KOPANA Spring Seminar 2024

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UT MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Education:

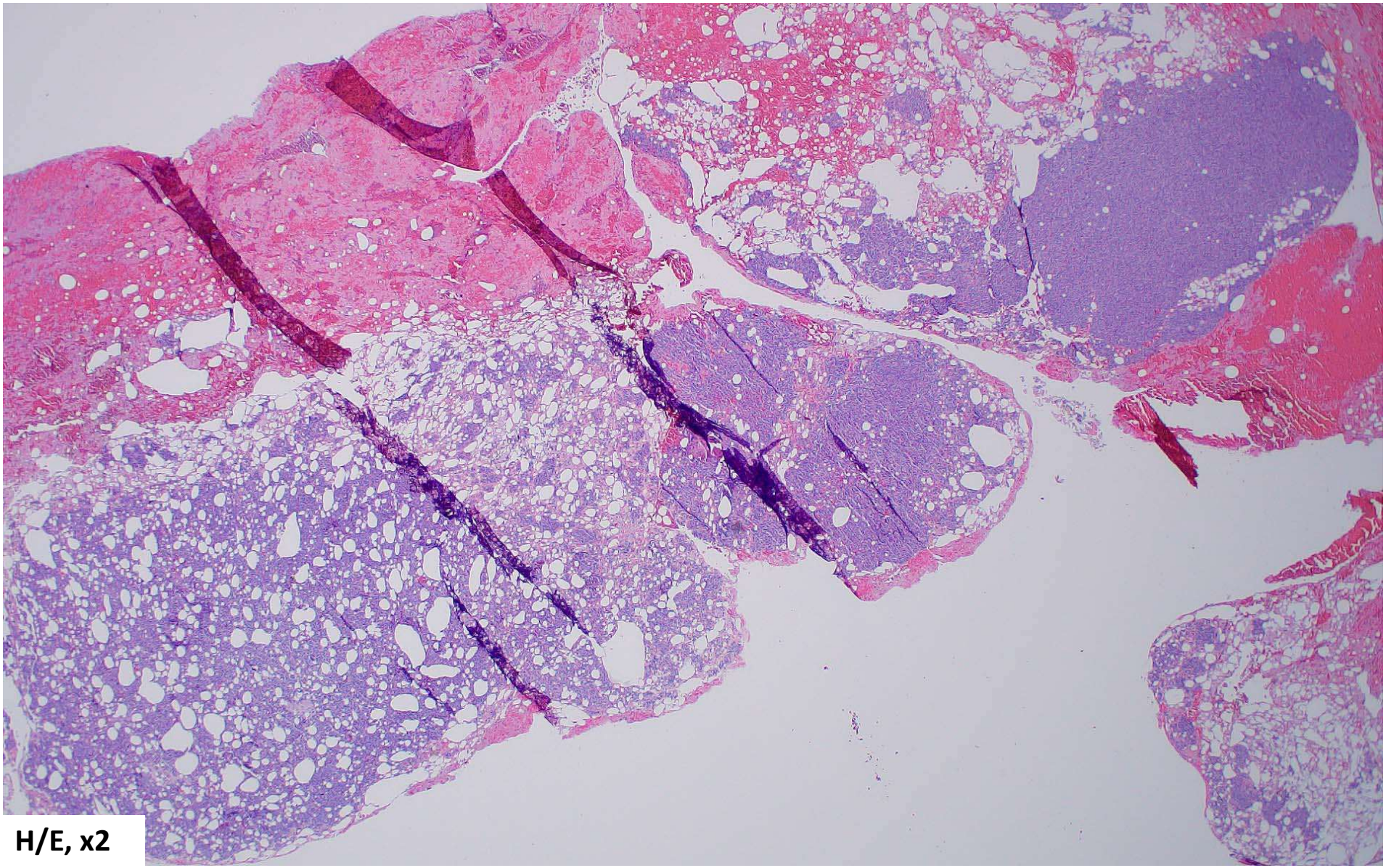
- Medical School: Yonsei University of College of Medicine
- Residency: University of Massachusetts
- Fellowship: UT MD Anderson Cancer Center

Current Position & Institution: Associate Professor, Department of Hematopathology, UT MD Anderson Cancer Center

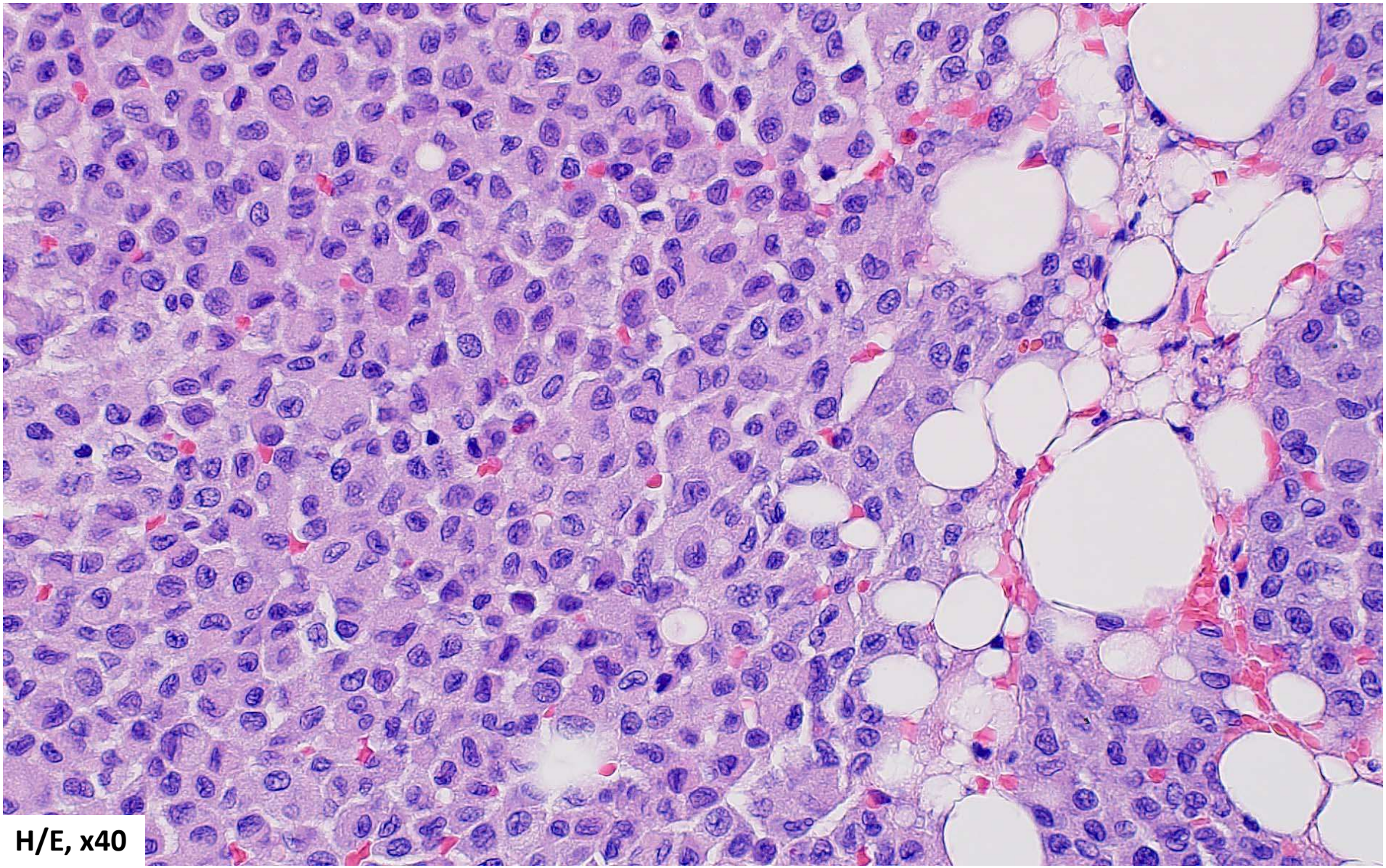
Subspecialty area: Hematopathology, molecular genetic pathology

Case 1

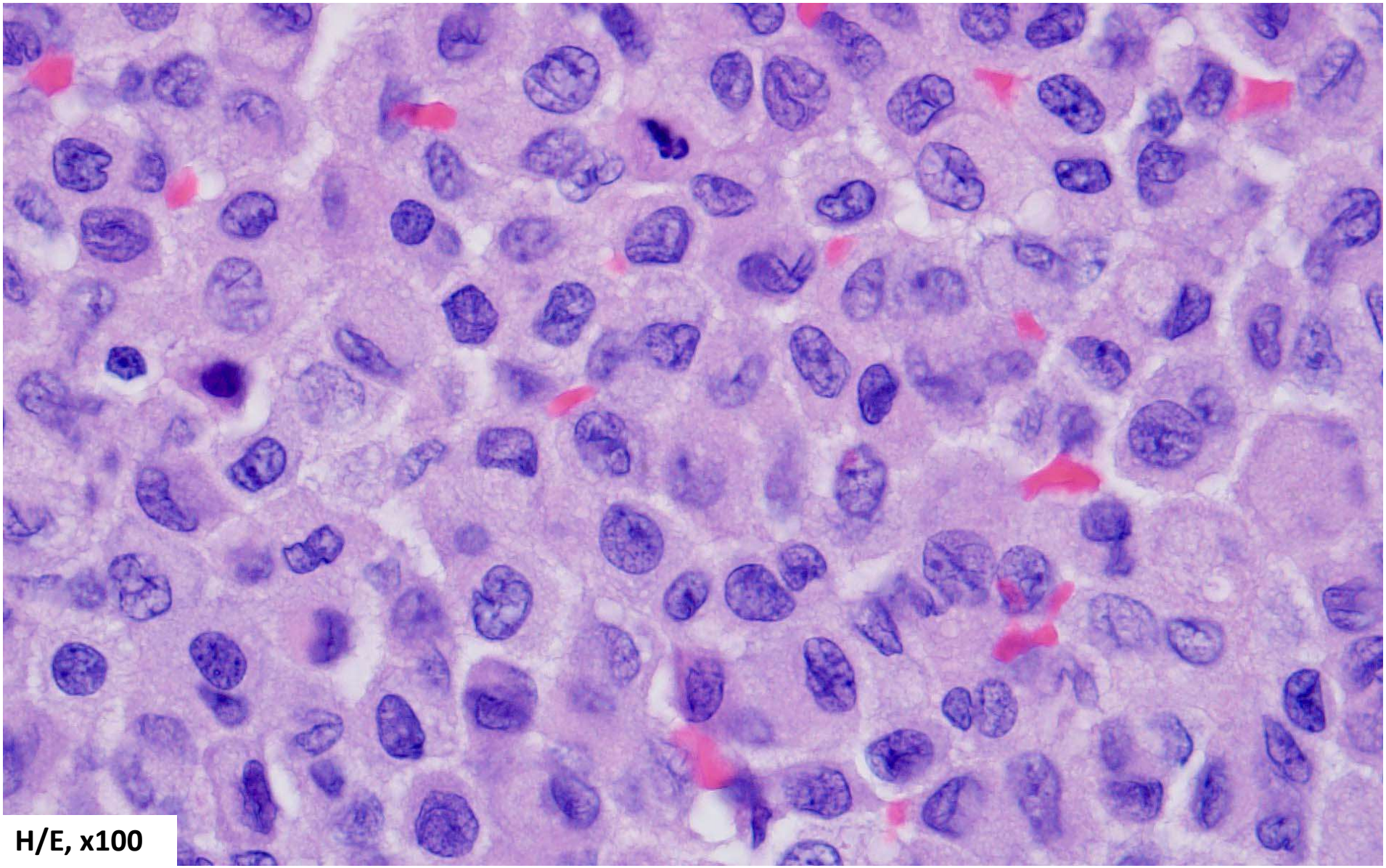
- 71 y/o man
- h/o squamous cell carcinoma at base of tongue (8 years ago)
- s/p chemoradiation, completed 8 years ago
- Visits hospital for aortic valve replacement
- Aortic valve: valve tissue with degeneration and calcification
- Atrial appendage and blood clot
  - Atrial appendage: no significant pathologic change
  - Blood clot



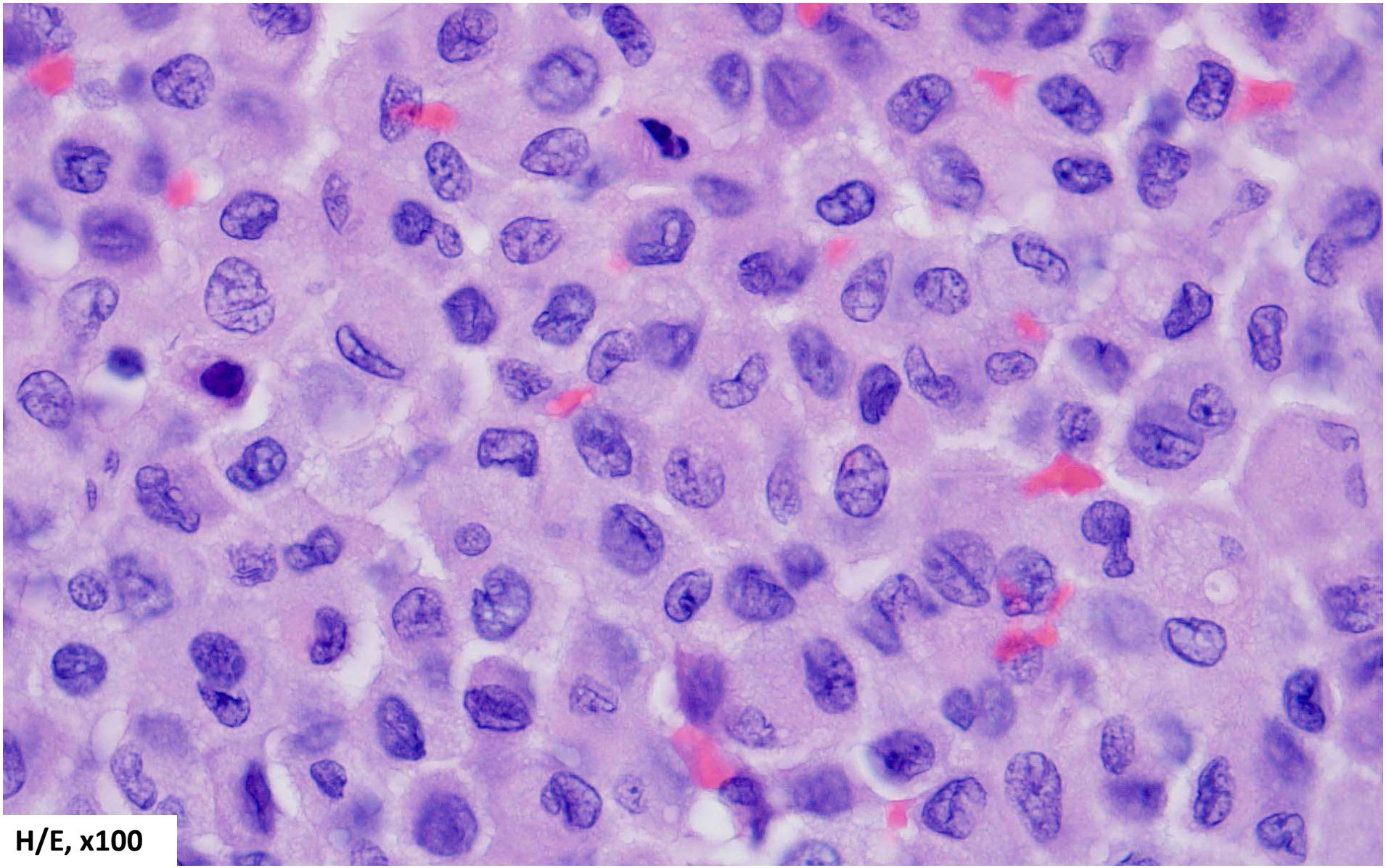
H/E, x2



H/E, x40



H/E, x100

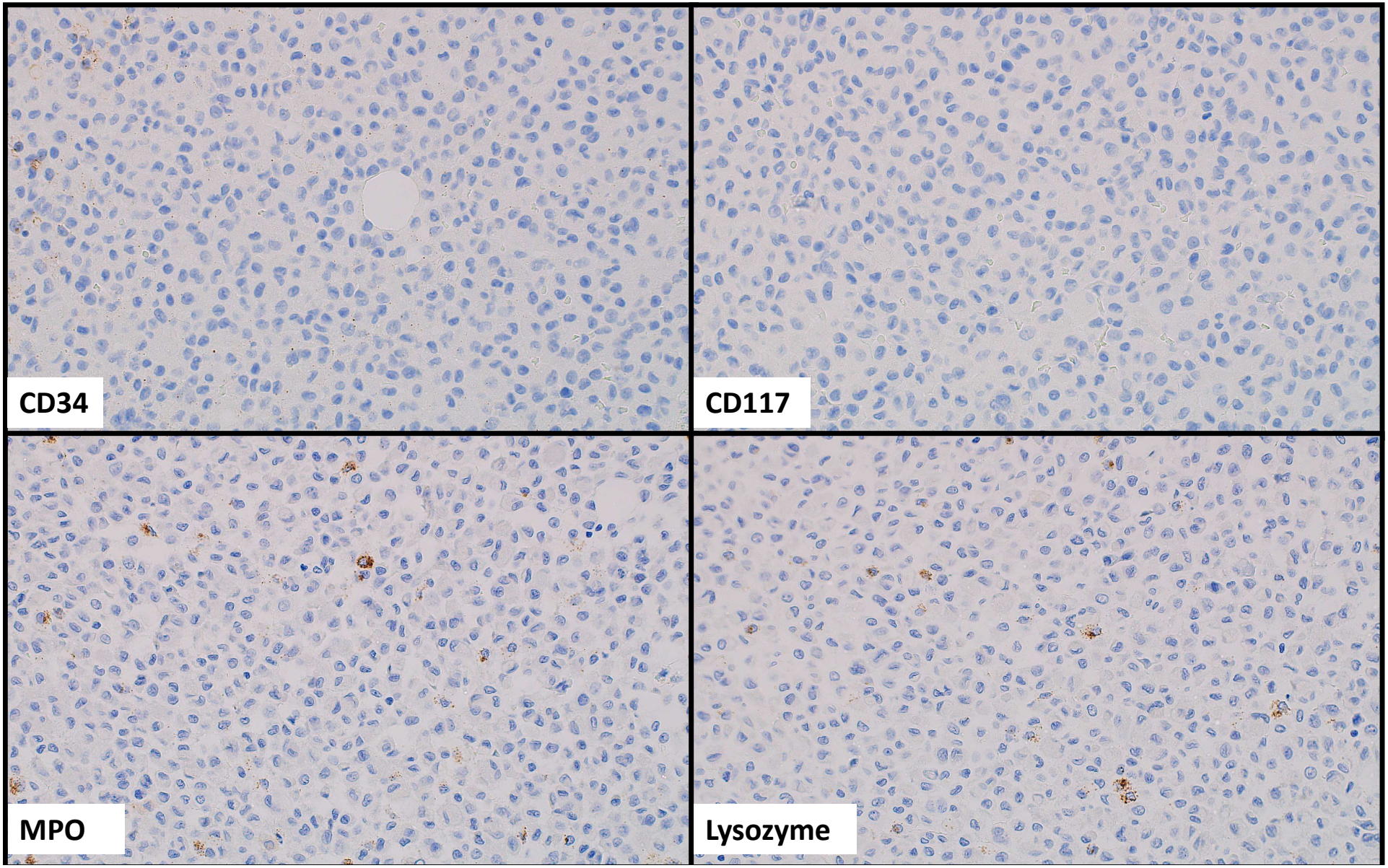


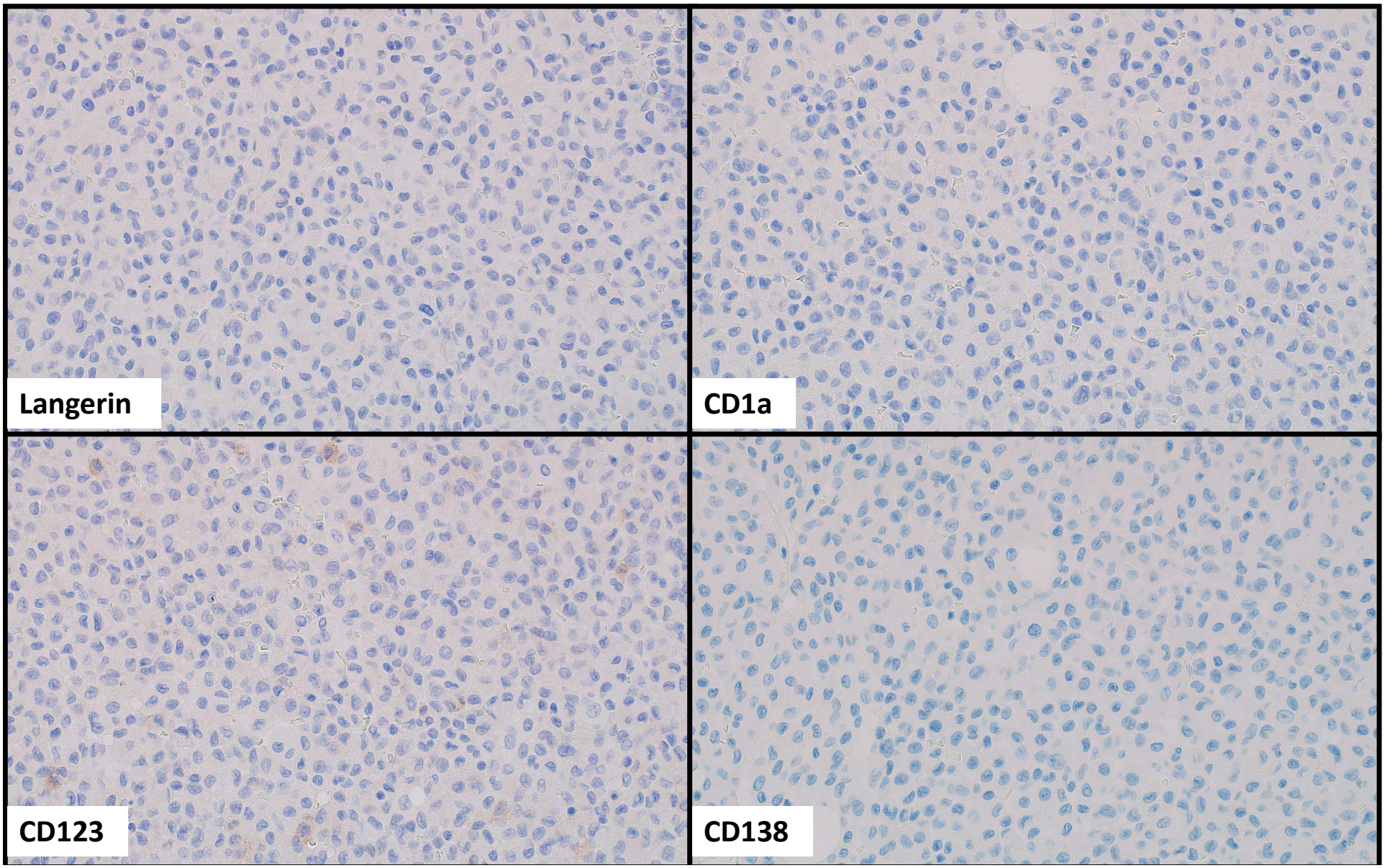
H/E, x100

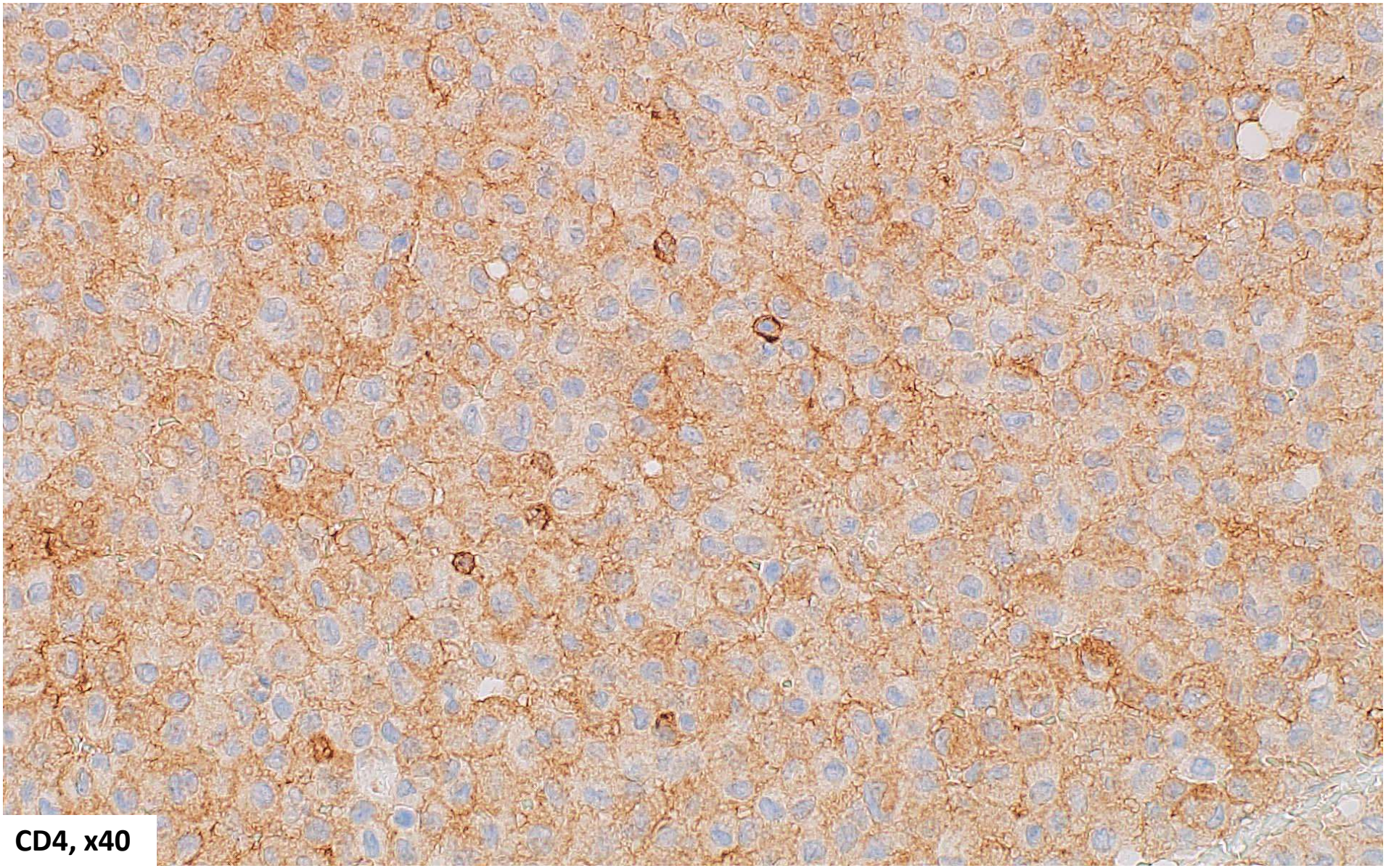

CROWN 죠리퐁 CROWN 죠리퐁 CROWN 죠리퐁
▲ 뜯는곳
크라운
죠리퐁®
Jolly pong
高 식이섬유
식이섬유 6%
과자(유처리제품)/74 g(320 kcal)
죠리퐁 CROWN 죠리퐁 CROWN 죠리퐁

Differential diagnosis

- Langerhans cell histiocytosis
- Myeloid sarcoma
- Histiocytic sarcoma


CD34
CD117
MPO
Lysozyme

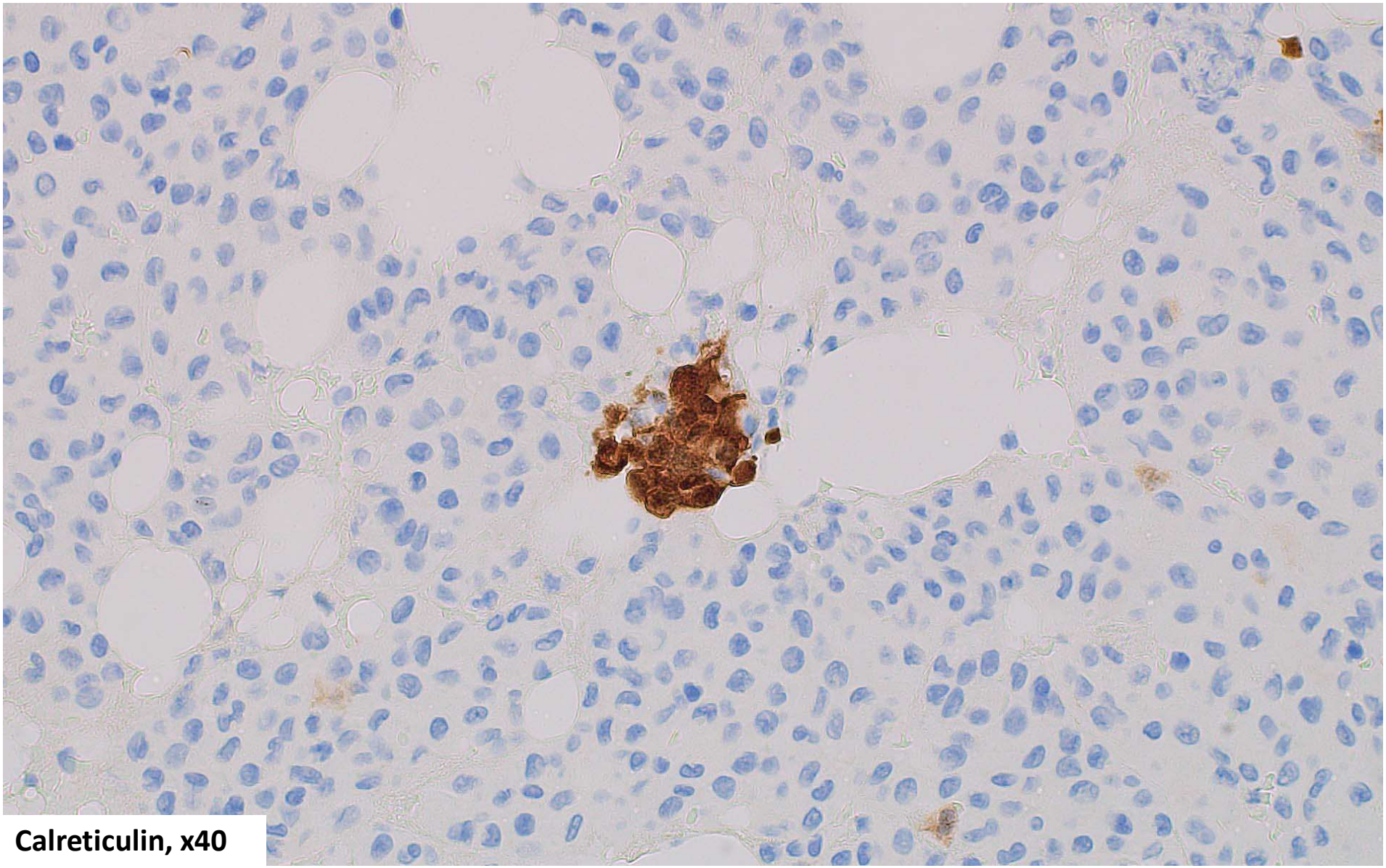

Langerin
CD1a
CD123
CD138



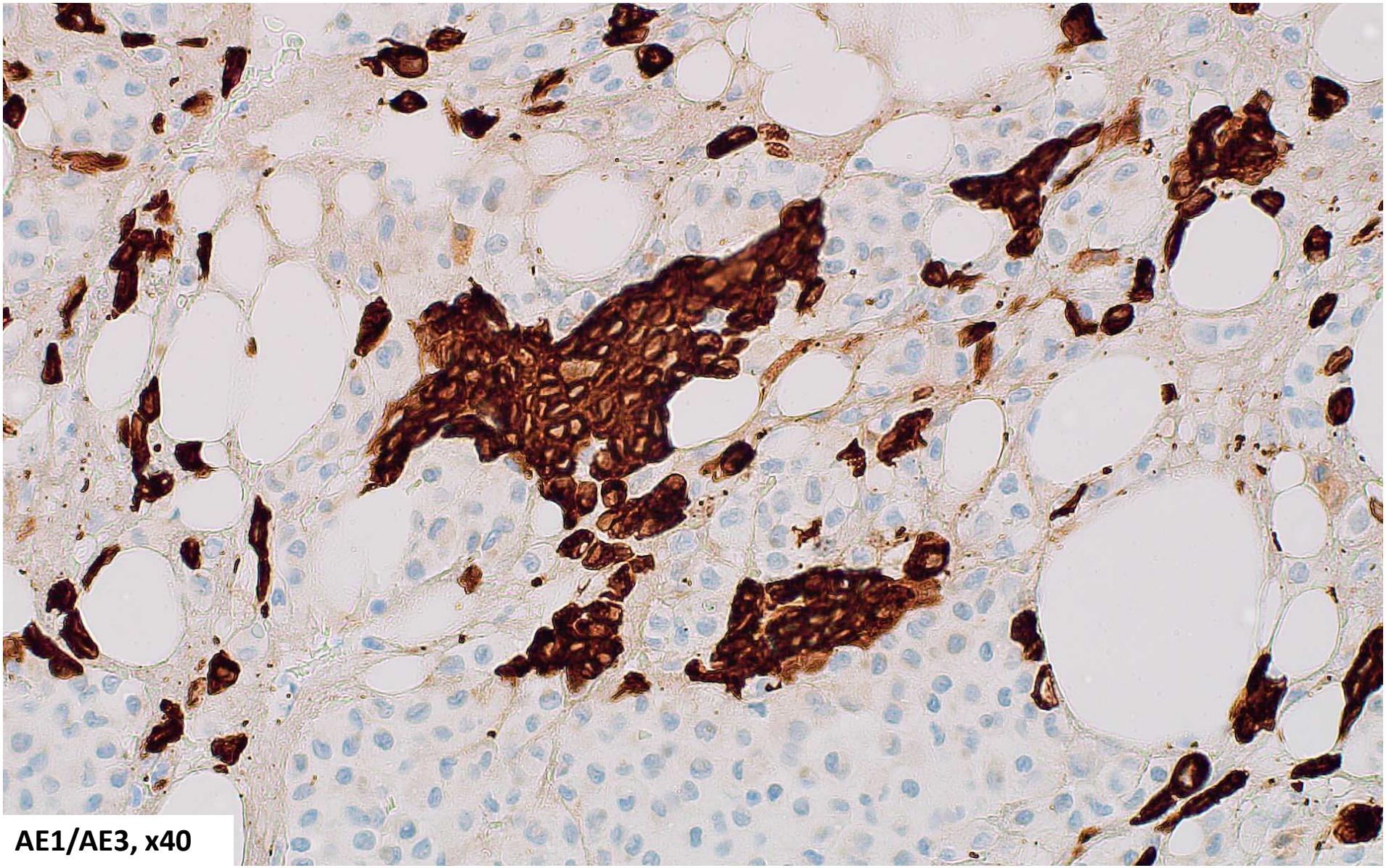
CD4, x40

Differential diagnosis

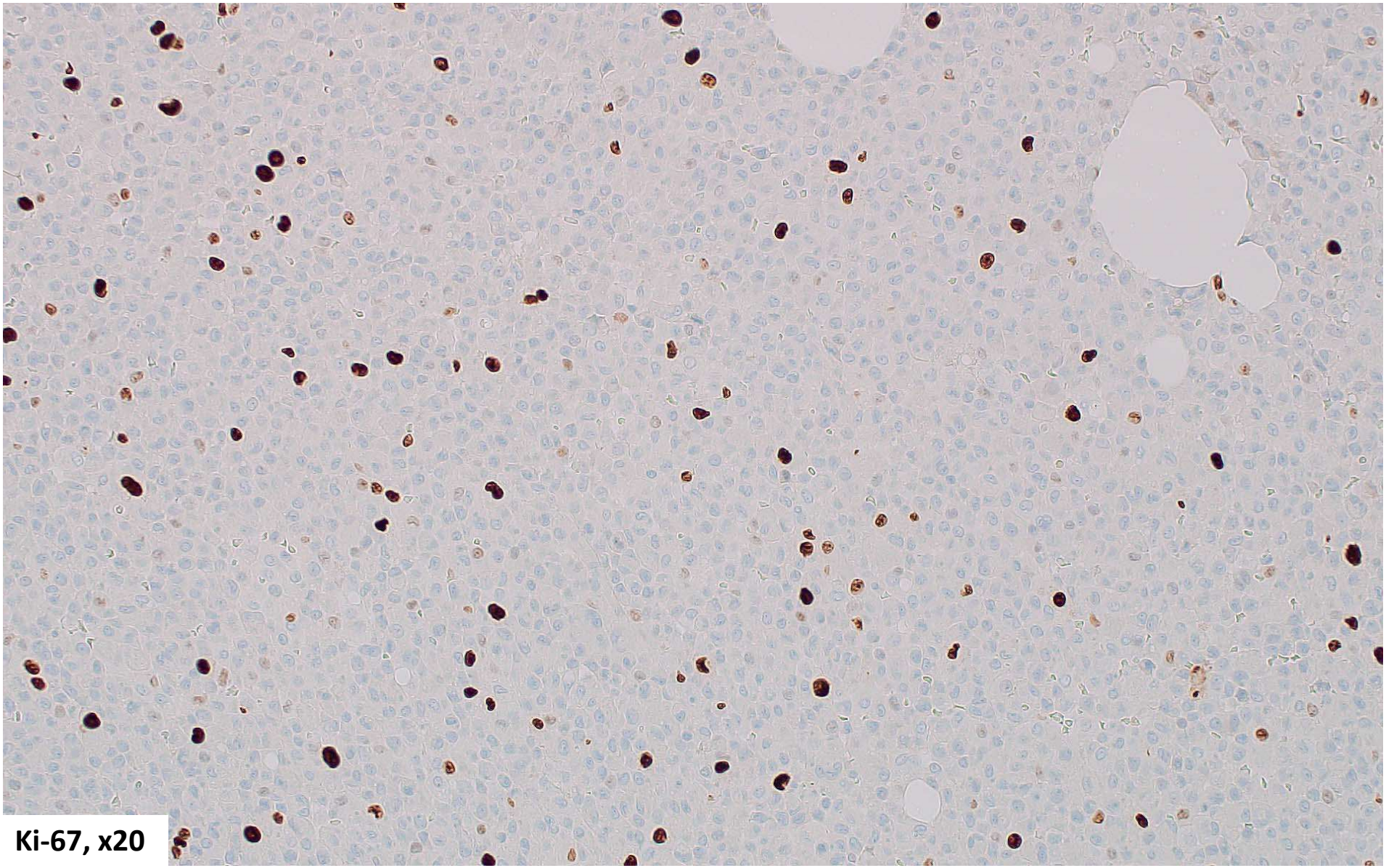
- ~~Langerhans cell histiocytosis~~
- ~~Myeloid sarcoma~~
- ~~Histiocytic sarcoma~~



Calreticulin, x40



AE1/AE3, x40



Ki-67, x20

Diagnosis

- Mesothelial/monocytic incidental cardiac excrescences (MICE)

Mesothelial/monocytic incidental cardiac excrescences

- Synonyms
  - Nodular mesothelial hyperplasia (NMH) by Rosai/Dehner
  - **Nodular histiocytic mesothelial hyperplasia** (**NHMH**) by JKC Chan
  - Nodular histiocytic aggregates
  - Nodular histiocytic hyperplasia
- Benign and reactive nature
- Pathogenesis
  - unknown
- Can occur in any age, gender or race group

Mesothelial/monocytic incidental cardiac excrescences (MICE)

- Usual sites
  - Mesothelial-lined surfaces: peritoneum, pericardium, pleura, hernia sac and spermatic cord
    - MICE: endocardial involvement of NHMH
  - Lung, urinary bladder, endometrium and endocardium
- Almost always incidental finding
- Gross finding
  - Brown-tan soft tissue excrescence
  - Size range: <1 mm to 3 cm

Mesothelial/monocytic incidental cardiac excrescences (MICE)

- Microscopic finding
  - Biphasic pattern composed of mildly to moderately pleomorphic cells (epithelioid, polygonal or ovoid cells with reniform or contorted nuclei, inconspicuous nucleoli with or without nuclear grooves and abundant cytoplasm) with distinct margins in cohesive clusters, and a lesser component of scattered, hyperchromatic and cuboidal cells
  - Lymphocytes and plasma cells can be seen, but no eosinophils
  - Mesothelial cells can be absent: entrapped?
- Immunohistochemistry
  - Histiocytes: CD4, CD68, CD163
  - Mesothelial cells: calretinin, WT-1, D2-40, CK5/6 and cytokeratin

Table 1
Common differential diagnoses of nodular histiocytic/mesothelial hyperplasia.

Differential Diagnosis (DDx)	DDx Features	NHMH
Neuroendocrine tumor	Lesional cells are keratin-positive, synaptophysin- and/or chromogranin- positive.	Constituting cells are of histiocytic and mesothelial origin, synaptophysin- and chromogranin negative
Hematolymphoid malignancy	Histomorphology and immunoprofile is dependent on the classification of leukemia/ lymphoma	Constituting cells are of histiocytic and mesothelial origin.
Malignant mesothelioma	Bulky disease with stromal invasion, complex architecture, and necrosis may be seen, proliferating cells are of mesothelial origin, loss of BAP1 immunoexpression [12]	Usually microscopic lesion without stromal invasion, nodular growth, mixed with histiocytic component, intact BAP1 expression
Well-differentiated papillary mesothelioma	Bland mesothelial cells arranged in a predominantly papillary pattern with or without focal glandular/ tubular/nesting pattern. PAX8 immunohistochemistry shows at least partial staining in most cases [13]	Predominant nodular growth pattern mixed with histiocytic component, PAX8-negative

Contents lists available at ScienceDirect

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Review

Nodular histiocytic/mesothelial hyperplasia, a benign entity posing diagnostic challenge

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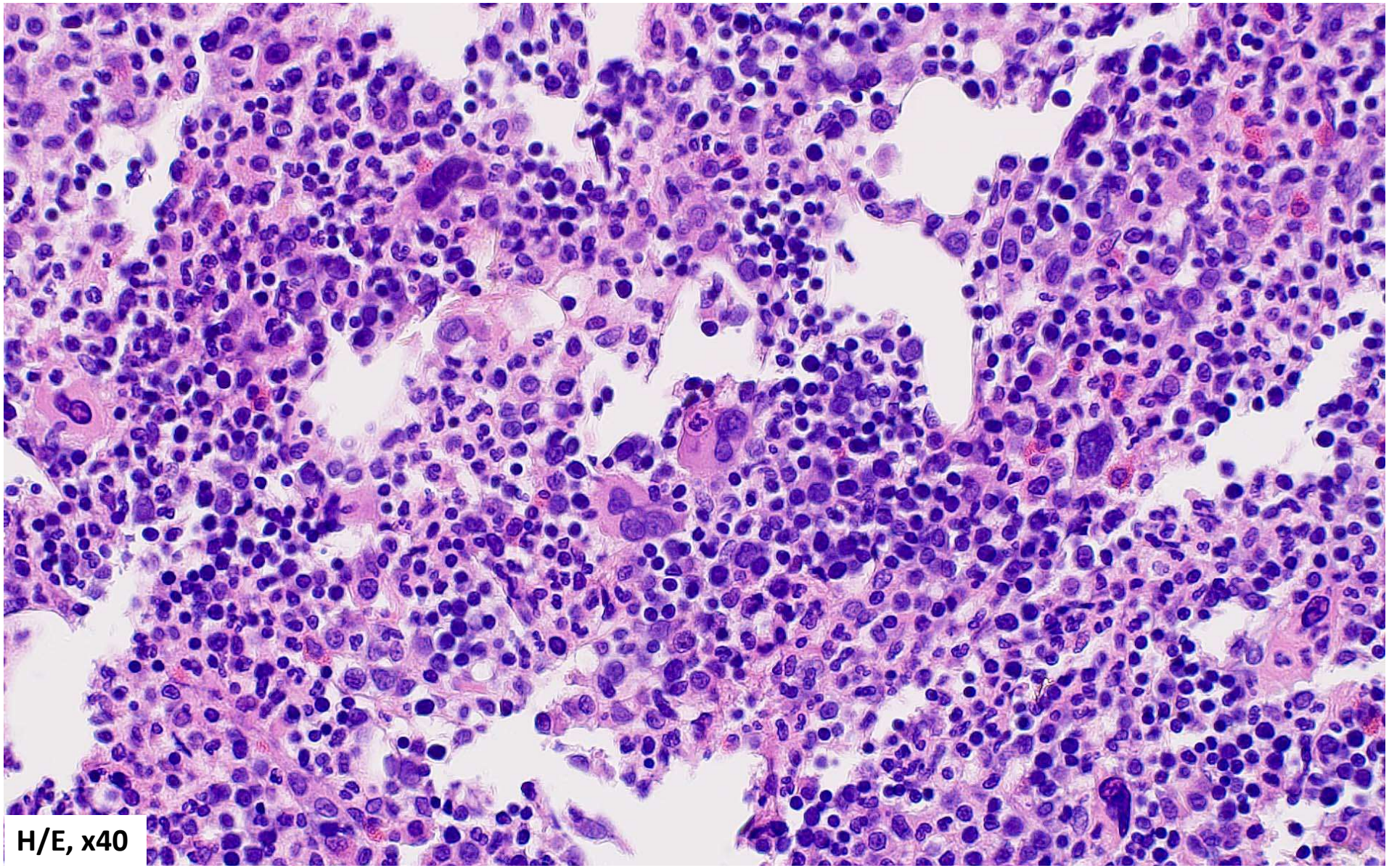
Case 2

- 23-year-old man
- Leukopenia and thrombocytopenia for 4 years
- Complains of occasional epistaxis and easy bruising
- Hgb: 16.7 d/dL
- WBC: 2.5 x 10^9/L
- Platelet: 89 x 10^9/L
- Hepatomegaly (17.7 cm) and splenomegaly (15.2 cm)
- Vitamin B12: 2,841 pg/mL (reference: 232 -1,245 pg/mL)



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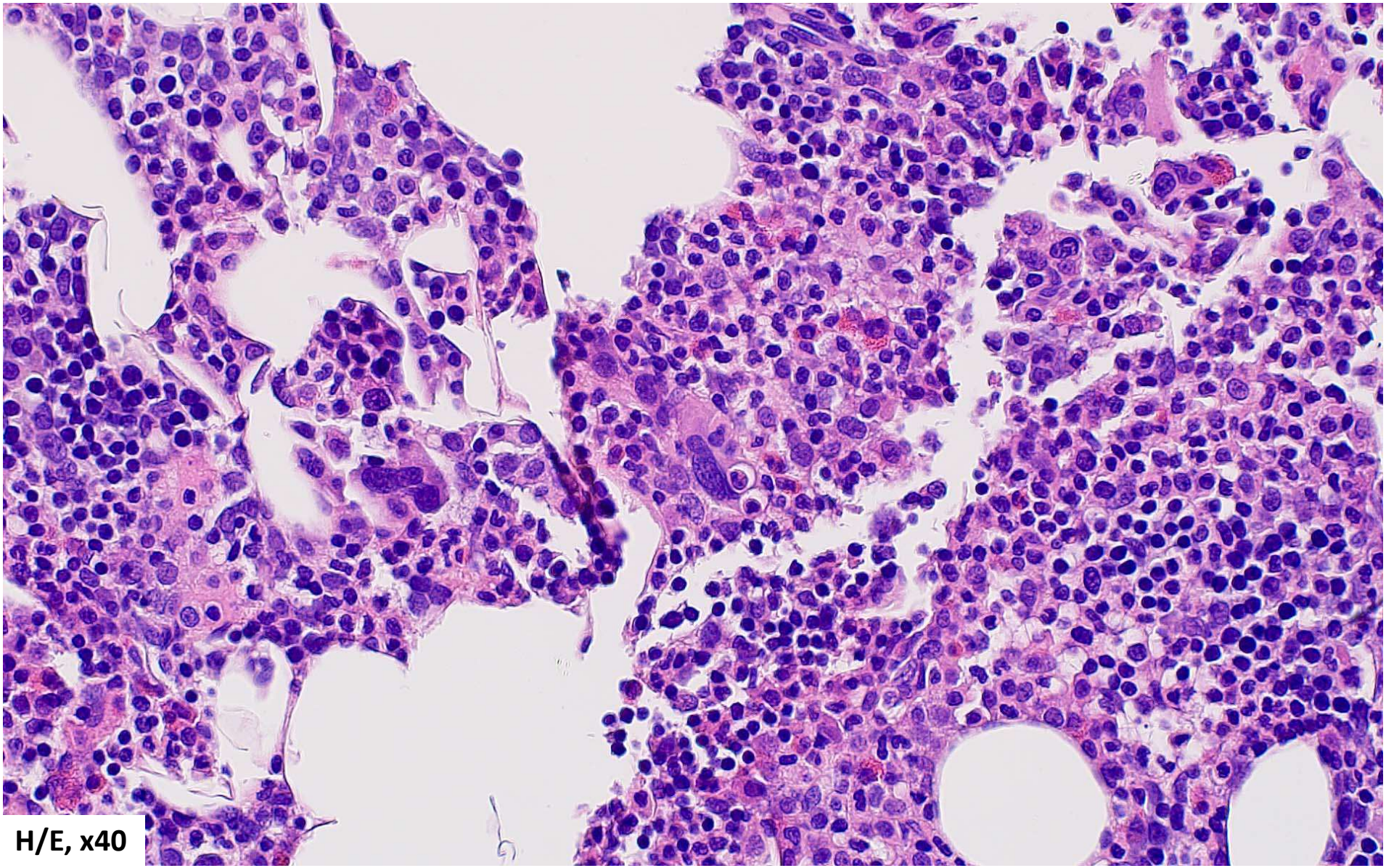

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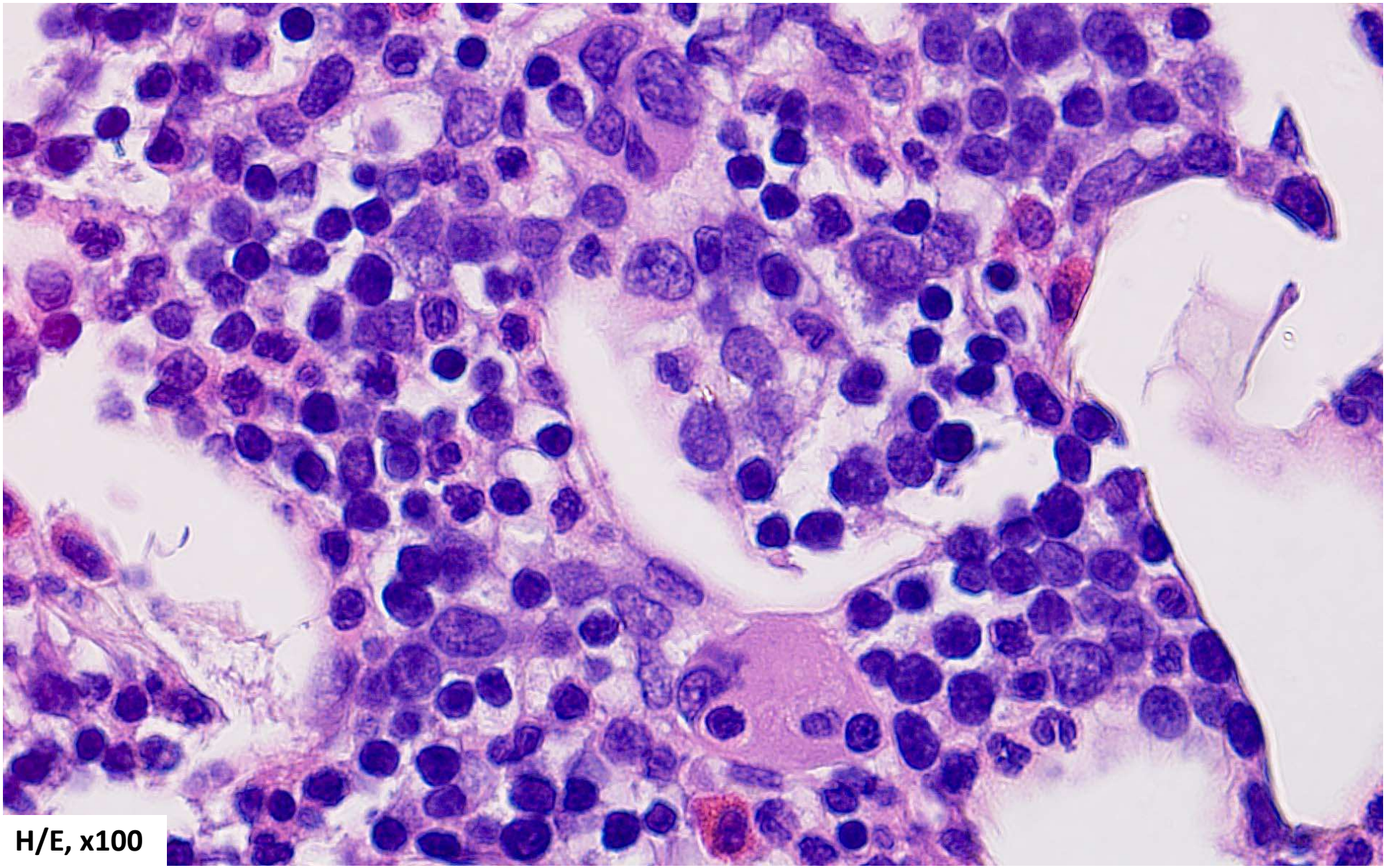

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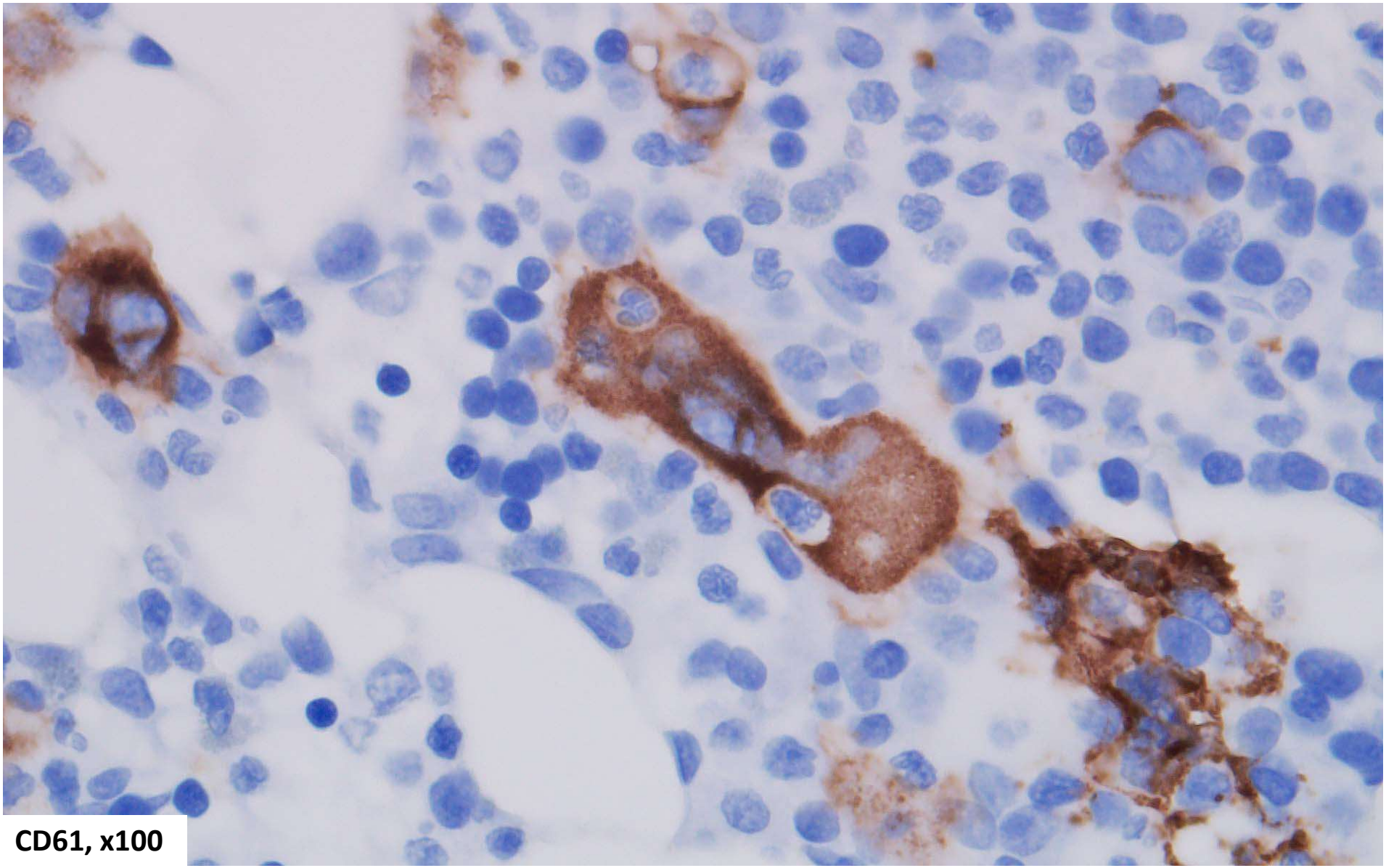
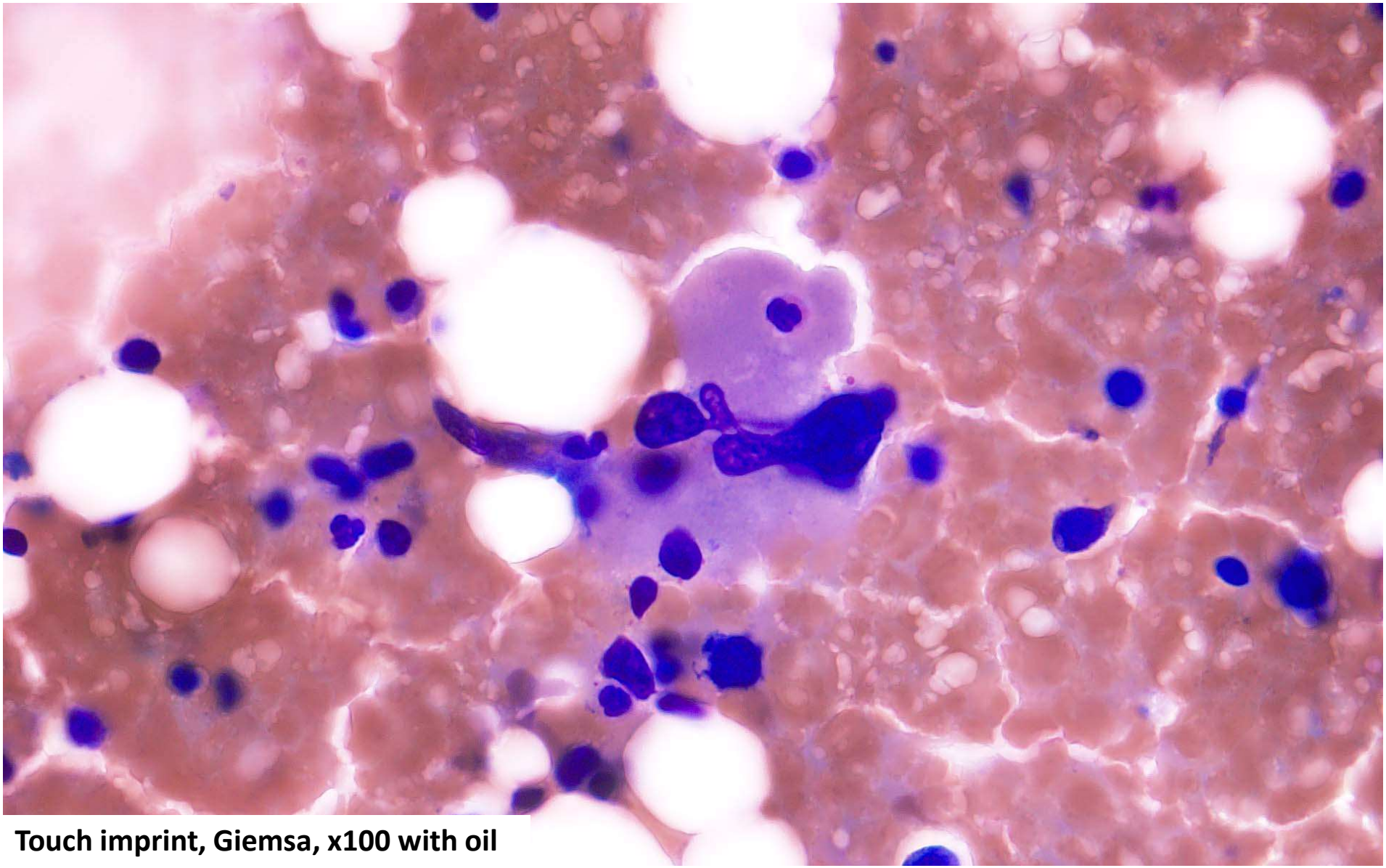
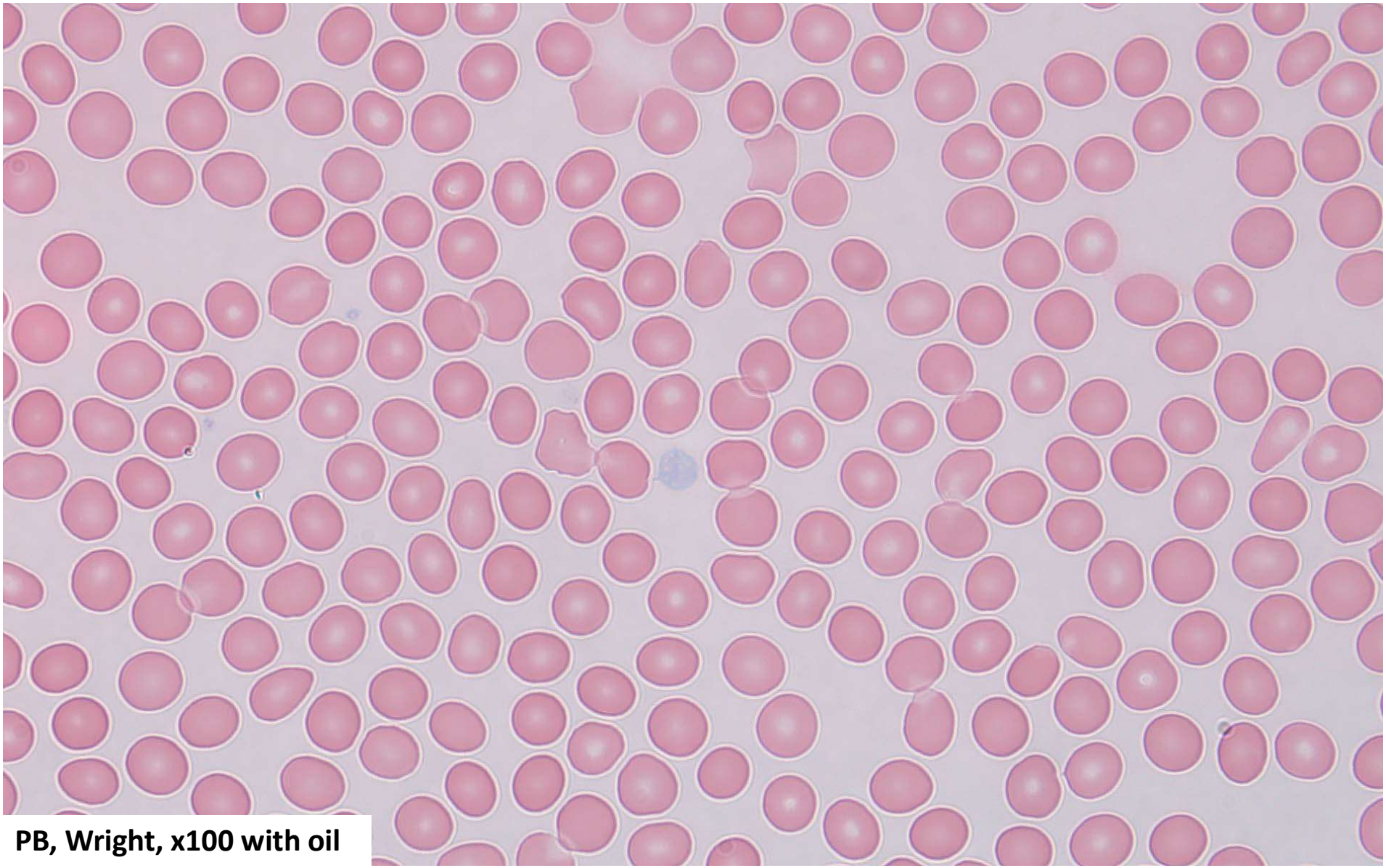


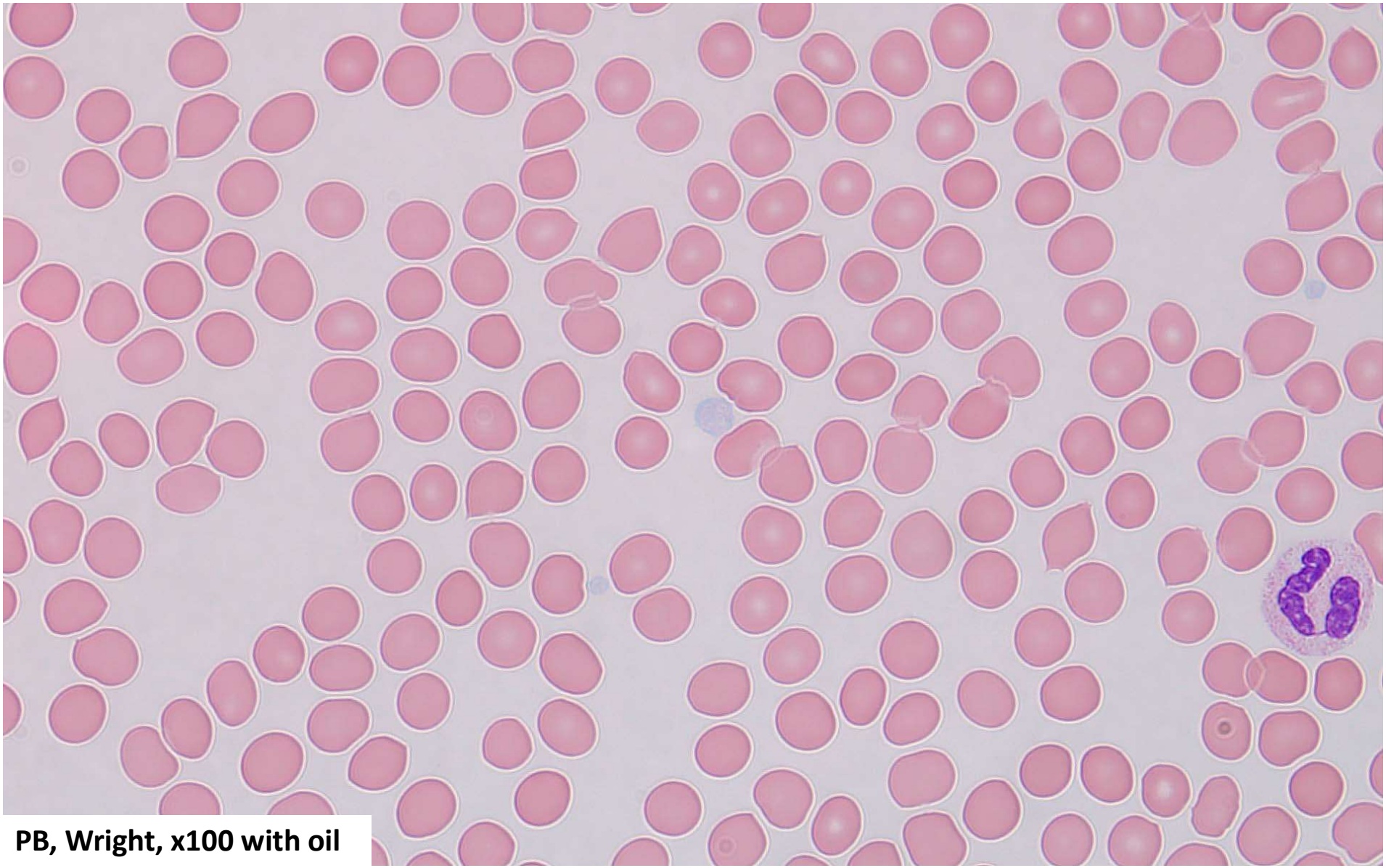
CD61, x100



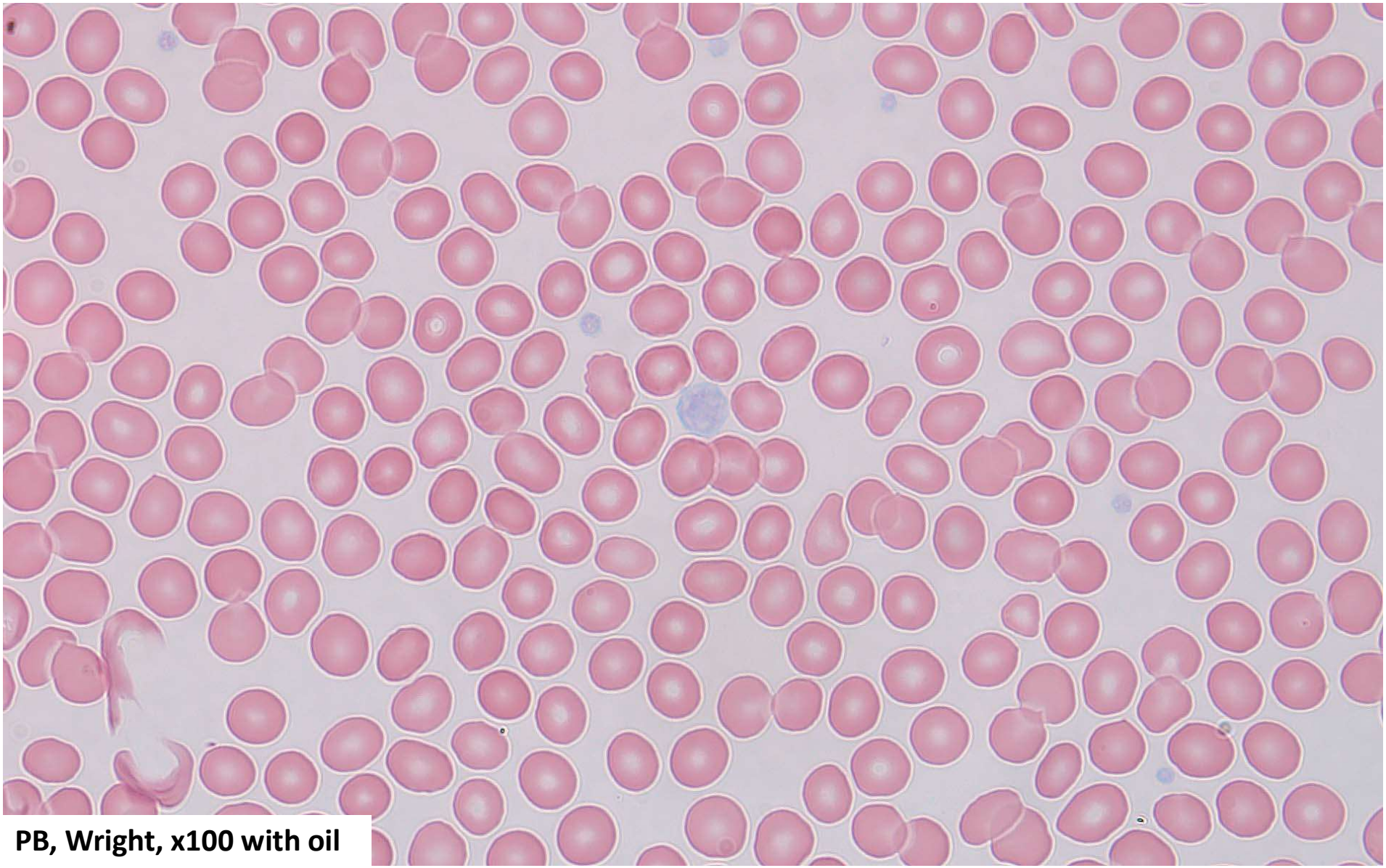
Touch imprint, Giemsa, x100 with oil



PB, Wright, x100 with oil



PB, Wright, x100 with oil



PB, Wright, x100 with oil

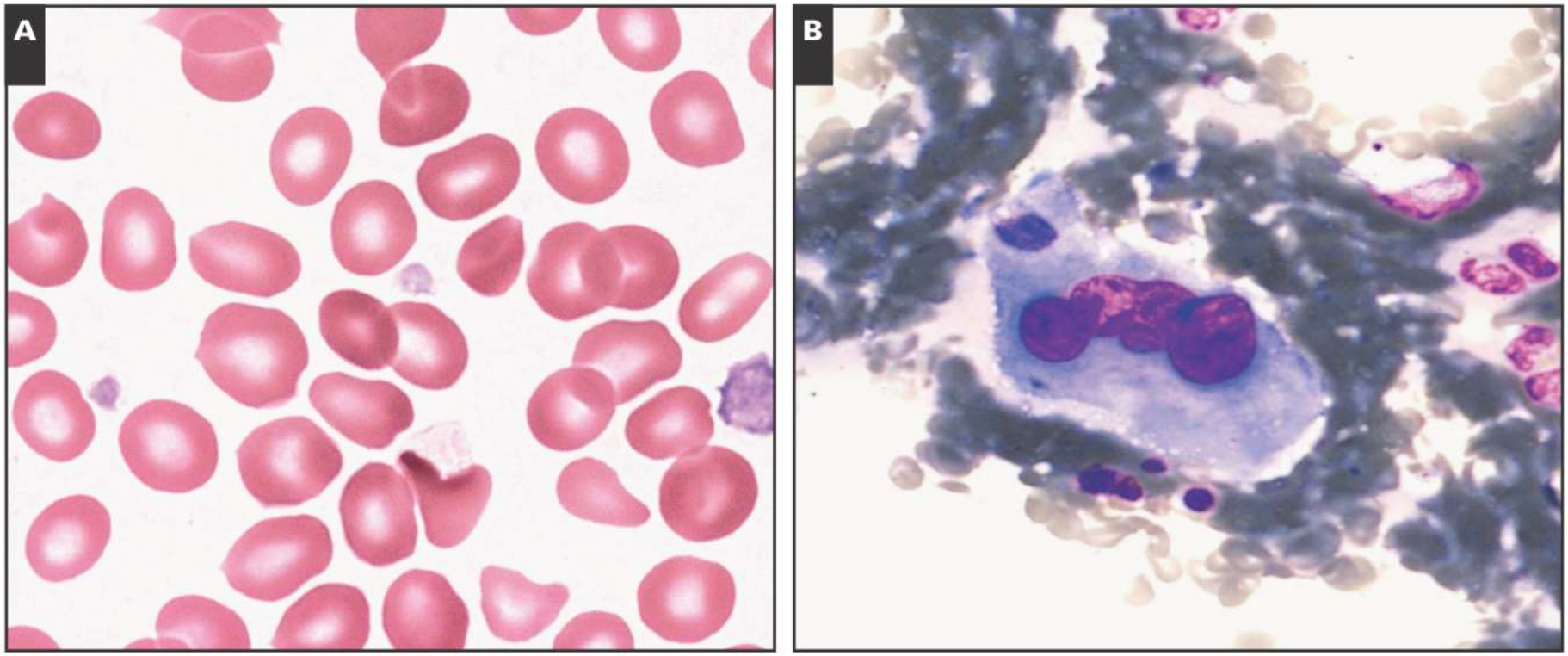
Differential Diagnosis for macrothrombocytopenia

- Bernard-Soulier syndrome
- Gray platelet syndrome
- May-Hegglin anomaly

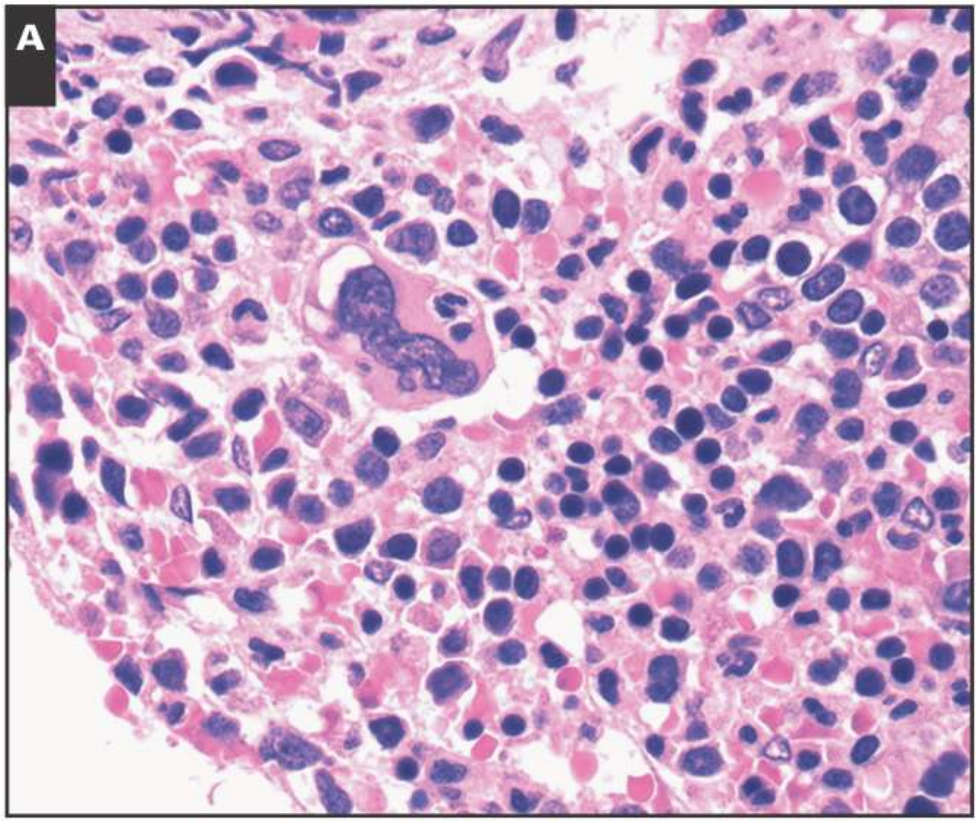
Gray platelet syndrome (OMIM #139090)

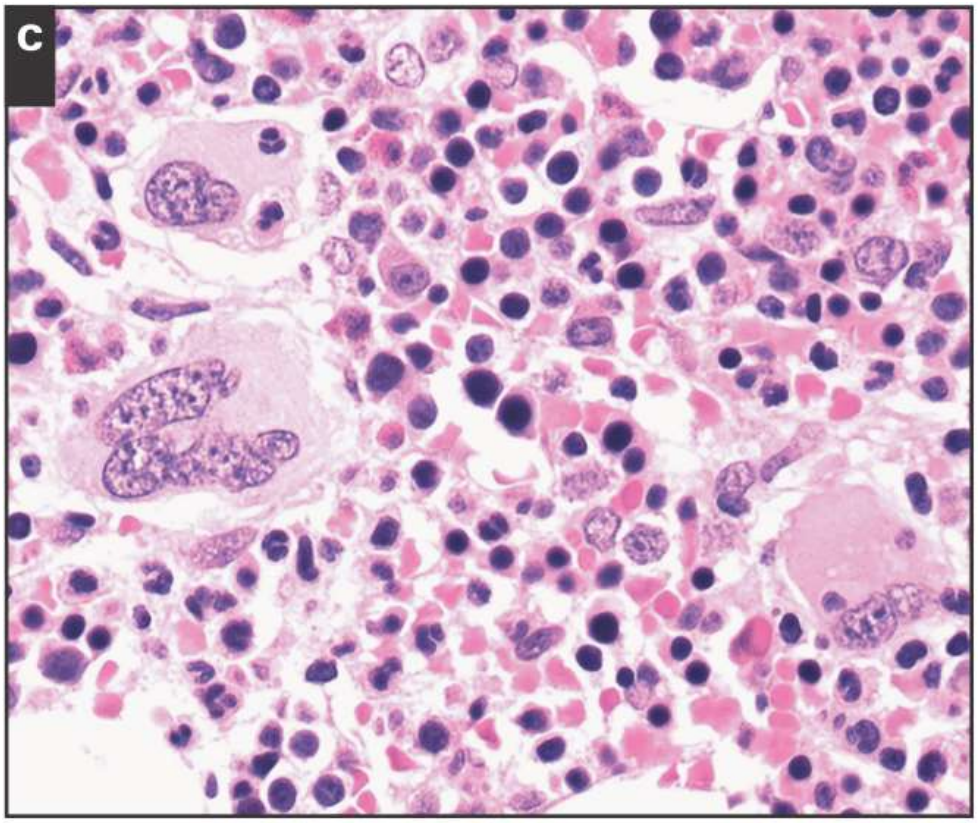
- Autosomal recessive disorder
- Moderate macrothrombocytopenia
- Marked decrease or absence of platelet alpha-granules
- Mild to moderate bleeding
- Splenomegaly
- Bone marrow fibrosis
- Elevated vitamin B12
- *NBEAL2* mutations

Gray platelet syndrome



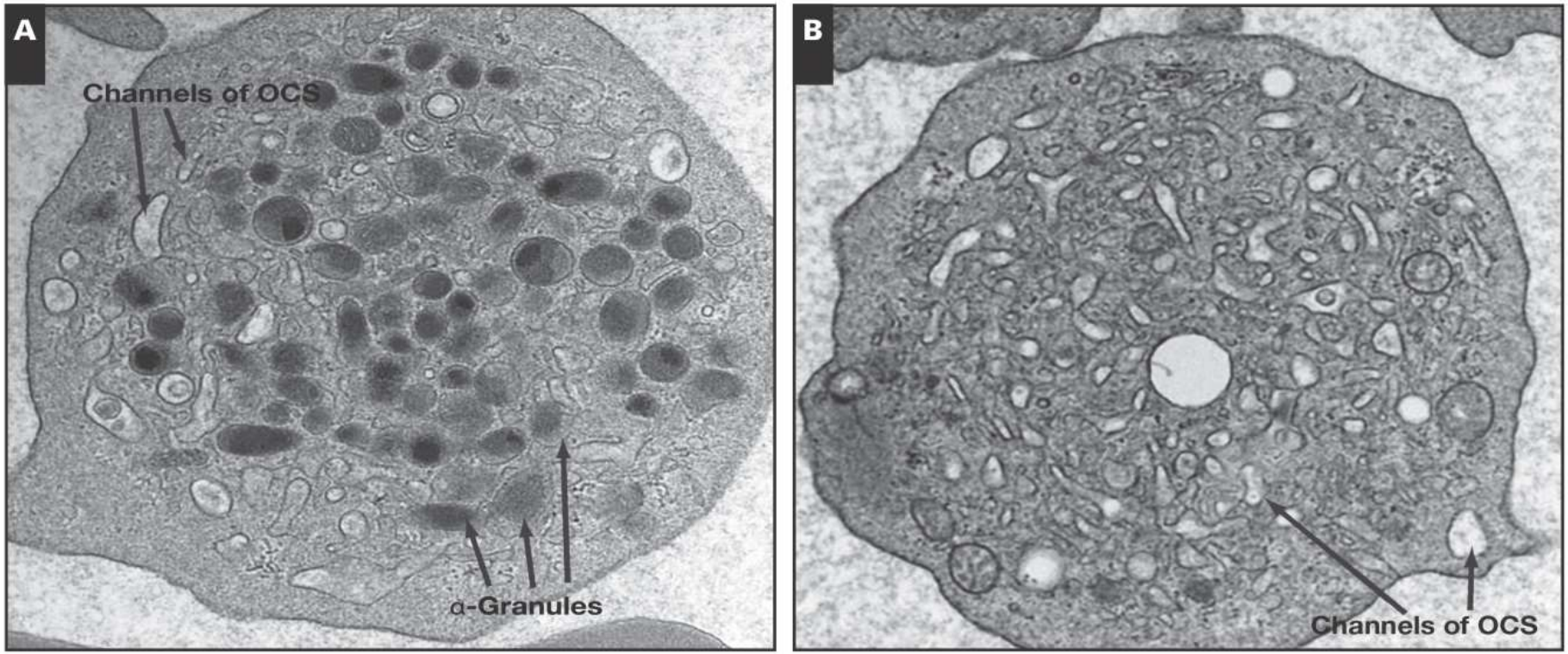
Gray platelet syndrome





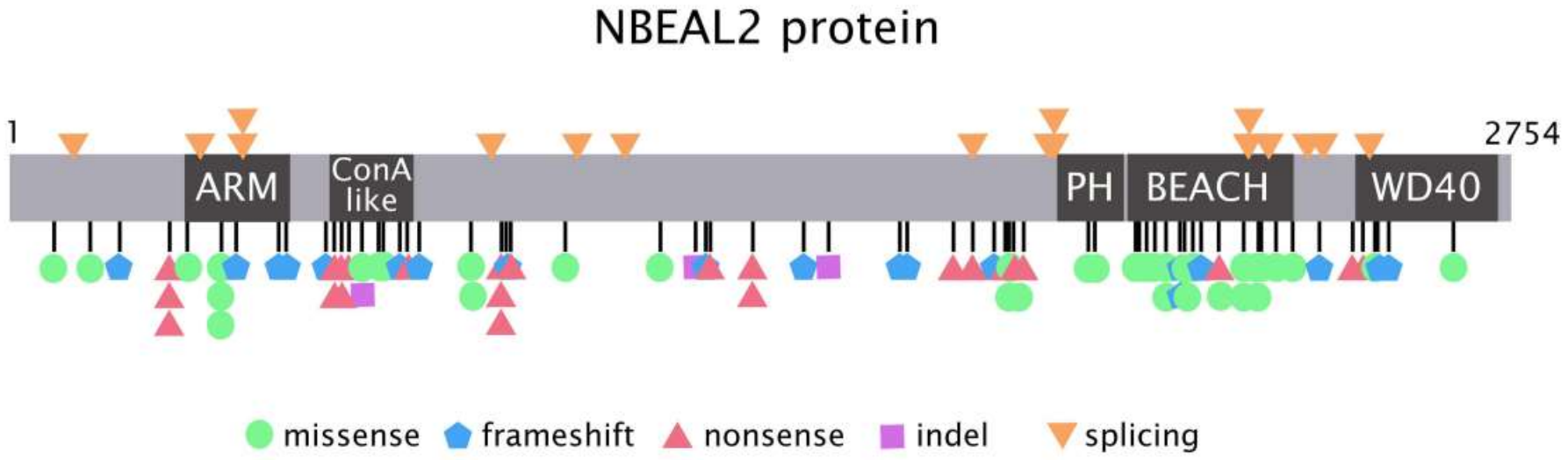
Am J Clin Pathol. 2021 Jul 6;156(2):253-258.

Gray platelet syndrome



Am J Clin Pathol. 2021 Jul 6;156(2):253-258.

Gray platelet syndrome

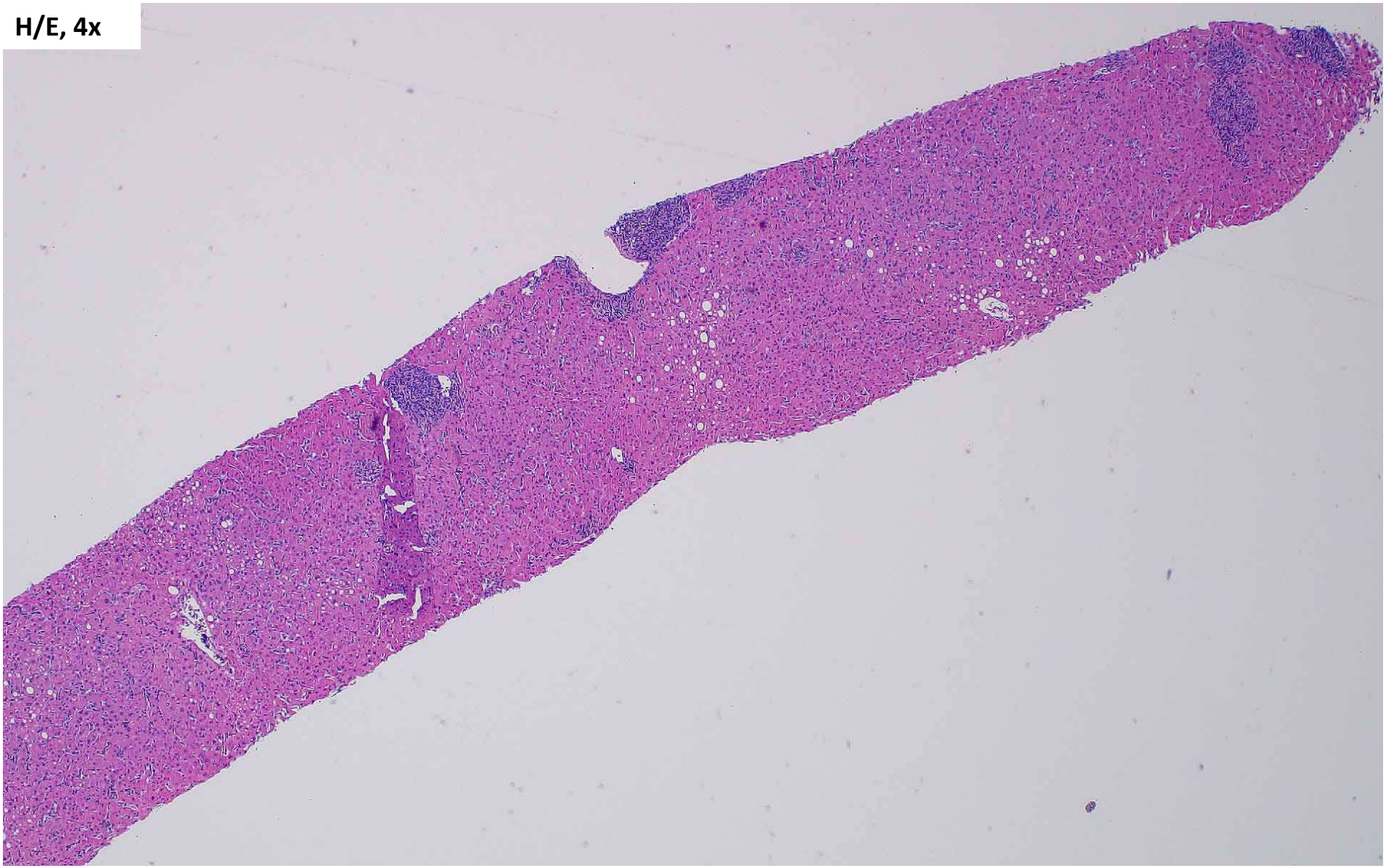


J Blood Med. 2021 Aug 11:12:719-732

Case 3

- 60 y/o man
- Drenching night sweat, fever, persistent N/V for 1 month
- CT scan
  - Hepatomegaly (23 cm) without mass or biliary ductal dilation
  - Splenomegaly (23%) with multiple infarcts
  - Adenopathy in the mediastinum, right hilum, retroperitoneum, porta hepatis
- PET-CT
  - Diffuse adenopathy
  - Splenomegaly
  - Small-to-moderate left pleural effusion
- Liver biopsy and bone marrow biopsy

H/E, 4x



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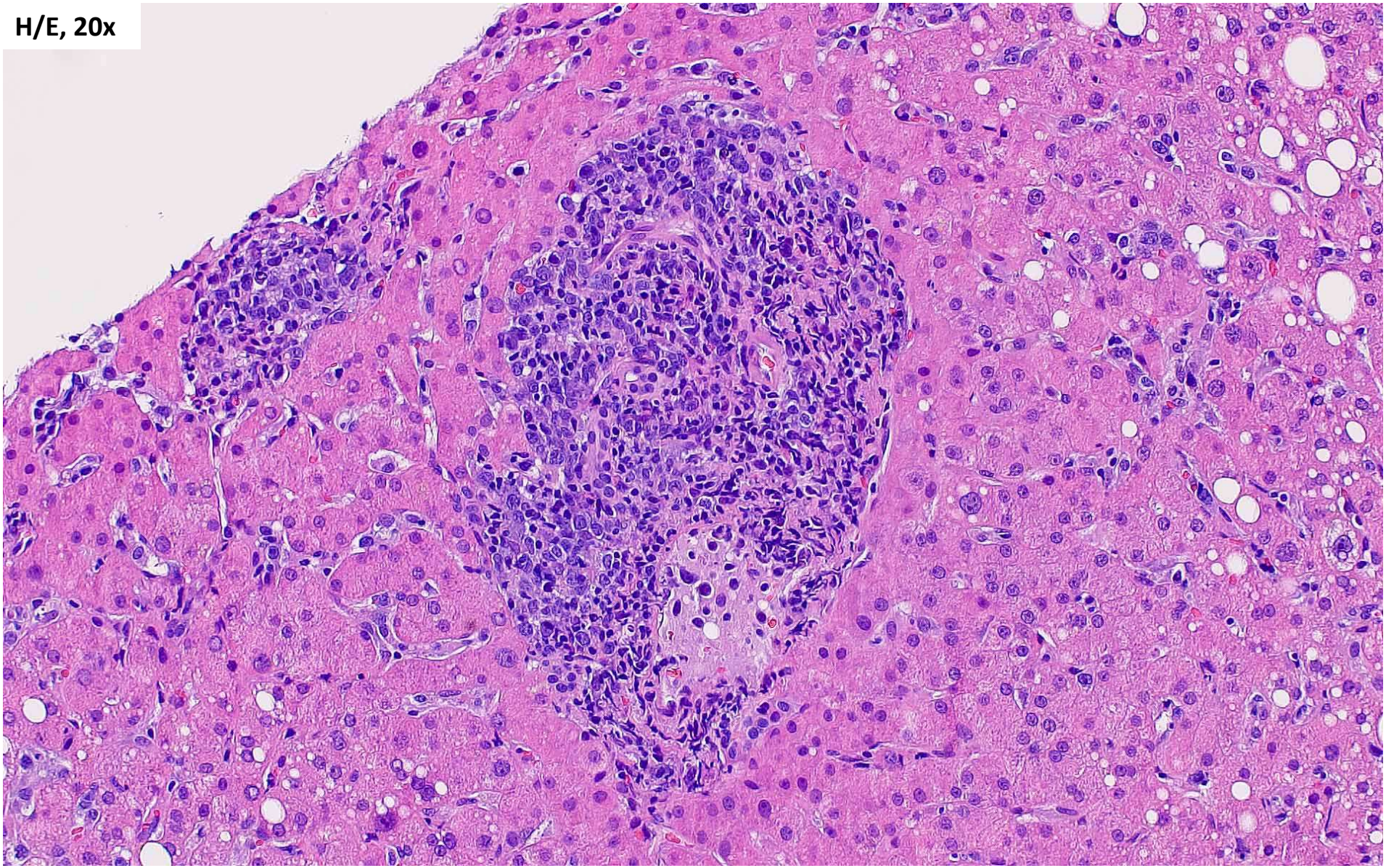

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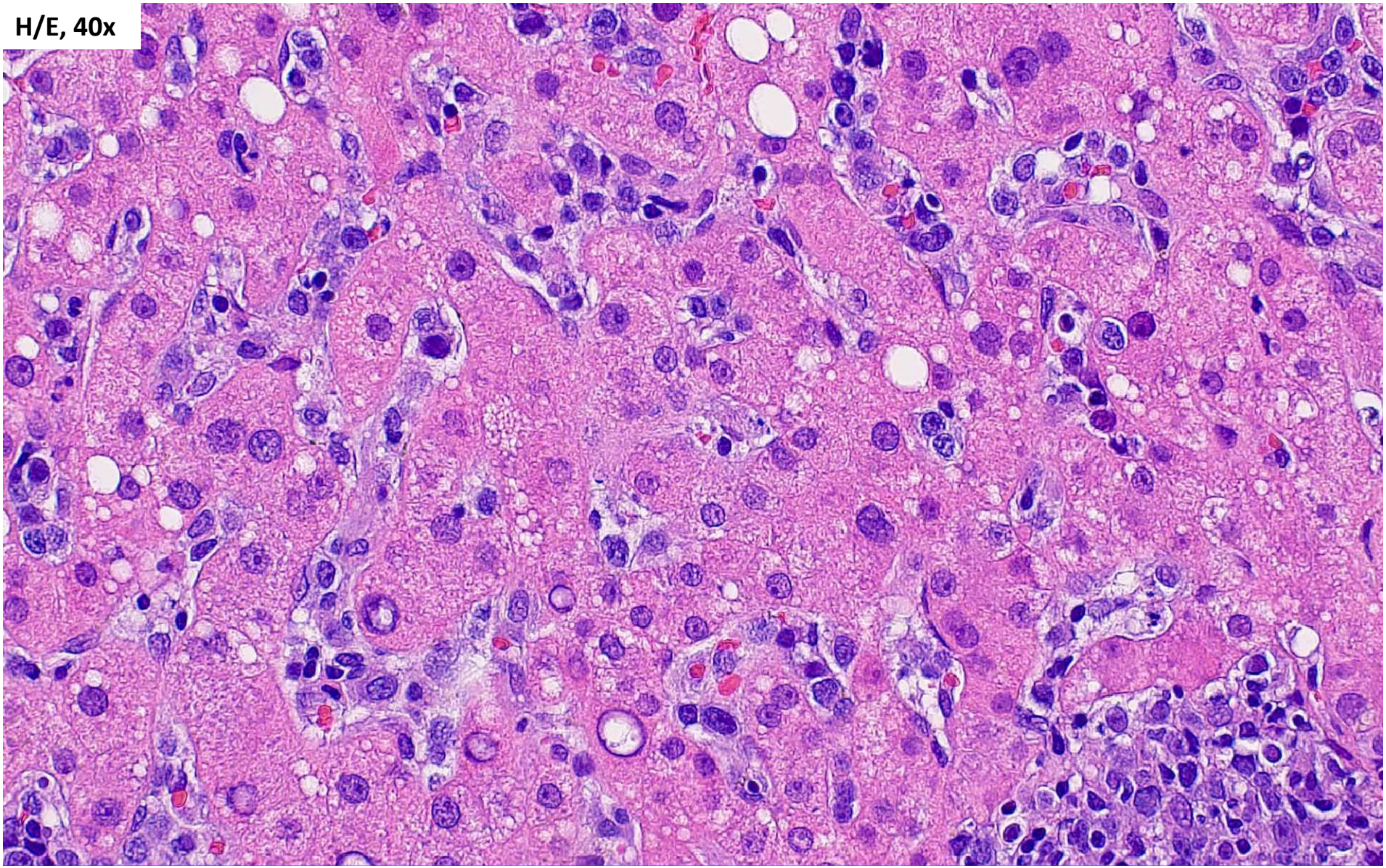

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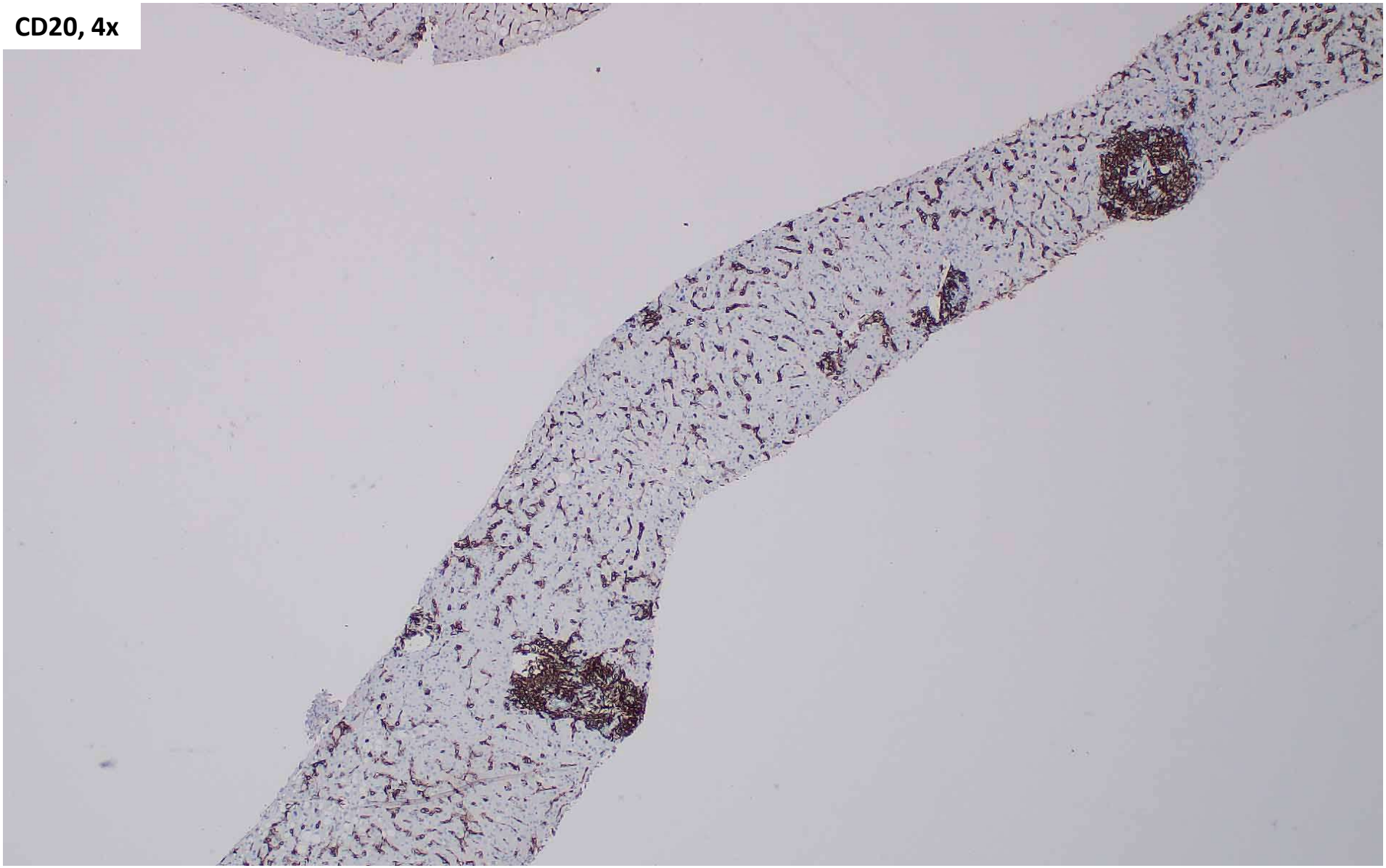

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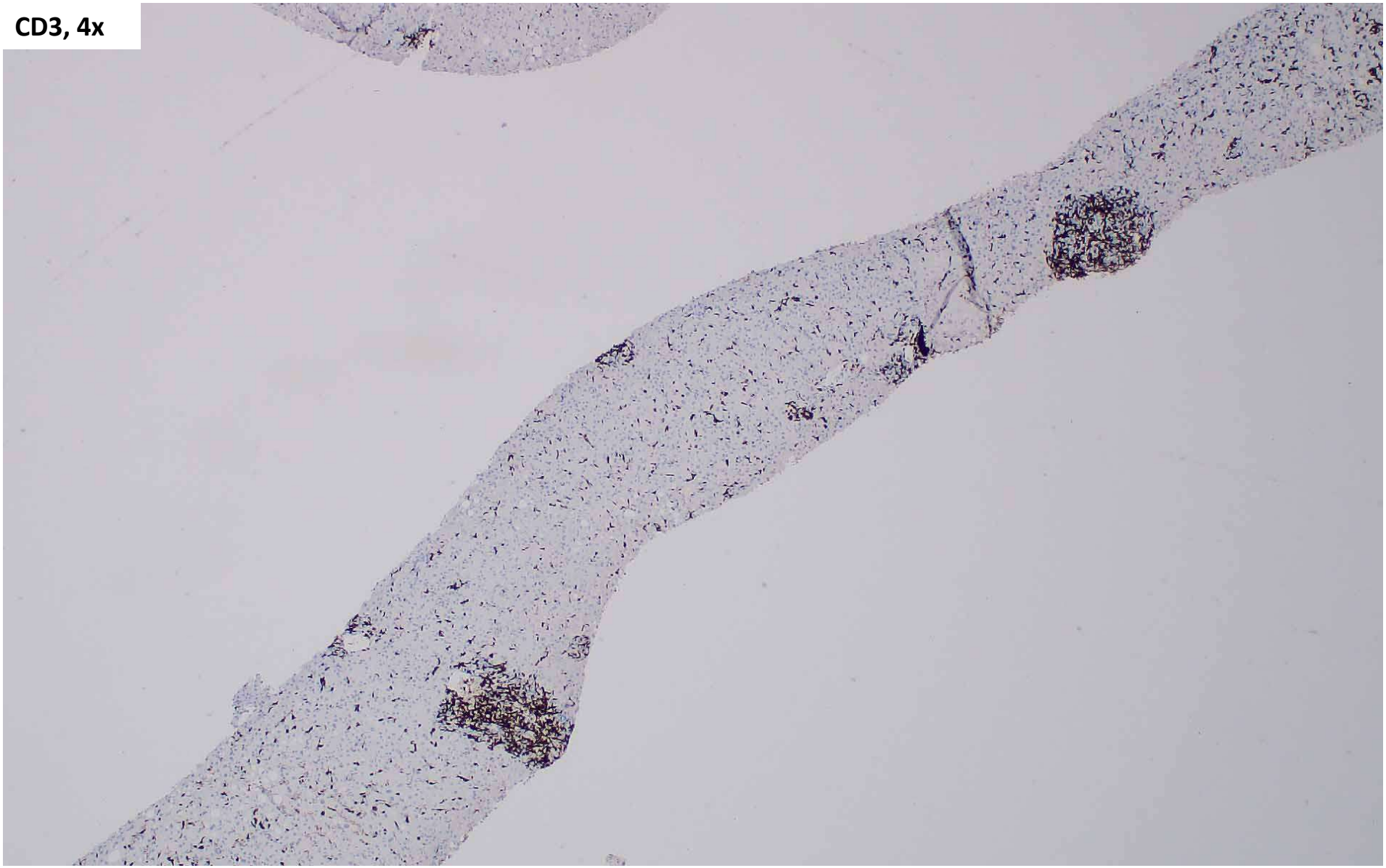

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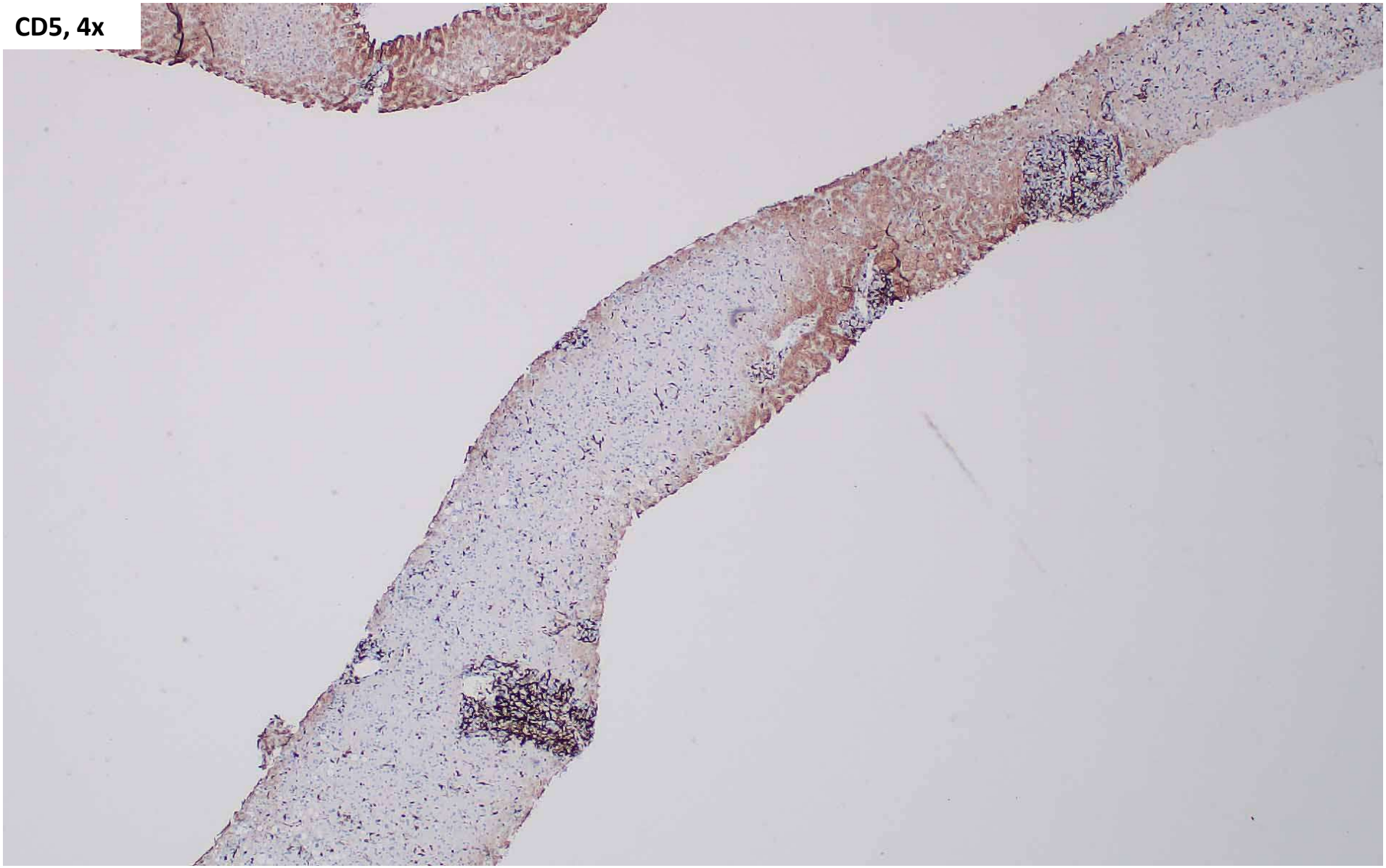

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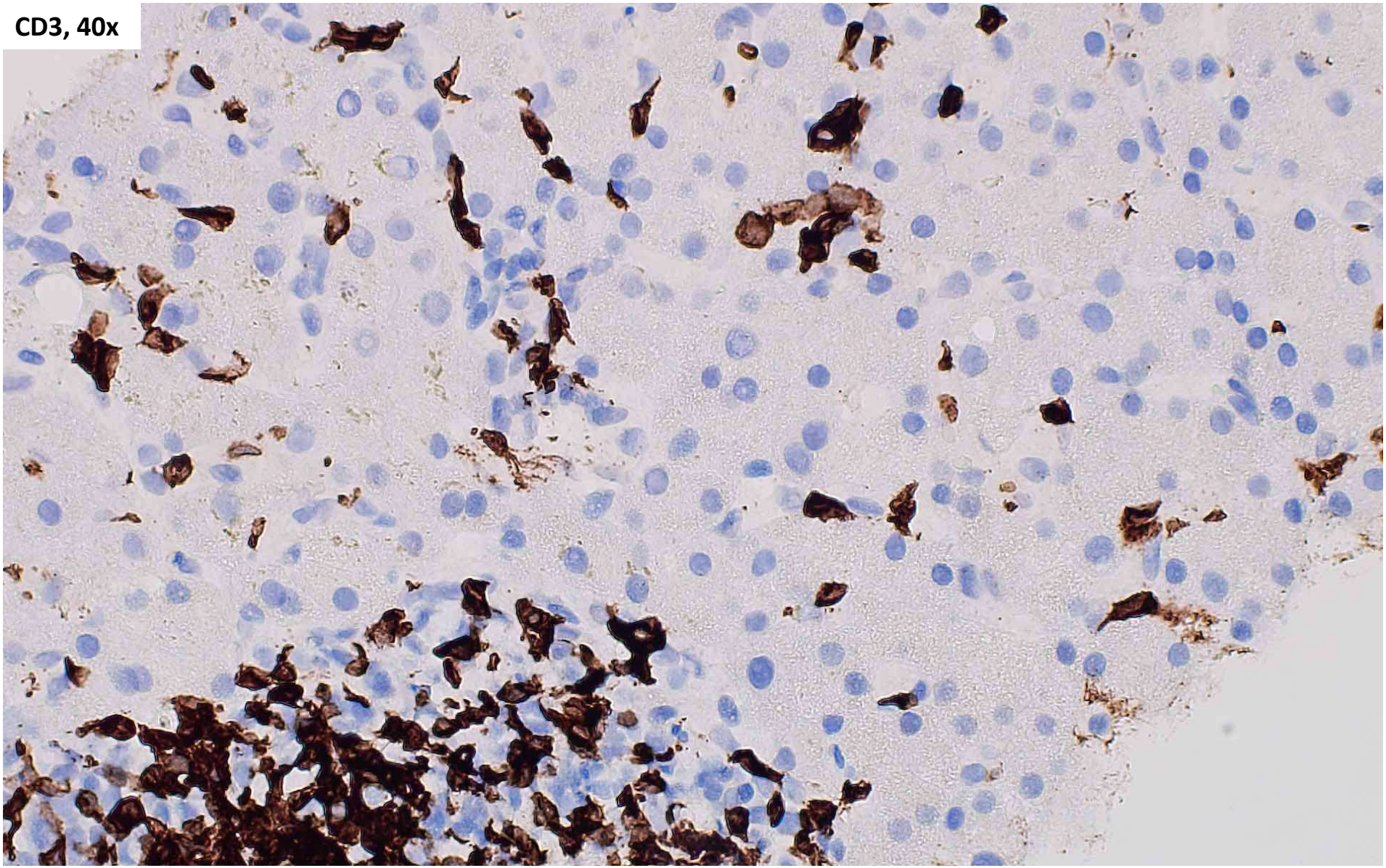

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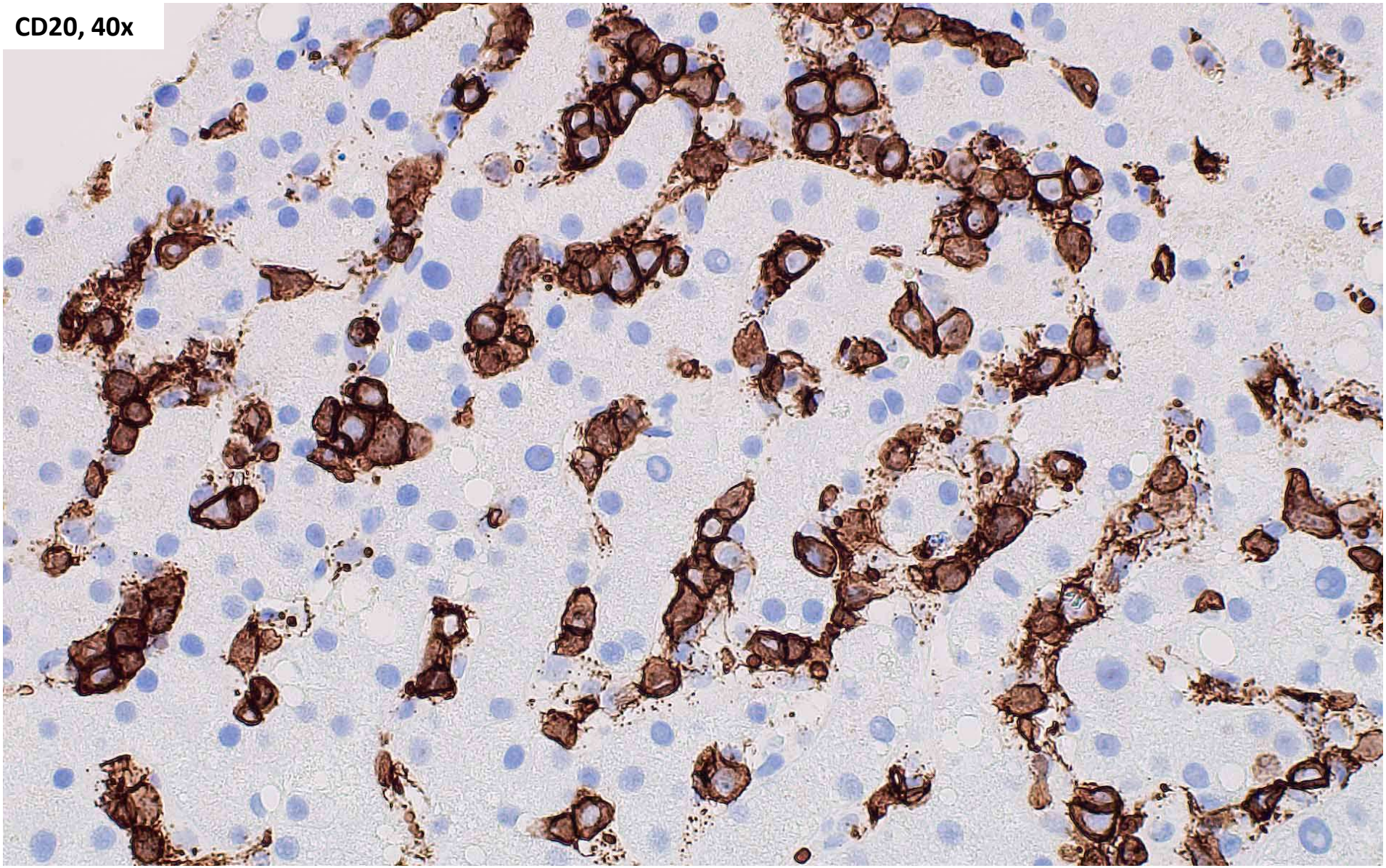
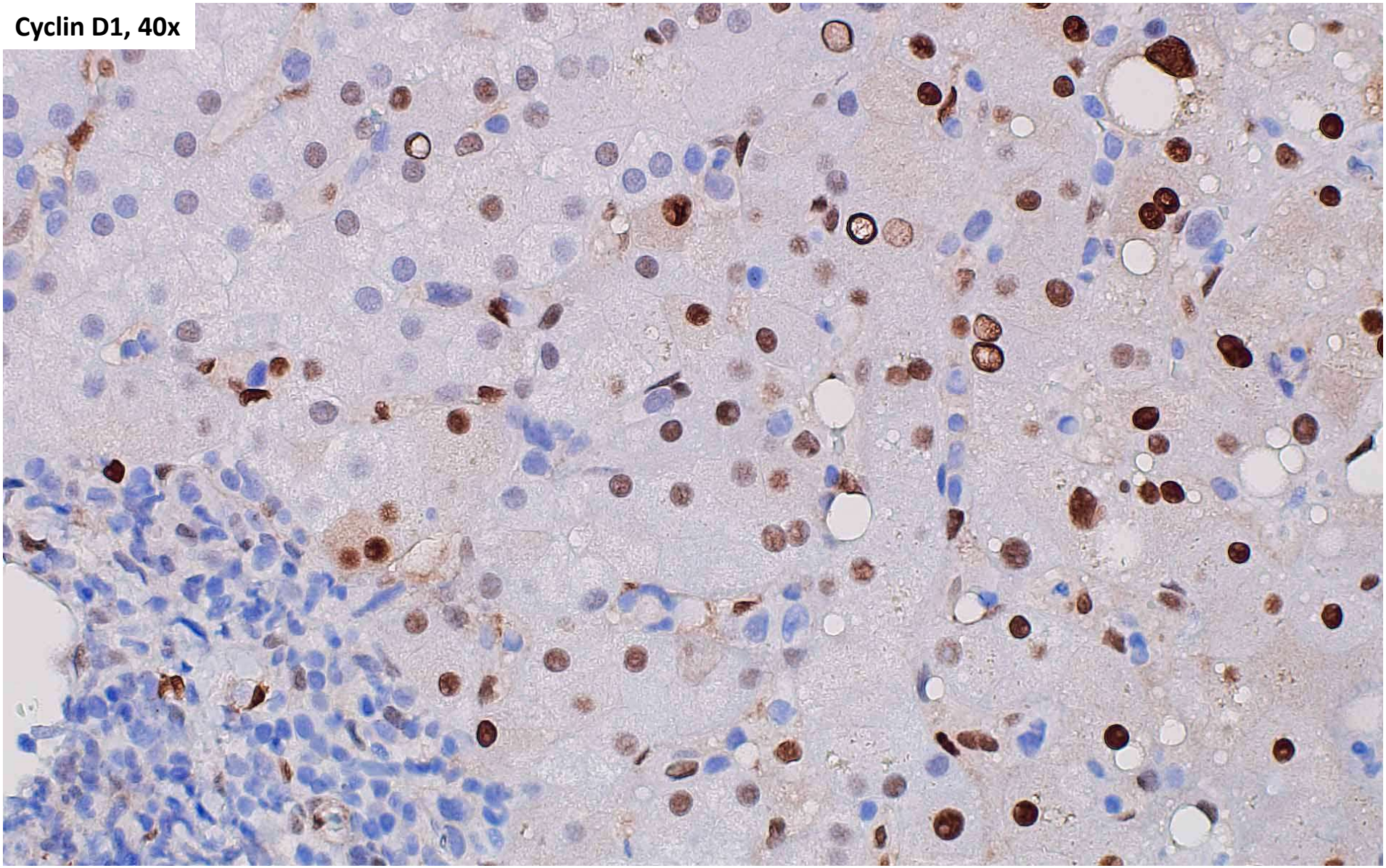
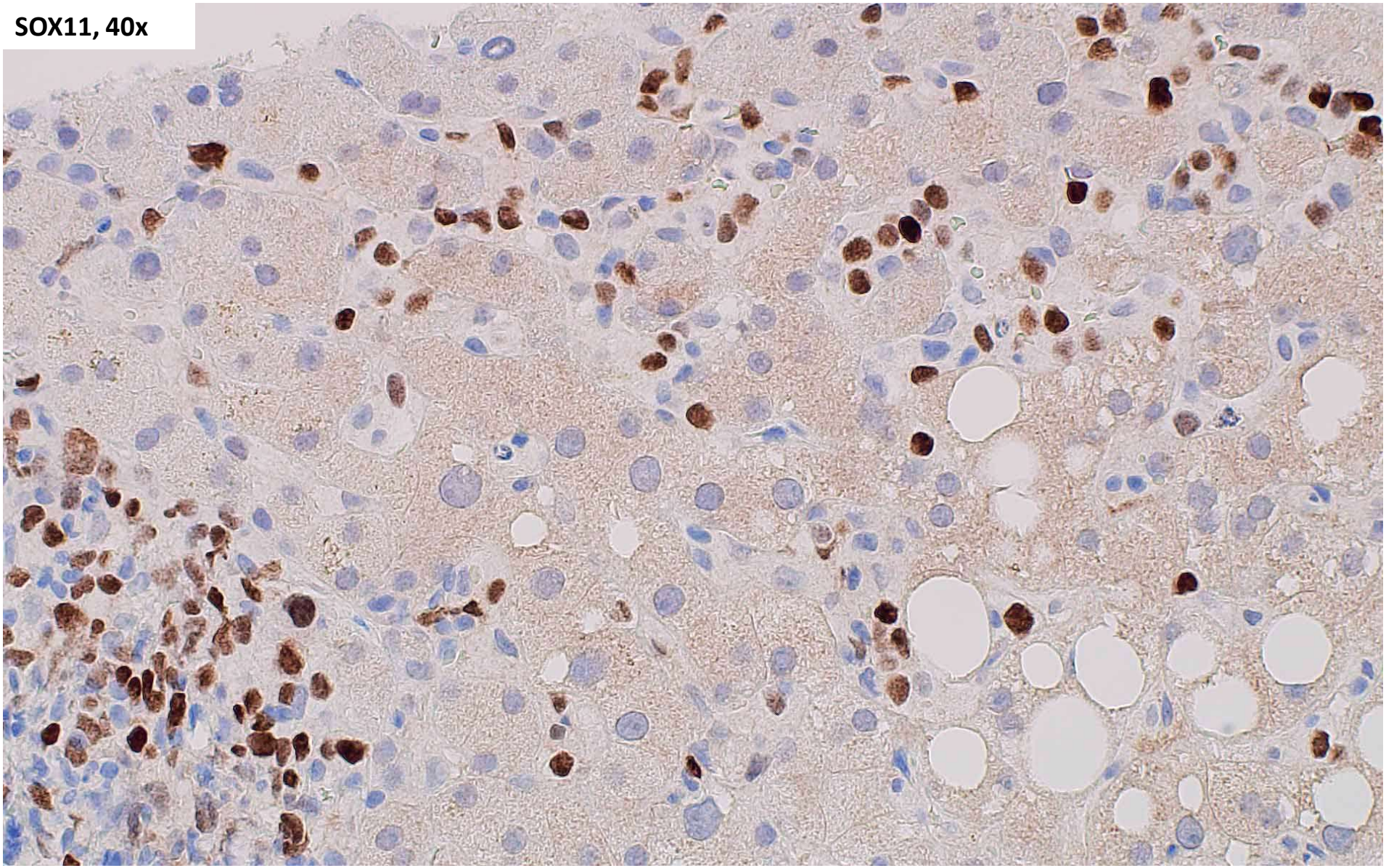


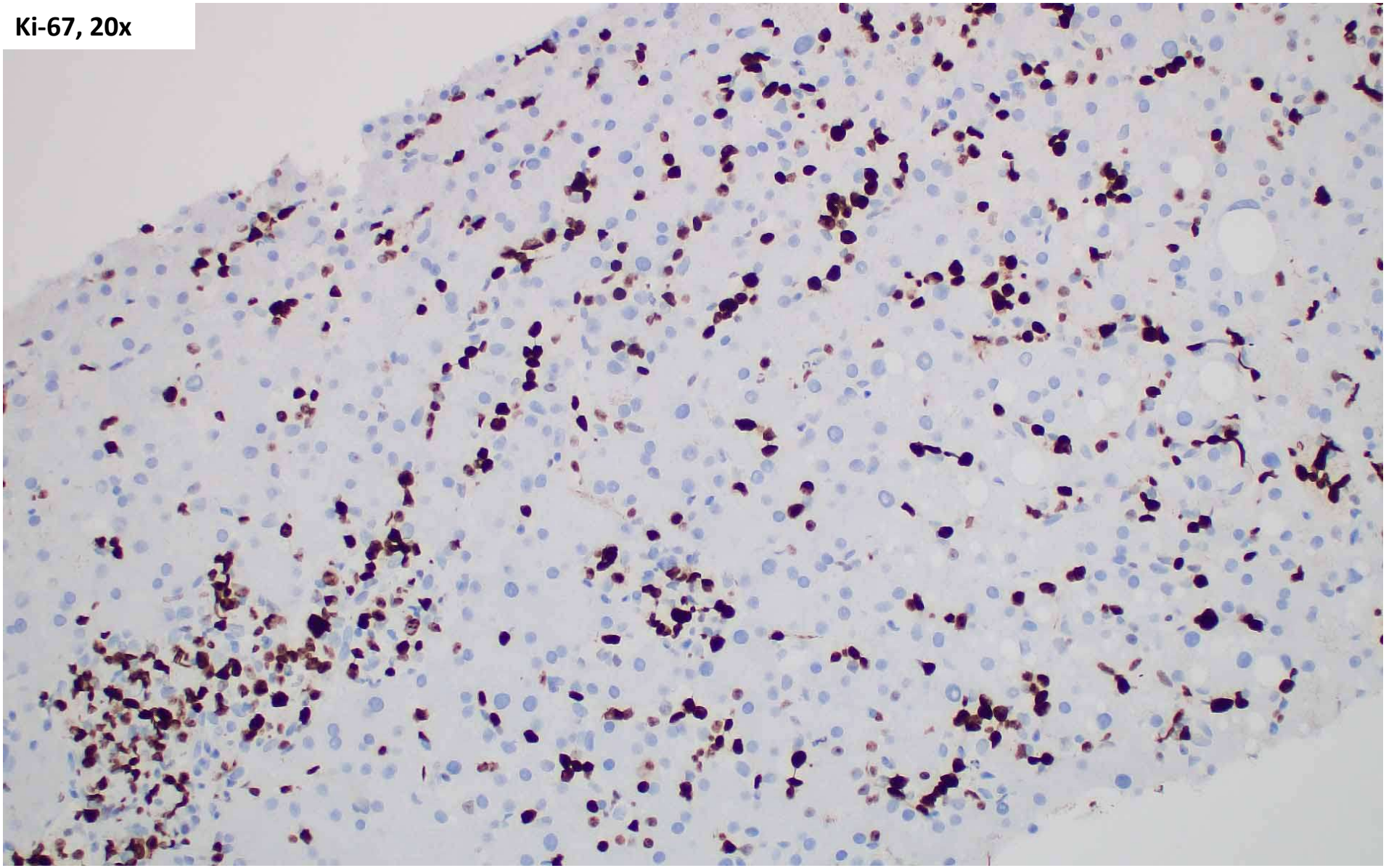
Cyclin D1, 40x



SOX11, 40x

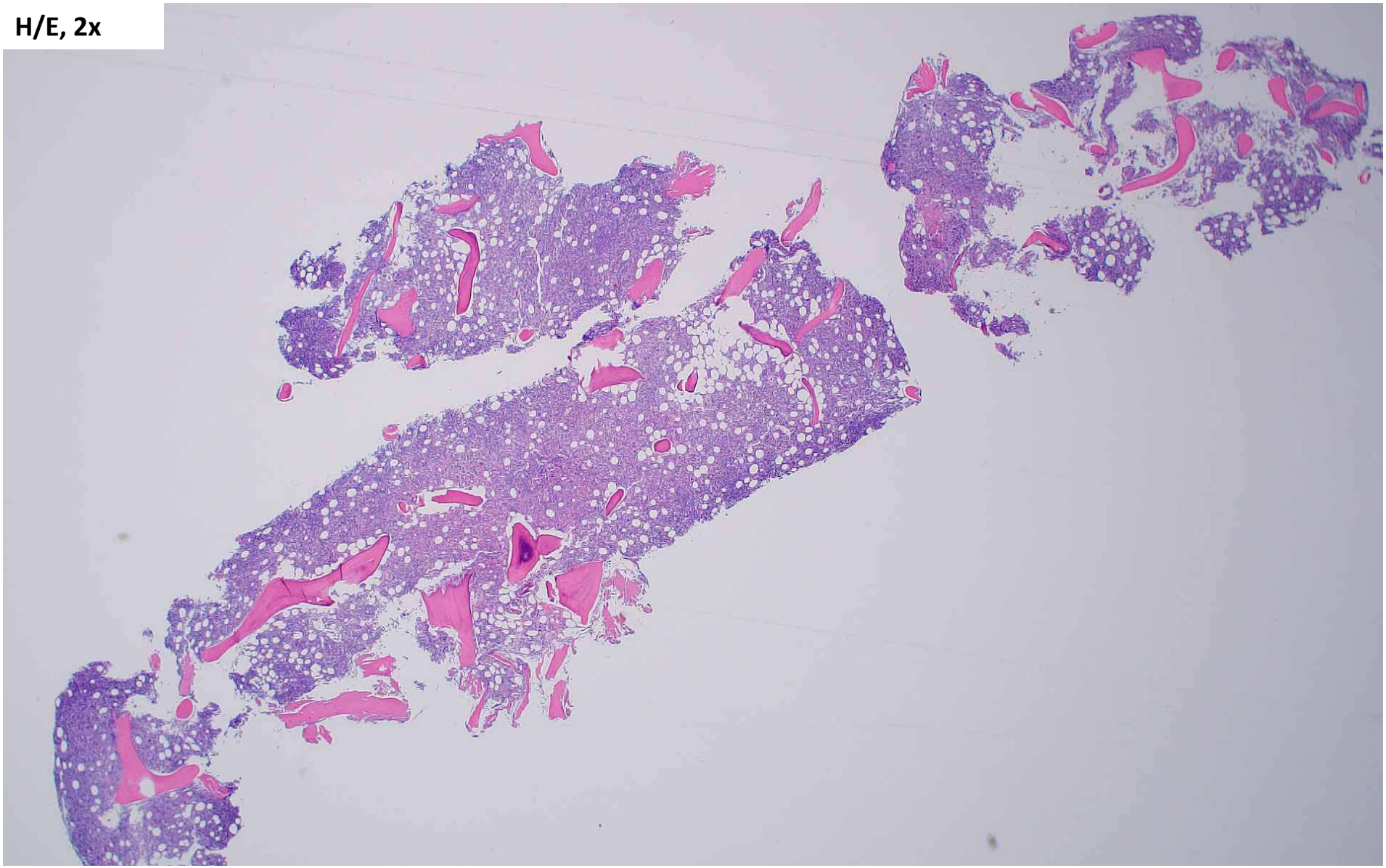


Ki-67, 20x

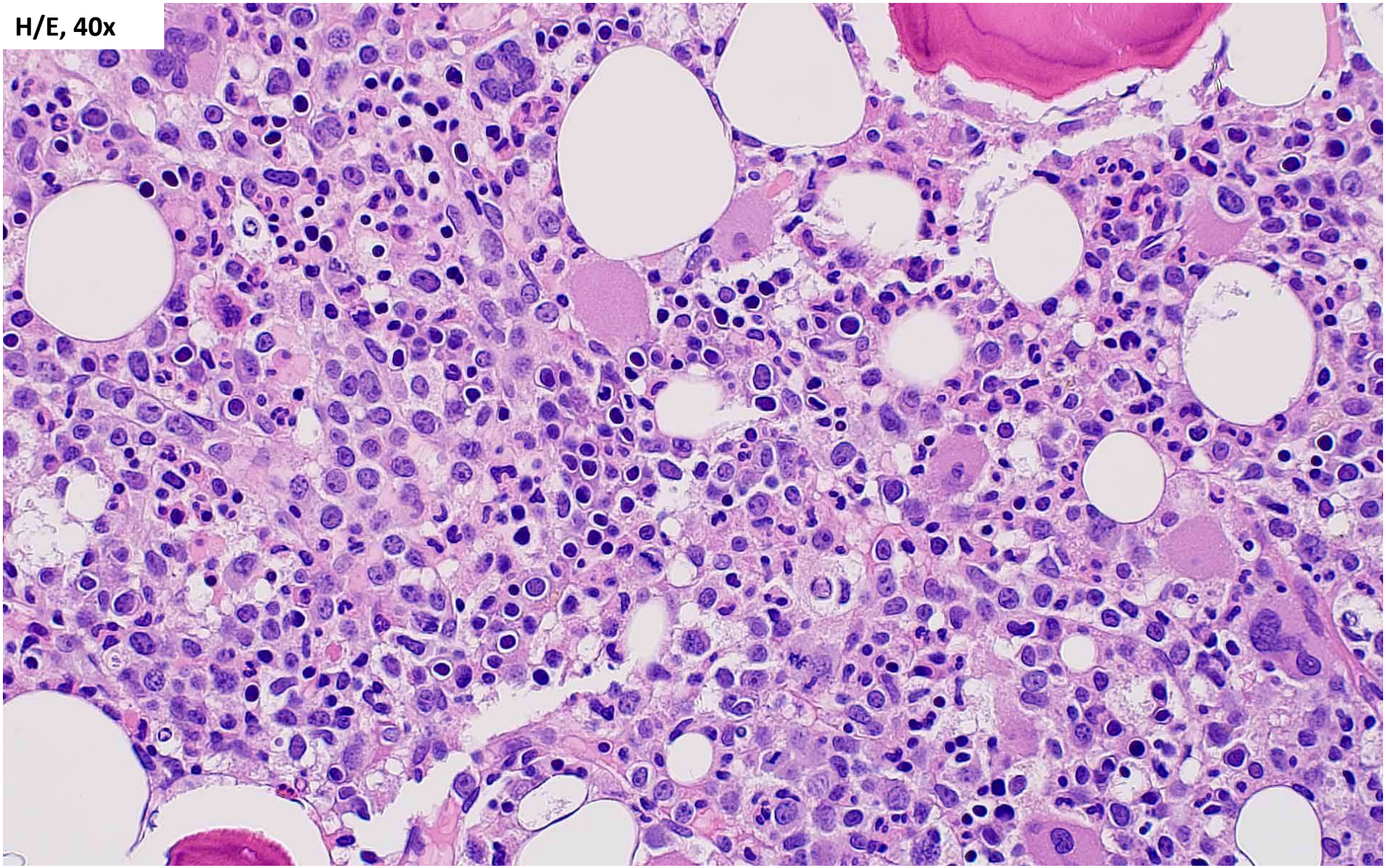


Bone marrow biopsy

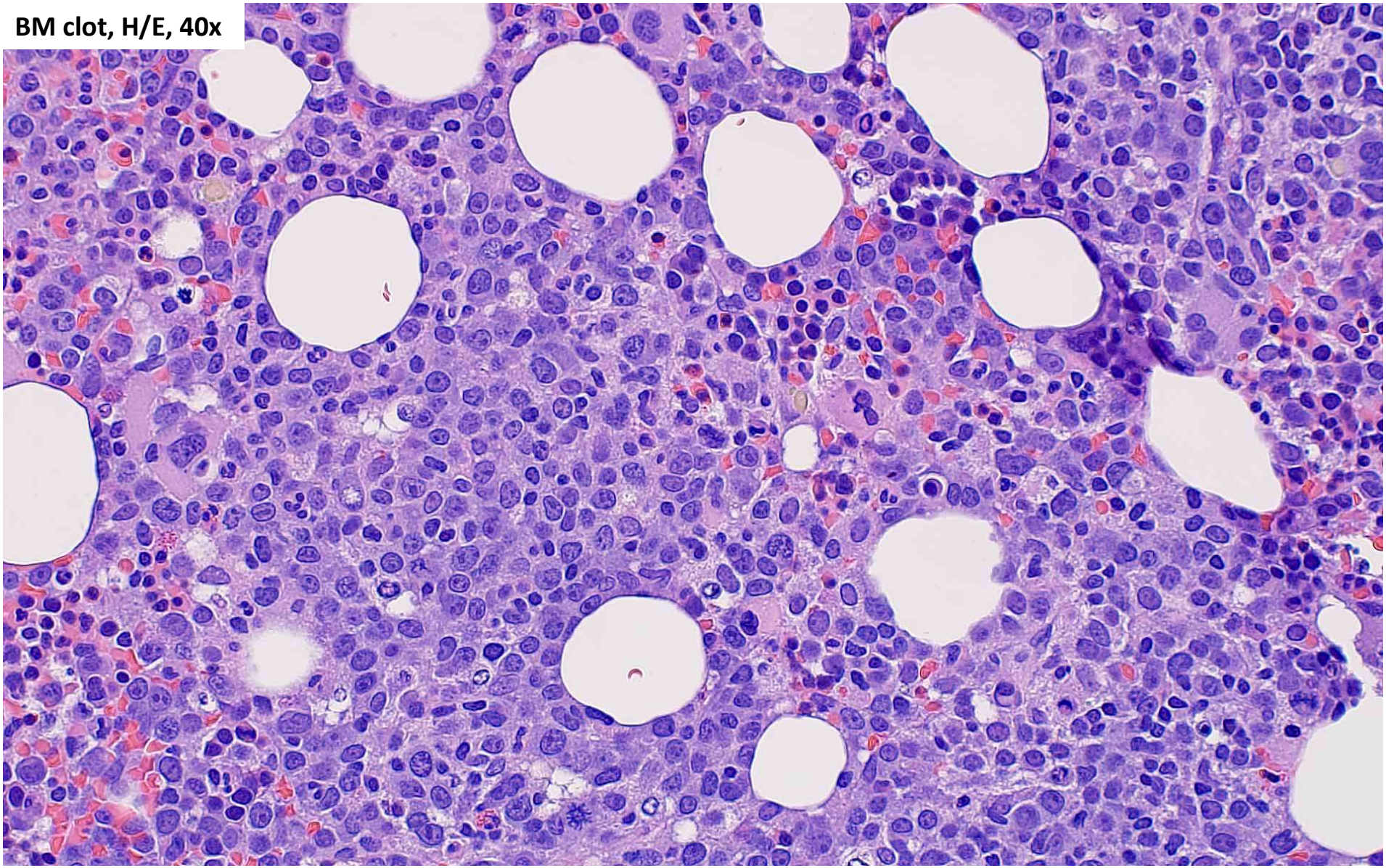
H/E, 2x



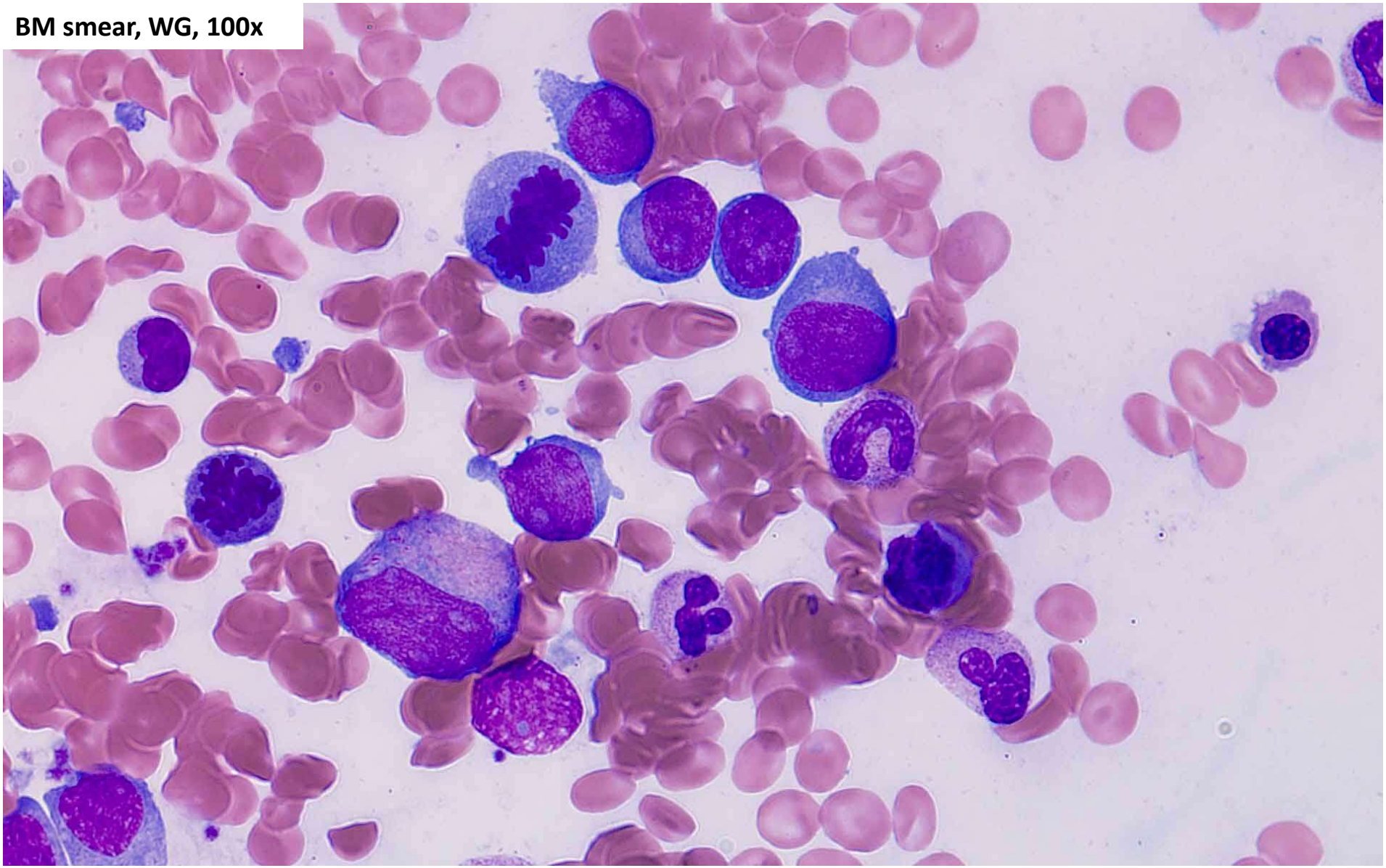
H/E, 40x



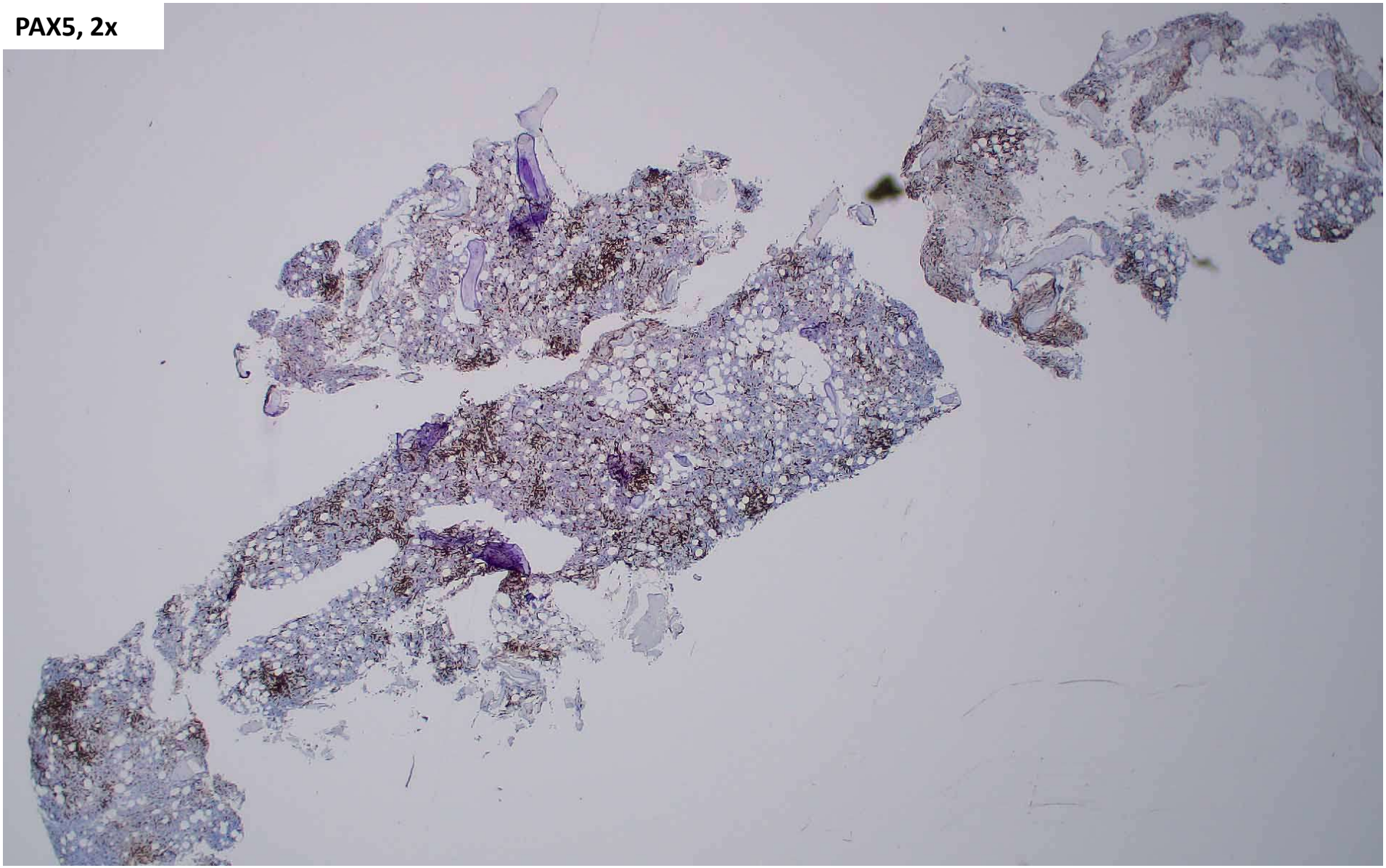
BM clot, H/E, 40x



BM smear, WG, 100x



PAX5, 2x



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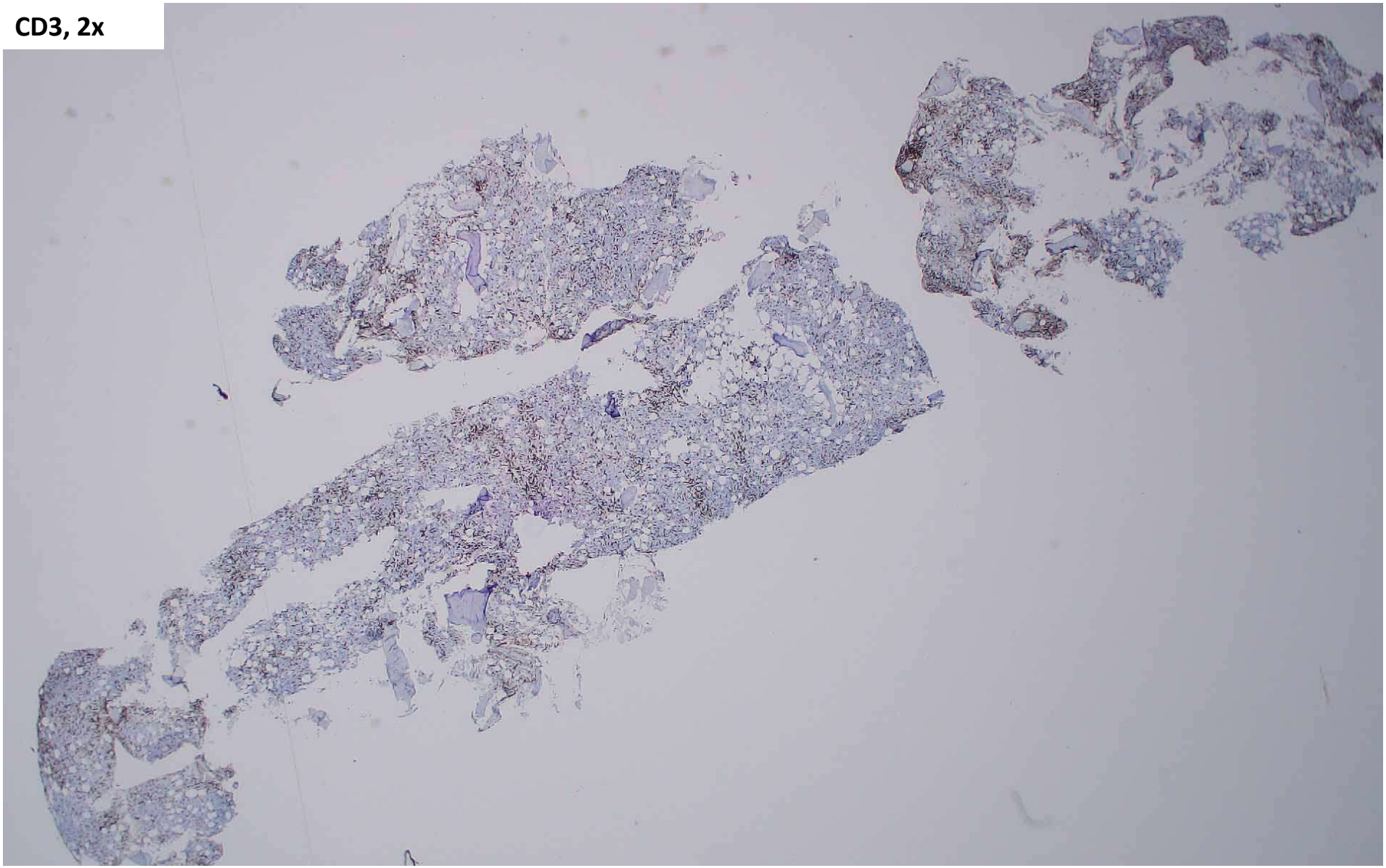

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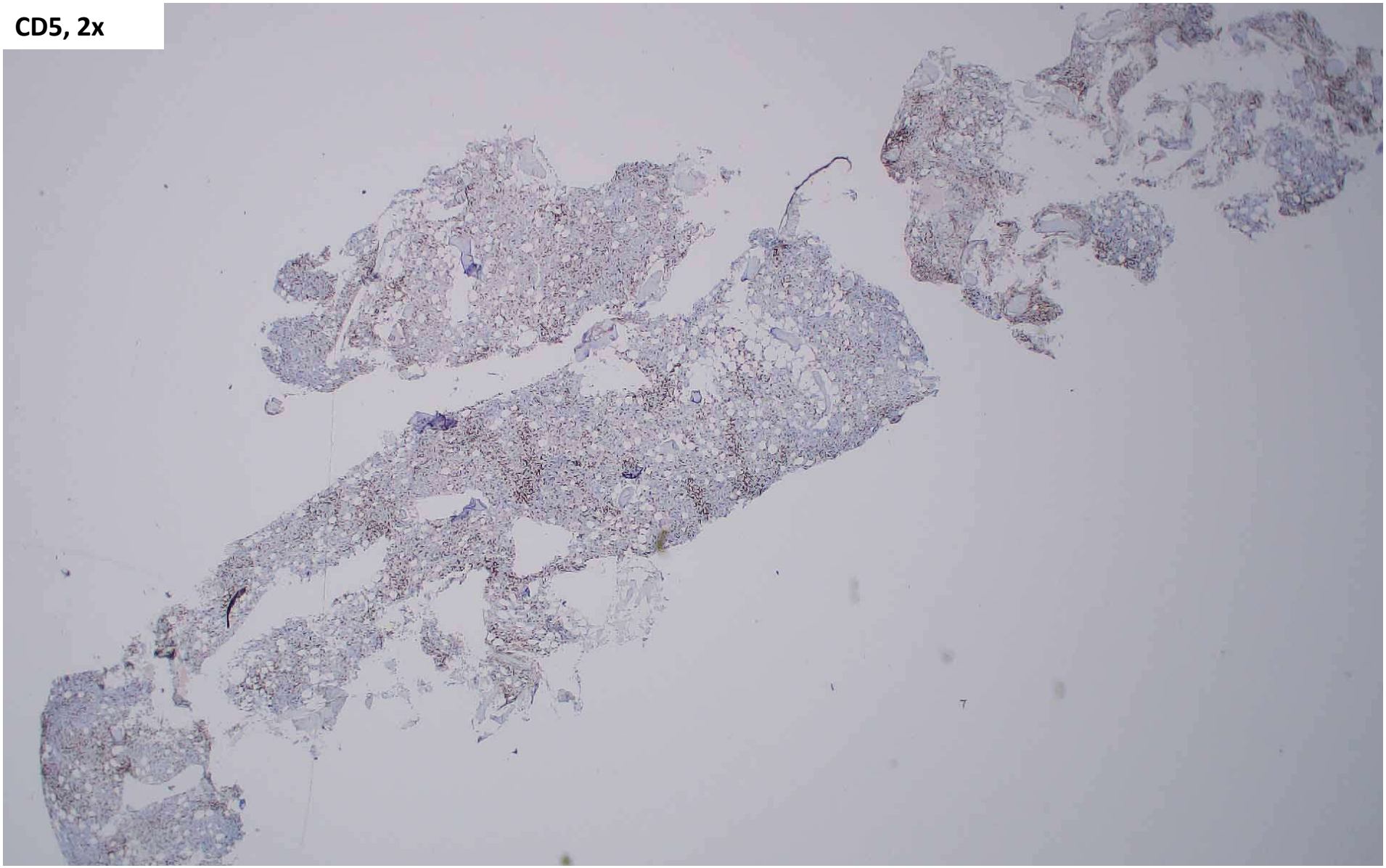

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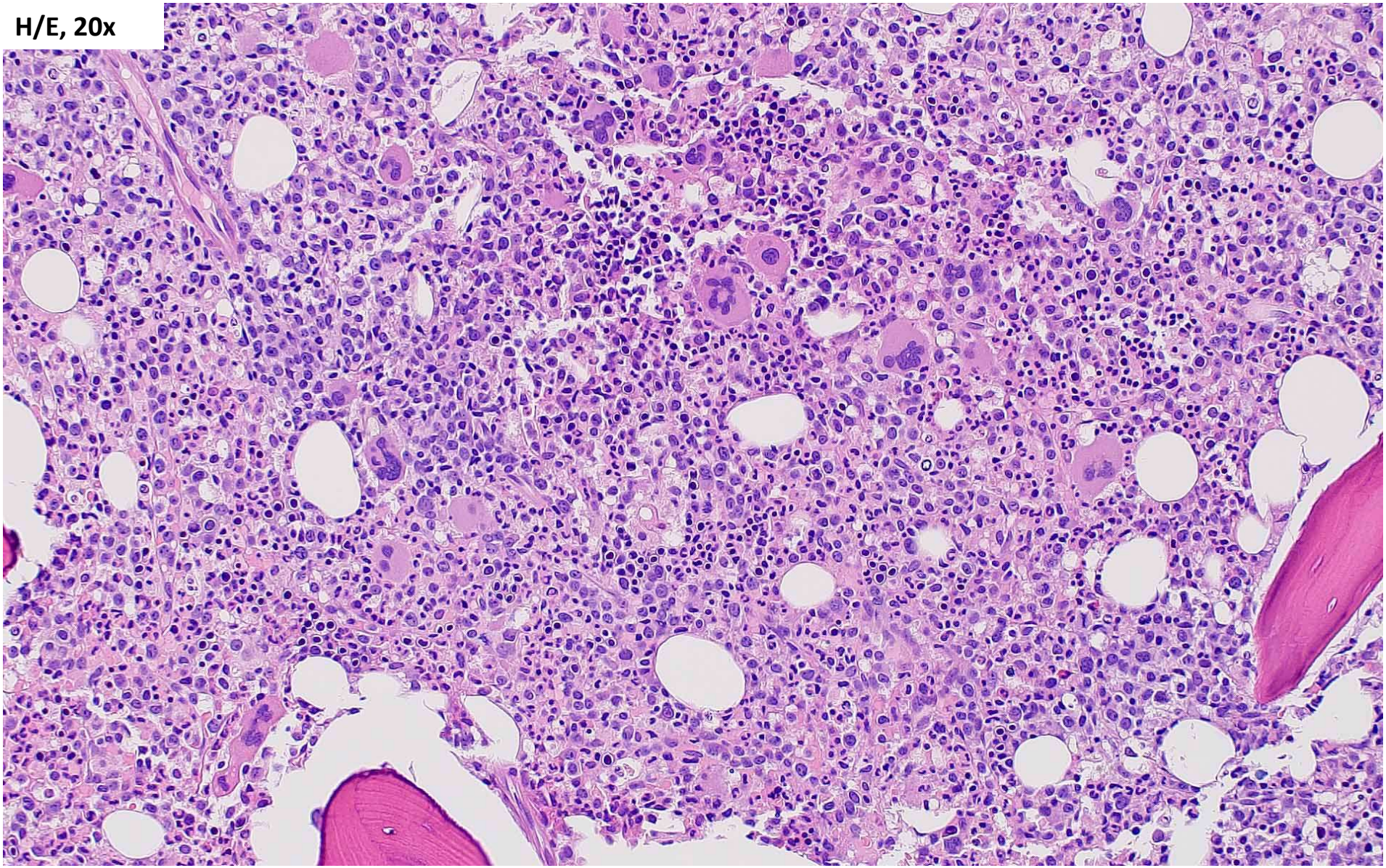

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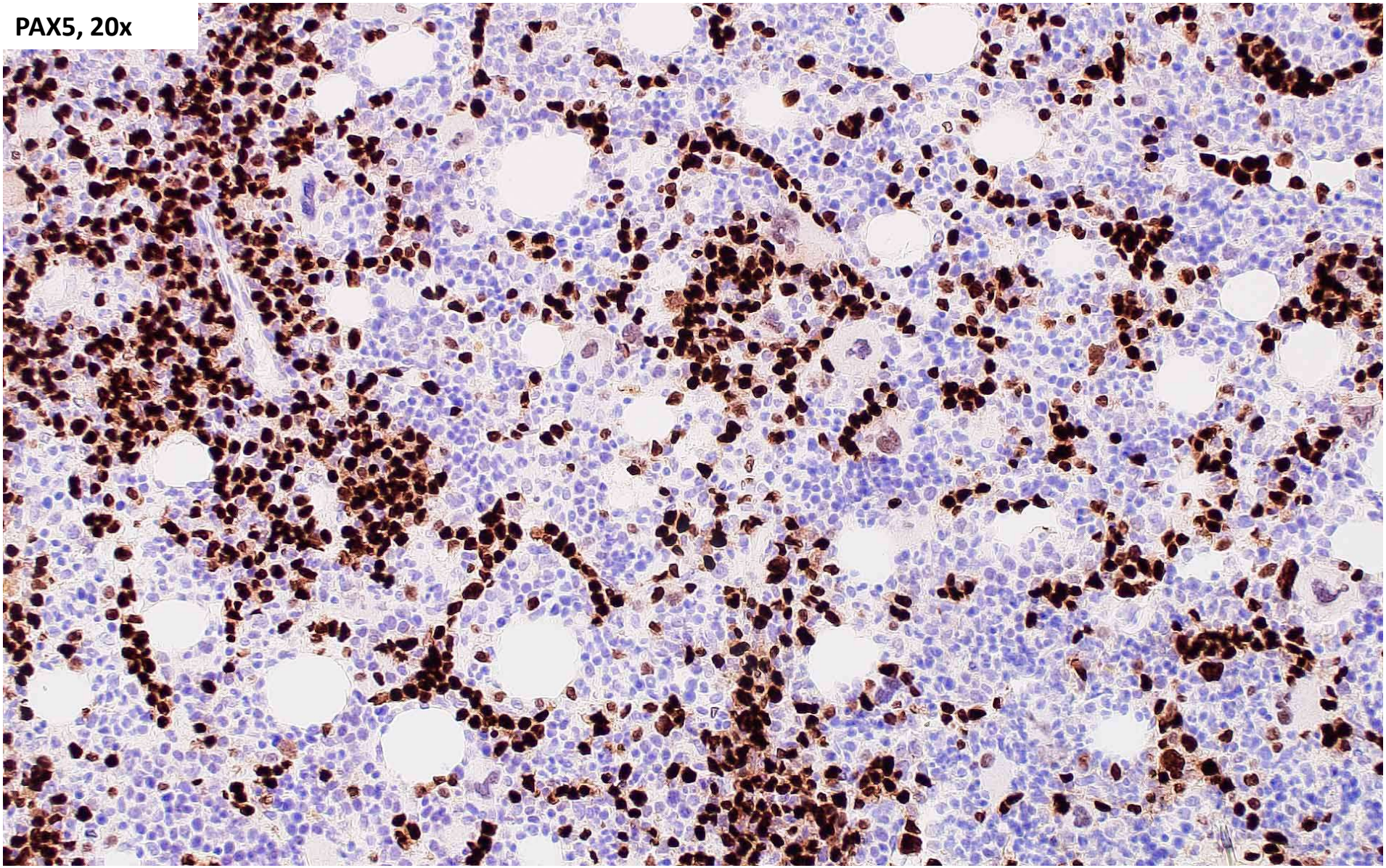
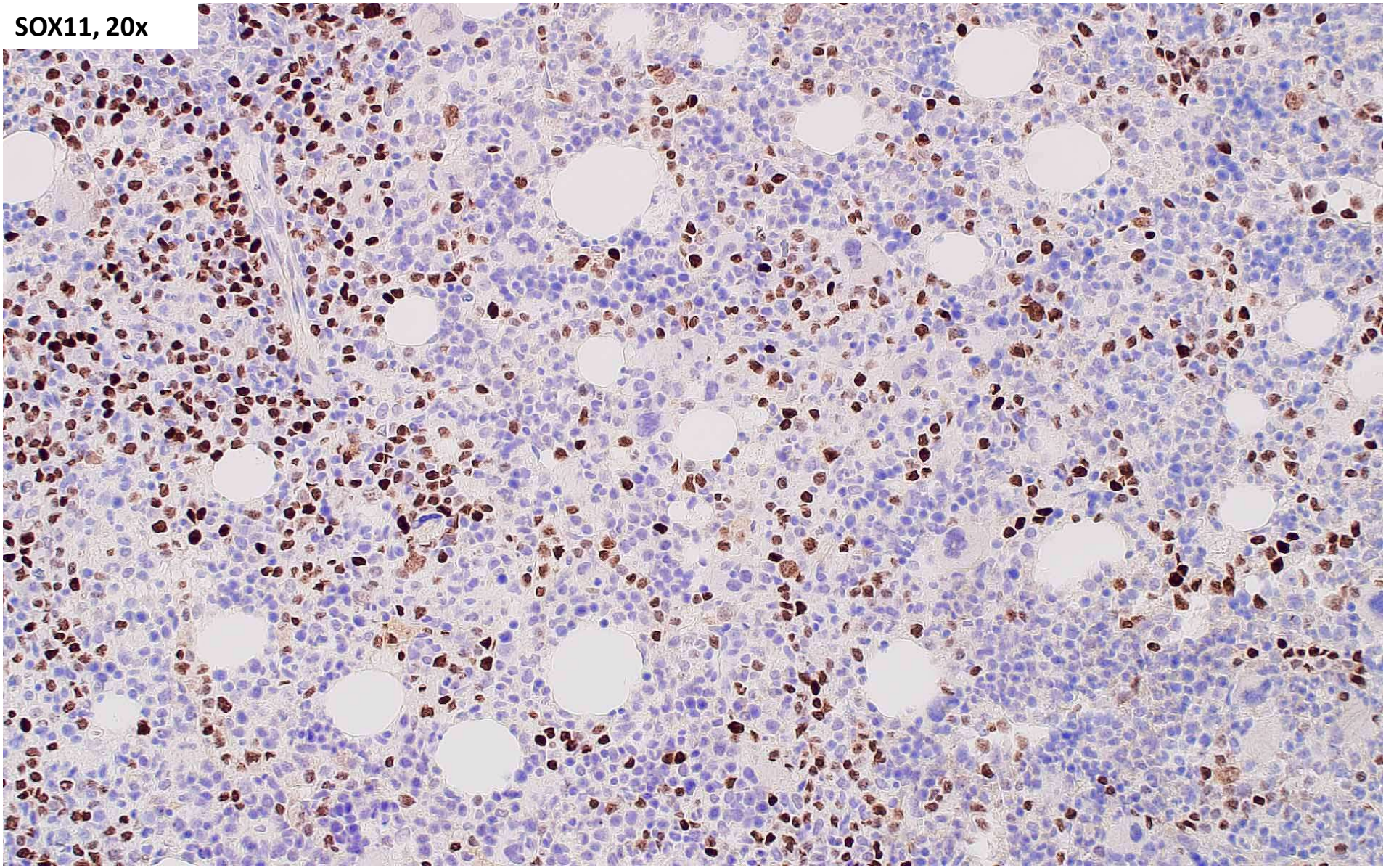
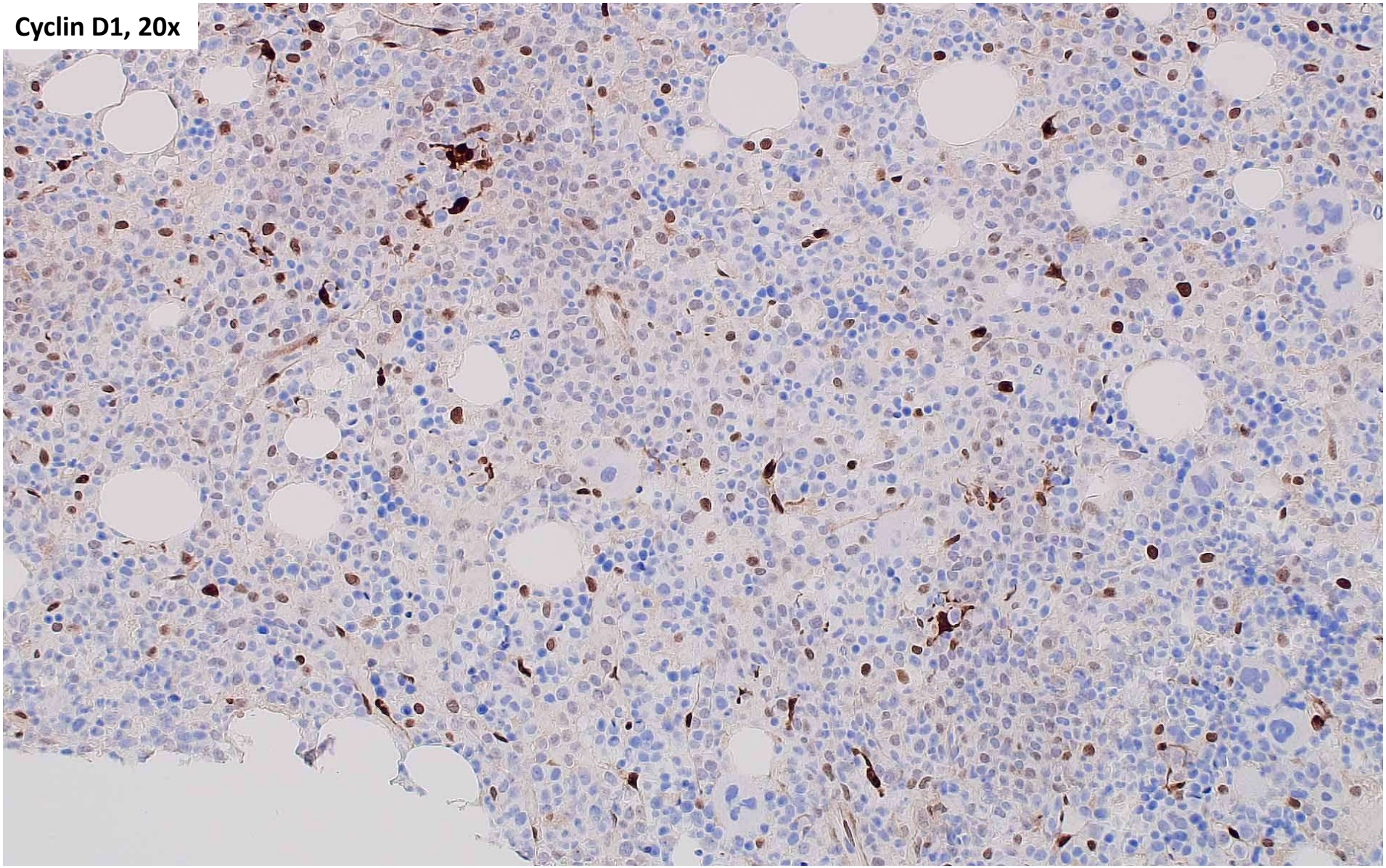


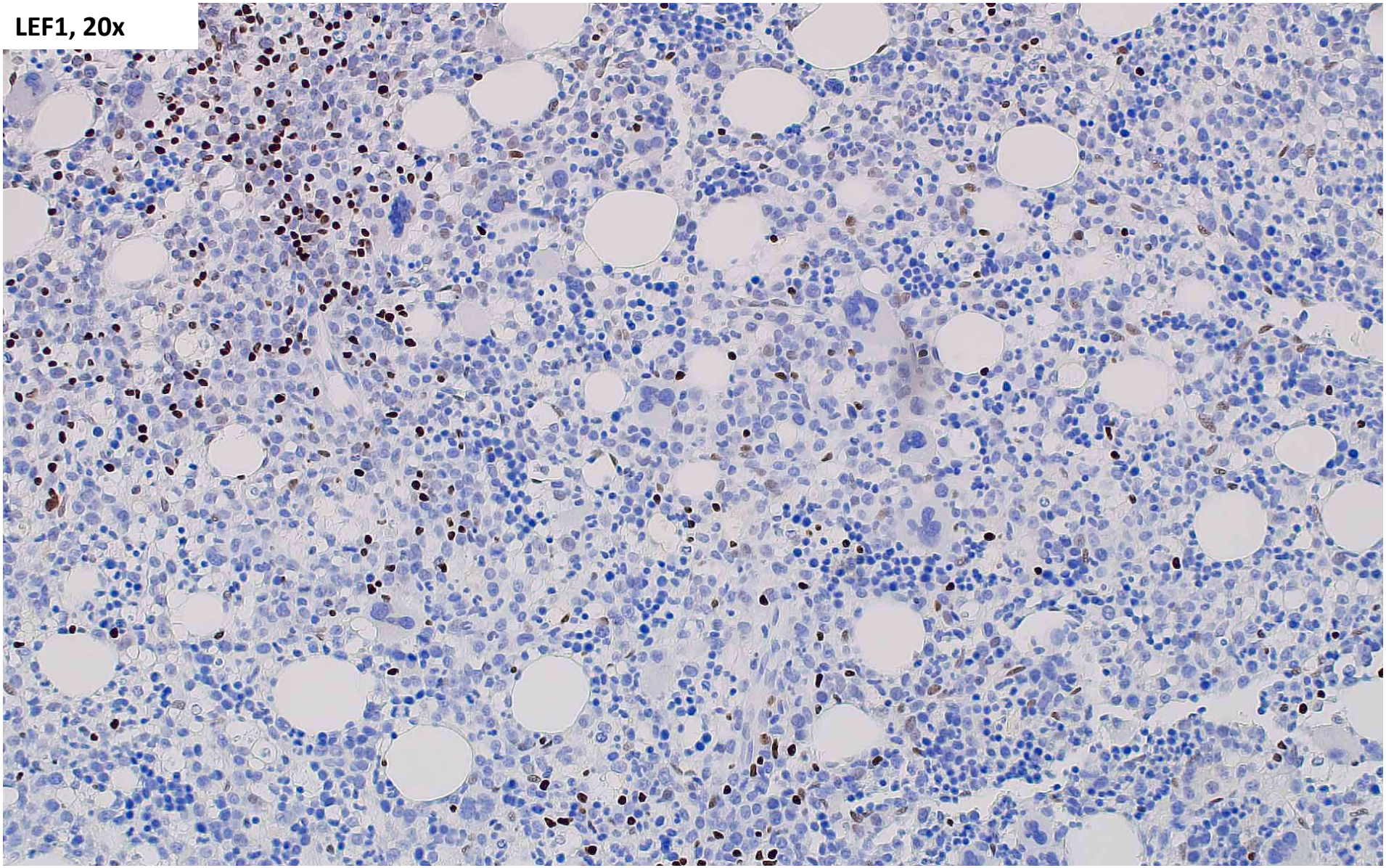
SOX11, 20x



Cyclin D1, 20x

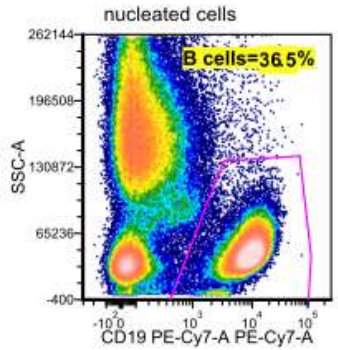


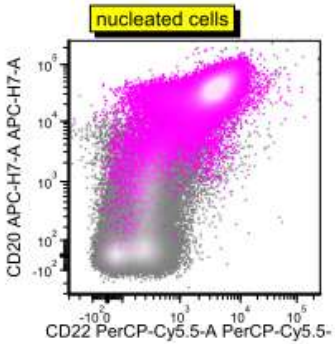
LEF1, 20x

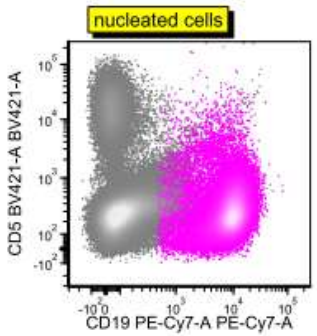


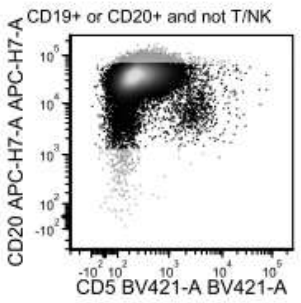
Ancillary studies (BM sample)

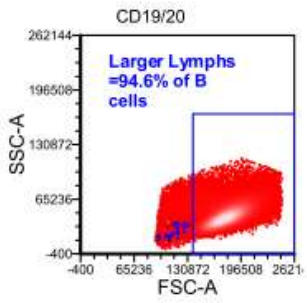
- Flow cytometry
- Chromosome analysis
- FISH for *IGH::CCND1* (dual color dual fusion probe)
- *IGH* somatic hypermutation
- NGS panel
- OGM

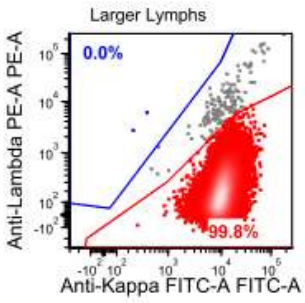


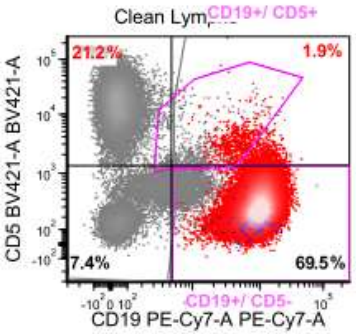


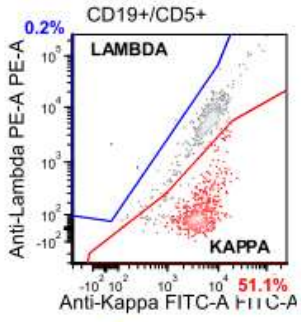


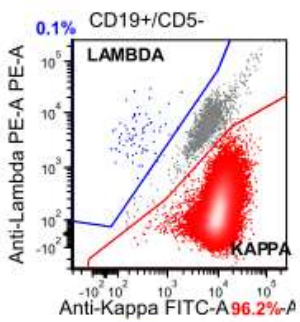


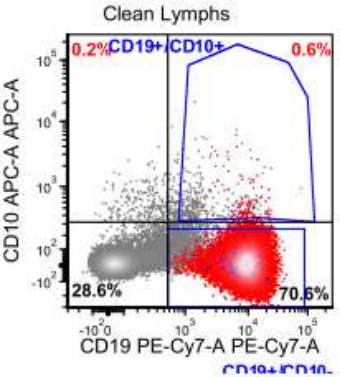




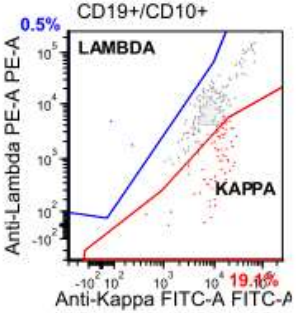




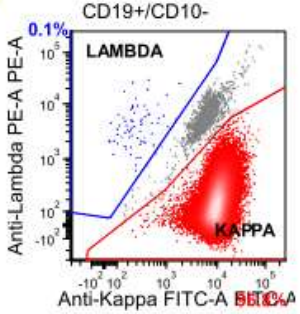


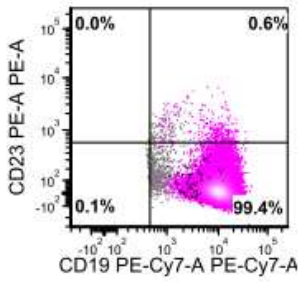


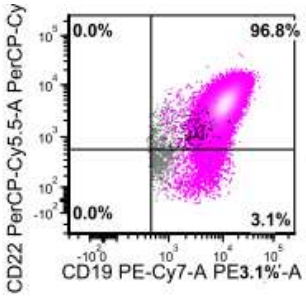
CD19+/10+ gate is 0.4% of lymphocytes
CD19+/10+ gate is 0.2% of total events

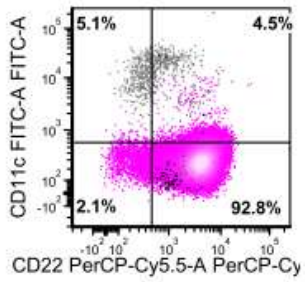


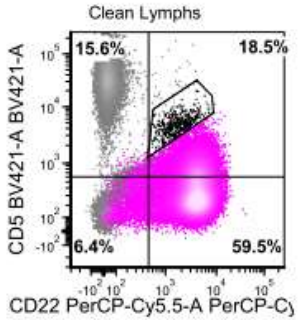
CD19+/10- gate is 70.3% of lymphocytes
CD19+/10- gate is 32.3% of lymphocytes

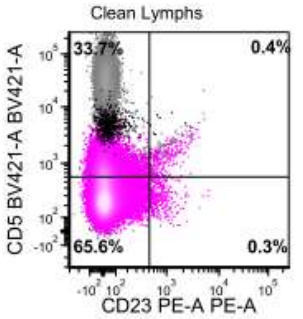


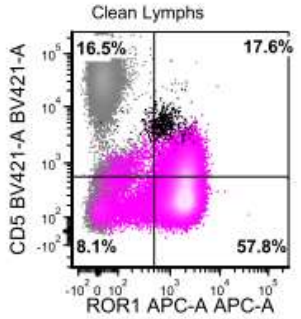


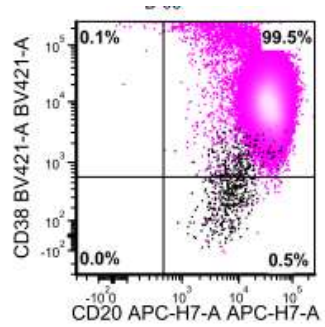


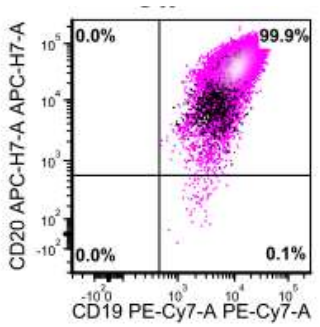


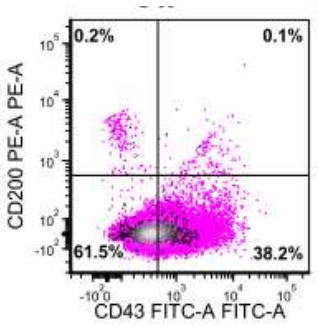


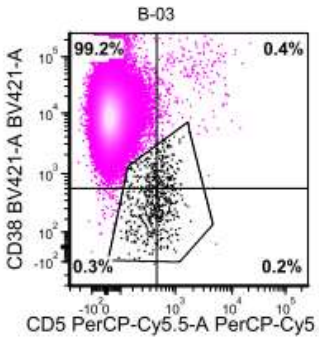


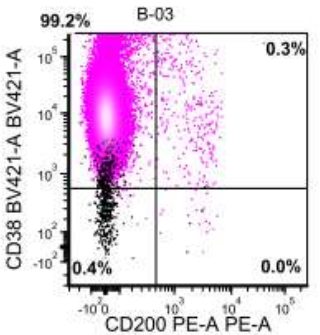


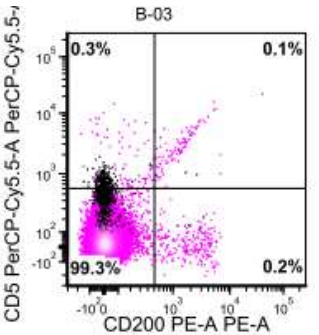

0.1%
99.5%
0.0%
0.5%
CD38 BV421-A BV421-A
CD20 APC-H7-A APC-H7-A

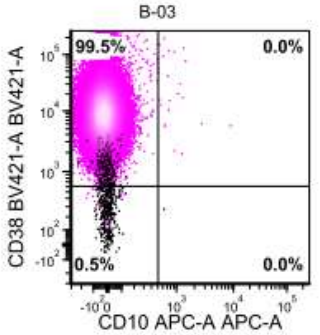

0.0%
99.9%
0.0%
0.1%
CD20 APC-H7-A APC-H7-A
CD19 PE-Cy7-A PE-Cy7-A

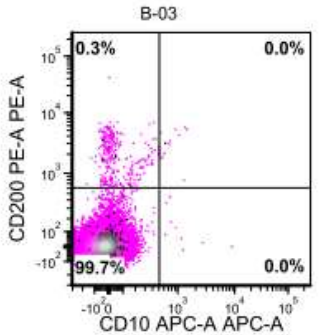

0.2%
0.1%
61.5%
38.2%
CD200 PE-A PE-A
CD43 FITC-A FITC-A

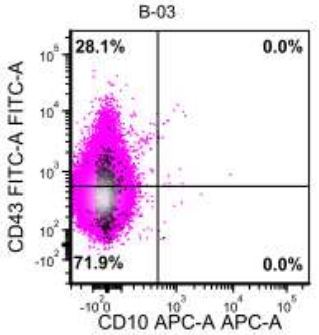

B-03
99.2%
0.4%
0.3%
0.2%
CD38 BV421-A BV421-A
CD5 PerCP-Cy5.5-A PerCP-Cy5

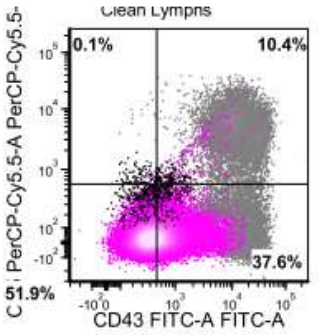

B-03
99.2%
0.3%
0.4%
0.0%
CD38 BV421-A BV421-A
CD200 PE-A PE-A

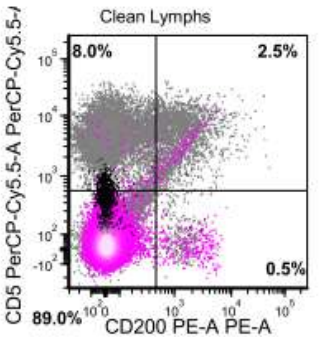

B-03
0.3%
0.1%
99.3%
0.2%
CD5 PerCP-Cy5.5-A PerCP-Cy5.5-A
CD200 PE-A PE-A

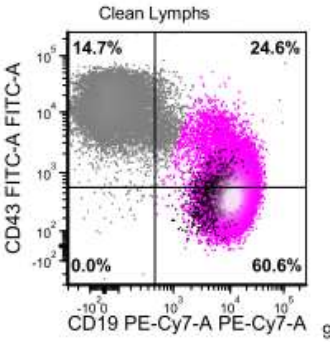

B-03
99.5%
0.0%
0.5%
0.0%
CD38 BV421-A BV421-A
CD10 APC-A APC-A

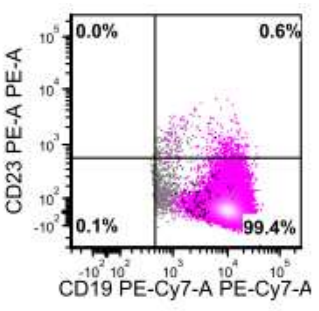

B-03
0.3%
0.0%
99.7%
0.0%
CD200 PE-A PE-A
CD10 APC-A APC-A

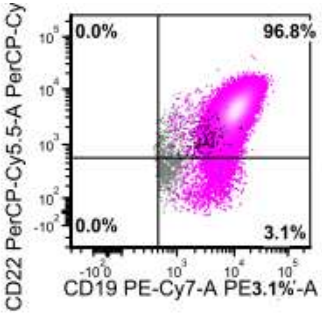

B-03
28.1%
0.0%
71.9%
0.0%
CD43 FITC-A FITC-A
CD10 APC-A APC-A

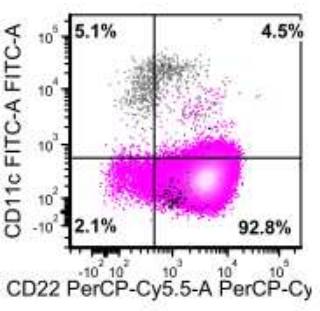

Clean Lymphs
0.1%
10.4%
51.9%
37.6%
CD5 PerCP-Cy5.5-A PerCP-Cy5.5-
CD43 FITC-A FITC-A

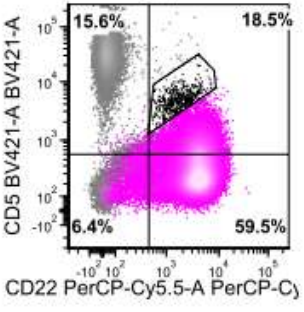

Clean Lymphs
8.0%
2.5%
89.0%
0.5%
CD5 PerCP-Cy5.5-A PerCP-Cy5.5-A
CD200 PE-A PE-A

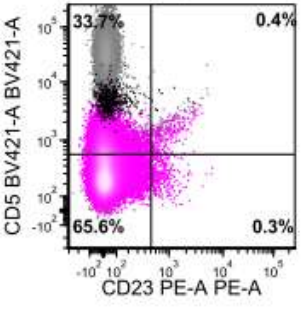

Clean Lymphs
14.7%
24.6%
0.0%
60.6%
CD43 FITC-A FITC-A
CD19 PE-Cy7-A PE-Cy7-A

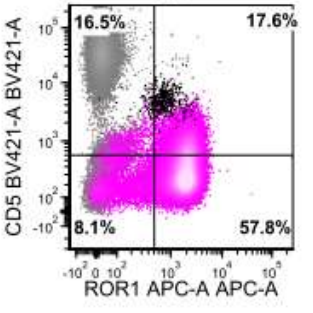

0.0%
0.6%
0.1%
99.4%
CD23 PE-A PE-A
CD19 PE-Cy7-A PE-Cy7-A


0.0%
96.8%
0.0%
3.1%
CD22 PerCP-Cy5.5-A PerCP-Cy
CD19 PE-Cy7-A PE-A


5.1%
4.5%
2.1%
92.8%
CD11c FITC-A FITC-A
CD22 PerCP-Cy5.5-A PerCP-Cy


Clean Lymphs
15.6%
18.5%
6.4%
59.5%
CD5 BV421-A BV421-A
CD22 PerCP-Cy5.5-A PerCP-Cy


Clean Lymphs
33.7%
0.4%
65.6%
0.3%
CD5 BV421-A BV421-A
CD23 PE-A PE-A


Clean Lymphs
16.5%
17.6%
8.1%
57.8%
CD5 BV421-A BV421-A
ROR1 APC-A APC-A

Flow cytometric immunophenotype

- High forward scatter value
- Positive
  - CD19, CD20, CD22, CD38, CD43, ROR1, kappa
- Negative
  - CD5, CD10, CD11c, CD23, CD200, lambda

- A small subset of B-cells with CD5 expression (0.5% of total events)

EndLymphoma panel

ARID1A	CCND1	DIS3	GPR183	JAK1	MYD88	PLCG2	S1PR1	TBL1XR1
ASXL1	CCND3	DNMT3A	H1-2	JAK2	NF1	PLEKHG5	S1PR2	TCF3
ATM	CCR4	DUSP2	H1-4	JAK3	NFKB2	POLE	SAMHD1	TENT5C
B2M	CCR7	EGR1	H3C2	KIT	NFKBIA	POT1	SETD2	TET2
BAZ2A	CD274	EGR2	HRAS	KLF2	NFKBIE	PRDM1	SF3B1	TMEM30A
BCL10	CD28	ELF4	HUWE1	KLHL6	NOTCH1	PTEN	SGK1	TNFAIP3
BCL2	CD58	EP300	HVCN1	KMT2D	NOTCH2	PTPN1	SMARCA4	TNFRSF14
BCL6	CD79A	EWSR1	ID3	KRAS	NPM1	PTPN11	SMO	TP53
BCL7A	CD79B	EZH2	IDH1	LTB	NRAS	PTPRD	SOCS1	TRAF2
BCOR	CDKN2A	FAM50A	IDH2	LYN	NSD2	RASSF1	SOX11	TRAF3
BIRC3	CDKN2B	FAS	IFNGR1	MAP2K1	NXF1	RB1	SP140	TRAF6
BLNK	CHD2	FAT1	IGLL5	MAP3K14	P2RY8	RBMX	SPEN	U2AF1
BRAF	CHEK2	FBXW7	IKZF3	MAPK1	PAX5	RFTN1	SRSF2	UBR5
BRCC3	CIITA	FGFR3	IL2RG	MAX	PCBP1	RHOA	STAT3	VAV1
BTG1	CNOT3	FOXO1	IRAK1	MED12	PIK3CA	RIPK1	STAT5B	XPO1
BTG2	CREBBP	FYN	IRF4	MEF2B	PIK3R1	RPS15	STAT6	ZFAT
BTK	CXCR4	GNA13	IRF8	MFHAS1	PIM1	RRAGC	STK11	ZMYM3
CARD11	DDX3X	GNAS	ITPKB	MYC	PLCG1	RRAS	SYK	ZRSR2

EndLymphoma panel

Variants of probable somatic origin (somatic mutations)

Gene	DNA change	Protein change	Location	VAF	Type
CDKN2A	c.238C>T	p.R80*	Exon 2	27%	SNV - Nonsense
DDX3X	c.908G>C	p.G303A	Exon 10	38%	SNV - Missense
IGLL5	c.166G>C	p.V56L	Exon 1	19%	SNV - Missense
KLF2	c.220_232del	p.Y74fs*63	Exon 2	17%	Deletion - Frameshift
NOTCH2	c.7081C>T	p.Q2361*	Exon 34	21%	SNV - Nonsense
STK11	c.511G>A	p.G171S	Exon 4	19%	SNV - Missense

Variants of uncertain origin (germline versus somatic origin cannot be determined unequivocally)

Gene	DNA change	Protein change	Location	VAF	Type
MAPK1	c.17_22del	p.A6_A7del	Exon 1	45%	Deletion - Deletion

Ancillary studies

- Flow cytometry
- Chromosome analysis
  - 46,XY[20]
- FISH for *IGH::CCND1* (dual color dual fusion probe)
  - Negative
- *IGH* somatic hypermutation
  - Unmutated (1.69% deviation from germline sequence, IGHV3-33)
- NGS panel
  - *CDKN2A, DDX3X, IGLL5, KLF2, NOTCH2, STK11* mutations
- OGM
  - t(2;12)(p11.2;p13.32) *IGK::CCND2*
  - t(8;14)(q24.21;q32.33) *IGH::MYC*

Diagnosis

- Mantle cell lymphoma with *CCND2* rearrangement

blood®

Regular Article

LYMPHOID NEOPLASIA

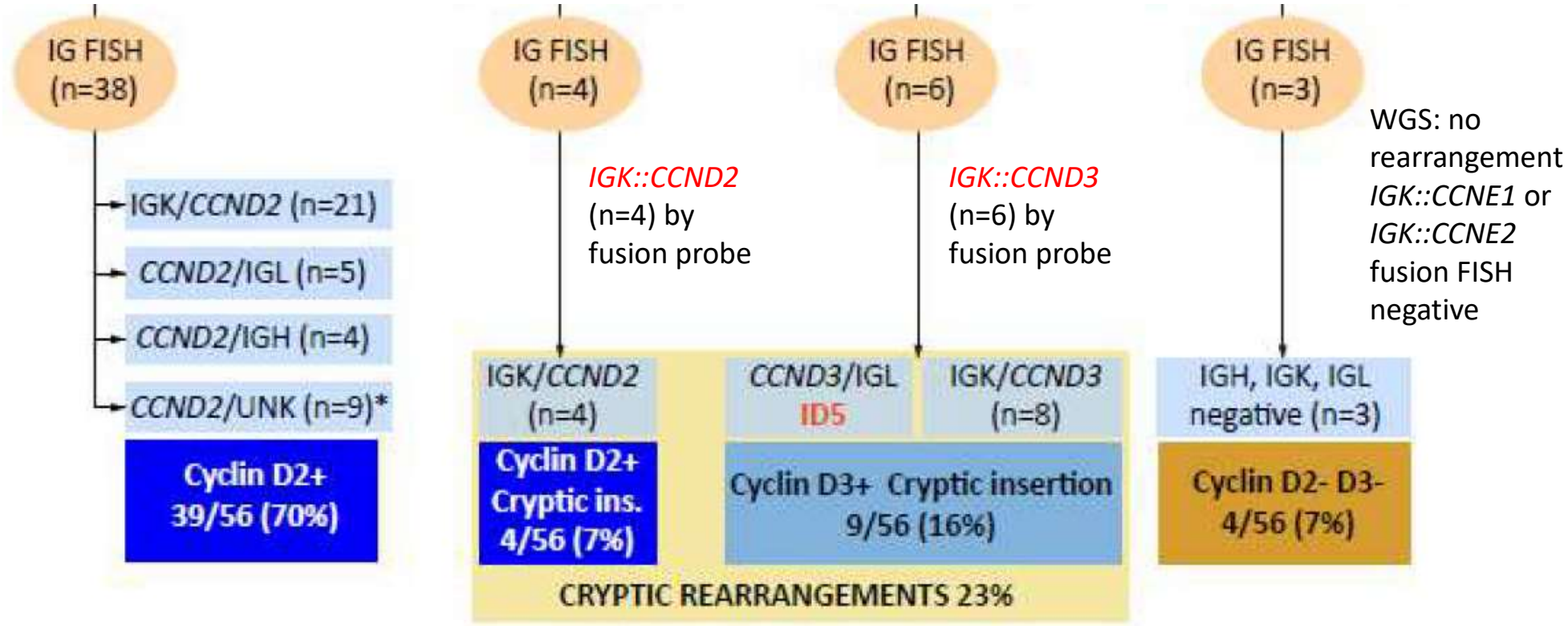
CCND2 and *CCND3* hijack immunoglobulin light-chain enhancers in cyclin D1$^-$ mantle cell lymphoma

David Martín-Garcia,[1,2,*] Alba Navarro,[1,2,*] Rafael Valdés-Mas,[3] Guillem Clot,[1,2] Jesús Gutiérrez-Abril,[3] Miriam Prieto,[1,2] Inmaculada Ribera-Cortada,[4] Renata Woroniecka,[5] Grzegorz Rymkiewicz,[6] Susanne Bens,[7,8] Laurence de Leval,[9] Andreas Rosenwald,[10,11] Judith A. Ferry,[12] Eric D. Hsi,[13] Kai Fu,[14,15] Jan Delabie,[16,17] Dennis Weisenburger,[18] Daphne de Jong,[19] Fina Climent,[20] Sheila J. O'Connor,[21] Steven H. Swerdlow,[22] David Torrents,[23,24] Sergi Beltran,[25] Blanca Espinet,[26,27] Blanca González-Farré,[2,28] Luis Veloza,[28] Dolors Costa,[2,28] Estella Matutes,[28] Reiner Siebert,[7,8] German Ott,[29,30] Leticia Quintanilla-Martinez,[31] Elaine S. Jaffe,[32] Carlos López-Otín,[2,3] Itziar Salaverria,[1,2] Xose S. Puente,[2,3,†] Elias Campo,[1,2,28,33,†] and Sílvia Beà[1,2,†]

Blood. 2019 Feb 28;133(9):940-951.

CCND2 and *CCND3* study in cyclin D1(-) MCL

- N=56 (28 patients included from the previous study)
- Inclusion criteria
  - Morphology typical for MCL
  - Immunophenotype (CD5+, CD23-)
  - Absence of cyclin D1 expression by IHC or t(11;14)(q13;q32)
  - Presence of SOX11 expression
- FISH for *CCND2, CCND3, CCNE1, CCNE2, IGH, IGK* and *IGL*
- NGS (WGS/WES) in 5 cases
- Gene expression and copy-number analysis



Blood. 2019;133(9):940-951

Thank you

- cok@mdanderson.org