Monthly Multi-Institutional Hematopathology Interesting Case Conference

Case 2

Andrea Coetzee, PGY1
Mount Sinai Hospital

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Mount Sinai

Clinical Presentation

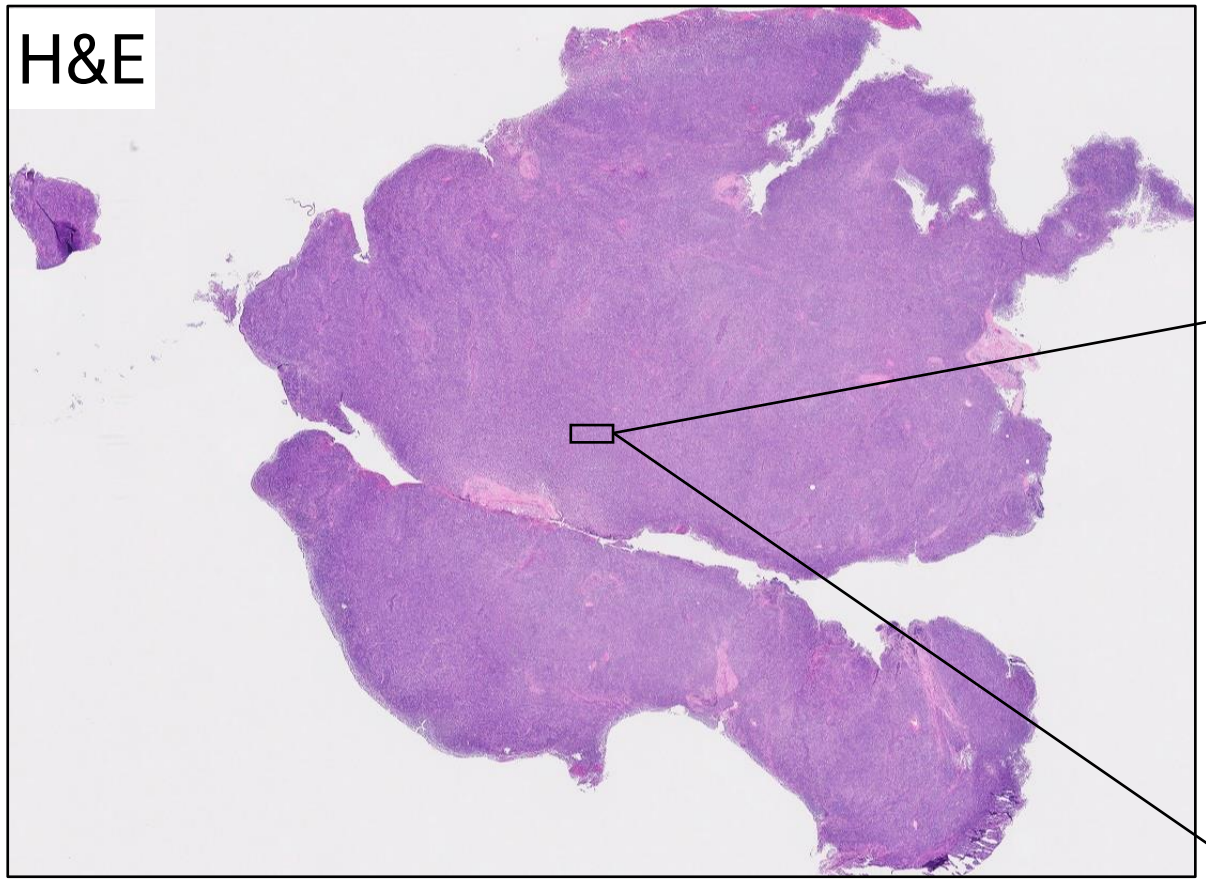
- 81-year-old woman
  - Past medical history of hypertension, CAD/MI, left locally advanced breast cancer status post surgery, radiation and chemotherapy (off treatment >1 year)
- April 2023
  - Visited oncologist for evaluation of new cervical lymphadenopathy
  - Also reports two weeks of fatigue, dysphagia with solid foods, and low-grade fevers
  - PET/CT
    - Multiple bulky hypermetabolic lymph nodes above and below the diaphragm with splenic involvement
    - Highest SUV 57.7 and largest lymph node 4.7 cm

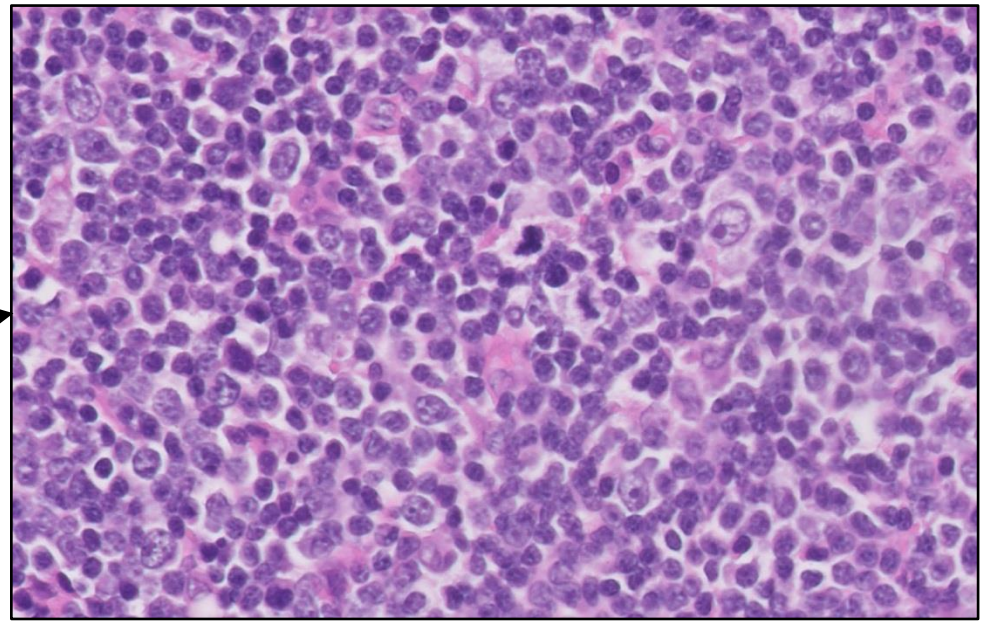
White blood cell count	8.5 K/uL
Hemoglobin	12.9 g/dL
Platelet count	93 K/uL

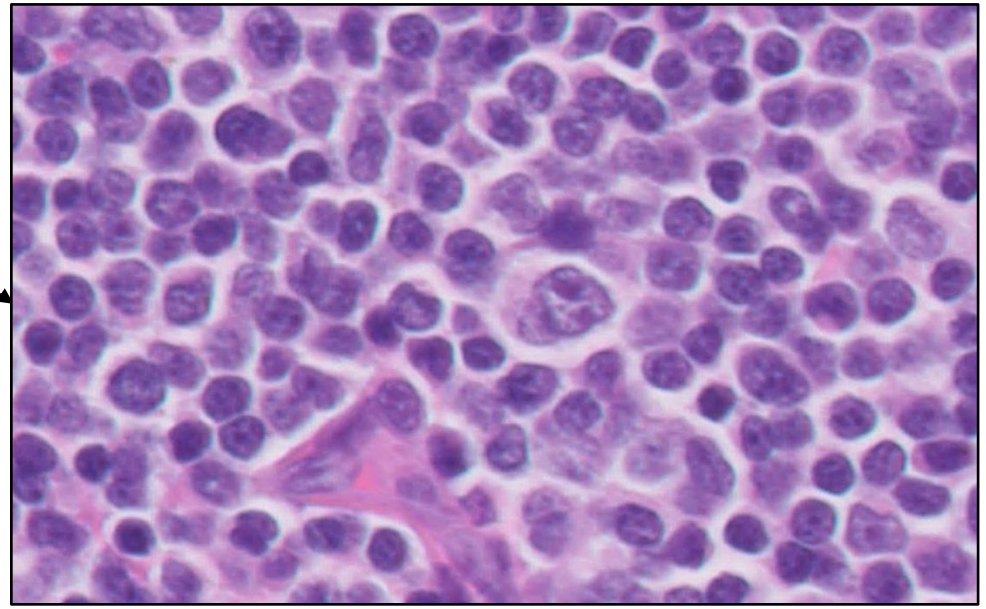
Neutrophils	47%
Lymphocytes	35%
Monocytes	11%

LDH	805 U/L
Uric acid	8.7 mg/dL
Basic Metabolic Panel	Within normal limits

Left Inguinal Lymph Node Excisional Biopsy







- Effacement of lymph node architecture by a diffuse atypical lymphocytic infiltrate
- Small to medium sized atypical lymphoid cells with scattered large cells with one or more distinct nucleoli resembling Hodgkin/Reed-Sternberg (HRS) cells

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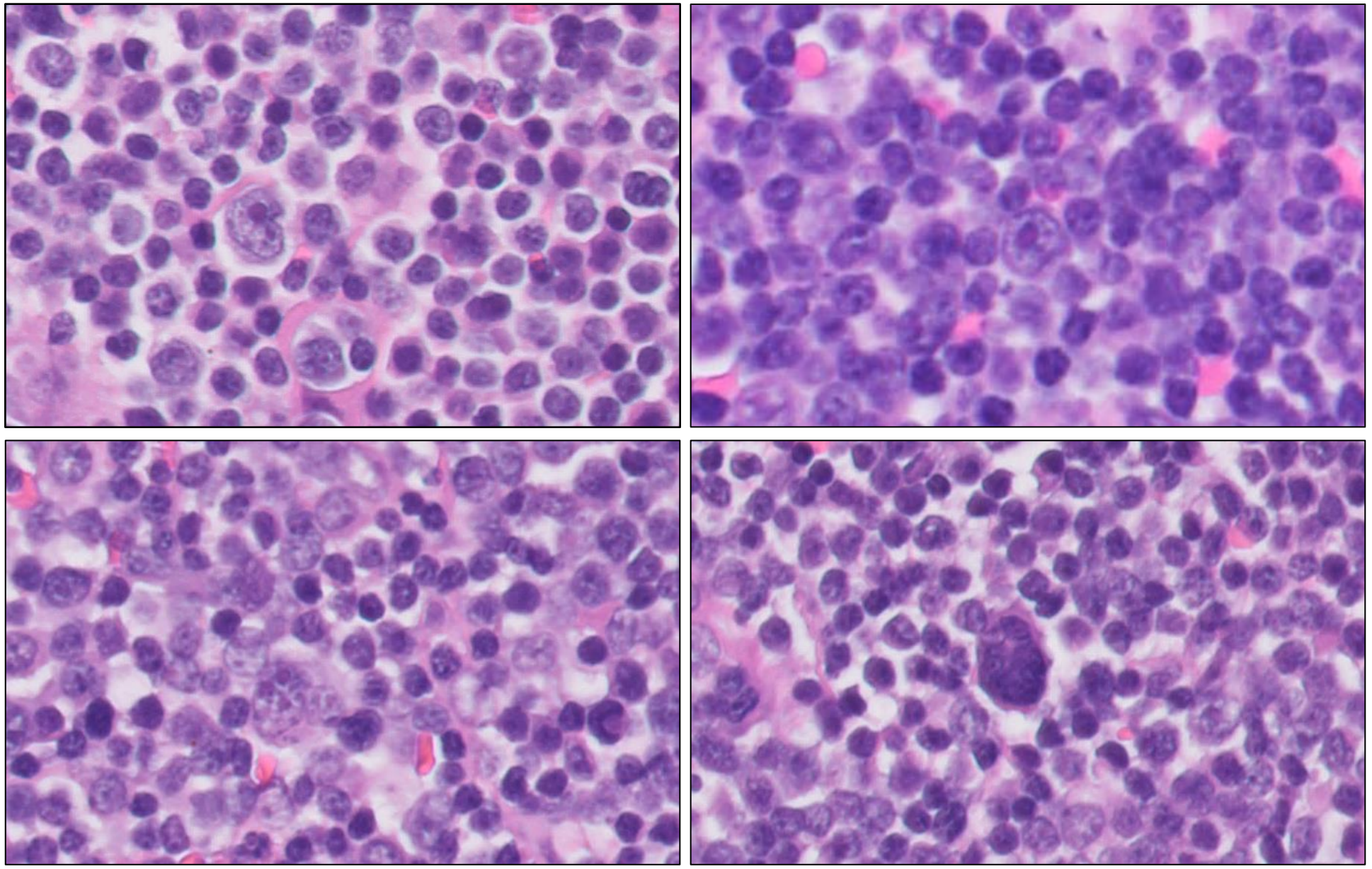

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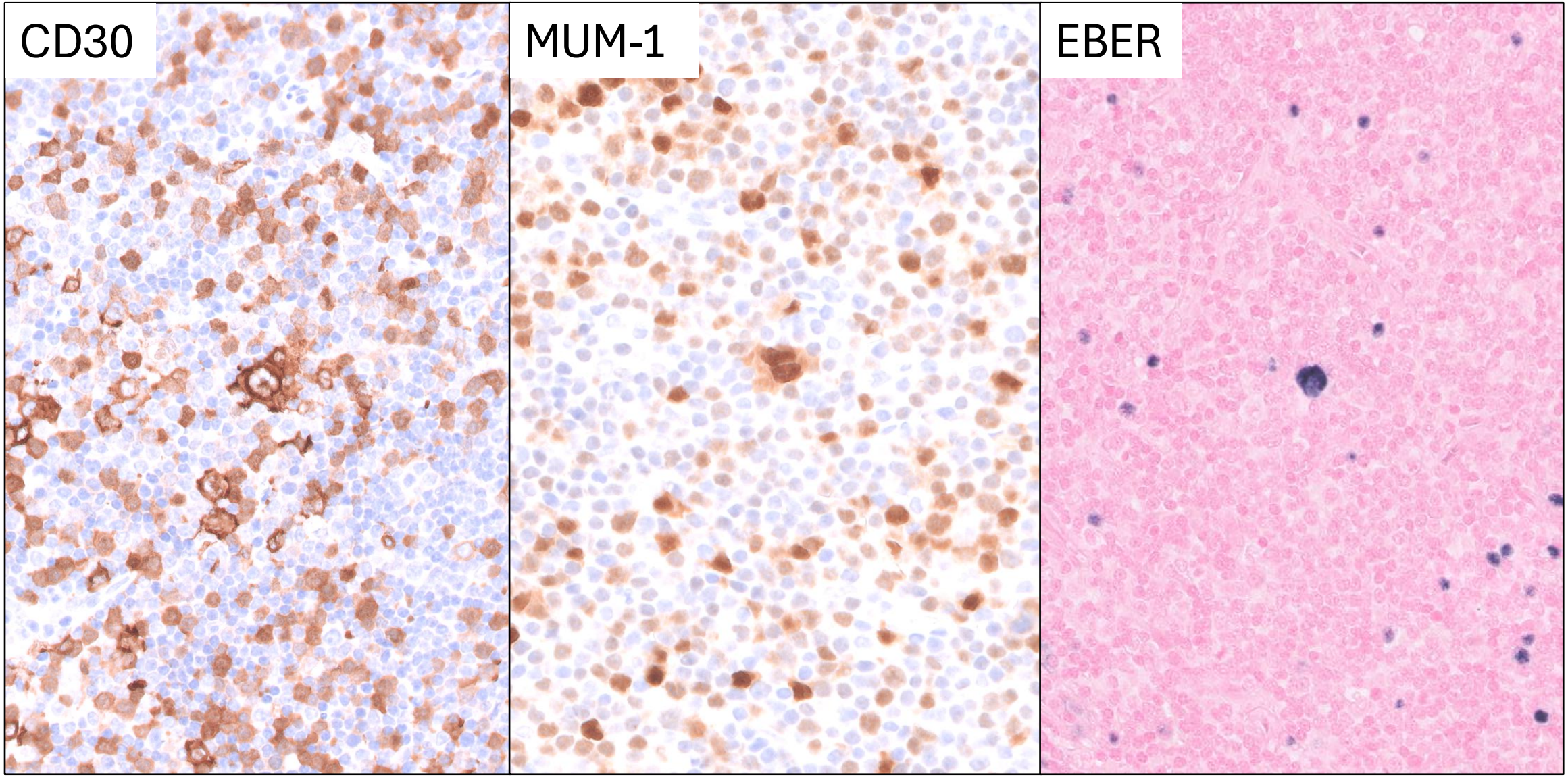

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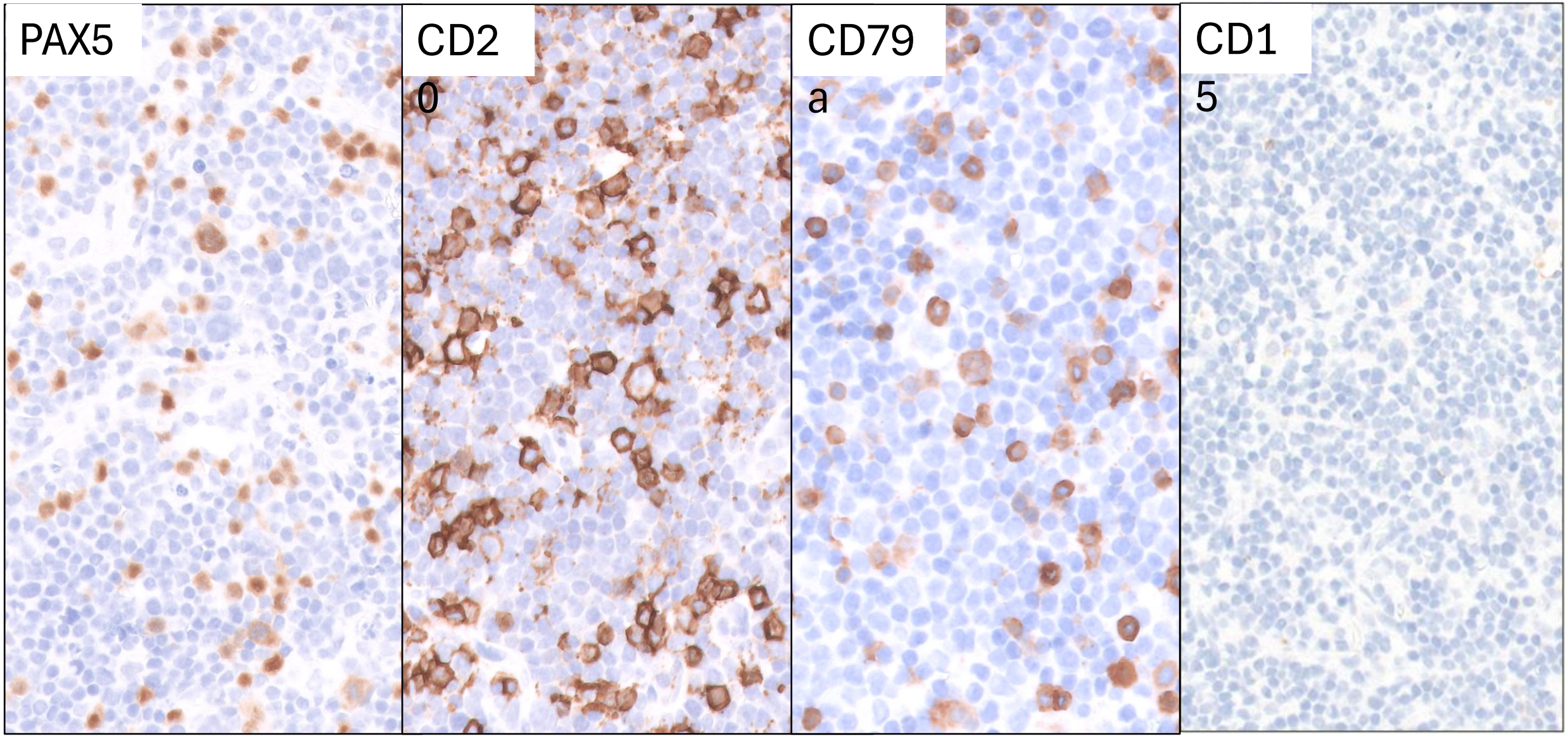

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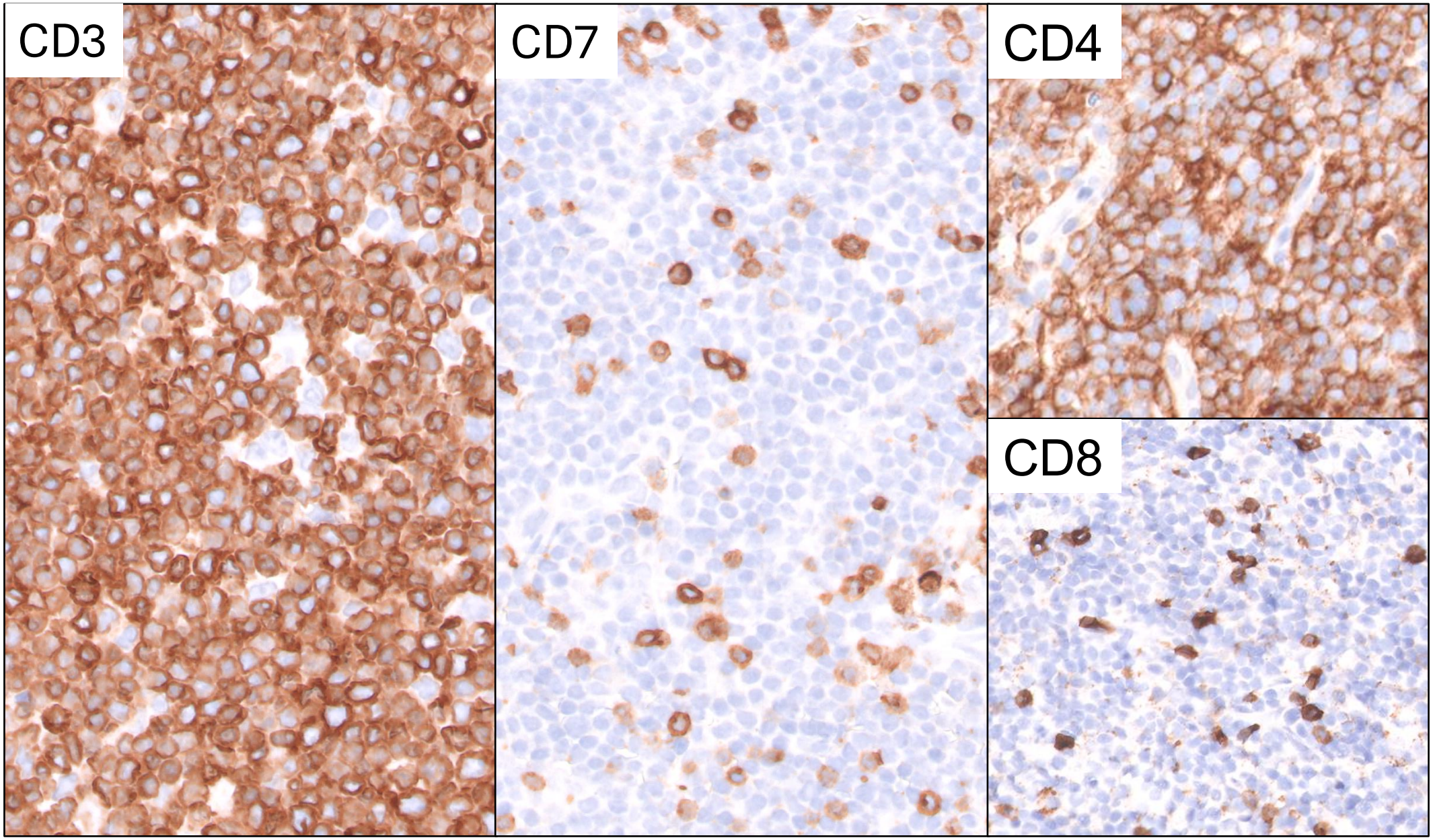

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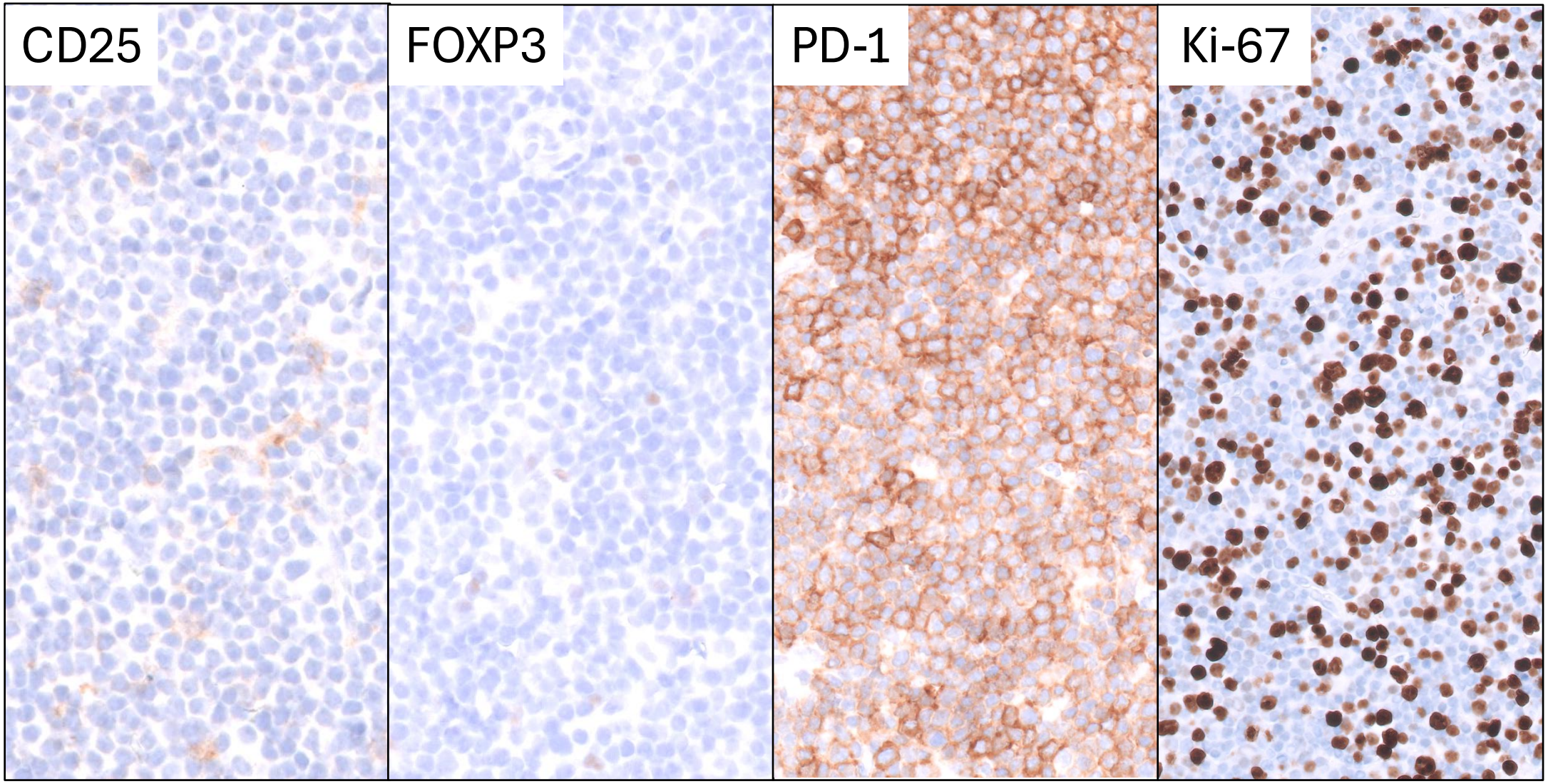
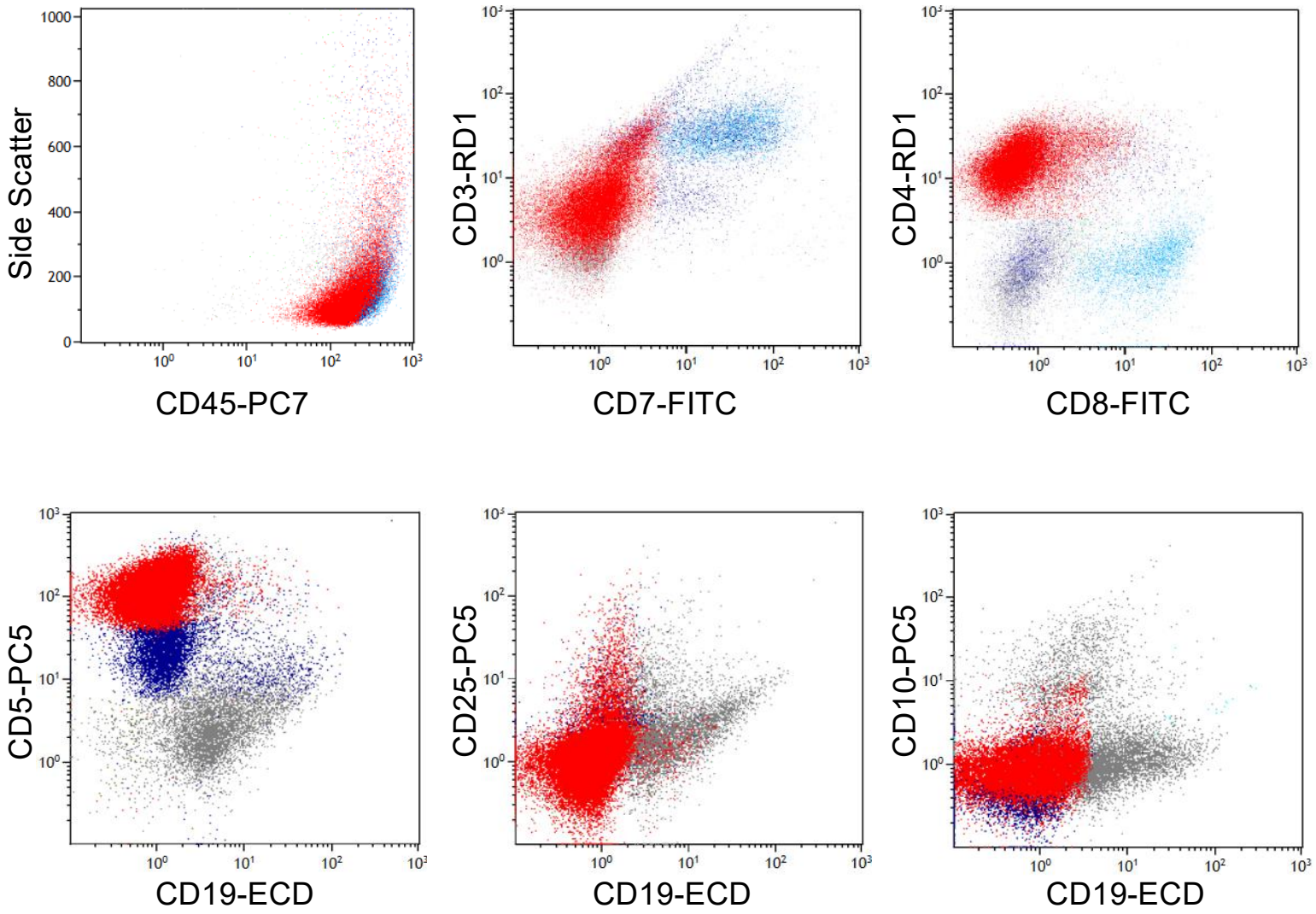


Flow Cytometry, Lymph Node

Abnormal cells

Aberrant T cell population, 60% of total

POSITIVE	NEGATIVE
Surface CD3 (partial dim)	CD7
CD4	CD8
CD2	CD10
CD5 (bright)	CD56 (not shown)
CD25 (minimal dim)	CD19/CD20



Summary: Immunophenotype

Atypical background T cells

POSITIVE	NEGATIVE
CD2	CD8
CD3	CD10
CD4	BCL6
CD5	EMA
PD1	FOXP3
MUM1	CD25
CD30	CD15
ICOS (minor subset)	
Ki67 (50-60%)	

Large atypical HRS-like cells

POSITIVE	NEGATIVE
CD30	CD15
PAX5	EMA
CD20	
CD79a	
MUM1	
EBER	

CD21 and CD23: Rare disrupted FDC meshworks

Final Diagnosis

- **T-cell lymphoma. See comment.**
  - Comment: Testing for HTLV-1 is recommended for definitive subclassification.

- At the time it was noted in the chart that the patient required a Haitian-Creole interpreter

Differential Diagnosis

Adult T-cell leukemia/lymphoma (ATLL) with HRS-like cells	▪ Haitian origin ▪ CD4+, CD7- ▪ EBV+ HRS-like cells ▪ PD-1 and ICOS+ in a subset of small cells (~10% of ATLL cases show TFH phenotype, specifically PD-1 and ICOS) ▪ CD25-, FOXP3- (~20% of ATLL cases do not show typical CD3+, CD4+, CD25+, CCR4+ phenotype)

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Nodal T-follicular helper cell (nTFH) lymphoma with EBV+ HRS-like B cells	▪ CD4+, PD-1+, ICOS+, CD25-, dim surface CD3+ ▪ EBV+ HRS-like cells ▪ Expression of other TFH markers is limited ▪ No characteristic morphologic features of nTFH, angioimmunoblastic-type (expanded FDC meshworks, HEV proliferation, polymorphous background)

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Classic Hodgkin lymphoma (CHL) occurring in an HTLV-1 carrier	▪ CD30+, MUM1+, EBV+ HRS-like cells ▪ Atypical T-cell background CD4+/CD7- ▪ Increased Ki-67%

Further Testing

- HTLV-1/2 antibody positive
  - Reflex confirmatory assay positive for HTLV-1
- Next Generation Sequencing not performed

Follow-up

- **ATLL, stage IV** disease
- Chemotherapy regimen= BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone)
- Poor response to treatment and **aggressive course**, passed away within 5 months

Discussion

- HRS-like cells in T-cell lymphomas
- Histologic variants of ATLL
- HRS-like cells in HTLV-1 infected individuals
- Pitfalls of peripheral blood HTLV-1/2 testing

HRS-like Cells in T-Cell Lymphomas – Diagnostic Pitfall

HRS-like cells can occur in a range of **mature T-cell lymphomas**

- Nodal T-follicular helper (nTFH) cell lymphoma
- Peripheral T-cell lymphoma (PTCL), NOS
- Adult T-cell leukemia/lymphoma (ATLL)

Immunophenotyping is critical

- Usually **EBV+, CD30+, CD15+/-, B-cell derived**

PITFALL!

- Can mimic classic Hodgkin lymphoma
- Neoplastic T cells in the background can be overlooked

Rarely, T-cell derived HRS-like cells **(PAX5-)** have been described in ATLL

Nicolae A et al., *Am J Surg Pathol*, 2014

Histologic Variants of ATLL

Major histologic variants

- **Pleomorphic cell variant** (90%)
- **Anaplastic large cell variant**
  - Uniformly large pleomorphic cells with strong CD30+, CD15+, dim CD3+, and EMA-
  - Consider in cases of ALK-negative cytotoxic marker-negative ALCL

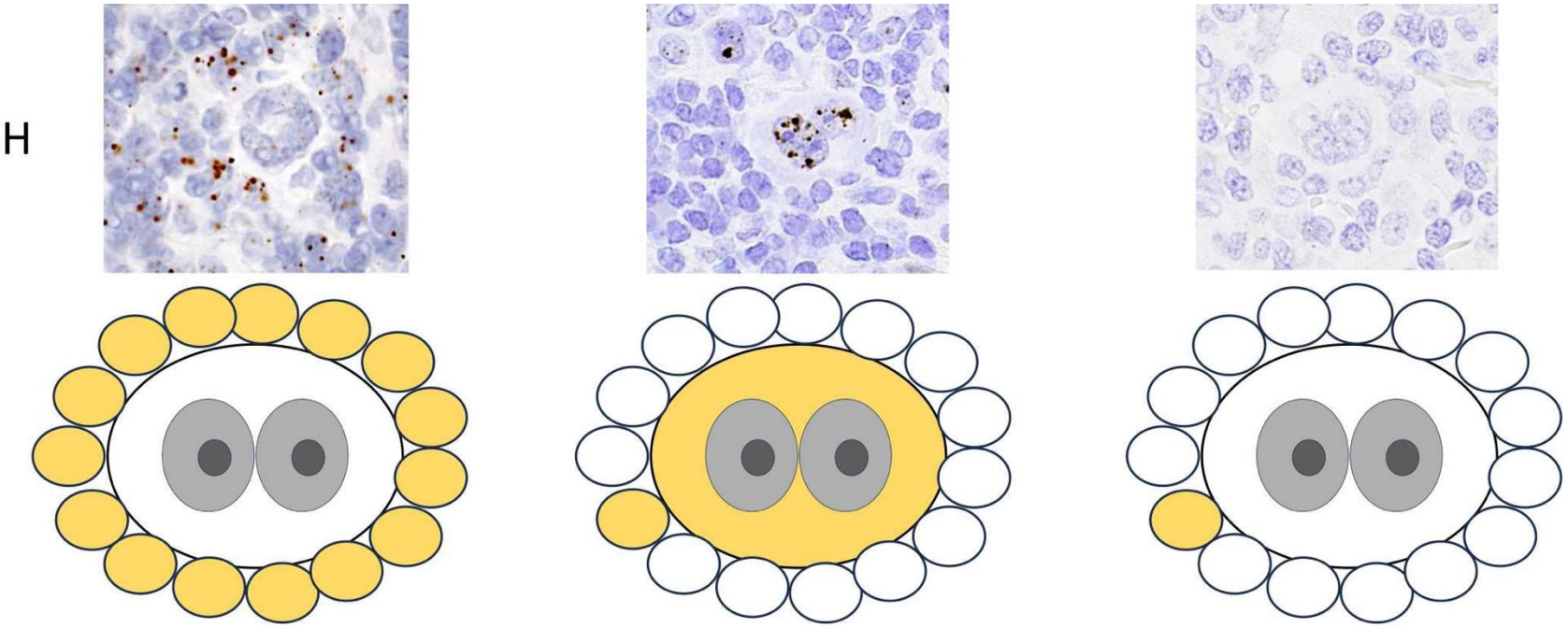
Minor histologic variants

- **ATLL with dermatopathic reaction**
- **Angioimmunoblastic T-cell lymphoma (AITL)-like variant**
  - Proliferating HEVs, polymorphous inflammatory background
  - Negative for TFH markers (though not reliable to distinguish ATLL from nTFHL-AI)
  - Absence of expanded FDC meshworks and evidence of HTLV-1 infection useful
- **Classic Hodgkin lymphoma-like variant**

Karube et al., *Leuk Res*, 2025

HRS-like Cells in HTLV-1 Infected Individuals – Diagnostic Possibilities

HBZ-ISH



ATLL with EBV+ HRS-like cells

ATLL, Hodgkin-like variant, HTLV-1+ HRS-like cells

Classic Hodgkin lymphoma in an HTLV-1 carrier

HTLV-1-infected

HTLV-1-uninfected

Other possibilities

- EBV reactivation in an HTLV-1 carrier
- Other T-cell lymphomas with HRS-like cells

Karube et al., *Leuk Res*, 2025

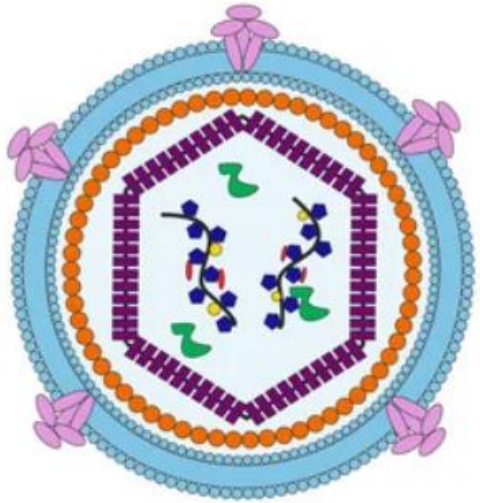
ATLL with HRS-like Cells

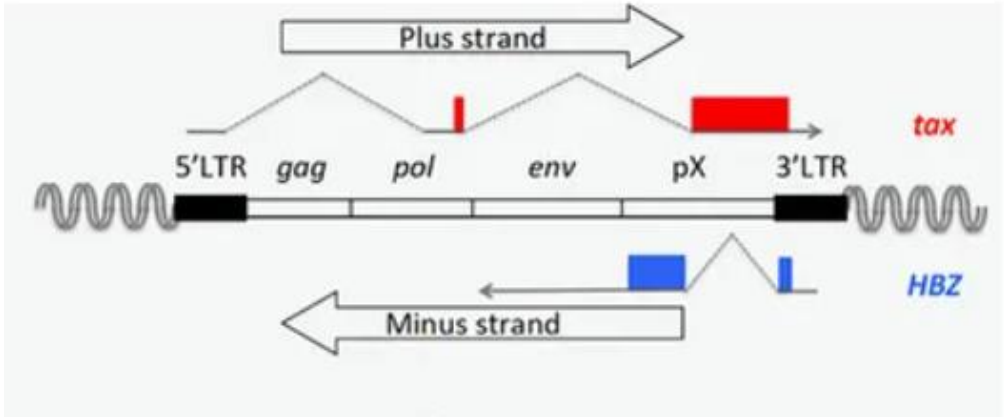
	ATLL, with EBV+ HRS-like cells	ATLL, Hodgkin-like variant HTLV-1 infected HRS-like cells
Frequency	More common variant	Rare (one published case series of 8 cases)
Pathogenesis	**EBV+ B cells** arising in an **immunosuppressive microenvironment**	**Neoplastic HTLV1+ ATLL cells** with HRS-like morphology
HTLV-1 distribution	HTLV-1 restricted to background neoplastic T-cells	HTLV-1 positive HRS-like cells
Immunophenotype of HRS-like cells	**B-cell lineage:** PAX5+, CD20+, CD79a+, OCT2+, BOB1+	**T-cell lineage:** Variable expression of T cell markers PAX5-, CD20-, lack B-cell program
	CD30+, CD15+/-	CD30+, CD15+
	EBER-ISH **positive**	EBER-ISH **negative**
	HBZ-ISH **negative**	HBZ-ISH **positive** (uniform/frequent positivity throughout)
Background cells	Neoplastic T-cells	Various inflammatory infiltrate Background T cells may be neoplastic or non-neoplastic

Karube K et al *Blood Adv.* 2021

Human T-lymphotropic Virus (HTLV) Type 1 Causes Profound Immunosuppression

RNA retroviruses





HTLV-1	Japan, Caribbean, South America, sub-Saharan Africa	ATLL, HAM/TSP
HTLV-2	Indigenous populations in the Americas Individuals who inject drugs	Rarely HAM/TSP
HTLV-3 and -4	Isolated cases in Cameroon	No disease association

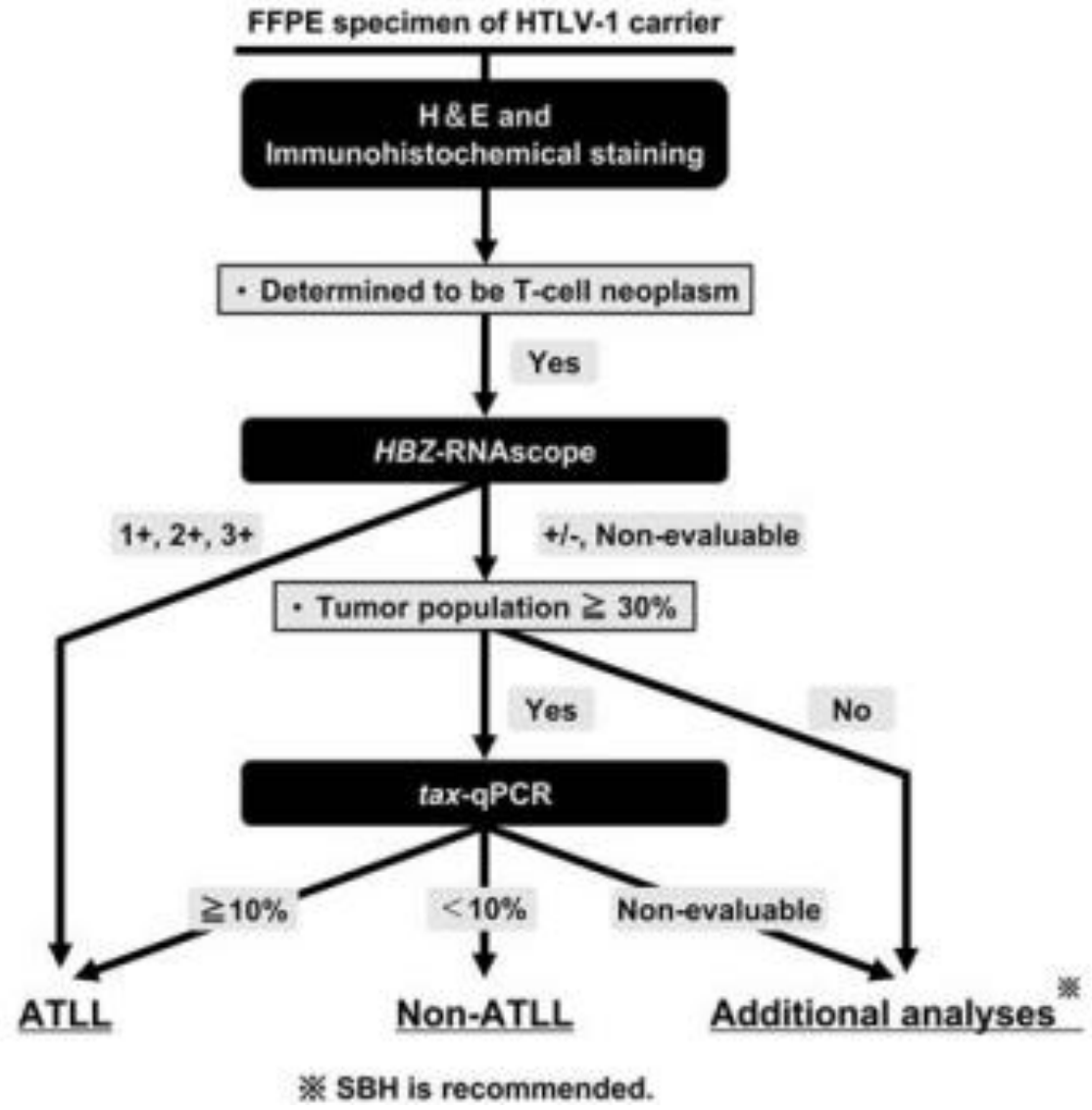
TAX	HTLV-1 basic leucine zipper factor (HBZ)
Transient expression, early in infection	**Constant** expression
Essential for initial transcription of viral genome	**Promotes:** Immune escape Viral latency Persistent infection
	Upregulation of genes associated with regulatory T-cells (T-regs), such as FOXP3 and CCR4

T-regs promote an immunosuppressive environment

Kemeter et al, *Microorganisms*, 2023
Yasunaga, *Front Microbiol*, 2020

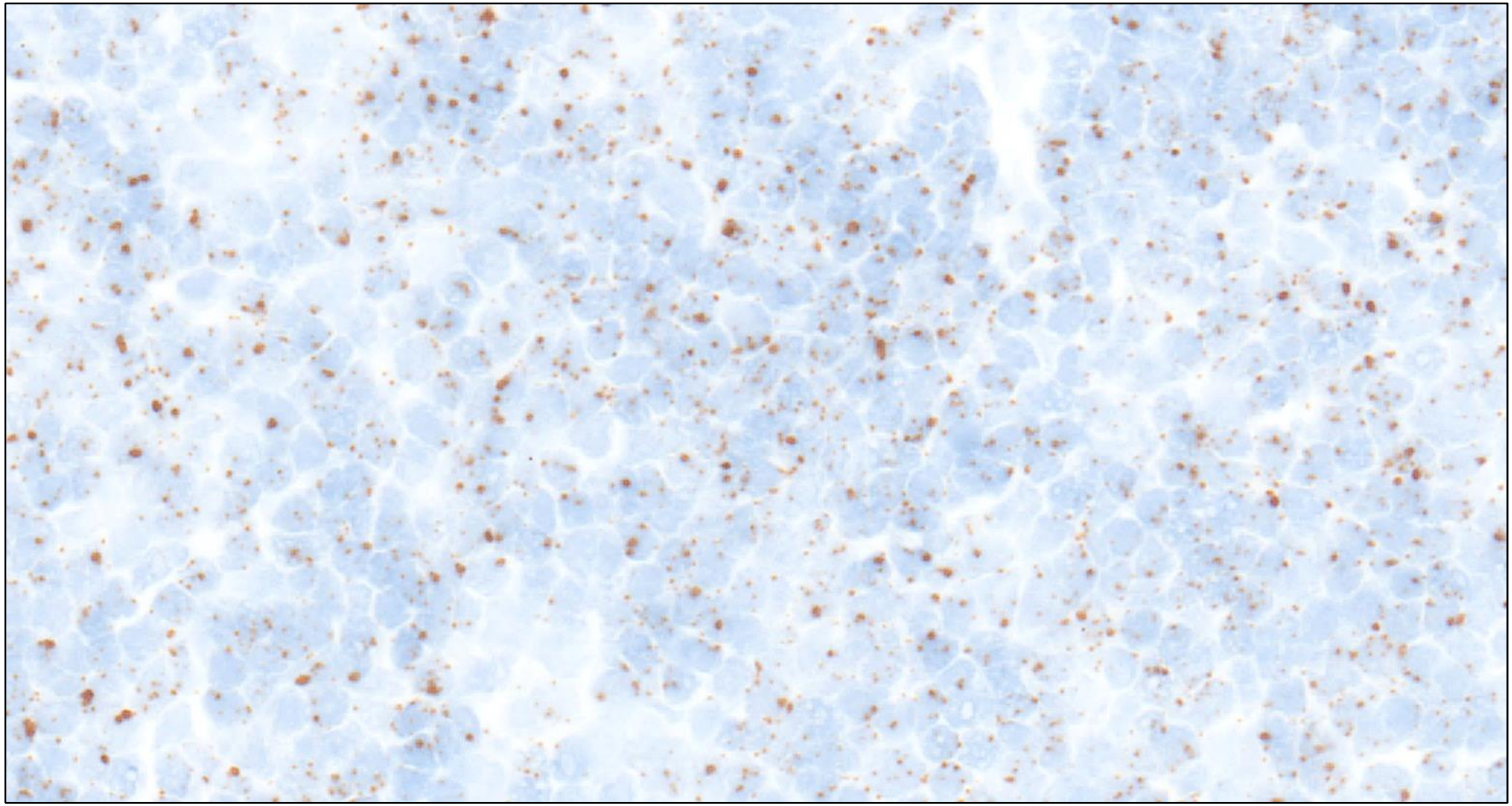
Pitfalls of Peripheral Blood HTLV-1/2 Testing

- Non-endemic areas = HTLV-1 seropositivity can be used as a surrogate for evidence of monoclonal integration
  - Yuan et al. (Taiwan)
    - ~10% of **HTLV-1/2-seropositive PTCL cases were not ATLL** on molecular testing
- Endemic areas = viral integration is often supported by tissue-based HTLV-1 molecular testing
  - **Southern blot** shows integration of HTLV-1 DNA in the host genome
  - **HBZ-ISH** uses labeled probes to detect viral transcripts in tumor cells
  - **Tissue *tax* qPCR** measures HTLV-1 viral DNA in tumor tissue and reports viral copies per total number of cells
- Evidence of proviral integration by molecular testing establishes ATLL diagnosis even if morphology is atypical



Takatori et al., *Mod Pathol*, 2021

HBZ-ISH



Take Home Points

- Testing for HTLV-1 infection is encouraged in all PTCLs
- HRS-like cells can occur in a range of mature T-cell lymphomas
  - Usually EBV+ B cells
  - Evaluate for atypical background lymphoid population in cases with HRS-like cells
  - In ATLL, HRS-like cells can be either T-cell (HTLV-1 infected) or B-cell derived
- ATLL, Hodgkin-like variant with HTLV-1+ HRS-like cells
  - HRS-like cells are HTLV-1 infected, possibly in a background of non-neoplastic T-cells
  - Demonstration of uniform/frequent HBZ-ISH labeling in HRS-like cells is critical
- ~20% of ATLL cases do not show a typical immunophenotype
  - CD25 negativity does not exclude ATLL
  - ~10% of ATLL cases show TFH phenotype
- Consider molecular testing for proviral integration in cases with atypical morphology and HTLV-1 seropositivity

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Thank You/Any Questions?

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