Hematopathology Tumor Board

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Session faculty

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Case presentations

Clinical portions : Kirk Cahill
Pathology portions : Aibek Akmatbekov and Leo Wu (Hematopathology Fellows, UChicago)

Disclosures

GV: None

AP: None

KC: None

AA: None

LW: None

Structure of session and goal for the next hour (or less)….

Path101 + Two case presentations

- Lymphoma rounds format (equal pathology and clinical discussions)
- Tricky situations that pathologists (and treating physicians) sometimes struggle with
- ARS questions

Content Covered

- Basic work up of T-cell lymphomas
- MYC/EBV+ lymphomas and pitfalls - 2 cases

….A pre-session ARS and handover to Dr. Perry for the Path101 around workup

ARS Question 1

Which of the following markers has **least** utility in the workup of Hodgkin lymphoma?

A. CD30
B. TdT
C. PAX5
D. CD20

ARS Question 1

Which of the following markers has least utility in the workup of Hodgkin lymphoma?

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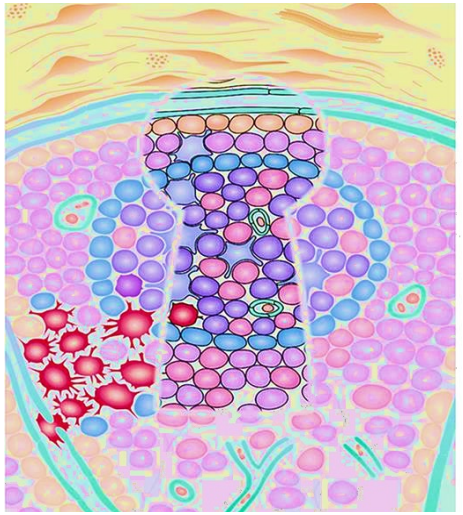
B. TdT
C. PAX5
D. CD20

Workup of lymph node specimen for suspected lymphoma

Lymph node biopsy evaluation - goals



1. Diagnosis and proper classification of disease
2. P

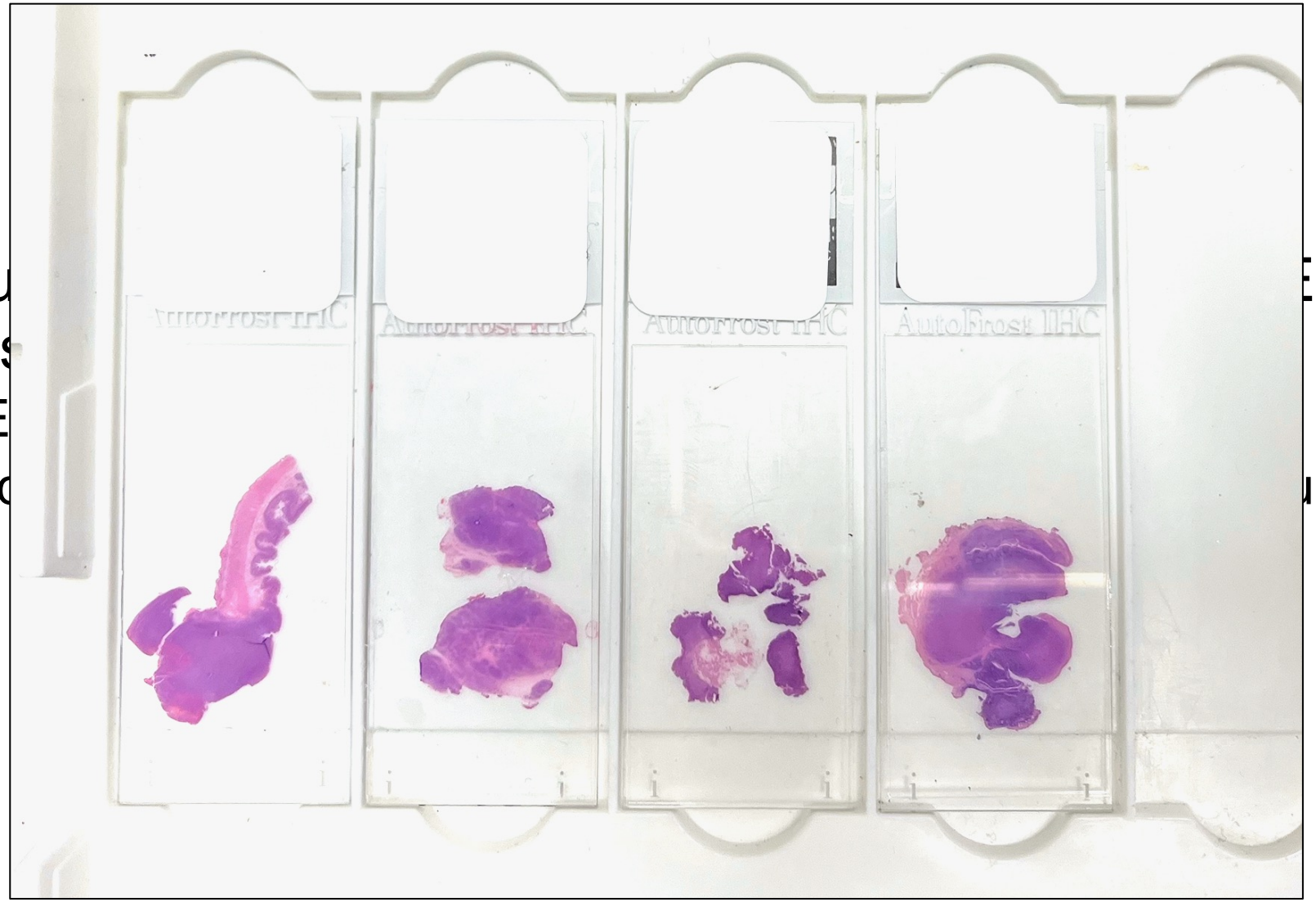
Guiding principle of both classifications – when making a diagnosis incorporate morphologic, immunophenotypic, genetic and clinical findings

Cur

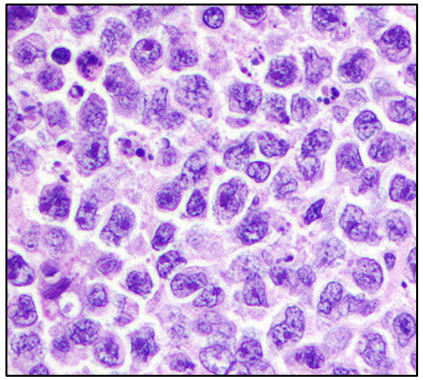
- World Health Organization (WHO) Classification, 5th ed
- International Consensus Classification (2022 ICC)

Lymph node biopsy evaluation - tools

1. Tissu)-stained slides
   - H&E
   - Usec rsue next

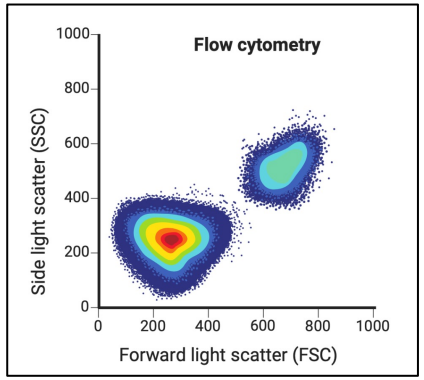


Lymph node biopsy evaluation - tools



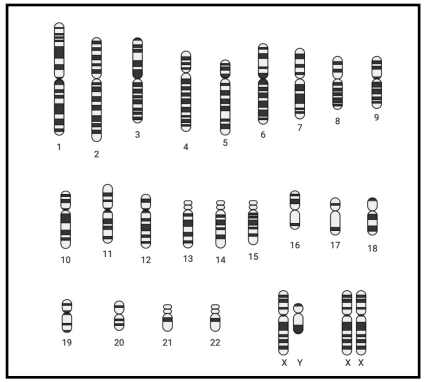
Tissue morphology

- IHC staining for CD markers



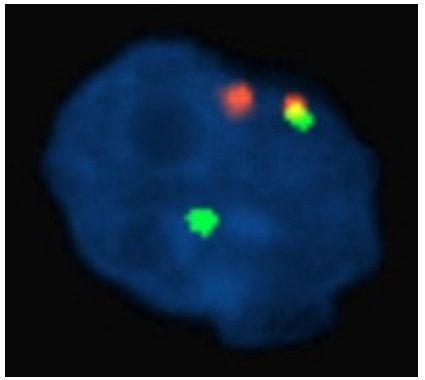
Flow cytometry

- Fluorescent antibody for CD markers
- Identify clonal populations



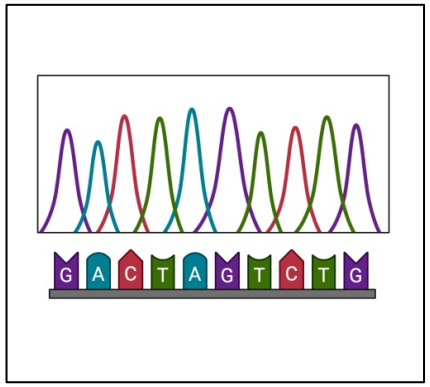
Karyotype

- General assessment of chromosomal abnormalities



FISH

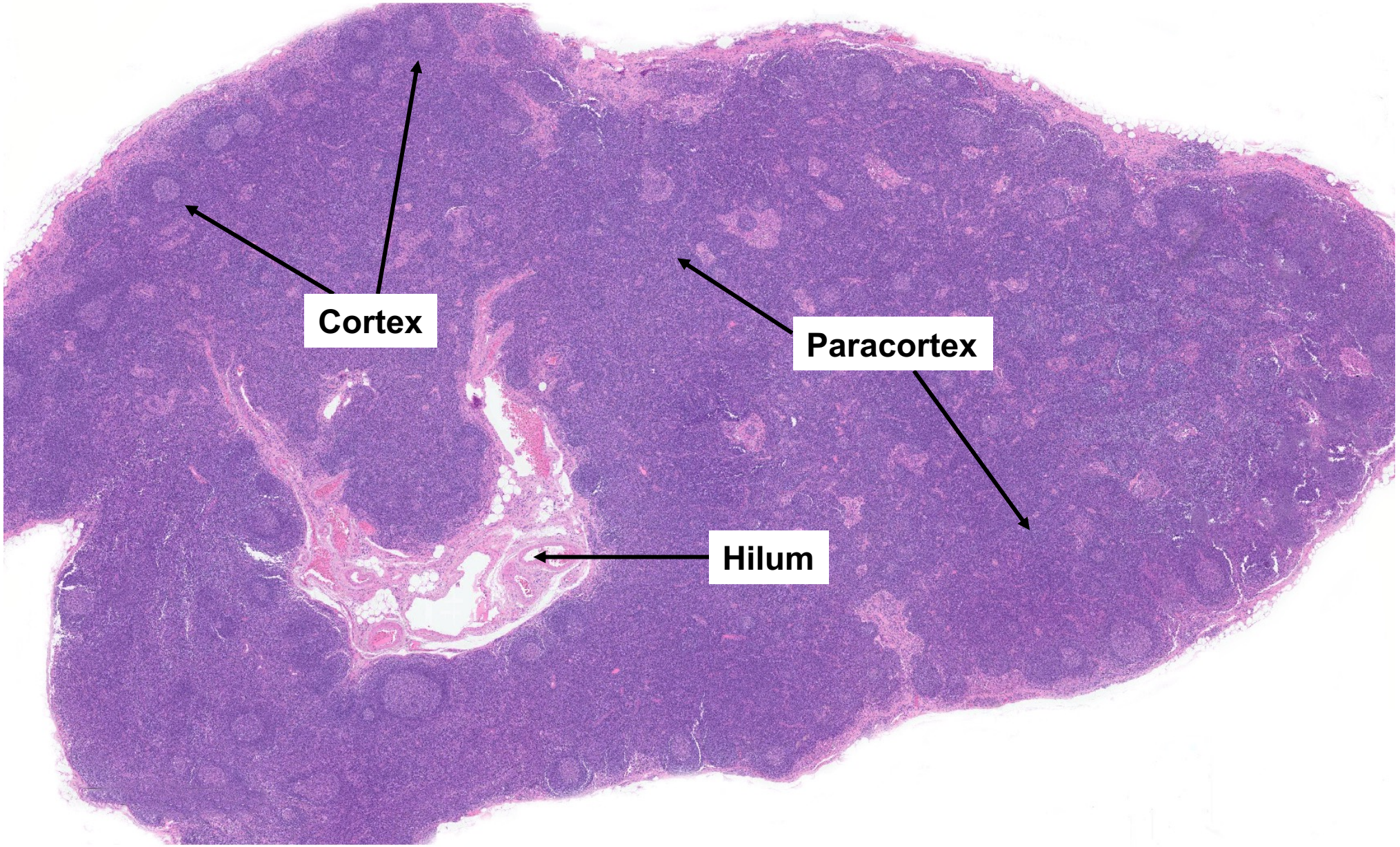
- Specific testing for chromosome deletions, additions, rearrangements



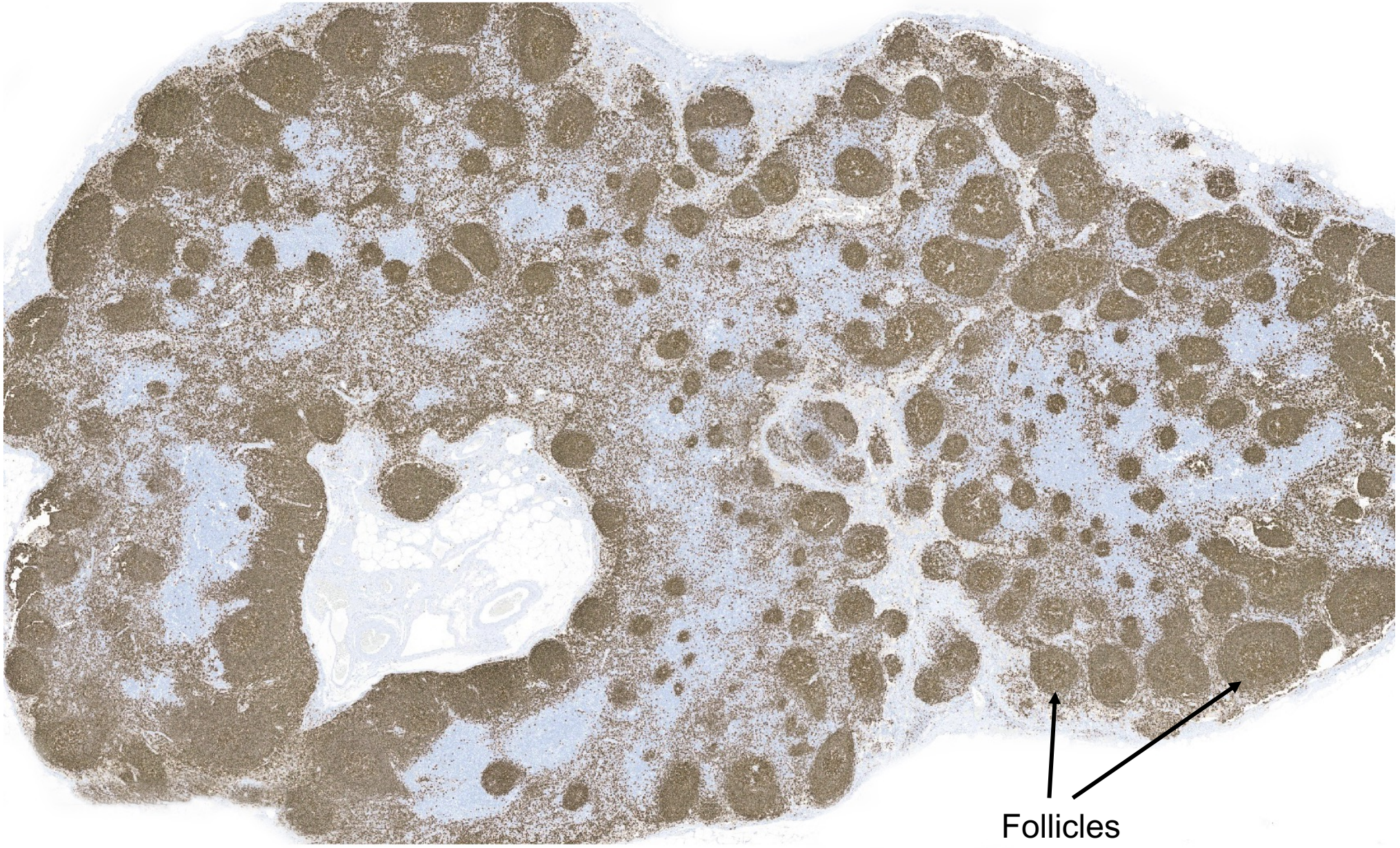
Next-generation sequencing

- DNA testing for pathogenic mutations

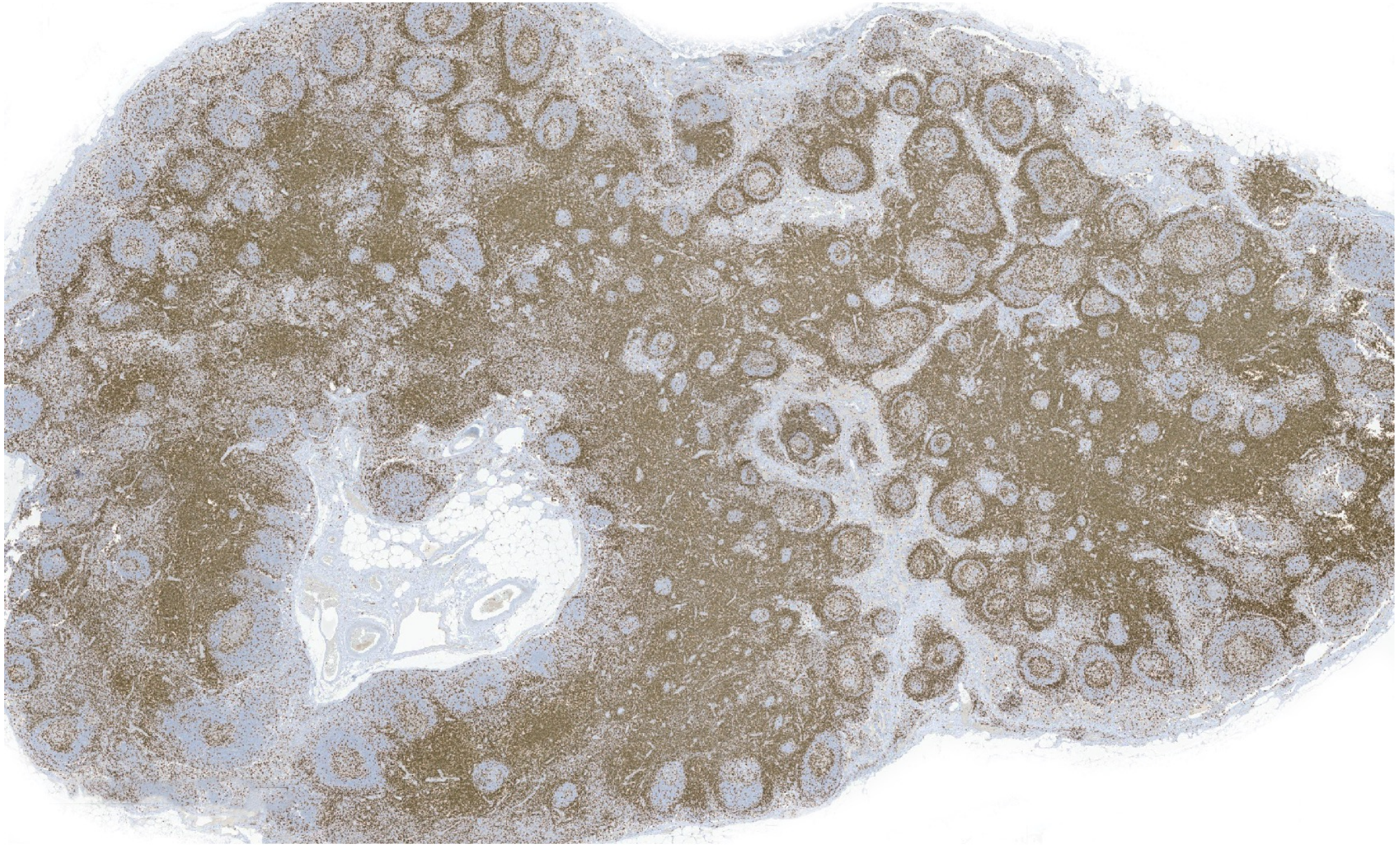
Know “normal” to recognize abnormal



CD20 – stains B cells



CD3 – stains T cells



Workup for suspected mature T-cell lymphoma

“T-cell lymphomas are hard!”

- Relatively uncommon specimen – <15% of NHL cases in the US
- Can be very challenging to diagnose on a needle core biopsy (and larger biopsy too!!)
  - Unable to properly assess architecture
  - Can look relatively bland and mimic benign condition
  - Can have Hodgkin/Reed-Sternberg cells and mimic other lymphomas (e.g. CHL)
  - Can have expanded B-cell areas and show more B-cells than T-cells on a needle core
  - Can only partially (focally) involve lymph node

Mature nodal T-cell lymphomas

- Mature T-cell lymphomas – nodal vs. extranodal
- Extranodal T-cell lymphomas can involve lymph node

- Primarily nodal lymphomas
  - Peripheral T-cell lymphoma, not otherwise specified (NOS)
  - Follicular helper T-cell lymphomas (Angioimmunoblastic TCL)
  - Anaplastic large cell lymphoma, ALK+ and ALK-

- Goal of the workup – try to classify T-cell lymphoma into one of the defined subtypes……if it does not fit (or material is too small) call it PTCL, NOS

Immunohistochemical markers –T-cell lymphoma workup

T-cell markers

Basic

- CD3 – pan T-cell marker
- CD4
- CD8

Aberrant loss

- CD2
- CD5
- CD7
- BCL2

Markers of follicular T-helper cells

- CD10
- BCL6
- PD-1
- CXCL13
- ICOS
- SAP

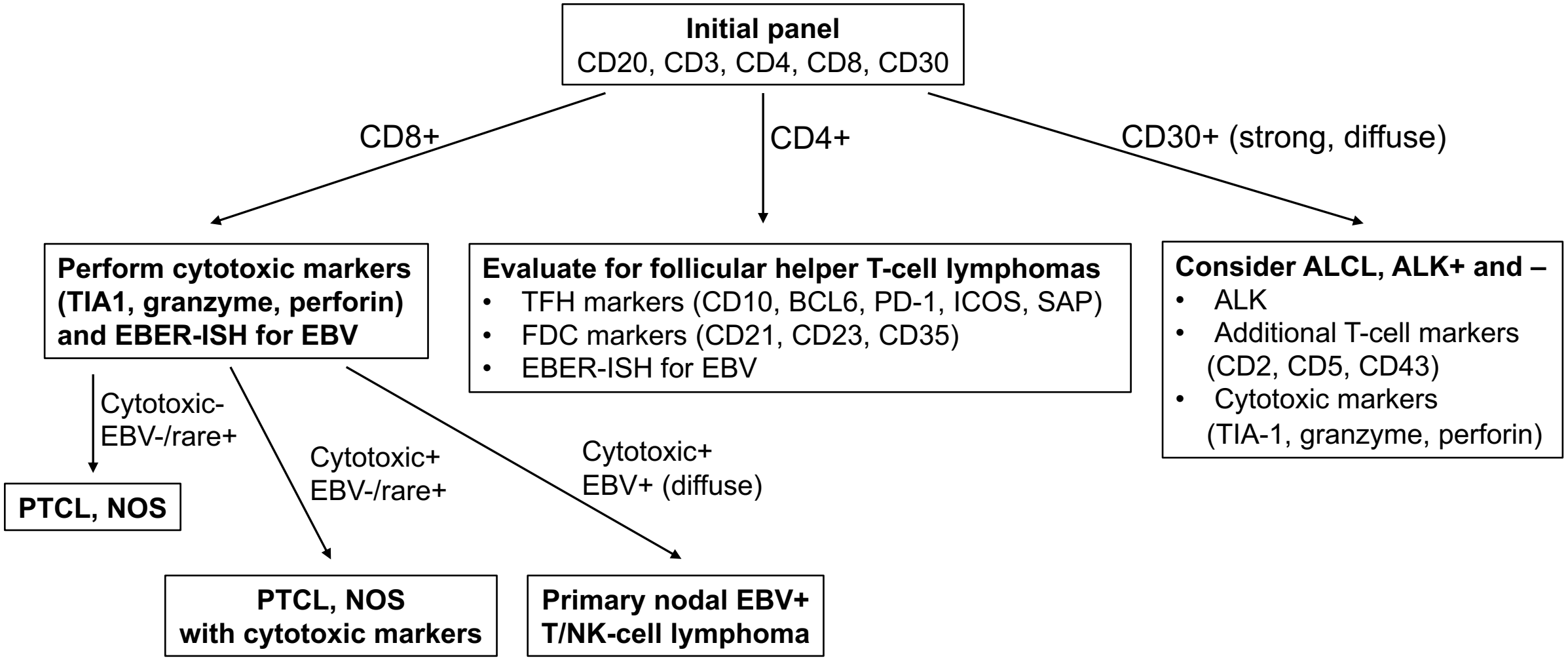
Cytotoxic markers

- TIA-1
- Granzyme
- Perforin

Other routinely used markers

- CD30, CD43, CD56
- EBER-ISH
- ALK
- TCR-B, TCR-D
- CD21, CD23 – follicular dendritic meshwork markers

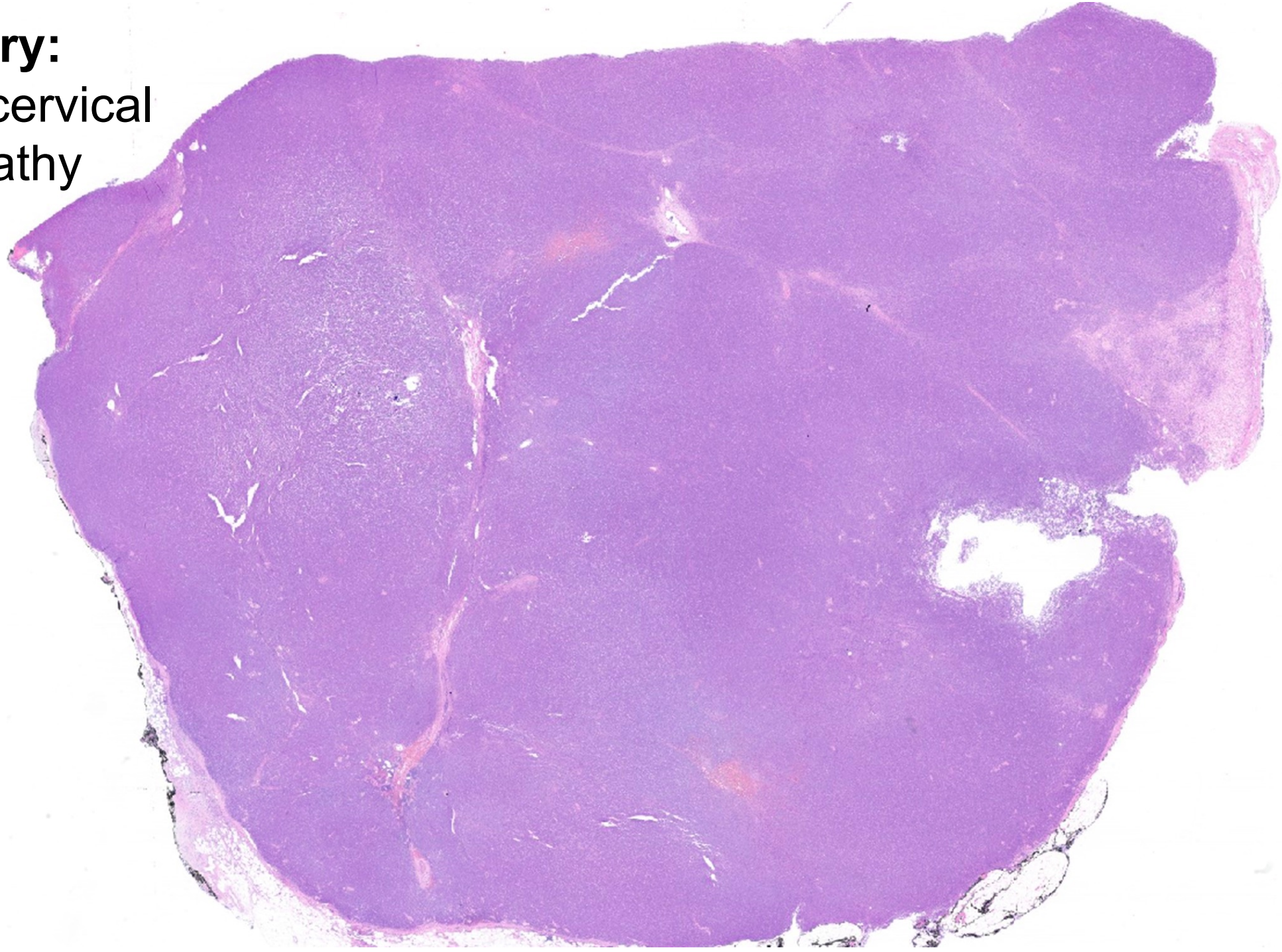
EVALUATION OF NODAL T-CELL LYMPHOMA

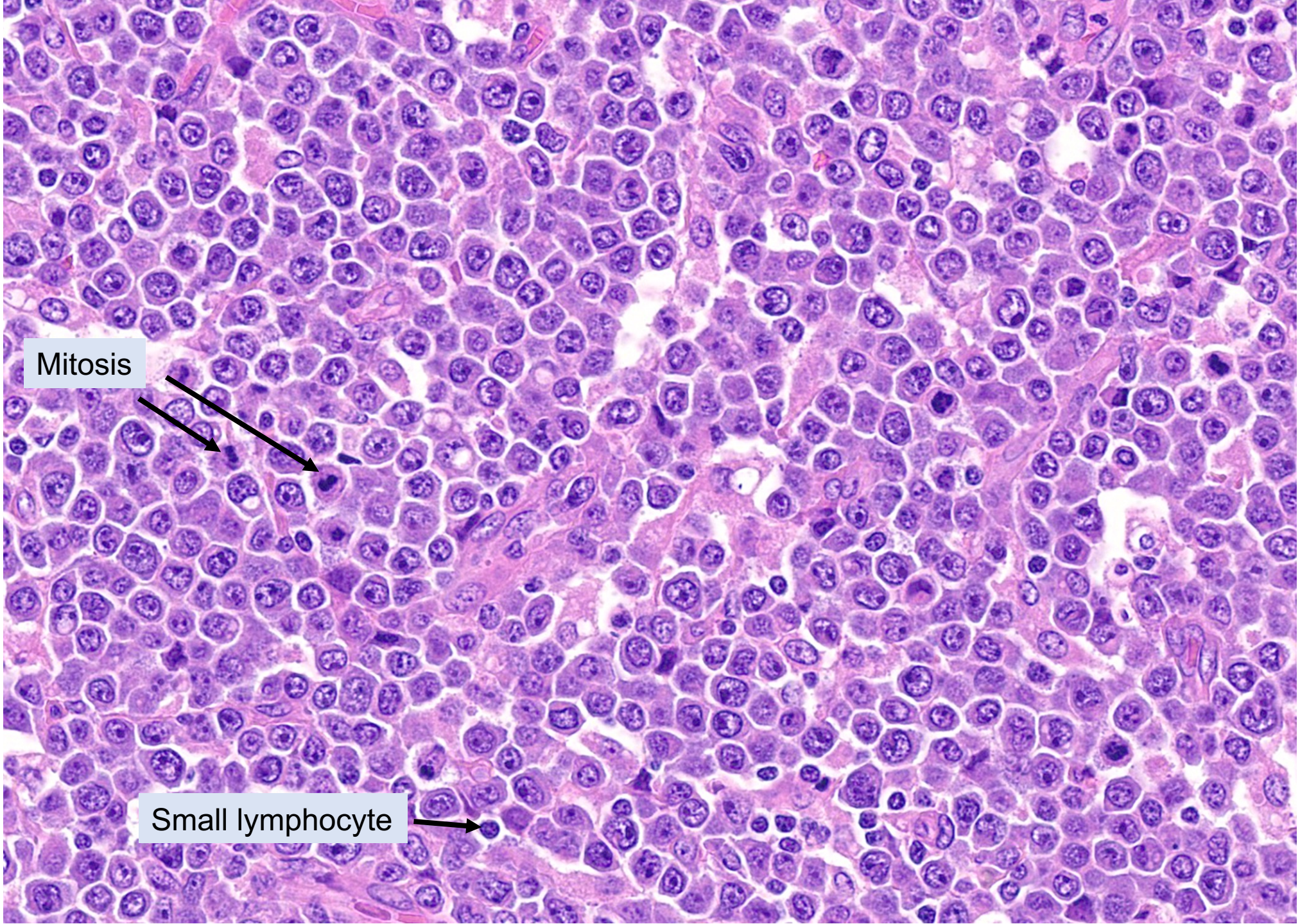


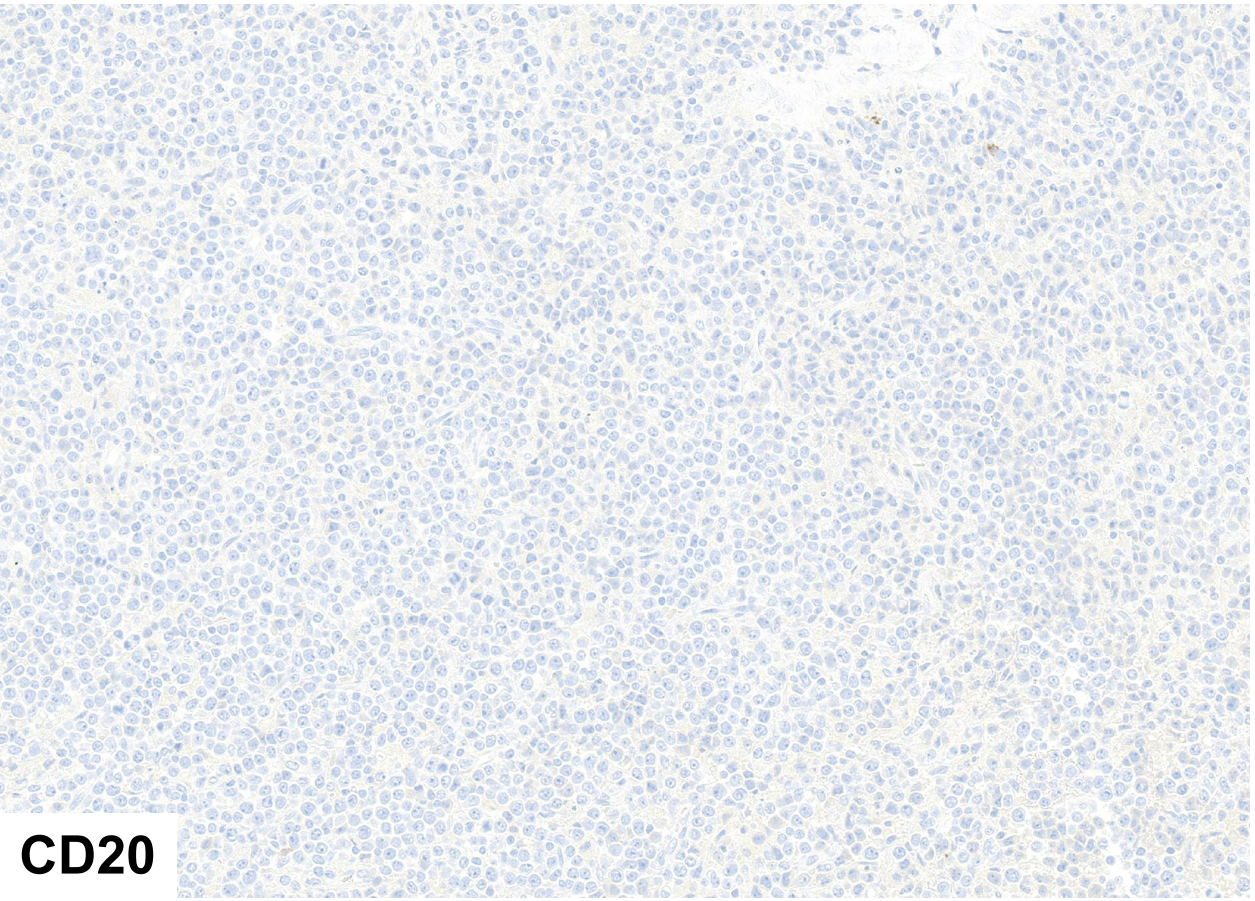
T-cell clonality studies – helpful in supporting the diagnosis (if morphology fits!!). **Clonality ≠ T-cell lymphoma**

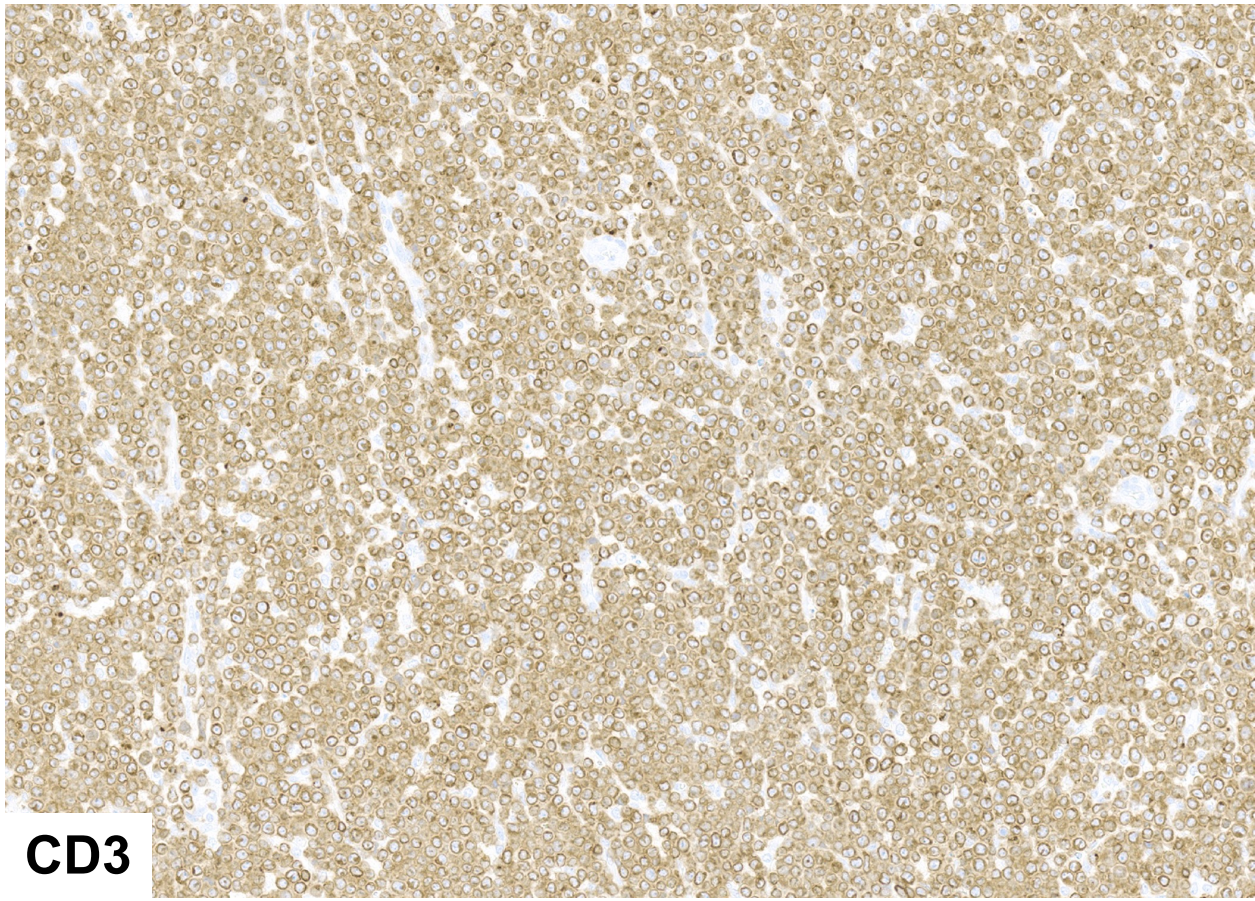
Example – diagnosis of anaplastic large cell lymphoma

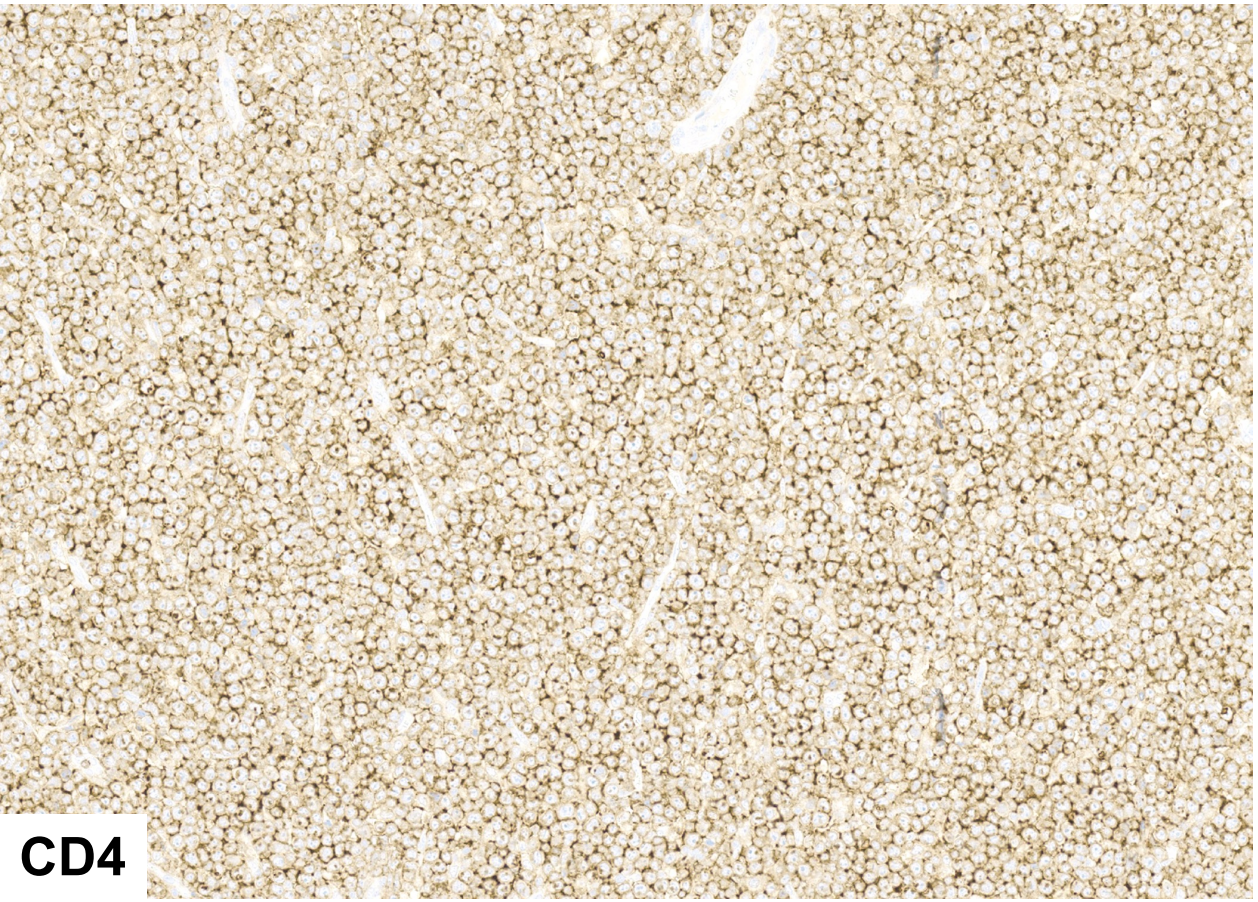
Clinical history:
67 y/o F with cervical lymphadenopathy

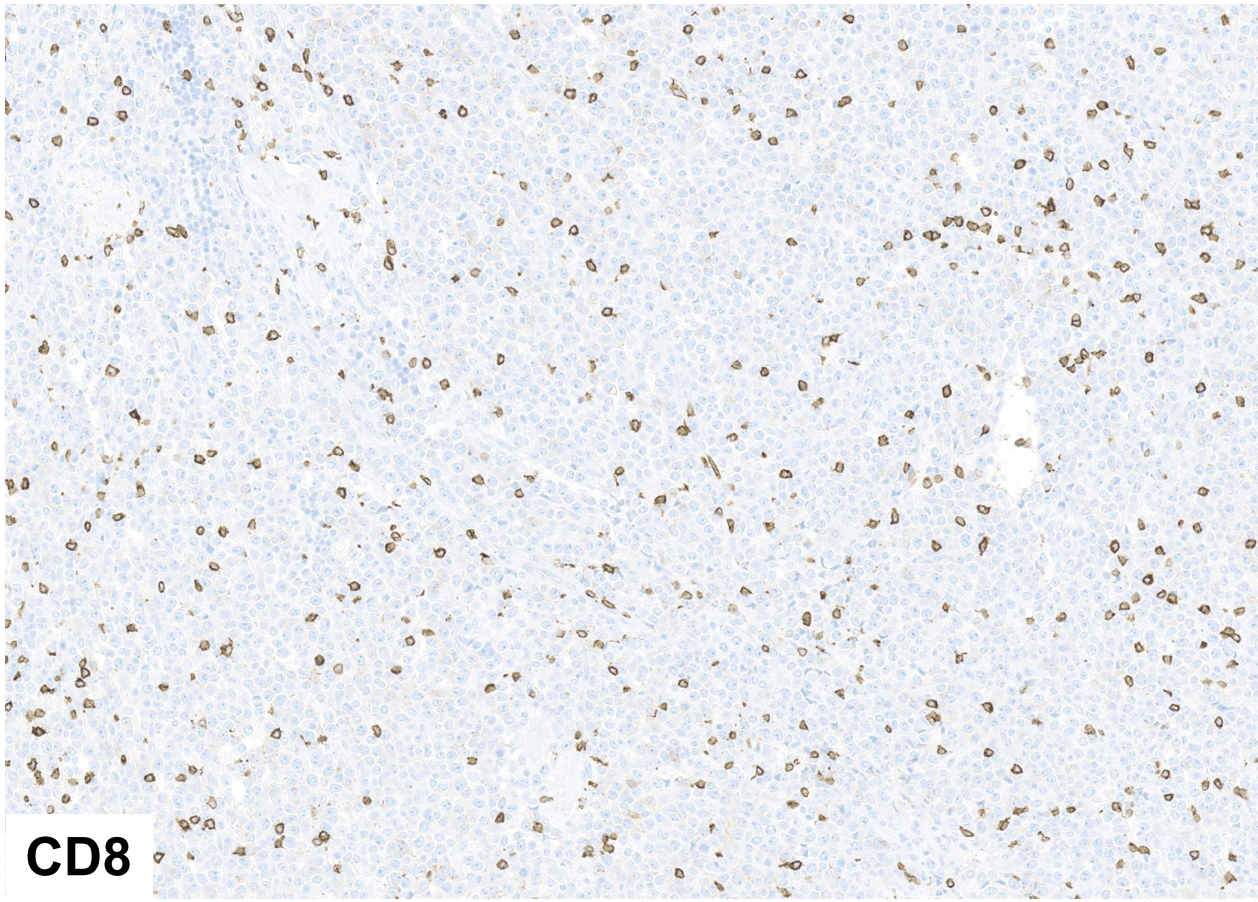


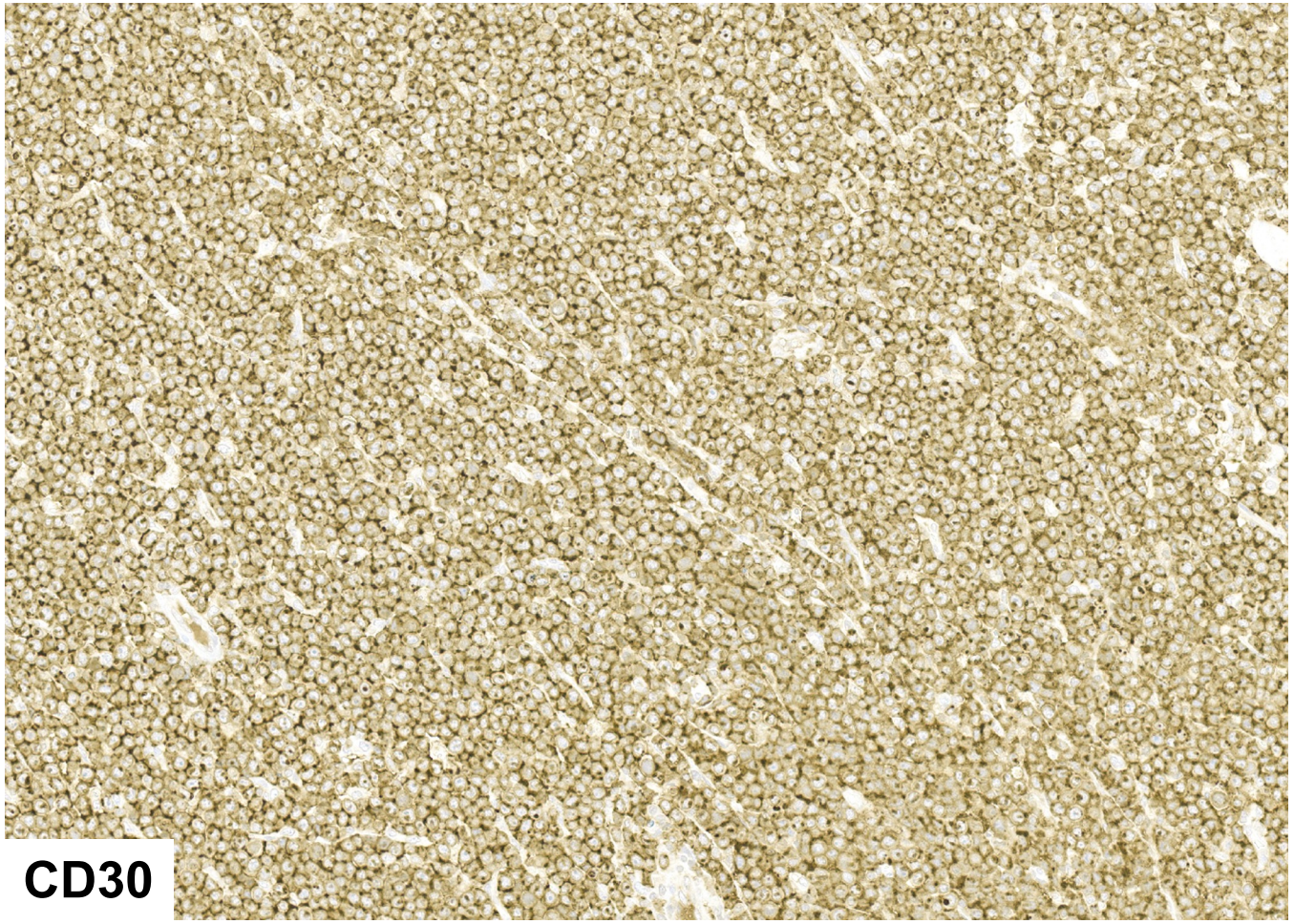

Mitosis
Small lymphocyte


CD20

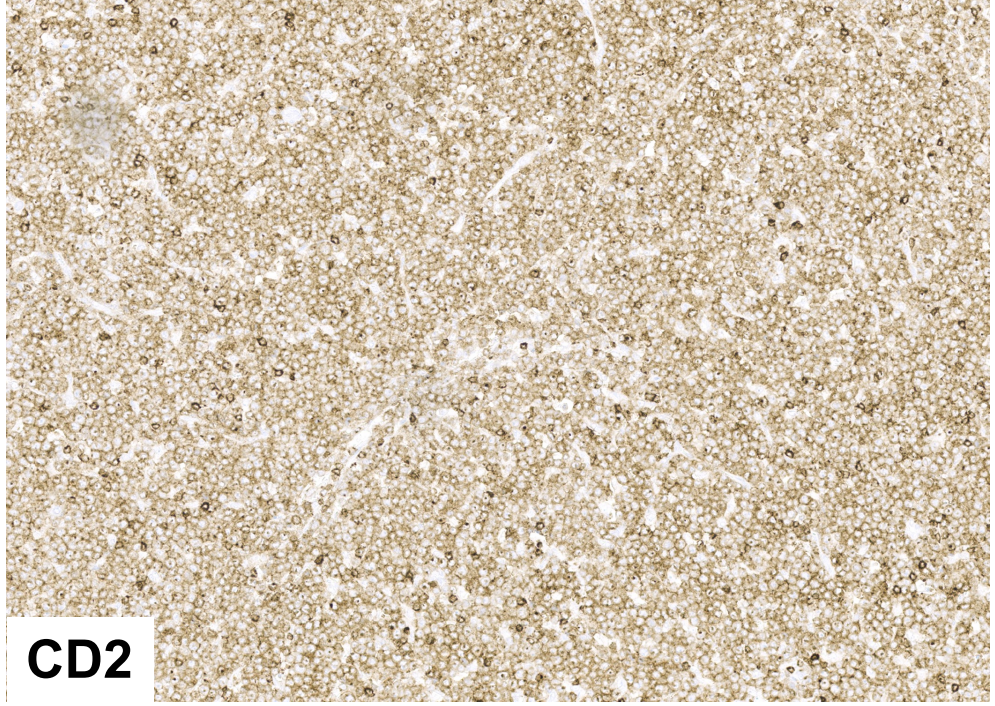

CD3

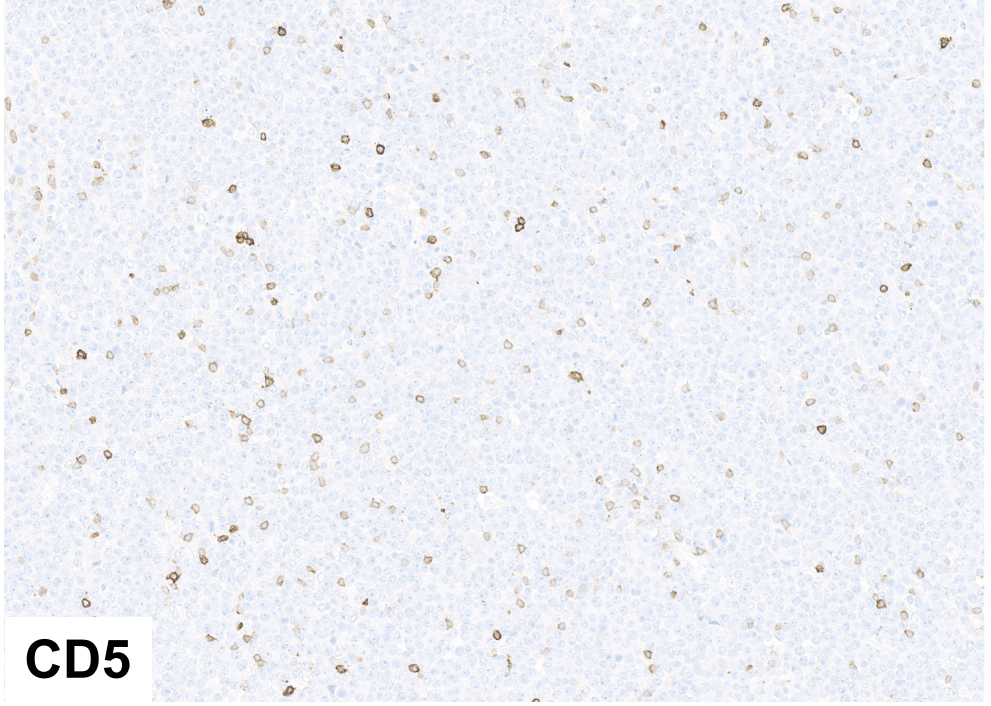

CD4

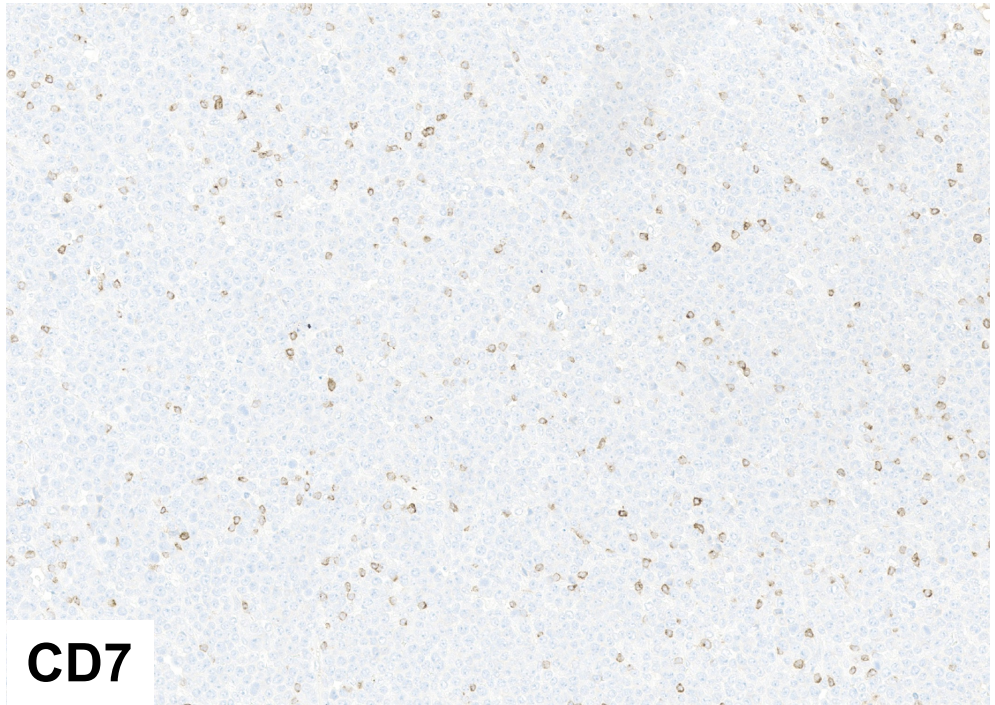

CD8

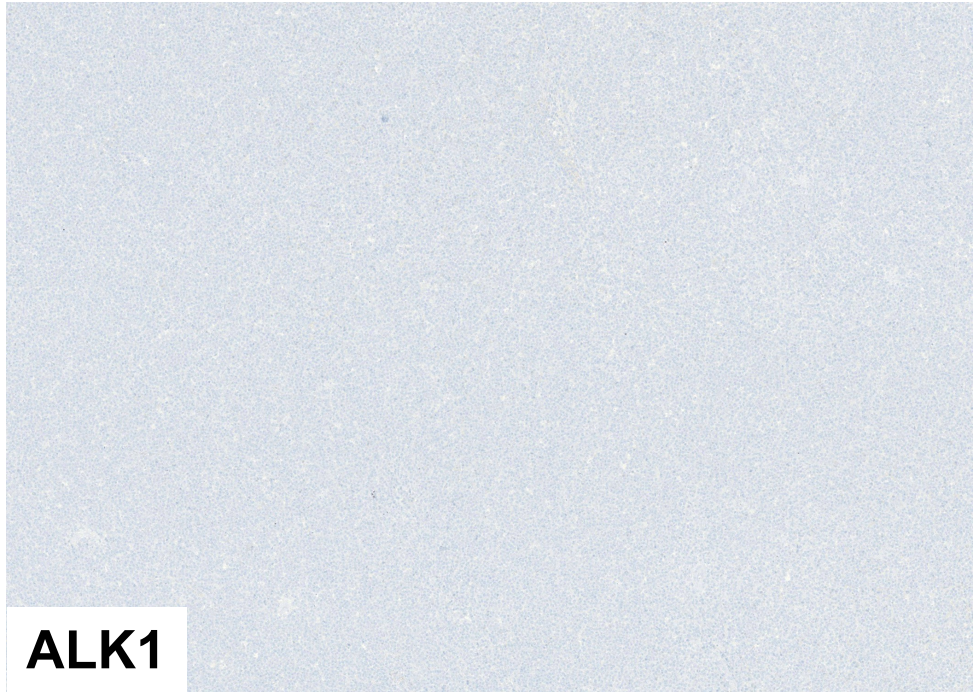


CD30

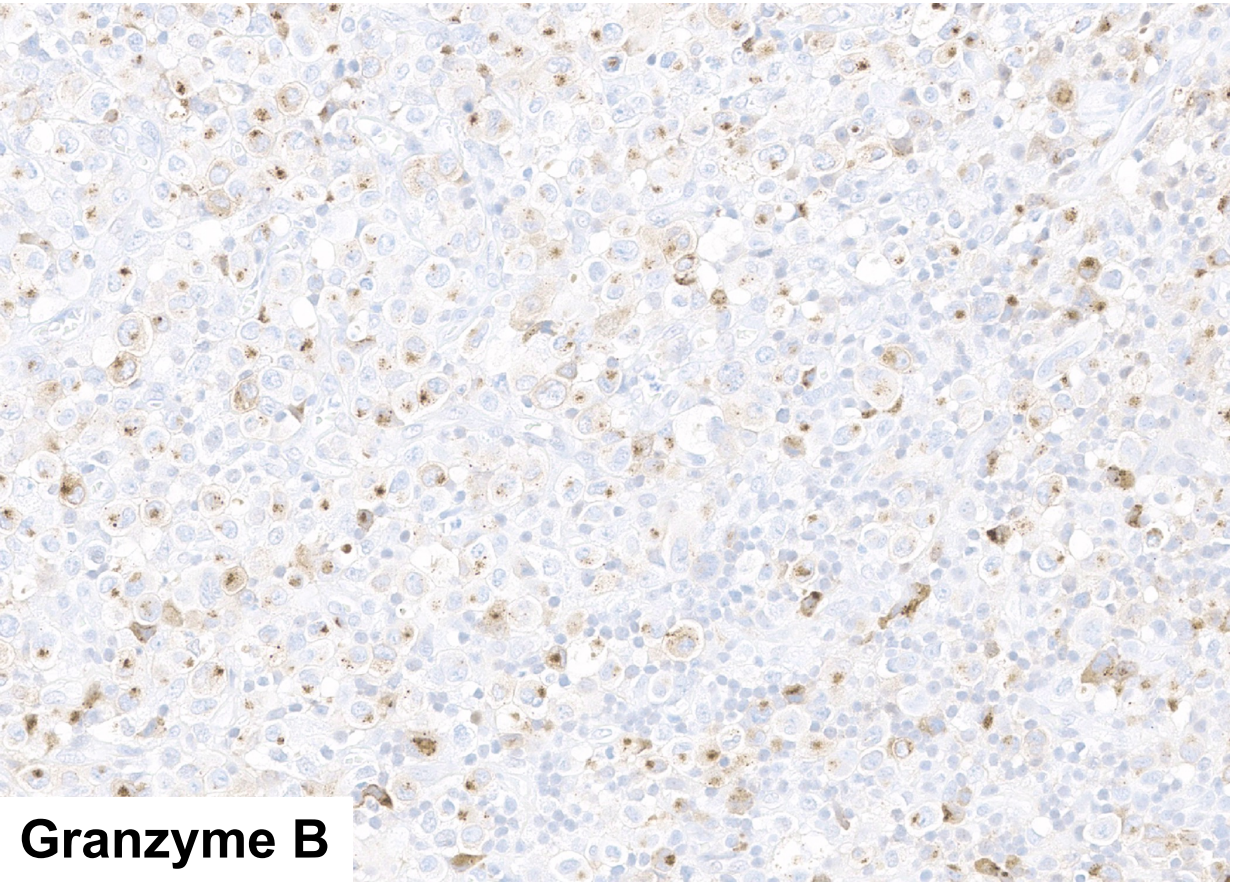

CD2


CD5


CD7

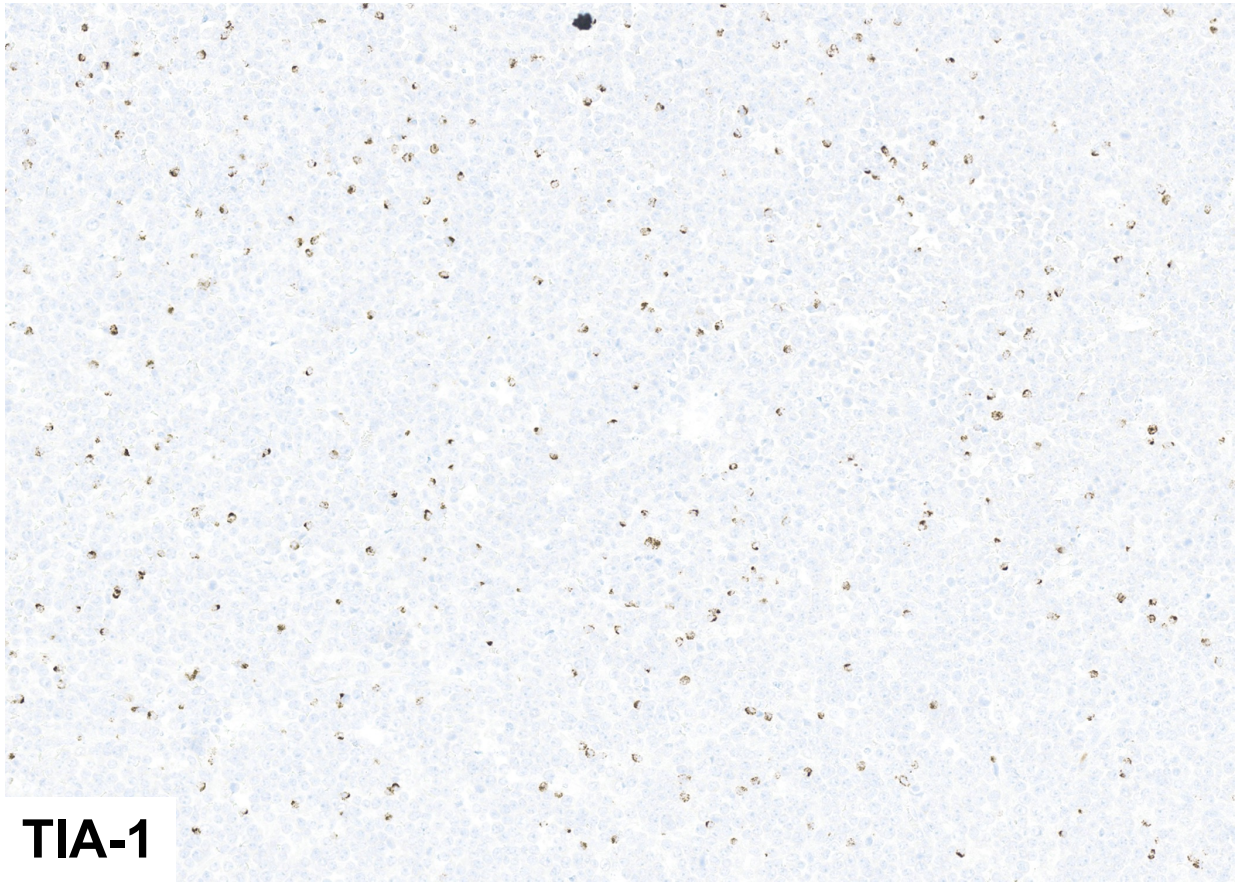

ALK1

Cytotoxic Markers



Granzyme B

(High Power)



TIA-1

(Low Power)

Summary of immunophenotype

- Positive: CD3, CD30, CD2, CD4, granzyme B
- Negative: CD5, CD7, CD8, TIA-1, ALK-1
- Final diagnosis - Anaplastic large cell lymphoma, ALK-negative

CD30 in ALCL

1. Required for diagnosis

ARS Question 2

A 62-year-old male presents with right axillary lymph node swelling. Needle biopsy performed shows anaplastic large cell lymphoma (ALK negative). PET shows abnormal uptake in the cervical, axillary, and inguinal lymph nodes consistent with stage III disease. No cytopenias. Bone marrow biopsy-negative for lymphoma. ECOG performance status is 1. TTE shows a normal ejection fraction.

Which of the following is the preferred treatment?

A. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
B. Oral azacitidine + CHOP
C. Romidepsin + CHOP
D. BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone)
E. BV-CHEP (brentuximab vedotin, cyclophosphamide, doxorubicin, etoposide, prednisone)

ARS Question 2

Which of the following is the preferred treatment?

A. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
   - Acceptable regimen when BV is not available

B. Oral azacitidine + CHOP
   - Remains and investigational regimen for PTCL with TFH phenotype (PMID: 36796016)

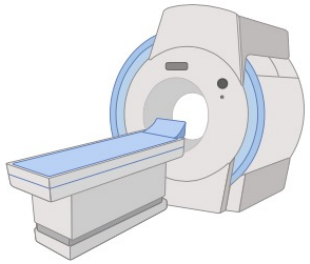
C. Romidepsin + CHOP
   - No benefit compared to CHOP in unselected PTCL. Remains investigational regimen for PTCL with TFH phenotype. (PMID: 38364196)

D. BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone)
   - NCCN preferred regimen for ALCL based on ECHELON-2

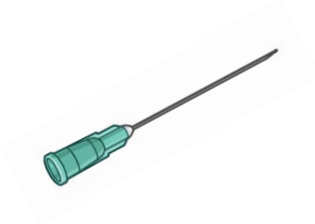
E. BV-CHEP (brentuximab vedotin, cyclophosphamide, doxorubicin, etoposide, prednisone)
   - Remains investigational regimen for PTCL (NCT03113500)

Case 1

ID: 70 year old male with HTN and prior PE presenting with hip pain.



- MRI pelvis showed incidental inguinal lymphadenopathy
- CT chest showed small axillary and mediastinal lymphadenopathy.



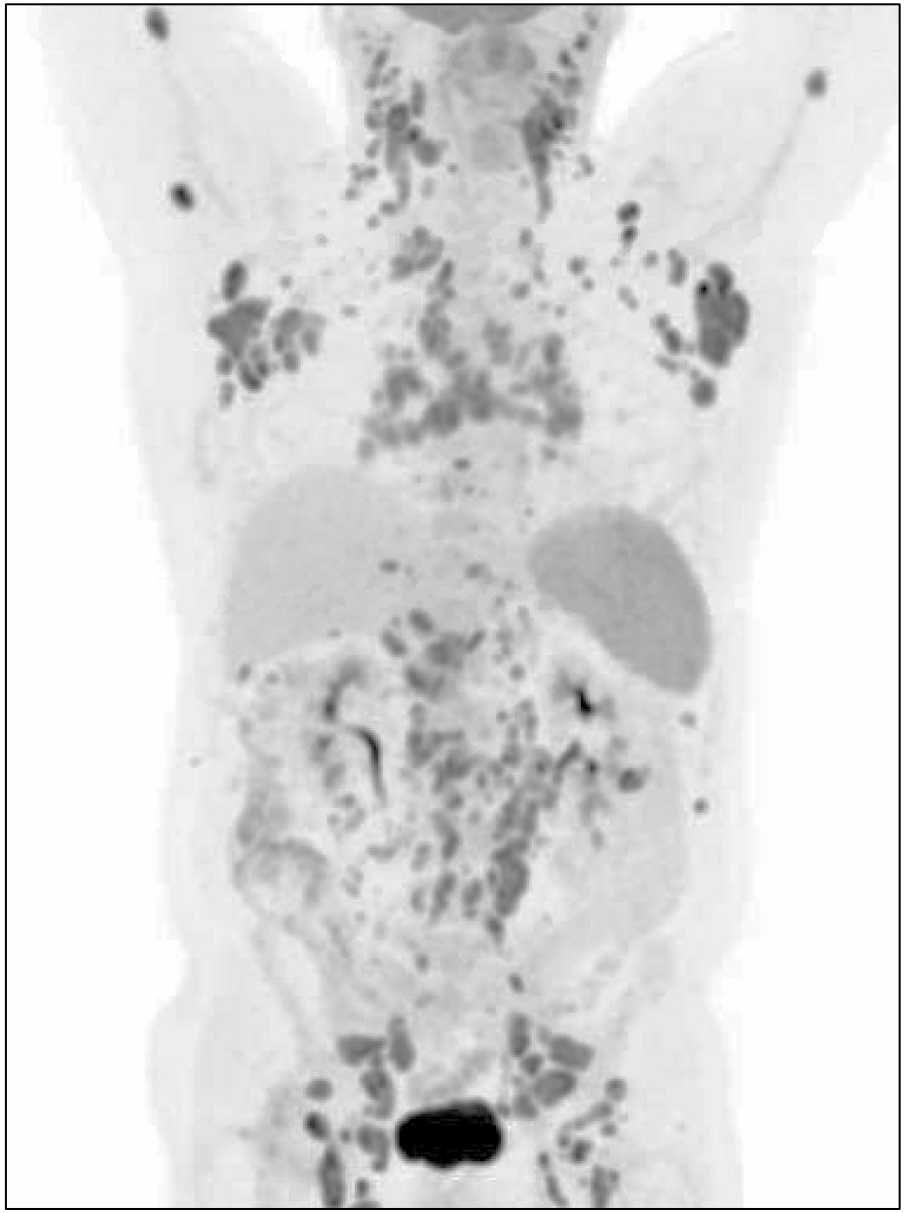
- Inguinal lymph node core needle biopsy:
  - ‘Atypical lymphoid infiltrate’

Case 1

- Inguinal lymph node EXCISIONAL biopsy:
  - ‘Atypical lymphohistiocytic proliferation’
  - Flow cytometry: abnormal CD8+ T lymphocytes (21%)
  - CD4-, CD8+, CD5-, CD7 heterogeneous
  - **NGS: Pathogenic** *TET2* mutation (10% VAF)

Case 1

- Initial PET showed resolution of lymphadenopathy.
- PET 2 months later ⟶
- Asymptomatic. HIV negative.
- Excisional biopsy of left axillary lymph node is done.



Pathology Timeline

4/2023

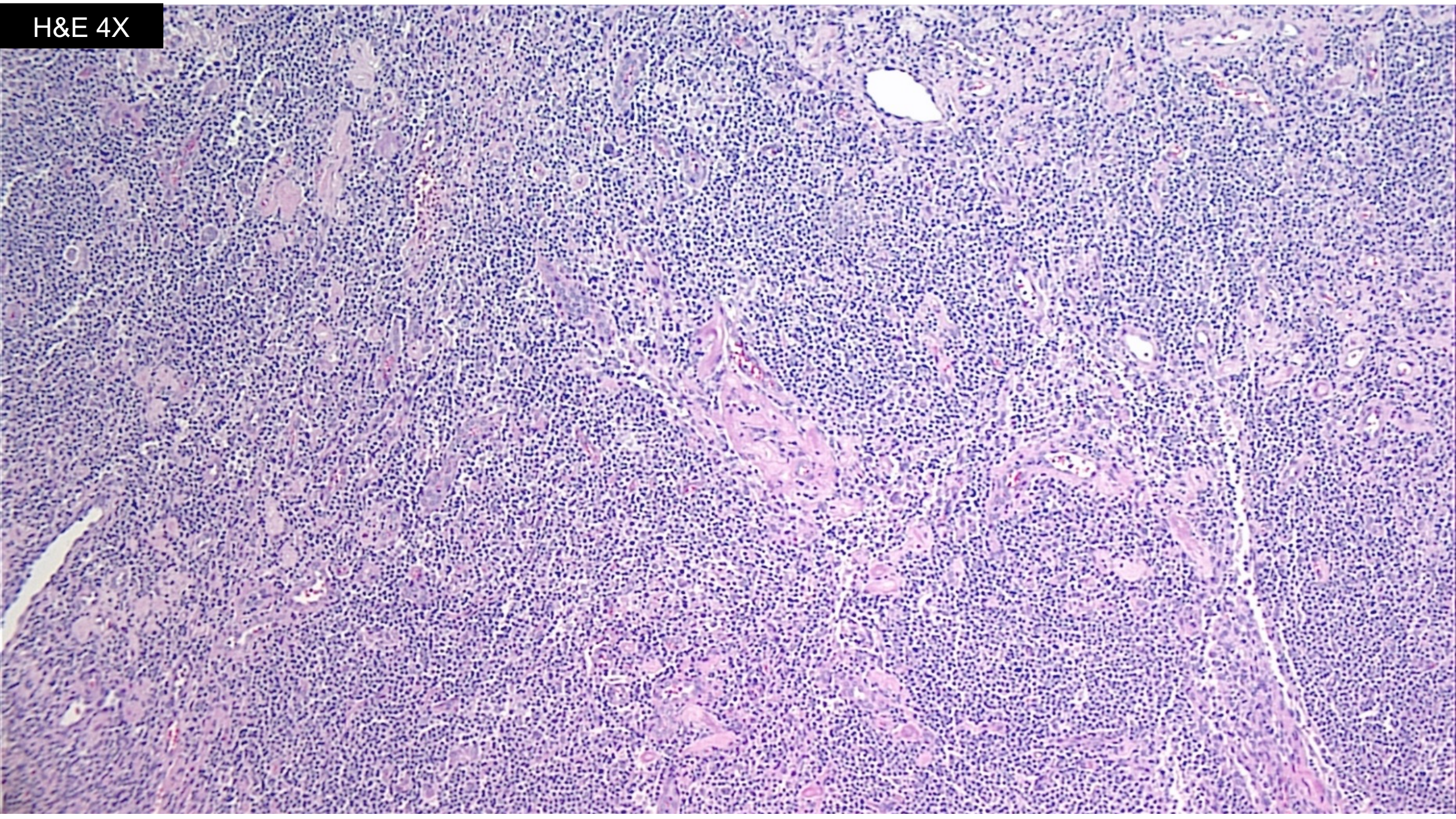
Inguinal lymph node:
- Atypical lymphoid proliferation

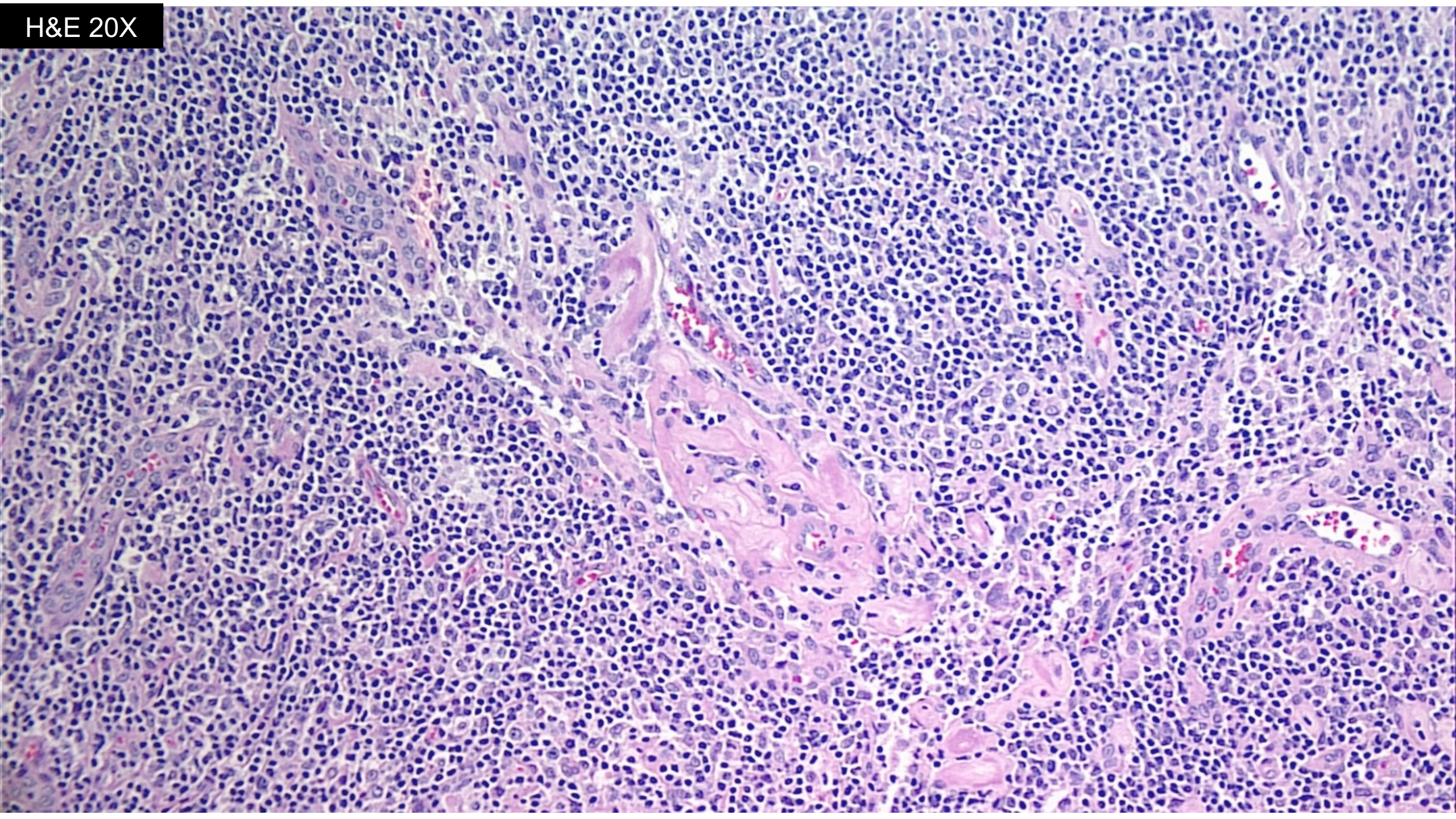
7/2023

Inguinal lymph node:
- Atypical lymphoid proliferation
- *TET2* mutation (VAF 10%)

10/2023

Left axillary lymph node:


H&E 4X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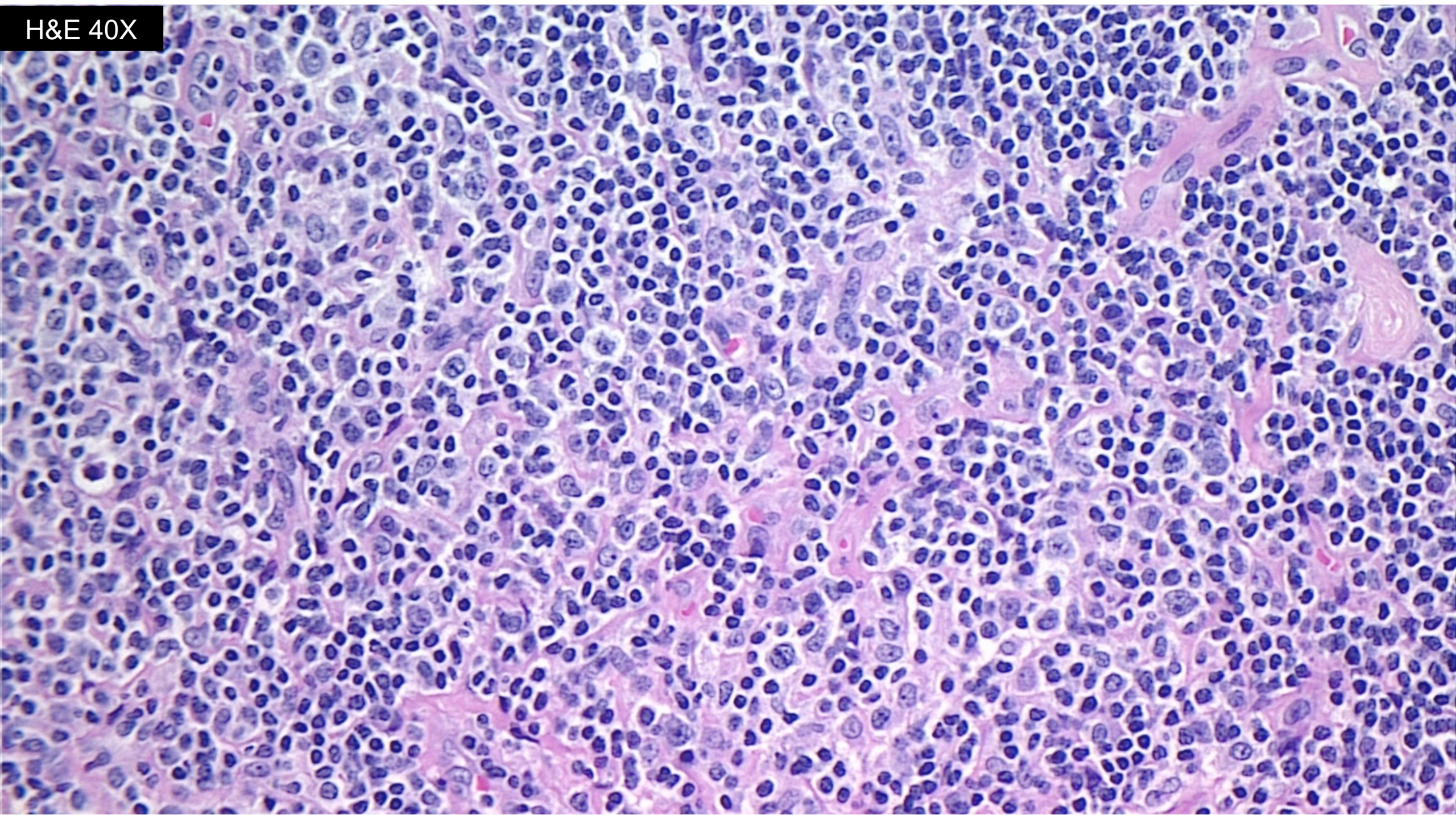
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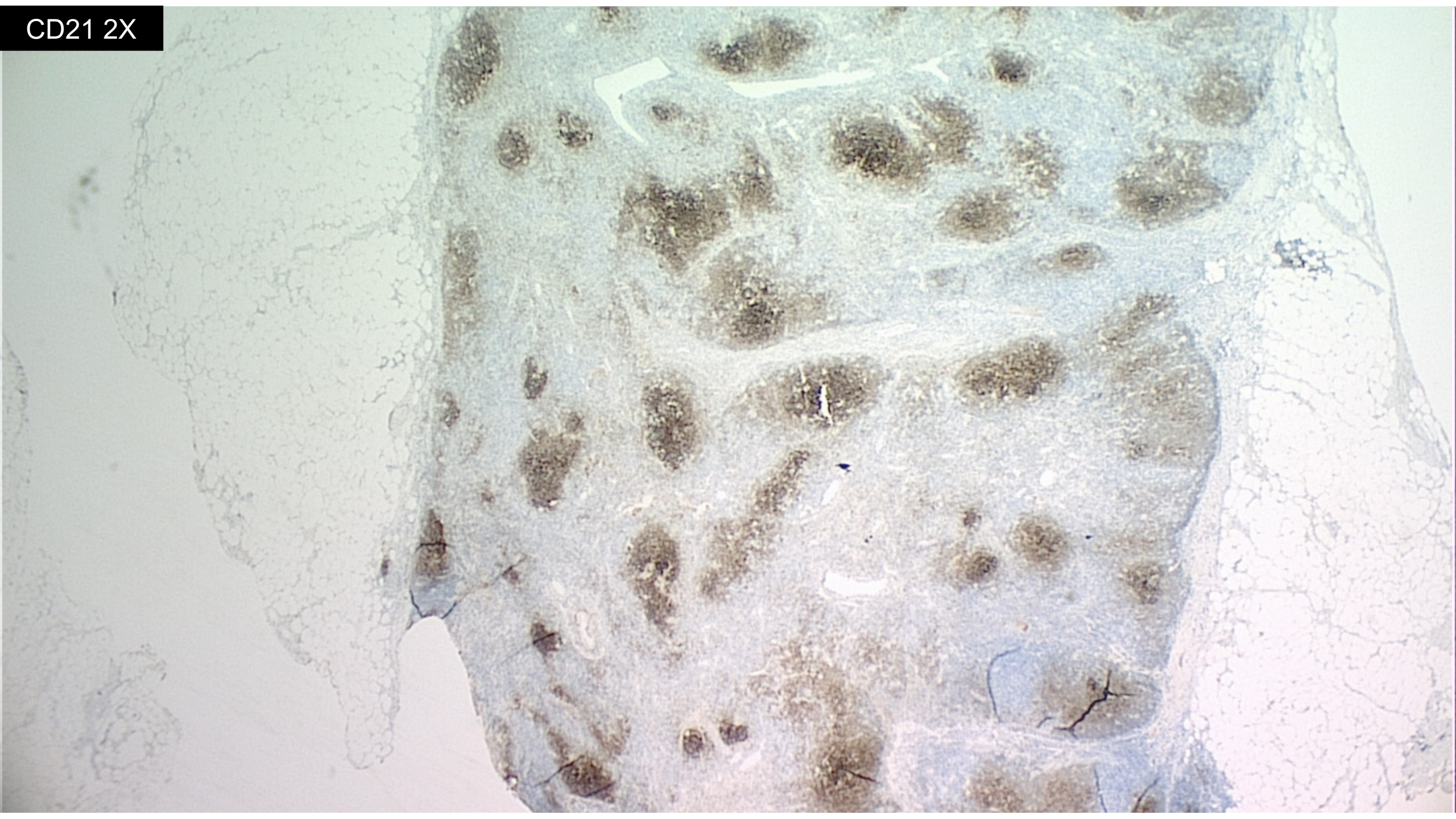
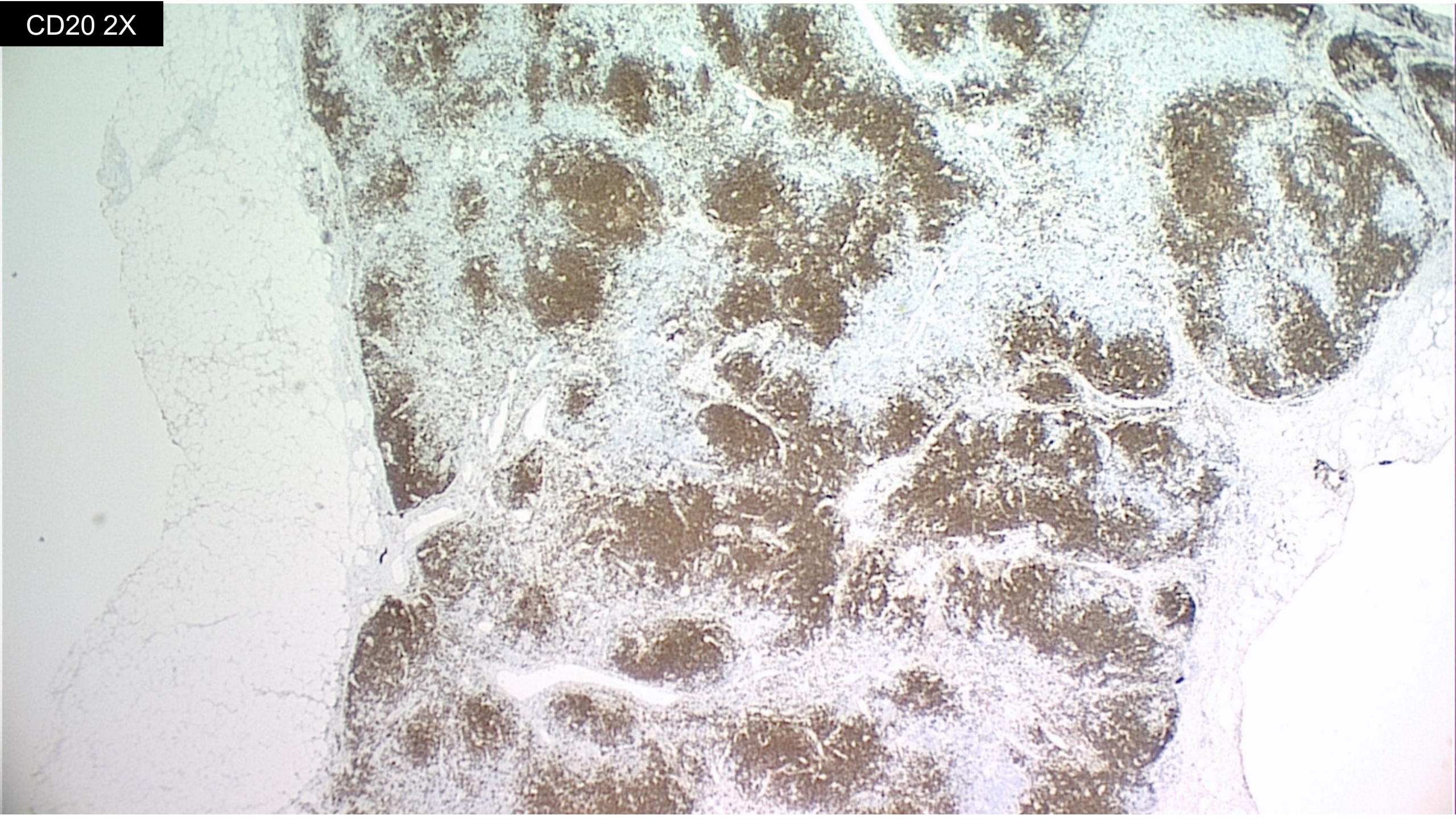
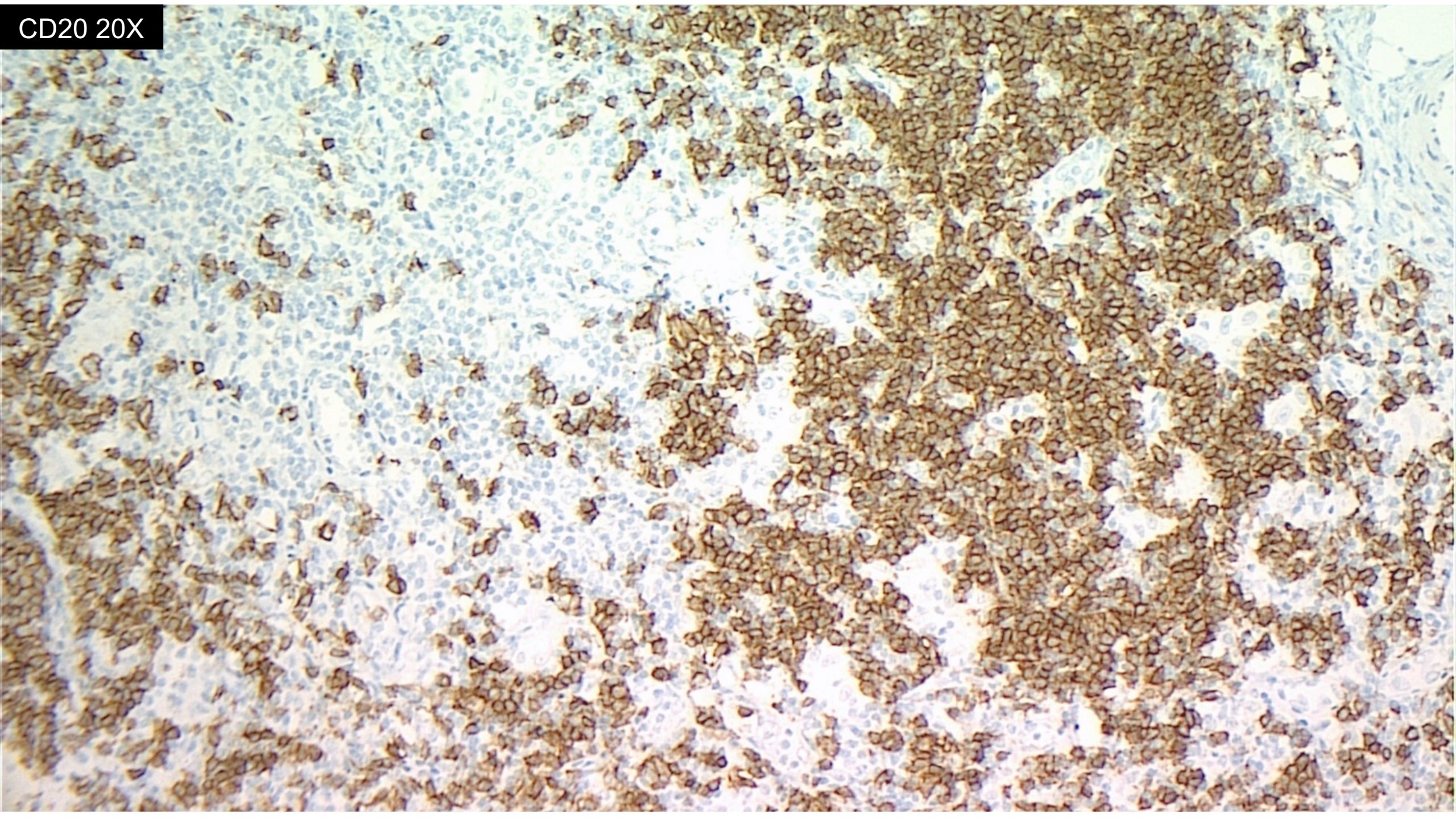
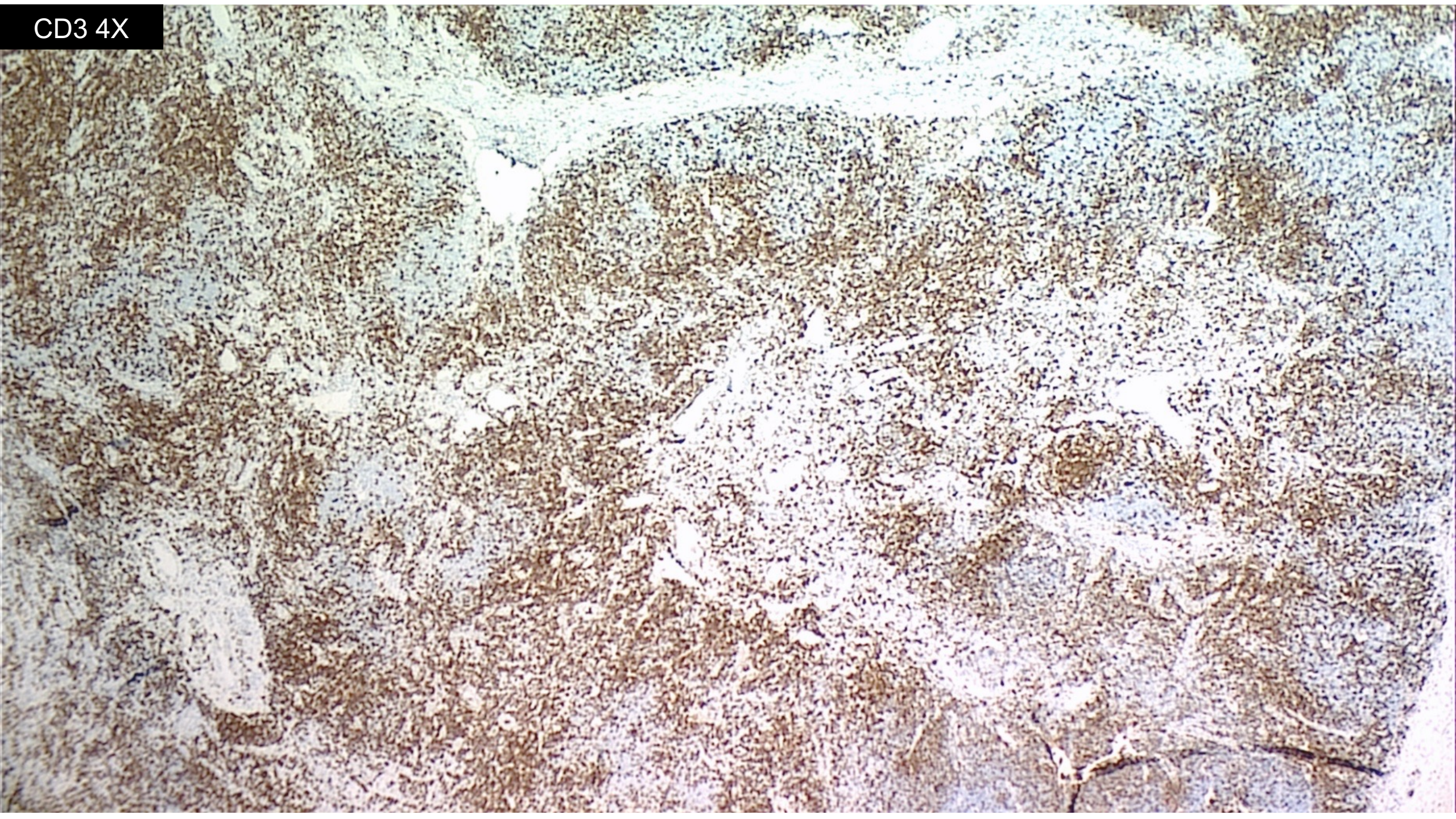
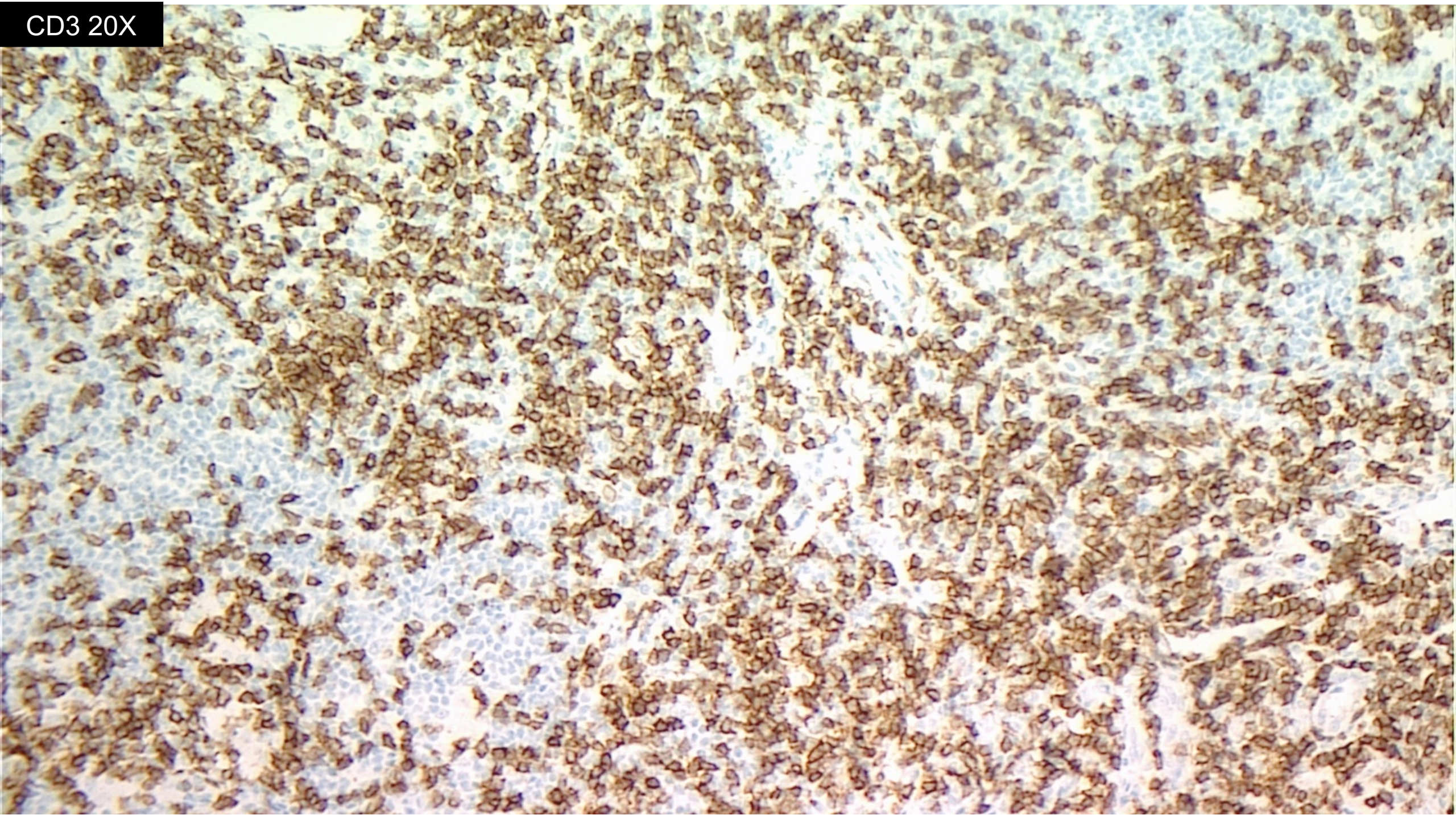
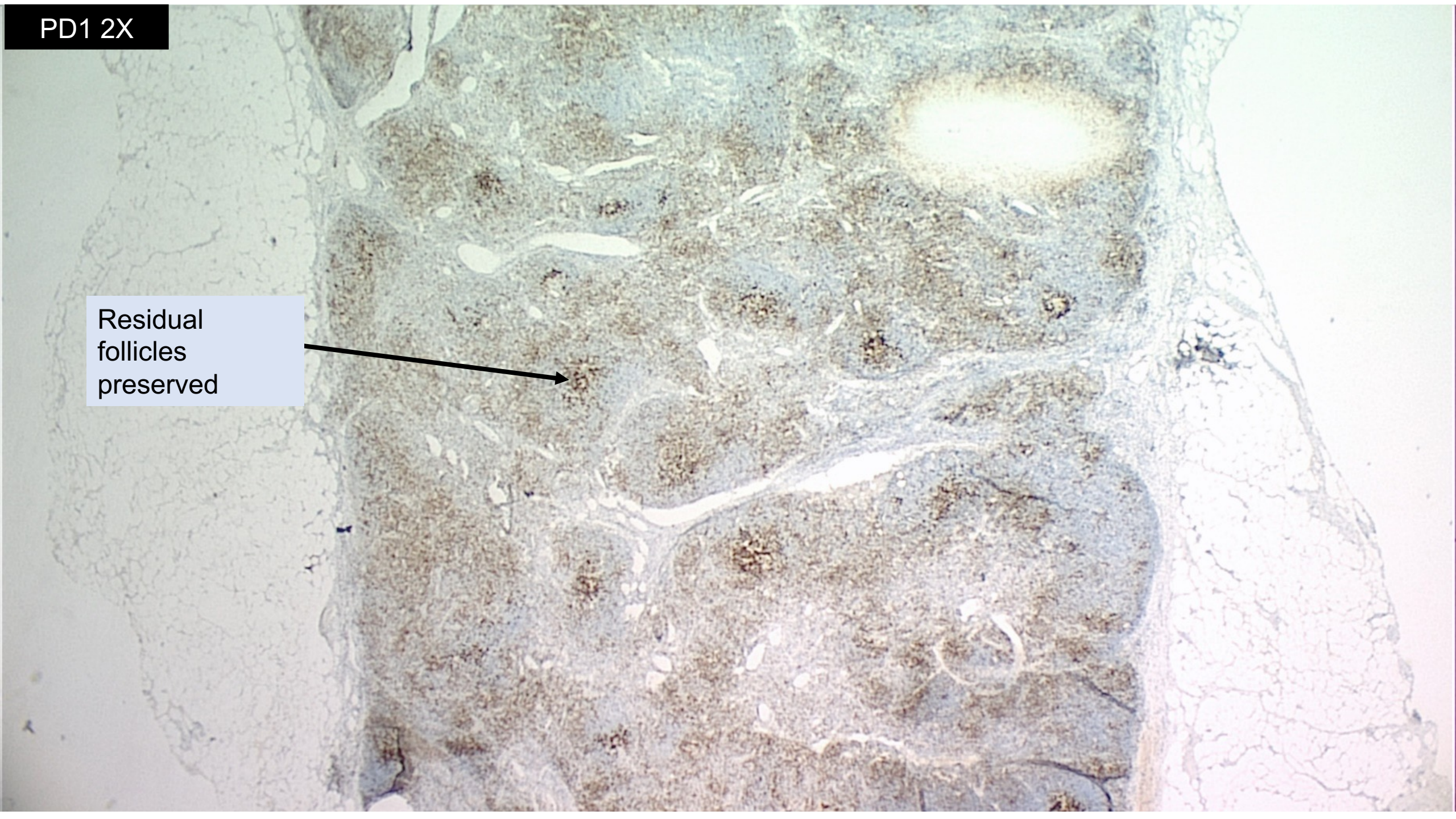

CD21 2X


CD20 2X


CD20 20X


CD3 4X


CD3 20X


PD1 2X
Residual follicles preserved

Left axillary lymph node, excisional biopsy

Morphology

Largely preserved architecture

Occasional immunoblasts

Immunostains

- CD20+ B cells in follicles (spatially appropriate)
- CD4+ T cells >= CD8+ T cells (normal)
- Pan T cell math : CD3=CD5=CD2>=CD7
- Rare EBV+ cells only

Ancillary studies

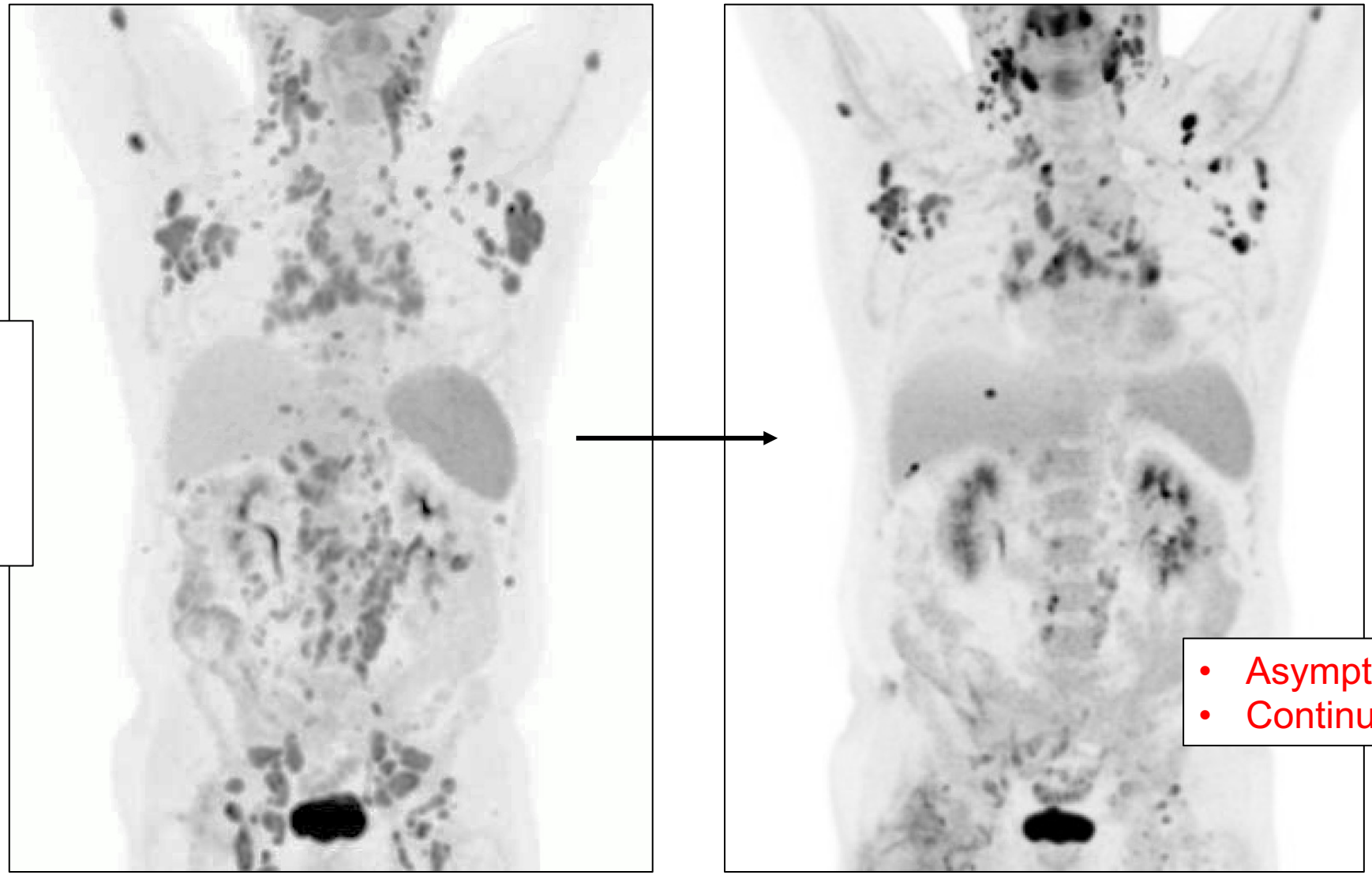
Normal Karyotype & no T-cell clonality (PCR)
NGS Panel: *TET2* c.623del, p.P208Lfs*42 (VAF: 7%)

FINAL DIAGNOSIS: Atypical lymphoid proliferation with scattered EBV+ cells

Case 1

4 months after presenting

7 months after presenting



L axillary node:
- Atypical lymphoid proliferation with scattered EBV cells
- *TET2* mutation

- Asymptomatic
- Continue observing

Case 1

- About 10 months after initial presentation he had worsening lymphadenopathy, fatigue, and fevers.

- WBC: 6.8
- Hb 11.5
- Platelets: 89

- Creatinine: 0.9
- LDH: 590
- Uric acid: 2.3

- EBV PCR: 61,700 IU/mL

Admitted for expedited work-up

Pathology Timeline

4/2023

Inguinal lymph node:
- Atypical lymphoid proliferation

7/2023

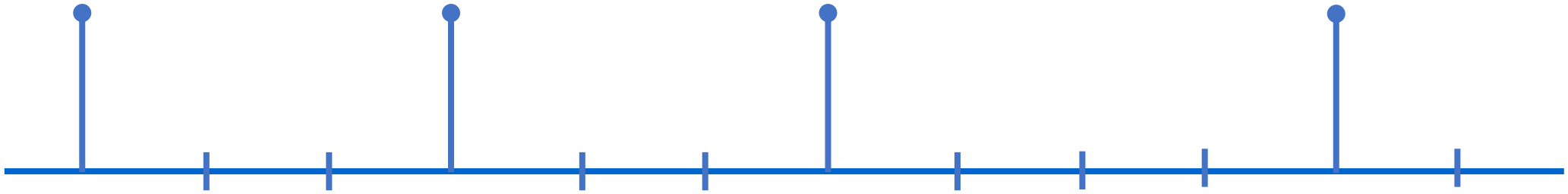
Inguinal lymph node:
- Atypical lymphoid proliferation
- *TET2* mutation (VAF 10%)

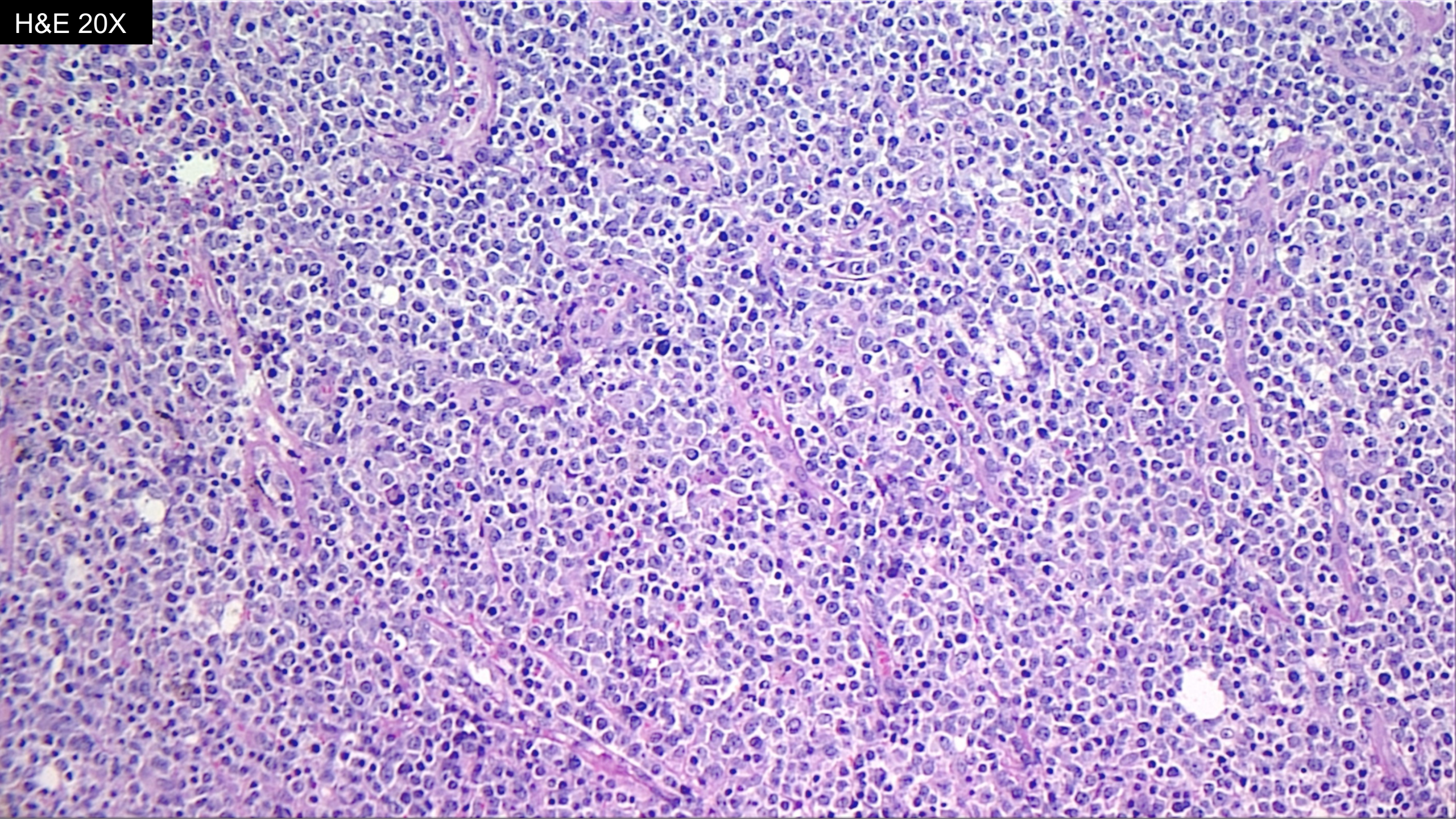
10/2023

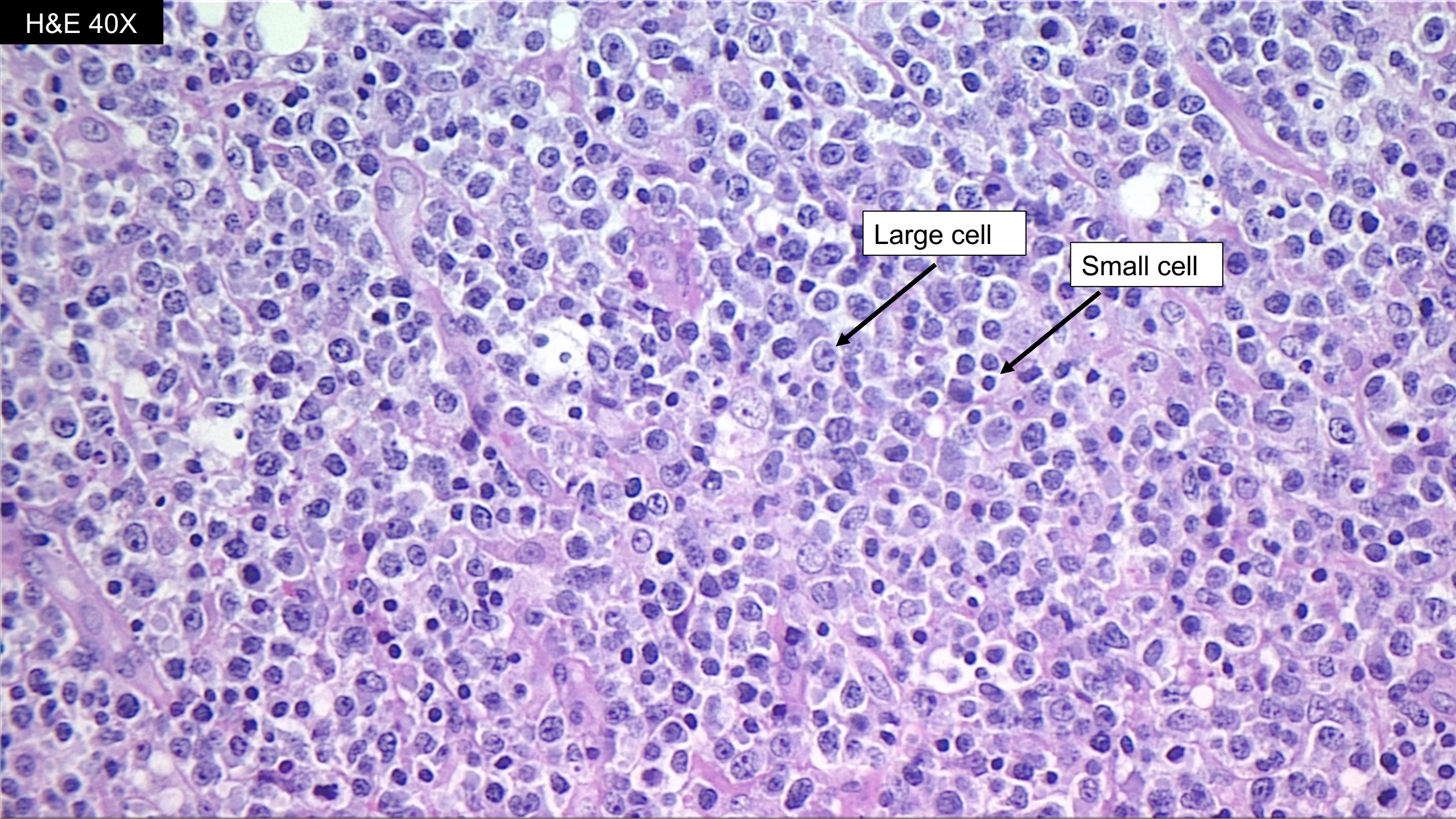
Left axillary lymph node:
- Atypical lymphoid proliferation
- *TET2* mutation (VAF 10%)
- Karyotype normal

2/2024

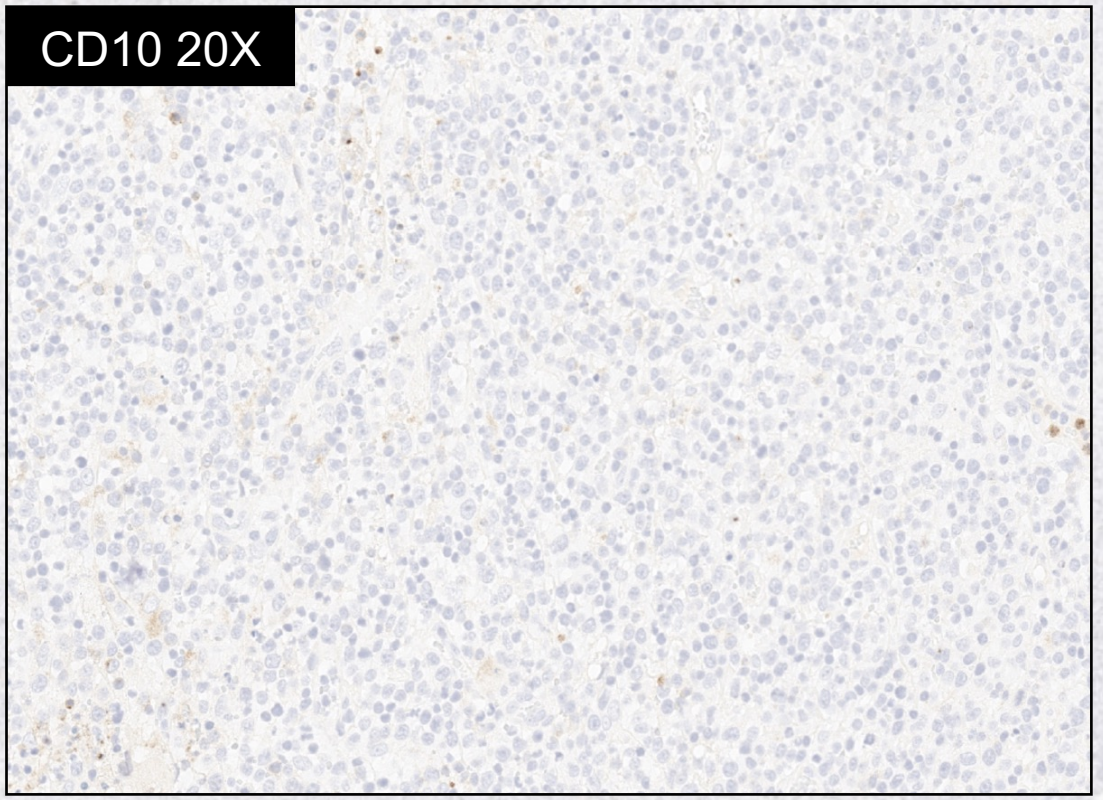
Right axillary lymph node and bone marrow biopsy

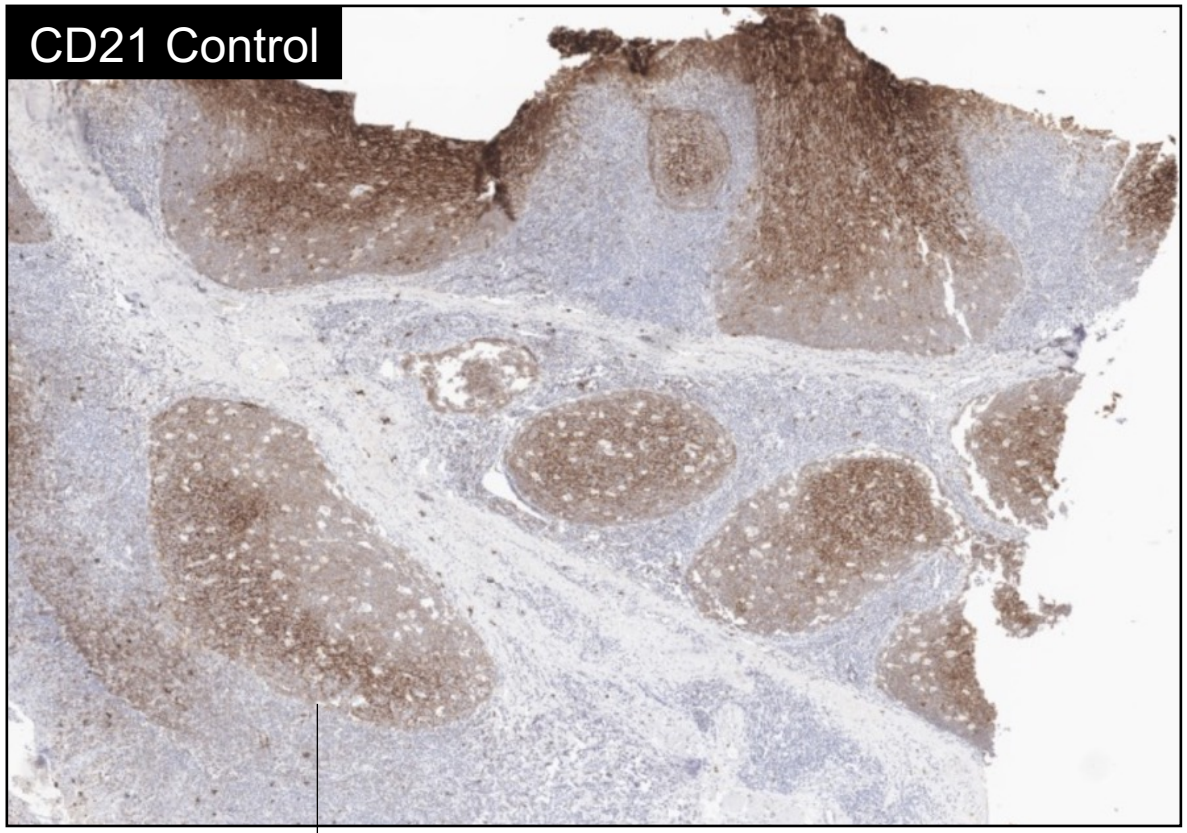



H&E 20X

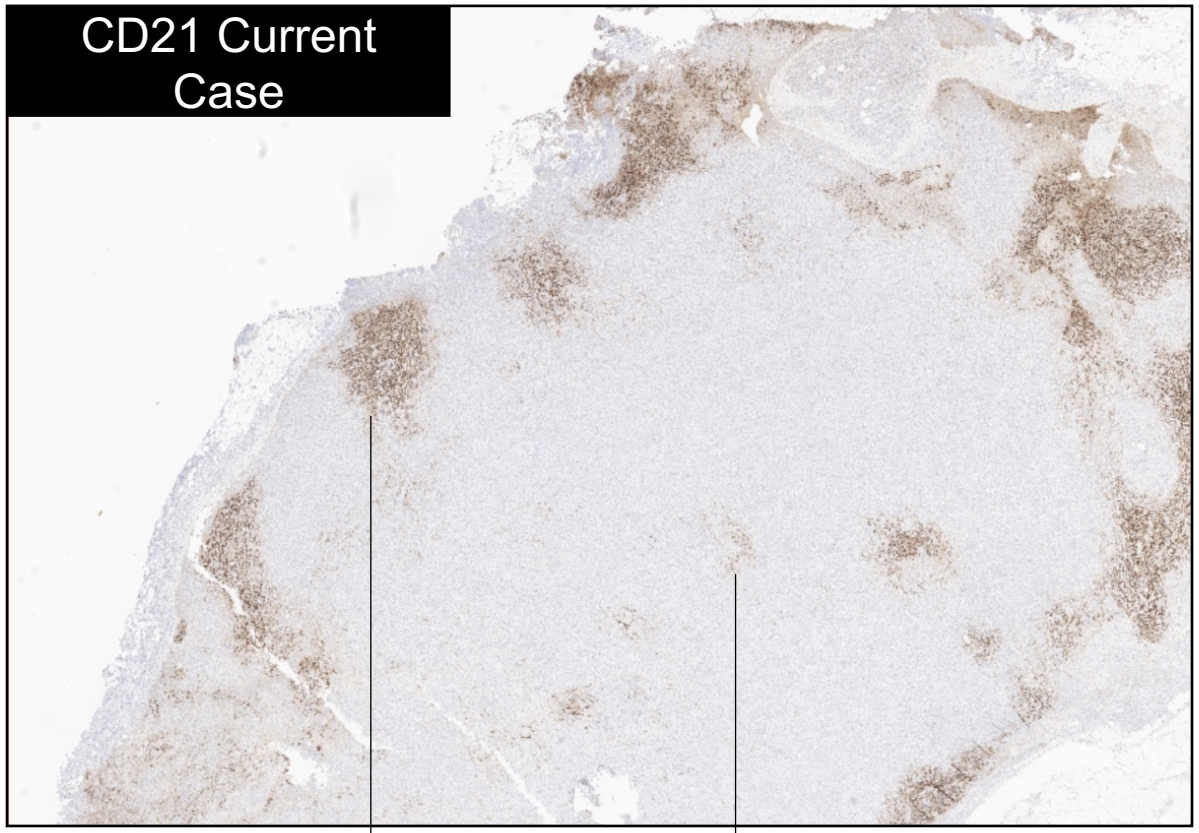

H&E 40X
Large cell
Small cell

CD10



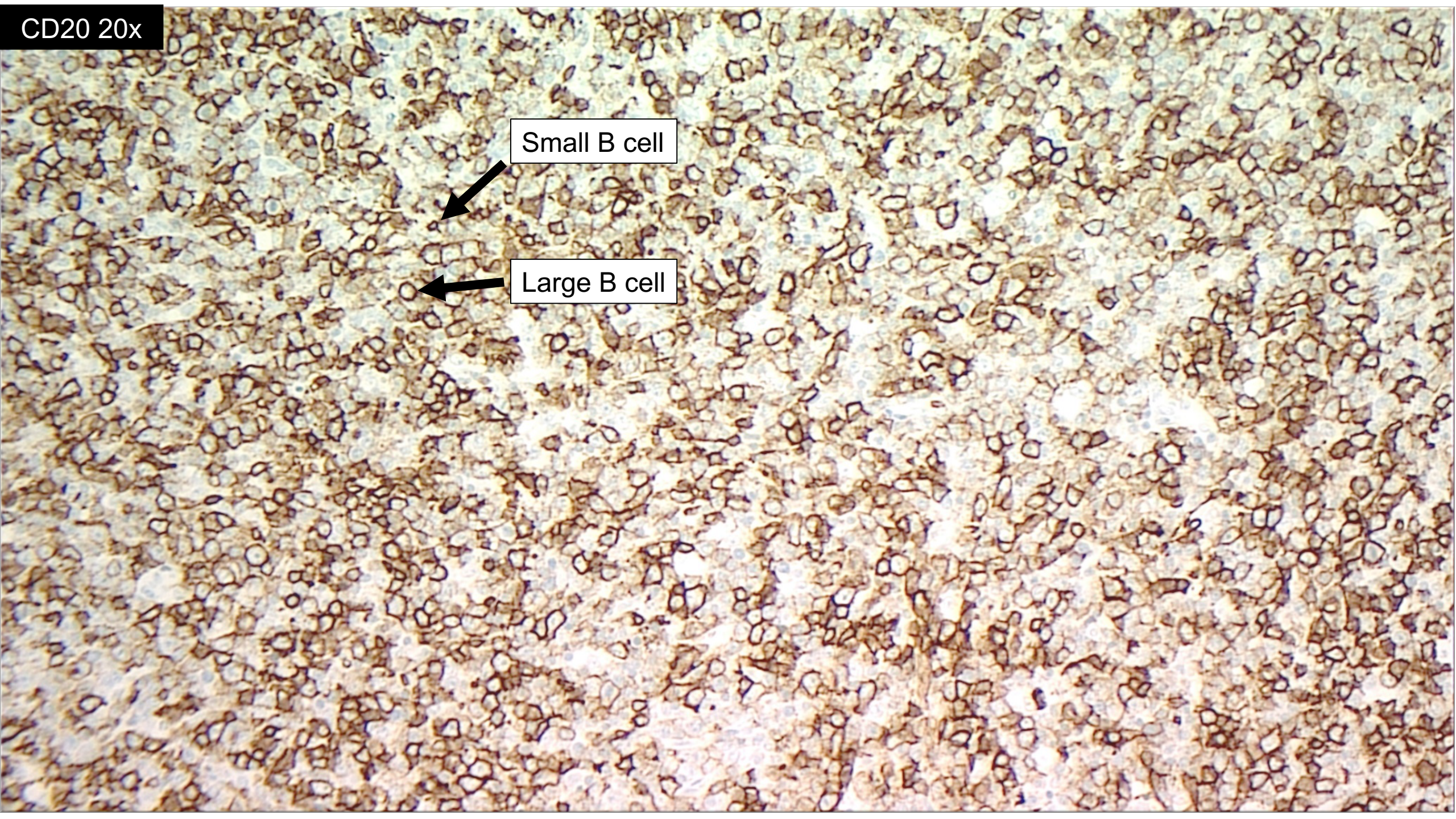


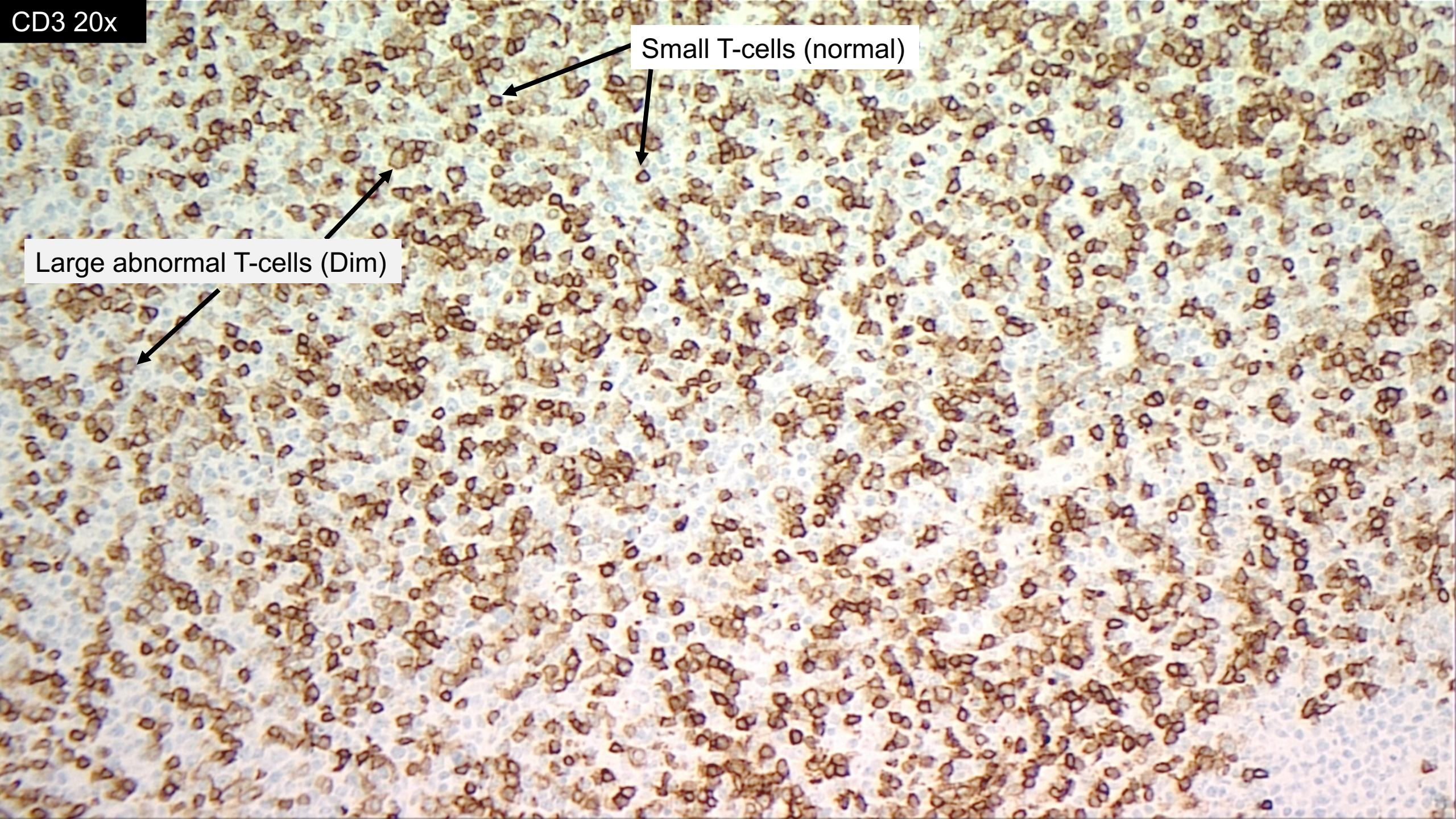
Nice rounded (“well-behaved”) CD21 pattern

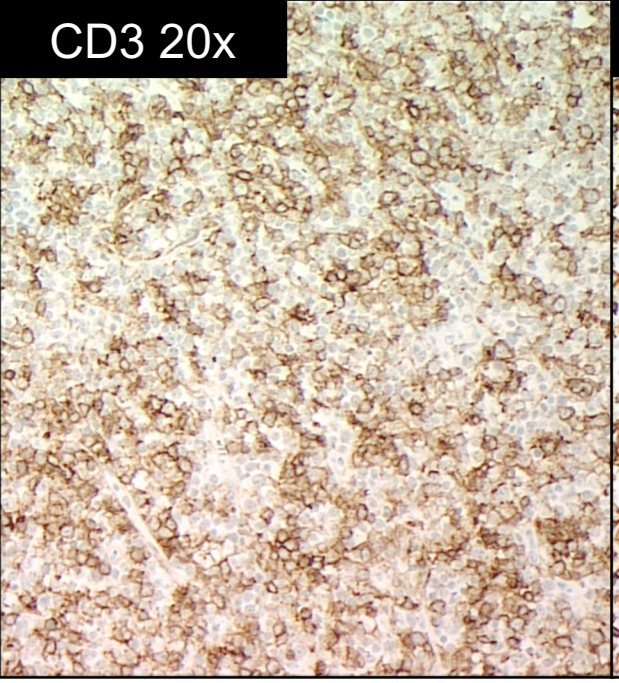


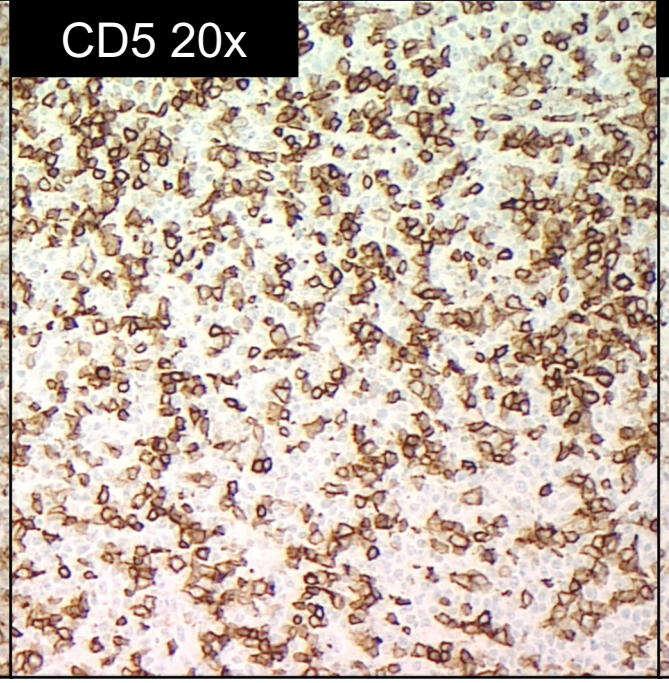
“Unruly” CD21 pattern

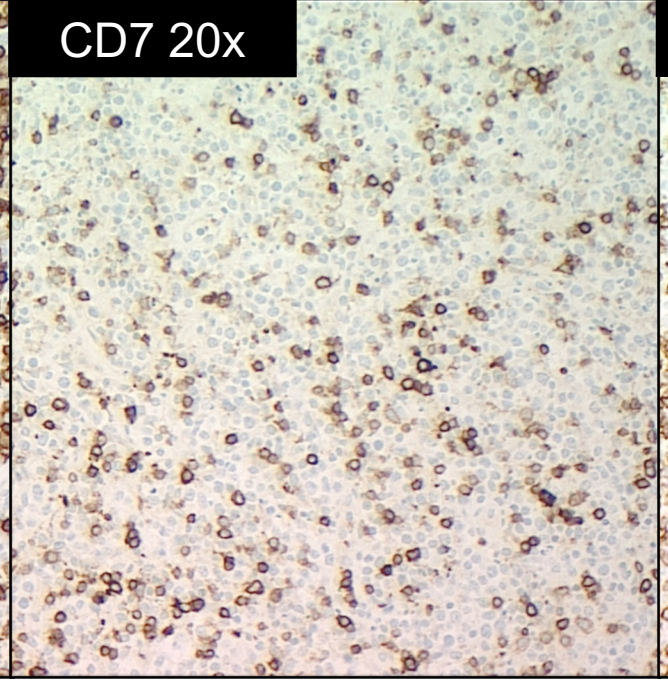
CD21 outside follicles

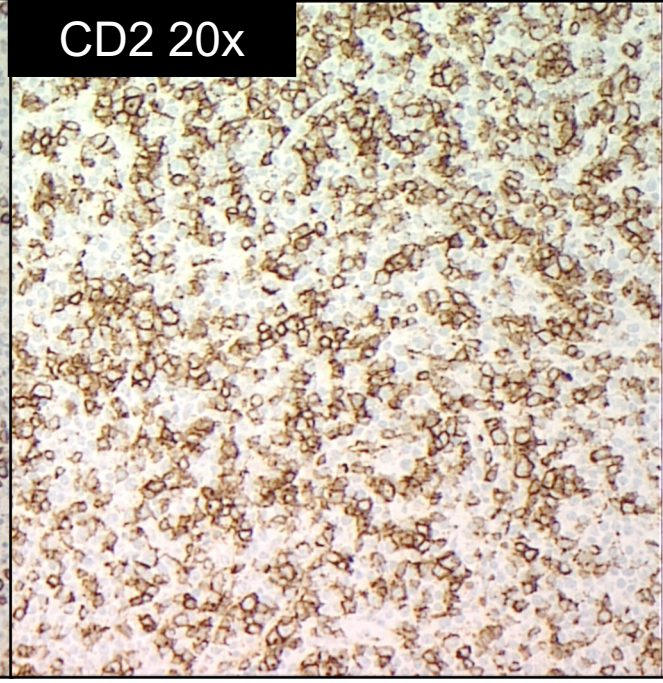

CD20 20x
Small B cell
Large B cell

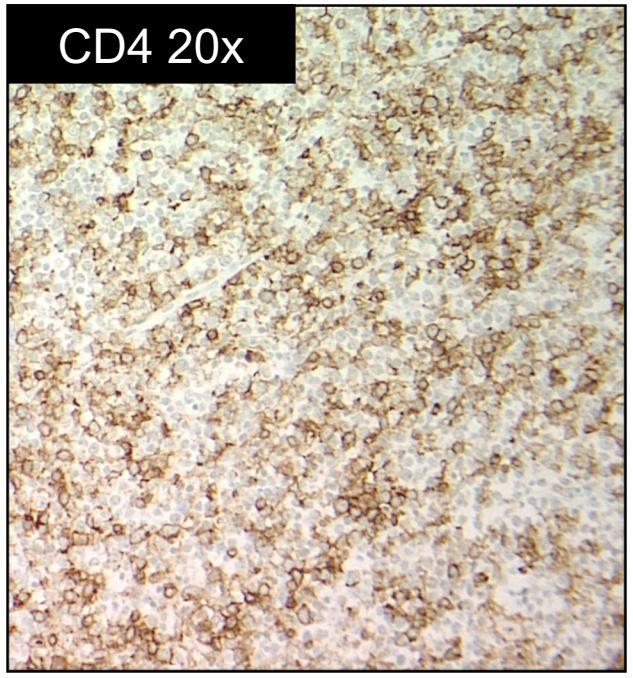

CD3 20x
Small T-cells (normal)
Large abnormal T-cells (Dim)

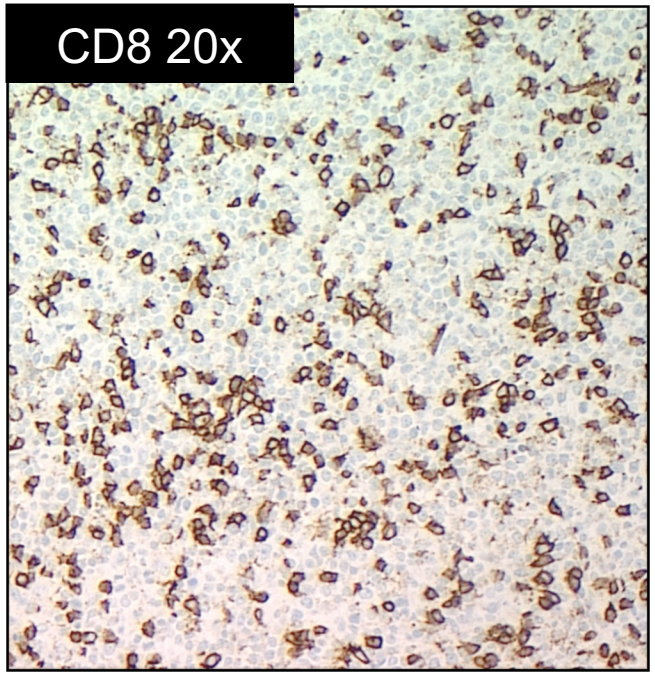






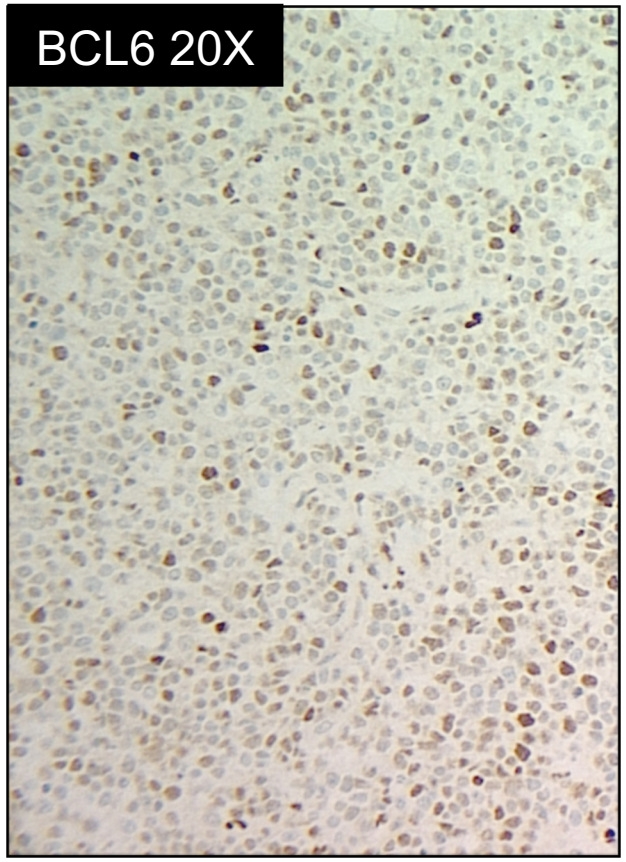


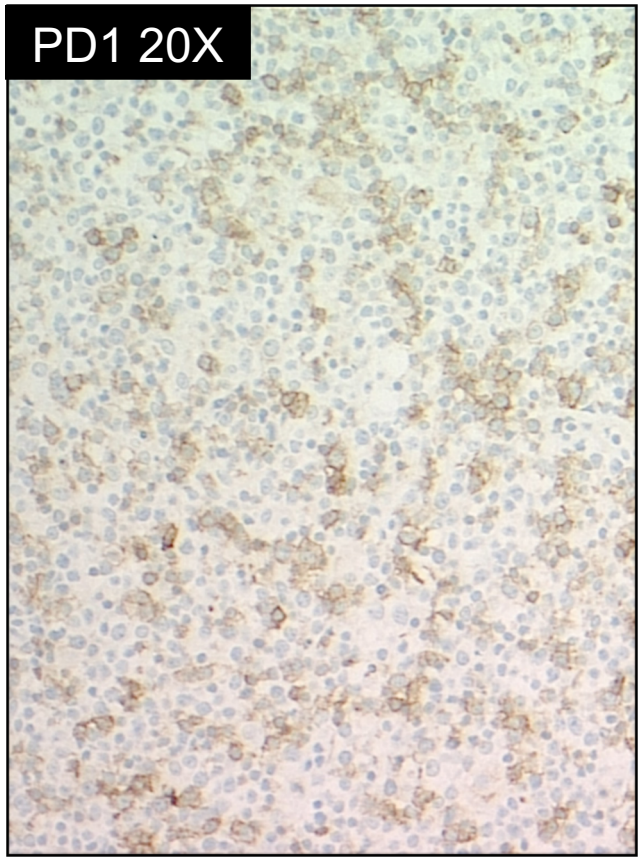


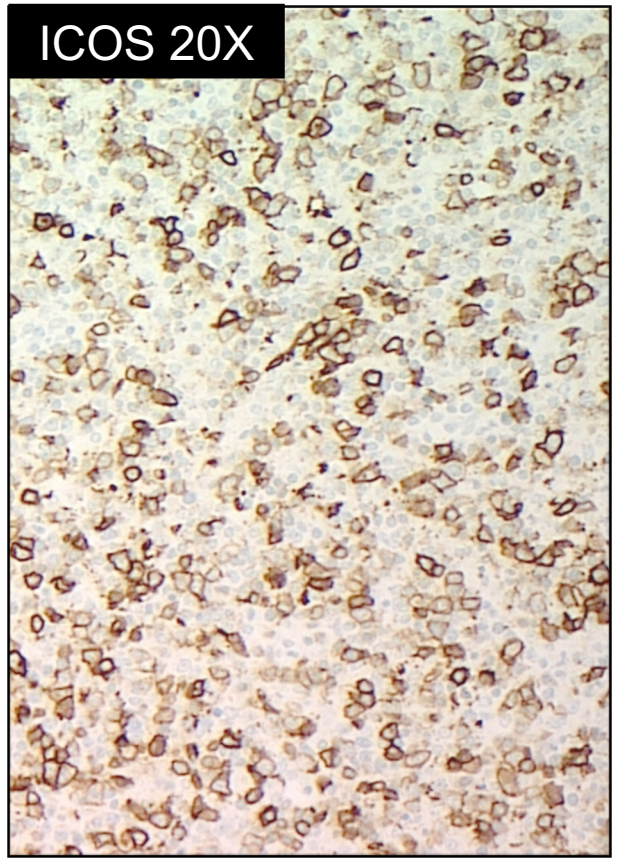


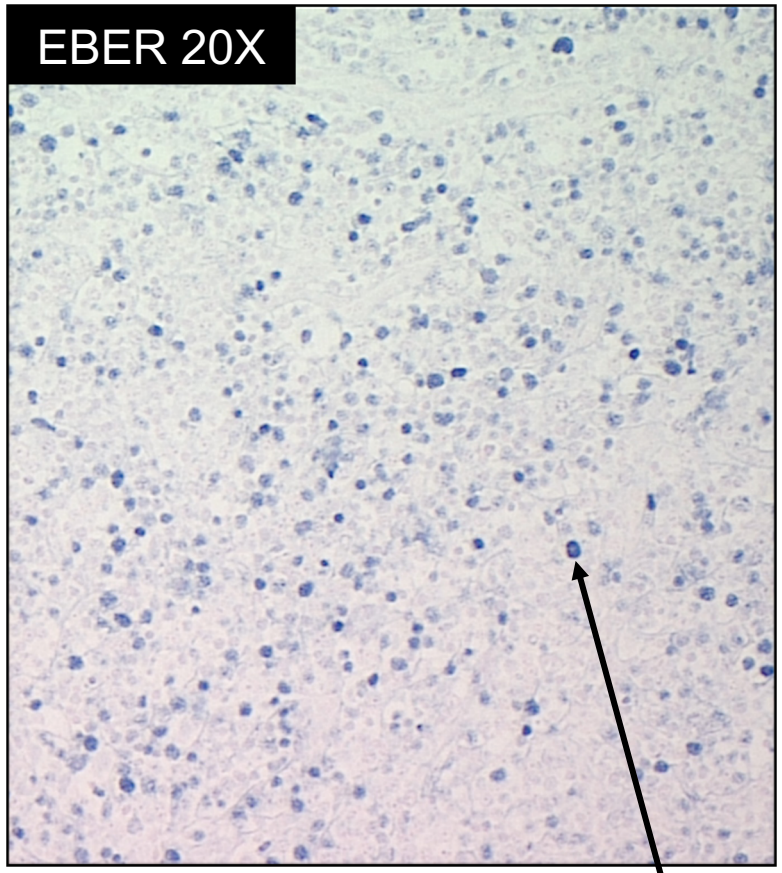
CD3	**Dim +**
CD5	**Uniform +**
CD7	**Loss**
CD2	**Uniform +**
CD4	**Dim +**
CD8	**Negative in lymphoma cells**

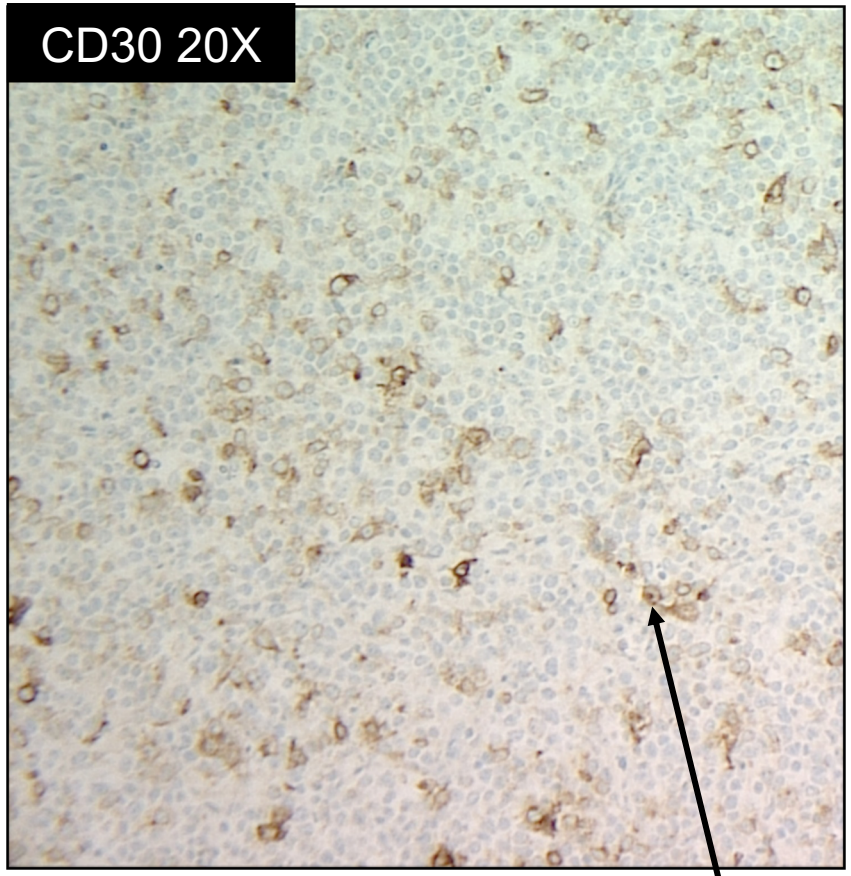
Follicular helper T-cell markers

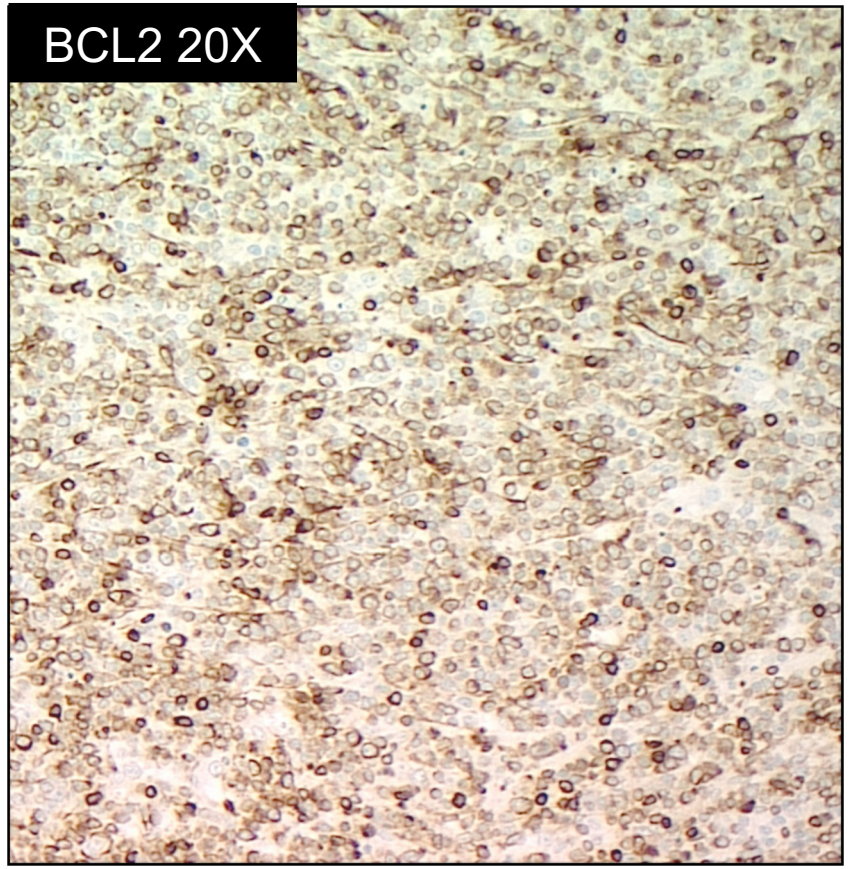












Too many EBV-infected B-cells

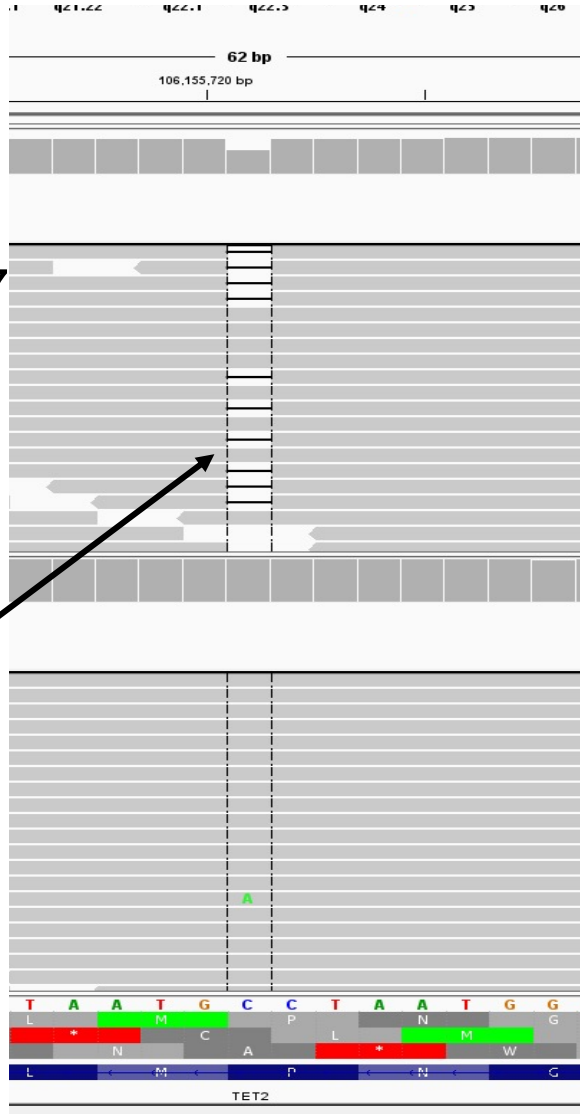
Likely in B-cells

Right axillary lymph node, excisional biopsy

Diagnosis: Composite EBV+ diffuse large B cell lymphoma arising within angioimmunoblastic T-cell lymphoma

Right axillary lymph node, excisional biopsy

- **Large B cell component (60% of the large cells):**
    - CD20+ and CD10 negative. EBER-ISH positive in 80%
- **Medium–large T lymphoid component (40% of the tissue):**
    - Positive for CD3 (dim), CD5 (dim), CD2, CD4, with loss of CD7
    - Positive PD1 (follicular helper T-cell marker)
- **Karyotype:**
    - -48,XY,+3,+5[cp3]/46,XY[18]
- **NGS:**
    - *TET2* c.4960C>T, p.Q1654* (VAF: 10%)
    - *TET2* c.623del, p.P208Lfs*42 (VAF: 32%)



Pathology Timeline

4/2023

Inguinal lymph node:
- Atypical lymphoid proliferation

7/2023

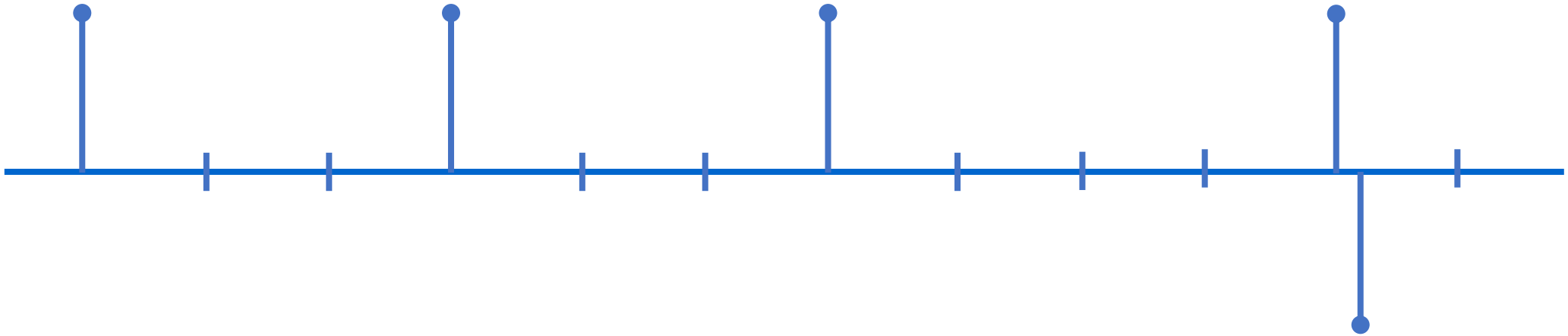
Inguinal lymph node:
- Atypical lymphoid proliferation
- *TET2* mutation (VAF 10%)

10/2023

Left axillary lymph node:
- Atypical lymphoid proliferation
- *TET2* mutation (VAF 10%)
- Karyotype normal

2/2024

Right axillary lymph node:
- EBV+ DLBCL and AITL
- *TET2* (VAF 10%)
- *TET2* (VAF 32%)
- Karyotype: +3, +5



Bone marrow biopsy:
- EBV+ DLBCL and AITL
- Karyotype: +X, +1q42, +8p23), del10p15

WHO Revised 4th	ICC	WHO 5th
“AITL and other nodal lymphomas of TFH origin”	**“Follicular helper T-cell lymphoma”**	**Nodal T-follicular helper cell lymphomas (nTFHLs)”**
AITL	Angioimmunoblastic-type	nTFHL angioimmunoblastic-type (nTFHL-AI)
Follicular helper T-cell lymphoma	Follicular-type	nTFHL follicular-type (nTFHL-F)
PTCL with TFH phenotype	NOS	nTFHL not otherwise specified (nTFHL-NOS)

Case 1

ID: 70 year old male with HTN and prior PE with new EBV+ DLBCL (CD30+) with TFH lymphoma angioimmunoblastic type with *TET2* mutation. ECOG PS = 3

- Stage IV with marrow involvement and IPI = 4

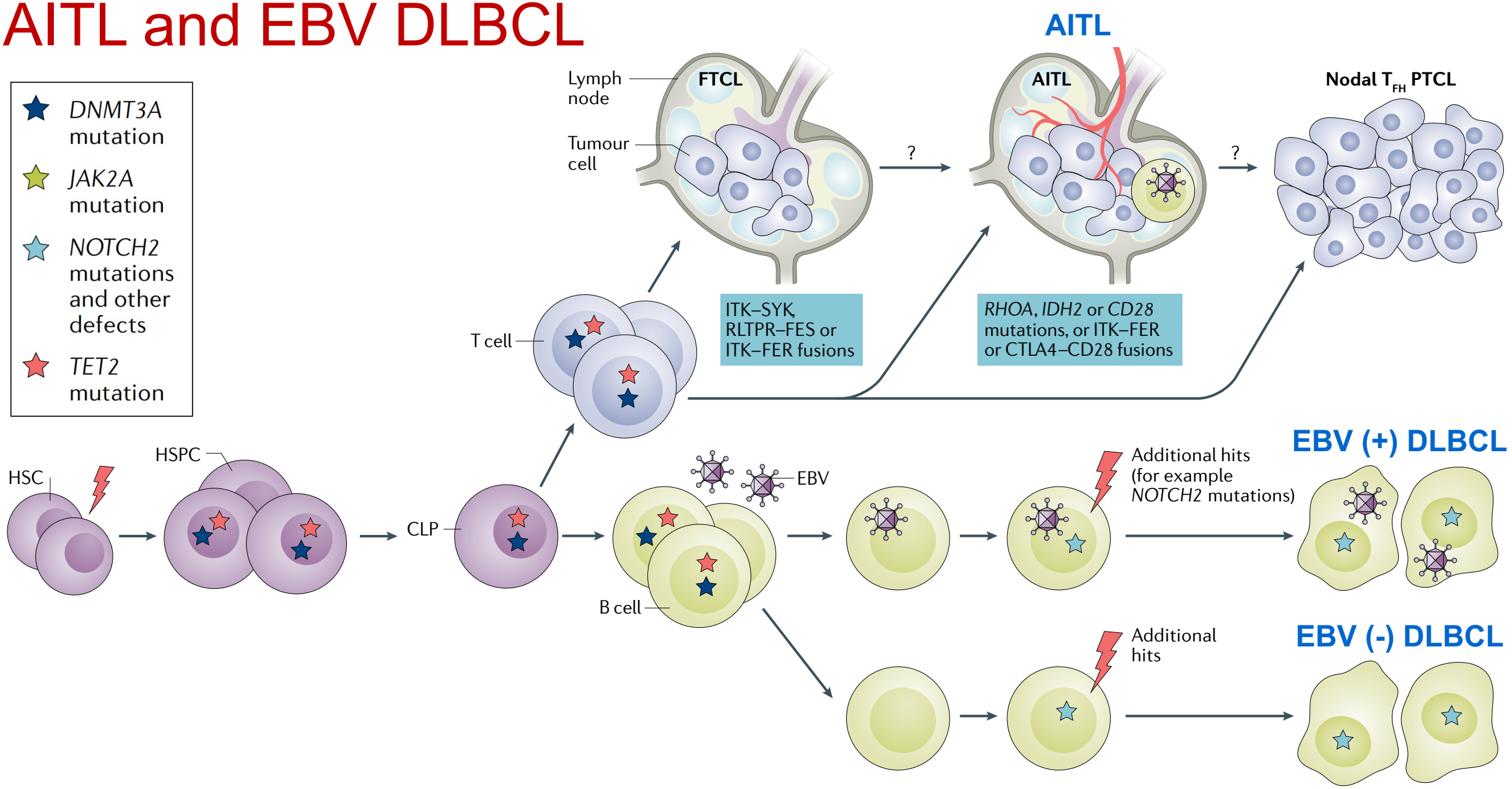
Treatment?

Case 1

ID: 70 year old male with HTN and prior PE with new EBV+ DLBCL (CD30+) with TFH lymphoma angioimmunoblastic type with *TET2* mutation. ECOG PS = 3

- Stage IV with marrow involvement and IPI = 4
- Treated with R-CHOP
- Current: Starting cycle 3 soon with plan for R-CHOP x6 cycles.

AITL and EBV DLBCL



Fiore D, et al. *Nat Rev Cancer* 2020; 20(6):323-342

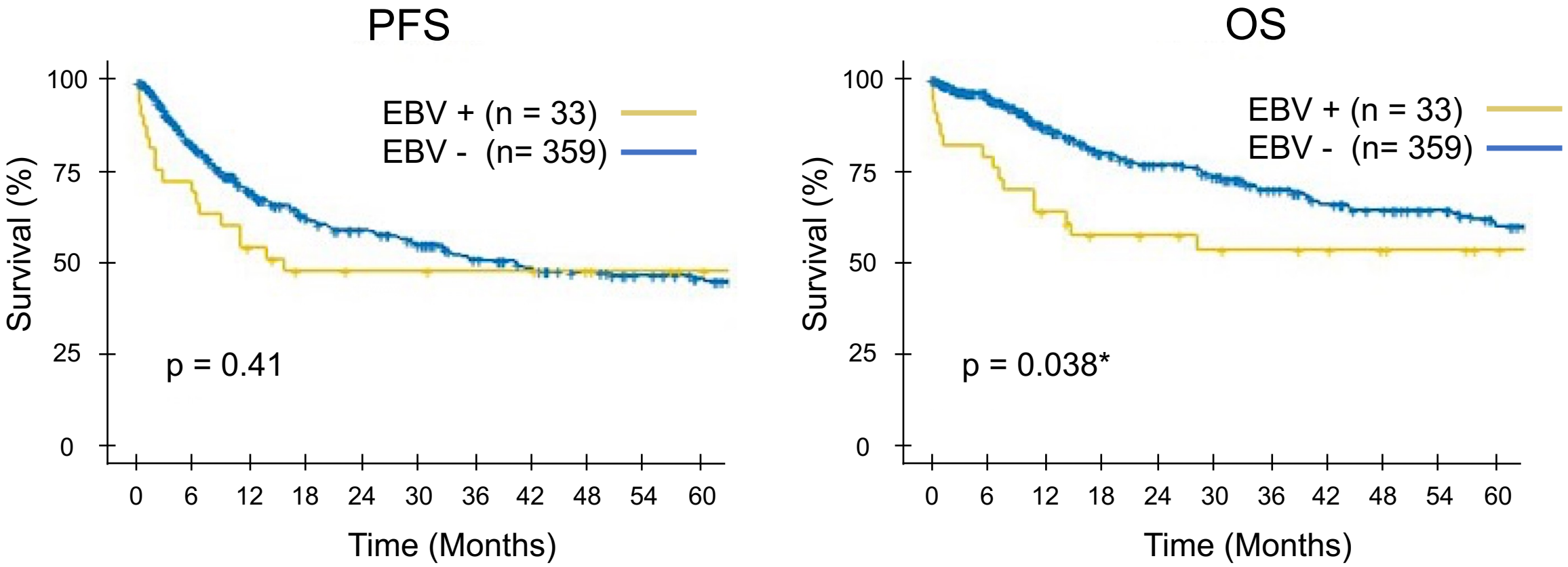
EBV+ DLBCL

- Recognized in WHO 5th and ICC
- Represents ~5% of DLBCL cases
  - Non-GCB, CD30+, PDL1+
- R-CHOP is standard treatment
- POLARIX (Polatuzumab-R-CHP): <5% were EBV DLBCL
- BV-R-CHP is investigational for CD30+ DLBCL

Bourbon E, et al. *Blood Adv* 2021; 5(16):3227-3239

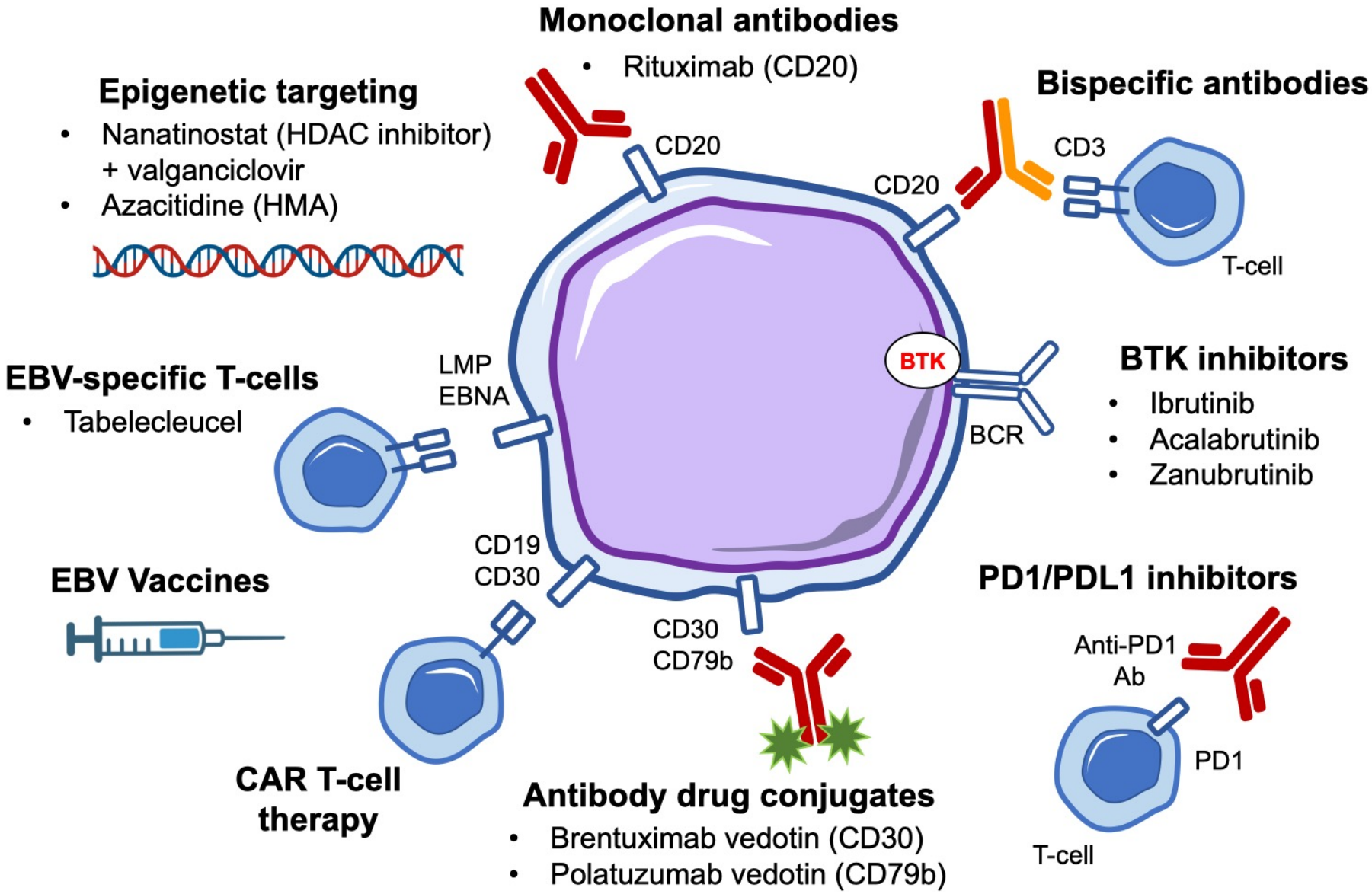
EBV+ DLBCL

Survival with curative intent treatment in DLBCL by EBV status (age >50)



Bourbon E, et al. *Blood Adv* 2021; 5(16):3227-3239

Targeting EBV Lymphomas



…ARS

ARS Question 3

EBV infection may be seen in which of the following lymphomas:

A. Classic Hodgkin lymphoma
B. Burkitt lymphoma
C. Plasmablastic lymphoma
D. All of the above

ARS Question 3

EBV infection may be seen in which of the following lymphomas:

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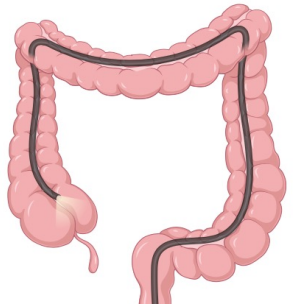
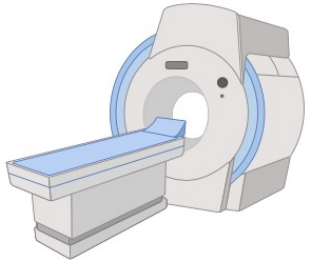
D. All of the above

Case 2

ID: 44-year-old male presenting with abdominal pain, constipation, and hematochezia.



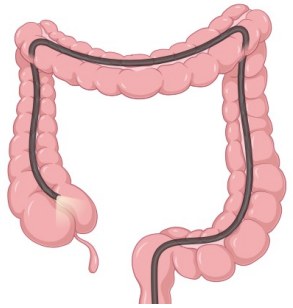
- Colonoscopy 3 months ago showed sessile serrated polyp and hemorrhoids.



- CT abdomen/pelvis showed 20 x 11 cm mesenteric mass and separate 8 x 5 cm mass, and hepatosplenomegaly.

Case 2

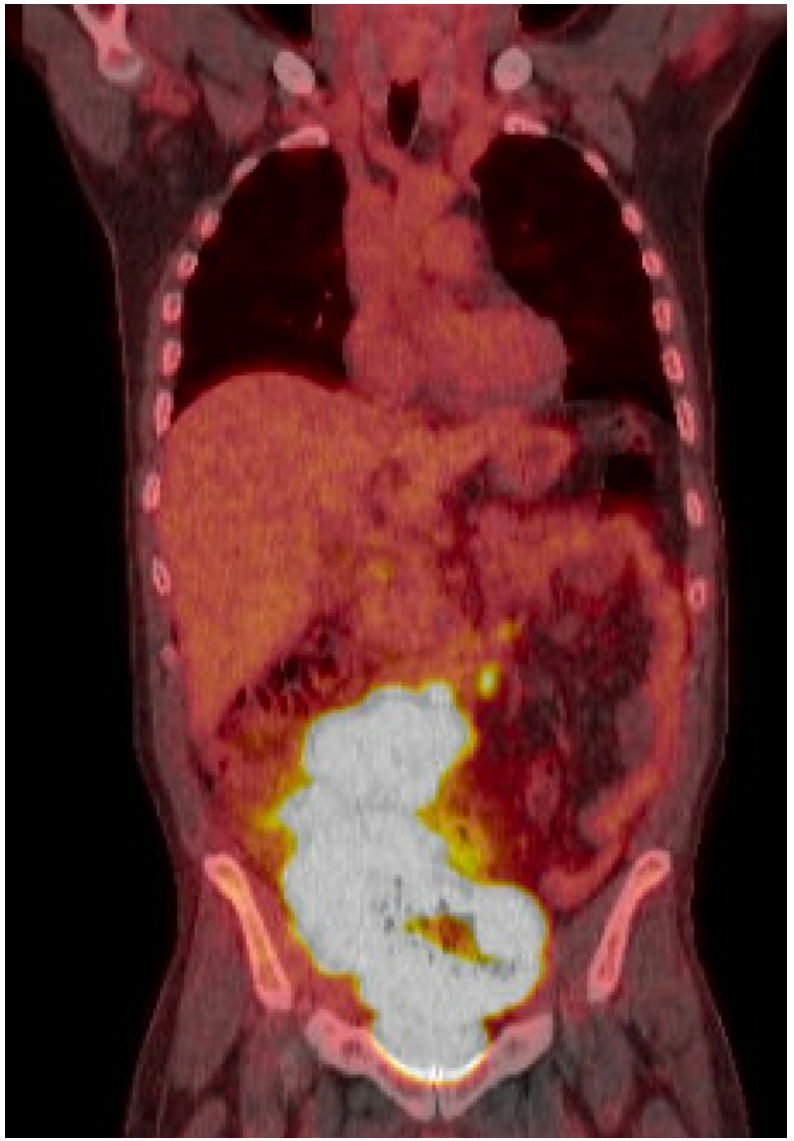
ID: 44-year-old male presenting with abdominal pain, constipation, and hematochezia.



- Repeat colonoscopy with biopsy showed:
  - ‘High-grade B-cell lymphoma with *MYC* rearrangement consistent with Burkitt Lymphoma’

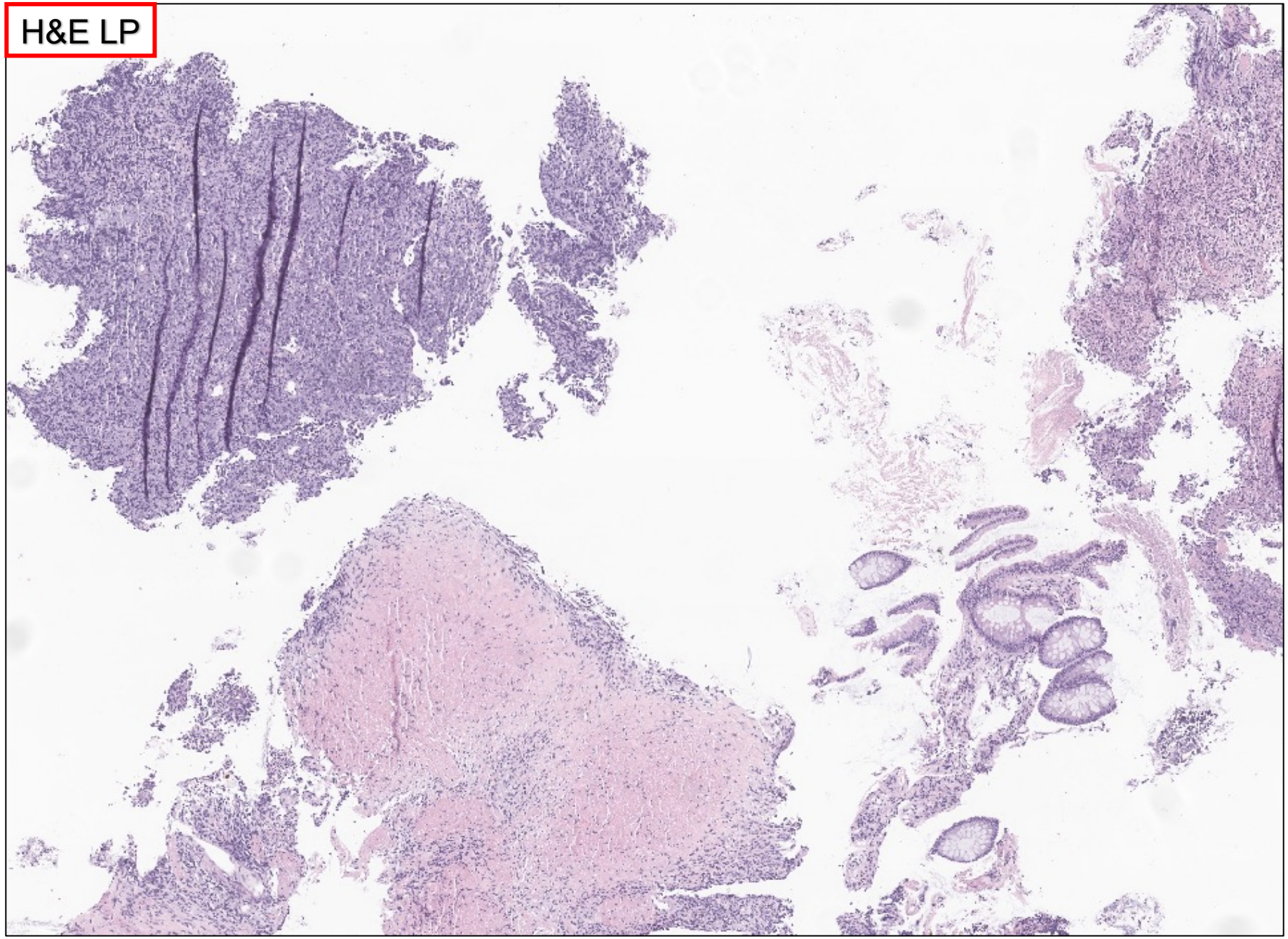
Case 2

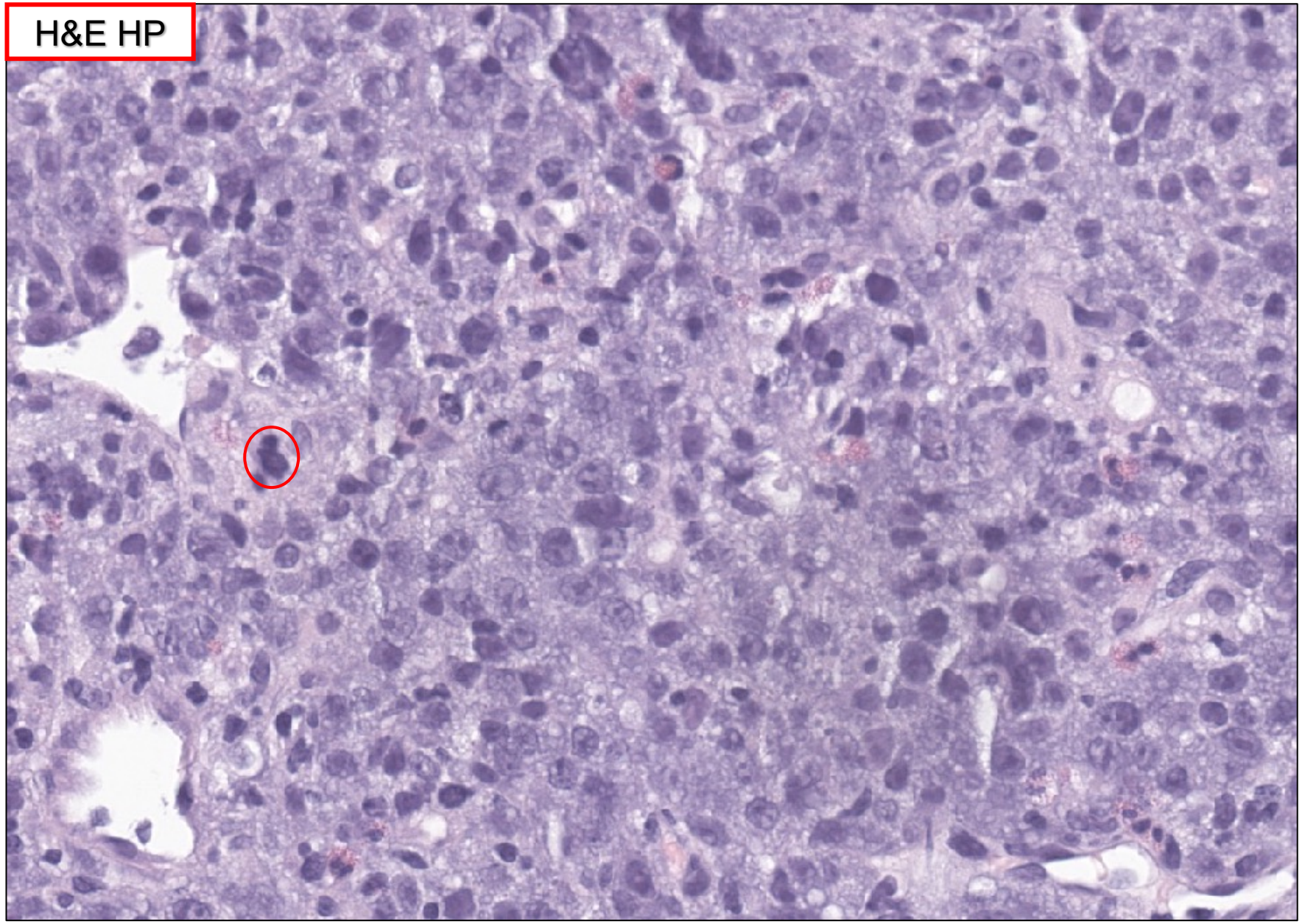
ID: 44-year-old male presenting with bulky abdominal lymphadenopathy.



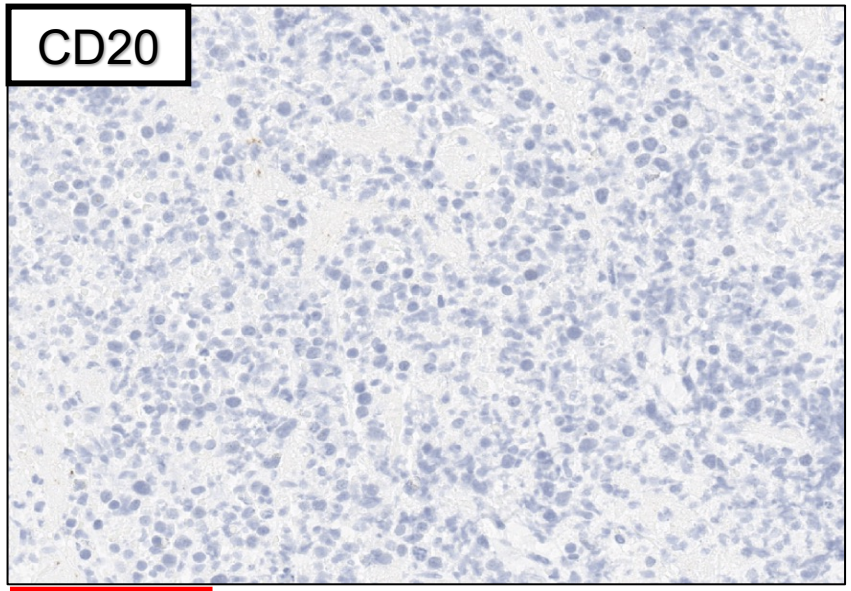
- Burkitt lymphoma.
- HIV negative. LDH in upper 200s
- Stage IV with bowel involvement.
- Starts DA-EPOCH-R + IT MTX

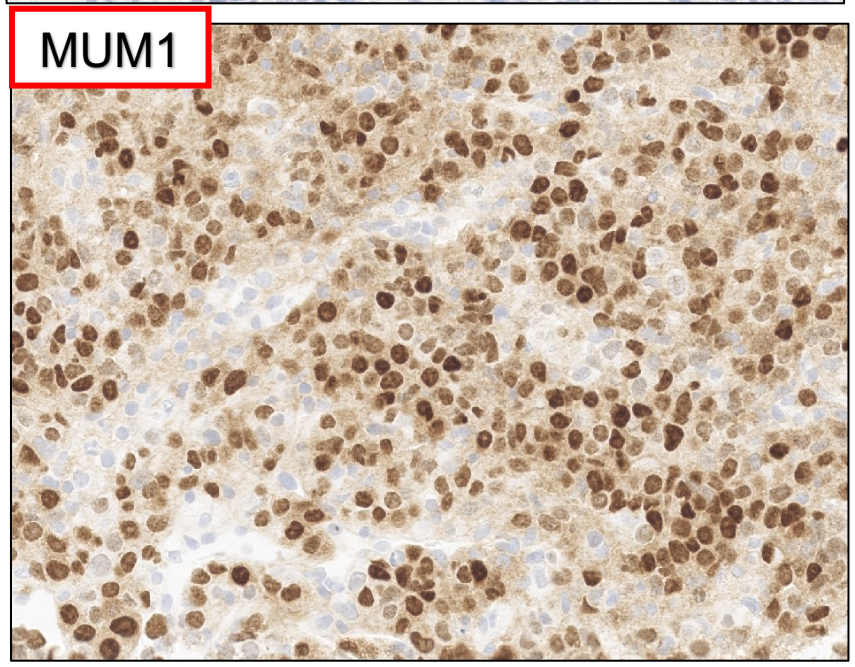
Second opinion consult/Pathology Review

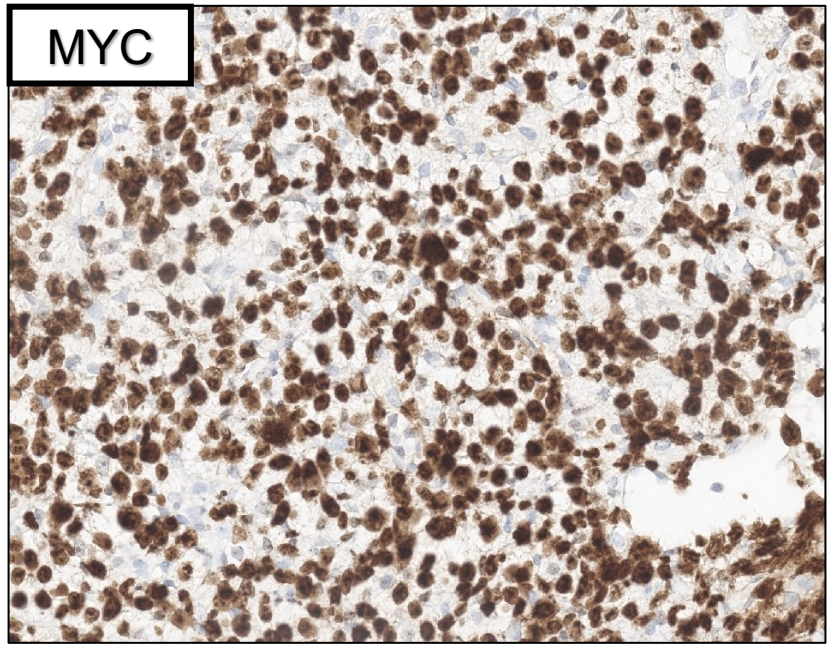

H&E LP

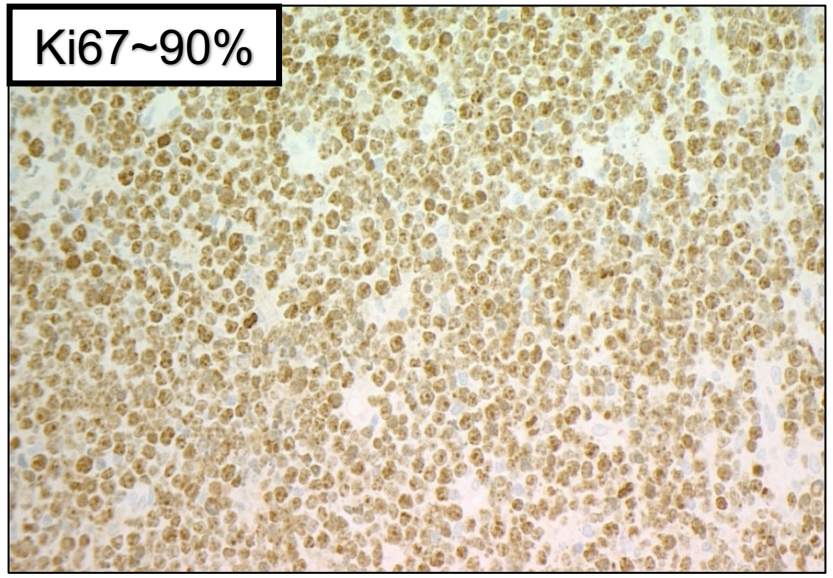

H&E HP

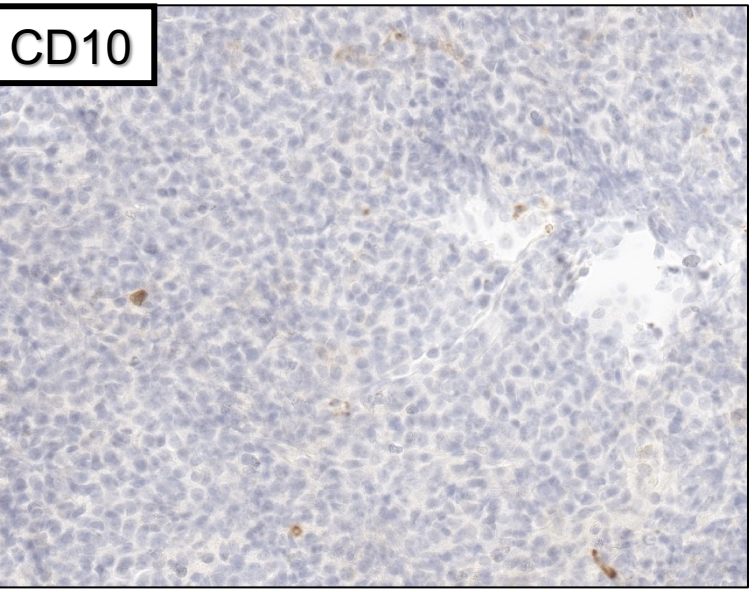
Immunochemistry

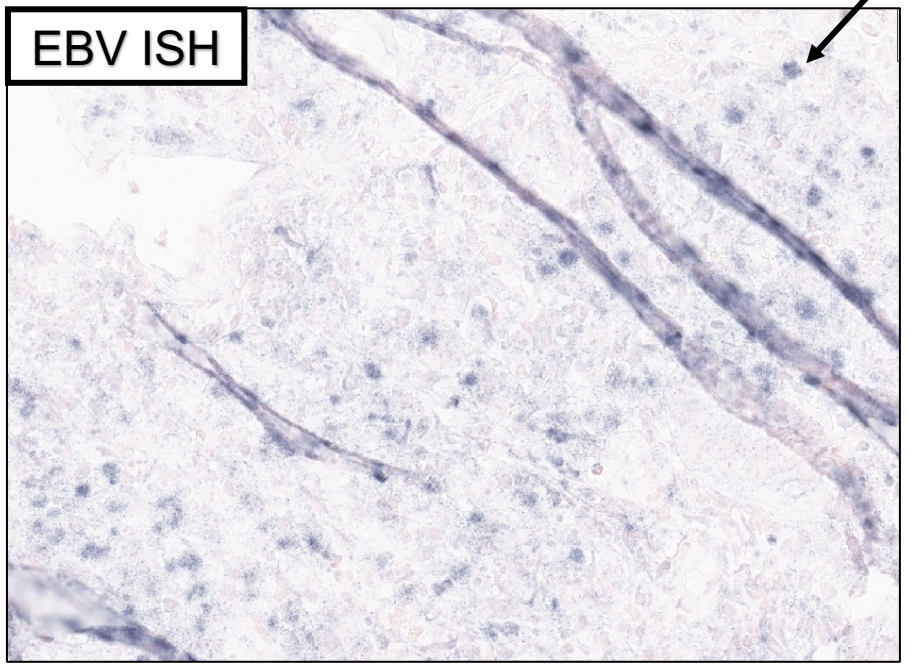


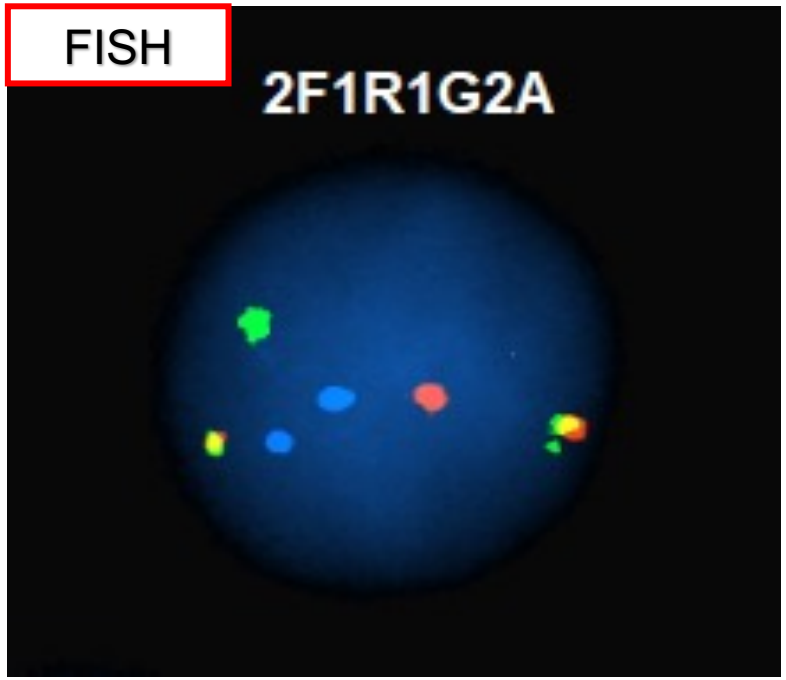












MYC rearrangements.

(Courtesy Dr. Angela Lager, Cytogenetics UChicago)

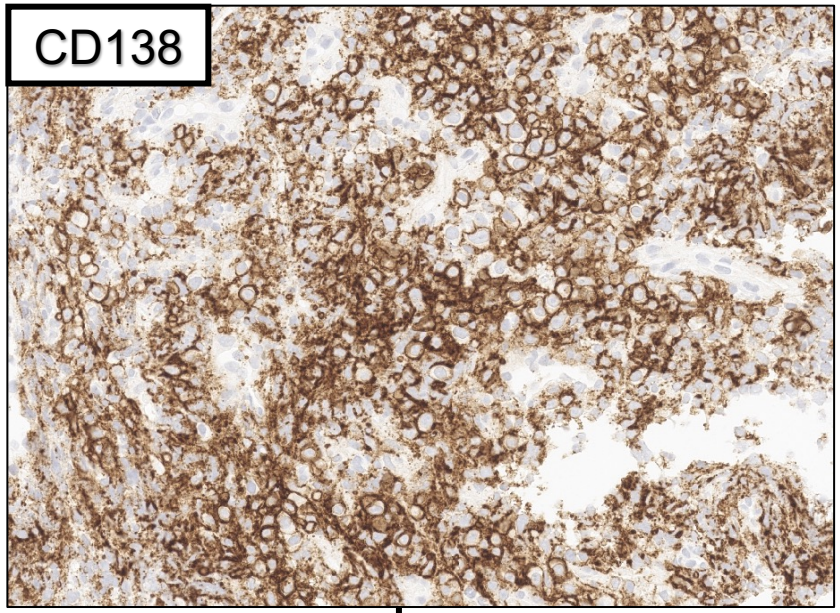
Extranodal + High Proliferation + MYC rearrangement + EBV

Outside Diagnosis:

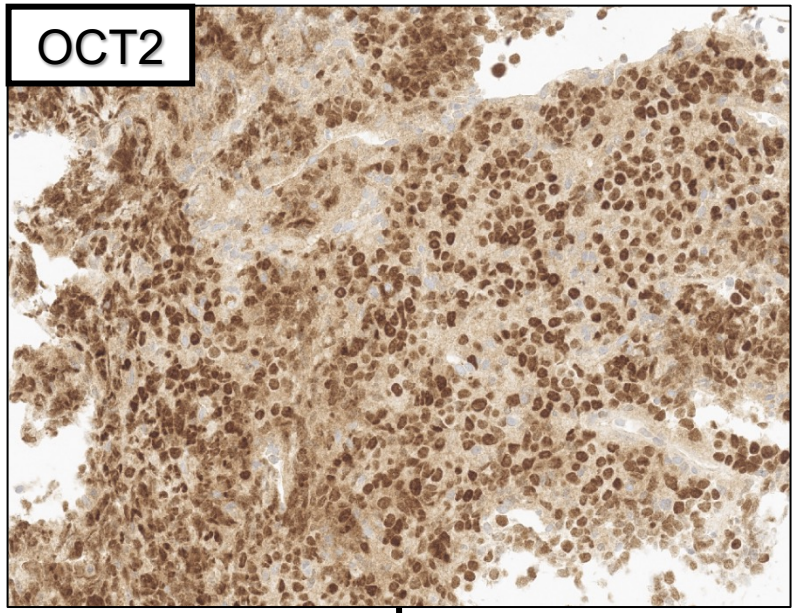
Burkitt Lymphoma

Something is not adding up…..

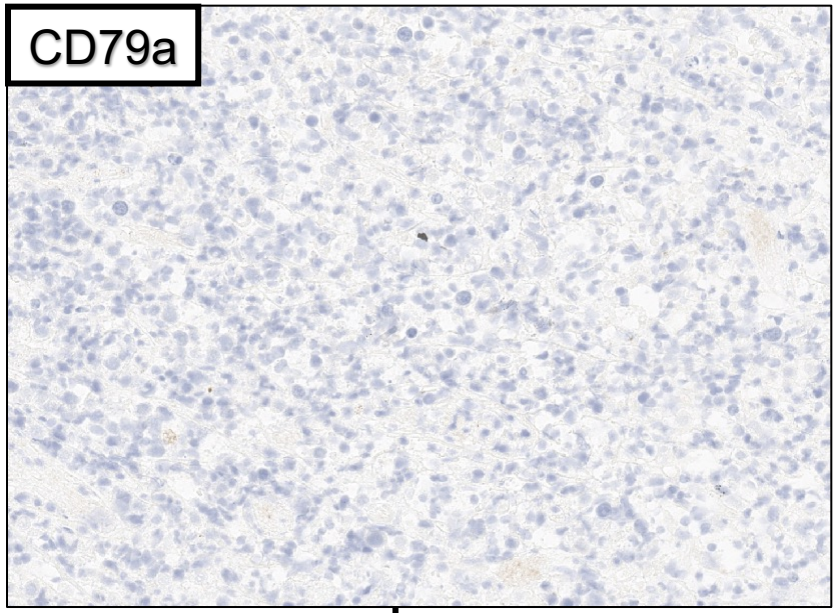
Immunochemistry



Plasmacytic marker



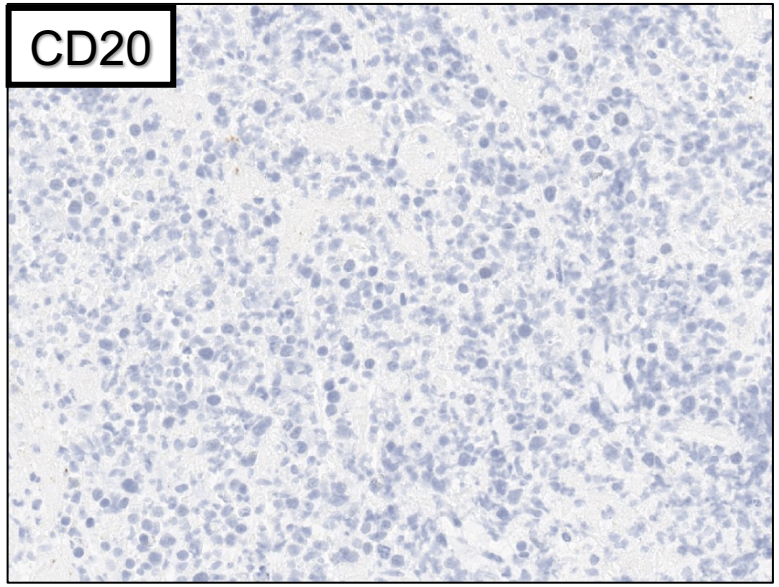
B/plasmacytic marker



B/Plasmacytic marker

Immunochemistry

Repeat



IHC	Immunoreactivity
BCL2	Negative - useful in context of Burkitt lymphoma
CyclinD1/SOX11	Negative - excludes Blastoid MCL
CD34	Negative - excludes lymphoblastic process
CD30	Negative - excludes ALCL

Revised Final Diagnosis:

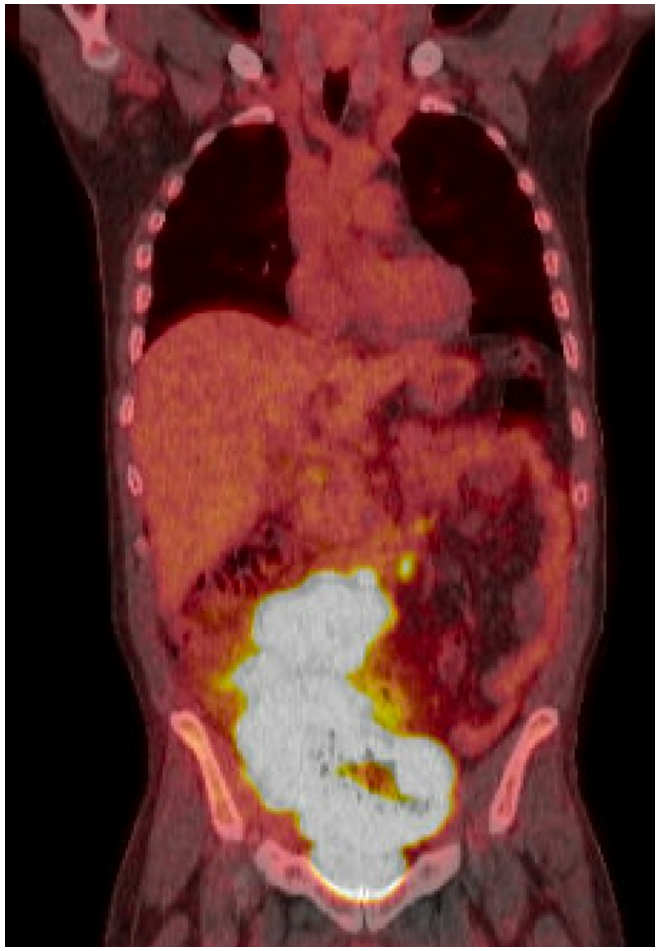
Plasmablastic Lymphoma with MYC rearrangement

Case 2

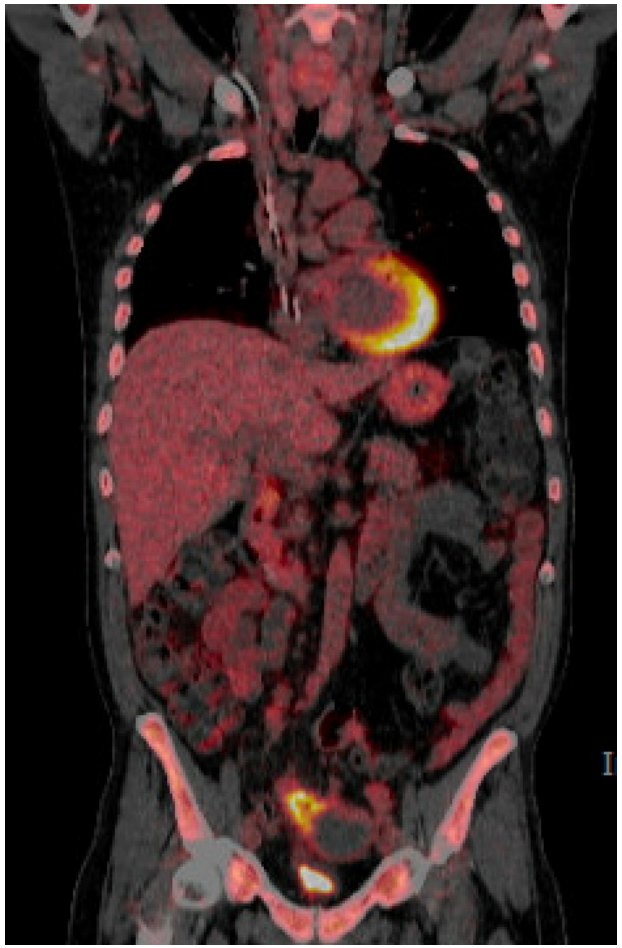
ID: 44-year-old male presenting with bulky abdominal masses and new plasmablastic lymphoma.

- Dropped the rituximab.
- Continuing with DA-EPOCH + IT MTX
- Plan for 6 cycles with consolidative auto-SCT.

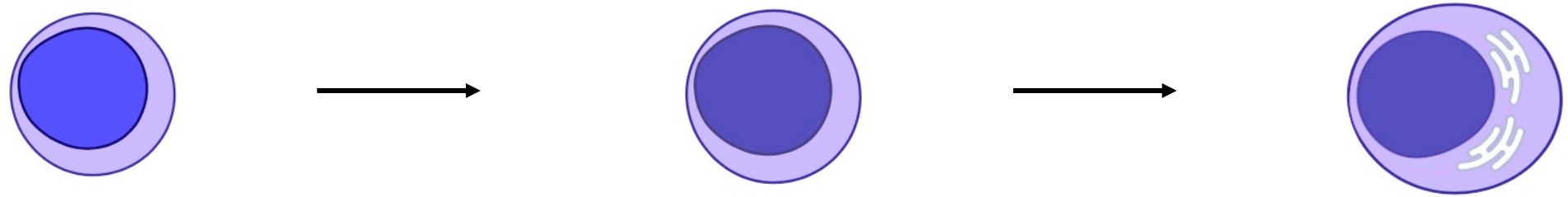
Baseline



After 3 cycles

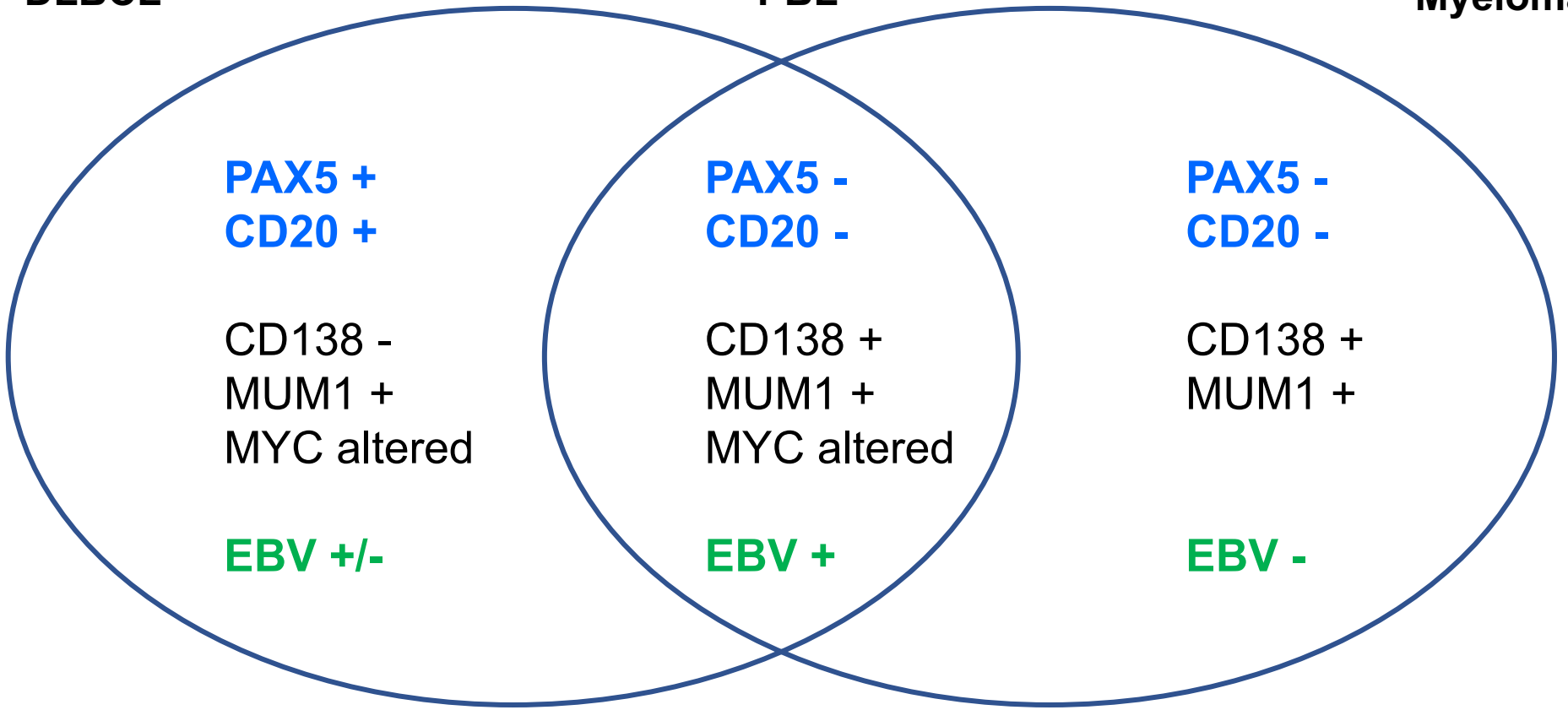


Plasmablastic Lymphoma



Post-germinal center B-cell → Plasmablast → Plasma Cell

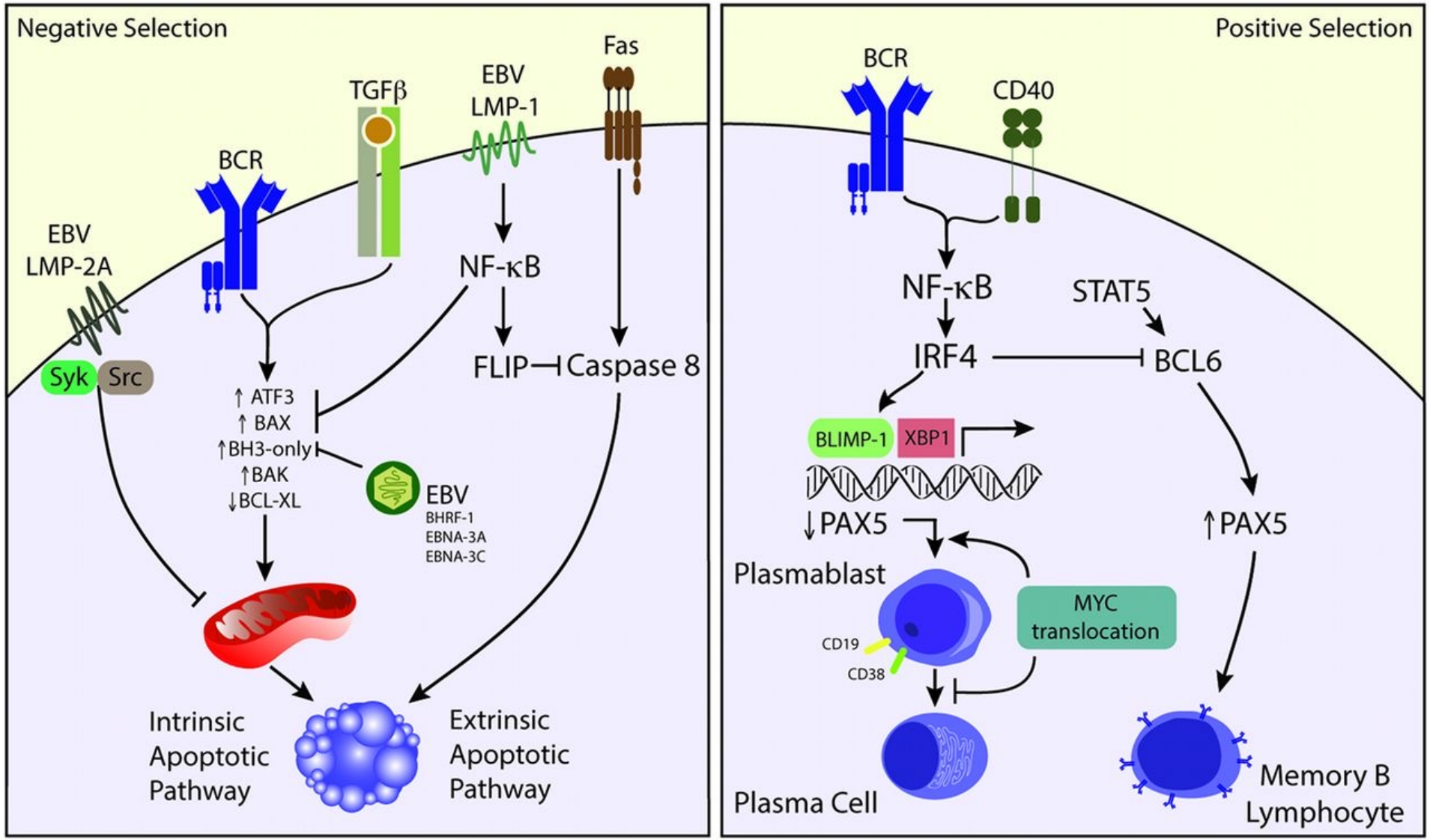
DLBCL | **PBL** | **Myeloma**



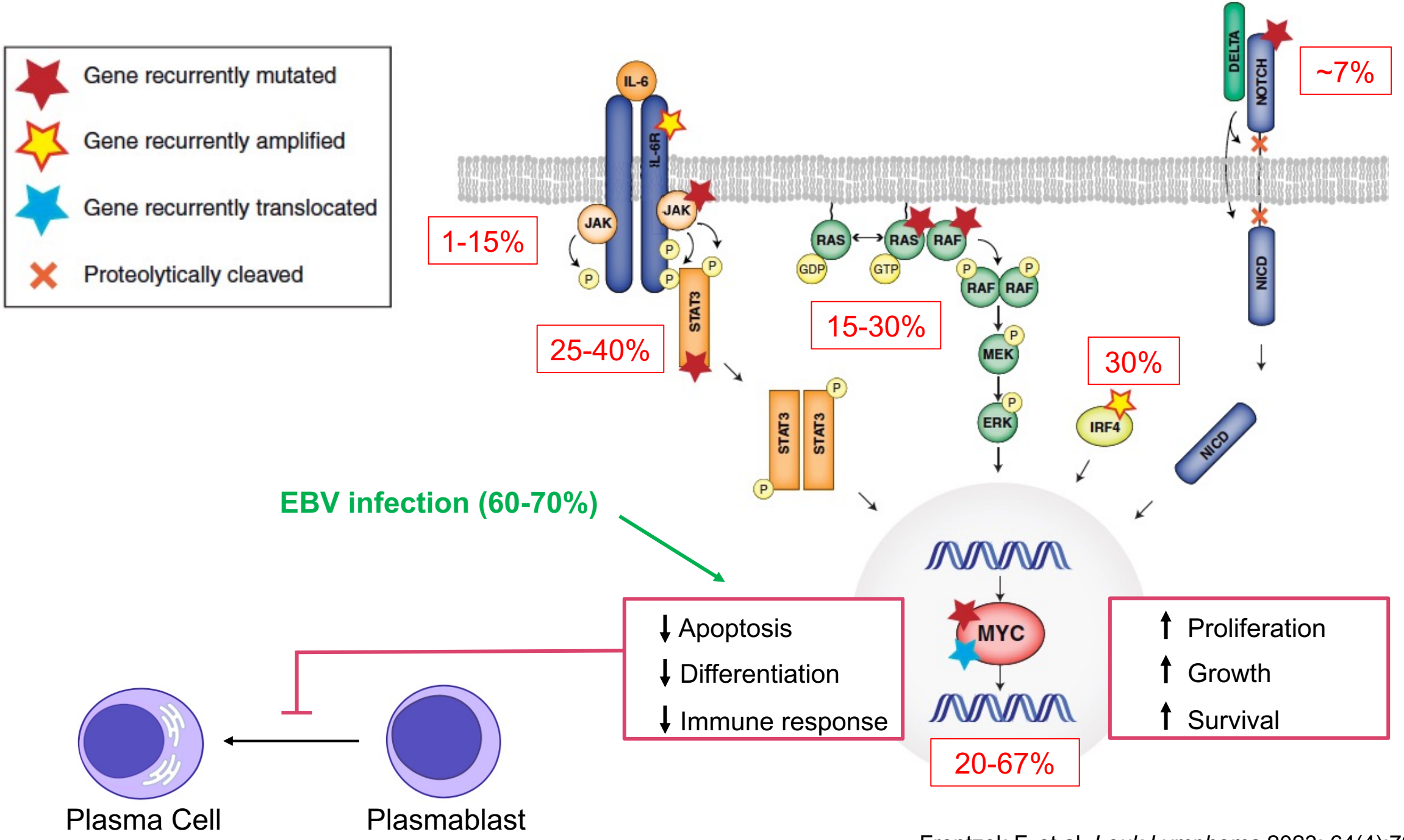
PBL Biology

EBV infection (60-70%)

MYC alterations (20-67%)



Castillo J, et al. *Blood* 2015; 125(15):2323-2330

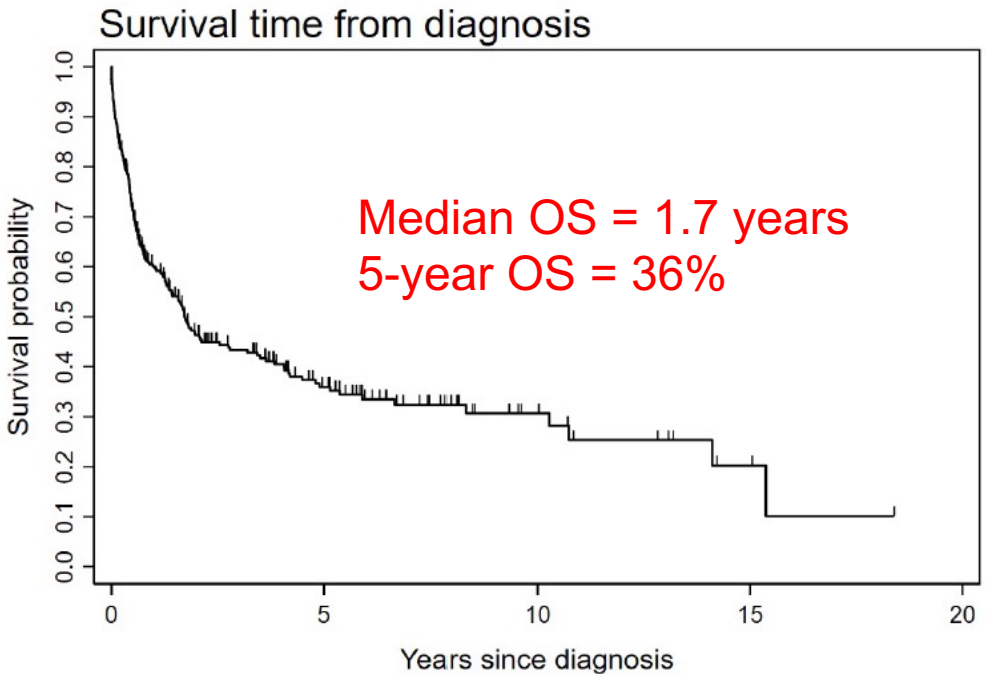


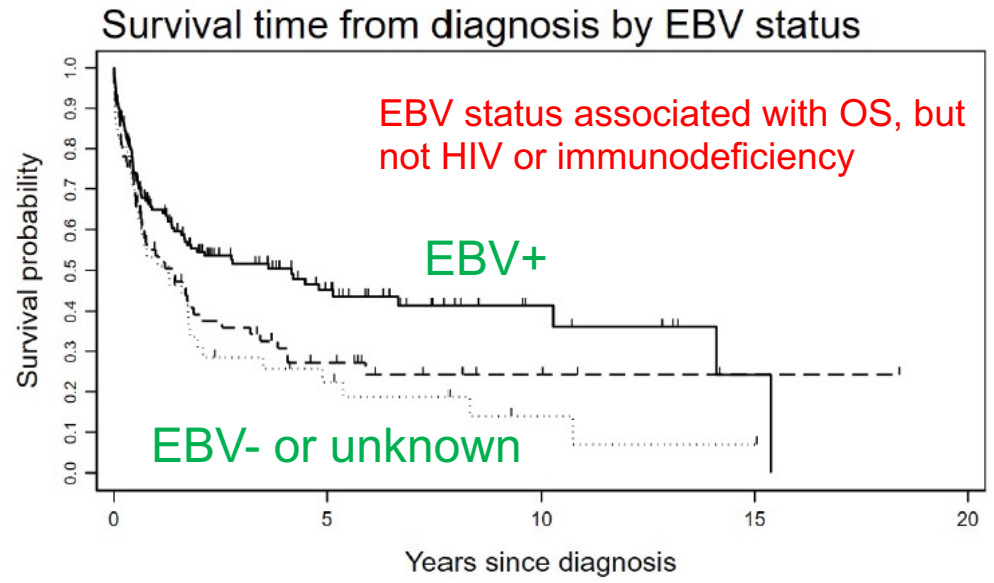
Frontzek F, et al. *Leuk Lymphoma* 2023; 64(4):799-807.

Retrospective PBL cases from 22 institutions in Australia, UK, Canada, and Singapore (1999 – 2020)

n=281
Median follow-up: 1.15 years

Characteristics	
Median Age (range)	55 years (44-69)
HIV positive	35%
Immunodeficient	56%
MYC rearranged	19%
EBV positive	57%
CD20+	9%
CD30+	16%
CNS involvement	5%





Di Ciaccio PR, et al. *Blood* 2024; 143(2):152-165.

Systematic Review in 173 patients with PBL

Characteristics	
Median Age (range)	49 years (2-86)
HIV positive	49%
Immunodeficient	?
MYC rearranged	67%
EBV positive	70%
CD20+	8%
CD30+	?

Median OS = ~2 years

Table 3 First-line Regimens' Response and Relapse Rates

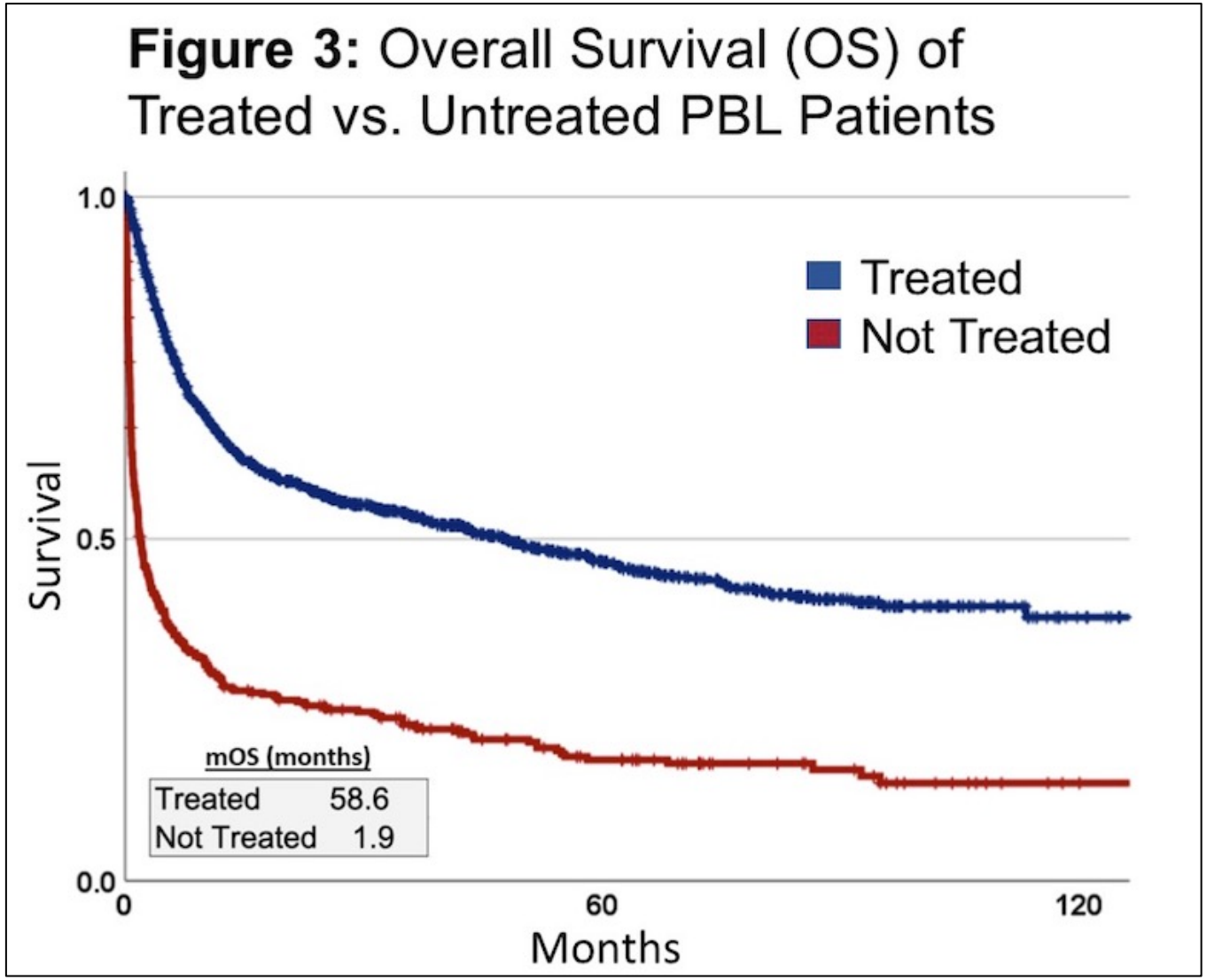
First Line	n/N (%)
CHOP	
CR	27/69 (39)
ORR	48/69 (69)
Relapse rate	16/45 (35.6)
EPOCH	
CR	9/19 (47.4)
ORR	15/19 (78.9)
Relapse rate	6/15 (40)
Bortezomib-based regimens	
CR	8/16 (50)
ORR	11/16 (68.8)
Relapse rate	1/11 (9.1)

Makady NF, et al. *Clin Lymphoma Myeloma Leuk* 2021; (21(3):e255-e263.

United States Retrospective Analysis
NCBD and SEER Data 2010 - 2020

n = 1,775 (HIV positive: 50%)

- Median OS ~2 years (all)
- Median OS ~ 5 years (treated)
- HIV status was not associated with OS



Hansen AR, et al. ASCO 2023 Abstract 7570.

Plasmablastic Lymphoma

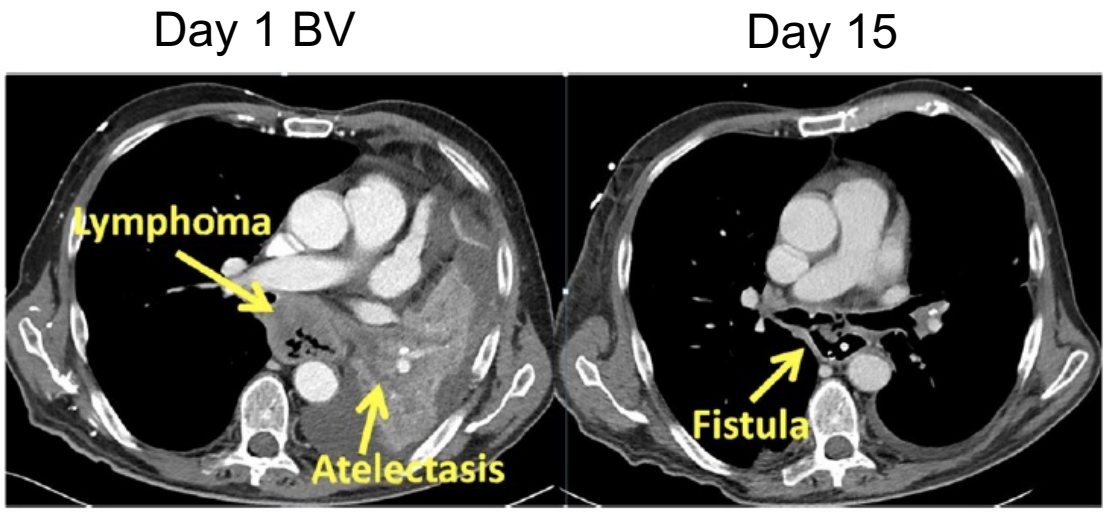
Table 1 Ongoing Trials

Regimen	Phase	Line of Therapy	Status	Location	Clinical Trial no
Dara-EPOCH **AMC105**	I	First line	Recruiting	USA	NCT04139304
Belantamab Mafodotin	II	Relapsed and Refractory	Recruiting	USA	NCT04676360
CARCD30	I	First line and relapsed	Active; not recruiting	USA	NCT01192464
Dara, bortezomib and Dexamethasone	II	Relapsed and refractory	Recruiting	Italy	NCT04915248
Allogenic EBV-CTLs targeting CD 19 antigen	I	Relapsed and refractory	Active, not recruiting	USA	NCT01430390
Pomalidomide and Dose-adjusted EPOCH	I	First line	Recruiting	USA	NCT05389423
Nivolumab With or Without Varlilumab	II	Relapsed/Refractory	Active, not recruiting	USA	NCT03038672

Kaur S. and Kollimuttathuillam S. *Clin Lymphoma Myeloma Leuk* 2023; 23(9):e2253-e259

Brentuximab-vedotin in PBL

- CD30 is positive in ~30% of PBL cases.
- Case reports suggest some activity of BV used in PBL
  - **2013:** 48 year old with CLL transformed to PBL (CD30+) with neck mass
  - **2015:** 74 year old with refractory PBL (CD30+)



Castillo J, et al. *Blood* 2015; 125(15):2323-2330
Jessa R, et al. *Br J Haematol* 2022; 199(2):230-238
Holderness BM, et al. *J Clin Oncol* 2013; 31(12):e197-9
Pretscher D, et al. *Ann Hematol* 2017; 96:967-970

Conclusion: Case 1

- AITL can be very a challenging diagnosis.
- EBV+ cells are found in majority (80-95%) of cases.
- In subset of patients (rarely!), EBV+ proliferation can progress to EBV+ DLBCL.
- For EBV+ DLBCL, R-CHOP is the standard treatment and polatuzumab-R-CHP is an option.

Conclusion: Case 2

- PBL is a rare entity with plasmacytic markers (usually CD20 negative) and can be MYC positive.

- HGBCL is CD20 positive, although CD20 negative/dim can be seen in some cases.

- Extensive necrosis makes morphologic assessment challenging.

- PBL can occur in setting of immunodeficiency and EBV infection.

- Optimal first-line treatment of PBL is unknown and novel therapies are urgently needed.

In conclusion…

- The guiding principle of classification: incorporate ALL diagnostic and clinical information.

- TEAMWORK is essential for successful patient care.

Acknowledgements

- Dr. Alexandra Rojek
- Dr. Justin Kline
- Dr. Peter Riedell