Multi-institutional Hematopathology

Interesting Case Presentation

EMORY UNIVERSITY SCHOOL OF MEDICINE

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Financial Disclosure

- I have no financial interests or relationships to disclose

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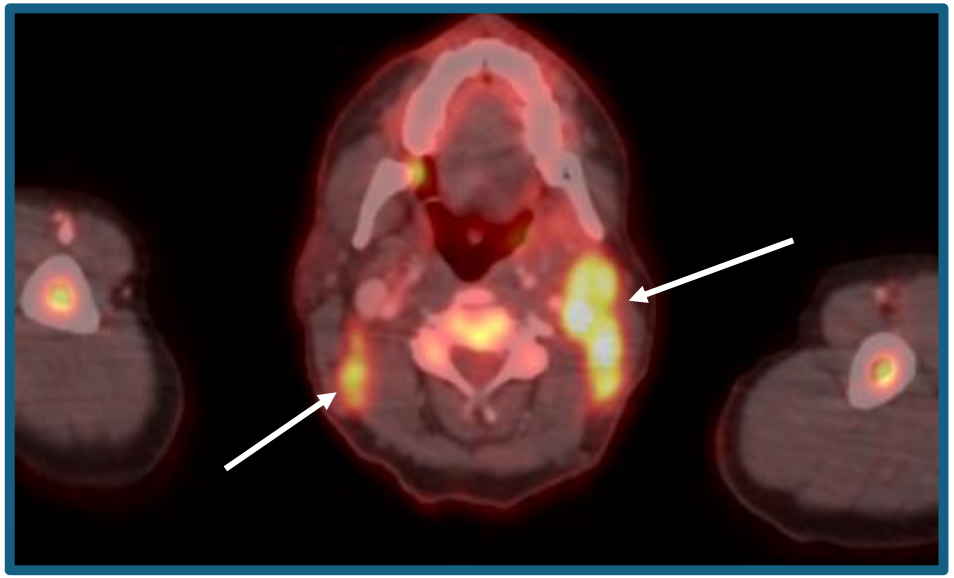
Case Presentation:

- **History**: 56-year-old male, with stage **IIIA follicular lymphoma** on observation since **2005** presented with rapidly enlarging bilateral neck masses and throat pain

Imaging

PET CT:

- **Bilateral cervical lymphadenopathy** (SUV **20.0**) and **left tonsil** enlargement suggestive of lymphoproliferative disease/metastases



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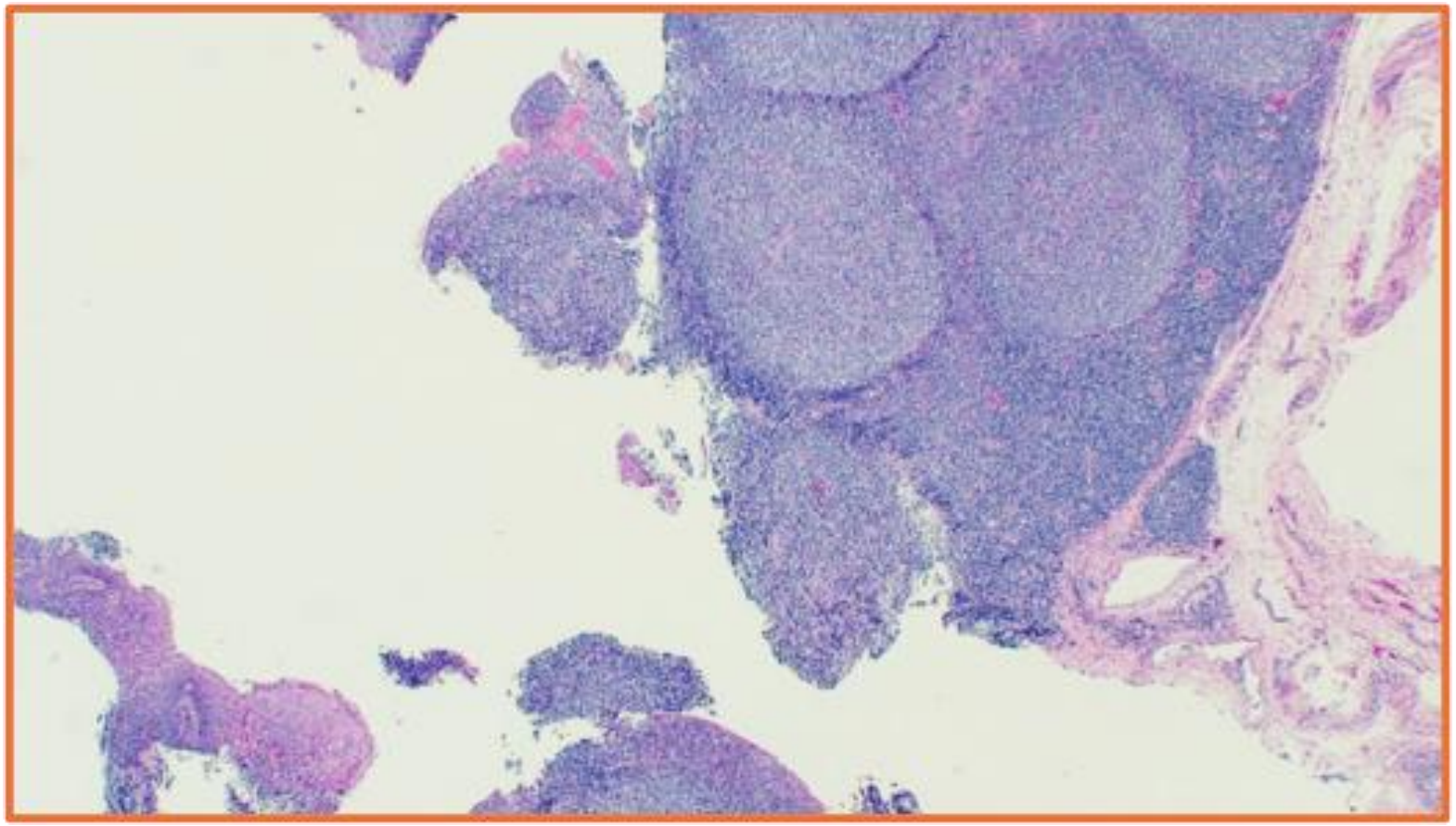
Tonsil mass, left, biopsy:

- Follicular lymphoma (persistent)
- **No** large cell lymphoma



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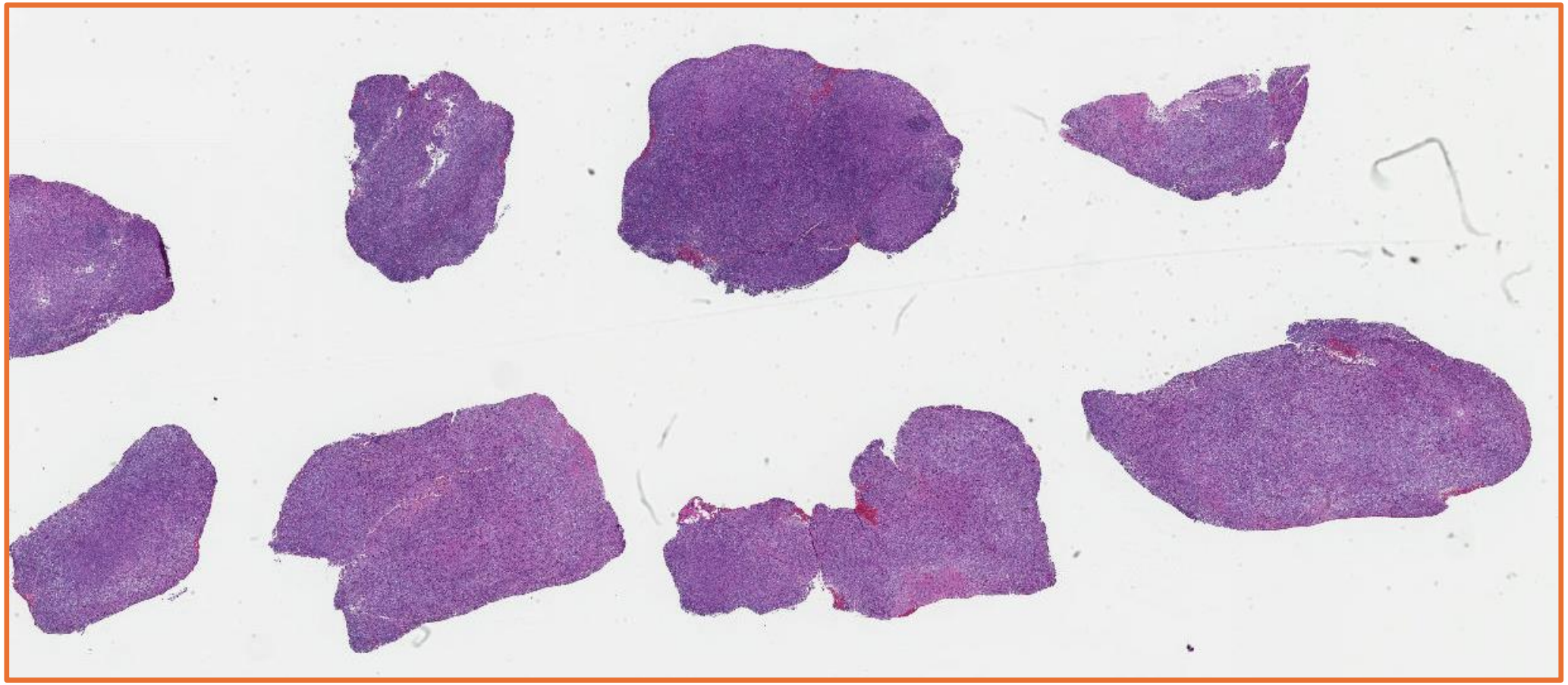
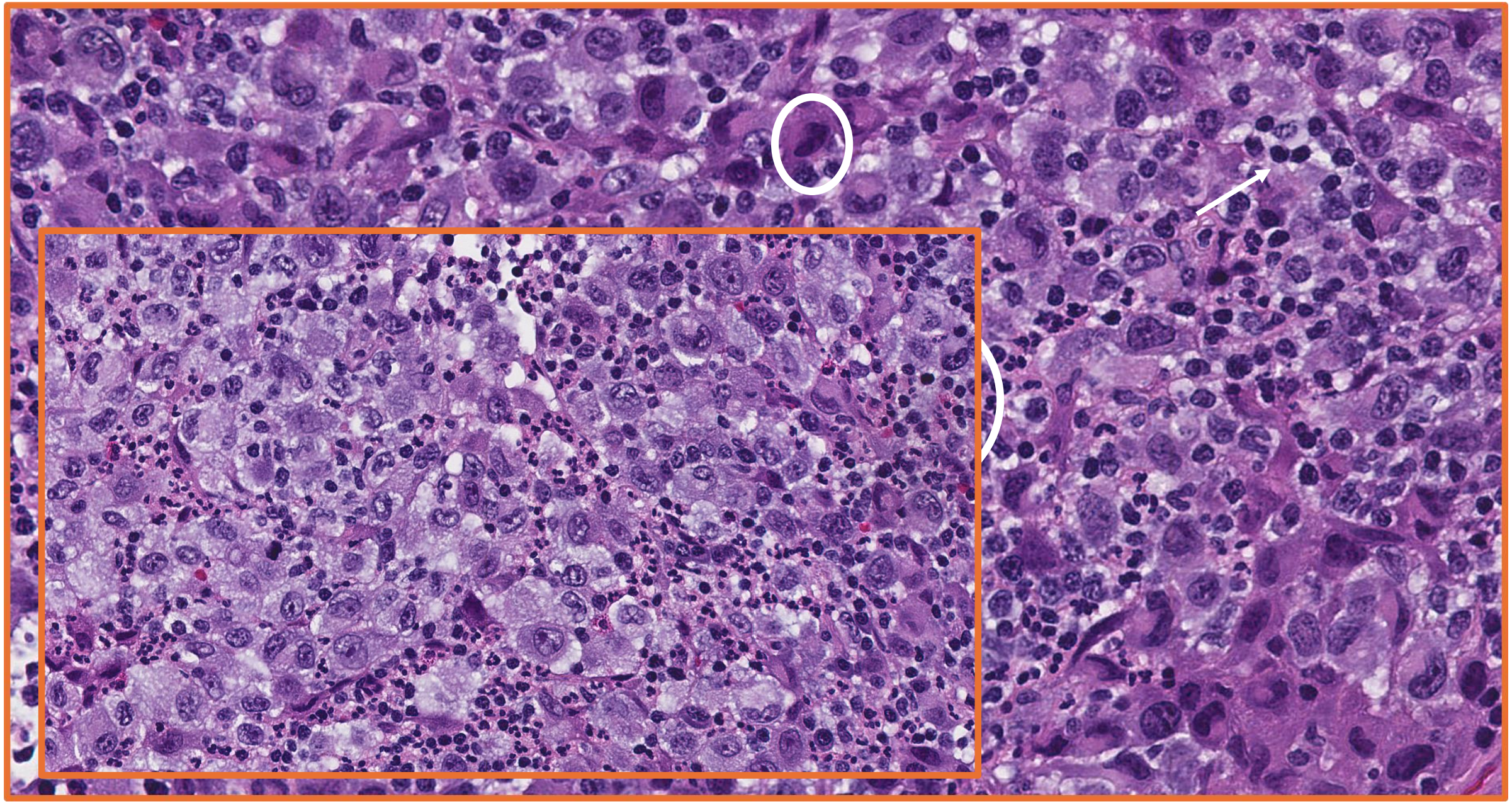
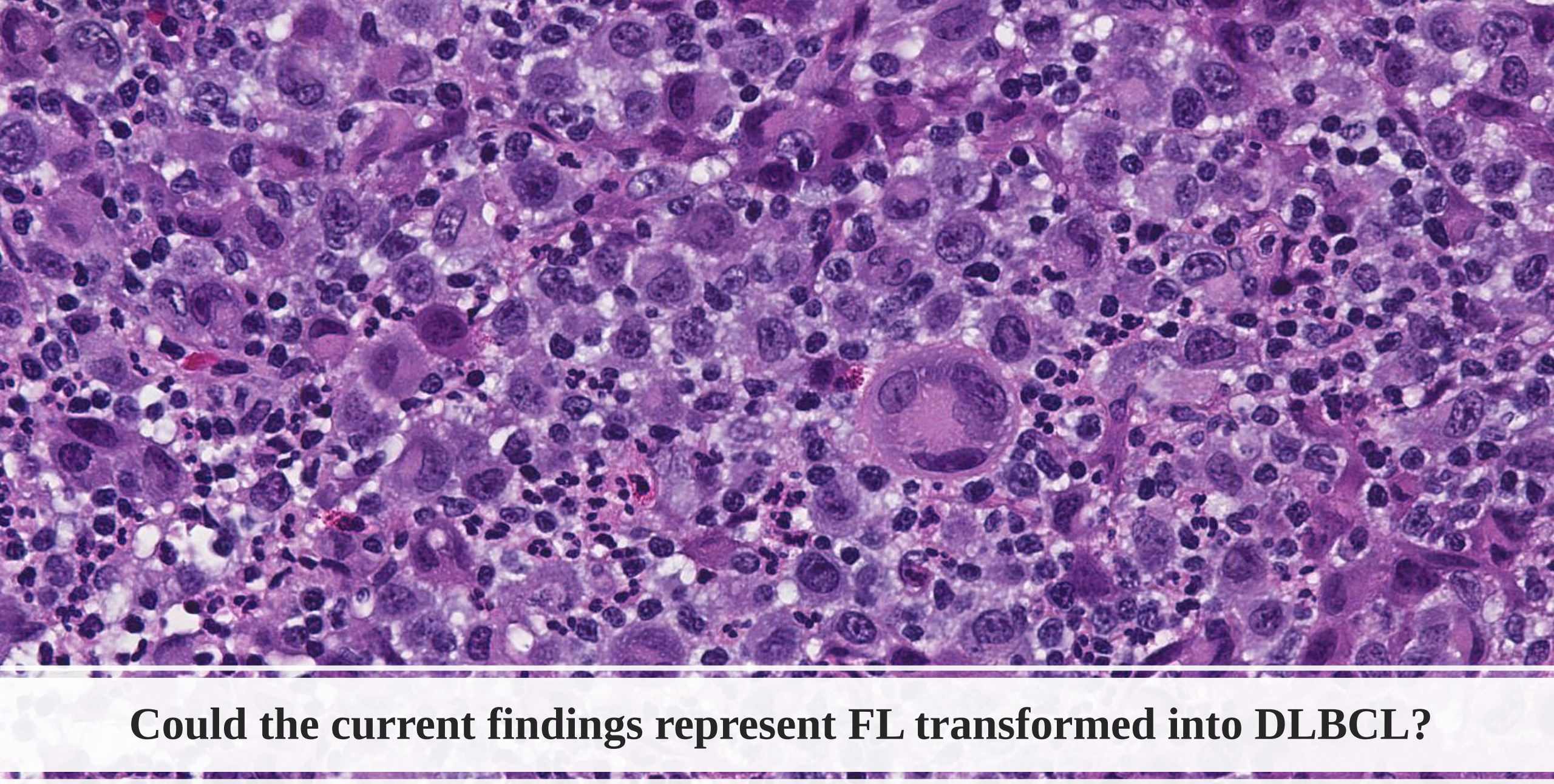
Because of persistent concern for **disease progression**, a cervical mass biopsy was performed

Cervical Mass

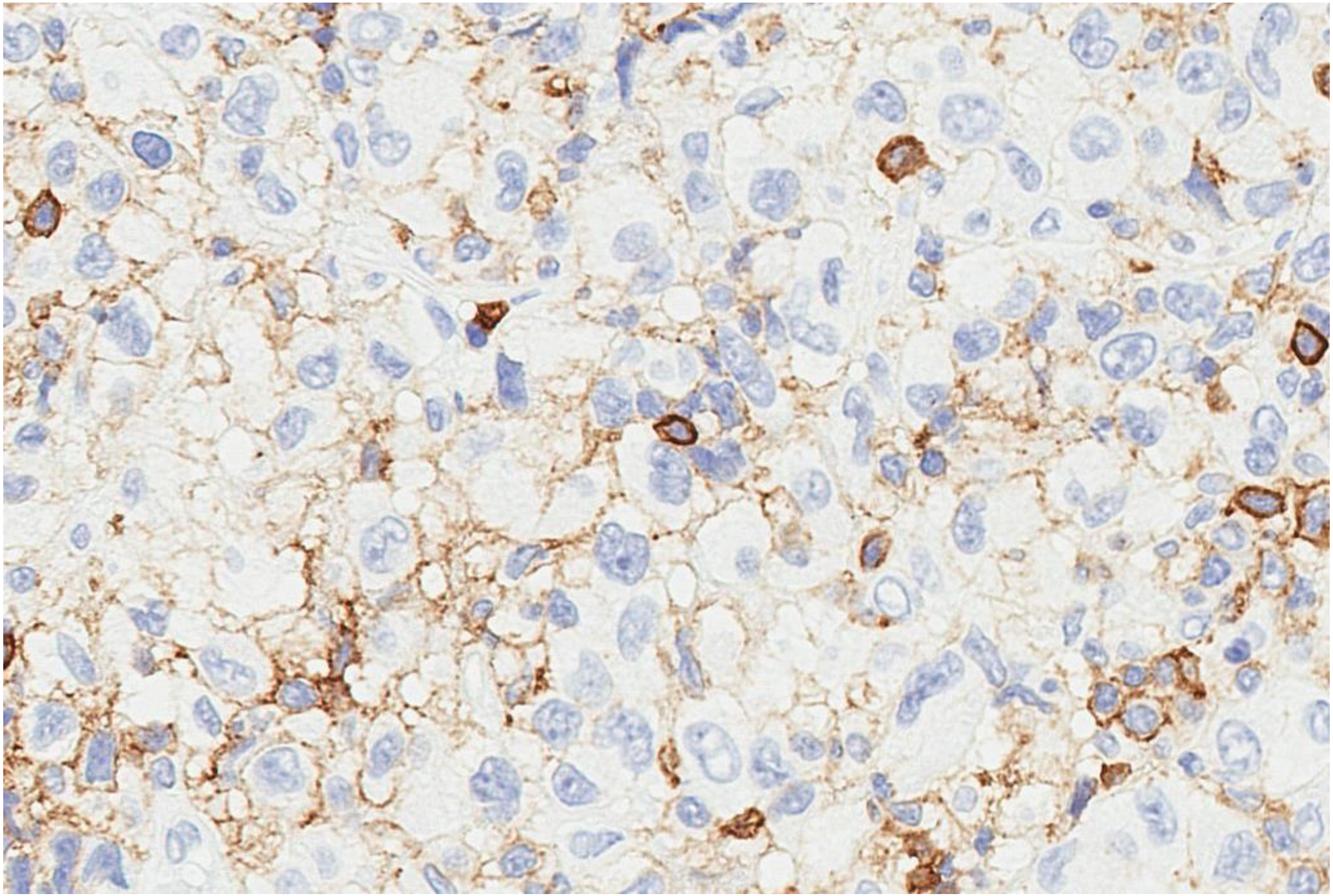






Could the current findings represent FL transformed into DLBCL?

CD45



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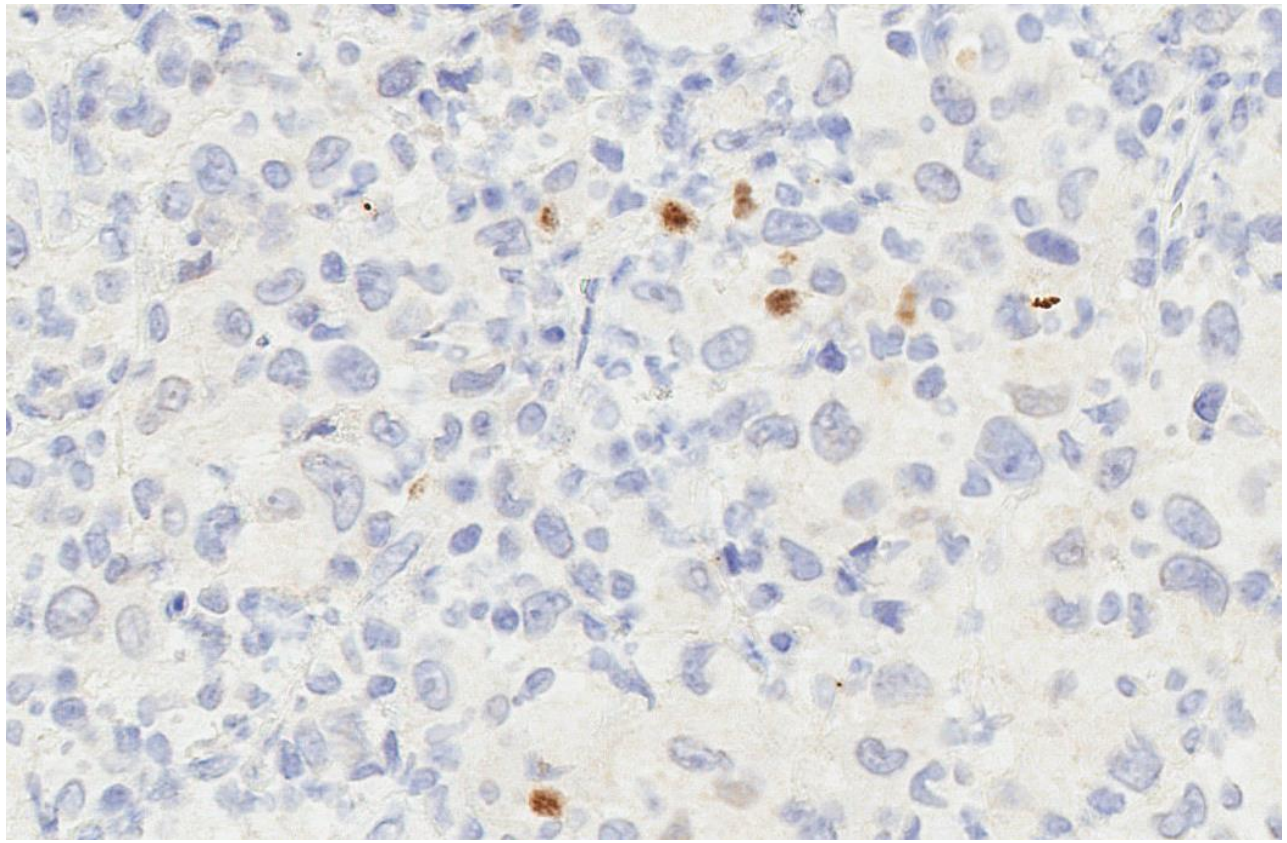
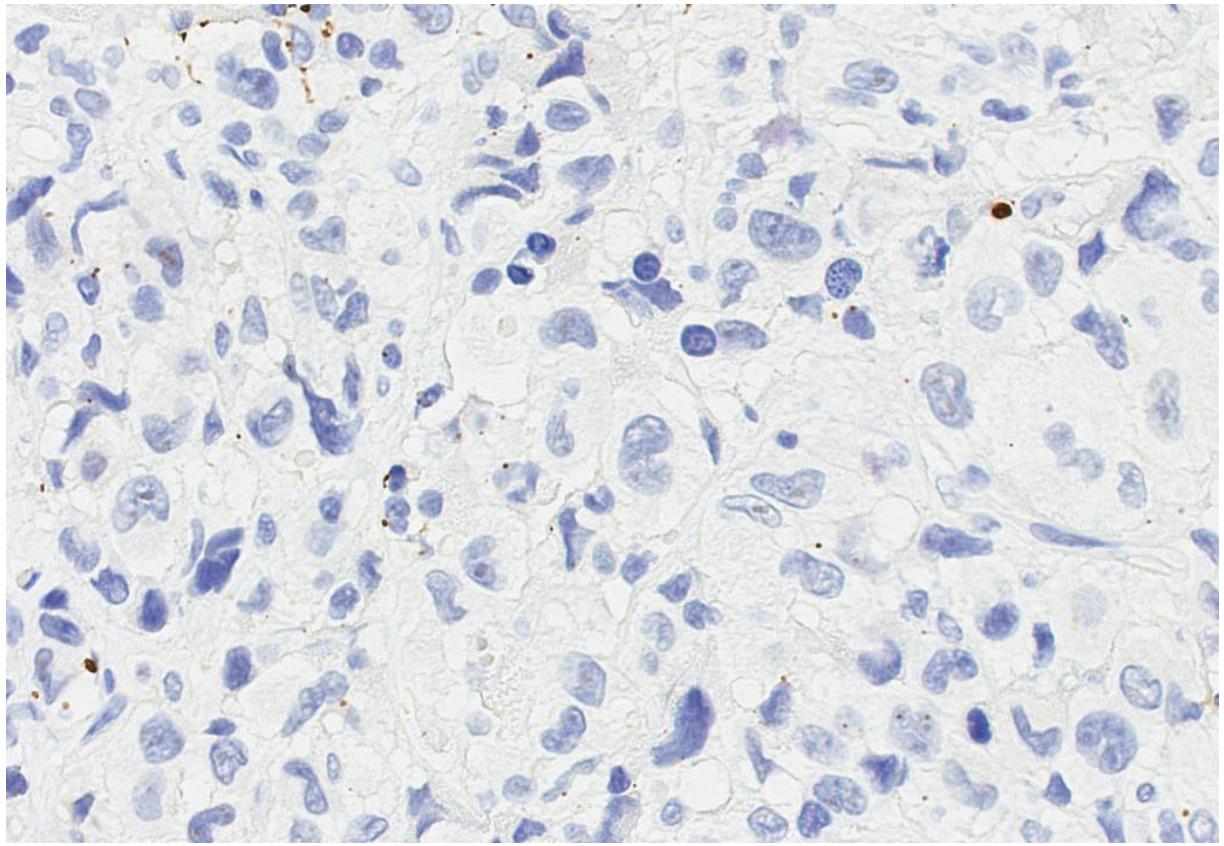
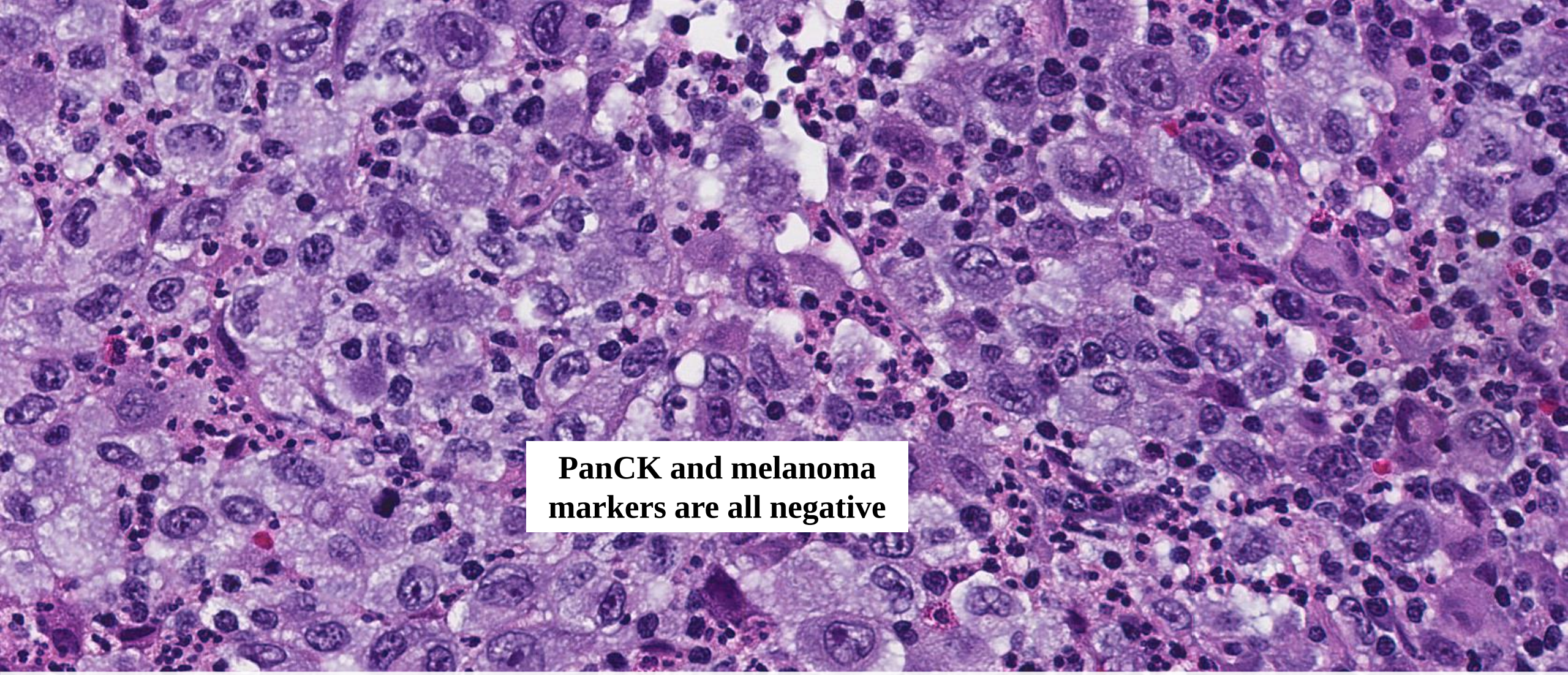


PAX5



CD20

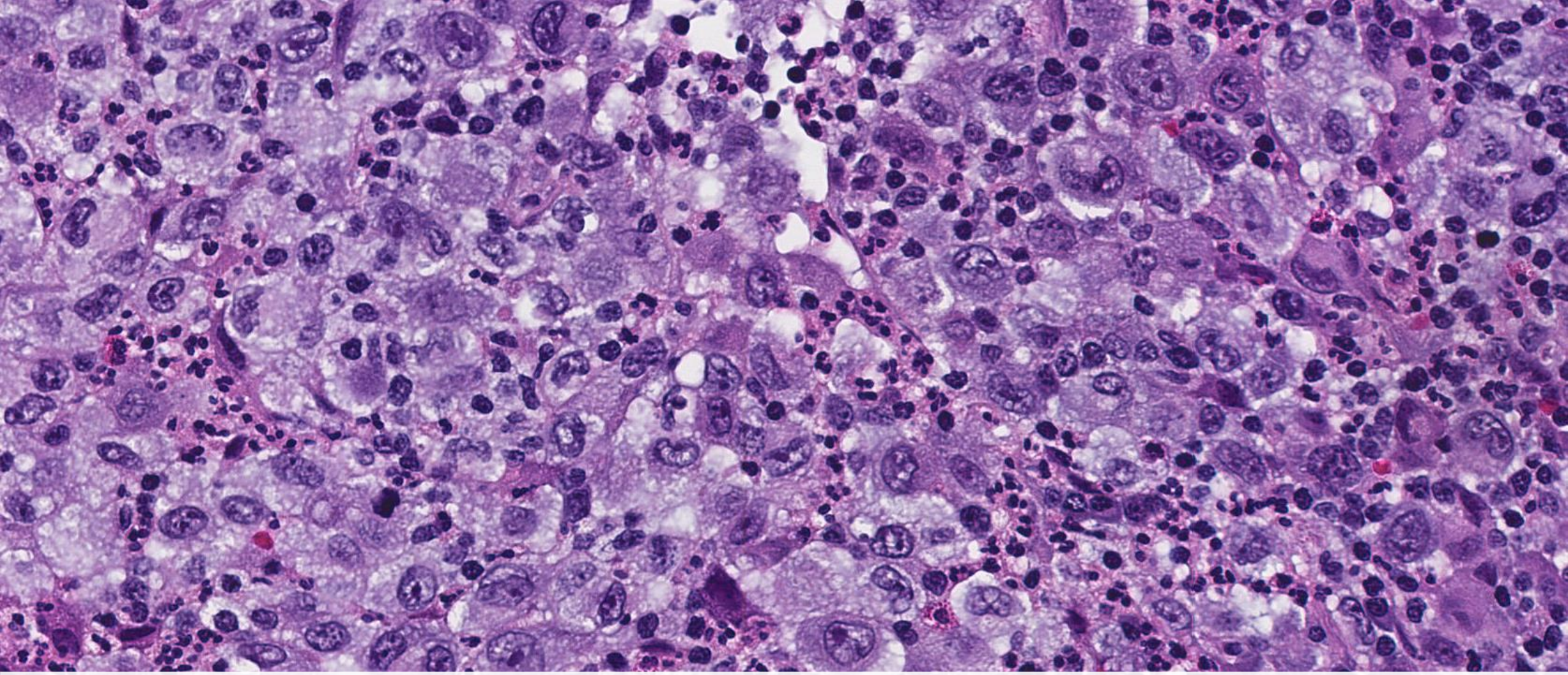
CD19, CD79a and CD22 negative



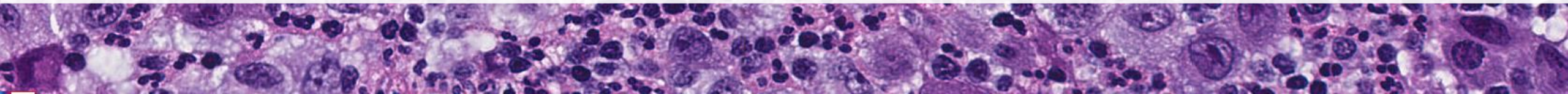
Carcinoma or melanoma with LN metastasis?

IHC

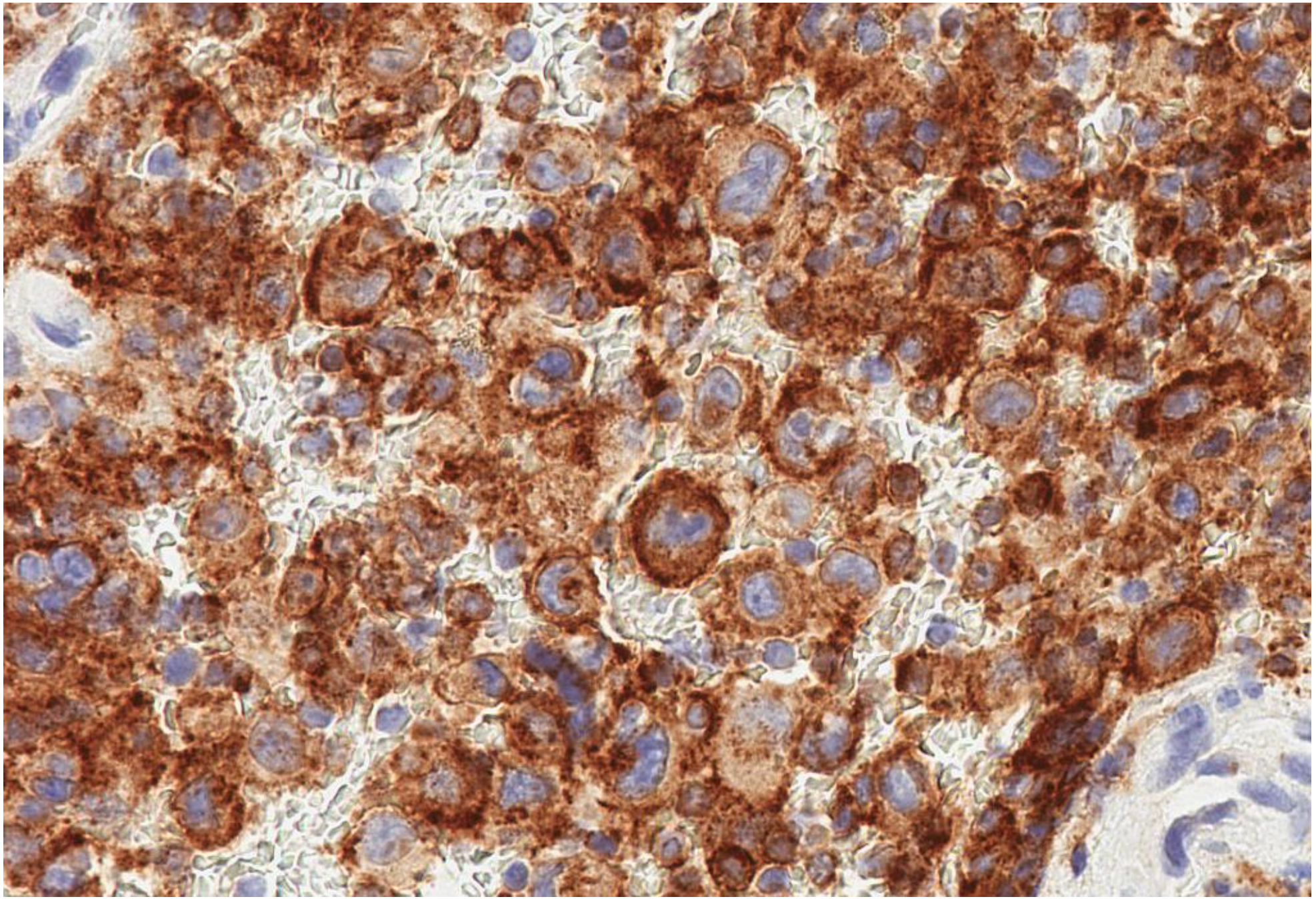
- T-cell markers (CD3, CD4)
- ALCL (ALK, CD30)
- FDC markers (CD21, CD23, CD35)
- Langerhans cell markers (CD1a)
- Interdigitating Dendritic Cell Sarcoma (S100)
- Myeloid markers (MPO, CD13, CD33, CD117)
- Histiocytic markers (CD68, CD163, lysozyme)



All additional IHC markers were negative, except…



CD4



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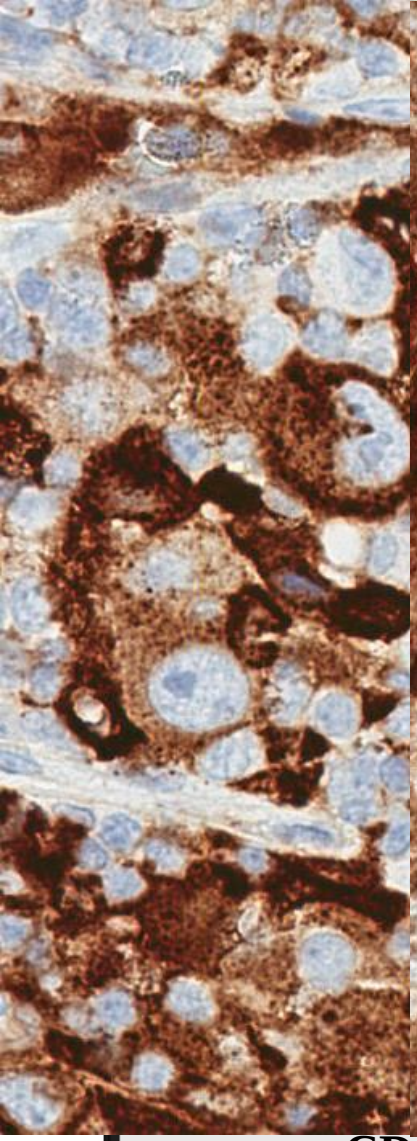
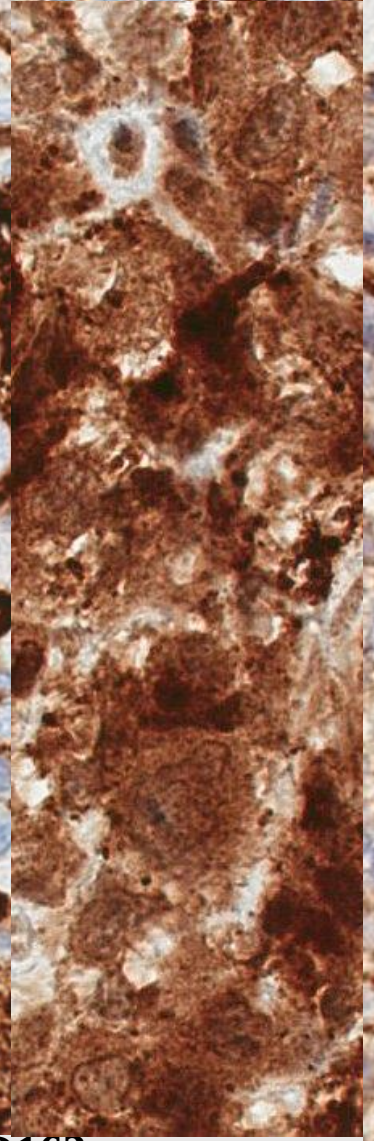
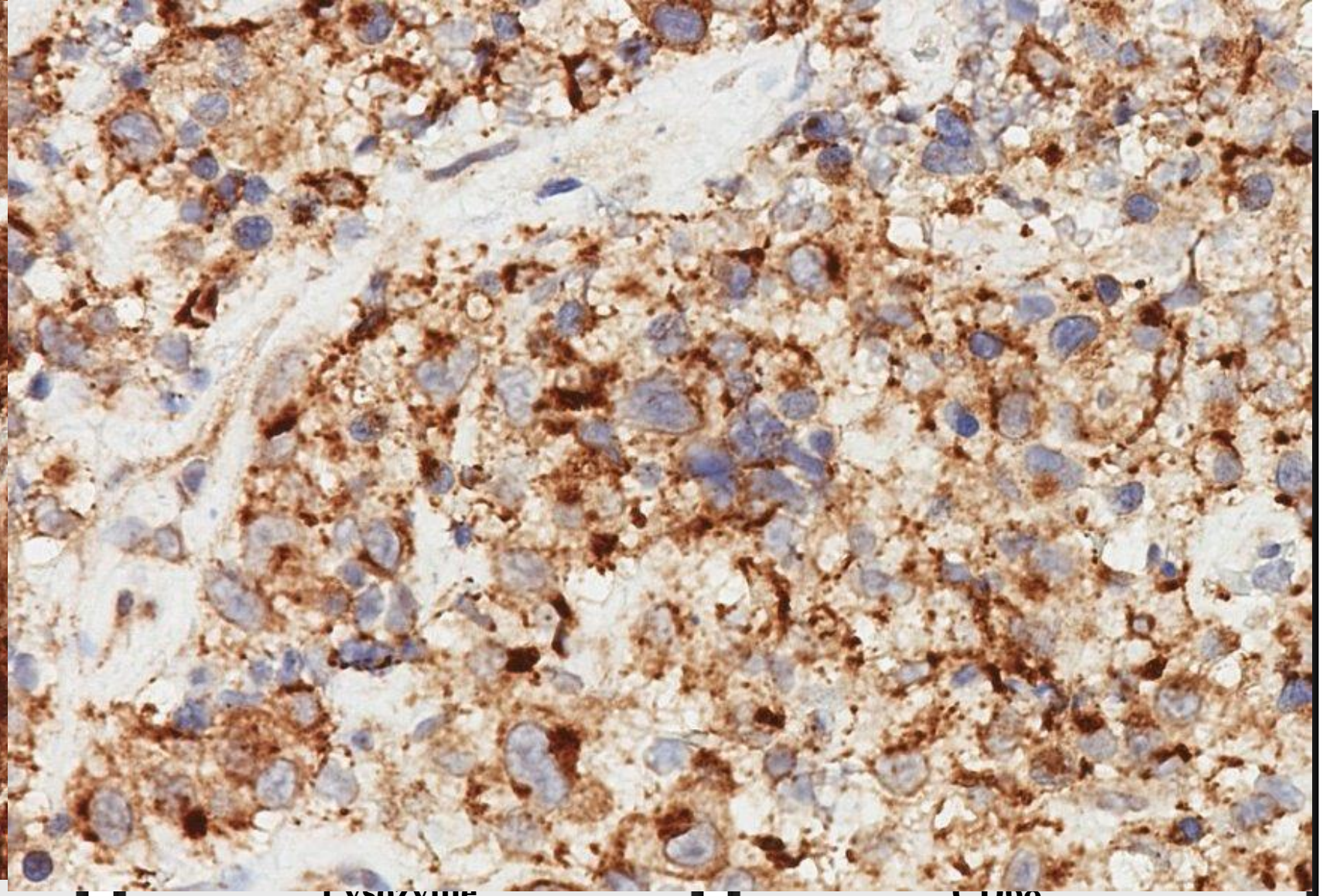


CD163



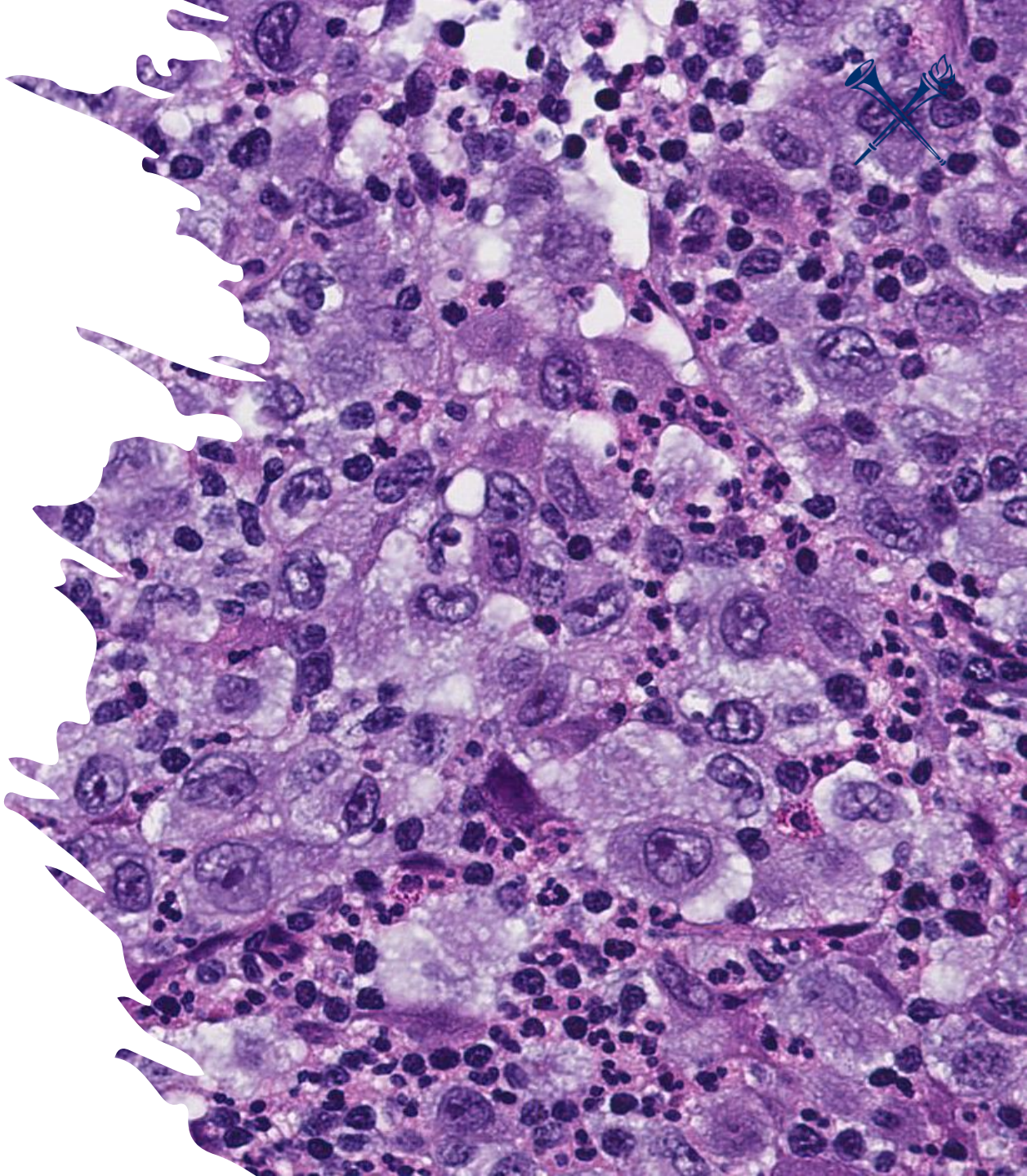


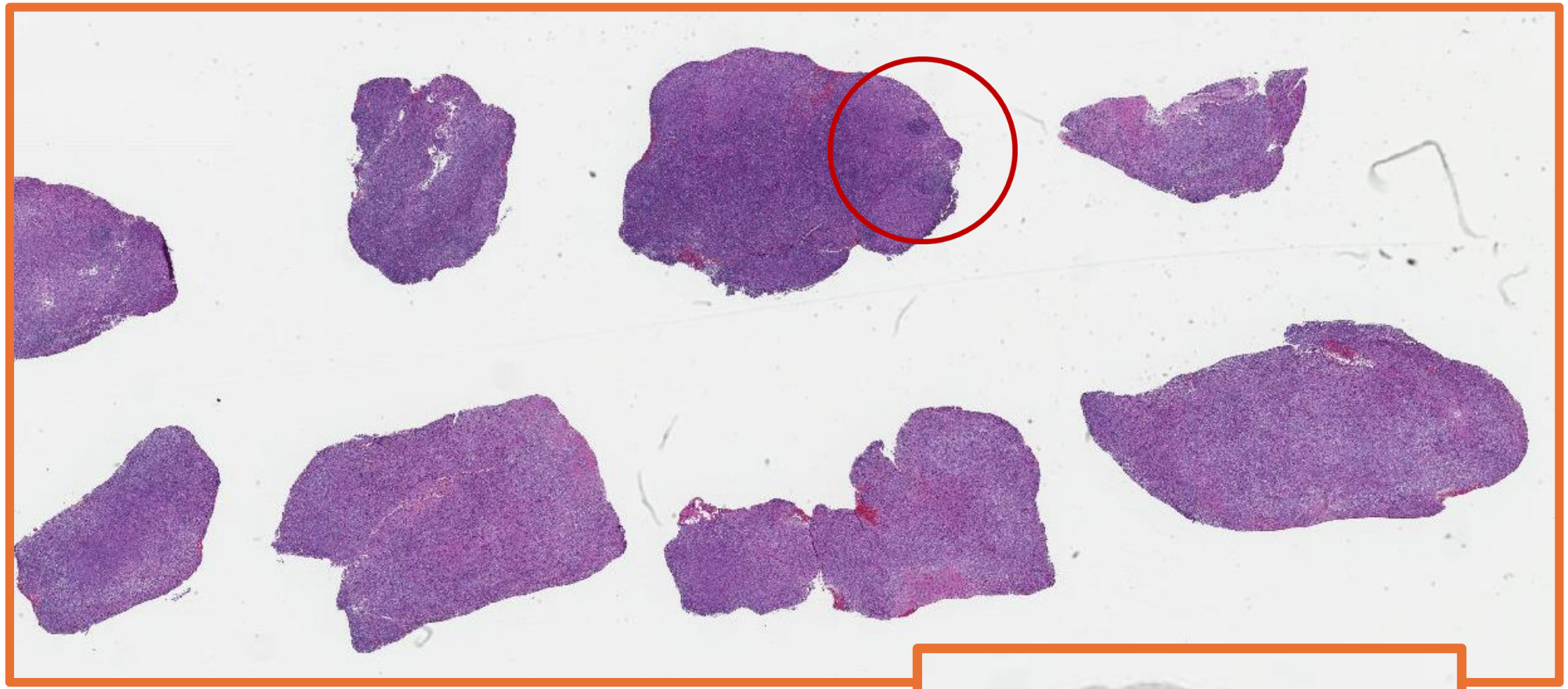
Lysozyme

CD68

Neck, mass, biopsy:

- Histiocytic sarcoma





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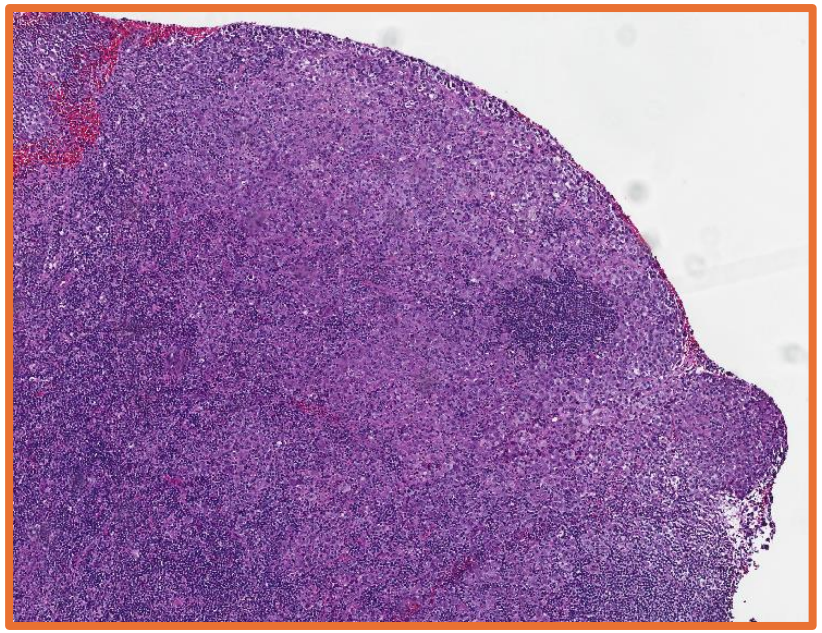
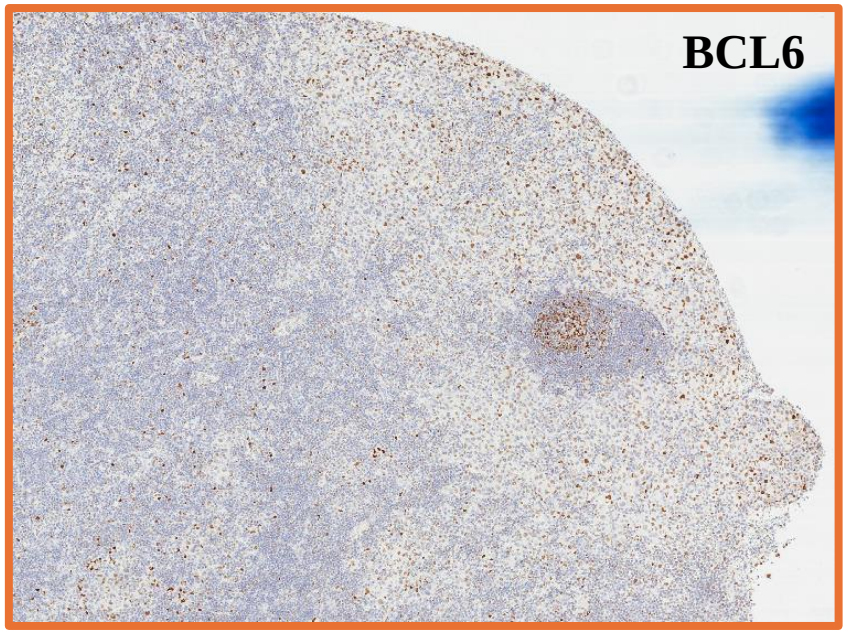
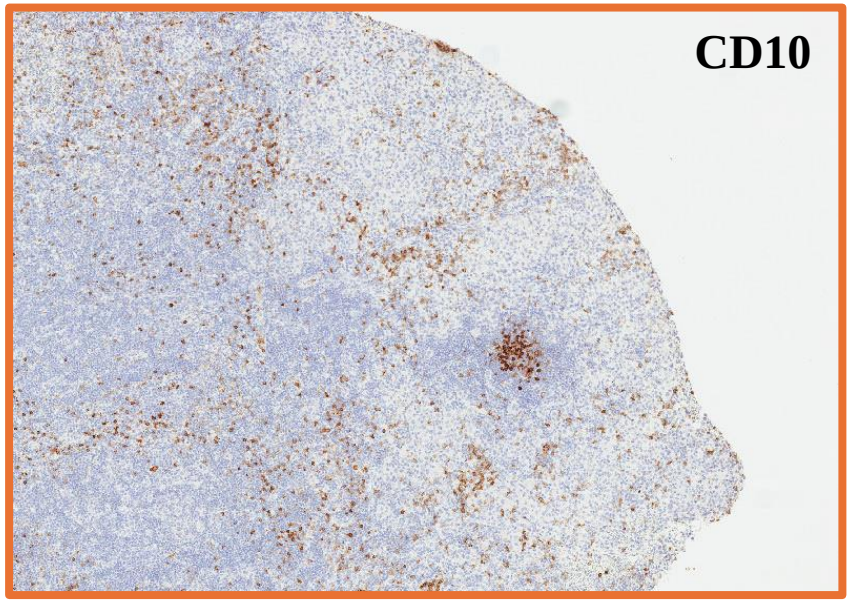
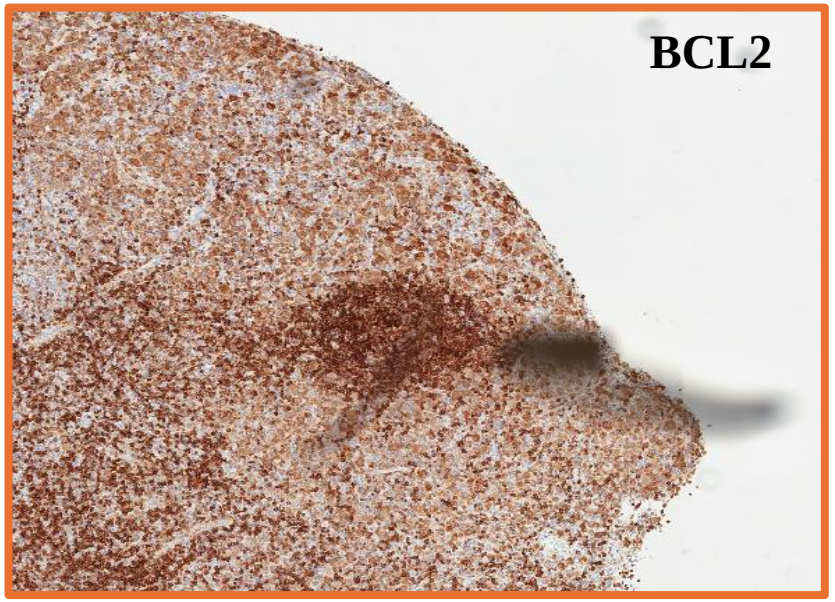



BCL6

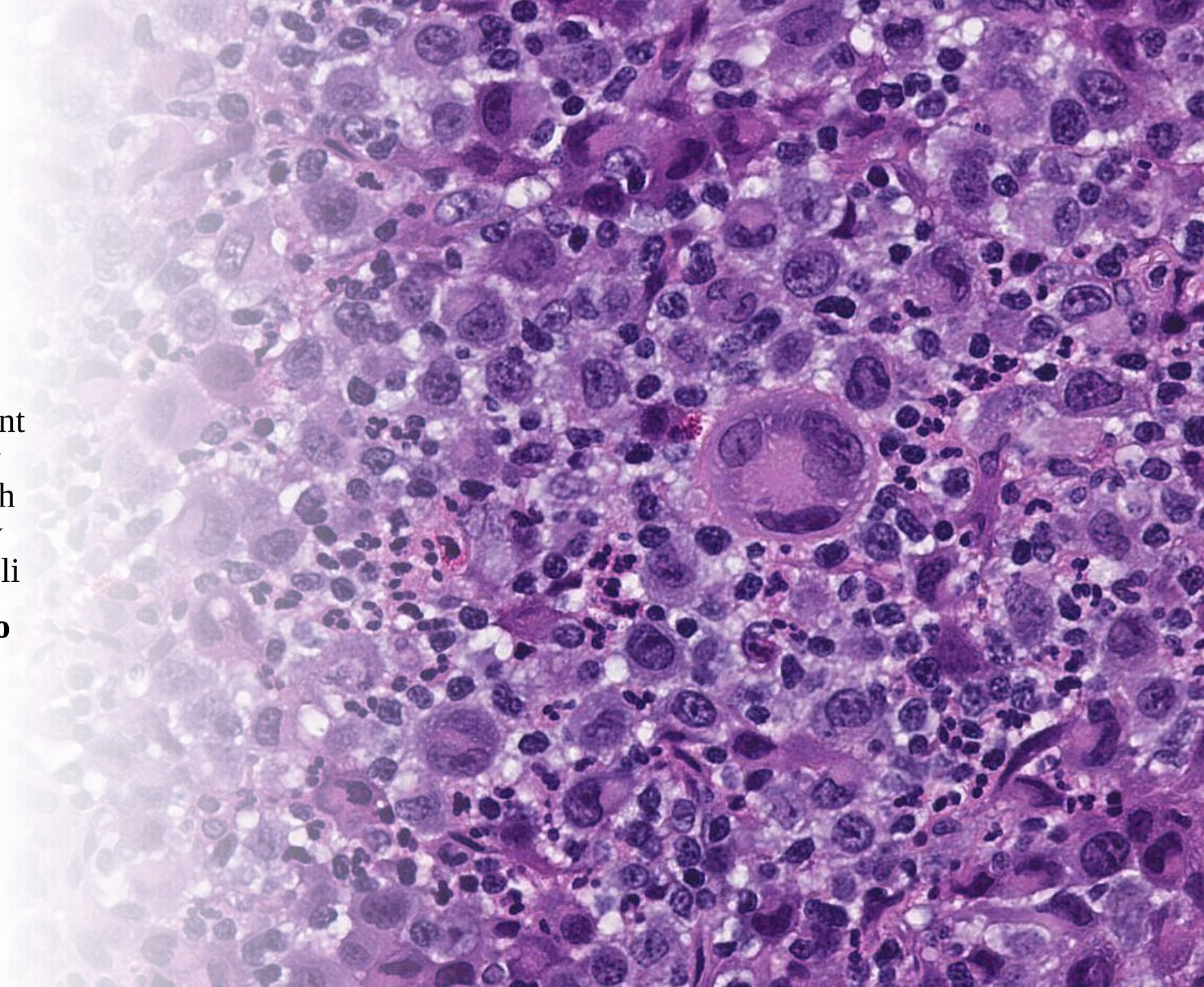

CD10


BCL2

WHO 5: HS

Essential:

- A tumor composed of non-cohesive large cells with abundant eosinophilic cytoplasm; variably pleomorphic neoplastic cells with reniform, grooved, or irregularly folded nuclei and distinct nucleoli
- **Positive** immunostaining for **two or more histiocytic** markers
- **Negative** for CD1a, CD207 (langerin), CD21, CD35



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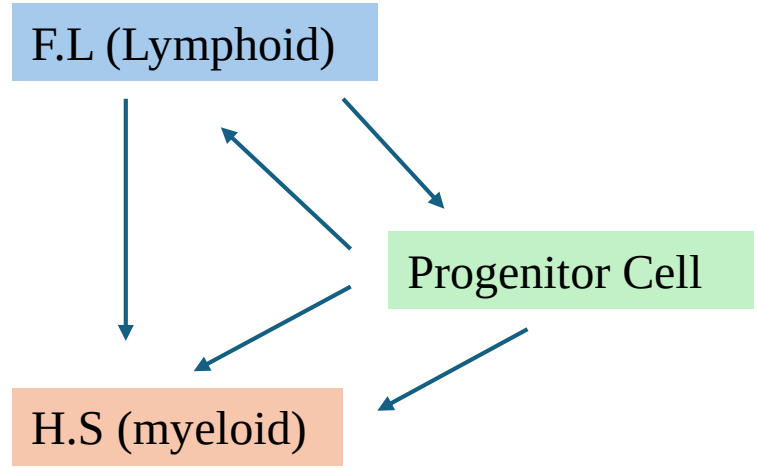
Histiocytic sarcoma

- **Rare and aggressive** neoplasm
- It occurs over a wide age range
- Frequently occur in extranodal sites
- The median overall survival (**OS**) is approximately **six months**
- HS can arise **de novo or transform/transdifferentiate** from a low-grade B-cell lymphoma (FL or CLL/SLL) and B- or T-lymphoblastic leukemia/lymphoma

Proposed Mechanisms Underlying Lineage Conversion

1. Origin from a **common** neoplastic **progenitor**
2. **Trans-differentiation** of a mature lymphoid cell to one of myeloid lineage
3. **Dedifferentiation** of a lymphoid cell to an immature progenitor with subsequent differentiation along the myeloid/dendritic lineage

Despite these hypotheses, the mechanism by which this process occurs remains **poorly understood**

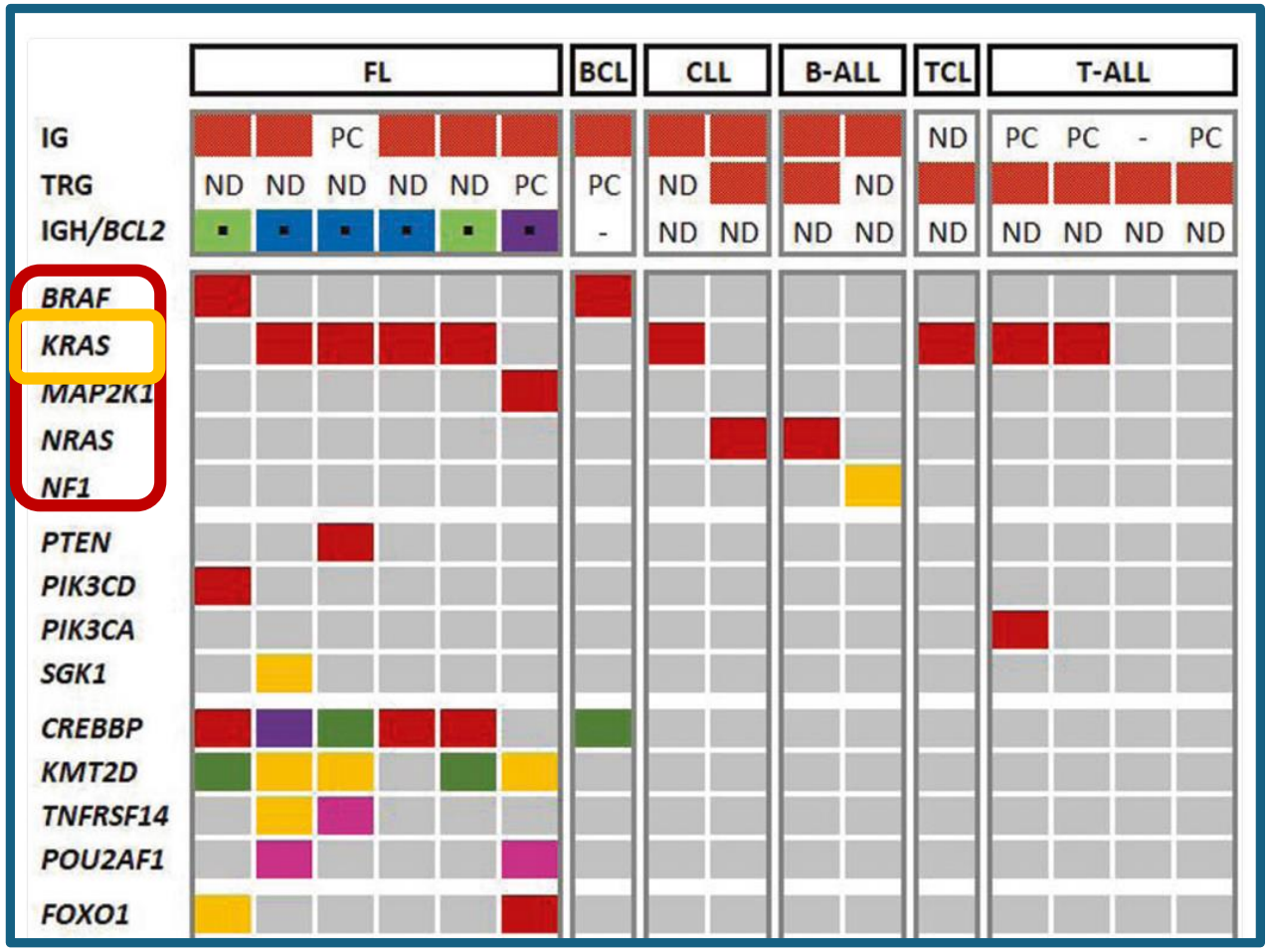


Mod Pathol. 2021 Feb;34(2):336-347. doi: 10.1038/s41379-020-00673-x. Epub 2020 Sep 14.

The mutational landscape of histiocytic sarcoma associated with lymphoid malignancy

Caoimhe Egan [1], Justin Lack [2], Shannon Skarshaug [1], Thu Anh Pham [1], Zied Abdullaev [1], Liqiang Xi [1], Svetlana Pack [1], Stefania Pittaluga [1], Elaine S Jaffe [1], Mark Raffeld [3]

- Whole exome sequencing was performed on **16** secondary histiocytic/dendritic cell tumors (15 H.S & 1 IDCT)
- Mutations in the **RAS/MAPK** pathway represent **87.5%** (14/16)
- The most frequently mutated gene was ***KRAS***



RAS-MAPK signaling pathway (***MAP2K1, KRAS, NRAS, BRAF, PTPN11, NF1, CBL***)

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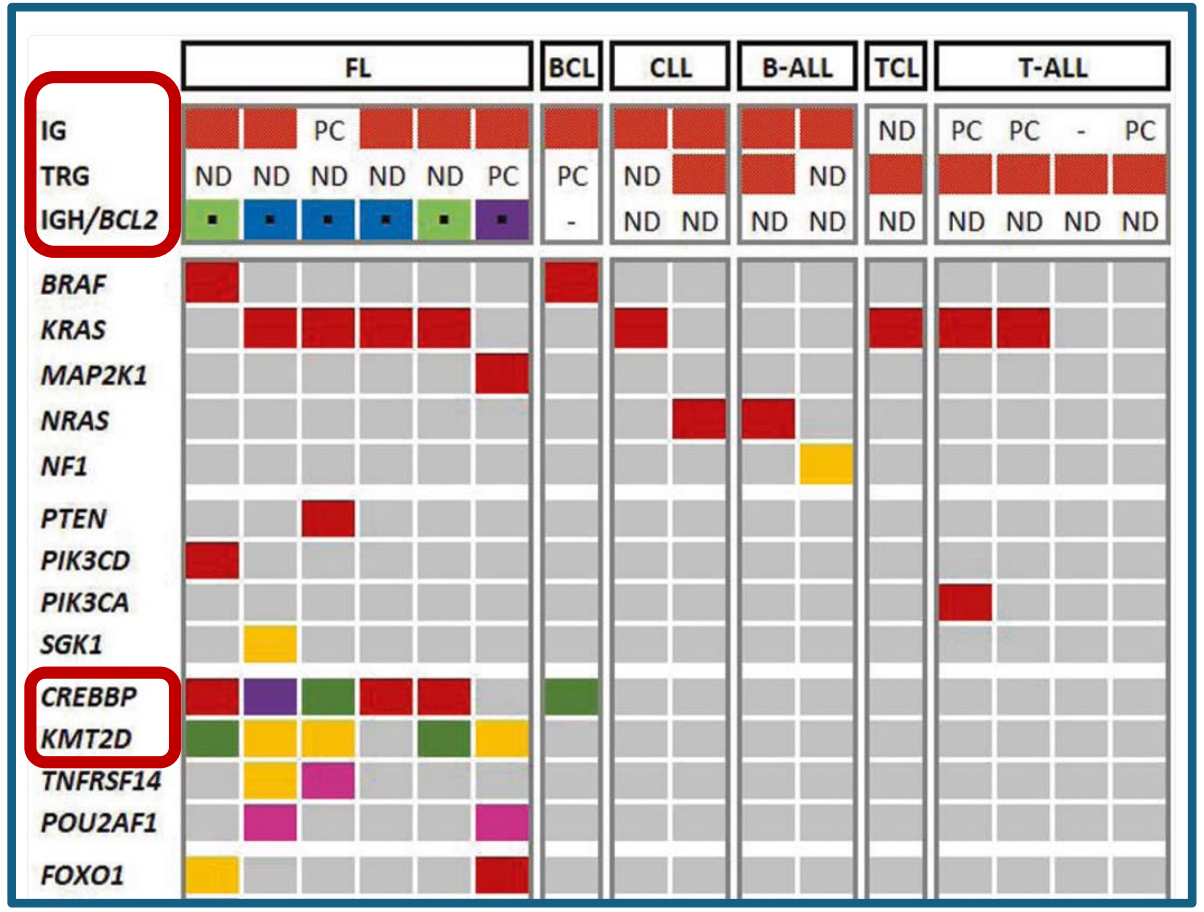
- All cases of sHDT, regardless of the associated lymphoma subtype, had **evidence of a clonal relationship** to the associated lymphoid tumor through clonal ***IG*** or ***TRG*** gene rearrangements, or ***IGH::BCL2*** sequence similarity
- All FL-associated cases had mutations that occur early in the pathogenesis of FL, ***CREBBP*** and ***KMT2D***



Mutation Type

- Missense mutation
- Nonsense mutation
- Inframe deletion
- Frameshift deletion
- Frameshift insertion
- Splice site mutation
- Multiple mutations

IGH/*BCL2* status

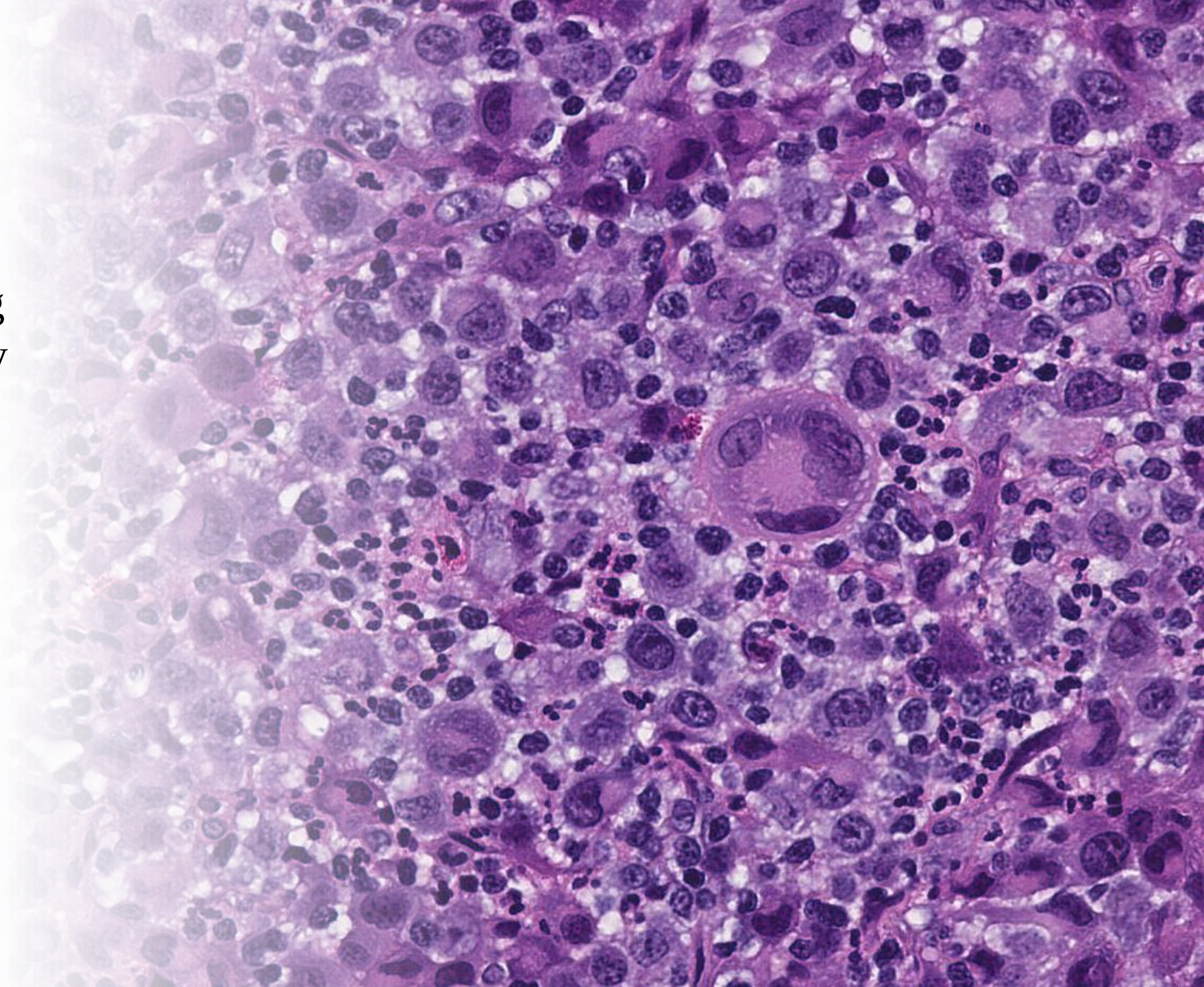
- *BCL2* translocation by FISH
- Positive by FISH and PCR
- t(14;18) by PCR
- \- Negative by PCR

IG and TRG status

- Monoclonal
- **ND** Not done
- **PC** Polyclonal
- \- No amplification

https://doi.org/10.1038/s41379-020-00673-x

Is the patient’s long-standing follicular lymphoma clonally related to the newly diagnosed histiocytic sarcoma?



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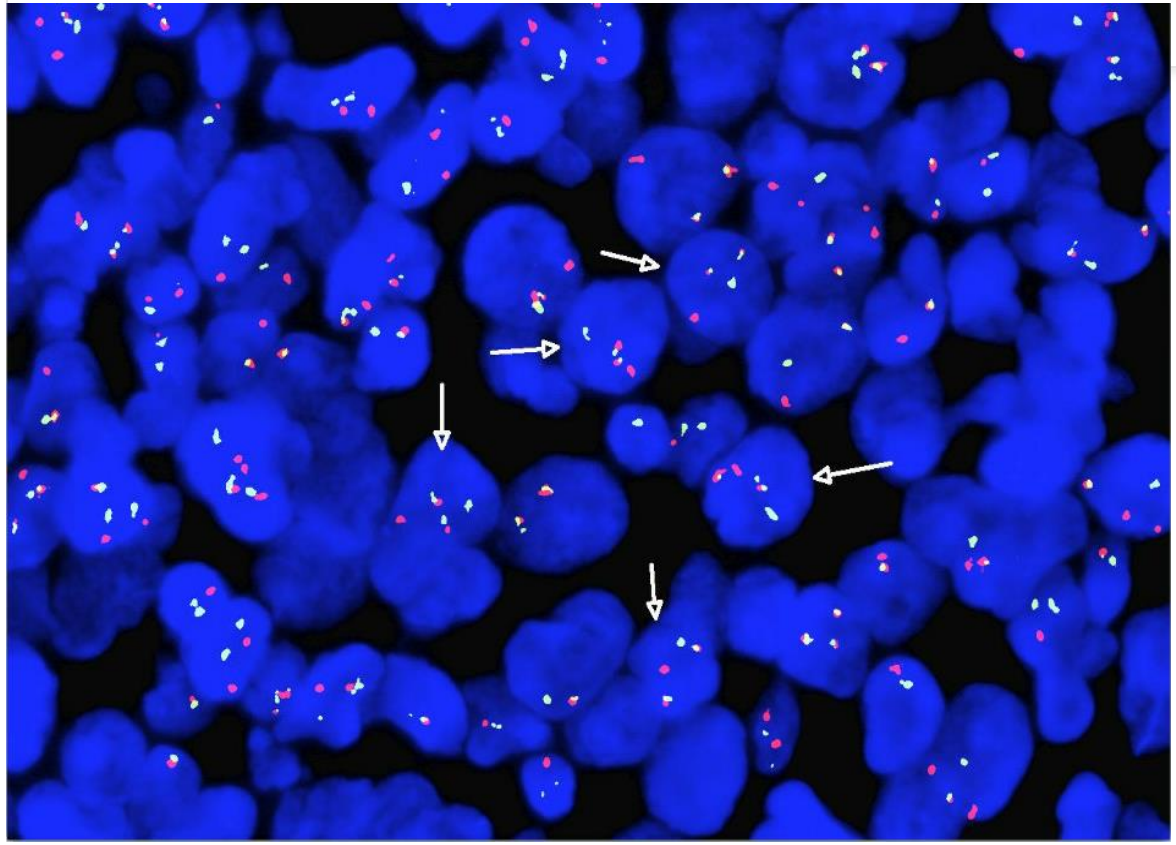
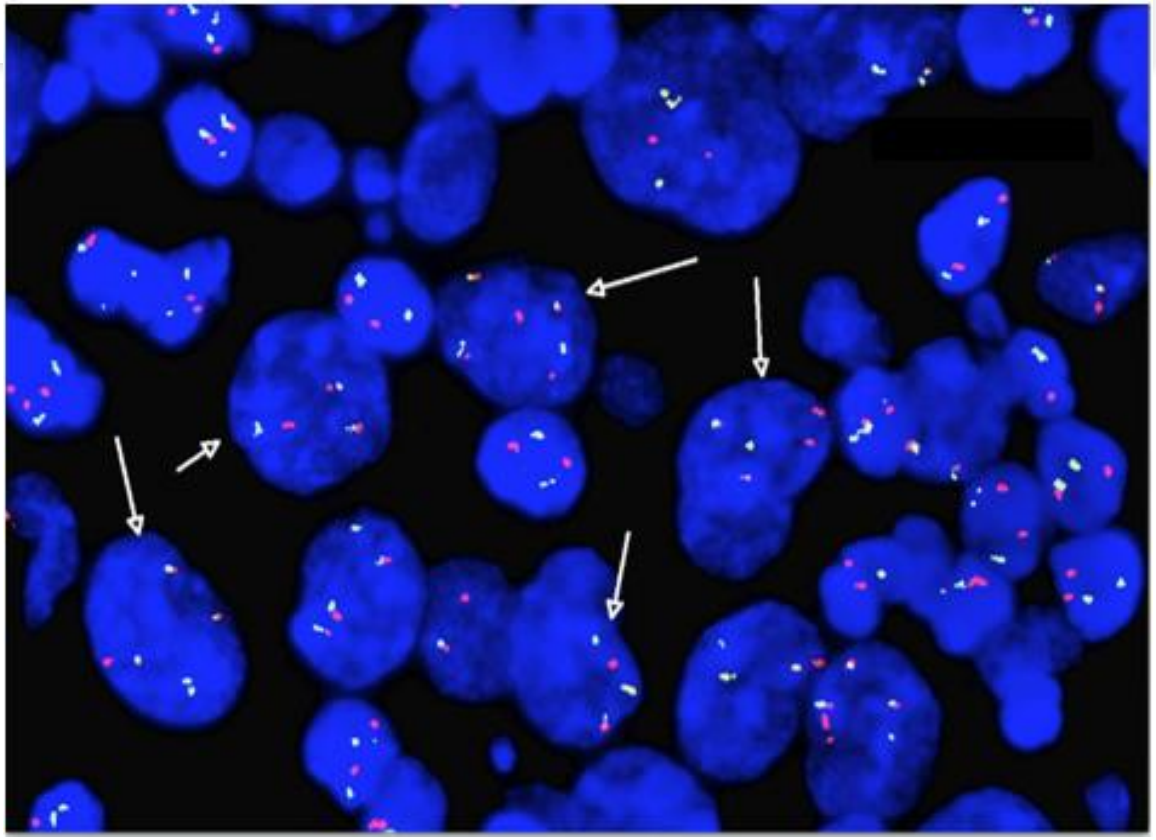
IGH::BCL2 Rearrangement



Follicular lymphoma (tonsil)



Histiocytic sarcoma (cervical mass)

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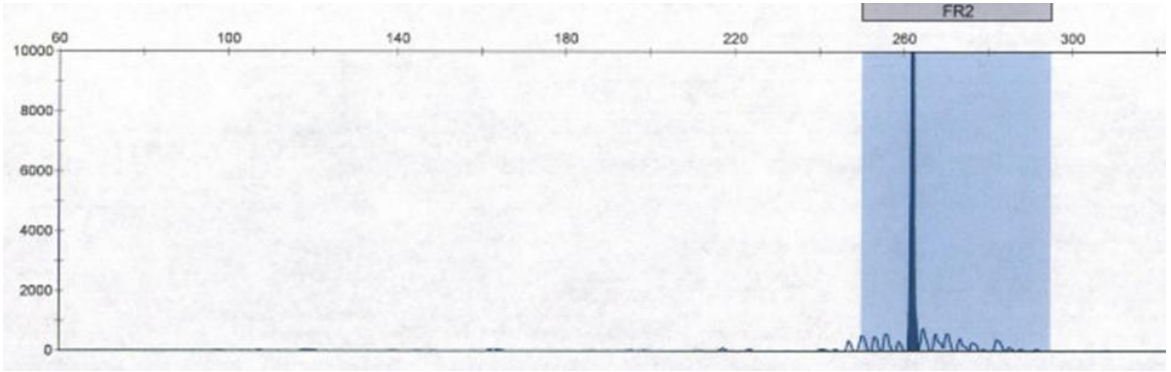
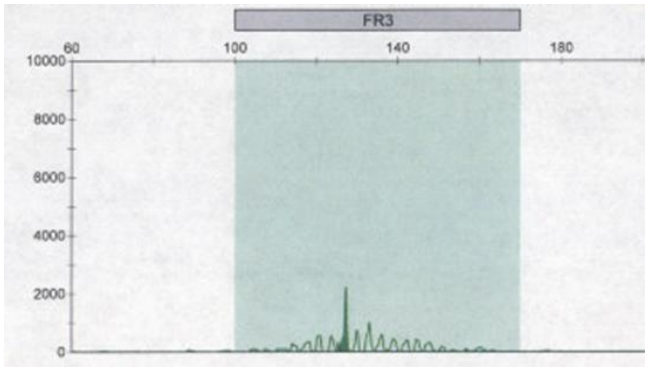
IGH/IGK: **Both samples shared identical clonal peaks**





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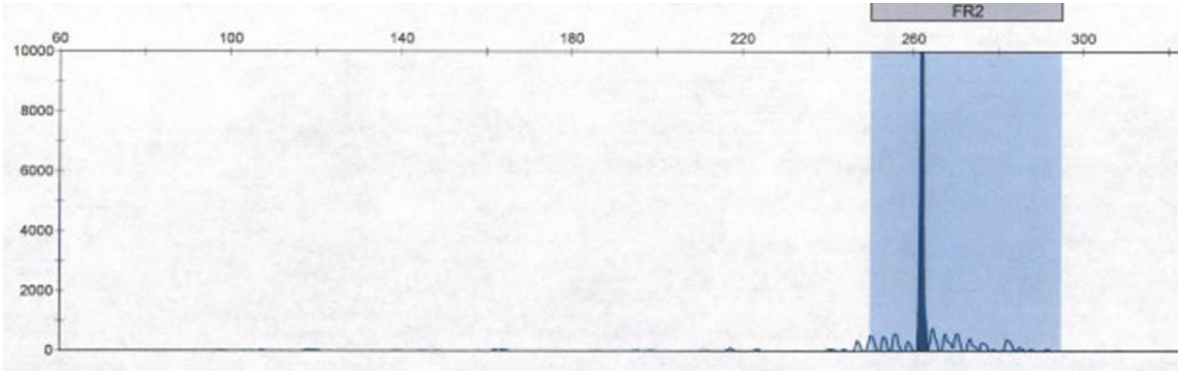
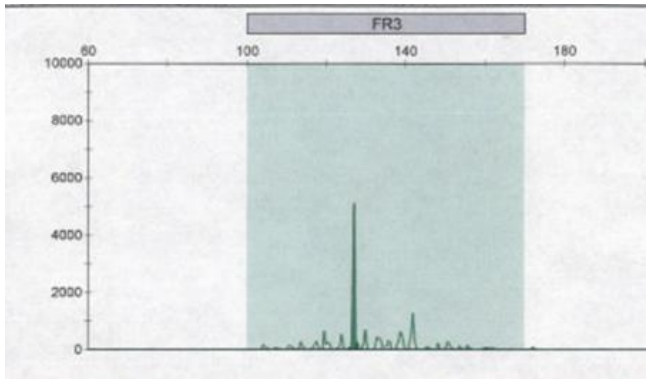


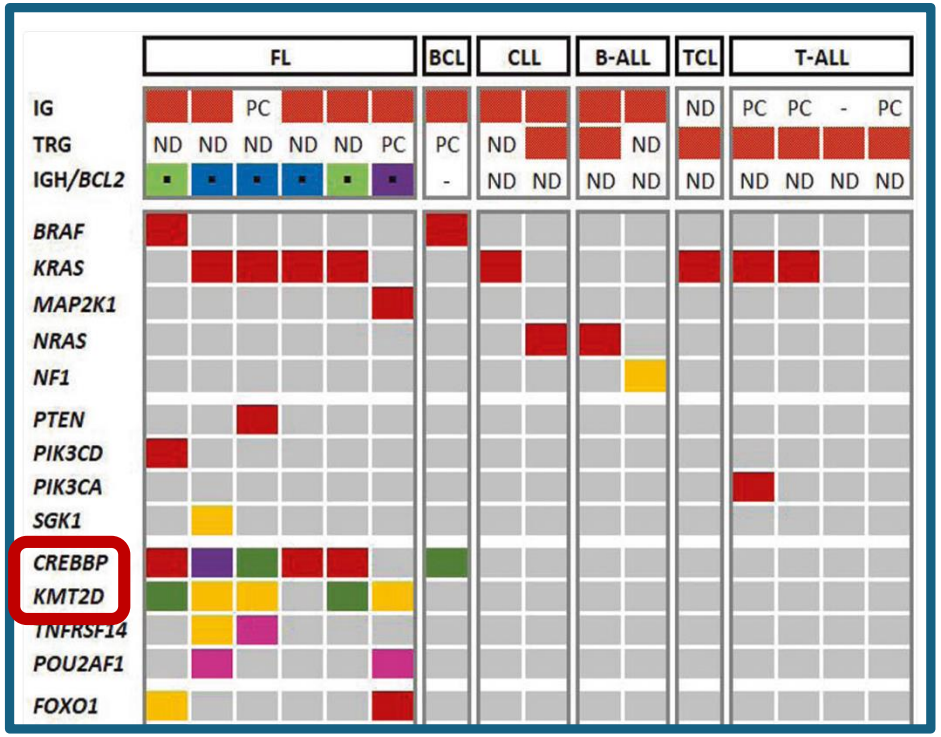


Histiocytic sarcoma (cervical mass)

NGS

Neck mass, HS

- ***CREBBP*** (c.4336C>T) (18%)
- ***KMT2D*** (C.303dupG) (10%)
- *KMT2D* (C.15716C>T) (6%)
- *KMT2D* (C.5062A>T) (11%)
- *BCL2* (c.495G>C) (18%)
- *CD79A* (c.543del) (17%)



- ***BCL2***: Apoptosis regulation
- ***CD79A***: BCR signaling/survival
- ***CREBBP & KMT2D***: Epigenetic / transcriptional regulation

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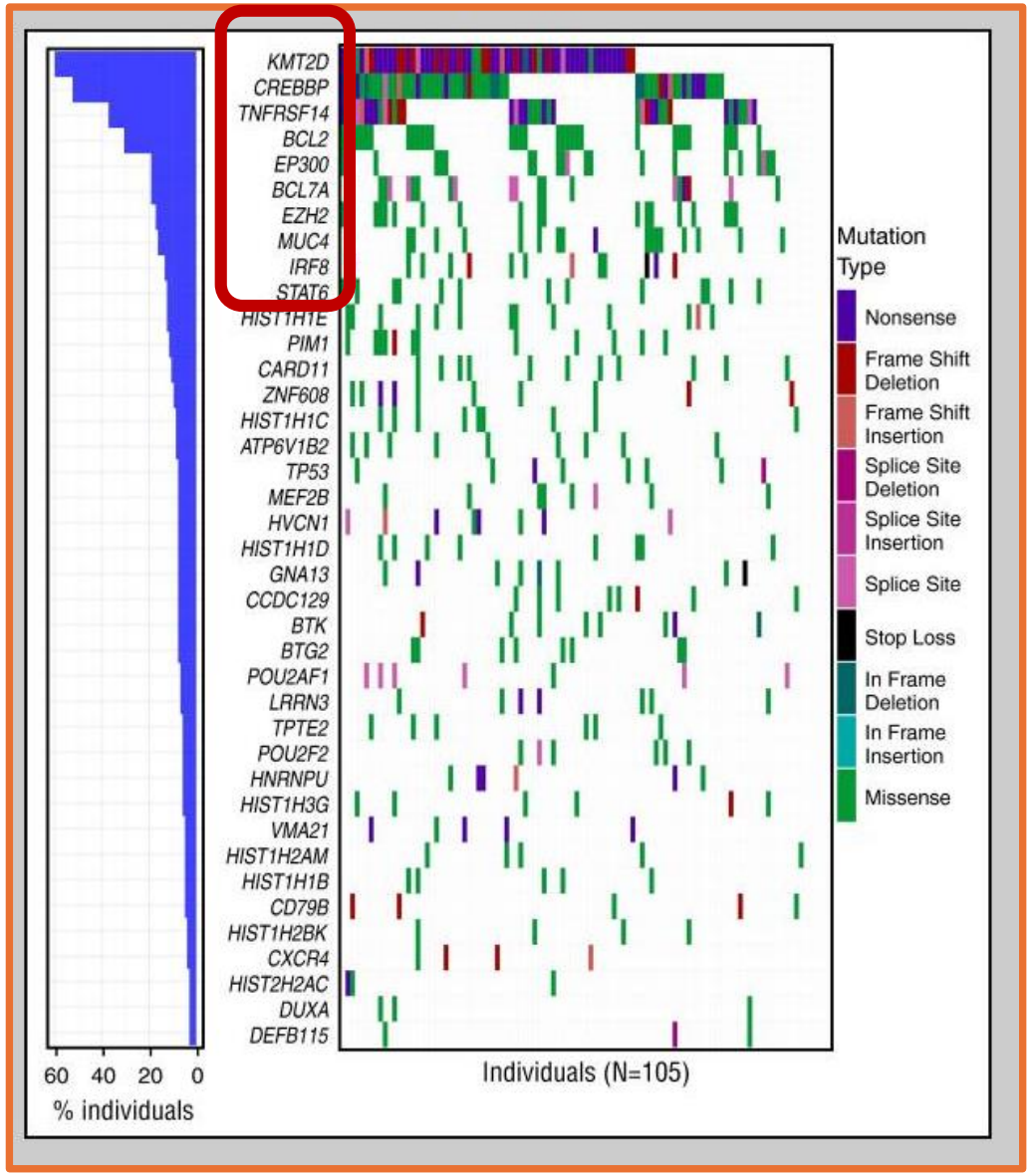
FL-associated HS have mutational hallmarks of FL

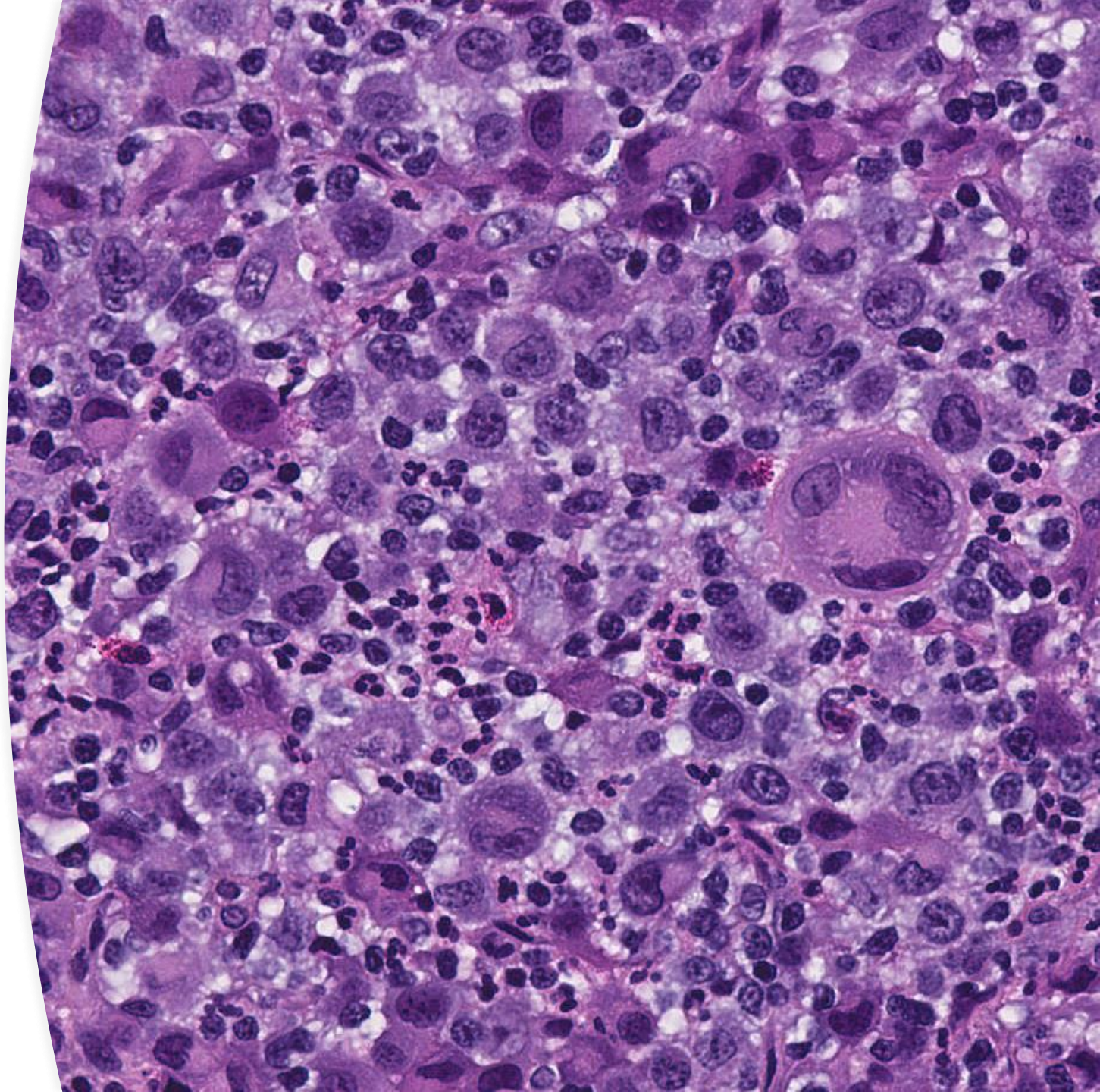
ASSOCIATED LYMPH/LEUK		FL	BCL	CLL	B-ALL	TCL	T-ALL
NUMBER OF CASES		6	1	2	2	1	4
FL GENES*	No (%)	No (%)	No	No	No	No	No
KMT2D	63 (60)	5 (83)	0	0	0	0	0
CREBBP	55 (50)	5 (83)	1	0	0	0	0
TNFRSF14	33 (35)	2 (33)	0	0	0	0	0
BCL2	32 (30)	1 (16)	0	0	0	0	0
EP300	20 (20)	0	0	0	0	0	0
BCL7A	20 (20)	0	0	0	0	0	0
EZH2	18 (15)	0	0	0	0	0	0
MUC4	17 (15)	0	0	0	0	0	0
IRF8	14 (14)	0	1	0	0	0	0
STAT6	14 (13)	0	0	0	0	0	0

*Top 10 mutated genes in FL as reported by Krysiak et al[34]. FL genes are significantly enriched in FL-associated cases as compared to non-FL associated cases (t-test: t=6.48, p=<0.0001).



H.S Treatment Modalities

- **Unifocal/localized :** Surgery is the treatment of choice +/- RT



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Current systemic therapies for multifocal/disseminated histiocytic sarcoma

Treatment Modalities	Agents
Chemotherapy	CHOP (first-line treatment)
	ICE
	ABVD
	CLAG-M
	Temozolomide
Targeted Therapy	Vemurafenib (BRAF inhibitor)
	Dabrafenib (BRAF inhibitor)
	Trametinib (MEK1/2 inhibitor)
	Cobimetinib (MEK1/2 inhibitor)
	Sirolimus (mTOR inhibitor)
	Alemtuzumab (humanized anti-CD52 monoclonal antibody)
	Thalidomide (antiangiogenic and immunomodulatory properties)
	Nivolumab (PD-1 inhibitor)
	Pembrolizumab (PD-1 inhibitor)

CHOP: cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone
ICE: Ifosfamide, carboplatin, and etoposide
ABVD: Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine
CLAG-M: Cladribine, high-dose cytarabine

Currently, there is **no consensus** regarding the optimal treatment strategy for multifocal/disseminated disease

https://doi.org/10.3390/ijms26178554

Our Patient/Treatment

- R-CHOP (2 cycles)
- Then Gemcitabine/docetaxel, IV (4 cycles)
- Due to residual neck disease: Proton beam, RT 60 Gy (RBE) in 30 fractions started

Patient's Current State

- PET: There is **no evidence** of systemic progression
- No further treatment needed

Conclusion

- HS is rare and accurate identification relies on key morphologic clues and IHC to confirm histiocytic lineage and exclude mimics
- HS can arise de novo or transform/transdifferentiate from a low-grade B-cell lymphoma as FL
- Management of HS remains challenging due to the absence of standardized treatment protocols
- Future studies are needed to guide optimal treatment strategies

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Questions?

Thank You

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