CASE 2

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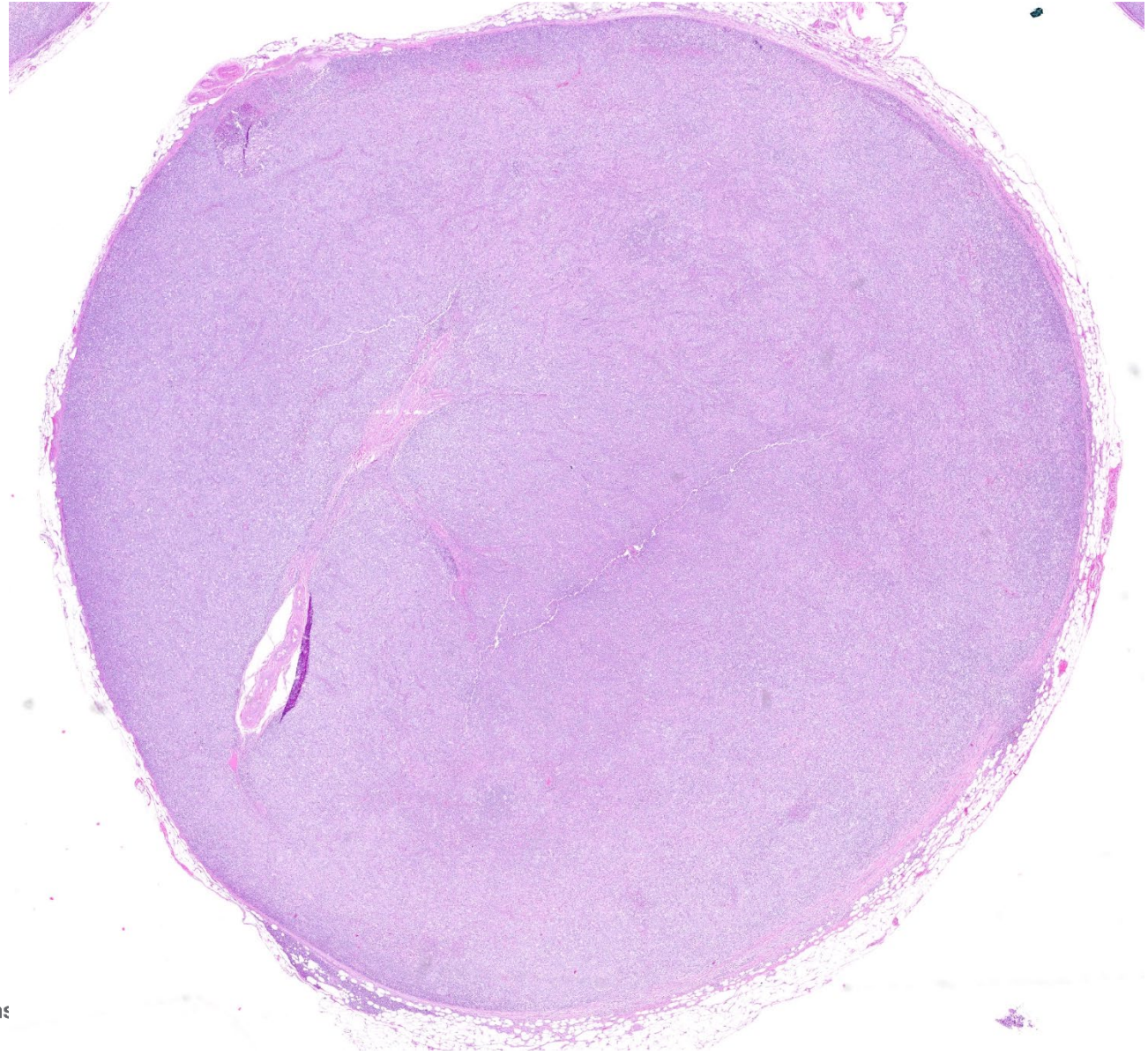
Clinical Center

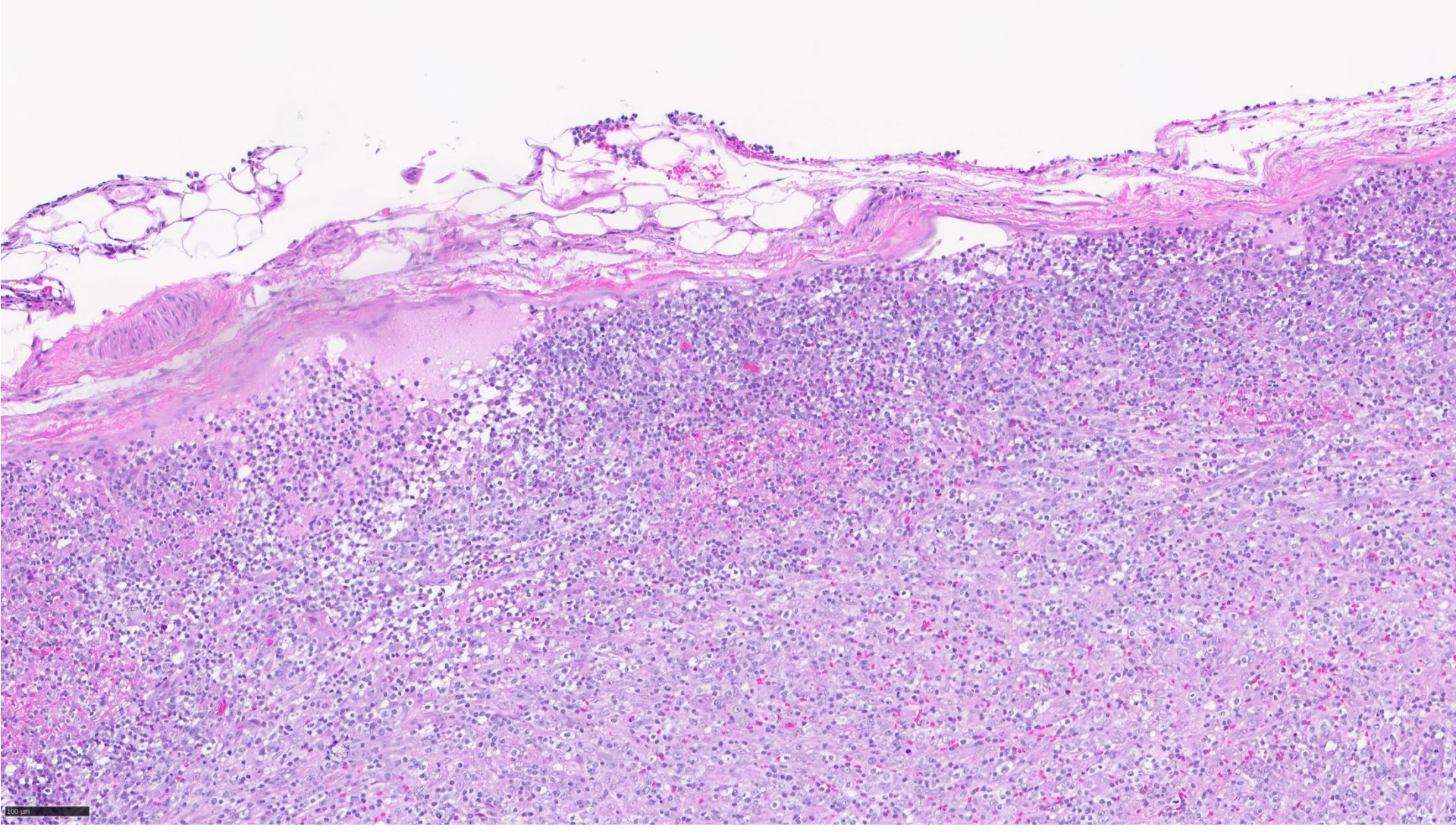
Clinical information

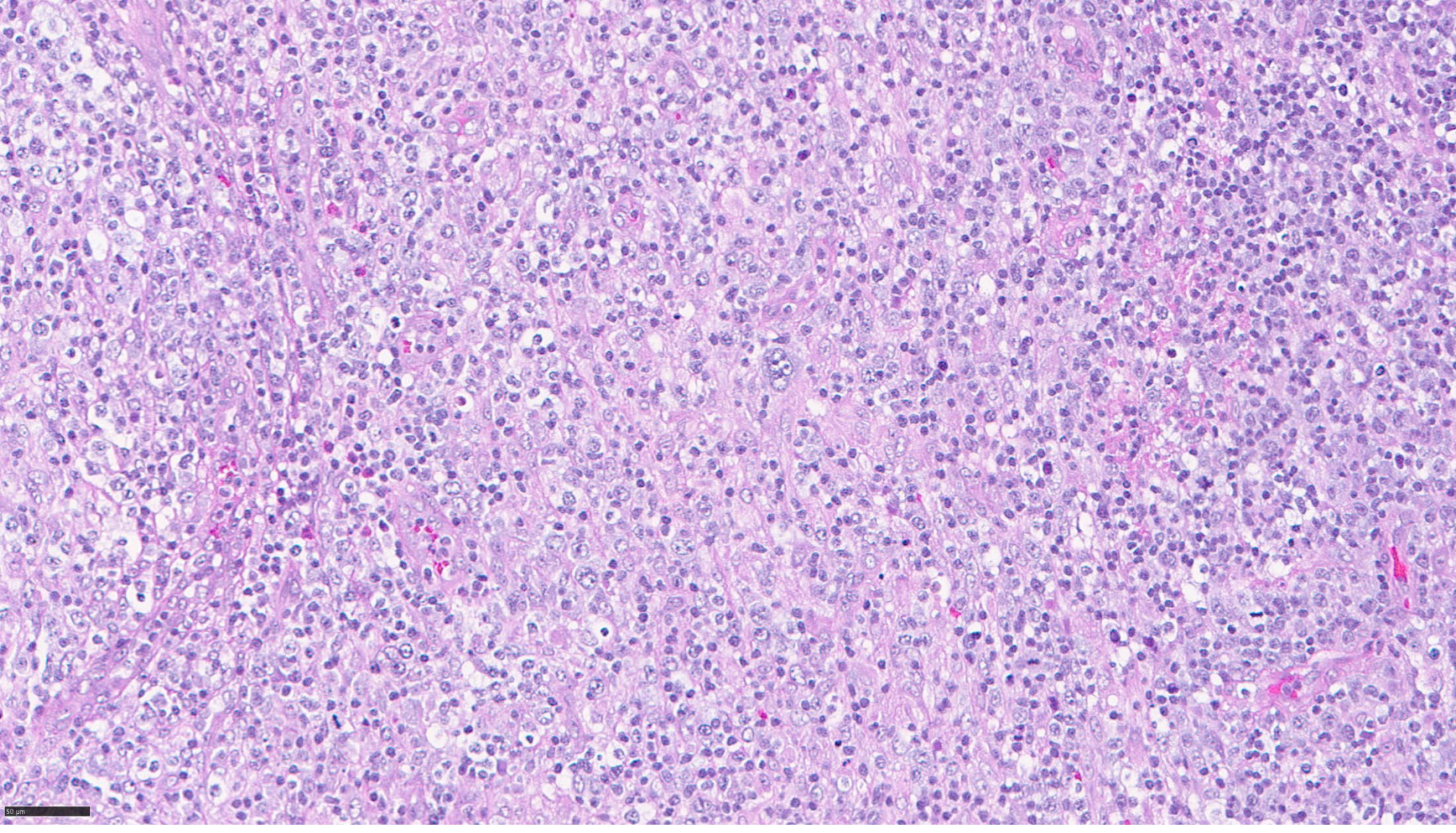
- 55-year-old female with a five-week history of lymph node swelling, fevers, and night sweats

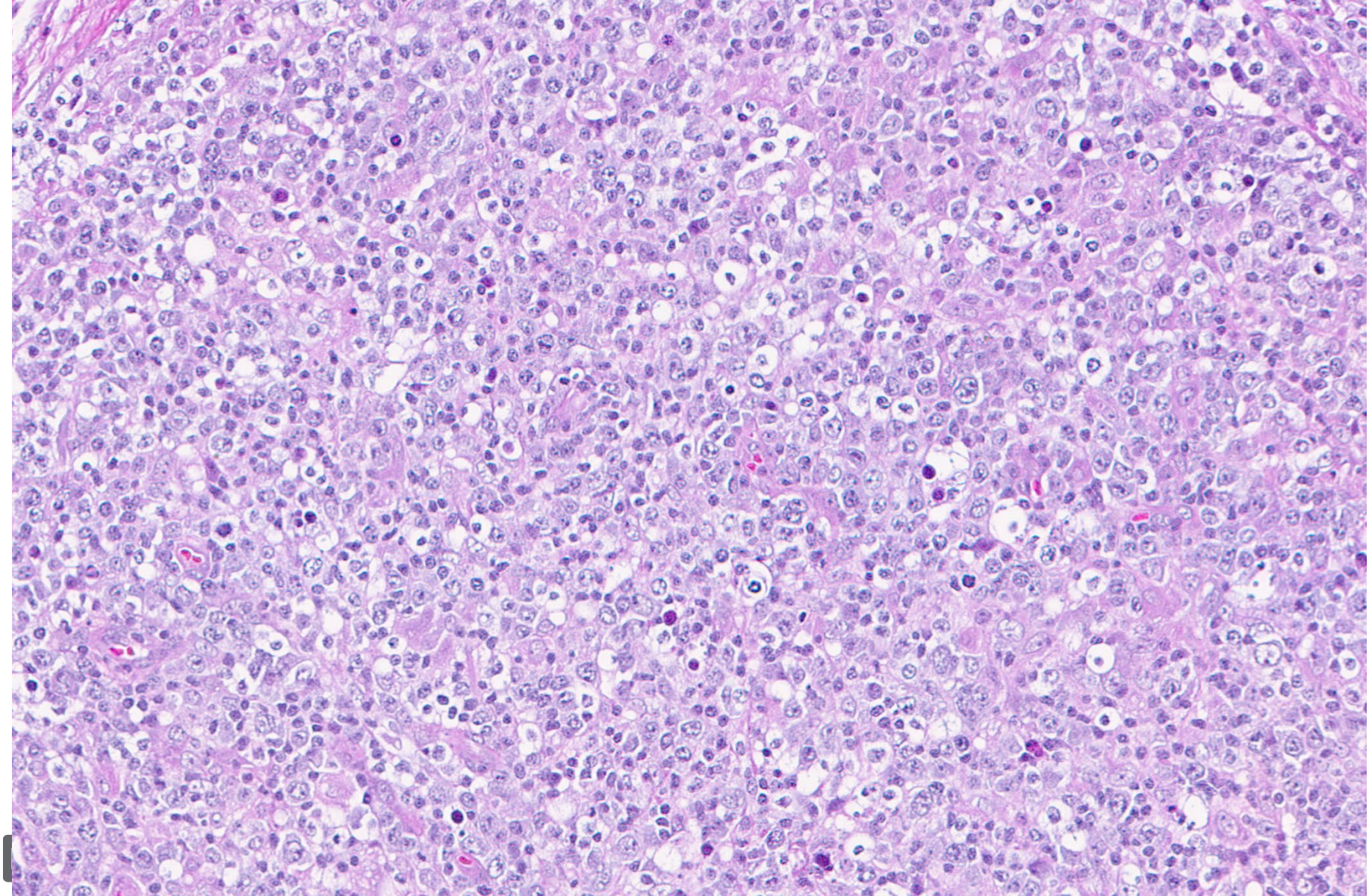
	04/08/25
WBC	**3.5 (ALC 784)**
HGB	**9.5** (MCV 88)
HCT	**29.3**
PLT	196

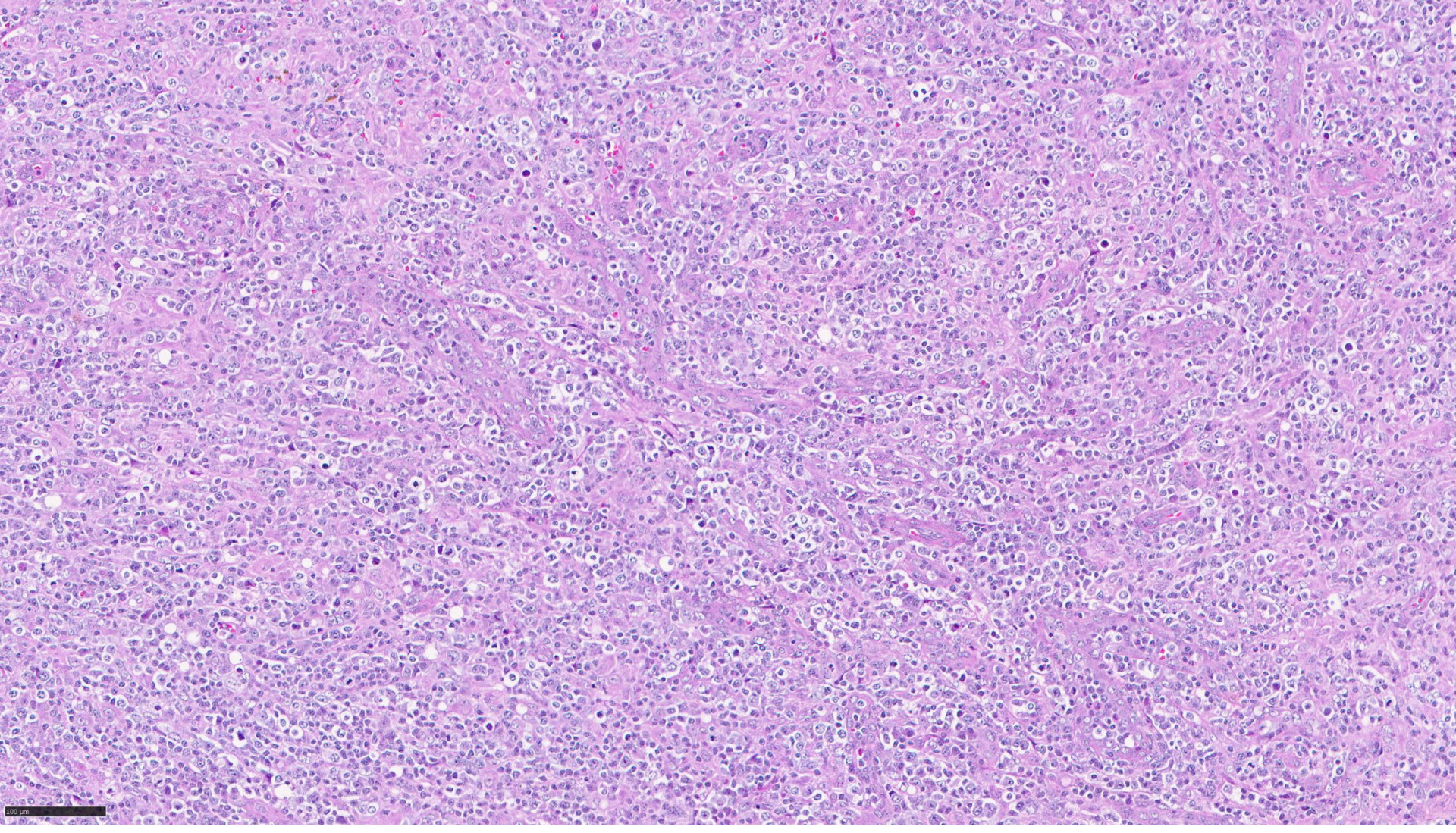
- CT chest/abdomen showed multiple enlarged lymph nodes in the chest, abdomen and pelvis
- Left interpectoral LN excision was performed→ Consultation

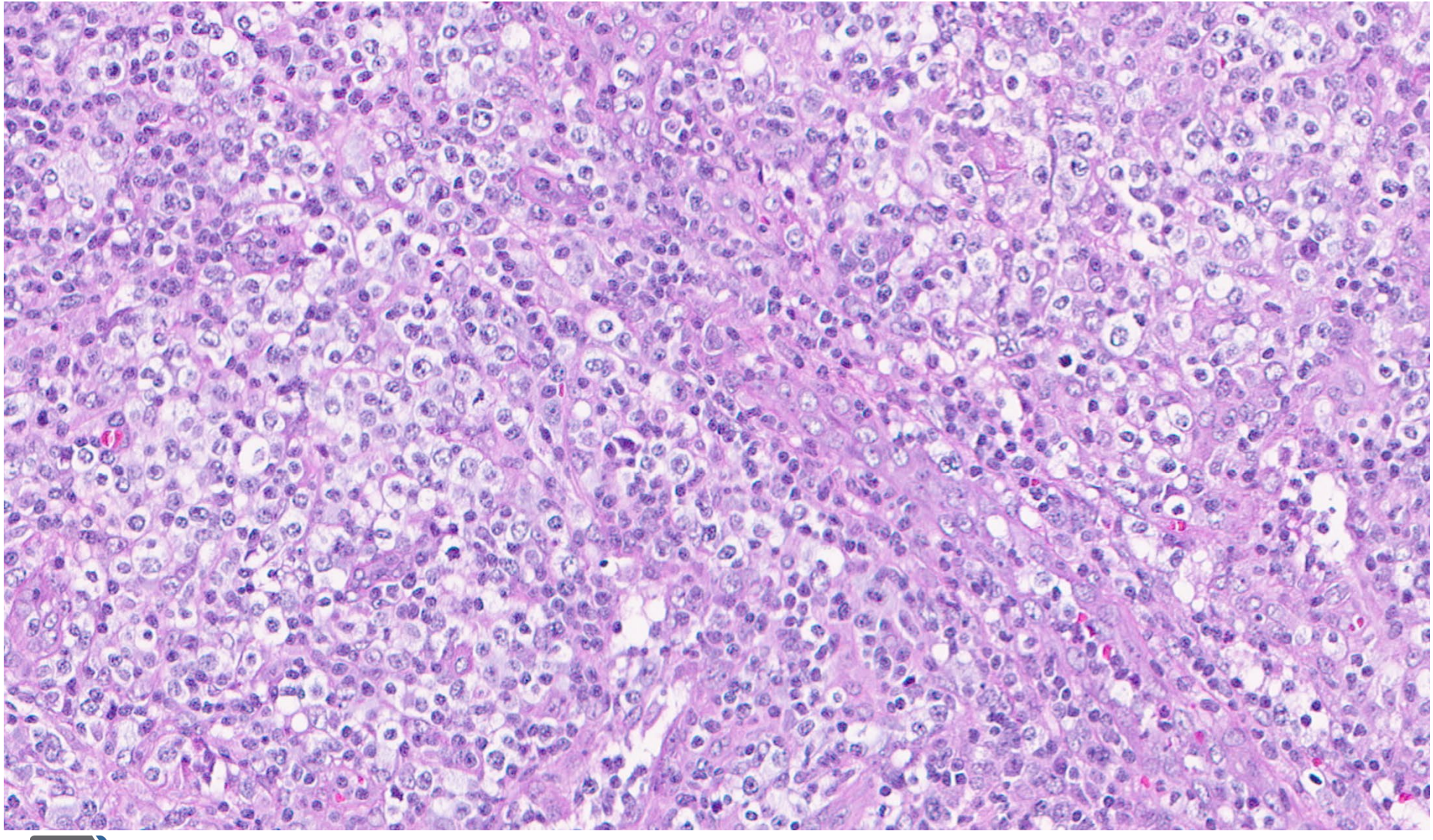



100 µm


50 µm




100 µm

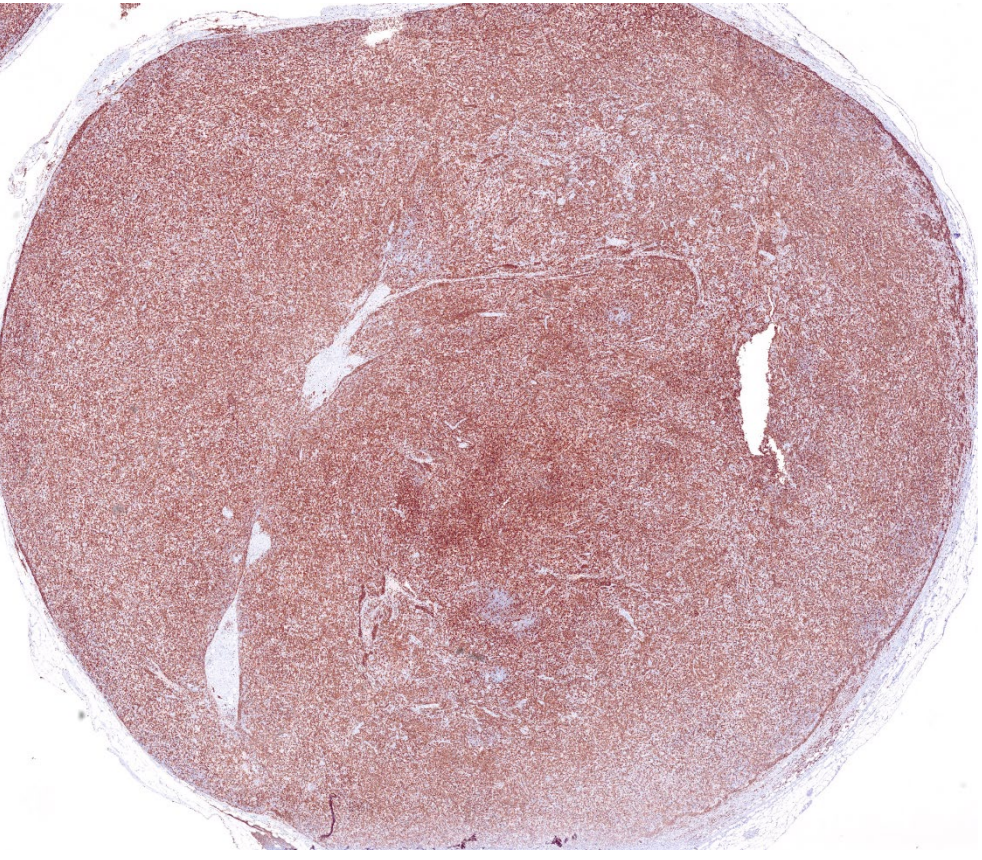


Differential diagnosis

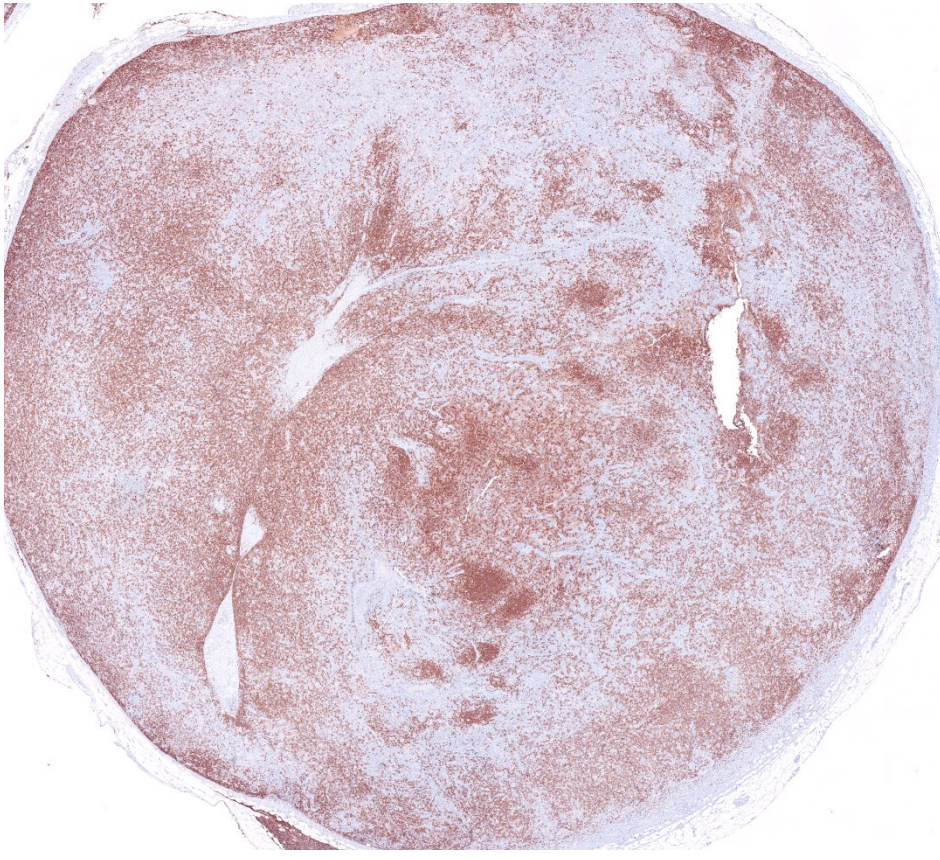
- Nodal T-follicular helper cell lymphoma, angioimmunoblastic type (WHO 5th)/ Follicular helper T-cell lymphoma, angioimmunoblastic type (ICC 2022)

- Peripheral T-cell lymphoma, NOS

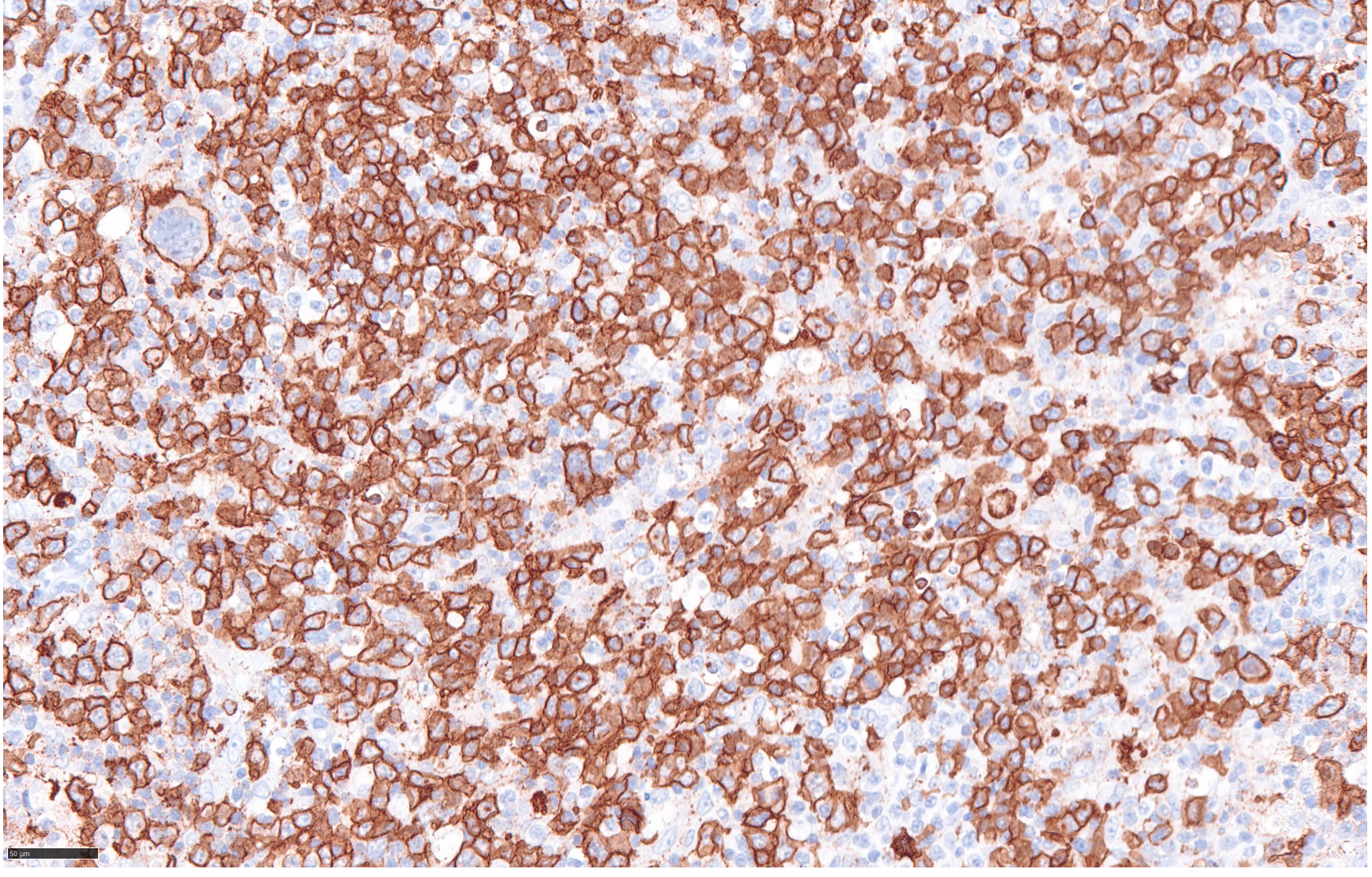
- Classic Hodgkin lymphoma, mixed cellularity type



CD3



CD20



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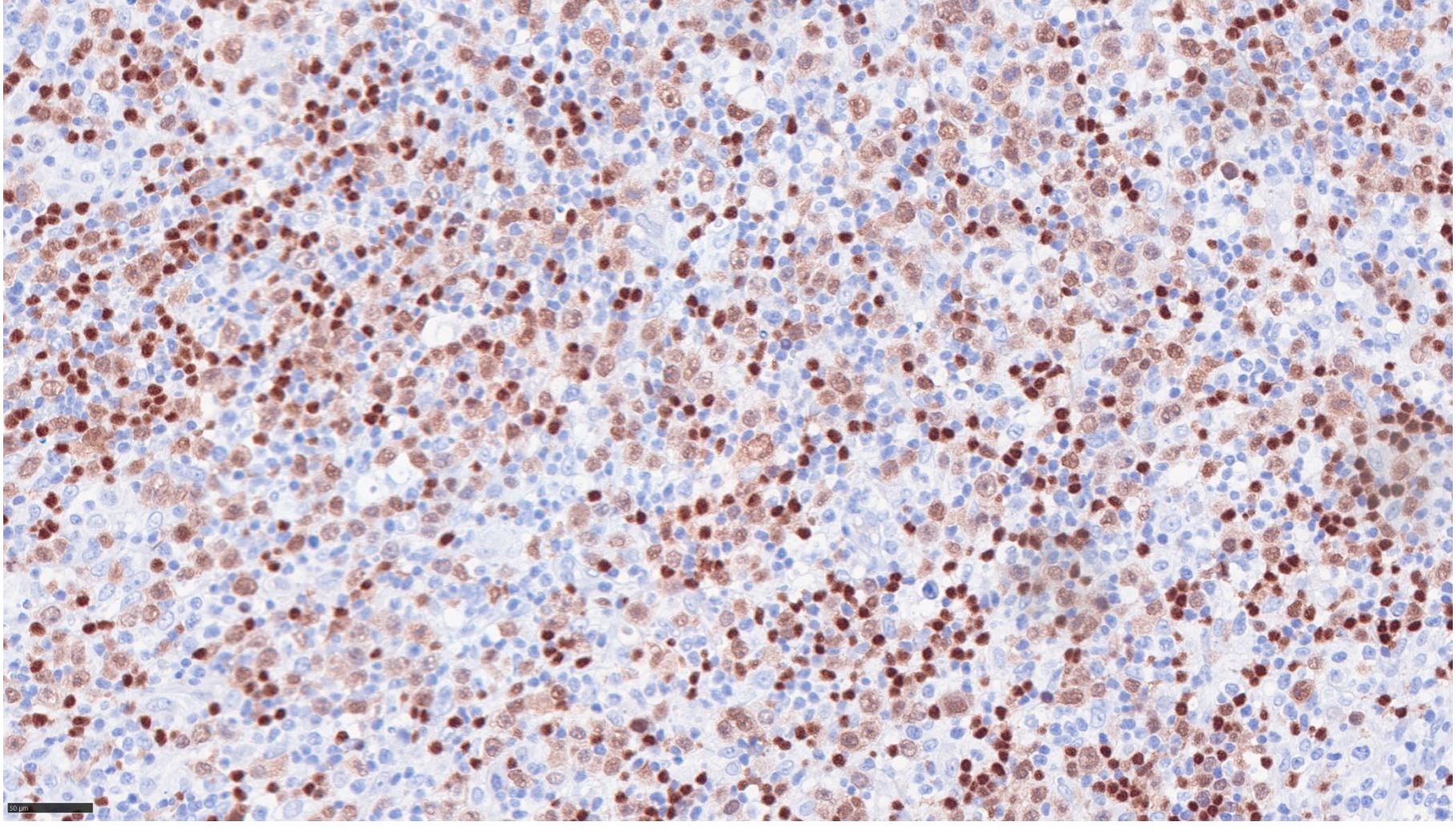
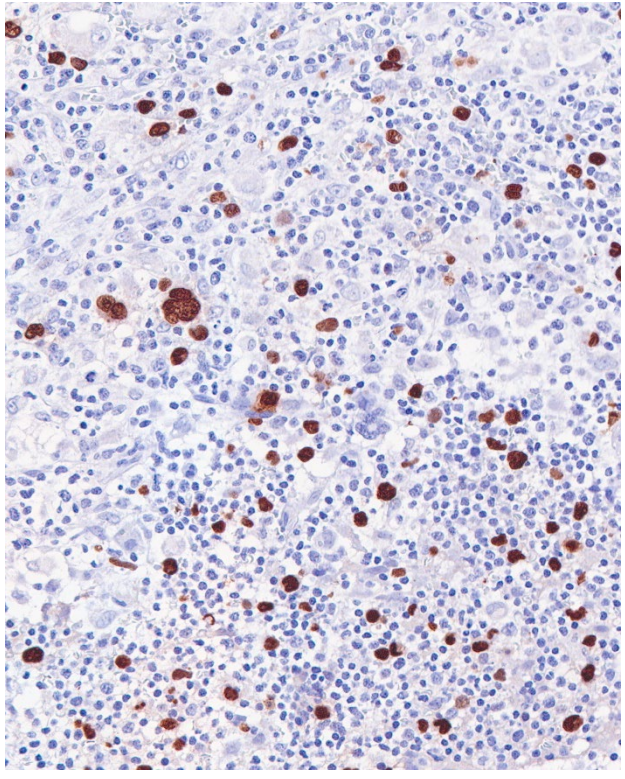
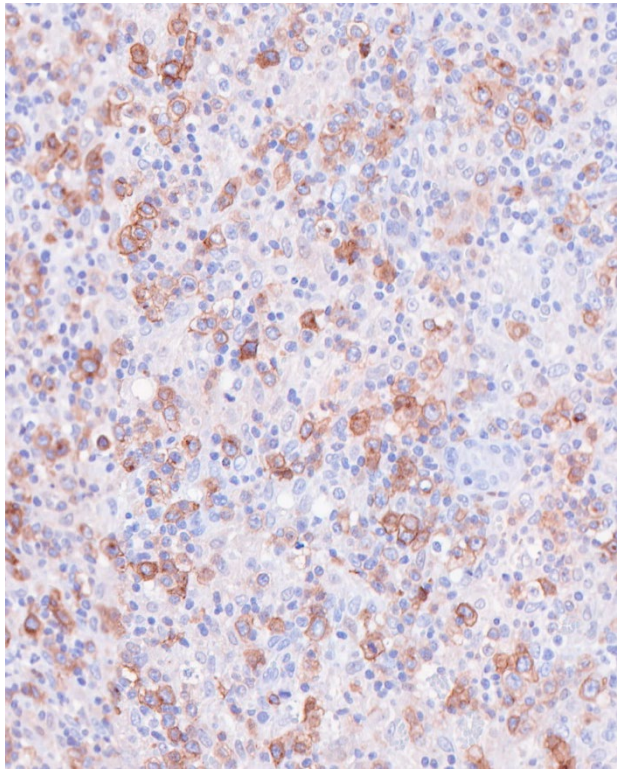


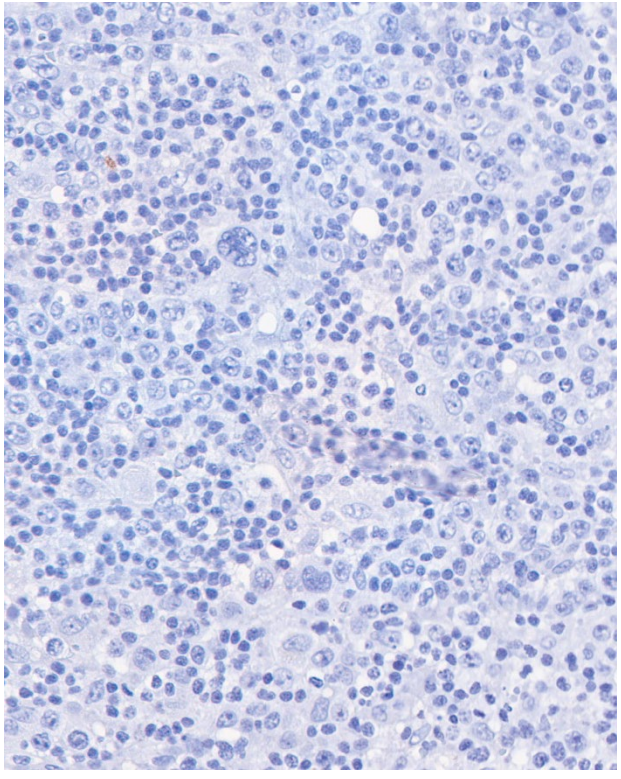
PAX5



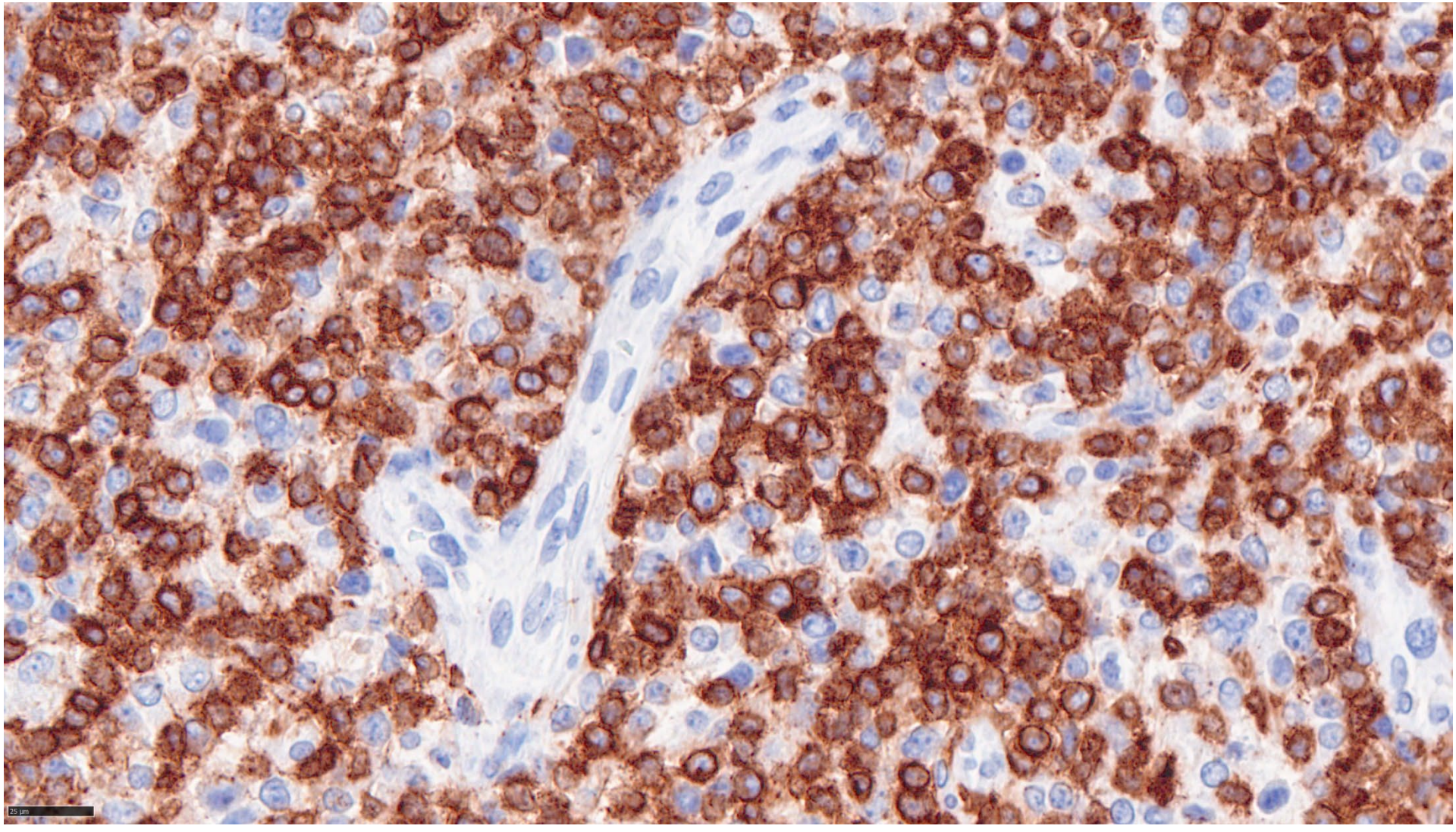
EBER

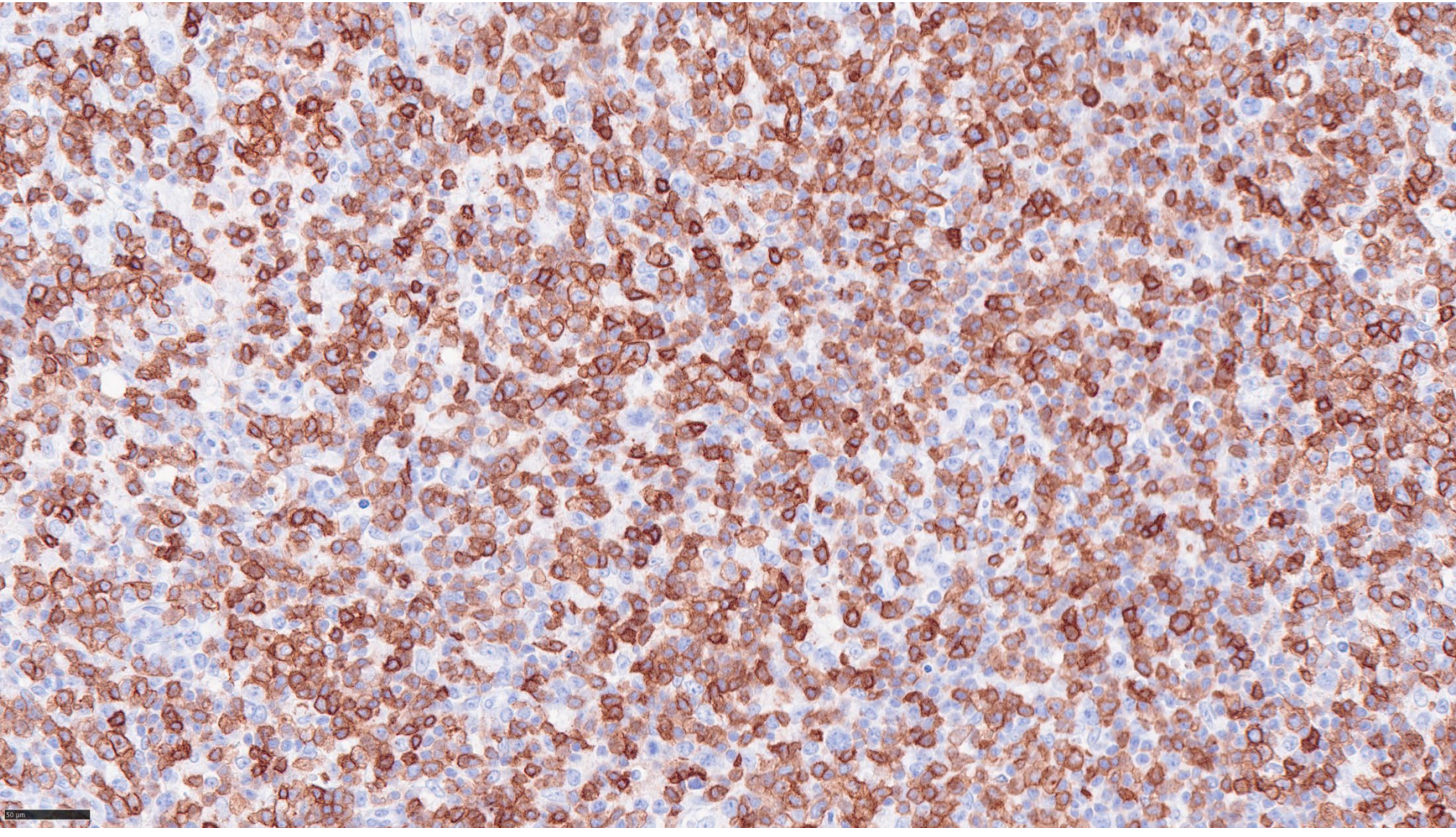


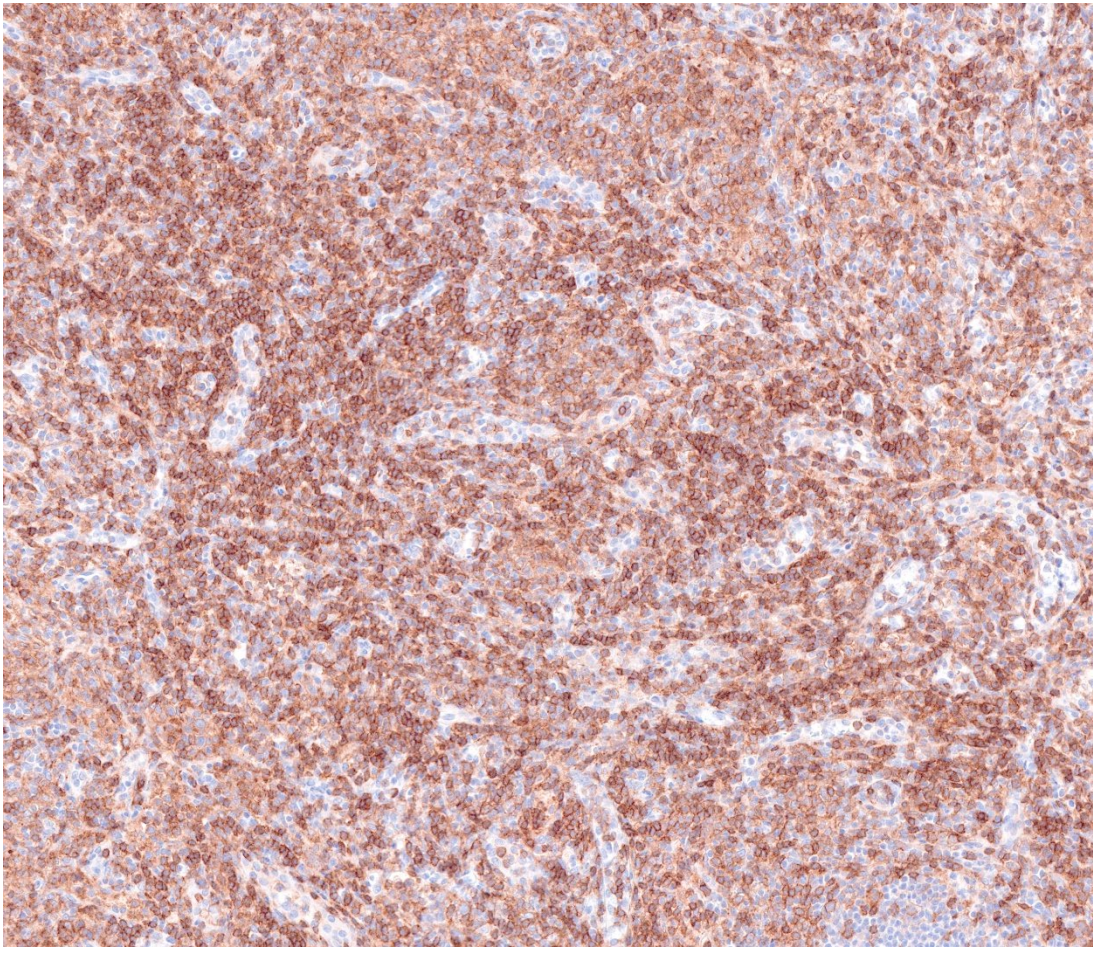
CD30



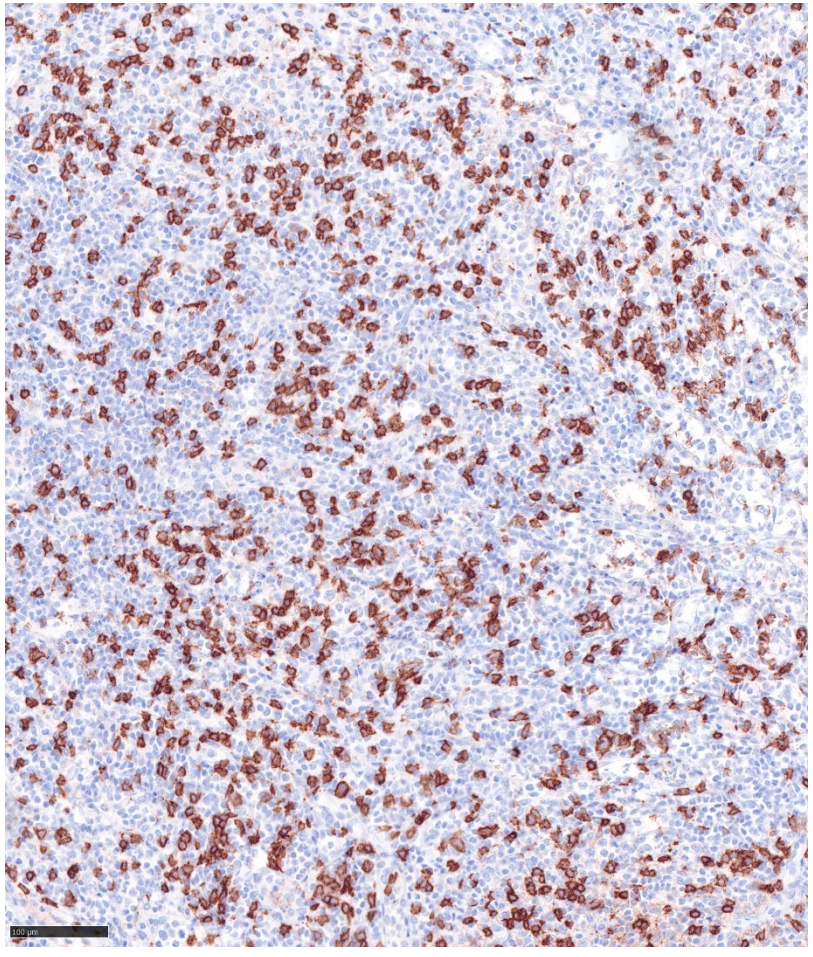
CD15


25 µm

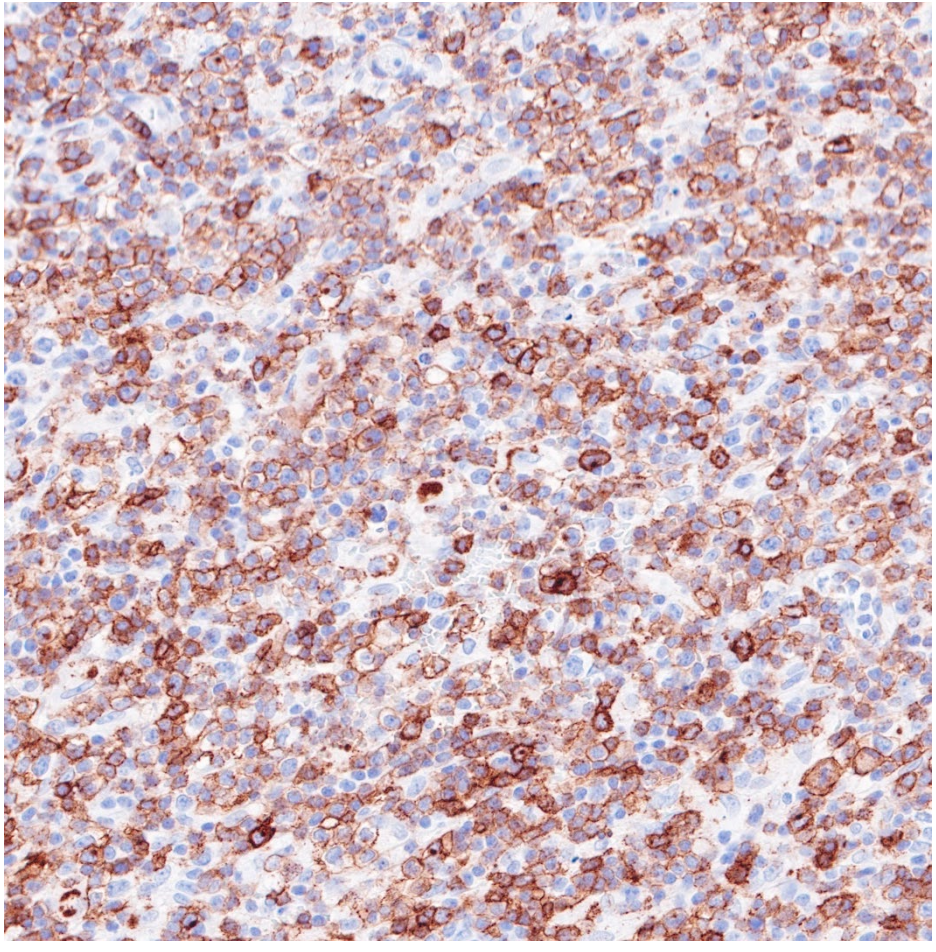

50 µm

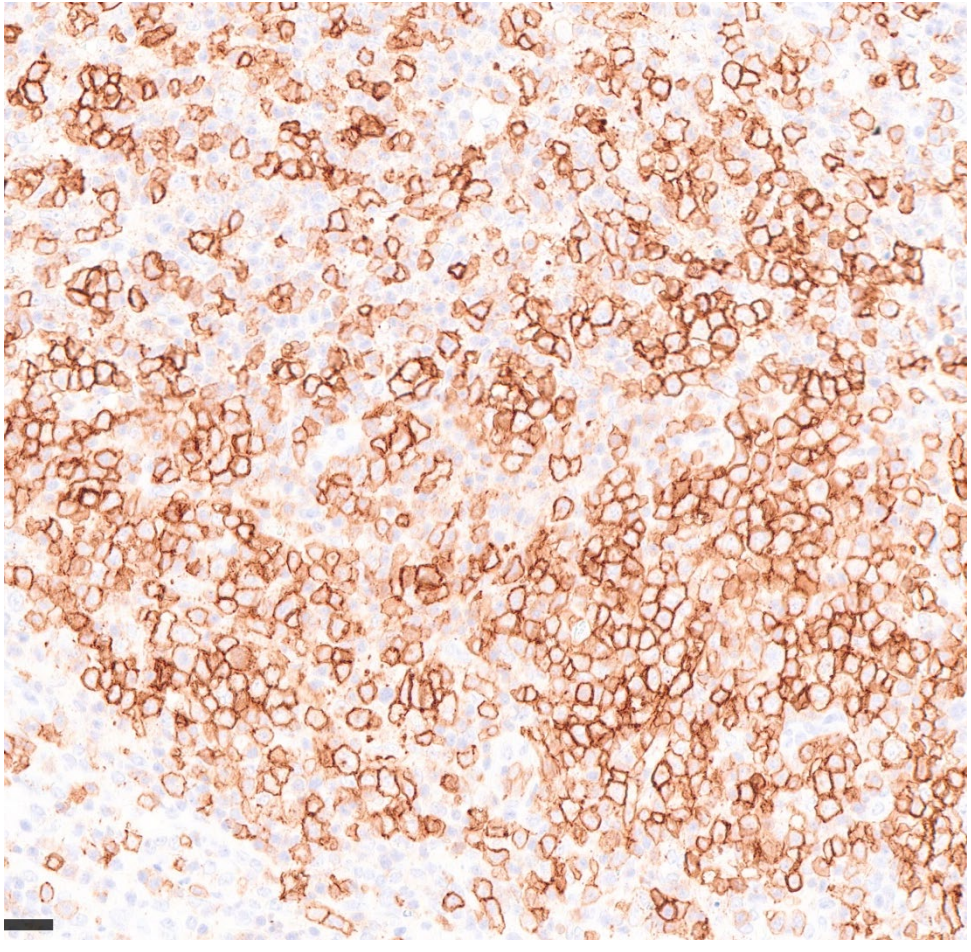


CD4



CD8



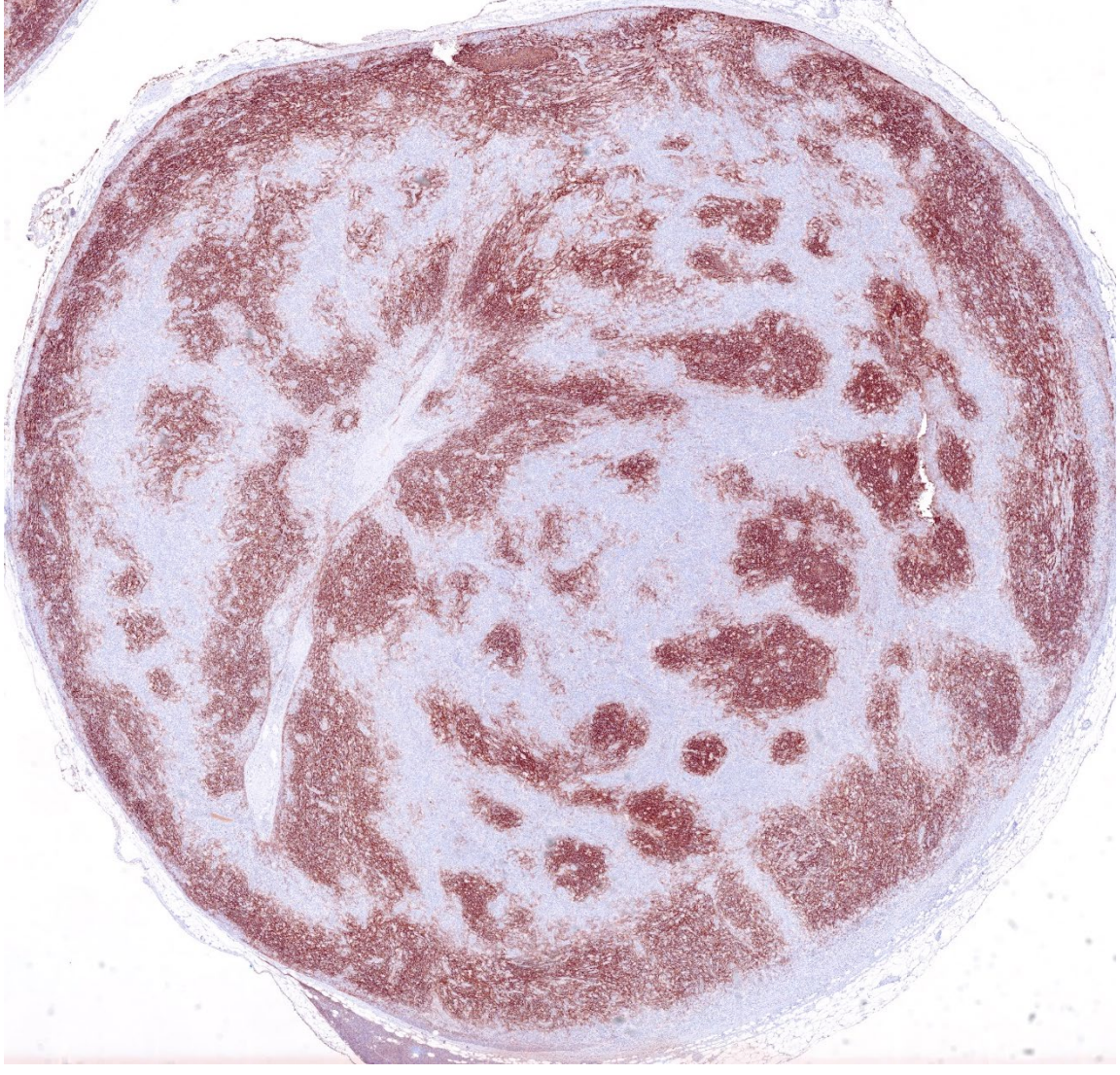


PD1

ICOS

CXCL13 +

CD10 -, BCL6 -



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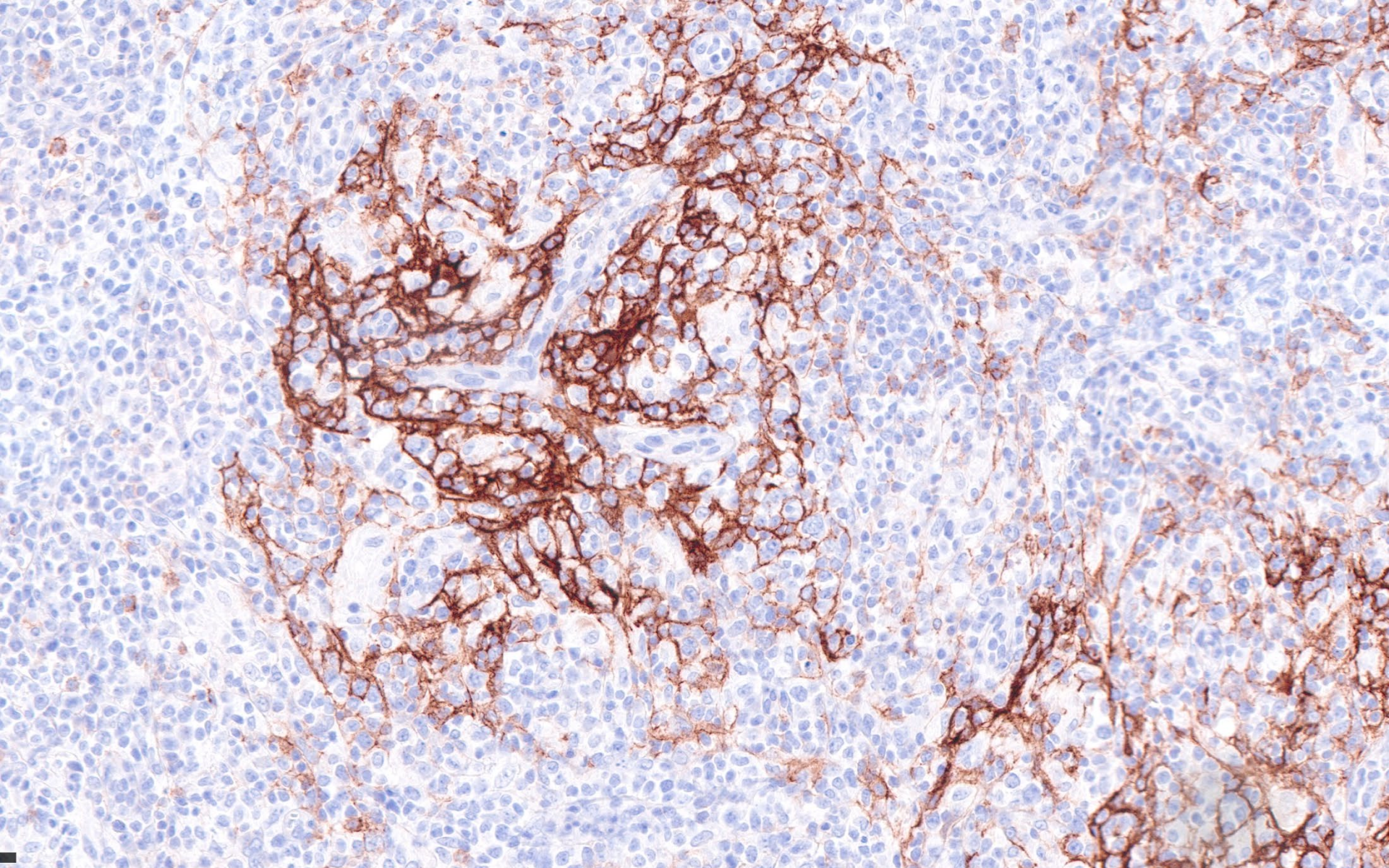
CD21



Summary

Polymorphous lymphoid infiltrate

Atypical T-cell proliferation	Atypical B-cell proliferation
Ass. w/ proliferating HEVs	Forming loose clusters
Positive: CD3, CD5, CD4, PD1, ICOS, CXCL13	Positive: CD20, PAX5 (weak), CD30, MUM1, EBER
Negative: CD8, CD10, BCL6	Negative: CD10, BCL6, CD15, ALK1, cyclin D1
CD21: expanded FDC/FRC meshwork ass w/ postcapillary venules	

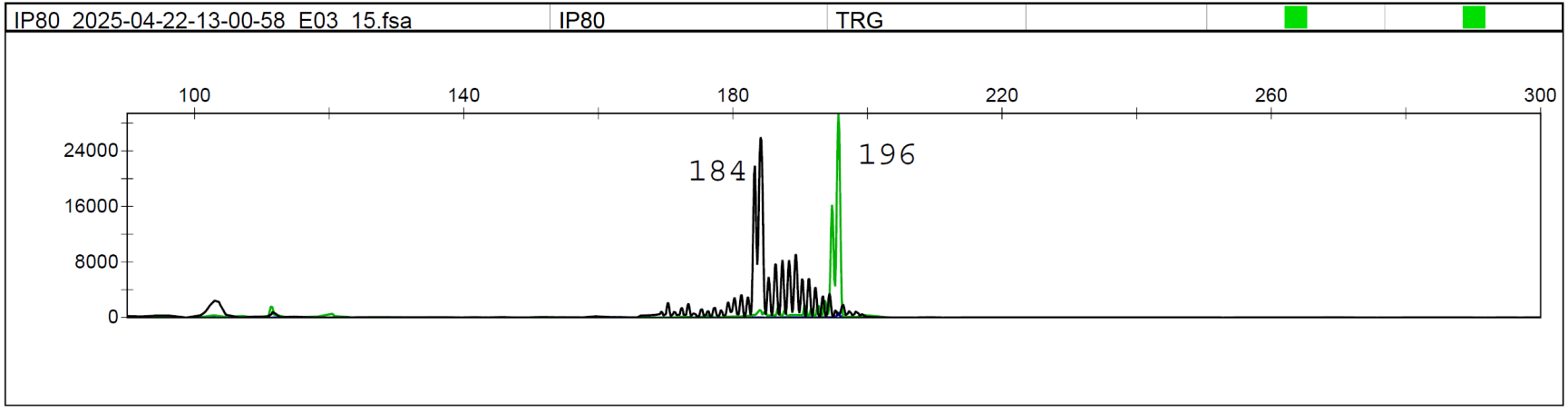
Differential diagnosis

- **Nodal T-follicular helper cell lymphoma, angioimmunoblastic type (WHO 5th)/ Follicular helper T-cell lymphoma, angioimmunoblastic type (ICC 2022)**

Reason for consultation

w/possible concomitant EBV-positive large B-cell lymphoma??

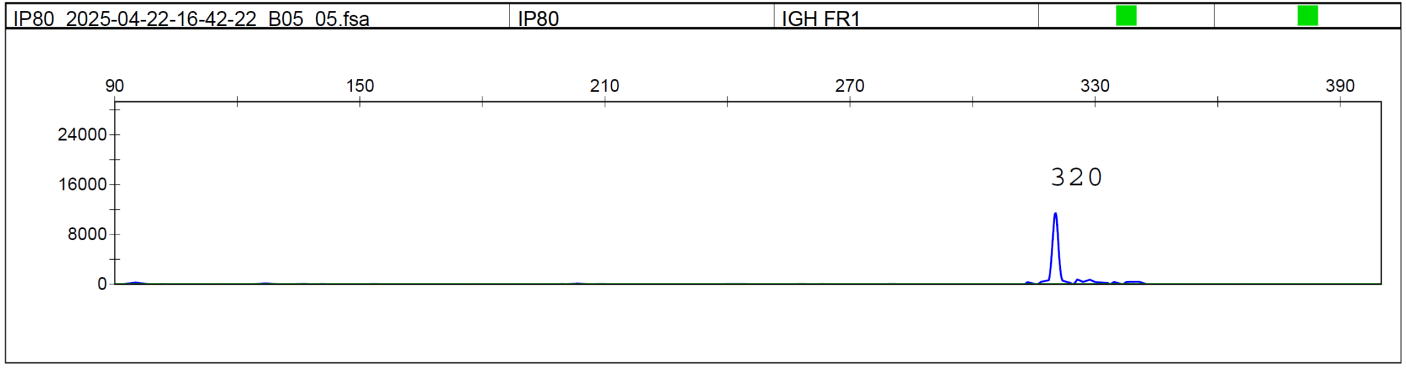
TRG PCR



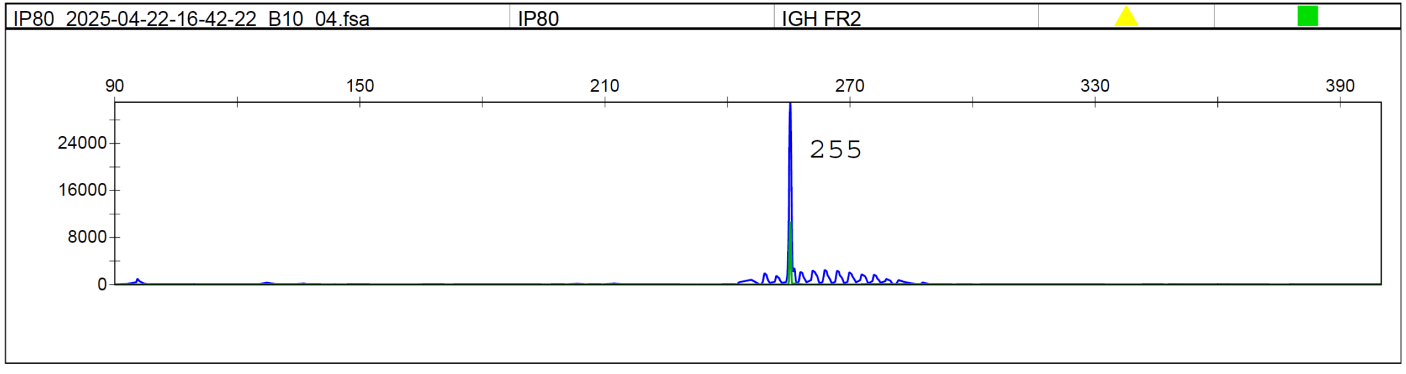
Clonal → Supports a TFH lymphoma

IG PCR

FR1
Clonal



FR2
Clonal



FR3: polyclonal
IGKA and IGKB: no specific peaks

B-cell proliferations in THF lymphomas

Gene expression profile

The gene expression profile demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells

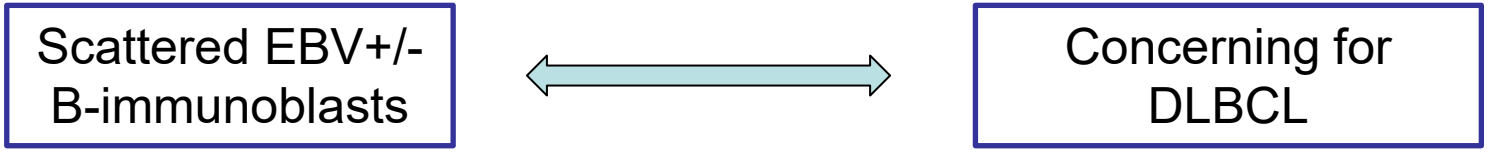
Blood. 2007 Jun 1;109(11):4952-63.

Like their normal counterparts, neoplastic TFH cells promote B-cell survival

B-cell proliferations in THF lymphomas

- B-cells are common in TFH lymphomas and can be **EBV-positive or negative**

Morphologic spectrum:



- Can be ass. w/ plasmacytosis (polyclonal>>>>monoclonal)
- In some cases, the plasma cell expansion can be so extensive and obscure the underlying T-cell neoplasm.

The utilization of clonality

Most TFH lymphomas show clonal or oligoclonal rearrangement of the T-cell receptor genes

In up to 50% of cases, IGH or IGK gene rearrangement is also present
(due to a clonal expansion of EBV-infected B cells)

A small group of cases (7%) with the morphology of AITL reveal clonal rearrangements of the **IGH genes alone**→ Nodal marginal zone lymphoma rich in PD-1 positive T-cells should be carefully excluded.

When should we diagnose a B-cell lymphoma?

In our practice, when there is clear evidence of TFH lymphoma in a sample, we avoid diagnosing a composite lymphoma.

The prognosis is dominated by a TFH lymphoma

Targeting intratumoral B cells with rituximab, in addition to standard chemotherapy, has not shown a clear benefit.

Haematologica. 2012 Oct;97(10):1594-602.

Diagnosis

- **Nodal T-follicular helper cell lymphoma, angioimmunoblastic type (WHO 5th)**
- **Follicular helper T-cell lymphoma, angioimmunoblastic type (ICC 2022)**
- **See note.**

NOTE:

Follicular helper T-cell lymphomas may show the presence of typical Reed-Sternberg-like cells and EBV positivity. In addition, **clonal B-cell populations are common in THF lymphomas, even in the absence of EBV** and some studies have shown that the B-cells may carry some of the same mutations as the T-cells.

Common molecular features

- **Recurrent somatic mutations**
  - Genes encoding the epigenetic regulators
    - TET2 (50-90%)
    - DNMT3A (30-40%)
    - IDH2 R172 (20-45%)
  - Small GTPase, RHOA G17V (50-70%)
  - Components of the TCR signaling pathways
    - PLCG1 (14%)
    - CD28 (9-11%)
    - VAV1 (5%)

- **Recurrent oncogenic fusions**
  - ICOS::CD28, ITK::SYK, VAV1 fusions

NGS (TSO500 DNA & RNA)

Pathogenic variants detected:

TET2: c.2815C>T; p.Gln939 (23.0%)*
TET2: c.2662C>T; p.Gln888 (21.0%)*
RHOA: c.50G>T; ***p.Gly17Val*** *(8.45%)*
IDH2: c526G>C; ***pArg172Ser*** *(7.39%)*

c/w TFH lymphoma

STAT3: c.1938C>G; pAsn646Lys (6.98%)

*NOTCH2: c.6909dup: p.Ile2304Hisfs*9 (3.78%)*

Activating mutations in NOTCH2 are more common in mature B-cell lymphoma rather than TFH lymphoma.

No fusions detected

TET2/DNMT3A mutations are not restricted to the T-cells

- TET2/DNMT3A mutations have been demonstrated in B-cells and hematopoietic stem cells→ Up to 80% of patient with TFHL also have clonal hematopoiesis.
- Myeloid neoplasms are more frequent in patients with TFHL than in the general population.
- In some patients, the myeloid neoplasms and TFHL share common ancestral mutations in TET2 and/or DNMT3A.

Suggesting multistep/ multilineage tumorigenesis and divergent evolution of a common CH clone

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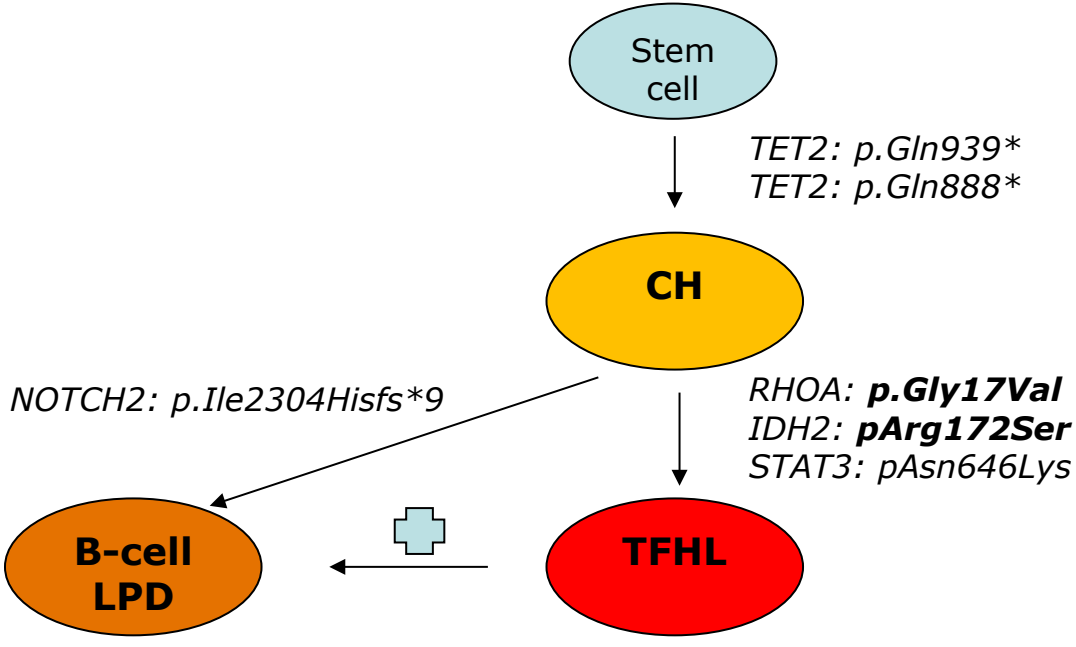

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