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Case 4: How Many Hits?

Monthly Multi-Institutional Hematopathology Interesting Case Conference

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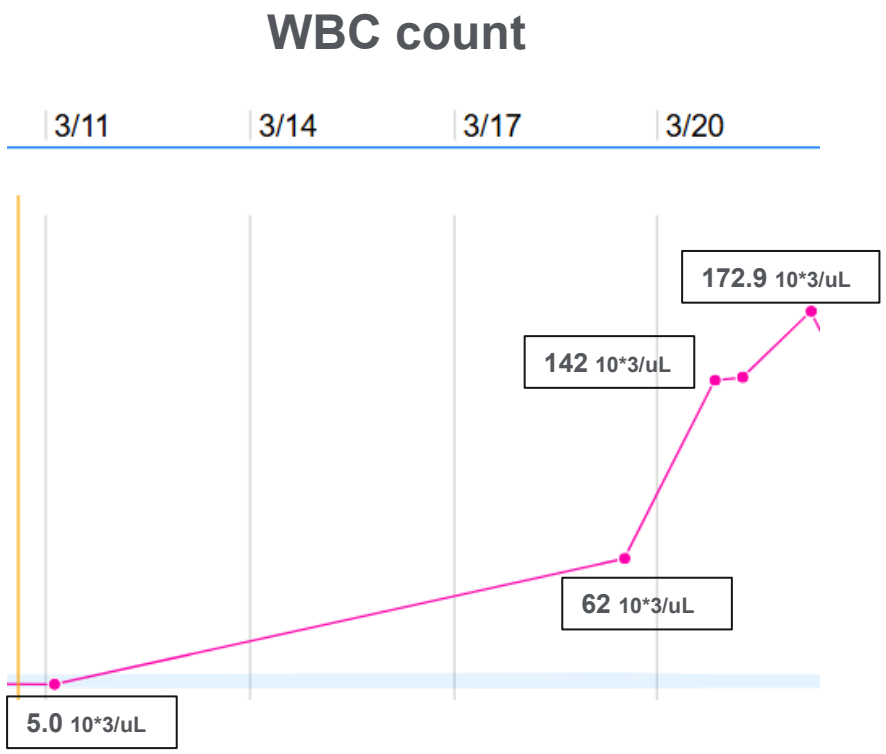
Clinical Presentation

- 93-year-old female with h/o breast cancer s/p mastectomy, hormonal treatment, and radiotherapy.
- Presented to NYU-ED with bilateral leg pain, abdominal pain, night sweats and unintentional weight loss for 2 weeks, found to have new onset anemia. CT of abdomen is normal.

CBC



Units	3/20/25
WBC COUNT	142 10*3/uL ↑
RBC COUNT	3.52 10*6/uL ↓
HEMOGLOBIN	10 g/dL ↓
PLATELET COUNT	249 THOUS/CMM
Lymphocytes %	21%
Neutrophils %	10% ↓
Monocytes %	1% ↓
Eosinophils %	1%
Basophils %	1%

LDH (125 - 220 U/L) **794** ↑

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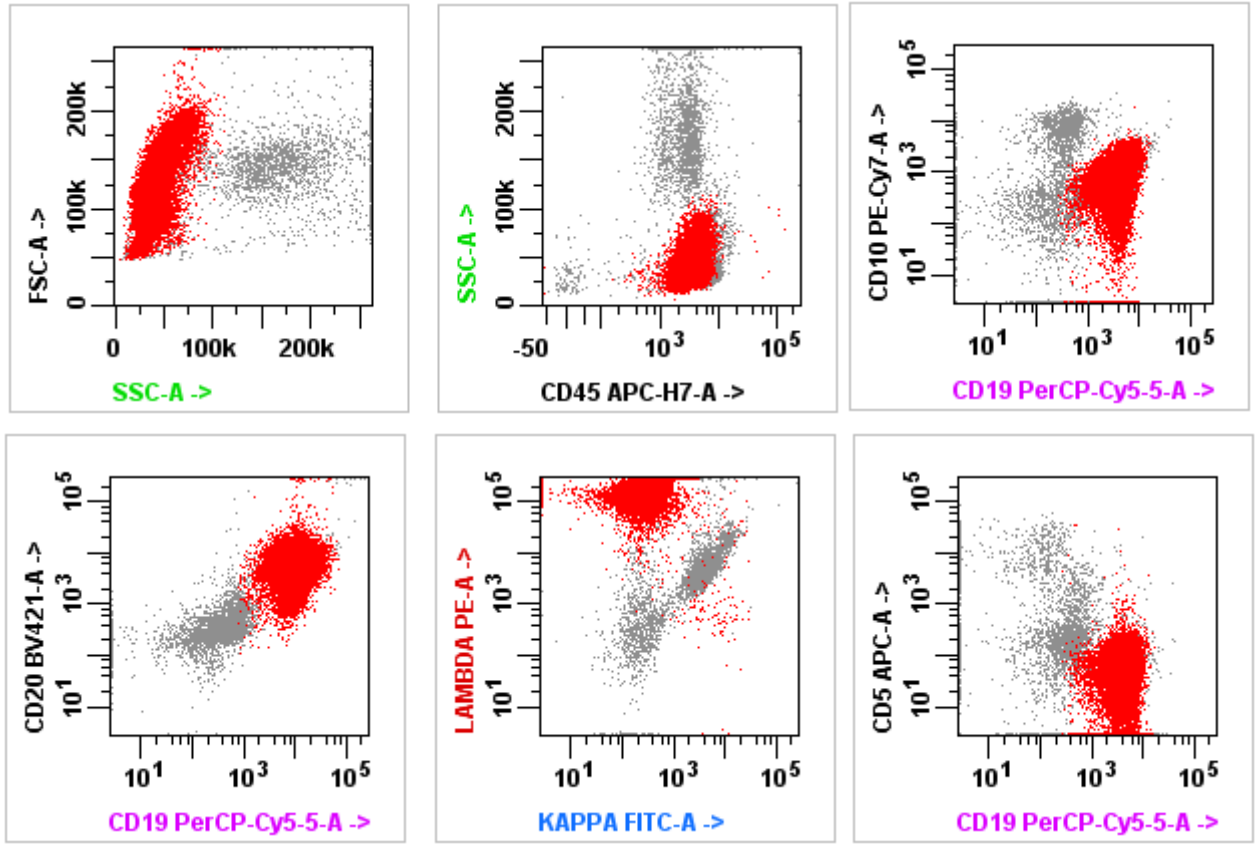
Flow cytometry on PB and BM



Positive: CD45, CD19, CD20, CD38, and surface lambda

Negative: CD5, CD10, CD11c, CD23, CD25, CD103, and surface kappa

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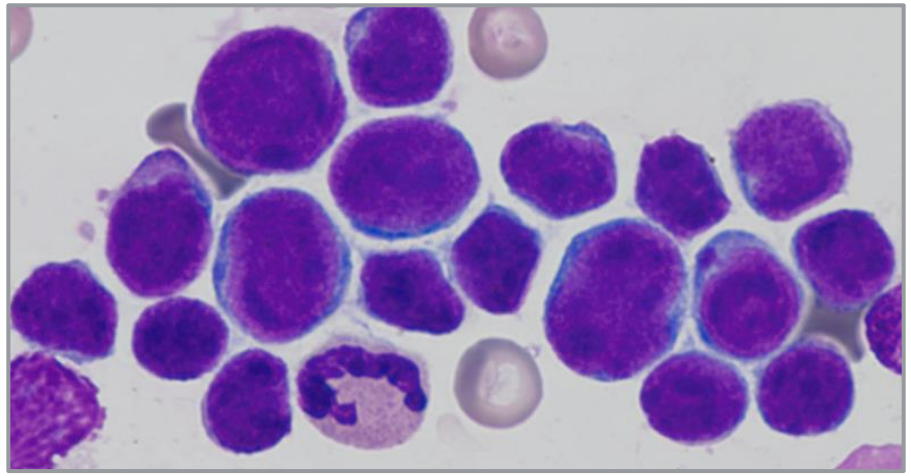
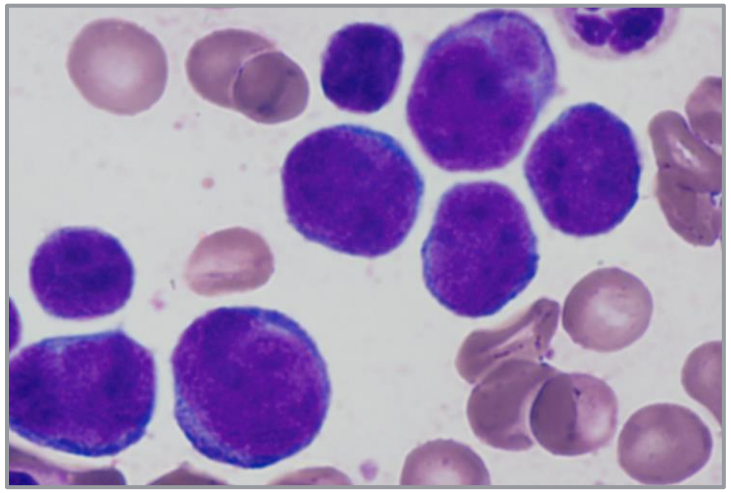
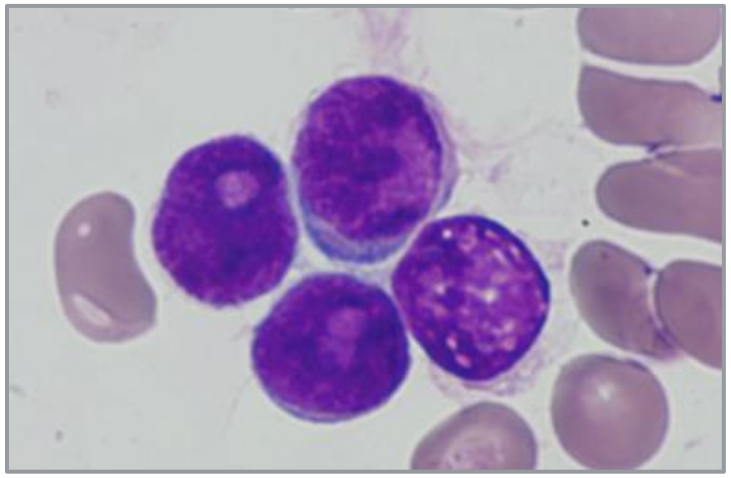
Aspirate Smears, Bone Marrow







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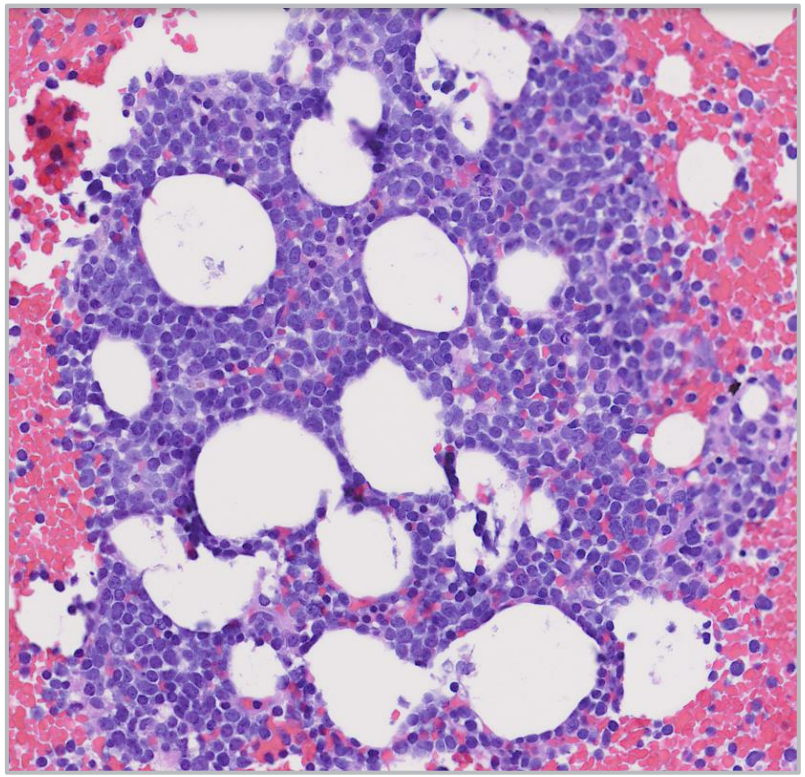
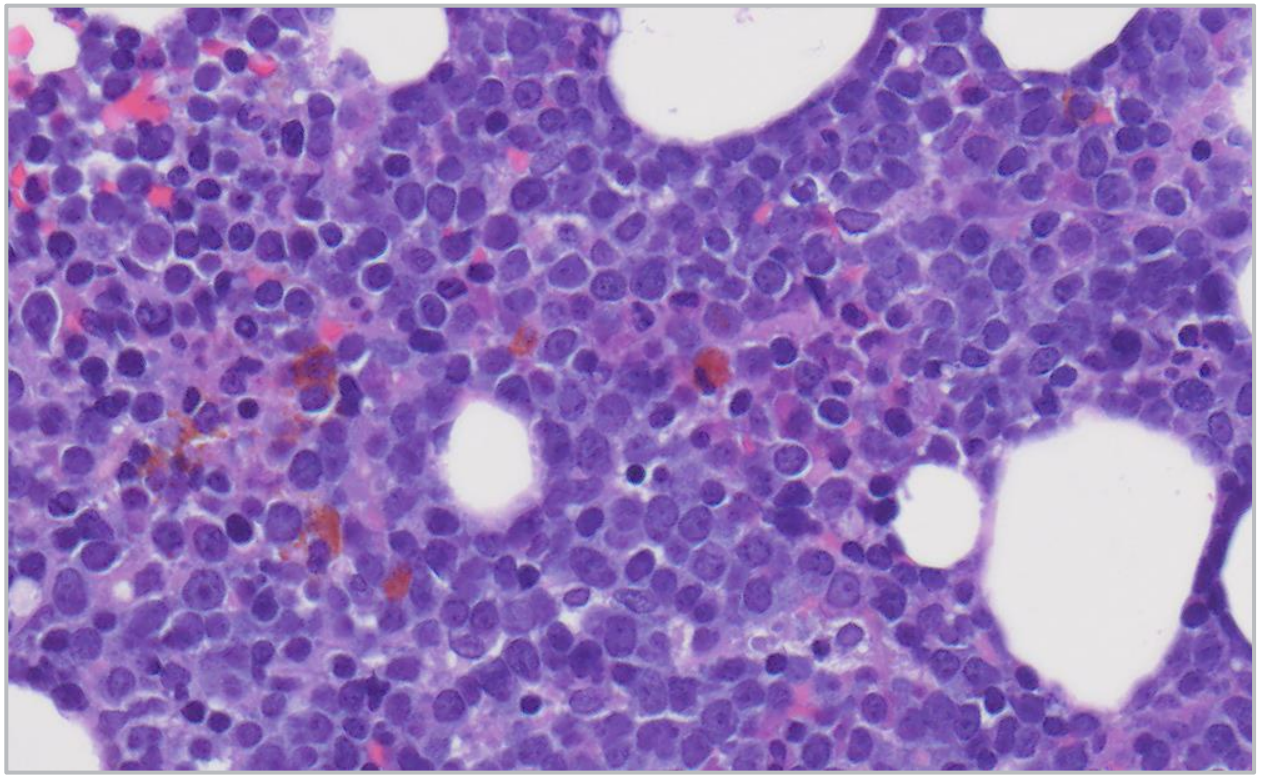
Bone marrow core biopsy and clot section, H&E Stain



x20, objective



x40, objective

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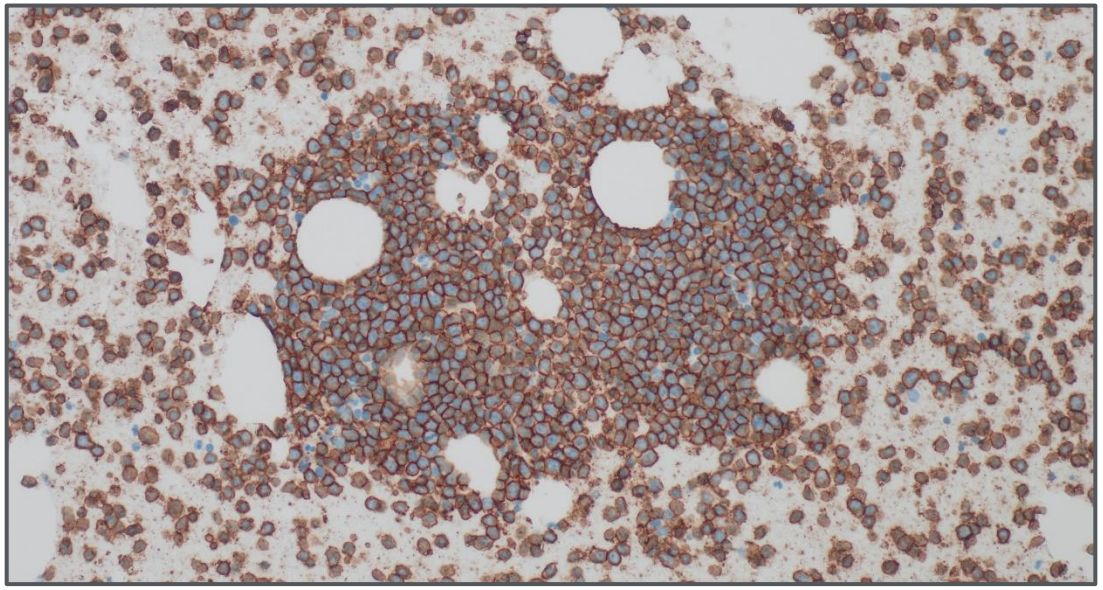
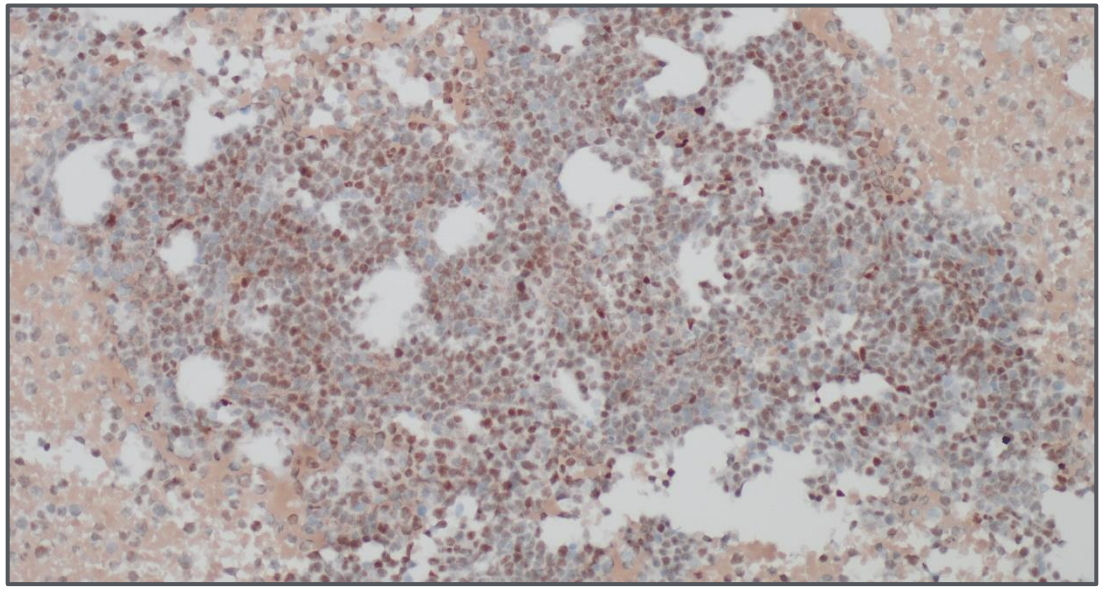
Immunohistochemical stains



CD20, x20, objective



BCL6, x20, objective

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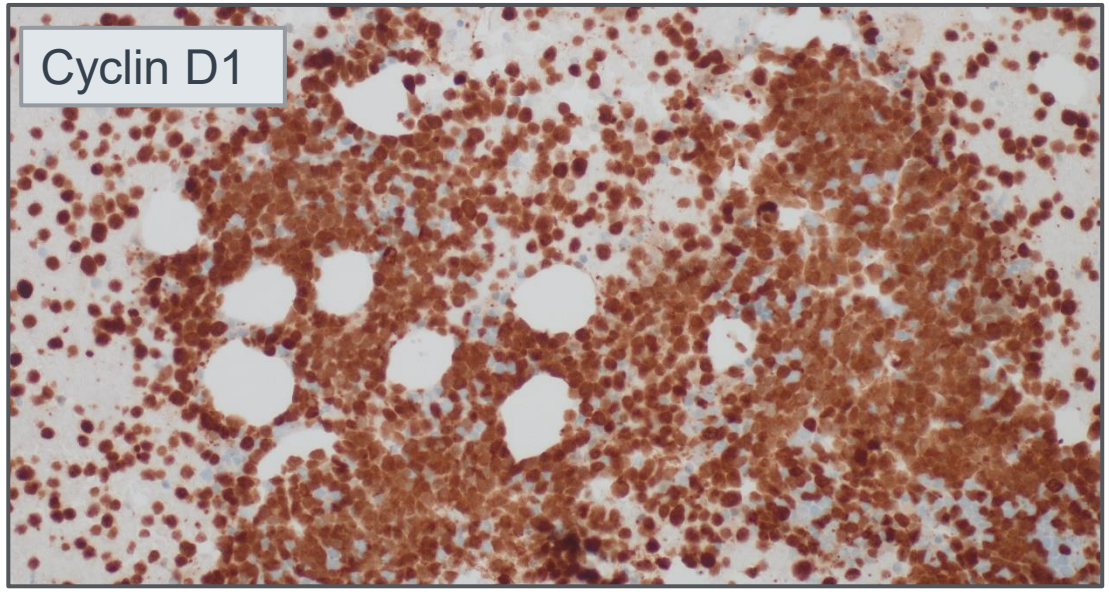
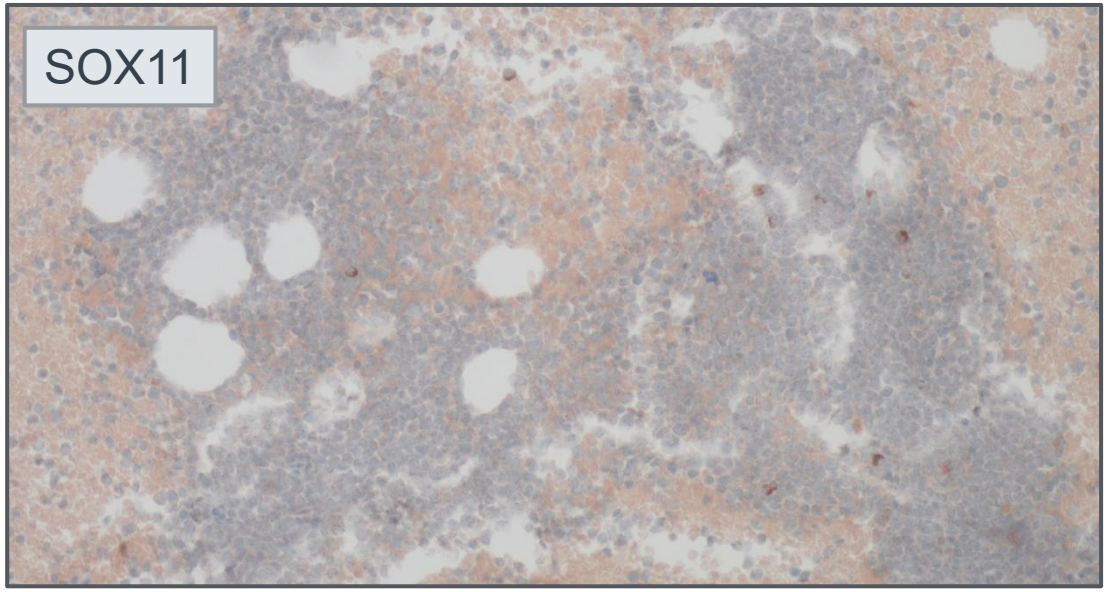
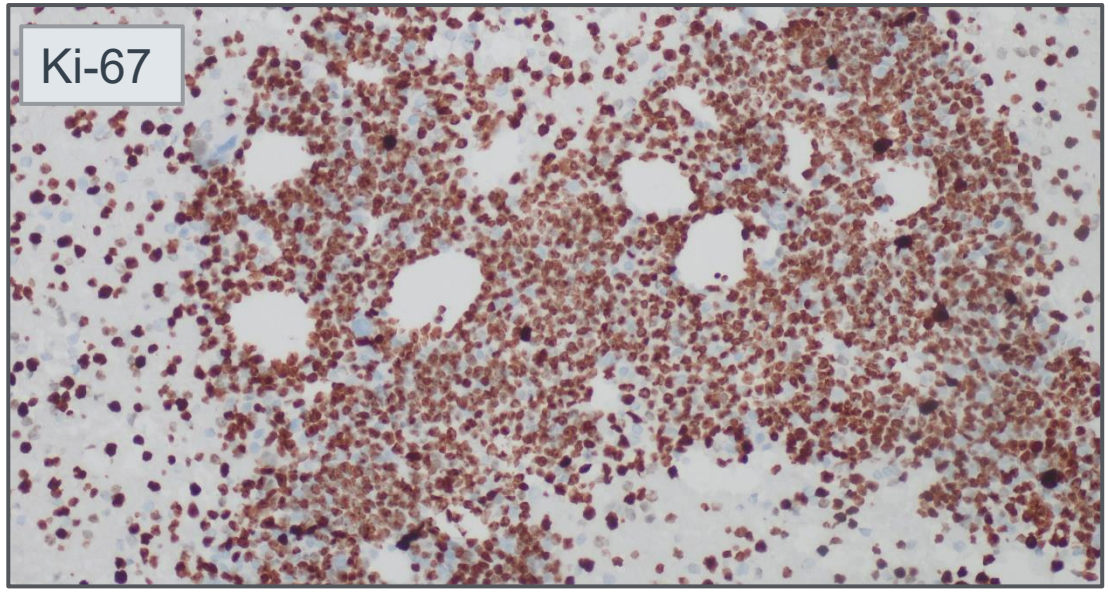
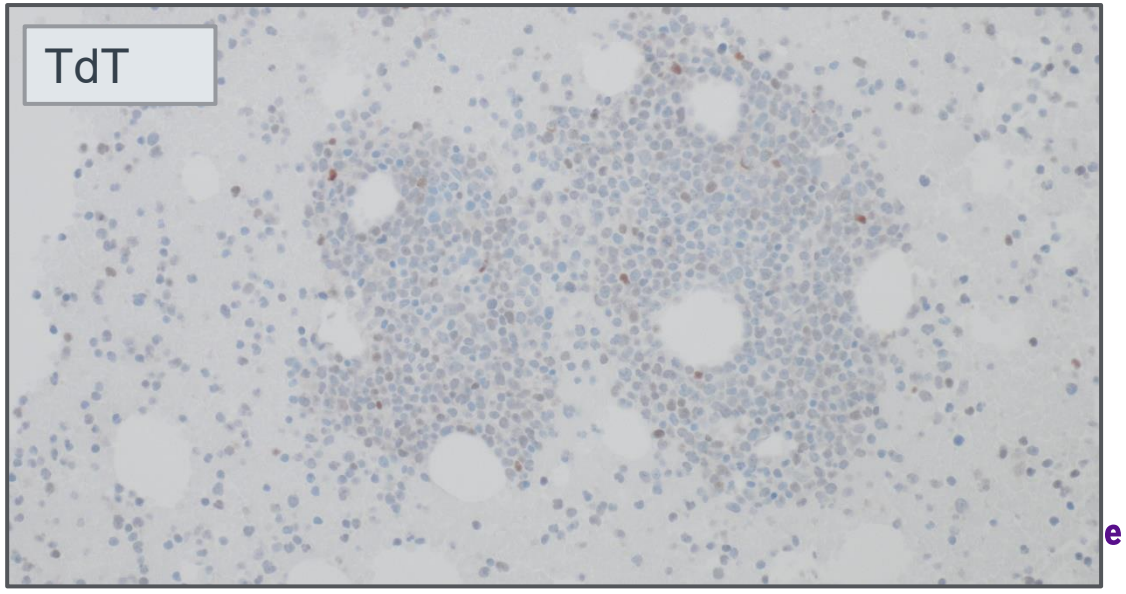
Immunohistochemical stains, cont'd, x20 objective









Summary of immunophenotype by IHC

Results	Markers tested
Positive Markers	CD20, PAX-5, BCL-2, BCL-6, c-MYC, Cyclin D1, LEF1, P53 (wild type pattern)
Negative Markers	CD5, SOX11, CD10 (largely-, rare+), MUM1, EBER ISH, HHV8, CD34, TdT
Ki-67	95%

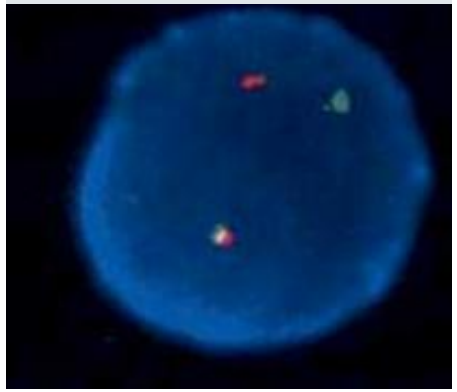
Diagnostic Differentials

Entity	Characteristic features and diagnostic criteria
High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBCL, double-hit or triple-hit)	Most likely given **BCL2, c-MYC positive** and **Ki-67 > 95%**. Often **CD10^{+}**, but ~20–30% can be CD10^{-}. **Requirement of MYC, BCL2, and/or BCL6 fusions**.
Mantle cell lymphoma (blastoid)	Cyclin D1 expression suggests MCL, but **CD5^{-} and SOX11^{-}** make it *very atypical*. Still, **rare CD5^{-}/SOX11^{-} blastoid MCL** cases exist. **(FISH)** as a primary event would be helpful to confirm MCL.
Diffuse large B-cell lymphoma, NOS (DLBCL, NOS)	A **CD10^{-} / MUM1^{-} / BCL6^{+}** pattern fits **germinal center B-cell (GCB) subtype** of DLBCL. High Ki-67 and MYC expression are compatible. Rare subset of DLBCL shows **Cyclin D1 positivity without CCND1 rearrangement**. These are usually **CD5^{-}/CD10^{-}** and aggressive. They're also post-germinal center and expresses MUM1. Also blastoid morphology argues against this.

FISH study

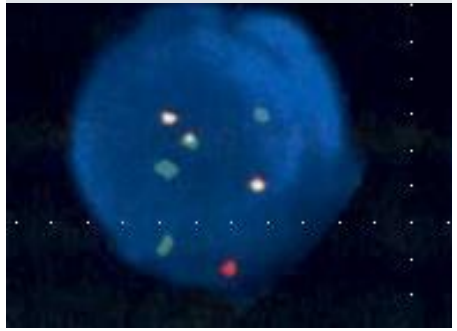
- **Positive for BCL6, IGH-BCL2, MYC-IGH, and CCND1-IGH gene rearrangements.**
  - Positive for the rearrangement of BCL6 (3q27) - 45.5%,
  - Positive for the rearrangement of MYC (8q24.1) - 43.5%
  - Positive for 2~3 fusion for CCND1/IGH (11q13/14q32)- 2~3F1R2~3G in 47%
  - Positive for 2~3 fusion for IGH/BCL2 (14q32/18q21) - 2~3F1R2~3G in 46.5%

BCL6 (3q27)

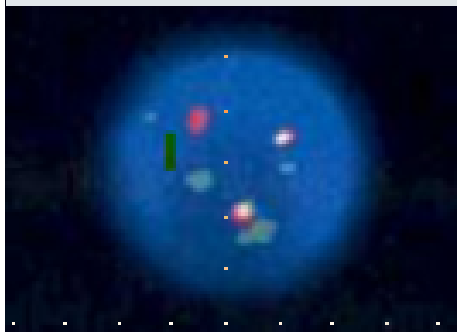


MYC (8q24)

IGH/BCL2 (14q32/18q21



CCND1/IGH (11q13/14q32)



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Proposed Final Diagnosis

High-grade B-cell lymphoma with *MYC, BCL2, BCL6, Cyclin D1* gene rearrangements (quadruple-hit)

Follow-up

- Patient was treated with mini-CHOP because of low performance status and multiple comorbidities; and also, Rituximab.

- Deceased shortly after diagnosis.

Literature Review of Quadruple-Hit

Case #	Sex/ Age	Presentation	CNS Involvement	BM Involvement	LDH 110-225 IU/L
1	M/72	CNS Sx and generalized LAD	Positive	Negative	582
2	F/81	Bone marrow involved by B-cell lymphoma	NA	Positive	NA
3	M/68	Bone marrow involved by B-cell lymphoma	NA	Positive	NA
4	F/51	Diffuse lymphadenopathy	Negative	Negative	522
5	M/79	CNS Sx, LAD, and skin infiltration	Positive	NA	989
6	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA
8	NA	NA	NA	NA	NA
9	F/74	Mediastinal mass	Negative	Negative	NA
10	M/76	Cervical LAD	Negative	Negative	Normal
11	M/73	Tonsillar mass and cervical LAD	Negative	Negative	Normal

Literature Review of Quadruple-Hit, cont'd

Case #	Diagnosis	IHC	Treatment / Response	Follow up/ Outcome
1	MCL Blastoid variant vs BCL UC	GCB Ki-67: 60%	R-CHOP and intracranial MTX/ CR to LAD, PR to CNS	NA/ died of CNS disease
2	DLBCL	NA	Cyclophosphamide therapy	9 days/ Death due to therapy related complications
3	BL/mature B-ALL	NA	NA	6 days/ Death due to unknown causes
4	DLBCL	GCB, Ki67: 80%	R-CHOP/ CR	30 months/ NA
5	DLBCL vs Pleomorphic MCL	GCB Ki67: 80%; SOX11-	Rituximab, Ifosfamide, Cytosine-arabinoside Intrathecal MTX/ NA	4 months/ Died of disease
6	HGBCL with quadruple hits	NA	Autologous BM transplantation	8 months/ Died of relapse
7	HGBCL	Non-GCB BCL1+	NA	NA
8	HGBCL	Non-GCB BCL1+	NA	NA
9	HGBCL with quadruple- hits	Non-GCB Ki67: 90%	R-CHOP/ PR	8 months/ Died of disease
10	Quadrupl-hit pleomorphic MCL	CD5-, SOX11- Ki67: 60%	Lenalidomide in combination with R2-CHOP/ CR	15 months NA
11	HGBCL with BCL2, BCL6, MYC and CCND1 R	GCB, CD5-, SOX11- Ki67: 90%	R-EPOCH/ CR	20 months/ Alive

Literature Review of Quadruple-Hit, NGS Results

NGS								
Case 1			Case 2			Case 3		
Gene	AA change	VAF	Gene	AA change	VAF	Gene	AA change	VAF
ARID1A	p.Ser280AlafsTer111	11%	CDKN2A	p.R80*	39%	ARID1B	p.Gln454fs	9.05%
BCL2	-	5%	KRAS	p.G13D	35%	BCL2	p.Ala131Val	3.00%
CCND3	p.Ser259Ala	42%	TP53	p.F270S	33%	BCL2	p.Arg146Lys	28.00%
FANCA	p.Arg1011His	7%	TNFRSF14	p.T169fs*65	32%	BCL2	p.Val134Met	1.00%
KMT2D	p.Arg2734Ter	43%				CCND1	p.Ala121Ser	19.00%
MYC	p.Leu159Phe	14%				CCND1	p.Glu162Ala	23.00%
MYC	p.Gln113His	13%				CCND1	p.Thr184Ile	3.00%
MYC	p.Tyr89Asn	12%				FOXO1	p.Thr24Ile	30.00%
PIM1	p.Tyr38Phe	9%				IL7R	p.Phe213Leu	21.00%
PIM1	p.Lys29Asn	8%				MGA	p.Gln1988*	27.00%
PIM1	p.Thr23Ile	7%				PIM1 SGK1	p.Ser97Asn	22.00%
PIM1	p.Val96Leu	7%				SGK1	p.Ala121Gly	24.00%
PXDNL	p.Thr453Ser	8%				SGK1	p.Met385Ile	27.00%
SF3B1	p.Lys666Asn	9%					p.Pro190Ala	25.00%
SOCS1	p.Ala16Thr	7%						
TNFRSF14	p.Gln158Ter	8%						
TSC2	p.Gly20Ter	8%						

Case 1 (HGBCL, quadruple-hit): The combination of mutations best fits in the EZB-DLBCL molecular cluster. PIM1, KMT2D, TNFRSF14 genes mutation frequently reported in DLBCL

Case 2(HGBCL, quadruple-hit): CDKN2A and TP53 can be seen in both cases. KRAS and TNFRSF14 are very atypical for MCL.

Case 3(quadruple hit MCL): Deletions or mutations of the *ARID1B* gene have been observed in lymphoplasmacytic lymphoma. The Y24I mutation in *FOXO1* gene has been identified in diffuse large B-cell lymphoma (DLBCL) and was associated with decreased overall survival. Mutations of the *SGK1* gene were common in DLBCL and the *PIMI* gene mutation has been identified in DLBCL (leg type). The *CCND1* mutations have been reported in MCL.

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Mutation profile between HGBCL and MCL

Mantle Cell Lymphoma (MCL)	High Grade B-Cell Lymphoma (Adult HGBCL)
ATM, 41-61%	MYD88 (ABC subtype), CD79B, CARD11, TBL1XR1, TNFAIP3
TP53, 14-31%	PRDM1 (loss and/or mutation, 53%)
KMT2D, 12-23%	KMT2D (MLL2), TET2
CCND1, 14-34%	TP53 (loss/mutation, ~50%), ASPM
NSD2, 10-13%	PIM1 (20%)
BIRC3, 6-10%	DDX3X, GNA13, CCND3 (rare)
Notch1, 5-14%	

HGBCL w Quadruple-hit vs. MCL

- In DLBCL, the data suggests that the *CCND1* rearrangement is a **secondary event** during lymphoma evolution. This is in contrast to MCL, where *CCND1* rearrangement is considered to be a **primary genetic event**.
- Non-GCB phenotype is a point against the diagnosis of MCL because MCL is believed to originate from a naive pre–germinal center B cell
- Loss or marked reduction of p27 expression supports MCL, particularly when Cyclin D1 is positive or suspected.
- Treatment course may be helpful.
- Moreover, a yet unacknowledged diagnostic “gray zone” may exist between DLBCL and MCL.

Take Home Messages

- B-cell lymphomas with concurrent *MYC*, *BCL2*, *BCL6*, and *CCND1* rearrangements appear to be a rare occurrence; however, current standard approaches to DLBCL/HGBL classification do not require routine testing for *CCND1* rearrangement.

- With the current classification schemes de-emphasizing the importance of *BCL6* rearrangement, this may no longer be routinely assessed as well.

- The addition of *CCND1* rearrangement in the workup for a DLBCL/HGBL might only be sought in cases with BCL1 protein expression, as seen in our case.

- Sequencing may be of benefit for delineating DLBCL from MCL in the quadruple hit setting, although current data is limited.

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Thank you!

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