MIHCC
Case #2

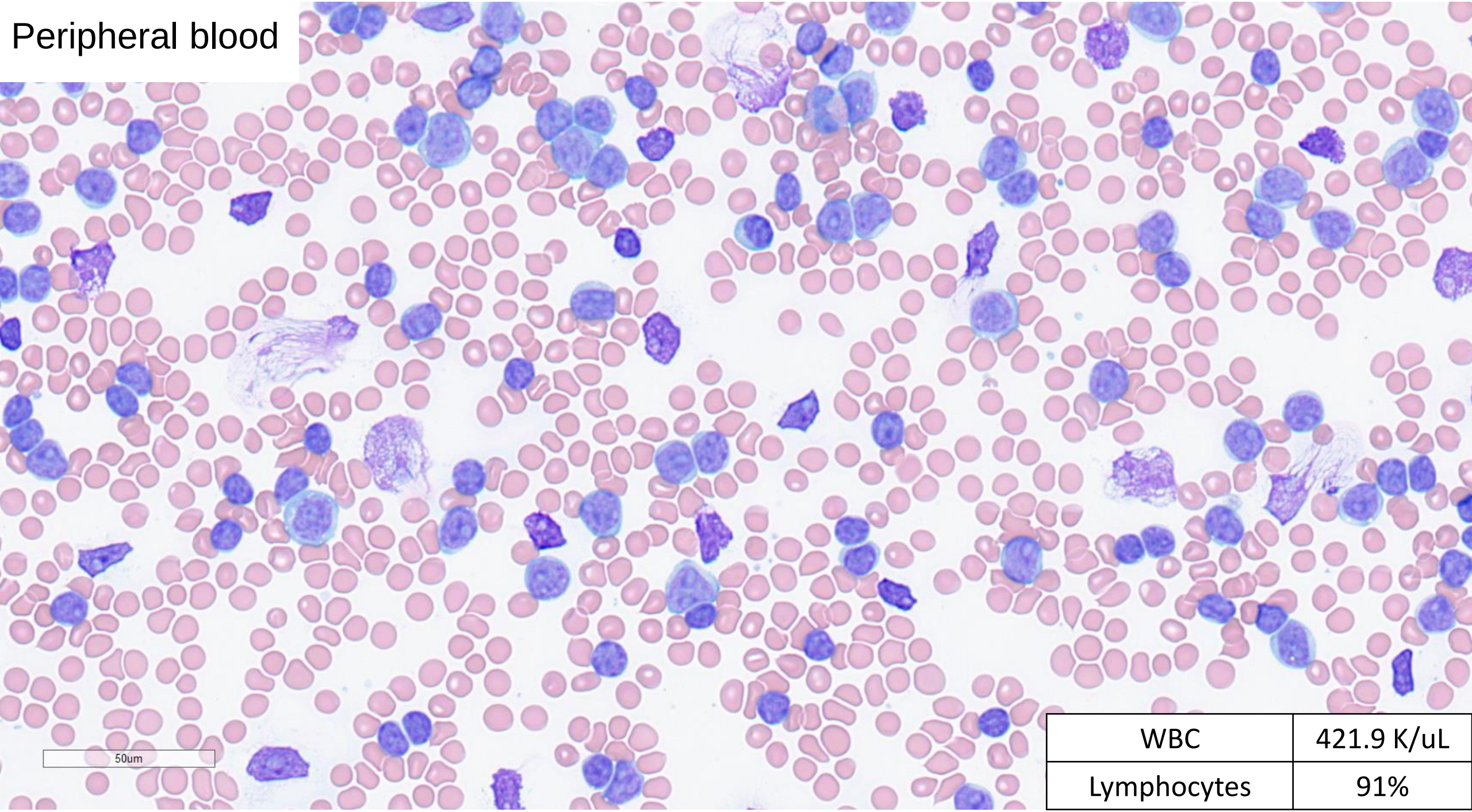
6/25/2025

Clinical Information

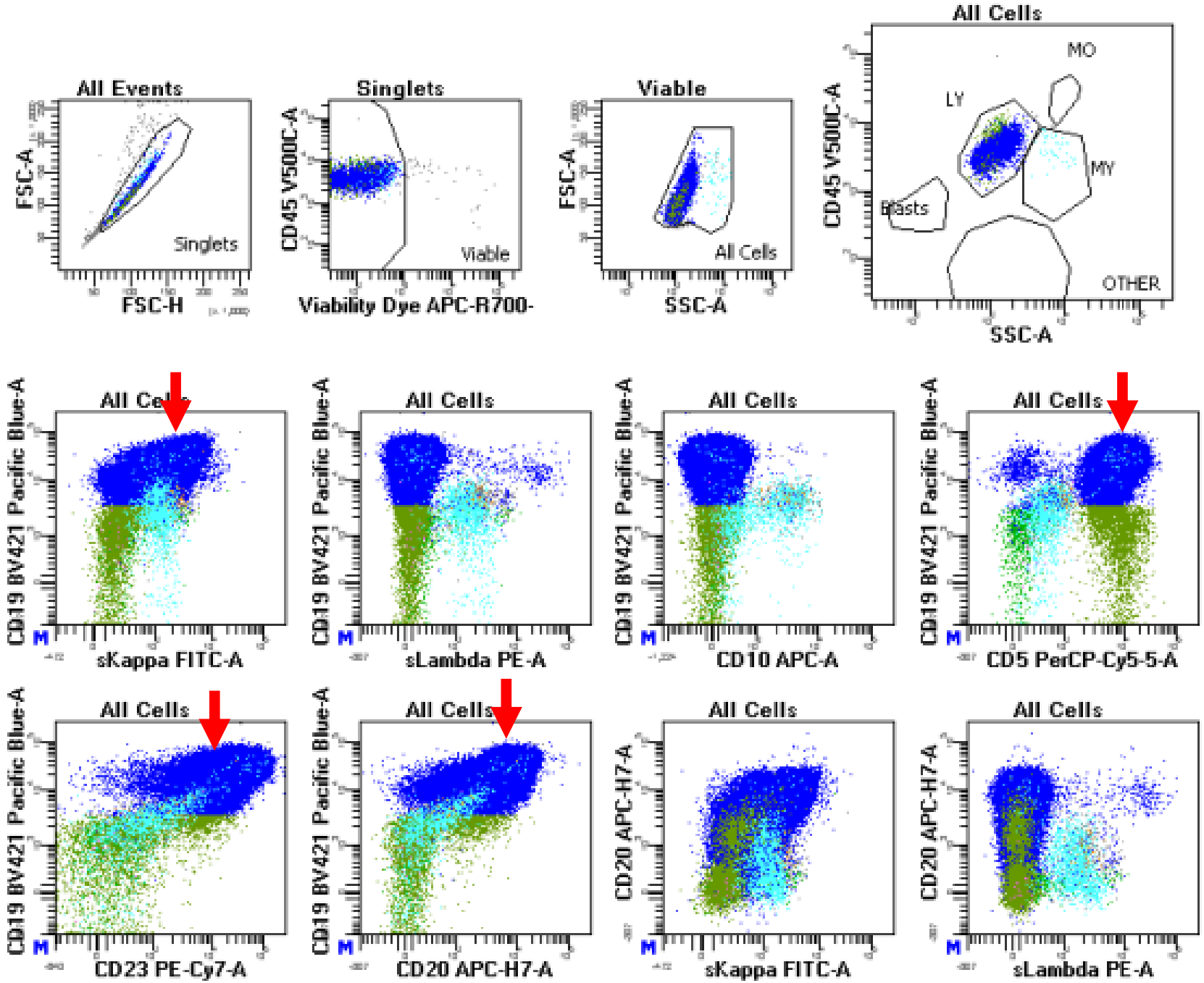
- 68-year-old women with chronic lymphocytic leukemia (CLL), under observation since January 2024.

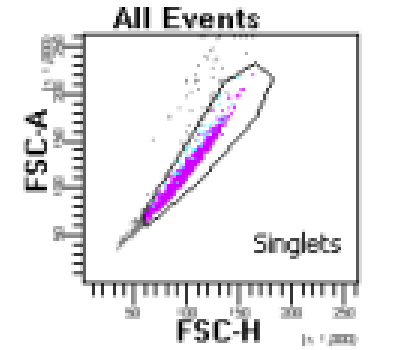
- In January 2025, she presented with worsening lymphocytosis and lymphadenopathy.

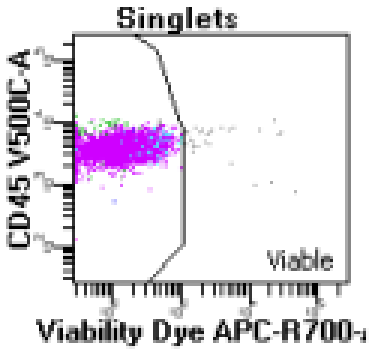
Peripheral blood

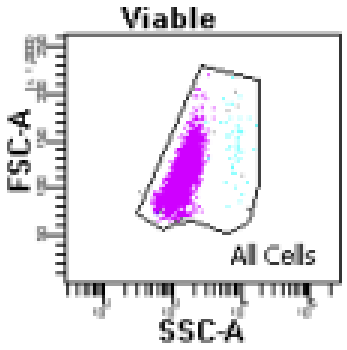


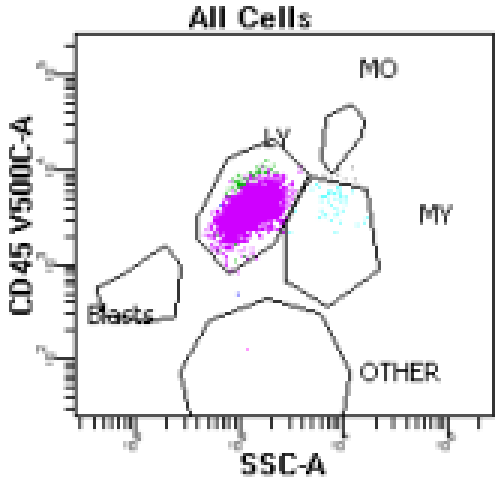
WBC	421.9 K/uL
Lymphocytes	91%

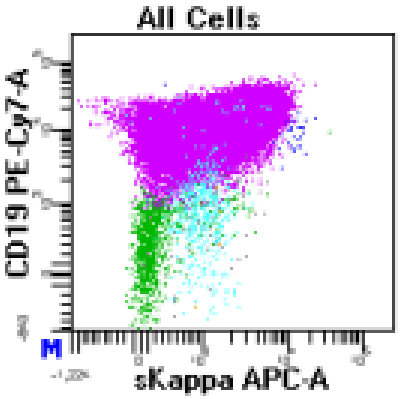

All Events
FSC-A
FSC-H
Singlets
Singlets
CD45 V500C-A
Viability Dye APC-R700-
Viable
Viable
FSC-A
SSC-A
All Cells
All Cells
MO
LY
MY
Blasts
OTHER
CD45 V500C-A
SSC-A
All Cells
CD19 BV421 Pacific Blue-A
sKappa FITC-A
All Cells
CD19 BV421 Pacific Blue-A
sLambda PE-A
All Cells
CD19 BV421 Pacific Blue-A
CD10 APC-A
All Cells
CD19 BV421 Pacific Blue-A
CD5 PerCP-Cy5-5-A
All Cells
CD19 BV421 Pacific Blue-A
CD23 PE-Cy7-A
All Cells
CD19 BV421 Pacific Blue-A
CD20 APC-H7-A
All Cells
CD20 APC-H7-A
sKappa FITC-A
All Cells
CD20 APC-H7-A
sLambda PE-A

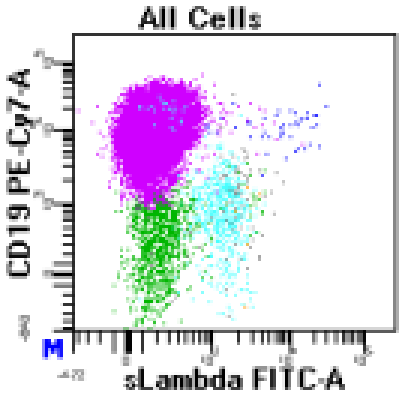

All Events
FSC-A
FSC-H
Singlets

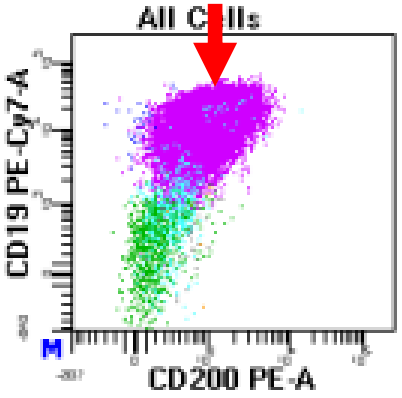

Singlets
CD45 V500C-A
Viability Dye APC-R700-
Viable

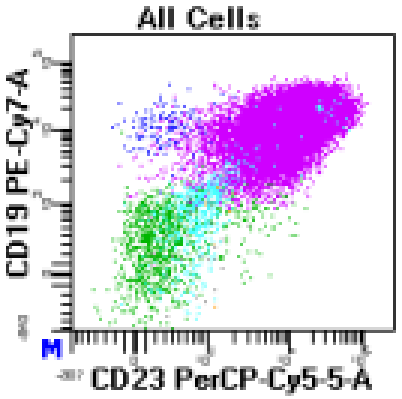

Viable
FSC-A
SSC-A
All Cells

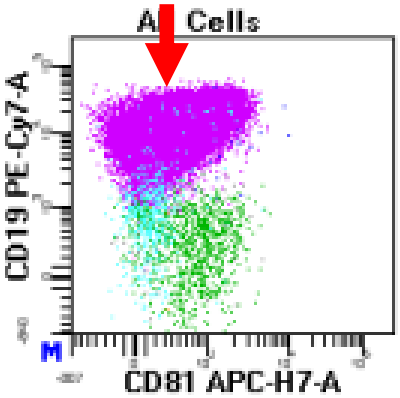

All Cells
MO
LY
MY
Blasts
OTHER
CD45 V500C-A
SSC-A


All Cells
CD19 PE-Cy7-A
sKappa APC-A
M


All Cells
CD19 PE-Cy7-A
sLambda FITC-A
M


All Cells
CD19 PE-Cy7-A
CD200 PE-A
M


All Cells
CD19 PE-Cy7-A
CD23 PerCP-Cy5-5-A
M


All Cells
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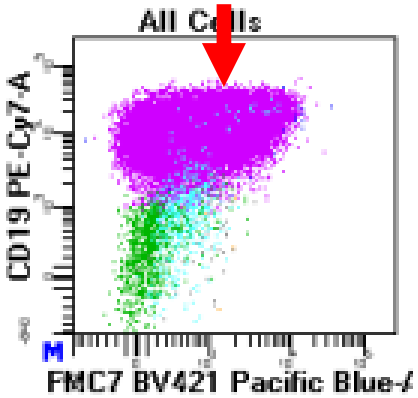
CD81 APC-H7-A
M


All Cells
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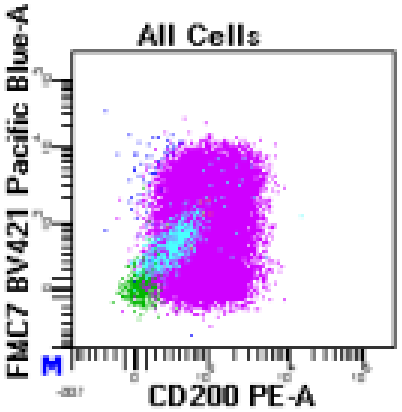
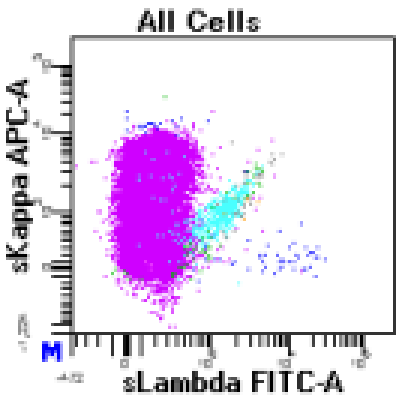
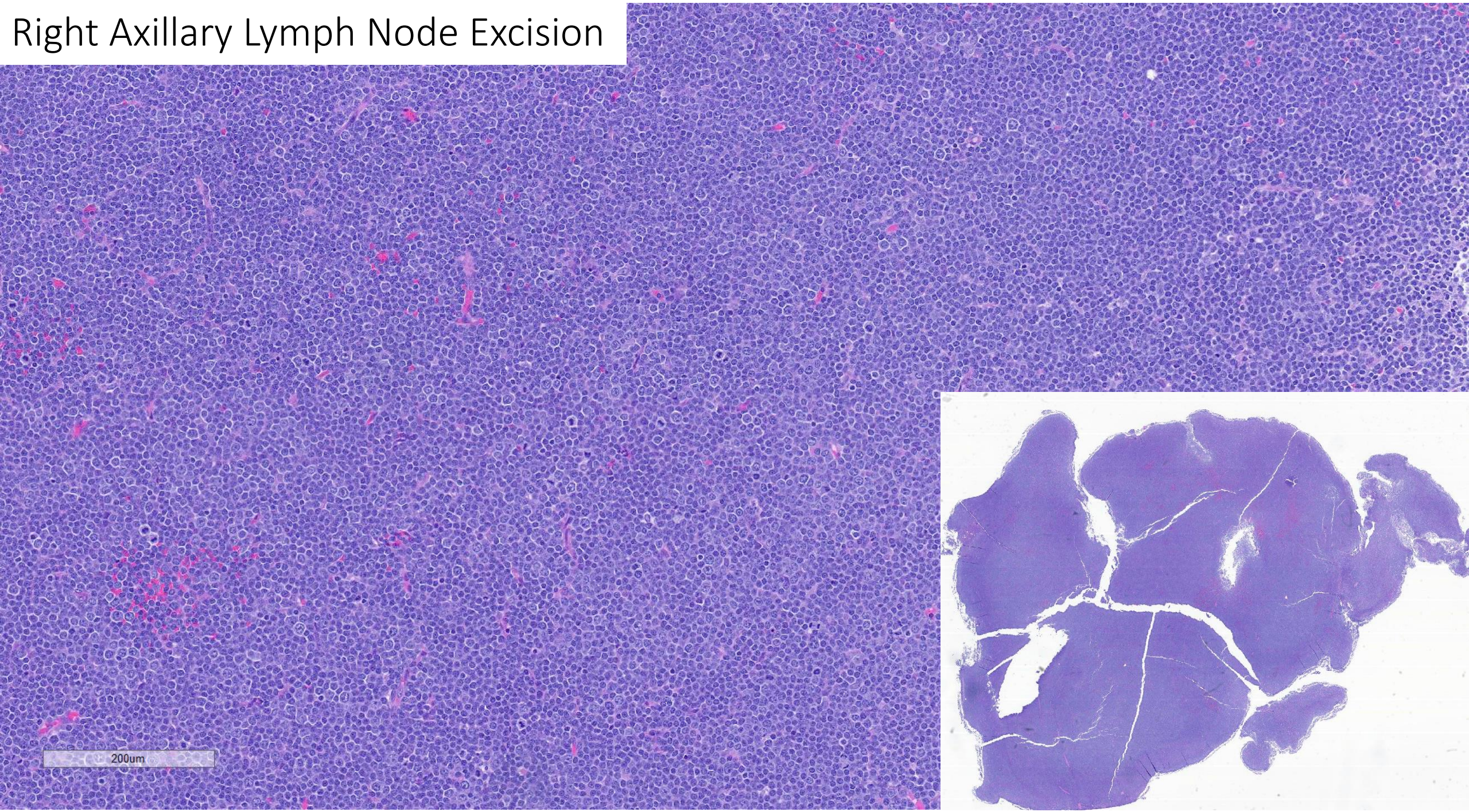
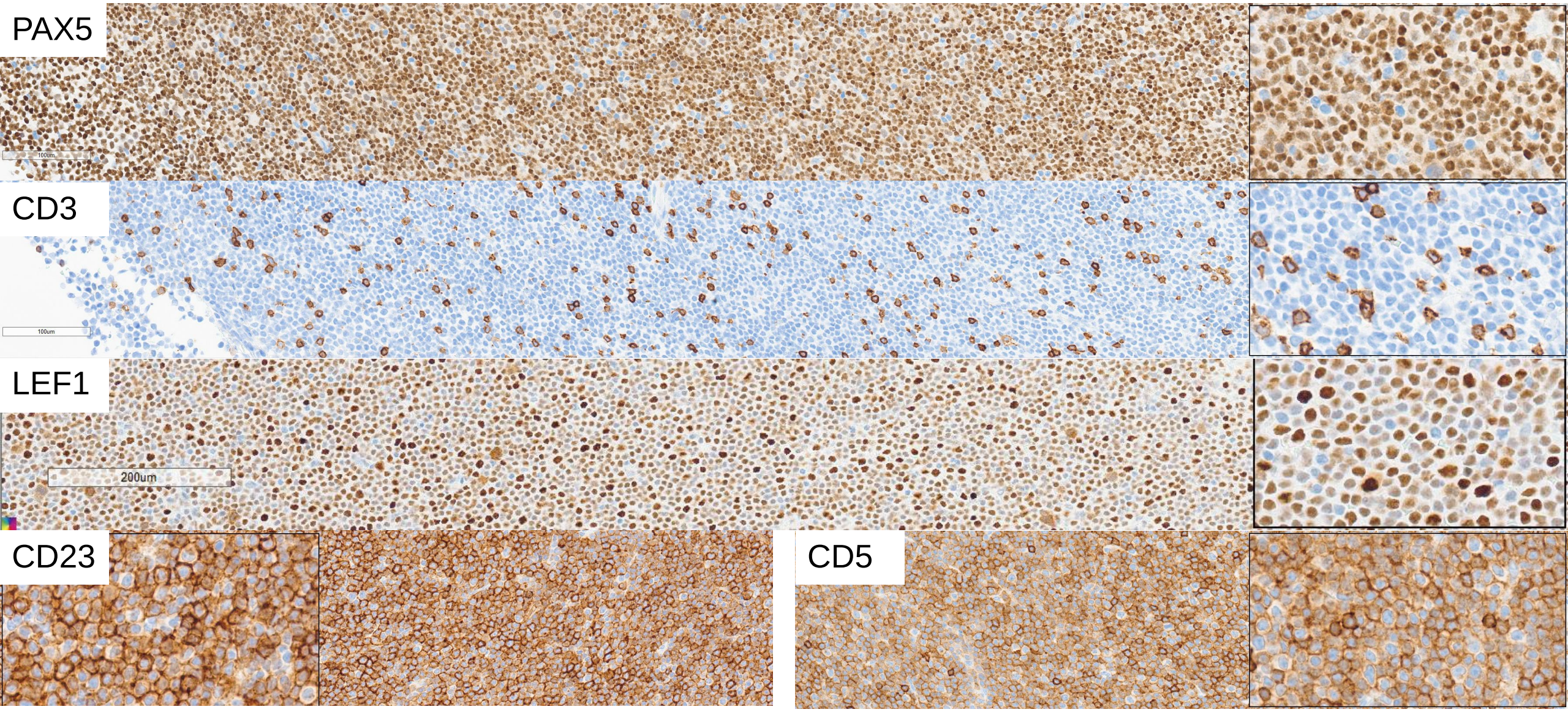
FMC7 BV421 Pacific Blue-A
M


All Cells
FMC7 BV421 Pacific Blue-A
CD200 PE-A
M


All Cells
sKappa APC-A
sLambda FITC-A
M

Right Axillary Lymph Node Excision





Diagnosis: Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

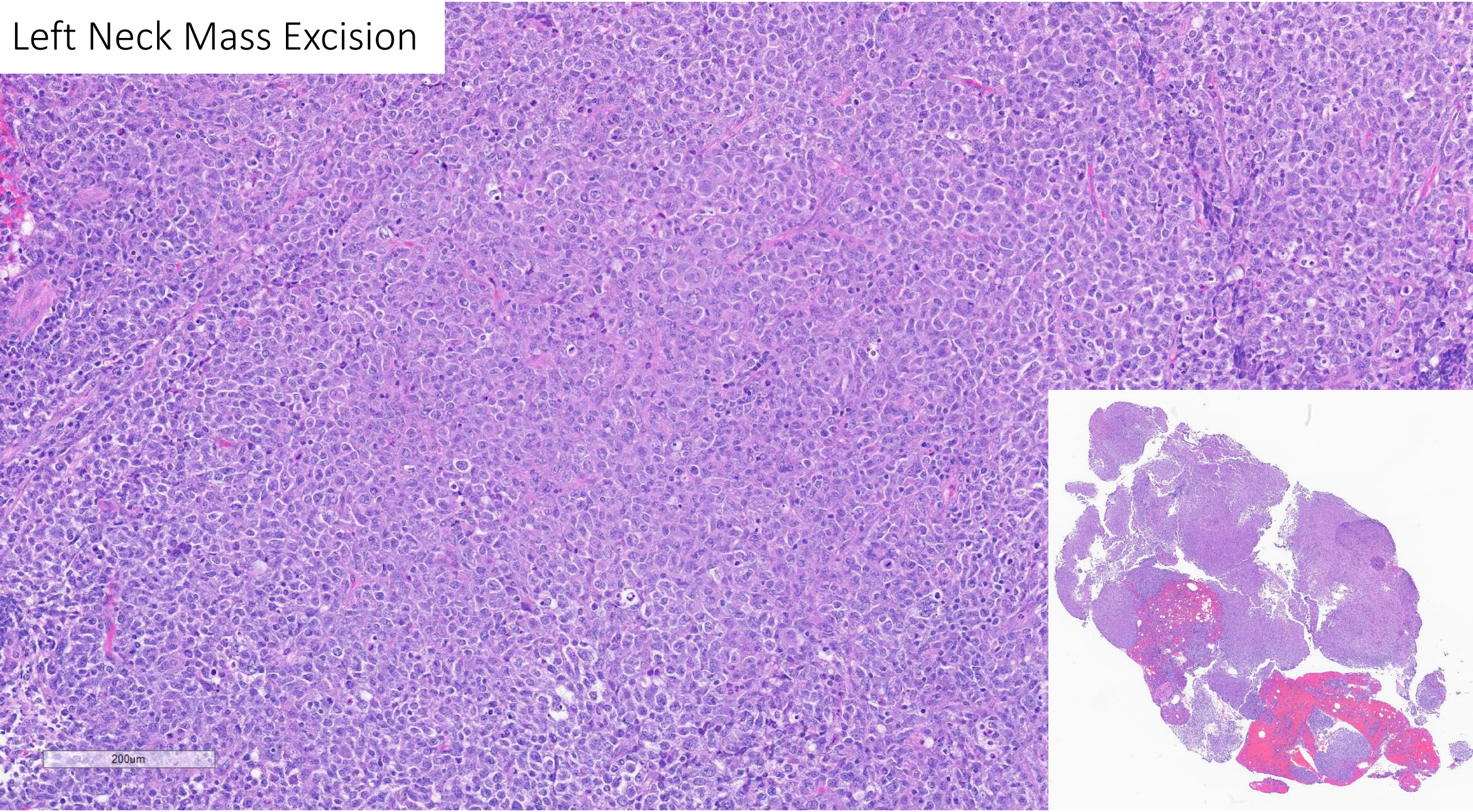
Clinical Information

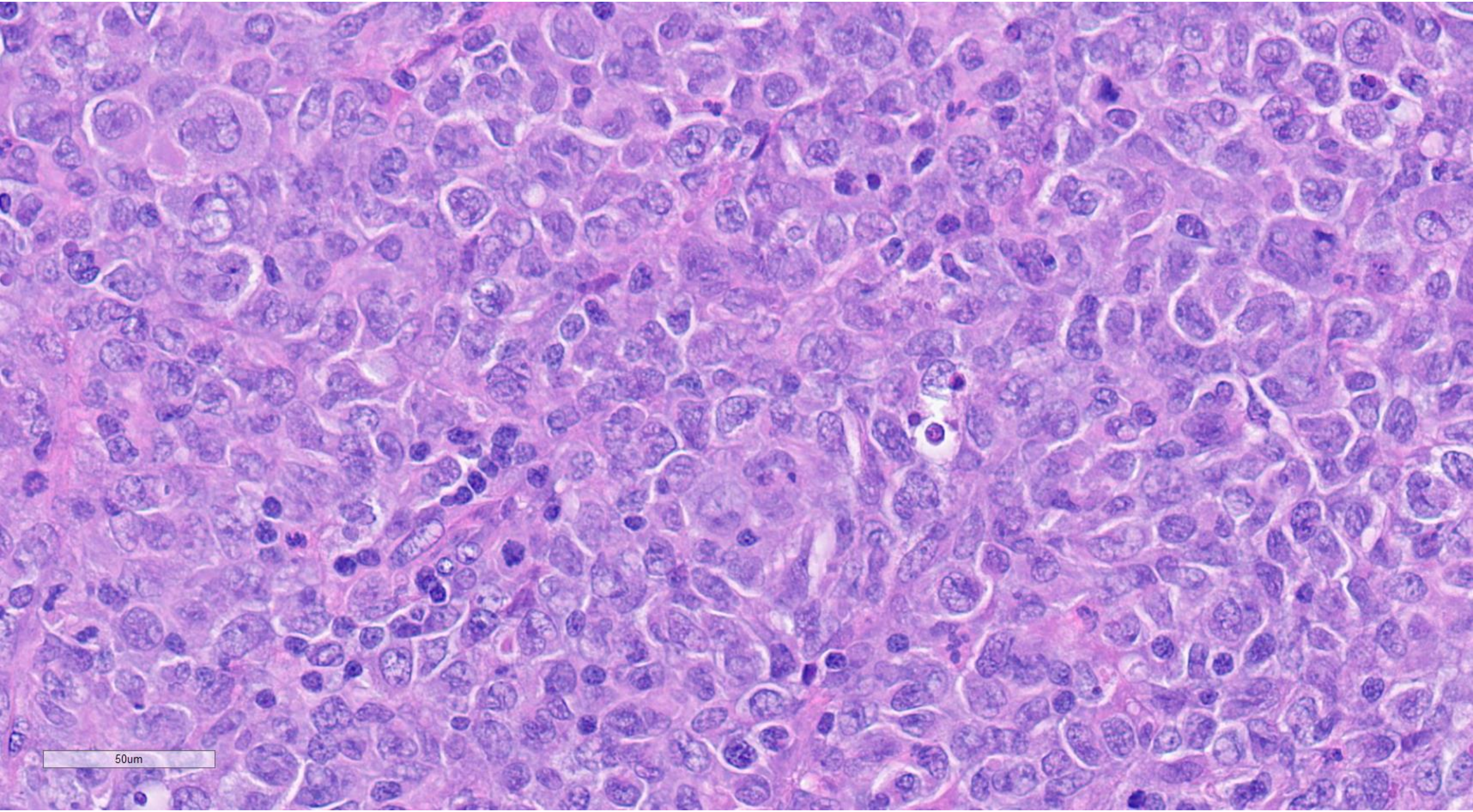
- The patient was treated with rituximab, zanubrutinib, venetoclax, and obinutuzumab.

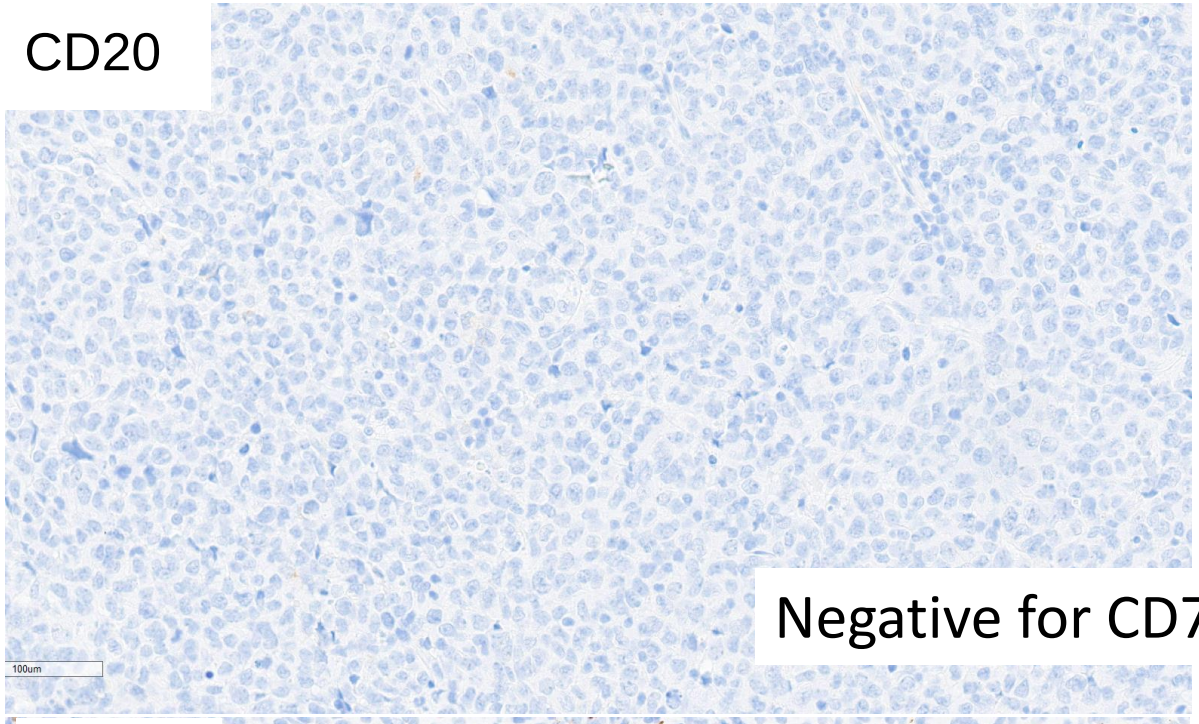
- Subsequent peripheral blood analysis showed normalization of white blood cell and lymphocyte counts, with a marked reduction in abnormal monotypic B-cell populations.

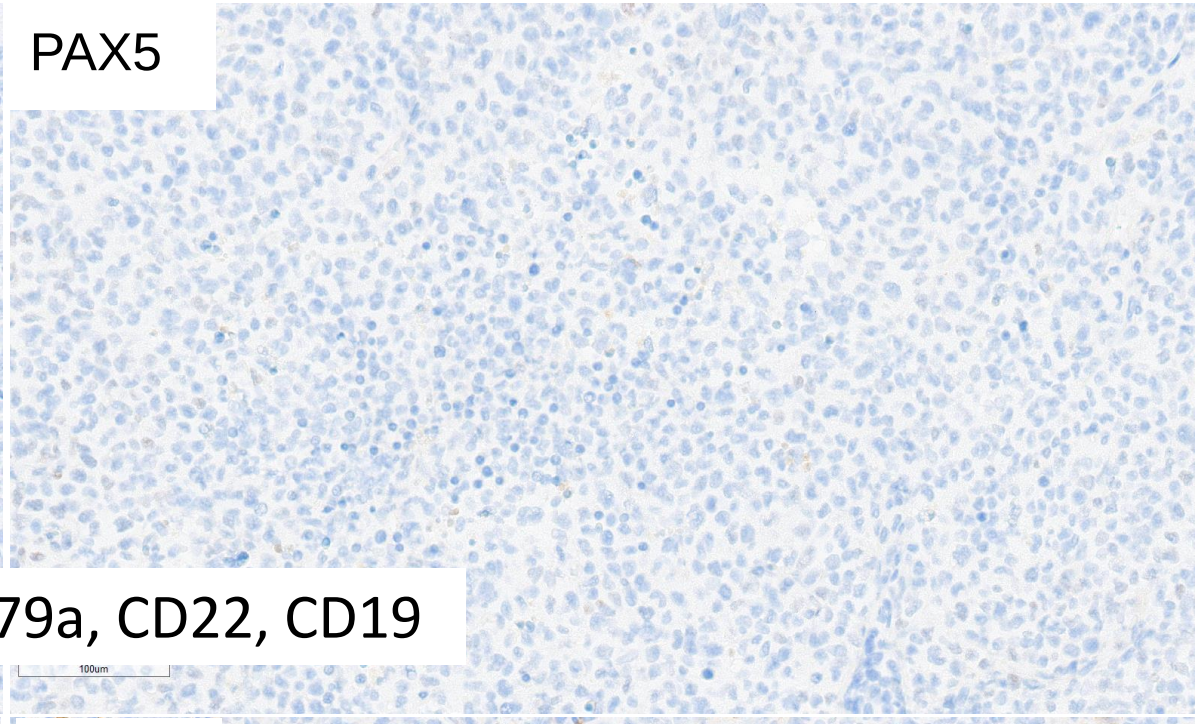
- In March 2025, the patient developed worsening abdominal pain. PET-CT revealed new FDG-avid lymphadenopathy and multiple lesions in the liver and spleen. A left neck mass excision was subsequently performed.

Left Neck Mass Excision

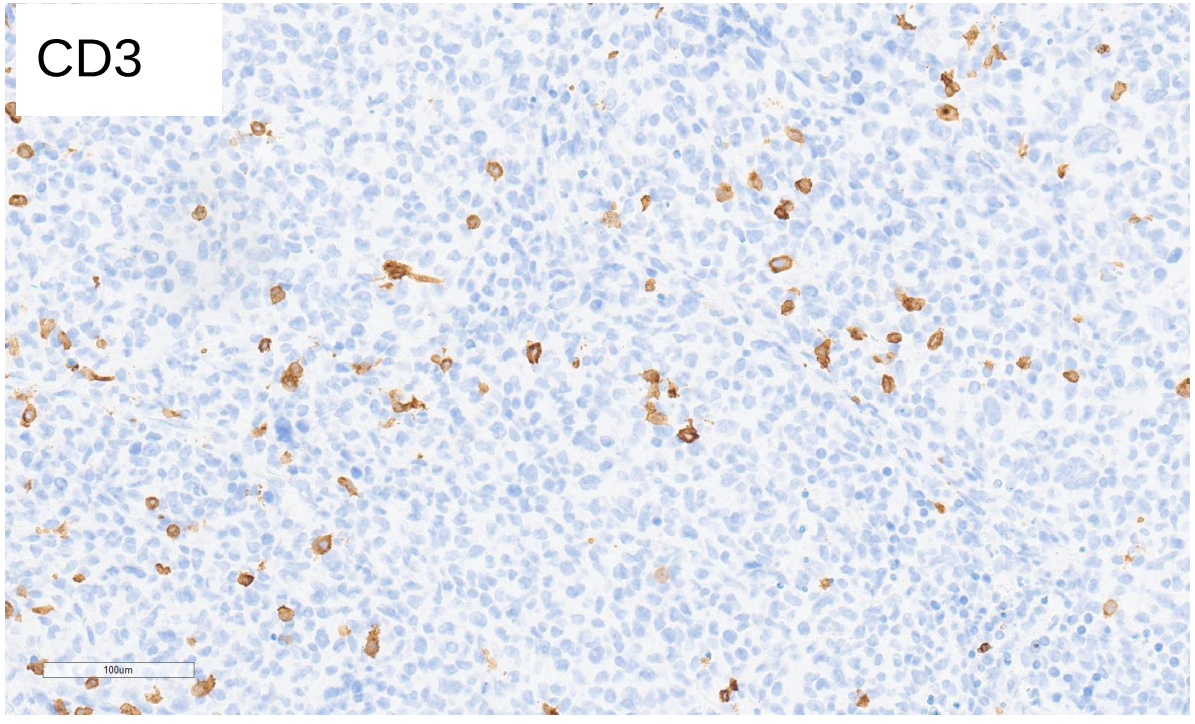


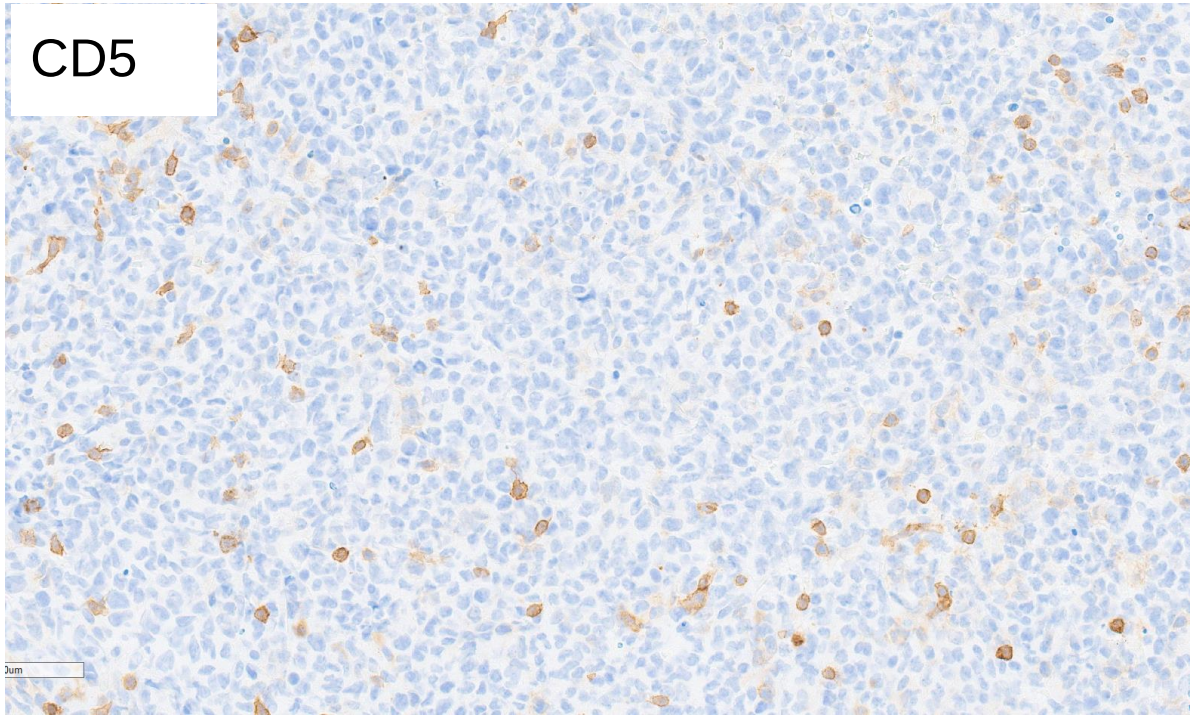

50um

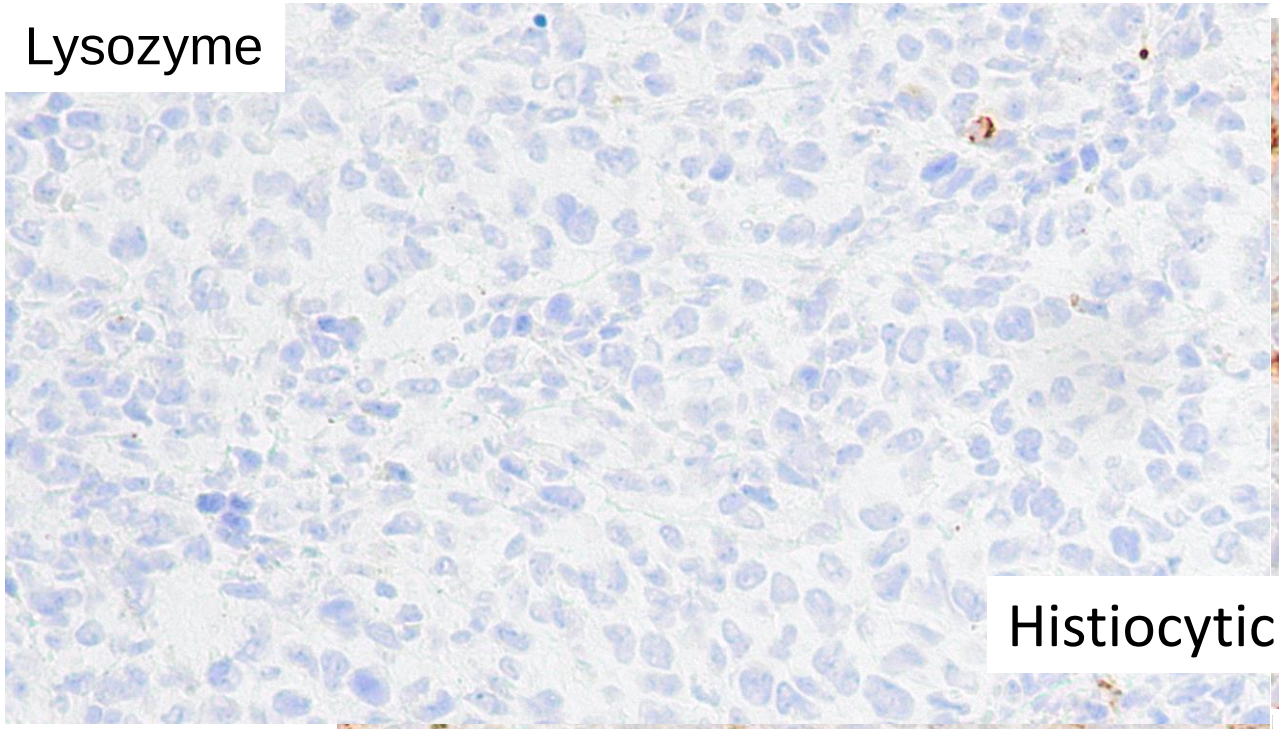


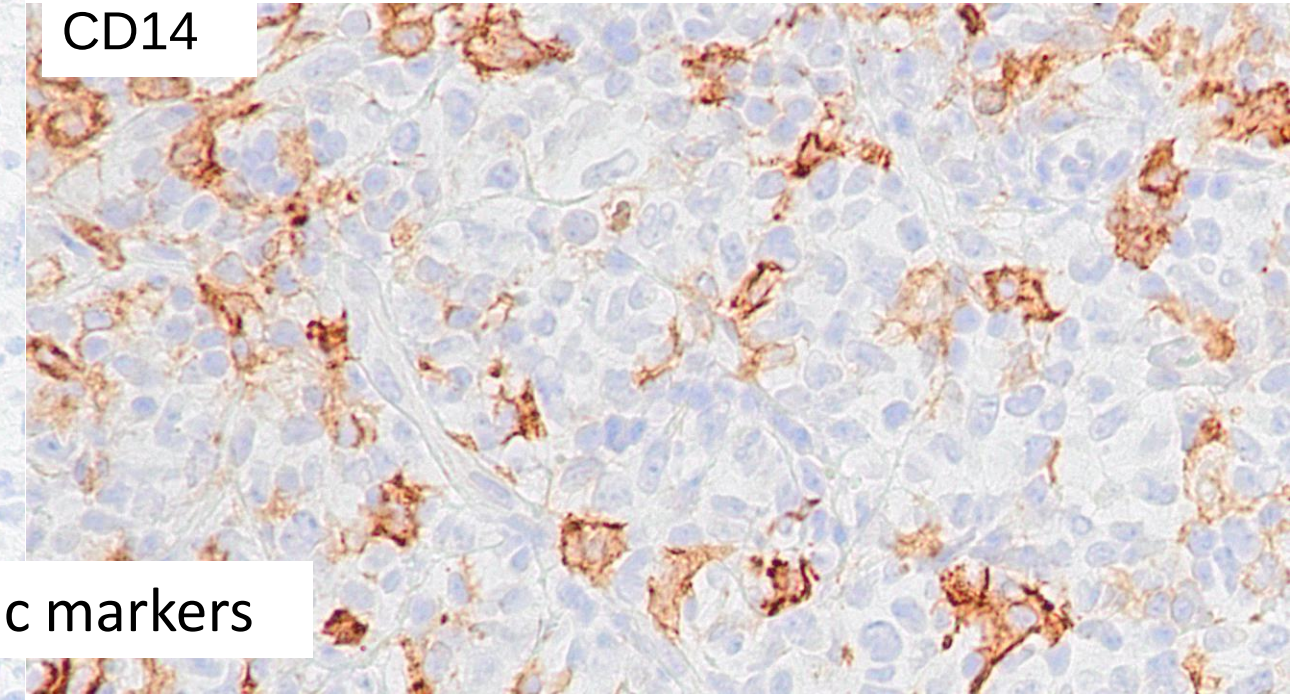


Negative for CD79a, CD22, CD19

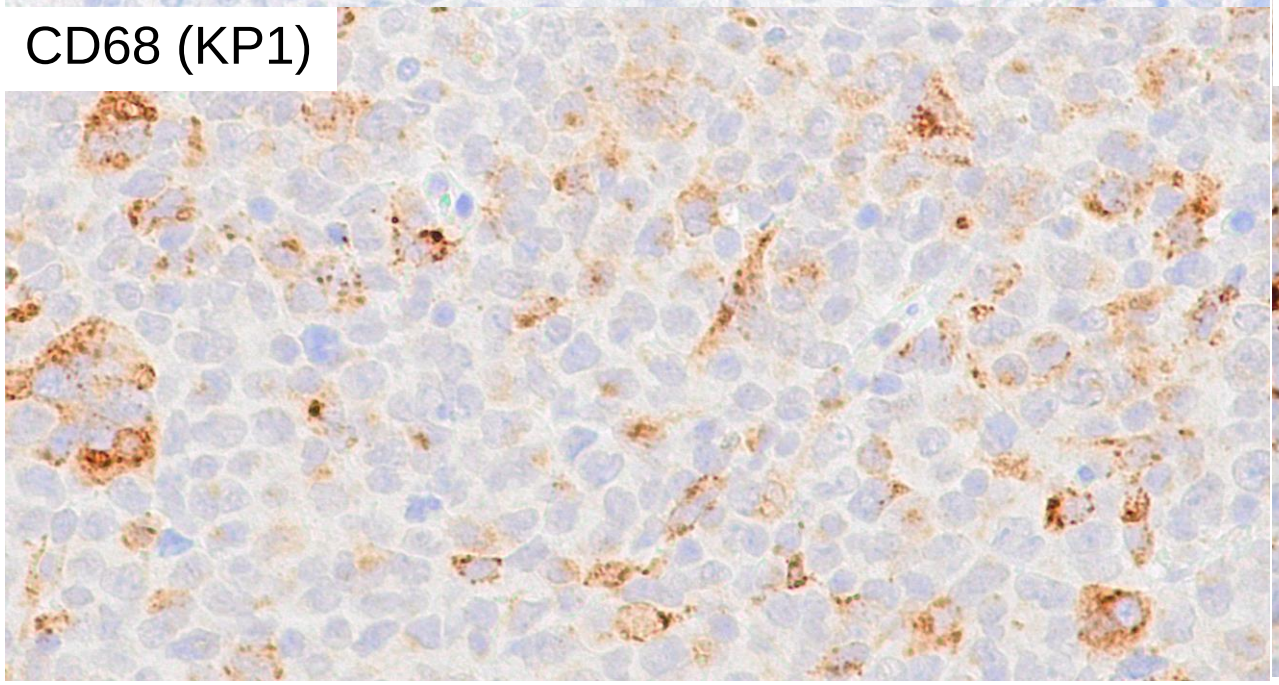


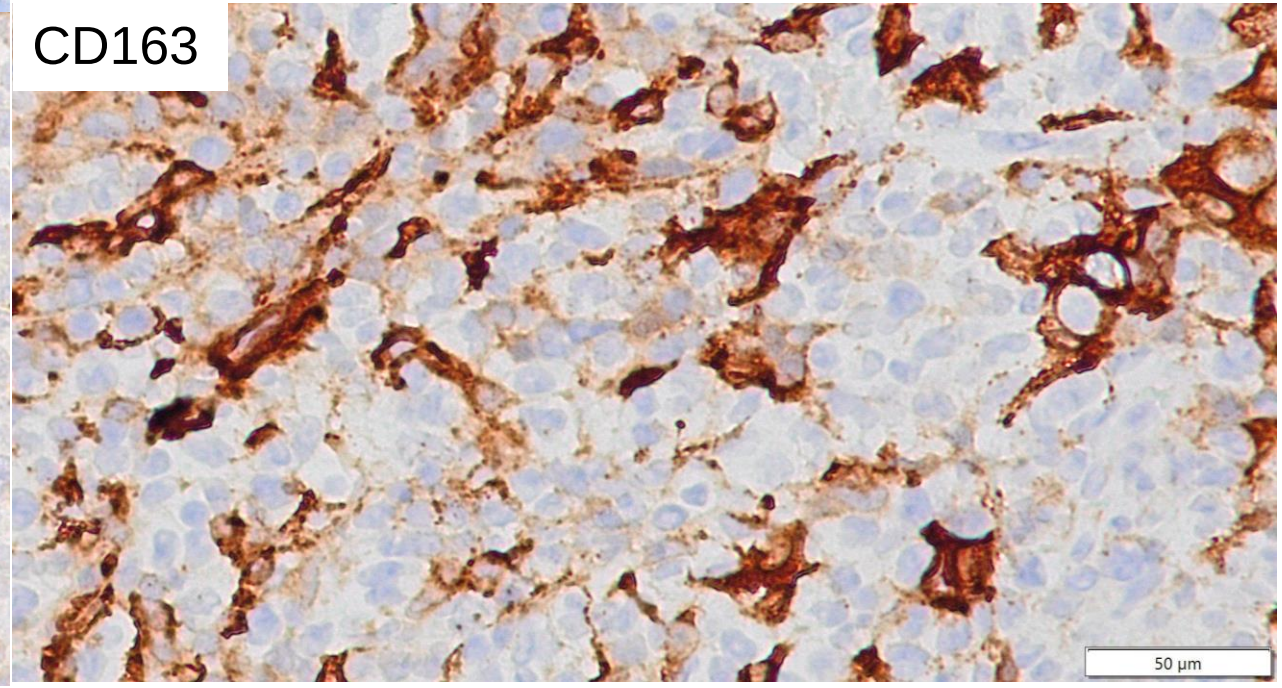


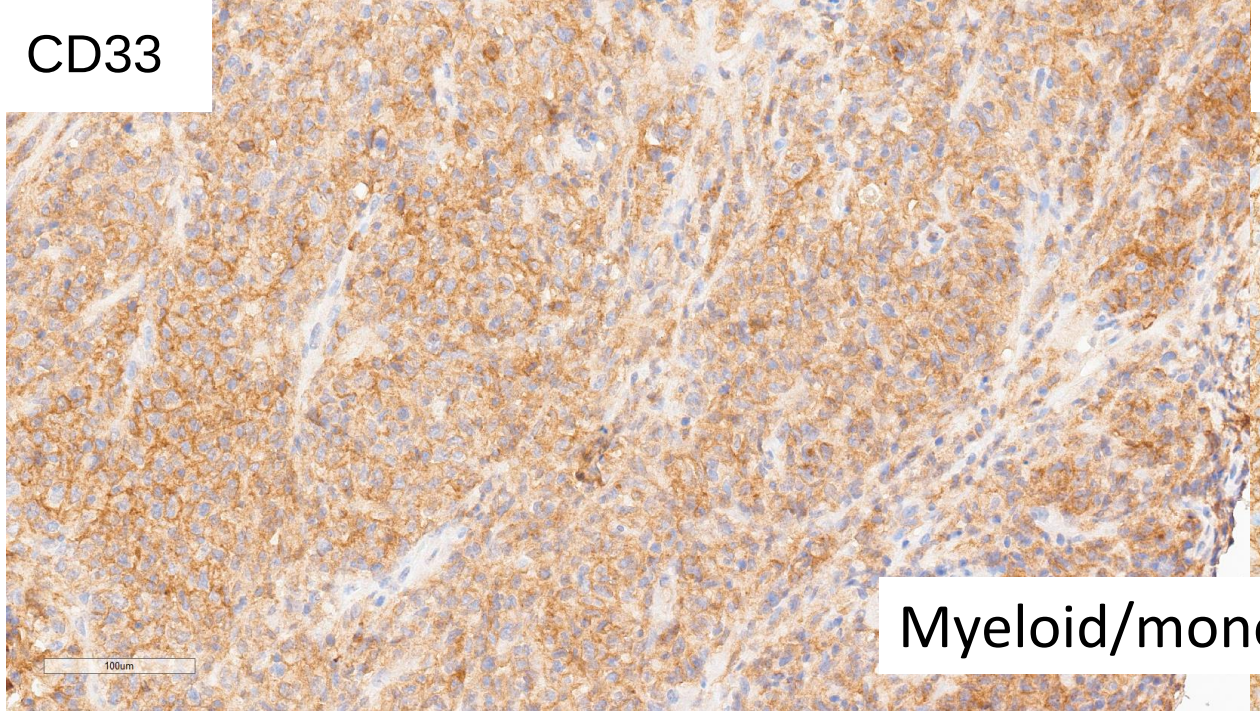


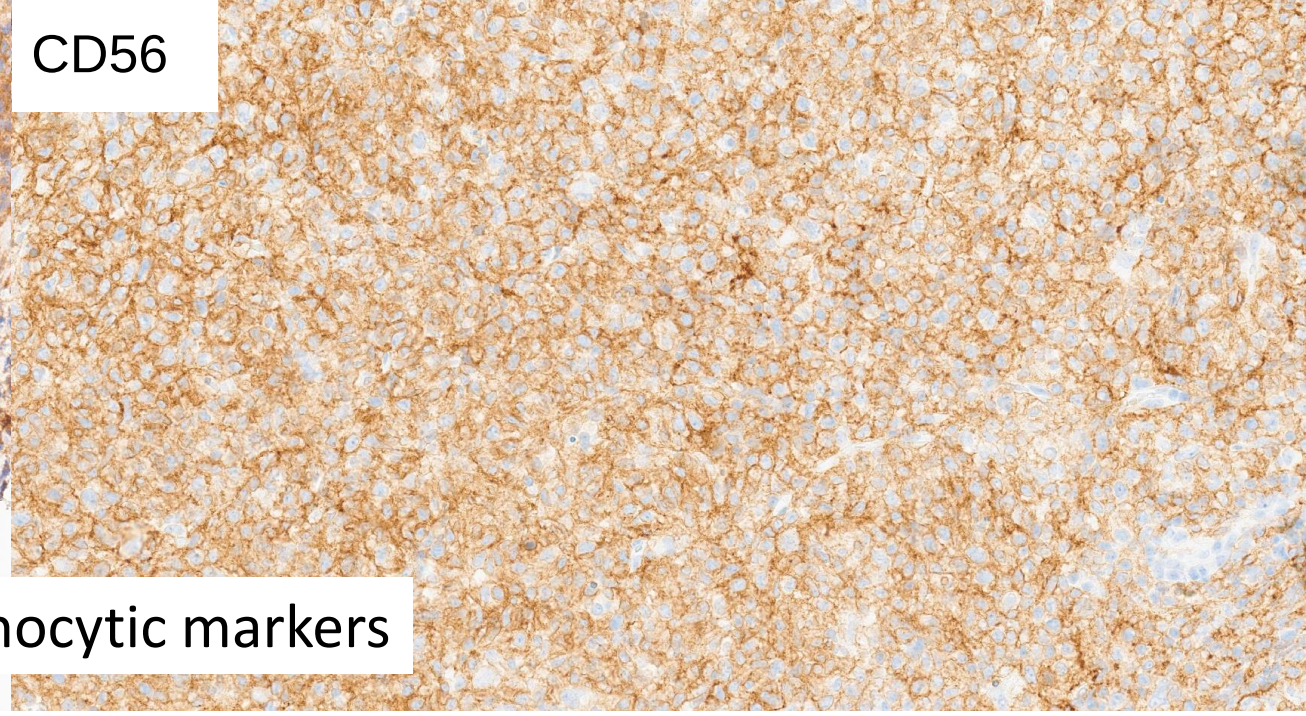


Histiocytic markers

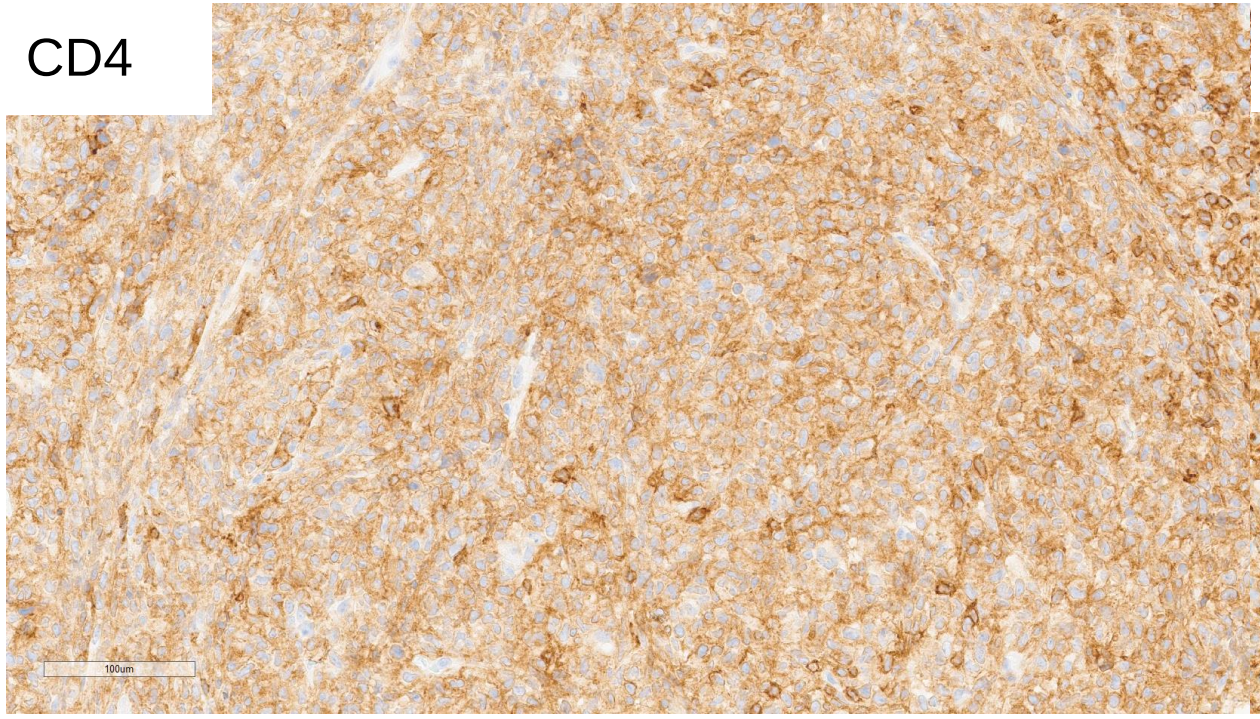


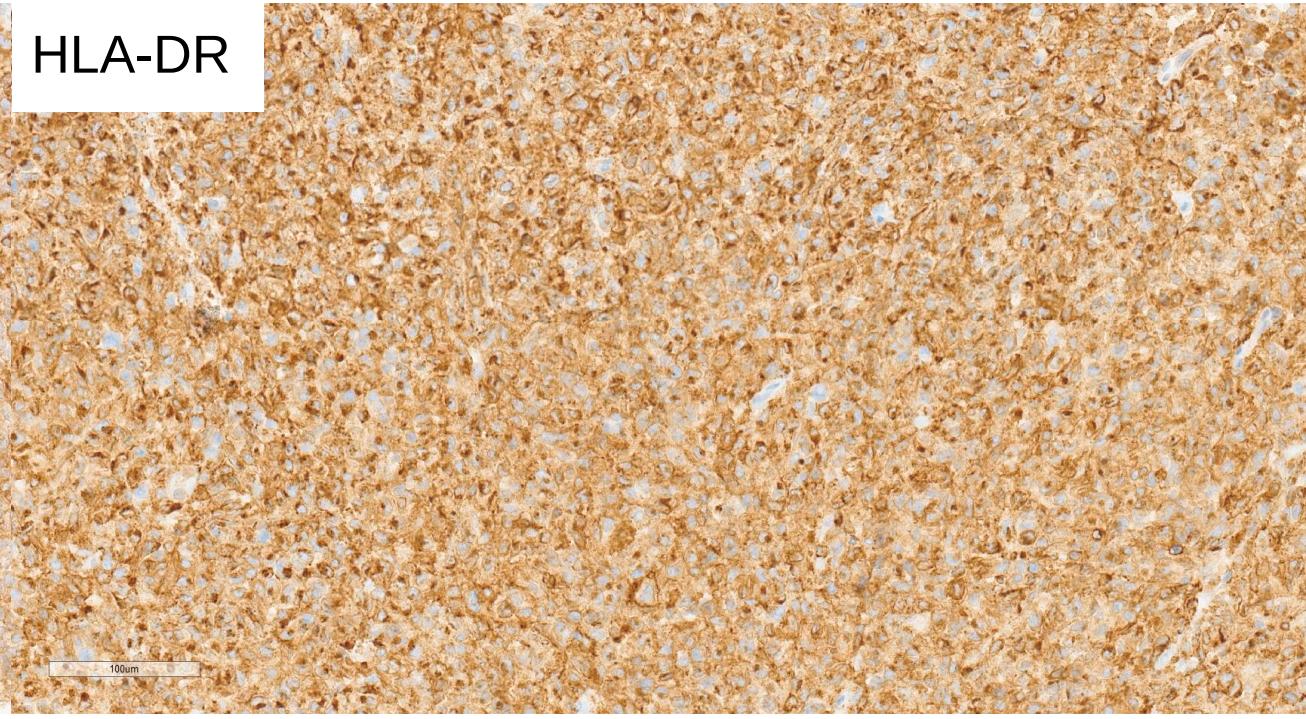


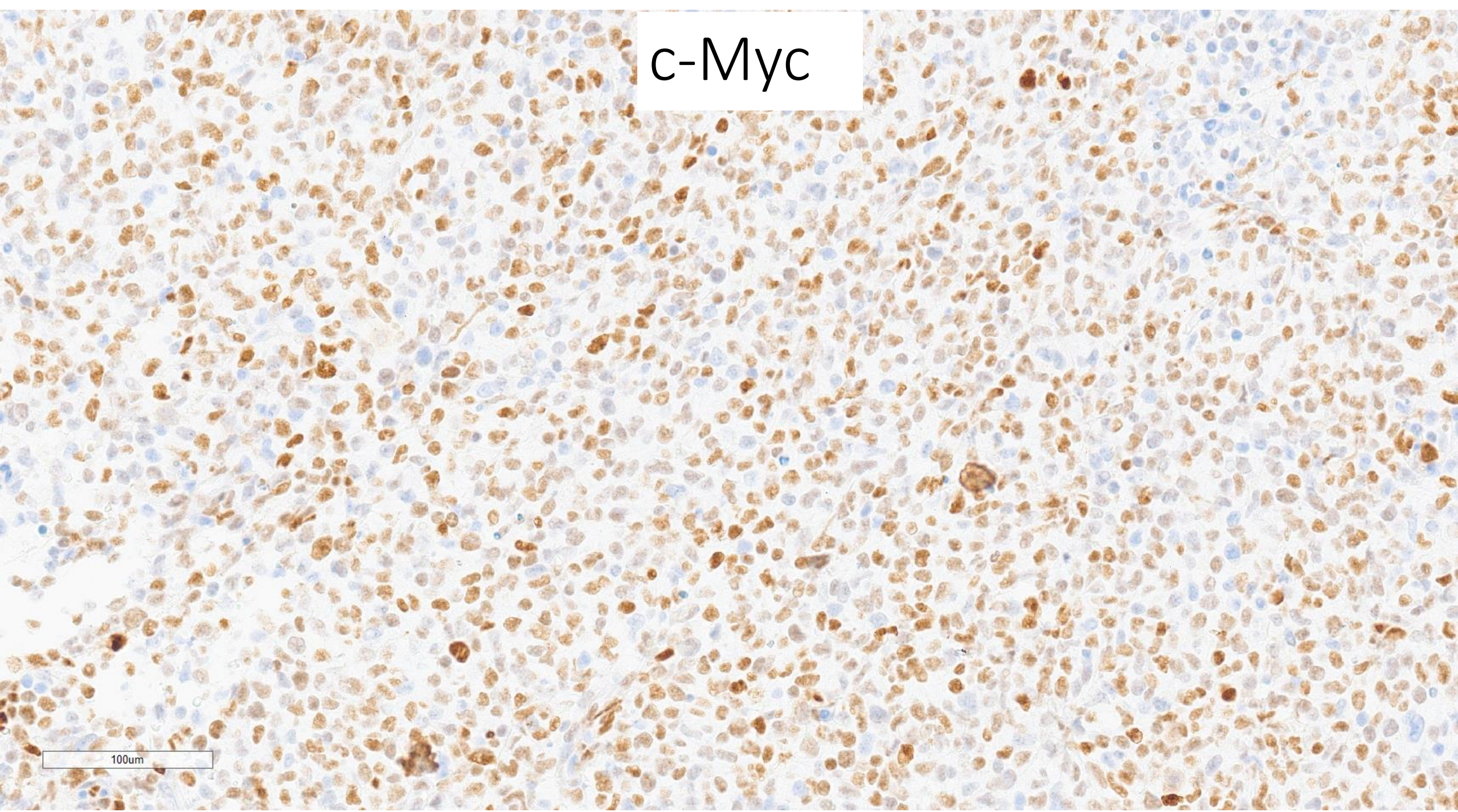


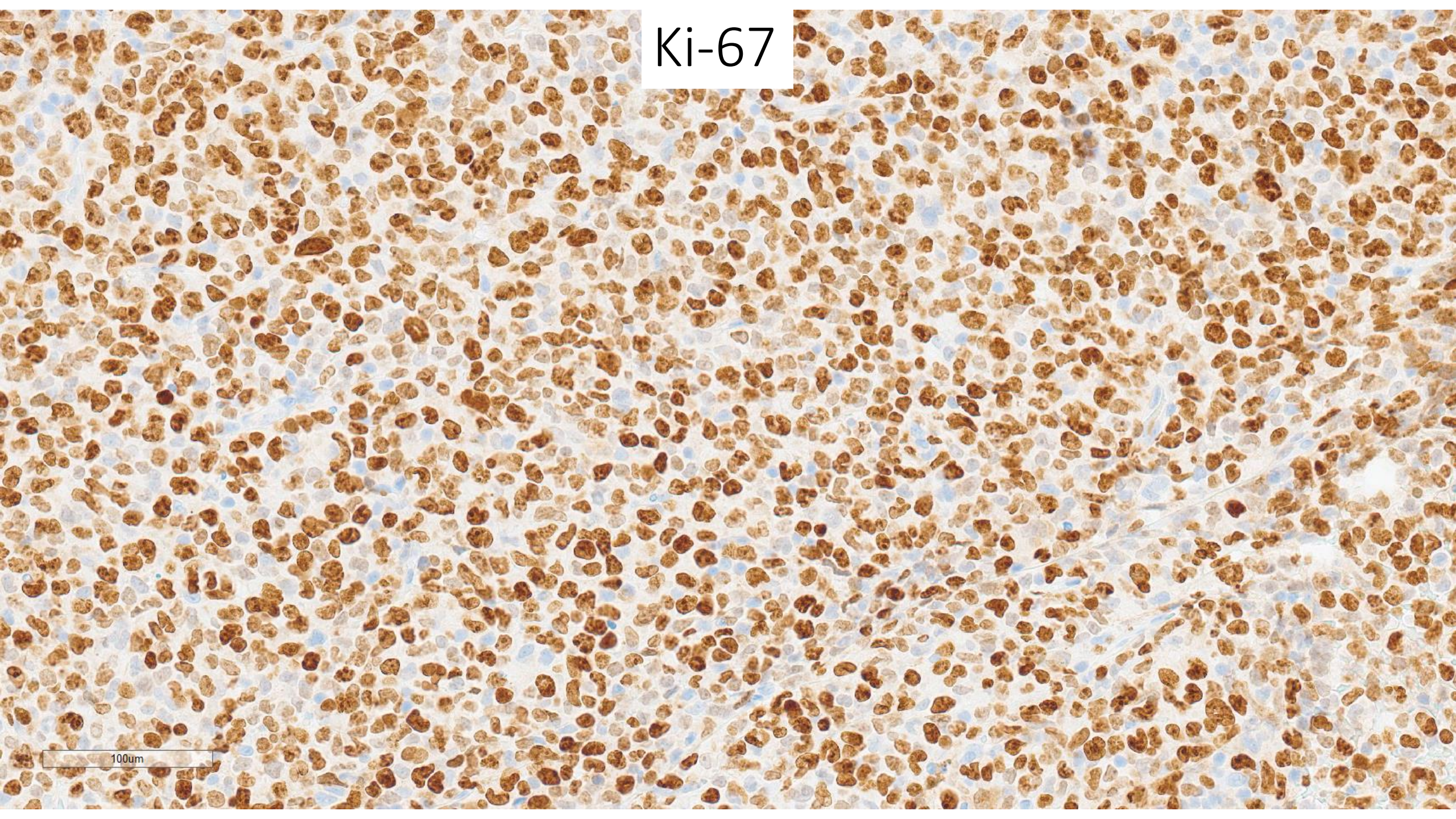


Myeloid/monocytic markers





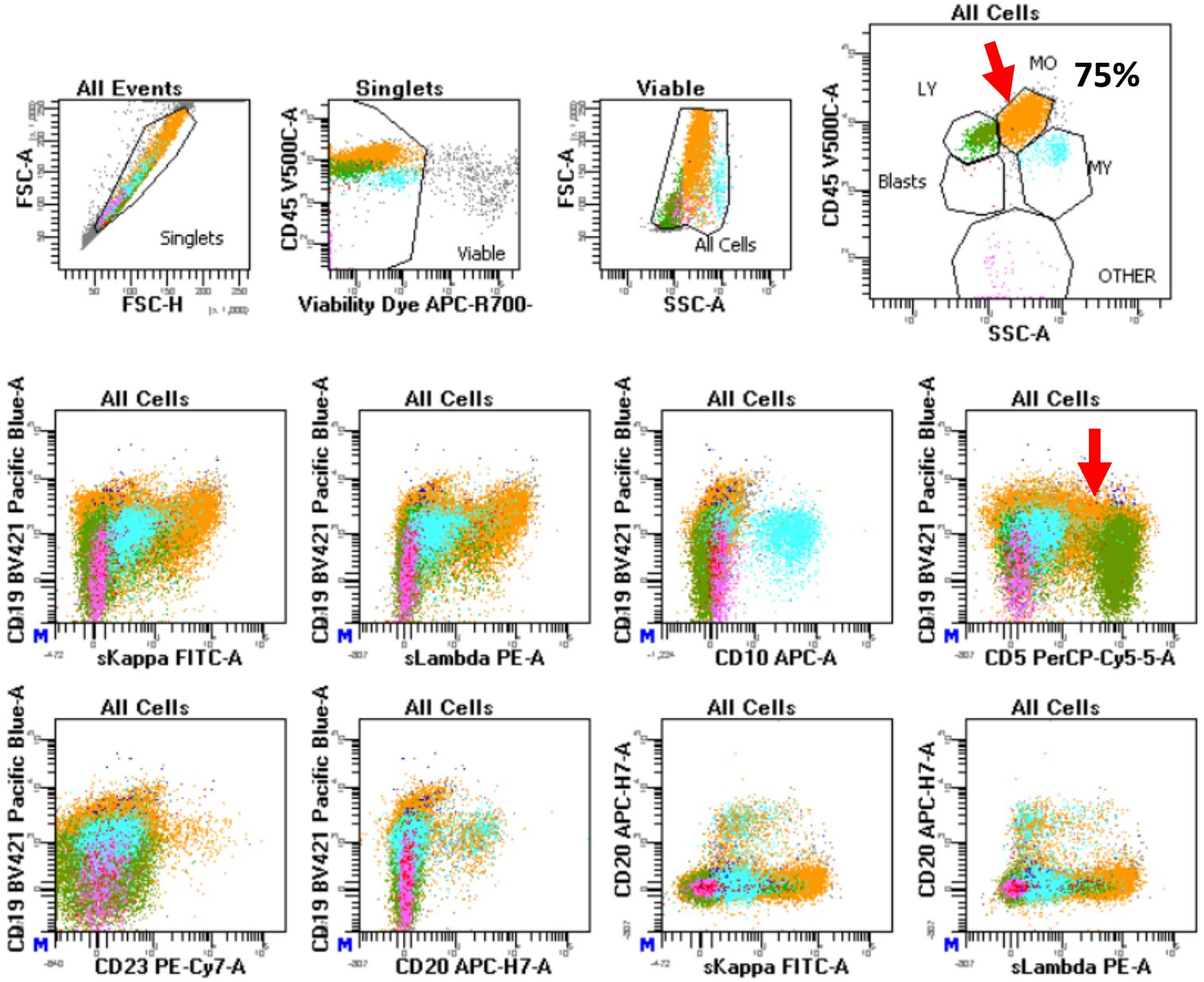

c-Myc
100um


Ki-67
100um

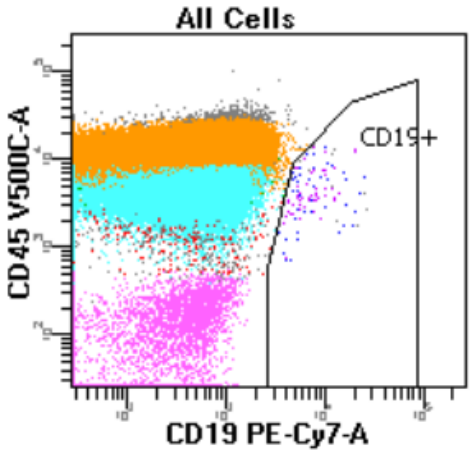
Summary of immunohistochemistry stains

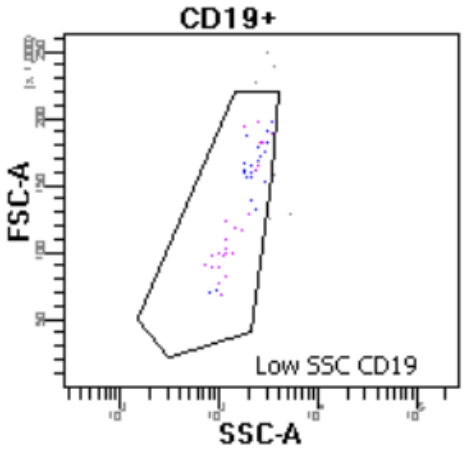
Positive	Negative
HLA-DR, CD33, CD56, CD4, fascin, CD31, c-Myc, LEF1, CD38 (weak/partial), CD5 (small subset/partial), BCL2 (small subset/weak), and BCL1 (partial/weak)	CD3, CD19, CD20, CD22, Pax-5, CD79a, MUM1, CD30, EMA, CD21, CD23, CXCL13, D2-40, CD34, CD117, MPO, Lysozyme, CD15, CD11c, CD14, CD68/KP1, CD68/PGM1, CD163, S100, CD1a, Langerin, PD-L1, CD123, p53, mutant NPM1, Kappa ISH, Lambda ISH, EBER ISH

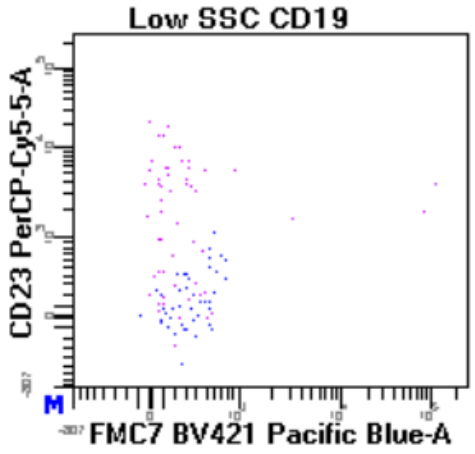
The specimen is predominantly composed of cells with elevated forward and side scatter properties localized within the conventional monocyte gate.

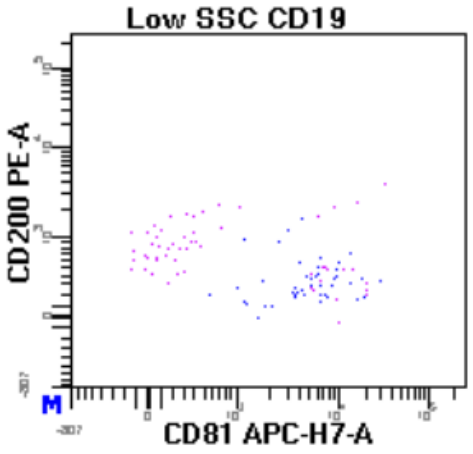


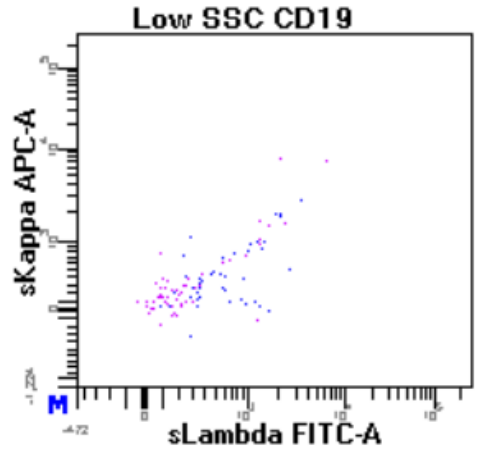
Minute kappa-monotypic B cell population

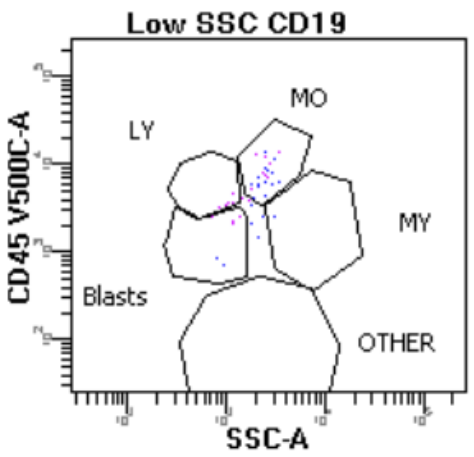


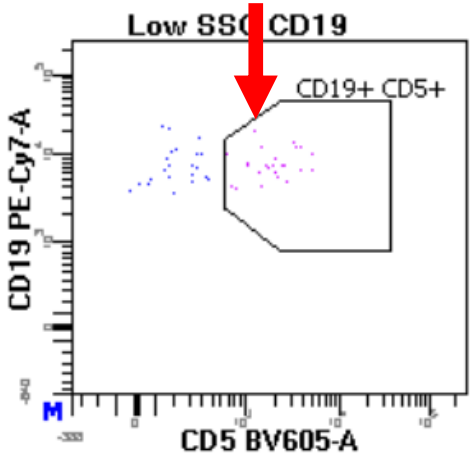


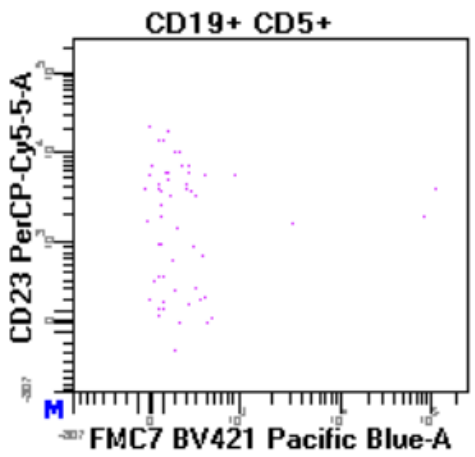


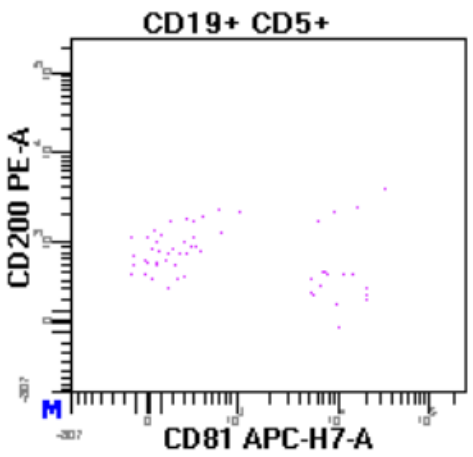


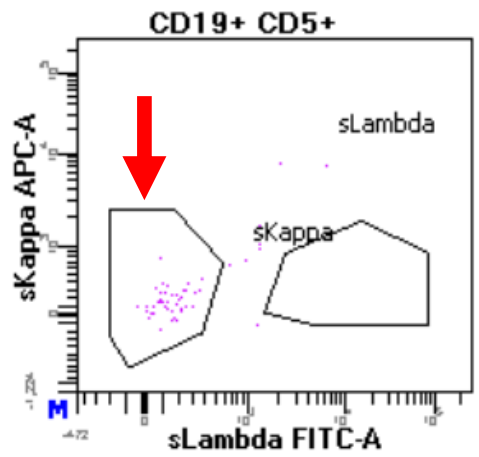












Diagnosis

- Involvement by a myeloid sarcoma.

- Transdifferentiation of the patient’s CLL/SLL into a myeloid sarcoma?

RESULTS OF GENE REARRANGEMENT ANALYSIS

SPECIMEN: A. Peripheral Blood for Molecular **CLL/SLL**

RESULTS:

Ig Heavy Chain: Monoclonal

Ig Kappa Light Chain: Monoclonal

INTERPRETATION: For IGH, a monoclonal pattern was identified (149bp). For IGK, a monoclonal rearrangement was detected (152bp, 200bp in tube A).

SPECIMEN: A. Left Neck Mass for Molecular **Myeloid sarcoma**

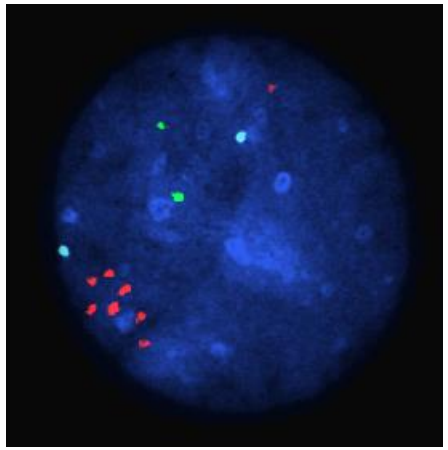
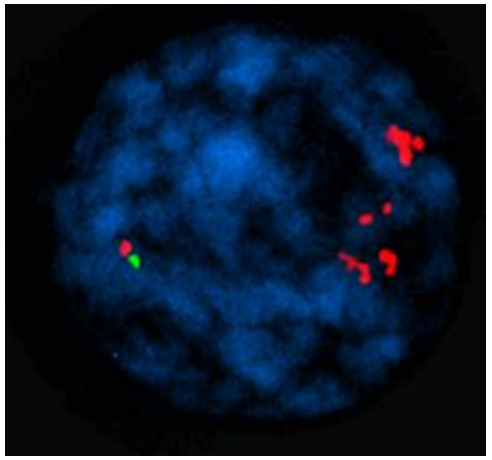
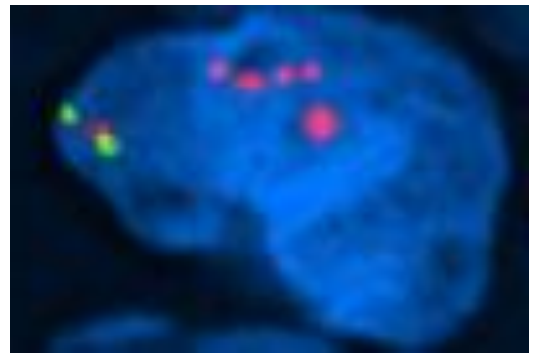
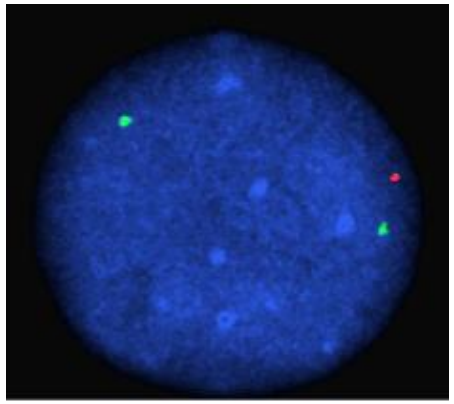
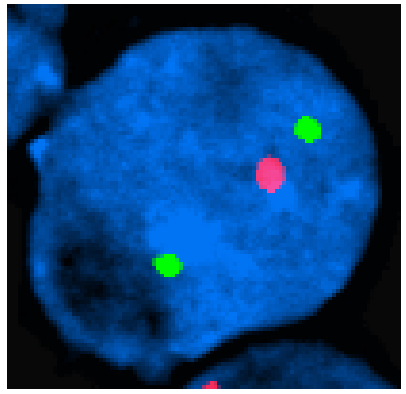
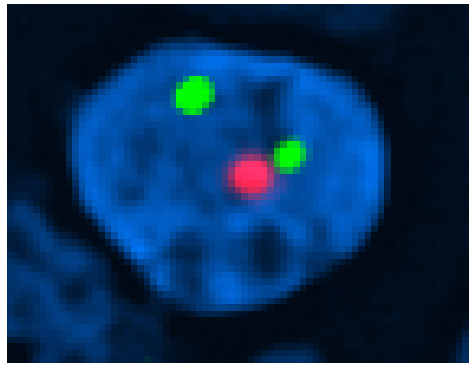
RESULTS:

Ig Heavy Chain: Monoclonal

Ig Kappa Light Chain: Monoclonal

INTERPRETATION: For IGH, a monoclonal pattern was identified (149bp). For IGK, a monoclonal rearrangement was detected (152bp + 200bp in tube A).

FISH positive for MYC amplification and 7q deletion

	Peripheral blood **CLL/SLL**	Right axillary lymph node **CLL/SLL**	Left neck mass **Myeloid sarcoma**
MYC amplification			
7q deletion			

Bone marrow biopsy

Diagnosis:

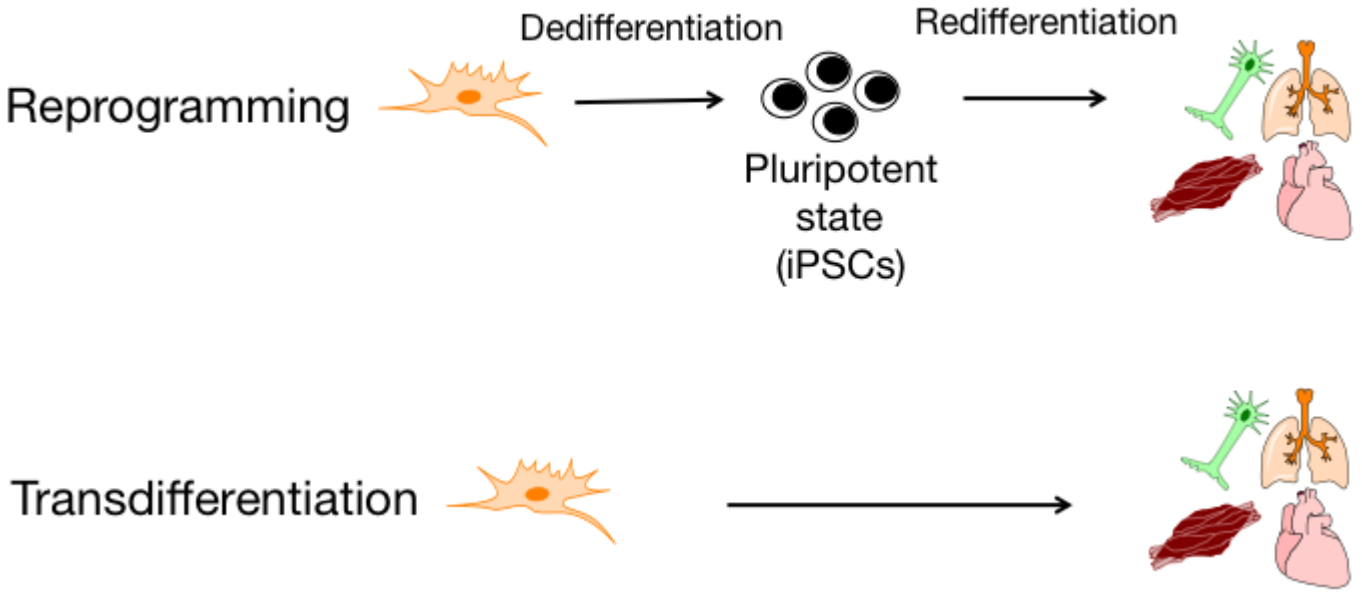
- Chronic lymphocytic leukemia/small lymphocytic lymphoma, residual focal bone marrow involvement (~5% of marrow cellularity).

Cytogenetics:

- 46,XX[20]
- FISH AML/MDS panels: Normal

Transdifferentiation

- Transdifferentiation refers to a process in which a mature cell type switches lineage identity into a phenotypically and functionally distinct lineage without reverting to a pluripotent state.



Post by Kusumika Mukherjee.

- In hematologic malignancies, transdifferentiation is most notably observed in low-grade B-cell lymphomas (follicular lymphoma, CLL/SLL, and marginal zone lymphoma) that transdifferentiate into histiocytic/dendritic cell neoplasm.

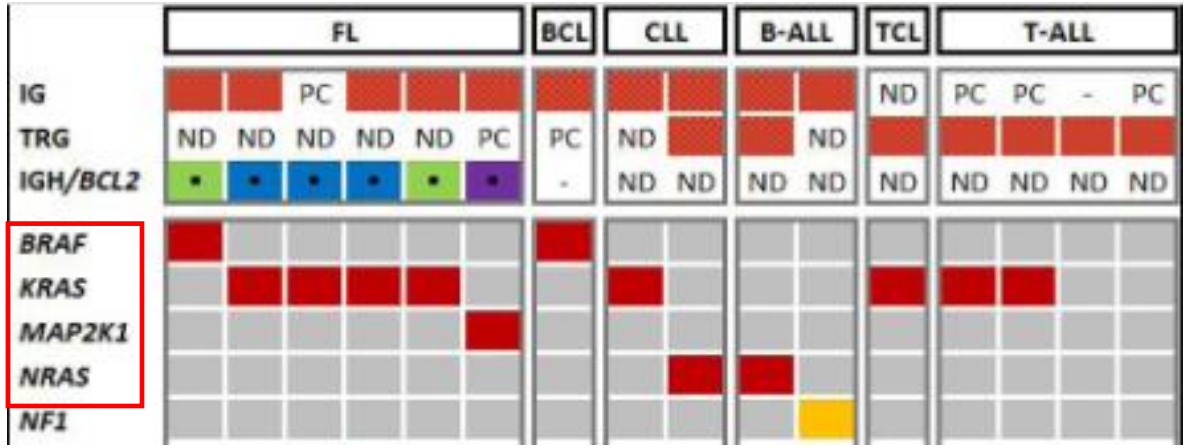
- These cases often occur in the setting of disease progression or relapse and may follow targeted therapies such as rituximab or BTK inhibitors.

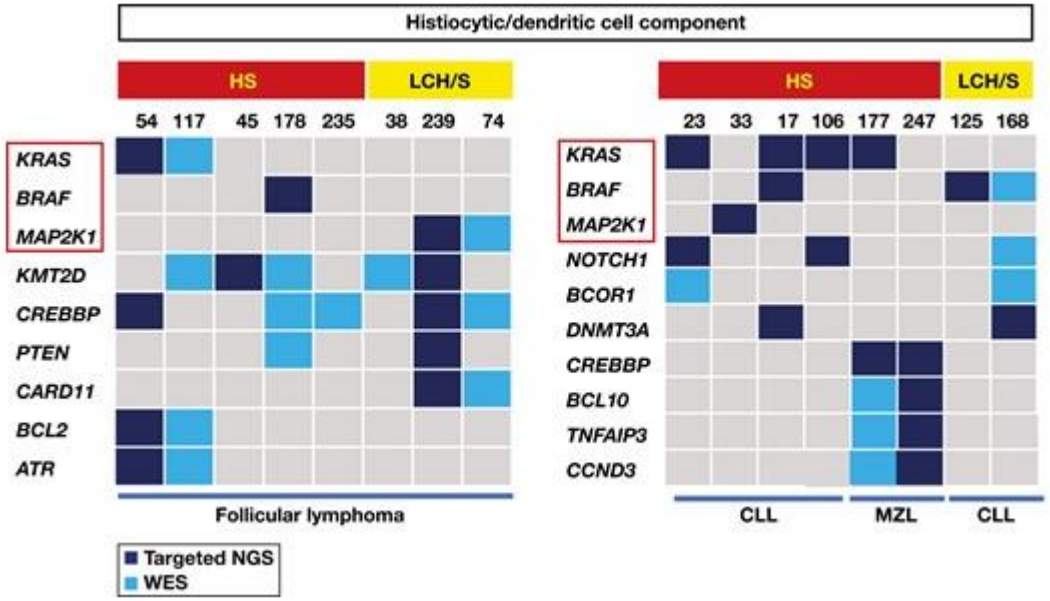
- To the best of our knowledge, transformation of CLL/SLL into a lesion most consistent with myeloid sarcoma has not been previously reported in the literature.

Xiao W. et al. Am J Clin Pathol. 2023 Jun 1;159(6):522-537.

Mutational profile

- A high frequency of mutations in the RAS/MAPK pathway was found in secondary histiocytic/dendritic neoplasms associated with diverse lymphoid malignancies.





Egan C. et al. Mod Pathol. 2021 Feb;34(2):336-347.
Xiao W. et al. Am J Clin Pathol. 2023 Jun 1;159(6):522-537.

Left Neck Mass NGS findings

Genomic Findings

IA	IB	IIC		IID	
No variants reported.	No variants reported.	***NRAS***	p.G12D c.35G>A VAF 41.4%	***FBXW7***	p.R361P c.1082G>C
		KRAS	p.G13D c.38G>A VAF 53.3%	***CDKN2B***	Copy number loss in *CDKN2B* (1 copy)
		0 Clinical Trials		***CDKN2A***	Copy number loss in *CDKN2A* (0 copies)
				ATM	Copy number loss in *ATM* (1 copy)
				MYC	Copy number gain in *MYC* (5 copies)
				0 Clinical Trials	

Proposed mechanism

- Transdifferentiation is driven by disruption of lineage-specifying transcription factors (e.g., PAX5) and induction of myeloid-associated regulators like PU.1 and C/EBPα.

- In murine models, the deletion of *Pax5* in B cells results in reprogramming toward macrophage lineages.

Mikkola I, et al. Science. 2002;297(5578):110-113.
Xie H, et al. Cell. 2004;117:663–676.

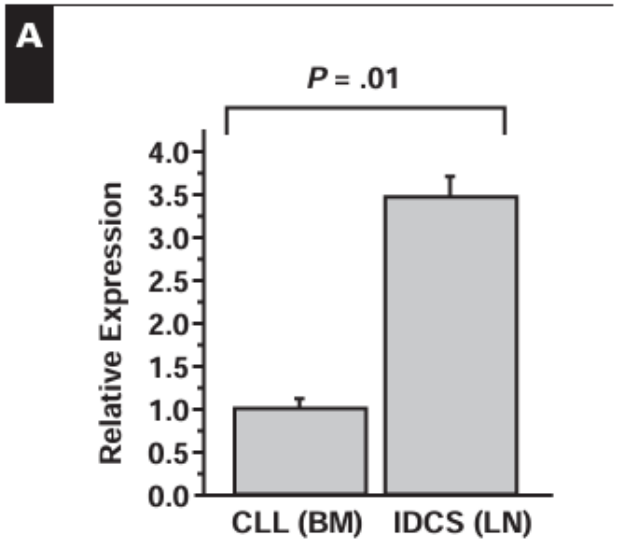
Case Reports > Am J Clin Pathol. 2009 Dec;132(6):928-39. doi: 10.1309/AJCPWQ0I0DGXBMHO.

Transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma to interdigitating dendritic cell sarcoma: evidence for transdifferentiation of the lymphoma clone

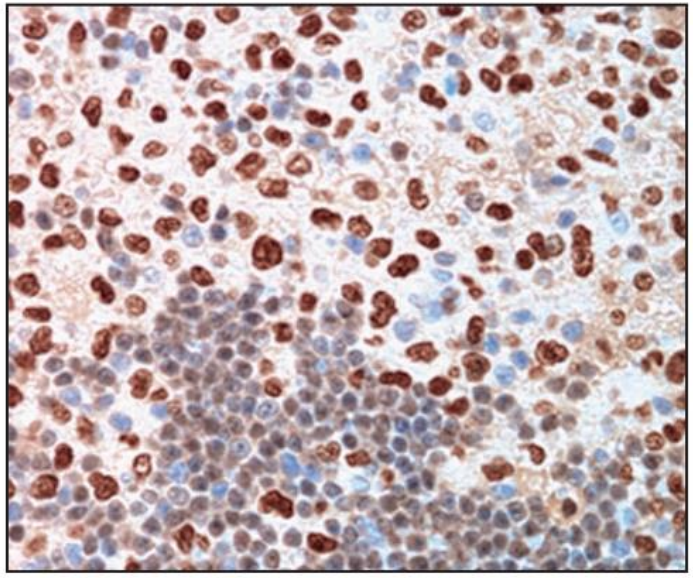
Cory R Fraser [1], Wei Wang, Mario Gomez, Taotao Zhang, Susan Mathew, Richard R Furman, Daniel M Knowles, Attilio Orazi, Wayne Tam

Affiliations + expand

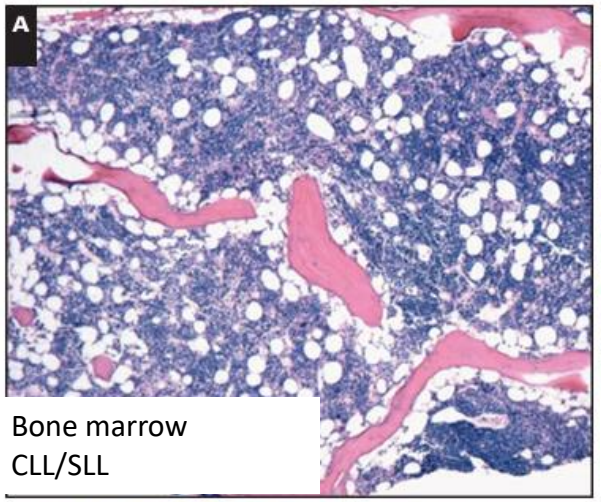
PMID: 19926586 DOI: 10.1309/AJCPWQ0I0DGXBMHO



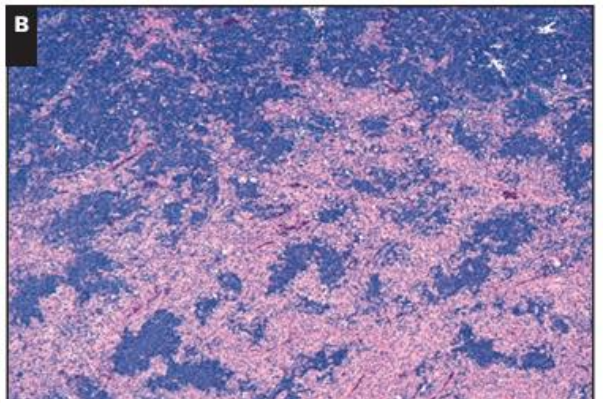
PU.1 RT-PCR



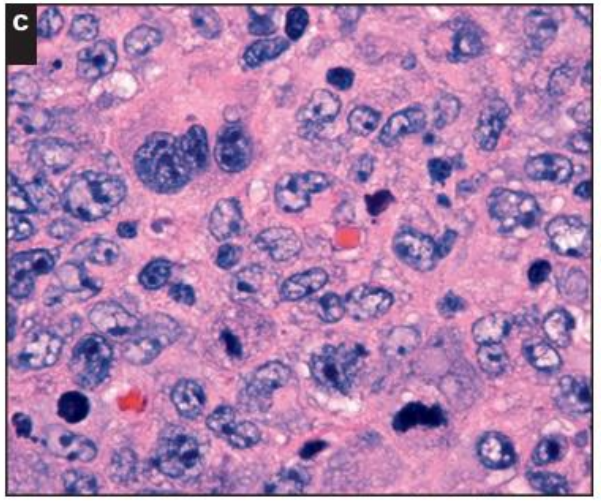
High expression of PU.1 in IDCS cells compared with the weak expression in the adjacent CLL cells

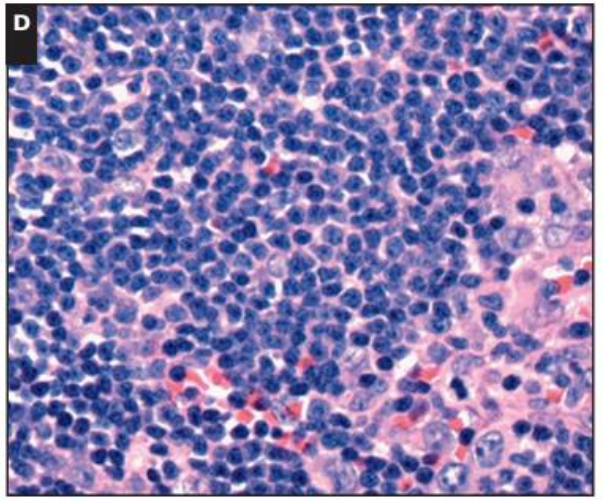


Bone marrow
CLL/SLL

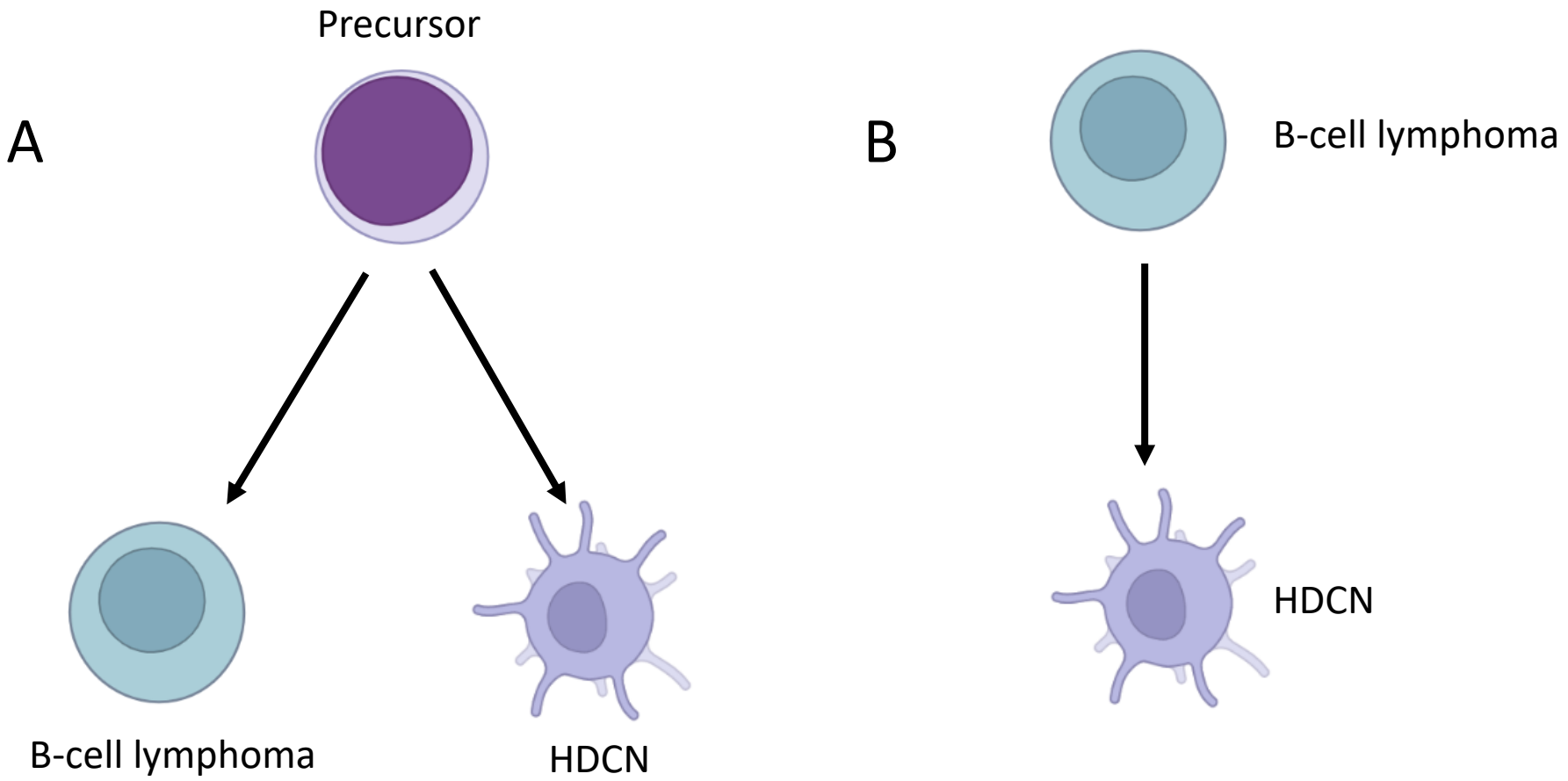


Lymph node
Interdigitating dendritic cell sarcoma (IDCS)





Patterns of clonal evolution



A, Divergent clonal evolution.

B, Linear evolution.

Xiao W. et al. Am J Clin Pathol. 2023 Jun 1;159(6):522-537.

Prognostic and therapeutic implications

- These transformed neoplasms are typically clinically aggressive, with limited response to conventional therapies. Median survival is often less than two years following transformation.

- Treatment strategies are not standardized and may rely on phenotype-directed regimens.

- Emerging therapies targeting lineage plasticity, epigenetic modifiers, and tumor microenvironmental signaling are currently under investigation.

Kommalapati A, et al. Blood. 2018;131(2):265-268.

Thank you!