Multi-Institutional Hematopathology Interesting Case Conference (MHICC)

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04/22/2026

Disclosure

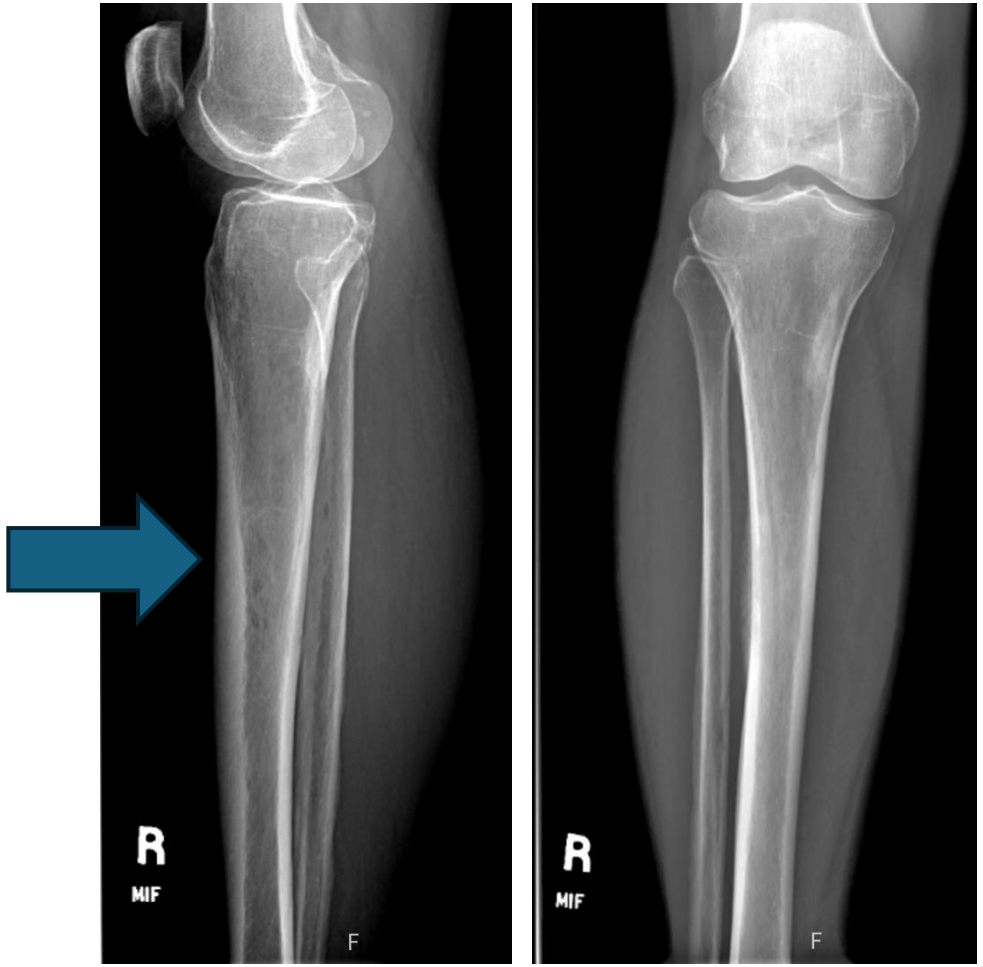
I have nothing to disclose

73, F

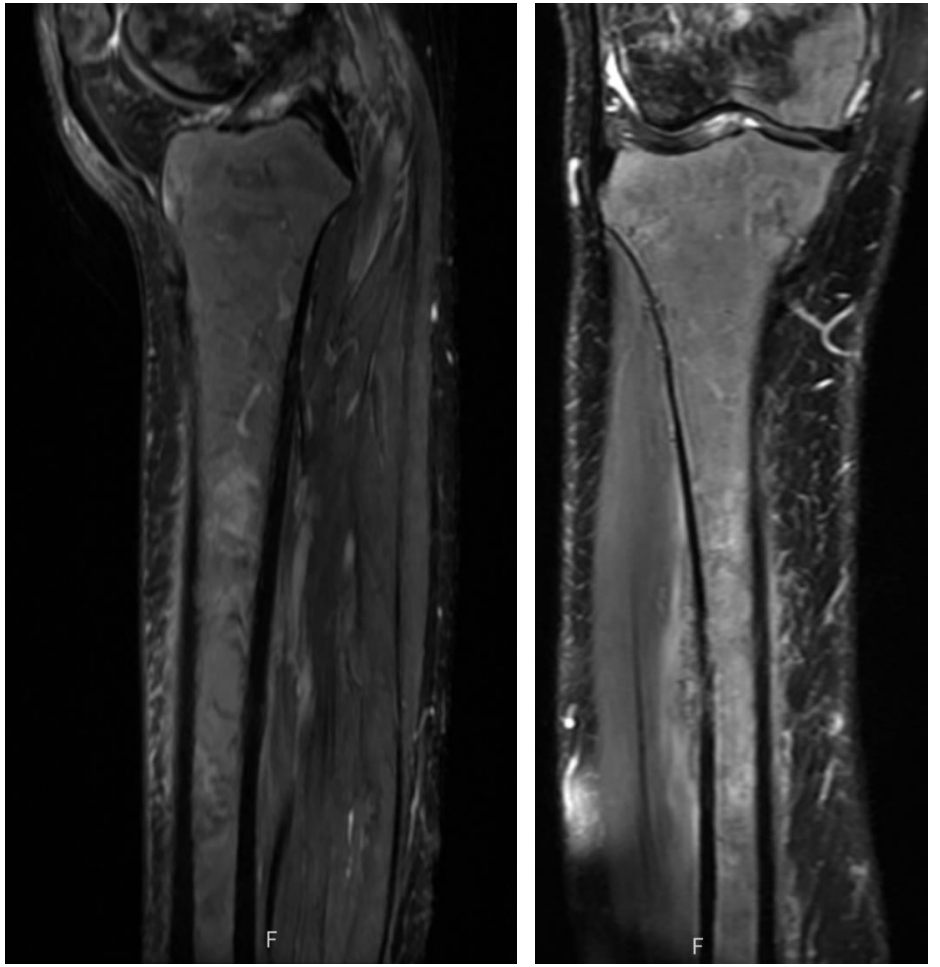
- weight loss and persistent right leg pain

Medical Hx

- Familial Mediterranean Fever
- Osteoarthritis
- Bilateral DCIS, post-lumpectomy (2002)
- CLL (2018), observation



11/12/2025



11/22/2025

Proximal to mid right tibial diaphysis aggressive lesion with cortical erosions and extraosseous soft tissue. Differential diagnosis includes leukemic involvement, primary osseous lesion, and metastasis.

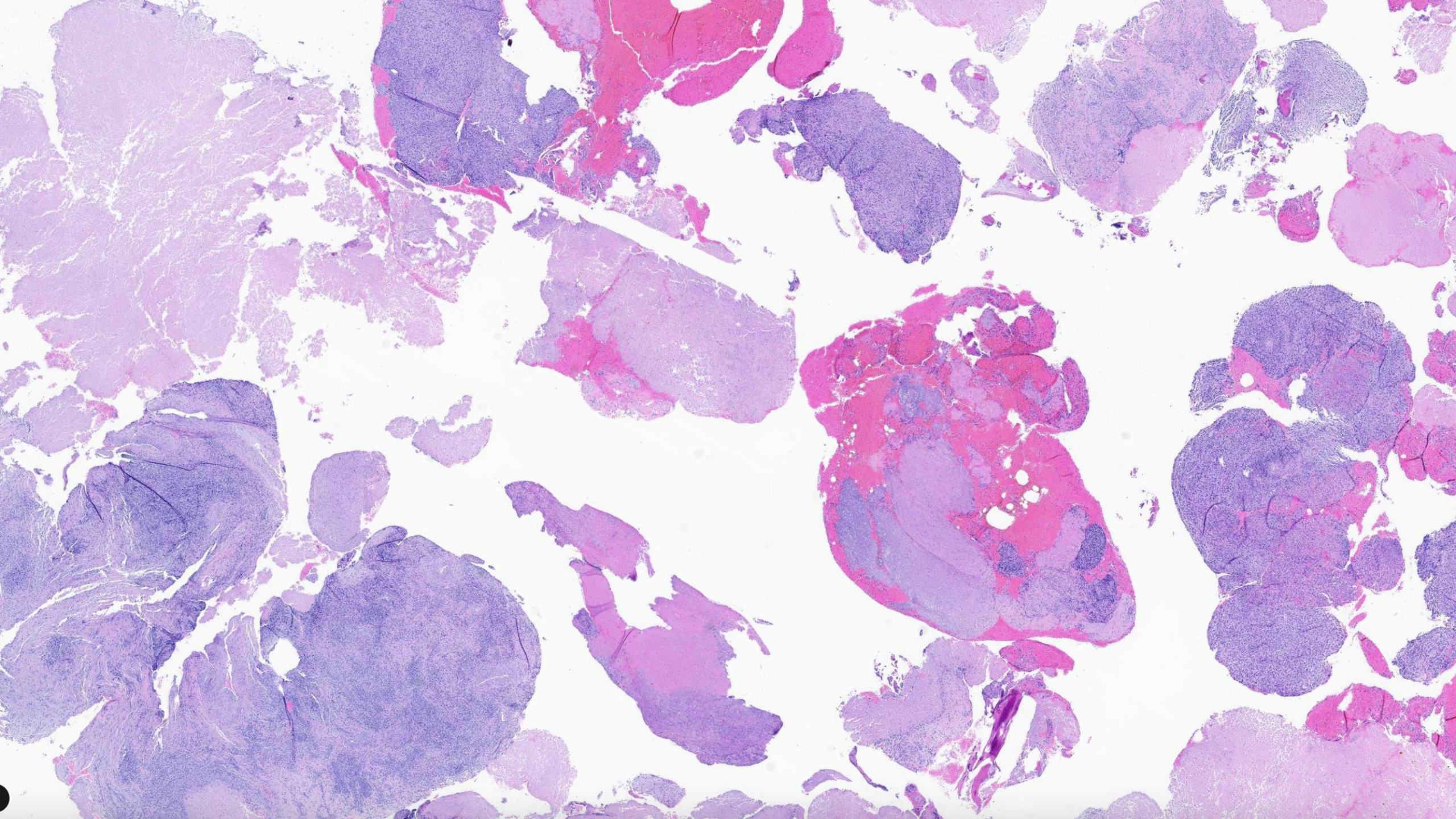
1. Abundant normal sized and slightly enlarged lymph nodes throughout the body with only minimal FDG uptake (SUV <2), consistent with CLL.

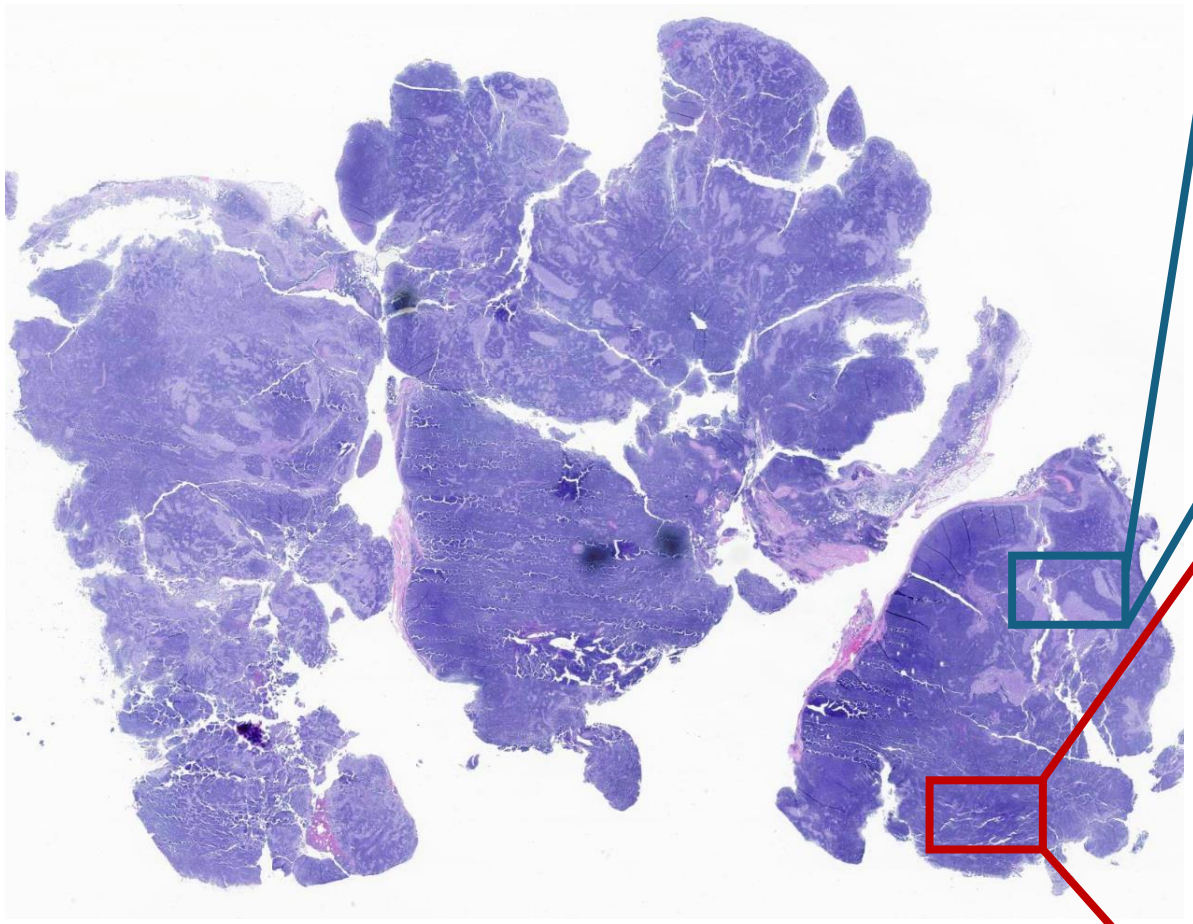
2. Splenomegaly without focal abnormal FDG uptake, consistent with CLL.

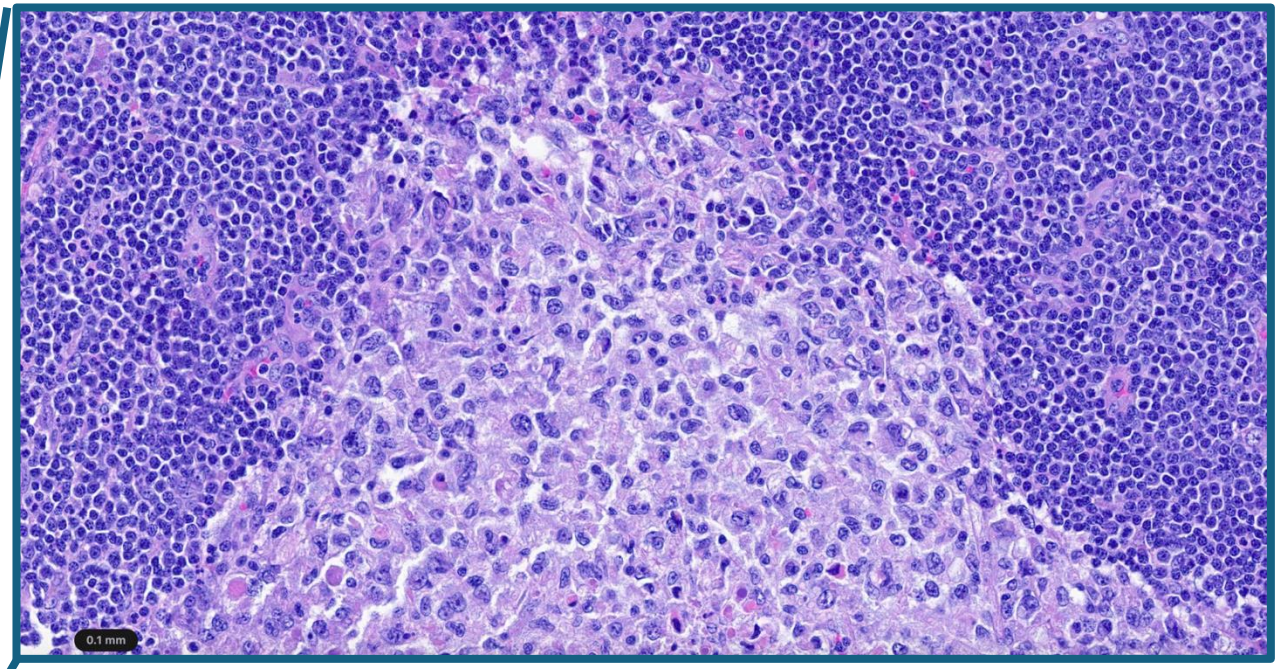
3. Prominent homogeneous marrow uptake is suspicious for CLL involvement.

A few areas of more prominent uptake, in particular in the right tibia (SUV 15.4) with destruction of lateral cortex and in the medial condyle of the right humerus (SUV 4.6) .

Since no FDG avid primary tumor is identified, these are possibly sites of transformed lymphoma; biopsy is recommended.



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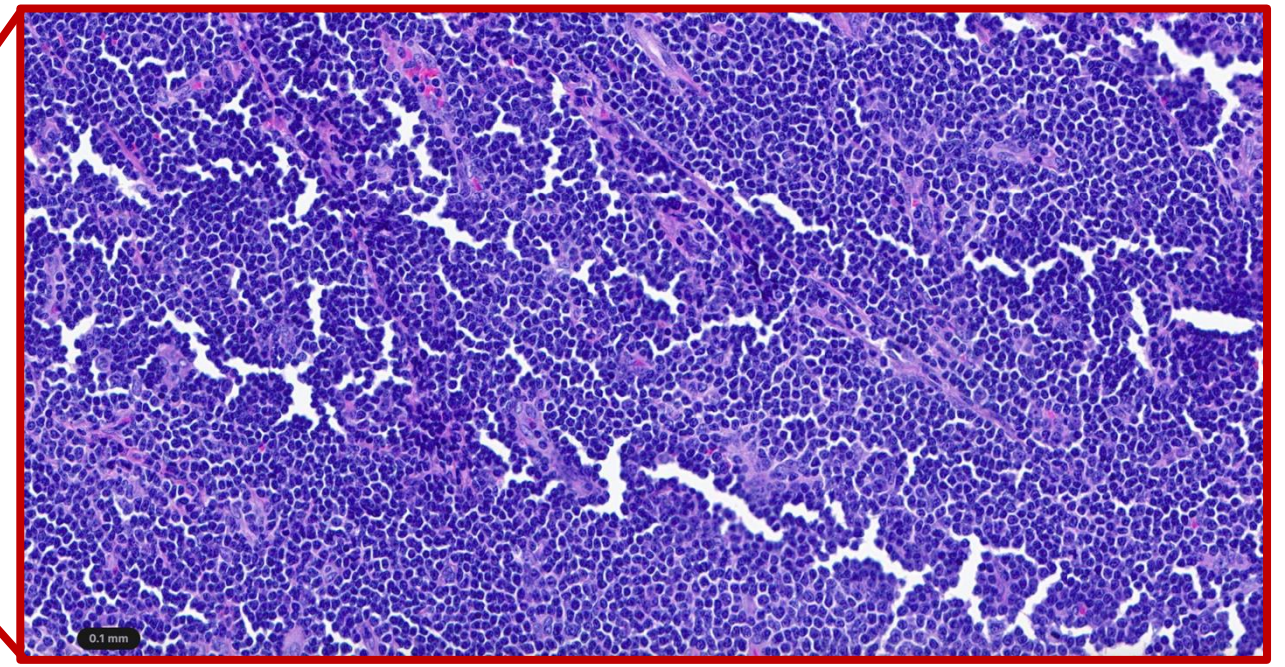
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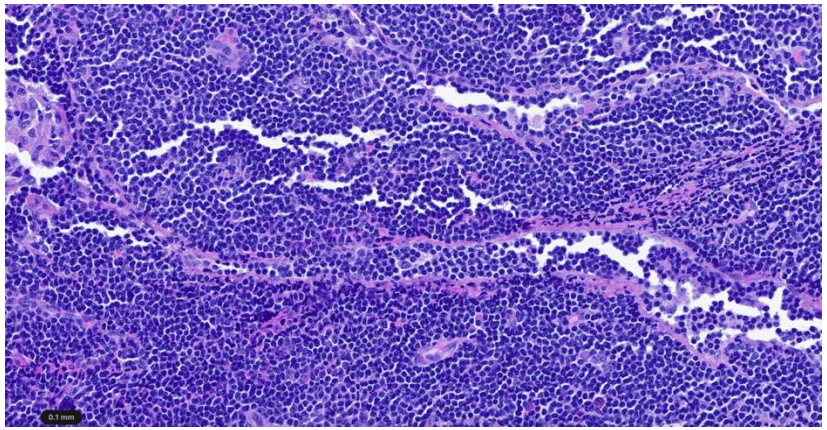

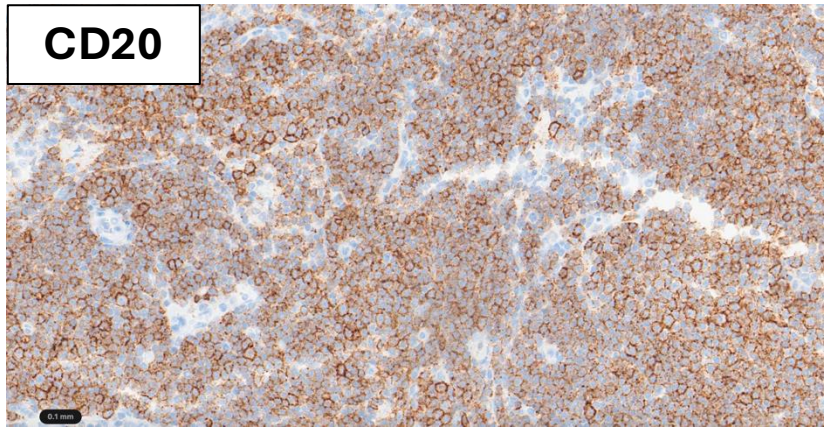
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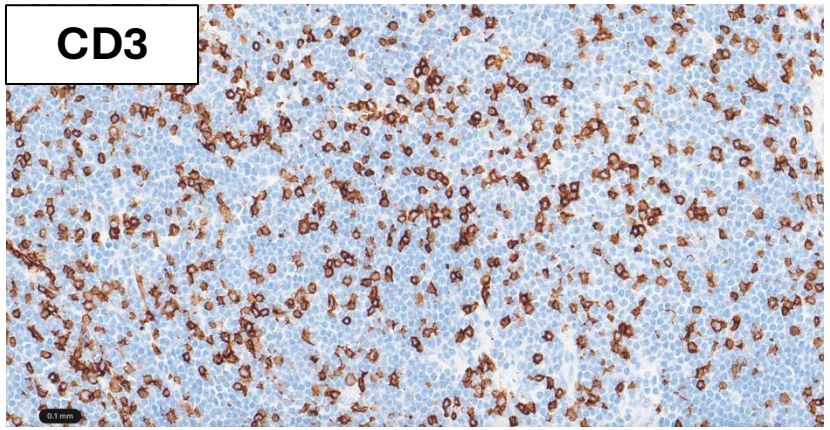
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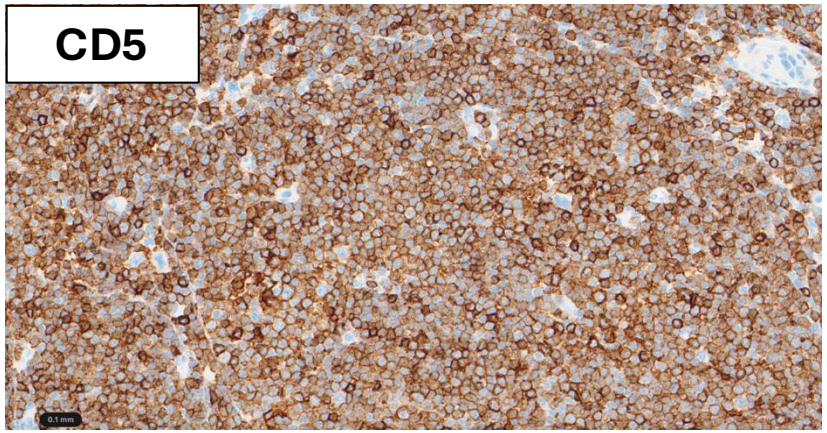
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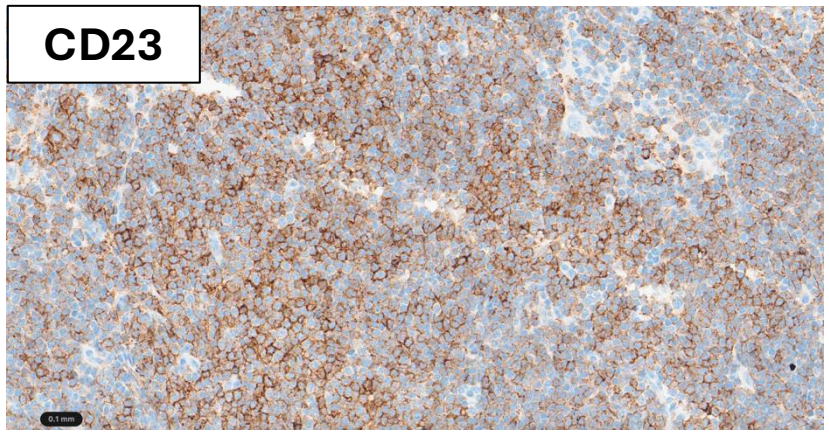
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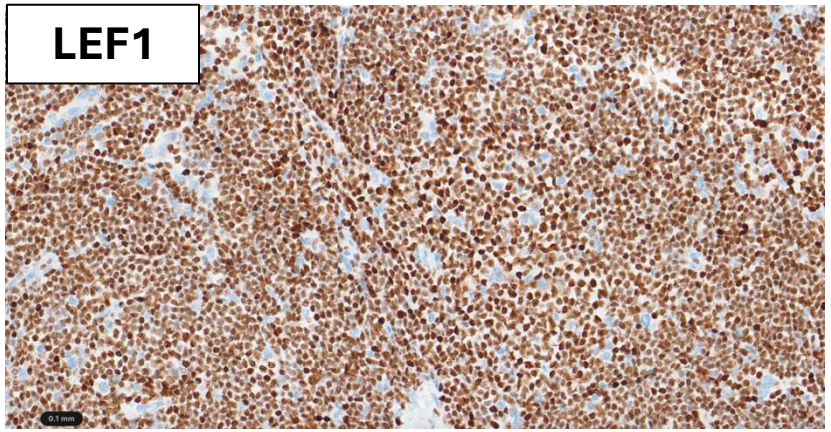
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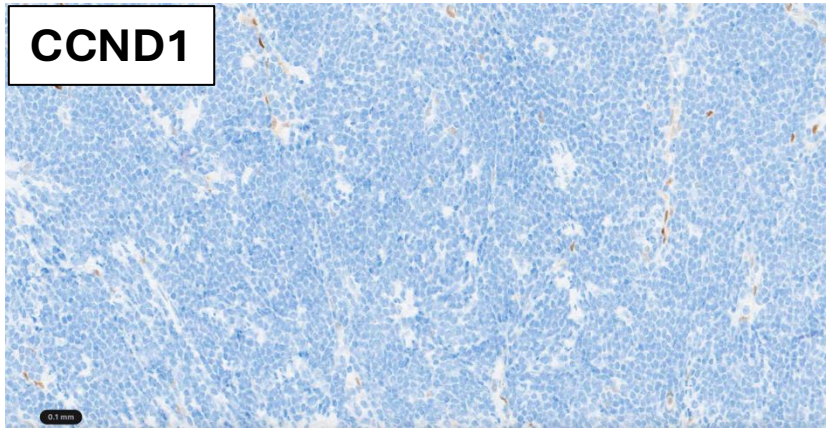
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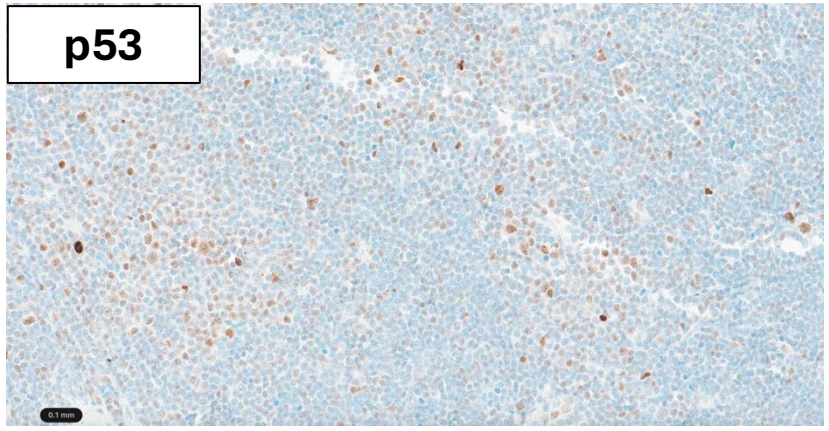
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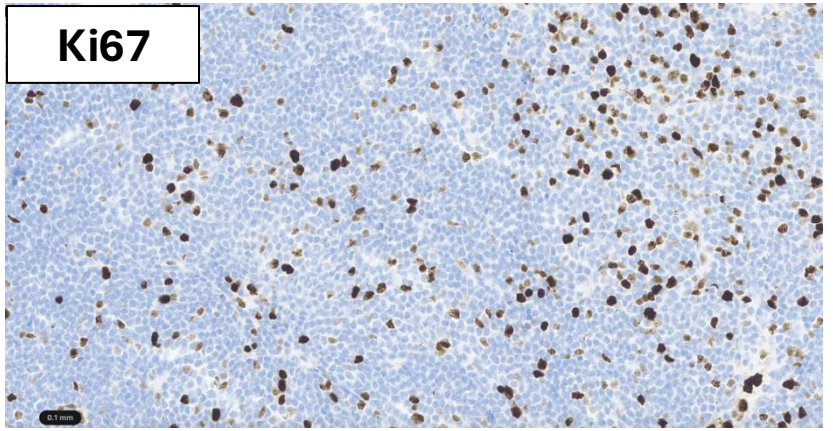
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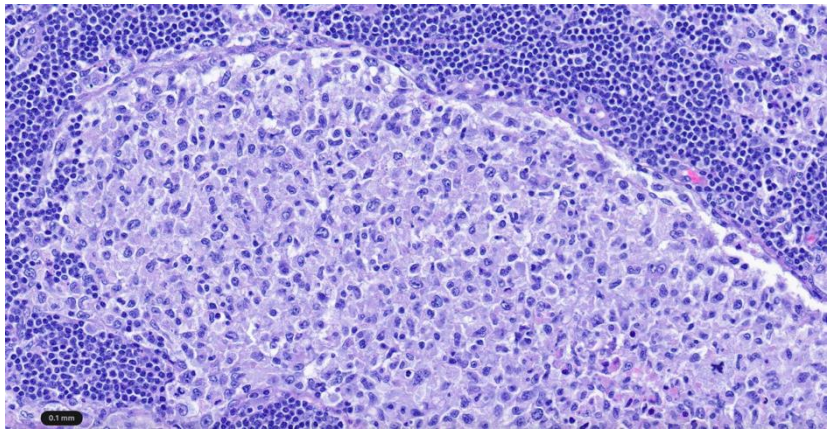

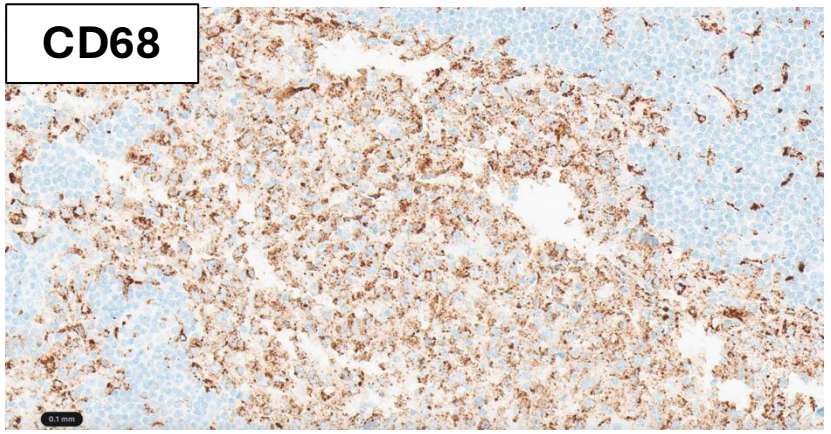
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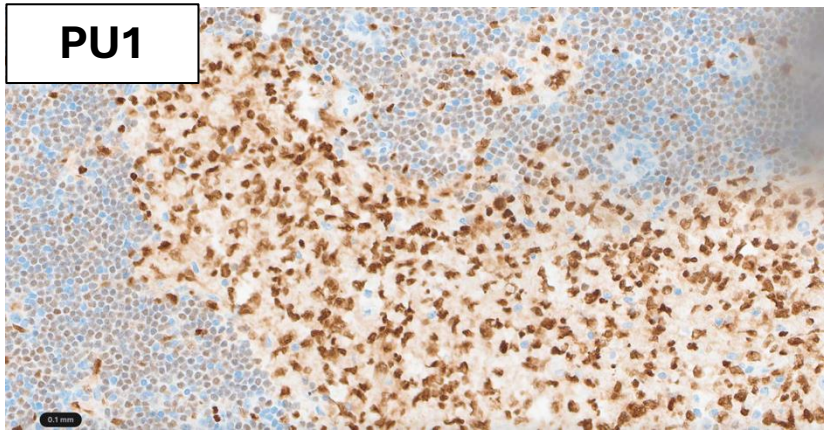
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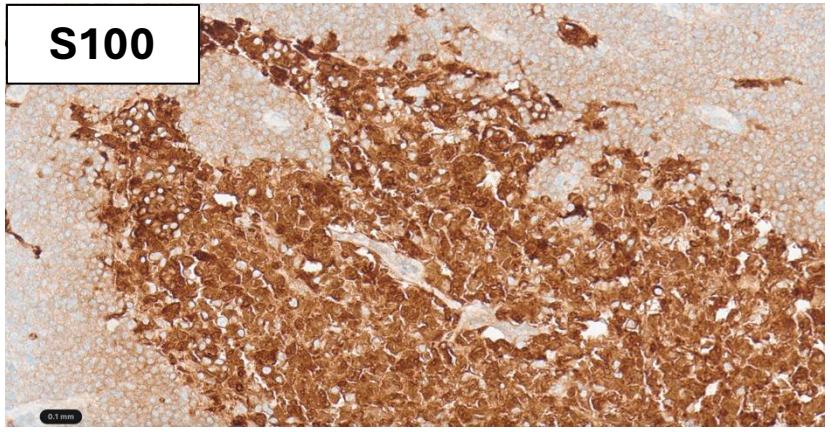
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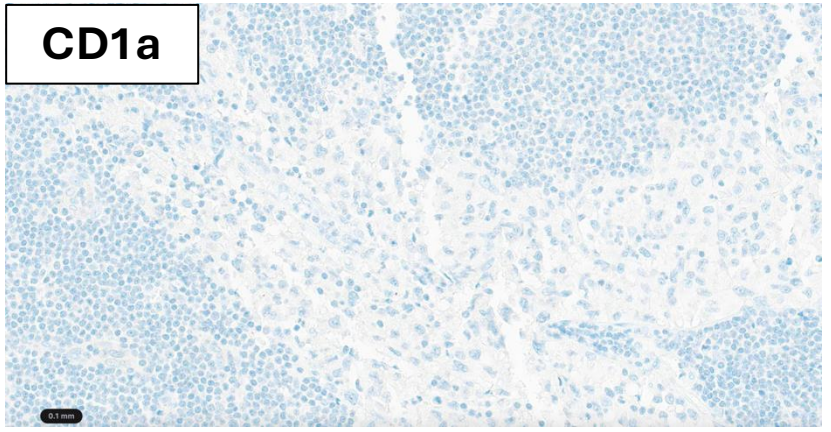
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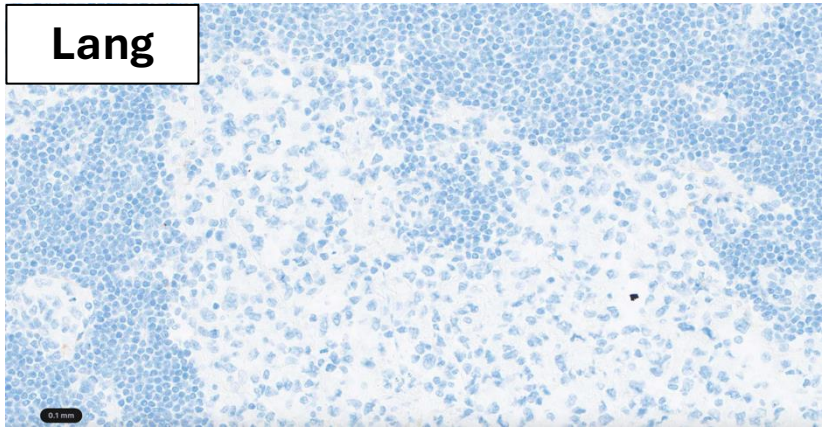
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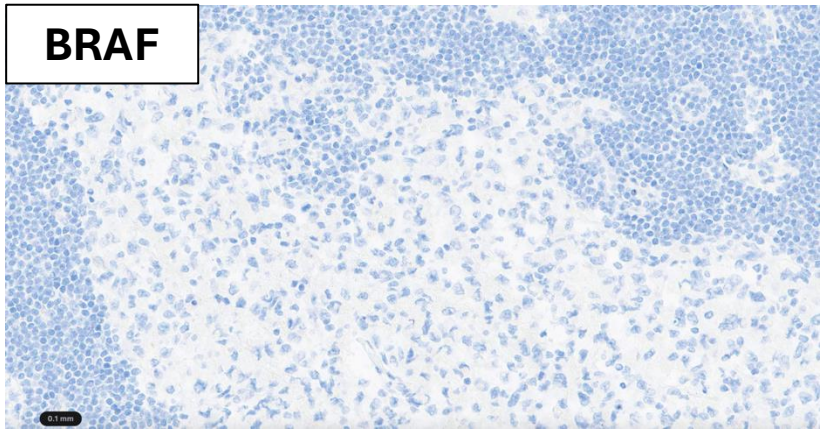
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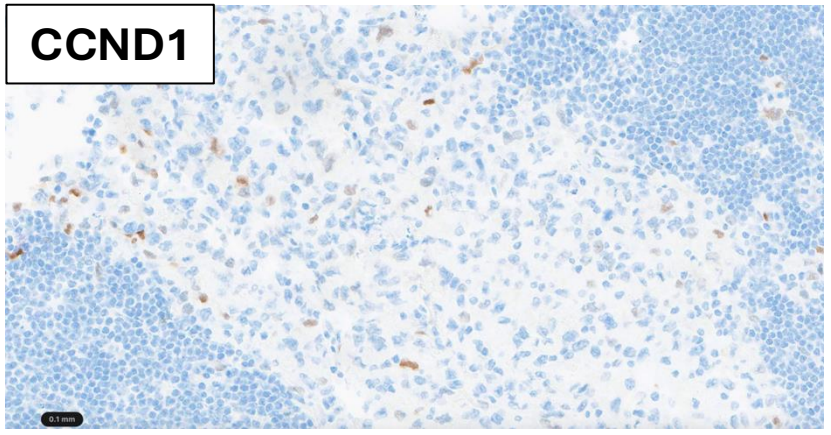
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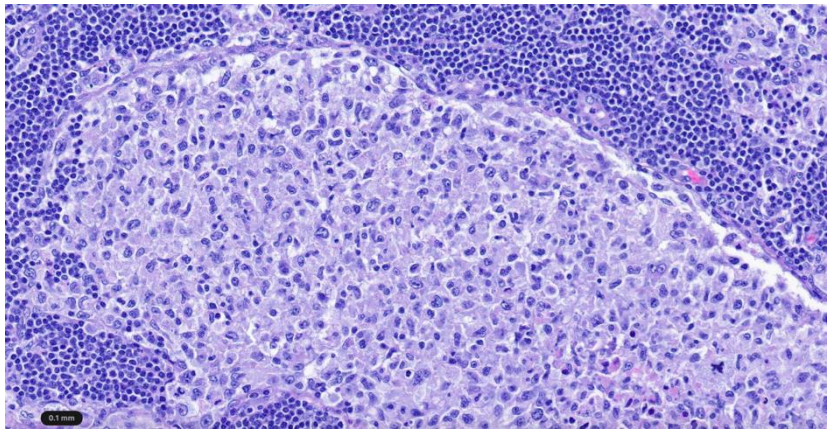

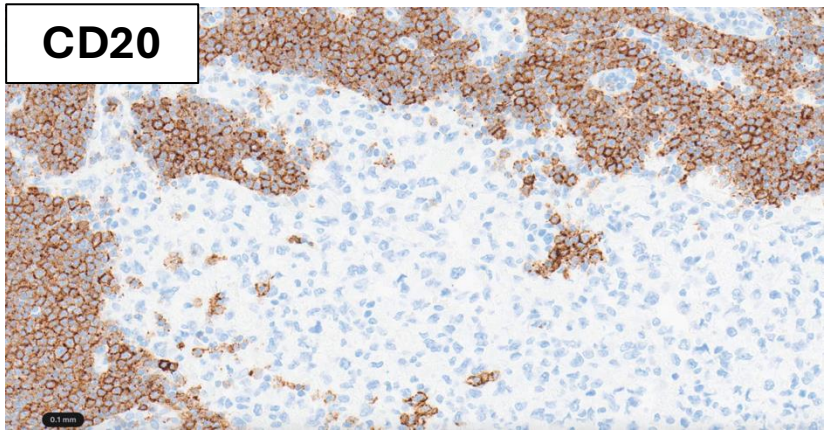
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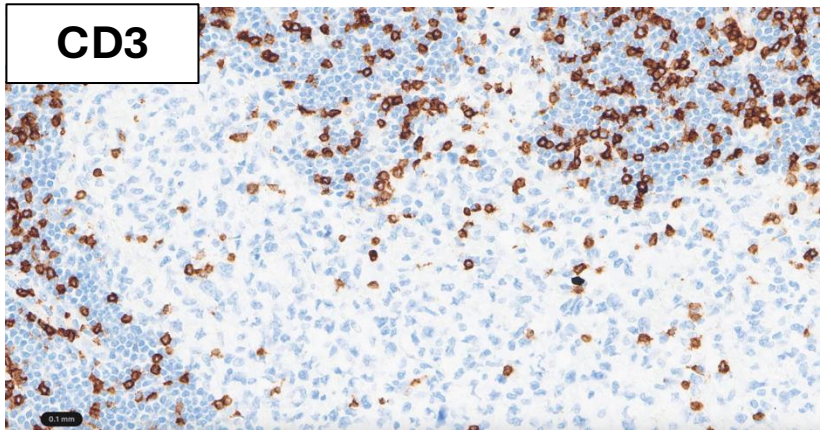
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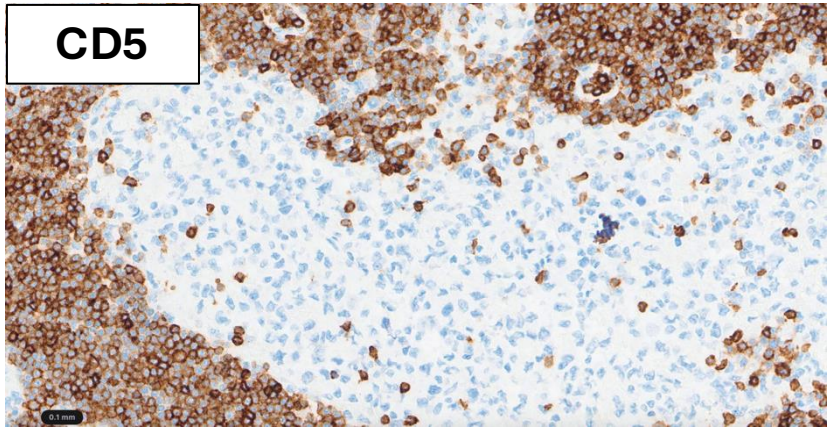
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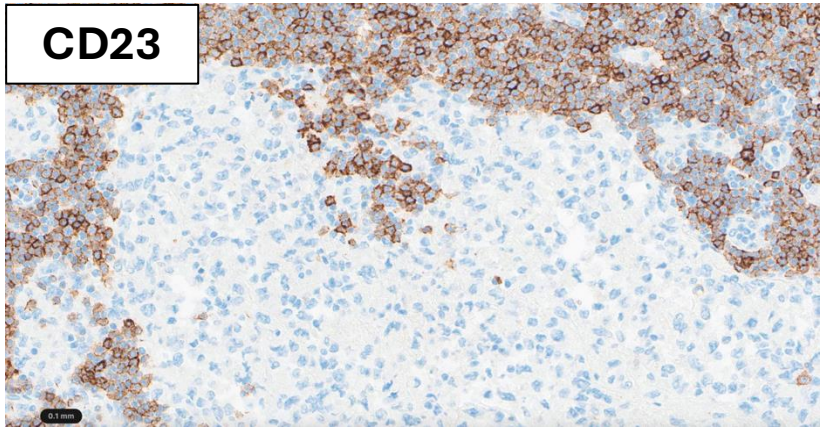
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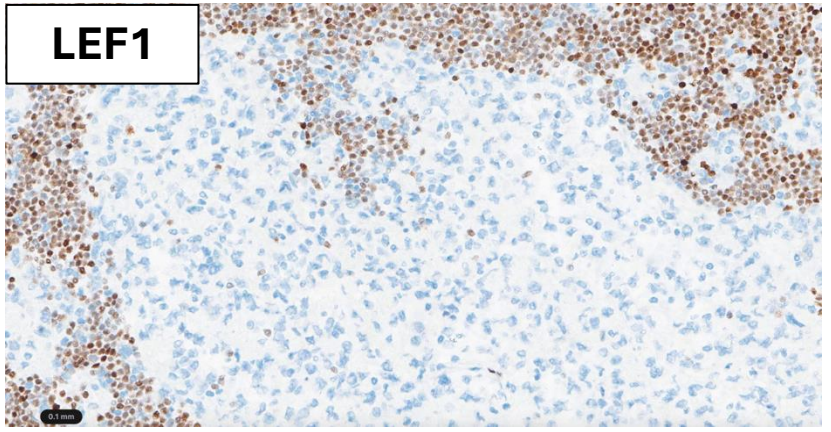
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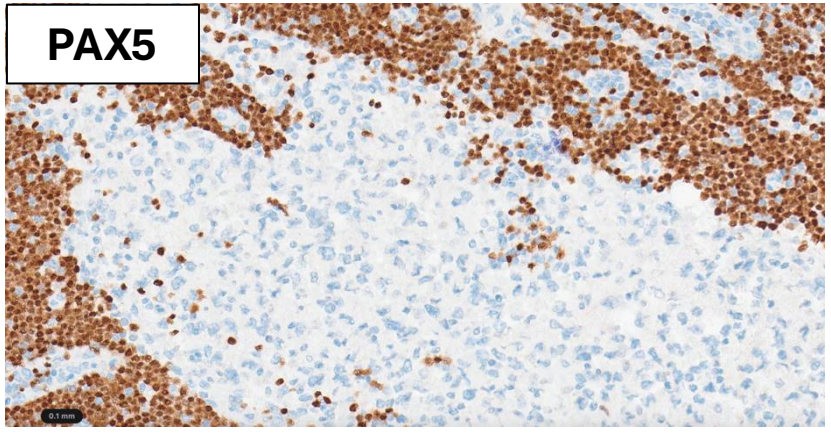
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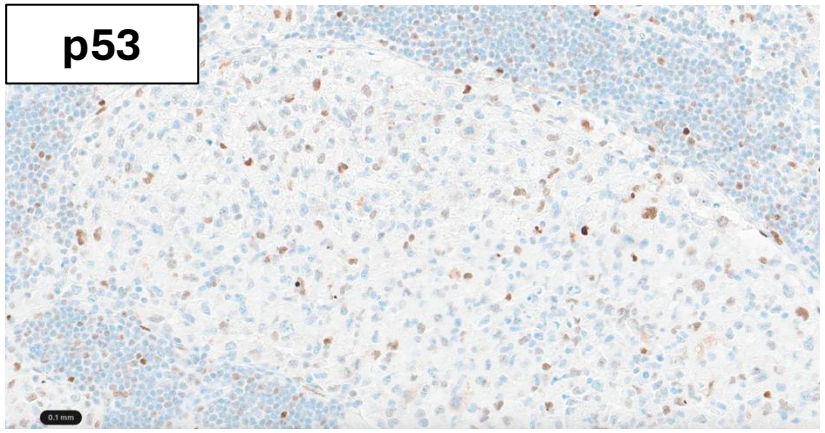
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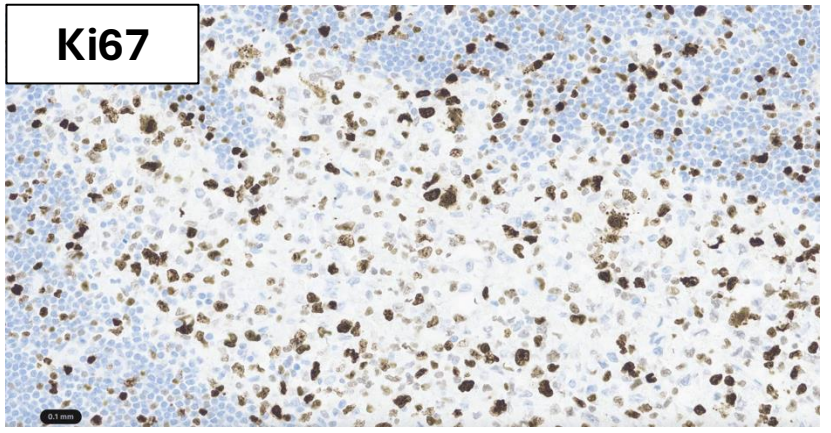
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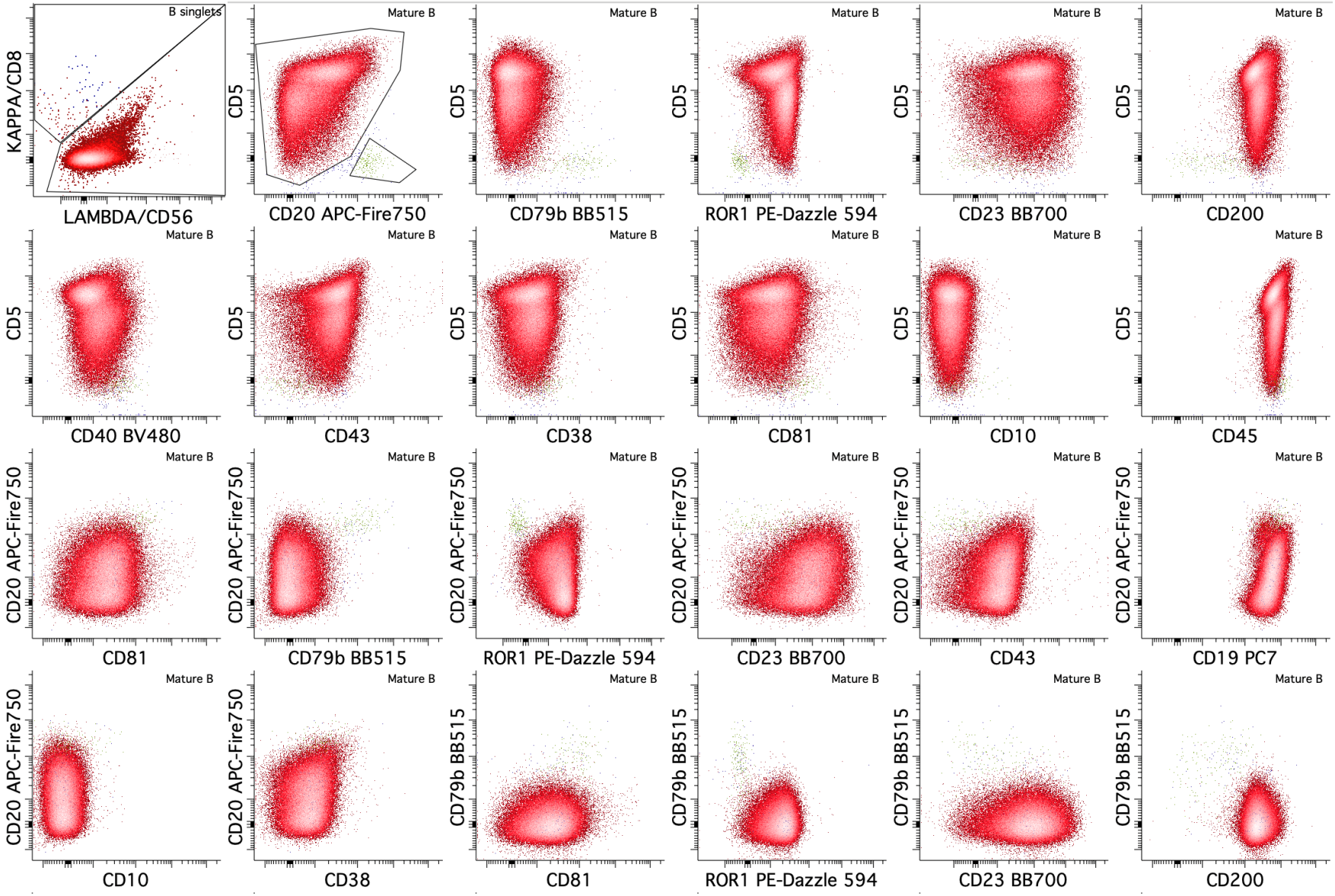
Flow Cytometry - Tibia

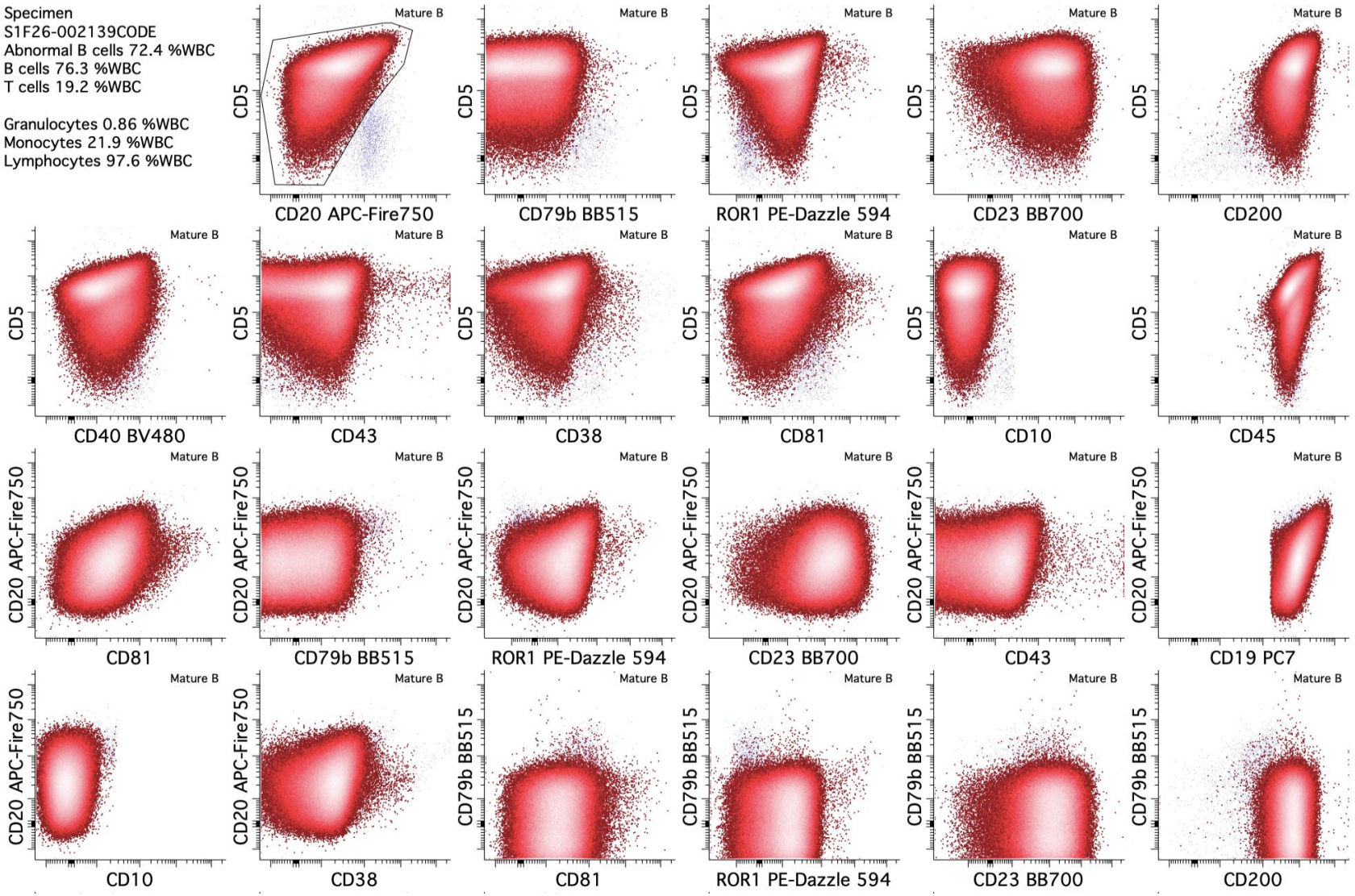


Abnormal B cell population detected (83.9% of WBC).

Immunophenotype:

- Abnormal: CD5 (positive), CD20 (dim), CD22 (negative to dim), CD23 (positive), CD43 (positive), CD79b (negative), CD81 (negative to dim), CD200 (bright), ROR1 (positive), surface Lambda (dim)
- Normal: CD19, CD40, CD45
- Negative: CD3, CD10, CD14, CD25, CD38, CD279 (PD1), surface Kappa

Flow Cytometry – Inguinal LN



Abnormal B cell population detected (59.9% of WBC).

Immunophenotype:

- Abnormal: CD5 (positive), CD20 (dim), CD22 (negative to dim), CD23 (positive), CD43 (positive), CD79b (negative), CD81 (negative to dim), CD200 (bright), ROR1 (positive), surface Lambda (dim)
- Normal: CD19, CD40, CD45
- Negative: CD3, CD10, CD14, CD25, CD38, CD279 (PD1), surface Kappa

MSK-IMPACT (Targeted NGS, DNA)

Tibia (lesion)

GENE	TYPE	ALTERATION	Allele Frequency
CHD2	Missense Mutation	D888Y (c.2662G>T)	3.49%
ATM	Missense Mutation	I2702R (c.8105T>G)	2.23%
KRAS	Missense Mutation	G12A (c.35G>C)	16.2%
DNMT3A	Splicing Mutation	X803_splice (c.2408+1G>A)	13.9%
DNMT3A	Missense Mutation	E733V (c.2198A>T)	12.12%
PIM1	Missense Mutation	H68N (c.202C>A)	13.31%
CIITA	Frameshift Insertion	A354Rfs*46 (c.1059dupC)	8.76%
TNFRSF14	Missense Mutation	G60S (c.178G>A)	29.54%
KLHL6	Missense Mutation	E568K (c.1702G>A)	11.58%
CD70	Missense Mutation	L167F (c.499C>T)	23.19%

Peripheral Blood

GENE	TYPE	ALTERATION	Allele Frequency
CHD2	Missense Mutation	D888Y (c.2662G>T)	47.77%
ATM	Missense Mutation	I2702R (c.8105T>G)	15.07%
ATM	Frameshift Deletion	F858Tfs*21 (c.2572_2575delTTTA)	1.4%

Molecular Studies – Peripheral Blood

SNP-ARRAY ANALYSIS

- Chromosome 11: low level loss in segment 11q21-q23.3, including the ATM gene
- Chromosome 13: loss in segment 13q14.2-q14.3, including the DLEU1, DLEU2, MIR16-1, and a portion of DLEU7 genes
- No evidence of 6q deletion by SNP-array analysis.
- No evidence of trisomy 12 by SNP-array analysis.
- No evidence of TP53 (17p13) gene deletion by SNP-array analysis.

NGS Clonality Testing – IGHV

- Clonal rearrangement involving the IG heavy chain gene is detected.
- IGHV mutation status is mutated

Clonal Sequence 1:
- IGHV Family: IGHV4-34
- IGHJ Family: IGHJ2
- Functionality: Productive
- Mutation Frequency: 6.48%
- Mutated

Clonal Sequence 2:
- IGHV Family: IGHV3-30
- IGHJ Family: IGHJ2
- Functionality: Unproductive
- Mutation Frequency: 11.82%
- Mutated

Final Diagnosis

- Atypical histiocytic proliferation most consistent with histiocytic sarcoma

- Involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma

TABLE 1 Cases Submitted to Session 1: B-Cell Neoplasms to Histiocytic/Dendritic Cell Neoplasms

Case	Age, y	Sex	Submitter	Panel diagnosis	MAPK variations in HDCN	Clonal relatedness
23[a]	62	M	Nichols	CLL/SLL with clonally related DLBCL variant Richter transformation and transdifferentiation to HS	*KRAS*	Shared trisomy 12 and *FGFR2* variations
168[a]	48	F	Yabe	CLL/SLL with clonally related transdifferentiation to LCS	*BRAF*	Shared variations (*BRAF/NOTCH1*)
33	80	F	Lytle	CLL/SLL with clonally related transdifferentiation to HS	*MAP2K1*	Shared trisomy 12 and peaks of fragment analysis
52	54	M	Hollander	Low-grade B-cell lymphoma with clonally related transdifferentiation to HS	Not done	Shared peaks of fragment analysis
125	59	F	Wong	CLL/SLL with clonally related transdifferentiation to LCS	*BRAF*	Shared *ATM* deletion and peaks of fragment analysis
17	61	M	Ravindran	CLL/SLL with clonally related transdifferentiation to HS	*BRAF* and *KRAS*	Shared trisomy 12
106	61	F	LaValley	Composite CLL/SLL and HS with a history of DLBCL	*KRAS*	Shared trisomy 12 and other karyotypic abnormalities
28[a]	56	F	Yu	MCL with clonally related transdifferentiation to HS	*BRAF* and *KRAS*	Shared *CCND1* rearrangements by FISH and peaks of fragment analysis
177[a]	63	F	Grzywacz	Splenic MZL with clonally related transdifferentiation to HS	*KRAS*	Shared del7q by FISH and *MYD88* and *CREBBP* variations
247	53	F	Sakhdari	MZL with clonally related transdifferentiation to HS	Not detected	Shared peaks of fragment analysis, CDR3 sequence, and many variations
38[a]	70	M	Rohr	FL, grade 1-2, with clonally related transdifferentiation into LCH, and later transformation to DLBCL	Not detected	Shared peaks of fragment analysis, *BCL-2* FISH, and many variations
54[a]	70	F	Karrs	FL, grade 1-2, with clonally related transdifferentiation to HS	*KRAS*	Shared peaks of fragment analysis, *BCL-2* FISH, and many variations
34	31	F	Tashakori	FL, grade 1-2, with clonally related transdifferentiation to LCS	Not done	Shared *BCL-2* FISH
117	64	F	Merzianu	DLBCL with clonally related transdifferentiation to HS during CAR T-cell therapy	*KRAS*	Shared *BCL-2* FISH and many variations
239	65	F	Yuen	FL, grade 1-2, with clonally related transdifferentiation to LCS	*MAP2K1* and *PTEN*	Shared *BCL-2* FISH
45	58	F	Wotherspoon	FL, grade 1-2, with clonally related transdifferentiation to HS	Not detected	Shared *BCL-2* FISH and peaks of fragment analysis
74	60	F	Cook	FL, grade 1-2, with clonally related transdifferentiation to LCS and transformation to DLBCL	*MAP2K1*	Shared *BCL-2* FISH and many variations
86	50	M	Shet	Composite FL and HS	Not done	Unclear
178	57	F	Madrigal	FL, grade 1-2, with clonally related transdifferentiation to HS	*BRAF* and *PTEN*	Shared *BCL-2* FISH and peaks of fragment analysis
235	71	F	Hergott	FL, grade 1-2, with clonally related transdifferentiation to HS	Not detected	Shared *BCL-2* FISH
133[a]	–	–	Zemmour	Clonally related LCH and BPDCN, with concurrent FL and HDCN, unclassifiable	Not detected	Shared variations between LCH and BPDCN but unclear on the nodal biopsy; many shared variations across tissue by whole-exome sequencing
139[a]	56	F	Goodlad	FL, grade 1-2, with clonally related transdifferentiation to HDCN, unclassifiable	Not detected	Shared *BCL-2* by FISH
79	13	F	Aljudi	B-ALL to HS	Not done	Shared SNV array abnormalities
203	14	M	Fitzpatrick	B-ALL to HS	*NRAS*	Shared *DNMT3A* and *NRAS* variations

AJCP | REVIEW ARTICLE

B-cell lineage neoplasms transdifferentiating into histiocytic/dendritic cell neoplasms: diversity, differentiation lineage, genomic alterations, and therapy

Report from the 2021 SH/EAHP Workshop

Wenbin Xiao, MD, PhD,[1,•] Catalina Amador, MD,[2] James R. Cook, MD, PhD,[3,•] Magdalena Czader, MD, PhD,[4] Sandeep Dave, MD, MS,[5] Ahmet Dogan, MD, PhD,[1] Amy Duffield, MD, PhD,[1,] John Goodlad, MD,[6,•] Reza Nejati, MD,[7] German Ott, MD,[8] Mariusz Wasik, MD[7,•]*

KEY POINTS

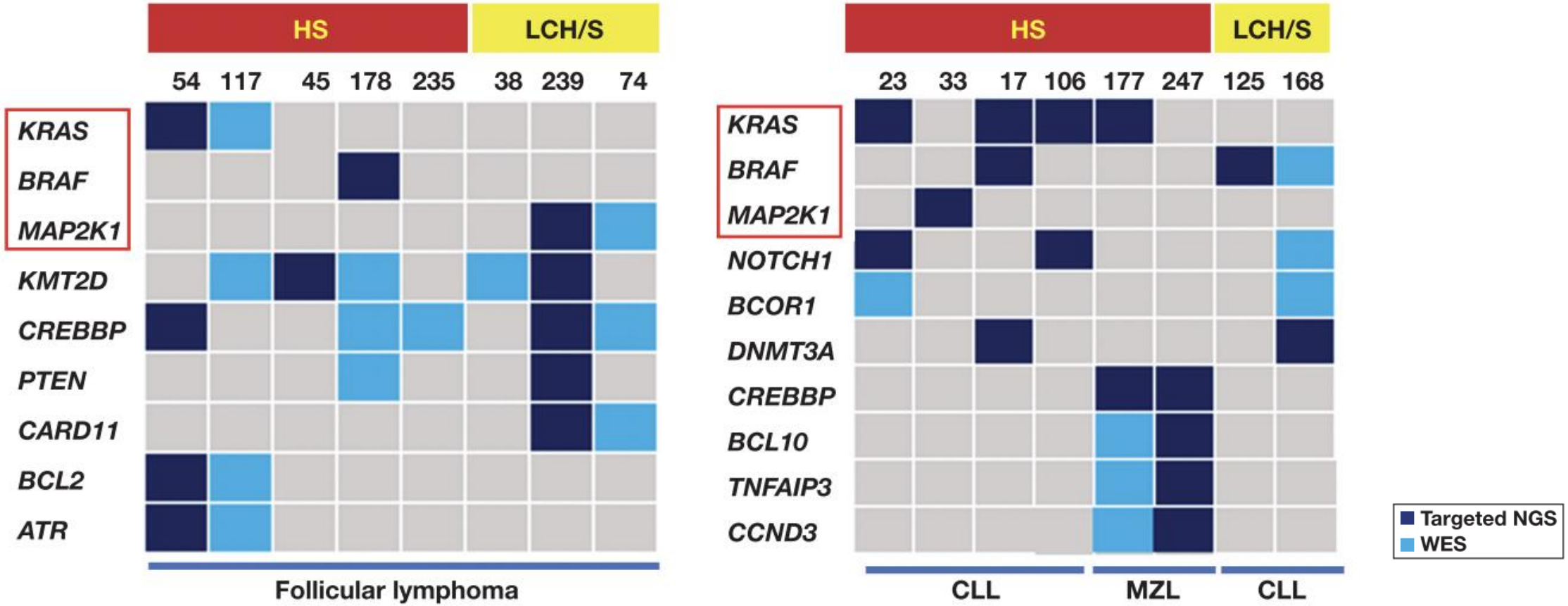
- Transdifferentiated histiocytic/dendritic cell neoplasms (HDCNs) show marked heterogeneity and overlapping immunophenotypic features.
- Variations in the MAPK pathway are enriched in HDCNs and may be therapeutic targets.
- Transdifferentiation into HDCNs occurs through both linear and divergent clonal evolution.

KEY WORDS

B-cell lymphoma; histiocytic/dendritic cell neoplasm; transdifferentiation

Xiao, Wenbin et al. *AJCP* (2023)

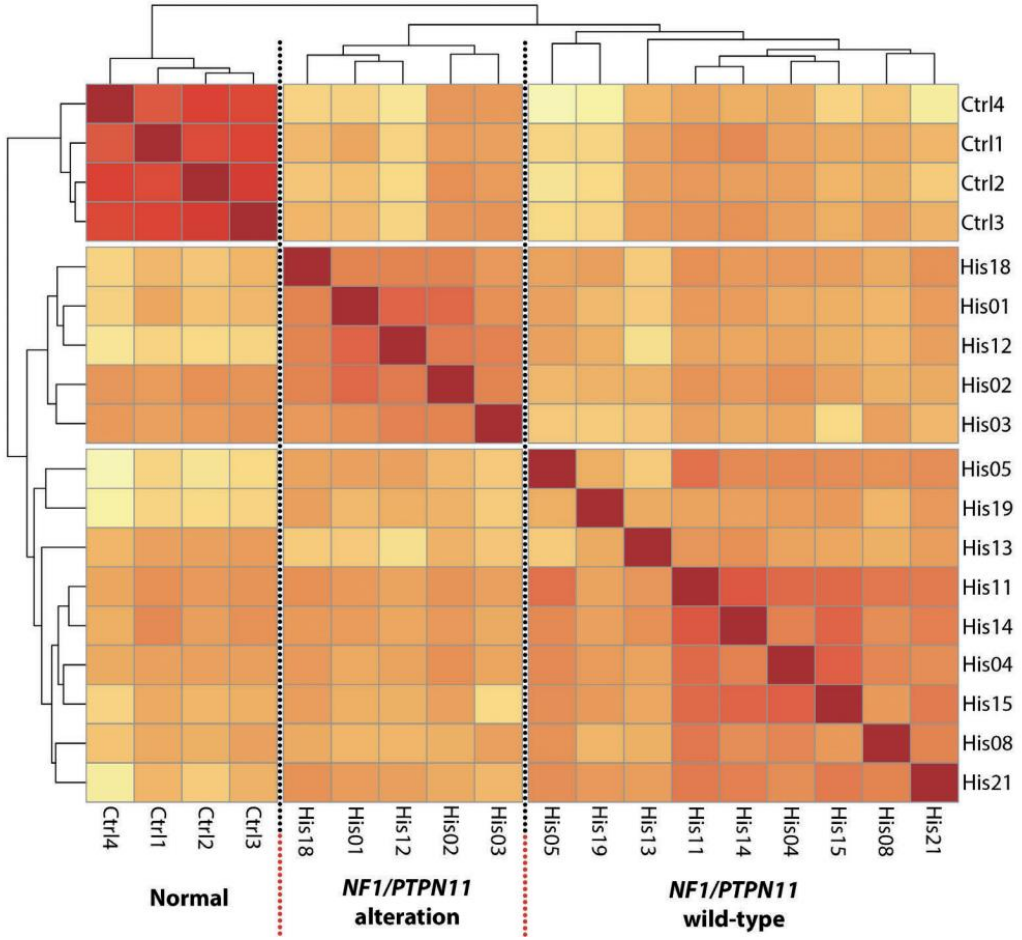
Mutational profile of histiocytic/dendritic cell neoplasms associated with B-cell lymphoma



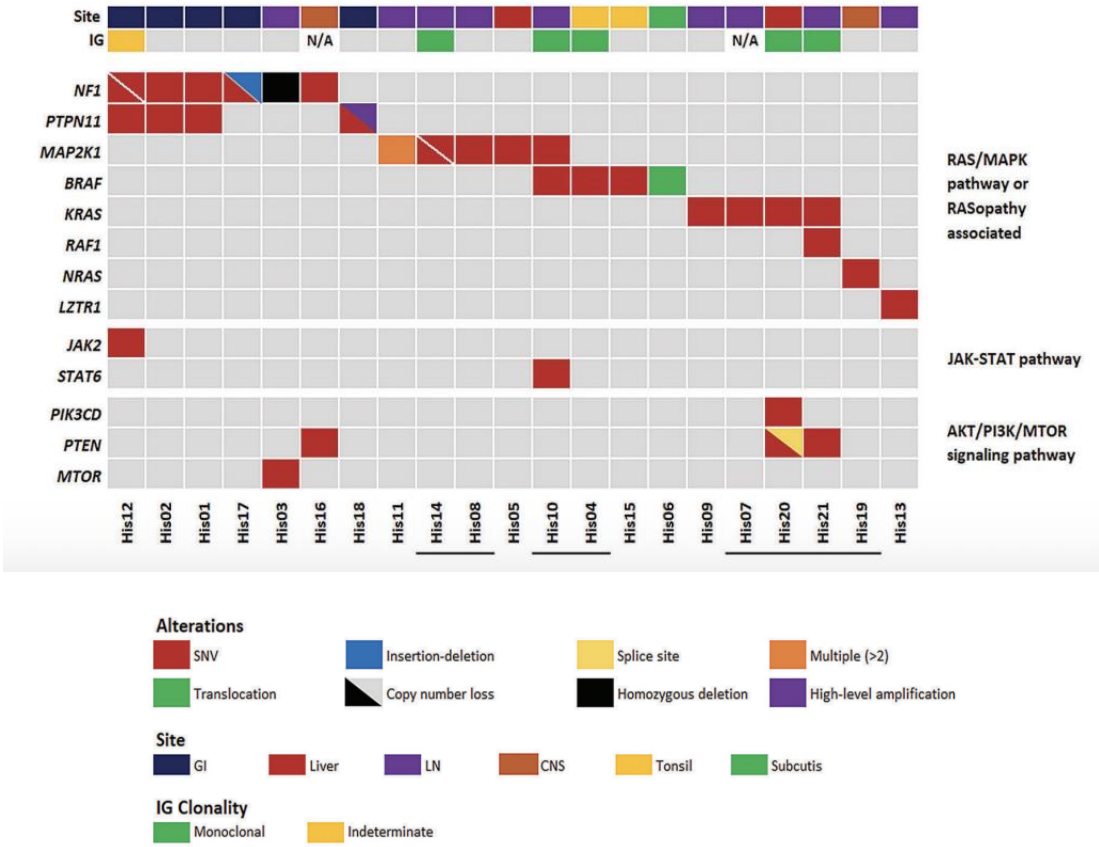
- B-cell neoplasms (FL > CLL > MZL > ALL) can give rise to HDCN.
- Clonal relatedness confirmed by shared mutations, IG rearrangements, FISH.
- MAPK pathway activation is the critical switch.

Xiao, Wenbin et al. *AJCP* (2023)

Two Molecular Subgroups of HS



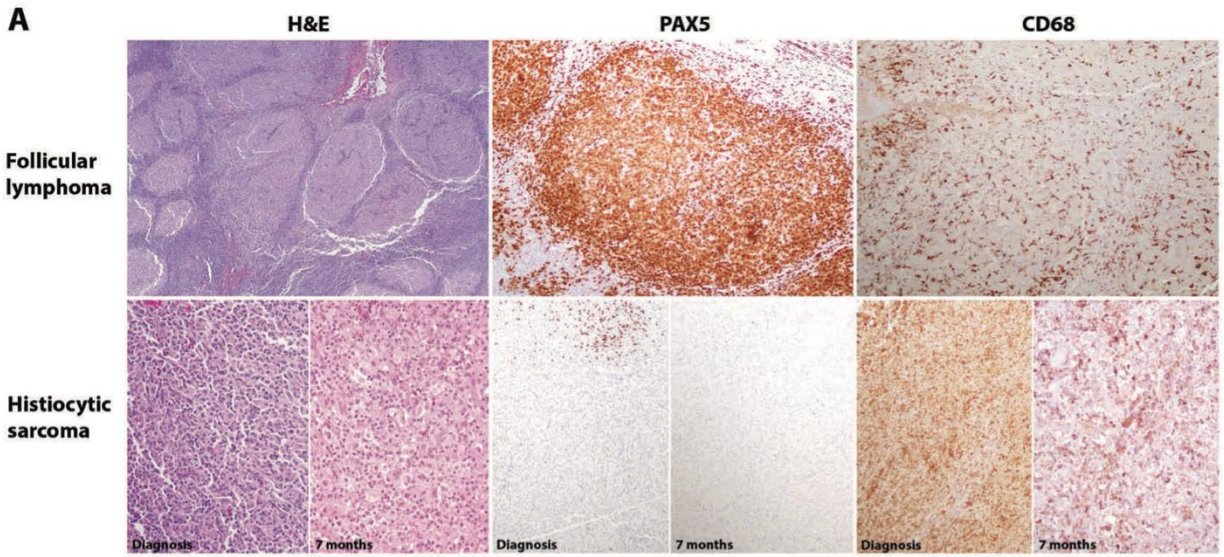
Selected molecular alterations in primary histiocytic sarcoma (pHS) cases

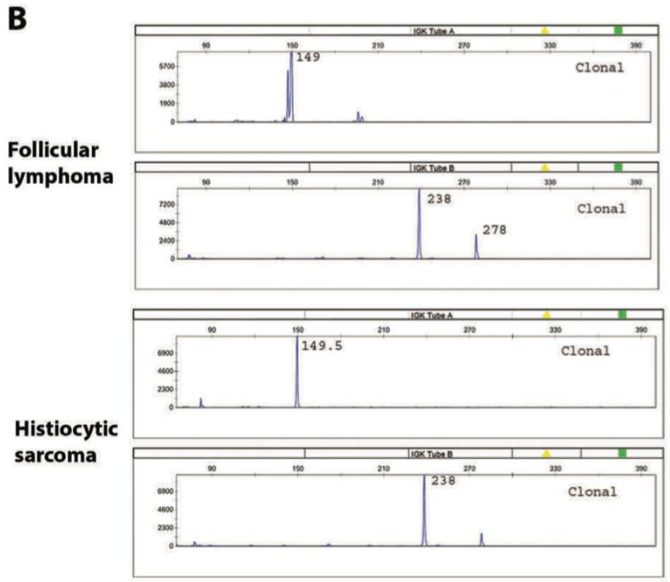


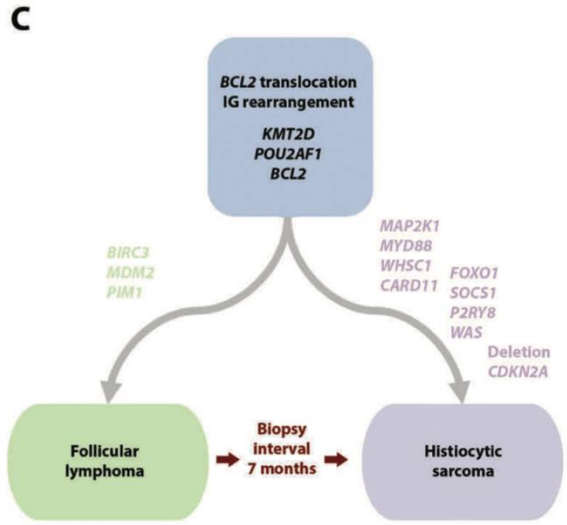
- NF1/PTPN11 (GI-tropic) vs. WT (B-cell–like).
- WT group often has clonal IG and B-lymphoma mutations even in "primary" HS.

Egan, Caoimhe et al. *Haematologica* (2020)

Secondary HS — Clonal Architecture



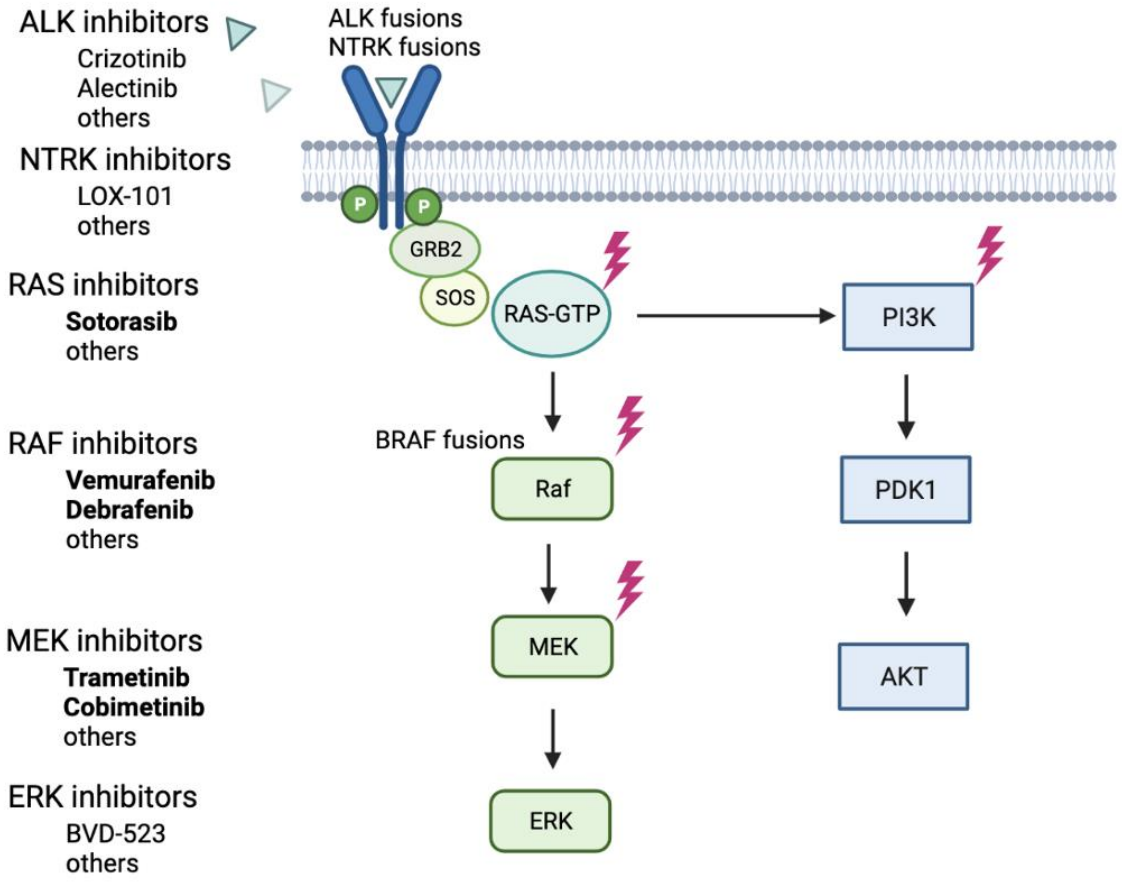




- Shared mutations = common precursor.
- RAS/MAPK acquired = transformation step.
- Clonal divergence in all matched pairs.

Egan, Caoimhe et al. *Modern pathology* (2021)

Treatment Implications



- MEK inhibitor cobimetinib → 89% ORR.
- BRAF inhibitor vemurafenib → 61.5% ORR.

Table S6. Therapy and outcome of HDCNs after transdifferentiation

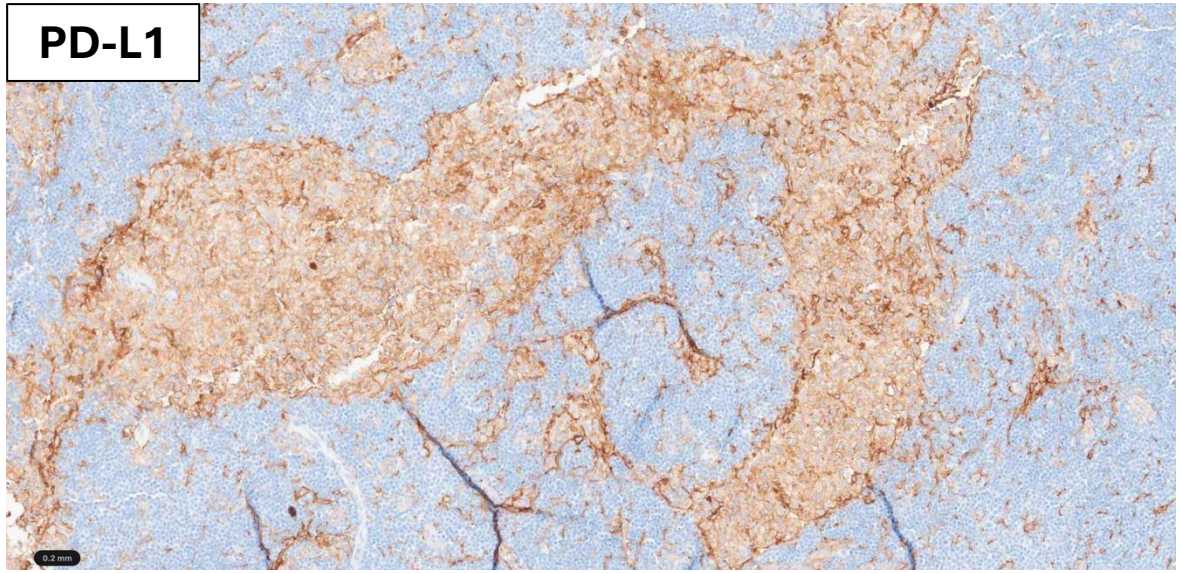
Case #	Diagnosis	treatment of HS/DC	live or death	follow up (months)
23	CLL/HS	Palliative Gemcitabine	died	<2
17	CLL/HS	Salvage chemo	died	<1
106	CLL/HS	RICE XRT	alive	?
177	MZL/HS	RCHOP for DLBCL	alive	12
38	FL/LCH	Mustard based chemo	died	4
117	DLBCL/HS	None	died	<1
239	FL/LCS	REPOCH	alive but progressed	?
45	FL/HS	RCHOP	alive	1
74	FL/LCS	XRT	died	24
139	FL/HS-DC	Local XRT	alive	?
178	FL/HS	R-ICE then Vemurafenib, Dabrafenib and trametinib	alive	24

Abbreviations: RICE, rituximab, fractionated ifosfamide, carboplatin, etoposide; REPOCH, rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride; RCHOP, rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine and prednisone; XRT, radiotherapy.

Xiao, Wenbin et al. *AJCP* (2023)

Treatment plan

- Cobimetinib, 20 mg/day (MEK inhibitor)
  - 21 days on, 7 days off
- Pembrolizumab
- Radiation tx



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Multi-Institutional Hematopathology Interesting Case Conference (MHICC)

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