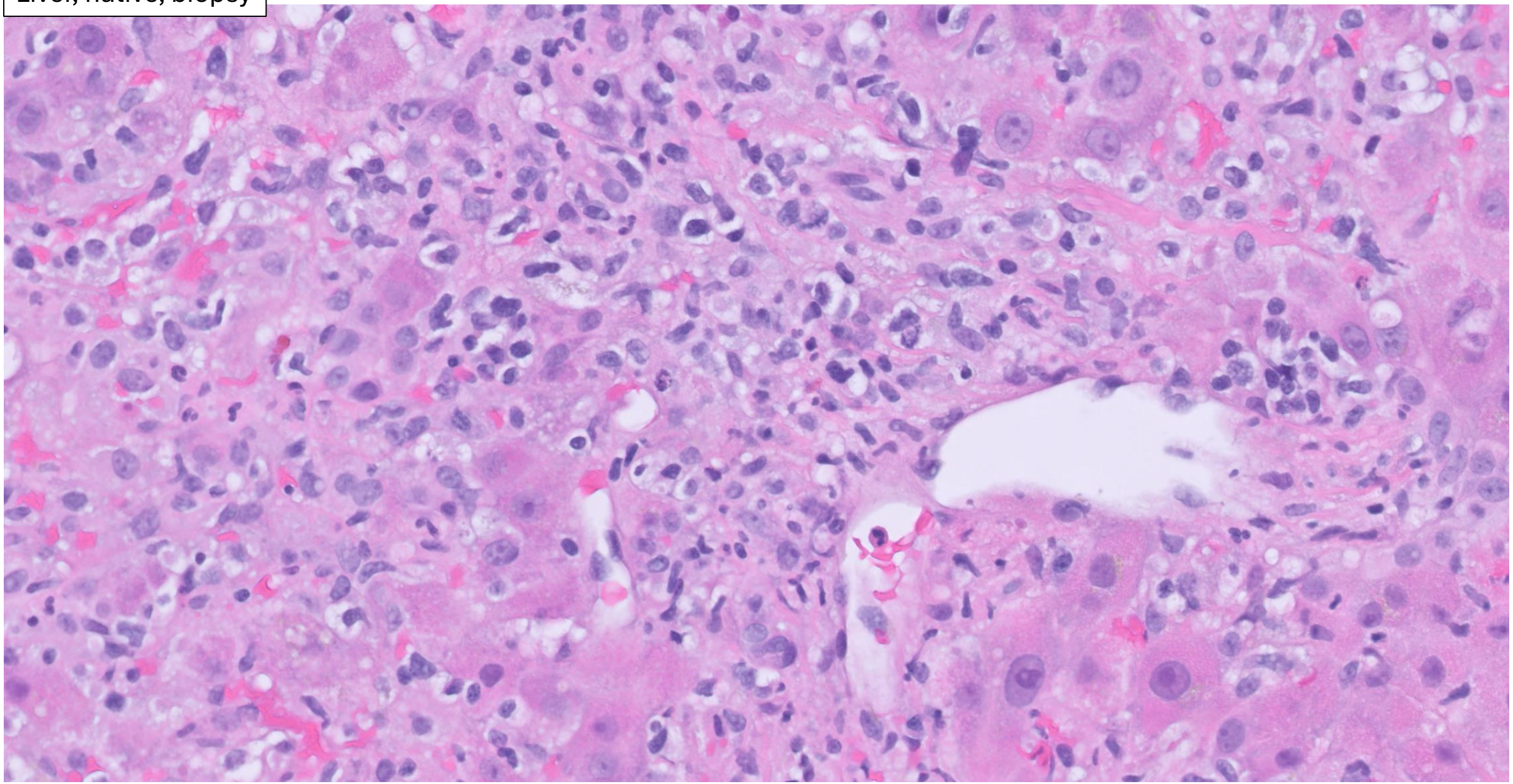

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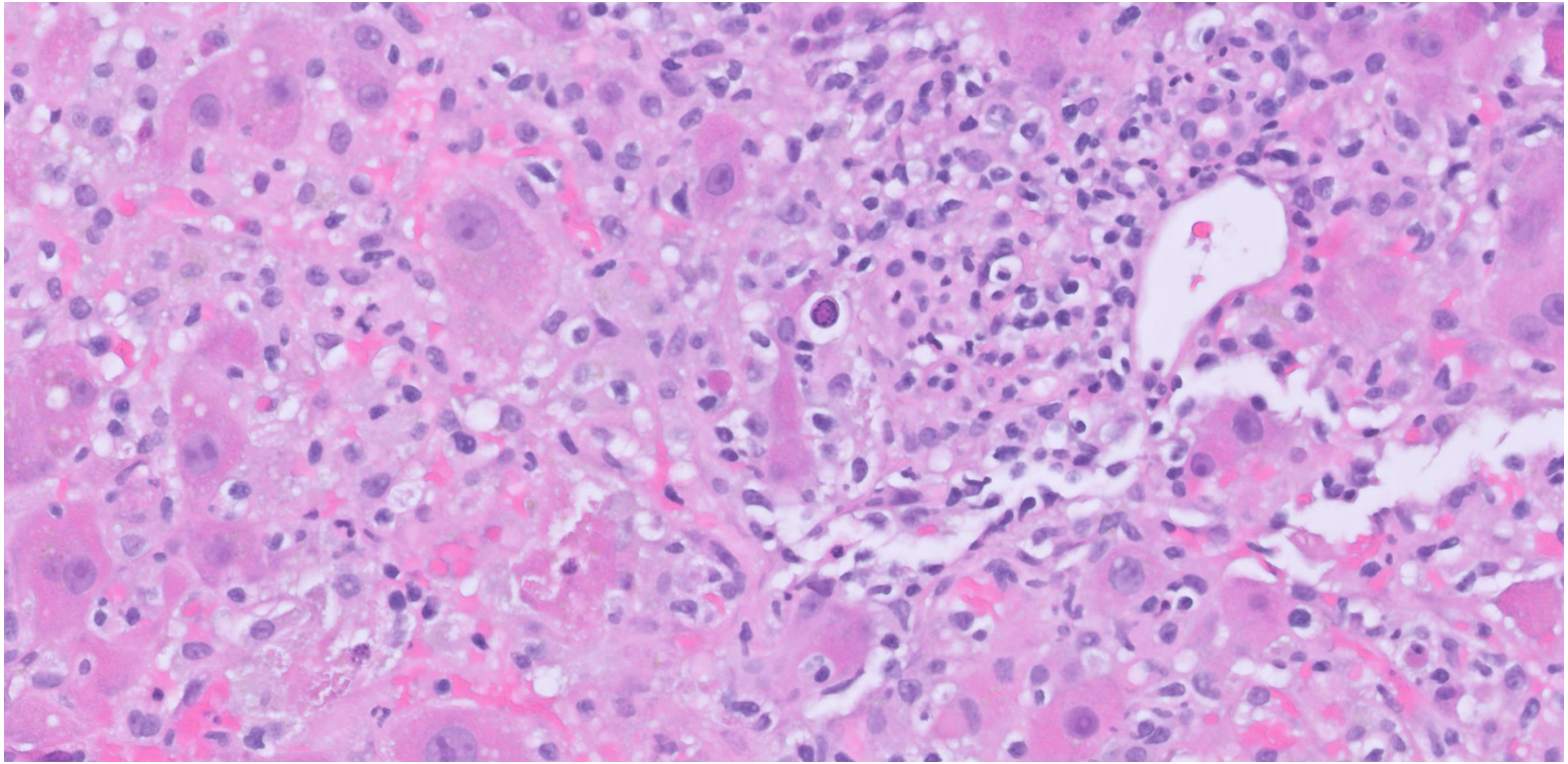
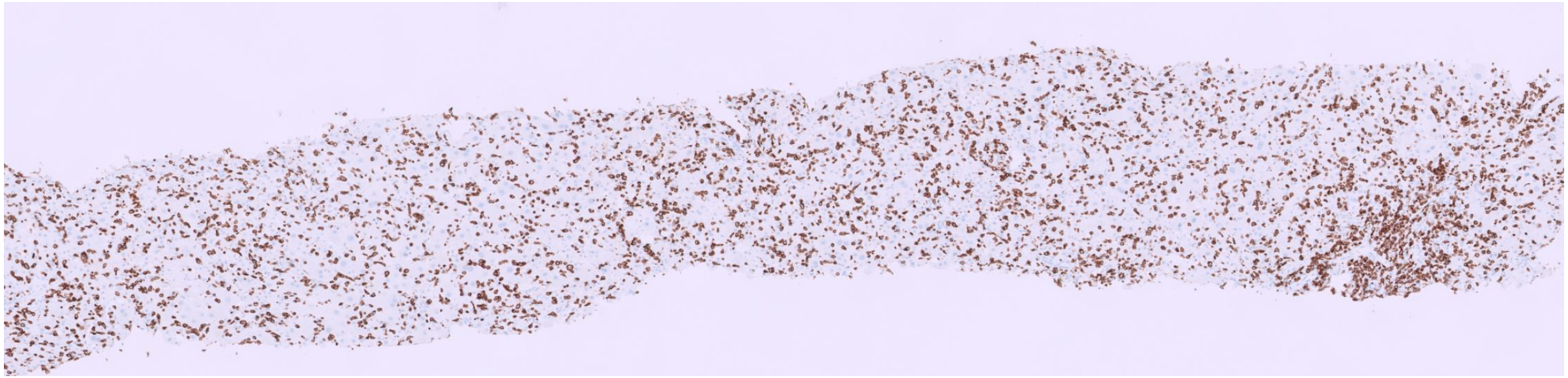


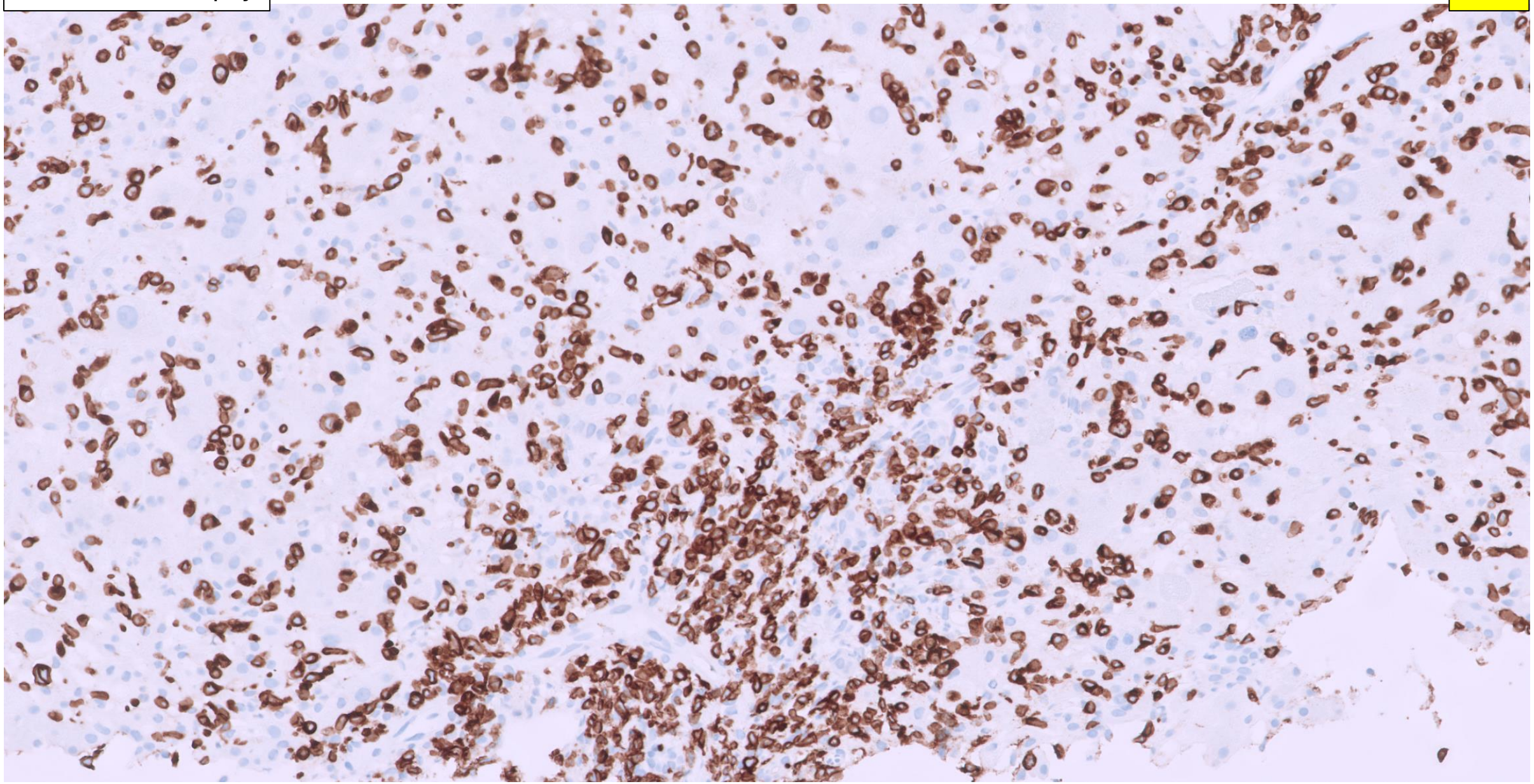
Liver, native, biopsy

CD3



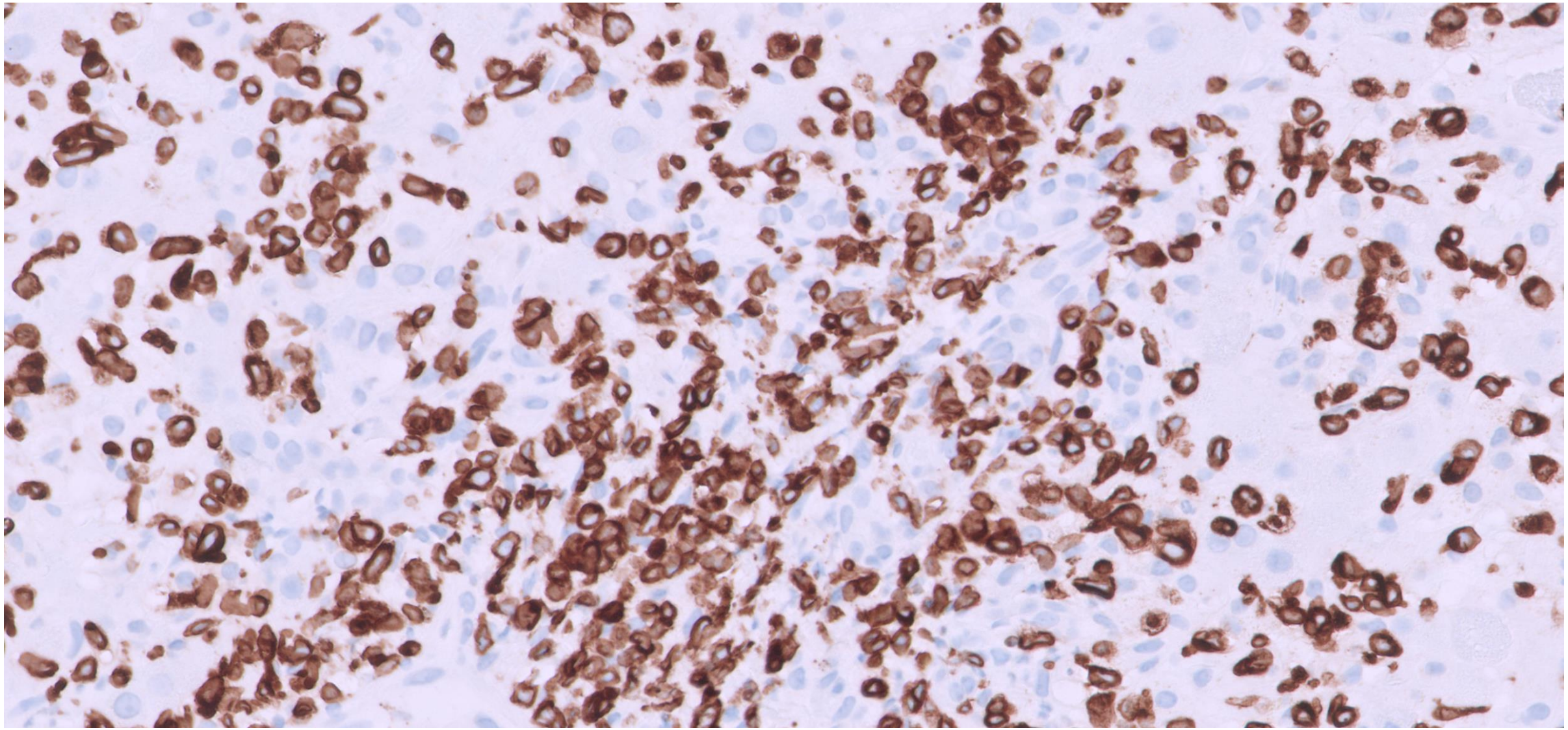
Liver, native, biopsy

CD3



Liver, native, biopsy

CD3



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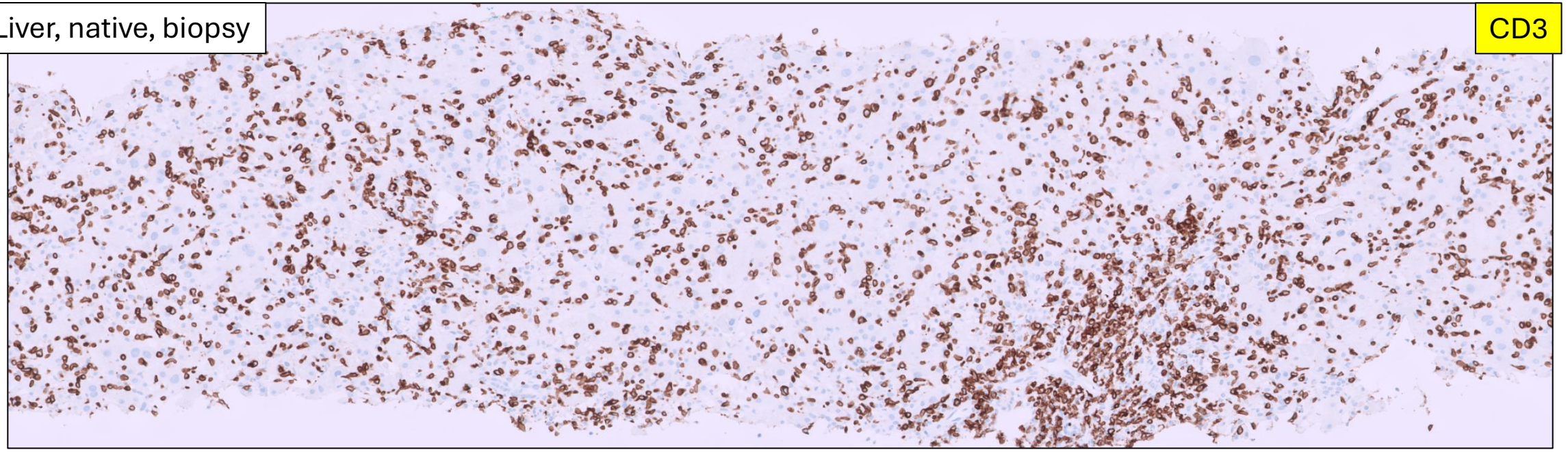
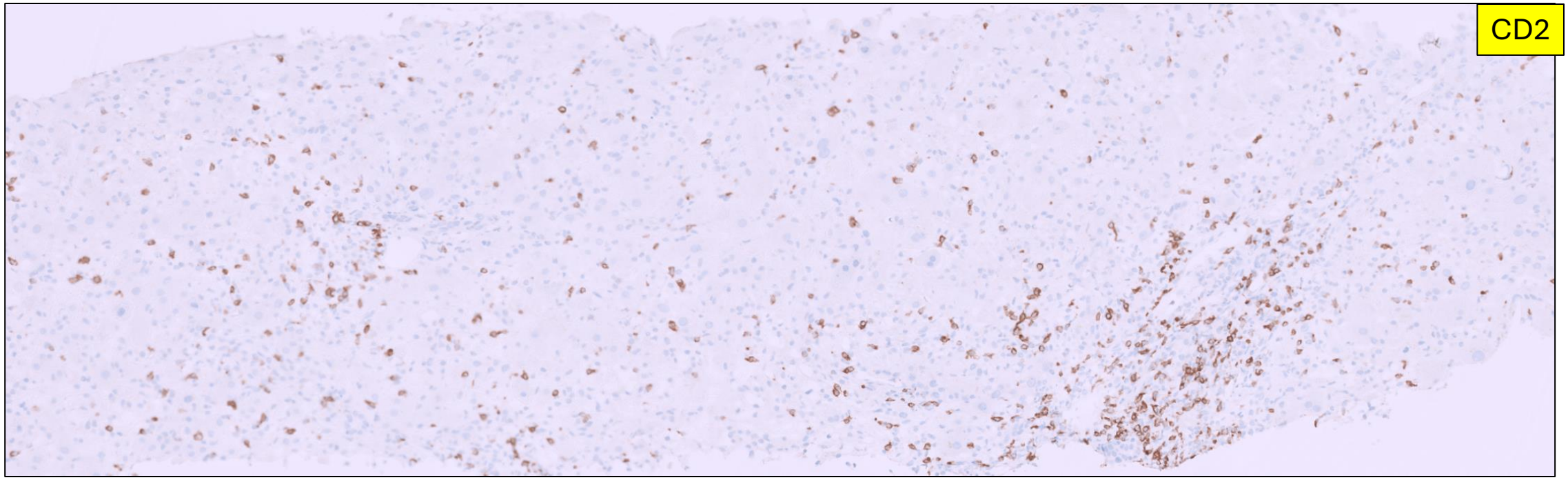
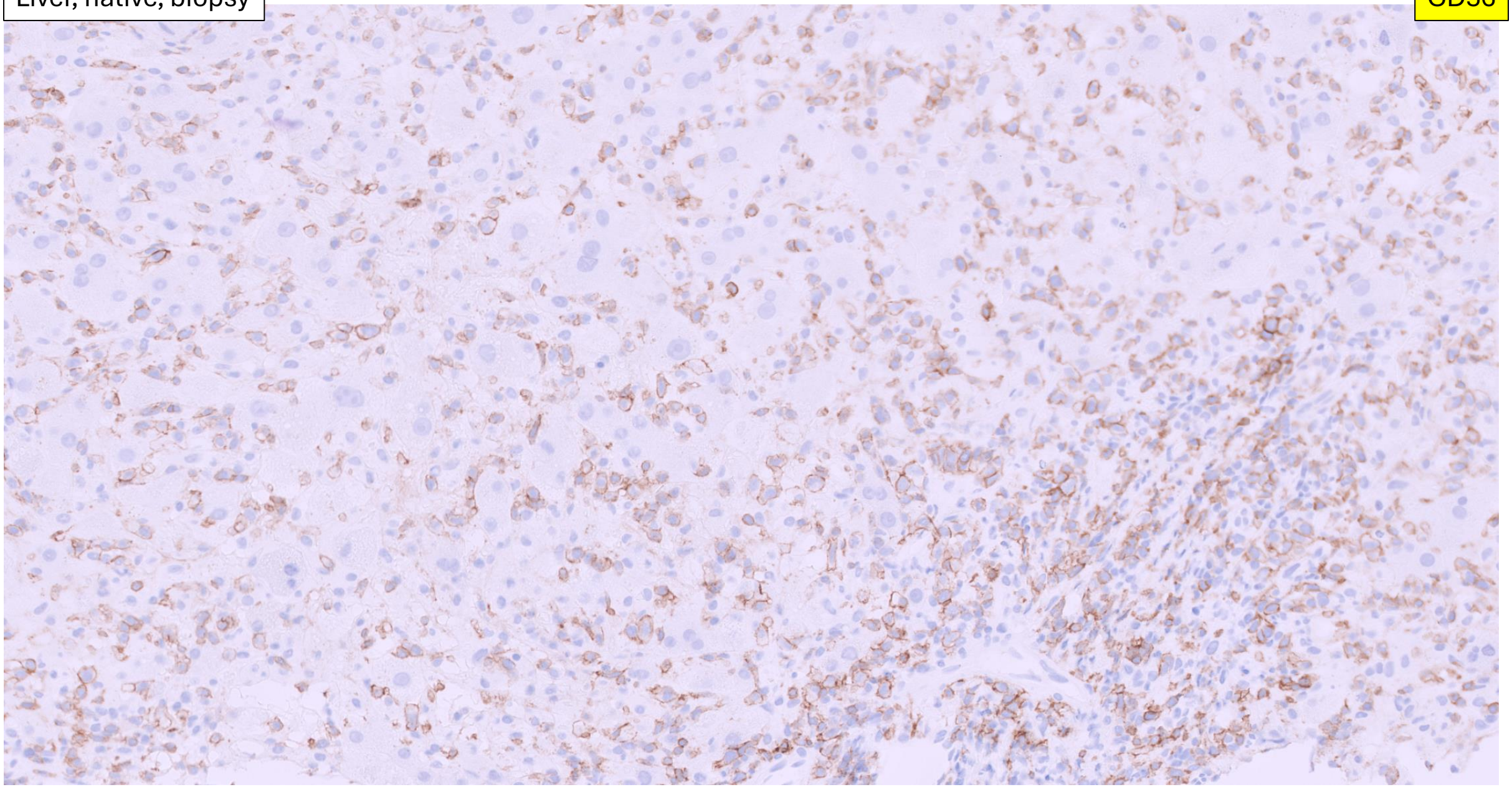


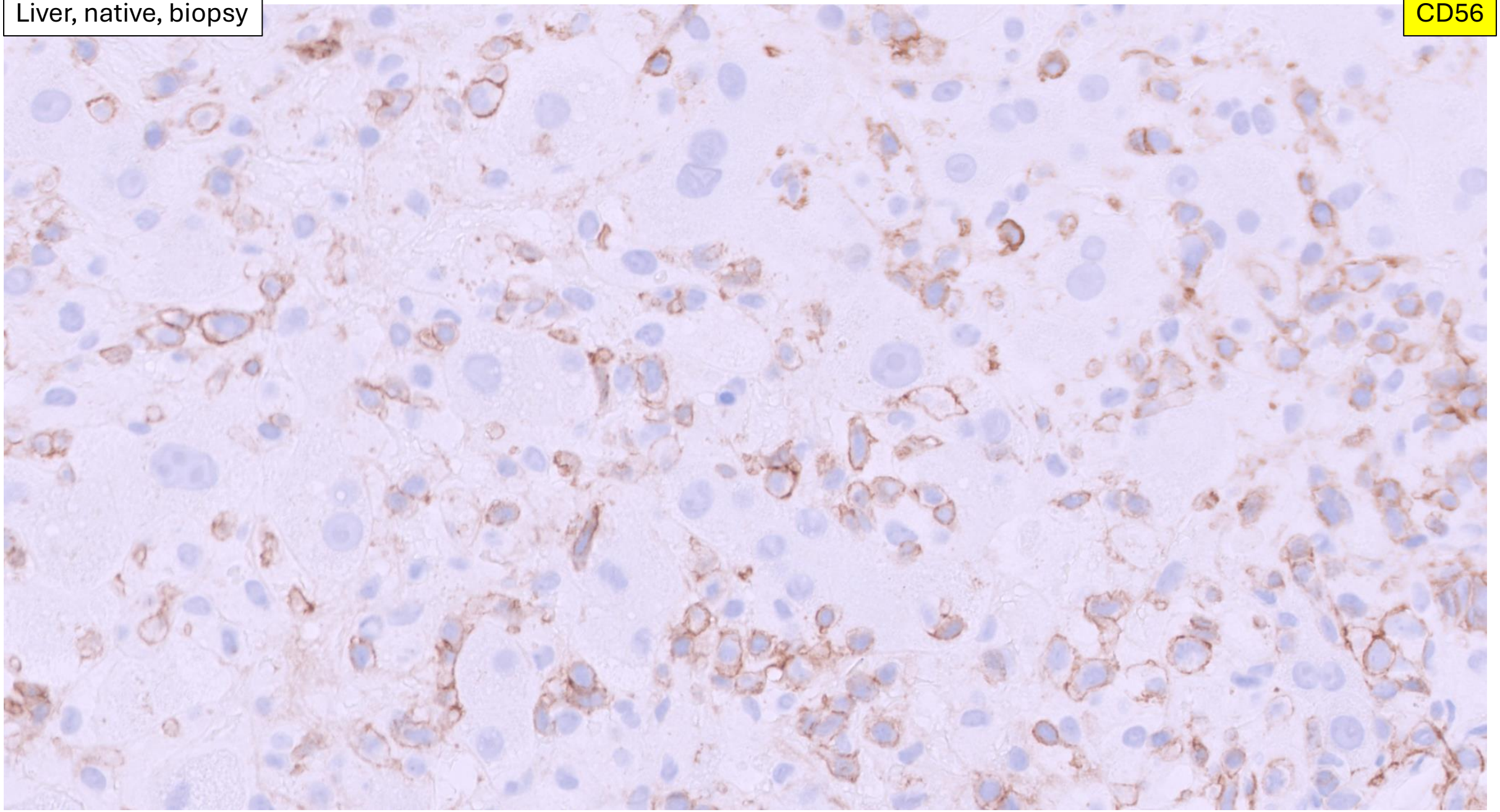


Liver, native, biopsy

CD56



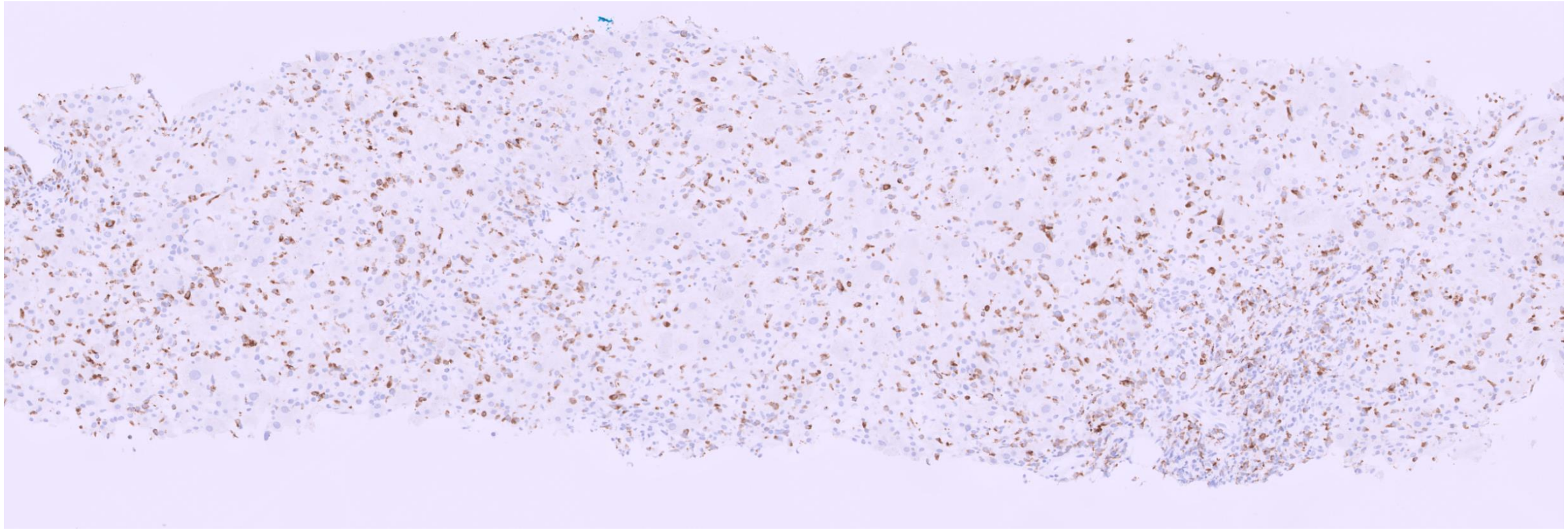
Liver, native, biopsy



CD56

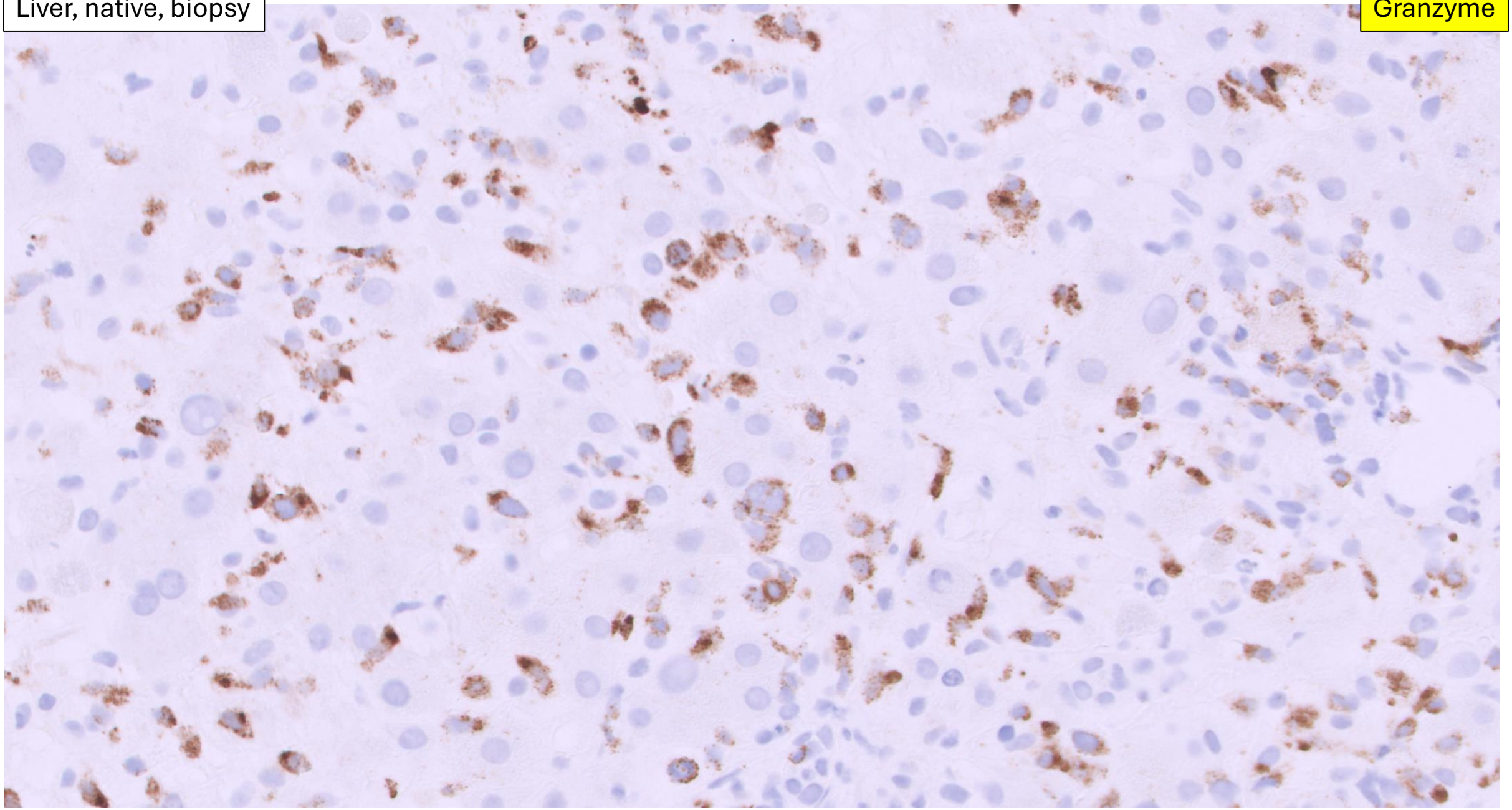
Liver, native, biopsy

Granzyme

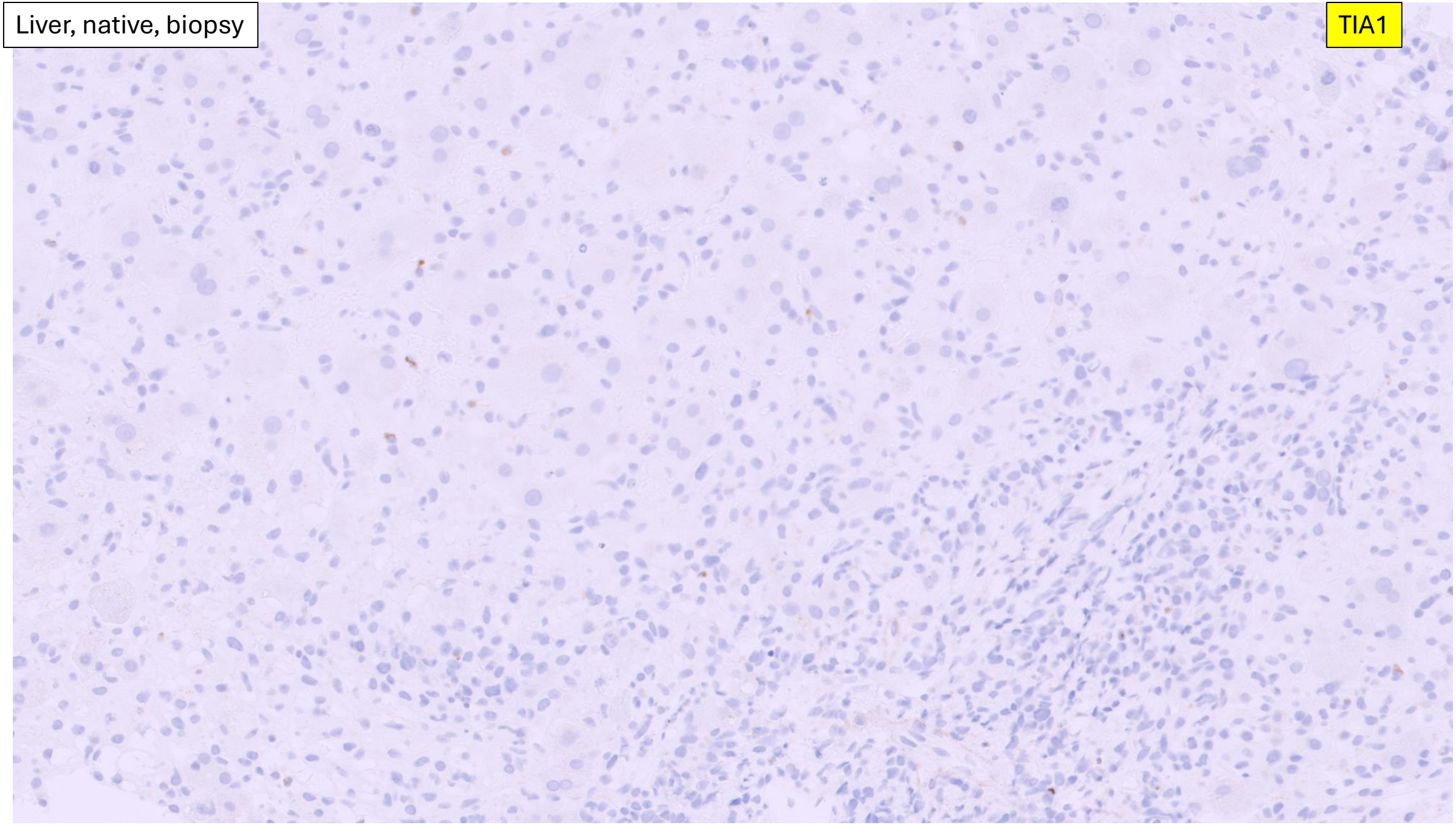


Liver, native, biopsy

Granzyme

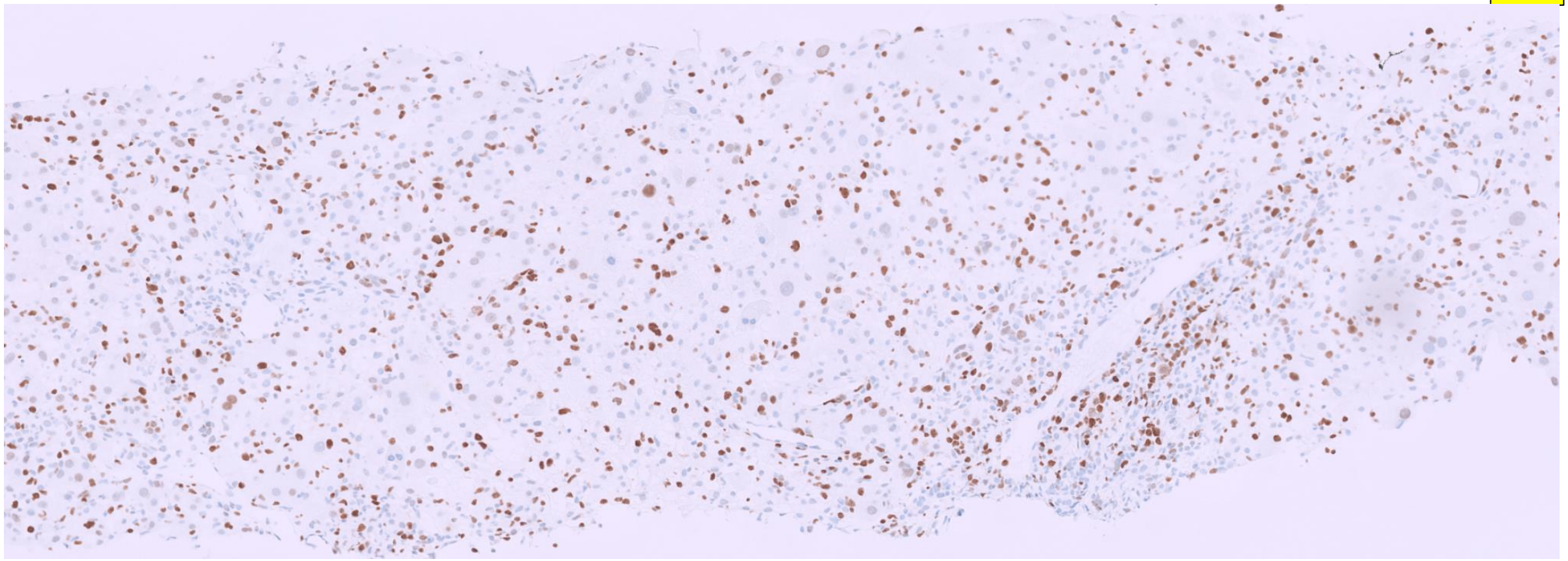


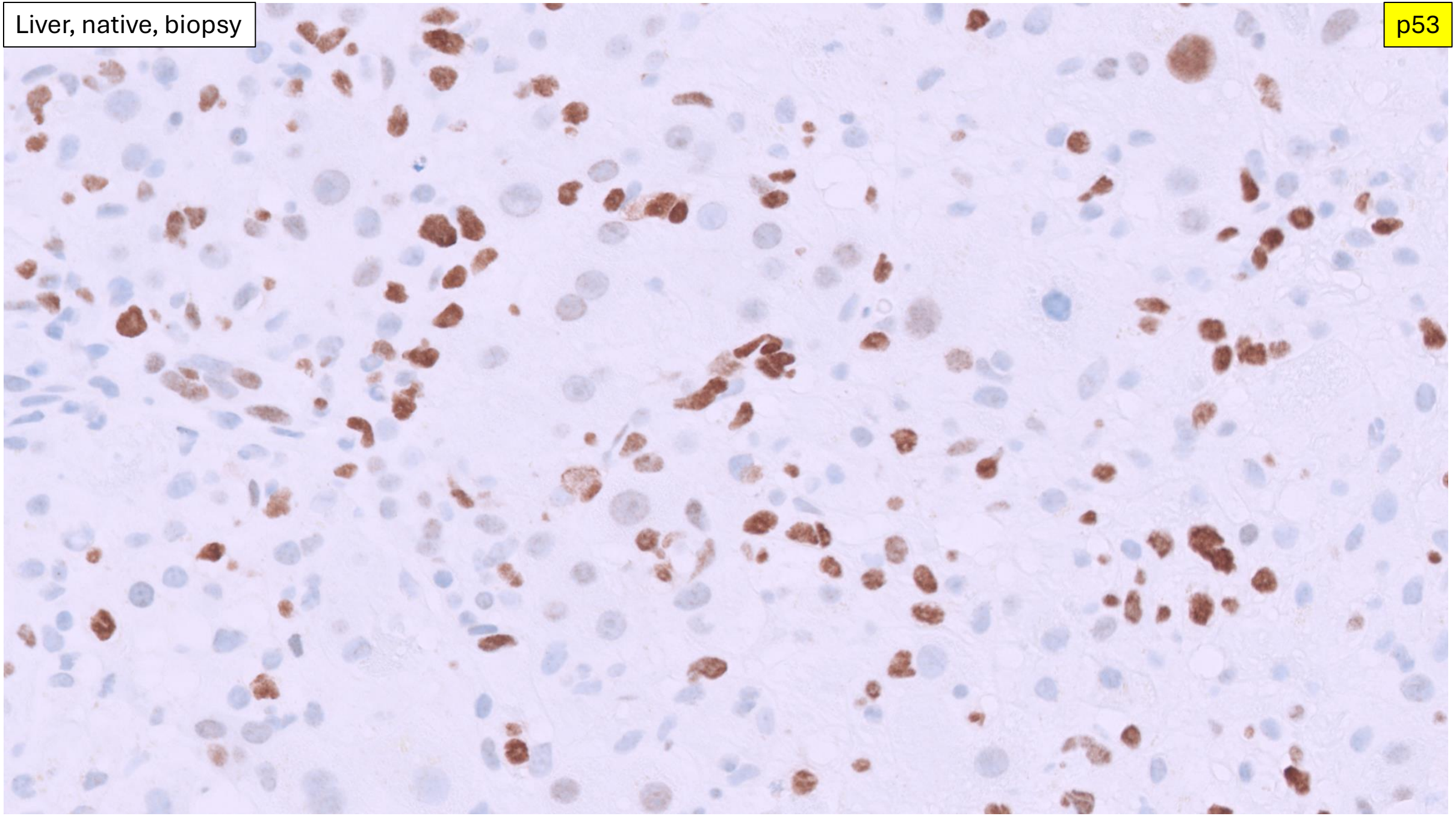
Liver, native, biopsy



Liver, native, biopsy

p53




Liver, native, biopsy
p53

- Liver, native, biopsy
  - Aggressive NK-cell leukemia, EBV-negative (see comment)
  - Severe active hepatitis with bridging necrosis (grade 4 of 4 activity, stage 0 of 4 fibrosis)

- Microscopic examination was performed. The native liver core needle biopsies contain adequate portal tracts for evaluation. The portal tracts show a mild to moderate mixed inflammatory infiltrate, consisting mostly of atypical lymphocytes with irregular nuclear contours. These atypical lymphocytes are also present within the liver sinuses. There is no significant bile duct injury. There are no granulomata, and minimal periportal bile ductular reaction. No cholestasis is seen. Areas of bridging necrosis are seen.
-

PET/CT

- Spleen - No FDG-avid lesion. 5 cm in vertical axis.
- Liver: No FDG-avid liver lesion.

- IMPRESSION:
-
- 1. Focal uptake in the left sella likely corresponding to a small pituitary lesion as seen on MRI 7/7/2024
- 2. Nonspecific mildly asymmetric uptake in left epididymal region. This can be further evaluated with ultrasound.
- 3. No hypermetabolic lymph nodes or evidence of high-grade lymphomatous involvement. No discrete hypermetabolic hepatic lesion.
- 4. Diffuse moderate bone marrow uptake, likely representing diffuse involvement given prior bone marrow biopsy although the degree of uptake is not specific. No focally hypermetabolic skeletal lesion
- 5. Mild subcutaneous stranding in lower torso.

Treatment history

Completed interventions:

- S/p daratumumab (7/24 – 1/25)
- S/p C1 Cytoxan 7/13/24
- S/p Jakafi 10mg BID (7/11-7/15; 10/14-11/25)
- Achieved CR s/p C3 ICE (12/24 – 1/25)
- Now s/p allo-HSCT (2/25)

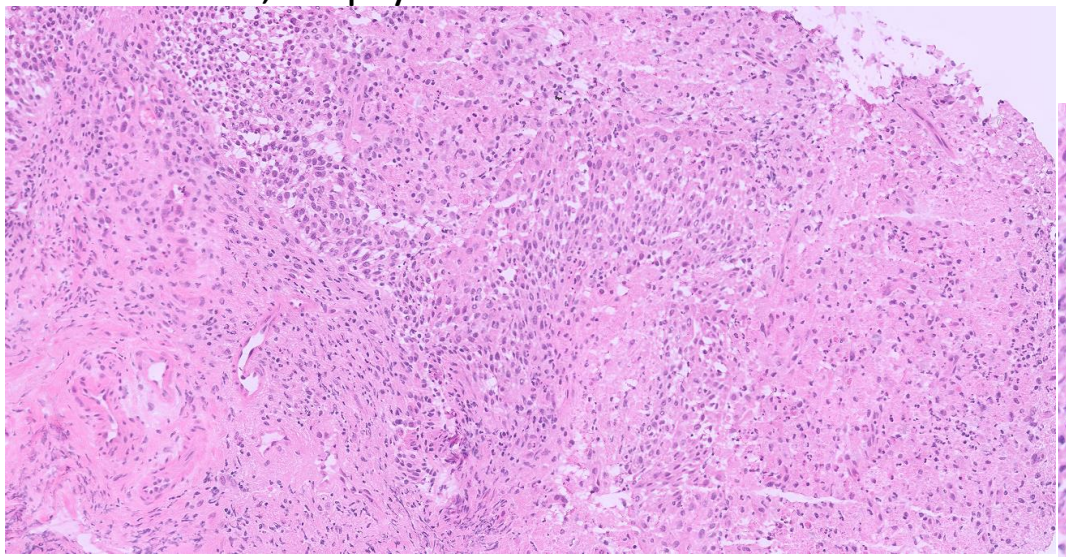
25-0402

Anne Cheng, Xiaoming Zhang; Stanford

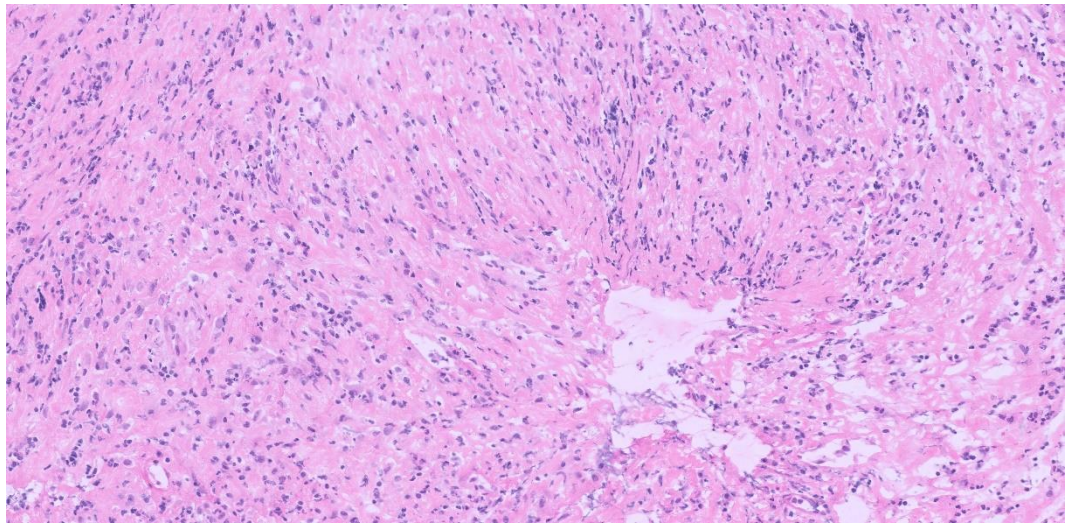
67-year-old woman with sepsis and hematuria. PET/CT findings showed a large complex cystic pelvic mass, concerning for primary malignancy. She has a prior path history of a vaginal mass diagnosed as smooth muscle neoplasm favored to be leiomyoma with degenerative changes vs STUMP, s/p excision. Op Note: 15 to 20 cm pelvic mass intimately involved with the bladder anteriorly, rectosigmoid posteriorly and encompassing the uterus and bilateral adnexa. Numerous small polypoid lesions on the bladder

Three specimens were sent for frozen:

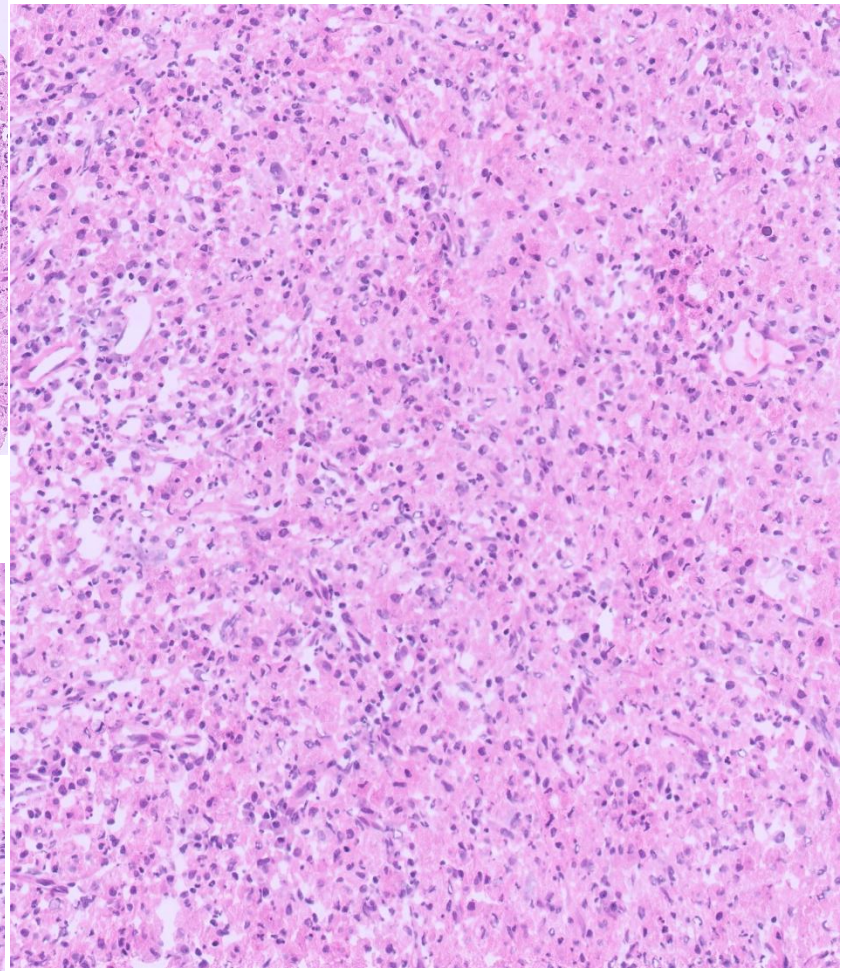
FSA. Bladder, biopsy



FSB. Pelvic mass, biopsy

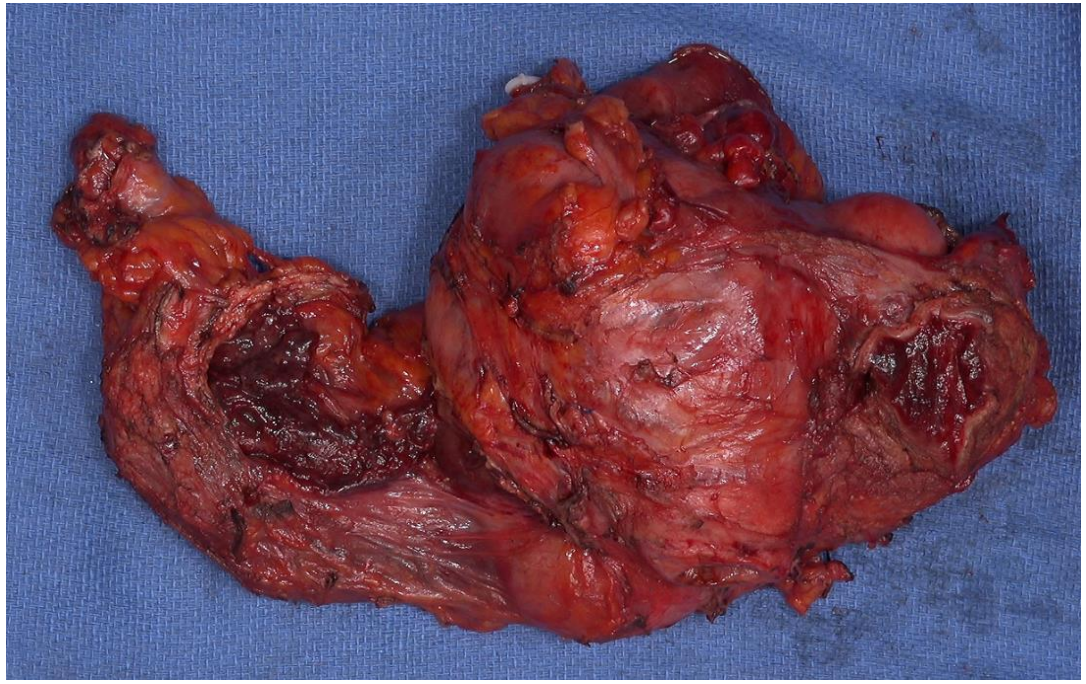


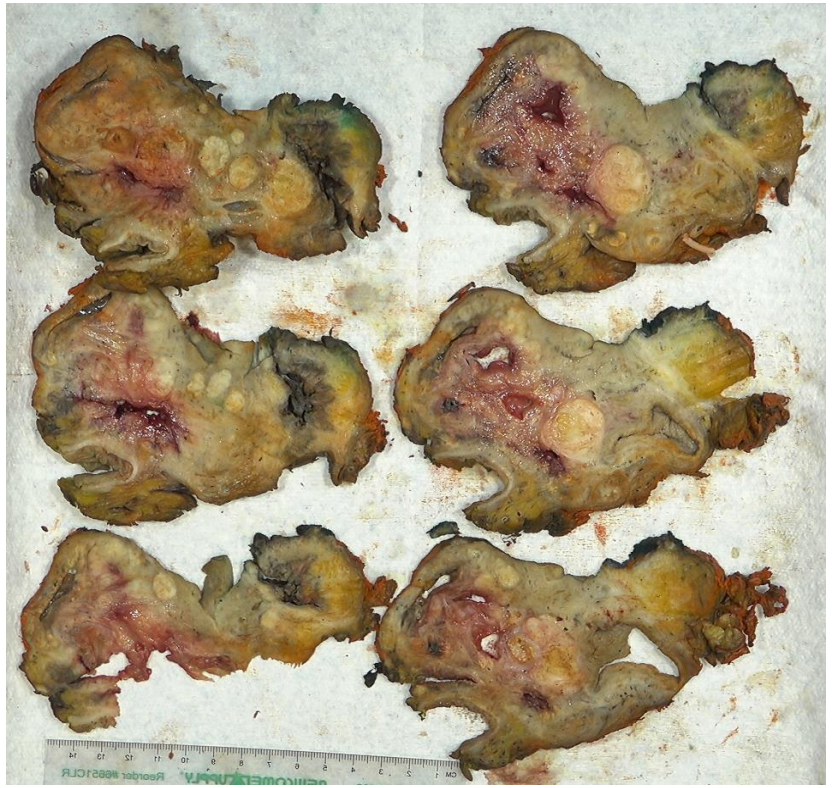
FSC. Bladder nodule, biopsy



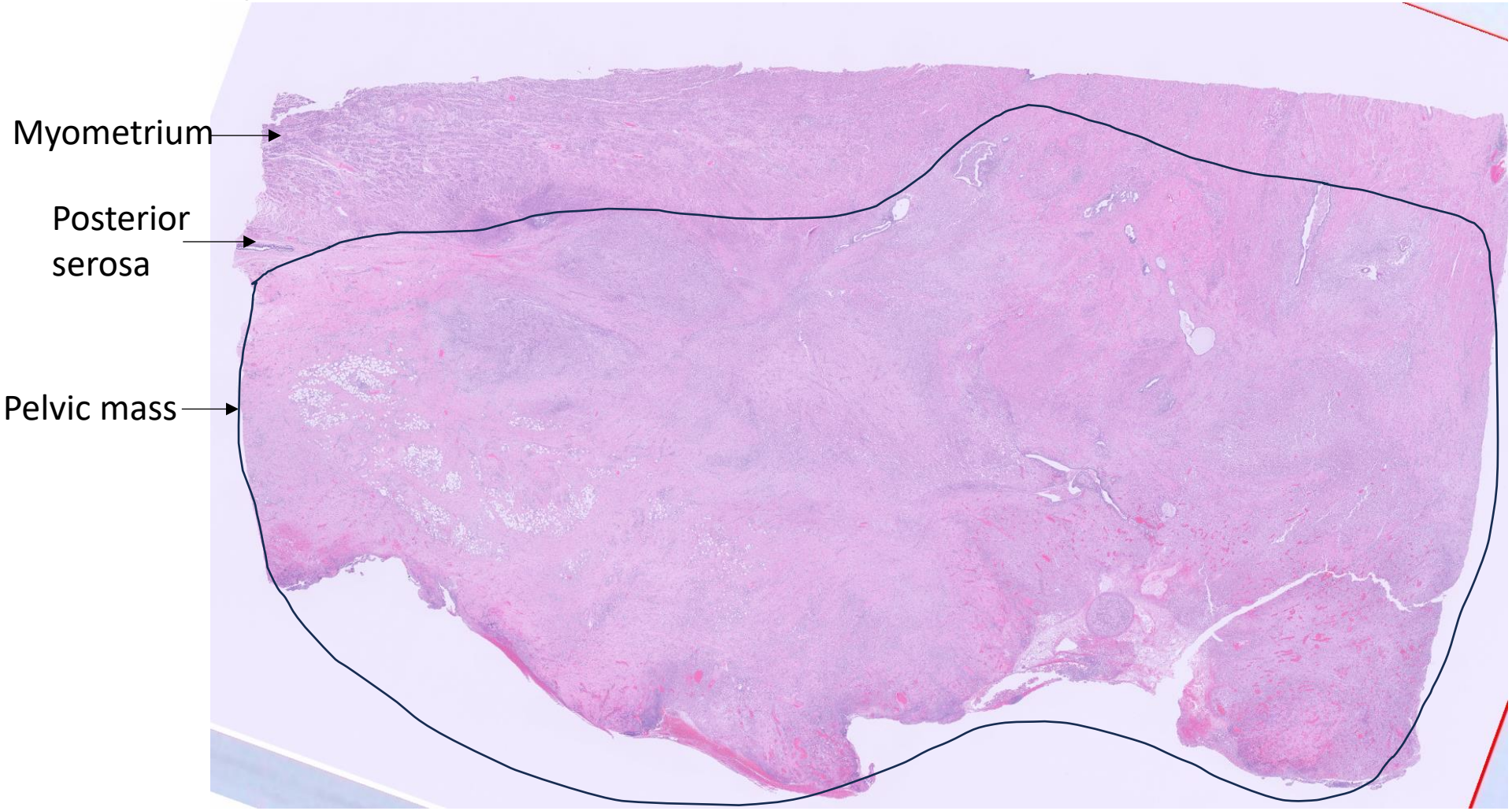
The specimen

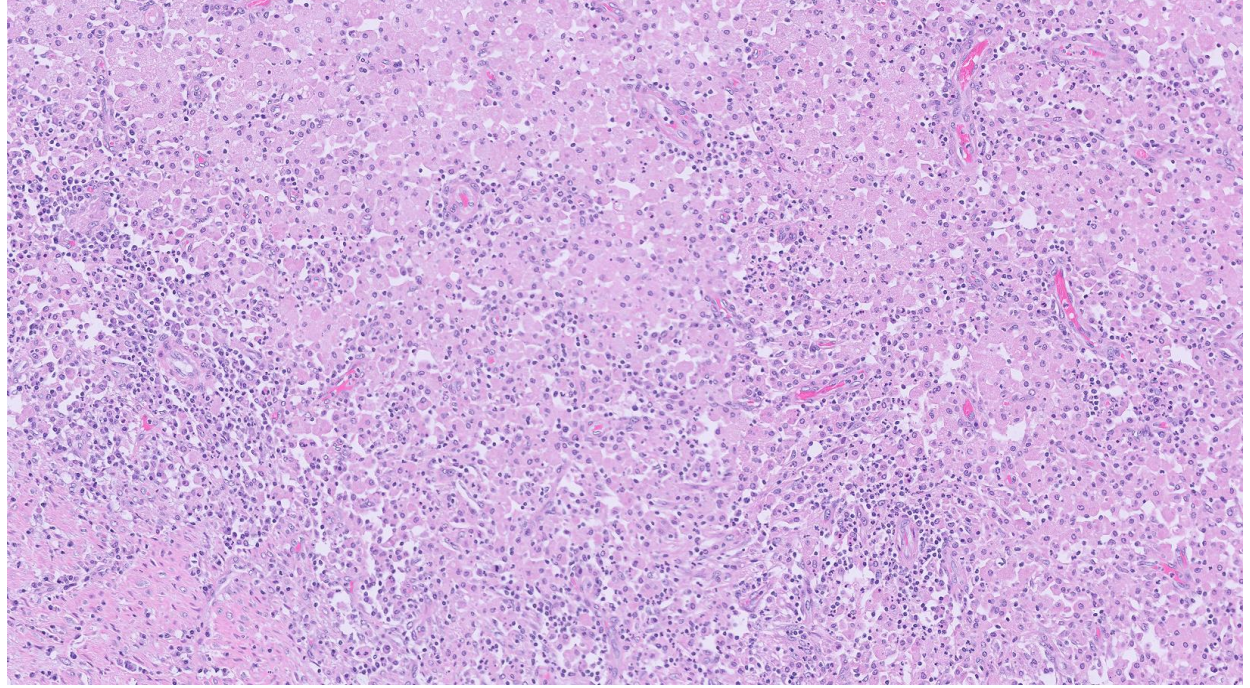
A pelvic exenteration was performed, resecting a portion of the left bladder, portion of vagina, uterus, cervix, fallopian tubes, ovaries, appendix, and rectosigmoid.

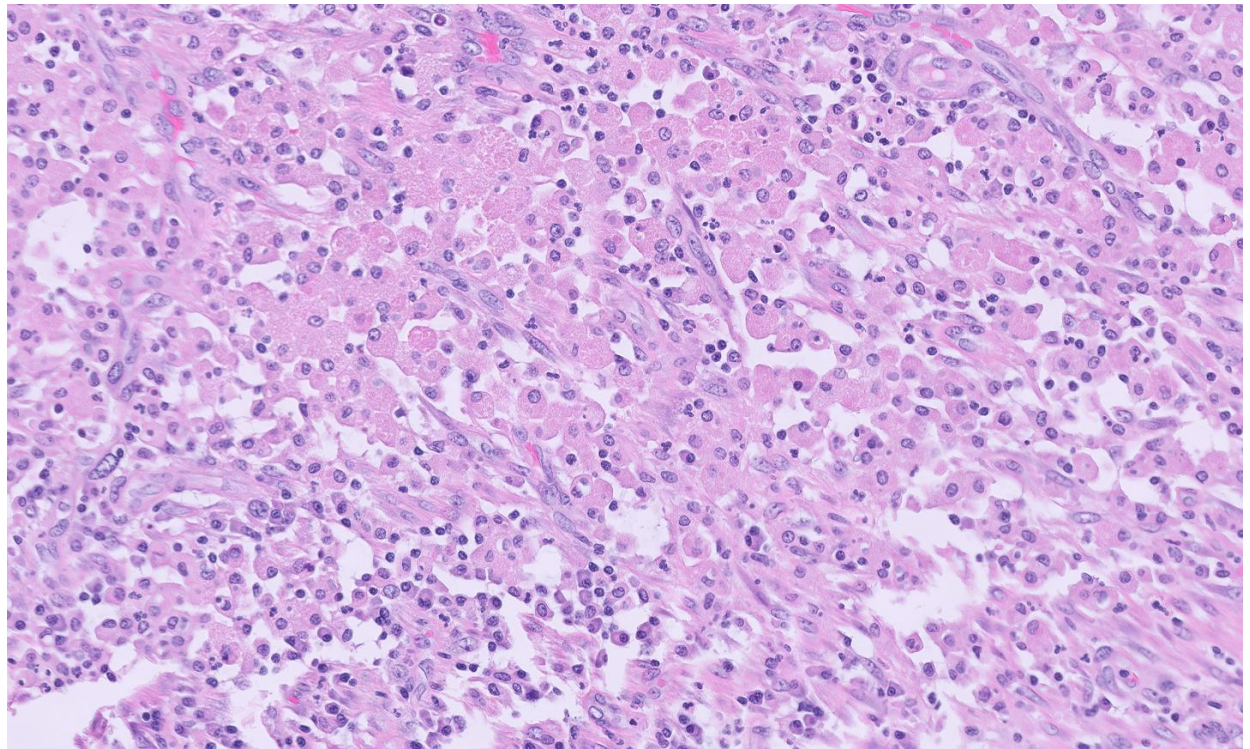


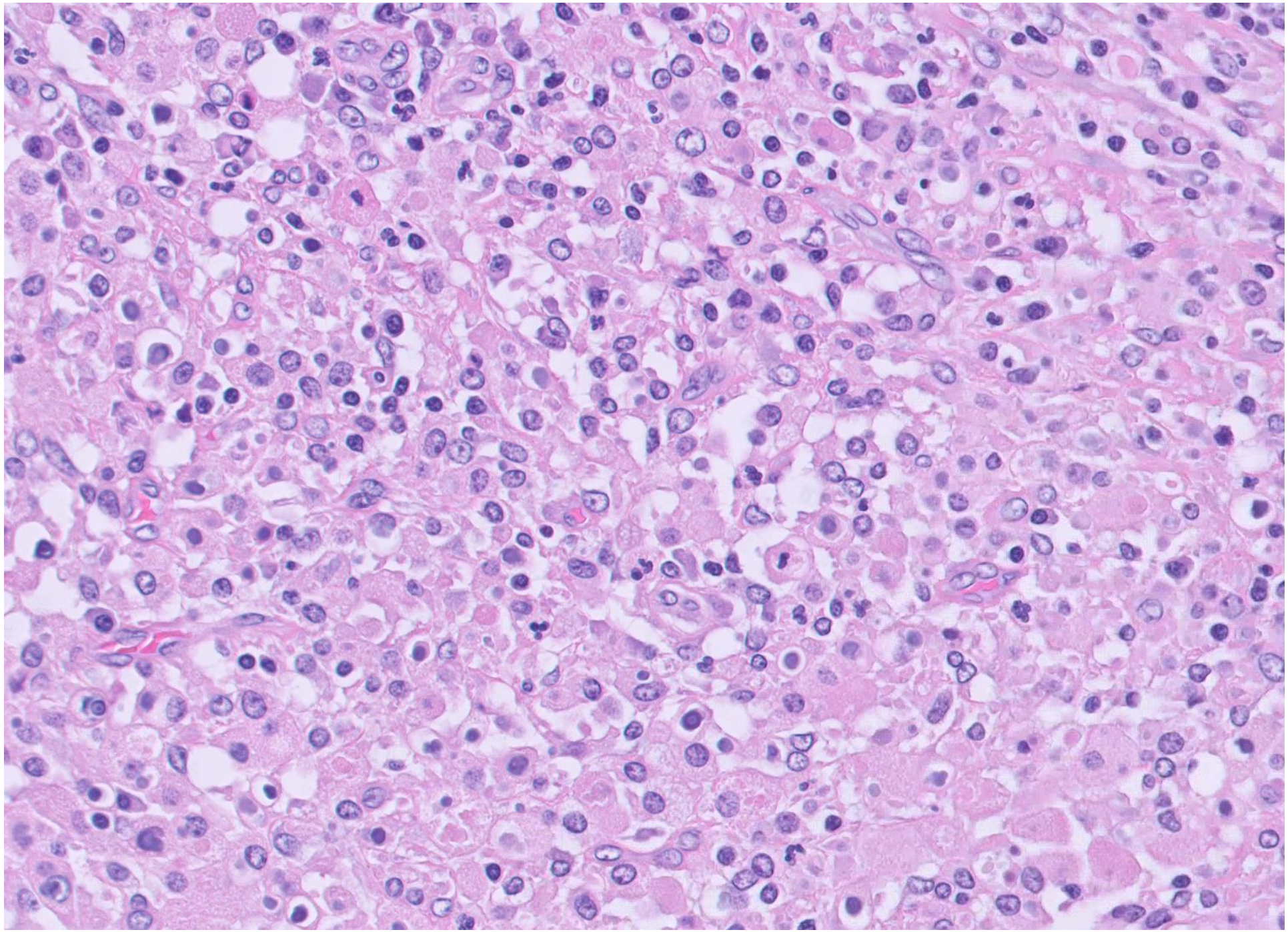


Microscopic

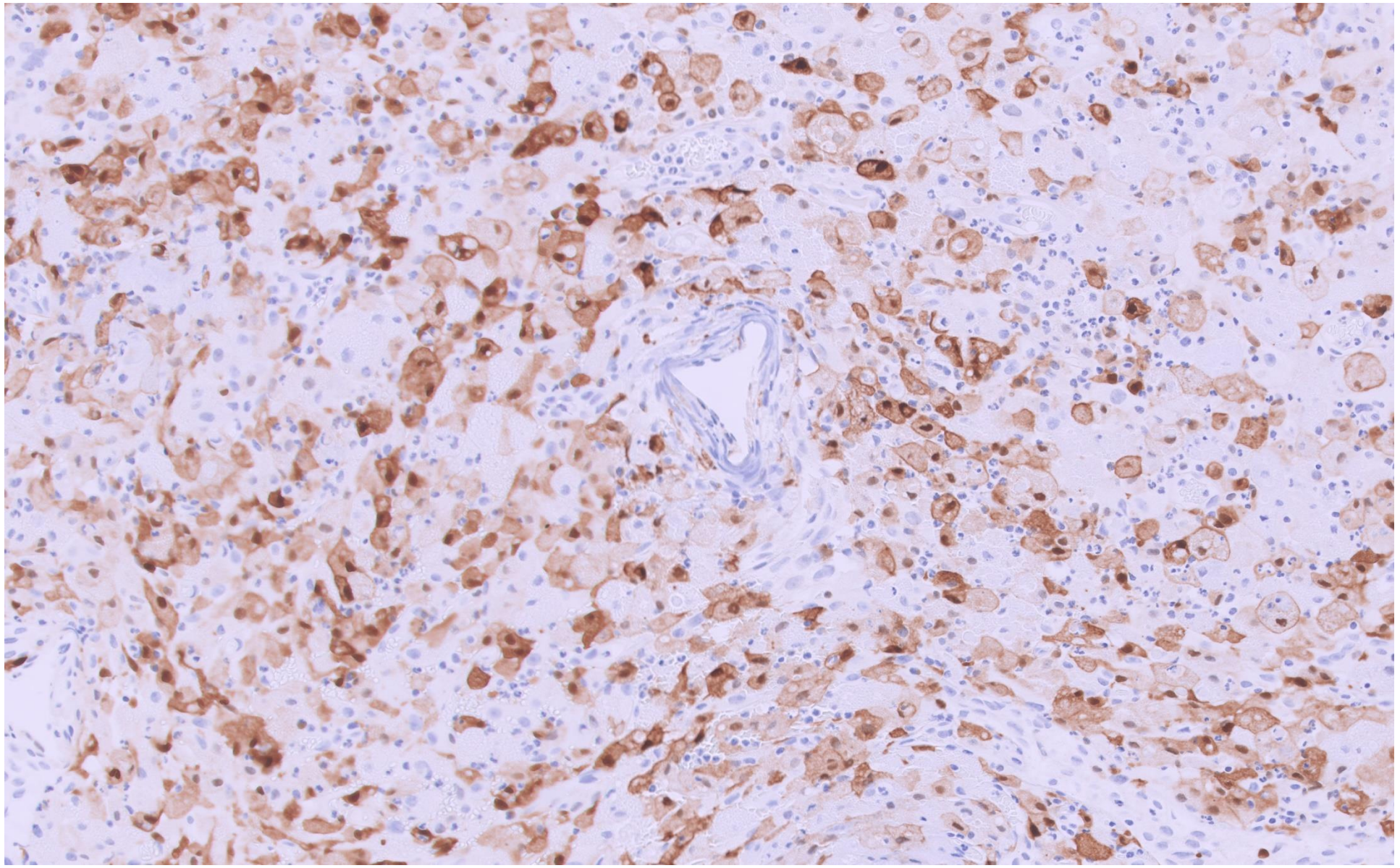








S100



DIAGNOSIS?

Differential diagnoses

1. Granular cell tumor
2. Rosai Dorfman Disease
3. Metastatic poorly differentiated/anaplastic carcinoma
4. Granulomatous inflammation (fungal/TB)
5. Malakoplakia
6. Melanoma

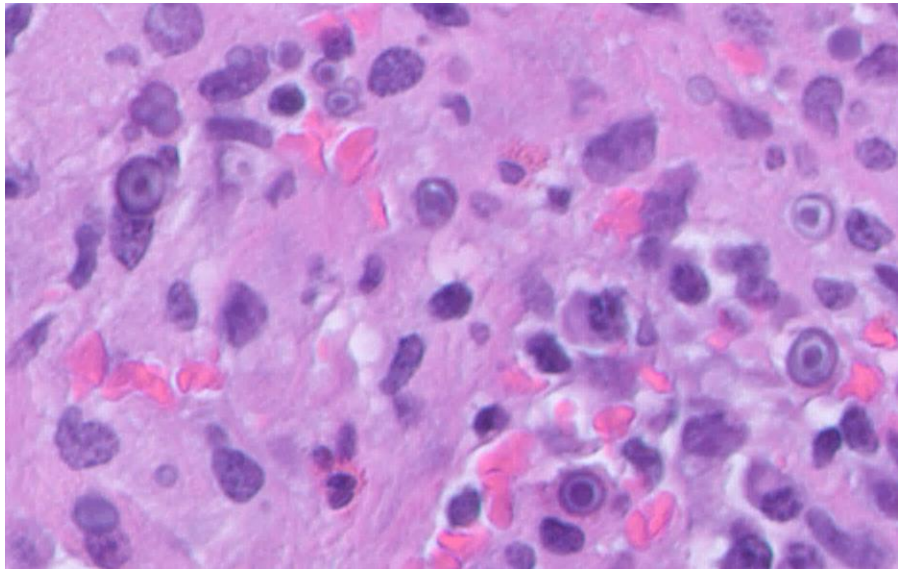
Other IHC

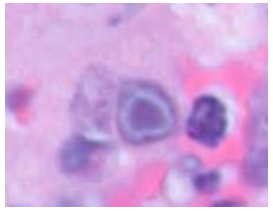
Negative

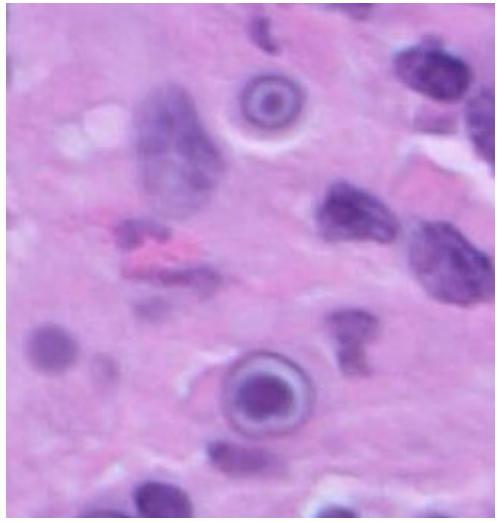
- SOX10
- OCT2 (patchy weak)
- BCL1 (cyclin D1)
- Langerin
- BRAF V600E
- ALK
- CMV, Parvovirus, HSV
- GMS, Gram, AFB l
- Inhibin

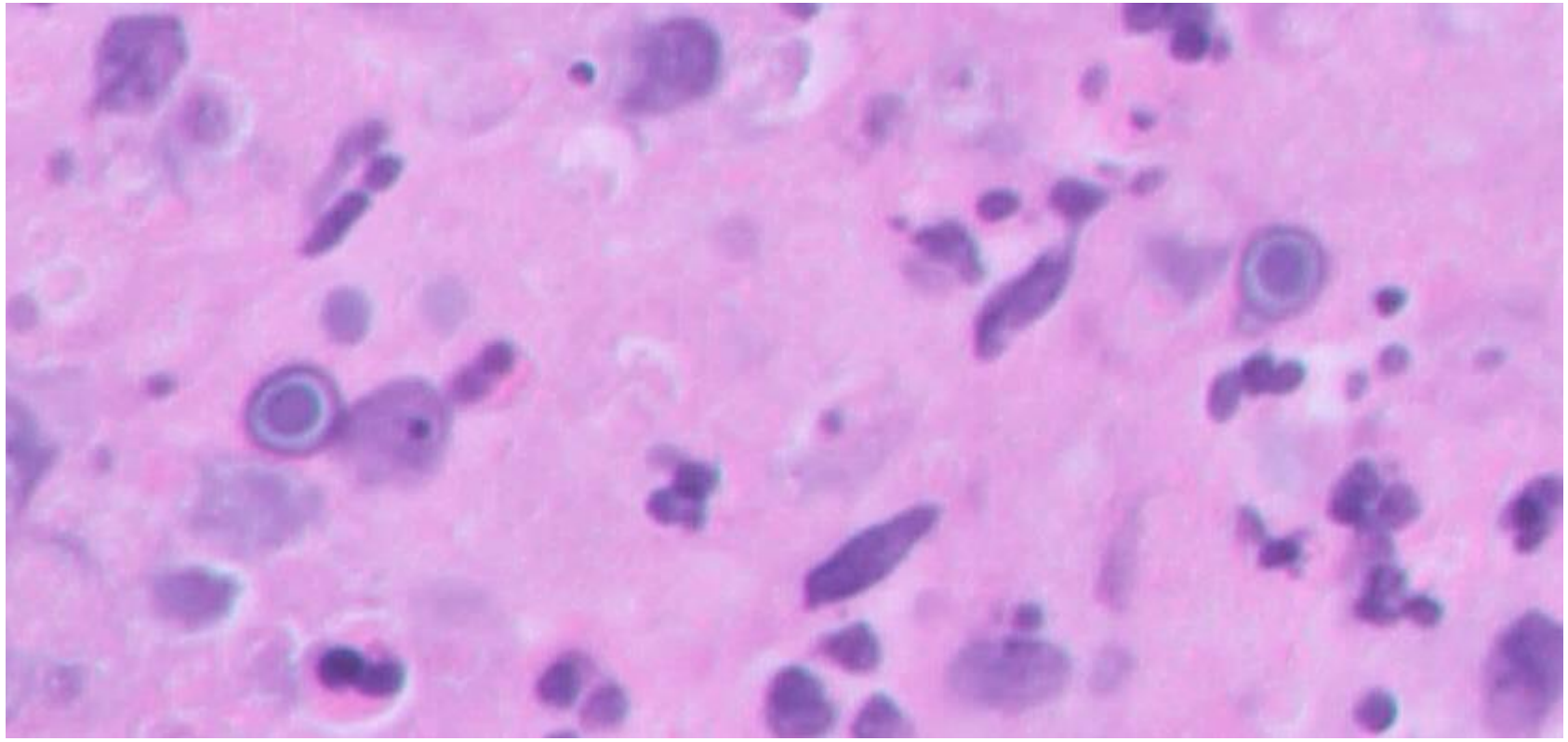
Positive

- S100 (subset)
- PU.1
- CD163

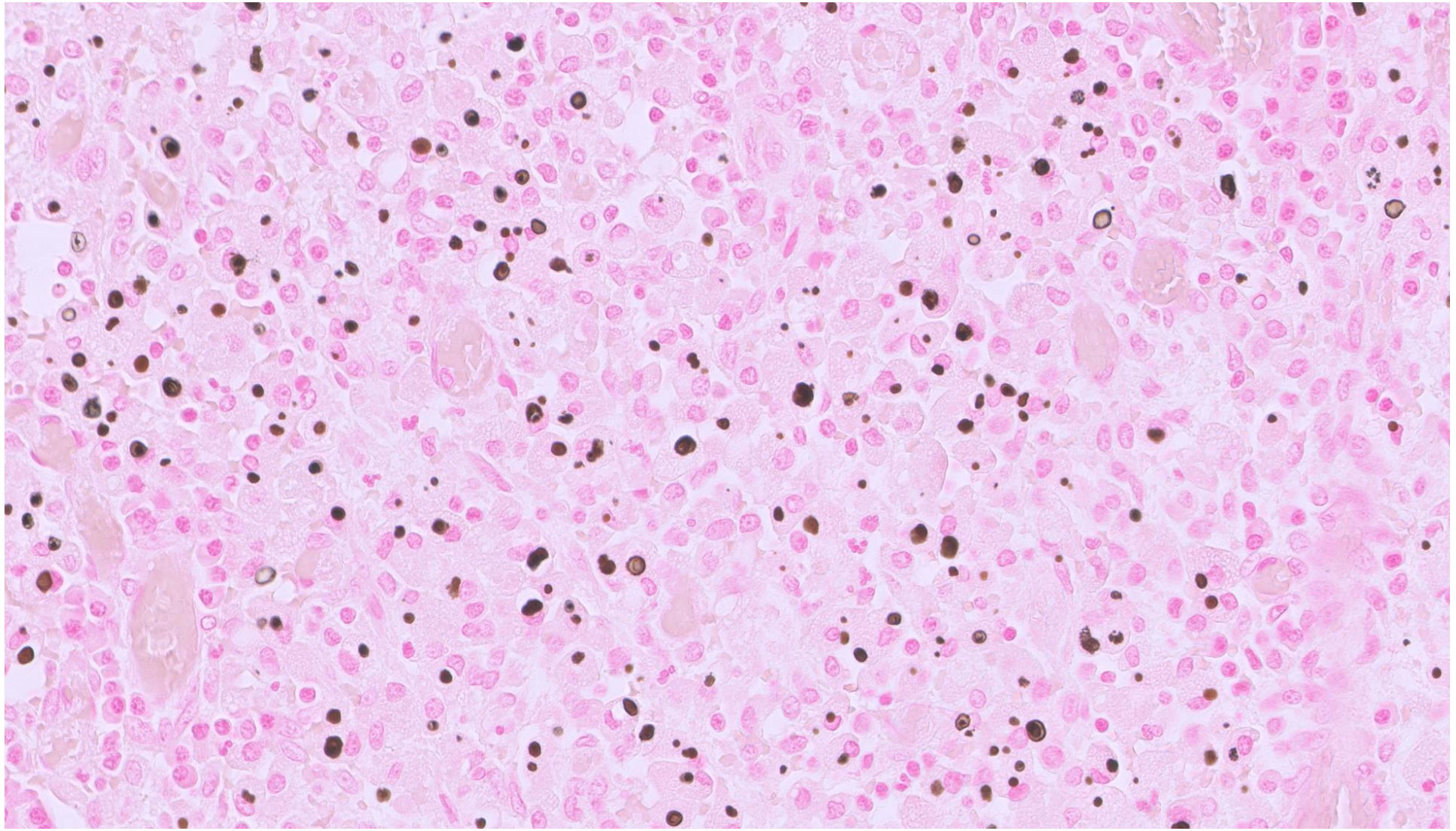




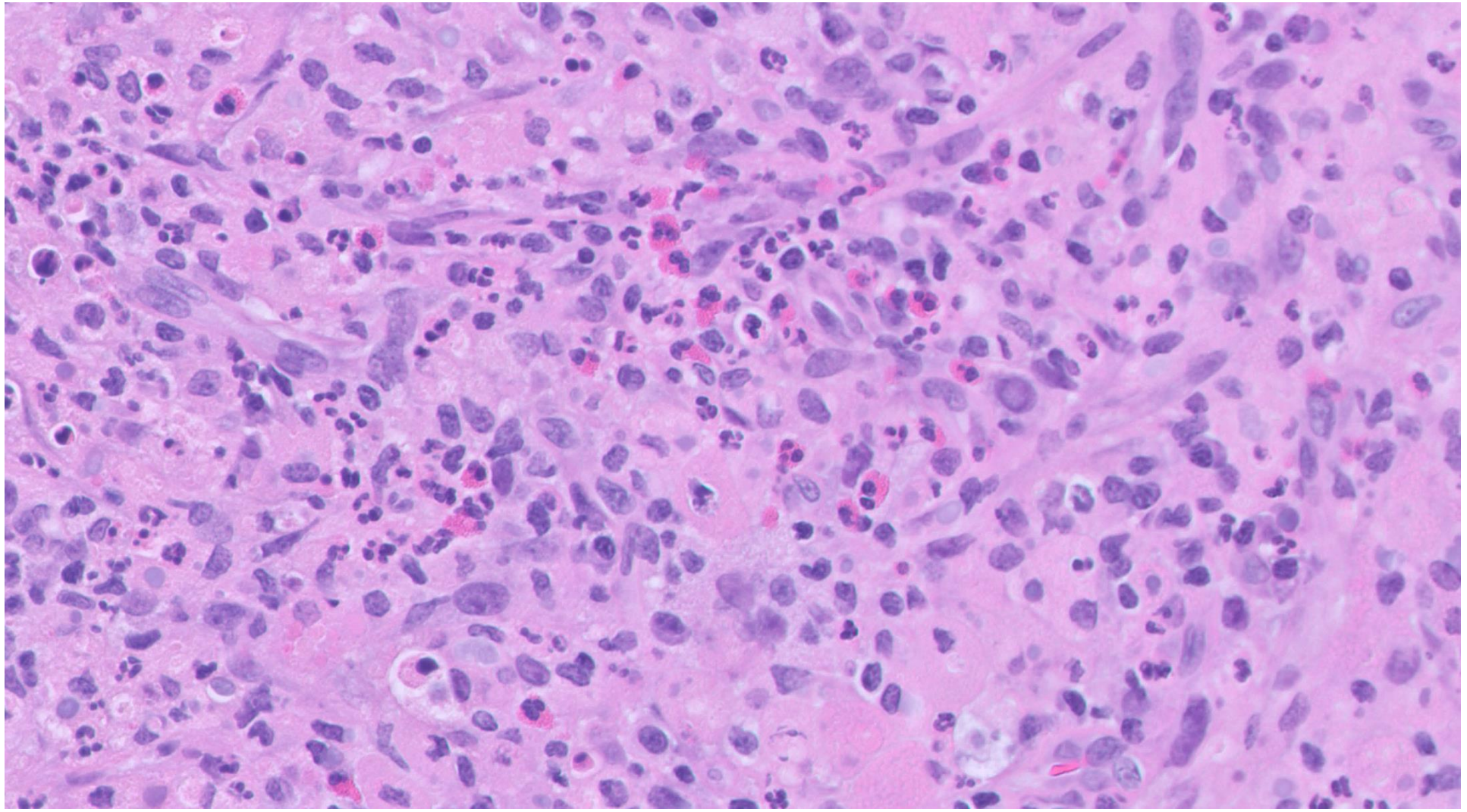




von Kossa



Eosinophils are easily identified



Answer

- Malakoplakia!
- Background endometriosis, adhesions

Why not RDD?

Has S100 positive histiocytes, emperipolesis, clusters of plasma cells, but...

- Negative cyclin D1
  - strong/diffuse cyclin D1 expression reported in 86%-97% of RDD cases
- Morphology, location, and clinical presentation is unusual
  - Histiocytes with usually paler cytoplasm, eosinophils usually absent to inconspicuous
  - Lymph nodes (majority) and/or extranodal sites, most often involving the head and neck, skin, and CNS
  - The typical presentation is that of painless, slow-growing lymphadenopathy,
- S100 can be variable in reactive histiocytic inflammation
- Rare instances of hemophagocytosis documented in florid inflammatory response
- Overall, insufficient evidence for RDD

S100 in other histiocytic reactions

TABLE 2 Histologic characteristics

Case #	Emperipolesis	Types of cells engulfed	S100 (+)	CD68 (+)	CD_{1a} (+)	Touton giant cells	Pathologic diagnosis
Group 1: Pathologic diagnosis consistent with XG							
1	Extensive	Lymphocytes	Diffuse, moderate	Y	N	Y	JXG
2	Extensive	Lymphocytes	Diffuse, moderate	Y	N	Y	XG
3	Focal	Lymphocytes	Negative	Y	N	Y	JXG
4	Focal	Lymphocytes, neutrophils, eosinophils	Focal, weak	Y	N	Y	XG
5	Focal	Lymphocytes eosinophils	Diffuse, strong	Y	N	Y	XG
6	Focal	Lymphocytes	Focal, weak	Y	N	Y	JXG
7	Focal	Lymphocytes, eosinophils	Focal, weak	Y	N	Y	JXG
Group 2: Pathologic differential diagnosis includes XG and RDD							
8	Extensive	Lymphocytes, eosinophils	Diffuse, strong	Y	N	Y	JXG vs RDD
9	Extensive	Lymphocytes, eosinophils	Focal, strong	Y	N	Y	JXG vs RDD
10	Focal	Lymphocytes, eosinophils	Focal, weak	Y	N	Y	XG vs RDD

JXG, juvenile xanthogranuloma; N, no; RDD, Rosai-Dorfman disease; XG, xanthogranuloma; Y, yes.

J Cutan Pathol. 2018 May 24. doi: 10.1111/cup.13285. Online ahead of print.

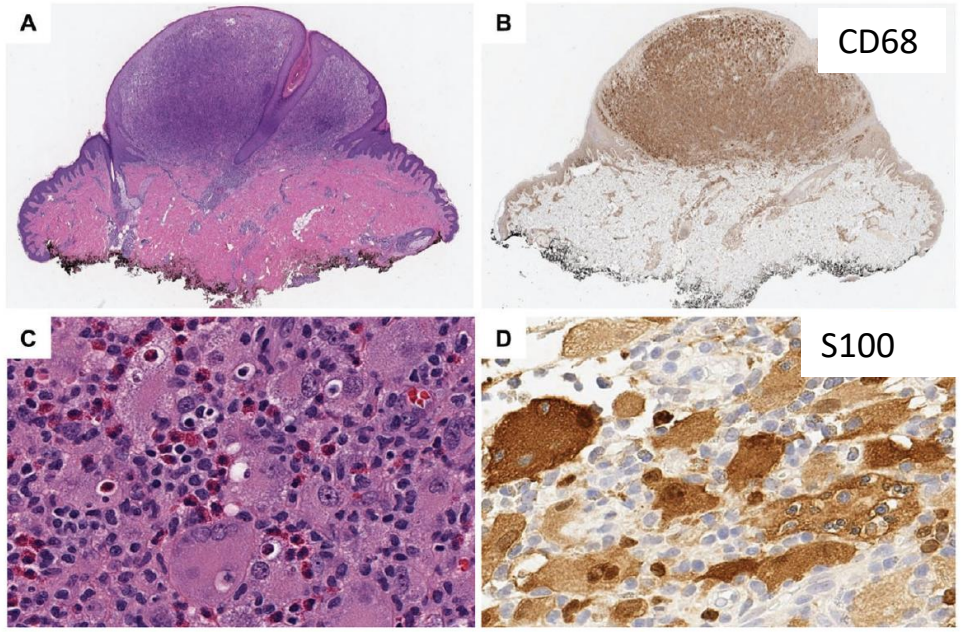
Emperipolesis and S100 expression may be seen in cutaneous xanthogranulomas: A multi-institutional observation

Kristen N Ruby [1], April C Deng [2], Jingwei Zhang [3], Robert E LeBlanc [1], Konstantinos D Linos [1], Shaofeng Yan [1]

Affiliations – collapse

Affiliations

1 Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.
2 Department of Pathology, University of Massachusetts School Medicine, Worcester, Massachusetts.
3 Pathology Service, Carolinas Dermatology Group, Columbia, South Carolina.



Xanthogranuloma

Learning points - Malakoplakia

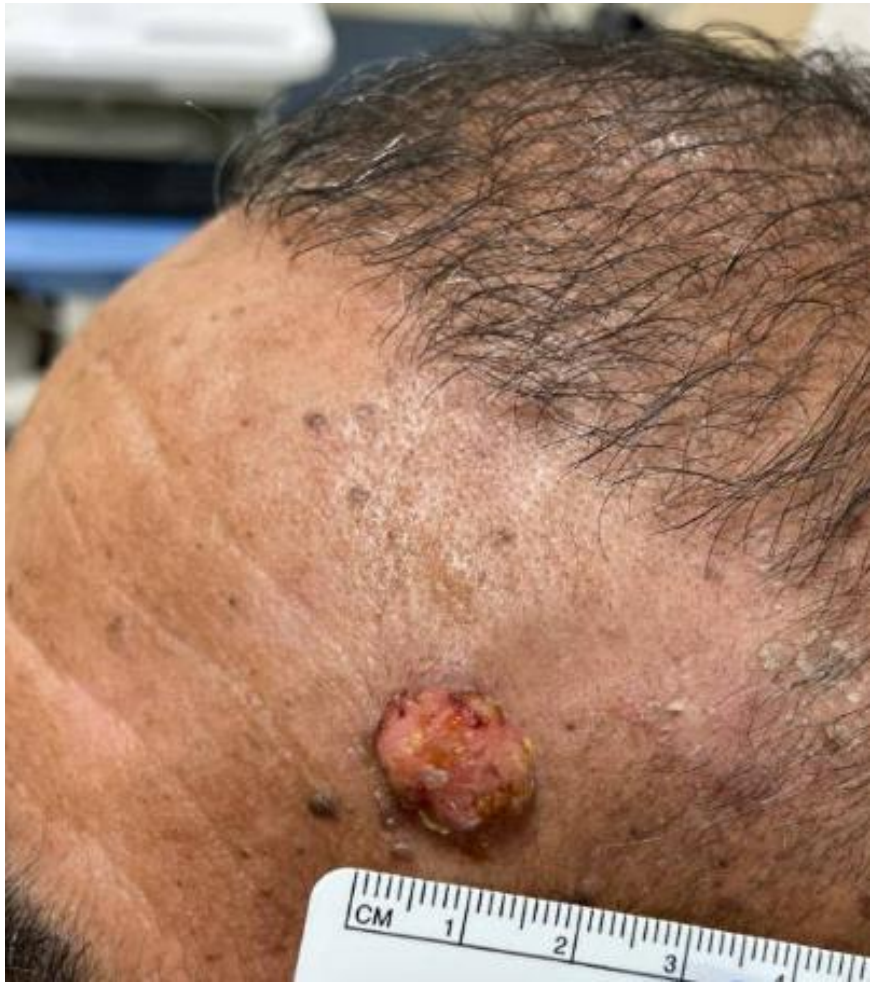
- Chronic inflammatory process
- Impaired histiocytic response to infection (80% associated with E. coli)
- Most commonly in the bladder and genitourinary tract
- Michaelis-Gutmann bodies highlighted by von Kossa
- Can mimic malignancy with mass-forming lesion due to scarring and inflammation
- May present with hemophagocytosis in response to florid inflammatory response
- Variable S100 immunoreactivity reportedly seen in reactive histiocytic inflammation

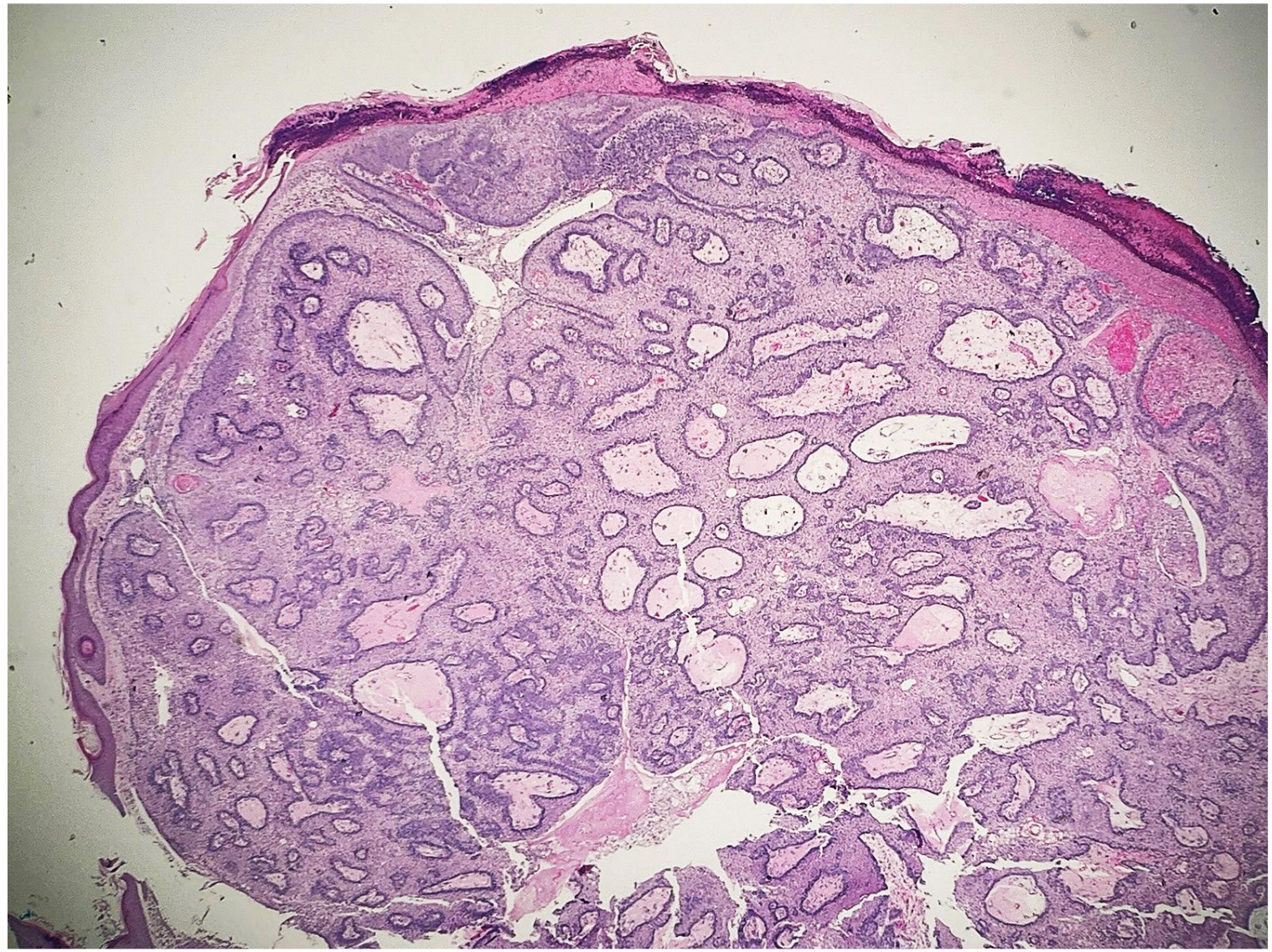
25-0403

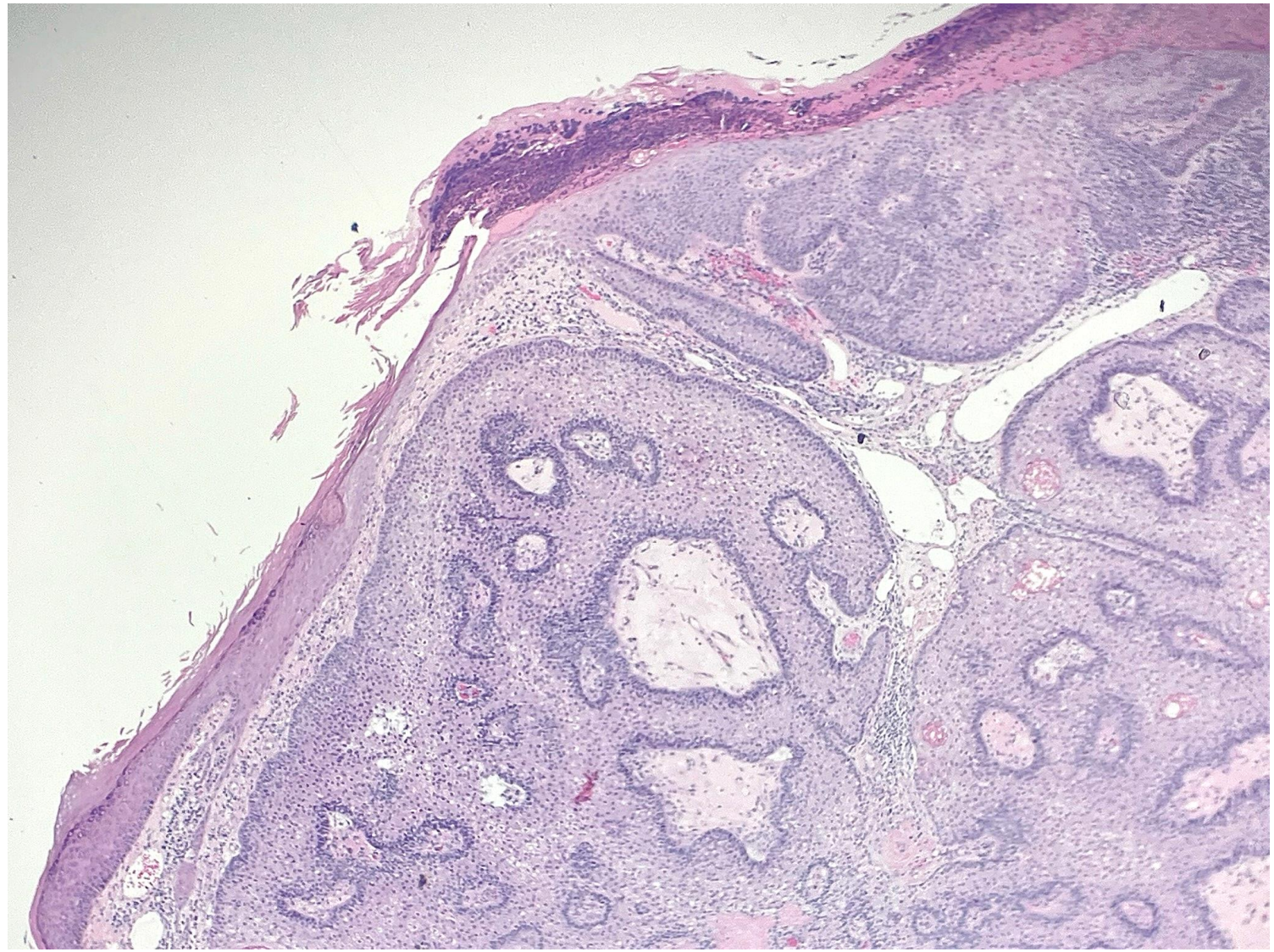
Harris Goodman; Alameda Health System

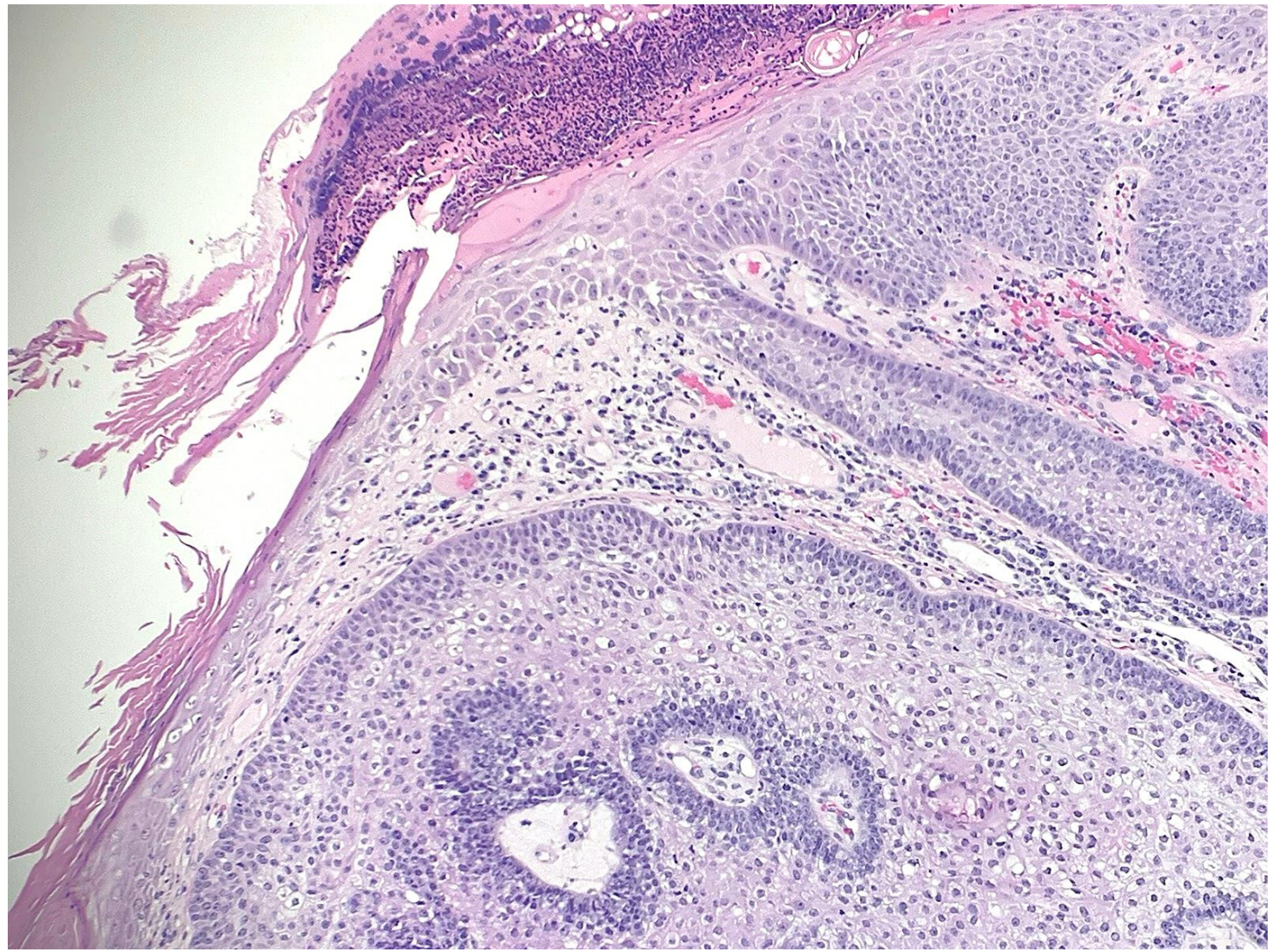
60-ish year old man with a complex medical history, including HTN, DMII, HLD and h/o renal transplant (6/2017) on prednisone, tacrolimus and MMF, presenting for consultation of growth on the left forehead for the last 3-4 months. He reports that it started as a small pimple and grew. It bled with manipulation. Exam reveals a 1.8 cm x 1.0 cm dome-shaped pink plaque on the left forehead x 4 months. Clinical differential diagnosis includes pyogenic granuloma, KA vs. other.

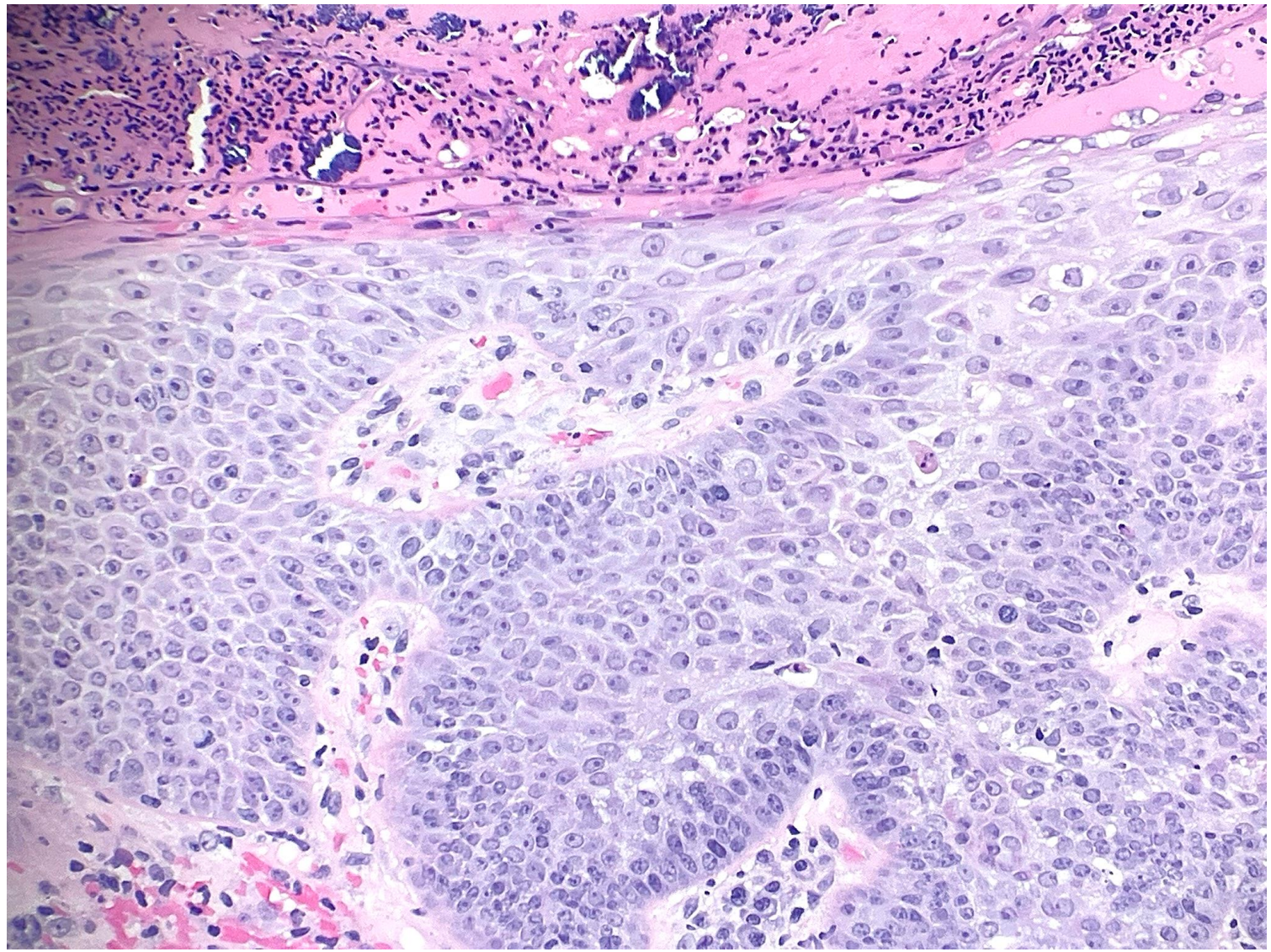
Clinical Examination:

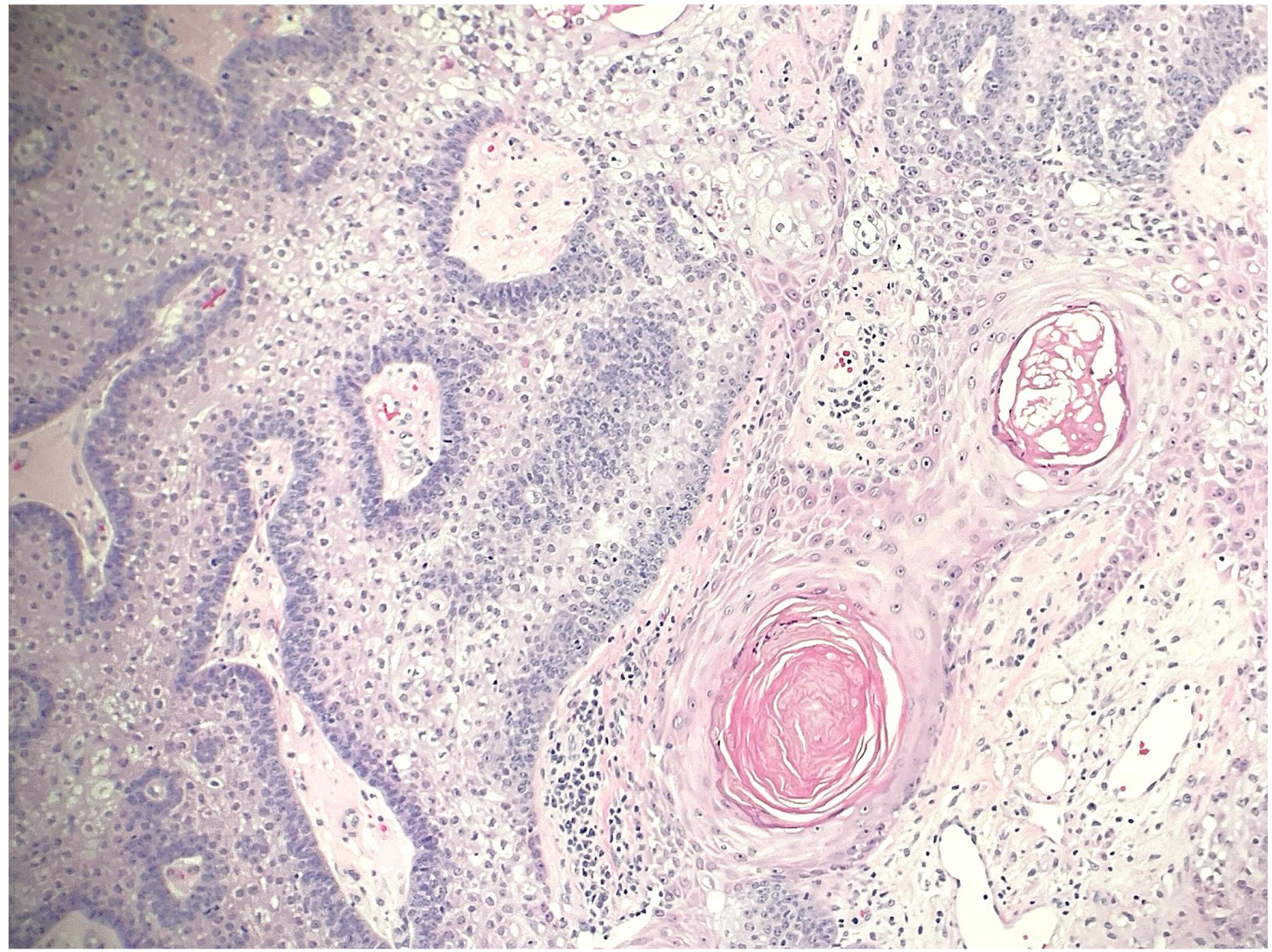


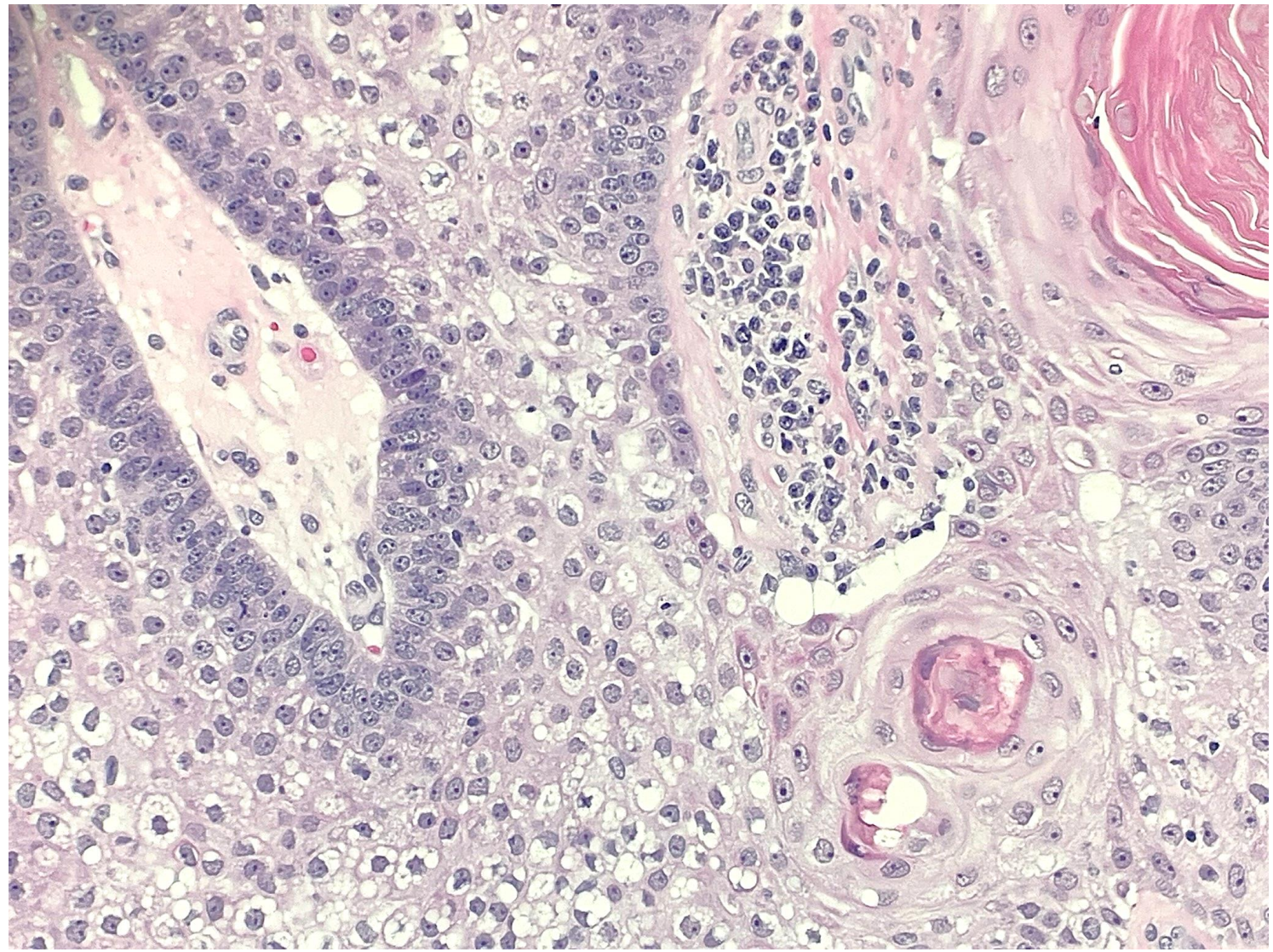


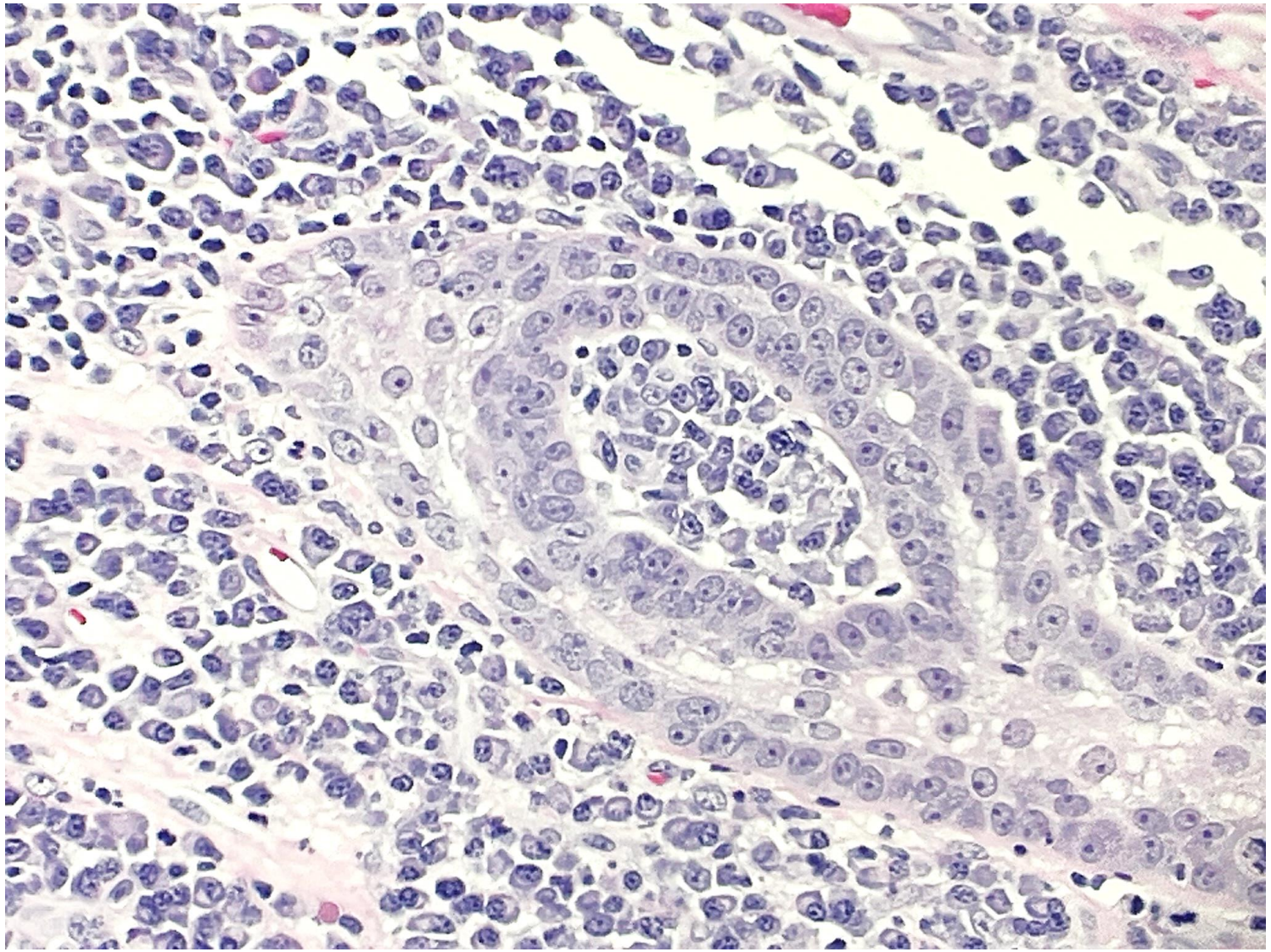


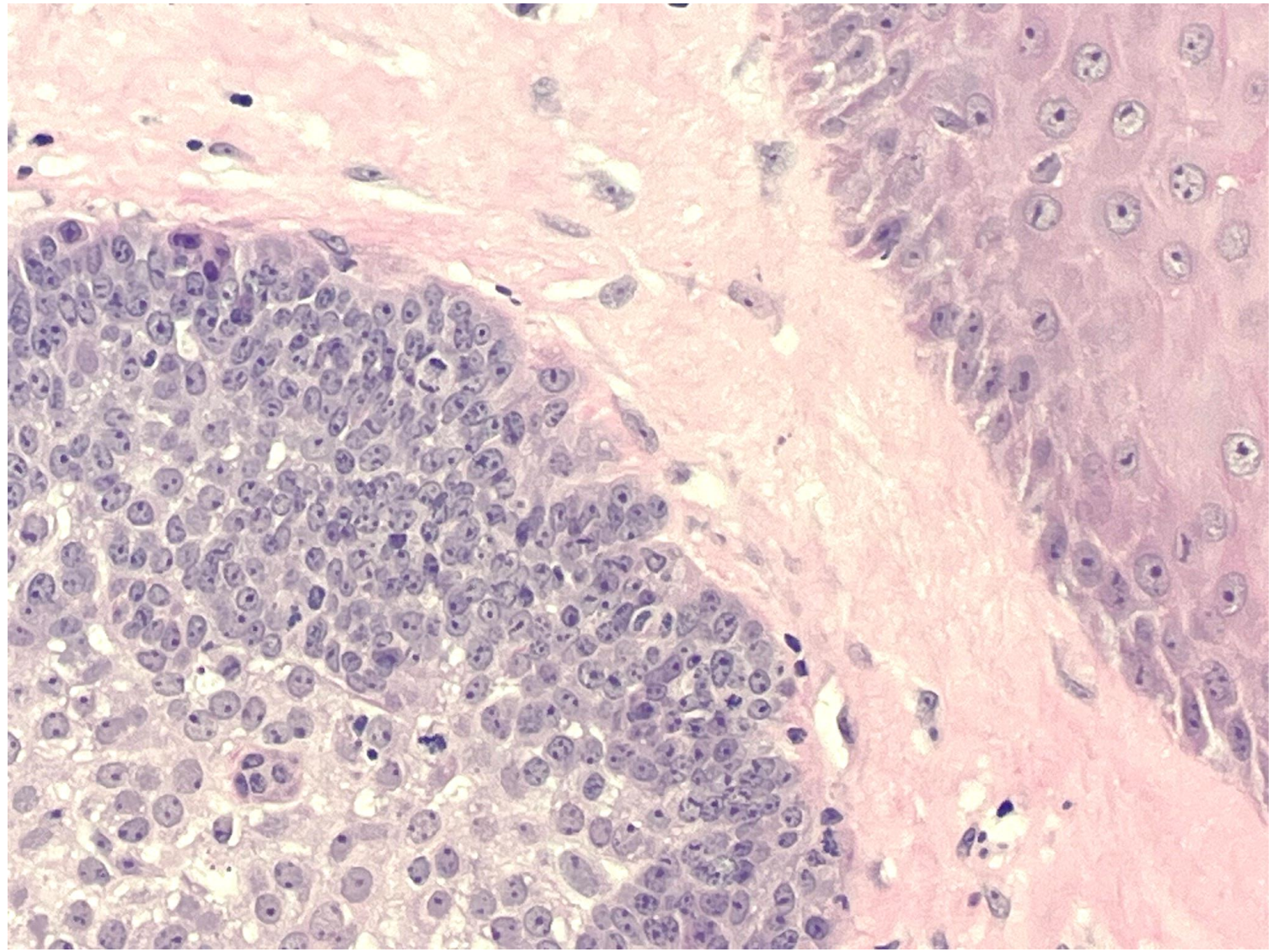












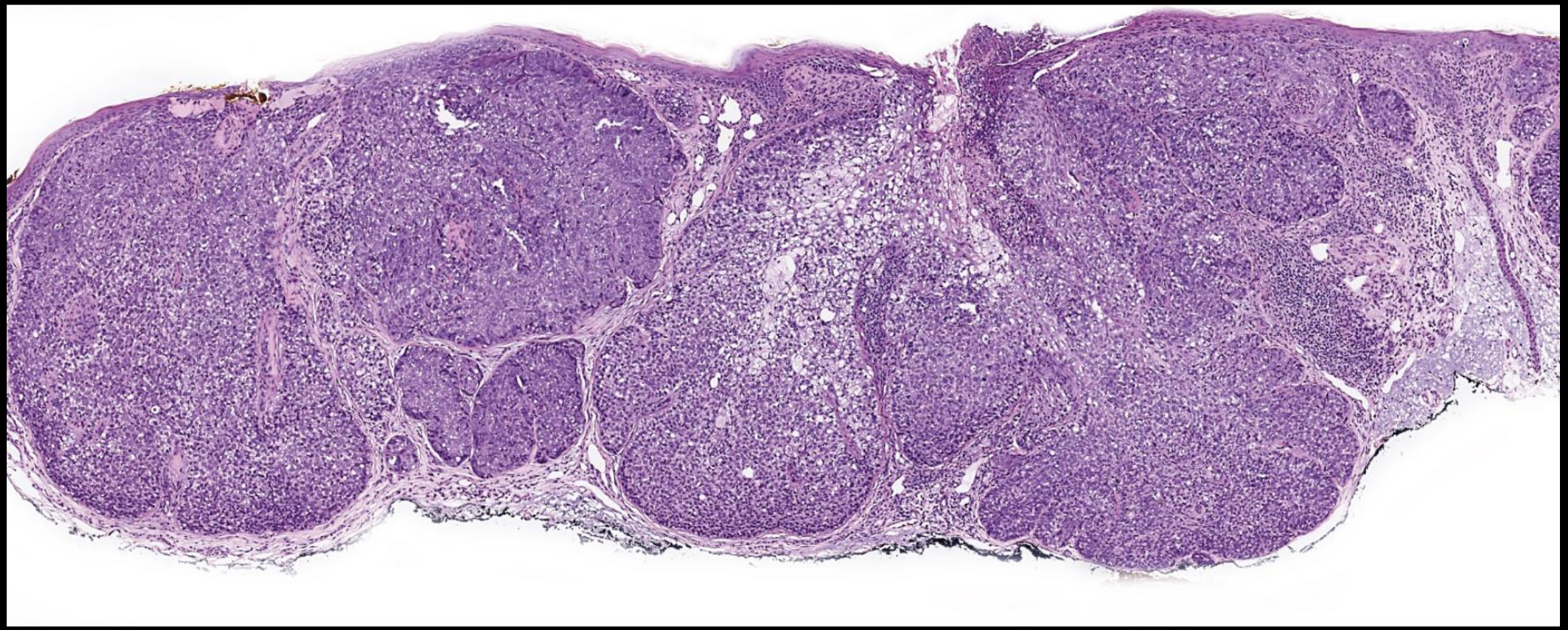
DIAGNOSIS?

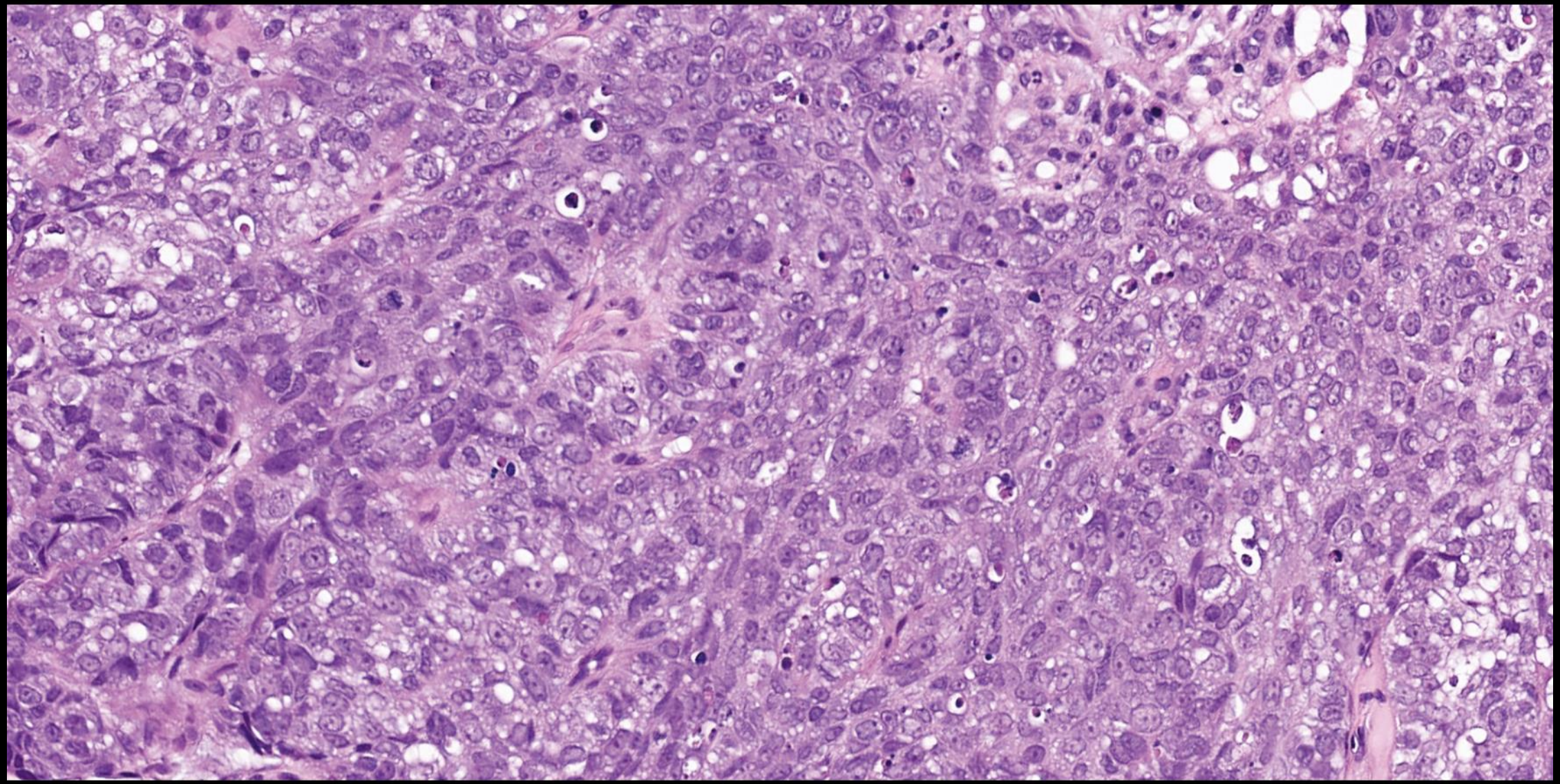
Sebaceous Carcinoma

Extraocular
Periocular (eyelid) aka meibomian gland carcinoma

Mean age: 73 years;
Risk factors: prior radiotherapy, sun exposure, immunosuppression;
Head and neck, most commonly around eyelids;

Additionally, this malignancy is associated with genetic cancer predisposition syndromes, such as MTS-I, which is a distinct variant of hereditary nonpolyposis colorectal cancer (HNPCC); Sebaceous carcinoma is also associated with MTS-II, a MUTYH-associated polyposis (MAP) variant.





Sebaceous Carcinoma – IHC

pan-CK
CK7
adipophilin
EMA
Ber-EP4
AR (androgen receptor)
p40
p63

Sebaceous Carcinoma – Differential Diagnosis

Basal cell carcinoma;
Sebaceoma;
Balloon cell melanoma;
Clear cell squamous cell carcinoma;
Metastatic clear cell carcinoma (e.g., RCC);
Clear cell sarcoma;
Proliferating pilar tumor (for this case).

Sebaceous Carcinoma – Differential Diagnosis

- Basal cell carcinoma (EMA, AR and adipophilin neg);
- Sebaceoma;
- Balloon cell melanoma (SOX10 and S-100 positive);
- Clear cell squamous cell carcinoma (BerEP4, AR and adipophilin neg);
- Metastatic clear cell carcinoma (e.g., RCC, which is CD10, CAIX and PAX8 positive).
- Clear cell sarcoma (SOX10 and S-100 positive);
- Proliferating pilar tumor (usually has a more cystic configuration and lacks sebocytic differentiation).

Sebaceous Carcinoma - Prognosis

Both periocular and extraocular sebaceous carcinomas have a 30-40% risk of local tumor recurrence, a 20-25% risk of distant metastasis, and a 10-30% risk of tumor-related mortality.

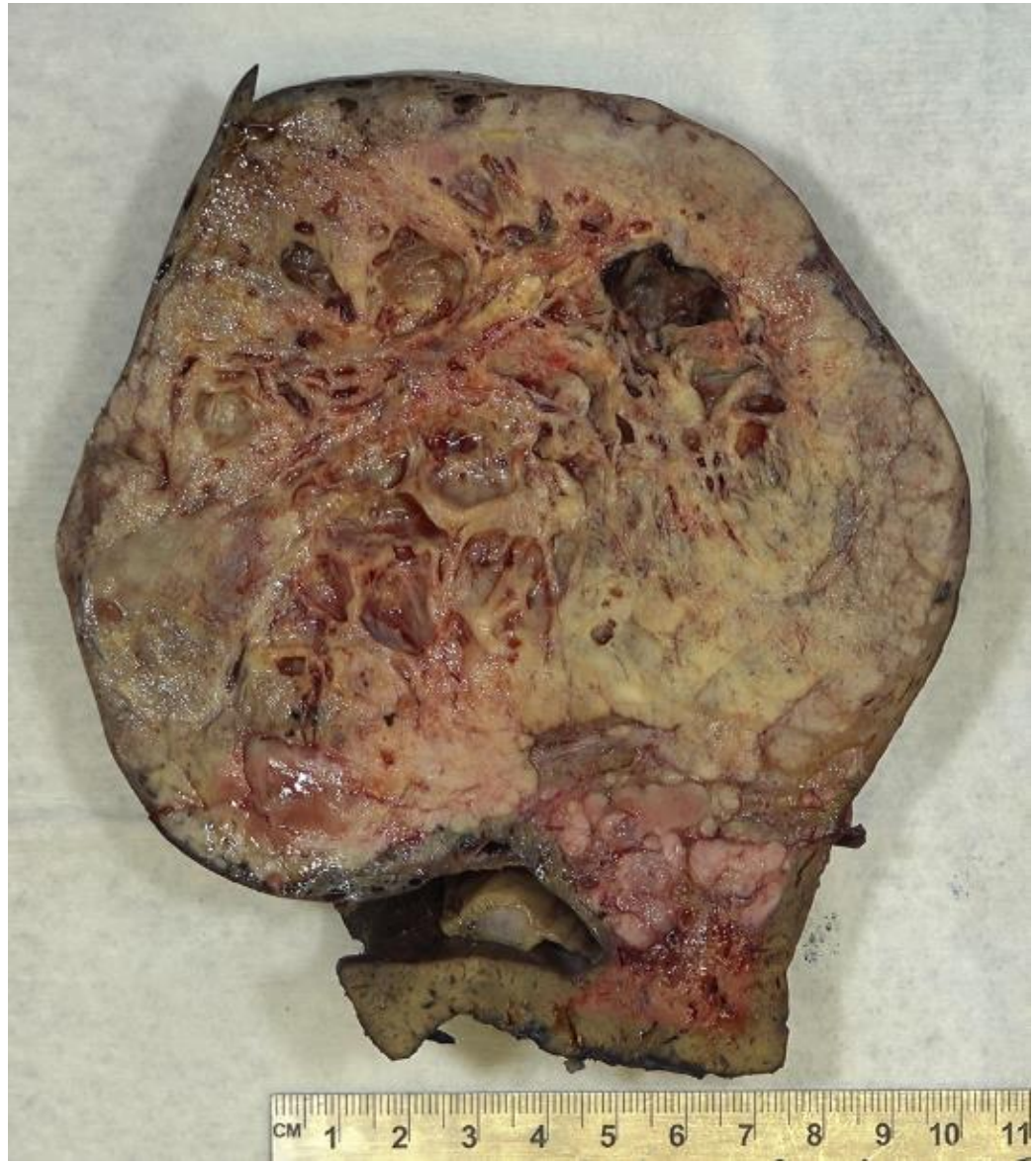
Approximately 70% of all patients with sebaceous carcinoma survive for ≥ 5 years after diagnosis.

25-0404

Iain Miller, David Bingham; Stanford

First case:

Early 30’s female with history of pT2N1a papillary thyroid cancer status post thyroidectomy and bilateral neck dissection (2023) found to have left hepatic lobe lesion (17 cm) suspicious for solitary metastasis on CT-scan. Undergoes left-sided hepatectomy.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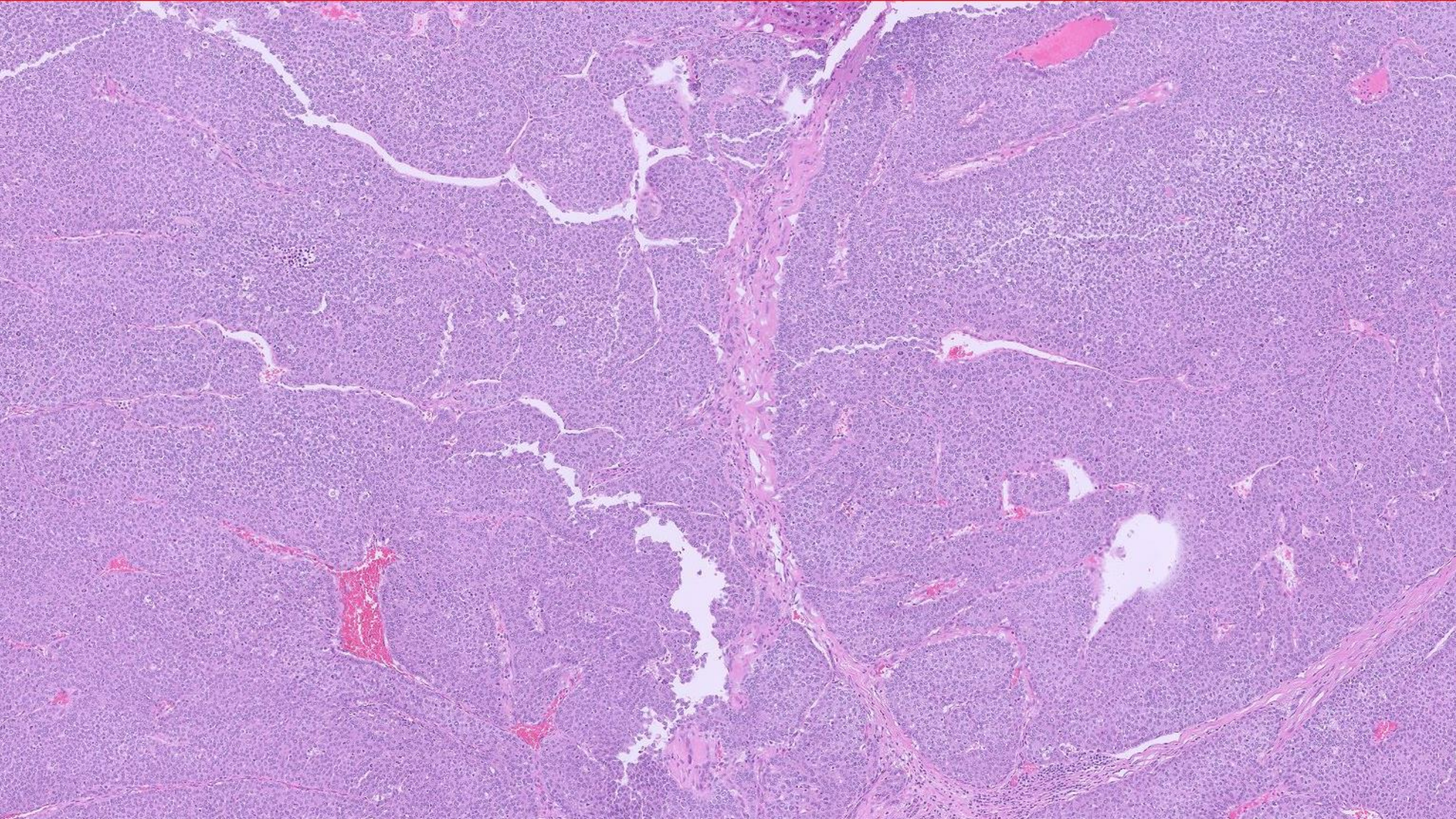
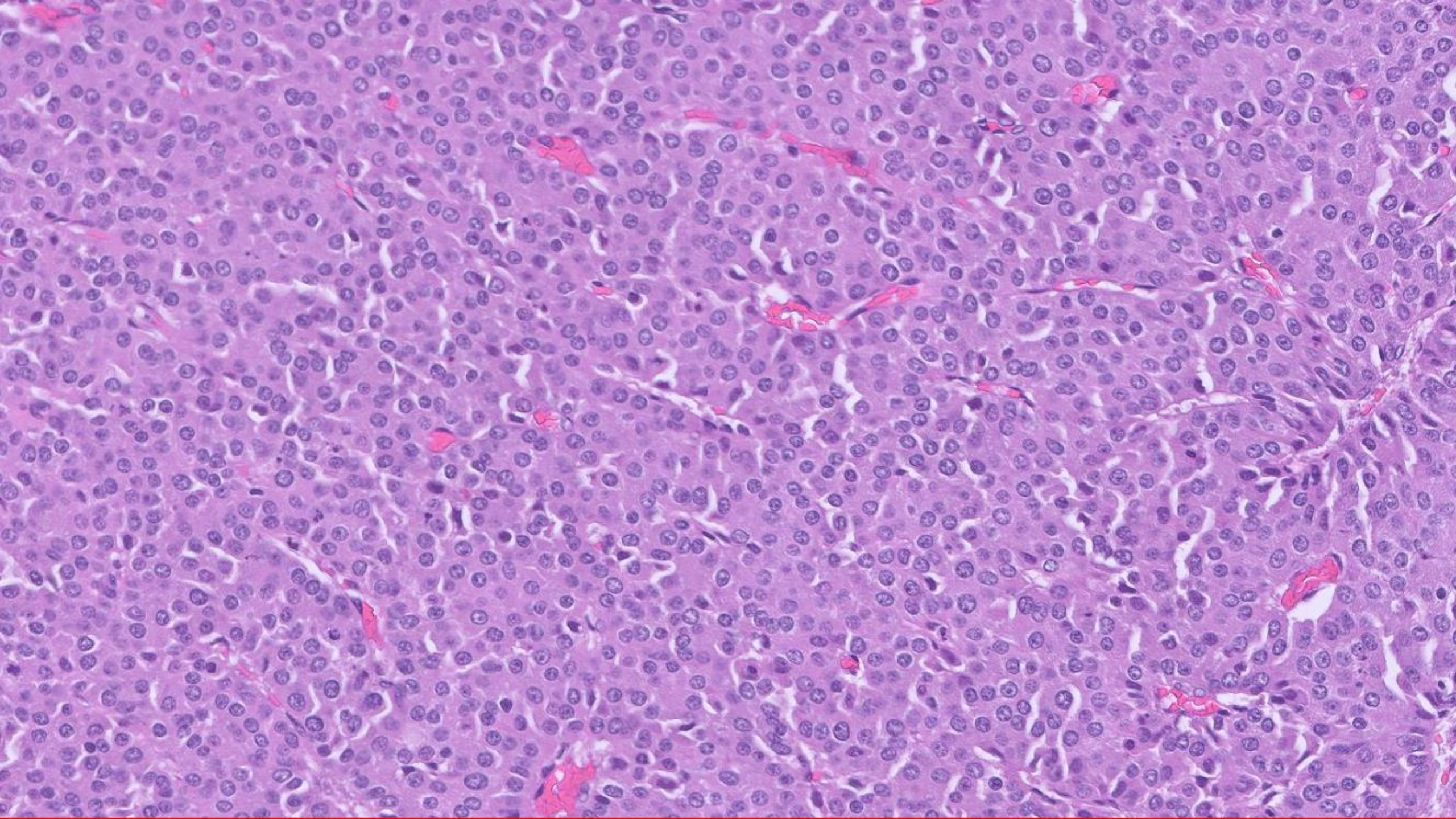
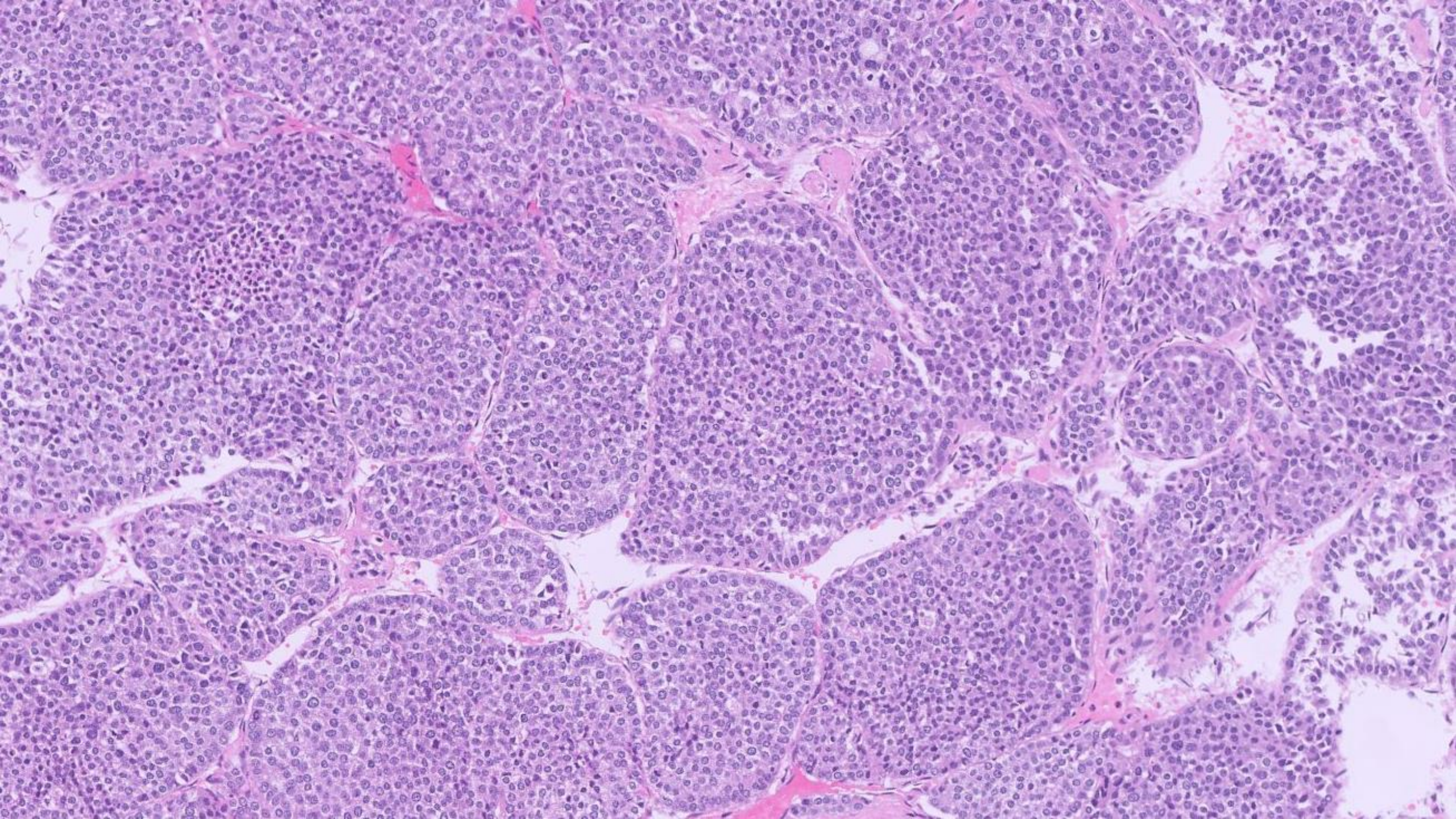
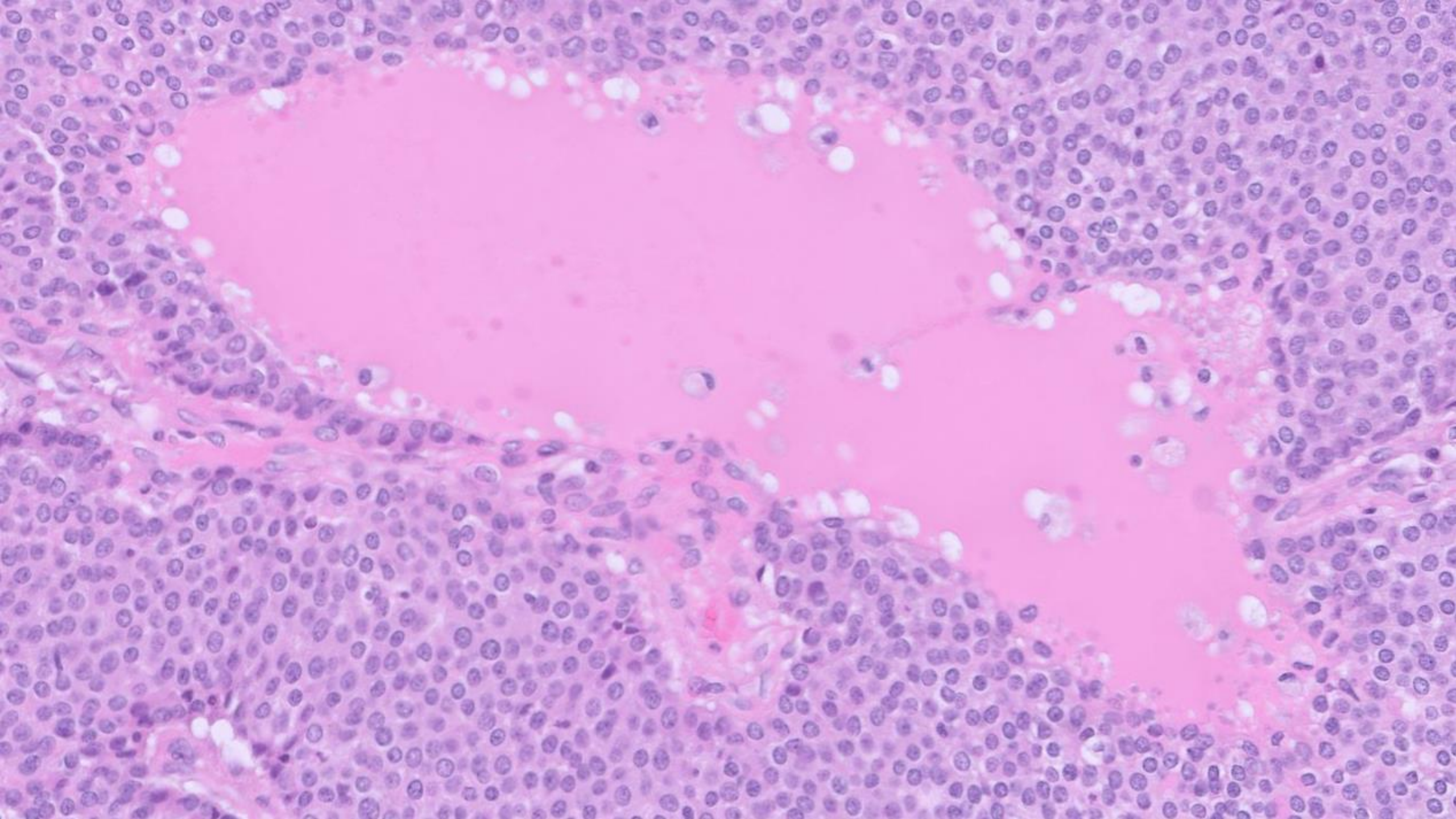
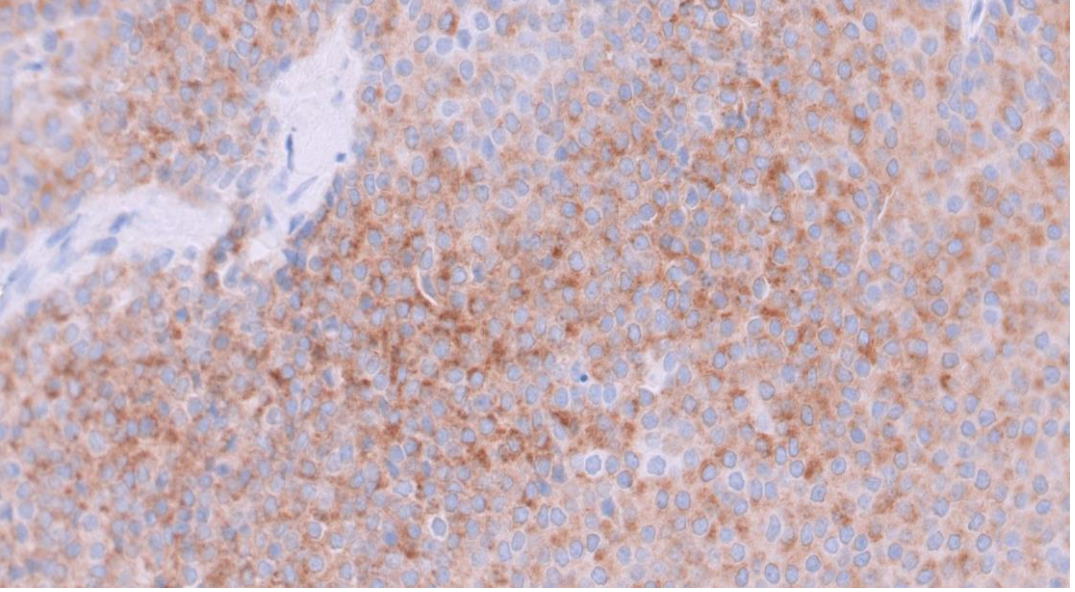


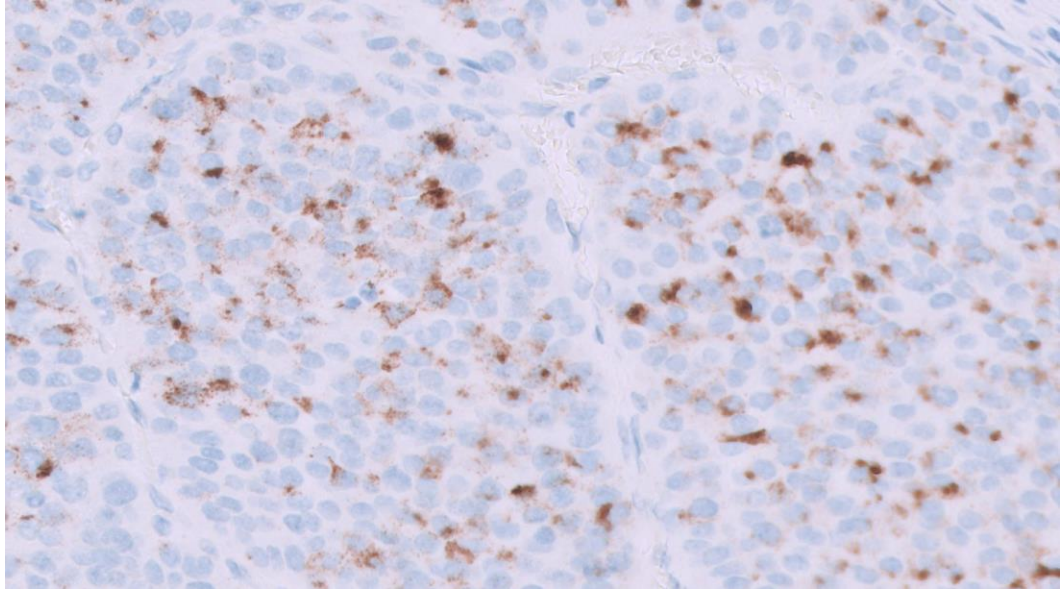






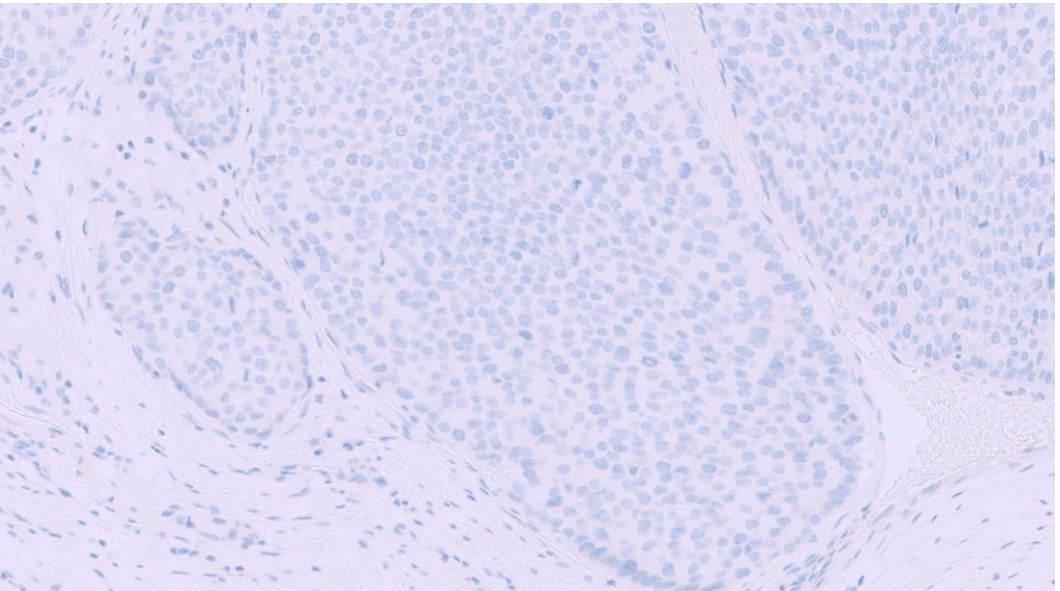


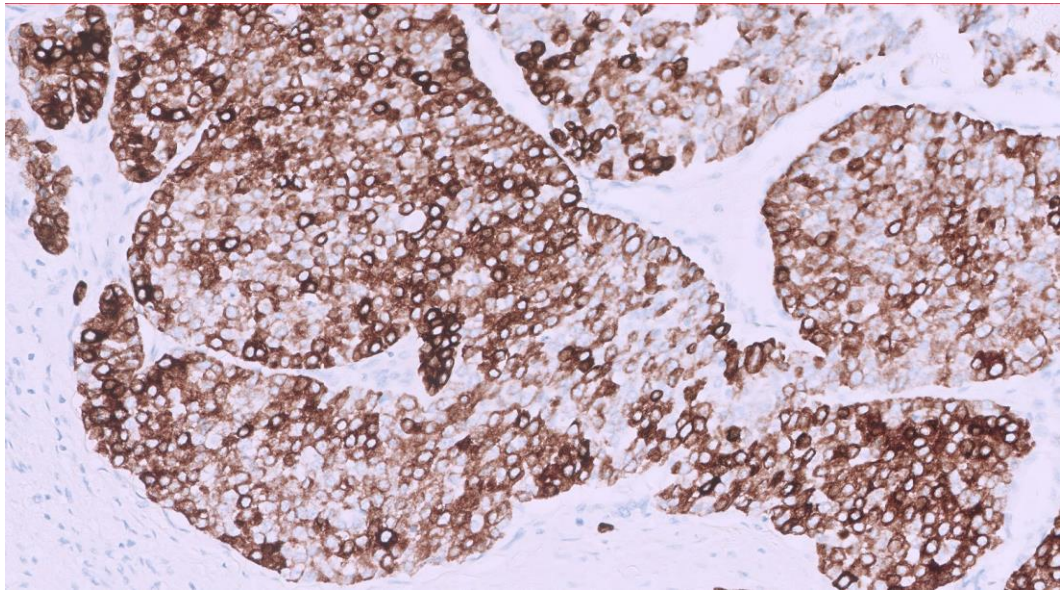
Synaptophysin



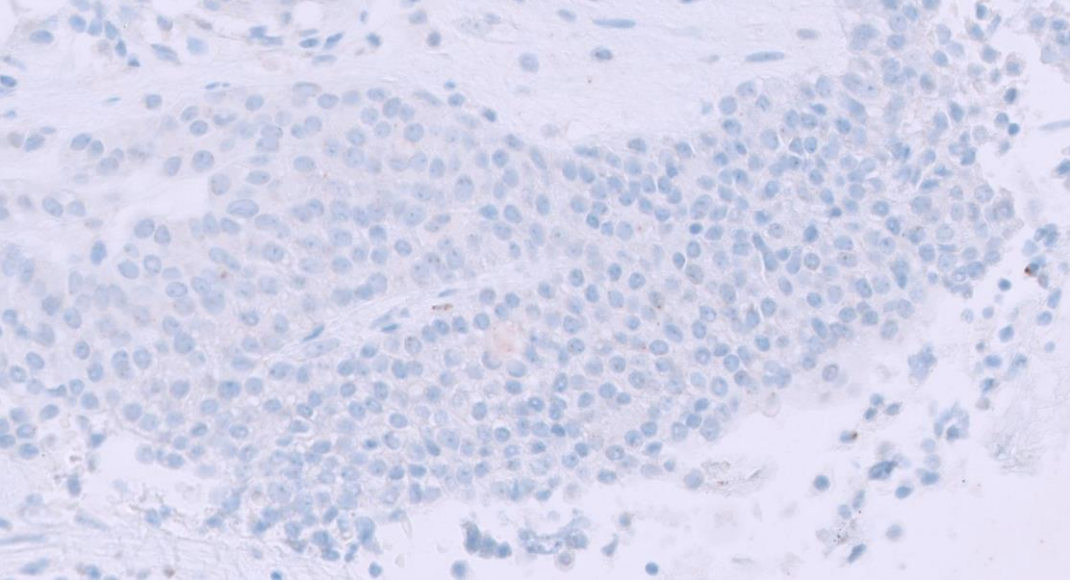
Chromogranin

TTF-1

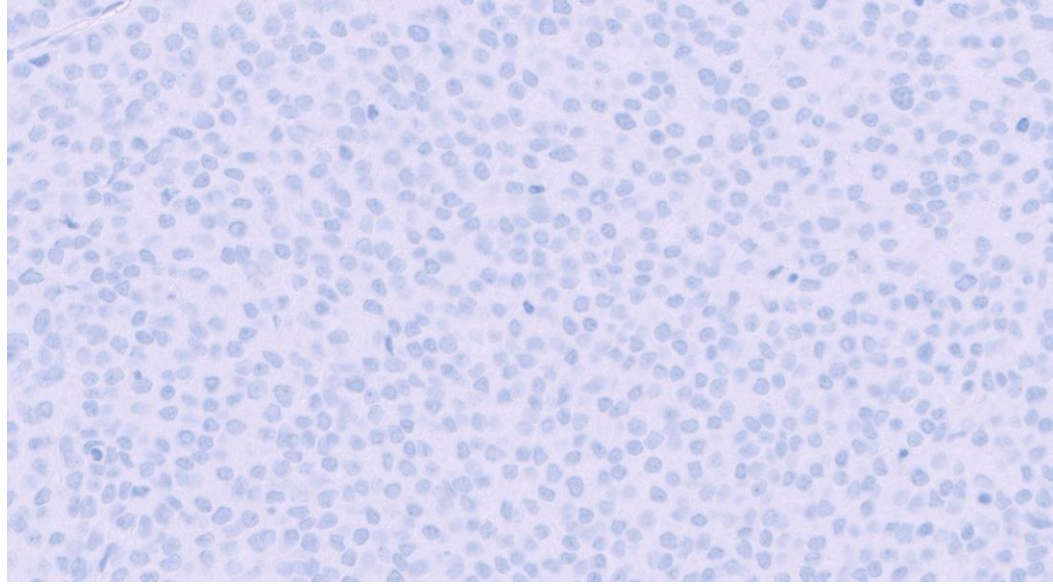




Pan-CK

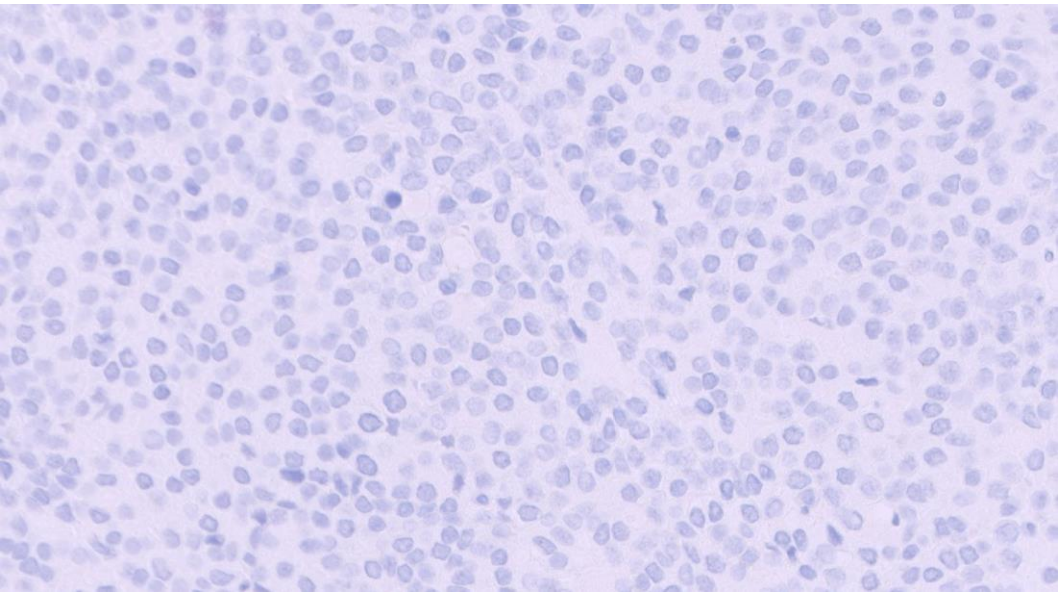


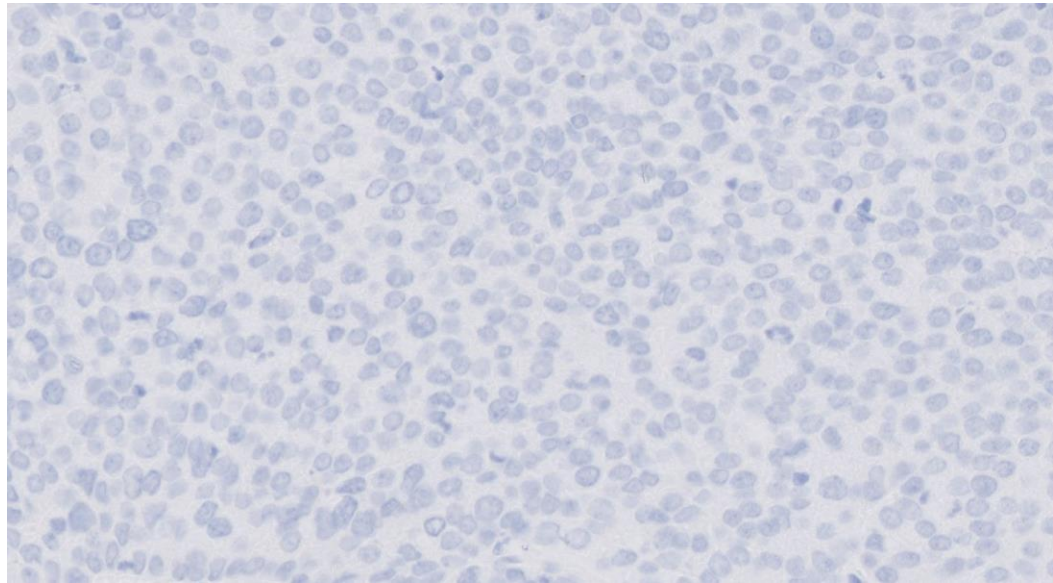
PAX8



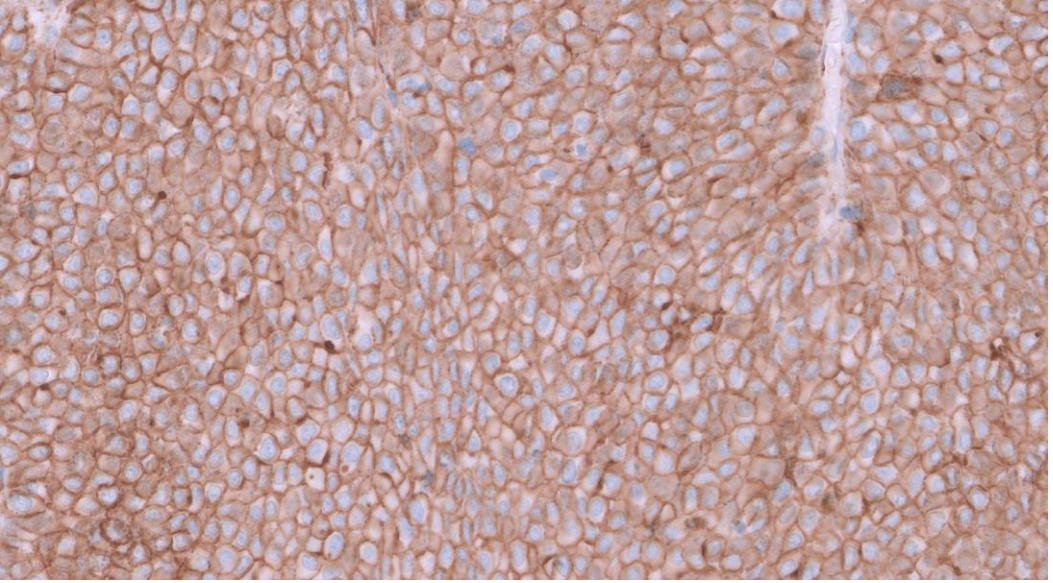
HEPPAR1

Arginase1

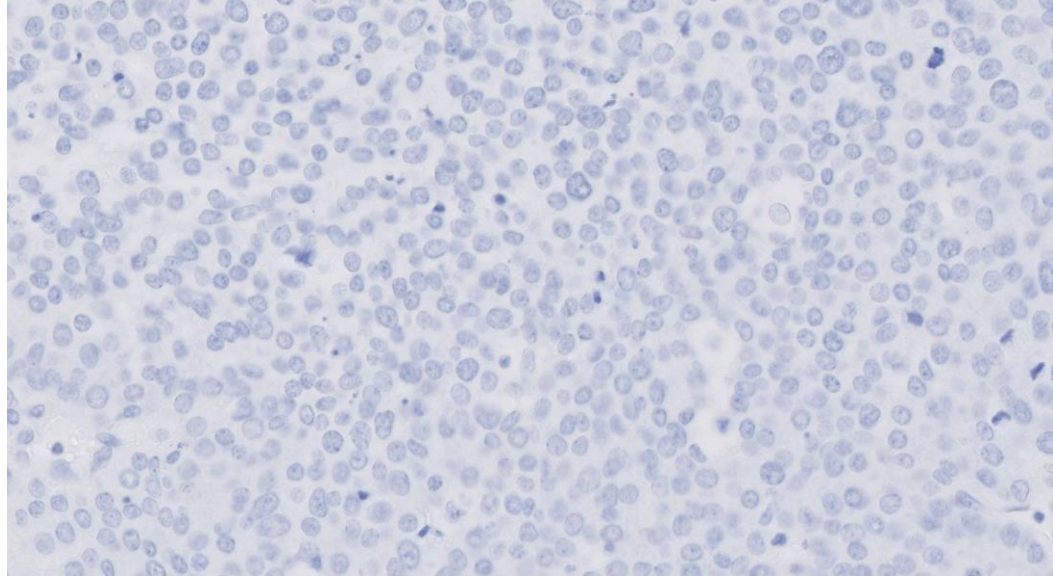




Glypican3

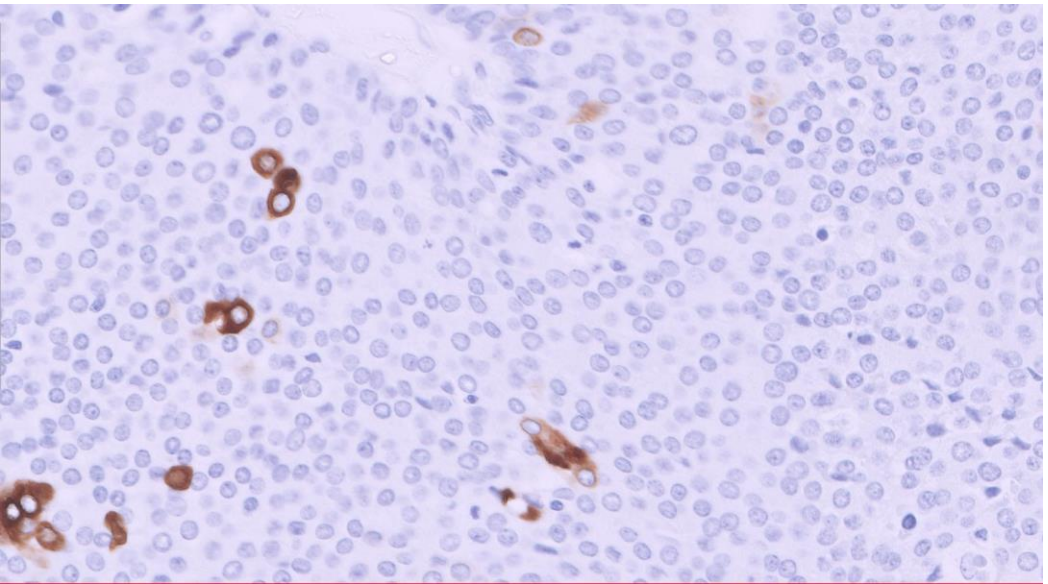


Beta-Catenin



S100

CK7



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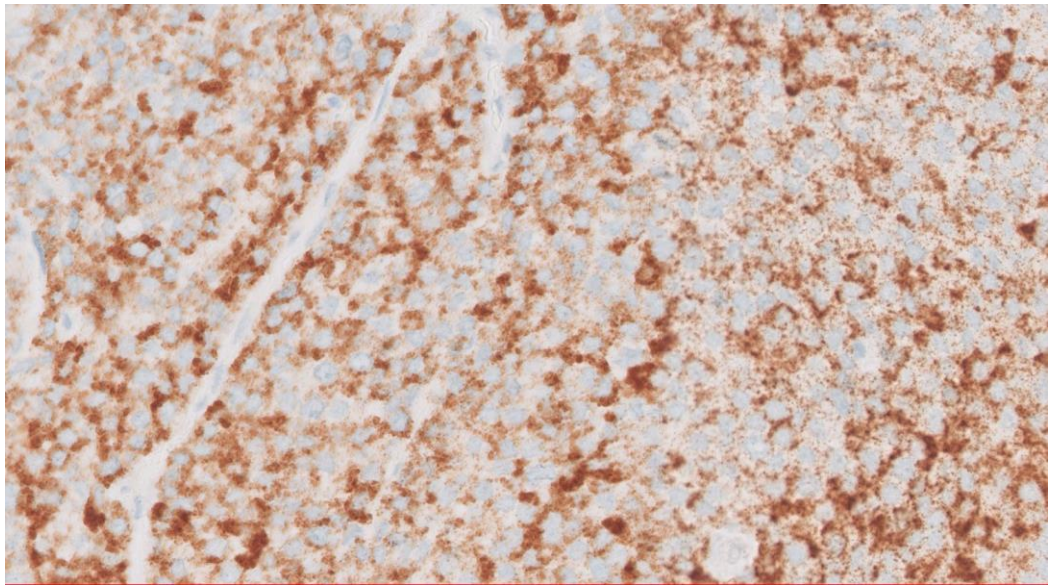
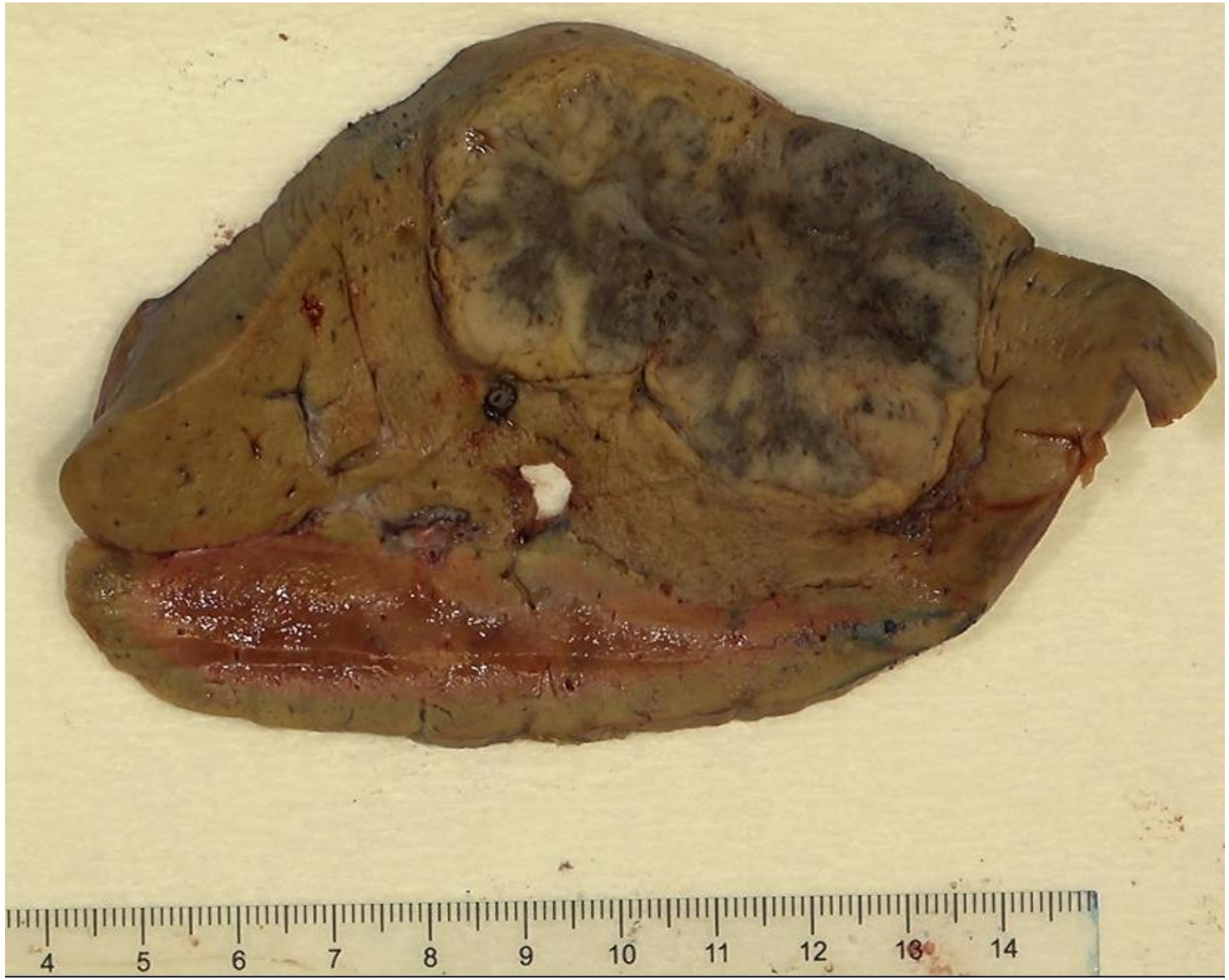


Clinical History of second case

- Mid 20’s female on oral contraceptives presenting with a large left-sided hepatic lesion. Lesion was 3.7 cm in 2021 with increase to 7.4 cm in 2024, probable hepatic adenoma by CT-scan.

- ➔ Undergoes left-sided hepatectomy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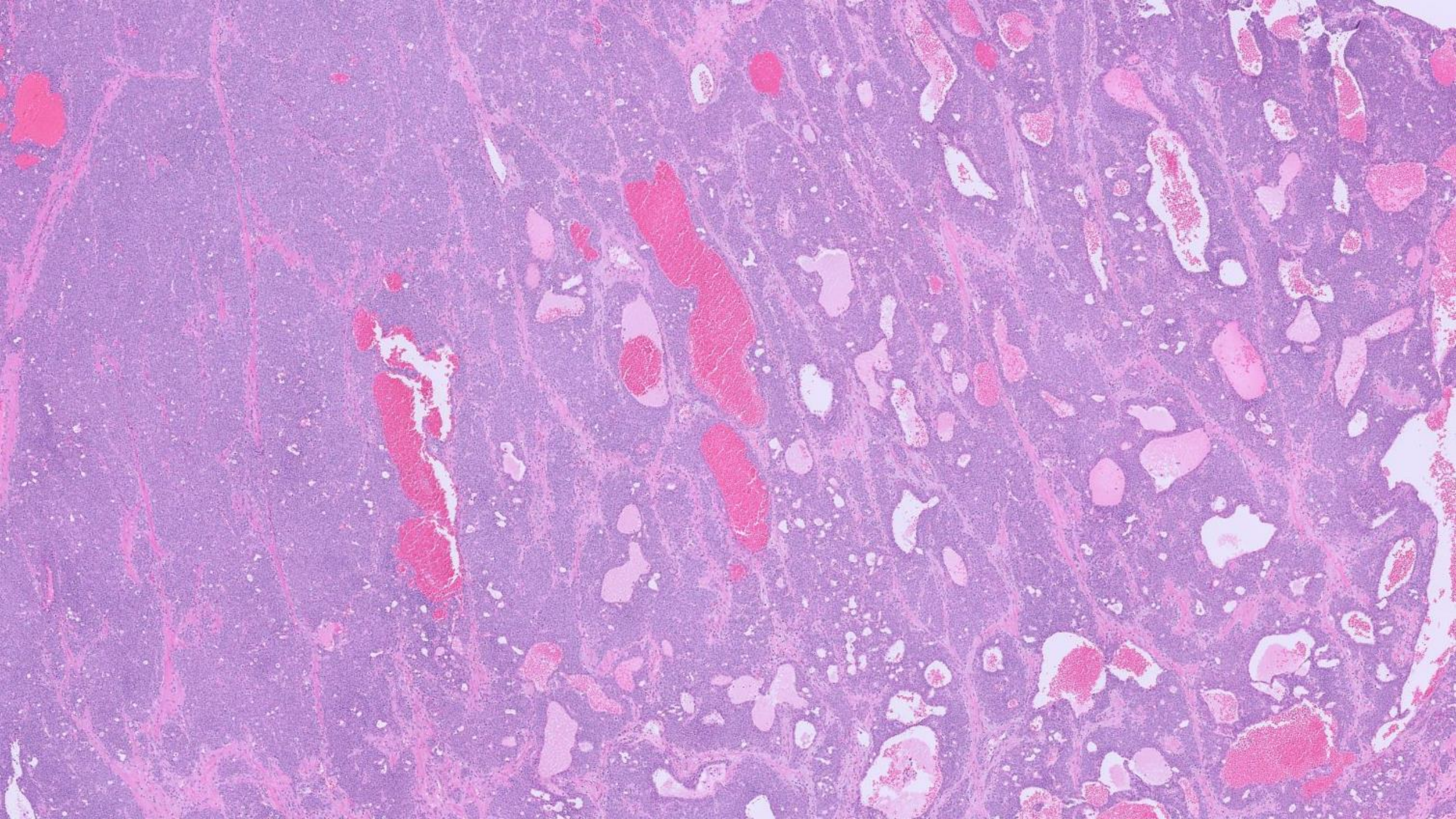
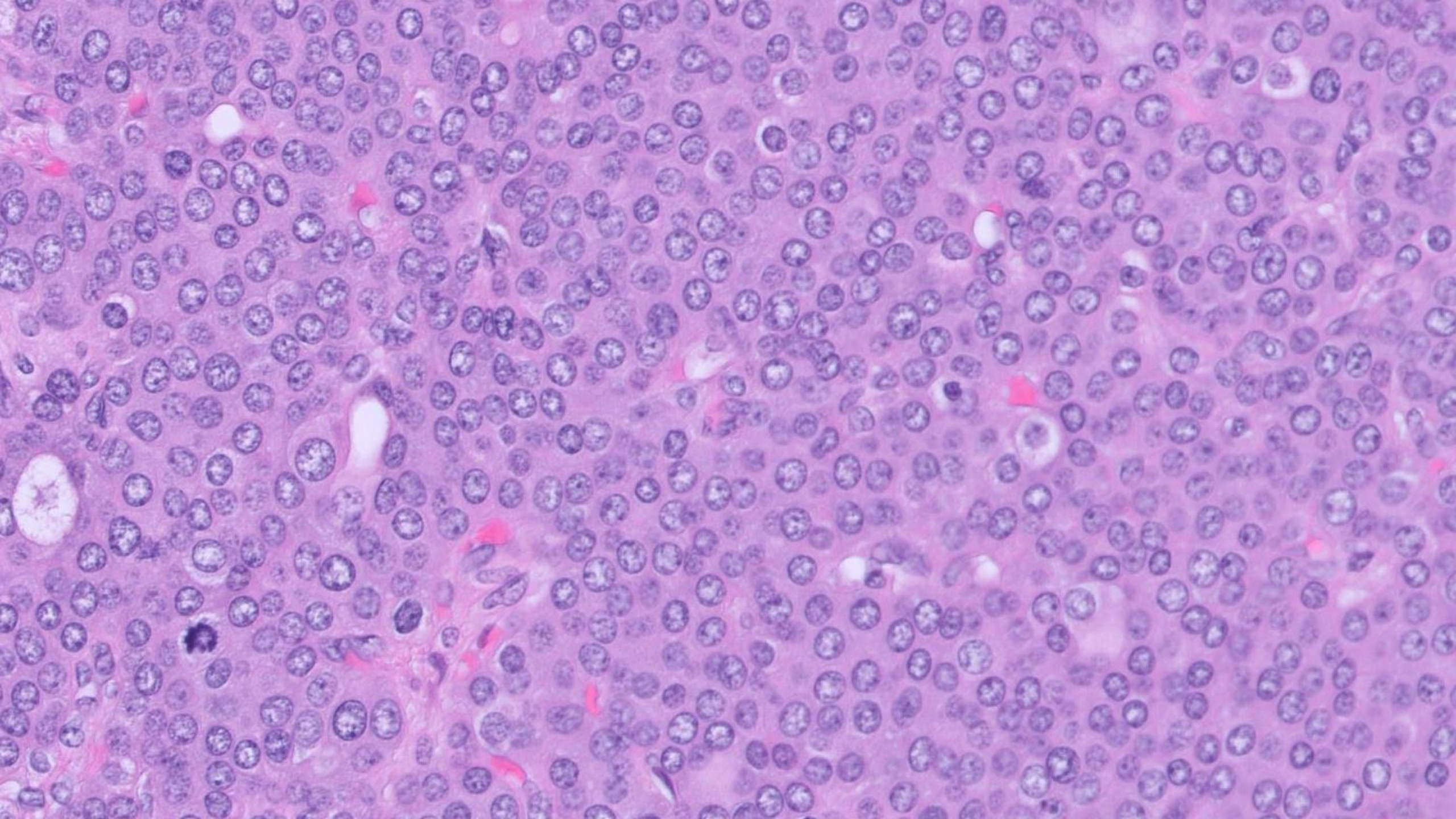
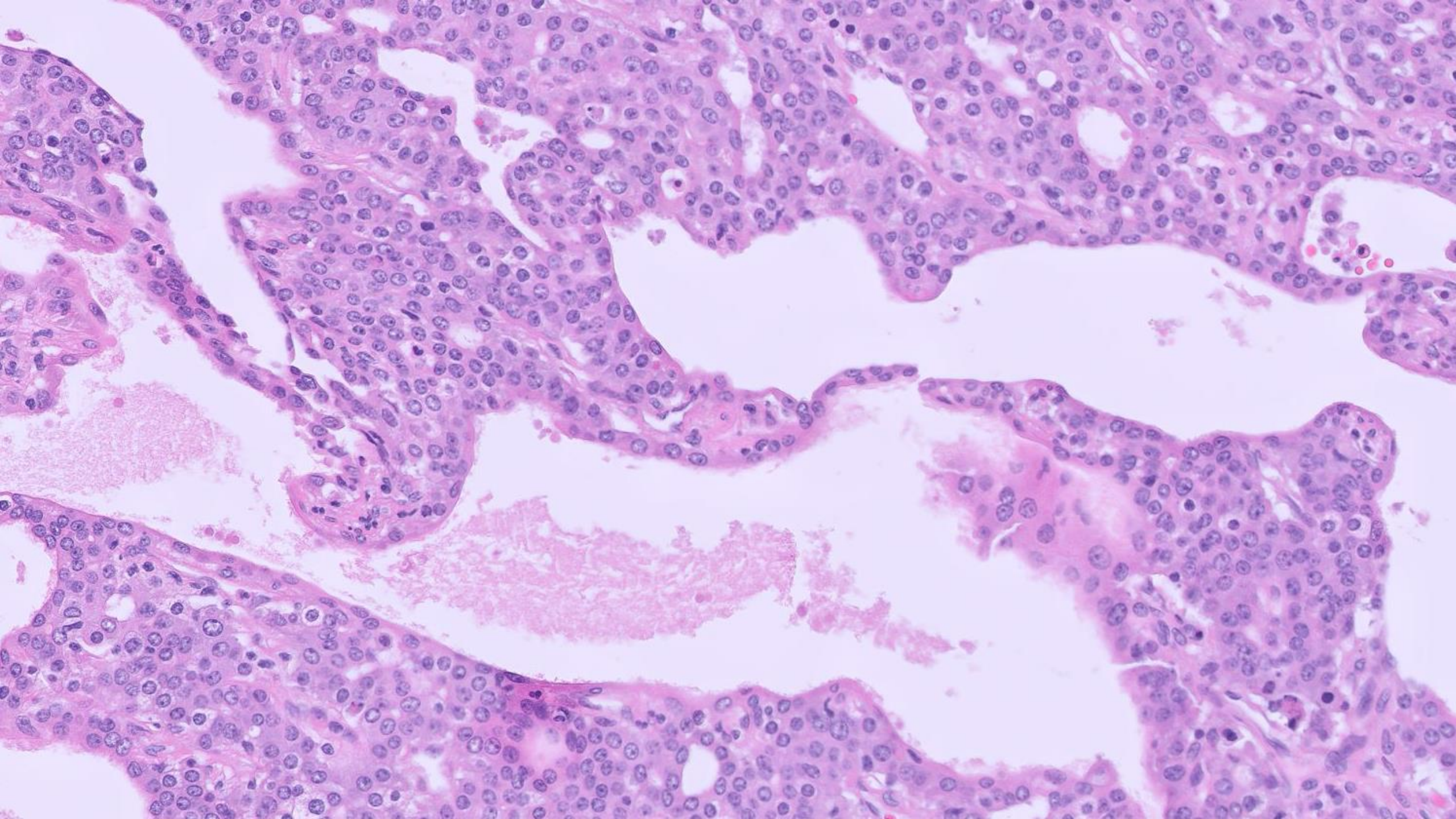
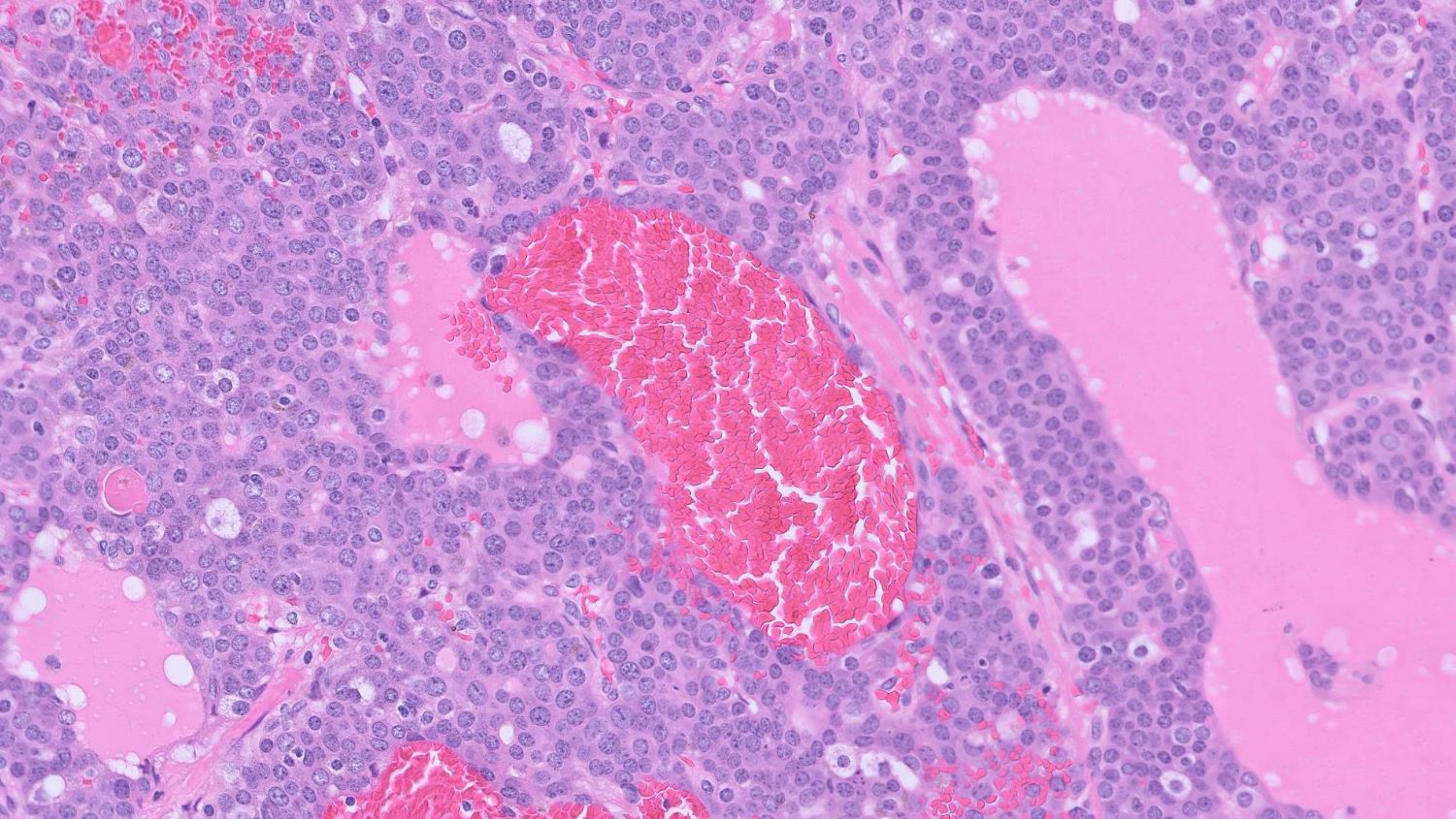
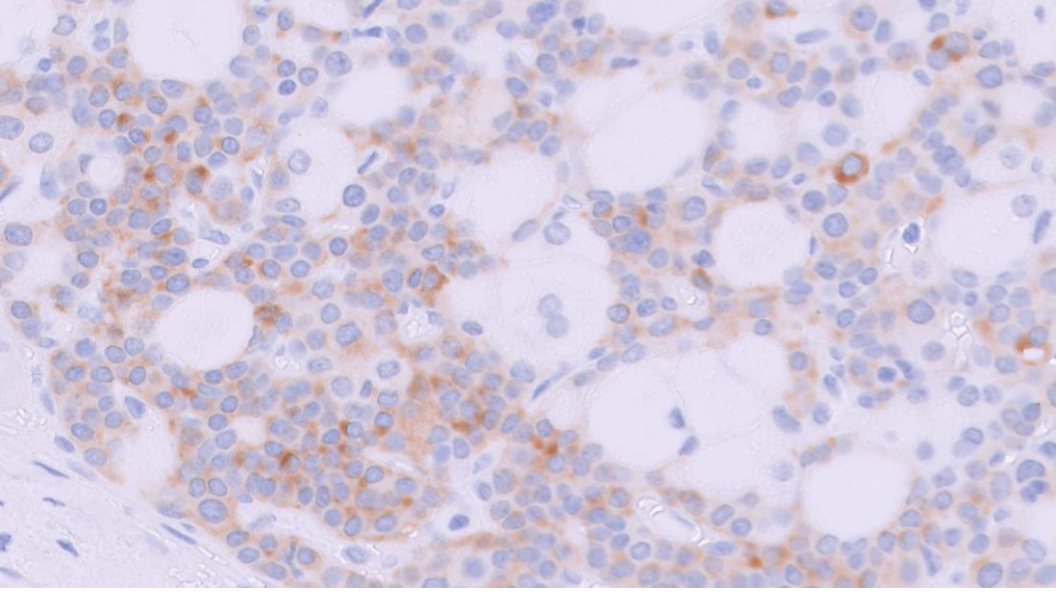


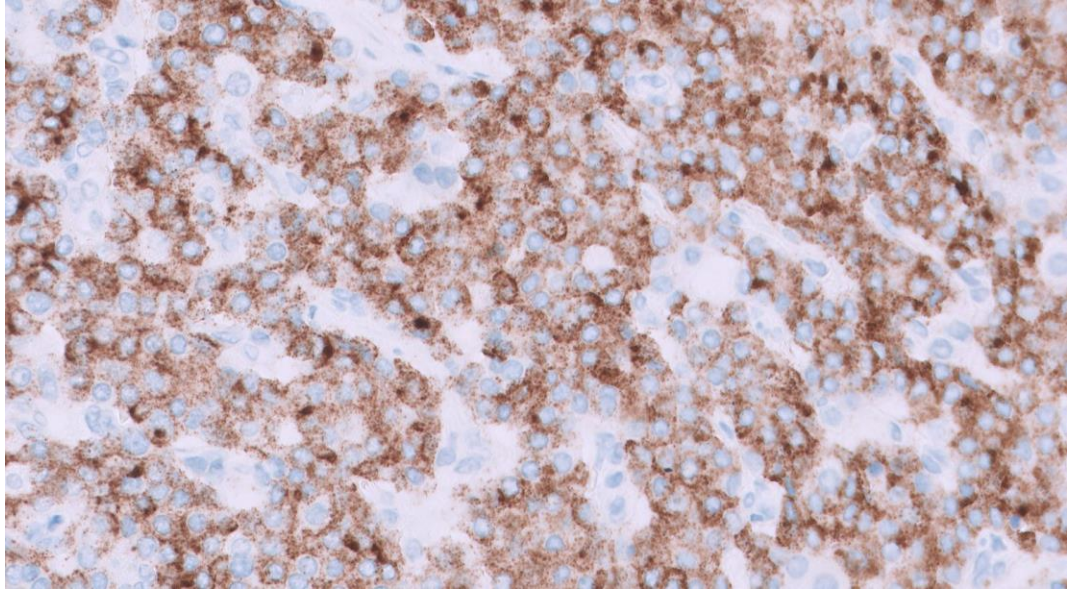






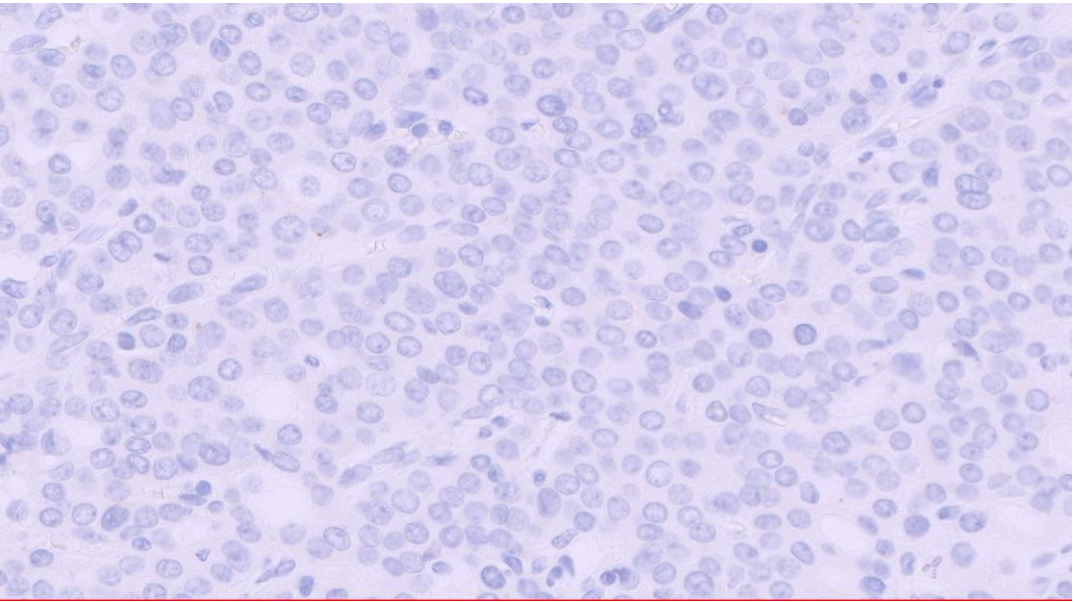


Synaptophysin

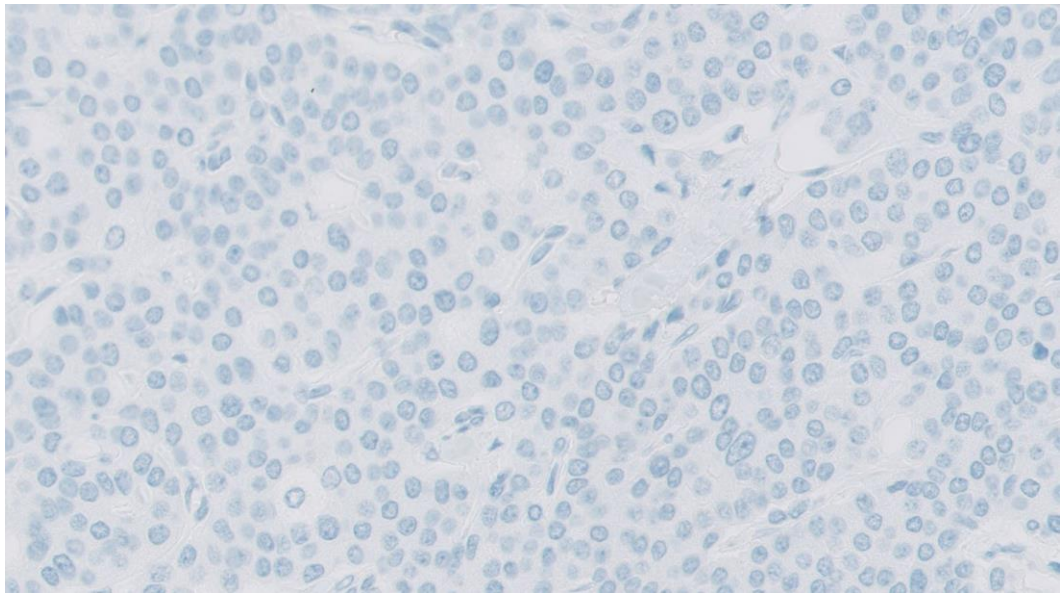


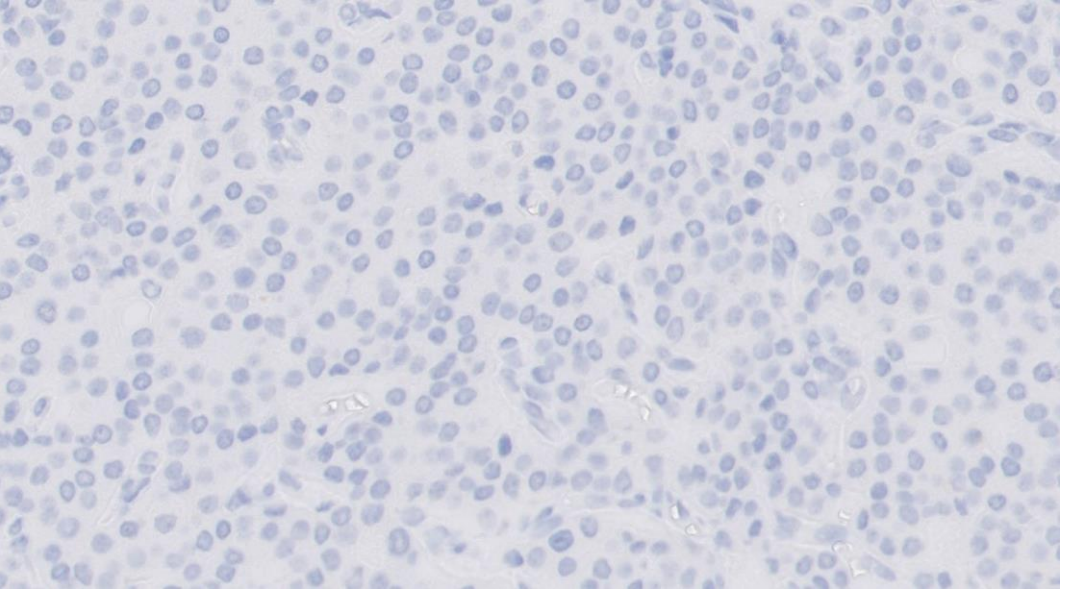
Chromogranin

Glipican-3

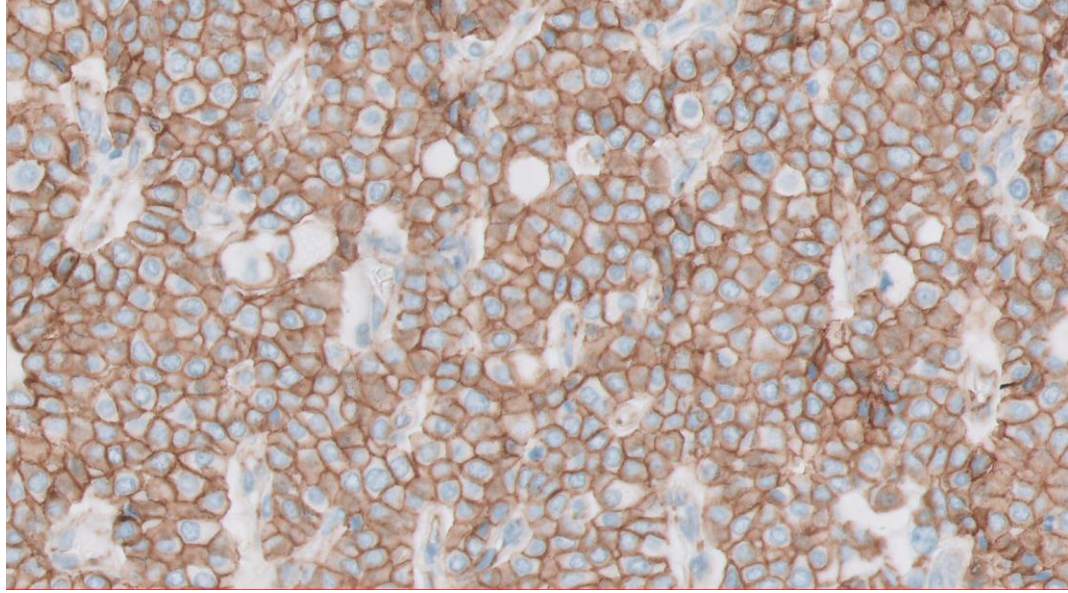


HEPPAR1



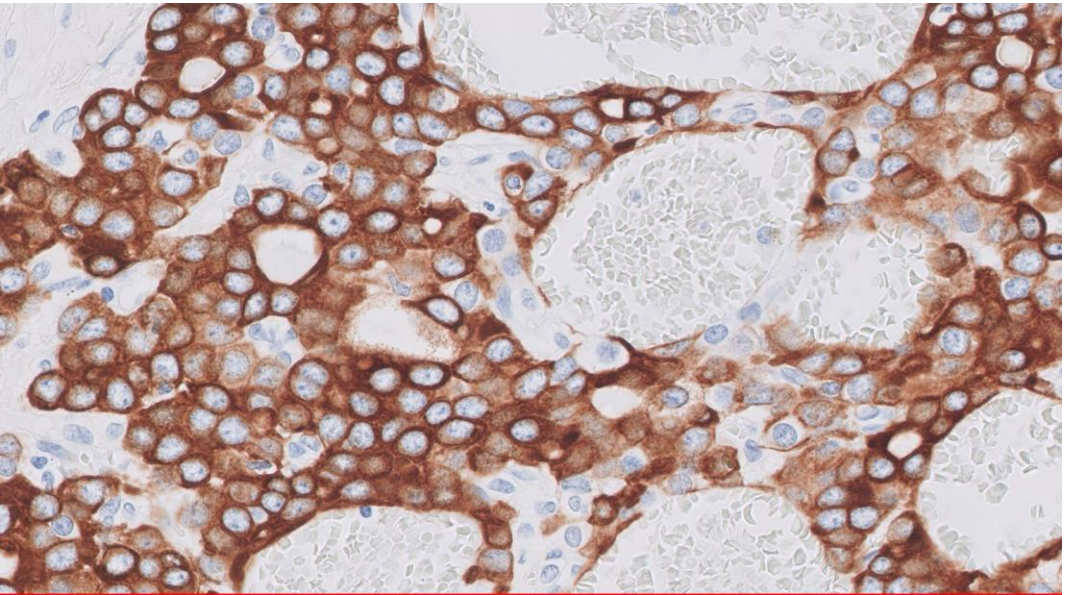


Arginase-1



Beta-Catenin

CK7



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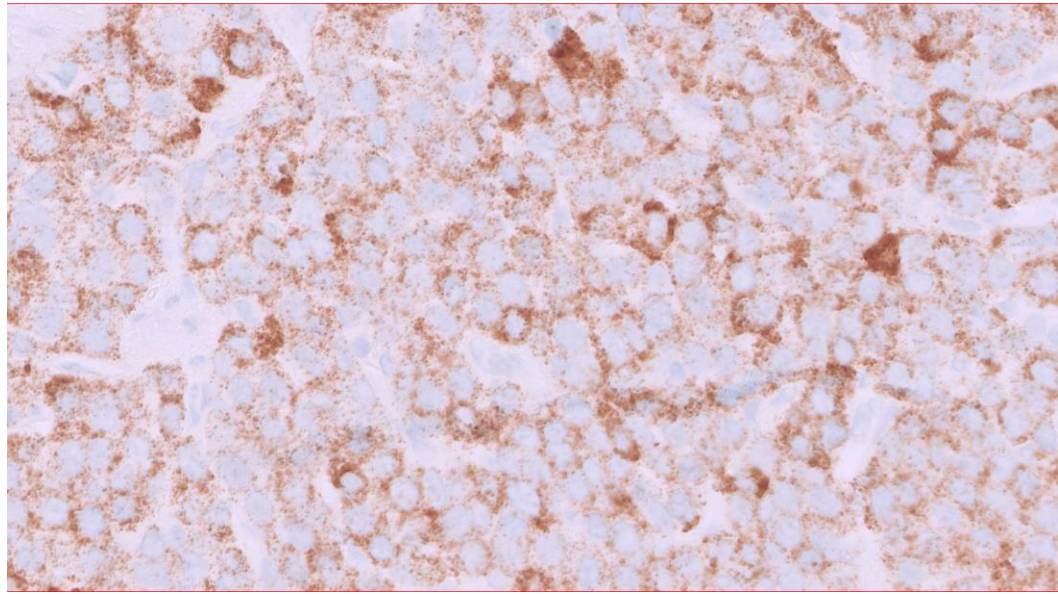
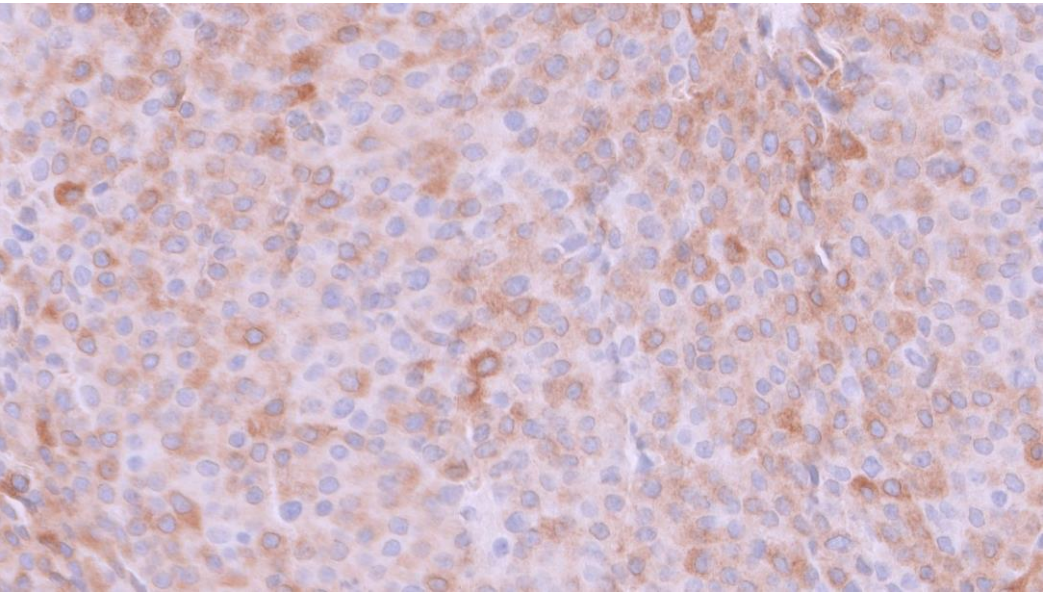


DIAGNOSES?



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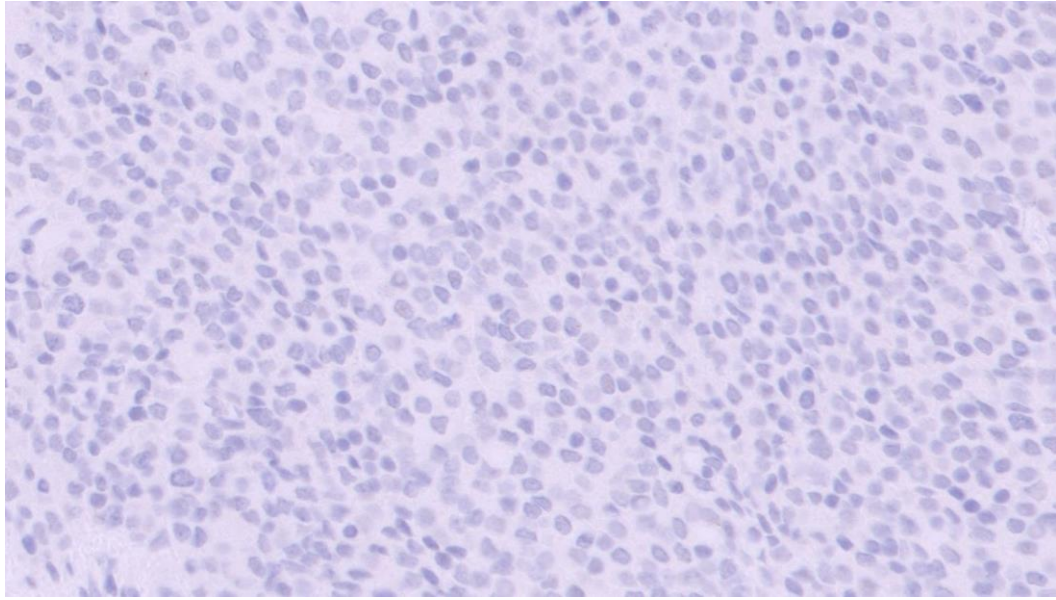

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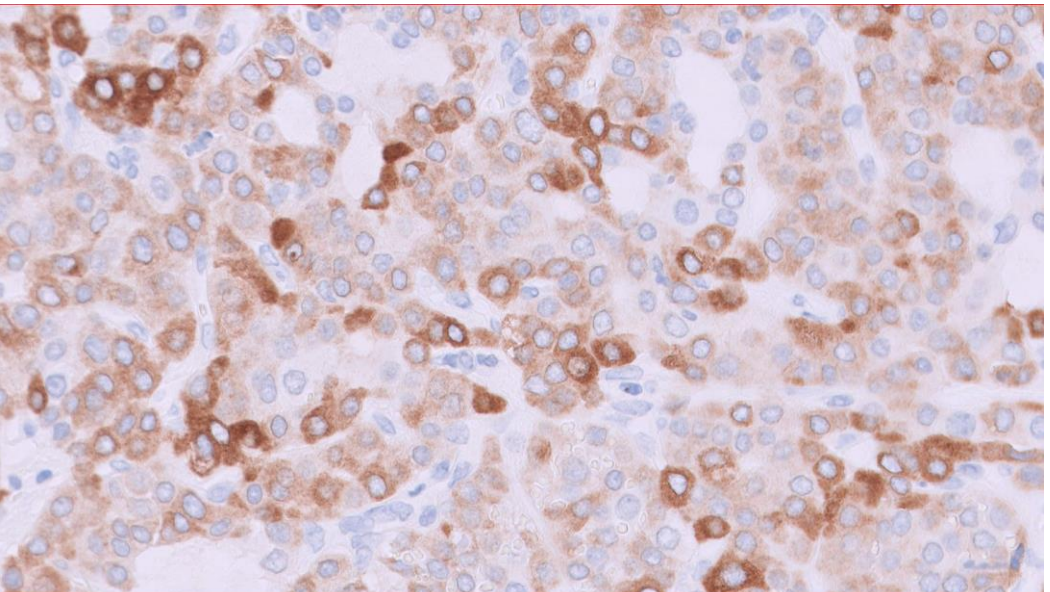
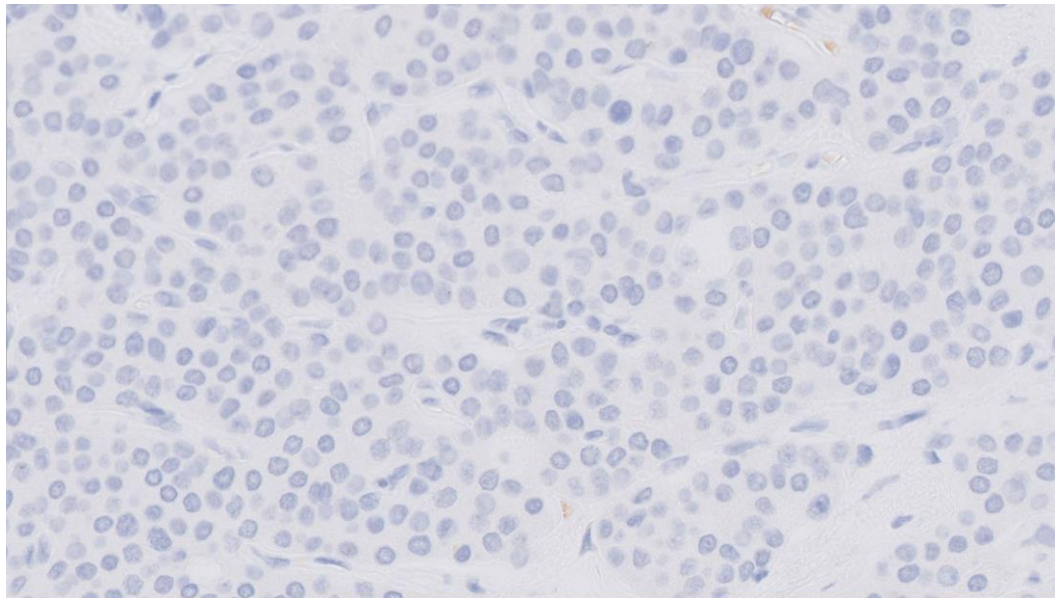
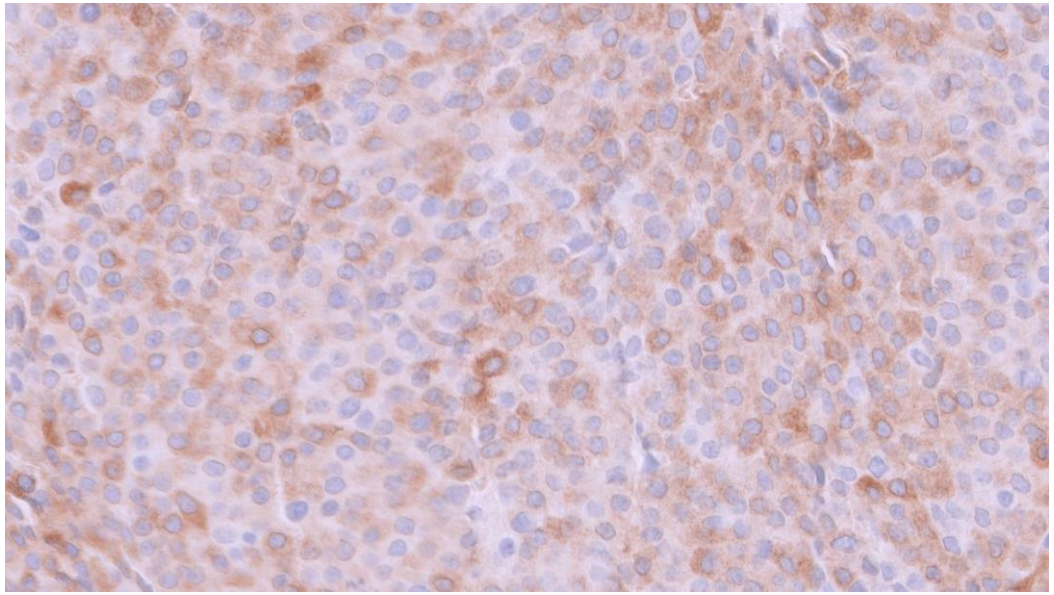
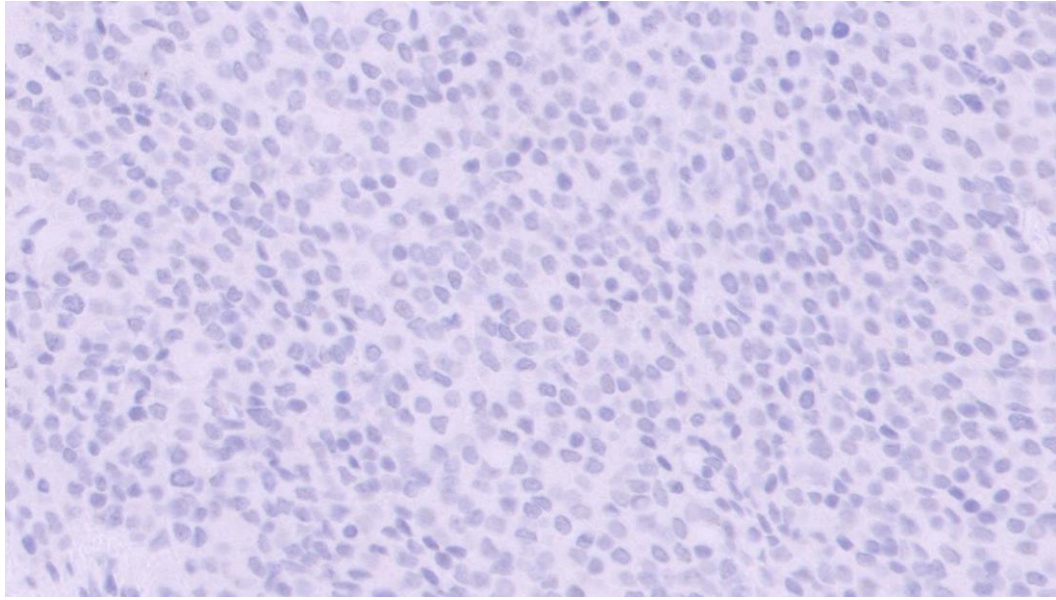


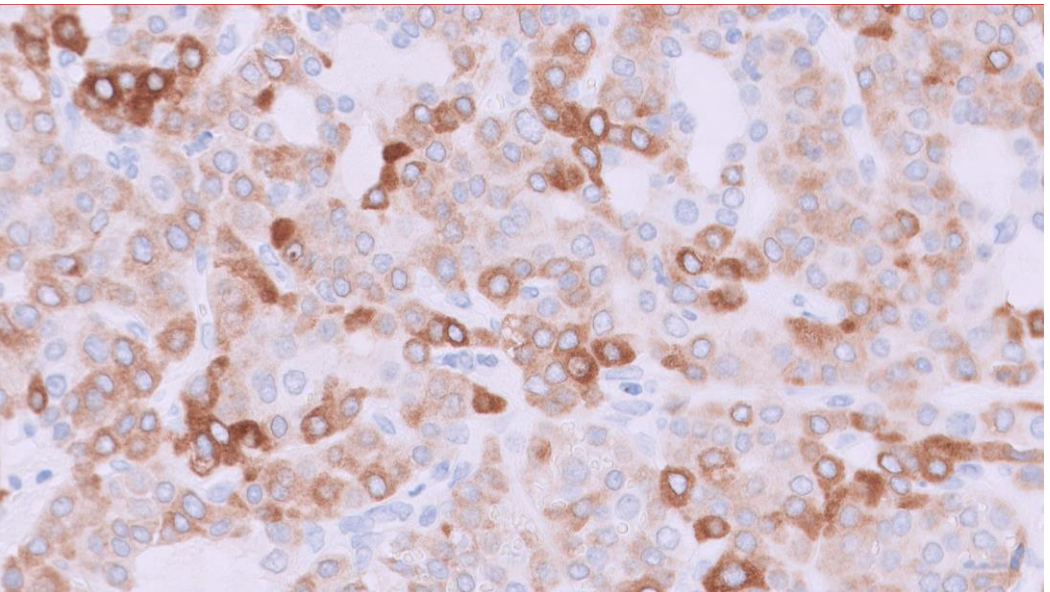
INSM1

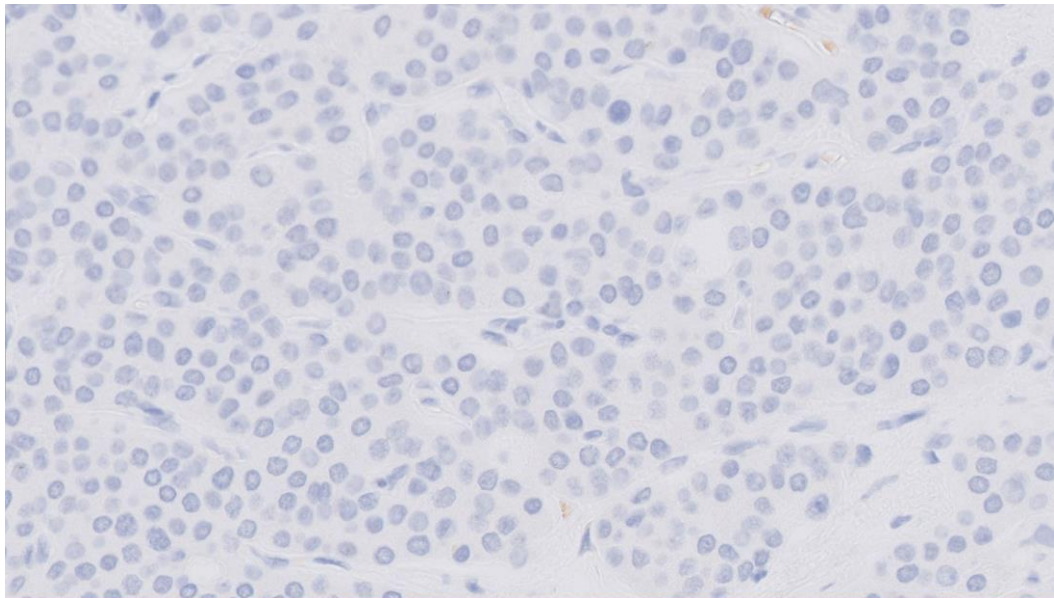






Solid-tubulocystic variant of intrahepatic cholangiocarcinoma (NIPBL::NACC1 Fusion)





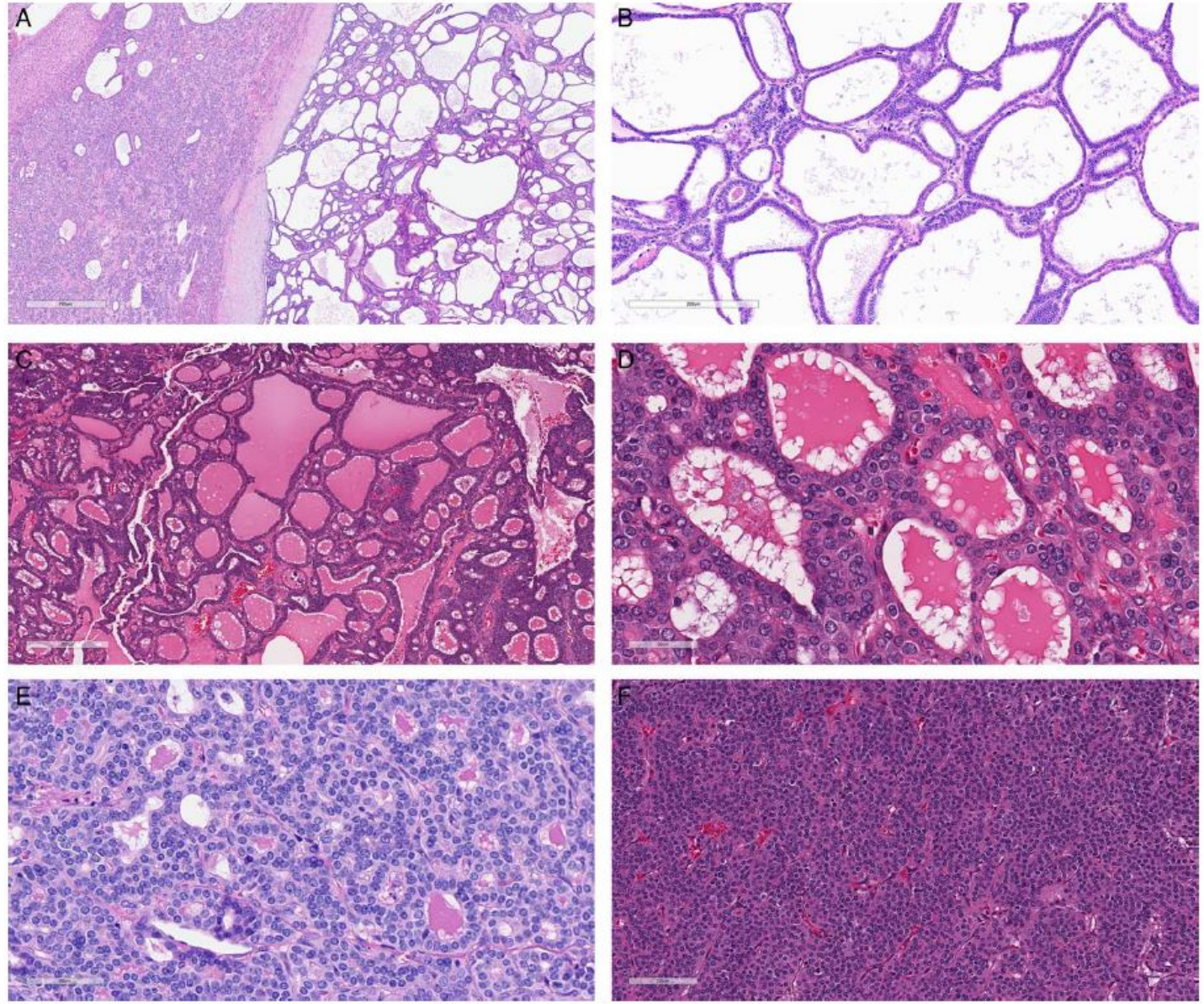


FIGURE 2. Histologically, *NIPBL::NACC1* fusion hepatic carcinomas show variable architectural patterns (A). All tumors contained a component of follicular/microcystic areas with variable dilatation (B, C), many of which contained colloid-like luminal material with peripheral vacuolization (D, E). Other components included solid or insular-like growth patterns (F). High power demonstrated monotonous round cells without significant mitotic activity or atypia (E, F).

How to diagnose this entity?

- Immunohistochemistry:
  - + Diffuse Albumin ISH
  - + Diffuse Inhibin
  - - INSM1
  - - Arginase 1
  - - HEPPAR1
  - - Glypican 3
    - Additional data shows high positive rate for nuclear MYC staining!
    - Variable low rates of RB loss
- Diagnostic pitfalls:
  - NET
  - Intrahepatic cholangiocarcinoma
  - Mixed HCC/Cholangiocarcinoma

What to call this tumor?

- “Solid-tubulocystic variant of intrahepatic cholangiocarcinoma”
  - Morphology: Variable
    - Solid
    - Trabecular
    - Tubulocystic
    - “Thyroid-like”
    - “Granulosa cell tumor like”
    - Biphasic small/large cell cytology vs uniform well differentiated NET-like
- “NIPBL::NACC1 Fusion Hepatic Carcinoma”
- “Cholangioblastic cholangiocarcinoma”
  - Taxonomy: Hepatocellular carcinoma and cholangiocarcinoma
    - Cholangiocarcinoma >> HCC
      - Could be the equivalent, in the cholangiocarcinoma family, of fibrolamellar hepatocellular carcinoma (DNAJB1-PRKACA fusion)
- “Inhibin-positive hepatic carcinoma”
  - Inhibin can stain with focal positivity in
    - HCC
    - Mixed HCC/Cholangiocarcinoma
    - Rarely in NET

What to tell the clinician?

TABLE 4. All Cases of Thyroid-like Cholangiocarcinoma or Inhibin-positive Cholangiocarcinoma That Have Been Reported in the Literature to Date, Including the Current Study

No.	Reference	Age	Sex	Liver disease	Inhibin	Gene fusion	Treatment	Follow-up (mo)	Outcome
1	Hissong et al[4]	60	F		+	Present	Resection	156	NED
2	Vrettou et al[11]	52	M		+	Present	Resection	168	NED
3	Chablé-Montero et al[9]	23	F		+	Present	Resection	81	NED
4	*Current series*	46	F		+	Present	Resection	12	NED
5	*Current series*	33	F		+	Present	Resection	22	DOD
6	*Current series*	32	F		+	Present	Resection	7	NED
7	*Current series*	61	F		+	Present	Chemotherapy/Radiation	NA	AWD
8	*Current series*	48	F	Steatohepatitis	+	Present	Resection/chemotherapy	4	NED
9	Fornelli et al[10]	26	F	Cirrhosis	+	Present	Resection/chemotherapy	18	DOD
10	*Current series*	42	F	Steatosis	+	Present	Resection	6	NED
11	*Current series*	45	F		+	Present	NA	NA	NA
12	Wen et al[7]	24	F		+	Present	Resection/chemotherapy	53	AWD
13	Wen et al[7]	54	M		+	Present	Resection	10	AWD
14	Wen et al[7]	51	M		+	Present	Resection	17	NED
15	Huang et al[29]	15	F		+	Present	Resection/chemotherapy	30	NED
16	Wen et al[7]	41	F	Steatohepatitis	+	Present	Resection	17	NED
17	Braxton et al[13]	17	F		+	Not performed	Resection/chemotherapy	41	DOD
18	Braxton et al[13]	44	F		+	Not performed	Resection	NA	NA
19	Braxton et al[13]	25	F		+	Not performed	Resection/chemotherapy	30	DOD
20	Chen et al[30]	68	F		+	Not performed	Resection/chemotherapy	72	NED
21	Mittal et al[8]	37	F		+	Not performed	Resection	24	NED
22	Mittal et al[8]	28	F		+	NIPBL exons 9-48 del	Resection	5	NED
23	Mittal et al[8]	19	F		+	Not performed	Resection/chemotherapy	24	DOD
24	Mittal et al[8]	34	F		+	Not performed	Resection	12	NED
25	Mittal et al[8]	44	F		+	Not performed	Resection	15	AWD
26	Mittal et al[8]	33	F		+	Not performed	Resection	1	AWD
27	Bardia[14]	26	F		NP	Not performed	Chemotherapy	2	DOD
28	Khan et al[31]	59	F	Cirrhosis	NP	Not performed	Resection	16	NED

AWD indicates alive with disease; DOD, died of disease; NA, not available; NED, no evidence of disease.

NIPBL (Nipped-B-like protein)::NACC1 (Nucleus accumbens associated 1)

- NIPBL is a key component of the cohesin loading complex, which helps attach cohesin to DNA, facilitating the folding of the genome
- NACC1 gene, is a transcriptional regulator and a member of the (BTB for Broad-complex, Tramtrack, and Bric-a-brac; POZ for Pox virus and Zinc finger) family
- NACC1 has been proposed to affect the acetylation patterns
  - including HIF1A, CTTN, and FOXP3
  - Preposed to alter the TGFbeta signaling pathway through similar interactions with histone deacetylases
    - Inhibin-A goes but a lot of the pathway decreases
- NACC1 also preposed to directly bind to the MYC promoter

References:

- Argani, Pedram, et al. Cholangioblastic Cholangiocarcinoma (NIPBL :: NACC1 cholangiocarcinoma): Expanded Morphologic Spectrum and Further Genetic Characterization. The American Journal of Surgical Pathology, vol. Publish Ahead of Print, January 16, 2025, doi: 10.1097/PAS.0000000000002365.

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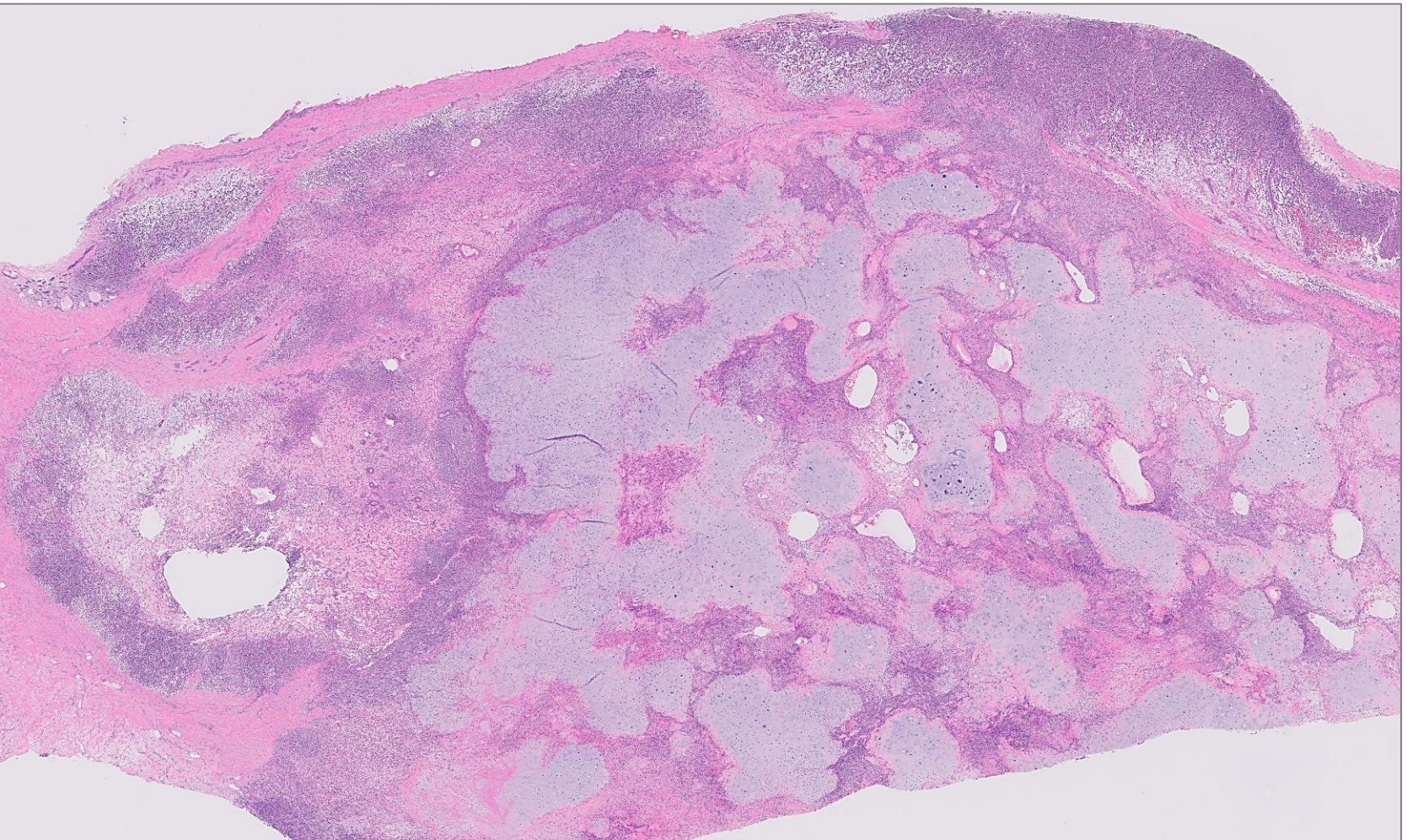
- Hissong E, Al Assaad M, Bal M, Reed KA, Fornelli A, Levine MF, Gundem G, Semaan A, Orr CE, Sakhadeo U, Manohar J, Sigouros M, Wilkes D, Sboner A, Montgomery EA, Graham RP, Medina-Martínez JS, Robine N, Fang JM, Choi EK, Westerhoff M, Delgado-de la Mora J, Caudell P, Yantiss RK, Papaemmanuil E, Elemento O, Sigel C, Jessurun J, Mosquera JM. NIPBL::NACC1 Fusion Hepatic Carcinoma. Am J Surg Pathol. 2024 Feb 1;48(2):183-193. doi: 10.1097/PAS.0000000000002159. Epub 2023 Dec 4. PMID: 38047392; PMCID: PMC11238093.

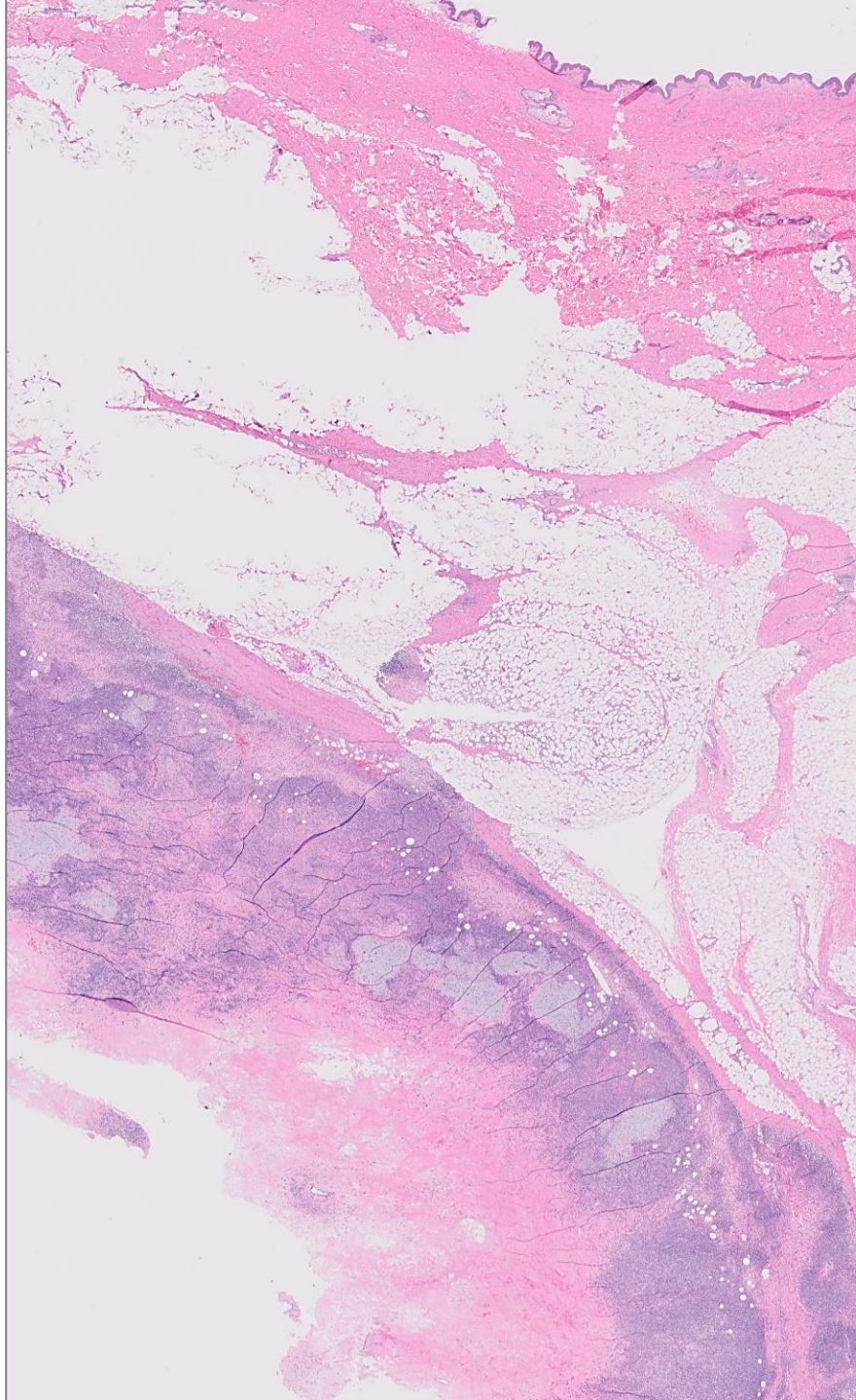
25-0405

Joanna Solarewicz, Greg Bean; Stanford

29-year-old postpartum female with right breast mass. Prior biopsy showed fibroadenoma in 2020 (not reviewed at Stanford or by referring pathologist). The mass has increased size and now measures 7 cm. She underwent a mastectomy in August of 2023.

H&E Sections





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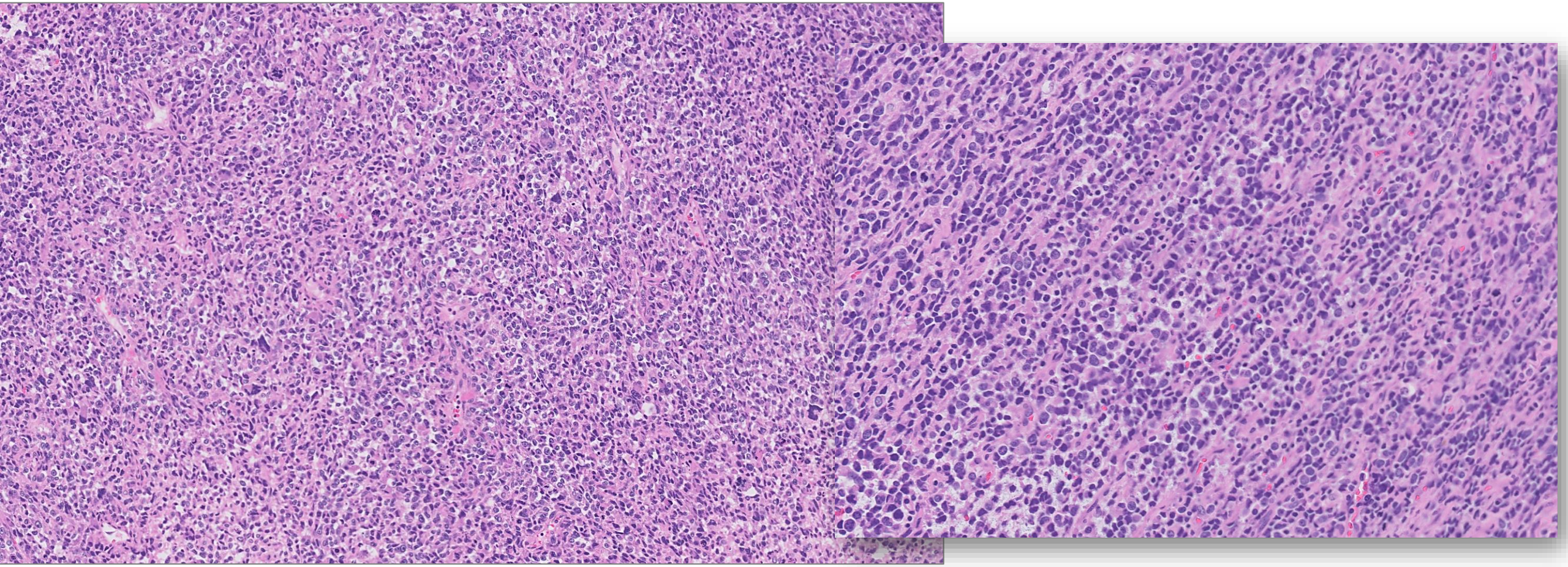

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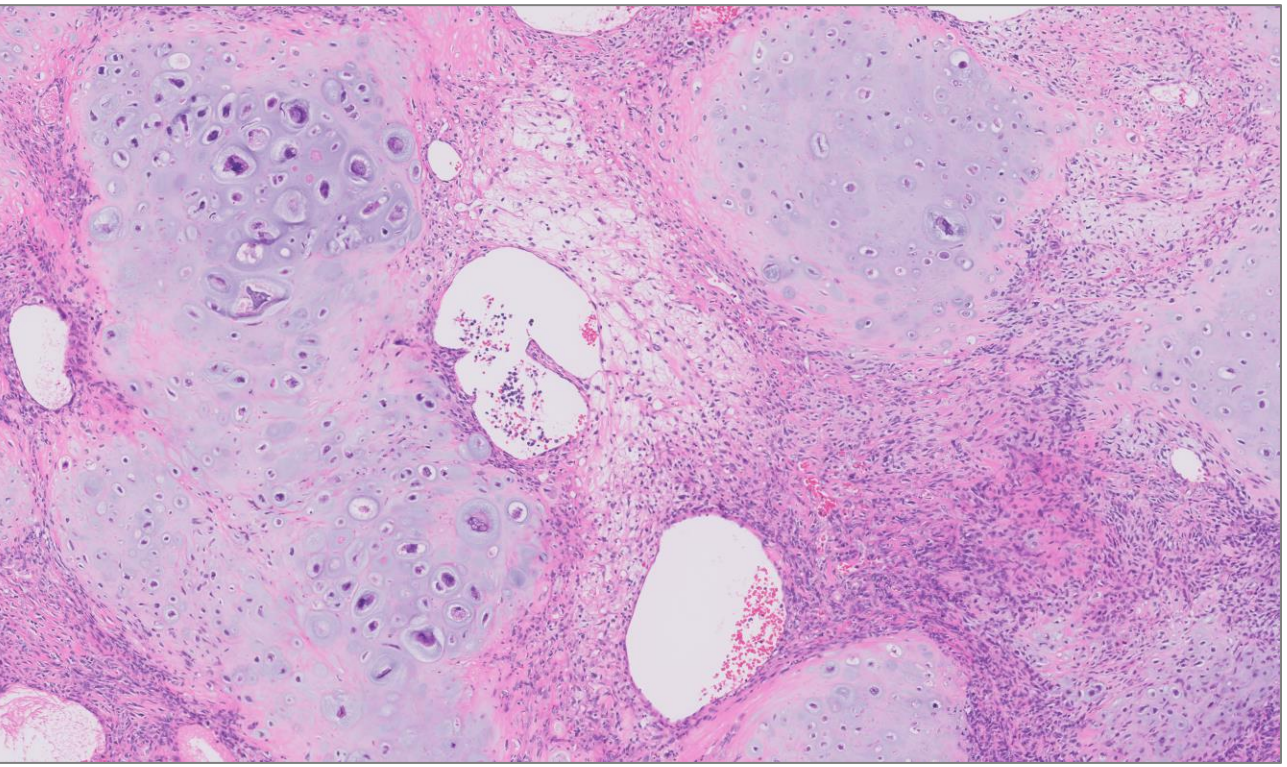
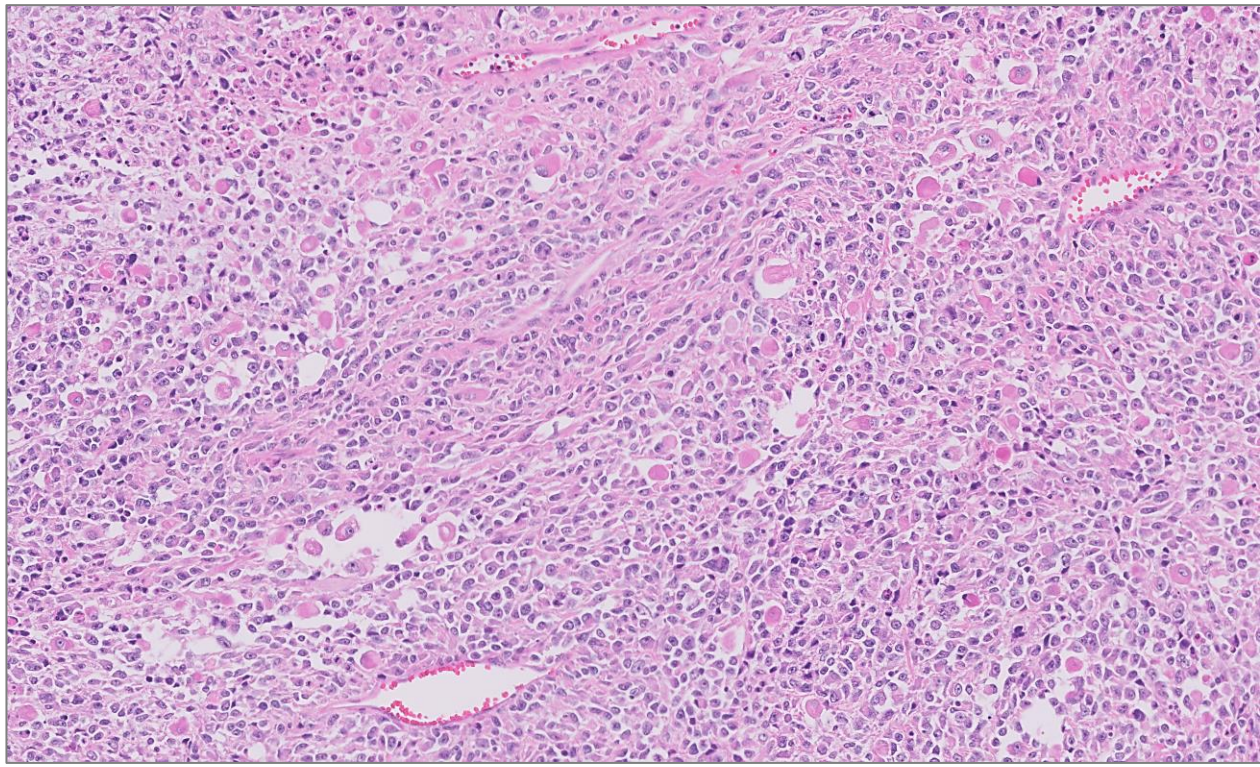
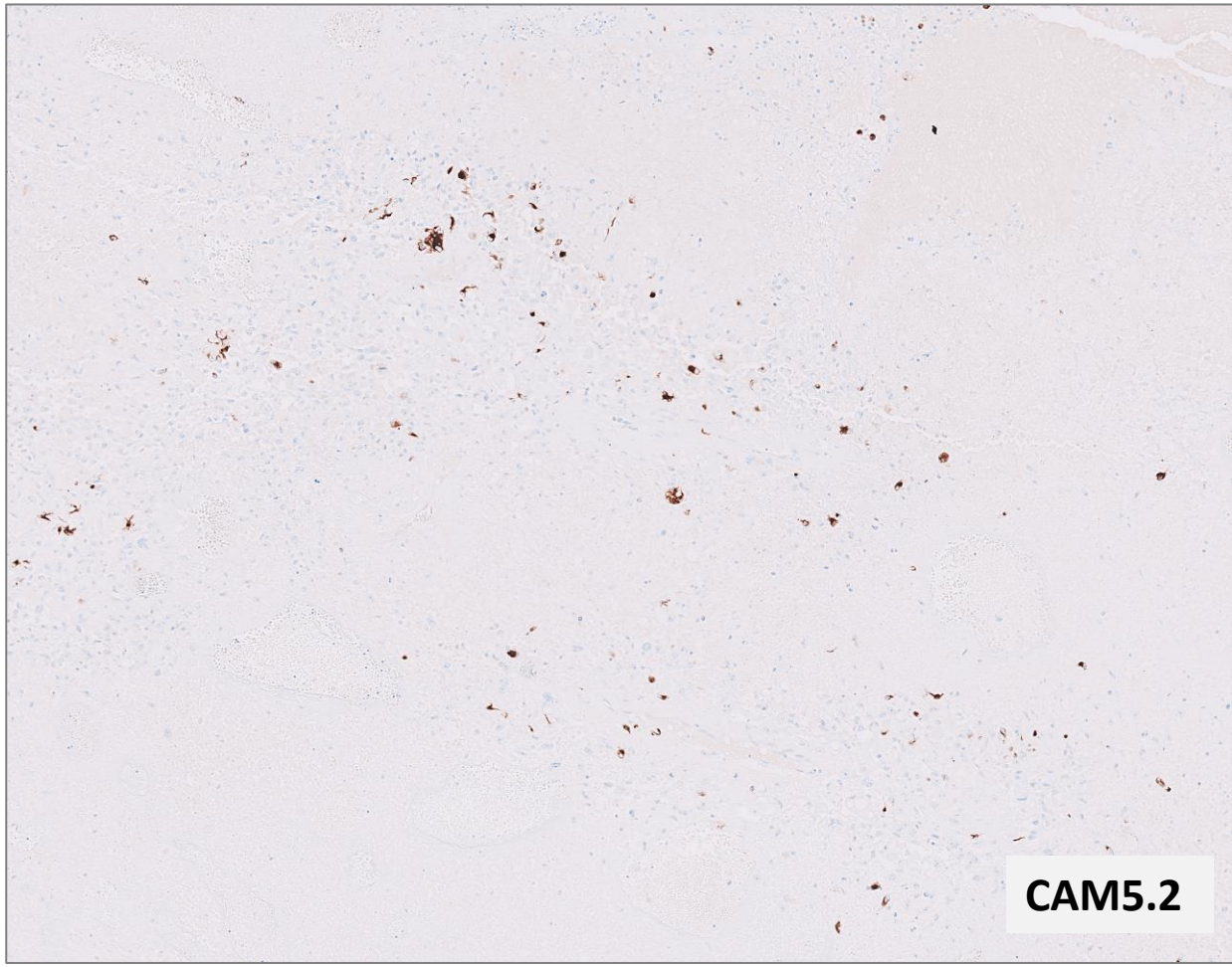




IHC

- Pan-keratin – Negative
- CAM5.2 and CK14 – Focally Positive
- P63 – Rare Positive
- CD34 – Negative
- Desmin – Focally Positive
- S100 – Focally Positive



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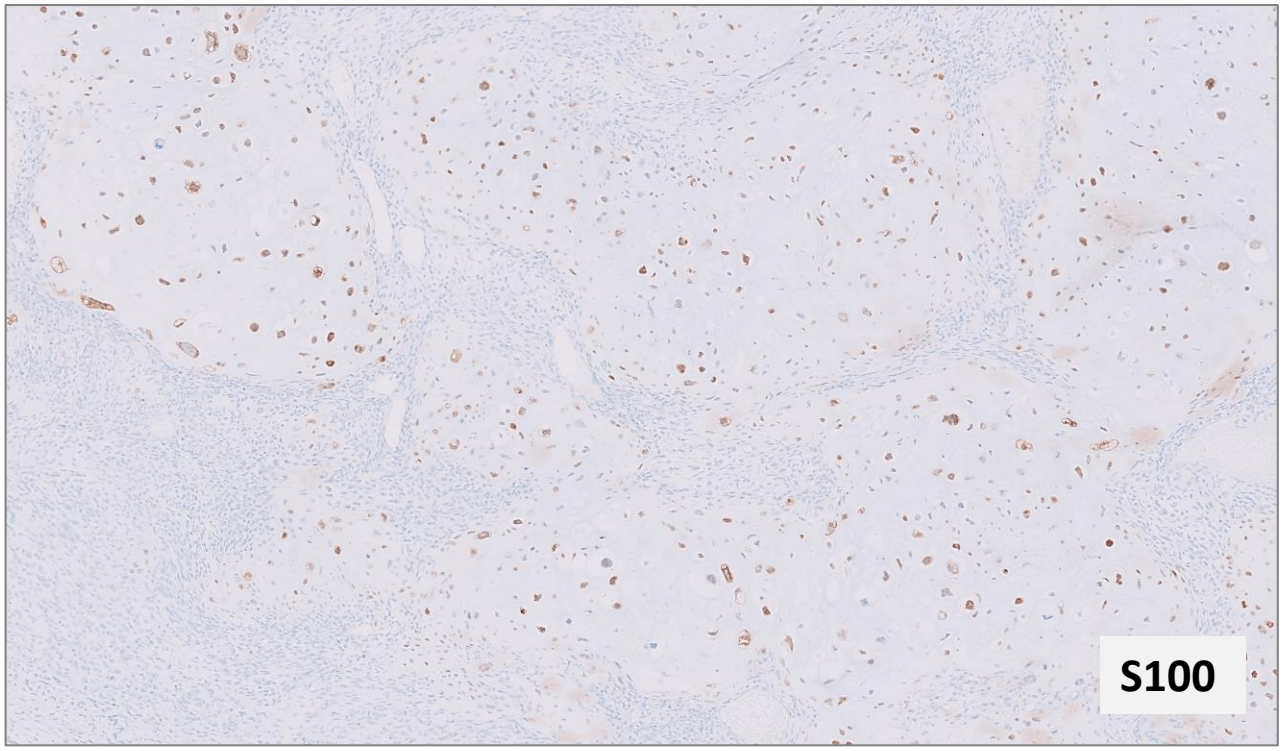
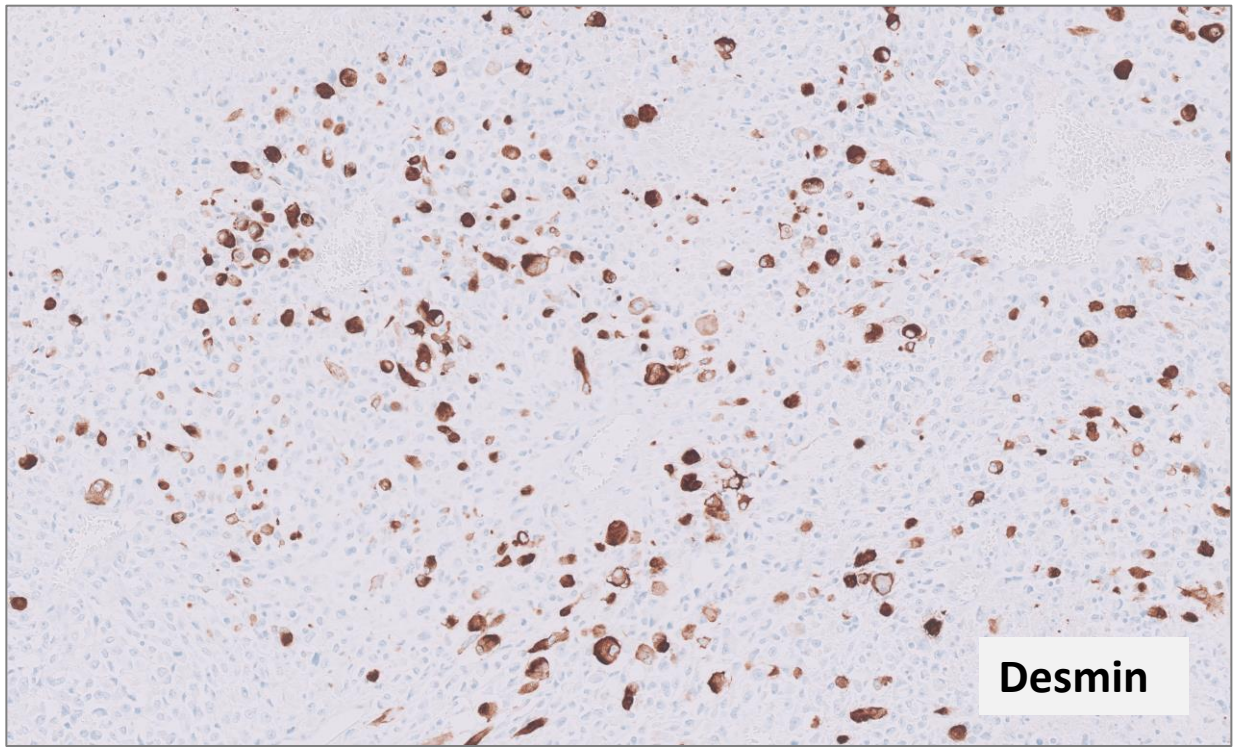




DIAGNOSIS?

Breast Case

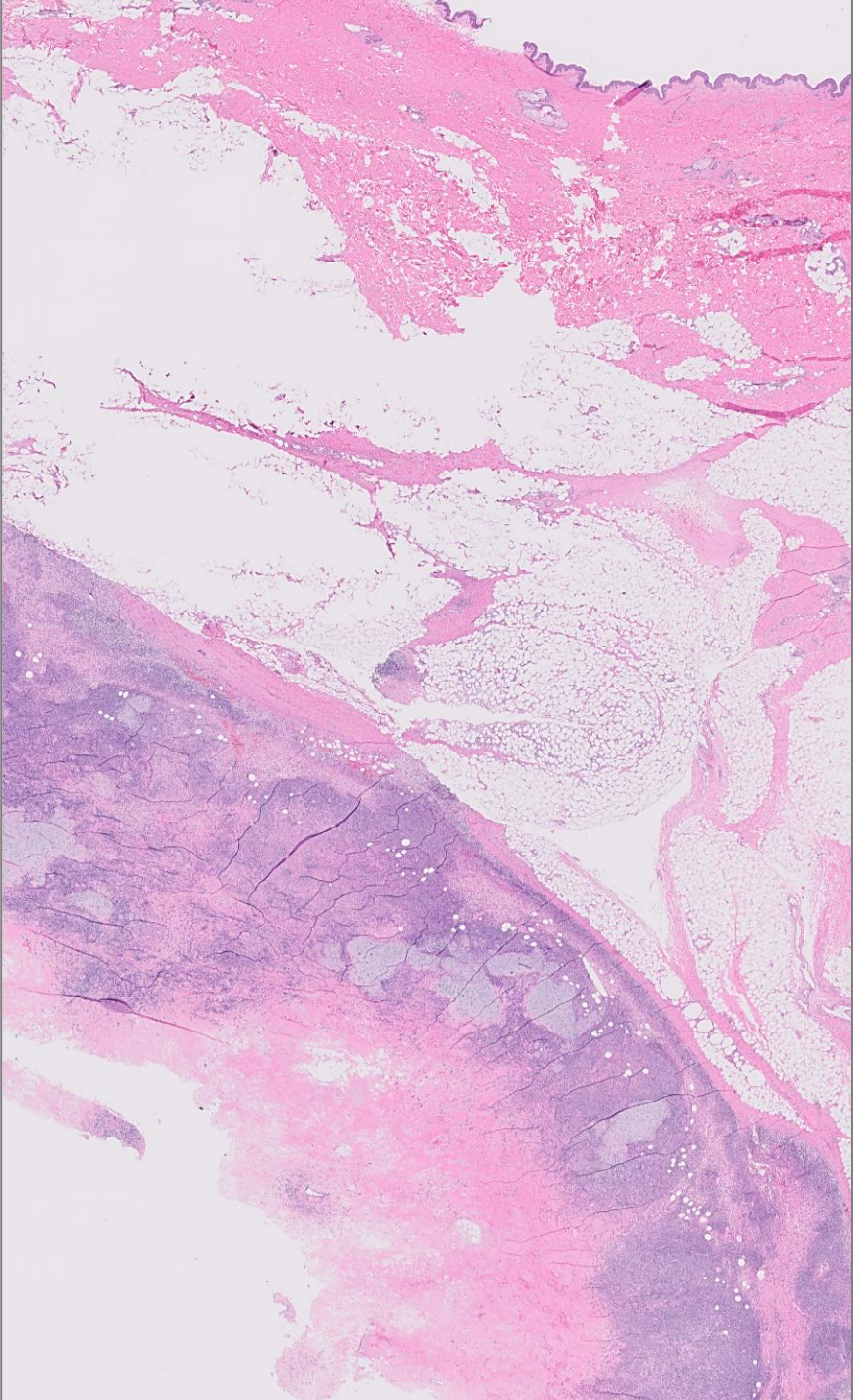
Joanna Solarewicz, DO, MS
Breast Pathology Fellow
Stanford University

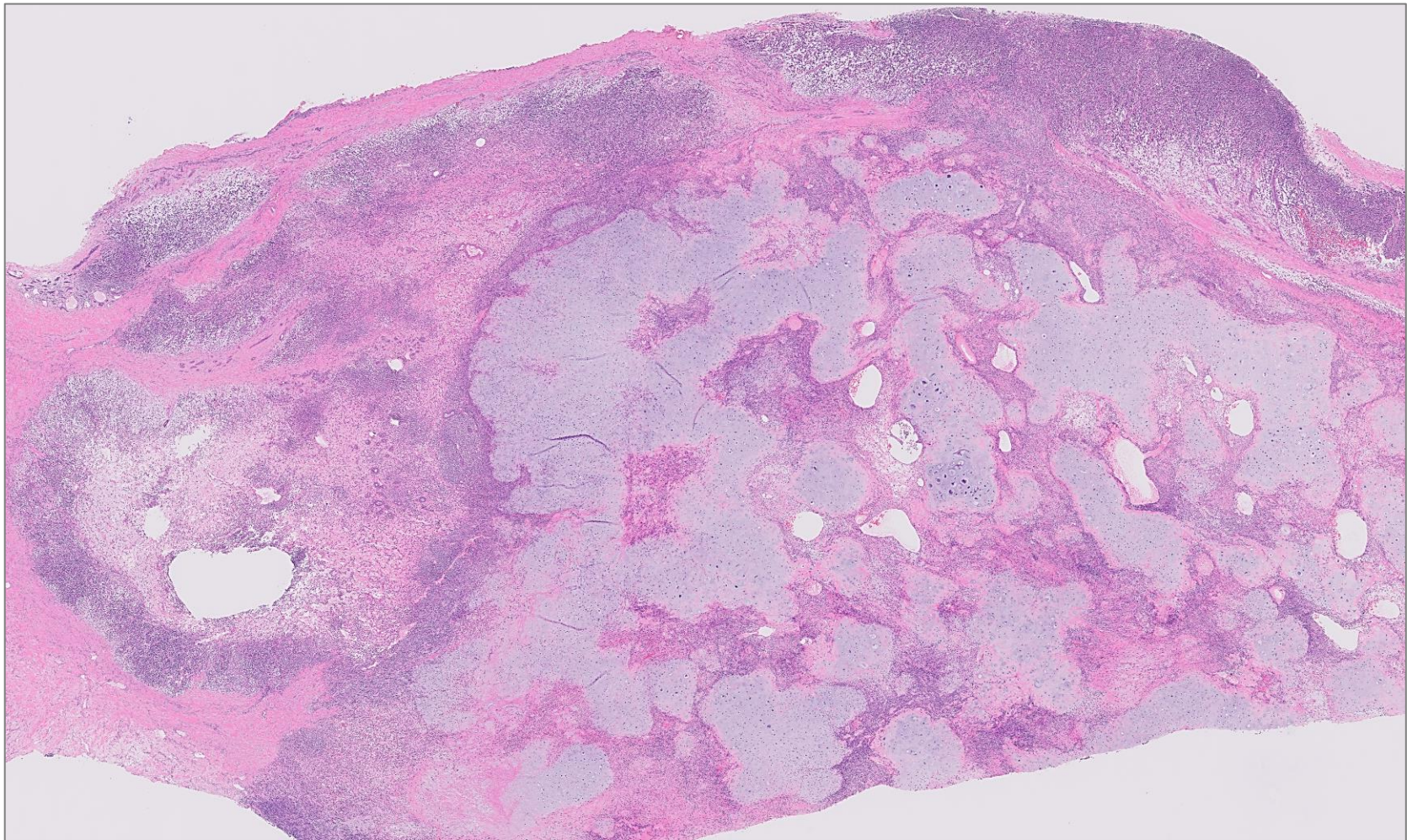
Consult Case: 29-year-old woman

- Postpartum
- Right breast mass
- Prior biopsy → **Fibroadenoma** in 2020 (not reviewed at Stanford or by referring pathologist)
- Mass has increased in size and now measures **7 cm**

→ She underwent a mastectomy in August of 2023

H&E Sections





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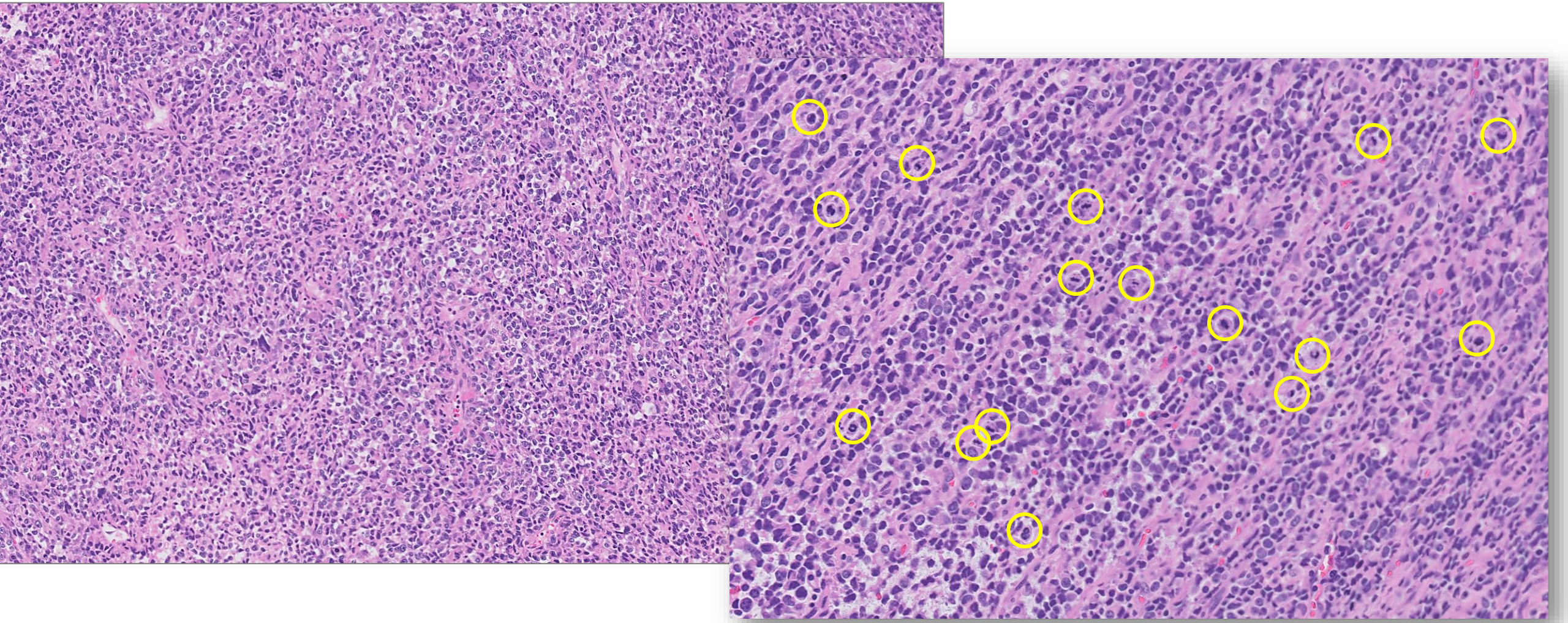

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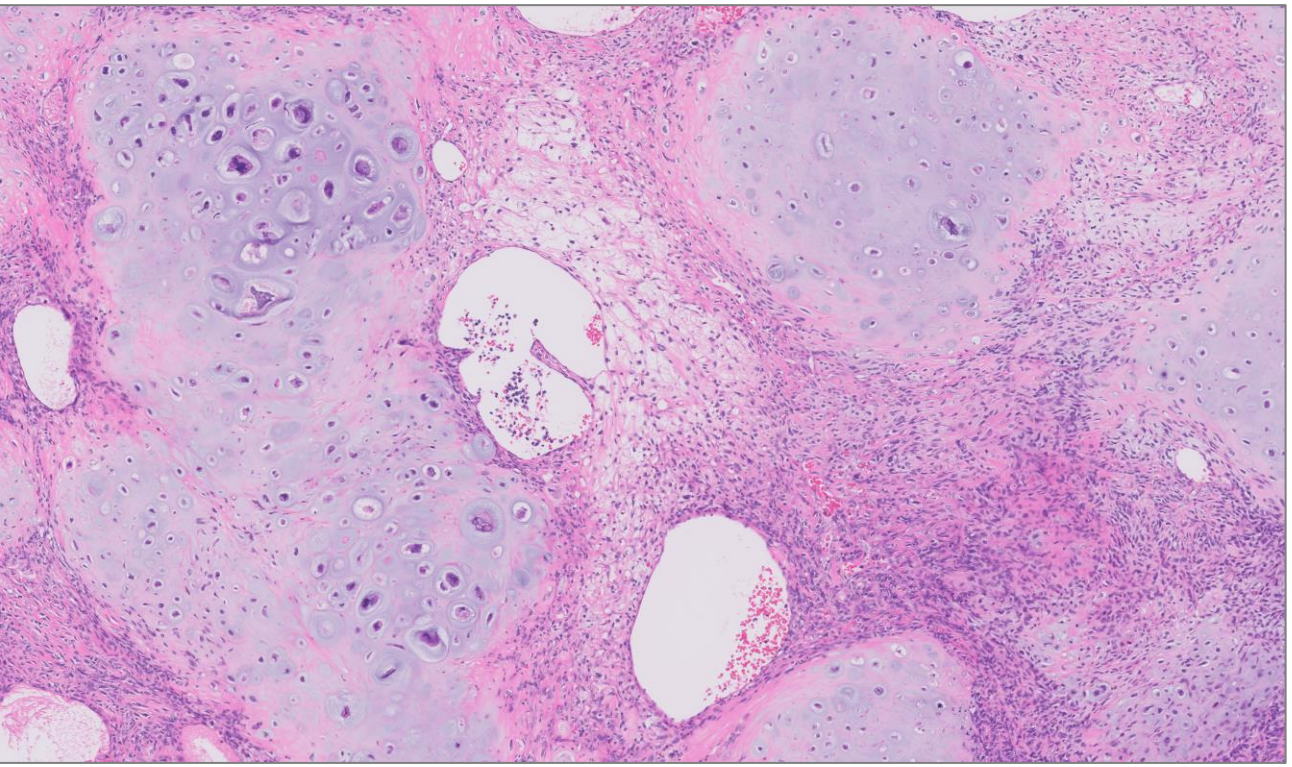

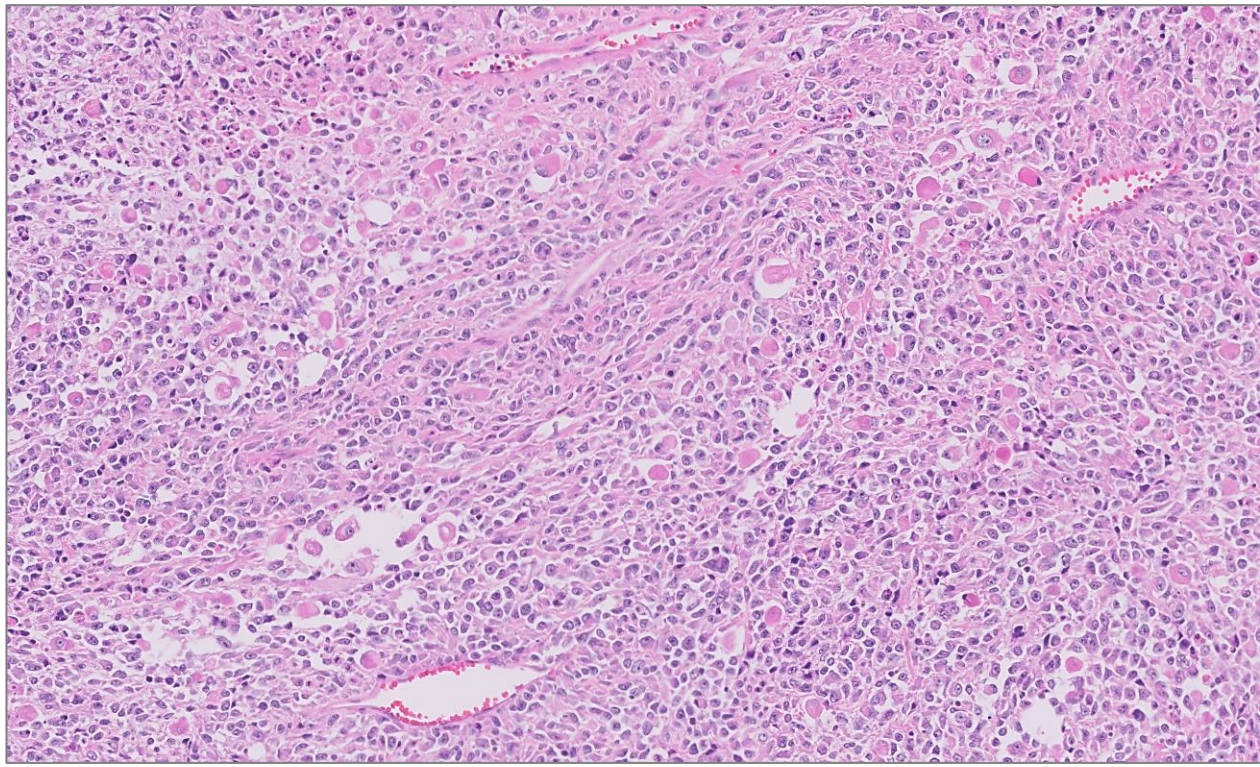

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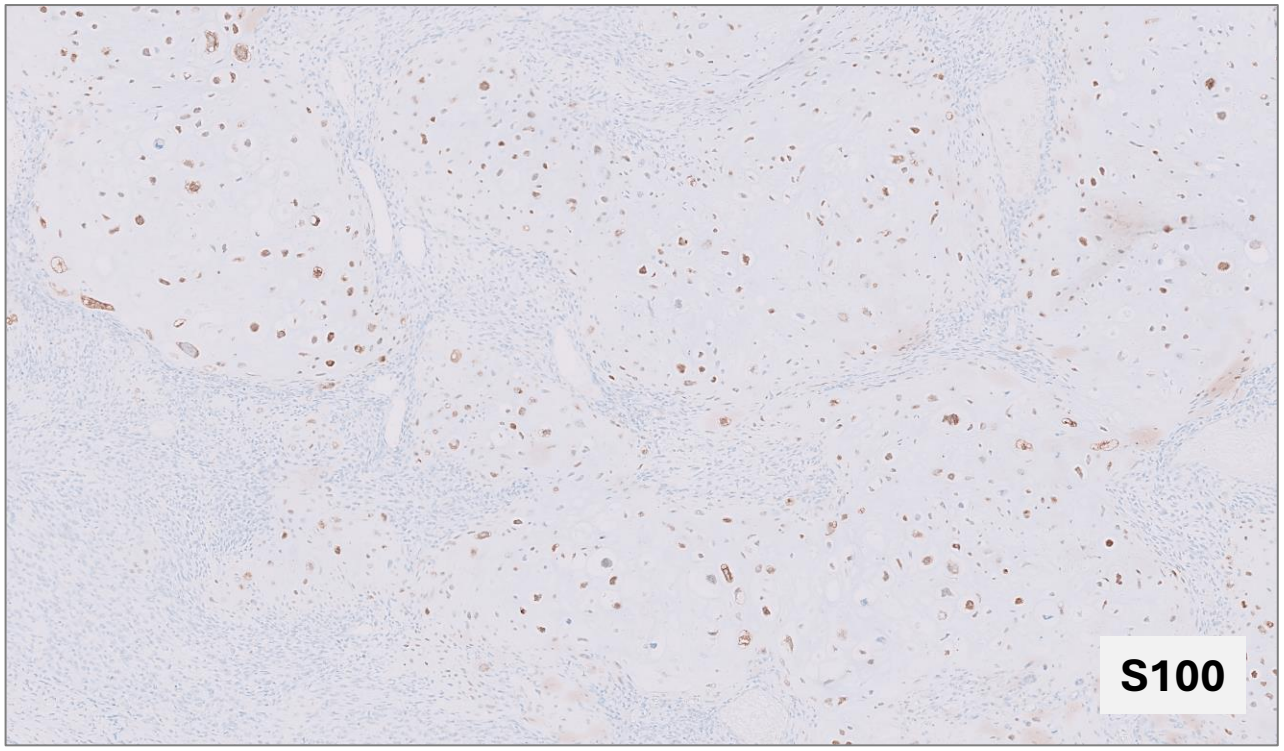

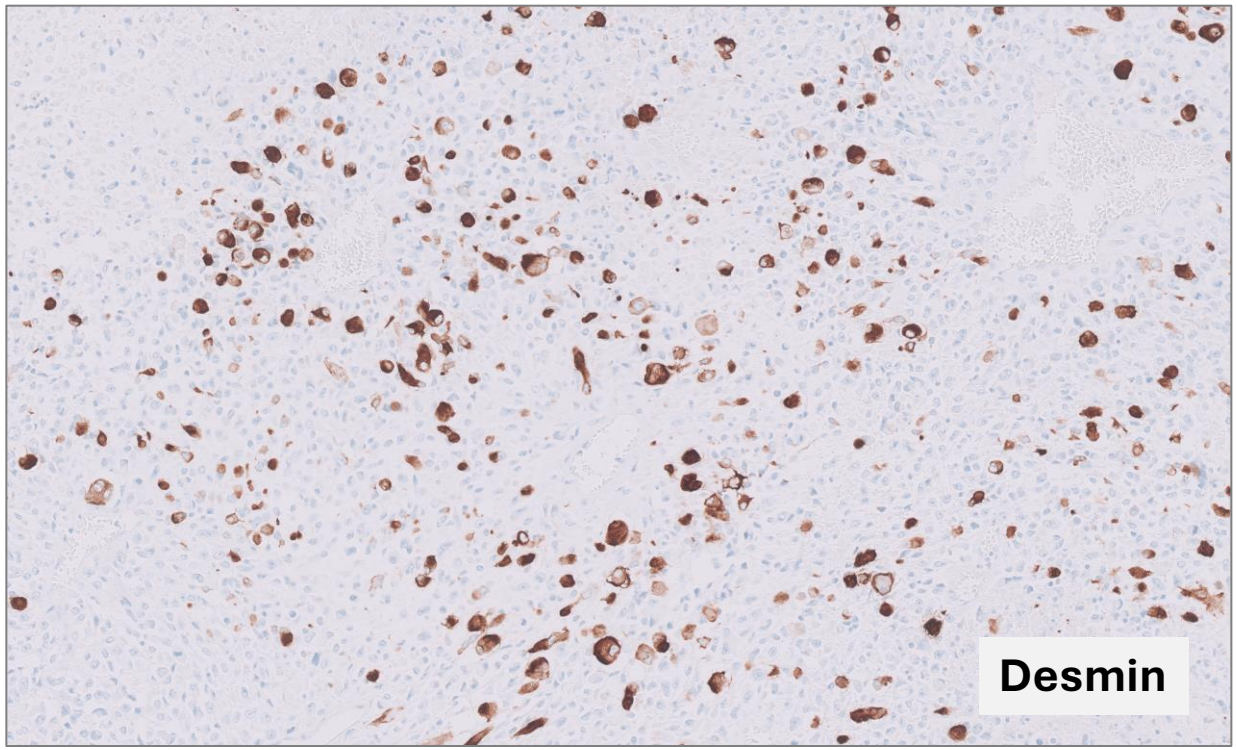

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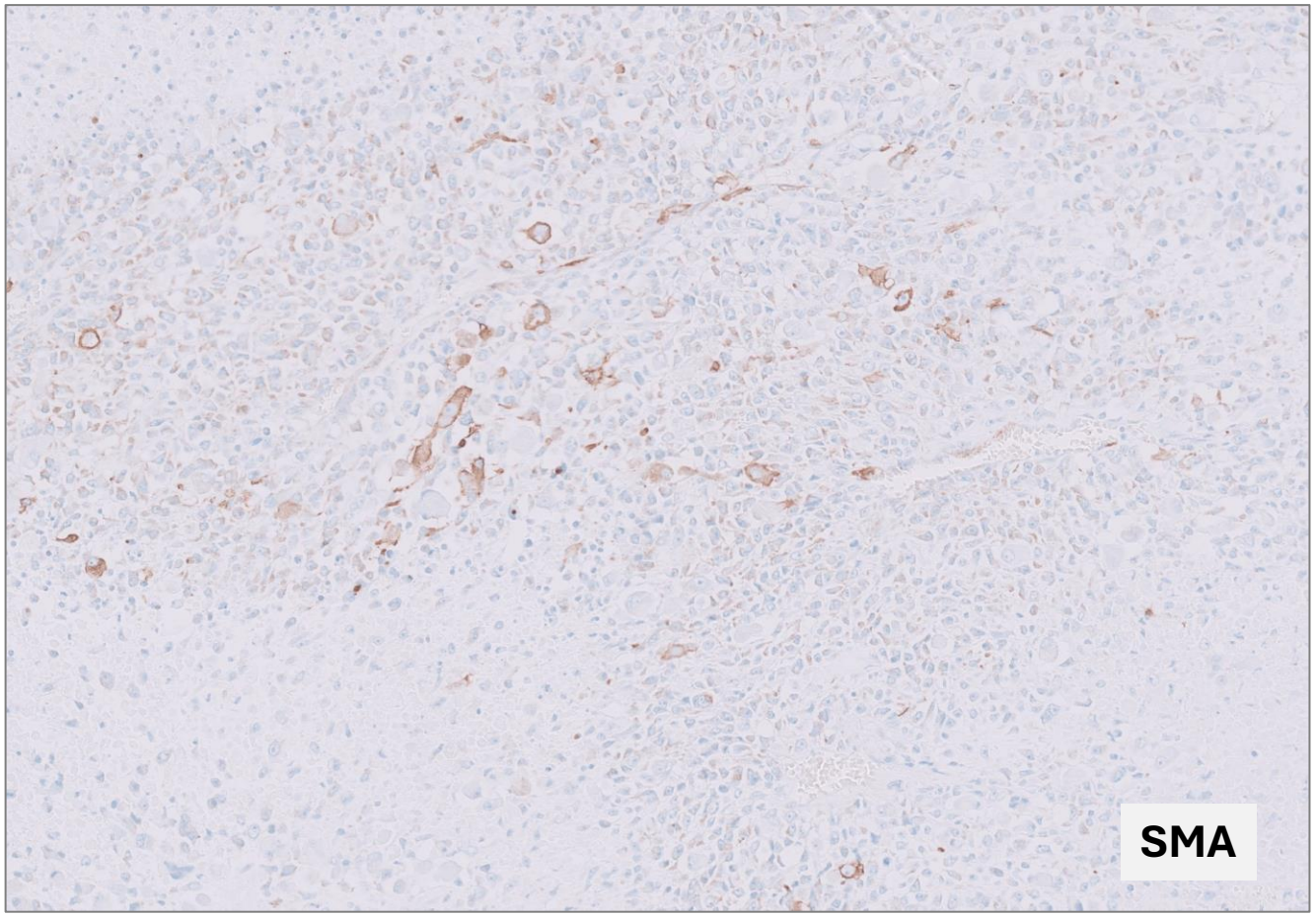
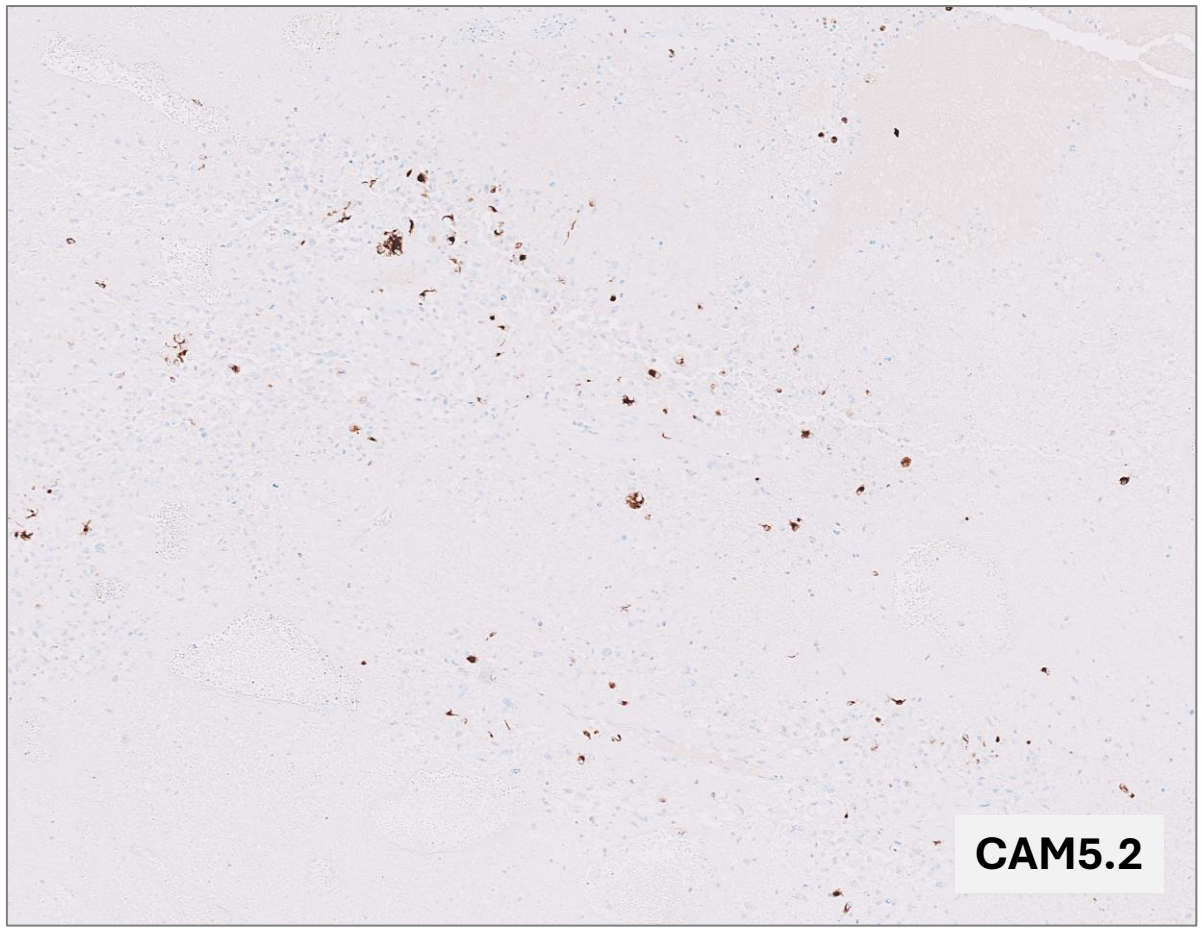




IHC Stains

Immunohistochemical Stains	Interpretation
Pan-keratin	Negative
CAM5.2	**Positive (focally)**
CK14	**Positive (focally)**
CK5/6	**Positive (rare)**
CK7	Negative
p63	**Positive (rare)**
CD34	Negative
SMA	**Positive (focally)**
Desmin	**Positive (focally)**
S100	**Positive (focally)**
SOX10	Negative

Initial Tissue Sections

- Benign epithelial elements are rarely identified
- NO in situ carcinoma present

→High grade malignancy

Top differentials:

1. *Metaplastic carcinoma*
2. *Malignant phyllodes tumor*
3. *Sarcoma*

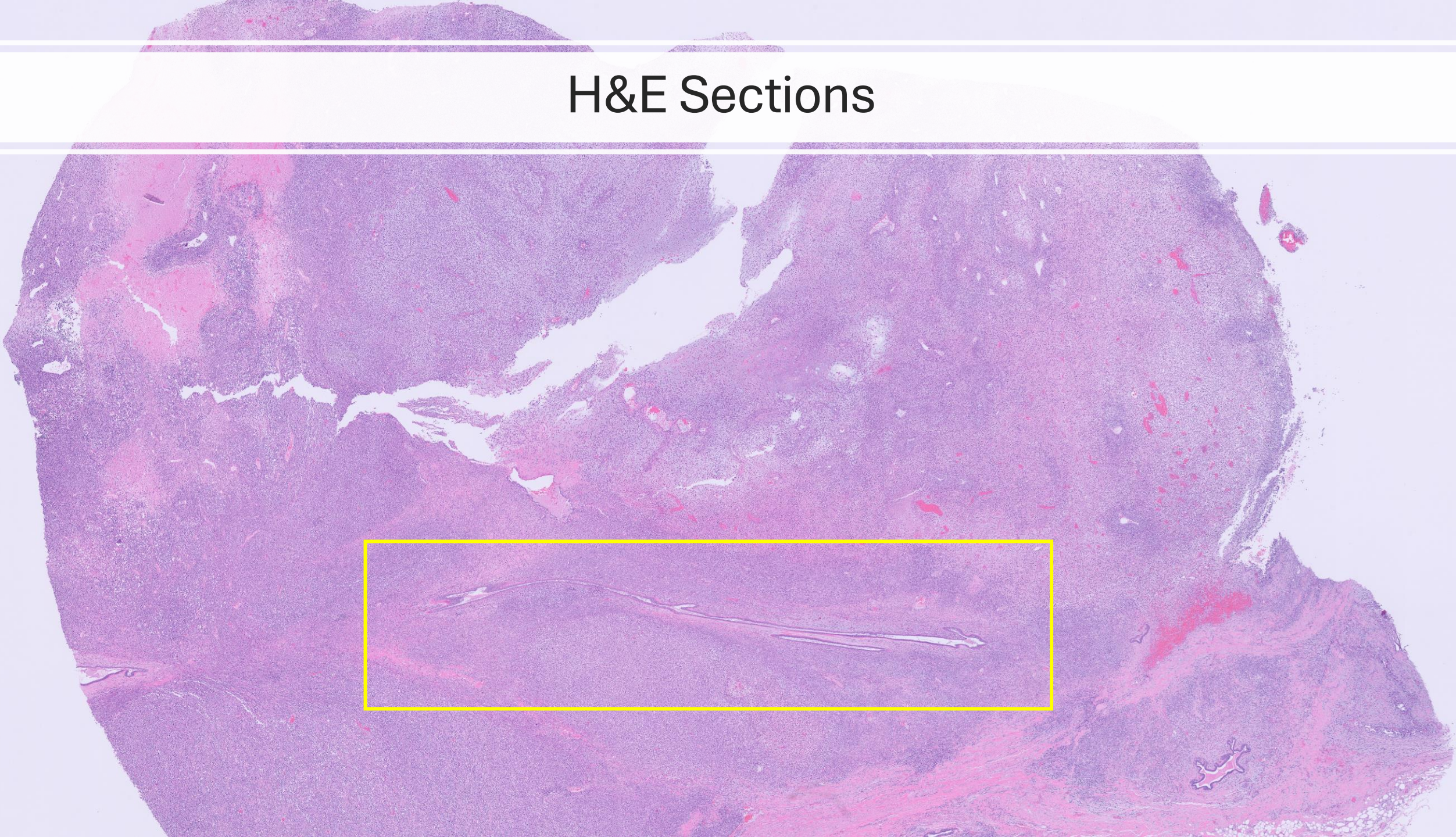
Differential Diagnoses

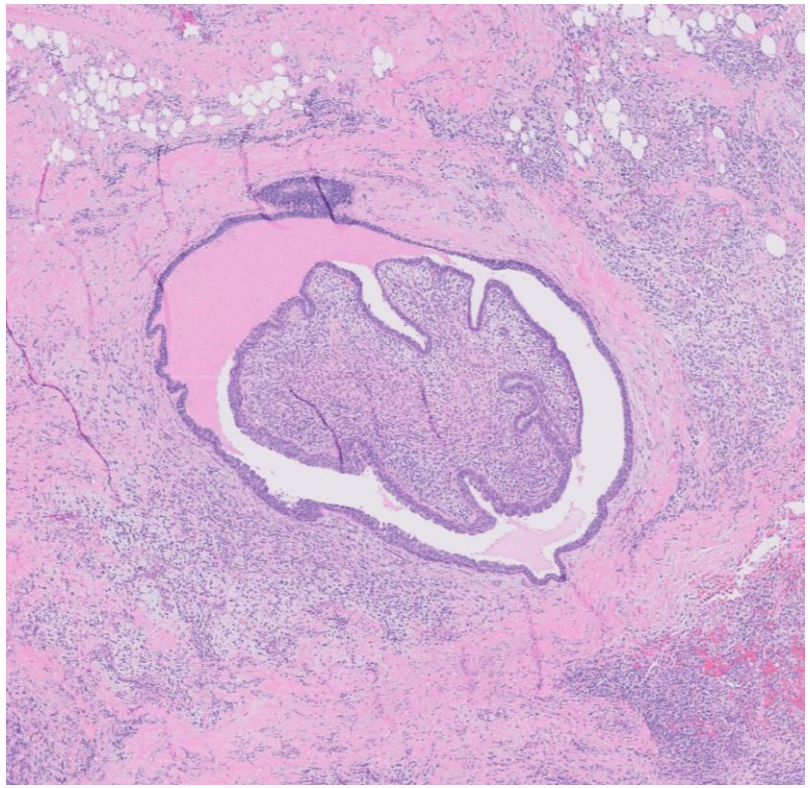
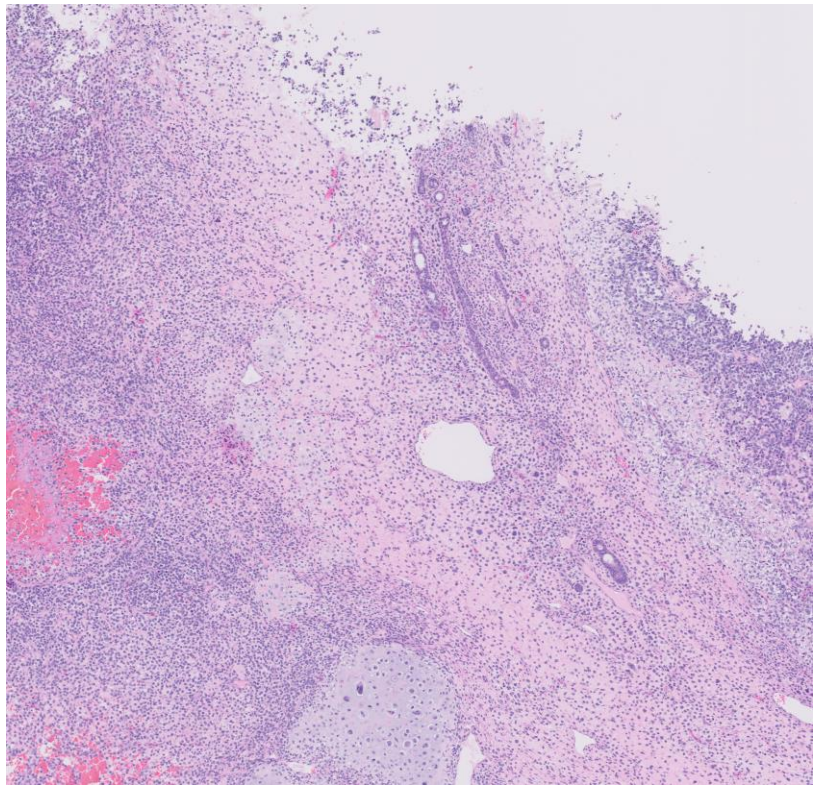
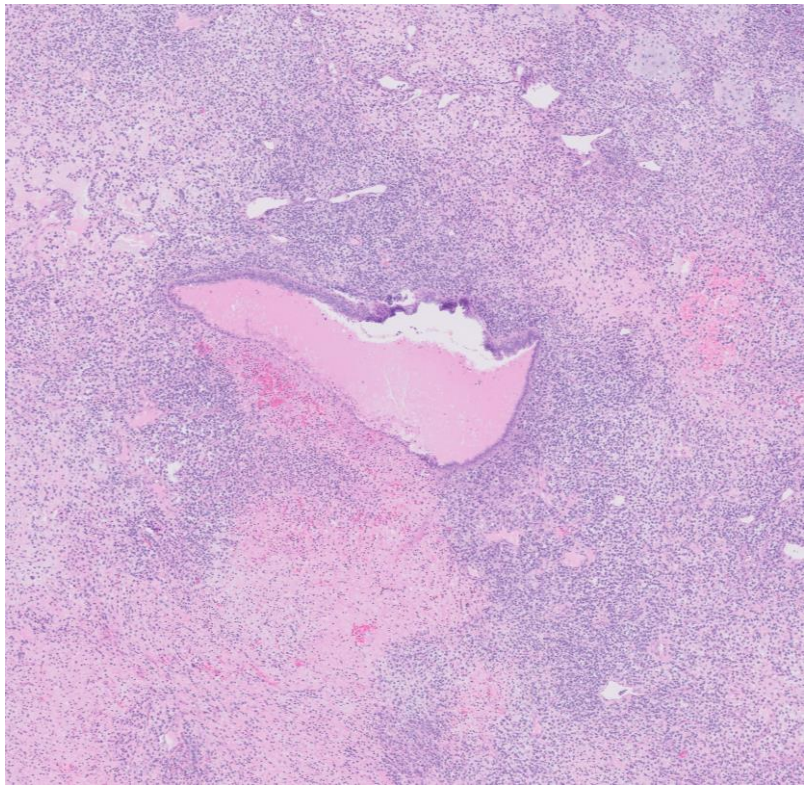
- Malignant Phyllodes Tumor
  - Fibroepithelial architecture
  - Distinct genetic alterations in PT (such as MED12) can help confirm the diagnosis
- Metaplastic carcinoma
  - IHC demonstration of diffuse epithelial differentiation
  - Caution in interpreting focal keratin expression and p63 positivity → positivity has been reported in PT
  - CD34 positivity essentially excludes metaplastic carcinoma and is compatible with PT
- Primary or metastatic sarcomas
  - Diagnosis of exclusion
  - Extensive sampling to find residual epithelial structures is crucial
  - However, clinical outcomes of primary breast sarcomas and malignant phyllodes tumors appear to be similar

Additional Tissue Sections

***Requested the referring pathologist to submit additional tissue sections from the mastectomy specimen
***Sent specimen for NGS testing

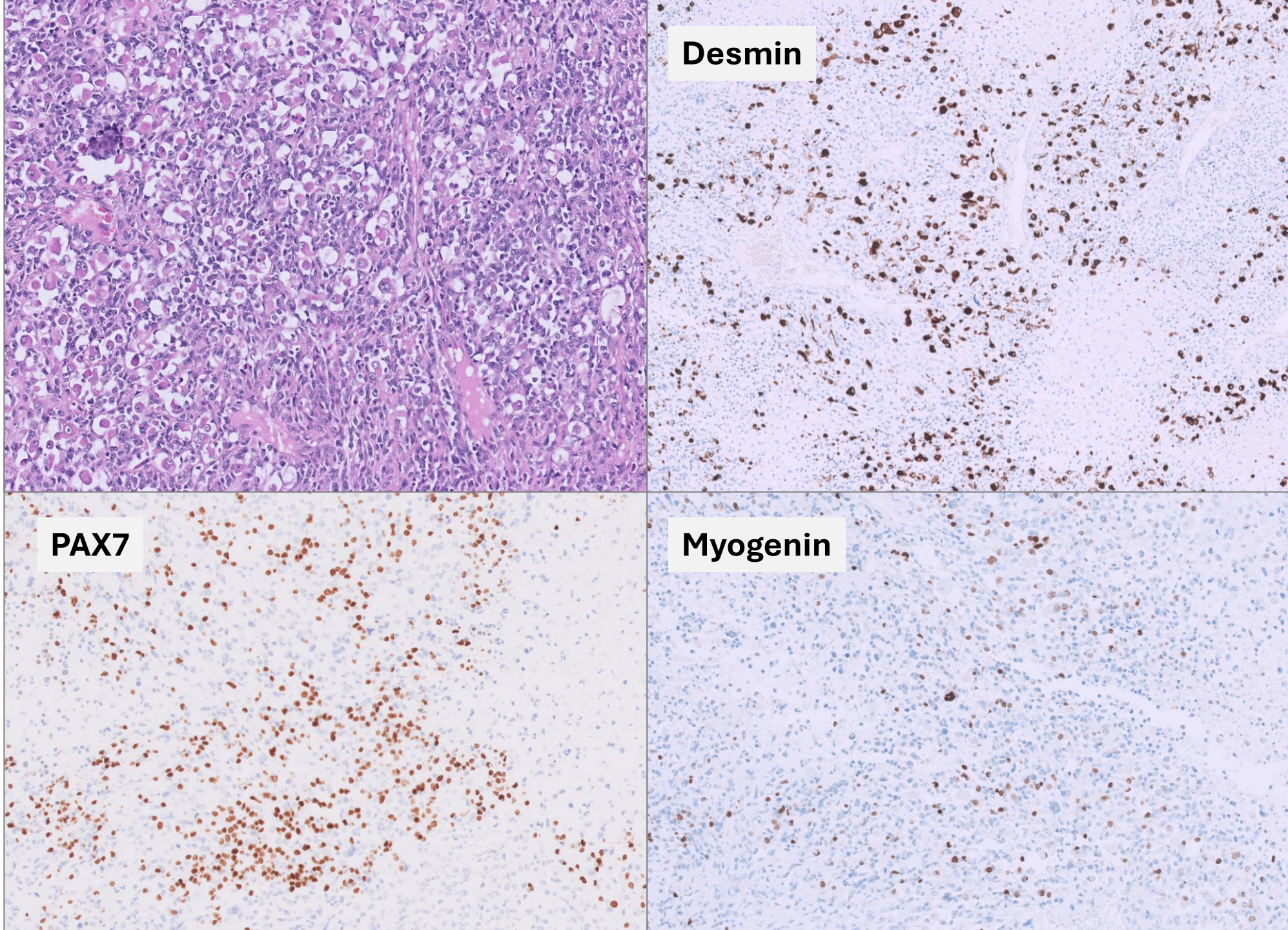
H&E Sections



Epithelial Components

Rhabdoid Elements



IHC Stains Performed at Stanford

Immunohistochemical Stains	Interpretation
CK34betaE12	Negative
CD34	Negative
Desmin	**Positive in rhabdoid elements**
Myogenin	**Positive in rhabdoid elements**
MyoD1	Negative
PAX7	**Positive in rhabdoid elements**
Caldesmon	Negative

FINAL DIAGNOSIS

Malignant phyllodes tumor, with chondro- and rhabdomyosarcomatous elements

- AJCC stage pT2 – 7 cm tumor
- Inked margins were uninvolved

Essential for differential diagnosis of benign versus malignant:

1. Number of stromal mitoses
2. Degree of stromal cellularity
3. Stromal atypia
4. Stromal overgrowth: absence of epithelial elements in at least one low-power field (4× objective)
5. Tumor borders
6. Malignant heterologous elements (excludes well-differentiated liposarcoma)

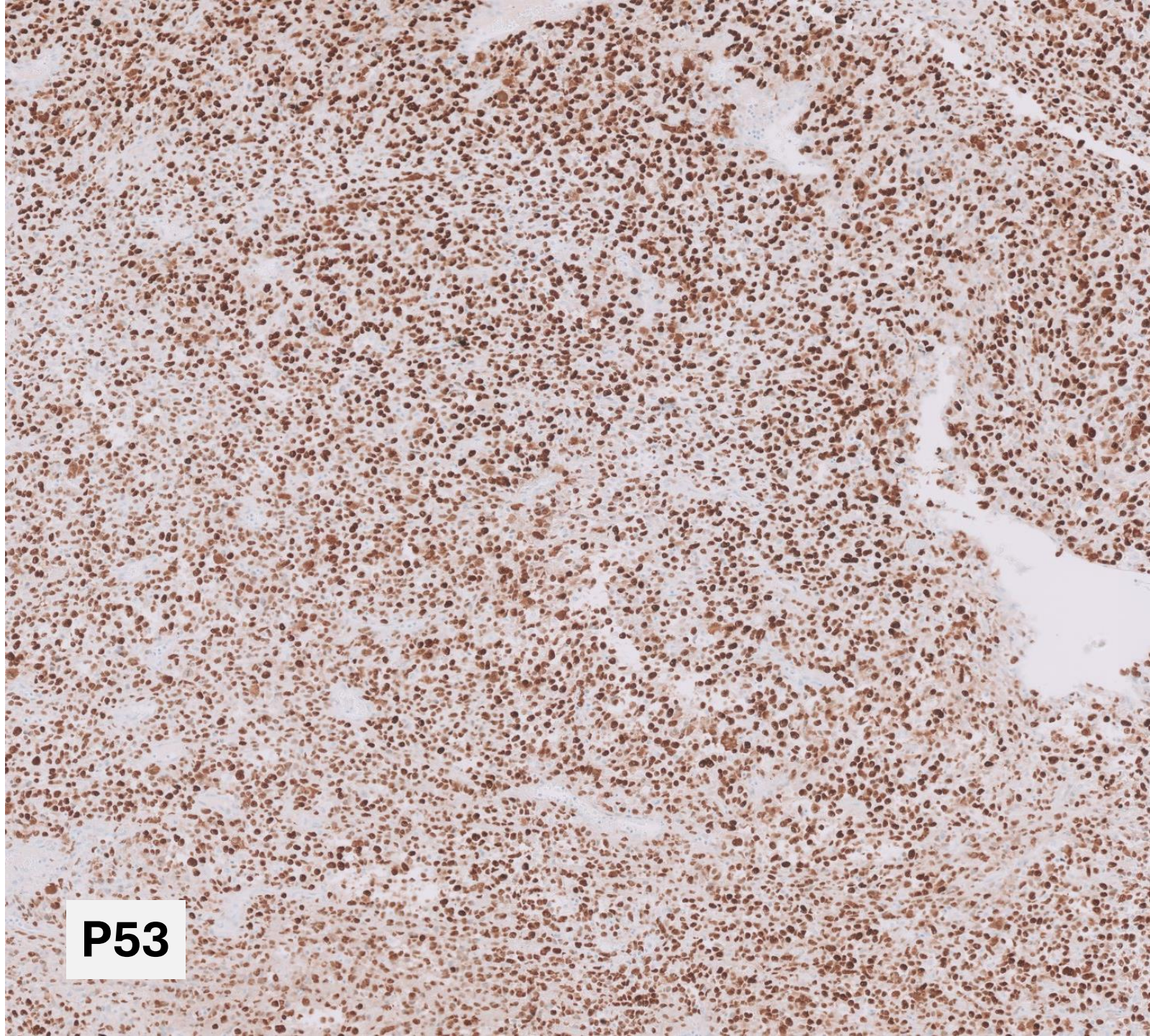
Rhabdomyosarcomatous Differentiation

Very RARE → *less than* 40 cases reported in the literature

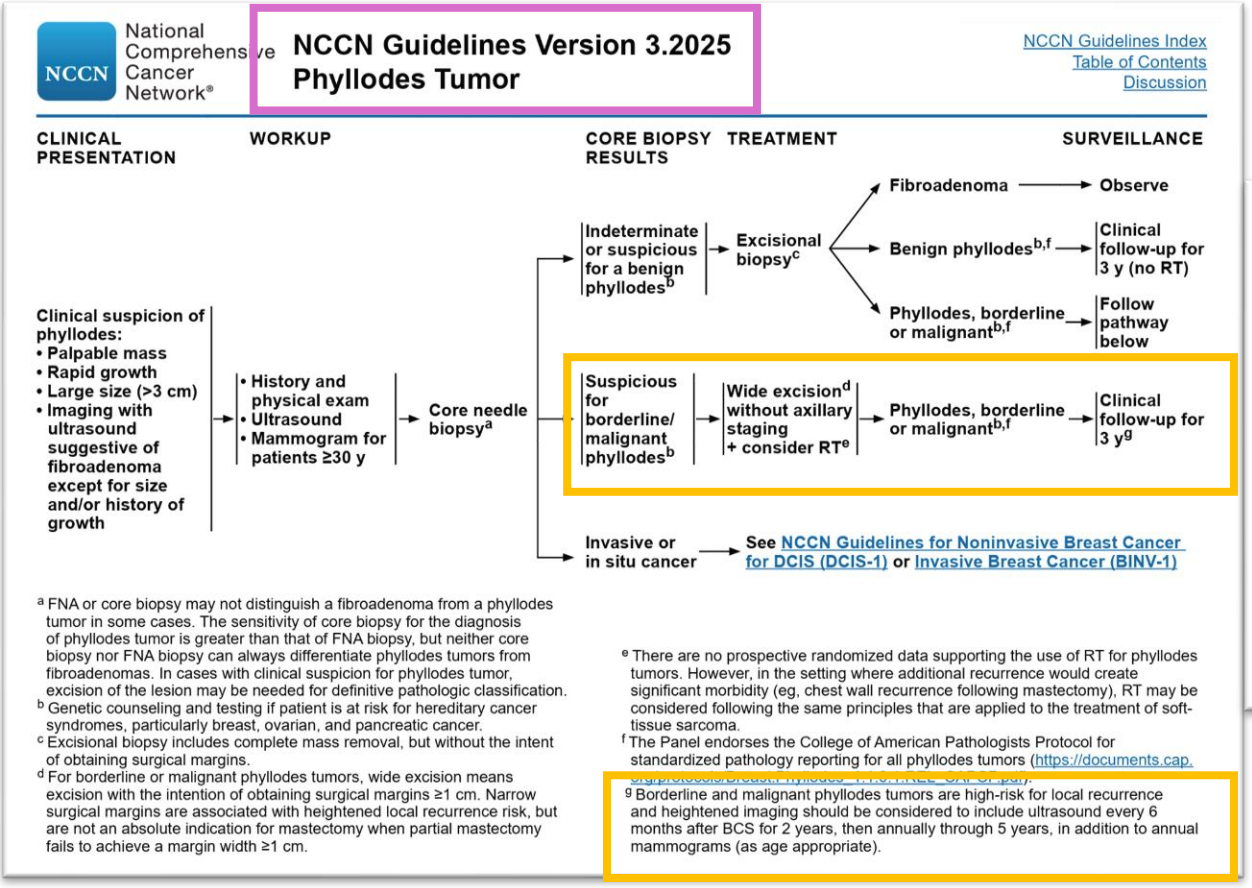
Next-generation Sequencing (STAMP) Results:

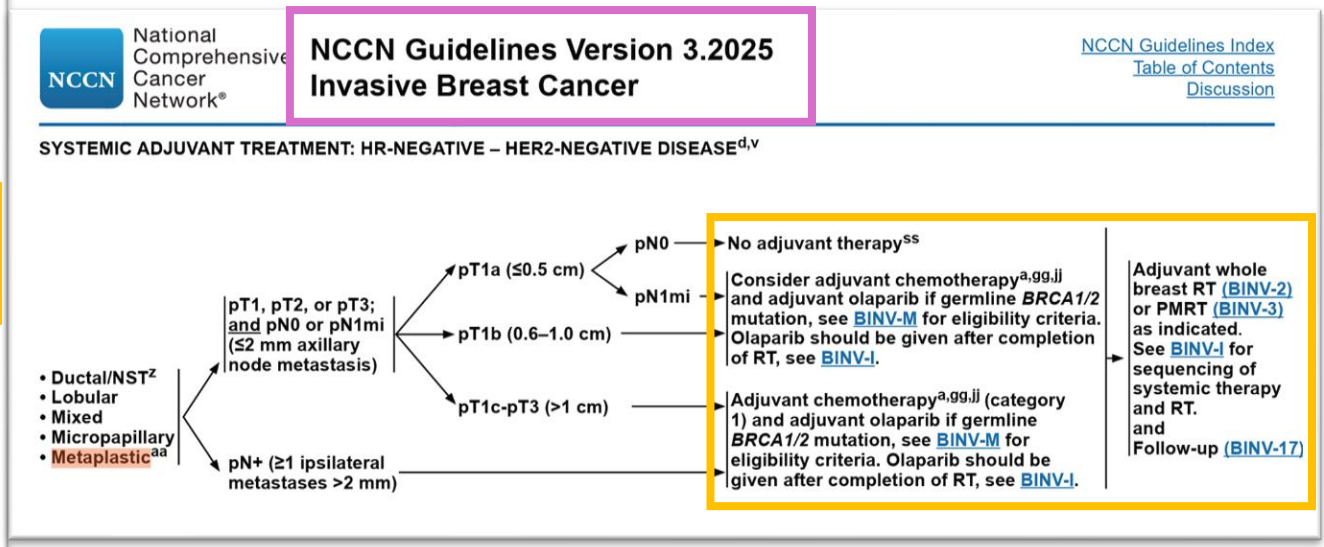
TP53 mutation – VAF 81%

SETD2 mutation – VAF 59%



Differences in Treatment – Metaplastic Carcinoma vs Malignant Phyllodes Tumor





Thank You

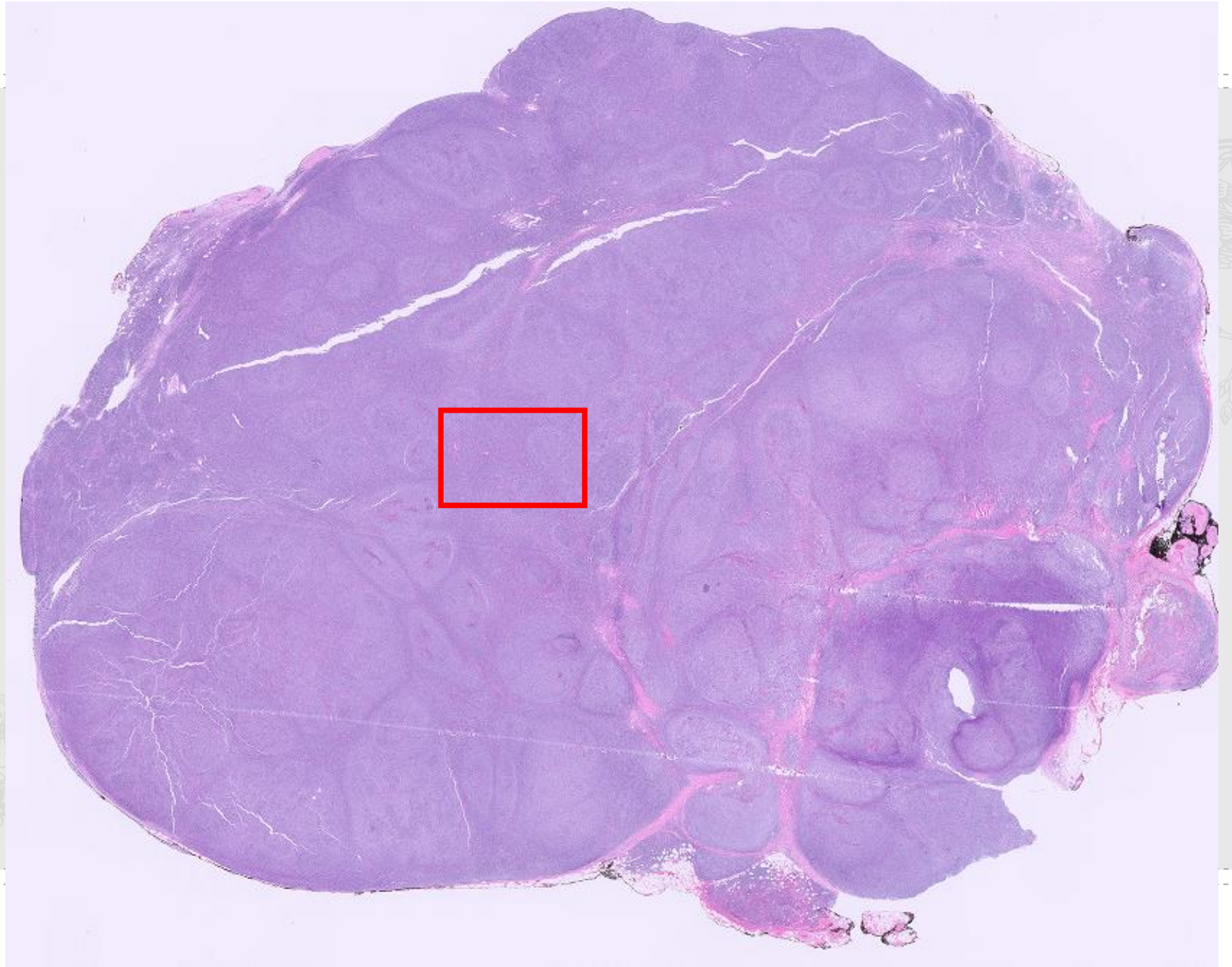
- Dr. Gregory Bean
- Stanford Pathology Department

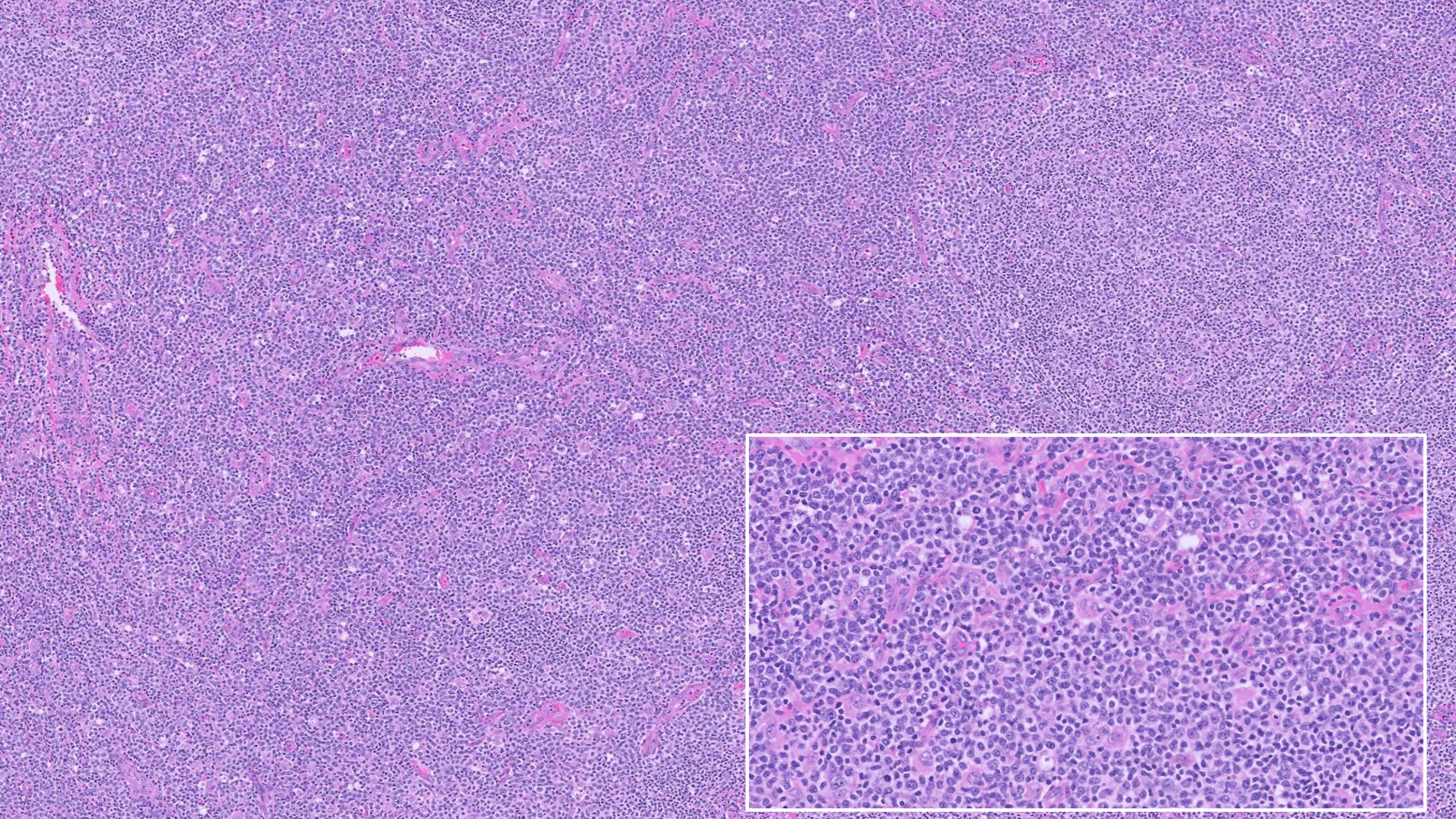
Stanford MEDICINE

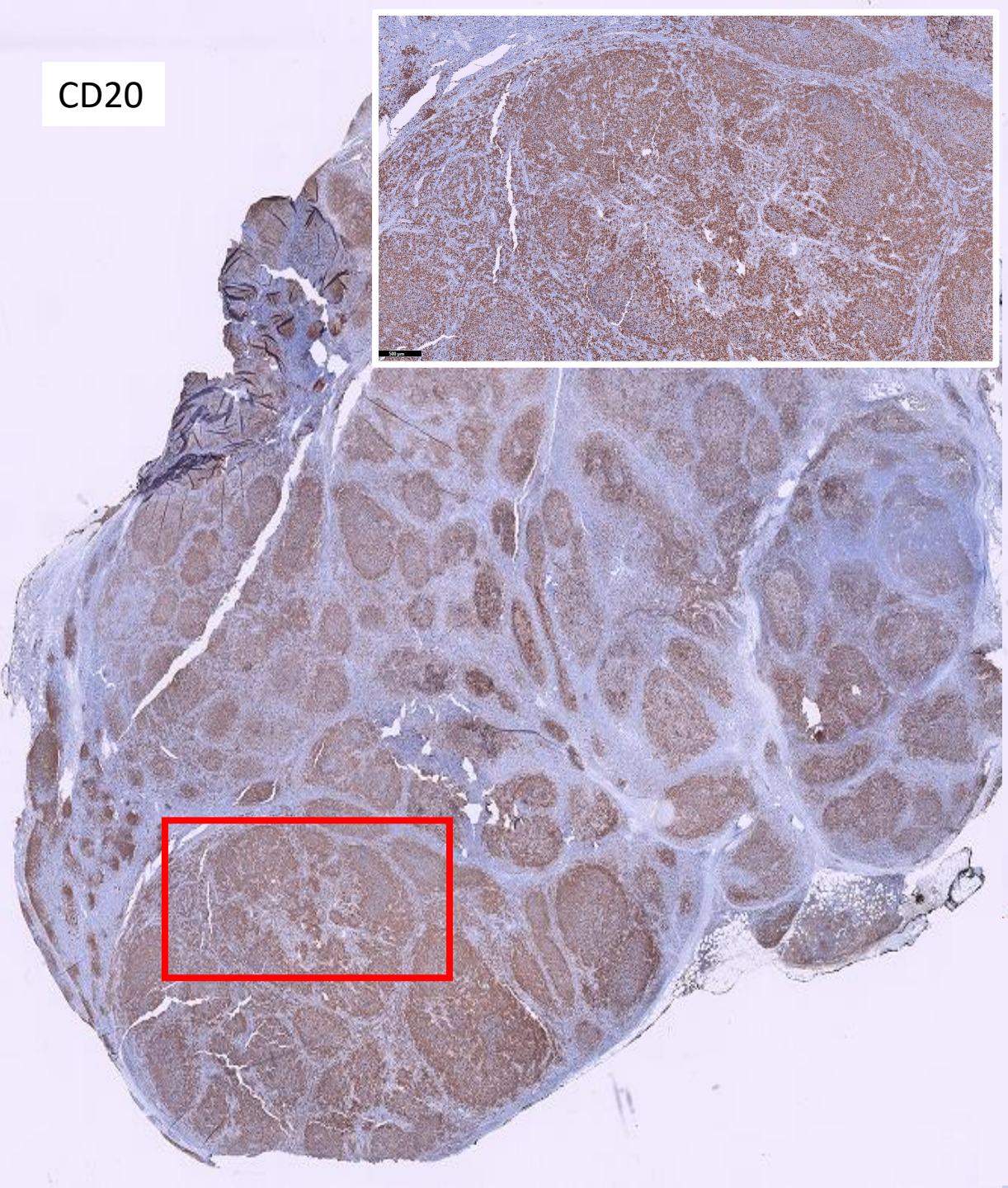
25-0406

Parnaz Daneshpajouhnejad, Yaso Natkunam; Stanford

48 year old female with splenomegaly, lymphadenopathy, and IgM kappa M protein. Inguinal lymph node was excised.



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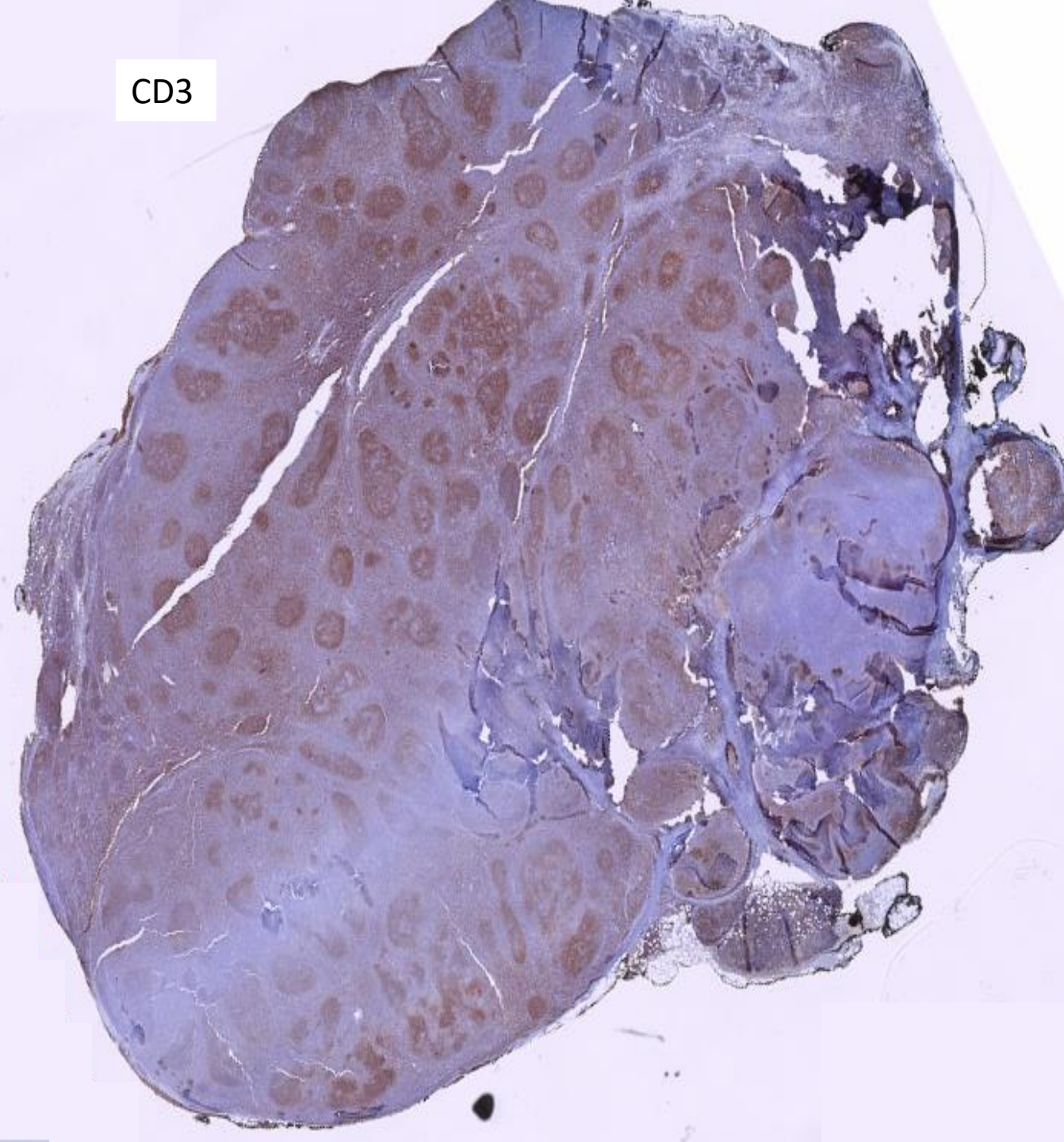
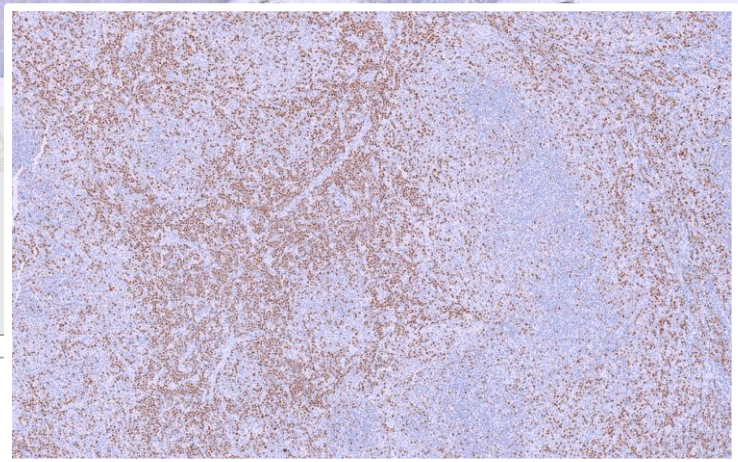
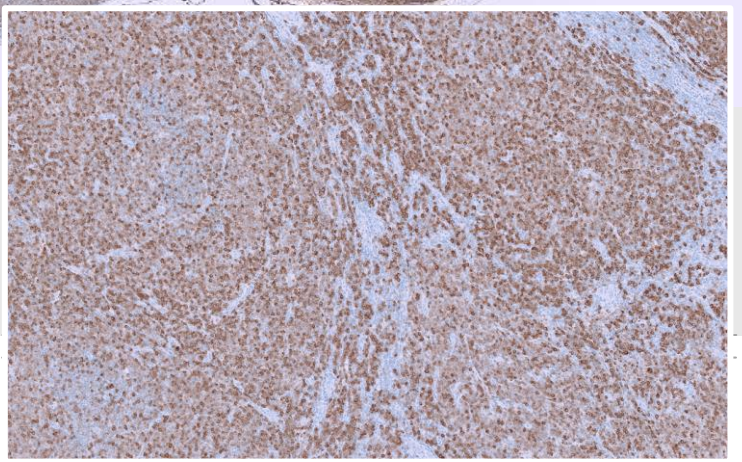

CD3

MUM1



CD79a



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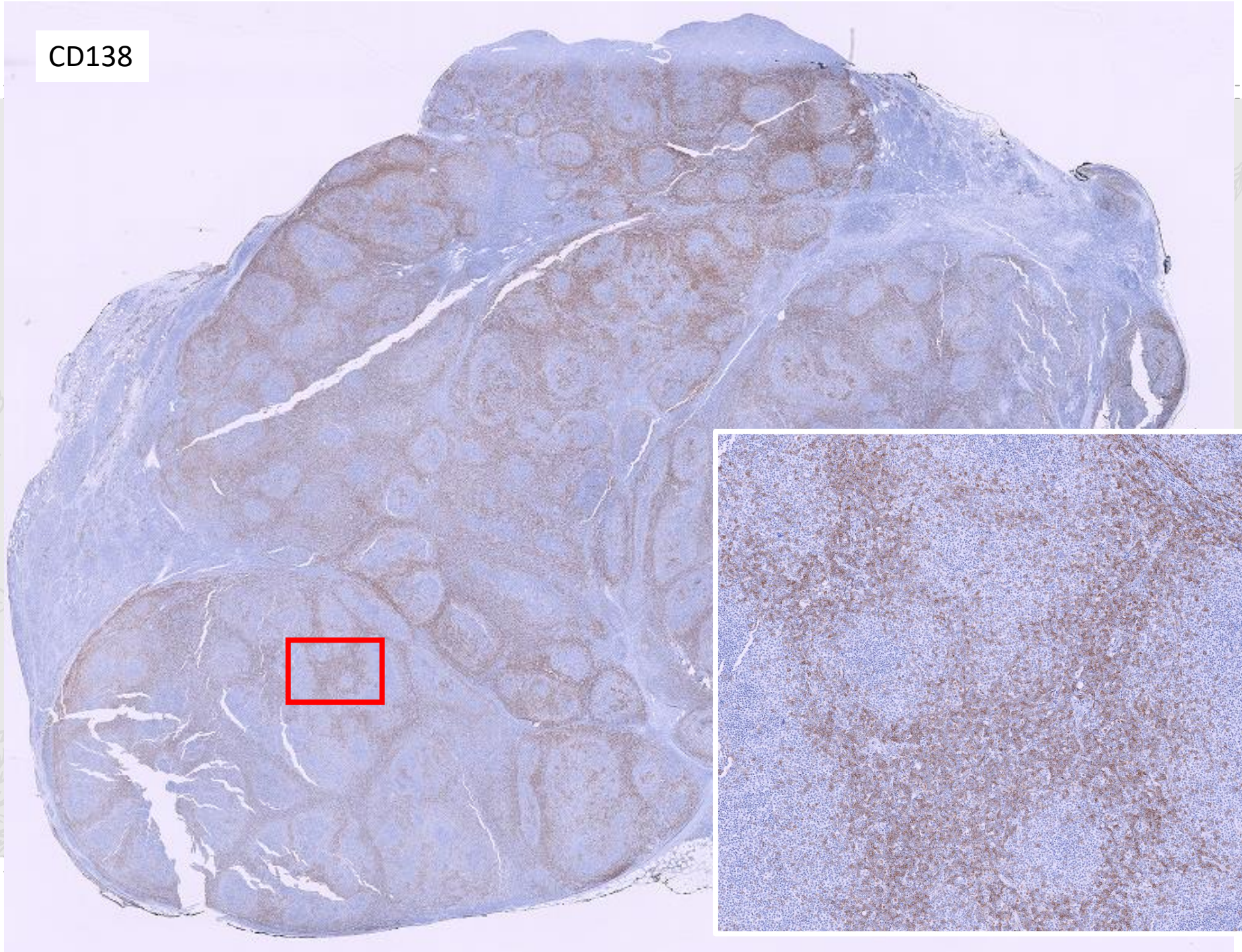

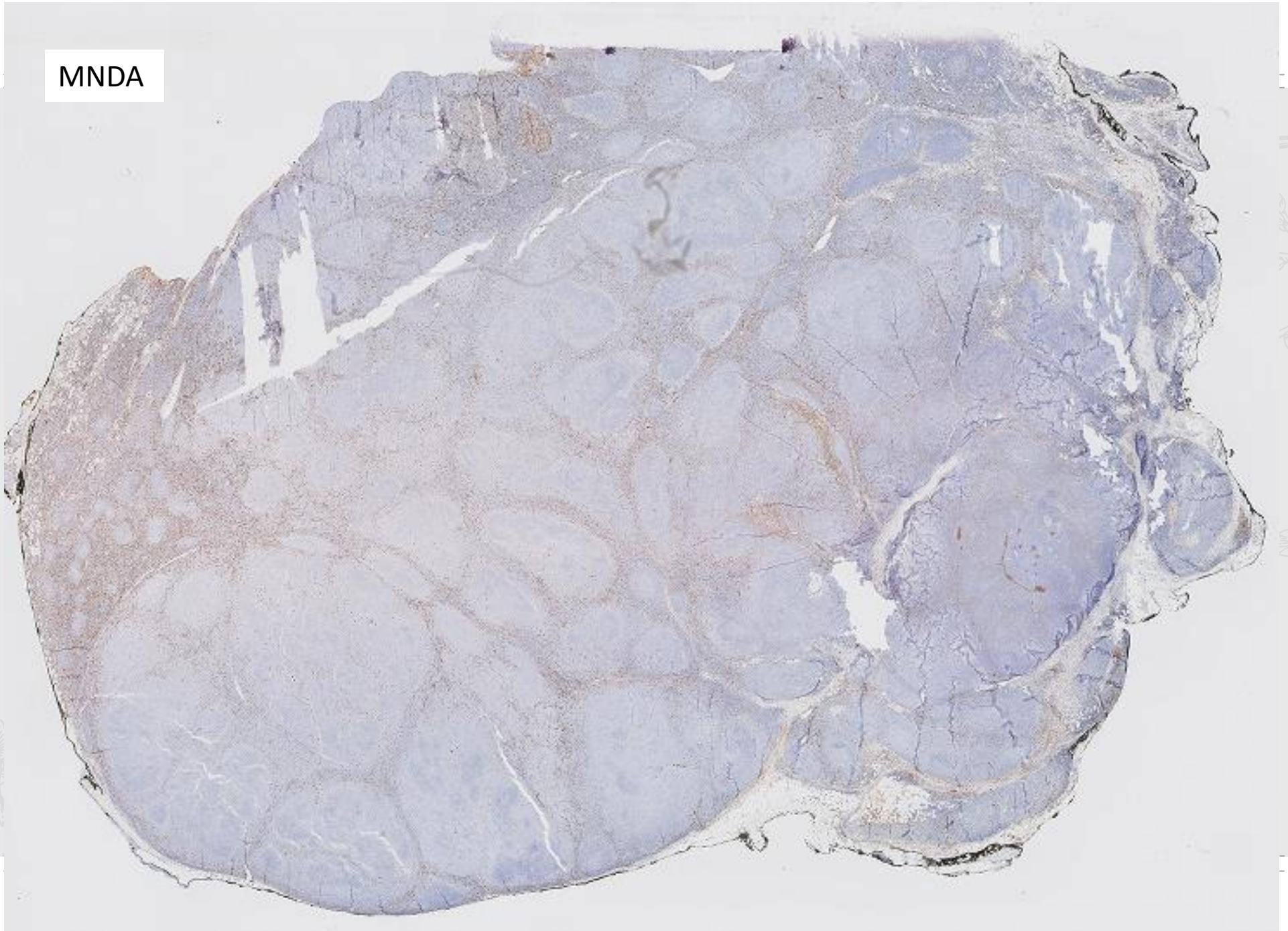
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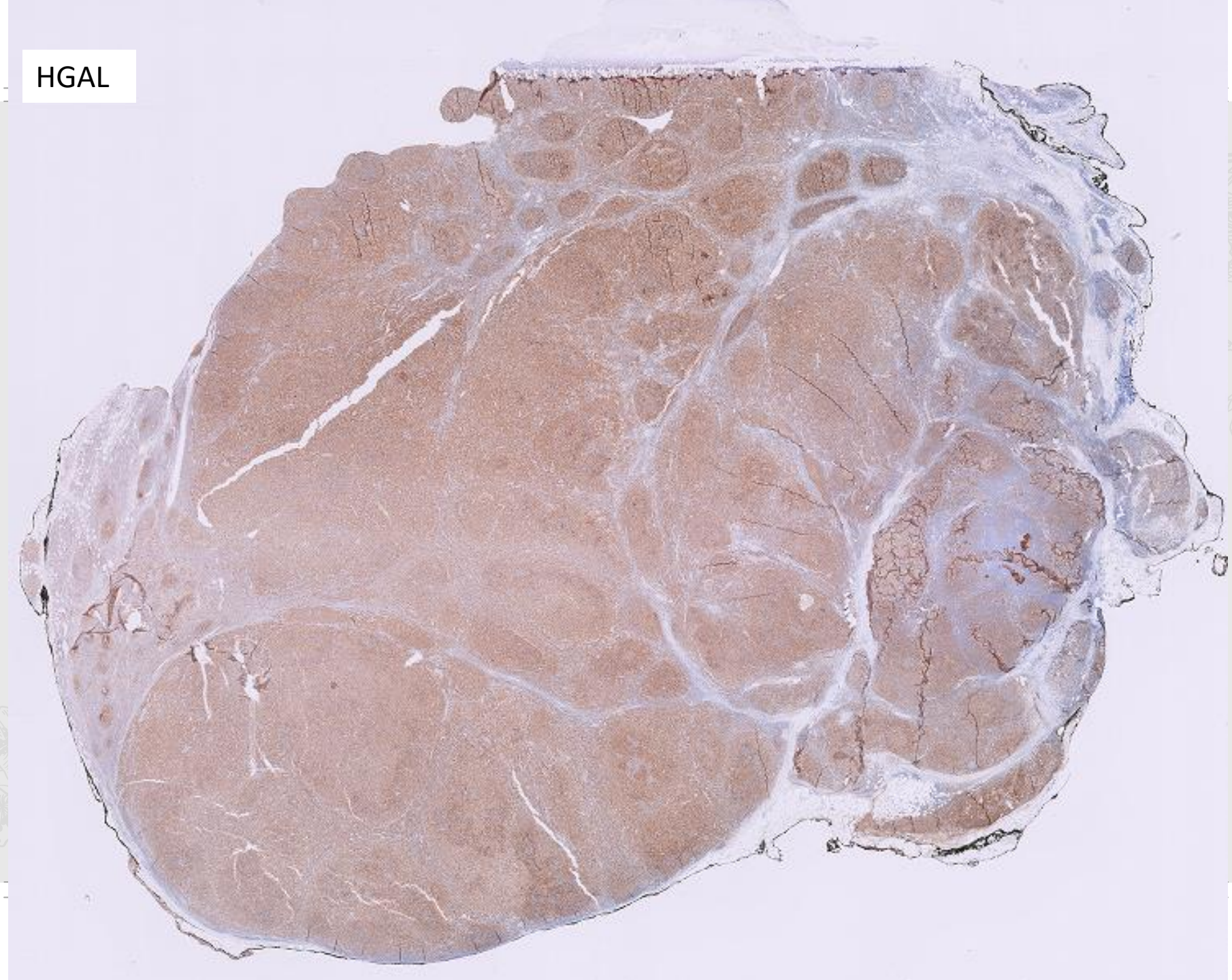
HGAL



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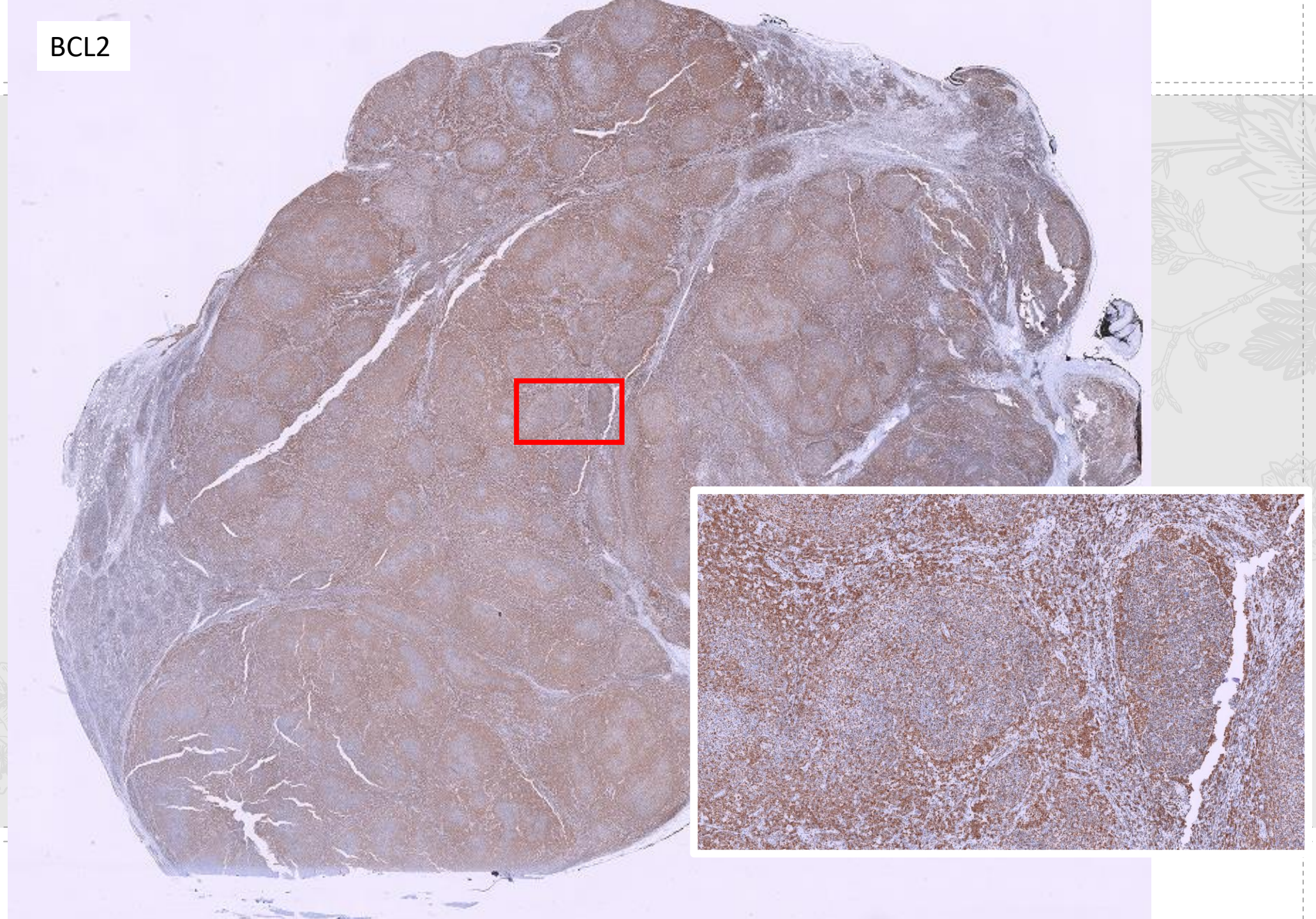
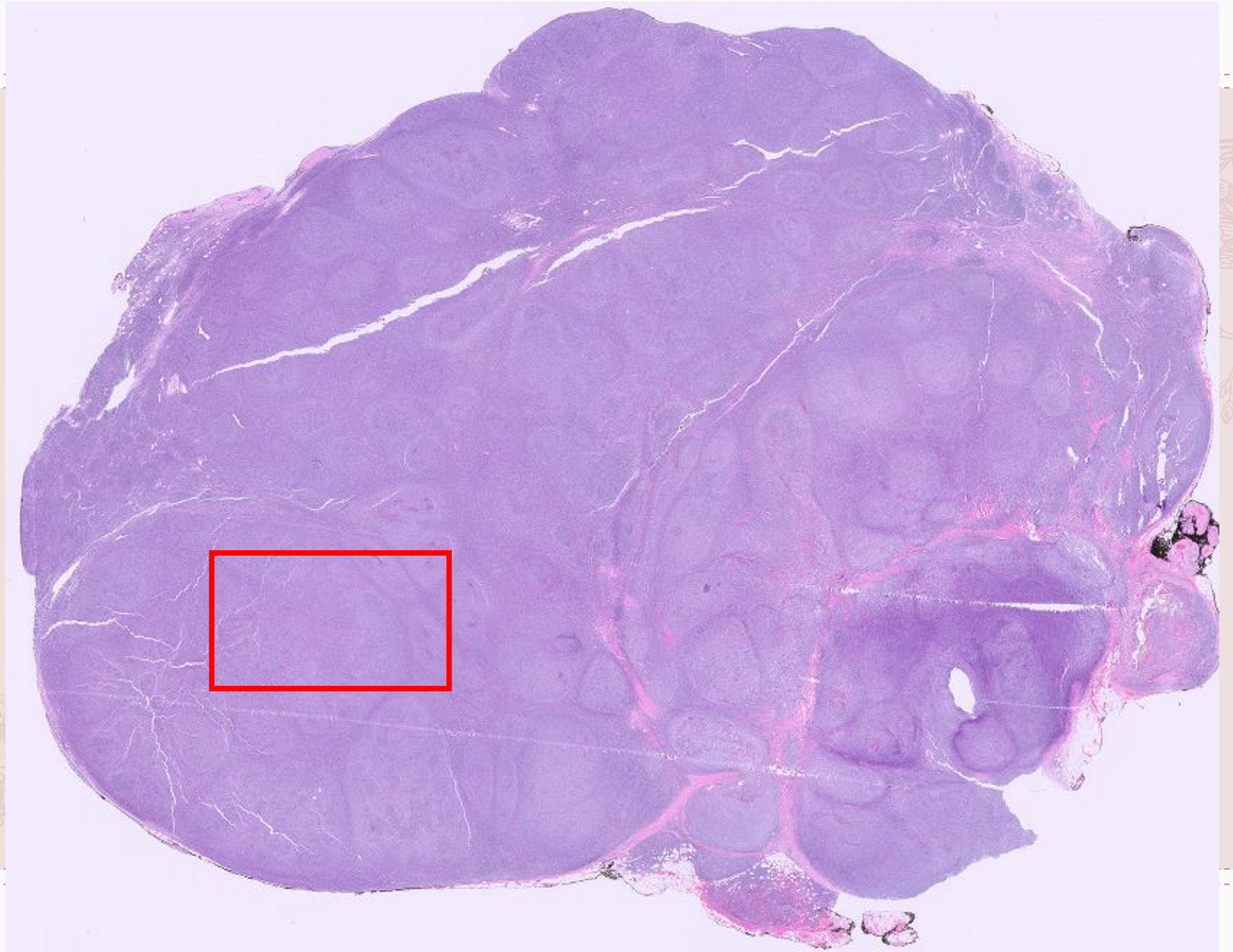


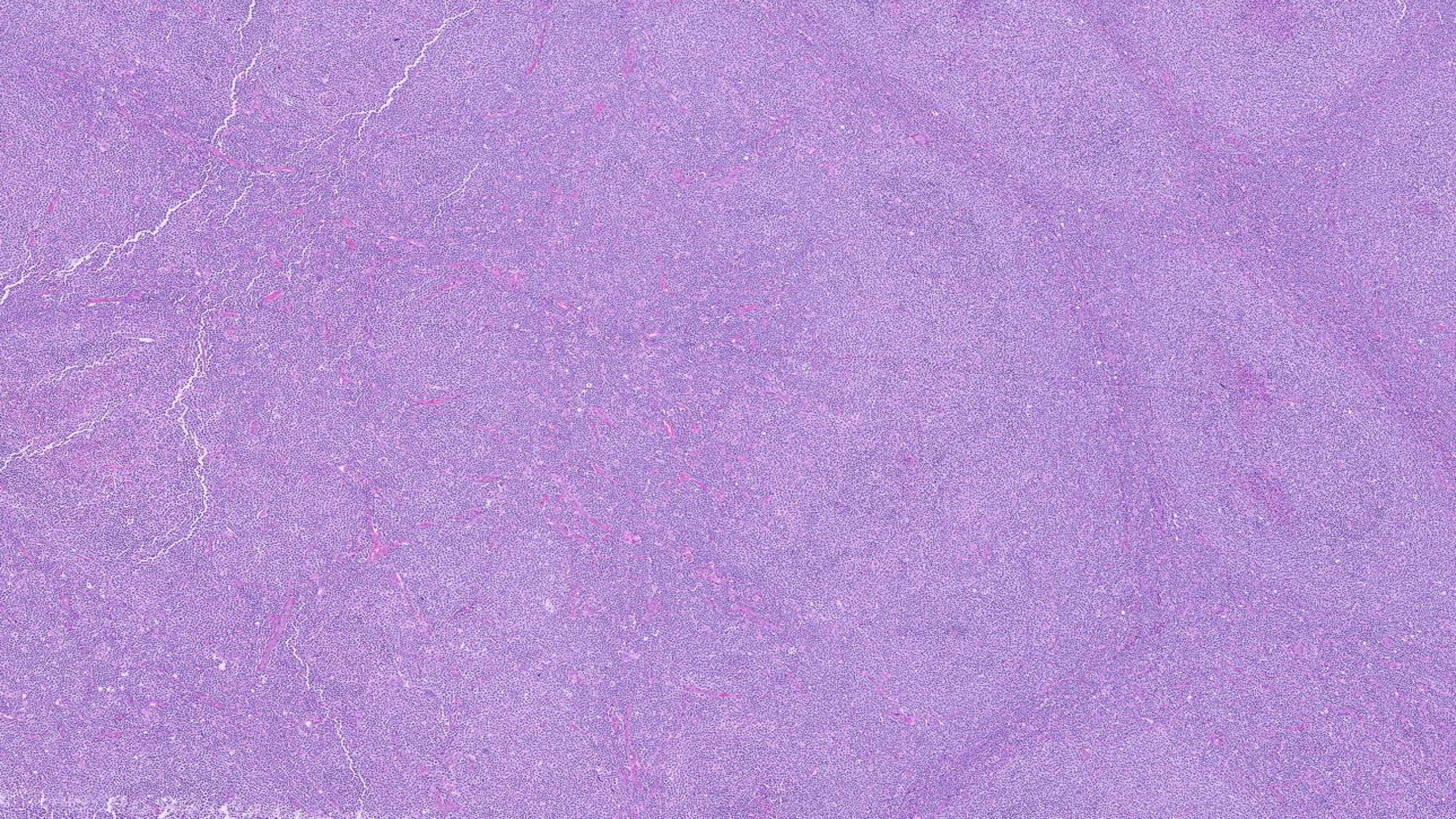
DIAGNOSIS?

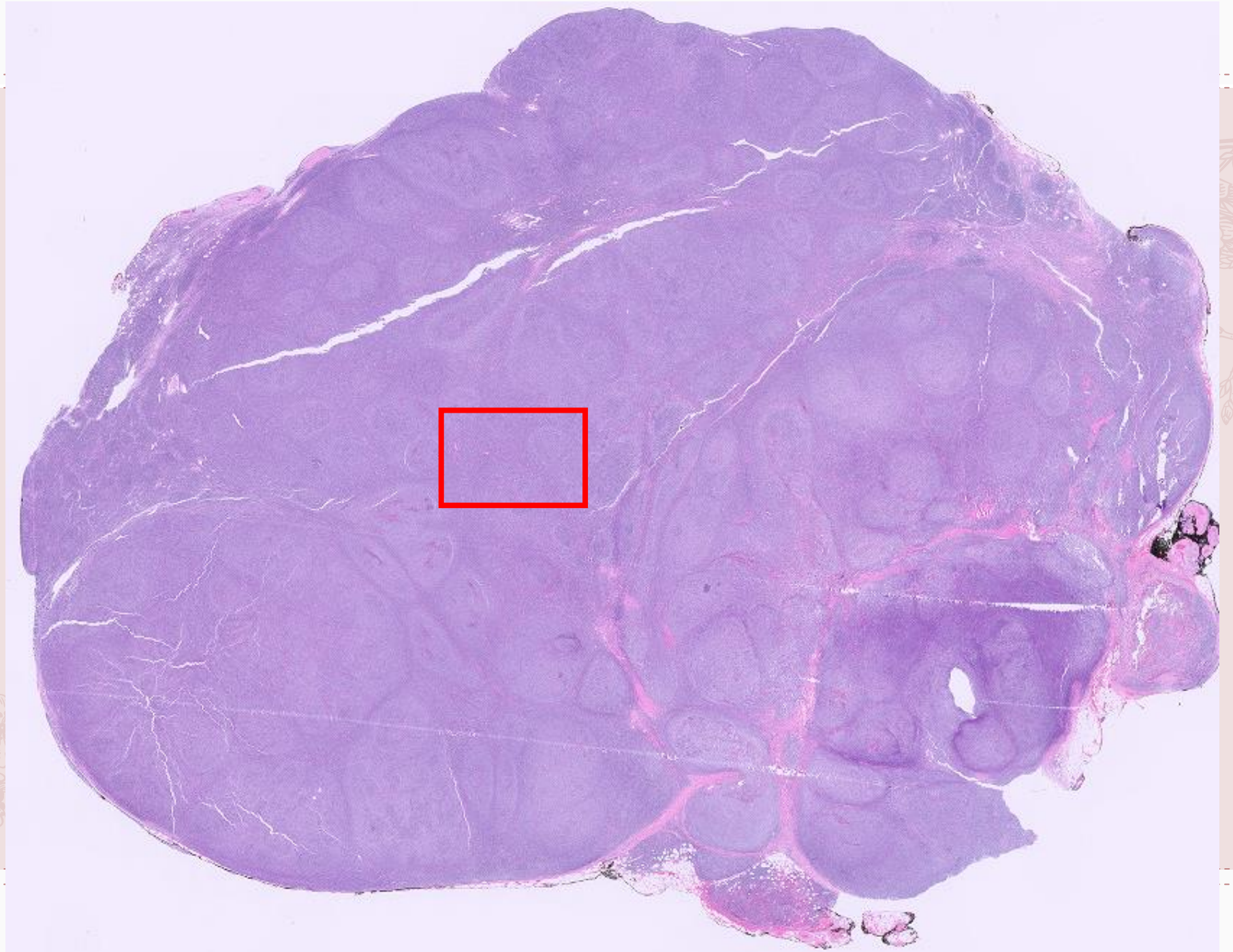
Inguinal Lymph Node Dilemma, Worth Exploring?

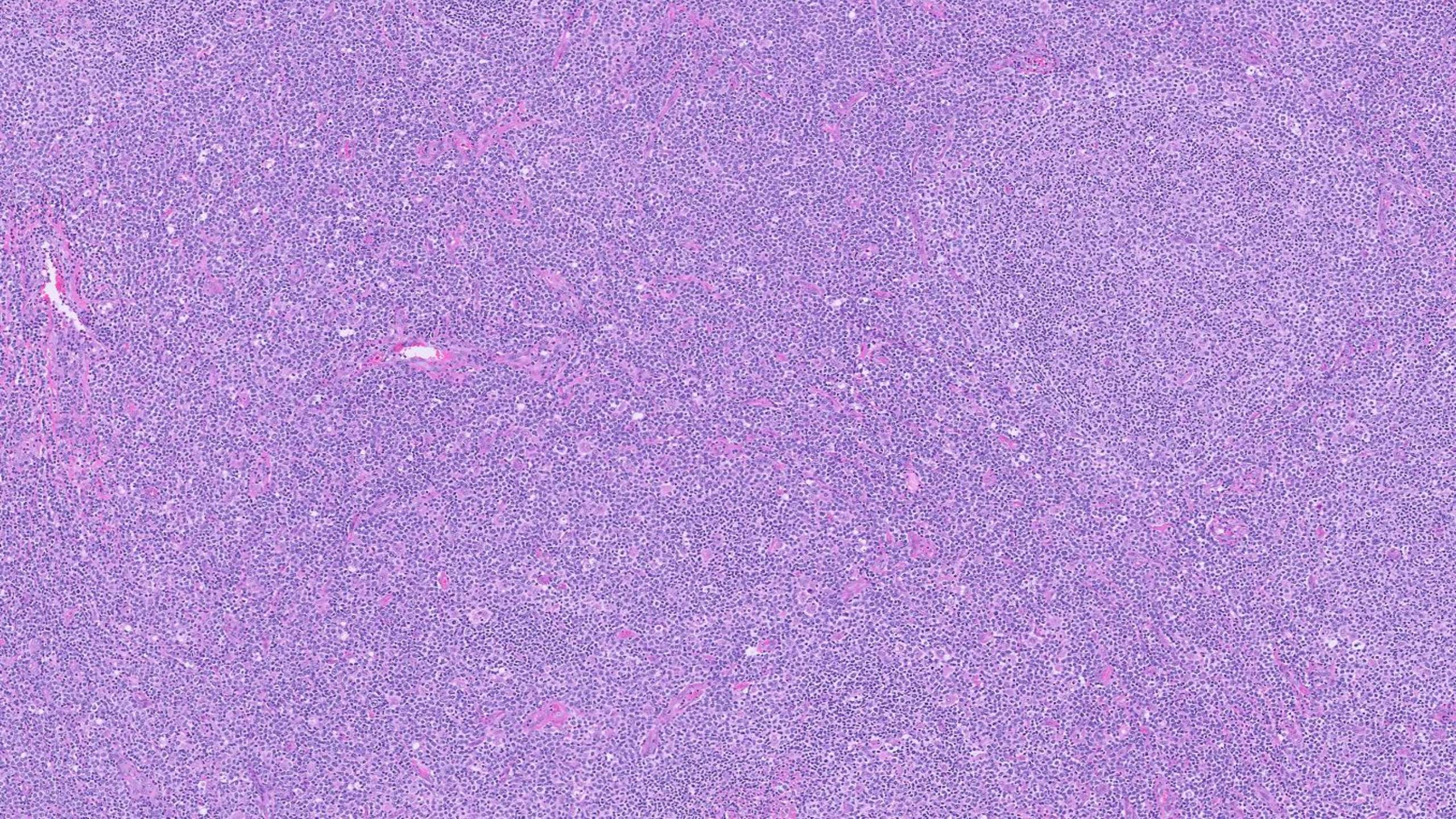
History

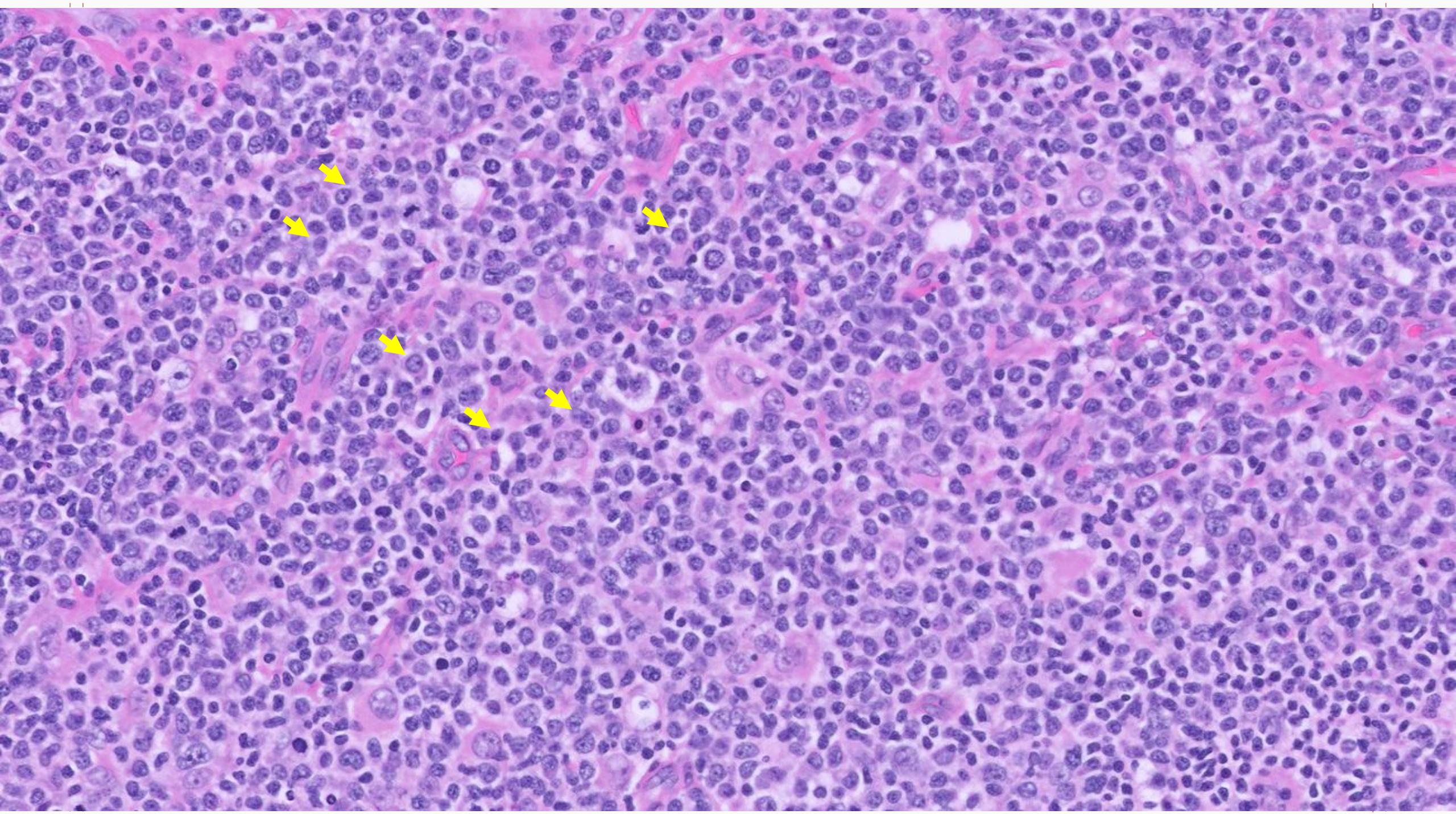
48 year old female with splenomegaly, lymphadenopathy, and IgM kappa M protein. Inguinal lymph node was excised.

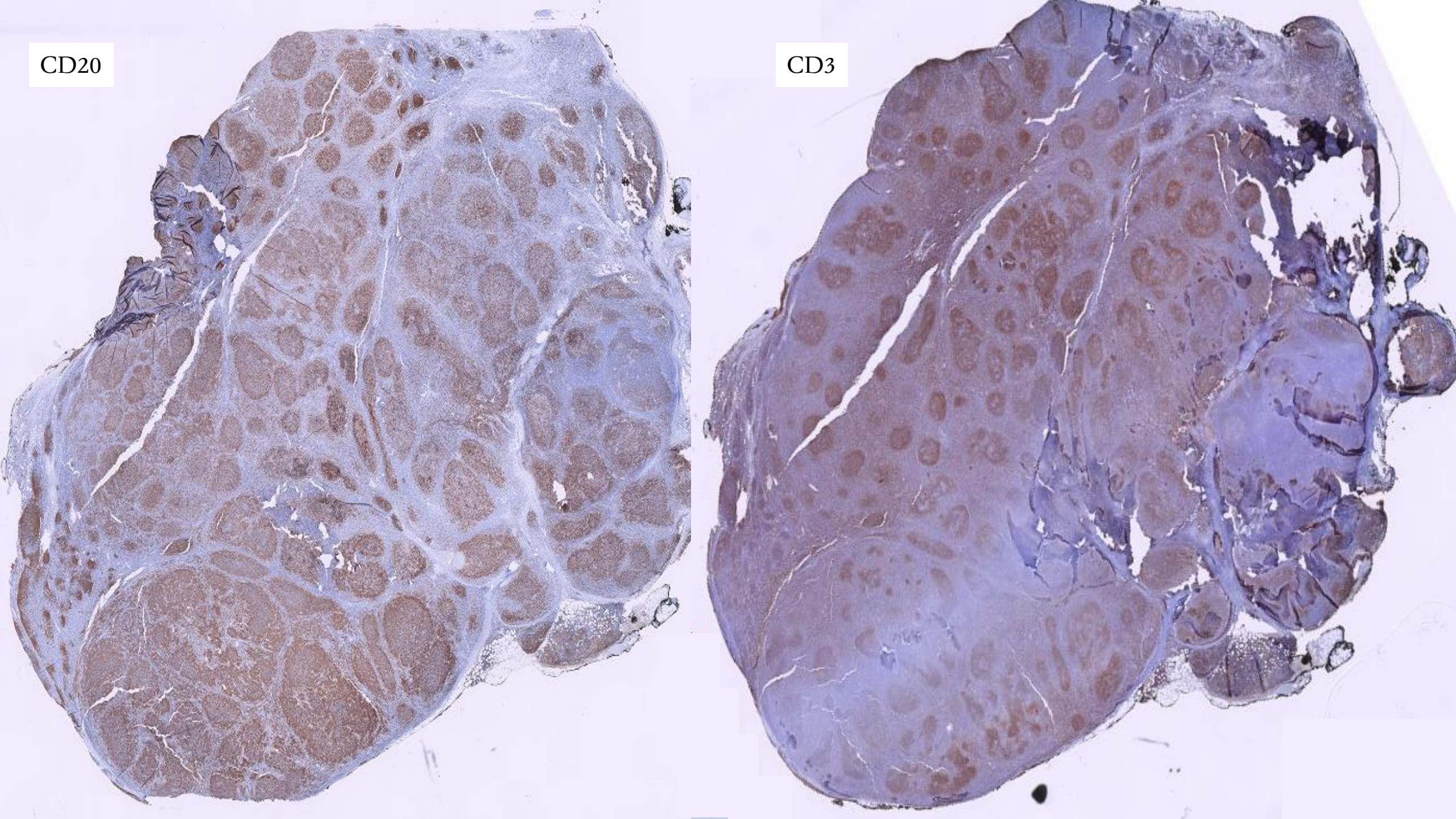


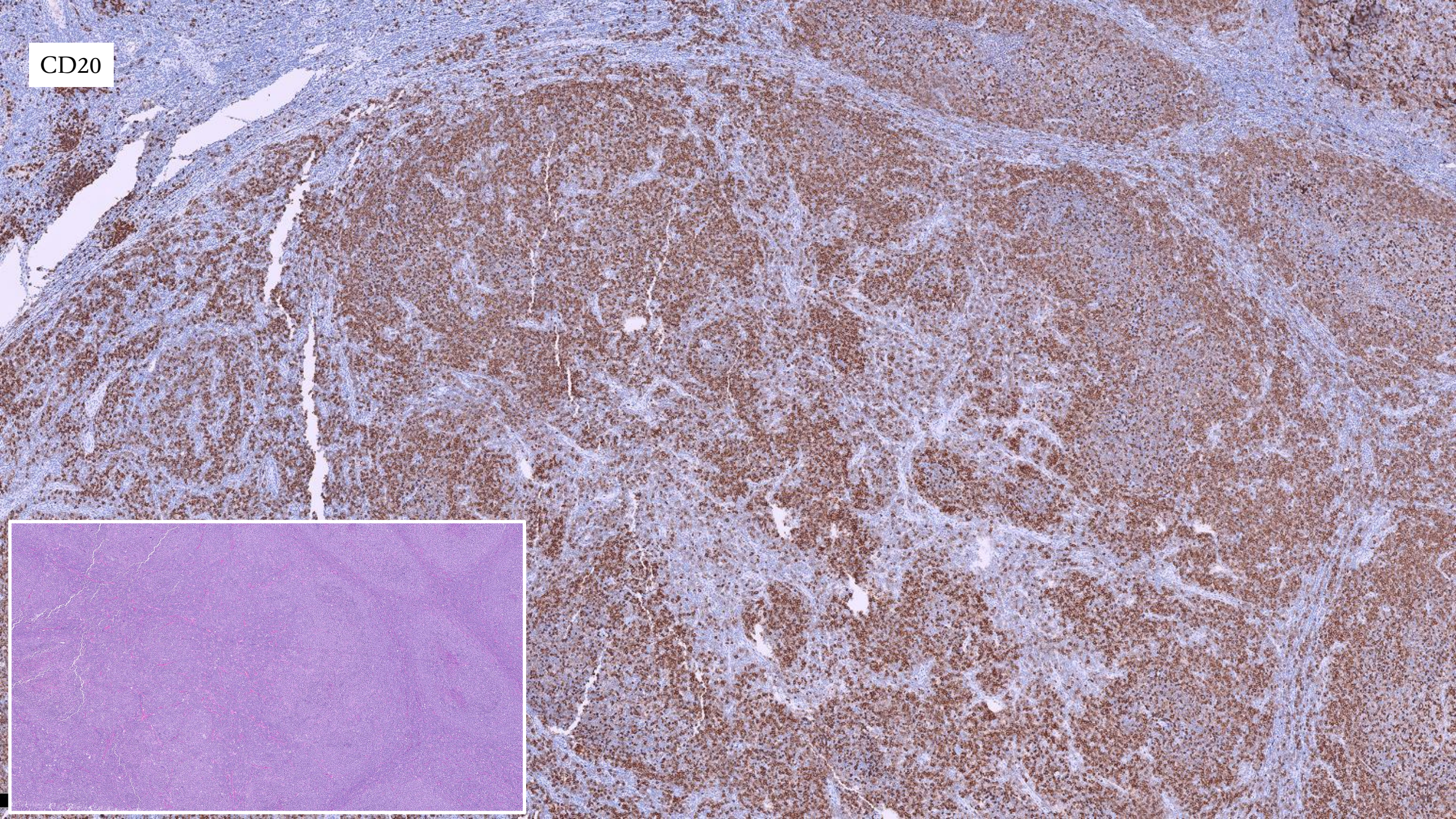








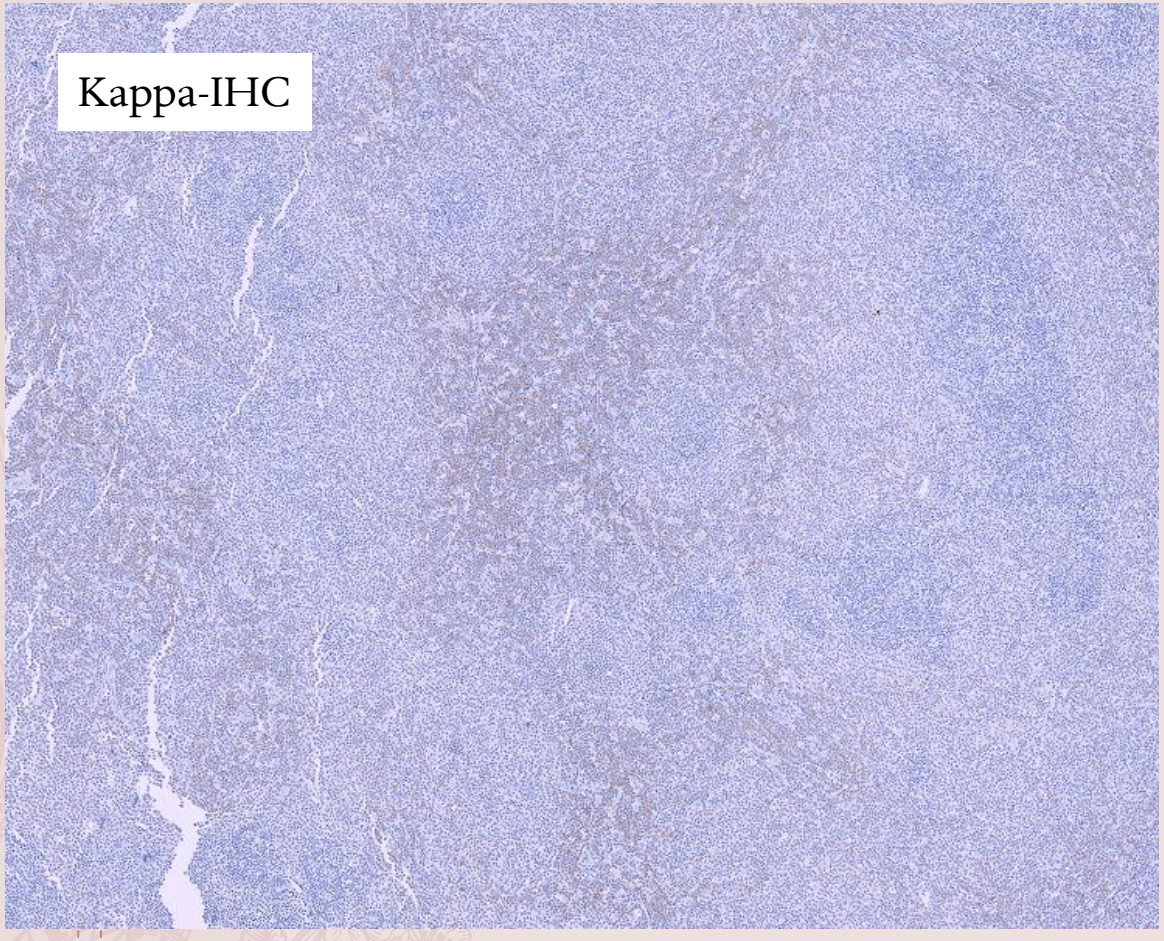

CD20
CD3

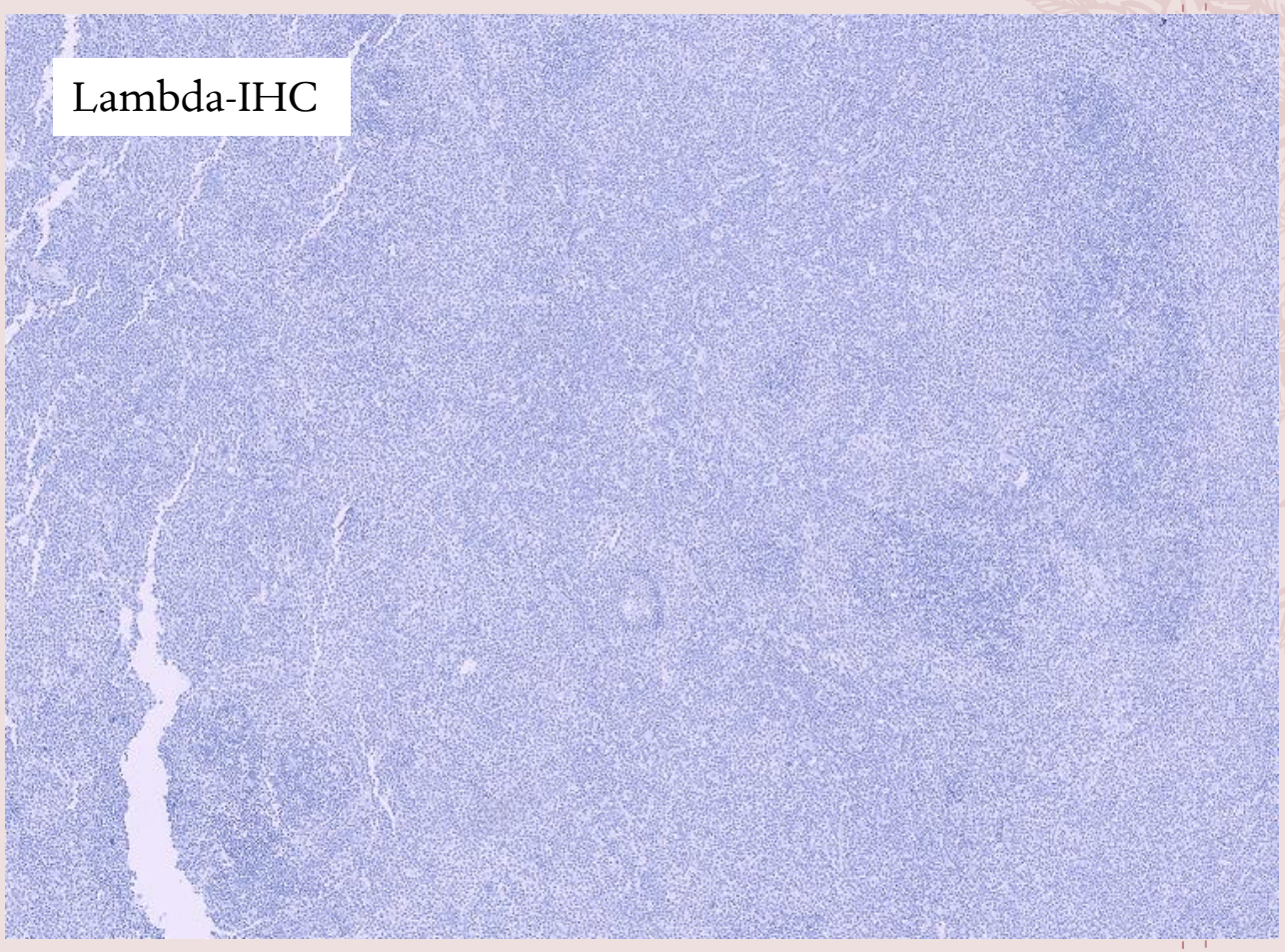

CD20

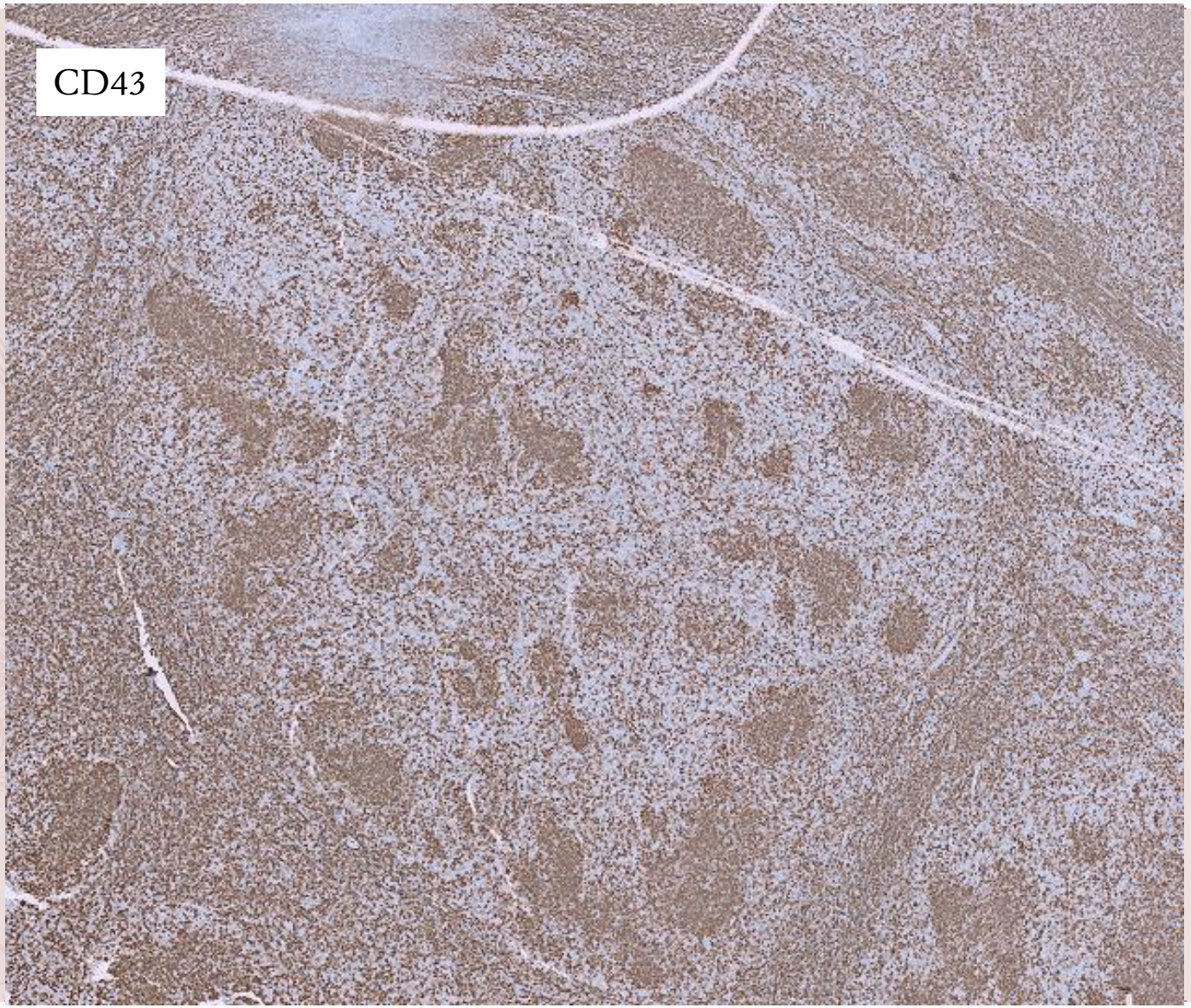
Differential Diagnosis

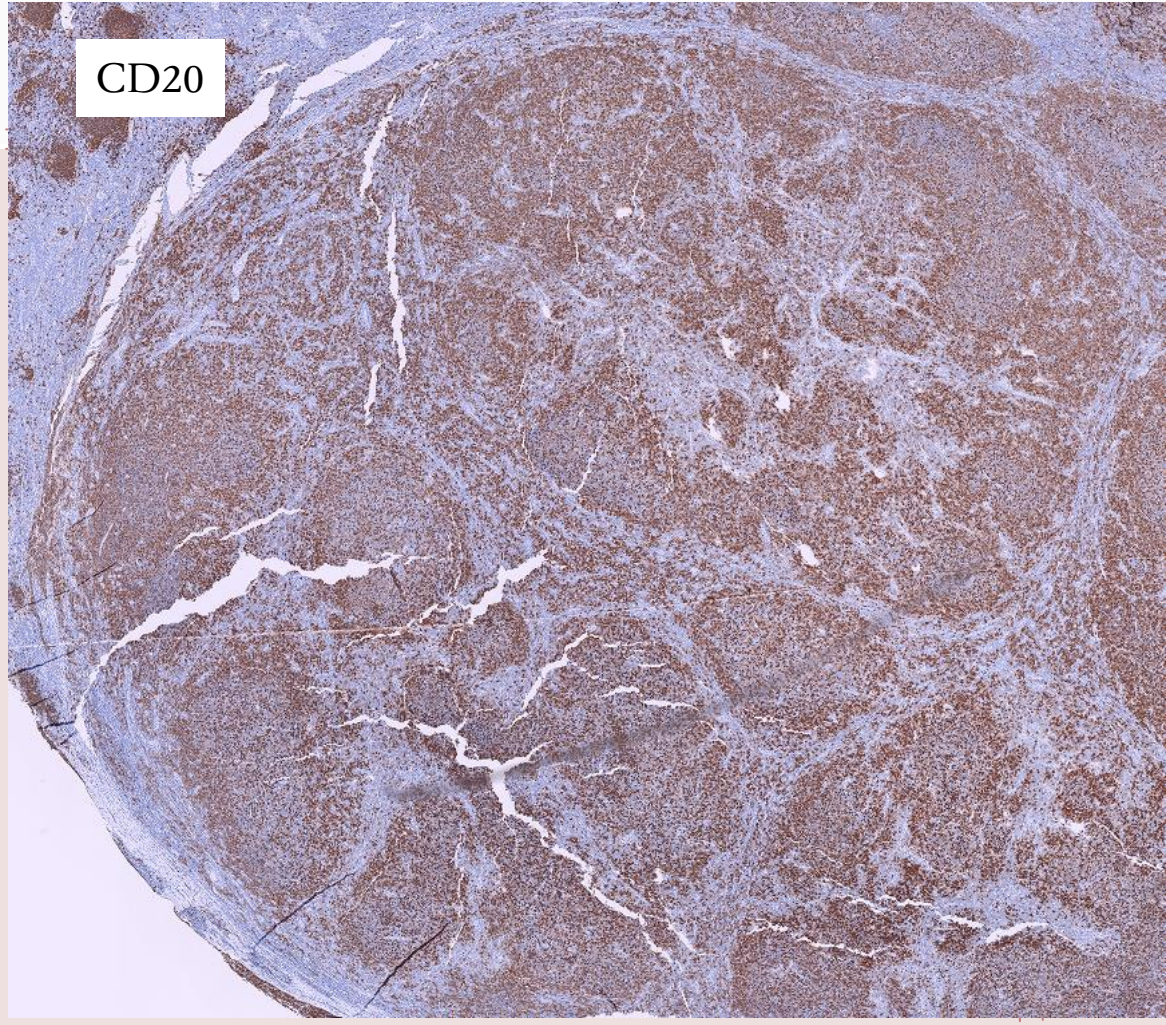
- History: 48 year old female with splenomegaly, lymphadenopathy, and IgM kappa M protein. Inguinal lymph node was excised.

- Marginal zone lymphoma
- Lymphoplasmacytic lymphoma
- Follicular lymphoma
- Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)
- Mantle cell lymphoma
- Plasma cell neoplasm

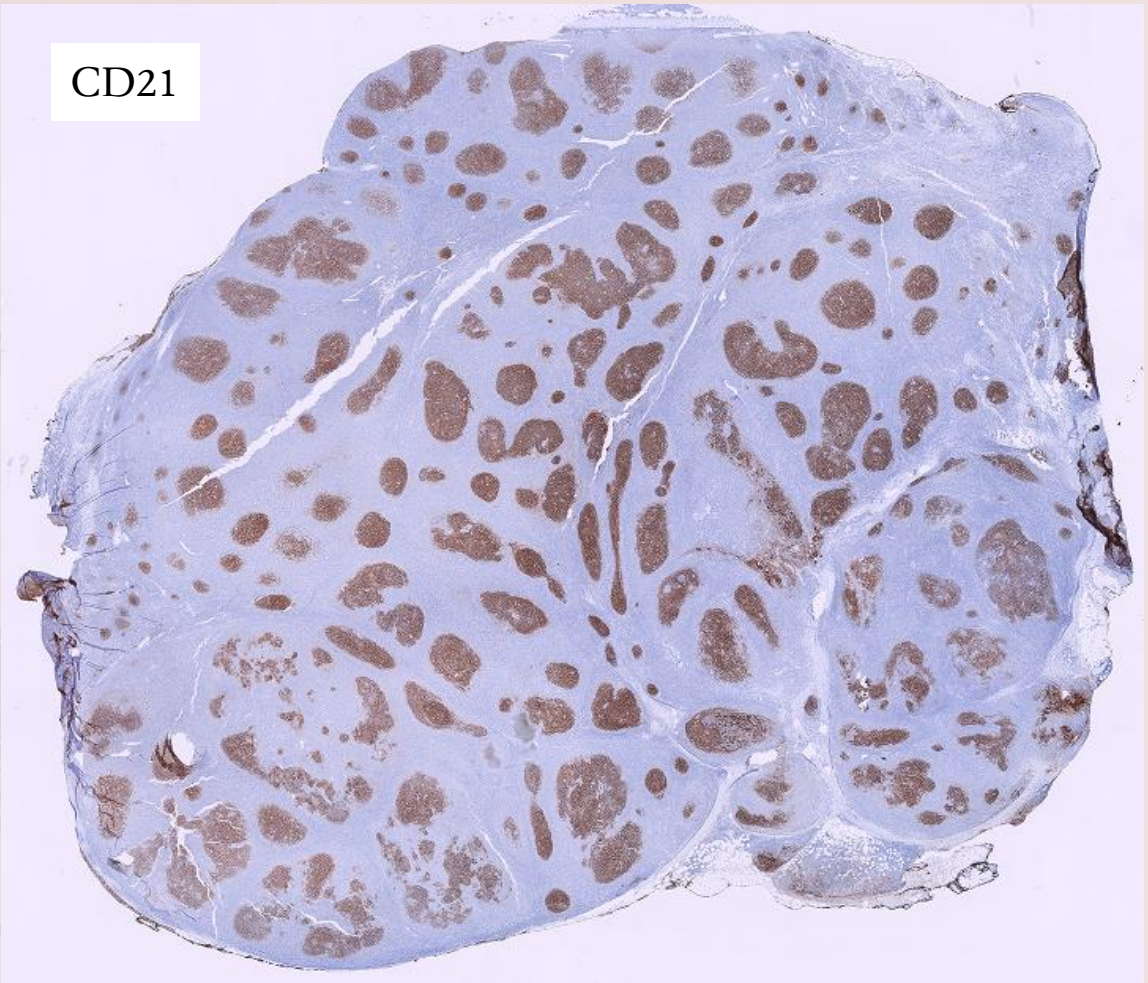

Kappa-IHC


Lambda-IHC


CD43


CD20

CD21



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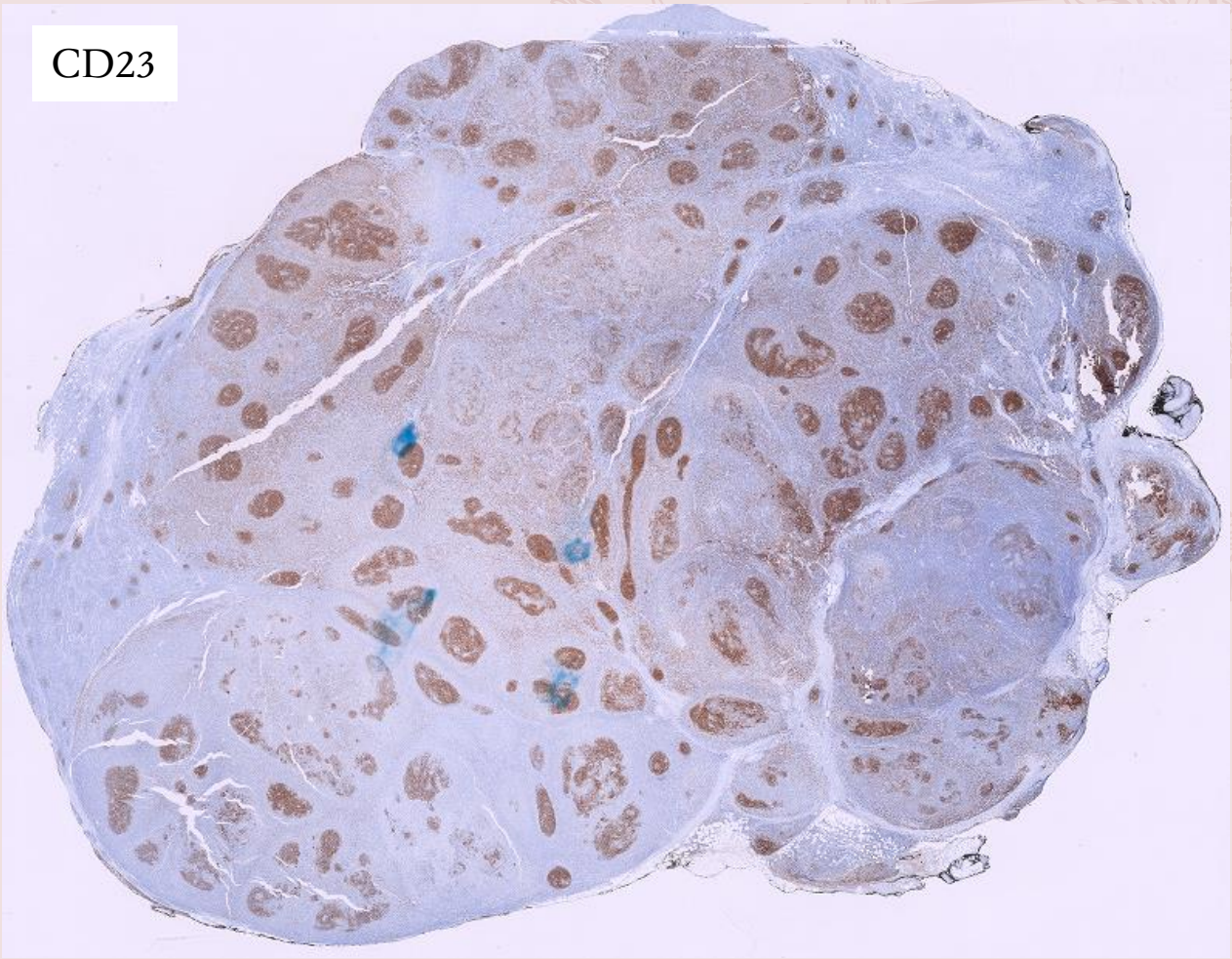
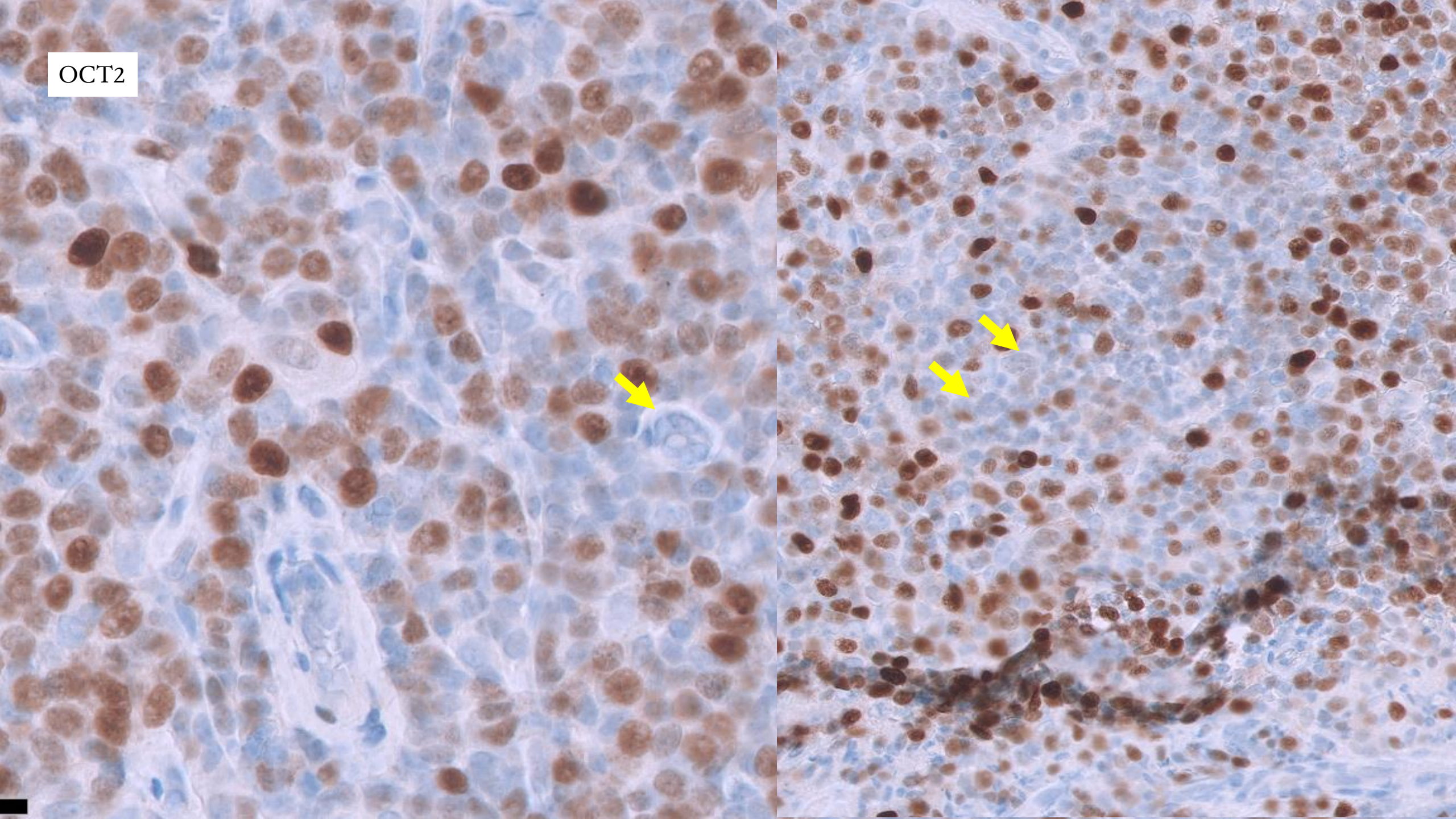
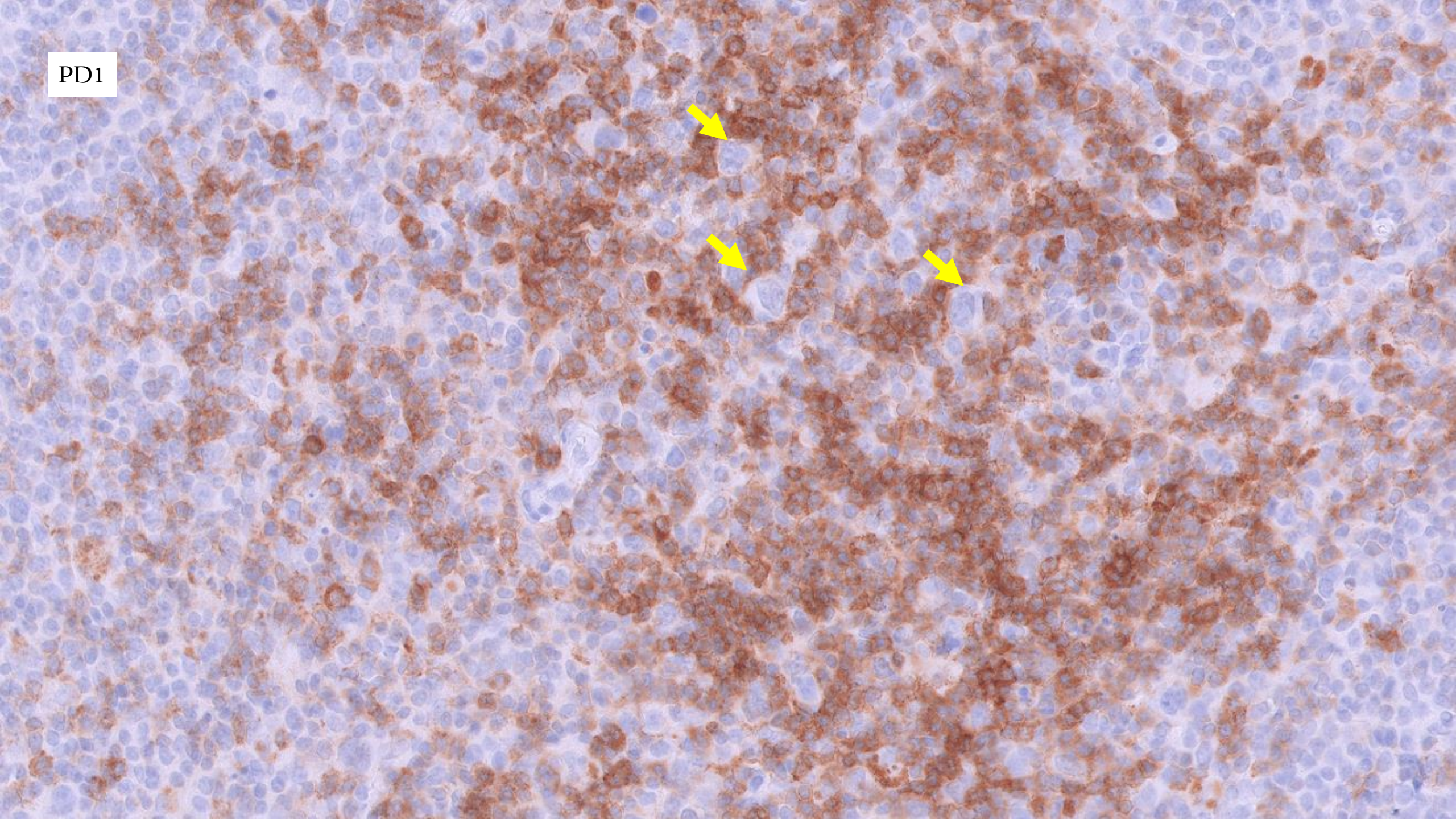
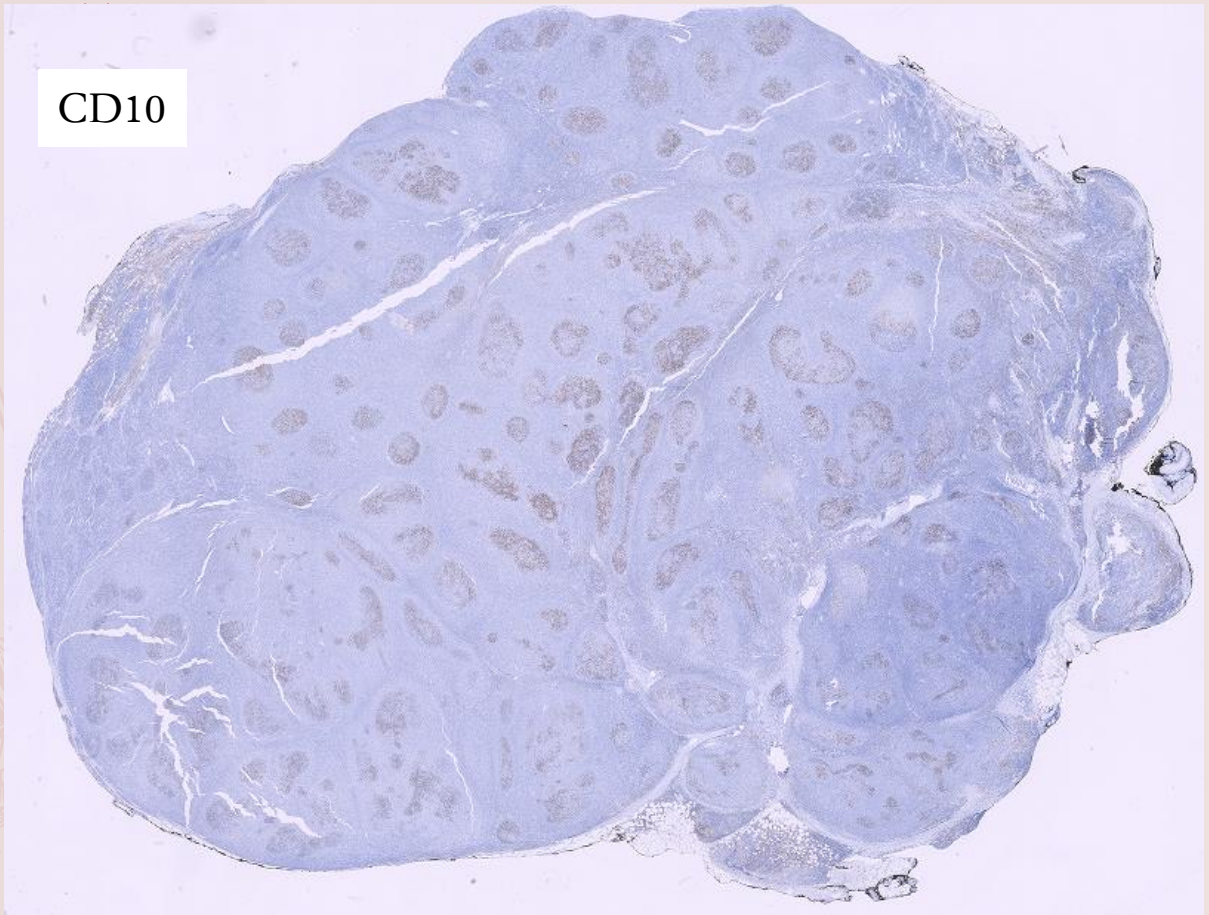


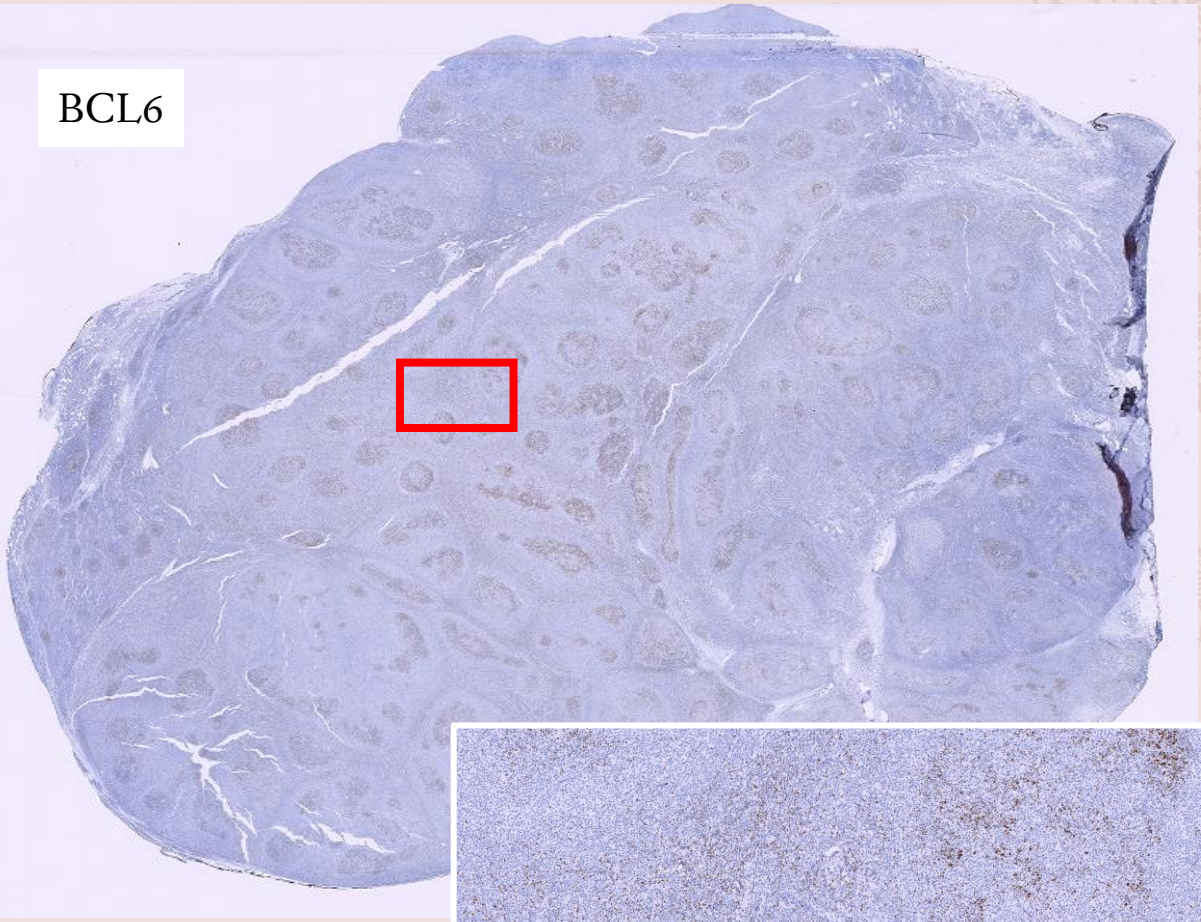

OCT2


PD1

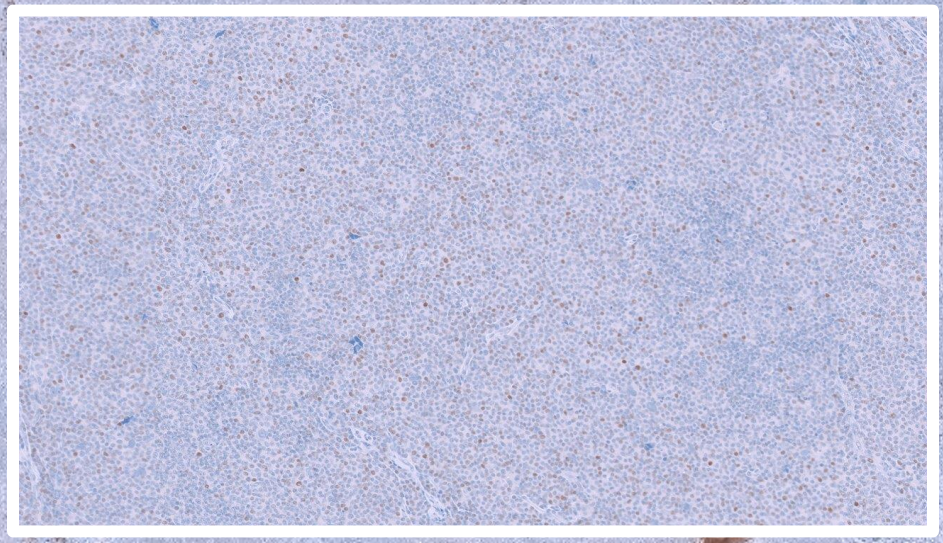
CD10

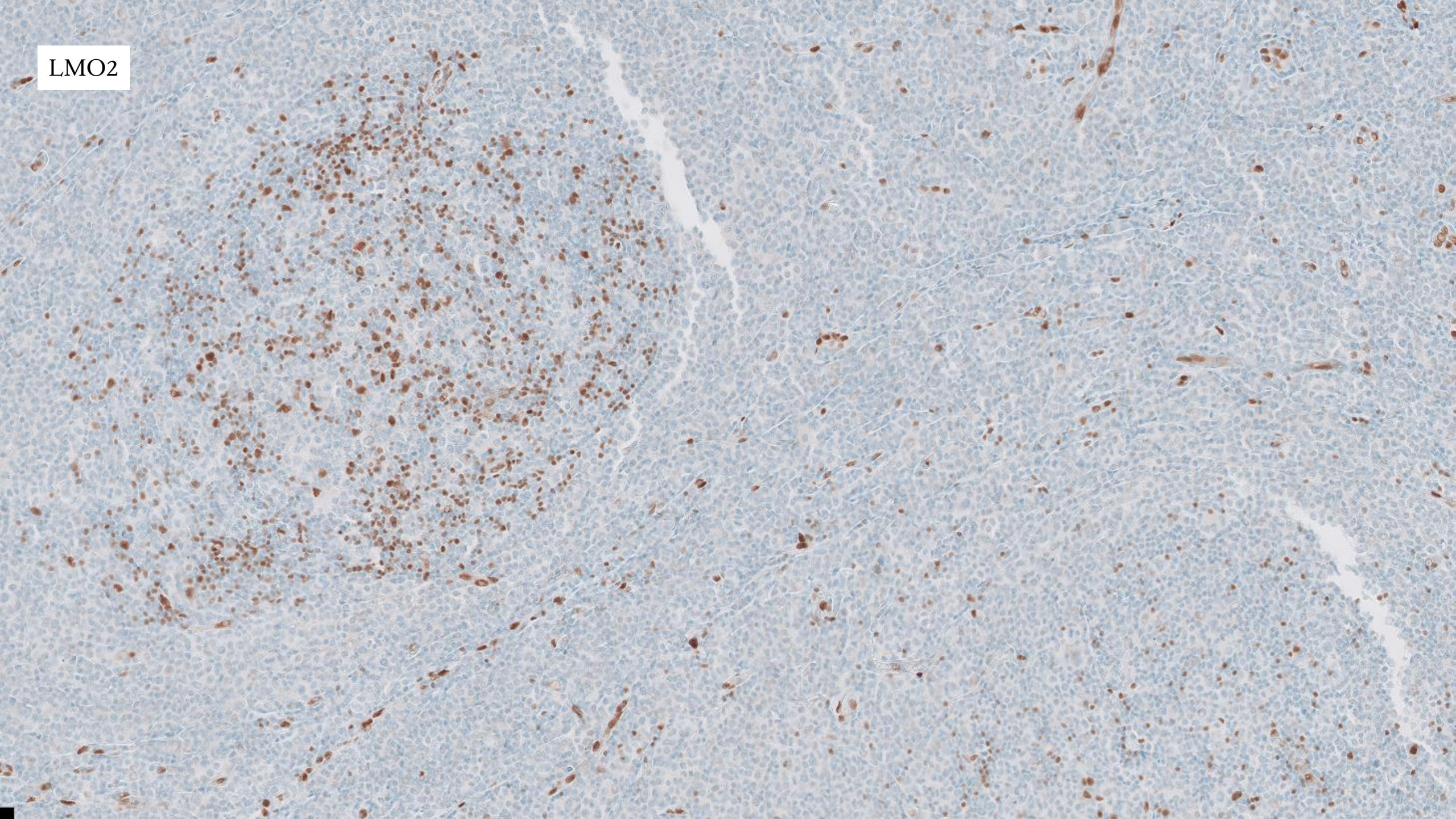


BCL6

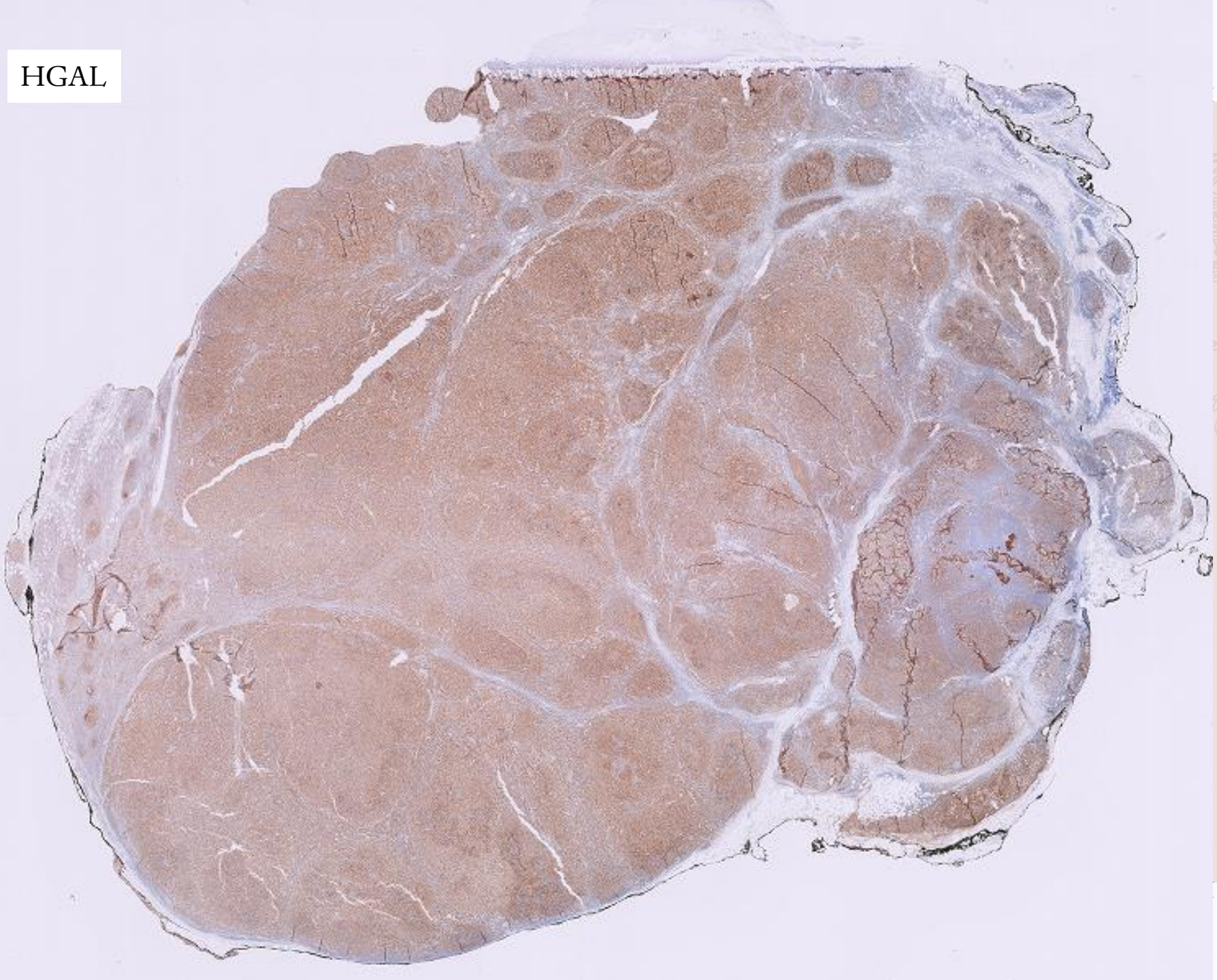


MEF2B

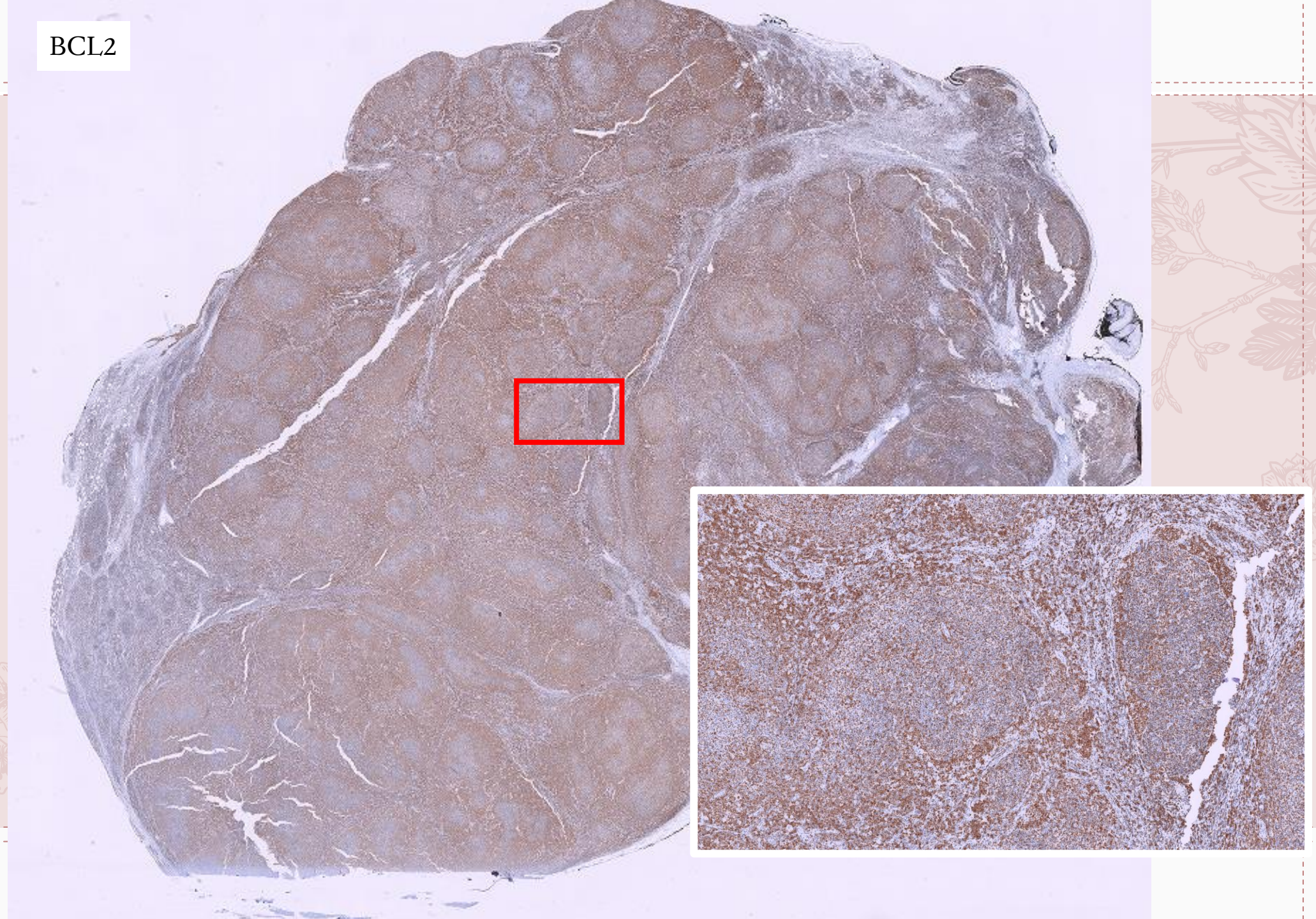



LMO2

HGAL



BCL2




Ki67

Flow cytometry (OSH)

- **Kappa-restricted B-cell population positive for CD19, weak CD20, CD22, variable CD38, and negative for CD5 and CD10**

NGS (UCSF 500 panel)

- EZH2 p.Y646N NM_004456.4 Pathogenic 13%
- NOTCH1 p.P2514fs NM_017617.3 Pathogenic 17%
- TNFAIP3 p.C627fs NM_006290.3 Pathogenic 21%
- AMER1 p.R601* NM_152424.3 Likely Pathogenic 11%
- IKZF1 c.851-2A>C NM_006060.4 Likely Pathogenic 15%
- XPO1, REL amplification; all Likely Pathogenic, approximately 3.0x N/A

FISH studies

- MYC, BCL2 and BCL6 rearrangements
  - Negative

Lymph node, Right femoral, Excisional biopsy

- Small B-cell lymphoma with plasmacytic differentiation
  - Favoring BCL2-negative follicular lymphoma

Mod Pathol. 2022 Jan;35(1):60-68. doi: 10.1038/s41379-021-00938-z. Epub 2021 Oct 2.

Histopathologic, immunophenotypic, and mutational landscape of follicular lymphomas with plasmacytic differentiation

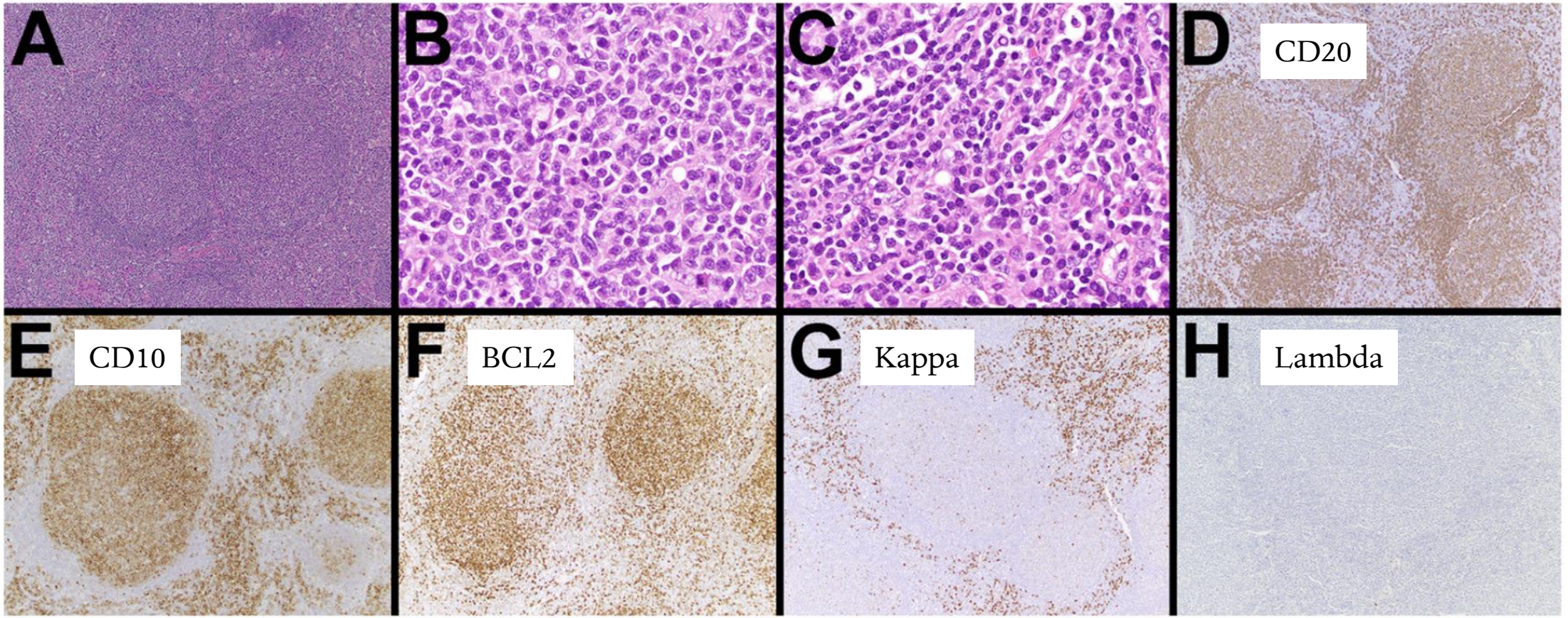
Sarah E Gibson [1 2 3], Yen-Chun Liu [4 5 6], Svetlana A Yatsenko [4 5], Nicholas J Barasch [5 7], Steven H Swerdlow [4 5]

Affiliations + expand

PMID: 34601504 DOI: 10.1038/s41379-021-00938-z

Free article

Follicular lymphoma with interfollicular plasmacytic differentiation



Follicular lymphoma with intrafollicular plasmacytic differentiation

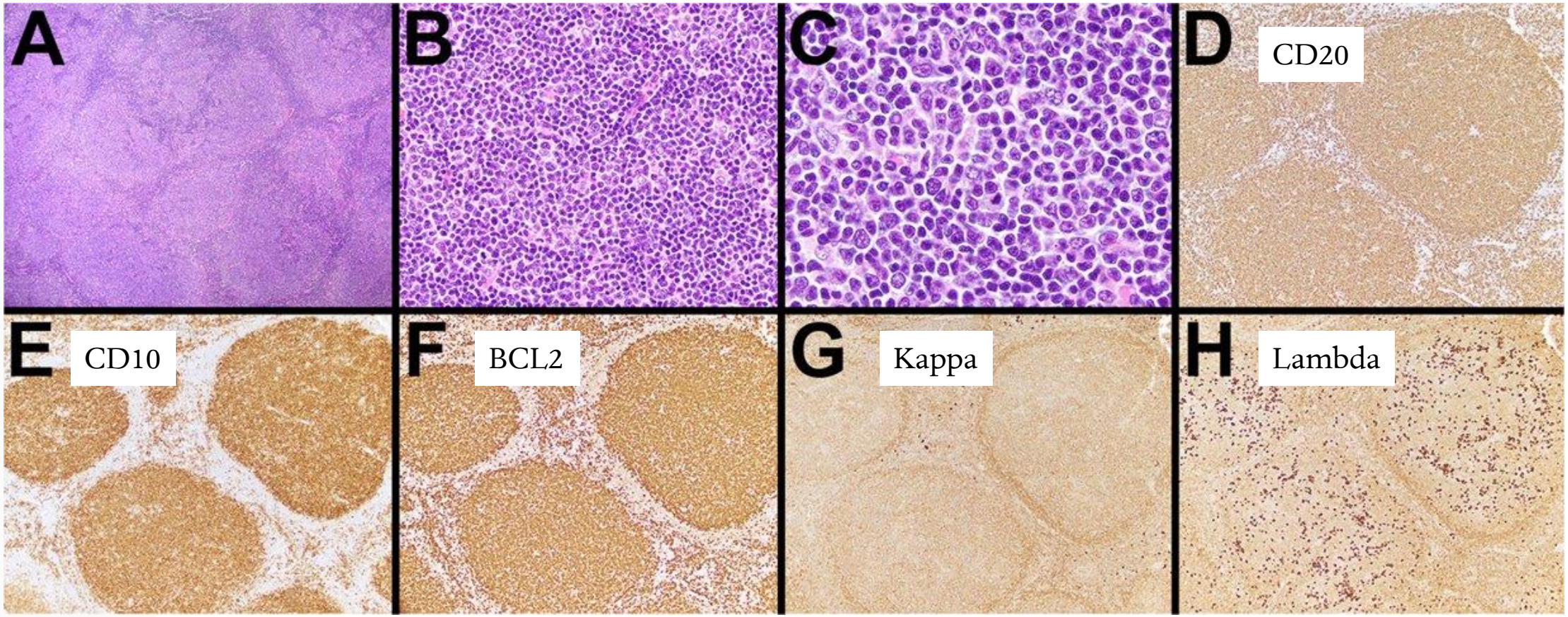
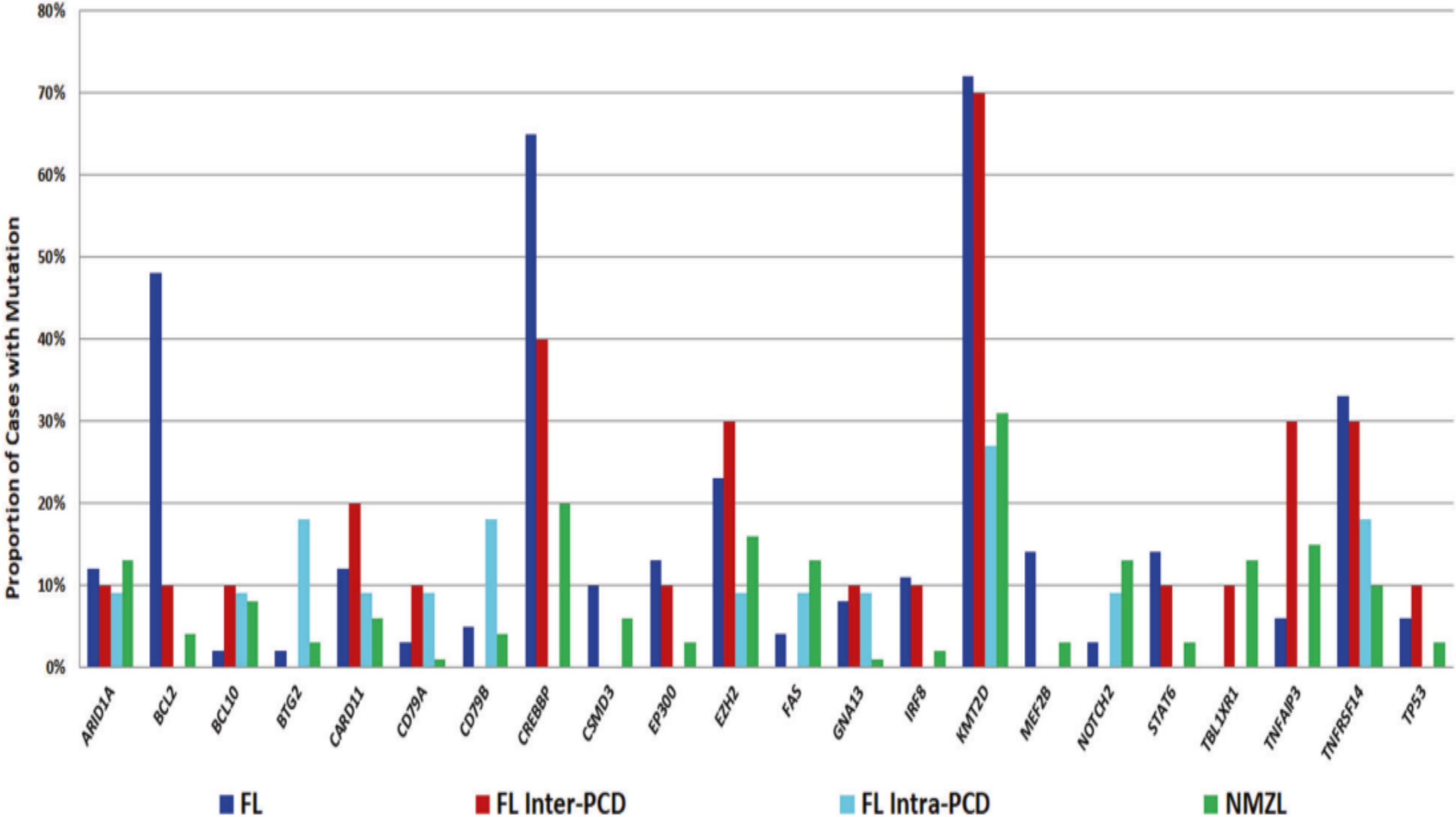


Table 2. Histopathologic and Immunophenotypic Features of 25 Follicular Lymphomas with Plasmacytic Differentiation.

	Intrafollicular PCD	Interfollicular PCD	Mixed intra/interfollicular PCD
No.	11	10	4
Histologic grade			
1-2	5 (45%)	7 (70%)	3 (75%)
3 A	5 (45%)	1 (10%)	0 (0%)
3B	1 (9%)	2 (20%)	1 (25%)
DLBCL present	3 (27%)	4 (40%)	0 (0%)
Predominant cytology of follicle center cells			
Plasmacytoid	4 (36%)[a]	0 (0%)	3 (75%)[a]
Centrocytes	1 (9%)	6 (60%)	1 (25%)
Centroblasts	4 (36%)	3 (30%)	0 (0%)
Small, round cells	2 (18%)	1 (10%)	0 (0%)
CD10 +	5 (45%)[b]	9 (90%)	1 (25%)[b]
BCL6 +	11 (100%)	10 (100%)	4 (100%)
MEF2B +	9 (100%)	3 (60%)	4 (100%)
HGAL +	7 (78%)	5 (100%)	3 (75%)
IRF4/MUM1 +[c]	4 (36%)	0 (0%)	2 (50%)
BCL2 +	10 (91%)	9 (90%)	4 (100%)
IgM +	8 (80%)[d]	3 (30%)	4 (100%)[d]
Kappa +	8 (73%)	3 (30%)	2 (50%)
Immunophenotype of monotypic plasmacytoid cells			
Plasmacytic (CD138 + /CD38 + /IRF4/MUM1 +)	3 (27%)	10 (100%)[e]	2 (50%)
Plasmacytoid (IRF4/MUM1 + only)	8 (73%)	0 (0%)	2 (50%)
Ki-67 ≥ 30%	6 (55%)	3 (30%)	3 (75%)


80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion of Cases with Mutation
ARID1A
BCL2
BCL10
BTG2
CARD11
CD79A
CD79B
CREBBP
CSMD3
EP300
EZH2
FAS
GNA13
IRF8
KMT2D
MEF2B
NOTCH2
STAT6
TBL1XR1
TNFAIP3
TNFRSF14
TP53
FL
FL Inter-PCD
FL Intra-PCD
NMZL

Conclusion

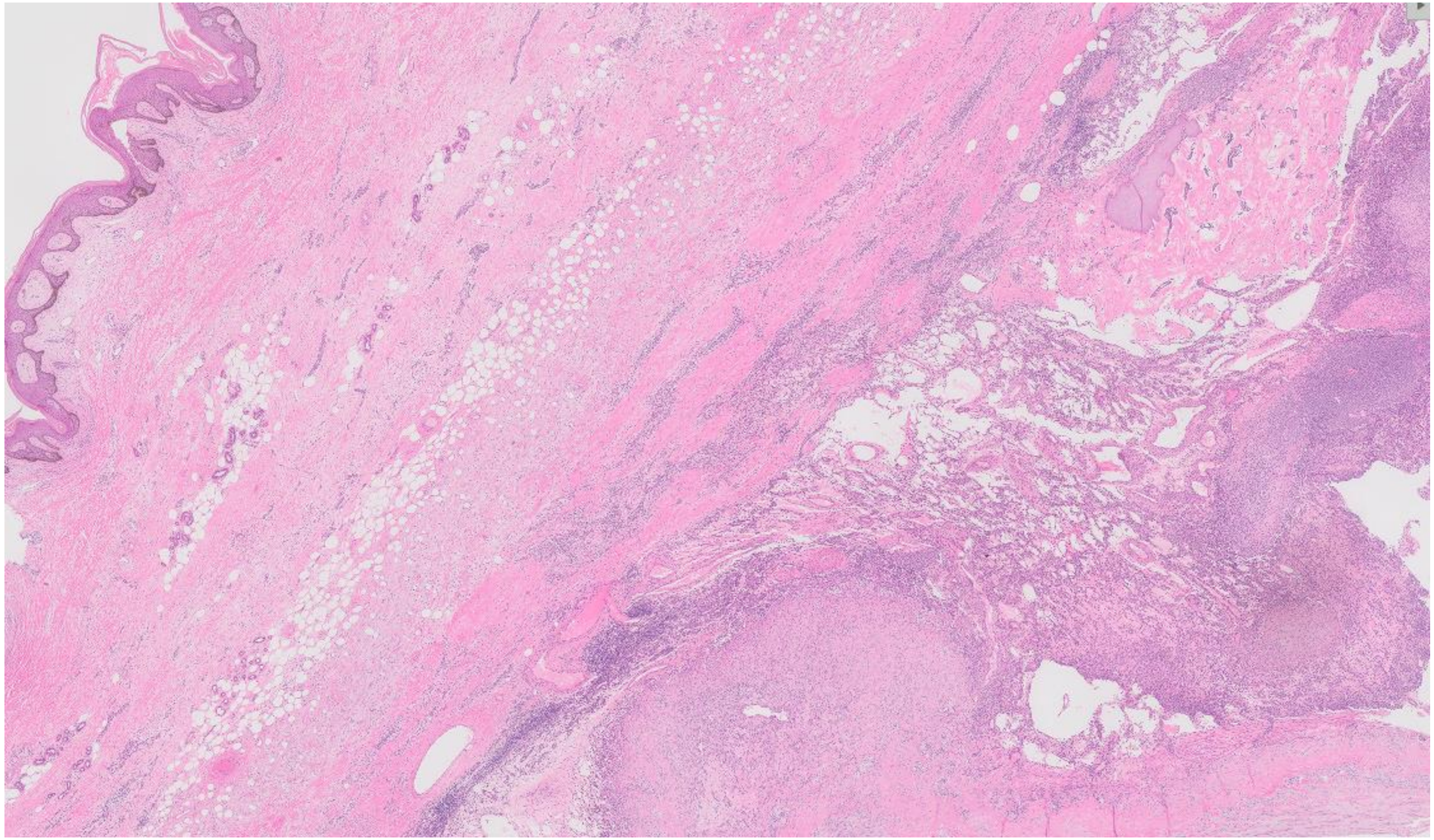
- Follicular lymphoma with plasmacytic differential is rare: 9% of FLs with easily visualized population of interfollicular lymphocytes resembling those seen in MZL
- FL-PCD histologically mimics MZL and LPL so need to do all GC markers and maybe even molecular (MYD88 to rule out LPL)
- Mutations in CREBBP, KMT2D, EZH2, and TNFRSF14 are most common (similar to conventional FL)
  - Interfollicular: share features with FL, harbor a BCL2 rearrangement
  - Intrafollicular: share features with MZL, absence of a BCL2-R
- 10–15% of cFL cases lack BCL2 rearrangement, More common in FLBCL, dFL, primary testicular FL, and pediatric-type FL. STAT6 and KMT2D, TNFRSF14 mutations, 1p36 deletion.
- Some studies suggested a worse clinical outcome

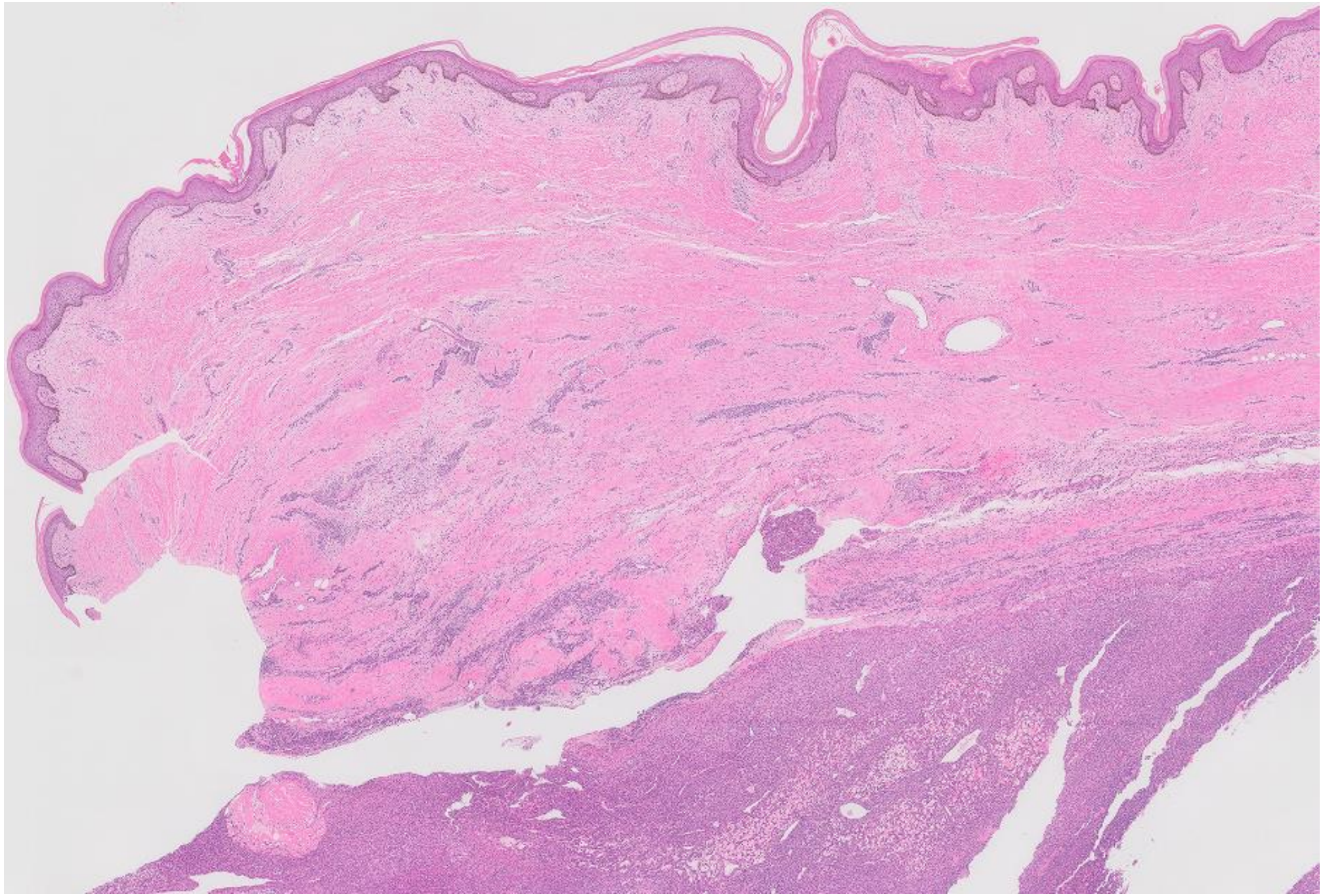
Thank You

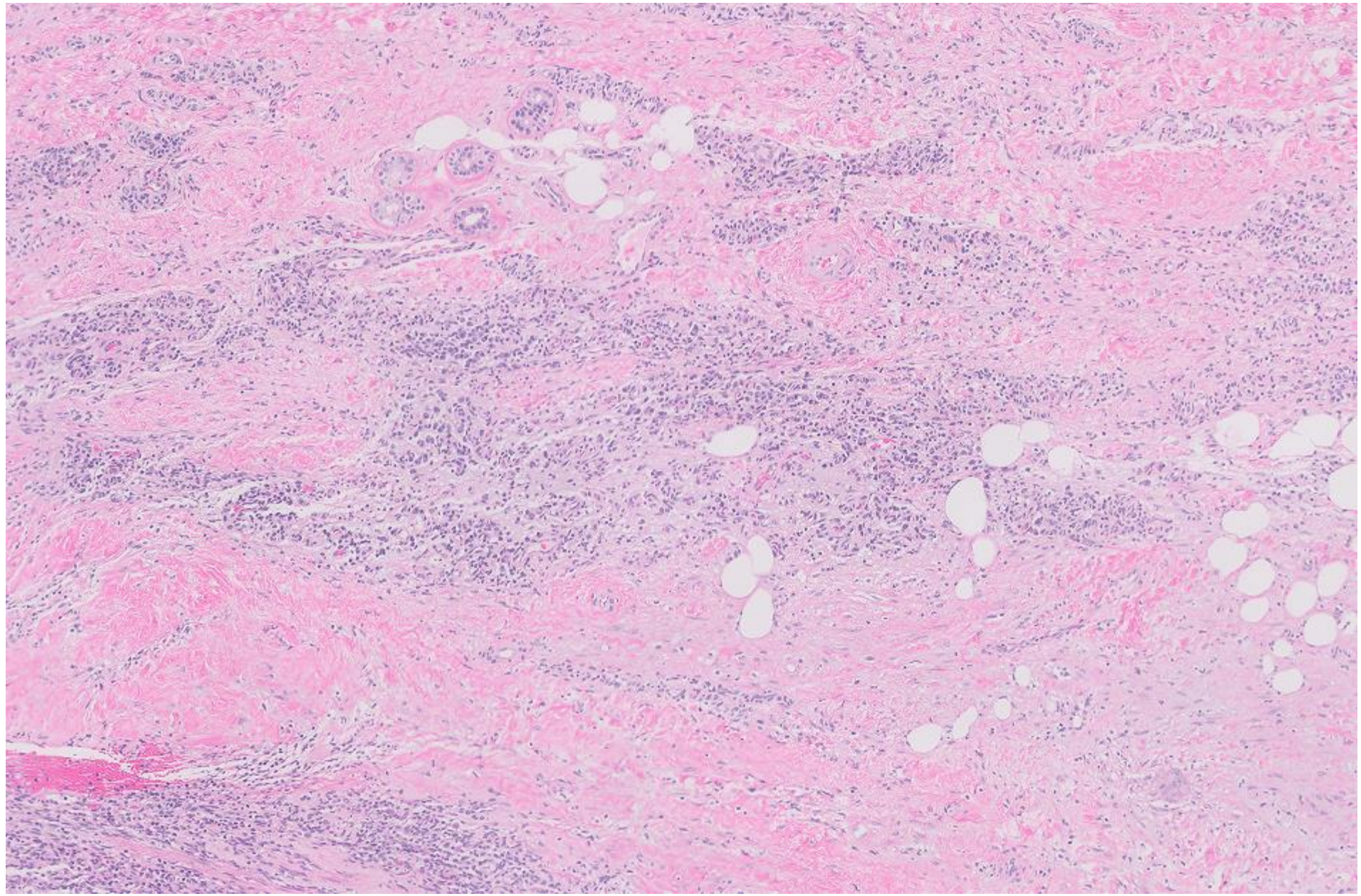
25-0407

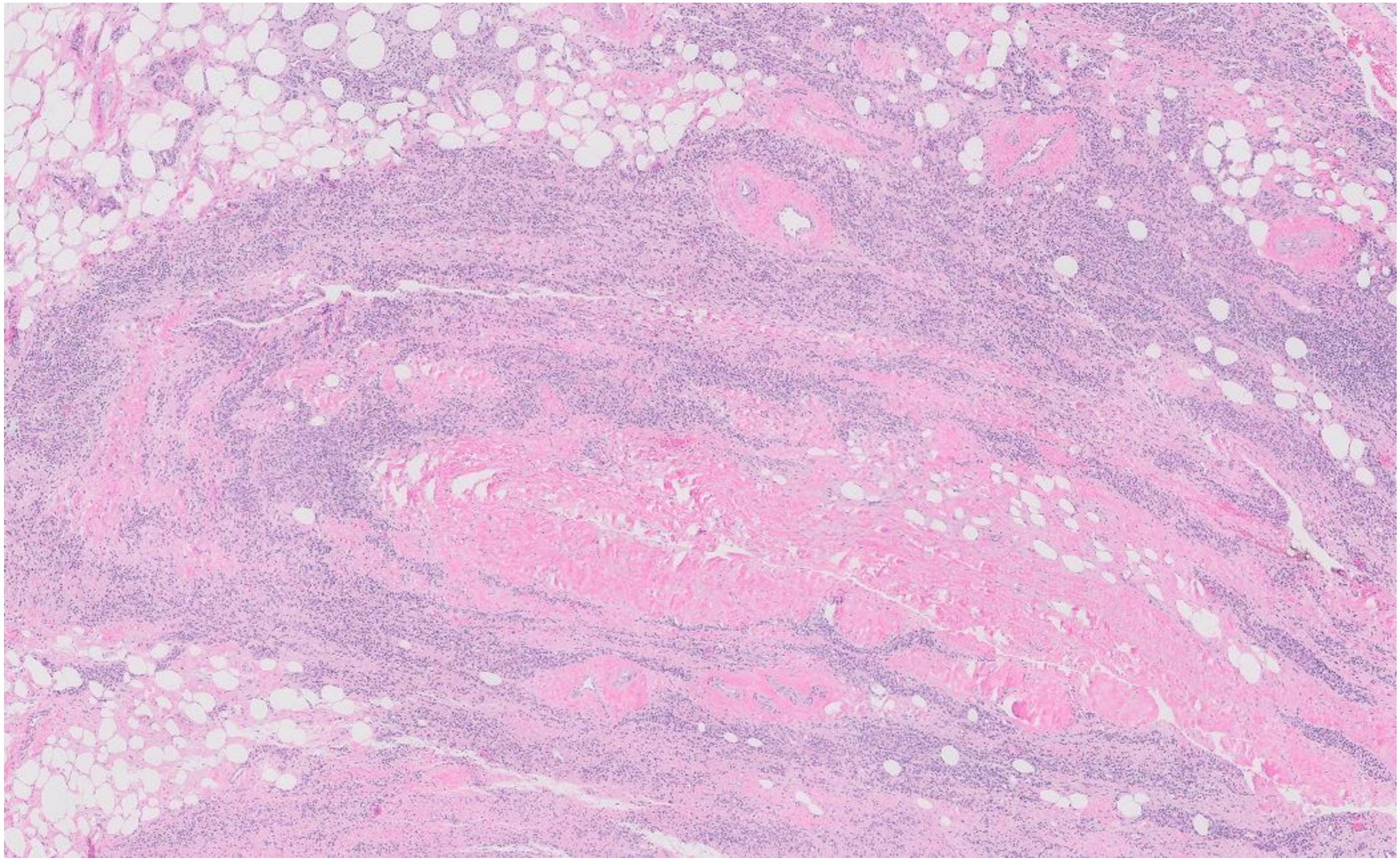
Sheren Younes; Xiaohua Qian; Stanford

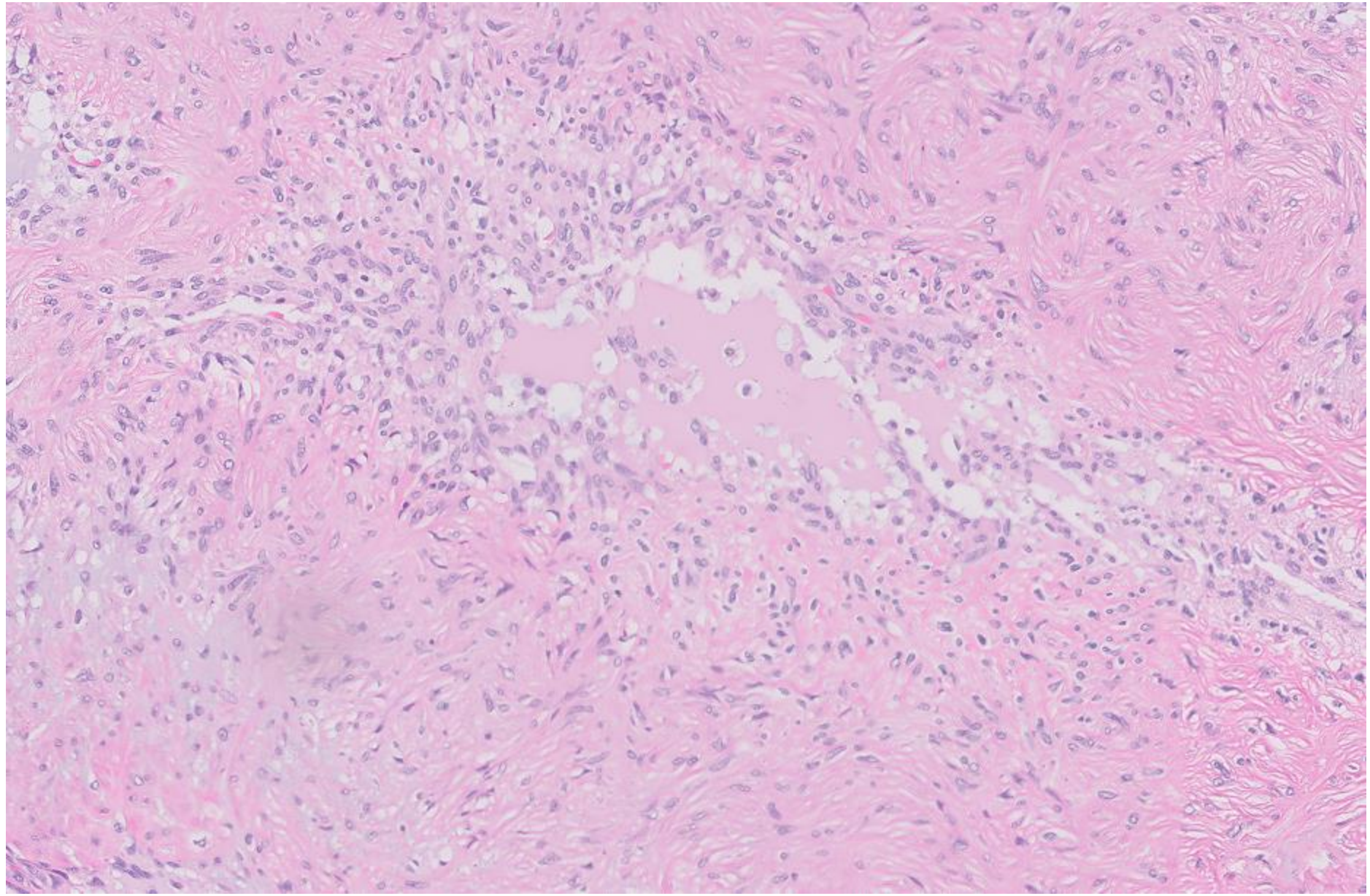
40 year-old female with left ankle mass

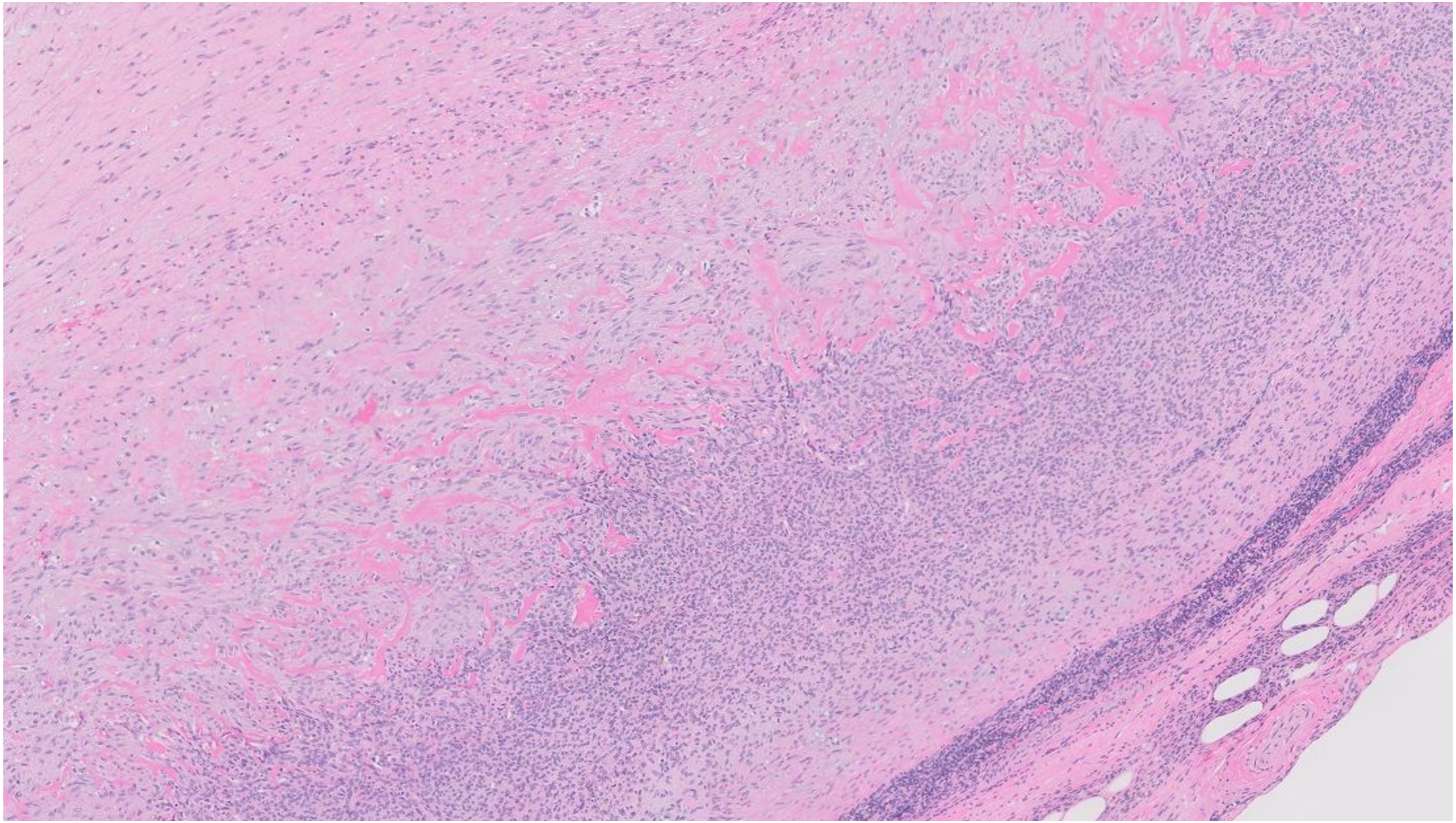


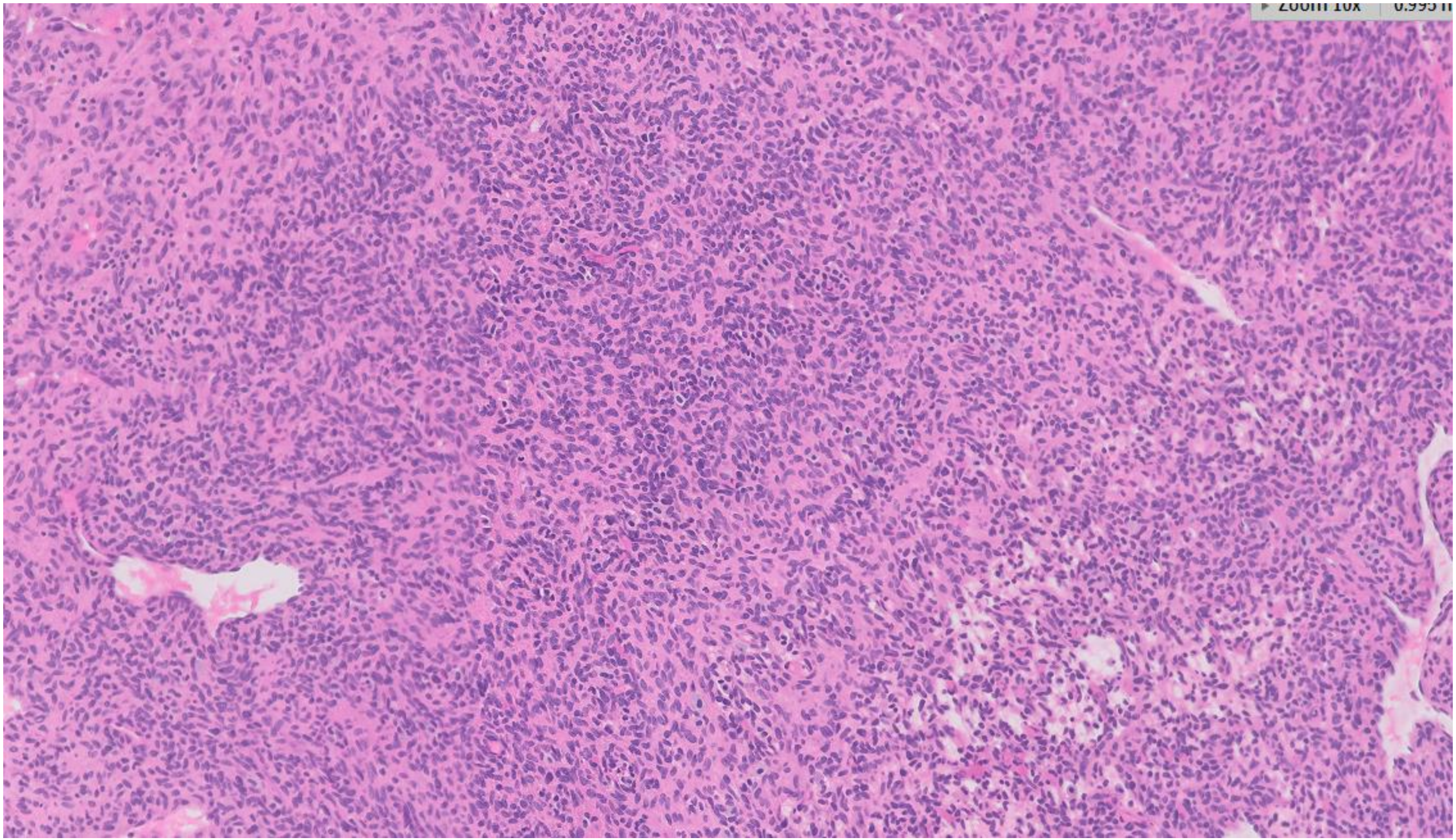


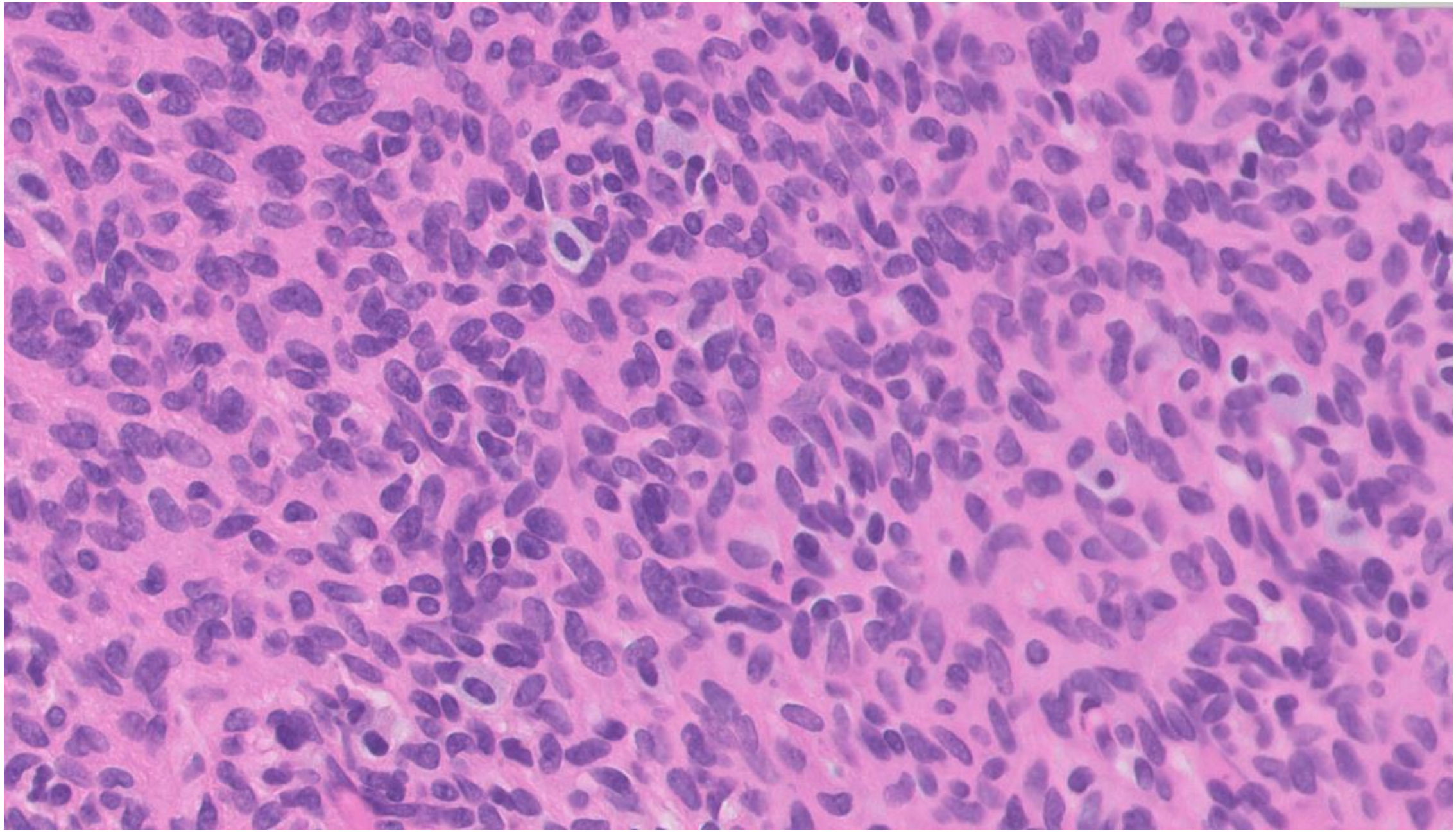


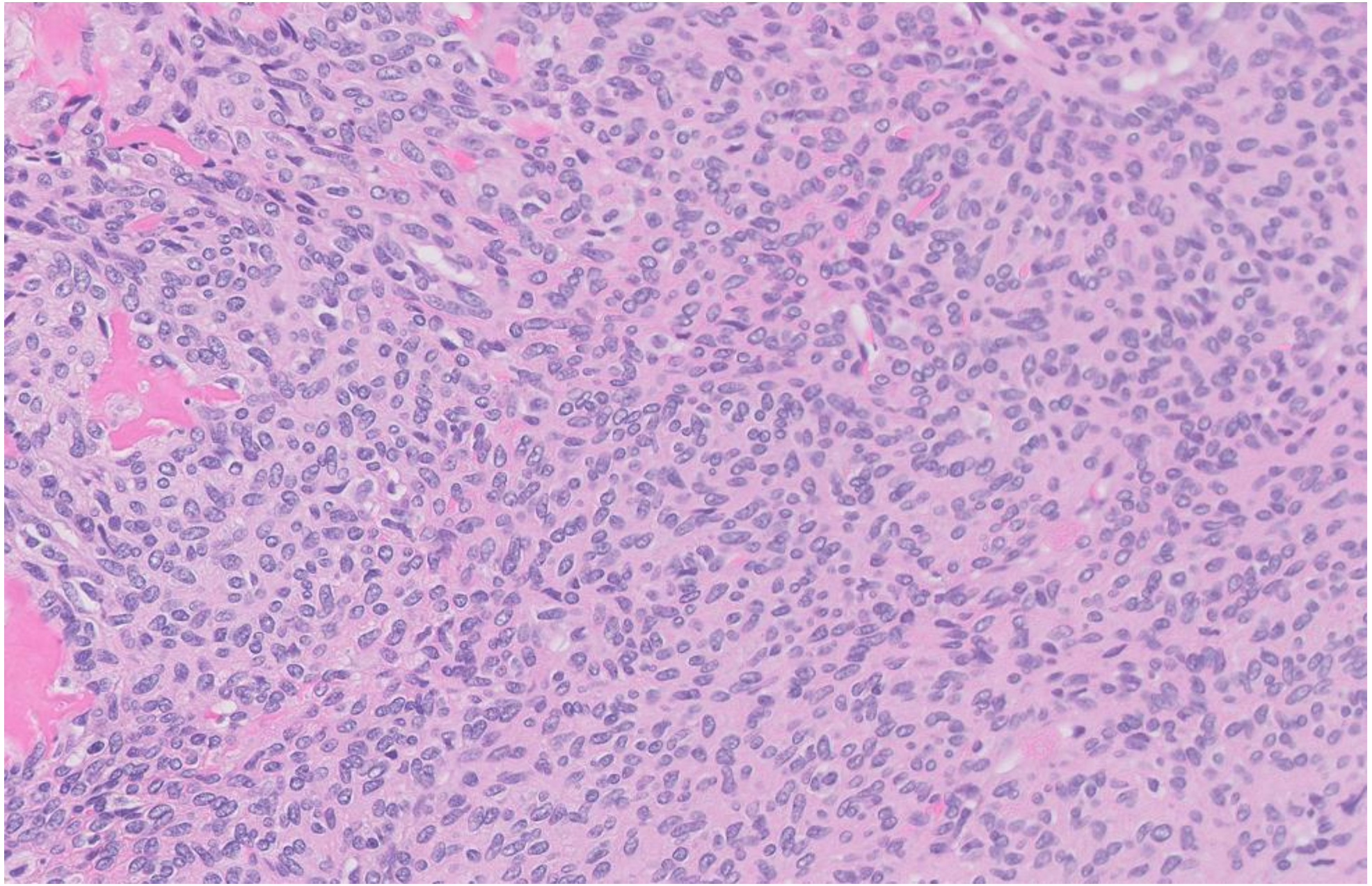


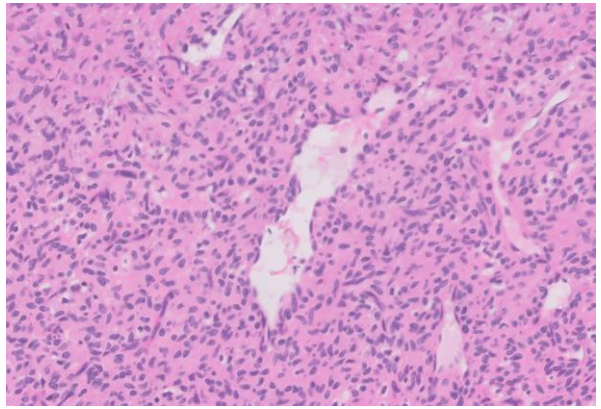


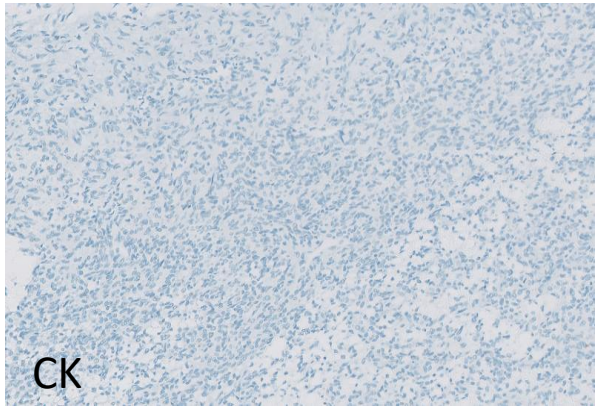








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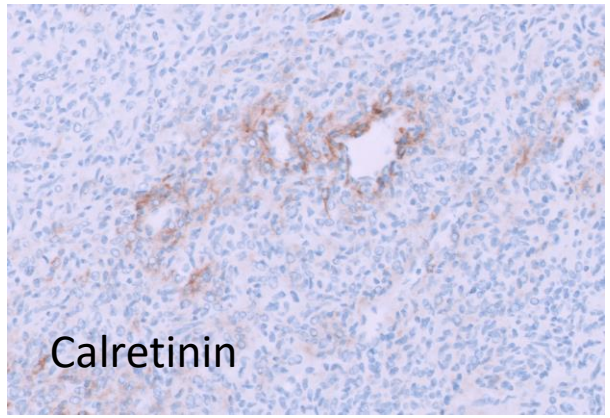
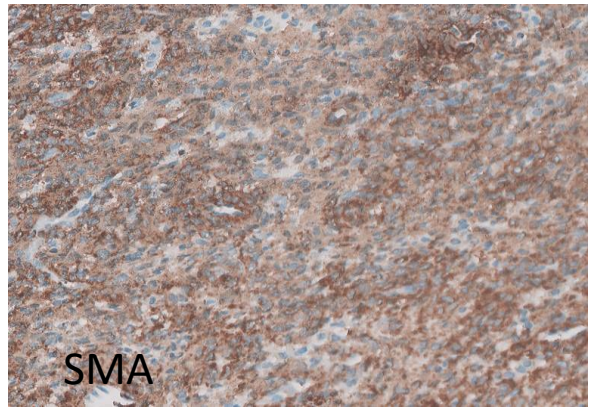

Calretinin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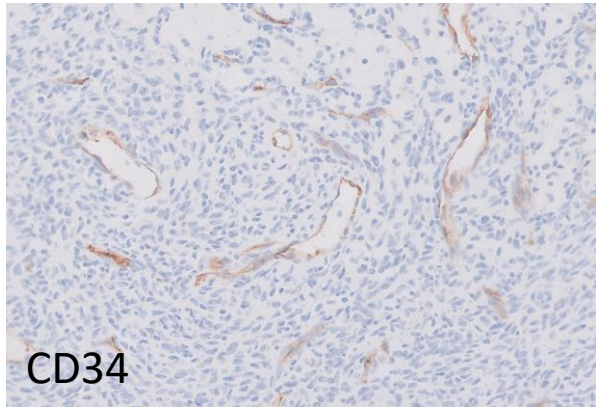
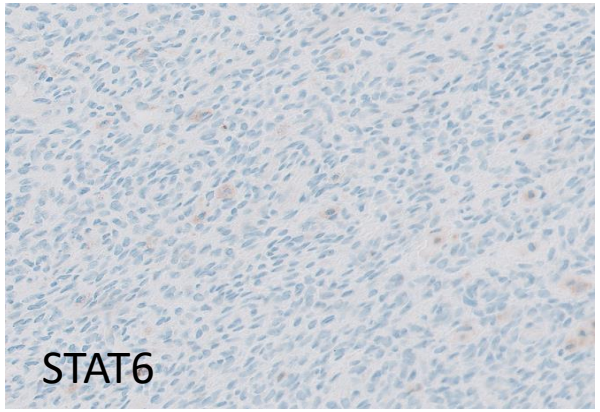
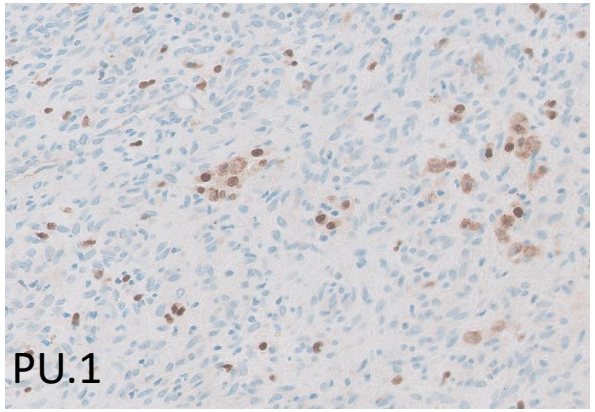

CD34


STAT6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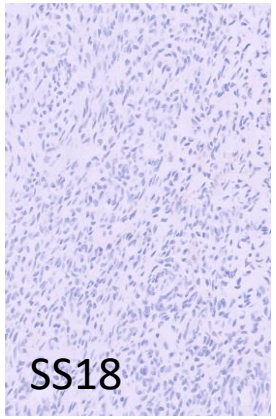
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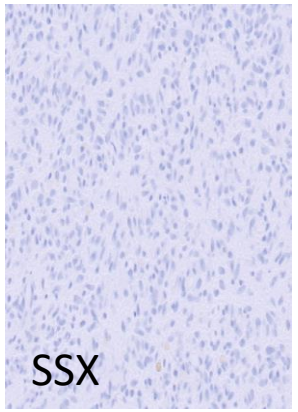
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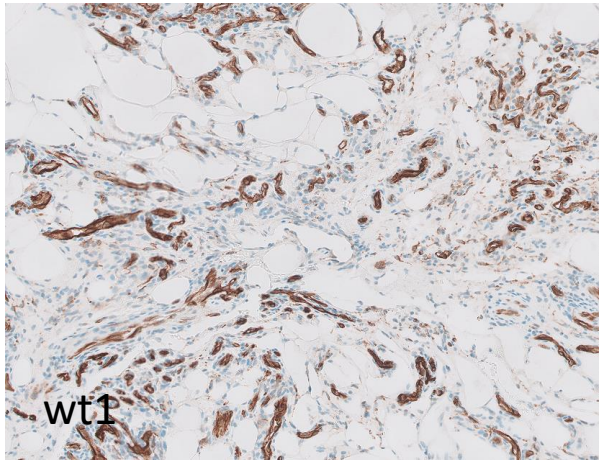
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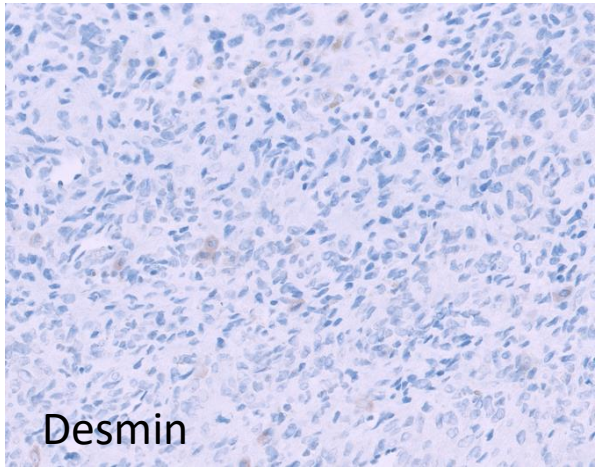
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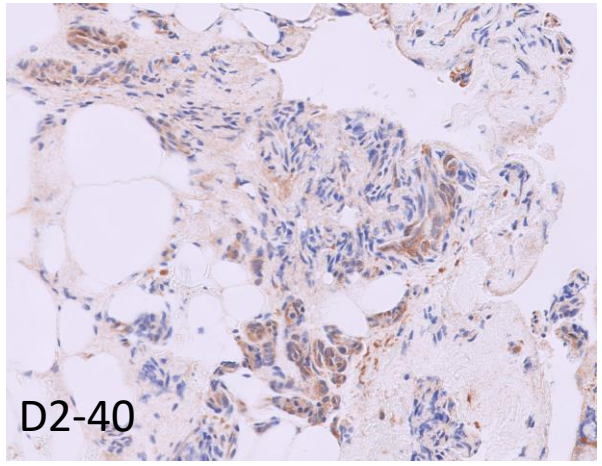
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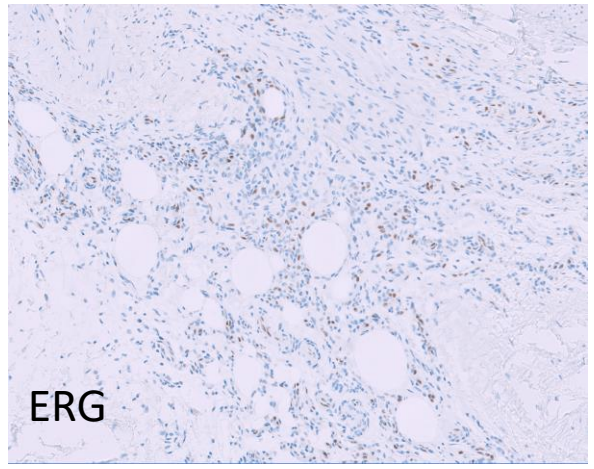

ERG

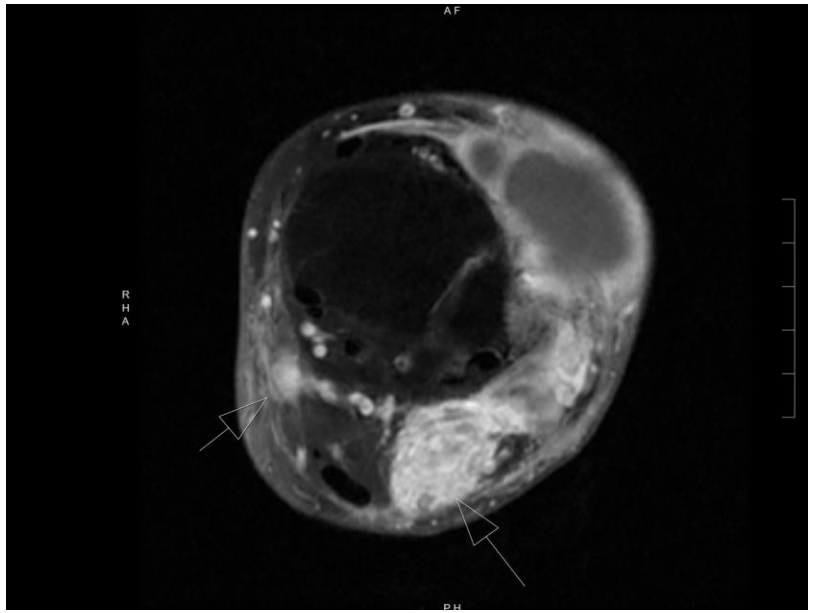
DIAGNOSIS?

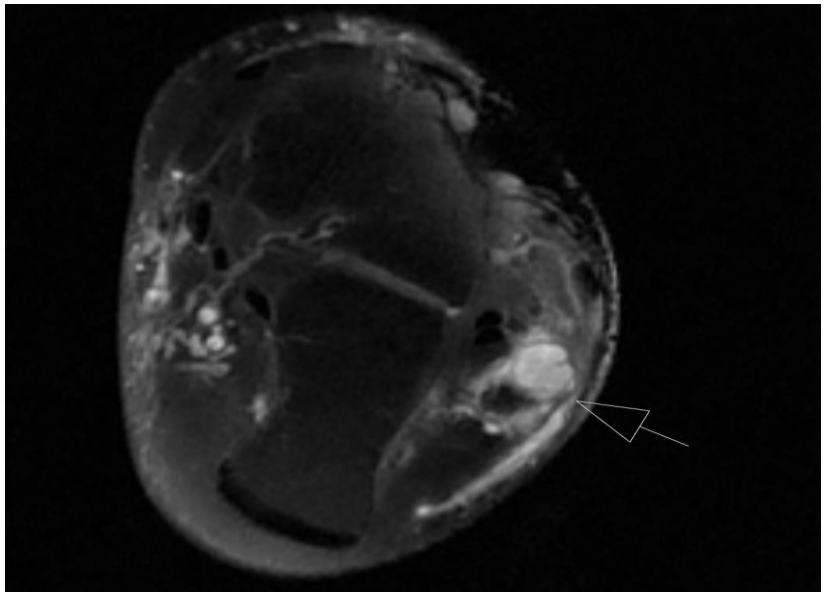
Sheren Younes, MD, PhD; Xiaohua Qian, MD, PhD

40 Y year old female with left ankle mass since the 1990s. She reports she had swelling at the lateral aspect of her ankle, with swelling throughout the left lower extremity. She had surgery done in India at age 14. Biopsy report from 1/20/1997 showed "synovial tissue with mild chronic inflammatory cell infiltrates. No evidence of tuberculosis or Rheumatoid disease." After moving to U.S. she had seen an orthopedic surgeon. MRI of the left ankle noted a large poorly circumscribed multilocular and septated mass centered in the soft tissues over the anterolateral distal tibia and fibular. Appearance is most suggestive of chronic soft tissue hemangioma or other vascular lesion.

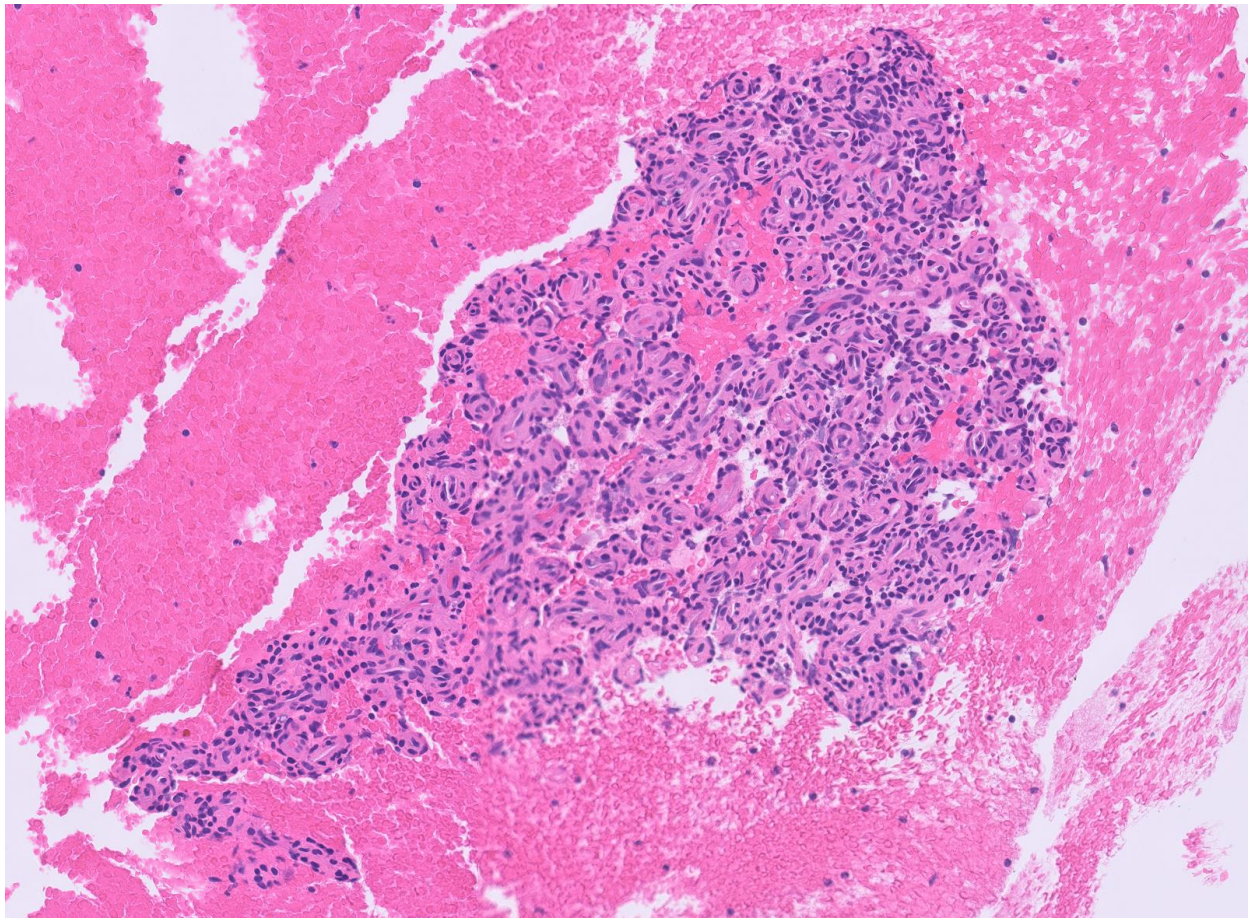
MRI

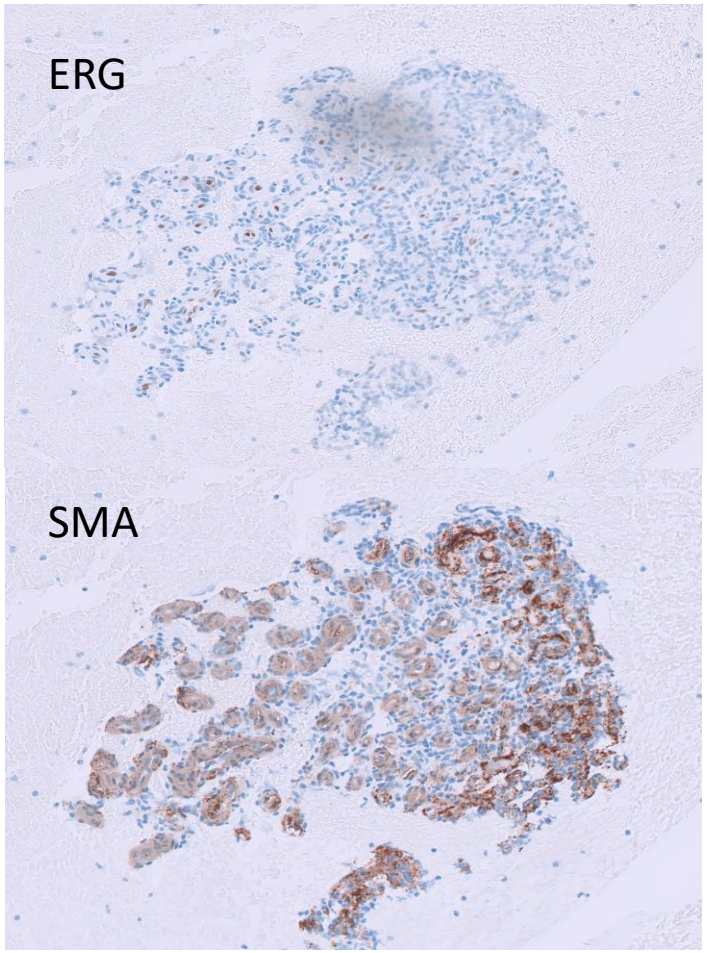
Along the anterior compartment of the left ankle, there is a large multilobulated septated mass, measuring 10 x5.7 x 7.9 cm. It demonstrates internal enhancing septae with a few nodular foci. There is increased vascularity and no bone destruction



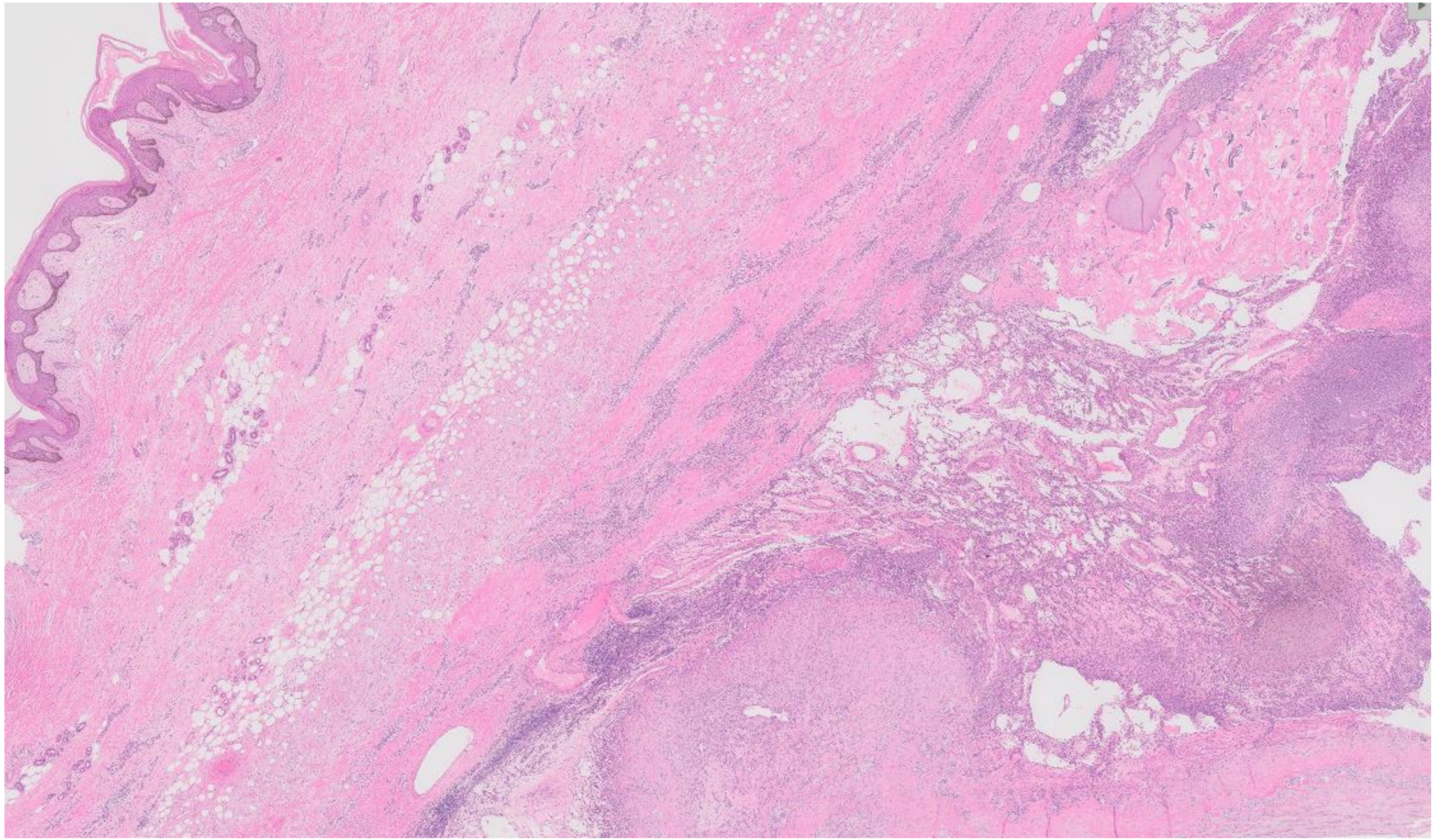


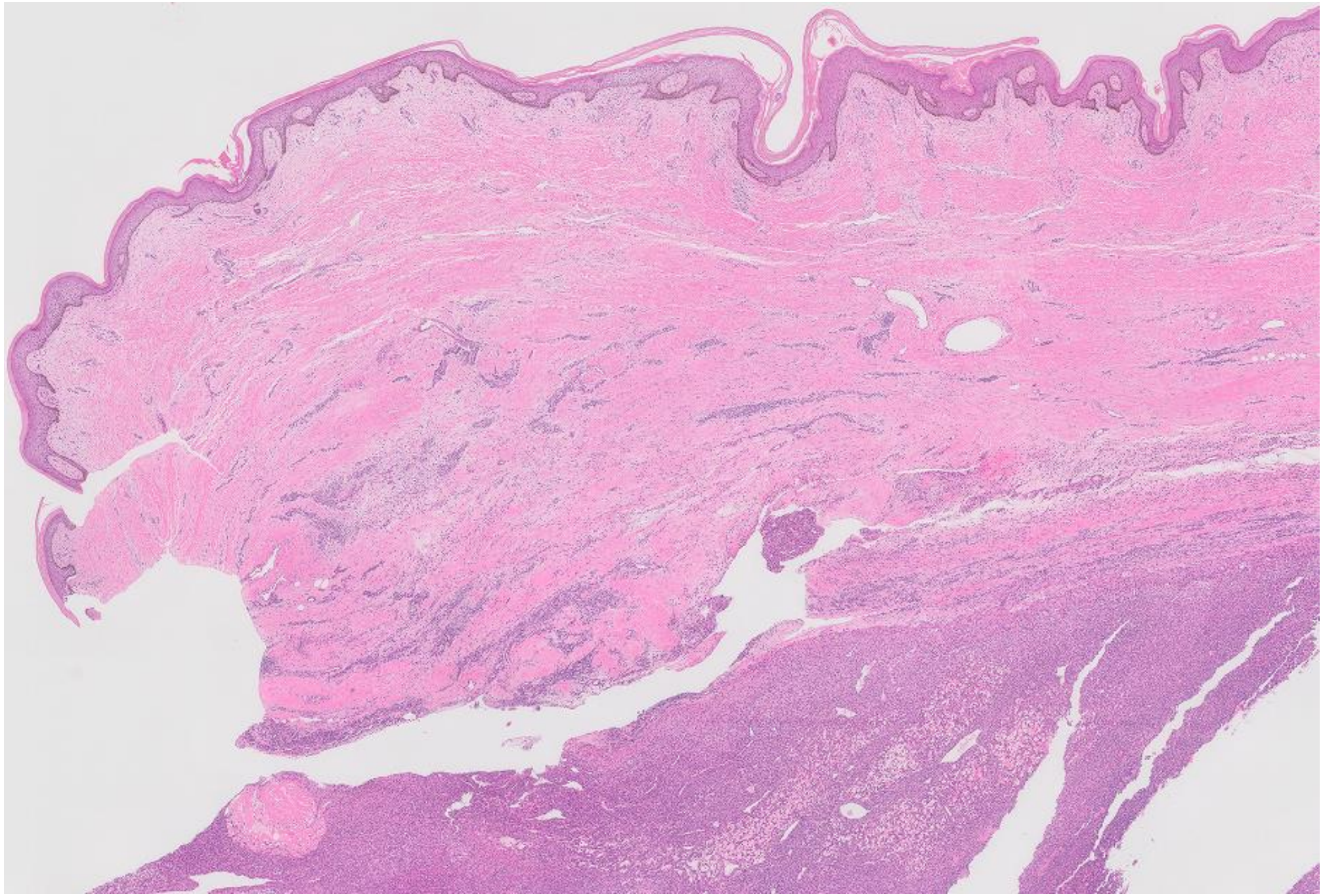
FNA, Hemorrhagic fluid with a rare fragment of a bland capillary proliferation

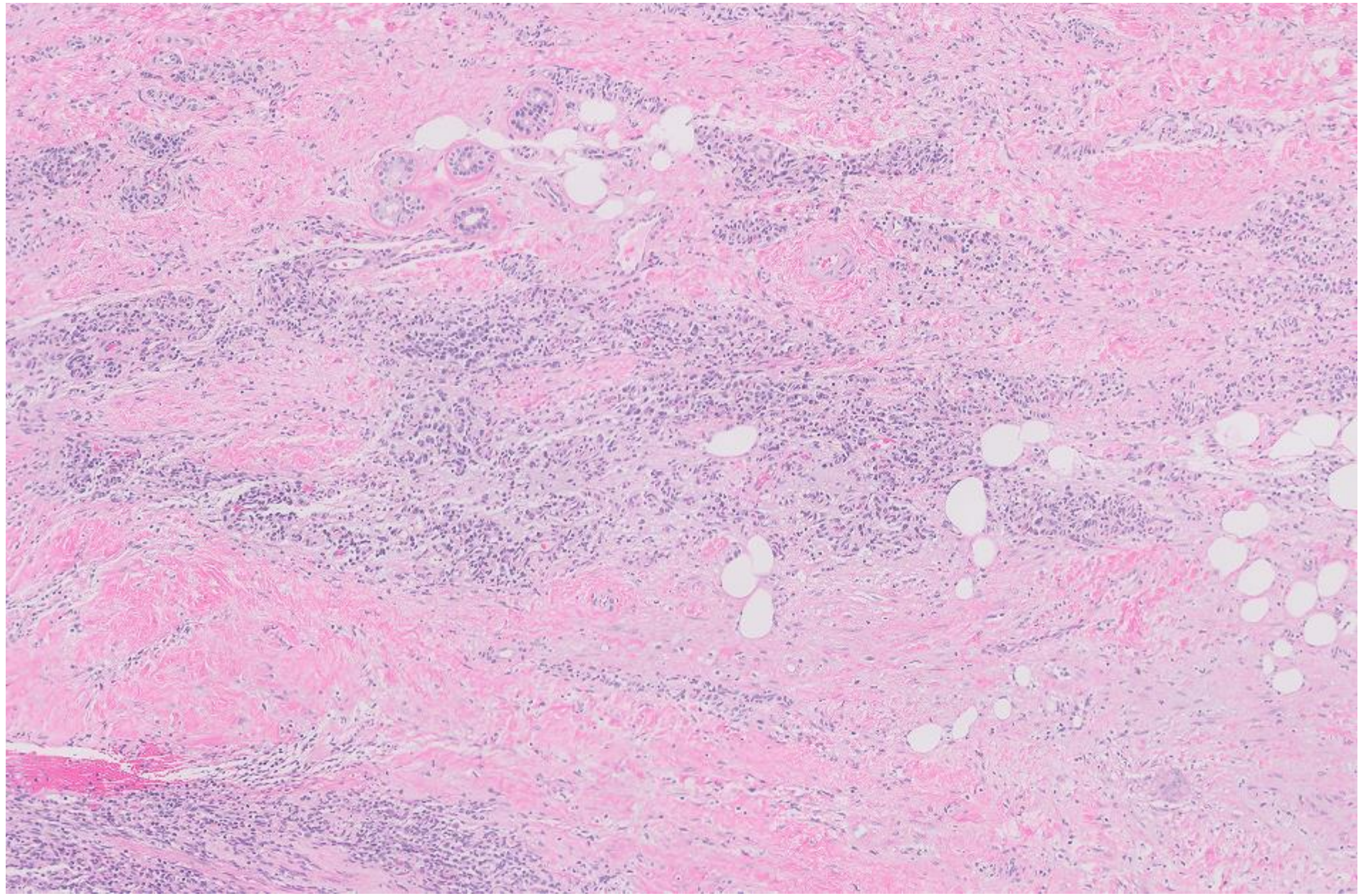


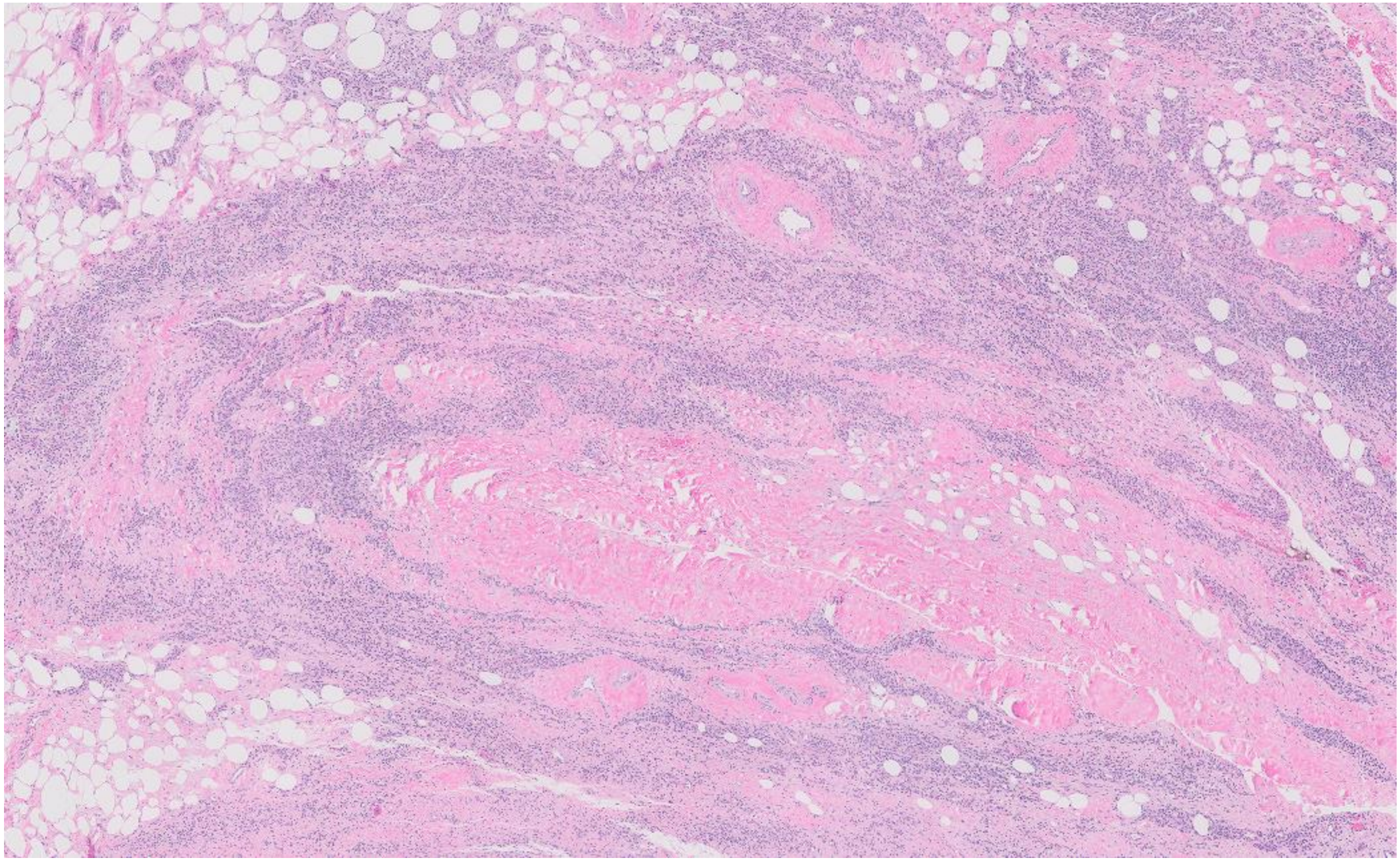


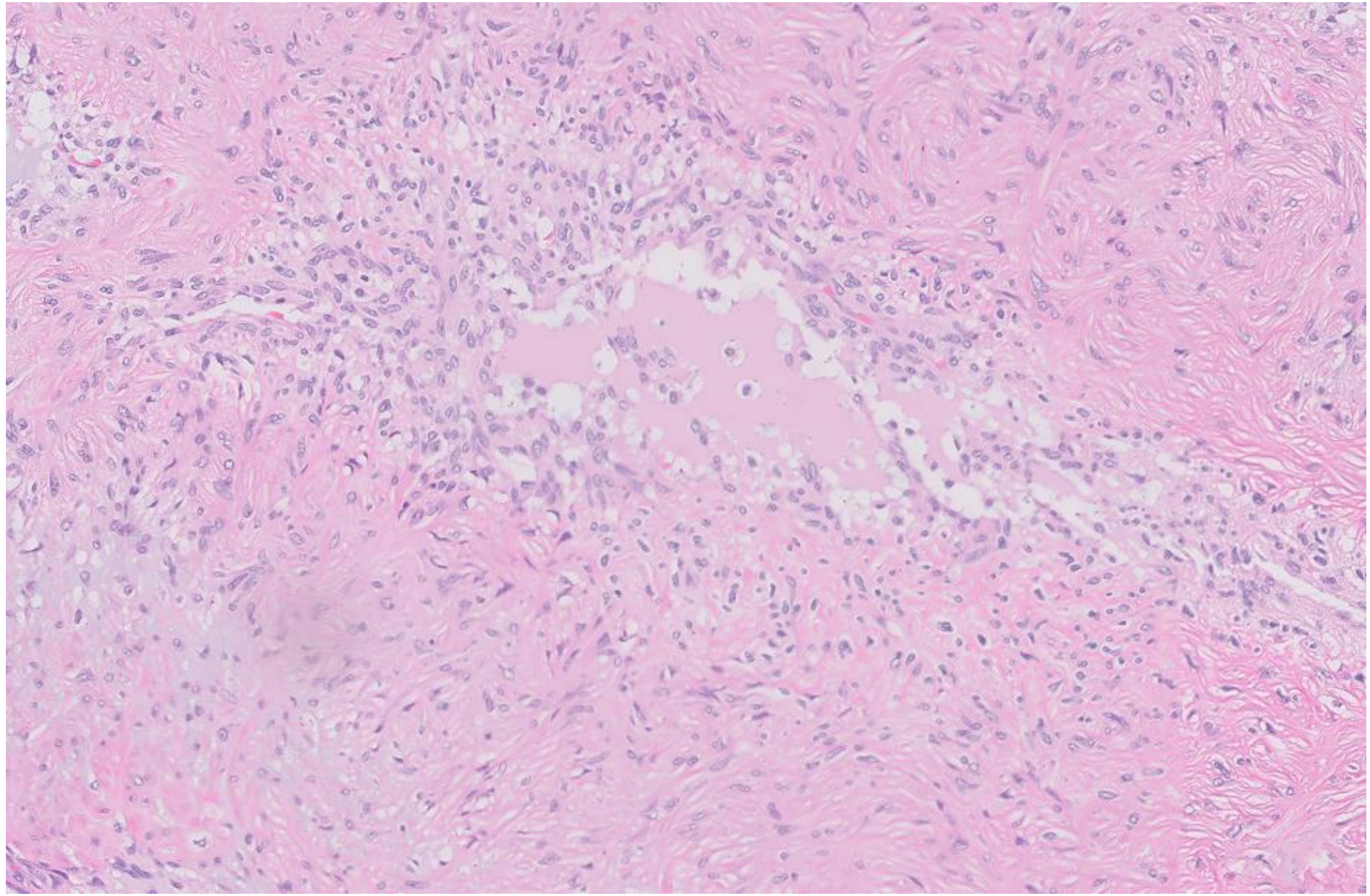
Excision of the mass

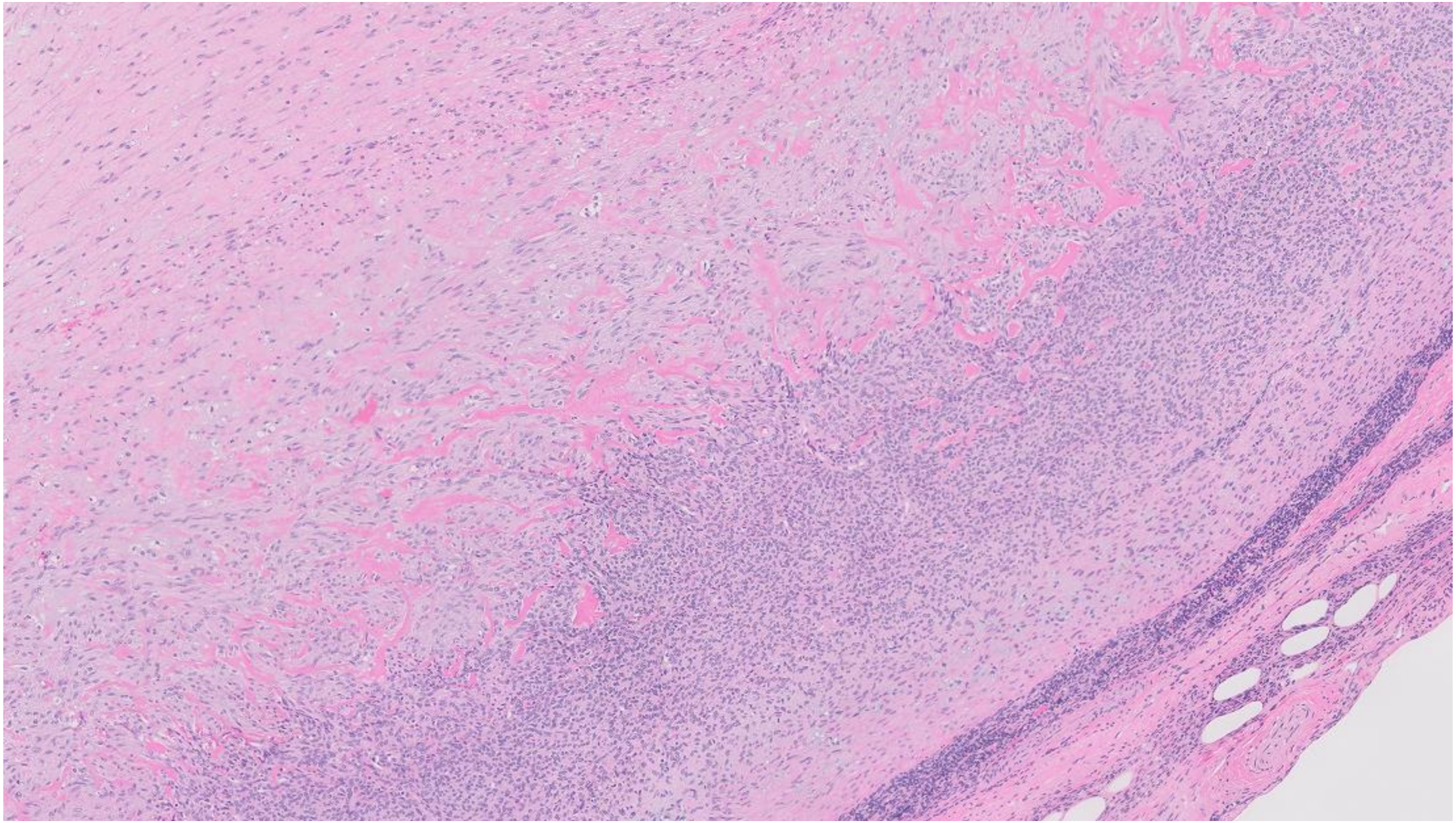


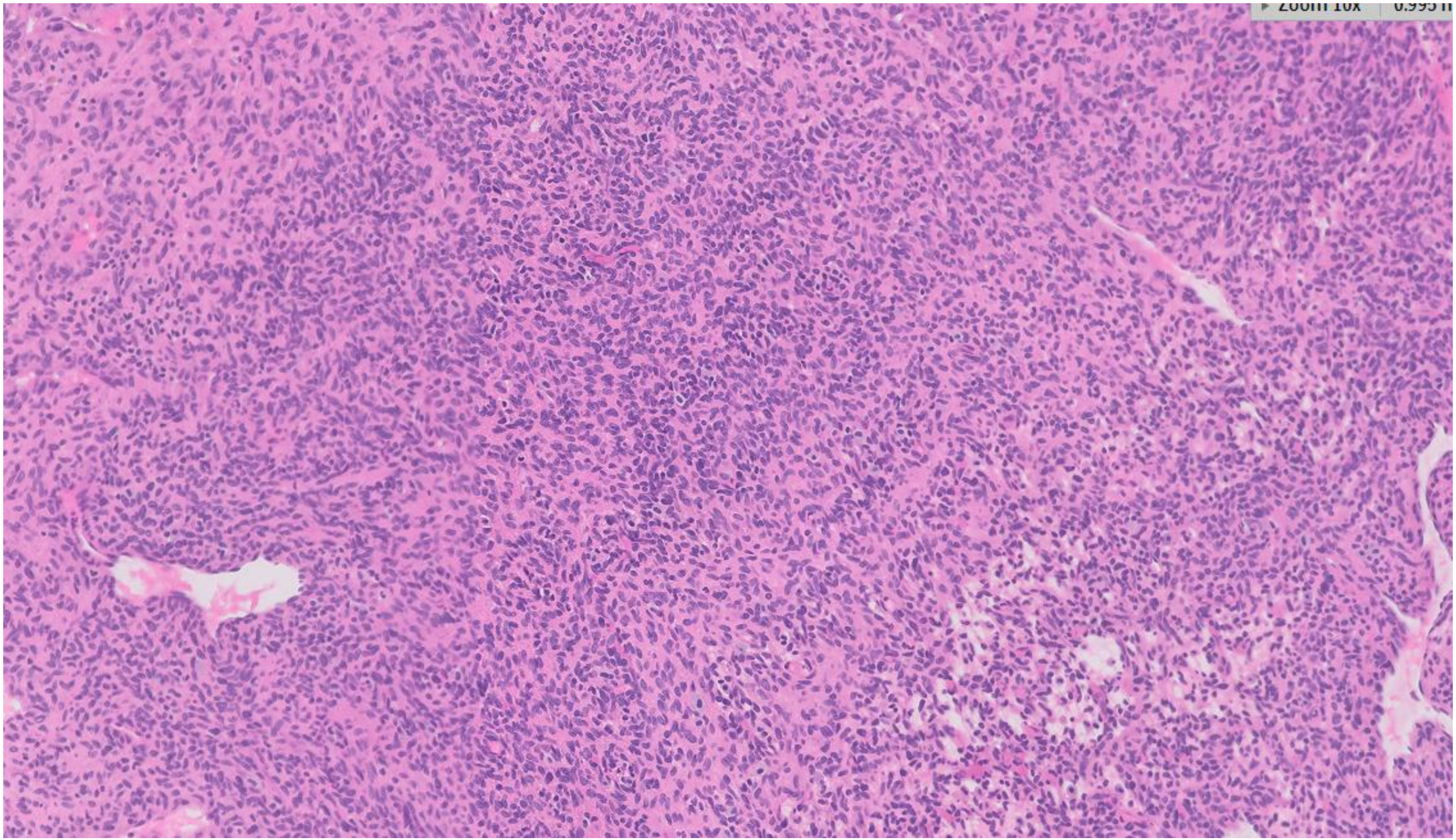


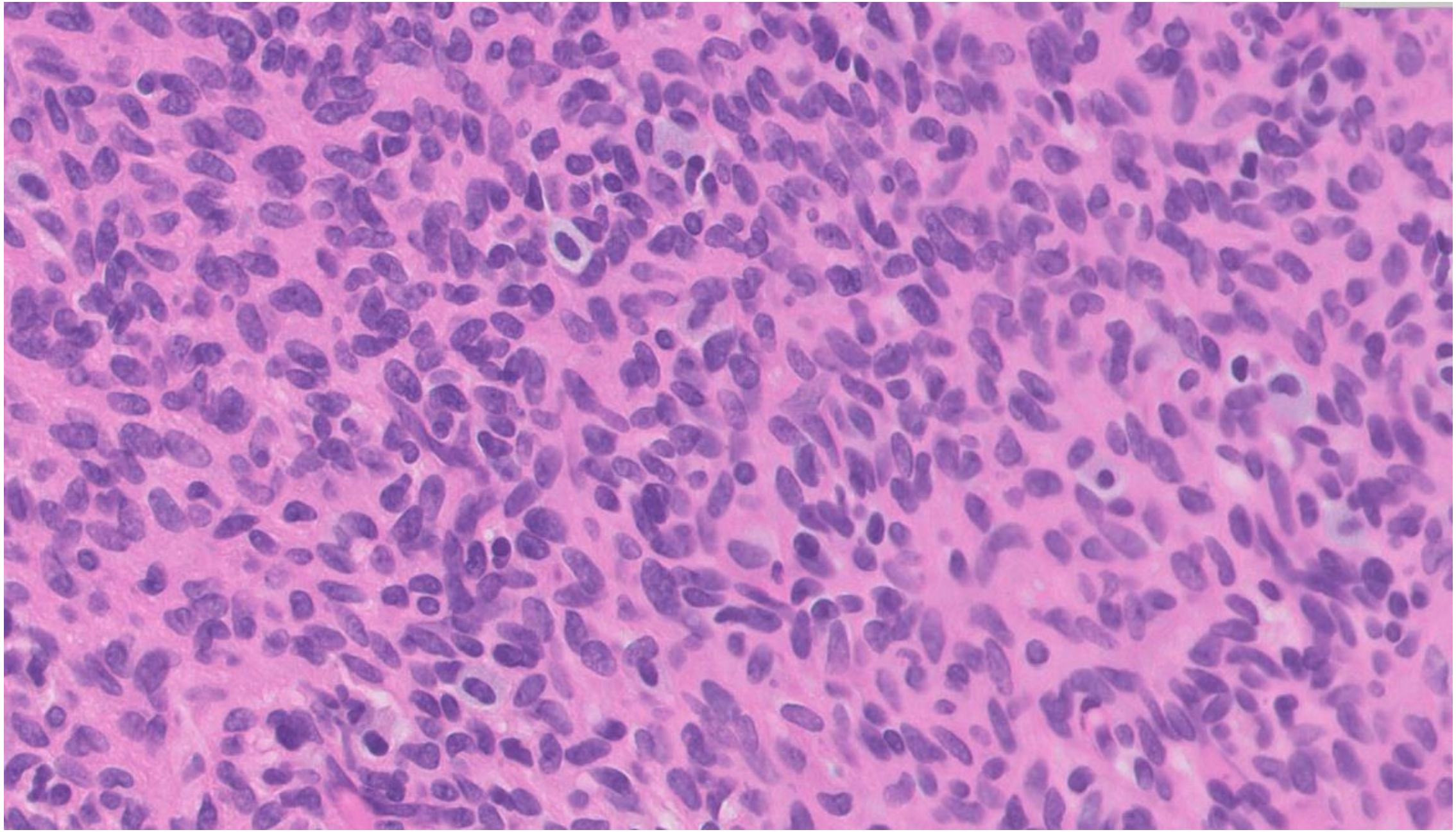








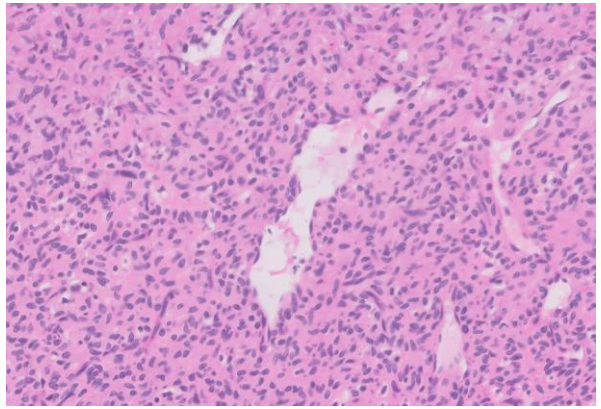


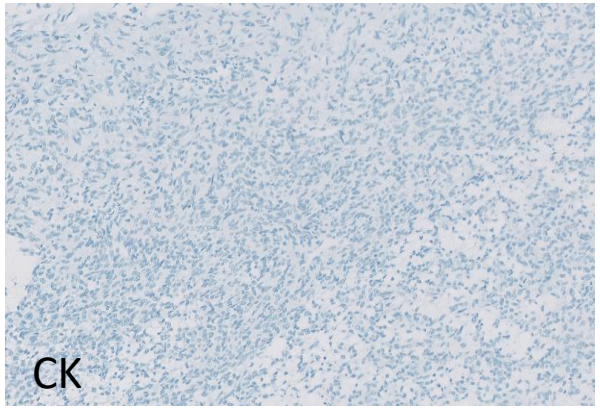


Differential diagnosis!

Differential diagnosis

- **Angioleiomyoma:** Can have a similar perivascular pattern but may show more prominent smooth muscle differentiation and may be associated with painful episodes.
- **Glomus tumor:** Usually presents as a small, painful nodule with a characteristic "epithelioid" cell pattern and may show expression of "glomus" markers. Vimentin (100%), SMA (99%), calopnin (80%), CD34 (32 - 53%;focal), Collagen type IV, laminin (pericellular), H-caldesmon
- **Myofibroma:** May have a similar spindle cell morphology but typically lacks the prominent vascular component seen in myopericytoma.
- **Solitary fibrous tumor:** May be difficult to differentiate based on morphology alone, but usually shows strong CD34 positivity and may have a more "storiform" pattern. CD34, STAT6, EMA and actin (20-30%)
- **Perivascular epithelioid neoplasm (PEComa):** Can have a similar perivascular arrangement but typically shows epithelial markers and may be associated with visceral involvement. Melanocytic markers as HMB45, Melan A. MiTF. Smooth muscle markers as SMA, desmin and Hcaldesmon. Catepsin K, ER, PR
- **Synovial sarcoma:** location, morphology, SS18-SSX1, t(X;18)

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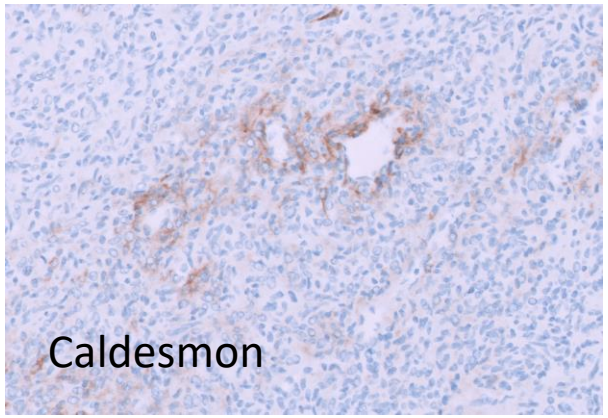
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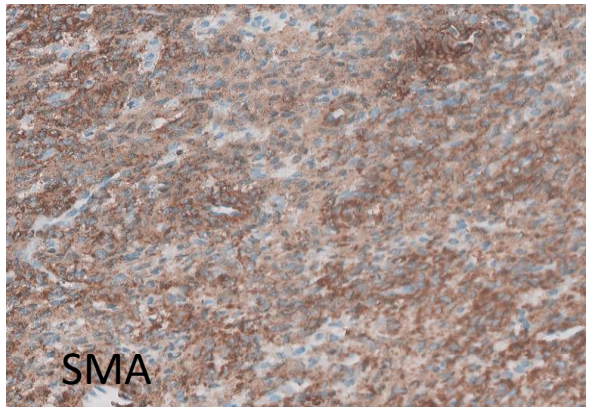
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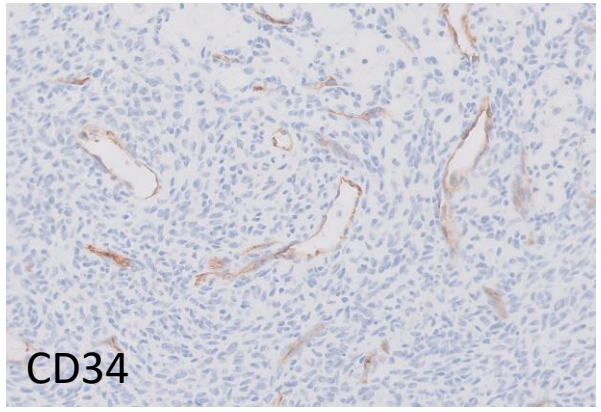
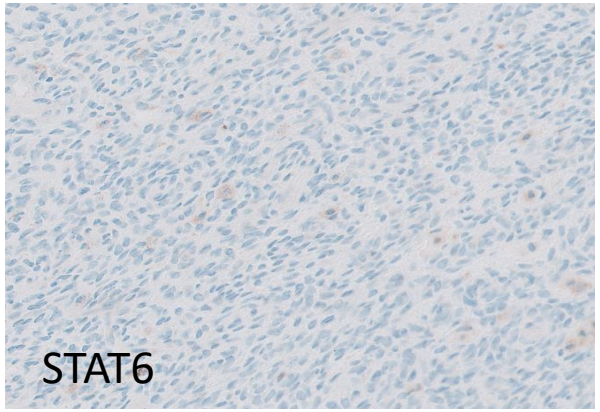
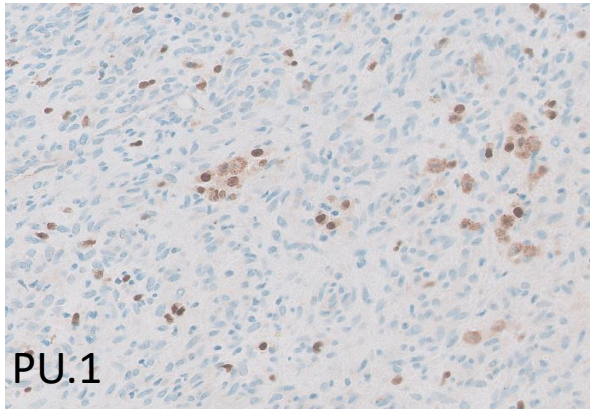
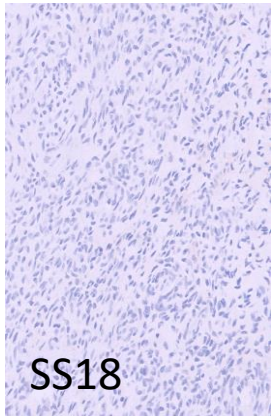

CD34


STAT6


PU.1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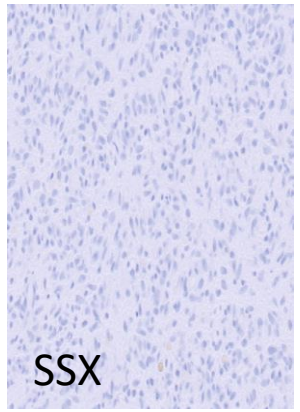
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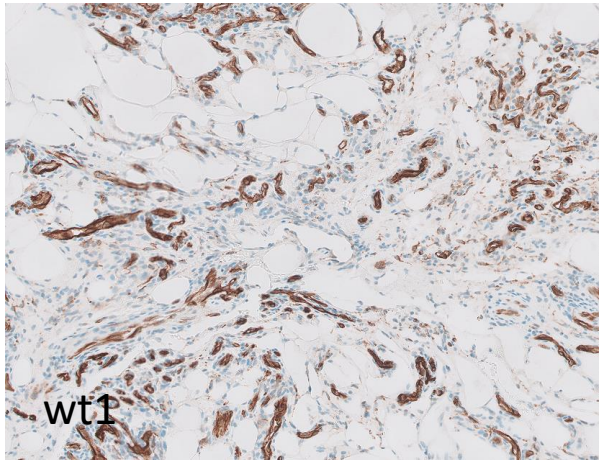
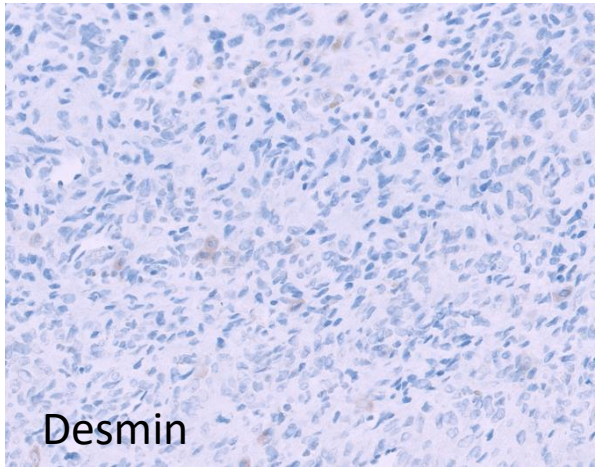

wt1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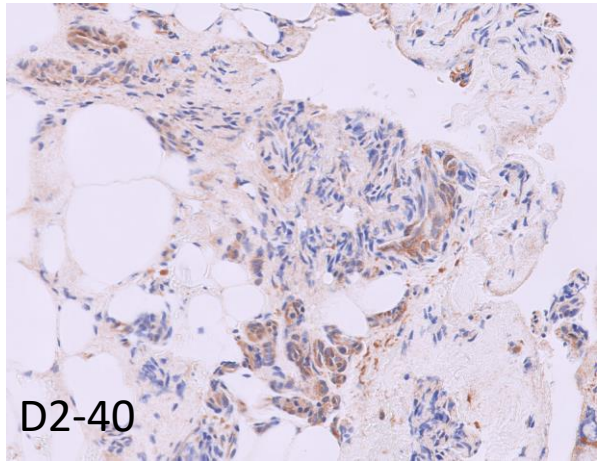
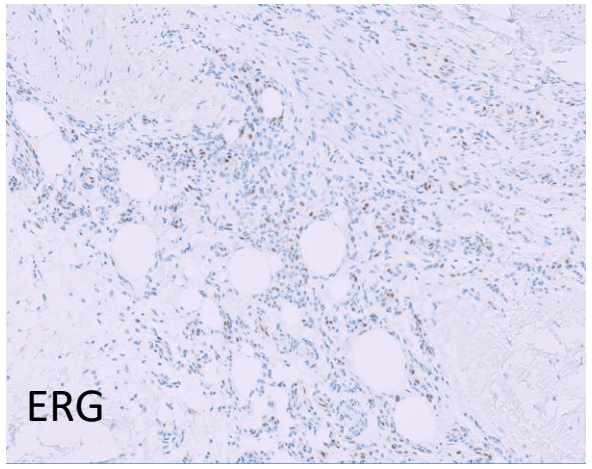
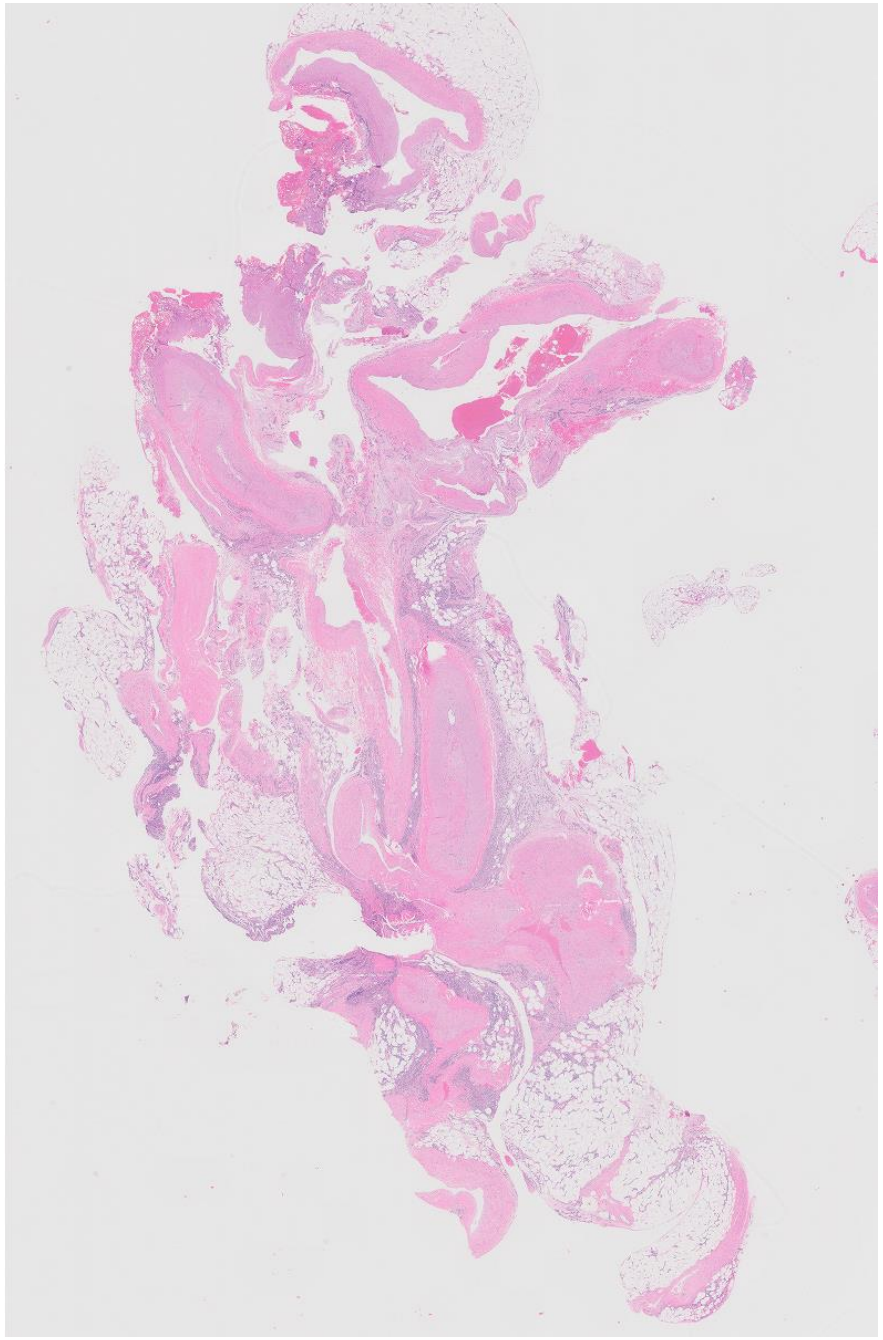
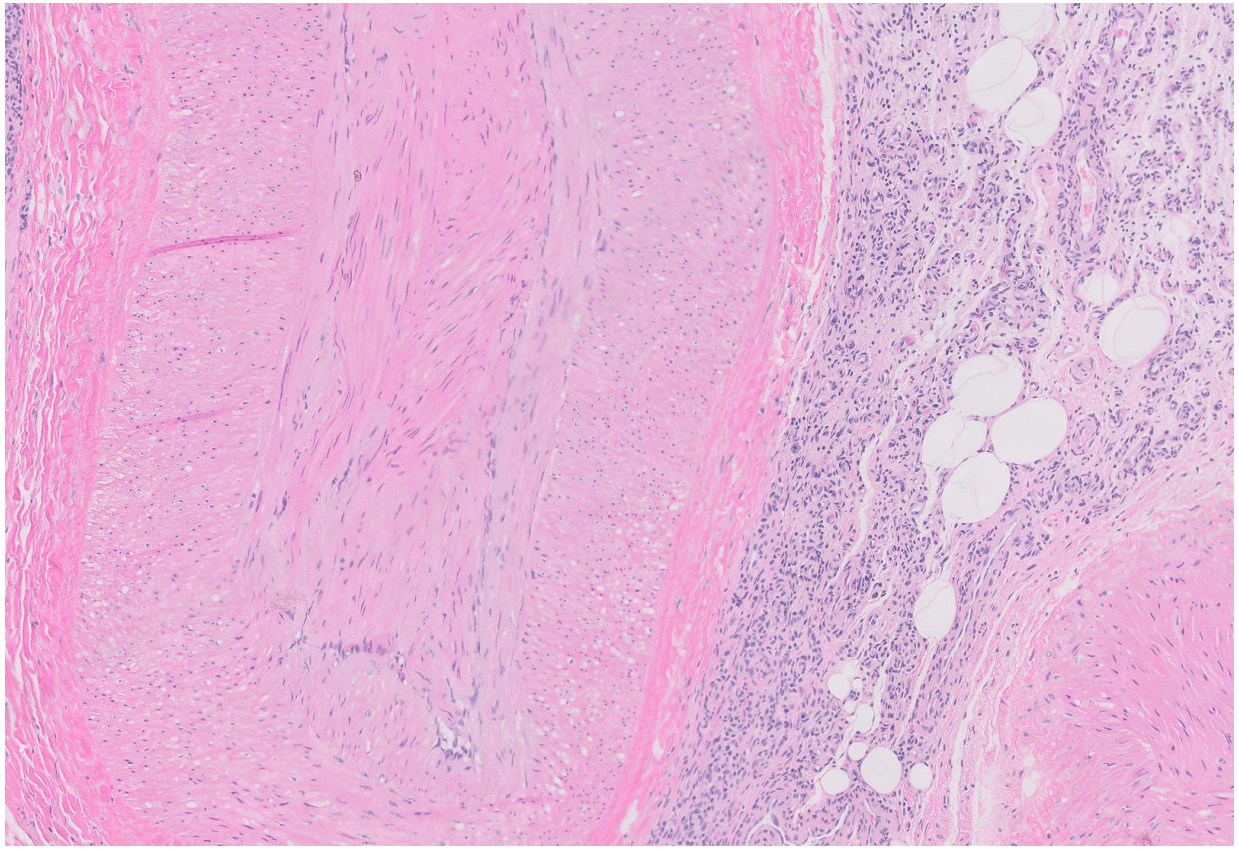

D2-40


ERG





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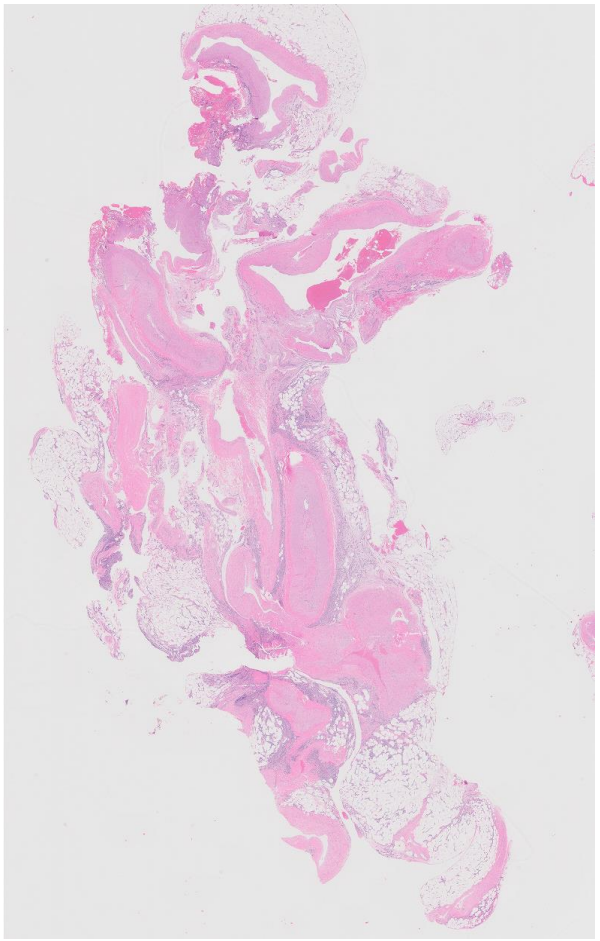
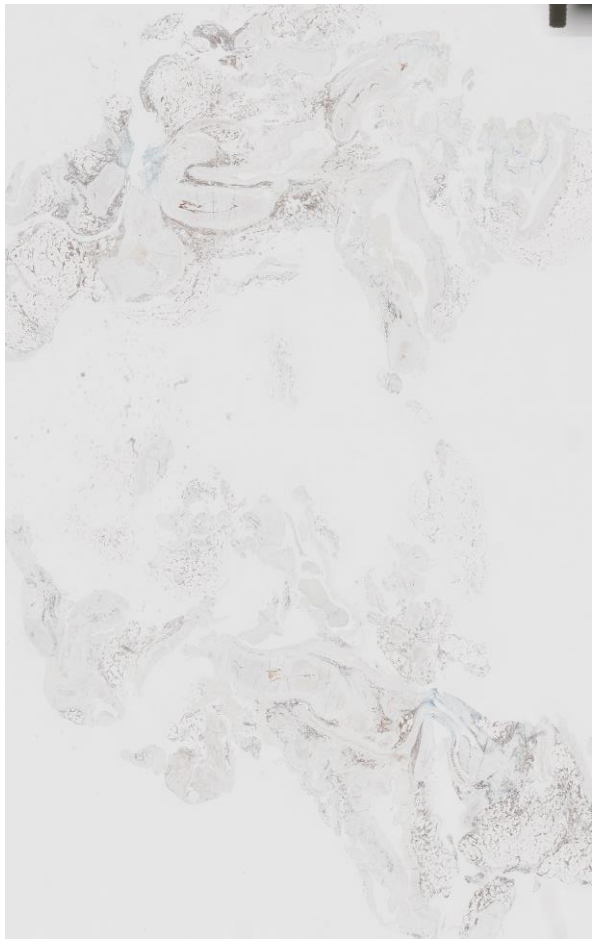
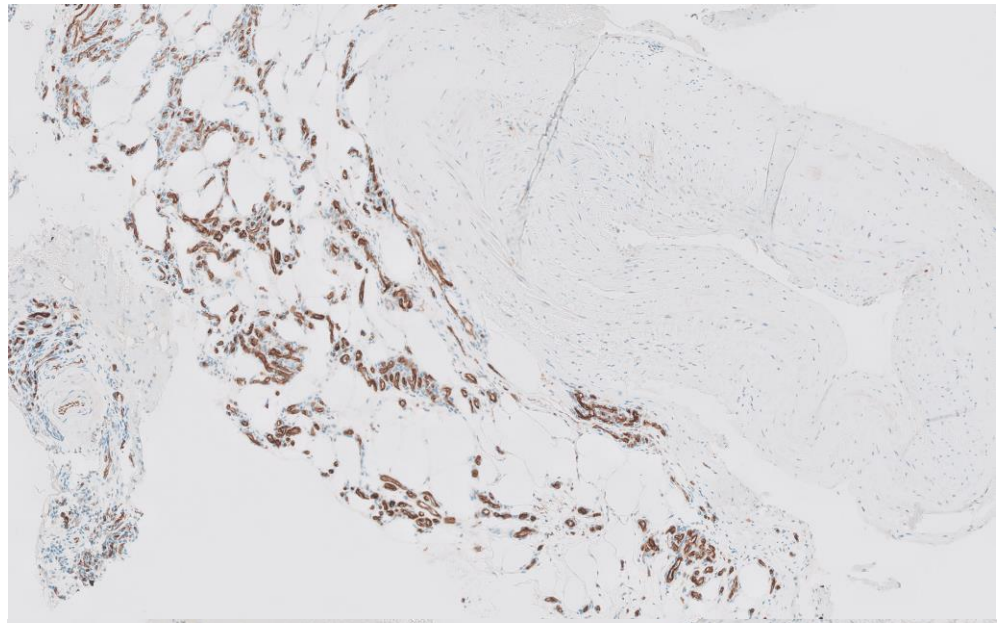
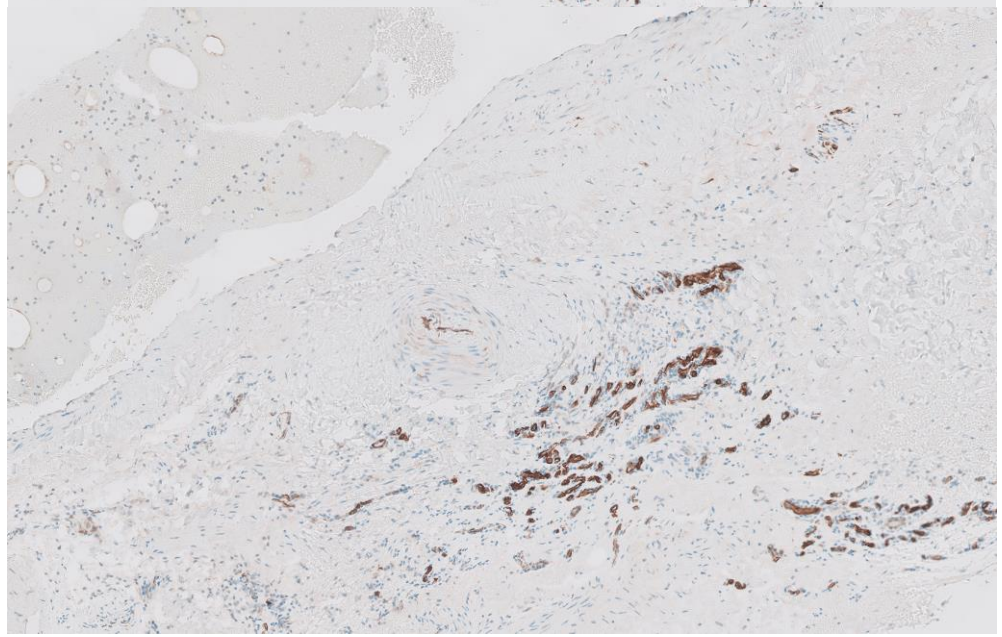








Diagnosis

Myopericytomatosis associated with vascular malformation

Myopericytoma, Clinical presentation

- Myopericytoma is a distinctive perivascular myoid neoplasm that forms a morphological spectrum with myofibroma.
- Rarely, myopericytomas show malignant features.
- Myopericytoma was first described in 1998 as a tumor characterized by numerous thin-walled blood vessels with concentric perivascular multilayered oval to spindle cell population.

Location

- Myopericytoma generally arises in the dermis or subcutis, rarely involves deep soft tissue.
- The distal extremities are most commonly involved, followed by the proximal extremities, neck, trunk, and oral cavity
- Very rarely, these neoplasms arise in visceral locations and intracranial sites
- The majority of solitary myofibromas arise in the skin and subcutis of the extremities, head and neck, and trunk
- Infants with myofibromatosis may have involvement of visceral locations, including the liver, heart, gastrointestinal tract, brain, and bone

Clinical picture

- Any age commonly in adults
- Myopericytoma usually presents as a painless, slow-growing, superficially located nodule, which can be present for years.
- Most cases arise as a solitary lesion, but multiple lesions involving a particular anatomical region or different regions are sometimes seen Myofibromas may present as solitary or multicentric lesions (myofibromatosis).

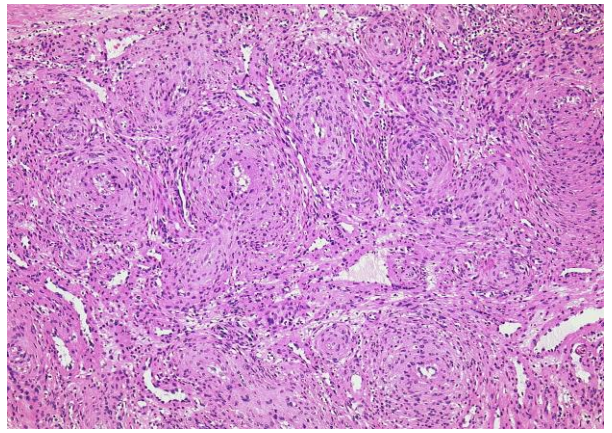
Myopericytoma, etiology and pathogenesis

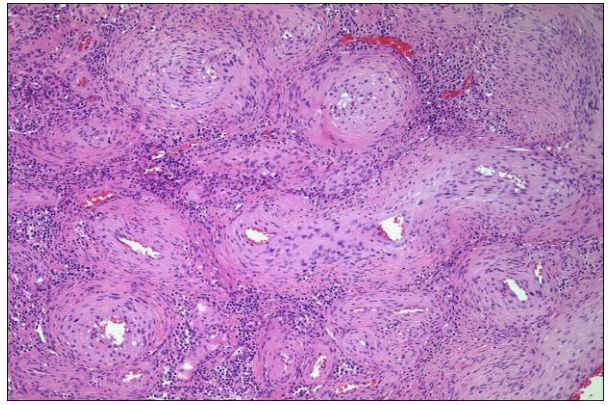
- A subset of solitary and multiple (non-visceral) forms of infantile myofibromatosis are familial, following an autosomal dominant mode of inheritance with variable penetrance and expressivity
- However, some reports have suggested instead an autosomal recessive inheritance
- An association between myopericytoma and EBV has been reported in patients with AIDS

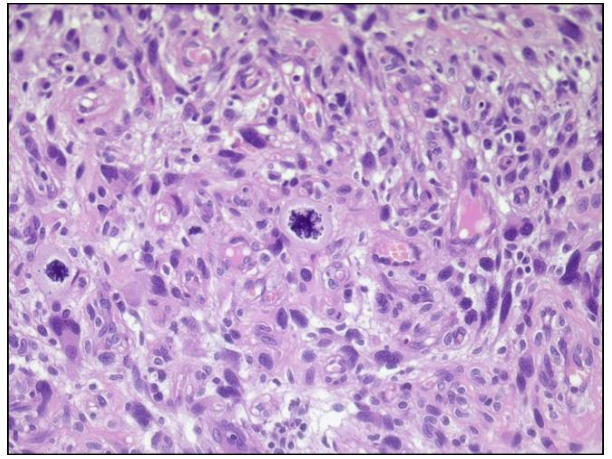
- Mutations in the *PDGFRB* gene appear to represent a common pathogenesis for myopericytoma, myopericytomatosis, and myofibroma
- Germline mutations in the *PDGFRB* gene have been shown to underlie familial, autosomal dominant infantile myofibromatosis
- Germline mutation in *NOTCH3*, a gene implicated in the pathogenesis of some glomus tumors has also been reported in a familial myofibromatosis
- Cellular/atypical myofibromas are associated with *SRF-RELA* gene fusions

Myopericytoma, pathology

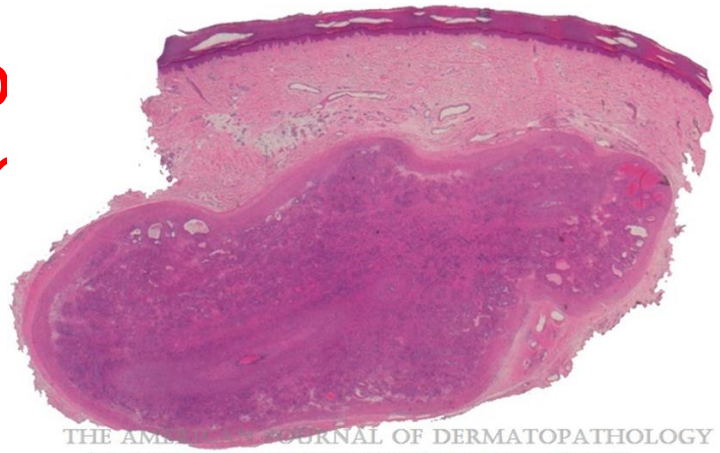
- Unencapsulated, usually well-circumscribed
- Nodular or lobular lesions
- Cytologically bland, oval to spindle-shaped, myoid tumor cells with characteristic multilayered, concentric growth around numerous small vessels.
- Variable cellularity, ranging from cellular and solid-appearing to hypocellular and collagenous/myxoid.
- Lesional blood vessels tend to be numerous and variable in size; branching, haemangiopericytoma-like vessels may be present.
- In some cases, a more prominent fascicular or whorled arrangement of neoplastic cells resembling myofibroma or angioleiomyoma is present
- Rarely, degenerative features, including symplastic nuclear atypia, stromal hyalinization, and cystic change
- A very unusual process of diffuse dermal and subcutaneous involvement by numerous microscopic myopericytomatous nodules has been reported under the term “myopericytomatosis”
- Rare malignant myopericytomas occur mainly in the deep soft tissues, as infiltrating neoplasms showing marked nuclear atypia and a high mitotic count, in addition to features more typical of myopericytoma
- By immunohistochemistry, myopericytomas express SMAs and h-caldesmon, and they are at most only focally positive for desmin and/or CD34.
- SRF and RELA gene rearrangements in cellular/atypical myofibromas can be identified by molecular studies



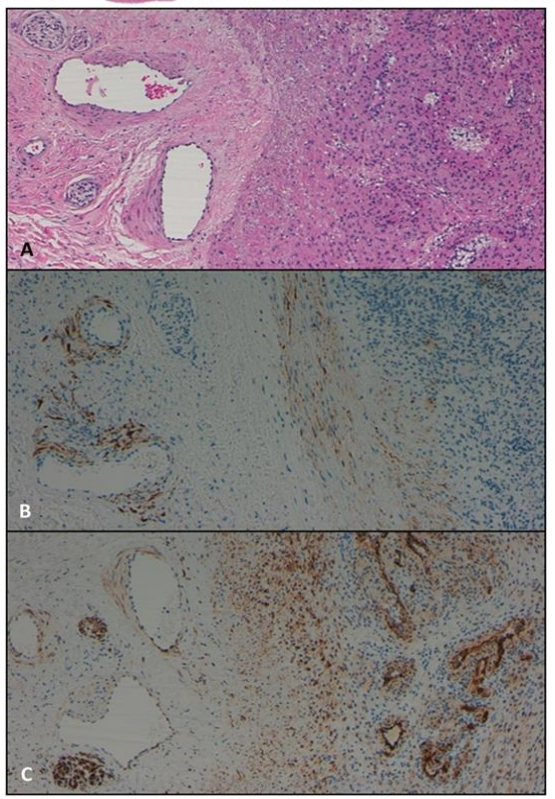




Intravascular Myopericytoma of the Plantar Regio Case Report and Discussion of the Probable Origir From a Cutaneous Vascular Malformation



- 1-cm sized subcutaneous nodule covered by normal skin. The lesion had been growing slowly during several years, without pain suggesting a lipomatous or cystic nature
- Histologically, a nodular solid mass surrounded by vascular muscular wall, reticular dermis and subcutaneous tissue.
- The lesion, that was entirely inside vascular wall, was composed of solid areas of round to spindle cells with eosinophilic cytoplasm arranged in a multilayered and concentric perivascular pattern (onion-skin appearance), admixed with thin-walled hemangiopericytoma-like areas
- Cellular atypia, pleomorphism, necrosis, and mitotic figures were not observed.
- Diffusely positive for SMA and h-caldesmon, whereas were negative for desmin and CD34 consistent with myopericytic origin.
- Endothelial cell were positive for CD34 and WT1.
- Therefore, a diagnosis of intravascular myopericytoma was rendered.



B, Desmin positivity for malformative component, including large-dilated vessel. C, Negativity for WT1 in malformative channels and intense positivity in myopericytoma component

The American Journal of Dermatopathology **38(7):p 546-548, July 2016.**

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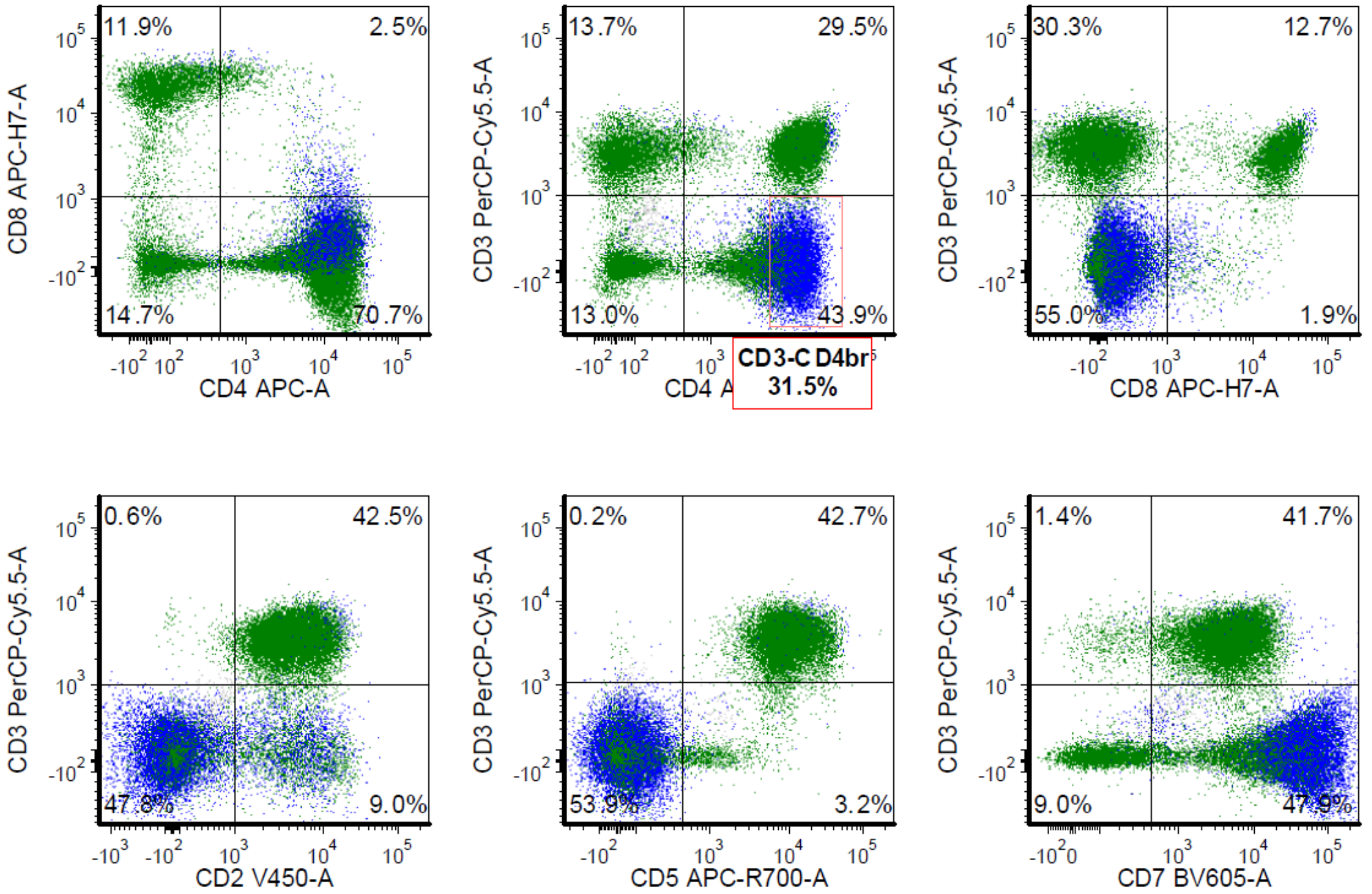
25-0408

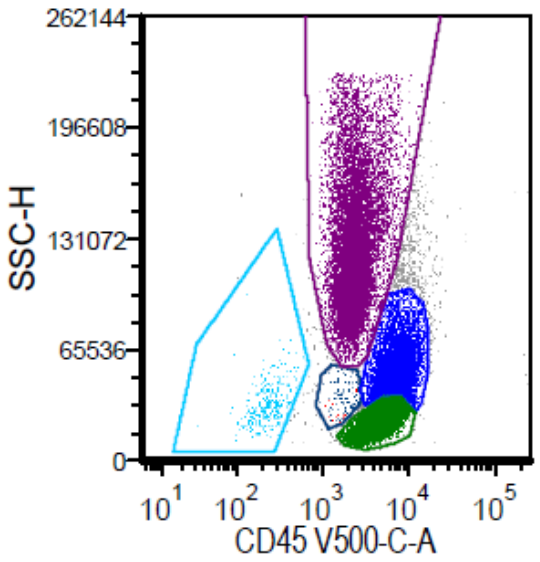
Sheren Younes; Sebastian Fernandez-Pol; Stanford

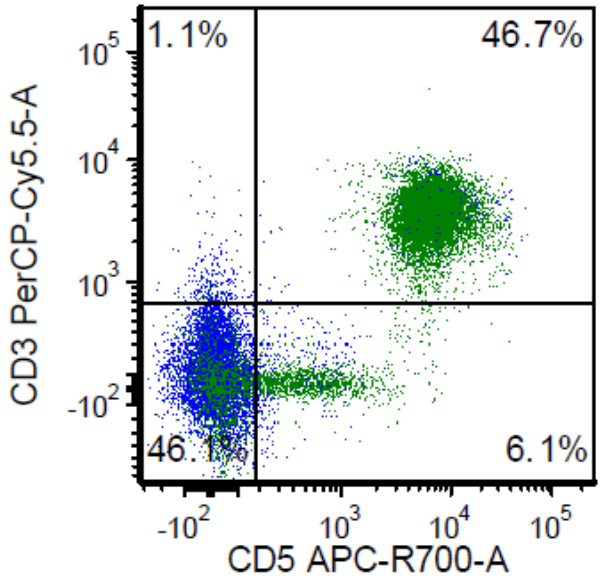
8 year old female with fever, respiratory failure, bilateral humerus lytic lesions

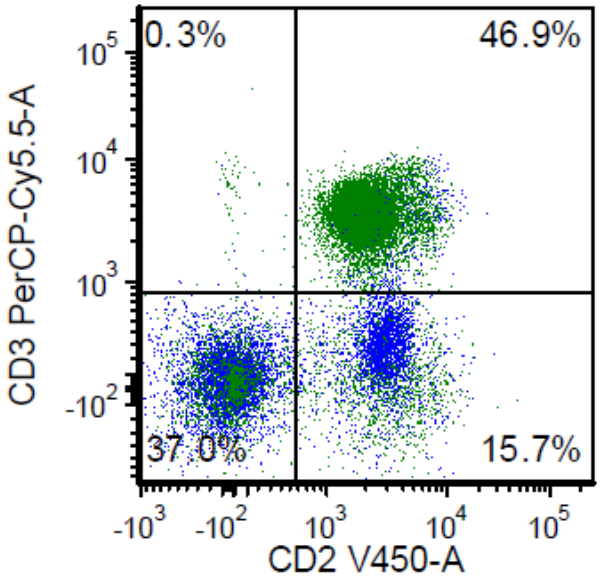
Pleural fluid flow cytometry

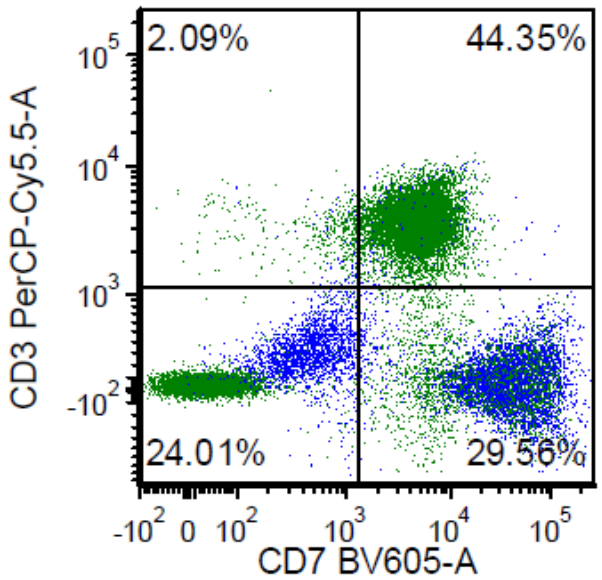


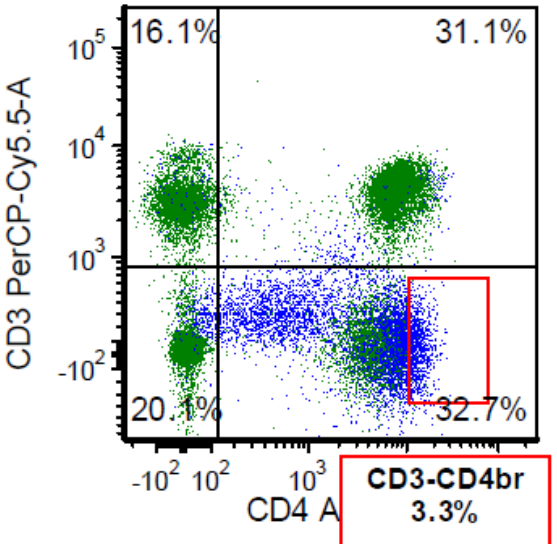
Peripheral blood flow cytometry

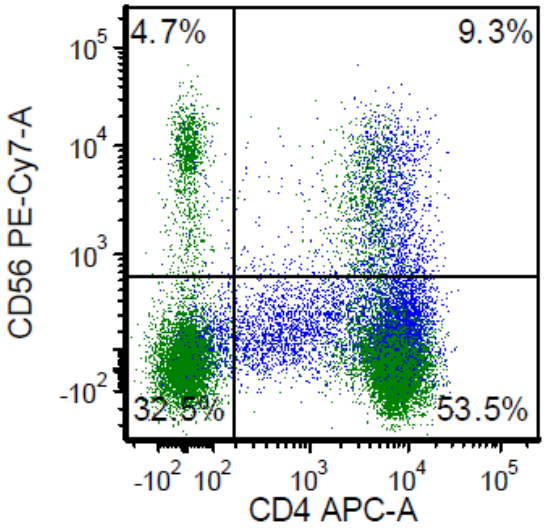


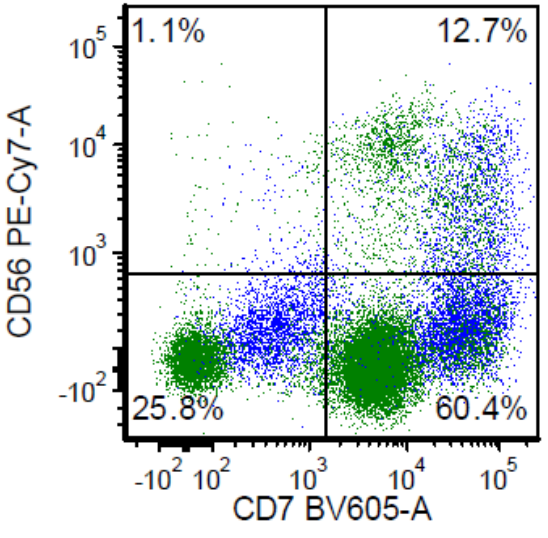


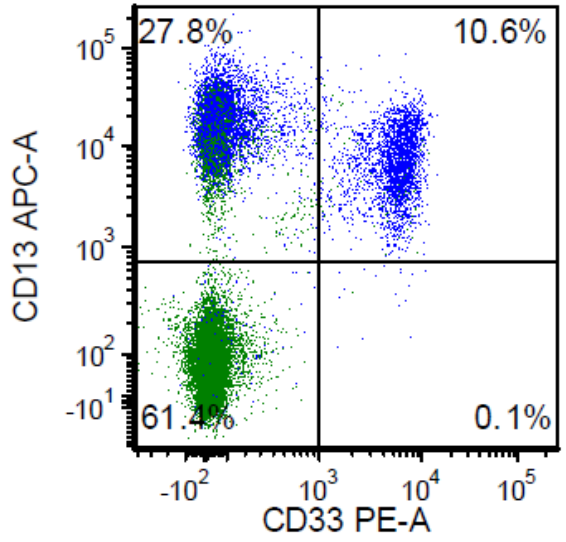




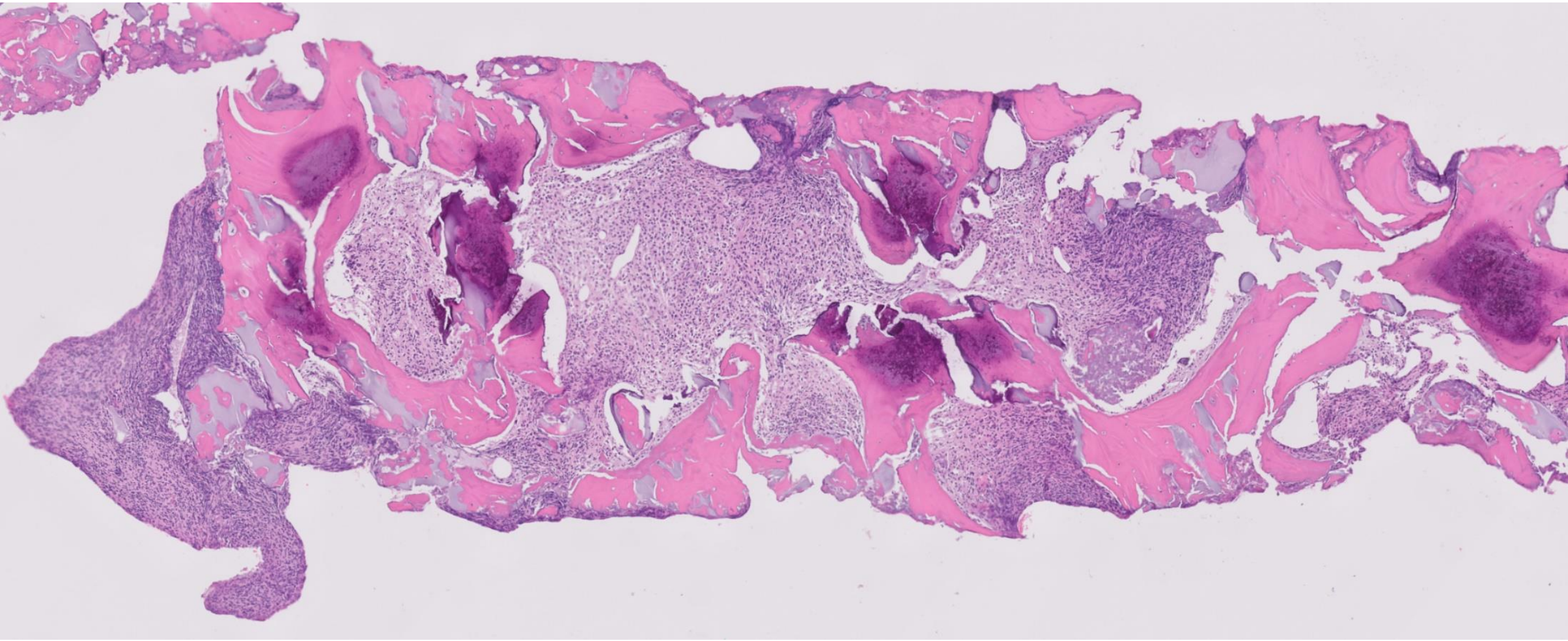




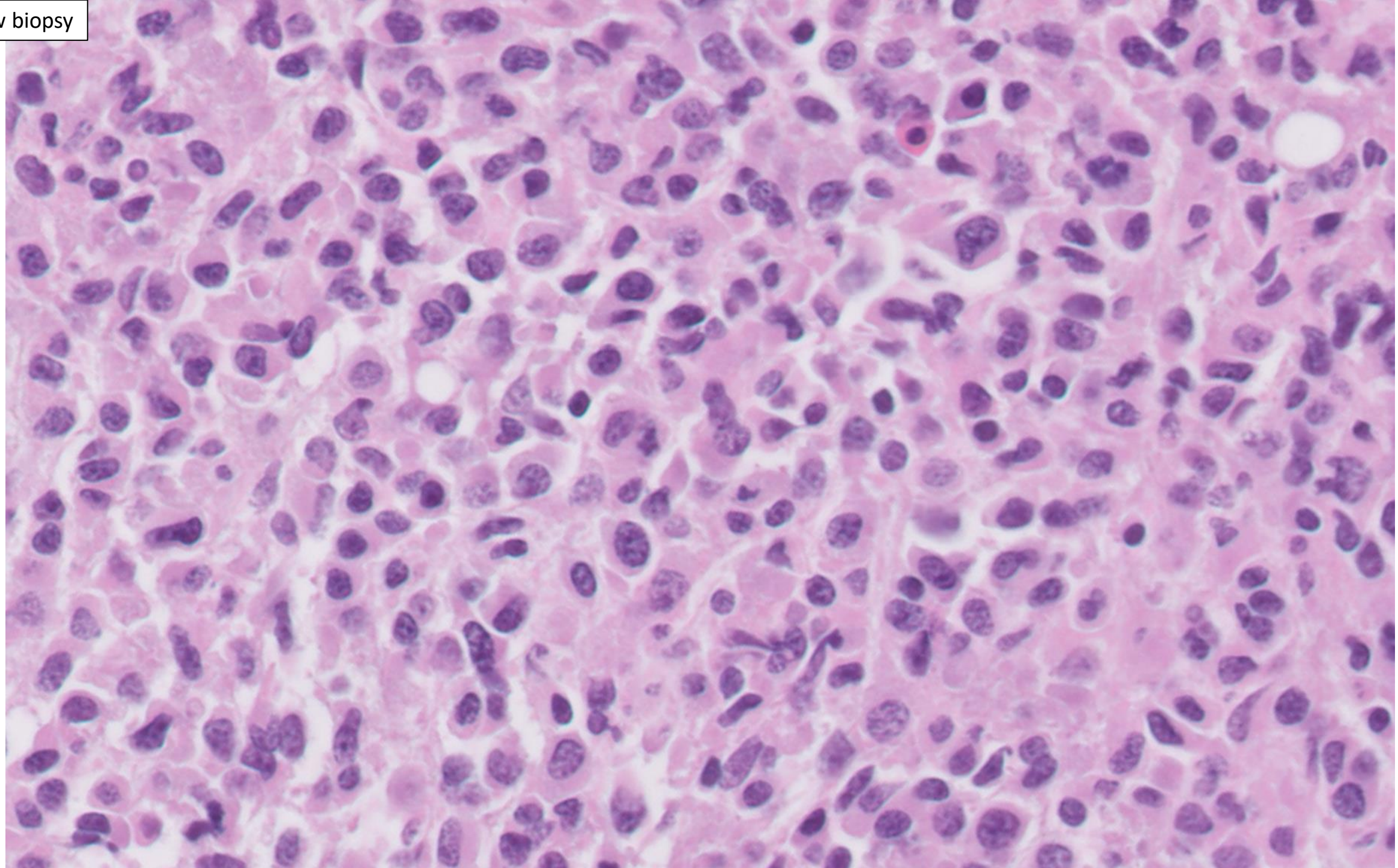


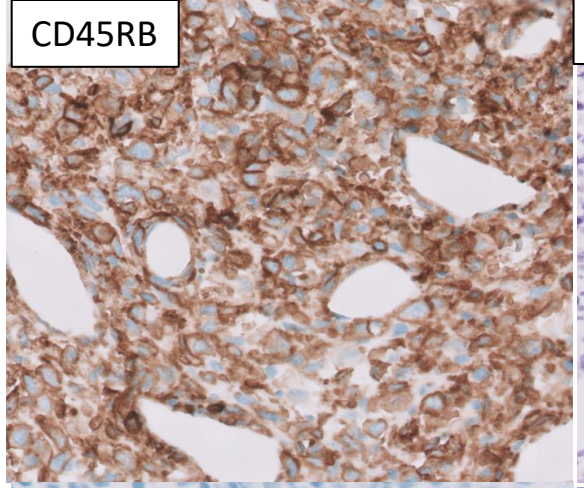


Bone marrow biopsy



Bone marrow biopsy

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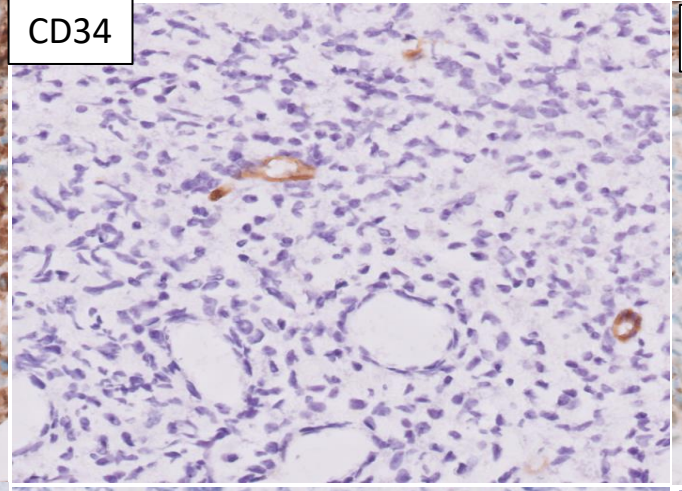
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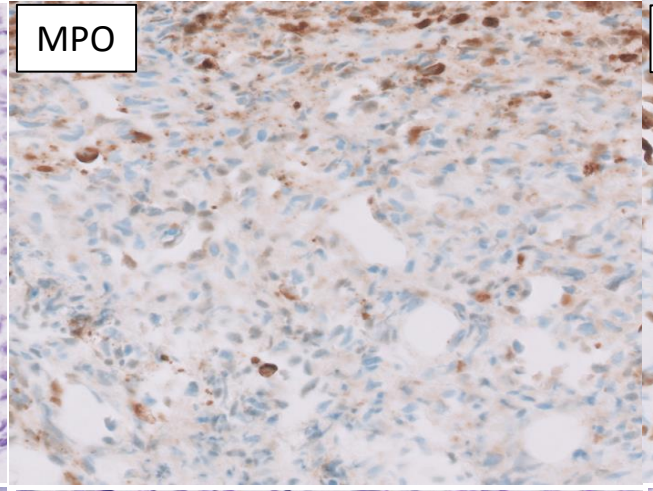
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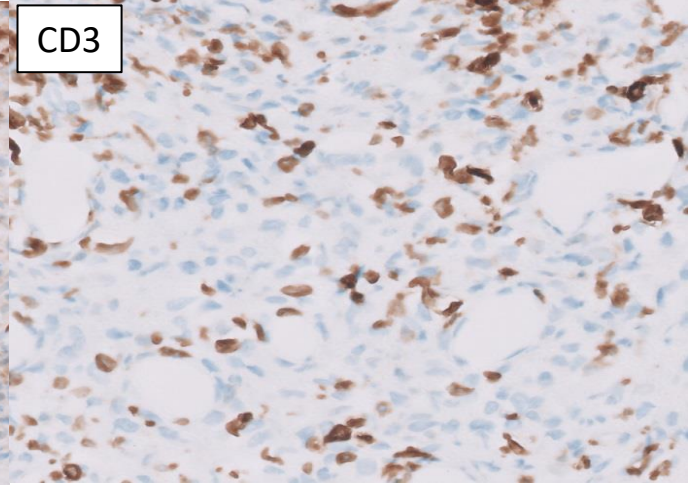
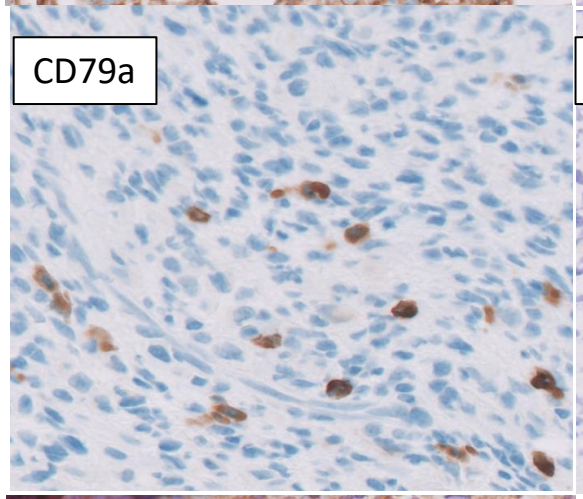

CD3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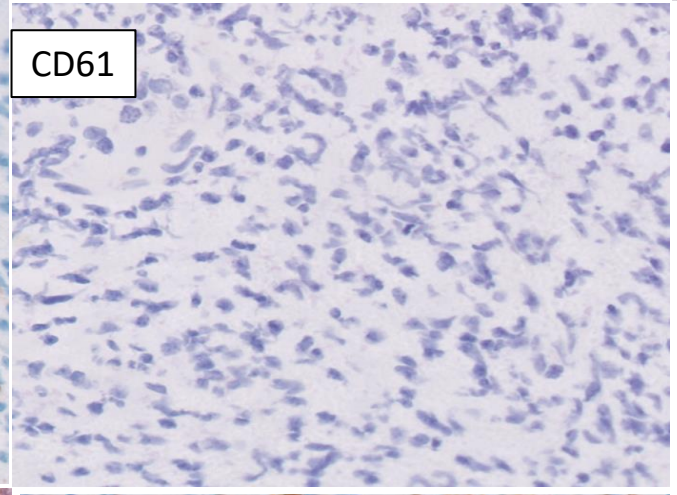
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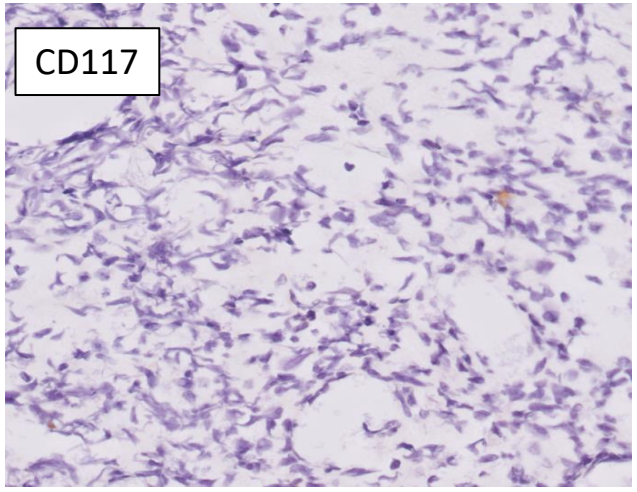
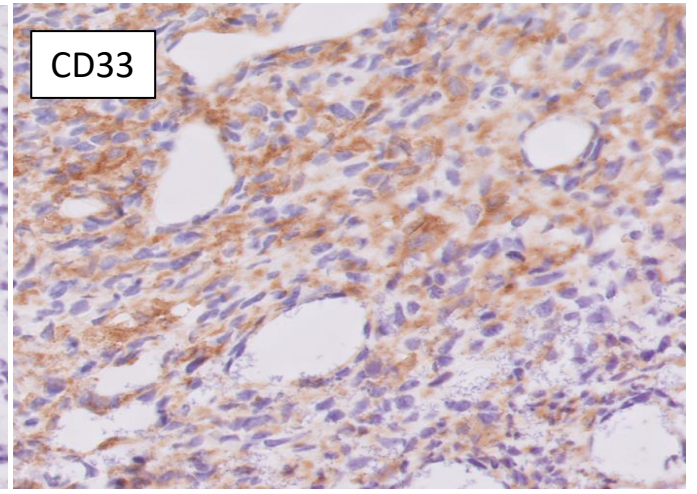
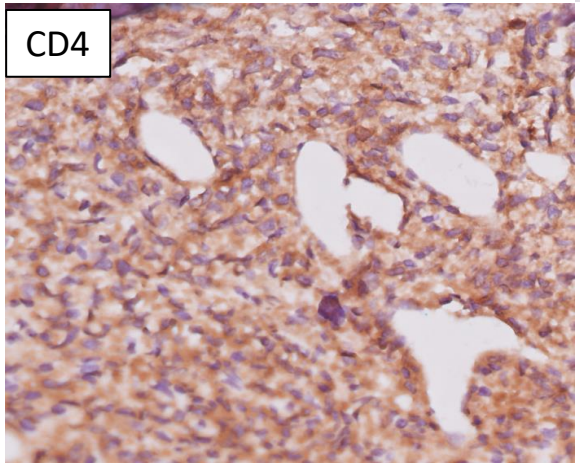
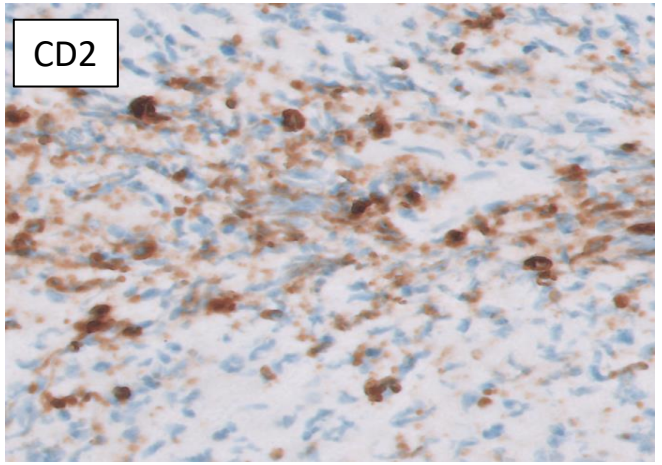

CD117


CD33


CD4


CD2

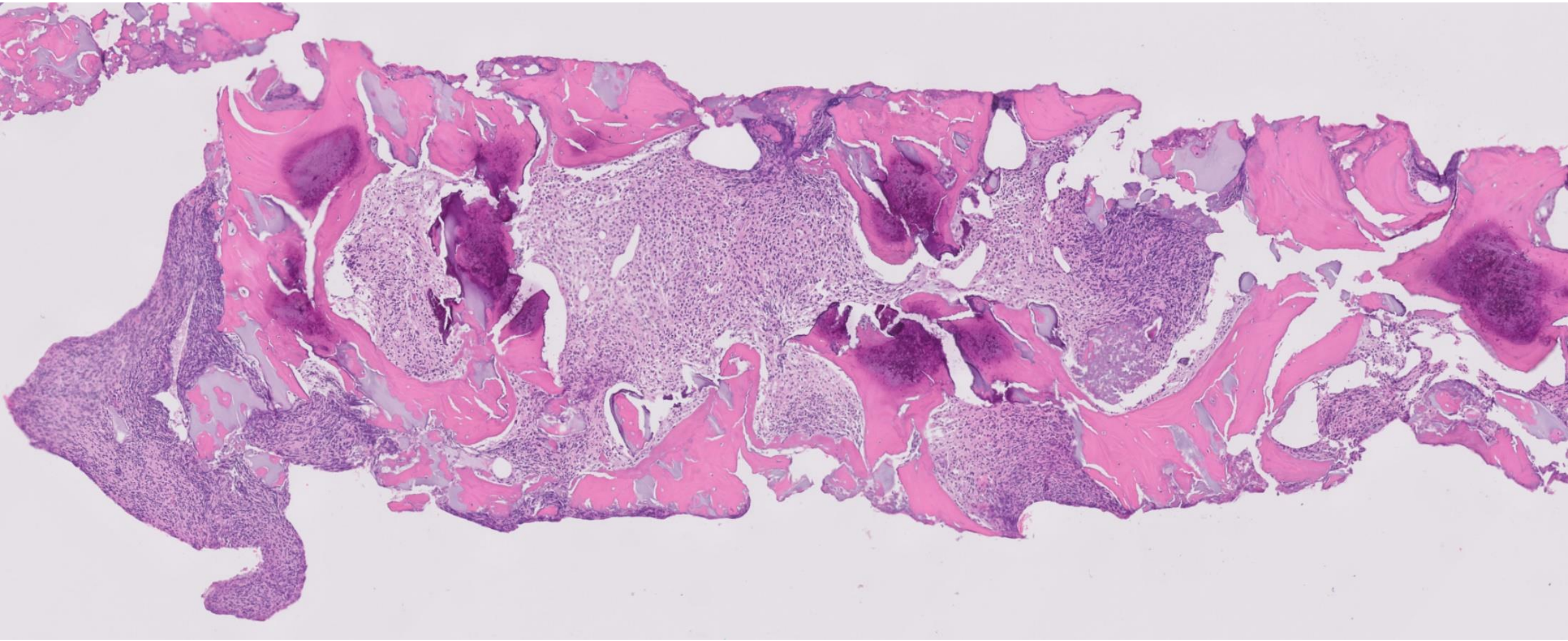
DIAGNOSIS?

Case

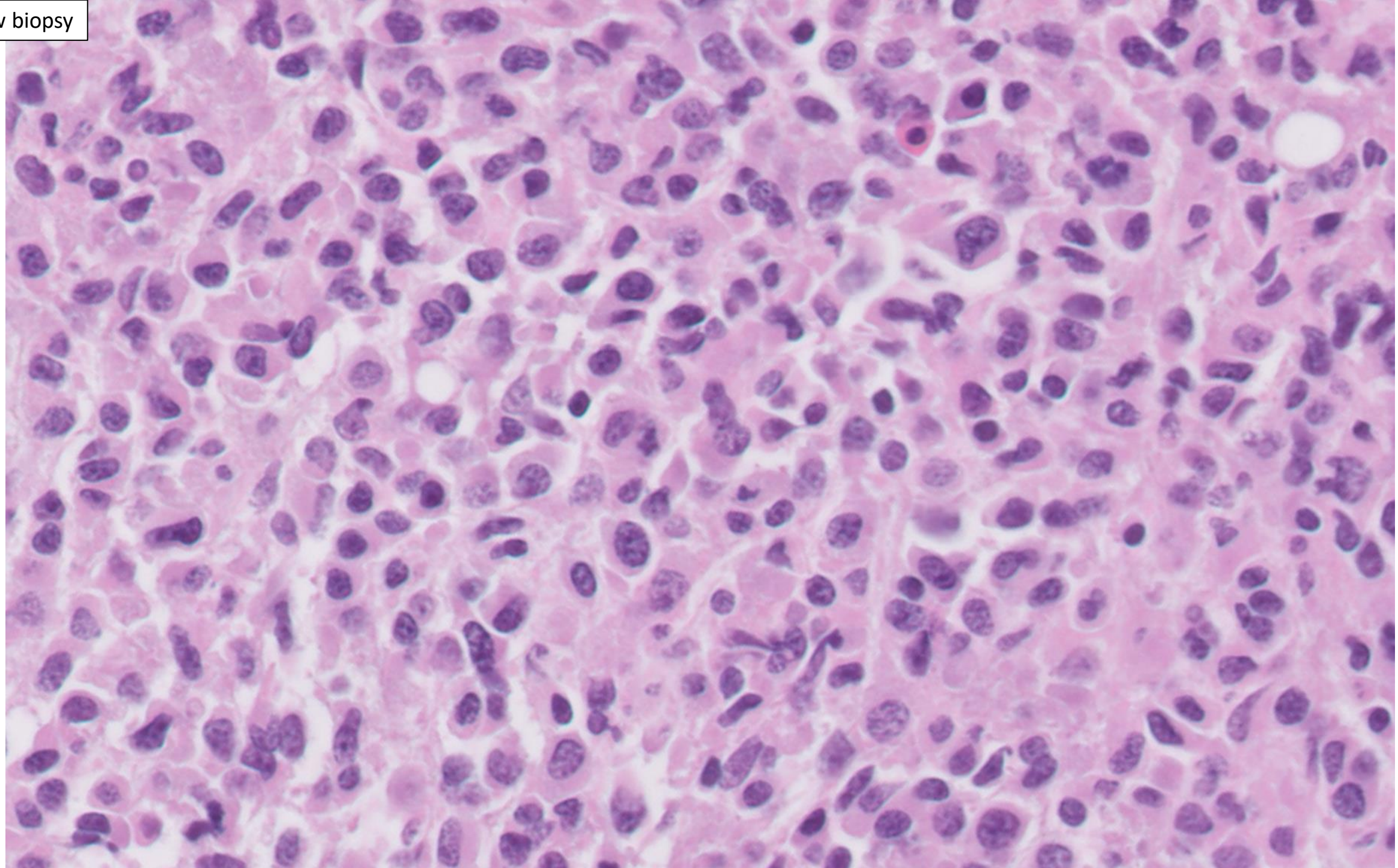
Sheren Younes, MD, PhD; Sebastian Fernandez-Pol, MD, PhD

8-year-old female with fever, respiratory failure, multiple lymph node masses and bilateral humerus lytic bone lesions concerning for oncologic vs infections process

Bone marrow biopsy



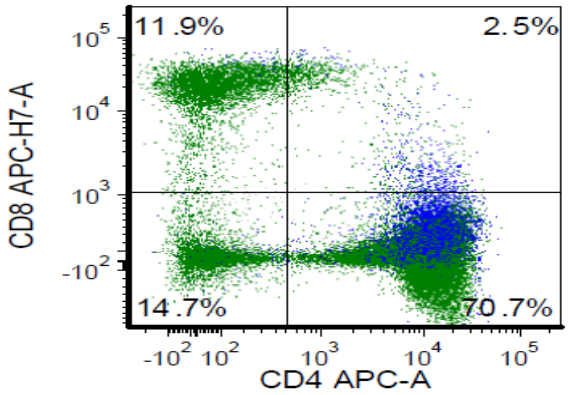
Bone marrow biopsy

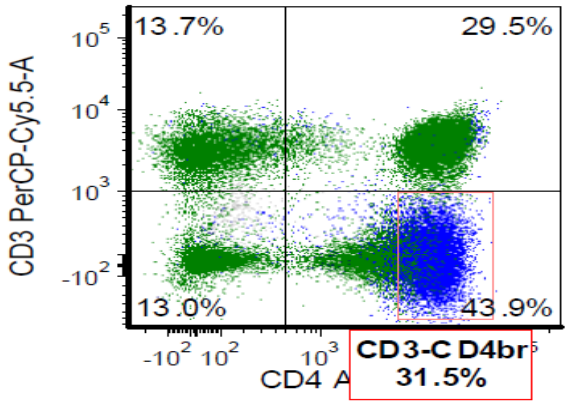


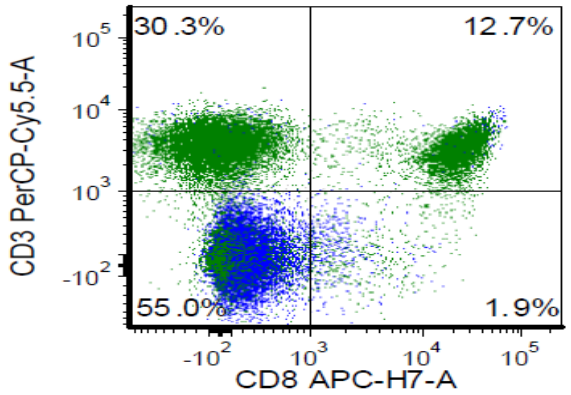
Differential diagnosis?

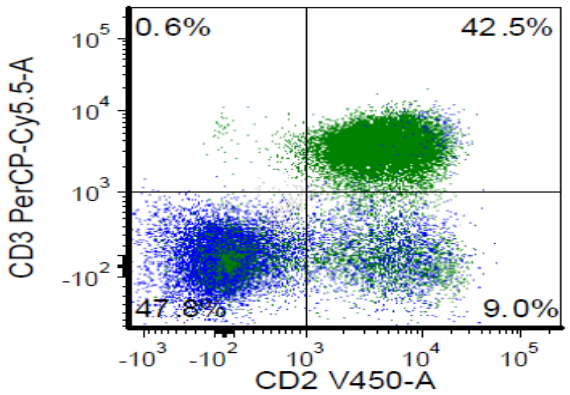
- Solid tumor?
- Mastocytosis/mast cell leukemia?
- Acute leukemia
  - Megakaryoblastic?
  - AML?
- ALK-positive anaplastic large cell lymphoma?
- Plasma cell neoplasm?

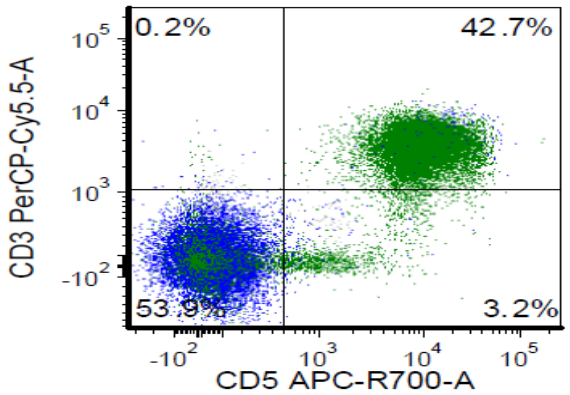
Pleural fluid flow cytometry

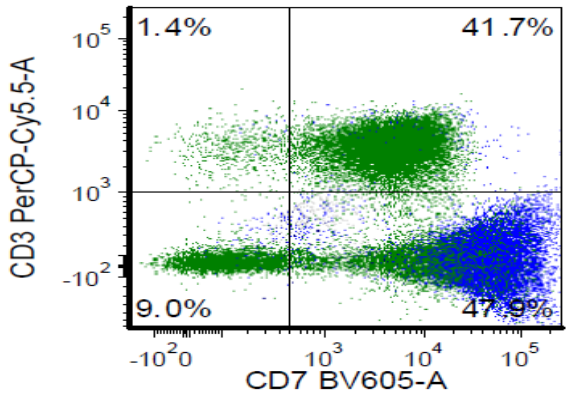










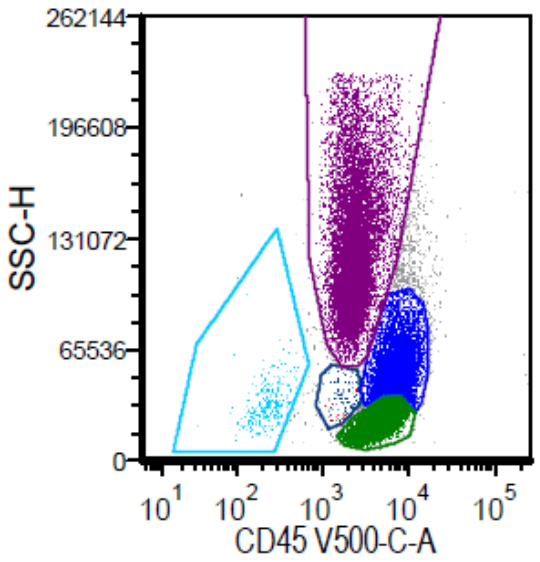


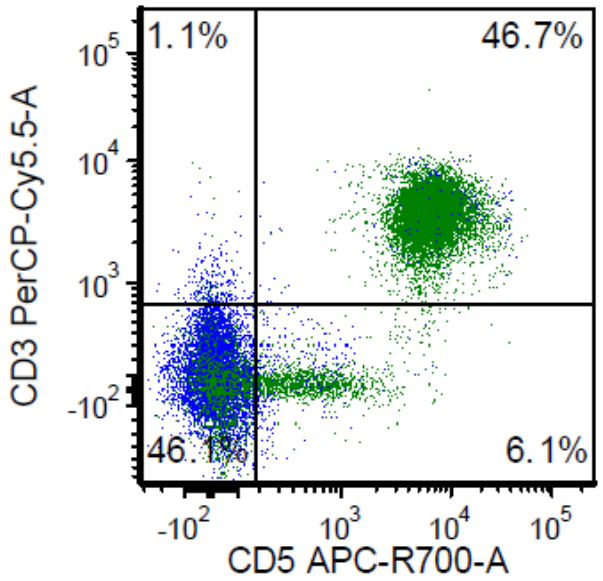
Positive	Negative
BRIGHT CD45, VARIABLE CD38, CD4, CD7, CD43, WITH MINOR SUBSETS WITH REACTIVITY FOR CD2 AND CD56	CD3 CD5

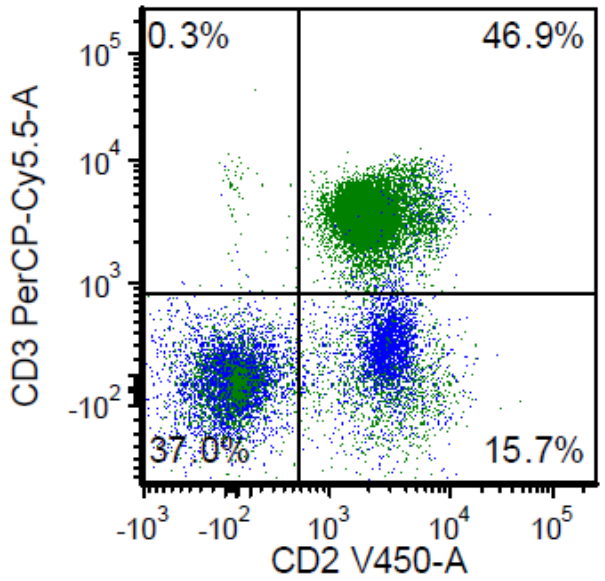
An atypical population of mononuclear cells is seen, compatible with abnormal monocytes or T cells with loss of typical T cell antigens.

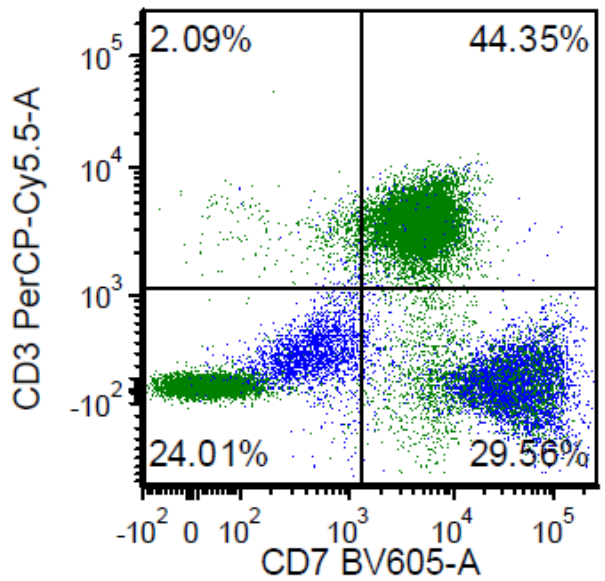
Peripheral blood flow cytometry

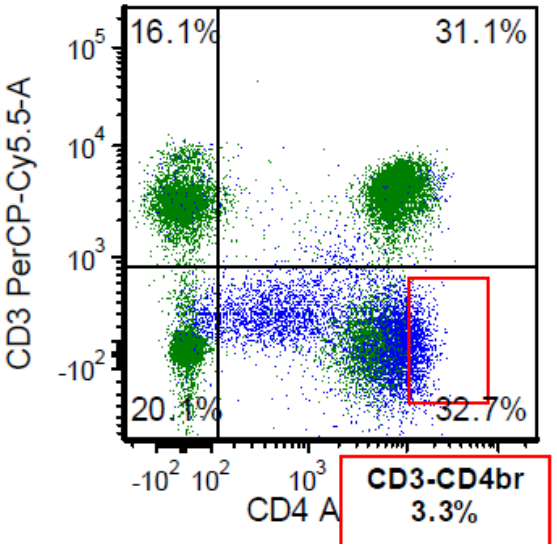
2 populations

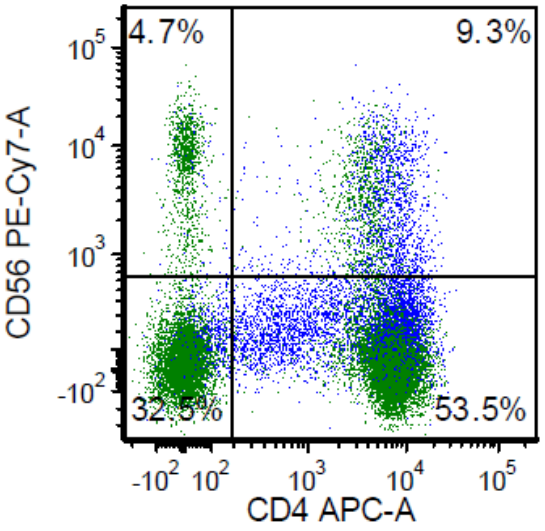


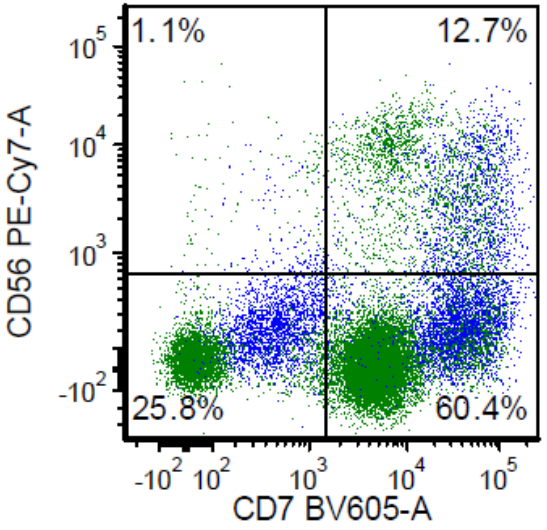


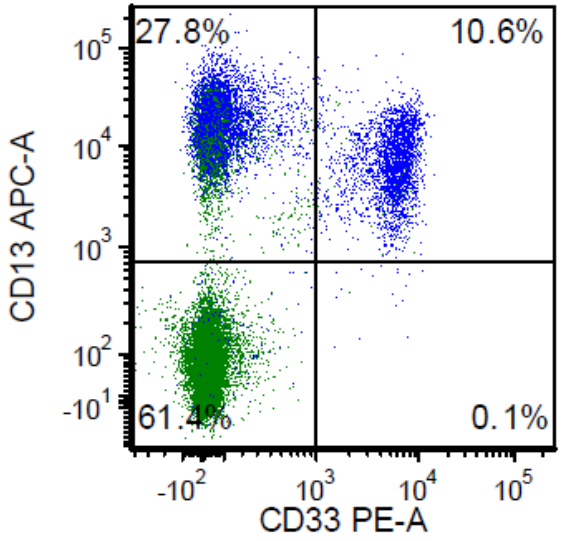


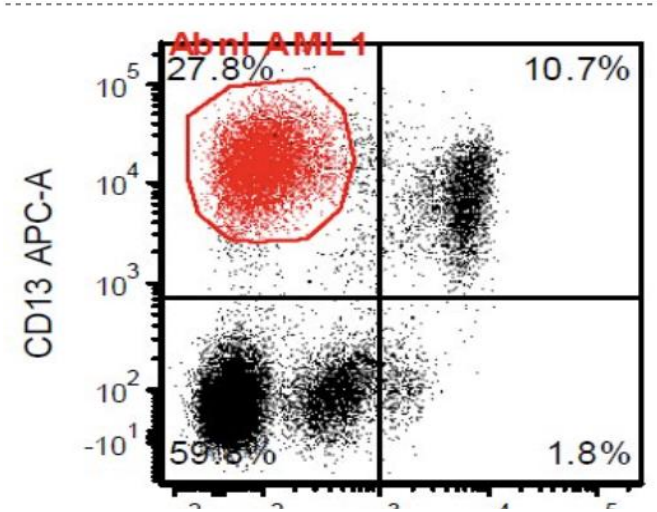


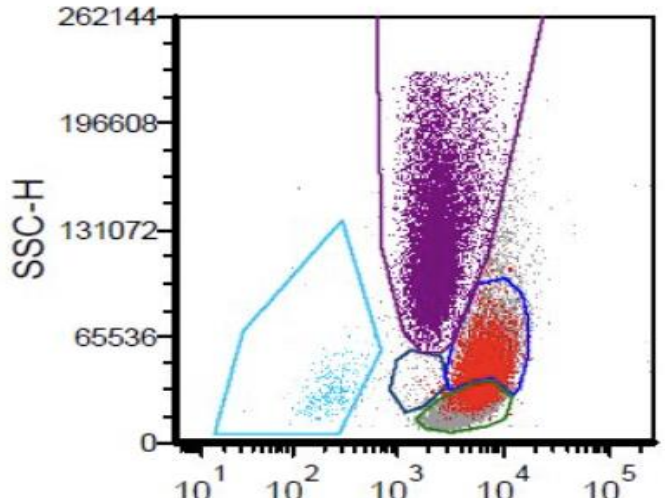


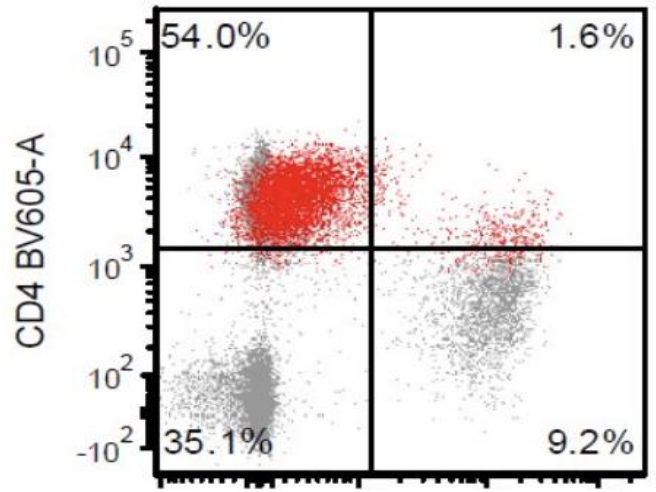


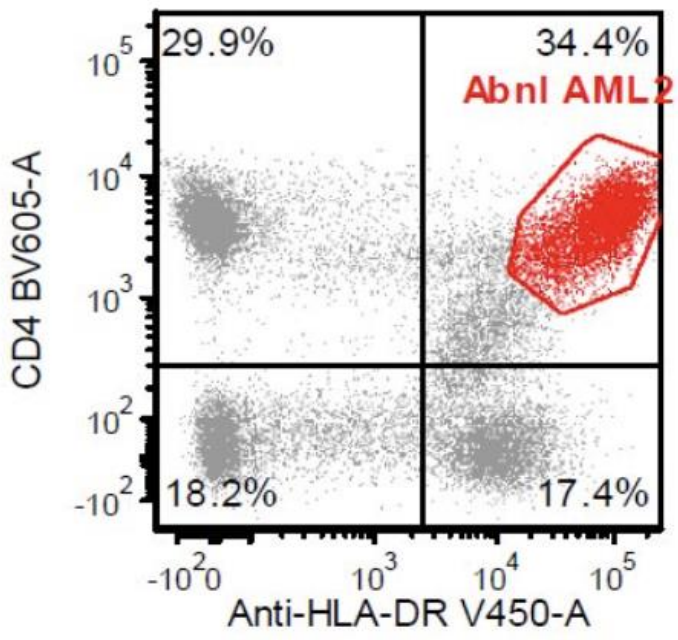


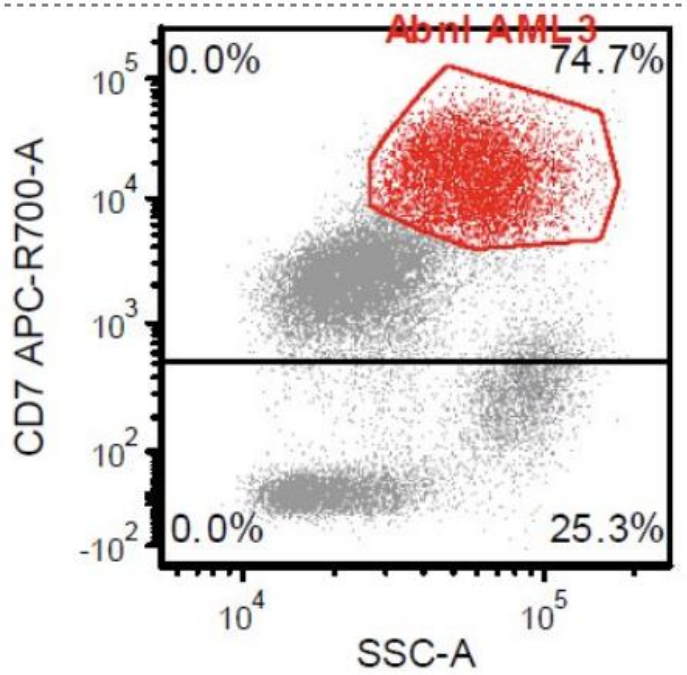



Abnl AML1
27.8%
10.7%
59.6%
1.8%
CD13 APC-A


262144
196608
131072
65536
0
SSC-H


54.0%
1.6%
35.1%
9.2%
CD4 BV605-A


29.9%
34.4%
Abnl AML2
18.2%
17.4%
CD4 BV605-A
Anti-HLA-DR V450-A


Abnl AML3
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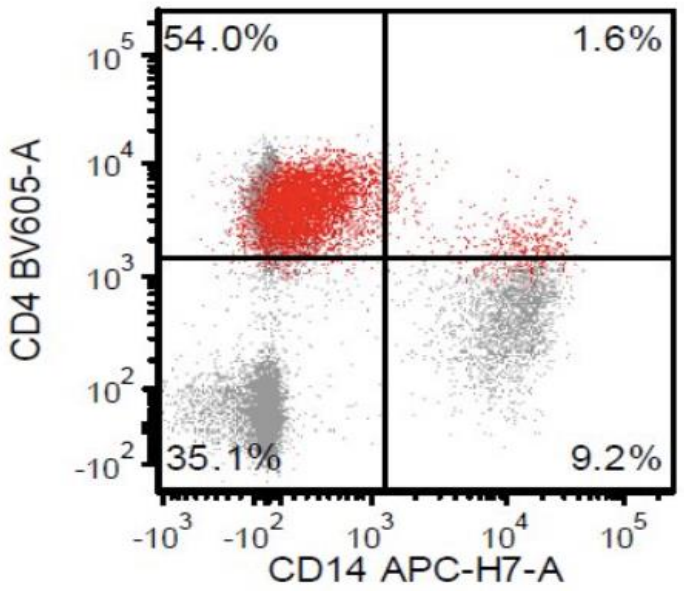
74.7%
0.0%
25.3%
CD7 APC-R700-A
SSC-A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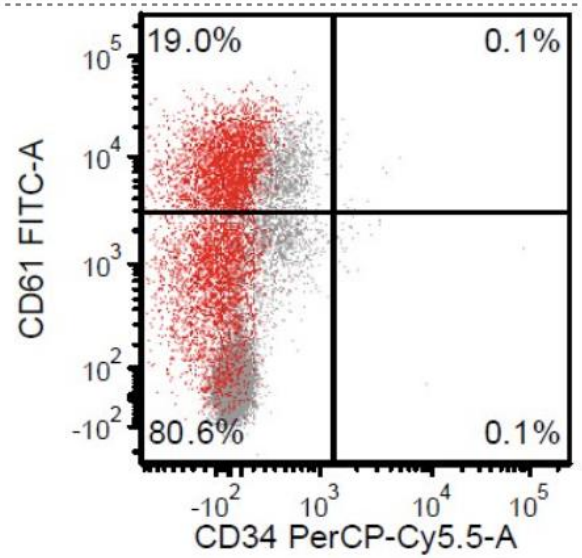
1.6%
35.1%
9.2%
CD4 BV605-A
CD14 APC-H7-A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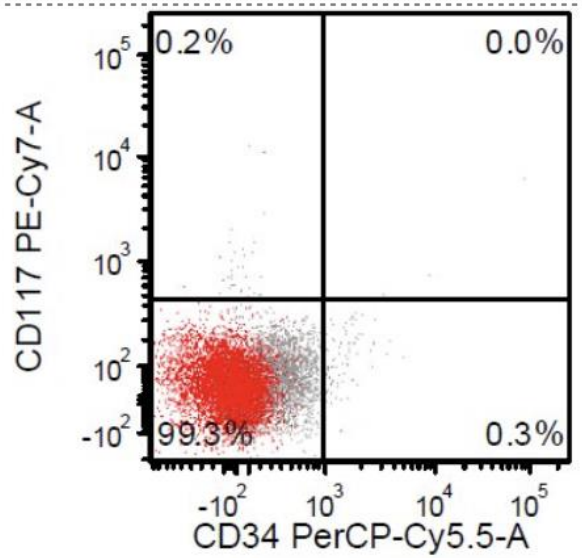
0.1%
80.6%
0.1%
CD61 FITC-A
CD34 PerCP-Cy5.5-A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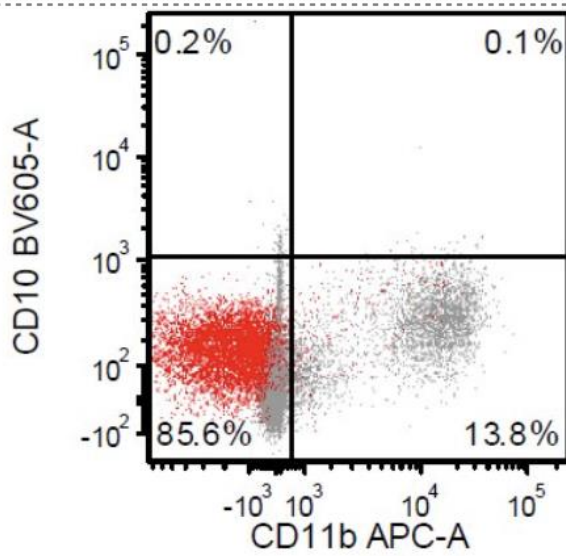
0.0%
99.3%
0.3%
CD117 PE-Cy7-A
CD34 PerCP-Cy5.5-A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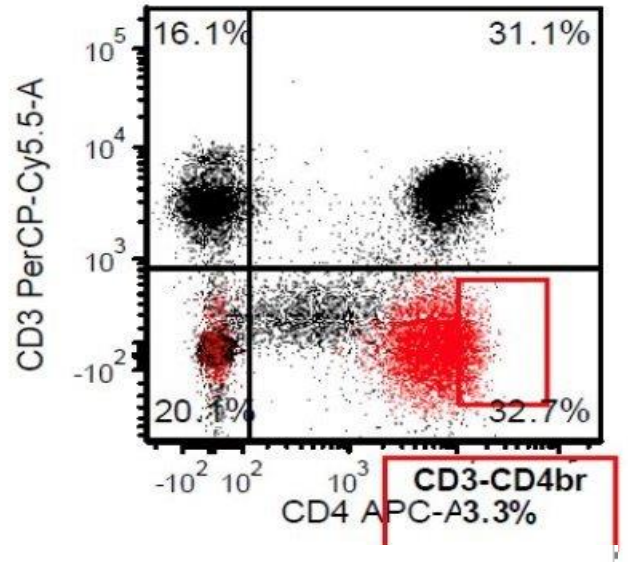
0.1%
85.6%
13.8%
CD10 BV605-A
CD11b APC-A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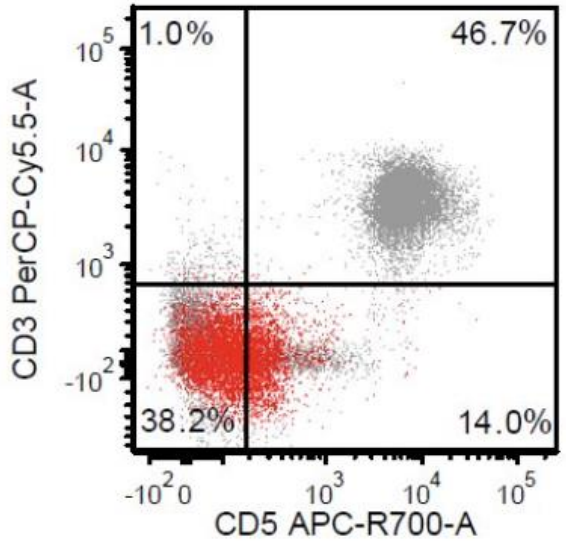
31.1%
20.1%
32.7%
CD3 PerCP-Cy5.5-A
CD3-CD4br
CD4 APC-A3.3%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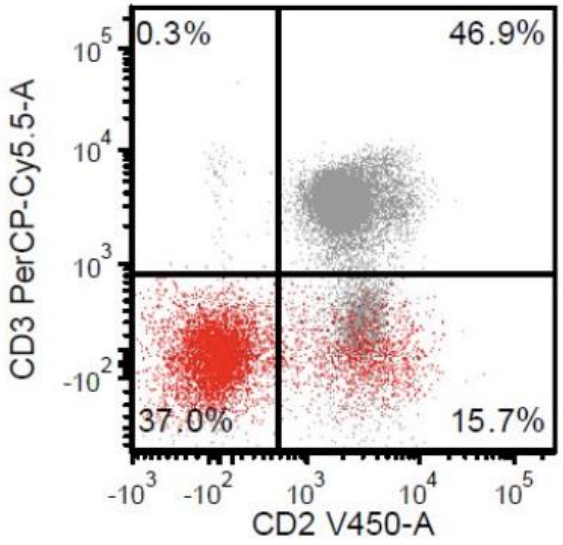
14.0%
CD3 PerCP-Cy5.5-A
CD5 APC-R700-A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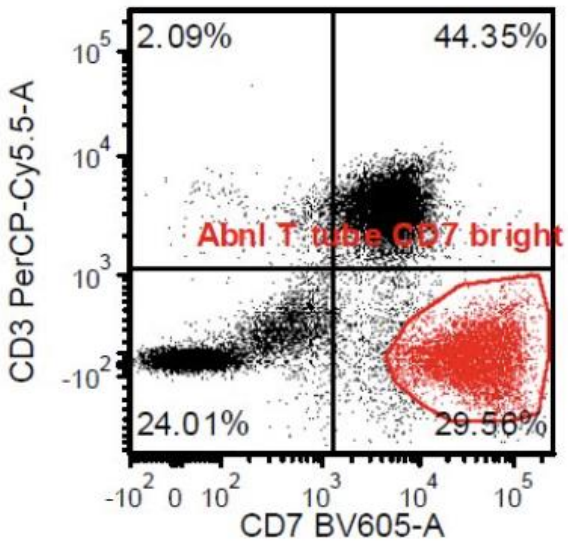
CD2 V450-A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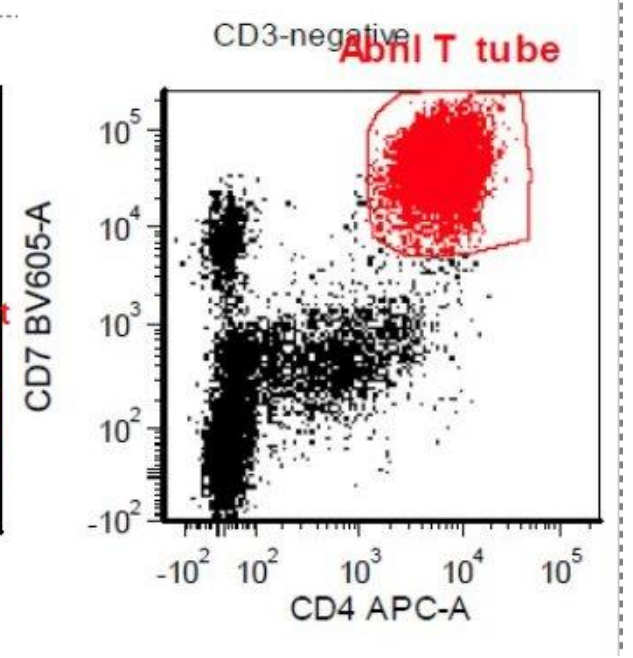
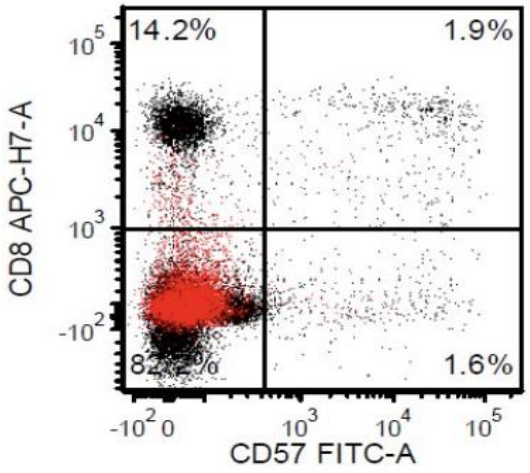
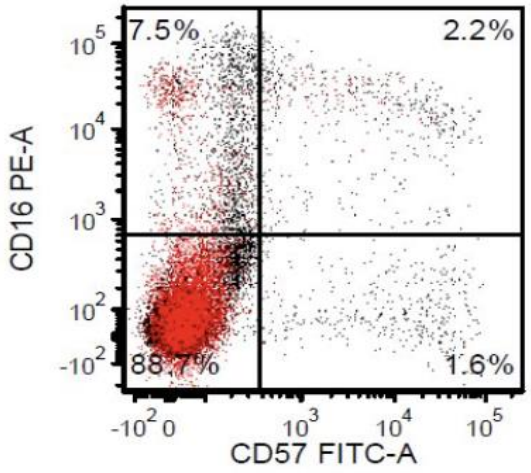
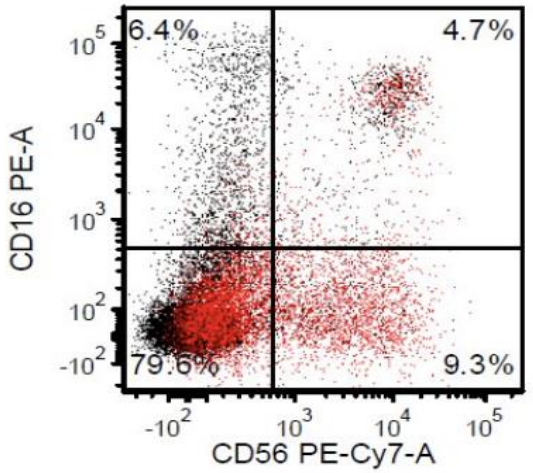
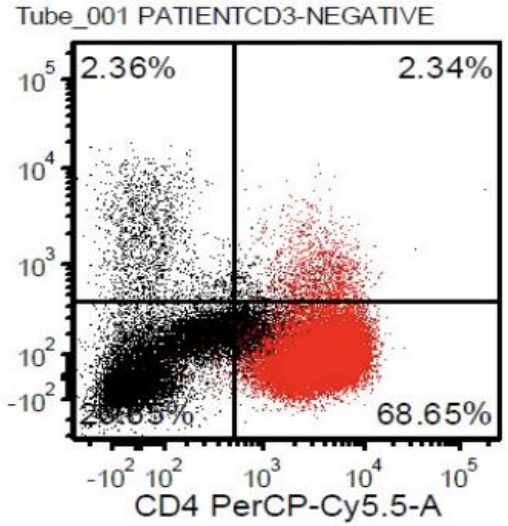
44.35%
Abnl T tube CD7 bright
24.01%
29.56%
CD3 PerCP-Cy5.5-A
CD7 BV605-A

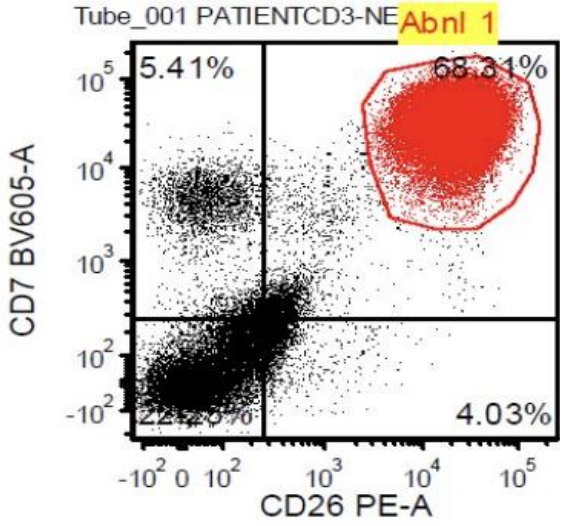

CD3-negative
Abnl T tube
CD7 BV605-A
CD4 APC-A

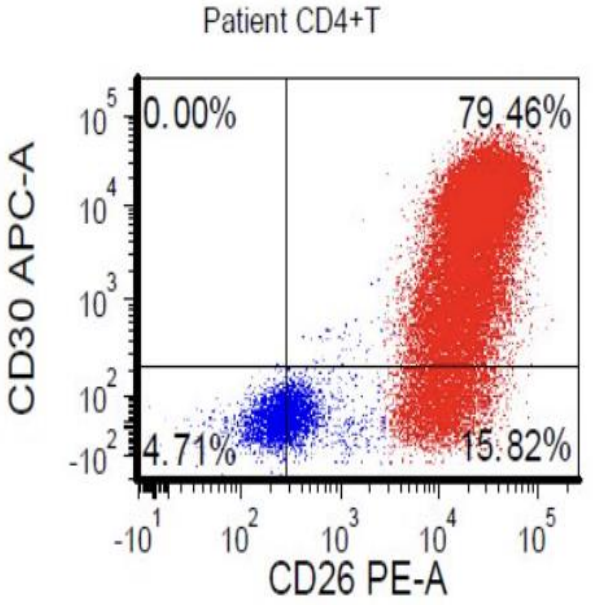






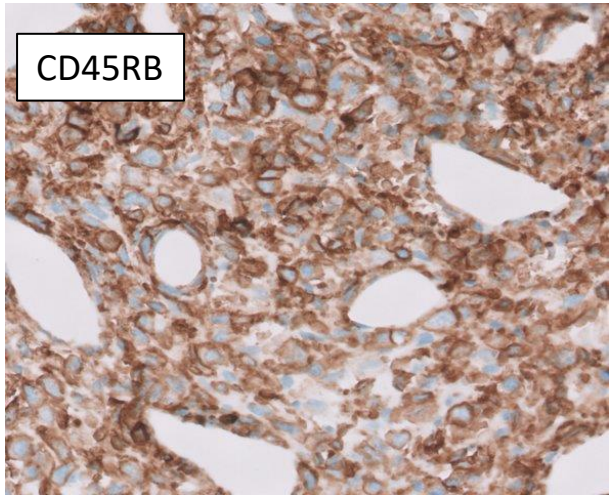


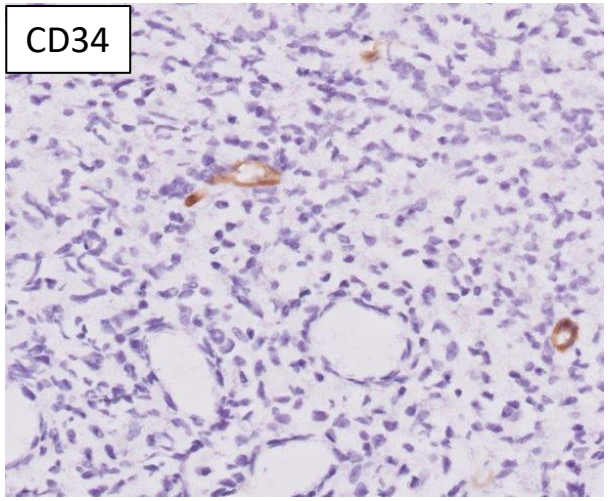


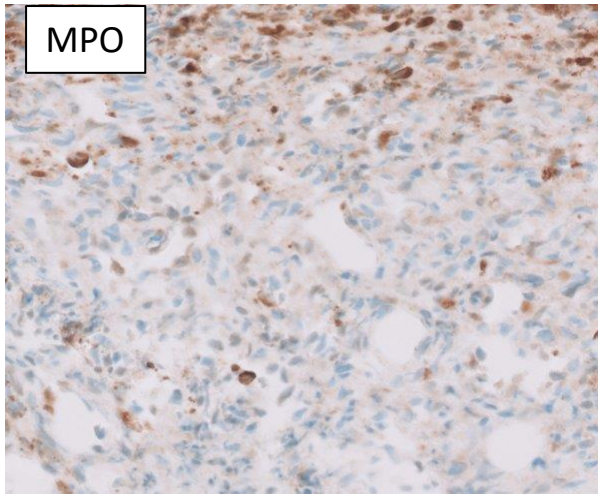


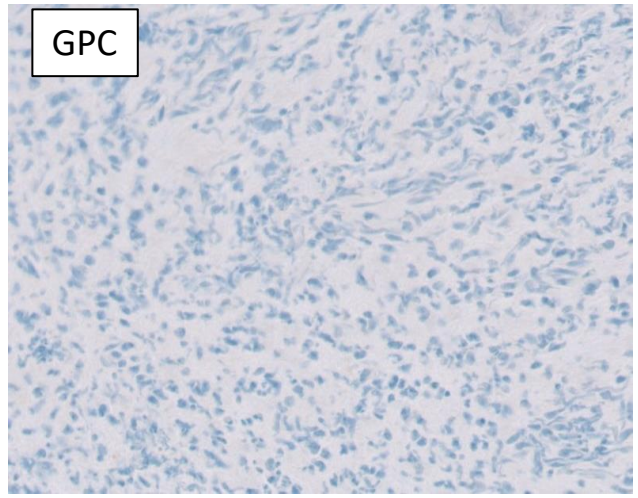
Positive	Negative
CD45 **CD30**(VARIABLE-BRIGHT) CYTOPLASMIC CD3 (VERY DIM) **CD2 (PARTIAL DIM)** **CD7(BRIGHT),** **CD4** CD8(MINIMAL PARTIAL DIM) CD56(PARTIAL DIM) CD26(BRIGHT CD25(partia) CD52(PARTIAl) **CD13** CD38 (PARTIAL DIM) HLA-DR (BRIGHT) CD71 (DIM)	SURFACE CD3 CD5 CD10 CD1A CD34 TDT CD79A CD33 CD19 CD14 CD16 CD64 CD117 CD11B CD20 CD22 CD57 CCR4

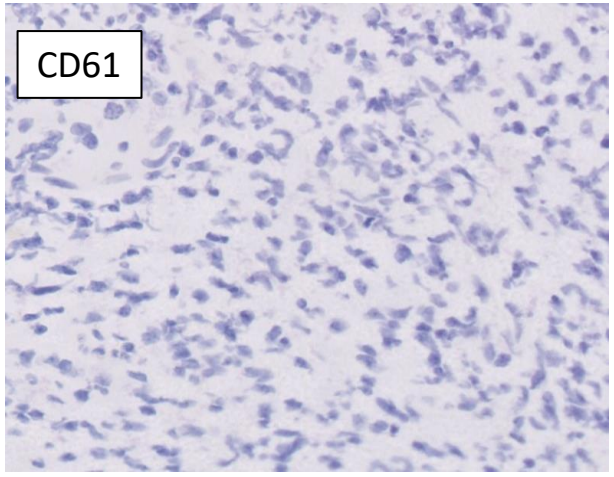
Bone marrow biopsy

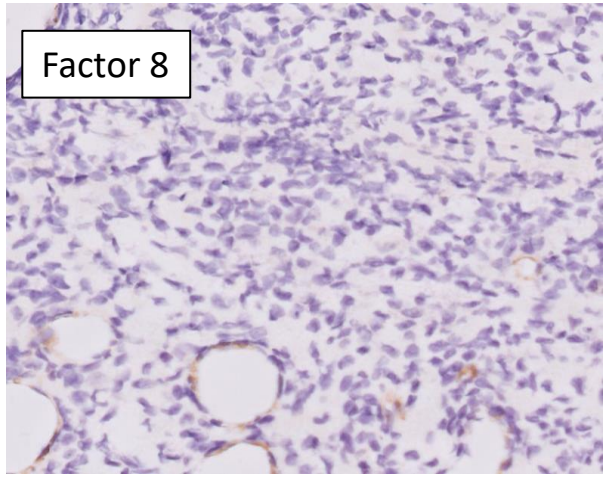


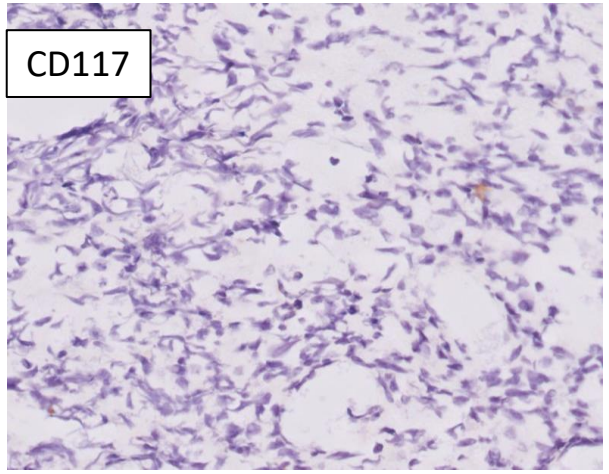


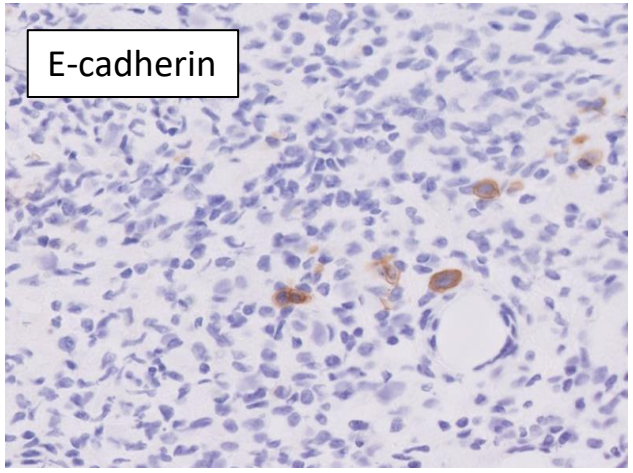


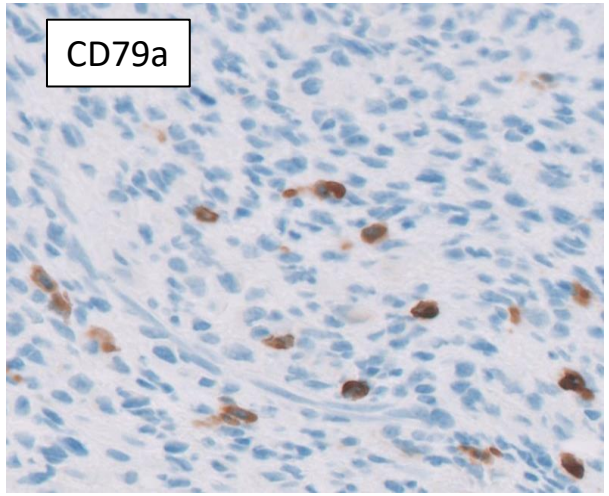


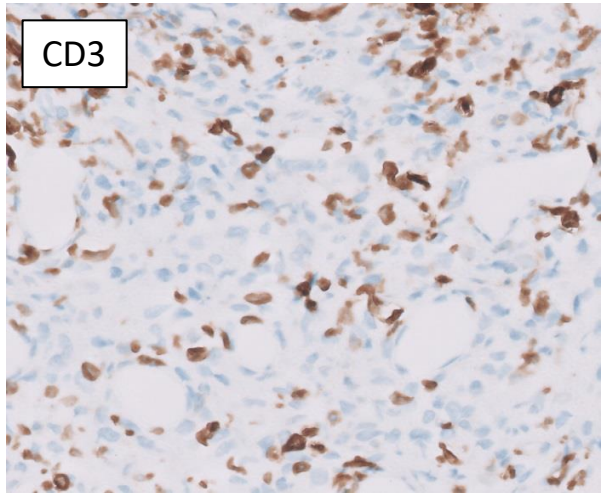









CD79a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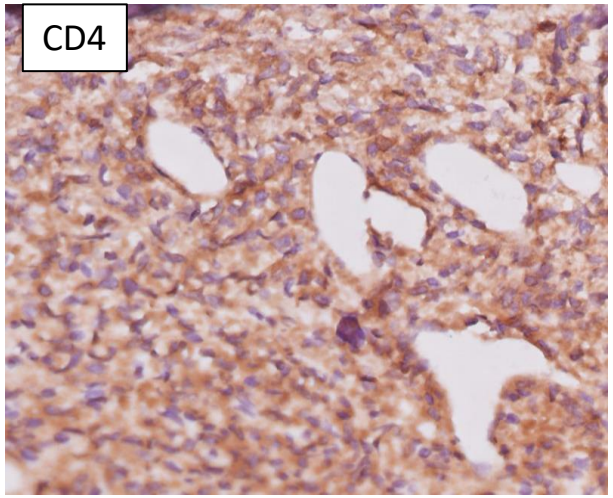
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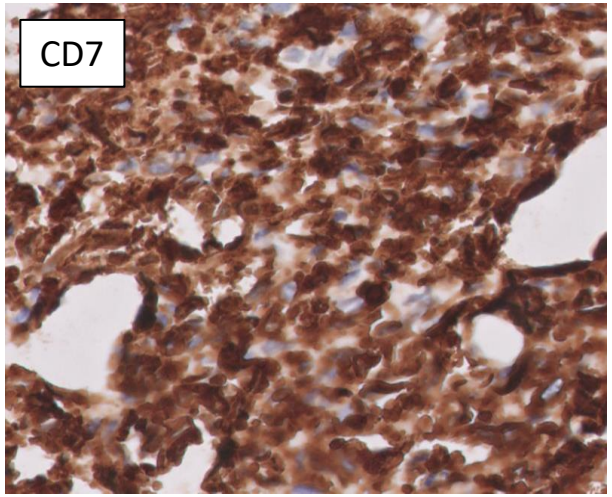
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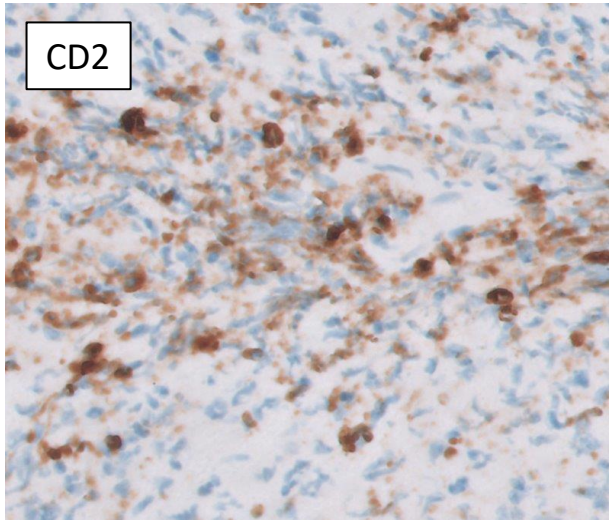
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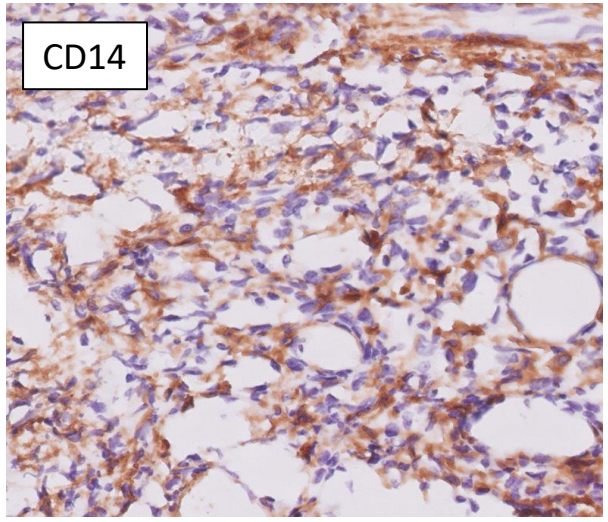
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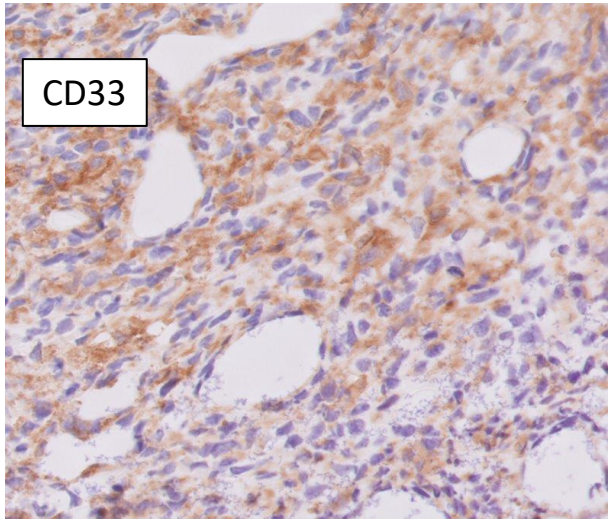
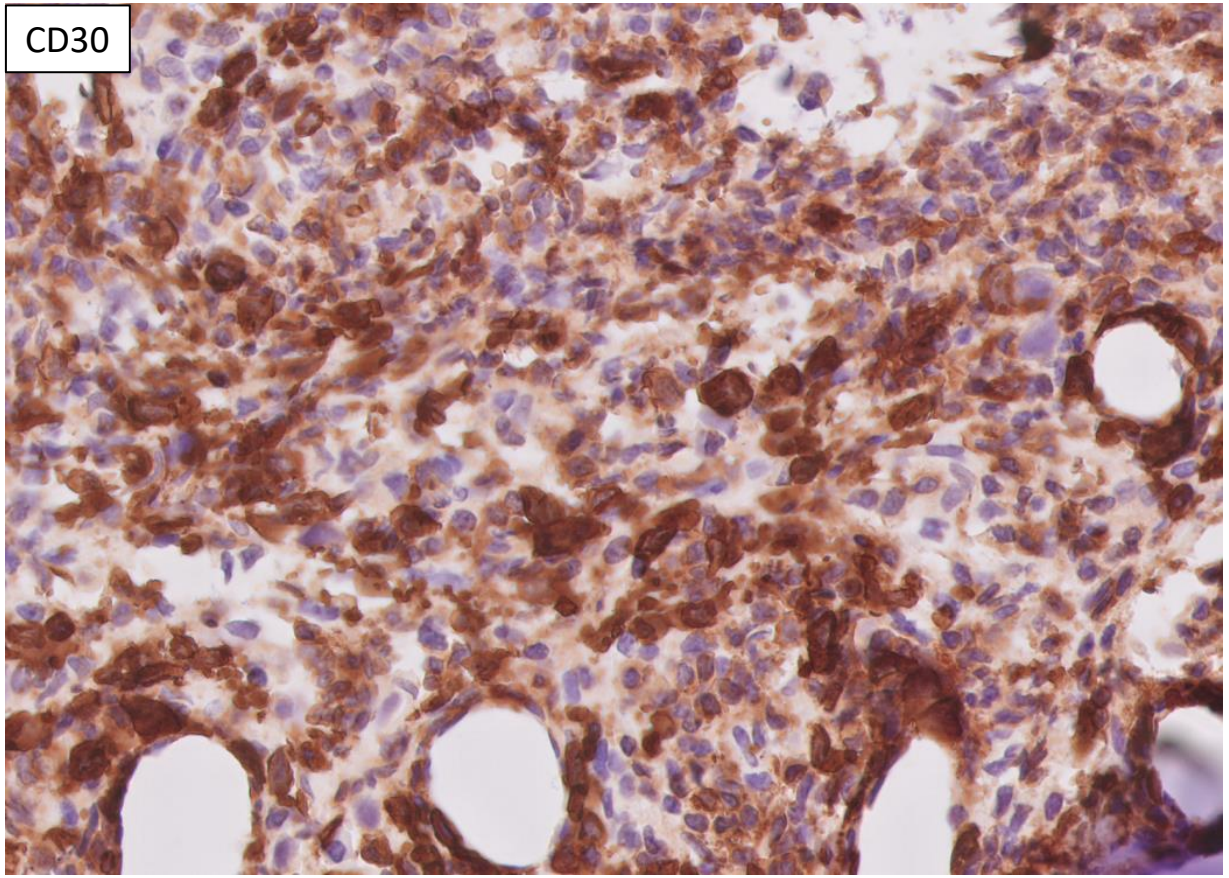
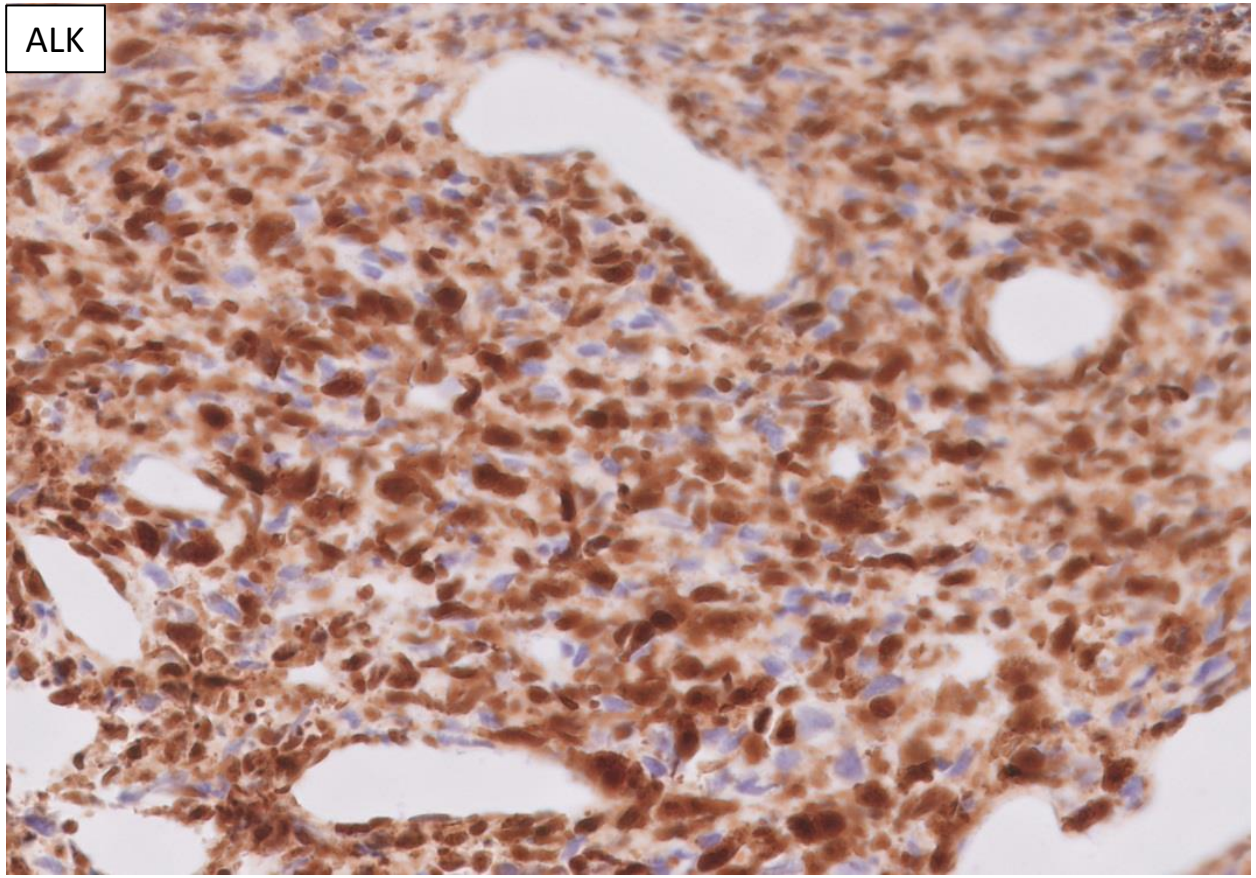

CD33





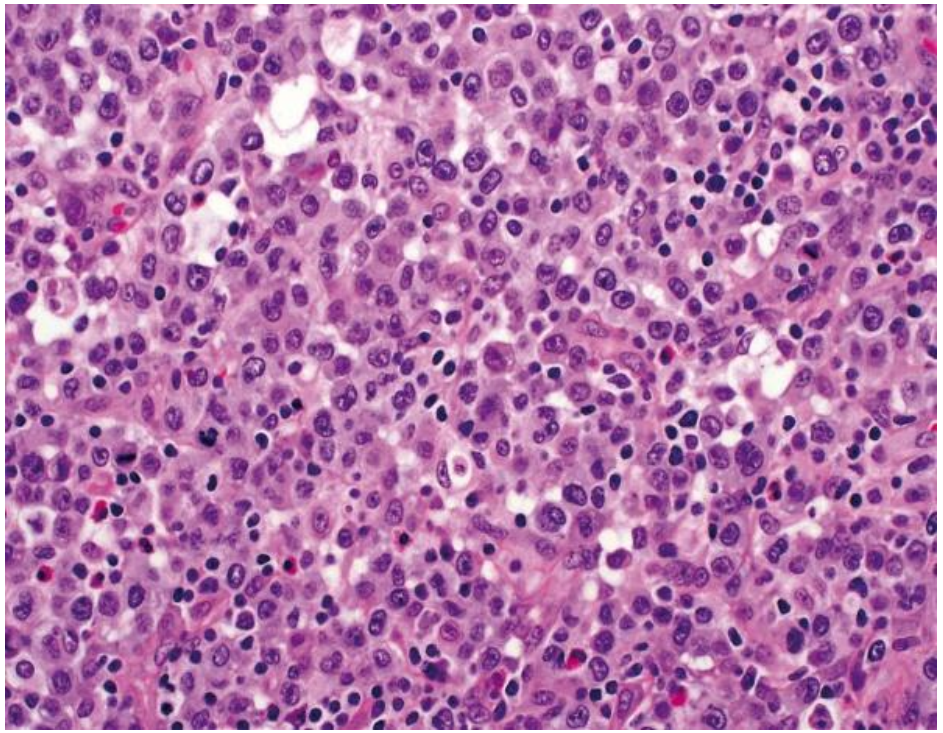
Cytogenetics:
46,XX,t(2;5)(p23;q35),add(4)(q?21),del(5)(q22q31),add(16)(q?23~24)[21]

Diagnosis

ALK-positive anaplastic large cell lymphoma

ALK-positive anaplastic large cell lymphoma

- CD30-positive mature T-cell lymphoma with aberrant expression of ALK secondary to rearrangements of the *ALK* gene.
- Lymph nodes (90%), and extranodal involvement is frequent (60%), most commonly the skin (26%), bone (14%), soft tissue (15%) and lung (14%)
- Bone marrow (10–14%)
- Advanced-stage 10–15% of pediatric and adolescent NHL and 3% of adult NHL
- t(2;5)(p23;q35) translocation, resulting in aberrant expression of the *NPM1*::*ALK* fusion protein
- Hallmark cells
- Long-term survival rates are about 80%, significantly better than the vast majority of ALK− ALCL



IHC

- CD30- strong uniform, membrane and Golgi area
- ALK -nuclear and cytoplasmic
- Frequent loss of T cell–associated antigens
- CD2 and CD4 are most commonly expressed (40–70%), whereas CD3 is negative in > 75% of the cases.
- CD43 and CD45RO expression is commonly observed
- The tumor cells express cytotoxic markers, including TIA1, granzyme B, and perforin
- Occasional cases aberrantly express CK, myeloid antigens (CD13 and CD33), NK-cell markers (CD56)
- EBV is characteristically negative

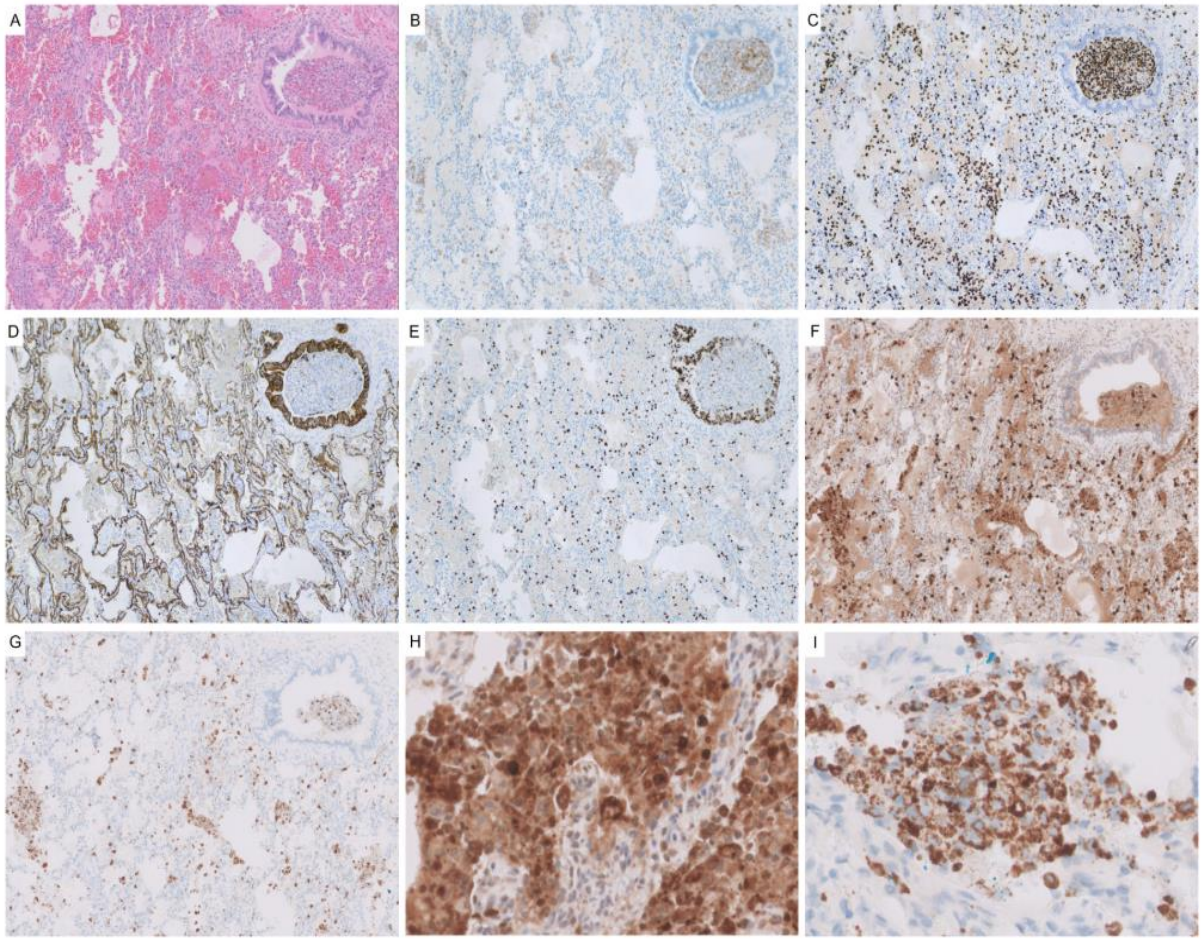
ALK-positive anaplastic large cell lymphoma- Take home!

- Can express CD13
- Bone involvement uncommon, but with age ALCL should be high in the differential
- Immunophenotypically and morphologically can resemble monocytes

Case Reports

The Histopathologic Features of Early COVID Pneumonia in a Pediatric Patient: New Insight into the Role of Macrophages

Philip L. Bulterys, MD, PhD , Guangwu Xu, MD, Benjamin A. Pinsky, MD, PhD, Megan L. Troxell, MD, PhD, Joshua R. Menke, MD, Gerald J. Berry, MD, Sebastian Fernandez-Pol, MD, PhD, and Florette K. Hazard, MD



Int J Surg Pathol. 2024 Dec;32(8):1595-1601

Nucleocapsid protein **Spike RNA**

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- Barik S, Goyal N, Paul S, Singh V, Arora S. Primary Bone Lymphoma: A Rare Case of Anaplastic Large Cell Lymphoma in Calcaneus in a Child. J Orthop Case Rep. 2019;9(4):14-18. doi: 10.13107/jocr.2019.v09.i04.1458. PMID: 32405479; PMCID: PMC7210905.
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