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CASE 3

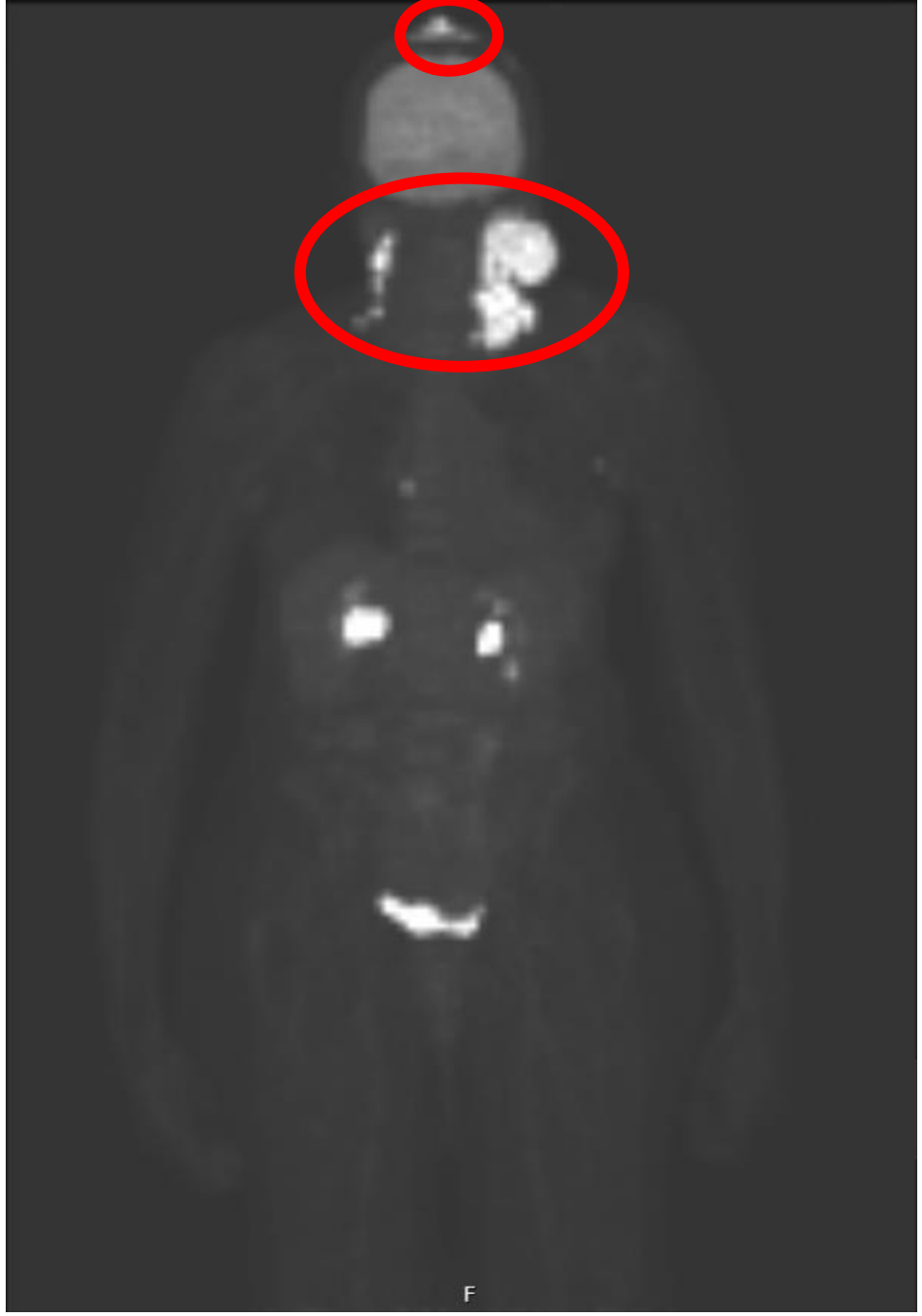
An 80-year-old female

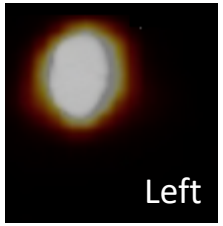
Clinical presentation

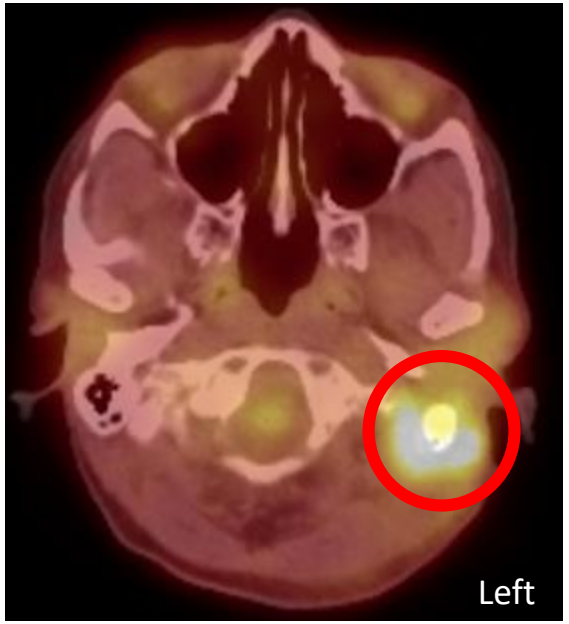
- Rapid progression of neck swelling
- 2.0 cm painful, pruritic, raised, ulcerated scalp lesion and Bilateral l 1 cervical lymphadenopathy
- Prior Diagnosis of T-cell lymphoma (outside institution)
- Treated with Brentuximab every 3 weeks s/p cycle 2 (Prior)

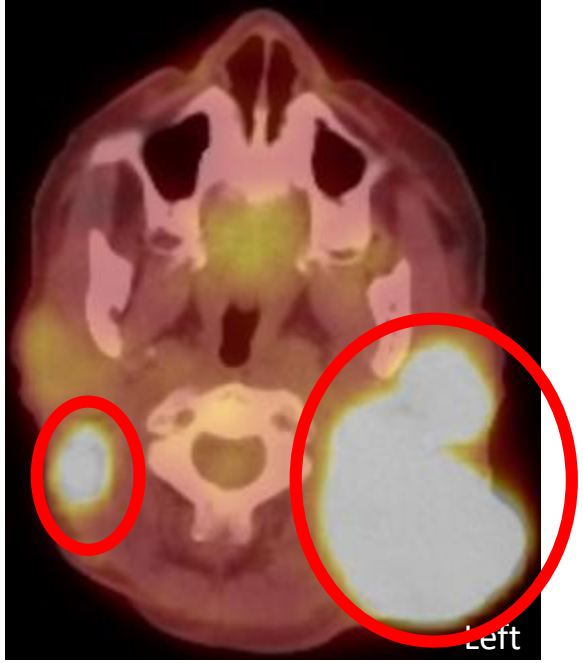
Procedure:

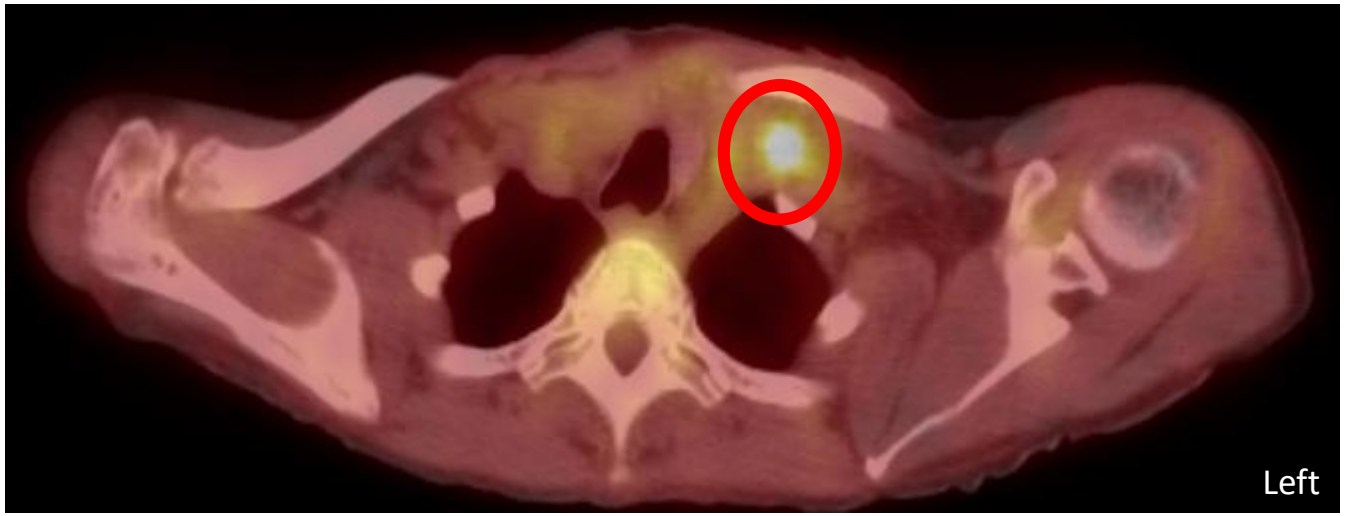
- Excisional biopsy Scalp lesion (4/23/2021 and 6/4/2021) received as consultation











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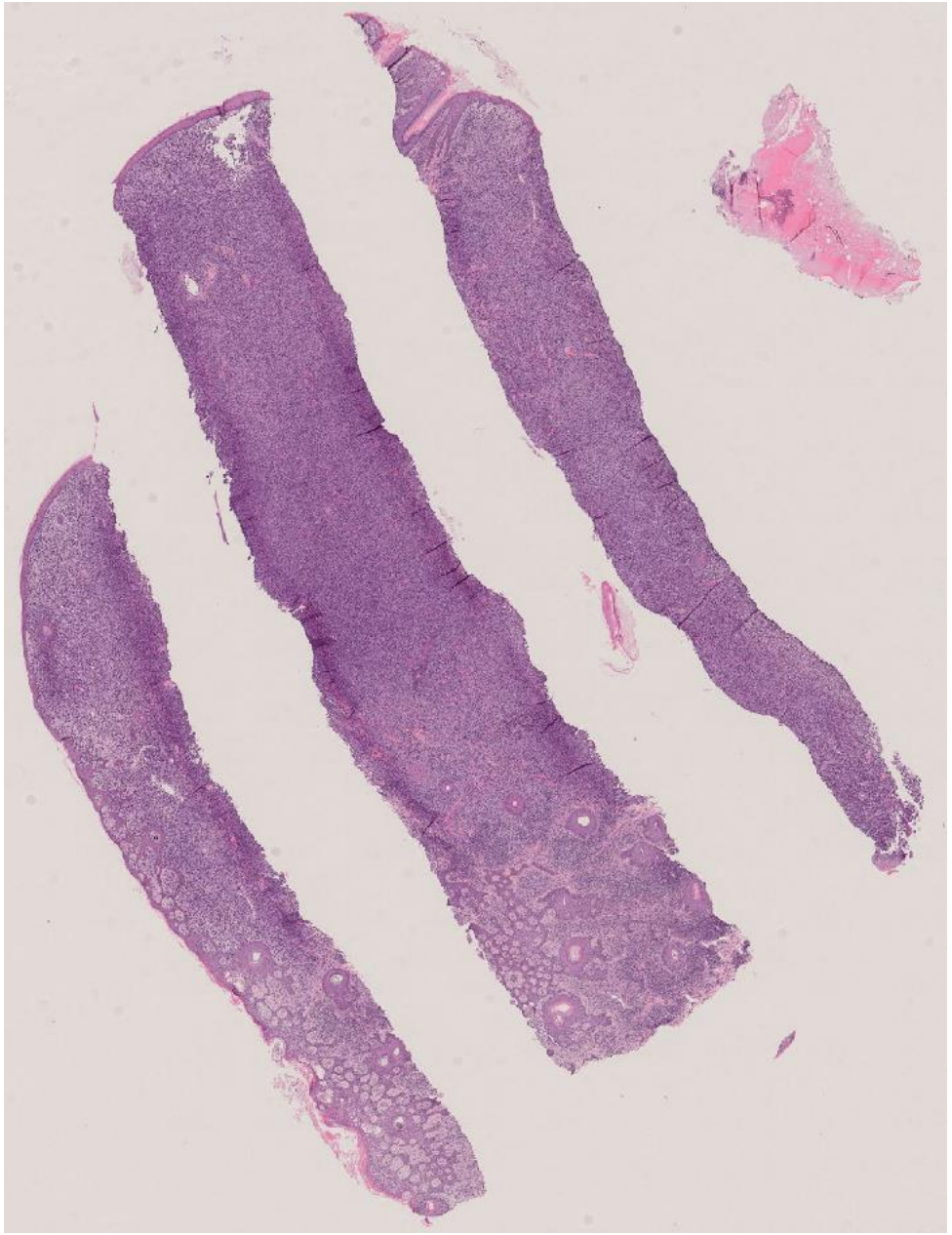
Original outside institution report (the immunostains were not submitted for review)

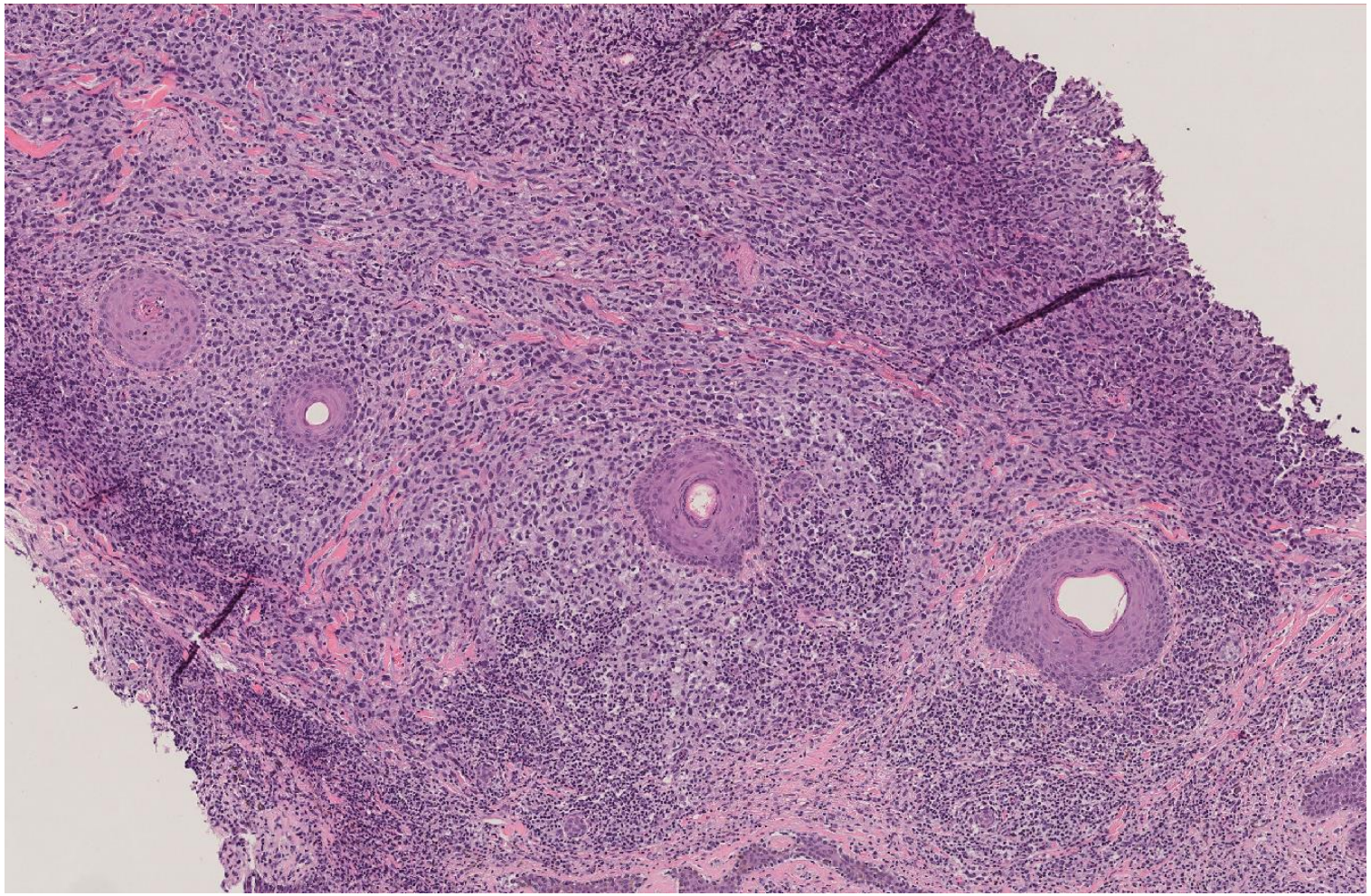
- T- cell lymphoma
- **neoplastic cells are positive for CD45, CD2, CD4, BCL6, CD3 (subset) and CD123 (scattered)**
- **neoplastic cells are negative for CD7, CD8, CD20, CD30, CD56, EBER ISH, PAX5 and lysozyme.**

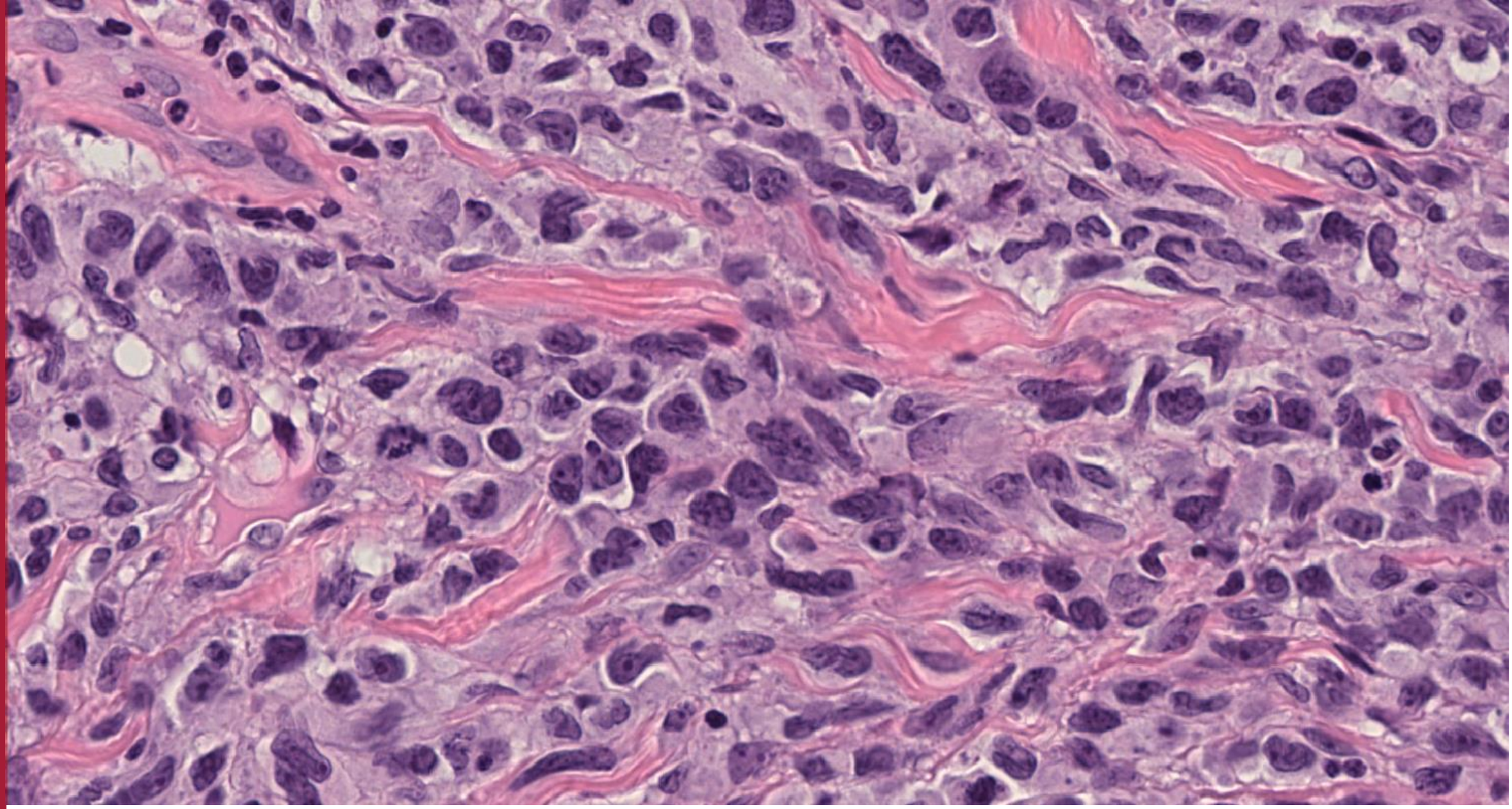
Consultation

- H&E and Unstained slides form the initial specimen were received
- Immunostains and molecular studies were done at Fox Chase Cancer Center

Histopathology and Immunohistochemistry







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Immunohistochemistry FCCC

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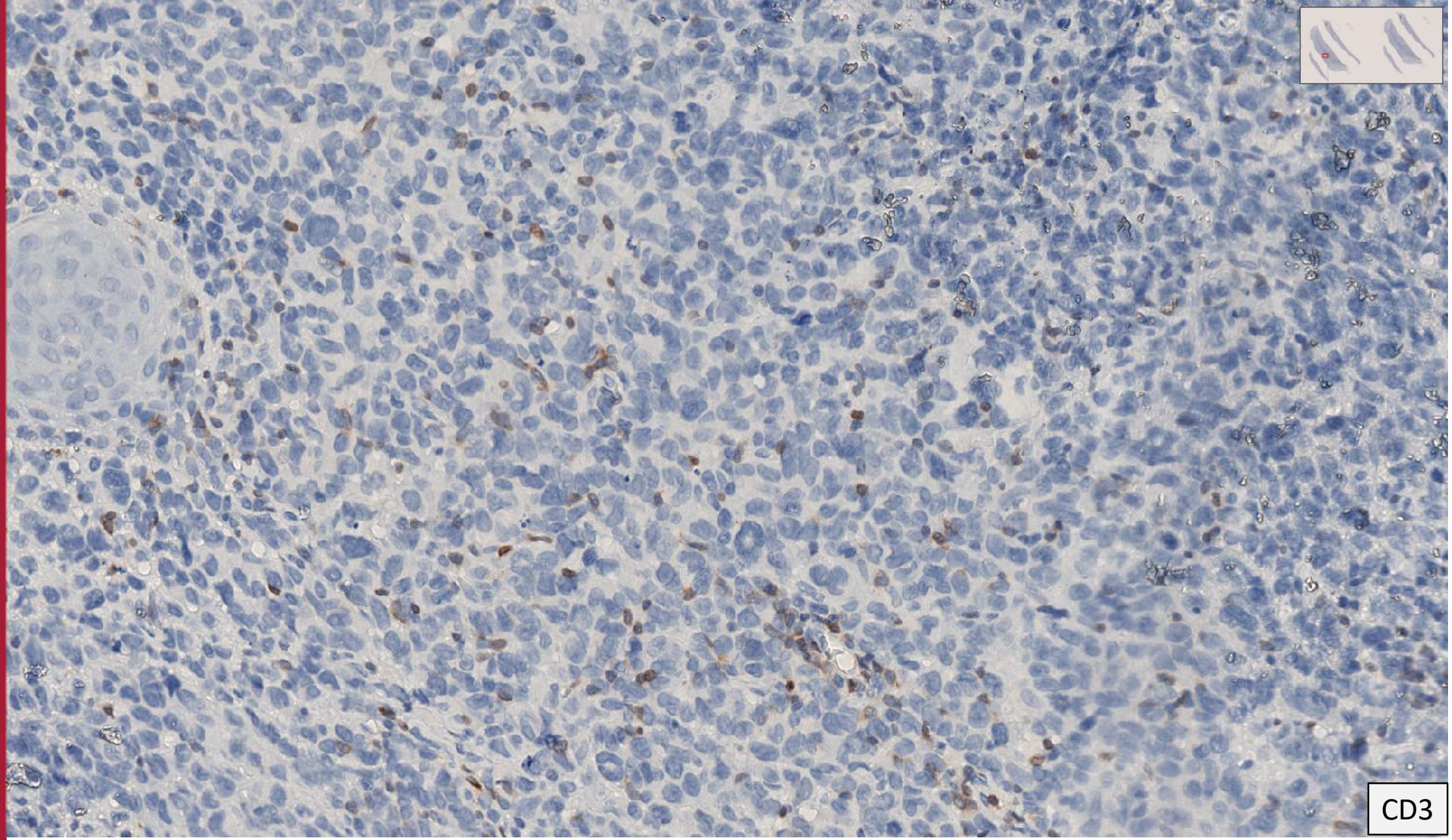

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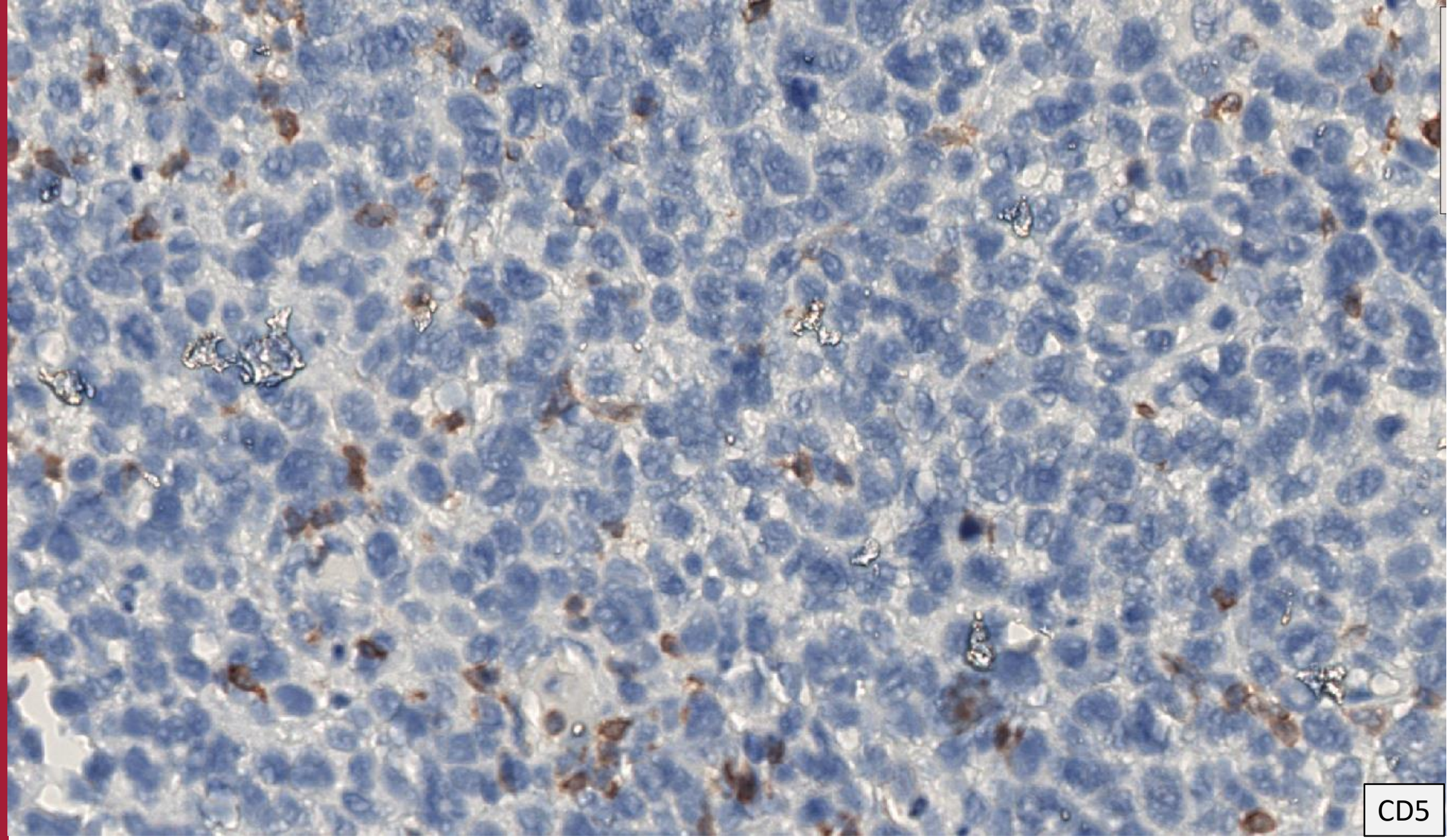

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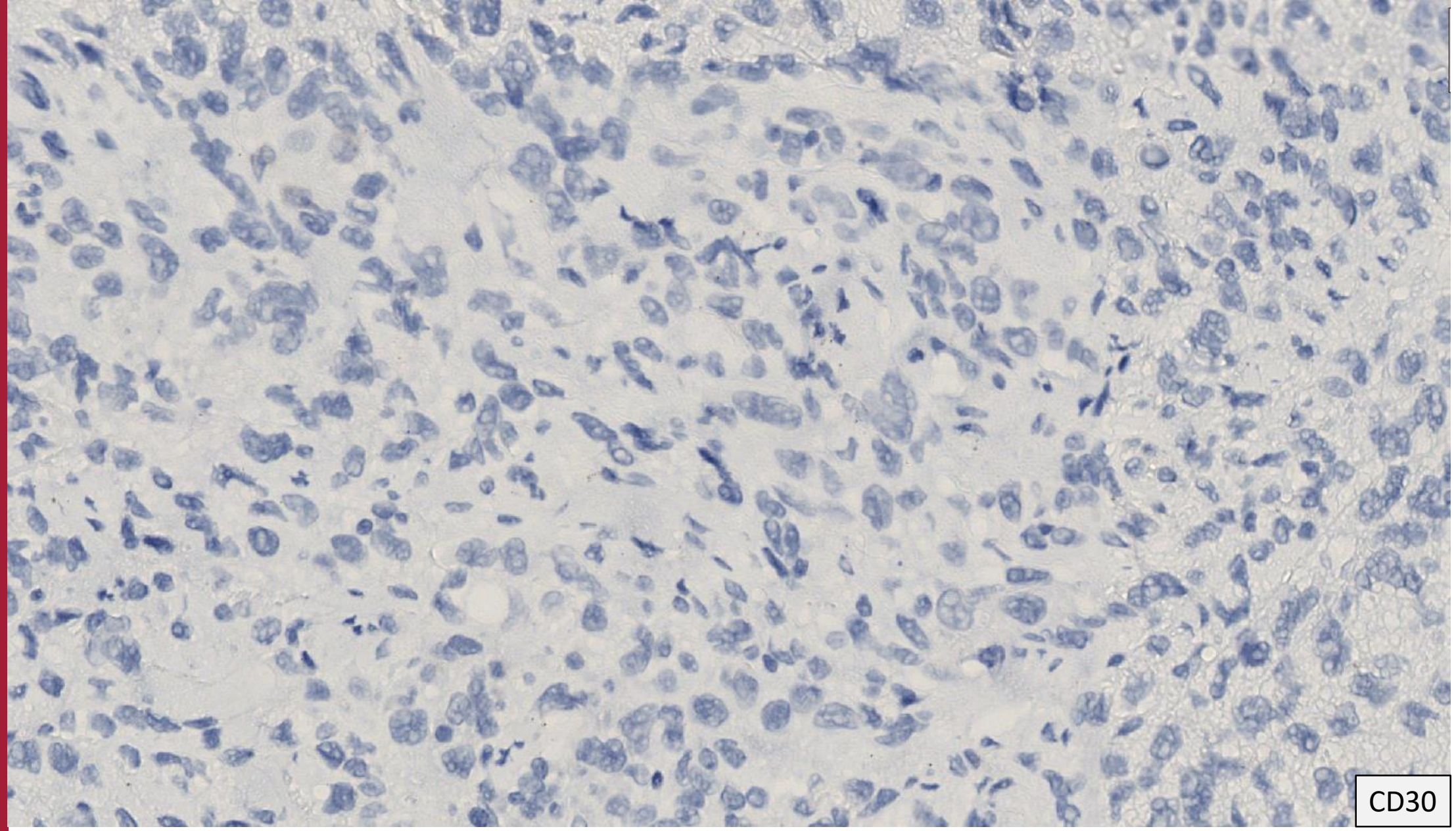
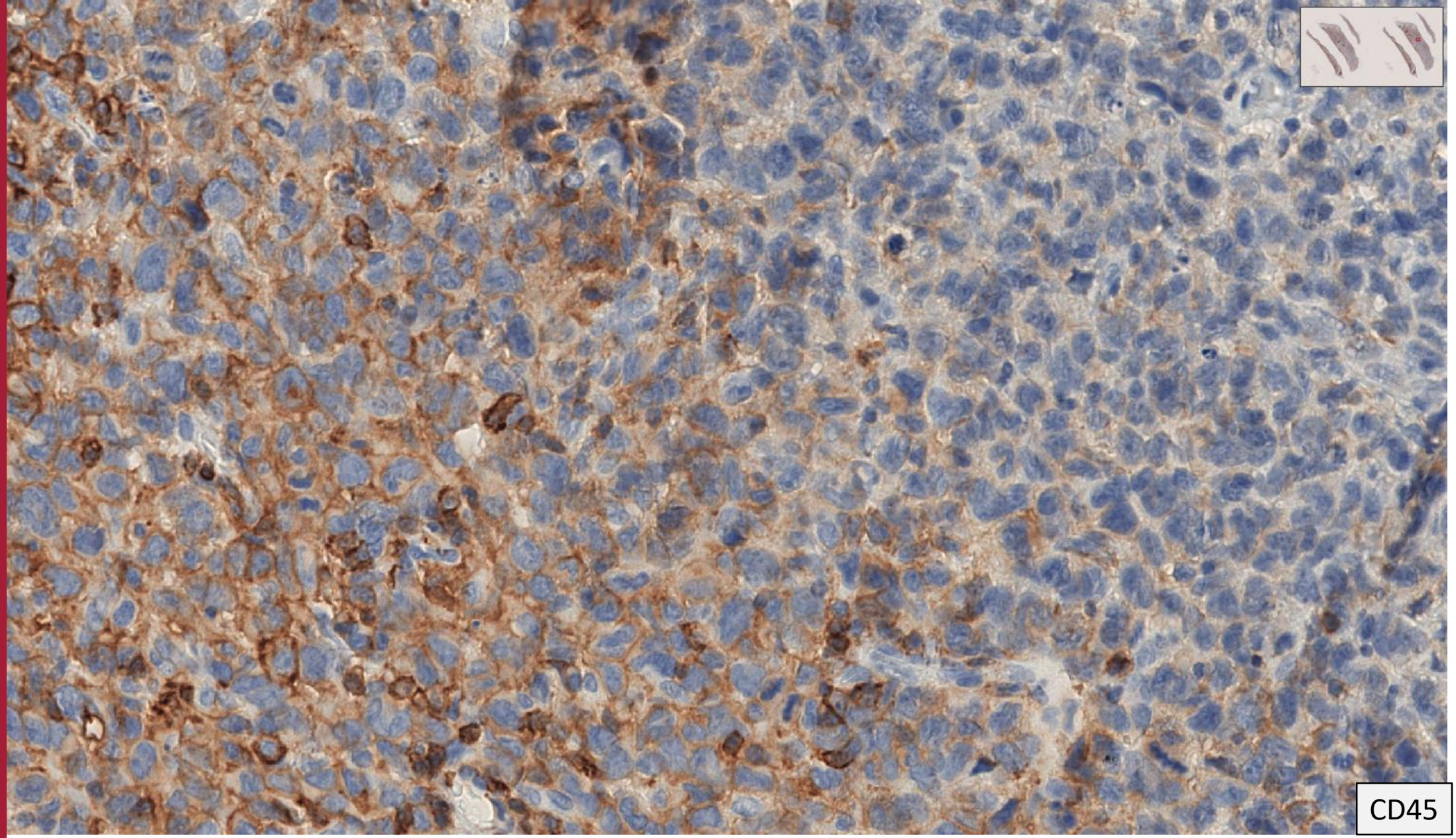

CD30



CD45

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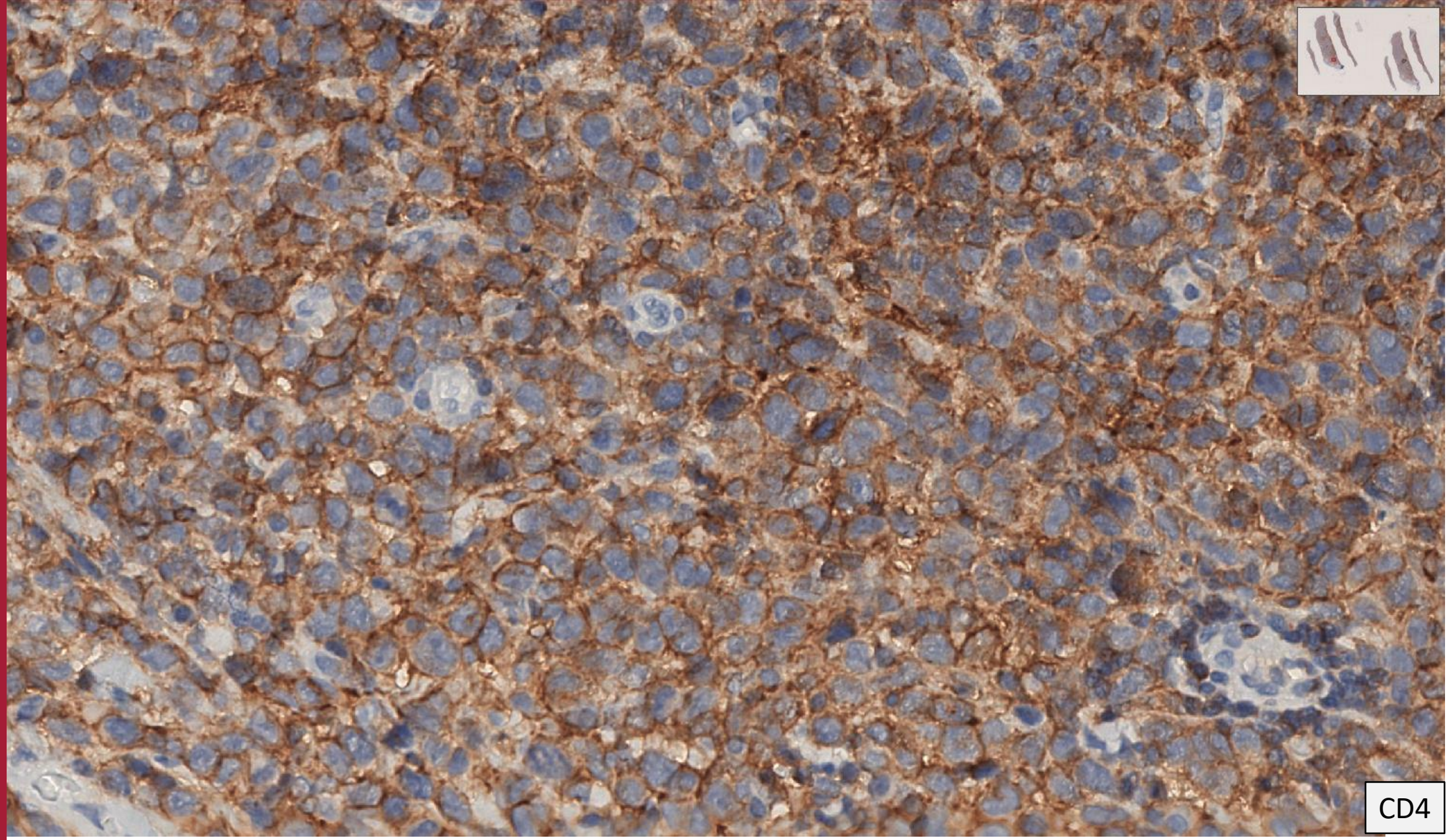

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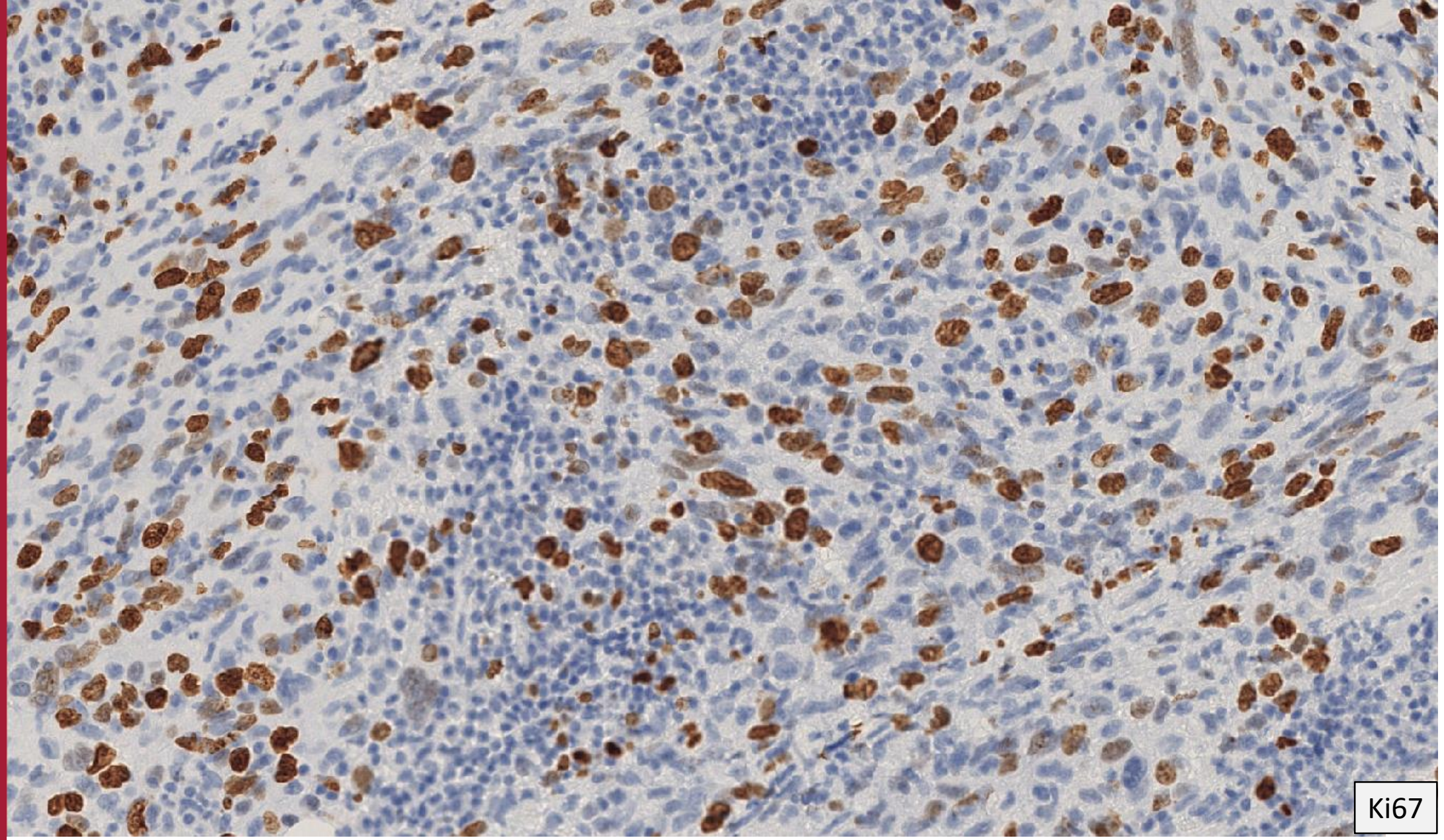
Differential diagnosis?

Additional Tests



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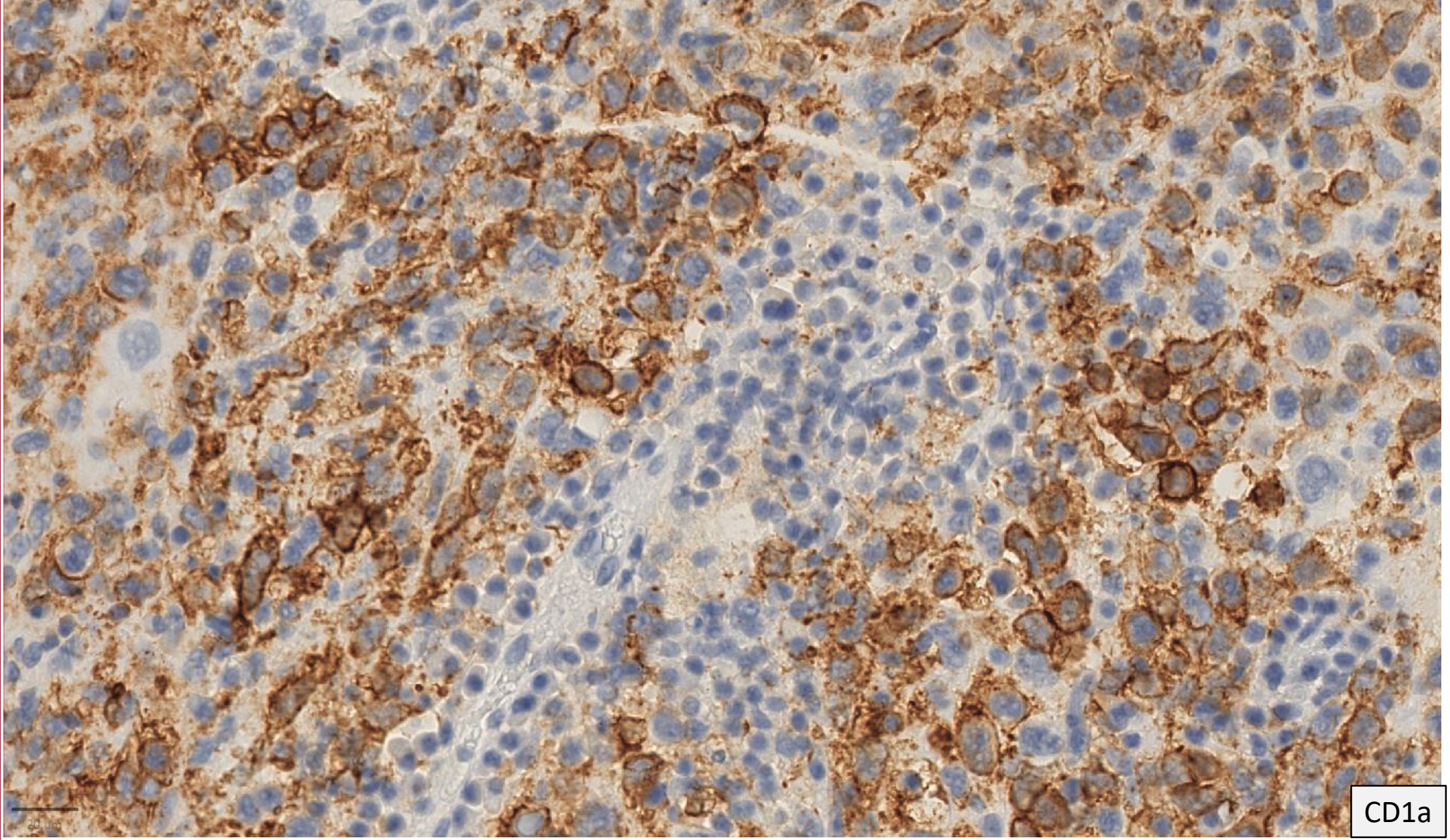

CD1a

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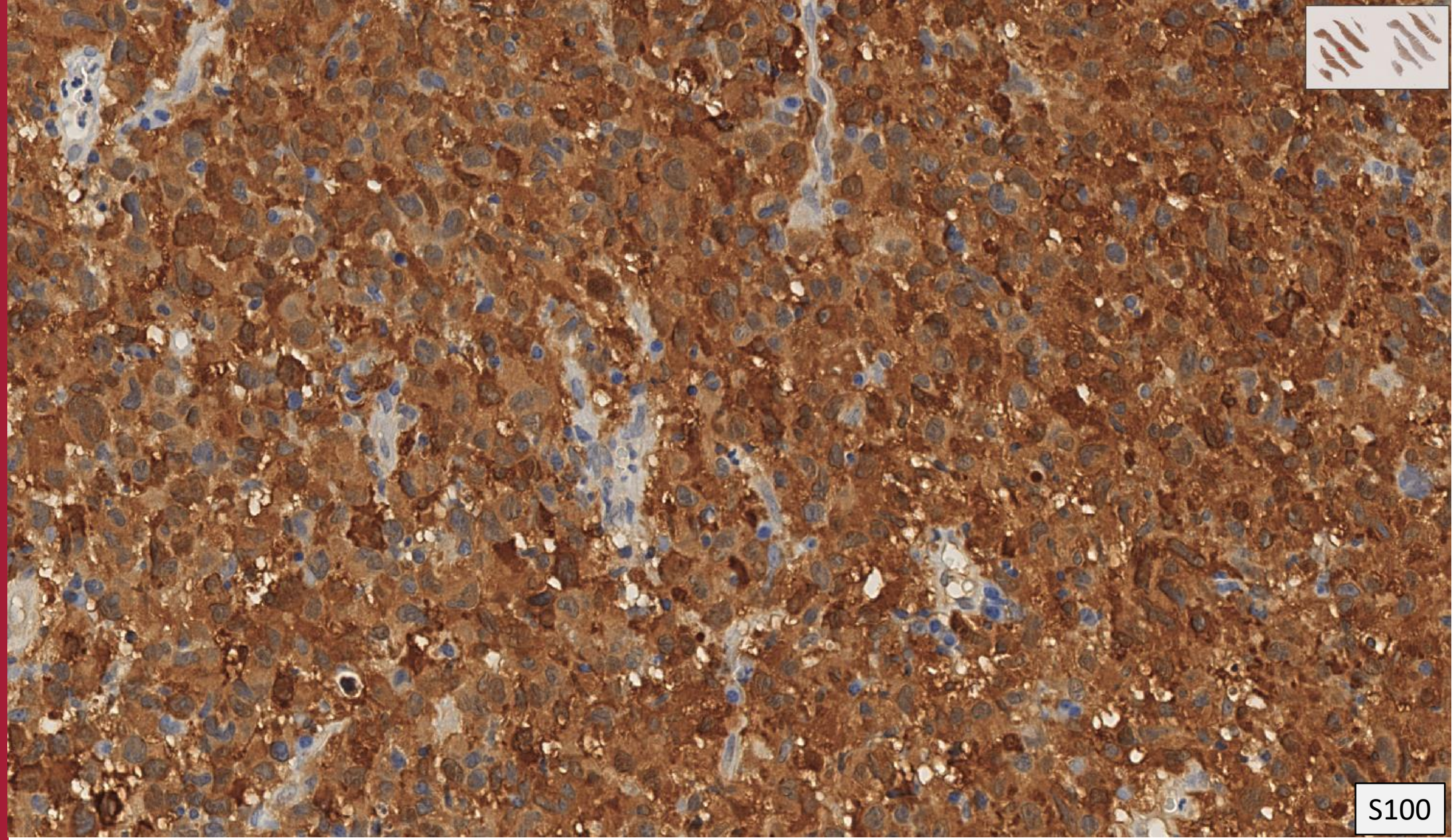

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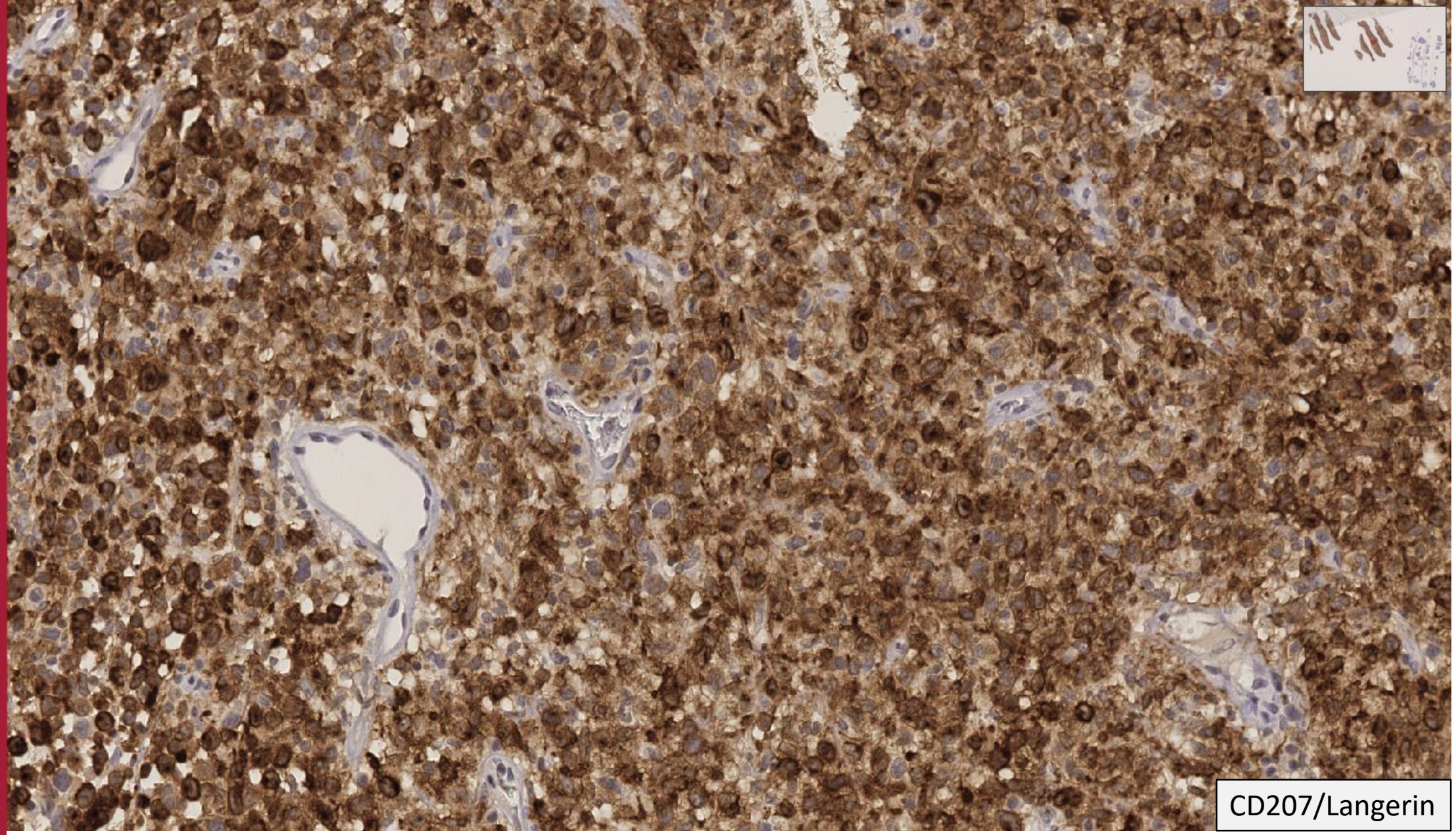

CD207/Langerin

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Additional Testing FCCC

Next Generation Sequencing

- Tumor mutation burden = 3.6Muts/Mb
  - **NF1 (p.Gln347*) VAF = 52.1% (Tier2)**
  - LRP1B (p.Gly4199Glu), VAF = 37.6% (Tier3)
  - ATRX (p.Phe1764Ile) VAF = 56.5% (Tier3)

Cytogenomic Microarray Analysis (CMA)

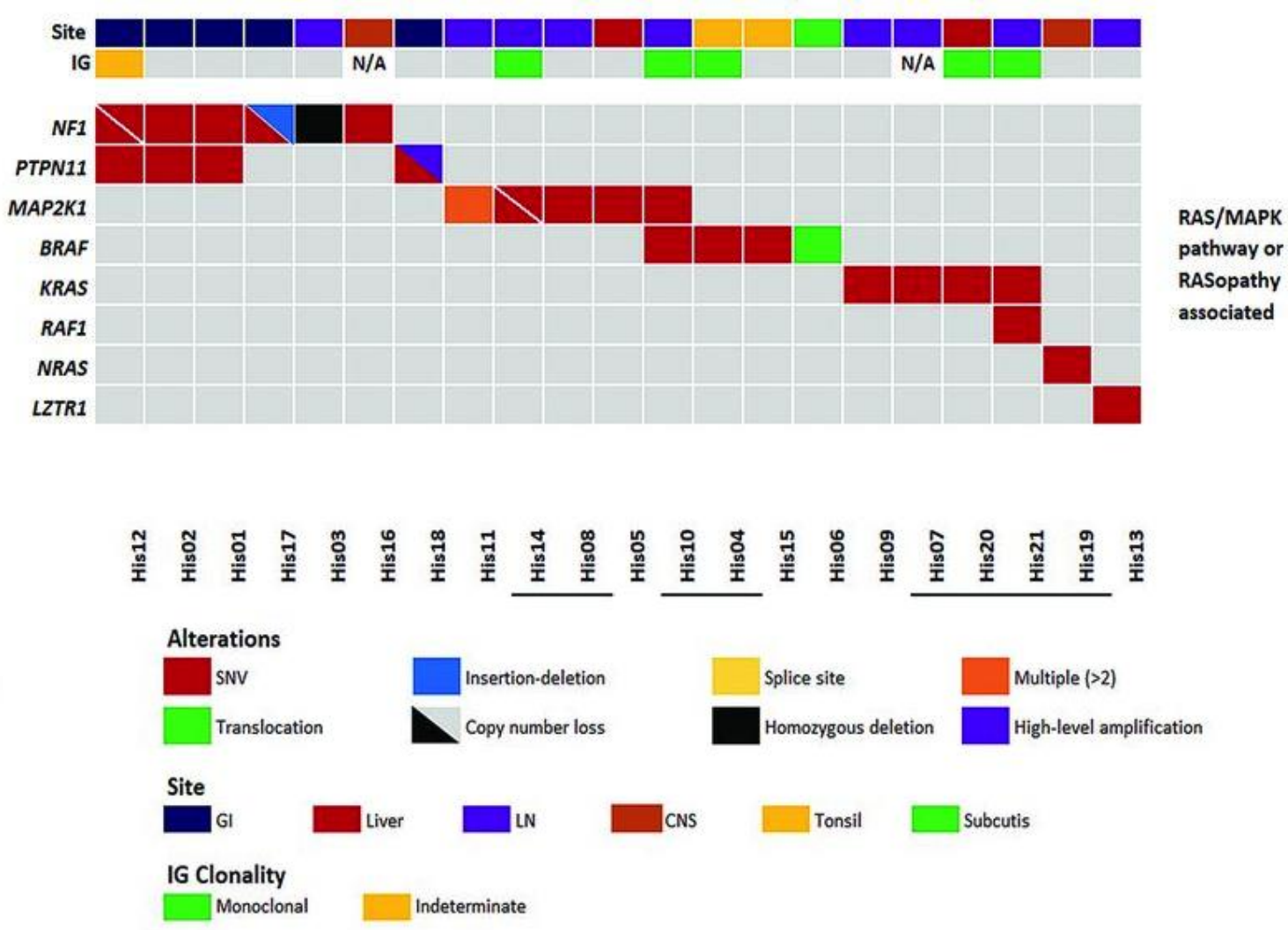
- Abnormal with **losses of** chromosomes or segments 3q, 4q, 6p, 6q, 11q, 13q, 14, **17p (Tp53 loss)**, 17q and 19q **and gains of** 3pq, 3q, 4p, 6p, 7q, 17q, 19pq, 21 and X and copy neutral Loss of Heterozygosity of chromosome 2 in mixed states representing clonal diversity. Gains of 18 and 21 are in about 30% - 40% of the cells.

RNA Fusion Analysis

- Negative

Final Diagnosis

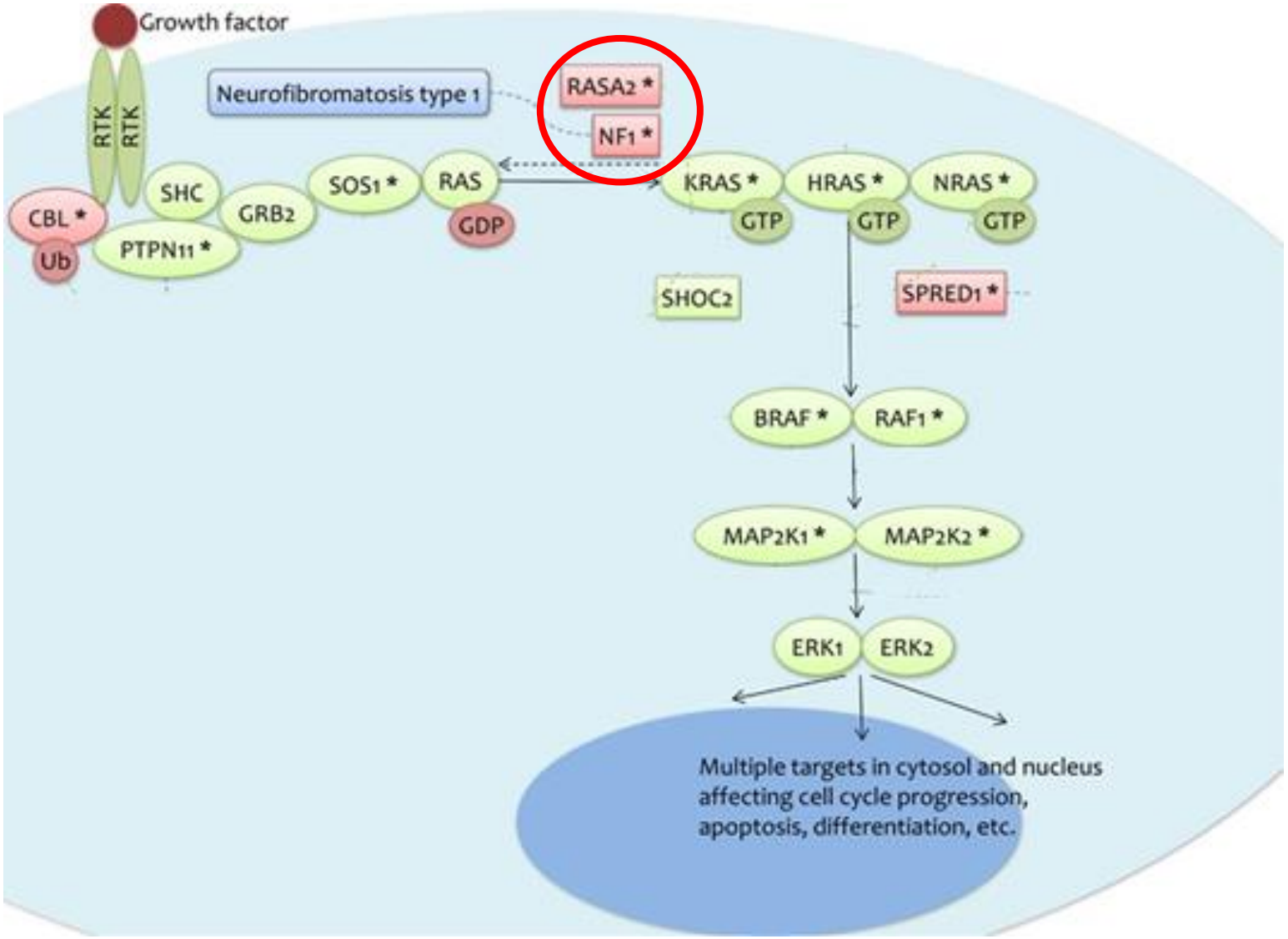
- **Langerhans cell sarcoma**
  - WHO Diagnostic criteria was met
    - Essential:
      - Pleomorphic histiocytes with high-grade cytology ✓
      - Increased mitoses ✓
      - Immunoreactivity for CD1a/Langerin and S100. ✓
    - Desirable:
      - Clinical evidence of rapid tumour progression ✓
      - Molecular alteration, preferably in the MAPK pathway ✓



Other genetic alterations in LCS include:

- Mutations in MAPK pathway genes (*KRAS* and less of *BRAF* p.V600E)
- Del *CDKN2A* and ***TP53***
- PTEN mutations

Egan, C., et al. (2020). *Genomic profiling of primary histiocytic sarcoma reveals two molecular subgroups*. *Haematologica, 105*(4), 951–960. https://doi.org/10.3324/haematol.2019.230375



NF1 is negative regulator in the RAS/MAPK Pathway

Patient has a NF1(p.Gln347*) results in a loss of function NF1 leading to proliferation of these dysplastic histocytes

Kiuru, M., Busam, K. The NF1 gene in tumor syndromes and melanoma. Lab Invest 97, 146–157 (2017). https://doi.org/10.1038/labinvest.2016.142

Patient Progress

- Patient is currently in Hospice care for terminal disease care (Admitted: October 2025).

Langerhans Cell Sarcoma (LCS)

Source: WHO Classification of Tumors (Hematolymphoid), 5th ed. — Langerhans cell sarcoma

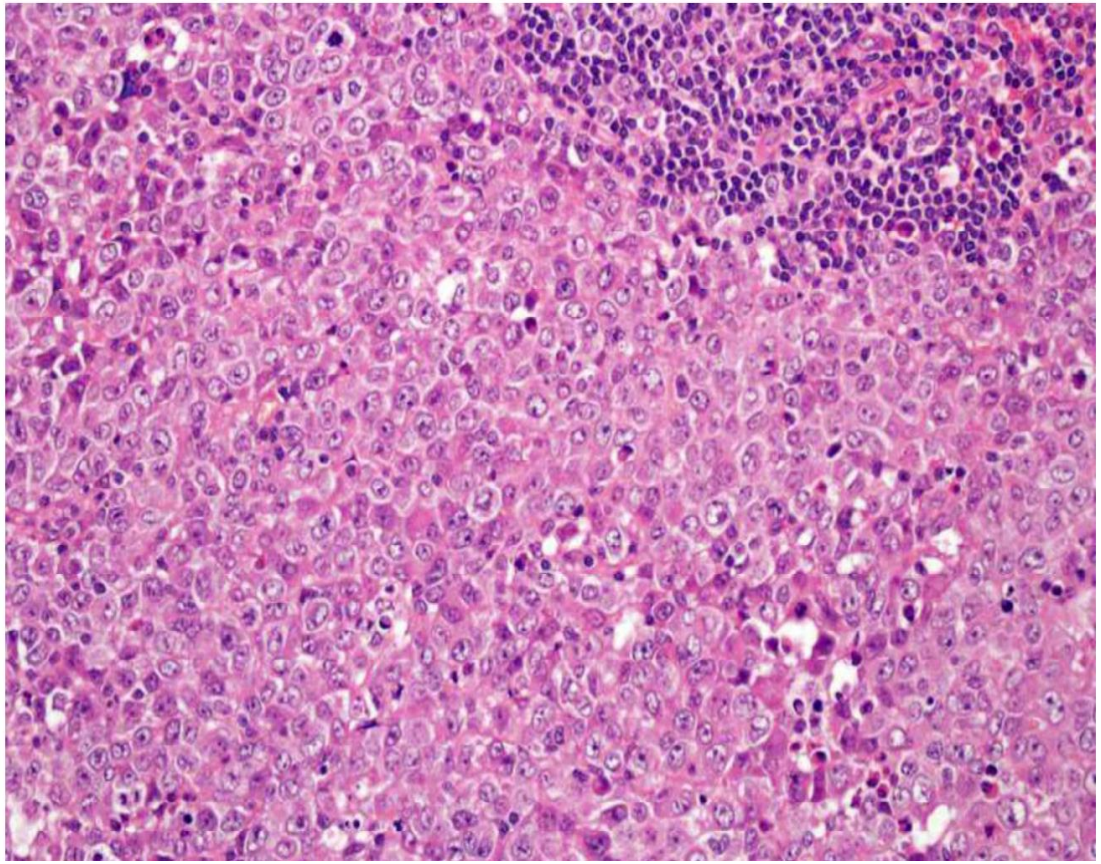
Key points

Rare, aggressive malignant neoplasm with Langerhans cell immunophenotype and high-grade cytology.

Often extranodal and may present with multiorgan disease.

Histopathology

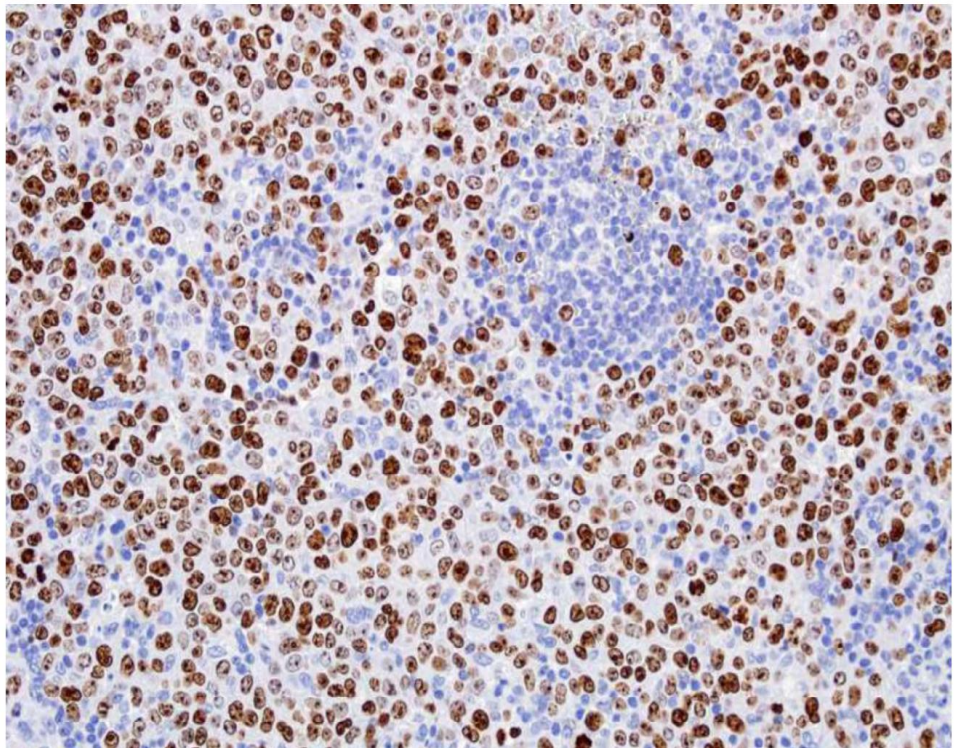
- Pleomorphic histiocytes (larger cells with abundant cytoplasm)
- Plump or elongated with clumped chromatin; nuclear grooves may be absent.
- Numerous and atypical mitosis
- Inflammatory background is variable; +/-eosinophils.
- Lymph nodes,
  - Sinusoidal proliferation.
  - Effacement at advanced stages.



Sheets of pleomorphic tumour cells with clumped chromatin (H&E).

Diagnosis: criteria & differential WHO 5th Edition

- **Essential**:
  - **Histology**: high-grade pleomorphic histiocytic neoplasm with increased mitoses.
  - **Immunohistochemistry**: immunoreactivity for LC markers (CD1a and/or S100 and/or CD207; may be focal).
- Desirable:
  - Clinical evidence of **rapid progression**.
  - supportive **molecular alteration** (preferably MAPK-pathway).
- Differentials: histiocytic sarcoma; dendritic cell sarcomas; metastatic melanoma; poorly differentiated carcinoma/lymphoma.



High proliferative index (Ki-67).

Source: WHO Classification of Tumours (Haematolymphoid), 5th ed. — Langerhans cell sarcoma

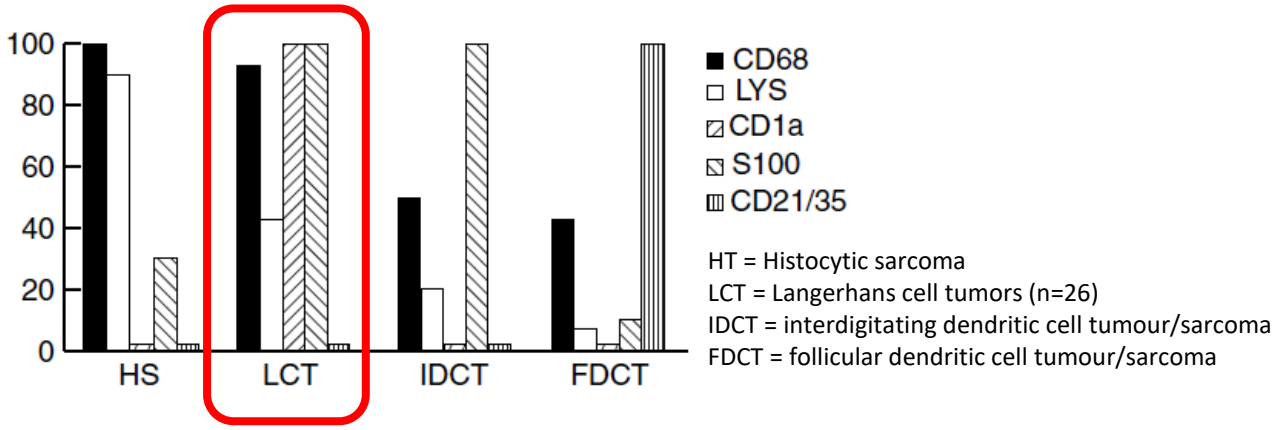
Localization & clinical presentation

- Most cases = extranodal sites: skin, lung, bone, and soft tissue.
- Multiorgan disease (lung, liver, spleen, lymph nodes, and bone)
- 20% cases = isolated lymph node involvement.
- Clinical presentation varies.

Epidemiology & etiology

Incidence = 0.02 per 1 million population (SEER); adults; male predilection.

Immunohistochemical classification of histiocytic/dendritic cell tumors (ILSG, 61 cases)



HT = Histocytic sarcoma
LCT = Langerhans cell tumors (n=26)
IDCT = interdigitating dendritic cell tumour/sarcoma
FDCT = follicular dendritic cell tumour/sarcoma

- Uses a practical paraffin IHC panel (e.g., CD1a/S100) to Diagnose LCT and LCS among other histocytic entities

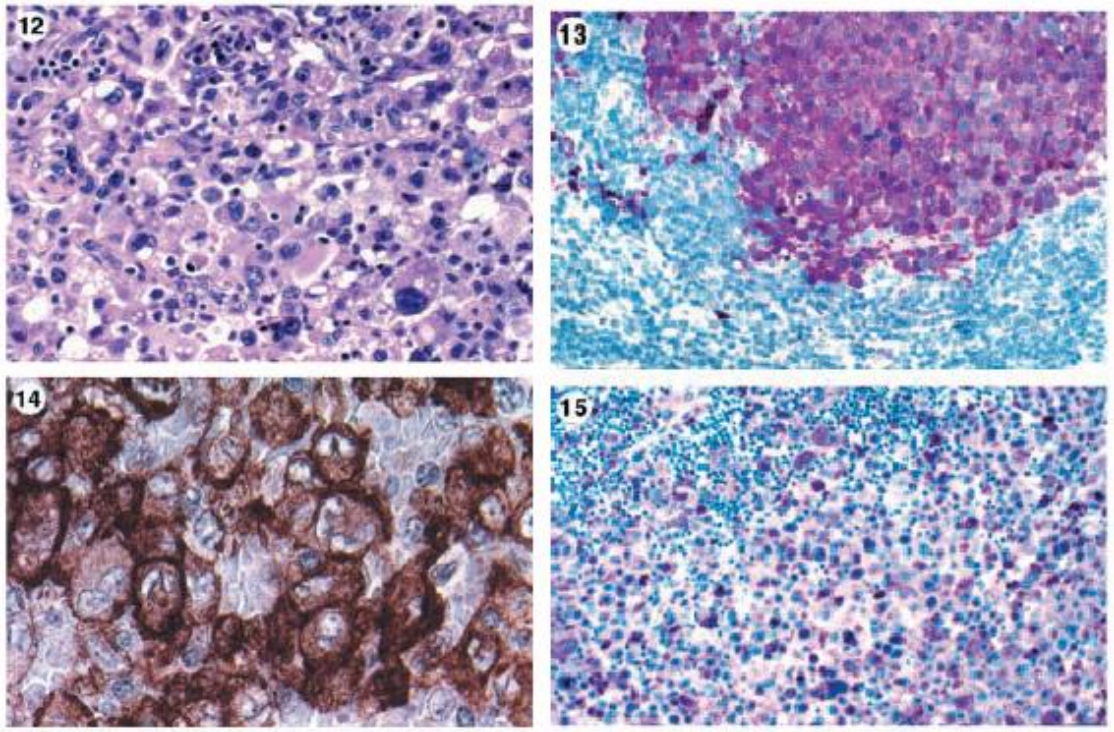
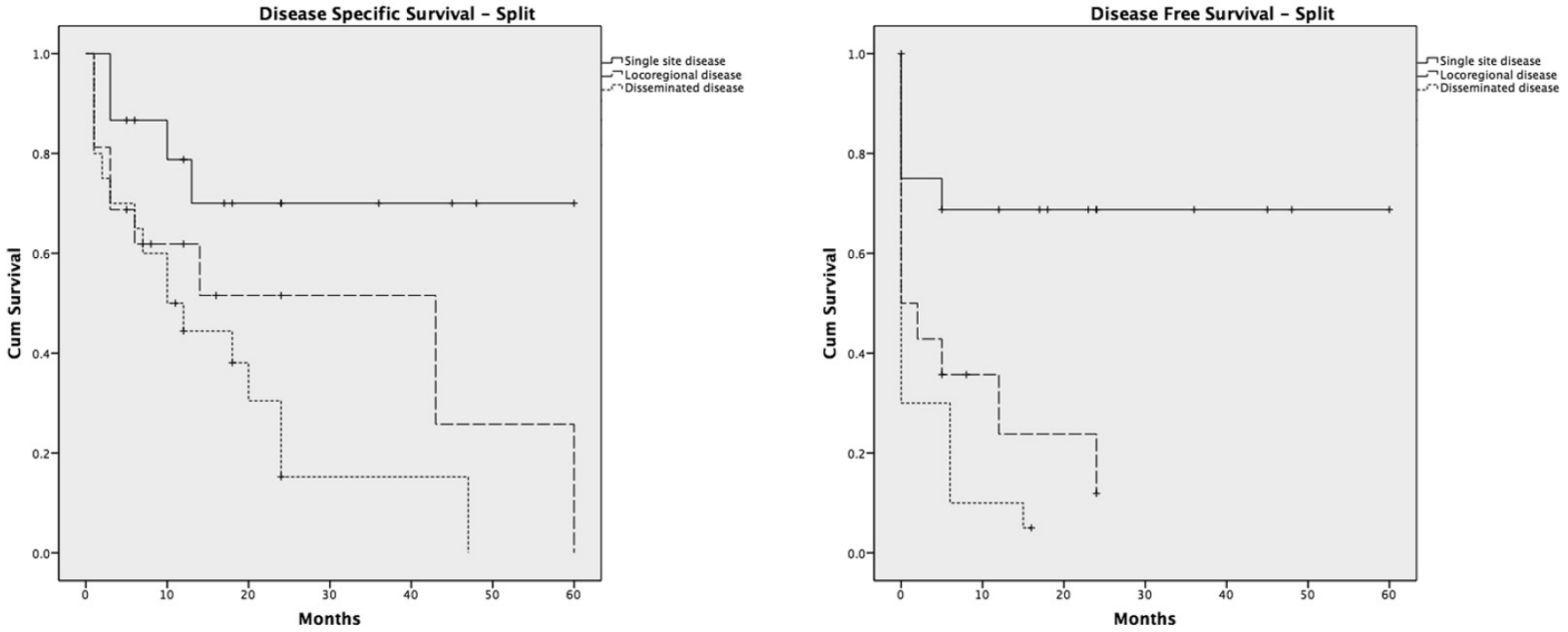


Figure 12. LCS: neoplastic cells show striking, overt cytologic atypia and pleomorphism. H&E.
Figure 13. LCT with mild atypia: strong expression of S100 protein. hematoxylin nuclear counterstaining.
Figure 14. LCT: the neoplastic cells show strong surface staining for CD1a.
Figure 15. LCT: expression of the CD68 molecule.

Pileri SA, et al. Histopathology. 2002;41:1–29. doi:10.1046/j.1365-2559.2002.01418.x

Langerhans cell sarcoma: systematic review (66 cases)



Disease specific and disease free survival calculations from Kaplan–Meier survival analysis.

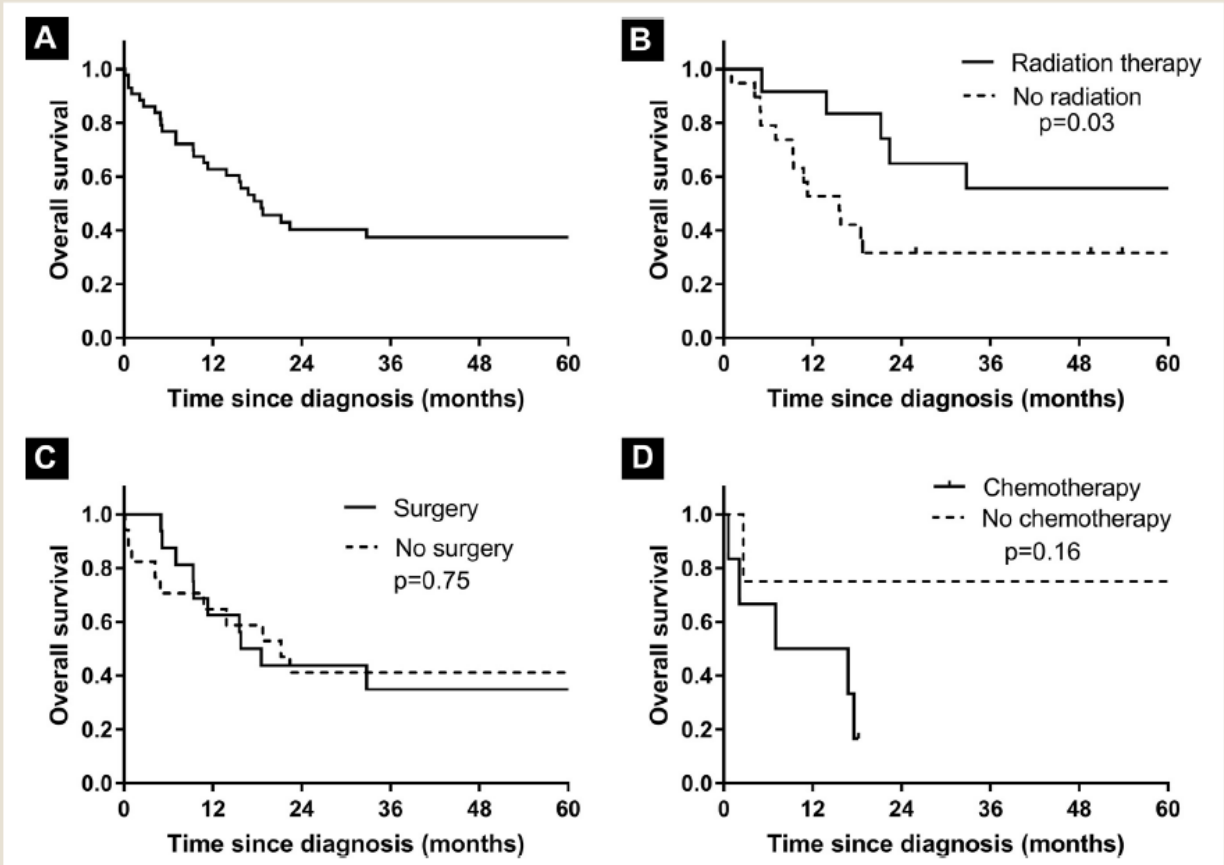
	Disease Specific Survival (Mean)			Disease Free Survival (Mean)		
	Estimate	Std Error	Mantel-Cox	Estimate	Std Error	Mantel-Cox
Overall	27.201	3.857		18.26	3.775	
Single site	44.346	6.625	$p = 0.014$	41.563	6.843	$p < 0.001$
Locoregional	28.973	7.471		7.643	2.767	
Disseminated	6.252	3.781		2.75	1.088	

- Overall prognosis remains poor; disease extent at presentation strongly influences survival.
- Proposes pragmatic management approach: local disease favors complete excision; disseminated disease often requires multimodality therapy.

Howard JEF, et al. Cancer Treat Rev. 2015;41:320–331. doi:10.1016/j.ctrv.2015.02.011

Epidemiology and outcomes of Langerhans cell sarcoma (US registries) SEER database (2000-2014; n=25)

Figure 2 OS of LCS Patients Using NCDB, 2004-2015. (A) Kaplan-Meier Curve Depicting OS of LCS. (B) Comparison of OS Based on Receipt or Not of Radiotherapy in LCS Patients After Censoring Patients With Hematopoietic and Reticuloendothelial System Involvement. (C) Comparison of OS Based on Receipt of Surgical Therapy in LCS Patients After Censoring Hematopoietic and Reticuloendothelial Involvement. (D) Comparison of OS Based on Receipt of Chemotherapy Among Patients With Hematopoietic and Reticuloendothelial System Involvement. $P < .05$ Is Considered Statistically Significant



Abbreviations: LCS = Langerhans cell sarcoma; NCDB = National Cancer Data Base; OS = overall survival.

Tella SH, et al. Clin Lymphoma Myeloma Leuk. 2019;19(7):441–446. doi:10.1016/j.clml.2019.03.026

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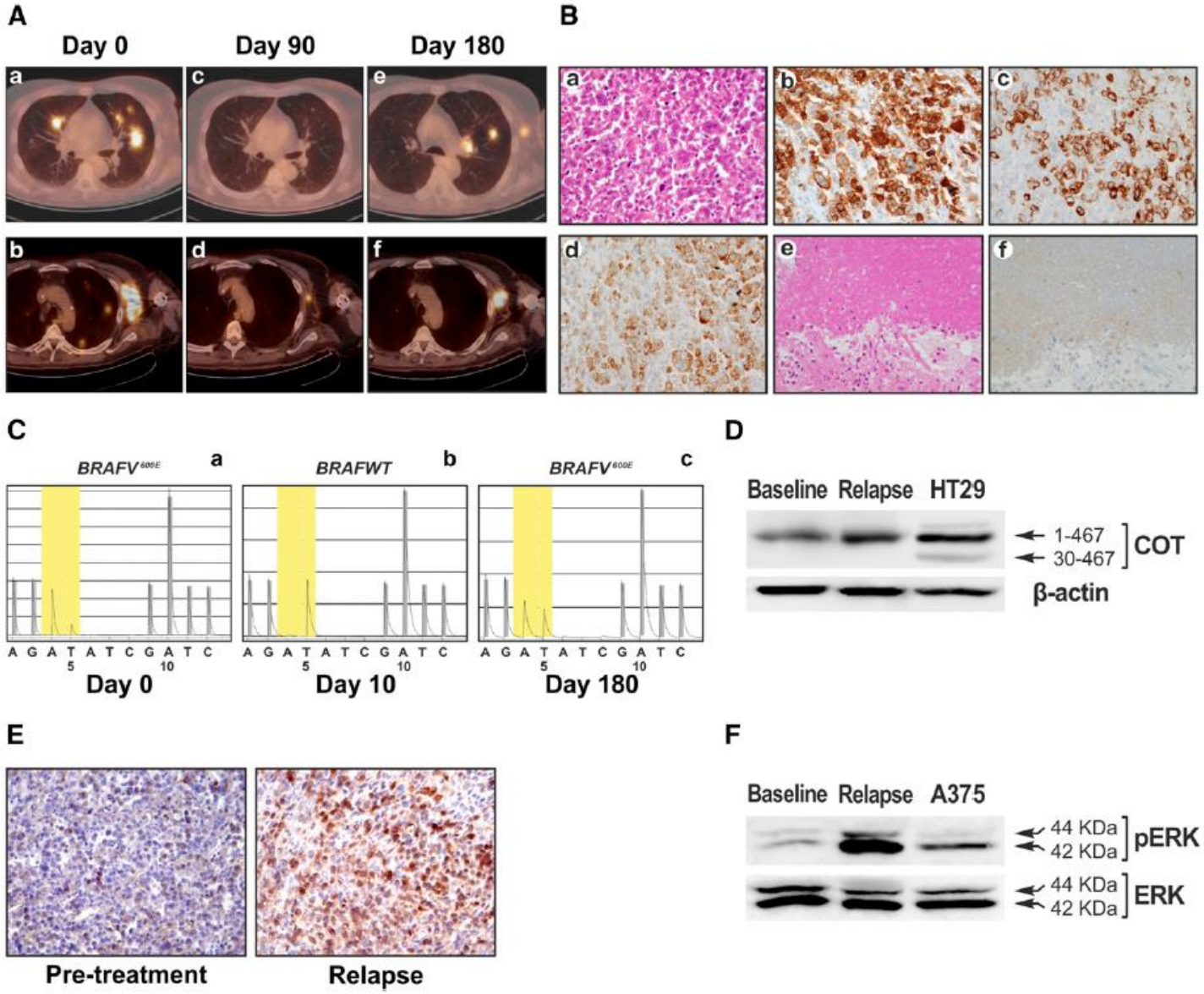
Dabrafenib in metastatic BRAFV600E Langerhans cell sarcoma (n=1)

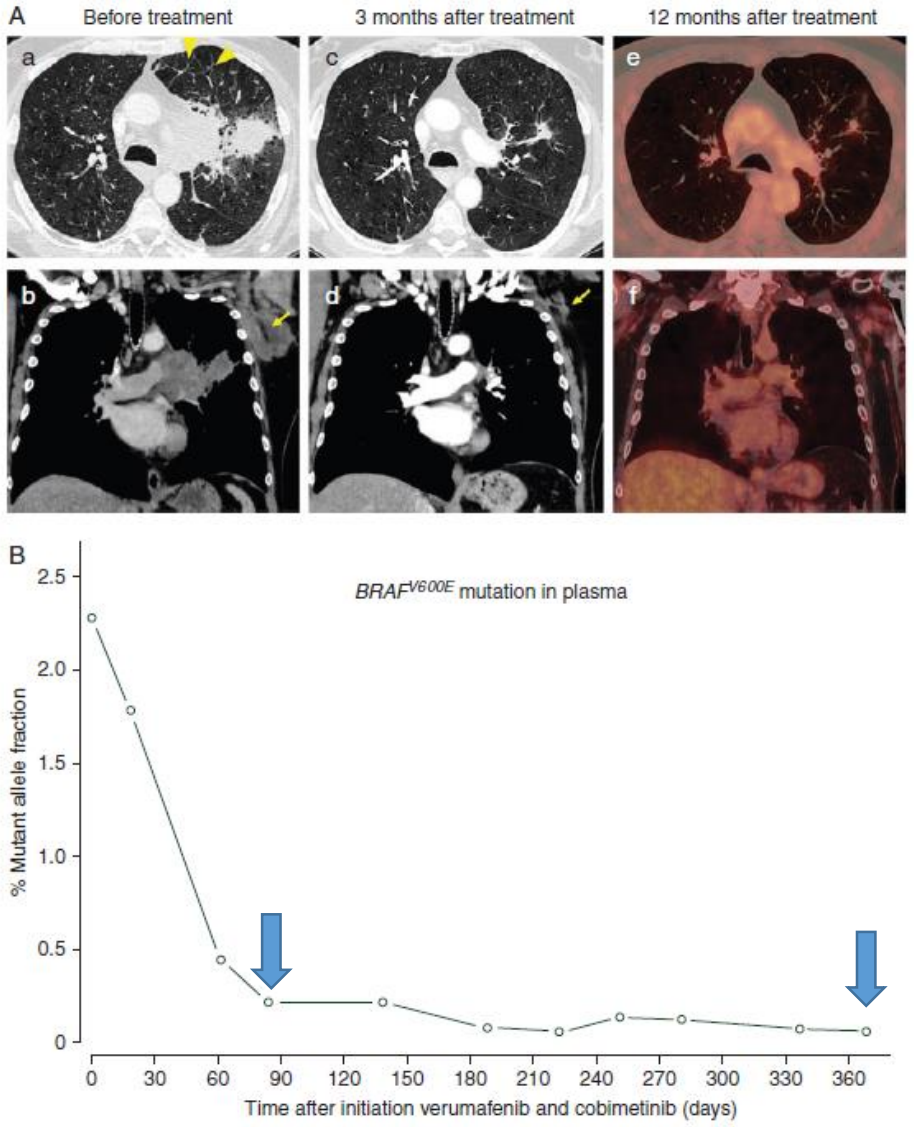


- Case report/letter of metastatic BRAFV600E-mutated Langerhans cell sarcoma treated with dabrafenib.
- Observed dramatic early clinical and radiographic improvement with tumor necrosis on biopsy soon after therapy.
- Molecular response documented by marked reduction in BRAFV600E allele burden, followed by later re-emergence at progression.
- Key takeaway: rapid on-target responses are possible, but acquired resistance can develop; supports molecular monitoring.

Mourah S, et al. Blood. 2015;126(24):2649–2652. doi:10.1182/blood-2015-09-670802

Salvage therapy after dabrafenib resistance in metastatic LCS(n=1)

- Letter describing dabrafenib-resistant metastatic BRAFV600E Langerhans cell sarcoma and subsequent salvage targeted therapy.
- Sustained response achieved using a combination of the BRAFi vemurafenib and the MAPK kinase inhibitor (MEKi) cobimetinib.
- Demonstrates meaningful objective and metabolic response after progression on BRAF inhibitor monotherapy.
- Uses plasma BRAFV600E monitoring (ultrasensitive method) as a response biomarker during therapy.
- Supports the concepts of (i) acquired resistance in MAPK-driven histiocytic neoplasms and (ii) value of ctDNA tracking.



Lorillon G, et al. Ann Oncol. 2016;27(12):2305–2307. doi:10.1093/annonc/mdw299

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SUMMARY:

- Diagnosis of Langerhans cell sarcoma is a rare diagnosis and suspicious cases should be worked up appropriately.

- CD1a, S100, CD207 immunostaining should be considered for these kinds of cases.

References:

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- Mourah S, Lorillon G, Meignin V, Vercellino L, de Margerie-Mellon C, Pagès C, et al. Dramatic transient improvement of metastatic BRAFV600E-mutated Langerhans cell sarcoma under treatment with dabrafenib. *Blood.* 2015;126(24):2649-2652. doi:10.1182/blood-2015-09-670802
- Pileri SA, Grogan TM, Harris NL, Banks P, Campo E, Chan JKC, et al. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. *Histopathology.* 2002;41(1):1-29. doi:10.1046/j.1365-2559.2002.01418.x
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- Howard JEF, Dwivedi RC, Masterson L, Jani P. Langerhans cell sarcoma: a systematic review. *Cancer Treat Rev.* 2015;41:320-331. doi:10.1016/j.ctrv.2015.02.011
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Thank you!

Multi-Institutional Hematopathology Case Presentation

A Special thanks to Drs. Nejati, Wasik, Mackrides for mentorship

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1/21/2026