



Mass General Brigham



HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL

# Multi-Institutional Hematopathology Interesting Case Conference (MHICC)

## Case 4

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Hematopathology Fellow, Mass General Brigham

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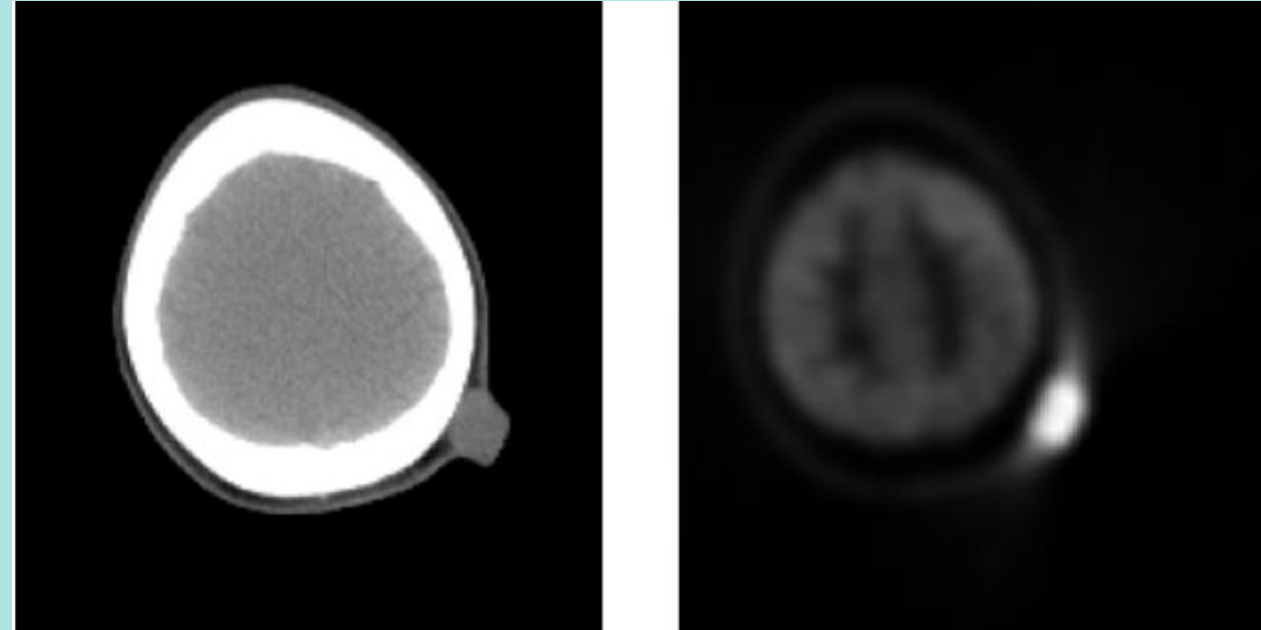
# Clinical summary

- 35 years old woman presented with a 3 cm scalp mass
- Previously biopsied at outside institution and diagnosed as “Aggressive B-cell lymphoma”

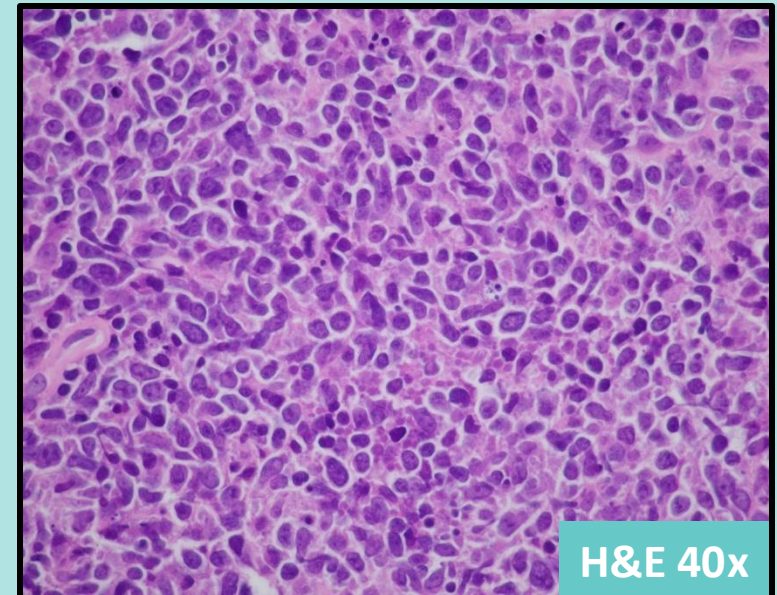
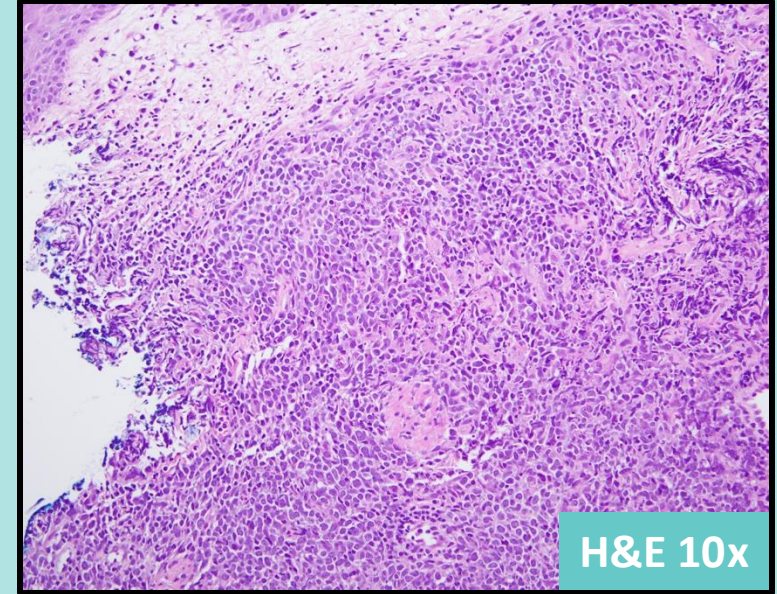
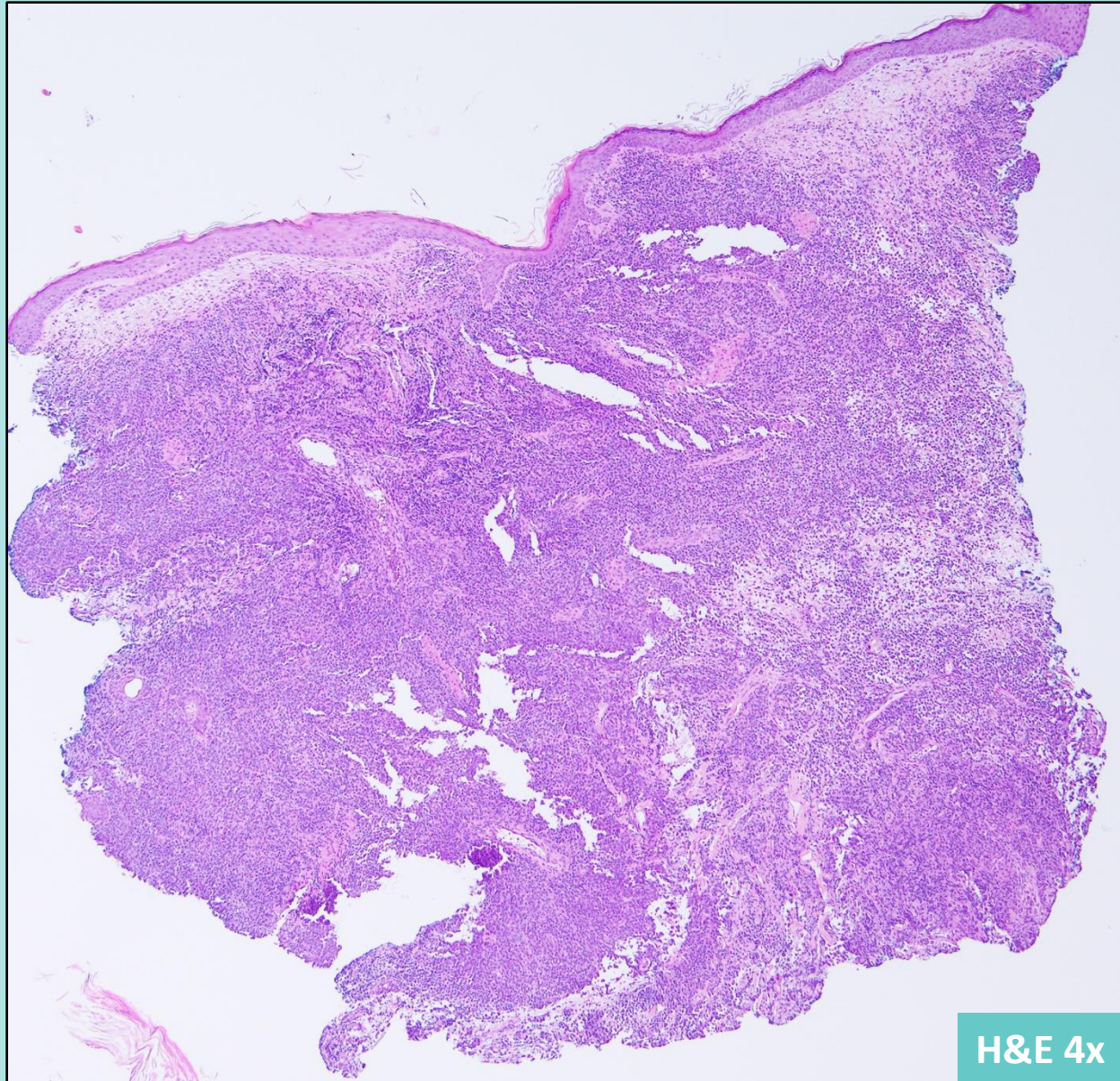


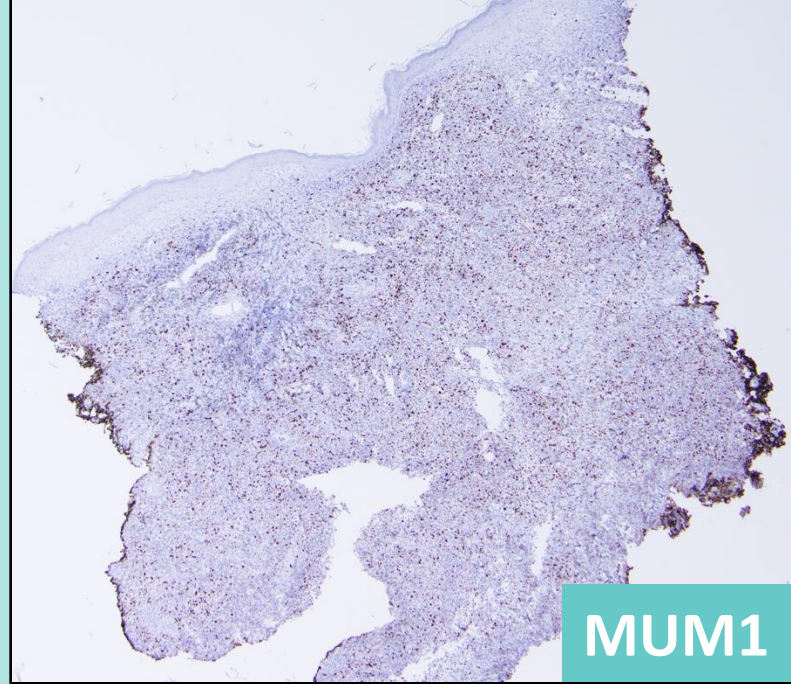
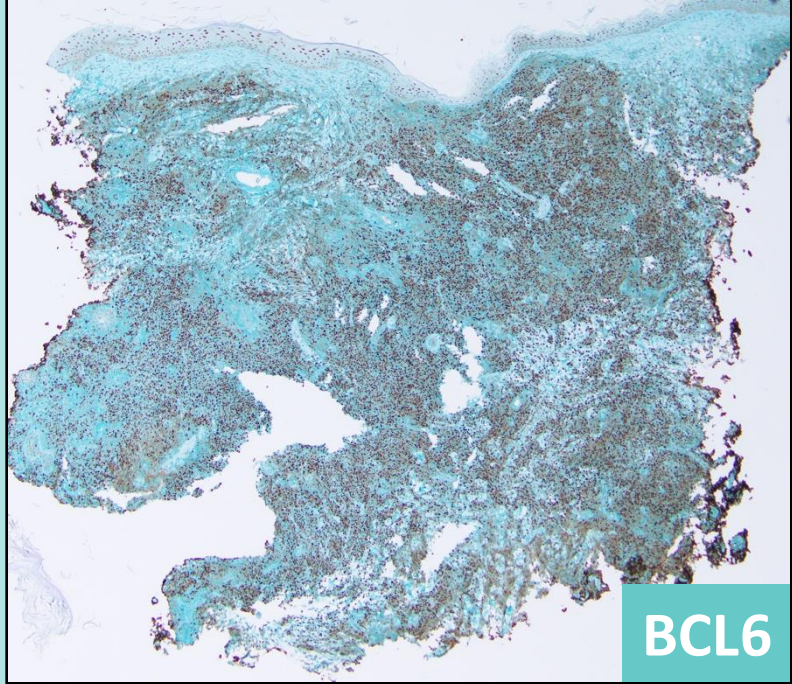
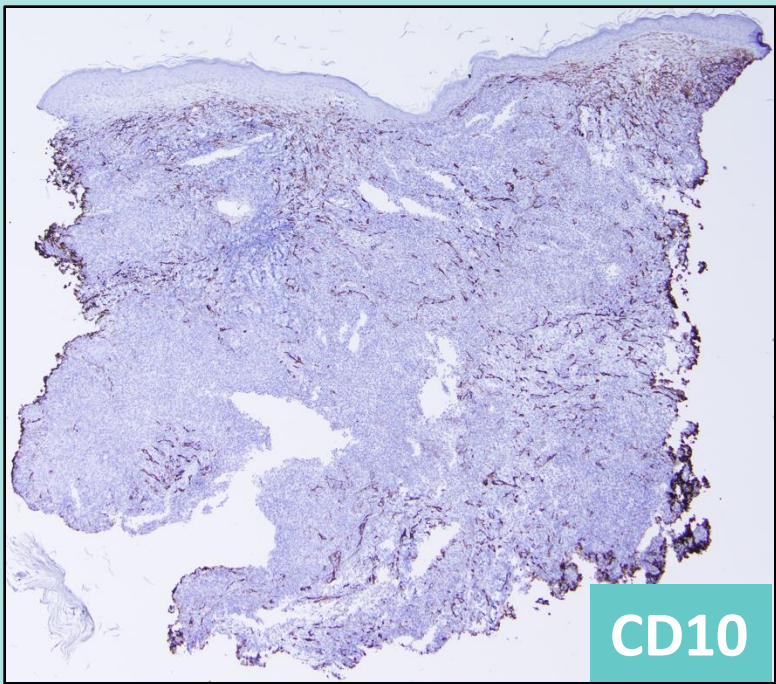
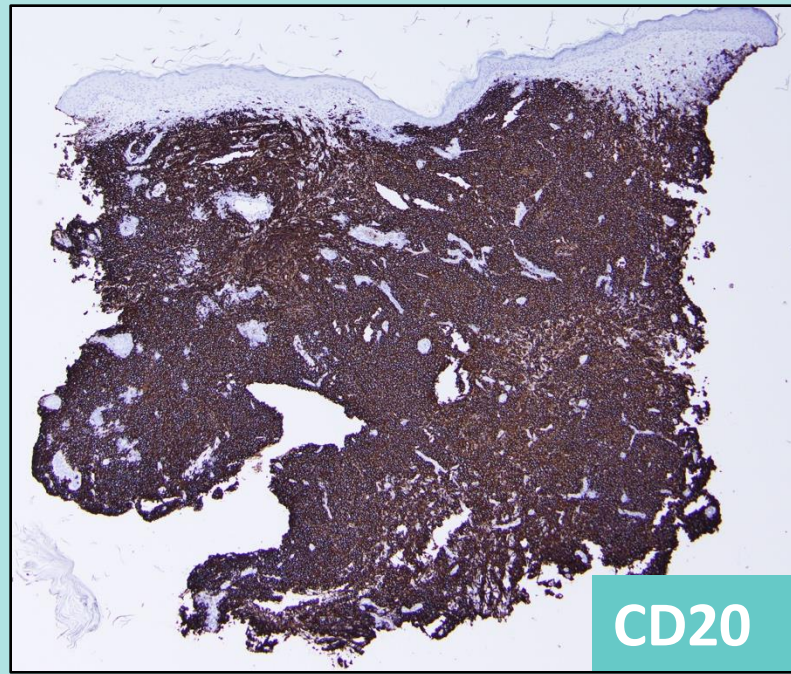
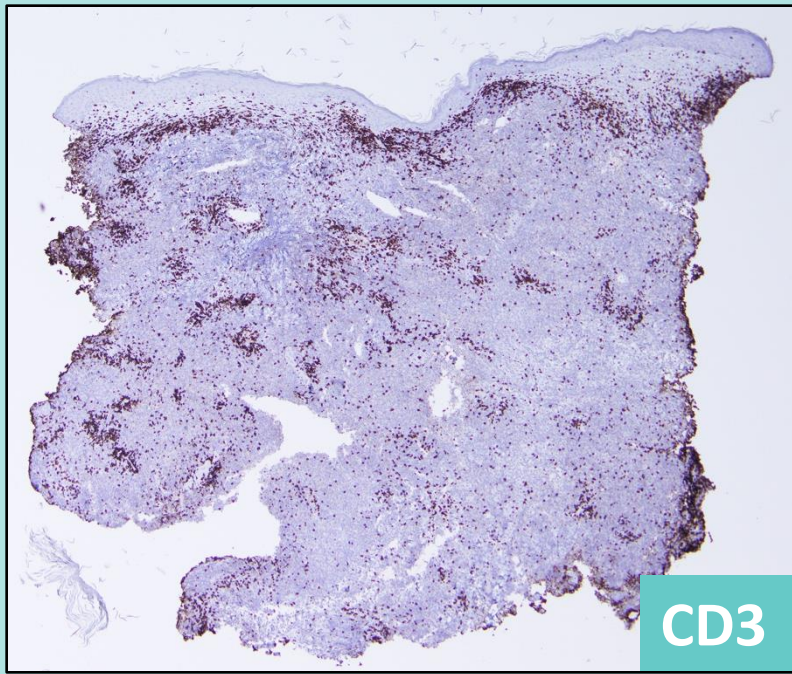
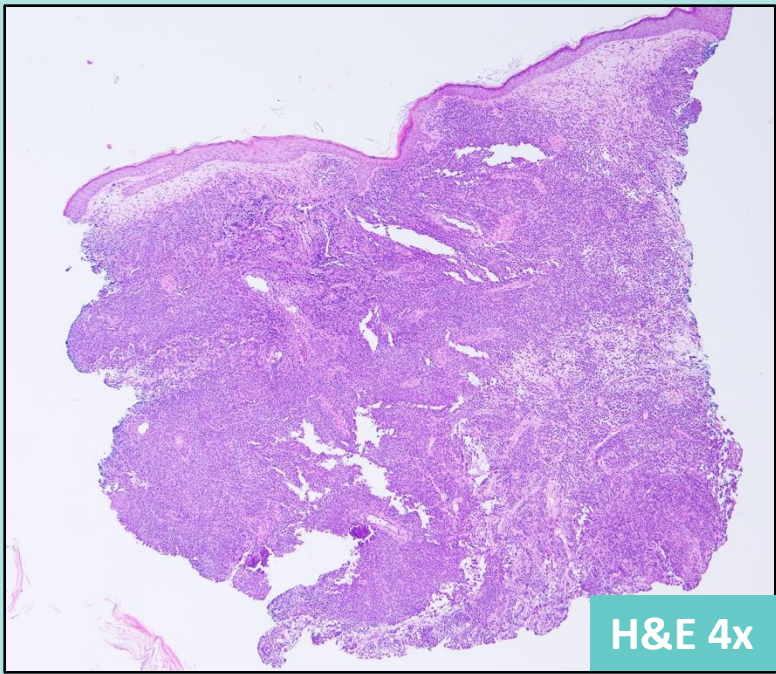
# Clinical summary

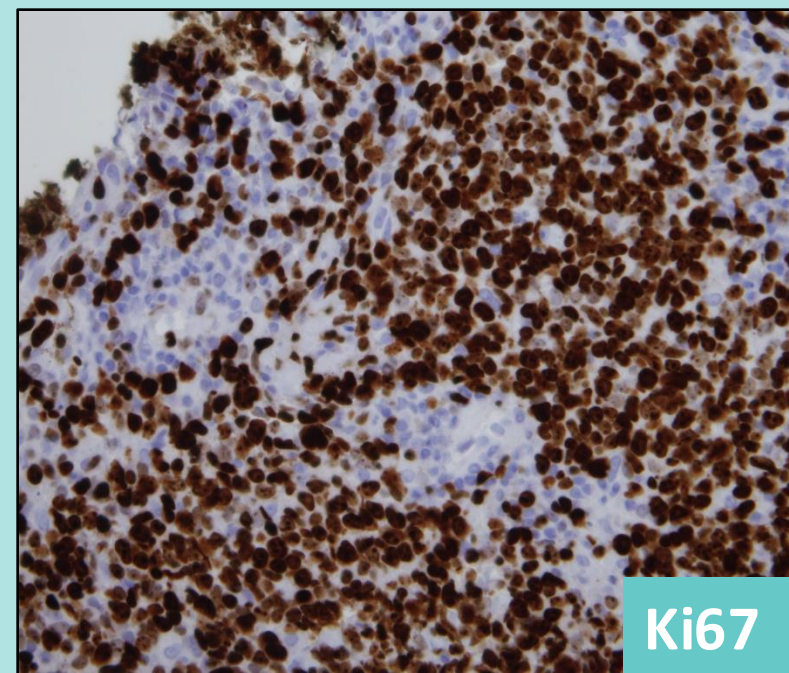
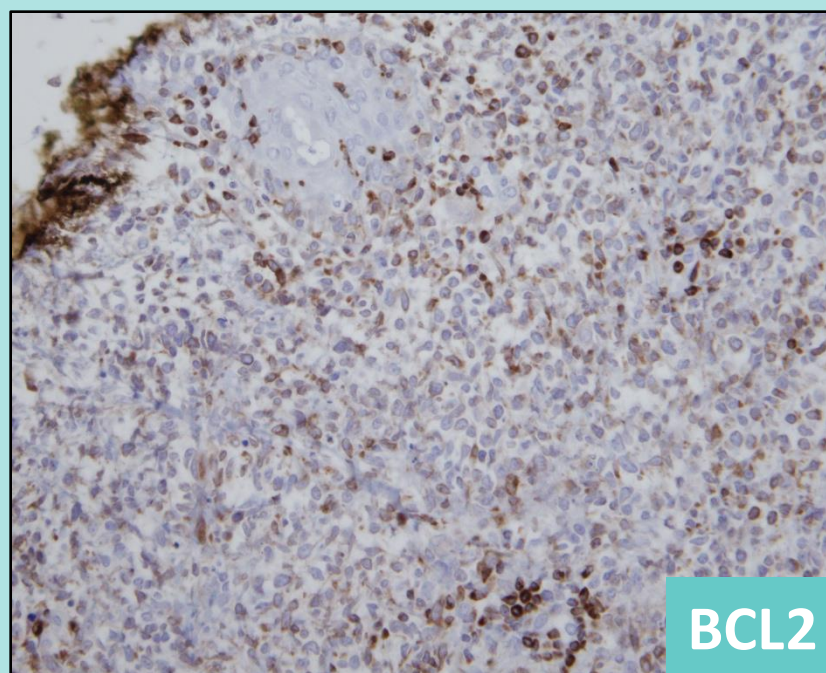
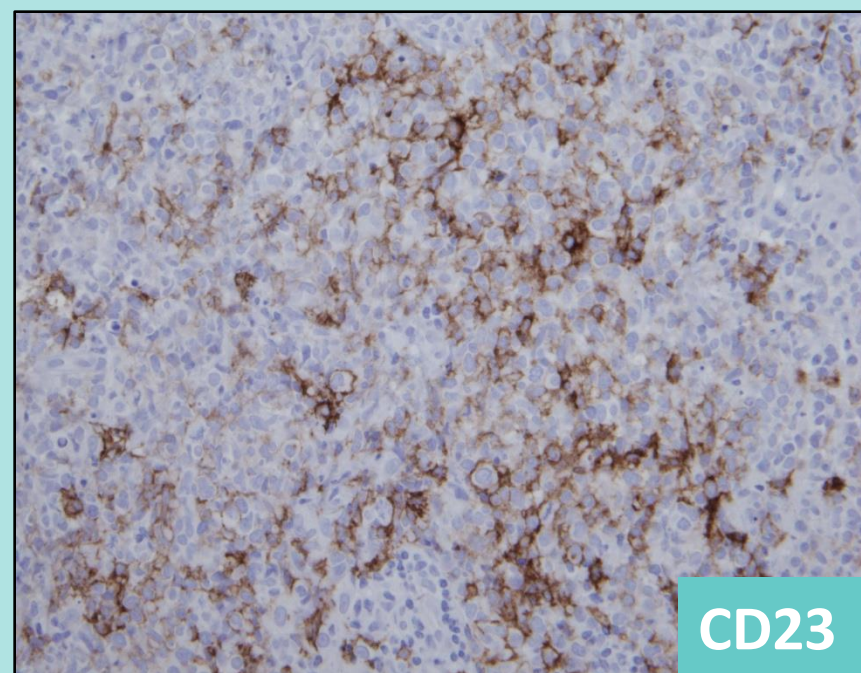
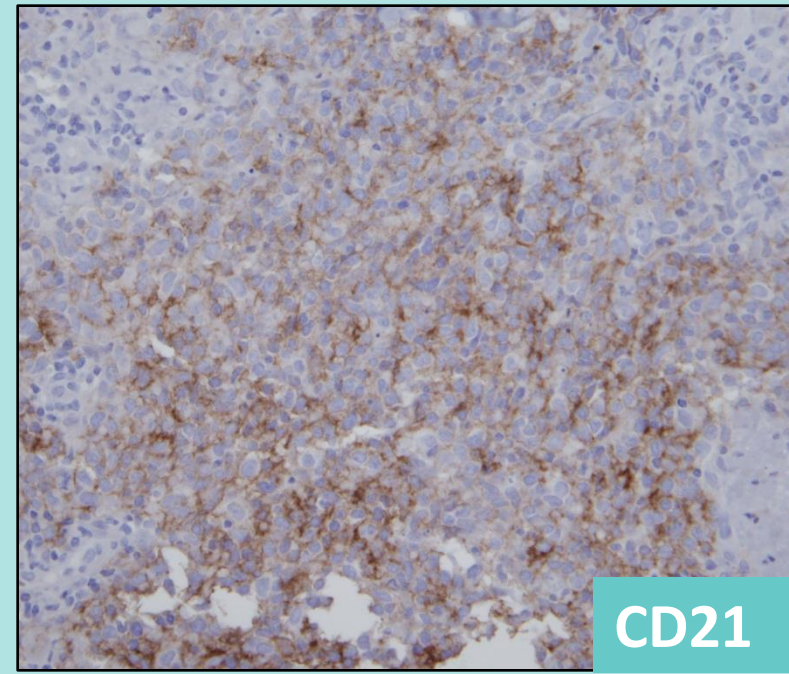
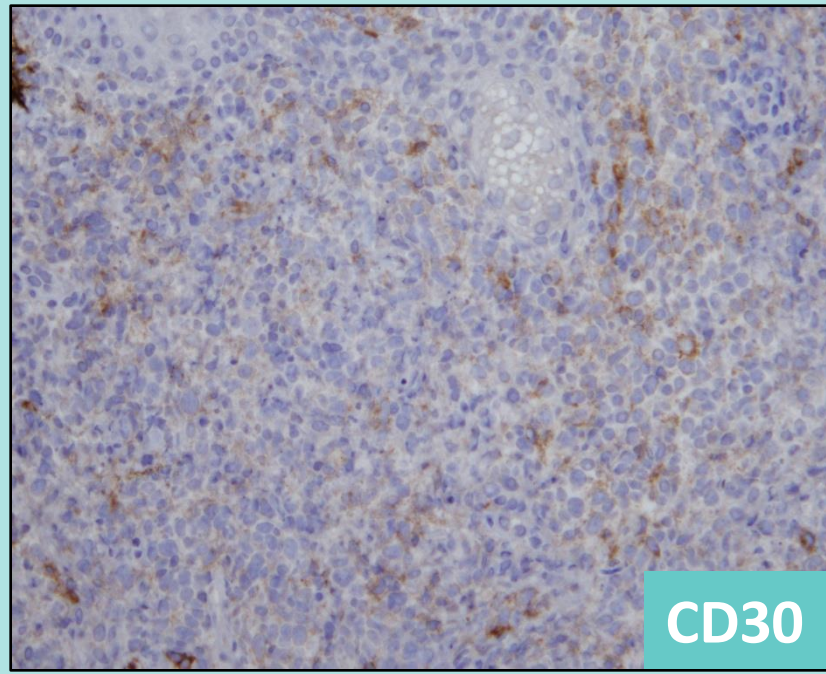
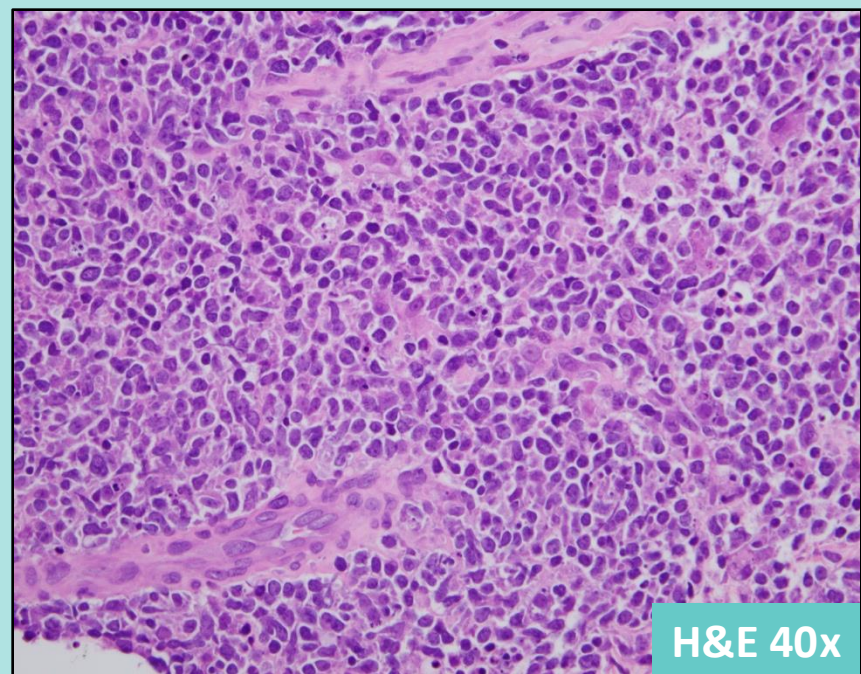
- The patient not ill-appearing. Good appetite, no weight loss.
- Abdomen: Soft, no hepato-splenomegaly, or palpable mass.
- No fever, chest pain, or shortness of breath.
- No lymphadenopathies
- LDH: slightly elevated
- CBC unremarkable



# Skin punch biopsy morphology












# Differential diagnosis

Adapted from WHO 5th edition Hematolymphoid Tumors

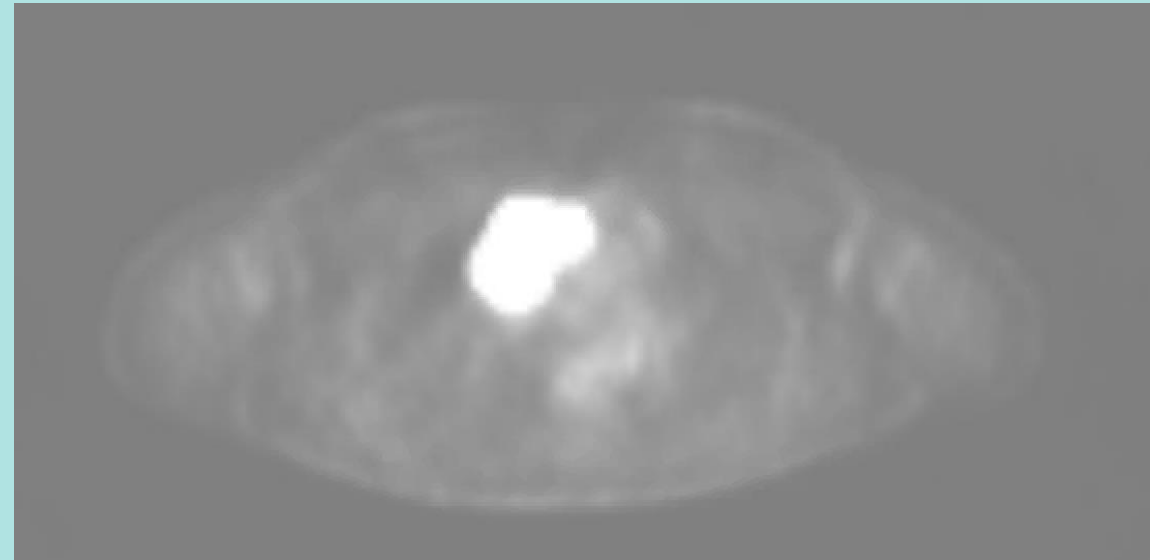
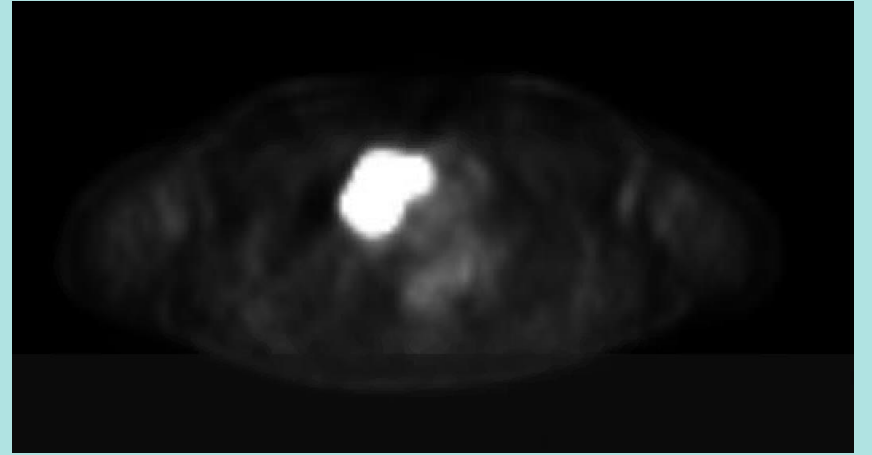
Differential diagnoses		PCFCL diffuse large cell / spindle cell variants	PCLBCL-LT
<b>Histopathology</b>			
<b>Morphology</b>		++ Predominance of large centrocytes including multilobated and spindle cells; centroblasts may be present, but not in confluent sheets	++ Predominance or confluent sheets of round centroblasts and/or immunoblasts, rare blastoid cells 
<b>High proliferative rate</b>		+, in diffuse PCFCL ++	++ 
<b>Diffuse growth</b>		-/+	++ 
<b>Follicular growth</b>		+/-	- (nodules possible)
<b>Reactive T cells</b>		++	+
<b>Immunophenotype</b>			
	IRF4 (MUM1)	-/+	++ <sup>a</sup>
	BCL2	-/+	++ <sup>a</sup>
	IgM	-	++ <sup>a</sup>
	CD10	-/+	- <sup>a</sup> 
	BCL6	+	+/-
	Cell-of-origin algorithm	GCB	Non-GCB <sup>a</sup>
	CD21 FDC networks	+/-	-
<b>Molecular alterations (in diagnostic setting)</b>		<i>MYD88</i> mutation is absent <i>BCL2</i> breaks ~10% No <i>MYC</i> breaks	<i>MYD88</i> and/or <i>CD79B</i> mutation ~70% <i>MYC</i> breaks ~30% No <i>BCL2</i> breaks
<b>Clinical presentation</b>		Scalp, upper body  Exceptional at leg Rare systemic progression	Leg, lower body, (arms) Exceptional at head/neck Most cases with systemic progression
<b>Treatment and outcome</b>		Local treatment, 95% DSS	Systemic treatment, ~50% DSS

# Additional imaging findings

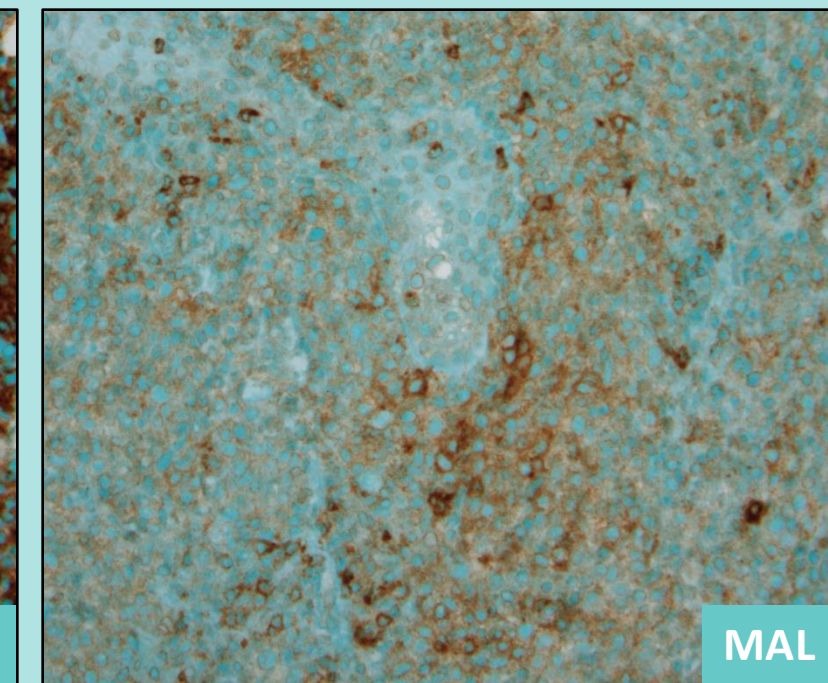
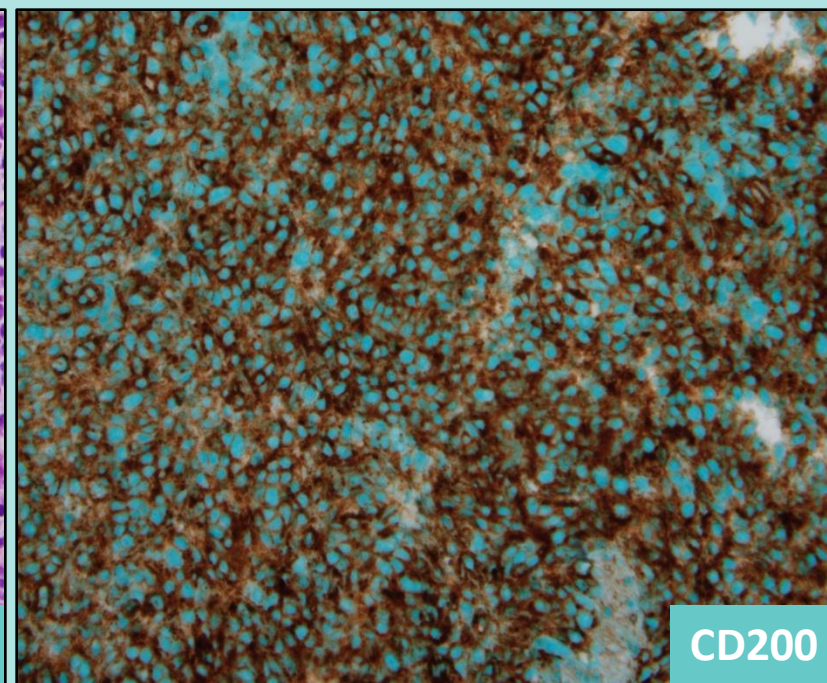
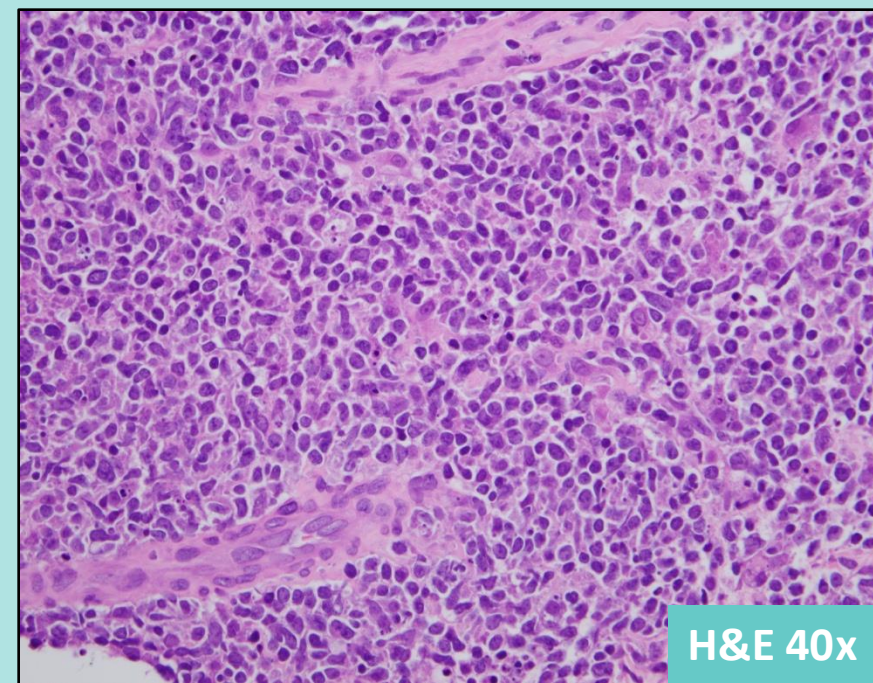
In addition to the scalp lesion:

**PET scan showed a mediastinal LAP (SUV 30) .**

**Clinical concern for  
Primary Mediastinal B-cell Lymphoma (PMBCL)!**



# Additional immunohistochemistry



# Additional molecular testing

FISH performed on paraffin sections showed:  
nuc ish(BCL6x2)[50],(MYCx2)[50],(IGH,BCL2)x2[50]

Rearrangements of *BCL6*, *MYC*, and *IGH::BCL2* were  
NOT OBSERVED.

**OncoPanel** is requested!

*a cancer genomic assay designed to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples.*

*This assay surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement detection.*



# OncoPanel results

## Mutational Burden:

**Tumor Mutational Burden/Megabase: 22.052**

This is higher than 95% of all Non-Hodgkin Lymphoma cases sequenced by this version of OncoPanel.

## Mismatch Repair Status:

**Deficient (MMR-D / MSI-H)**

## Copy Number Variants:

Cytoband/Size Type of Alteration Genes

**9p24.1 Amplification CD274 (estimated 6 copies)**



# OncoPanel results

## Mutations:

Tier 3 variants:

ARID1A c.5548dup (p.D1850Gfs\*4), exon 20 - in 41% of 615 reads##

**B2M c.35T>A (p.L12Q), exon 1 - in 64% of 361 reads##**

**B2M c.346+2T>G () - in 63% of 313 reads##**

CCND3 c.865\_870del (p.A289\_I290del), exon 5 - in 33% of 224 reads##

**CIITA c.25G>A (p.A9T), exon 1 - in 24% of 435 reads##**

**CIITA c.52+1G>A () - in 53% of 451 reads##**

EP300 c.1885T>C (p.Y629H), exon 10 - in 32% of 305 reads##

**NFKBIE c.759\_762del (p.Y254Sfs\*13), exon 1 - in 34% of 141 reads##**

**NFKBIE c.1136T>C (p.L379P), exon 4 - in 33% of 749 reads##**

PIM1 c.82+8C>T () - in 41% of 459 reads##

PIM1 c.3\_5dup (p.L3dup), exon 1 - in 39% of 501 reads##

**SOCS1 c.429C>G (p.S143R), exon 2 - in 33% of 326 reads##**

**SOCS1 c.7G>C (p.A3P), exon 2 - in 48% of 120 reads##**

**SOCS1 c.269\_282del (p.H90Rfs\*22), exon 2 - in 35% of 239 reads##**

**SOCS1 c.254G>A (p.S85N), exon 2 - in 35% of 206 reads##**

**SOCS1 c.456G>T (p.E152D), exon 2 - in 37% of 247 reads##**

**SOCS1 c.195\_210del (p.R66Afs\*14), exon 2 - in 40% of 139 reads##**

**SOCS1 c.3\_4delinsAC (p.MV1\_?2), exon 2 - in 45% of 111 reads##**

STAT6 c.1255G>C (p.D419H), exon 12 - in 38% of 1034 reads##

TNFAIP3 c.640dup (p.M214Nfs\*40), exon 5 - in 65% of 486 reads##

ZNF217 c.1798C>T (p.Q600\*), exon 3 - in 38% of 871 reads##

## Structural Variants:

Tier 3 variants:

Deletion - SOCS1 exon 2 (chr16:11349125) :: SOCS1 exon 2 (chr16:11349141)

Deletion - SOCS1 exon 2 (chr16:11349186) :: SOCS1 intron 1 (chr16:11349408)

**Rearrangement - CIITA intron 1 (chr16:10971268) :: CIITA intron 1 (chr16:10973710)**

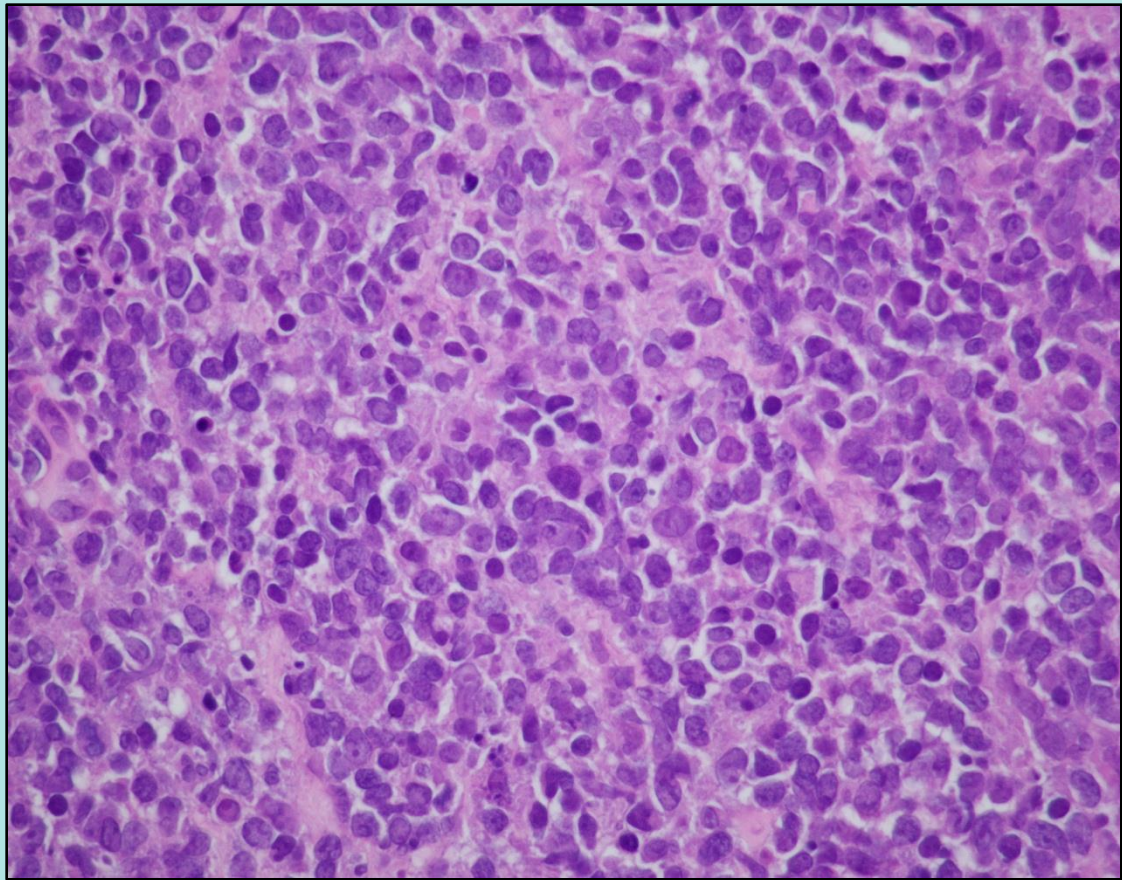
# OncoPanel results summary

Genomic analysis revealed several mutations, particularly in genes involved in immune regulation (*B2M*, *CIITA*, *SOCS1*) as well as those frequently mutated in large B-cell lymphomas (*NFKBIE*, *EP300*, *PIM1*, *STAT6*, and *TNFAIP3*).

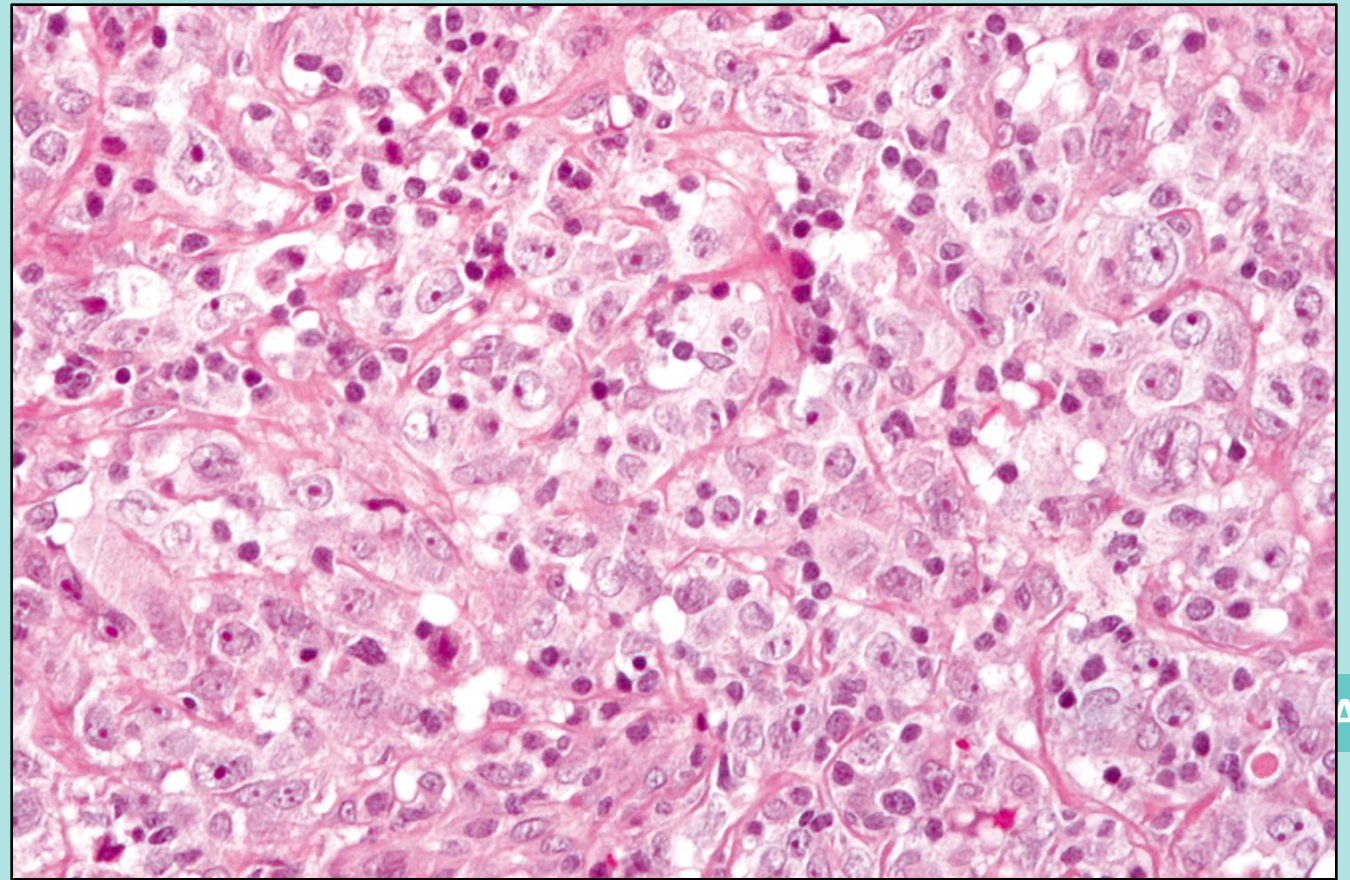
Additionally, a ***CIITA*** rearrangement was seen as well **copy number gains of 9p24 involving PD-L1/PD-L2/JAK2.**



# Morphologic comparison of our case



Our case

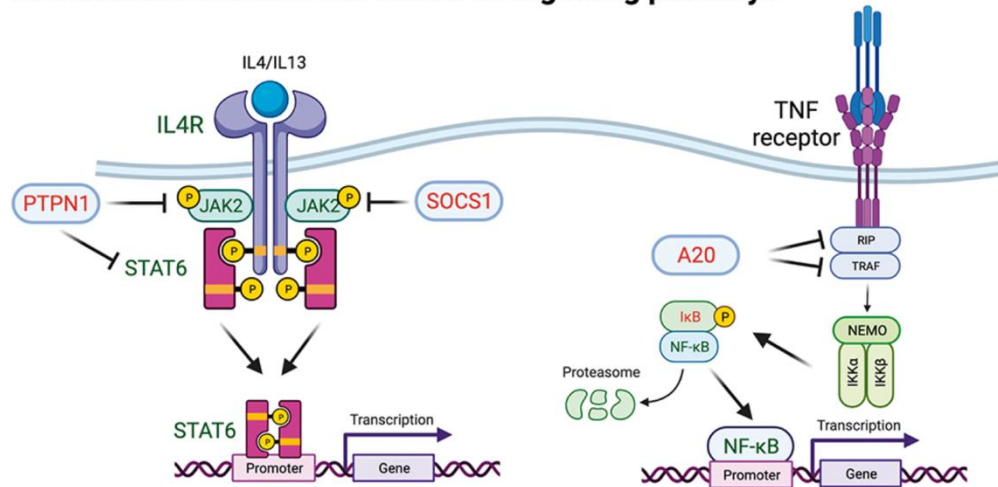


Diffuse infiltration of large clear cells with abundant cytoplasm and alveolar compartmentalizing by fine fibrosis



# Mechanistic pathway for PMBCL

## A. Mutations in JAK-STAT and NF-κB signaling pathways

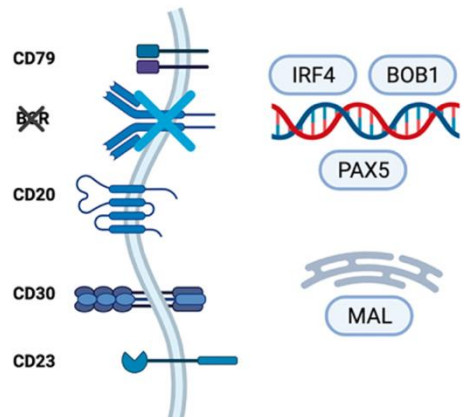


**Gain of function:** IL4R, JAK2, STAT6, REL (part of NF-κB complex)

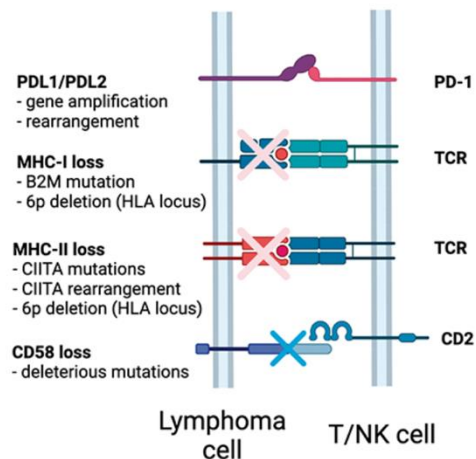
**Loss of function:** PTPN1, SOCS1, A20, NFKBIA/E (part of IκB)

## B. Expression profile

- Overlap with nodular sclerosis classical Hodgkin lymphoma
- Common B-cell markers and transcription factors
- Lack of B-cell receptor



## C. Acquired immune escape



Rearrangements of *CIITA* (*C2TA*) and abnormalities of the *JAK2/PDCD1LG2/CD274* locus at 9p24.1 recurrently found in PMBCL.

Rearrangements of *BCL2*, *BCL6*, and *MYC* are rare to absent

## Essential and desirable diagnostic criteria

**Essential:** large B-cell lymphoma in the anterior mediastinum; mature B-cell phenotype; at least partial expression of CD23 and/or CD30.

**Desirable:** distinctive stromal sclerosis; expression of at least one of the following markers: MAL, CD200, PDL1, and PDL2; copy gain or rearrangement of the *CD274/PDCD1LG2* locus and/or rearrangement involving *CIITA* (*C2TA*).

# Final Proposed Diagnosis

The patient's imaging revealing **mediastinal lymphadenopathy** is noted. Accordingly, the genomic findings are that of a hypermutated profile with multiple mutations in immune regulatory elements, NF- $\kappa$ B signaling, as well as those recurrently seen in DLBCL, **coupled with a *CIITA* rearrangement, copy number gain of PD-L1/PD-L2/JAK2 and REL**, as well as other copy number alterations conventionally seen in large B-cell lymphomas.

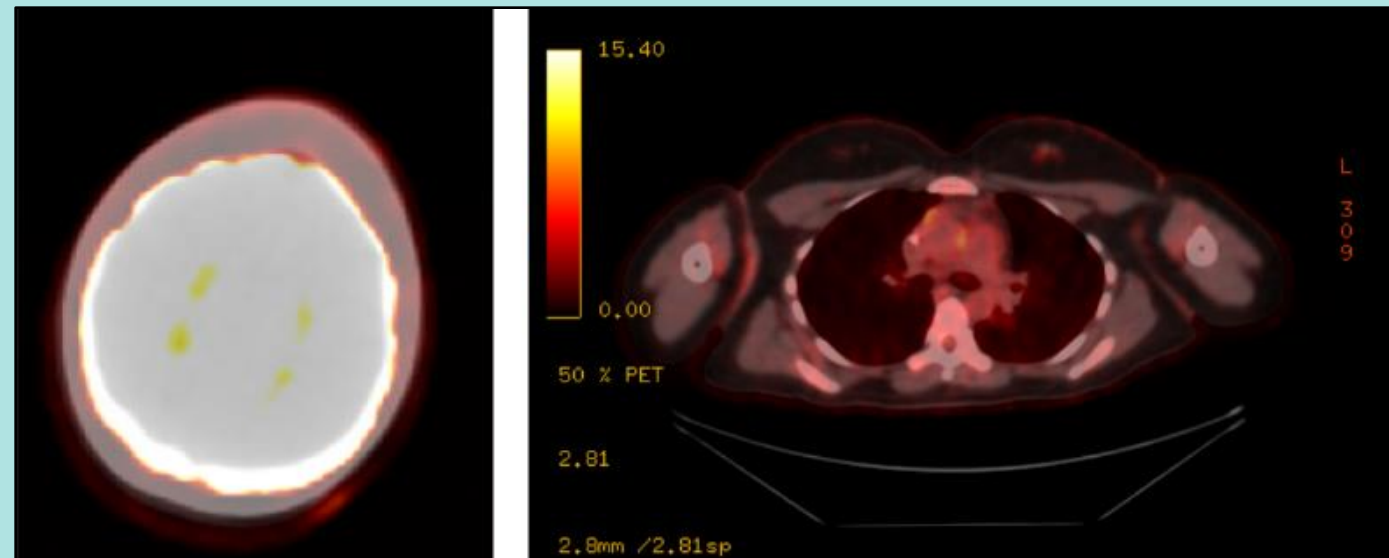
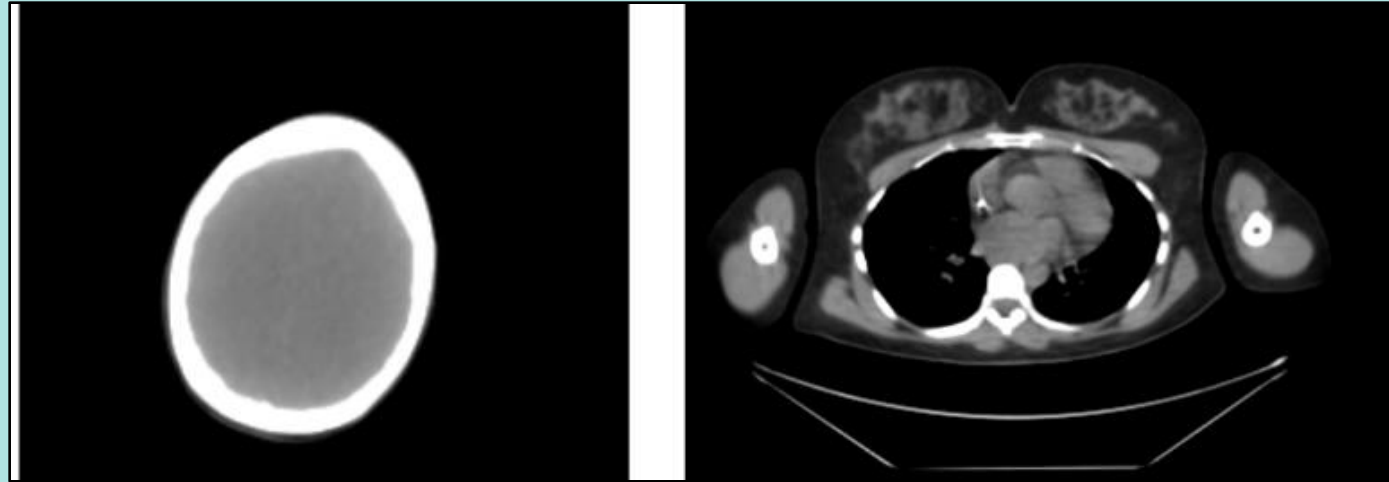
In conclusion, **the constellation of clinicopathologic and molecular genetic findings are more in support of extra-mediastinal (cutaneous) manifestation of a primary mediastinal large B-cell lymphoma (PMBCL).**



# Patient Follow up

3 cycles of R-CHOP

Repeat PET scan consistent with complete metabolic remission (CMR):



# Take home points

**1- Literature review shows no prior PMBCL case presenting as skin lesion**

2- Molecular analyses important for final classifications of large B cell lymphomas

3- Morphologic findings can be subtle in PMBCL



# Acknowledgements

Sam Sadigh, MD

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