Mass General Brigham

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

A 38-year-old man with cord compression and hyperleukocytosis

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History and clinical presentation

- 38-year-old man, with no significant past medical history
- Began having back pain that progressed to bilateral lower extremity weakness and bladder dysfunction
- Found to have T5-T10 epidural mass with associated T7-T9 cord compression, and diffuse marrow hypointensities on MRI

Peripheral blood smear

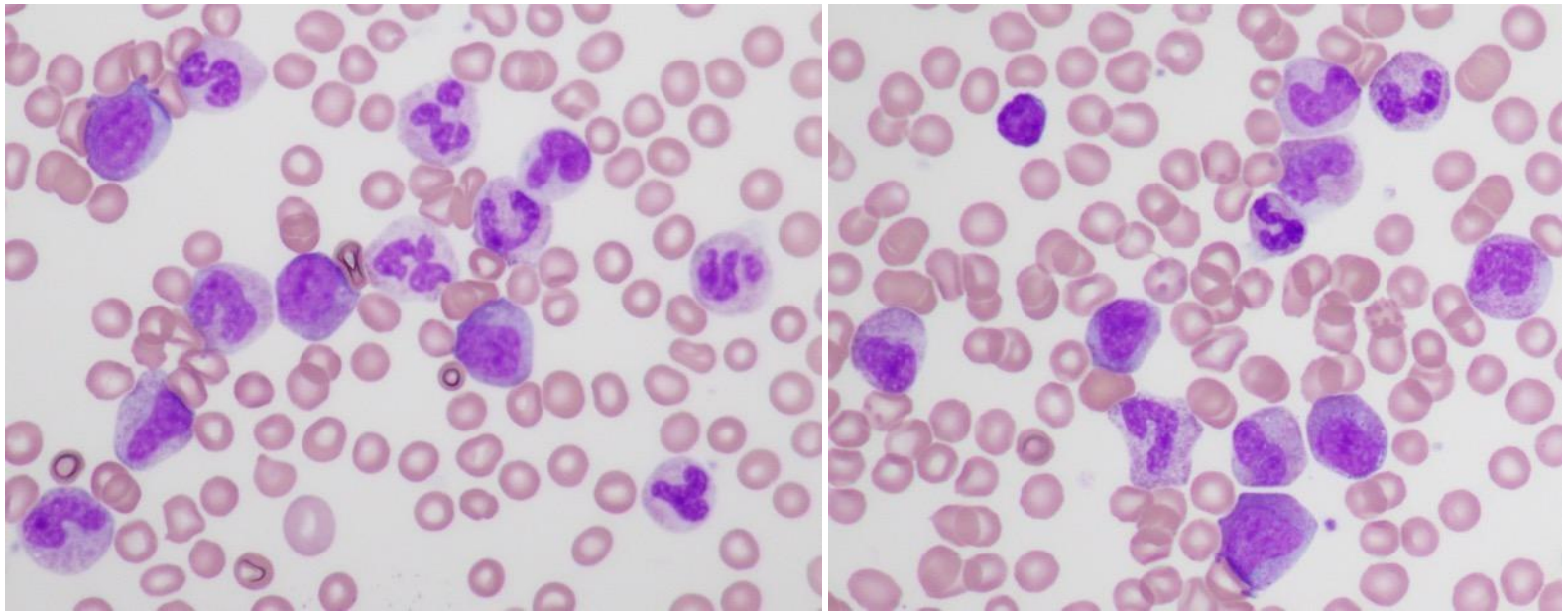
CBC:

WBC 123 K/uL

- 49% neutrophils
- 2% lymphocytes
- 2% monocytes
- 3% eosinophils
- 0% basophils
- 4% bands
- 15% metamyelocytes
- 11% myelocytes
- 12% promyelocytes
- 2% others

Hgb 10.9, MCV 103.8

PLT 142



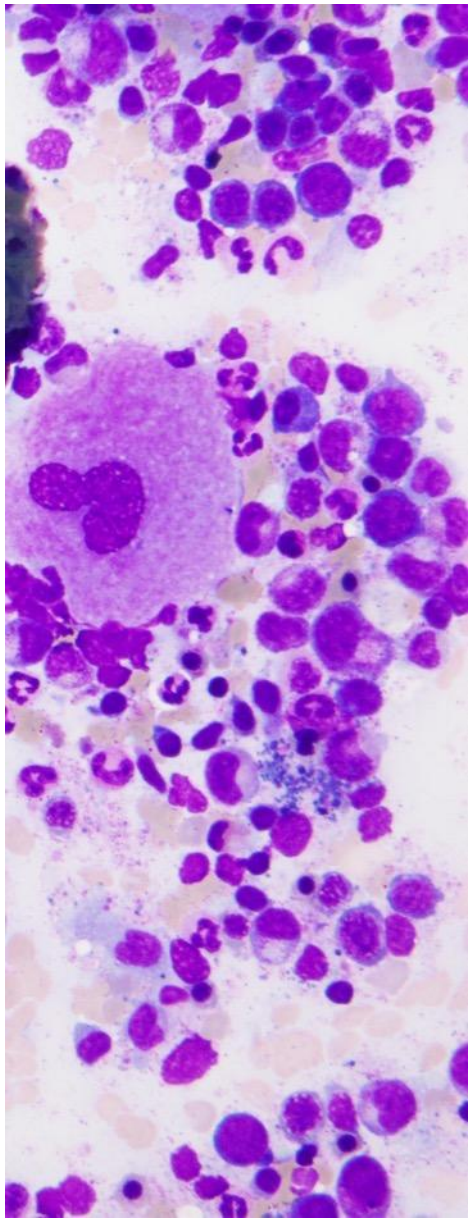
-Marked leukocytosis with mostly myeloid cells at all stages of maturation

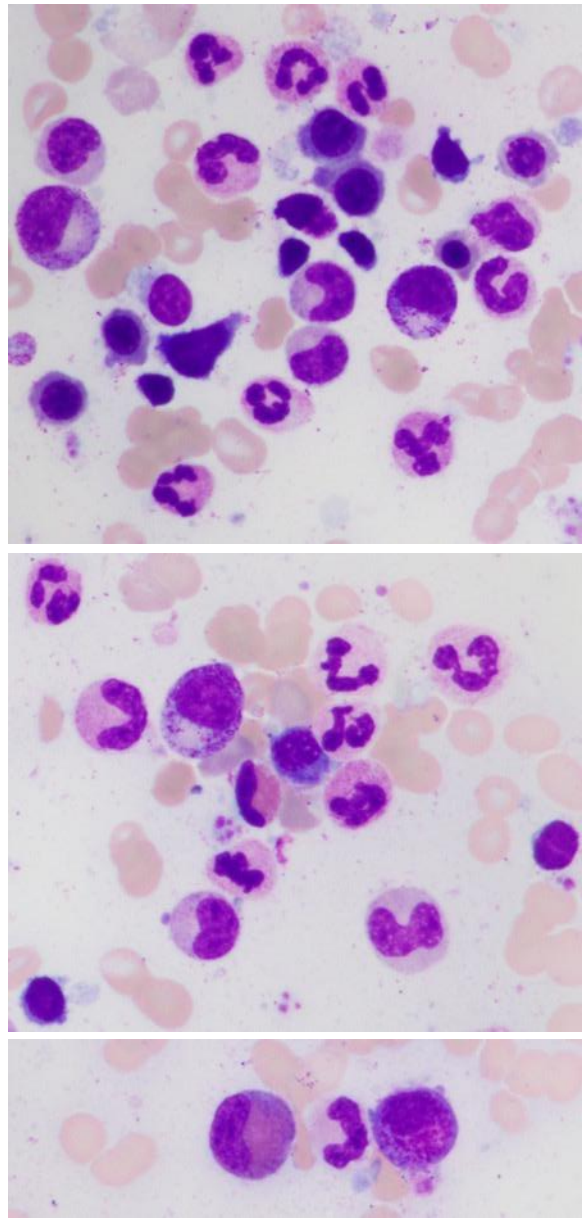
-No dysplasia

Bone marrow aspirate

400 cell-count:
Blasts: 0%
Promyelocytes: 4%
Neutrophils and precursors: 76%
Erythroid precursors: 7%
Monocytes: 1%
Eosinophils: 10%
Basophils: 0%
Lymphocytes: 2%

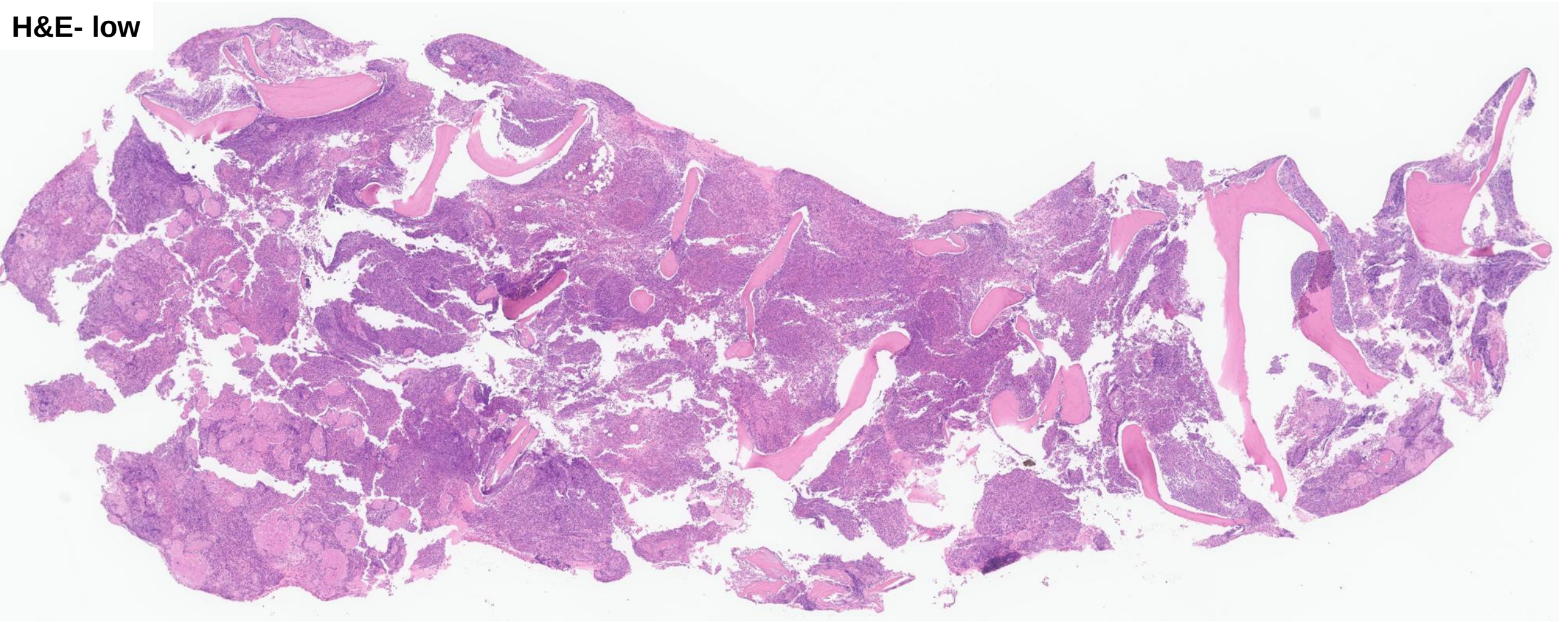
Myeloid maturation: left-shifted but complete.
Erythroid maturation: complete.
Megakaryocytes: present.
No significant atypia/dysplasia in any lineage.





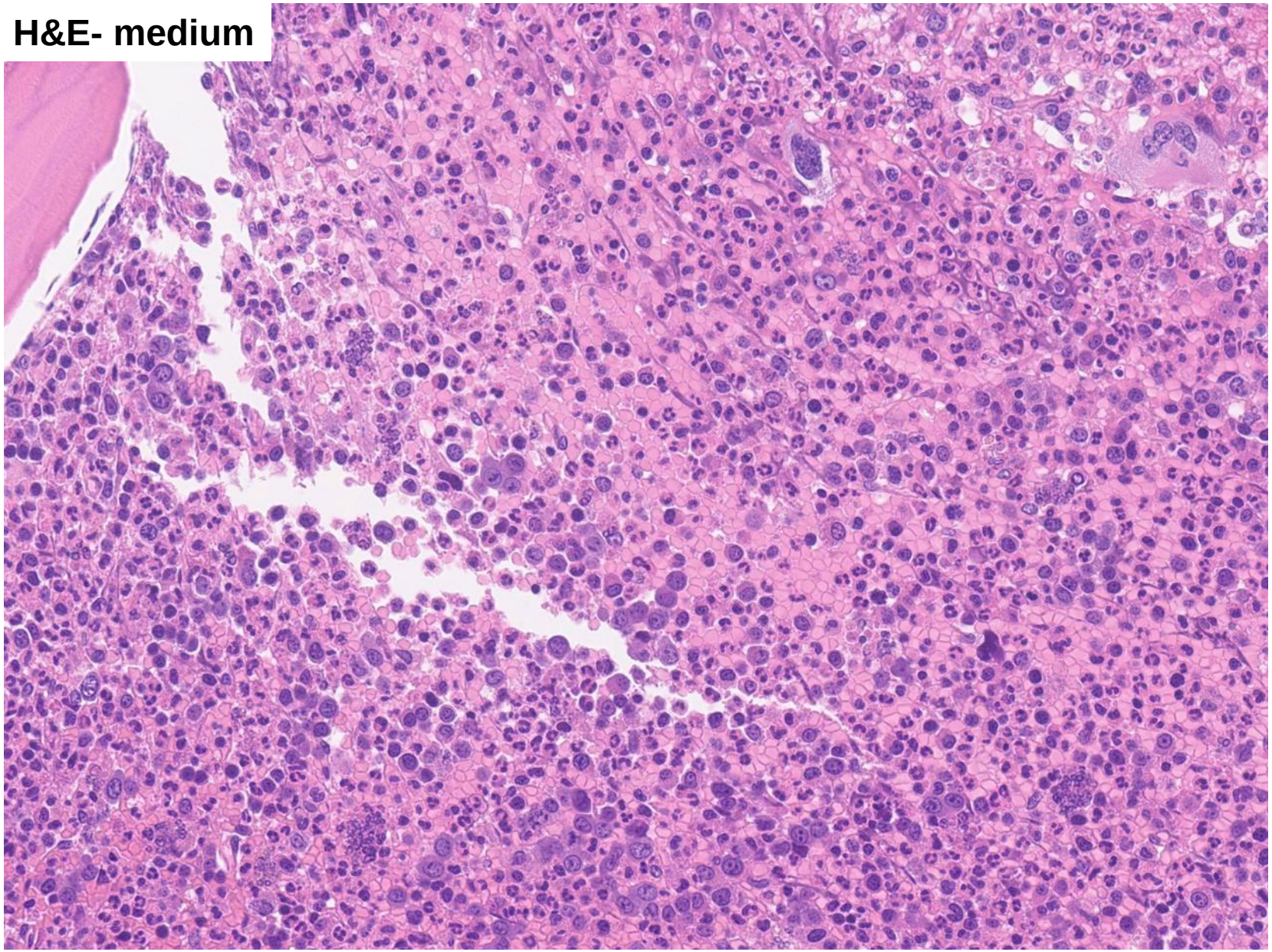
The bone marrow core was hypercellular

H&E- low

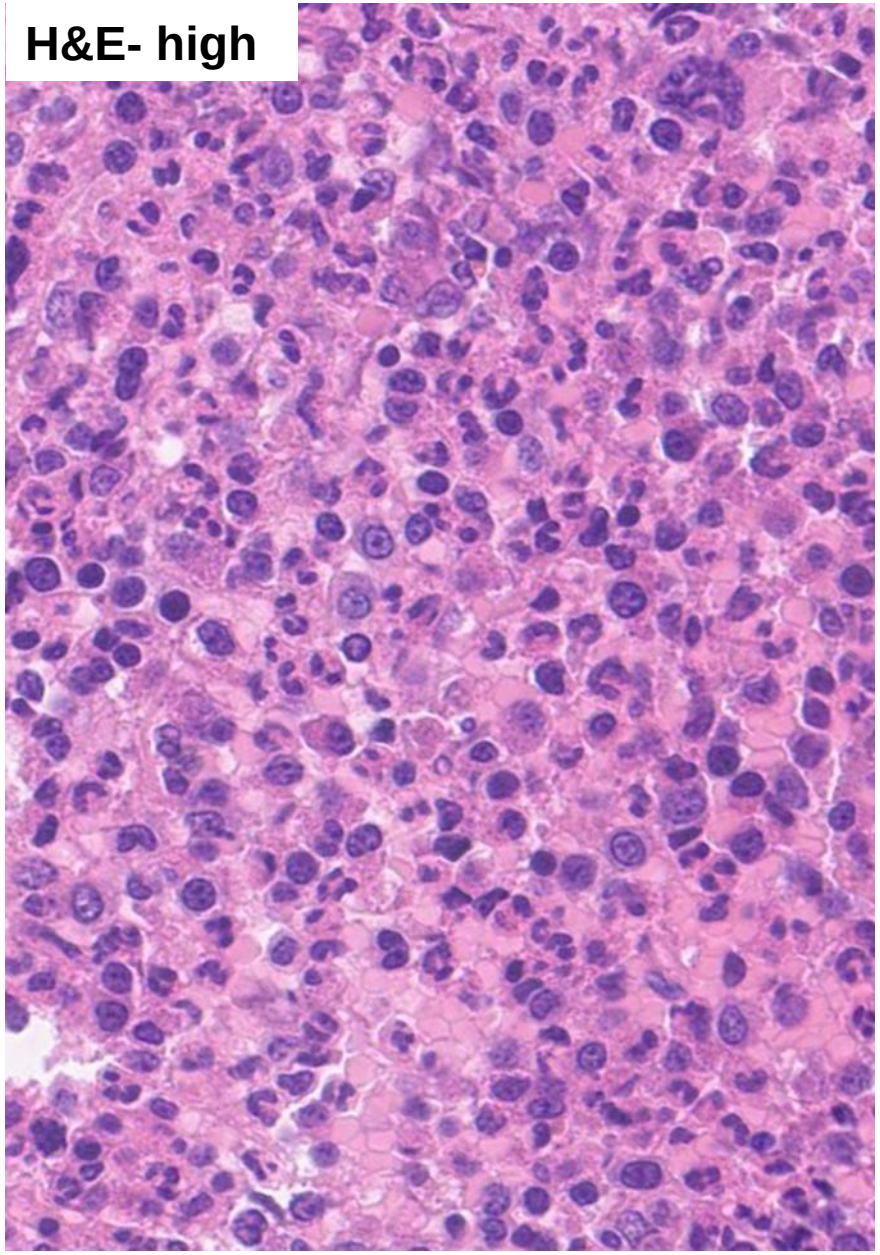


The marrow was myeloid-predominant and without megakaryocyte dysplasia

H&E- medium



H&E- high



Bone marrow- Differential Diagnosis (pending genetics)

-Myeloid neoplasm

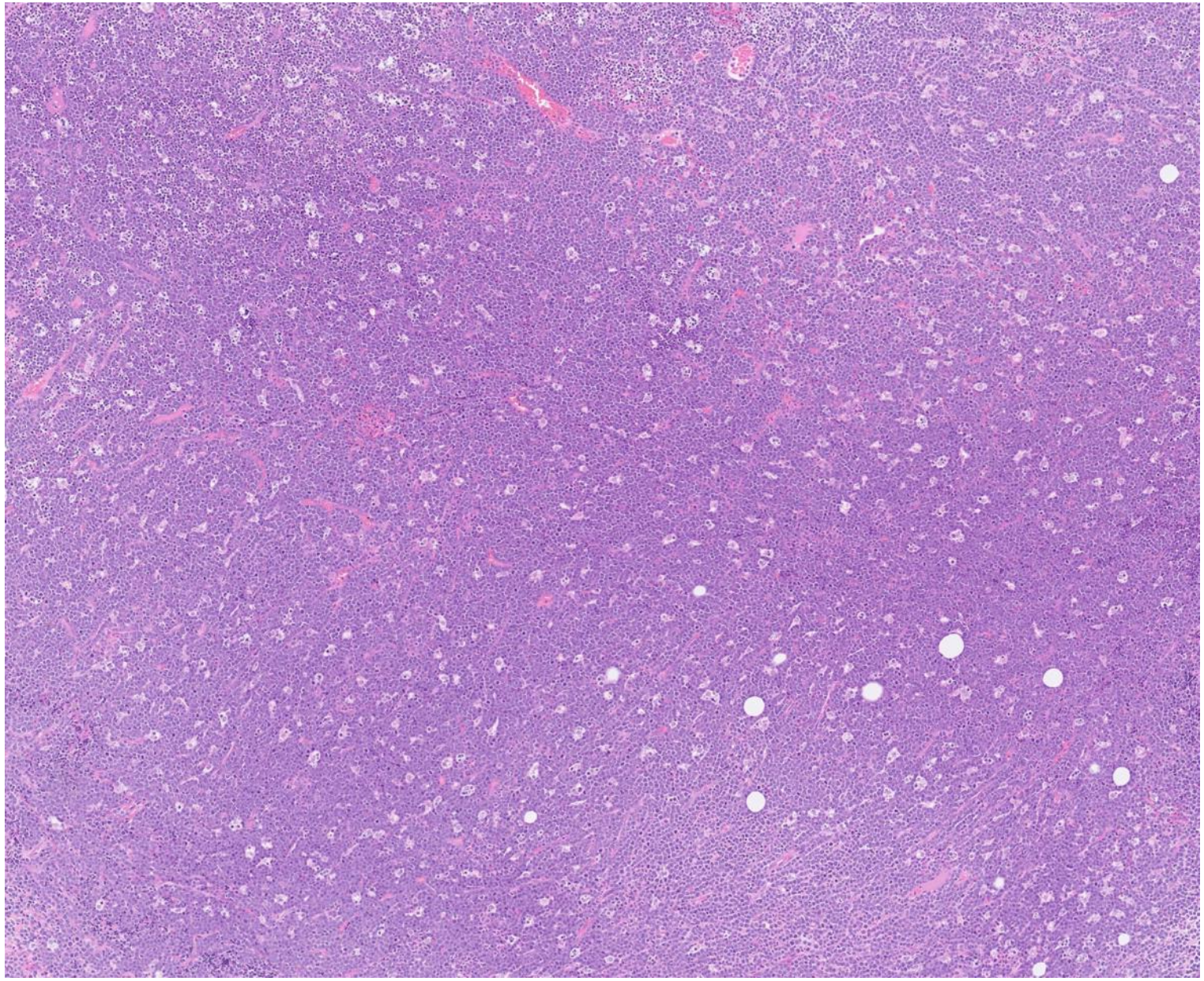
MPN (considered CML)

MDS/MPN (cytopenias present, but no significant dysplasia)

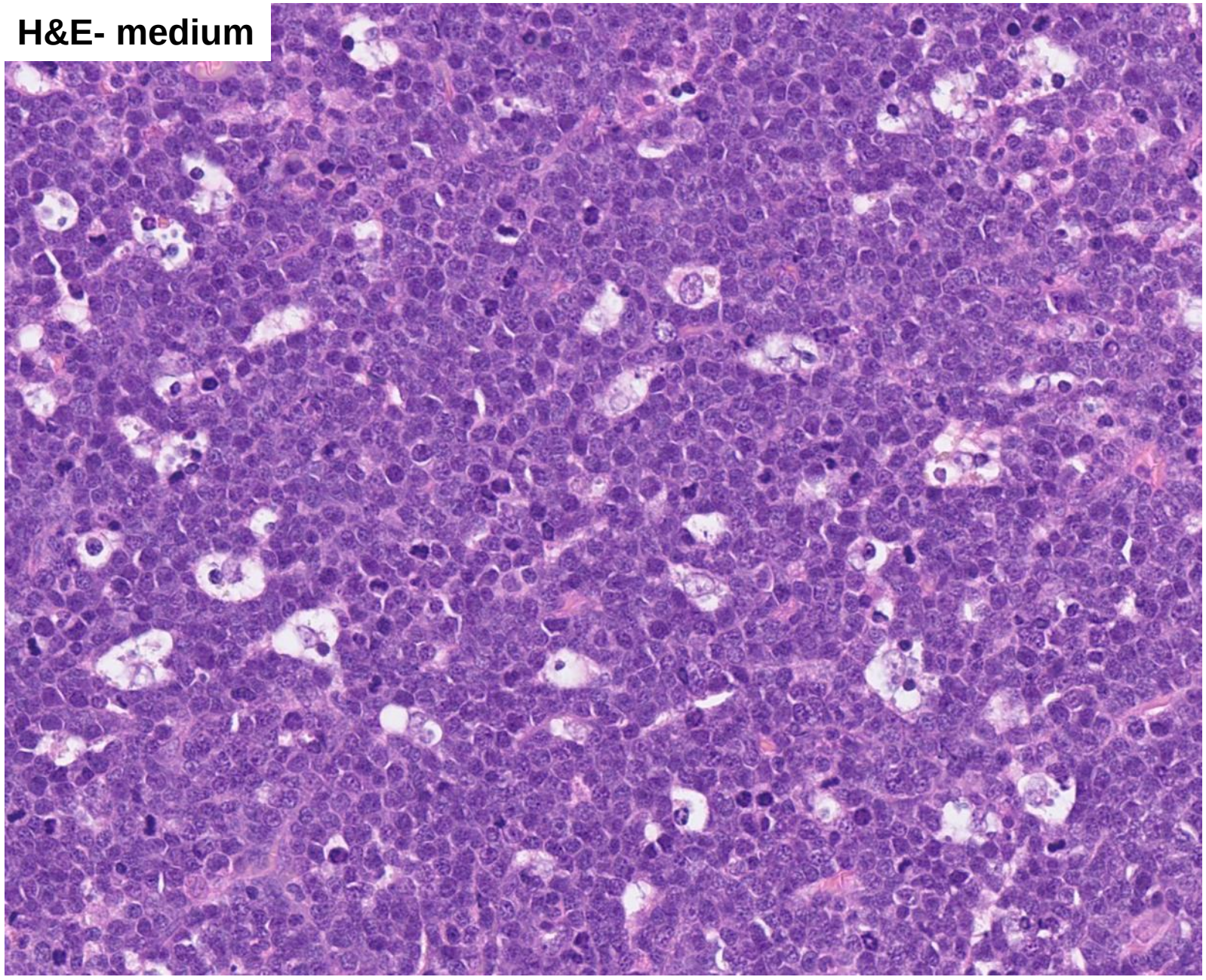
-Leukemoid reaction (WBC 123 K/uL would be unusually high)

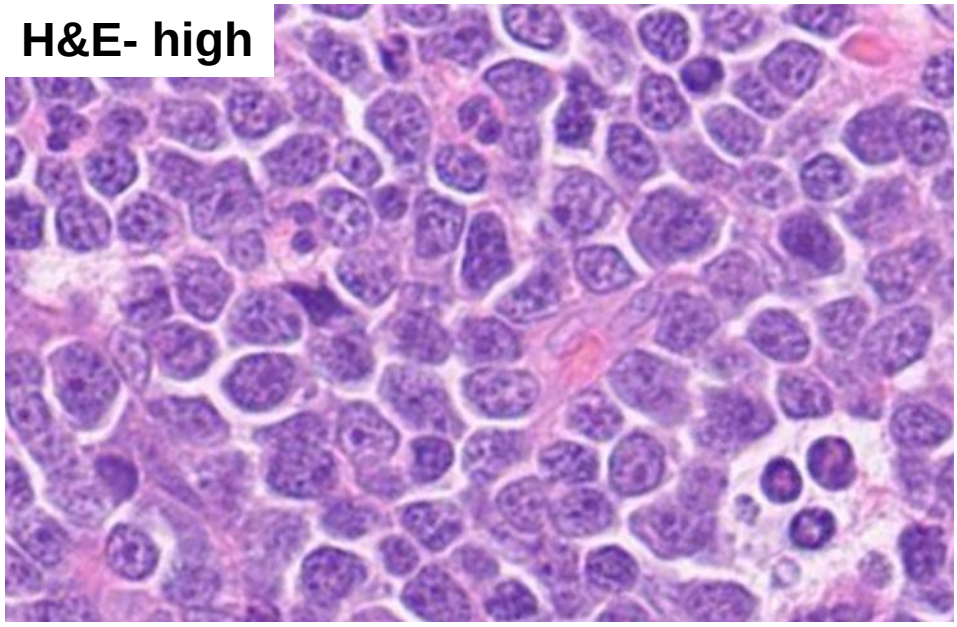
Thoracic Tumor

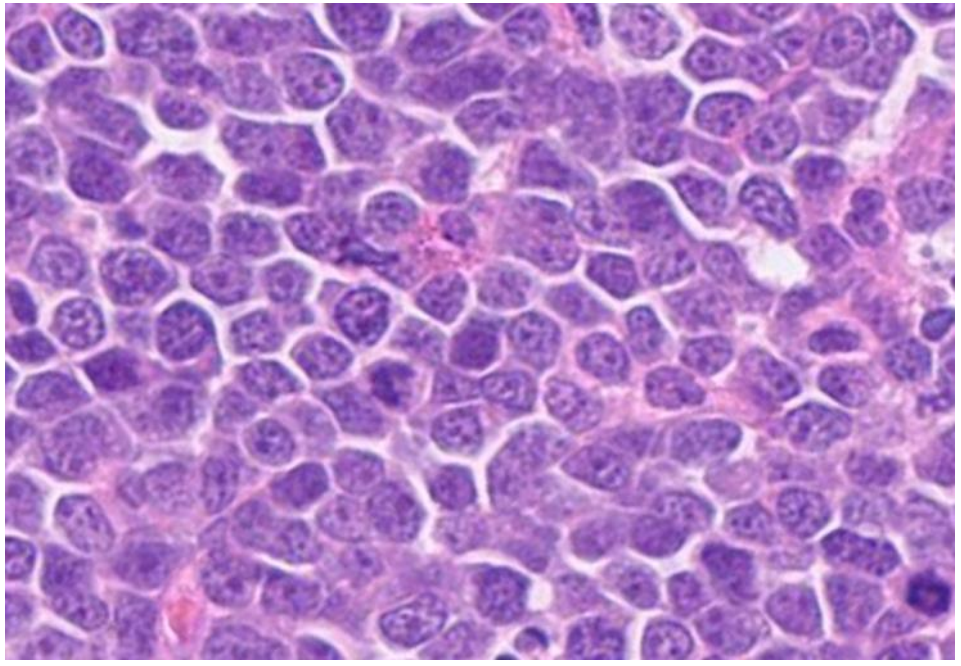
H&E- low

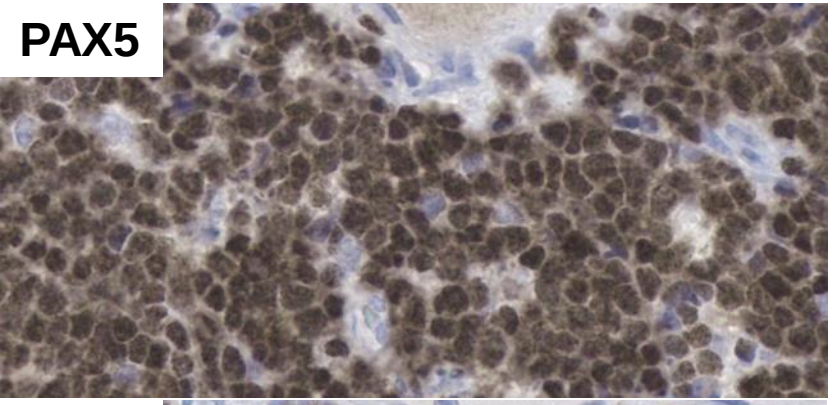


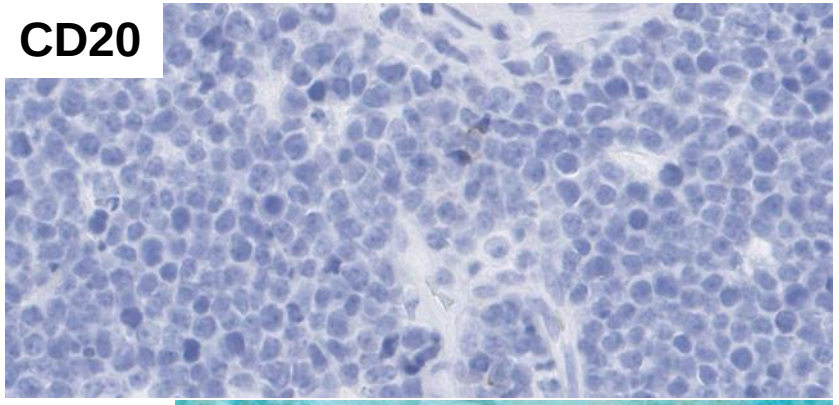
The tumor was “Burkitt-like” with some cells having finer chromatin

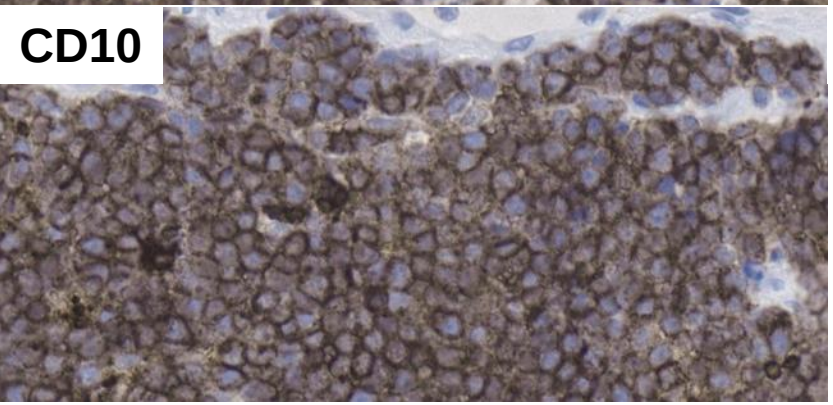


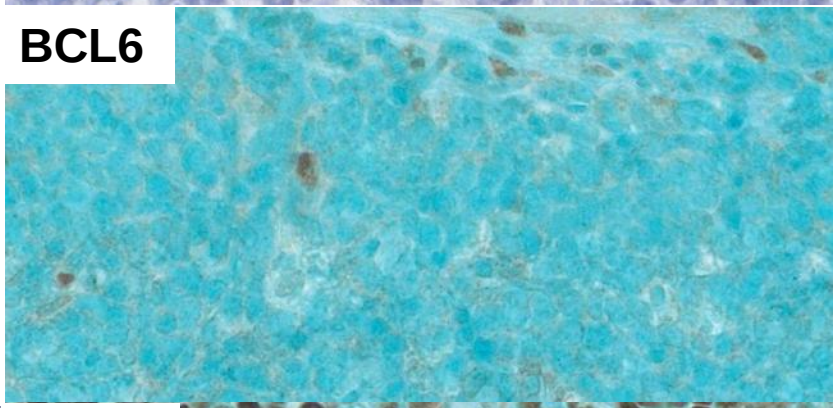


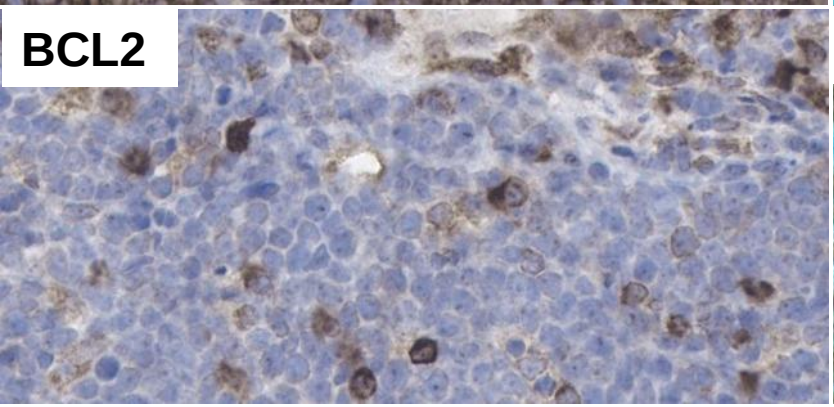


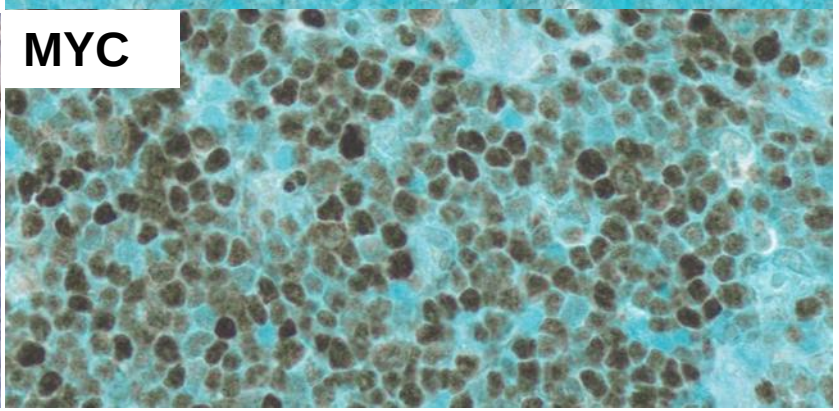

PAX5

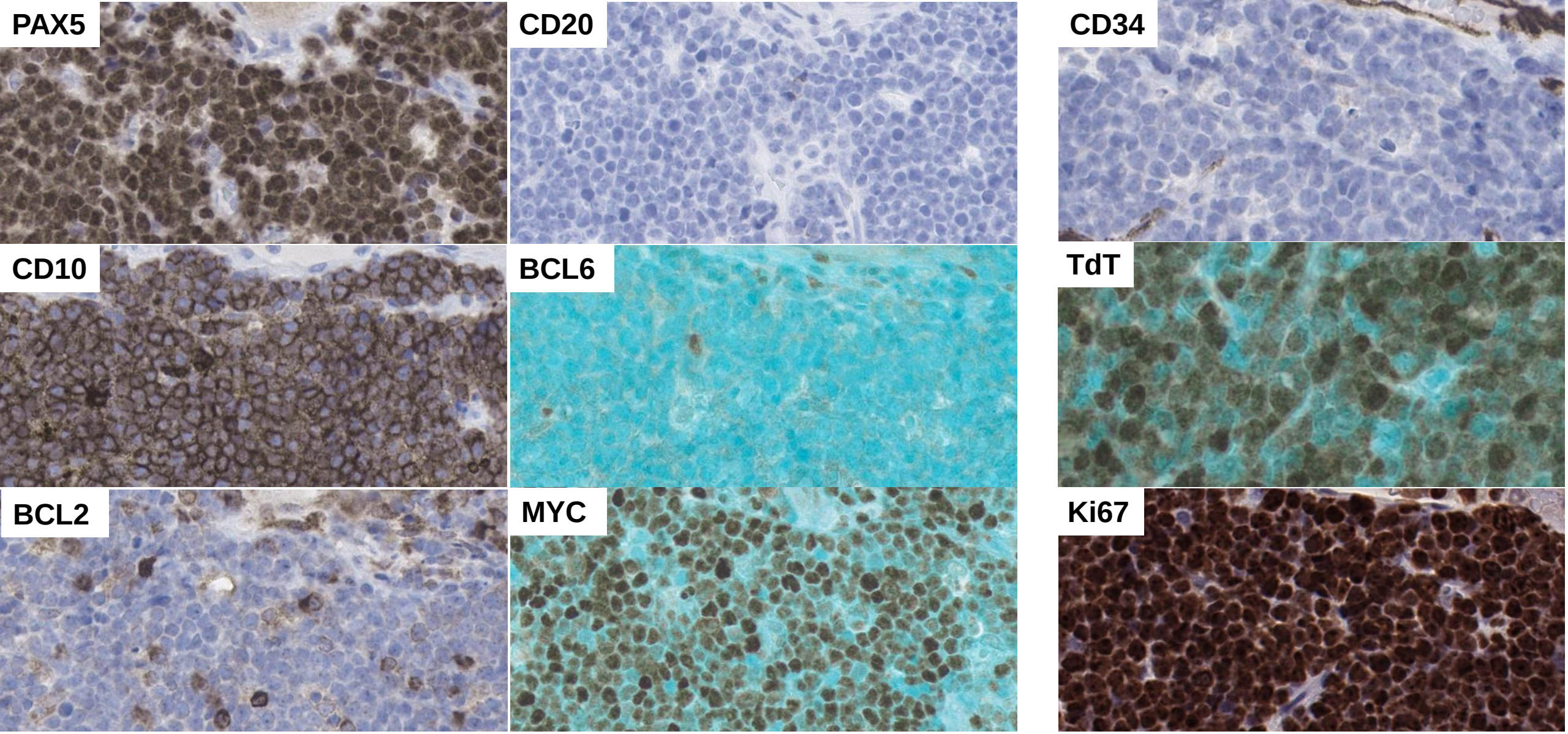

CD20


CD10


BCL6

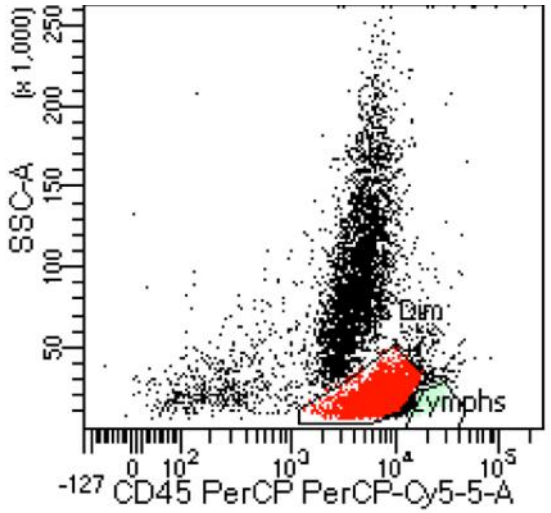

BCL2

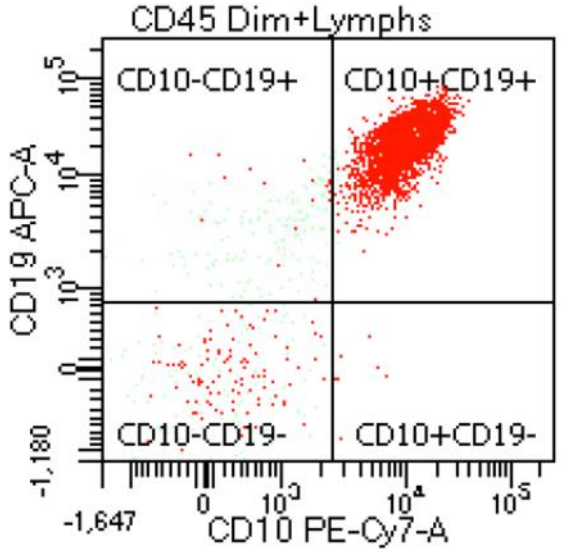

MYC

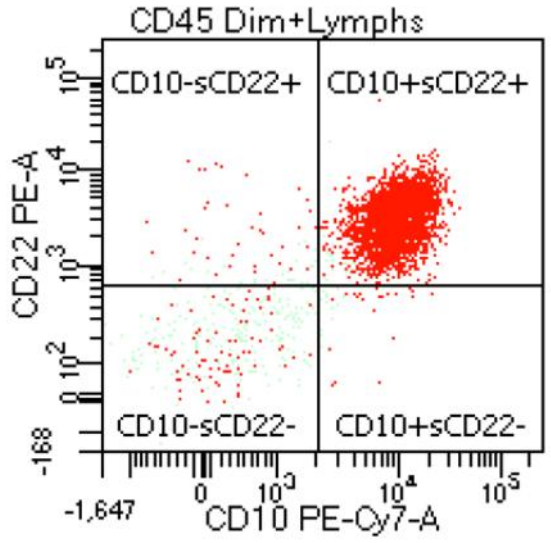


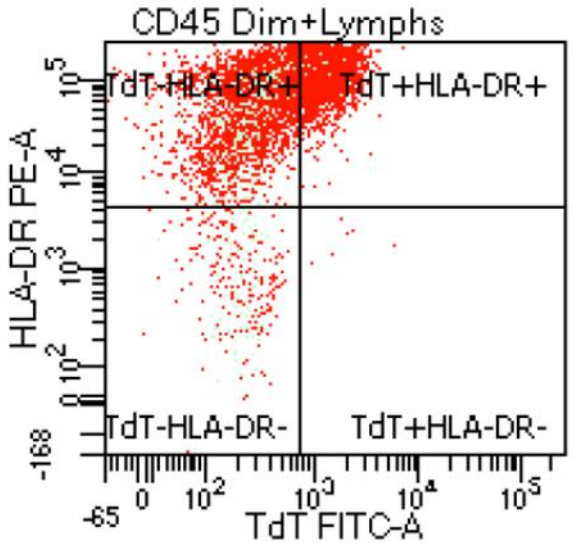
Thoracic Tumor IHC Summary:
Positive: **PAX5, CD10, TdT, MYC (>90%)**, Ki67 (>95%), CD45 (moderate), MUM1 (dim/variable), CD99 (dim/subset).
Negative: **CD34, CD20, BCL6,** BCL2, CyclinD1, EBER, CD3.

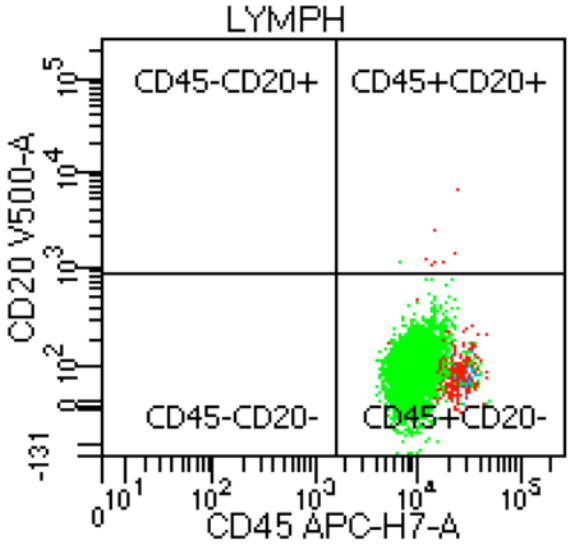
Thoracic Tumor- Flow Cytometry

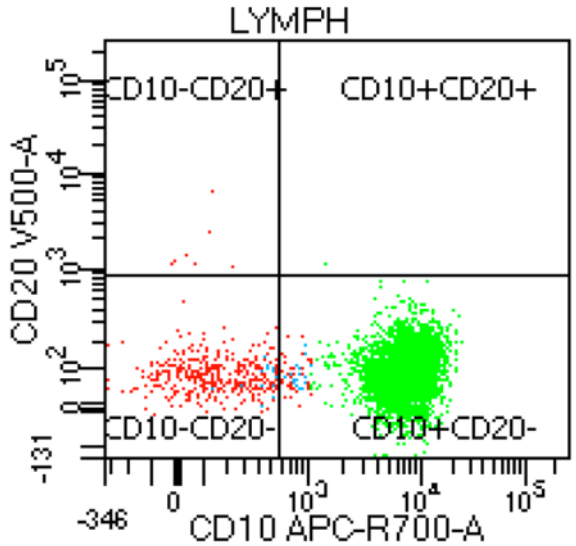


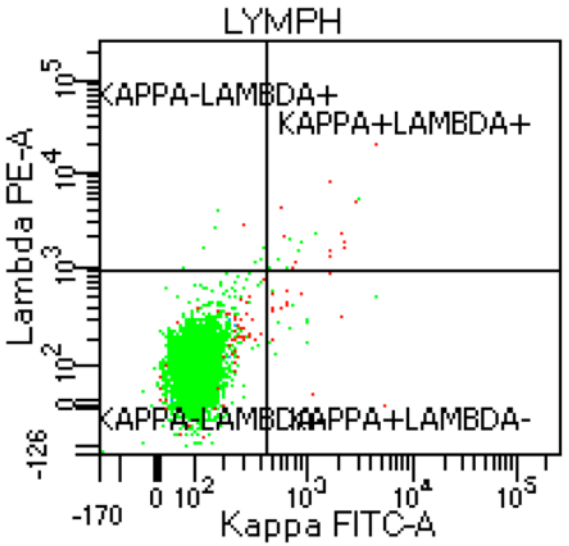












52% immature cells **positive for CD45(slightly dim)**, HLA-DR, CD38, **TDT(subset), B lymphoid markers CD19, CD10, and sCD22**, and **negative for** CD34, CD20, CD23, CD11C, CD123, CD56, **surface kappa and lambda light chains**, and other myeloid, monocytic, and T cell markers.

Thoracic tumor- Differential Diagnosis (pending genetics)

-B-lymphoblastic lymphoma (including with possible *MYC*r)

-Burkitt lymphoma (but was negative for CD20 and BCL6, and positive for TdT)

-High-grade B cell lymphoma with expression of TdT (but was negative for CD20 and surface light chains)

-Other

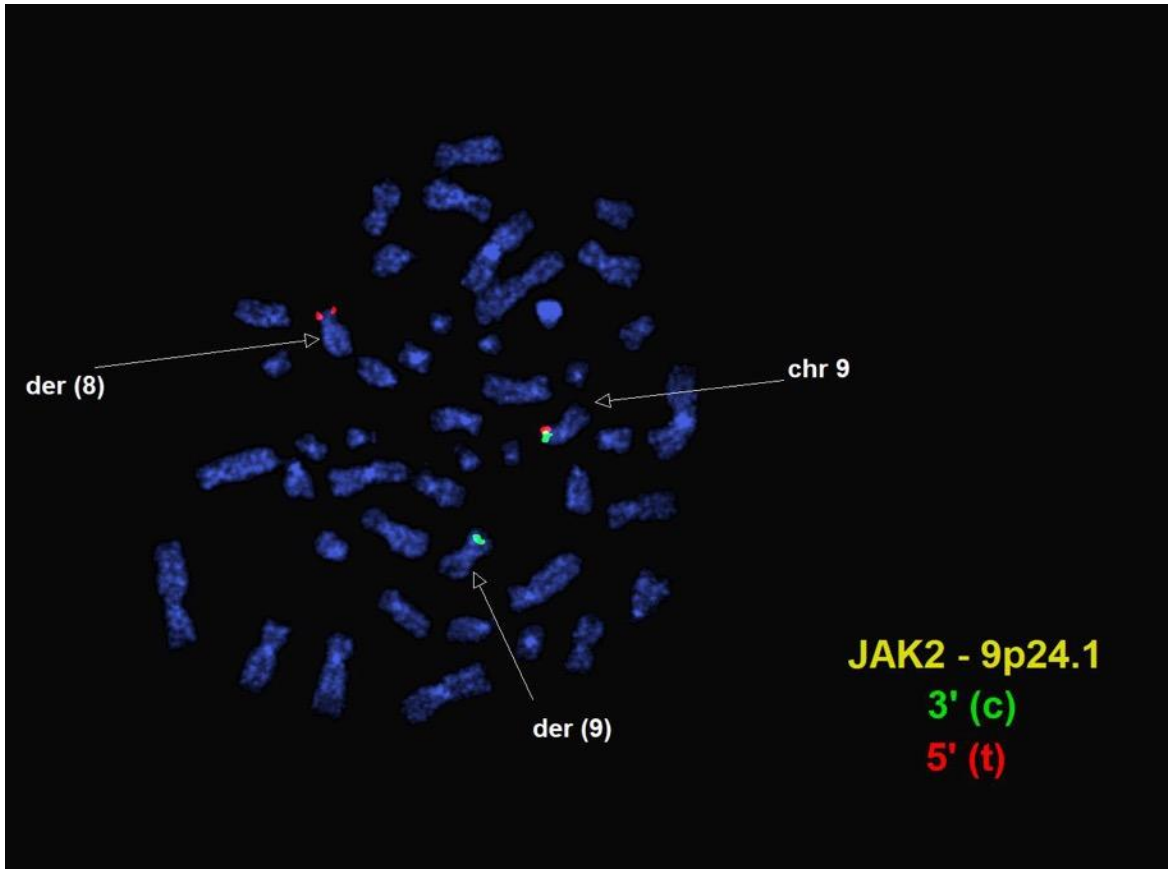
CML with B-ALL blast phase at extramedullary site?

CYTOGENETICS

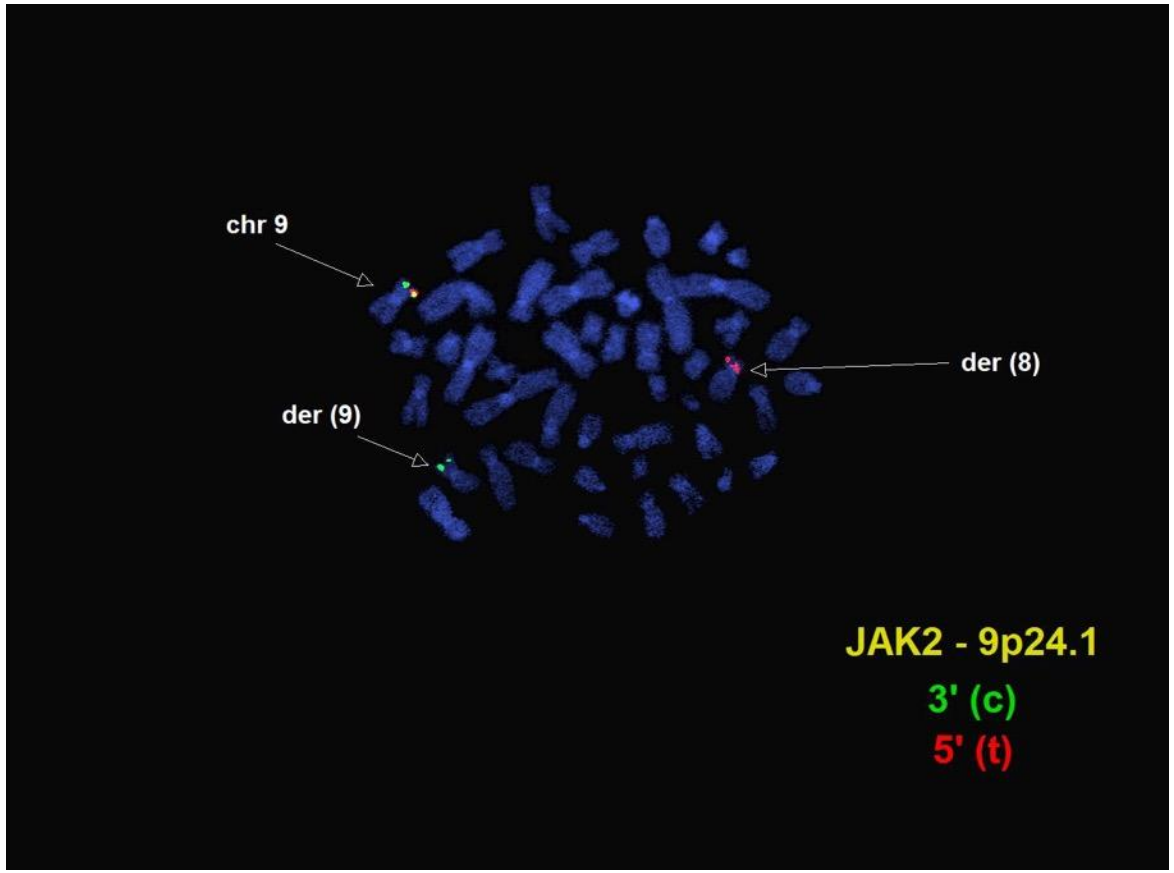
Bone marrow and peripheral blood showed the same karyotype of 46,XY,t(8;9)(p1?2;p2?2)[20], and had RT-PCR studies negative for *BCR::ABL1* p190 and p210.

FISH showed a *JAK2* rearrangement consistent with t(8;9):

Bone marrow

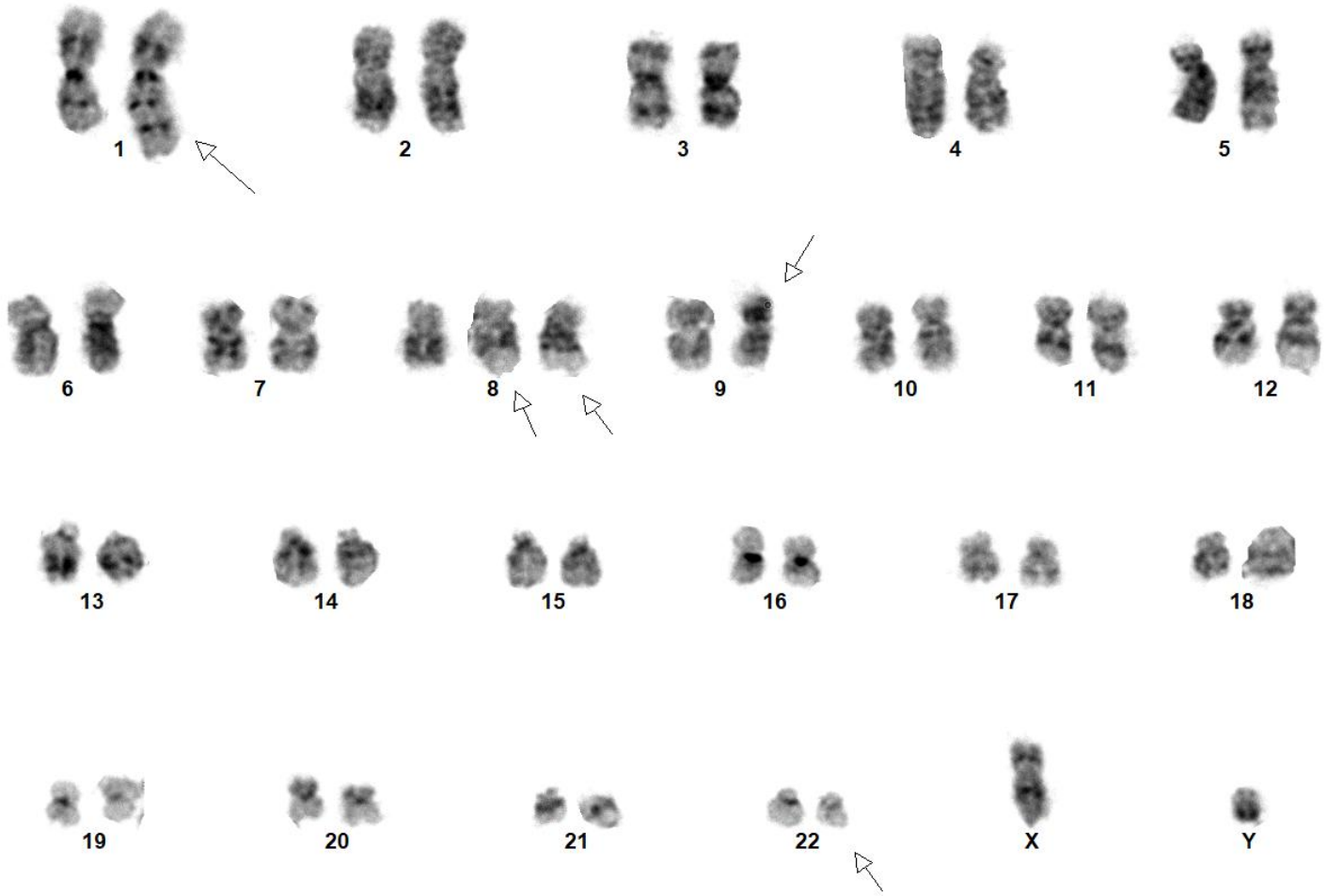


Peripheral blood



Note: No cytogenetic aberrations were identified from CpG-stimulated peripheral blood, suggesting the t(8;9) was not constitutional.

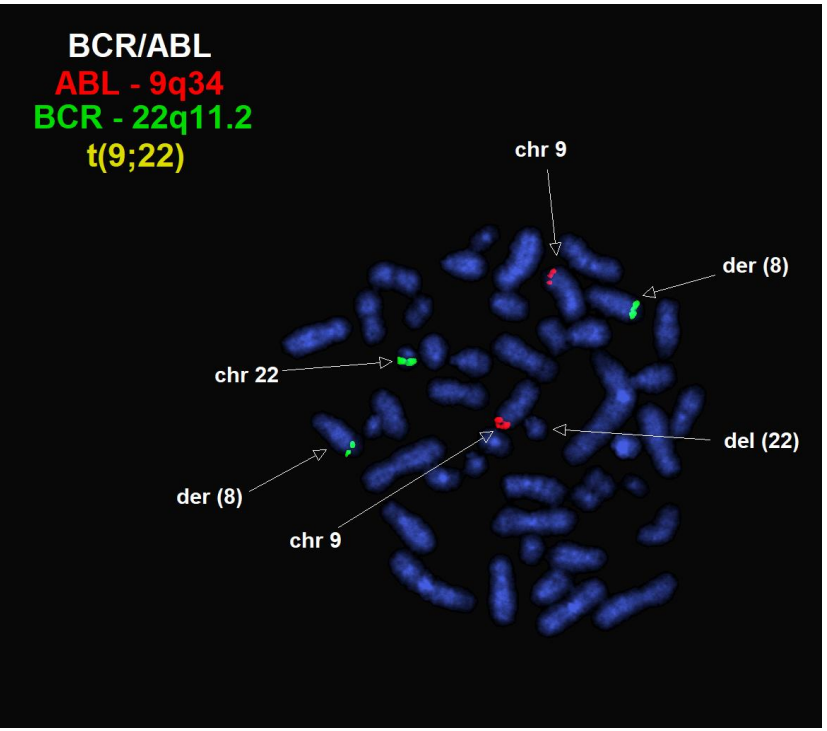
Thoracic tumor

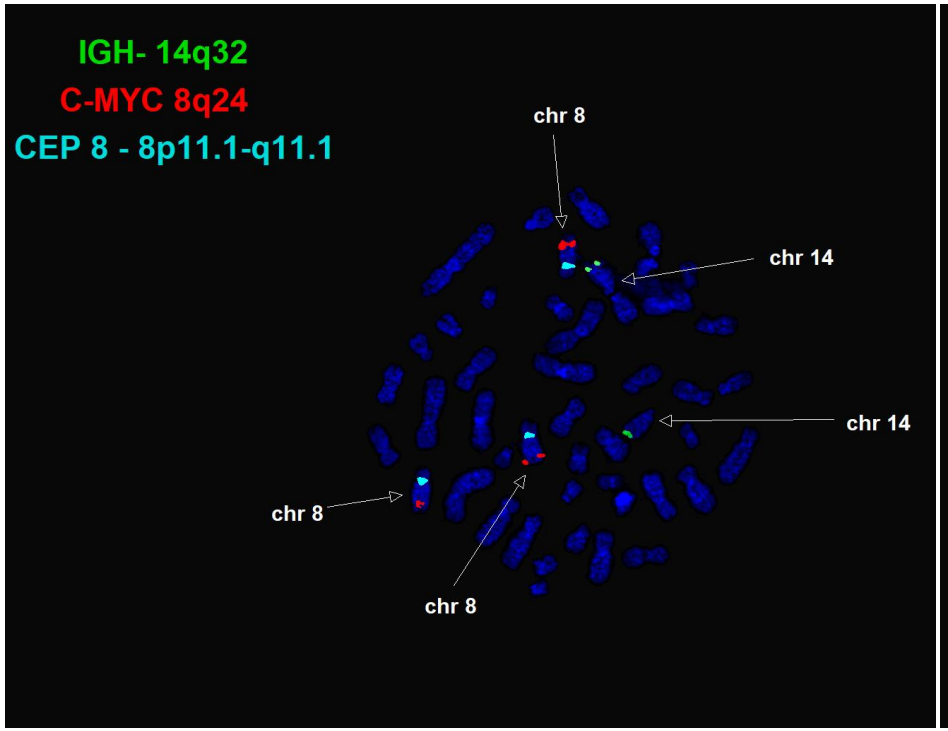


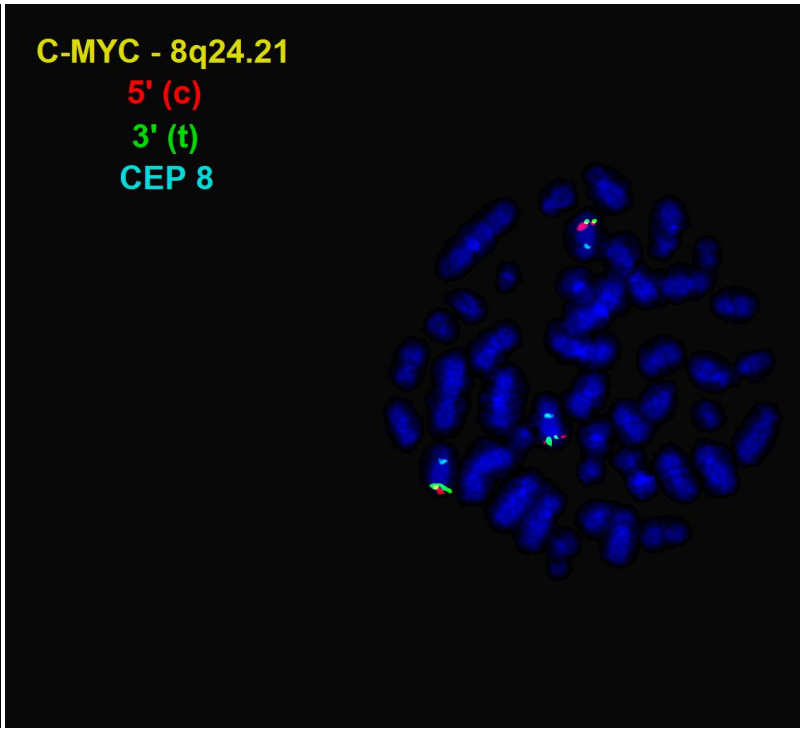
12/20 metaphases had:

(1) Duplication of 1q.
(2) Two copies of an abnormal chromosome 8, harboring both a t(8;22) **and the t(8;9) seen in BM/PB**, with corresponding der(9) t(8;9) and der(22) t(8;22).

Thoracic tumor







der(8) t(8;22)(q24;q11), x2.

No t(9;22) / *BCR::ABL*.

Three copies of chr 8.

No t(8;14) / *IGH::MYC*.

Three copies of chr 8.

No *MYC*r detected with 8q24 break-apart probe.

NOTE:

(1) The breakpoints of the t(8;22) involve regions near *MYC* on chr 8 and near *IGL* on chr 22.

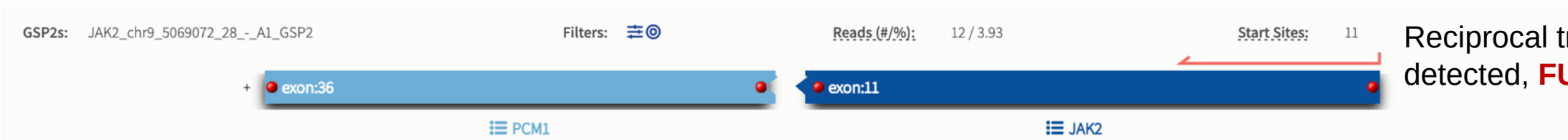
***(2)* *MYC* breakpoints can fall outside the detection range of standard *MYC* FISH probes.**

NEXT-GENERATION SEQUENCING

PCM1::JAK2 was detected in the BM and the thoracic tumor

BM, Archer Fusion Panel:

Fusion transcript with the most reads



Reciprocal transcript detected, **FUNCTIONAL**

DNA NGS (on BM and PB): No SNVs, Indels, CNVs, or VUSs.

Thoracic Tumor, Archer Fusion Panel:

Fusion transcript with the most reads

Reciprocal transcript detected, **FUNCTIONAL**

DNA NGS: Not performed.

NOTE: No *MYC*r seen, which can go undetected on this assay.

The *PCM1*::*JAK2* detected here is a recurrent fusion detected (rarely) in hematolymphoid neoplasms since at least 2005

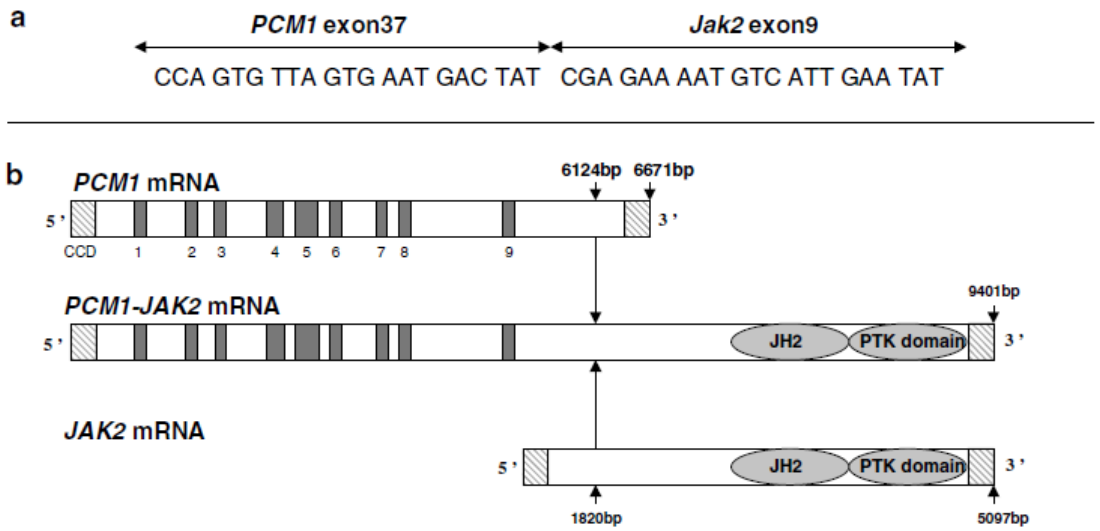


Figure 3 Sequence of the new fusion transcript: (a) Open reading frame of the chimeric *PCM1-JAK2* gene. (b) Structure of *PCM1*, *PCM1-JAK2* and *JAK2* mRNAs. CCD, coiled coil domain; JH2, JAK homology/pseudokinase domain of JAK2; PTK, protein tyrosine kinase

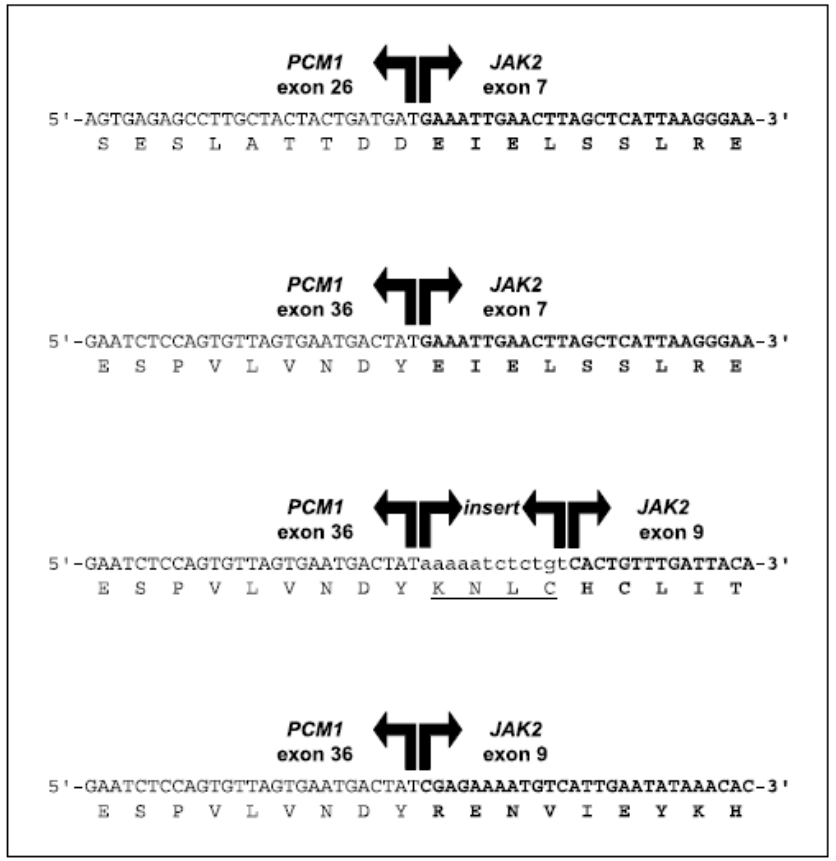


Figure 3. The four different in-frame *PCM1-JAK2* fusion junctions identified in this study. *PCM1* sequences are in plain type, *JAK2* sequences in bold, the 12 bp intron-derived insert seen in case 4 is shown in lower case with the corresponding amino acids underlined.

(1) Bousquet M, Quelen C, De Mas V, et al. The t(8;9)(p22;p24) translocation in atypical chronic myeloid leukaemia yields a new PCM1-JAK2 fusion gene. *Oncogene*. 2005;24(48):7248-7252. doi:10.1038/sj.onc.1208850

(2) Reiter A, Walz C, Watmore A, et al. The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2. *Cancer Res*. 2005;65(7):2662-2667. doi:10.1158/0008-5472.CAN-04-4263

Multicenter Study > Mod Pathol. 2019 Apr;32(4):490-498.
doi: 10.1038/s41379-018-0165-9. Epub 2018 Nov 6.

Hematopoietic neoplasms with 9p24/JAK2 rearrangement: a multicenter study

Guilin Tang [1], John Kennedy Sydney Sir Philip [2], Olga Weinberg [3], Wayne Tam [4], Sam Sadigh [5], Jonathan I Lake [5], Elizabeth M Margolskee [4], Heesun J Rogers [6], Roberto N Miranda [1], Carlos Bueso-Ramos C [1], Eric D Hsi [6], Attilio Orazi [4], Robert P Hasserjian [7], Daniel A Arber [2], Adam Bagg [5], Sa A Wang [8]

Cases	Karyotype	FISH for *JAK2*	Molecular mutations
1	46,XY,t(8;9)(p22;p24)[20]	Positive	Negative: All genes (NGS)
2	46,XY,t(8;9)(p22;p24)[19]	Positive	Negative: *JAK2*
3	46,XY,t(8;9)(p21;p24)[13]/46,XY[7]	ND	ND
4	46,XX,t(8;9)(p22;p24)[17]/46,XX[3]	Positive	ND
5	46,XY,t(8;9)(p22;p24)[20]	Positive	Negative: All genes (NGS)
6	46,XX,t(8;9)(p22;p24)[20]	Positive	Negative: All genes (NGS)
7	46,XX,t(8;9)(p22;p24)[20]	ND	Positive: *ASXL1, RUNX1, SRSF2, TET2* Negative: all others (NGS)
8	46,XY,t(8;9)(q22;p24)[20]	ND	ND
9	46,XY,t(8;9)(p22;p24)[1]/47,idem,+21 [19]	Positive	Positive: *ETV6, TP53* Negative: all others (NGS)
10	45,XY,-7,t(8;9)(p22;p24)[15]/45~46,idem [cp5]	Positive	Positive: *ASXL1, TET2, BCOR* Negative: all others (NGS)

ND not done, *NGS* next generation sequencing

Table 1 Clinical and Pathological Findings of patients with t(8;9)(p22;p24)

Case	Sex/age	Diagnosis	Organo-megaly	Peripheral blood				Bone marrow cell types, and percentages					Treatments	FU (mon)	Outcome
				WBC ($\times 10^9$/L)	HGB (g/dL)	PLT ($\times 10^9$/L)	Eos (%)	Cell (%)	Blast (%)	Eos (%)	MF	Dys			
1	M/37	MPN CP	Yes	15	10.7	316	8	100	0	8	MF-0	No	9-Nitrocamptothecin	24	Alive
2	M/71	MPN CP	Yes	6.1	14	180	6	100	0	21	MF-2	No	Observe	142	Dead
3	M/70	MPN CP	Yes	6	14.5	151	13	90	2	10	MF1-2	No	Supportive care	13	Alive
4	F/53	MPN CP	Yes	8.5	7.2	124	39	95	3		MF-3	No	Hydroxyurea	104	Alive
5	M/40	MPN CP	Yes	5.4	10.6	151	16	95			MF1-2	NA	Ruxolitinib, SCT	29	Alive
6	F/86	MPN AP/BP	No	74	12.3	74	2	95	2	19	MF-3	No	Hydroxyurea, ATRA	1	Dead
7	F/82	MDS-MLD	No	1.9	11.4	33		70	2	7	MF-0	E, G, Meg	Decitabine	8	Alive
8	M/43	CMML-2	Yes	99	6.7	559	4	100	13	6	MF-3	E, G, Meg	Hydroxyurea	35	Dead
9	M/47	B-ALL	No	75	8.9	32	1	100	91	2	MF-0	No	Hyper-CVAD	2	Dead
10	M/69	B-ALL	No	51	11.2	145	0	100	79	1	MF1-2	No	Hyper-CVAD, inotuzumab rituximab	7	Alive

AP accelerated phase, *ATRA* All-transretinoic acid, *B-ALL* B lymphoblastic leukemia, *BP* blast phase, *Cell* cellularity, *CMML* chronic myelomonocytic leukemia, *Dys* dysplasia, *CP* chronic phase, *E* erythroid precursor, *Eos* eosinophils, *F* female, *FU* follow-up, *G* granulocyte lineage, *HGB* hemoglobin, *Hyper CVAD* cyclophosphamide, vincristine, Adriamycin and dexamethasone alternating with methotrexate, *M* male, *MDS-MLD* myelodysplastic syndrome with multilineage dysplasia, *Meg* megakaryocytes, *MF* myelofibrosis, *MPN* myeloproliferative neoplasm, *PLT* platelet count, *SCT* stem cell transplant, *WBC* white blood cells

Only 3 extra-medullary in this series (2 LNs, 1 spleen)

(3) Tang G, Sydney Sir Philip JK, Weinberg O, et al. Hematopoietic neoplasms with 9p24/JAK2 rearrangement: a multicenter study. *Mod Pathol*. 2019;32(4):490-498. doi:10.1038/s41379-018-0165-9

2019 SH-EAHP Cases in category of:
M/L Neoplasms with eosinophilia and tyrosine kinase gene fusions (4)

Clinical and Morphologic Characteristics of Myeloid/Lymphoid Neoplasms Rearrangements in *PDGFRA*, *PDGFRB*, *FGFR1*, and *PCM1-JAK2*[a]

Characteristic	*PDGFRA* (n = 20)	*PDGFRB* (n = 12)	*FGFR1* (n = 5)	*PCM1-JAK2* (n = 11)
Sex, male/female ratio	20:1	11:1	3:2	10:1
Age, median, y	51 (27-82)	51 (26-86)	51 (33-59)	51 (1-86)
WBC, $\times 10^9$/L	13.9 (4.0-106.0)	34.4 (6.8-116)	46.6 (13.7-75.2)	50 (2.85-120)
Hypereosinophilia >1.5 × 10^9/L	15 (75)	10 (83)	4 (80)	8 (73)
AEC, $\times 10^9$/L	4.69 (0.35-81.0)	4.44 (0.07-73.5)	4.66 (0.93-33.1)	3.6 (0-85.2)
Abnormal eosinophil morphology of reported cases, No.	13/15	2/3	1/1	3/3
Monocytosis >1.0 × 10^9/L	4/11 (36)	7/12 (58)	NA	NA
AMoC, $\times 10^9$/L	0.8 (0.3-4.24)	1.86 (0.07-8.49)	NA	NA
BM involvement	18 (90)	12 (100)	5 (100)	11 (100)
BM eosinophilia	16 (89)	11 (92)	3 (60)	7 (64)
BM proerythroblast clusters	NA	NA	NA	6 (56)
Presenting as CEL, NOS	13 (72)	7 (58)	2 (40)	7 (64)
Presenting as	5 (28)	5 (42)	3 (60)	4 (36)
MPN, NOS	2	1		2
Systemic mastocytosis	2	1	1	
Acute myeloid leukemia	1		1	
Chronic myelomonocytic leukemia	1	2		
Basophilic leukemia[b]		1		
B-lymphoblastic leukemia[b]			1	1
T-lymphoblastic leukemia[b]				1
Extramedullary involvement	11 (55)	1 (8)	4 (80)	2 (18)
Lymph node	6	1	3	2
Spinal/epidural	4			
Oral	1			
Cutaneous	1		1	
Response to imatinib, No.	11/12	5/5	NA	NA

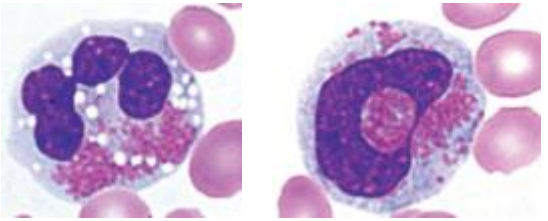
AEC, absolute eosinophil count; AMoC, absolute monocyte count; BM, bone marrow; CEL, chronic eosinophilic leukemia; MPN, myeloproliferative neoplasm; NA, not available; NOS, not otherwise specified.

[a]Values are presented as number (%) or median (range) unless otherwise indicated.

[b]Eosinophilia is not a prominent feature.

PCM1::JAK2:
11 / 53 (21%)
of cases in this category

Abnormal eosinophil morphology can be seen:



*PDGFRA*r:
4 (20%) spinal or epidural cases

***PCM1::JAK2*: Only 2 extra-medullary in this series (LNs)**

Ruxolitinib used for *JAK2*r,
but only alloSCT can potentially cure (5).

(4) Pozdnyakova O, Orazi A, Kelemen K, et al. Myeloid/Lymphoid Neoplasms Associated With Eosinophilia and Rearrangements of PDGFRA, PDGFRB, or FGFR1 or With PCM1-JAK2. *Am J Clin Pathol*. 2021;155(2):160-178. doi:10.1093/ajcp/aqaa208

(5) Kim AS, Pozdnyakova O. SOHO State of the Art Updates and Next Questions | Myeloid/Lymphoid Neoplasms with Eosinophilia and Gene Rearrangements: Diagnostic Pearls and Pitfalls. Clin Lymphoma Myeloma Leuk. 2022;22(9):643-651. doi:10.1016/j.clml.2022.03.008

DIAGNOSIS:

MYELOID/LYMPHOID NEOPLASM WITH *JAK2* REARRANGEMENT (WHO 5th ed.; ICC), with:

-solely a chronic myeloproliferative neoplasm in the bone marrow/peripheral blood.

-solely a B-lymphoblastic lymphoma with Burkitt-like features and additional/secondary t(8;22) translocation (suggestive of *MYC*::*IGL*, but negative for *MYC* rearrangement by FISH) in a thoracic tumor.

Diagnostic guide for MLNs, adapted for extramedullary presentation

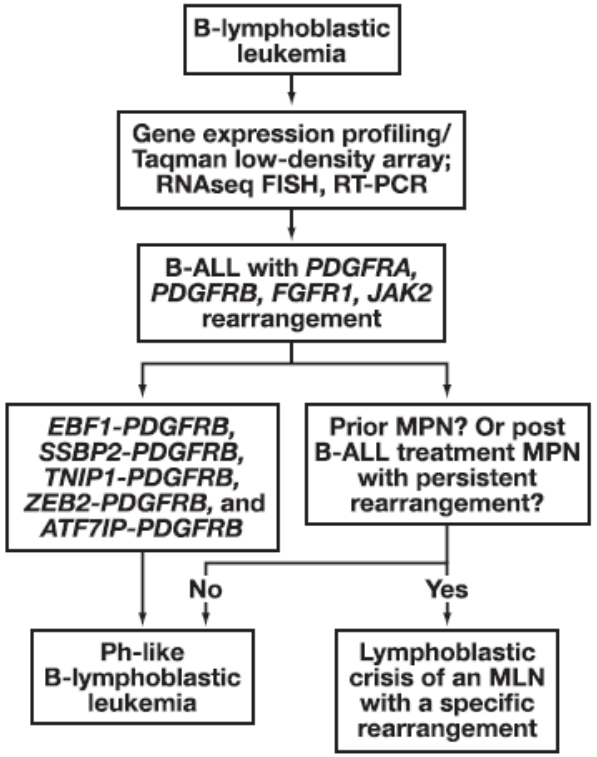


Figure 1 A guide for distinguishing Ph-like B-lymphoblastic leukemia/lymphoma from the myeloid/lymphoid neoplasms with a specific rearrangement. B-ALL, acute B-lymphoblastic leukemia; MLN, myeloid lymphoid neoplasm; MPN, myeloproliferative neoplasm.

Here: B-LBL in soft tissue.

Here: B-LBL with Burkitt-like morphology,
with IHC and t(8;22) raising question of *MYC::IGL*,
but also with a *JAK2*r.

Here: Concurrent chronic MPN seen in bone marrow.

Here: The thoracic tumor was a B-lymphoblastic lymphoma arising from a MLN with a *JAK2*r, now with secondary genetic abnormalities.

(4) Pozdnyakova O, Orazi A, Kelemen K, et al. Myeloid/Lymphoid Neoplasms Associated With Eosinophilia and Rearrangements of PDGFRA, PDGFRB, or FGFR1 or With PCM1-JAK2. *Am J Clin Pathol*. 2021;155(2):160-178. doi:10.1093/ajcp/aqaa208

Follow-up

- Treated with modified AYA regimen 06-254 for ALL (vincristine, doxorubicin, methotrexate, cytarabine, steroids, asparaginase).
- Achieved CR of B-LBL, proceeded with Blinatumomab consolidation.
- Now admitted for MAC 7/8 MMURD allogeneic PBSCT.
- Plan to include ruxolitinib with post-SCT medications.

THANKS!

Especially BWH hemepath, cytogenetics, and clinical teams!