Multi-Institutional Hematopathology Interesting Case Conference

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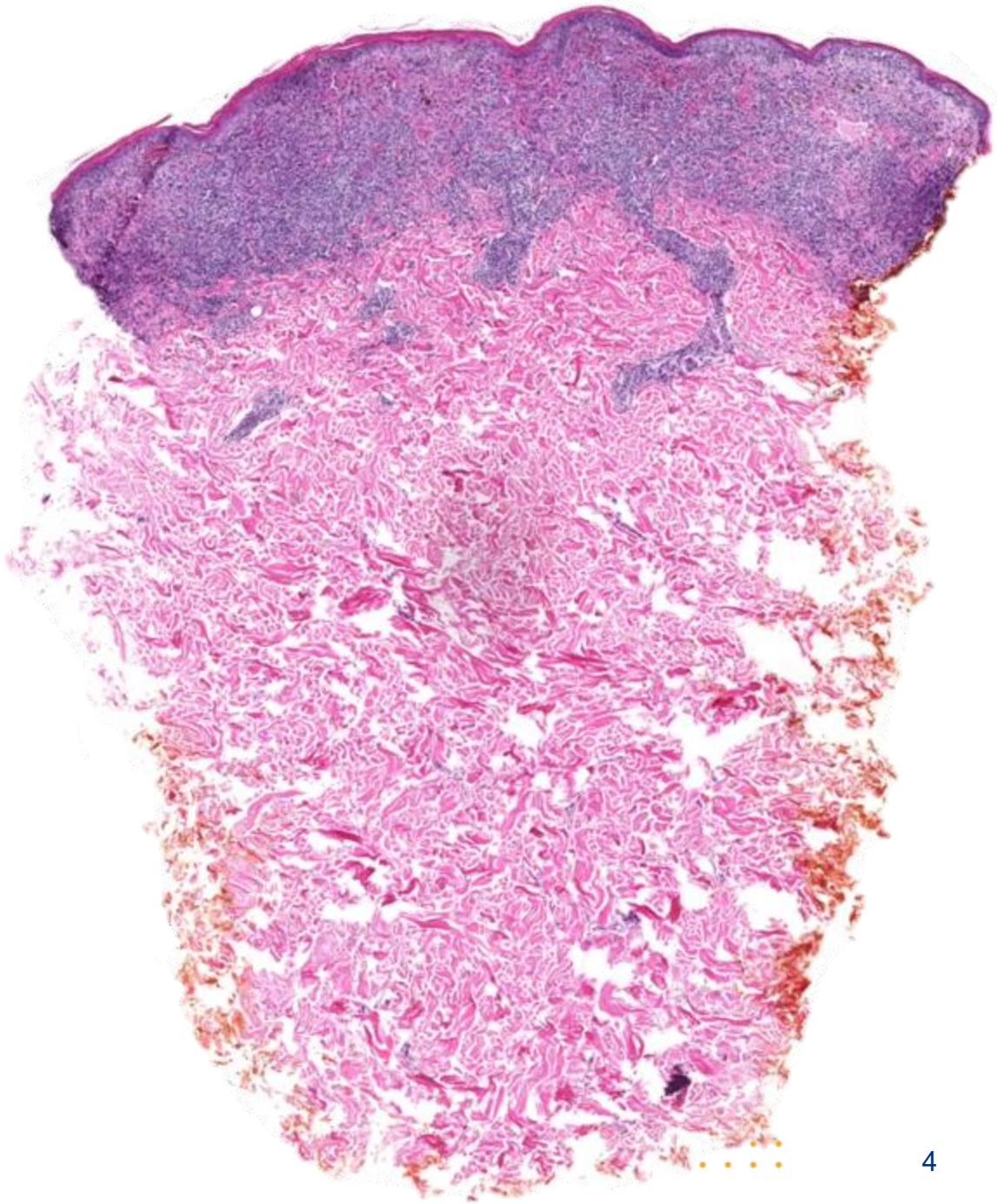
Clinical History

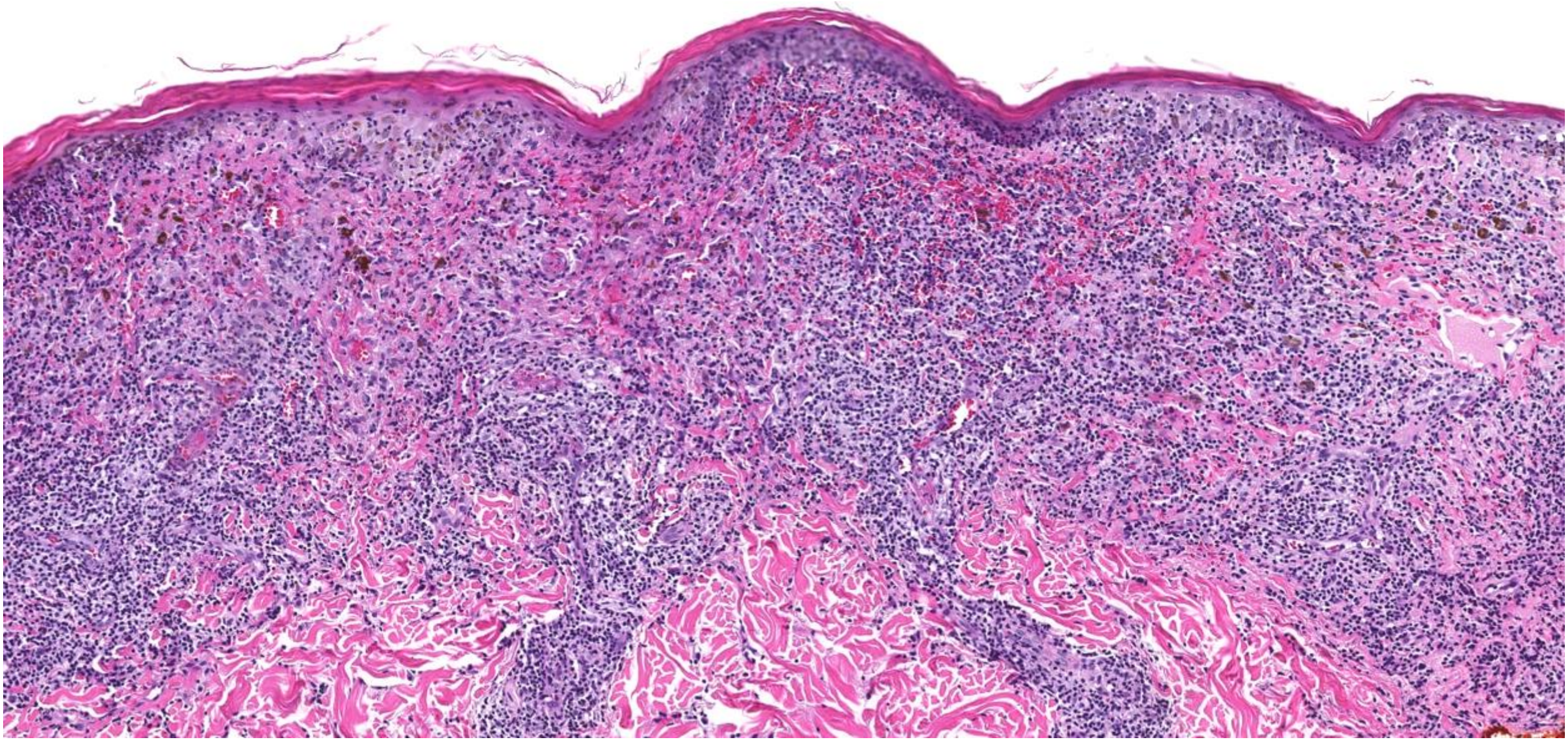
- 43-year-old male presented with a full-body pruritic skin rash that had been waxing and waning for the past 10 years
- No relief with oral and topical steroids, antihistamines or anti-itch cream
- Recently experiencing night sweats and weight loss
- Anemia and thrombocytopenia
- Physical exam
  - Diffuse erythematous papules on face/neck, trunk and extremities
  - Minimal palpable cervical, supraclavicular, axillary and inguinal lymphadenopathy
  - Mild splenomegaly

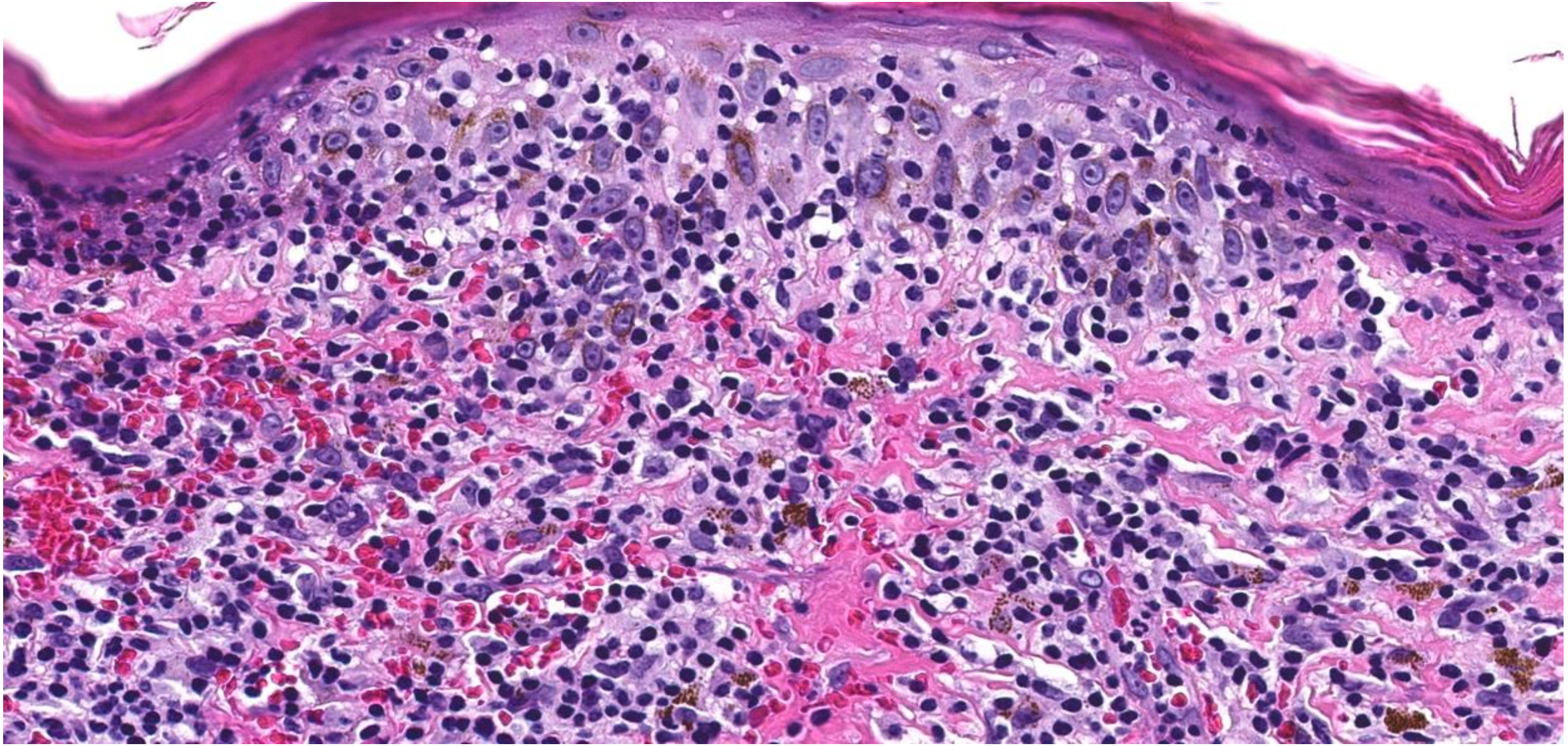
Lab	Result
WBC	**5.2 /µL**
RBC	**3.41 /µL ▼**
Hemoglobin	**10.8 g/dL ▼**
Hematocrit	**33.2% ▼**
Platelet	**102 /µL ▼**

Clinical Photos

Skin Punch Biopsy







Differential Diagnosis?

Infectious or inflammatory	Chronic dermatitis, drug reaction or viral exanthem can elicit lichenoid or epidermotropic lymphoid infiltrate
	Reactive pattern with pronounced spongiosis
Mycosis fungoides	Unusual clinical presentation for MF
	Classic morphologic features present, including band-like dermal infiltrate, epidermotropism and minimal spongiosis

Skin Biopsy

Immunophenotype:

- **POSITIVE:** CD2, CD3, CD4>>CD8, CD5, CD7, TCRβF1 (subset); rare + CD30, CD25 and CD56
- **NEGATIVE:** CD20, TCRɣ, ALK1, TIA1, EBV, infectious and special stains (spirochete, GMS, AFB)

DIAGNOSIS: Atypical T-cell infiltrate with epidermotropism

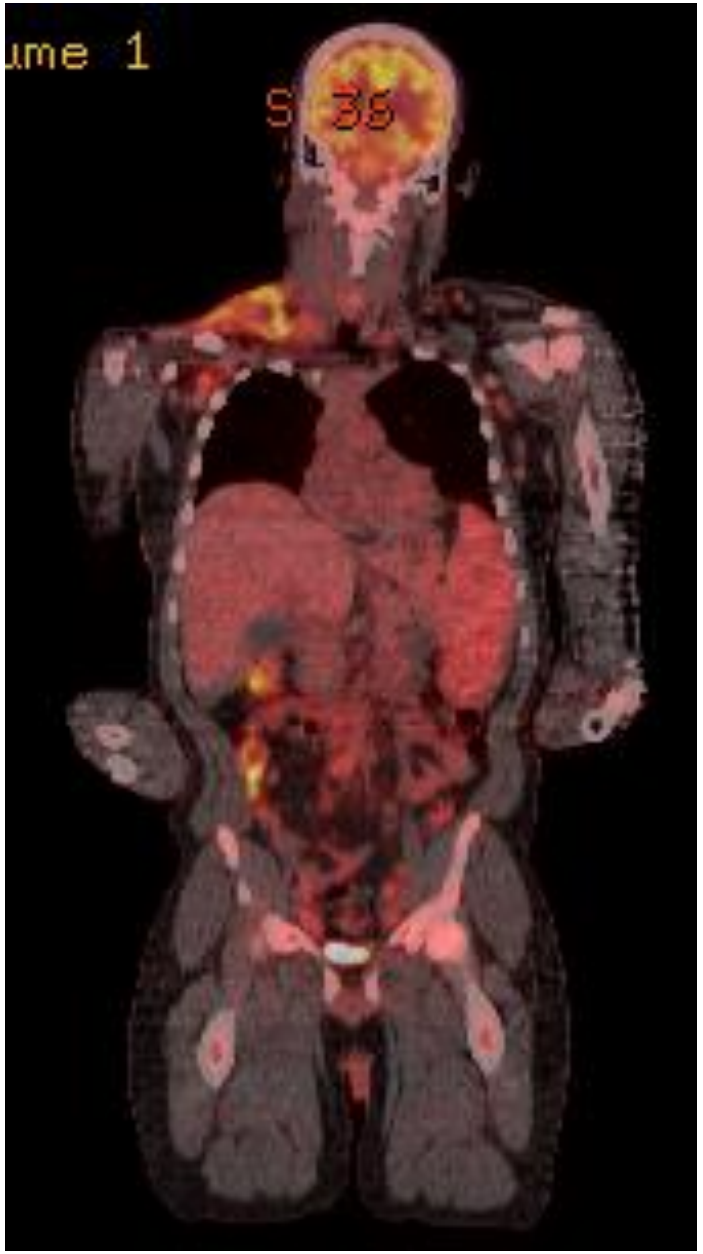
Clinical Follow-Up

- Worsening symptoms and cytopenias, concerning for systemic involvement
- CT chest and abdomen/pelvis → bulky multistation lymphadenopathy (largest 5.4 x 2.0 cm), splenomegaly (18 cm) and scattered bone lucencies
- PET/CT obtained

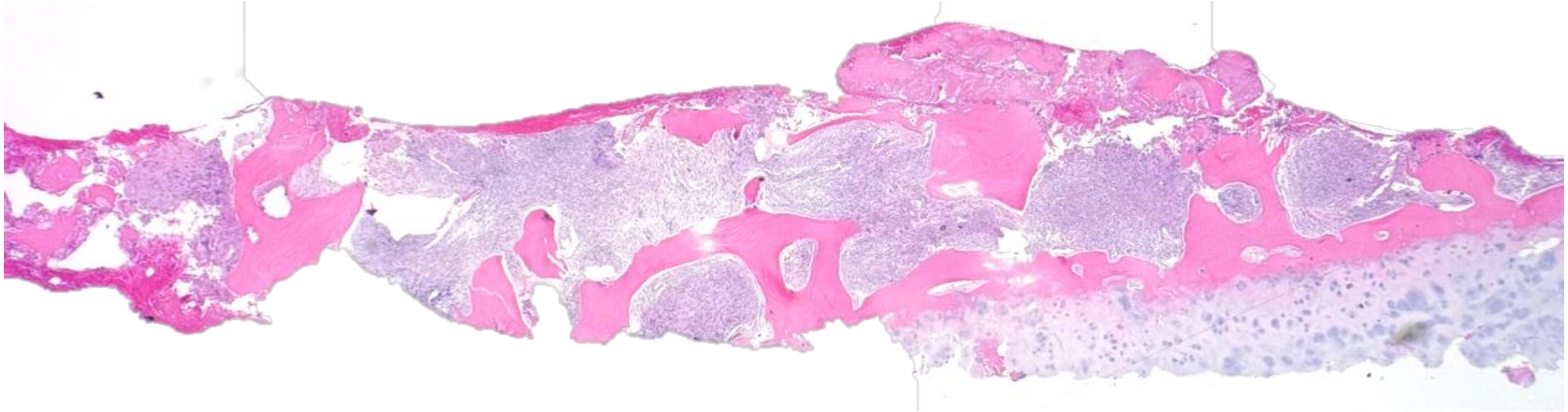
Lab	Result
HIV tests	Negative
EBV DNA by PCR	Undetected
HTLV I/II Ab	Negative
Hepatitis B/C	Negative
WBC	5.2 /µL
RBC	**2.93 /µL ▼**
Hemoglobin	**9.7 g/dL ▼**
Hematocrit	**27.4% ▼**
Platelet	**86 /µL ▼**
Neutrophil	39%
Lymphocyte	49%
Monocyte	5%
Eosinophil	6%
Basophil	0%

PET/CT

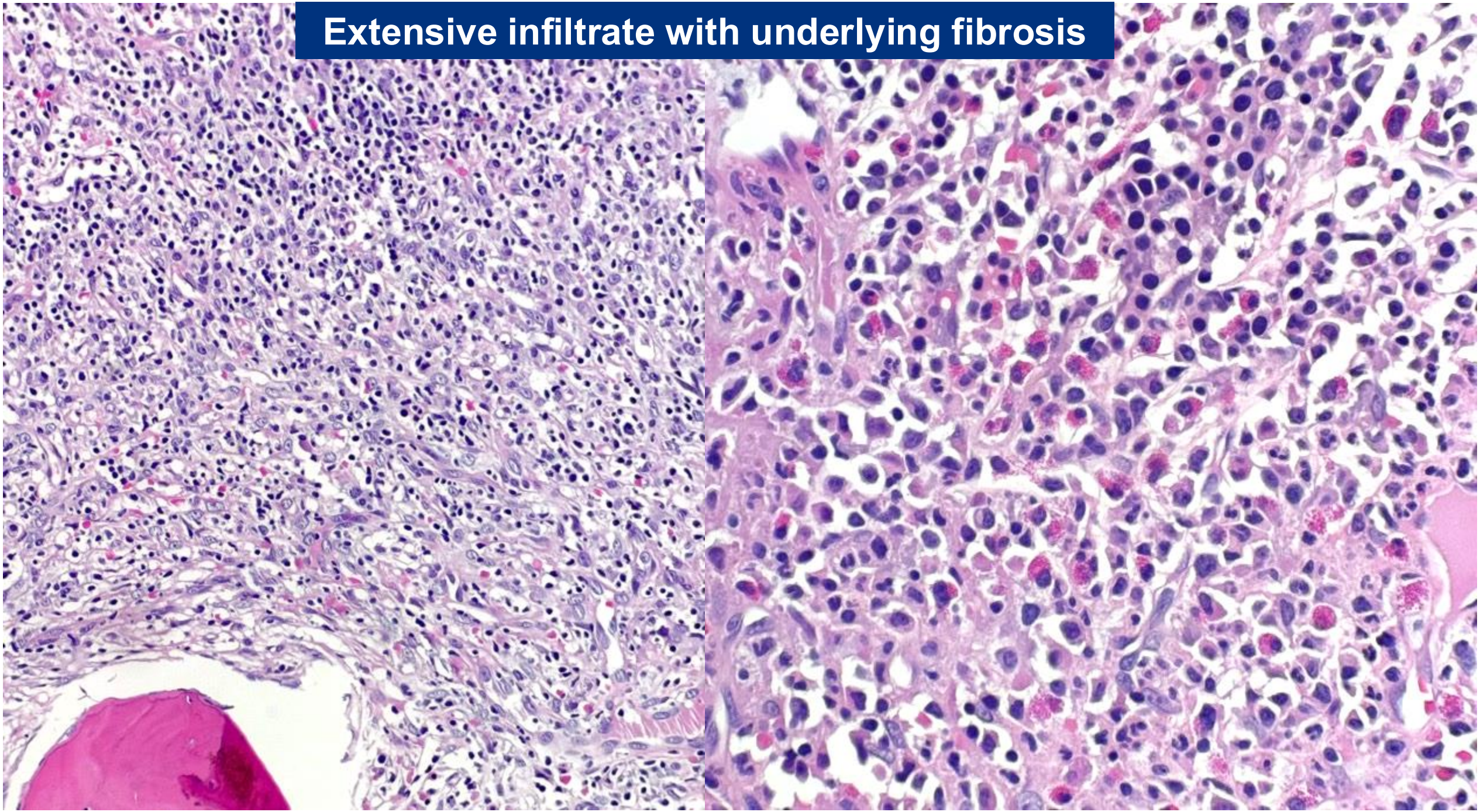
- Extensive LAD above and below diaphragm (max SUV 5.4) with **diffuse splenic and bone marrow involvement (stage IV disease)**
- Bone marrow biopsy performed

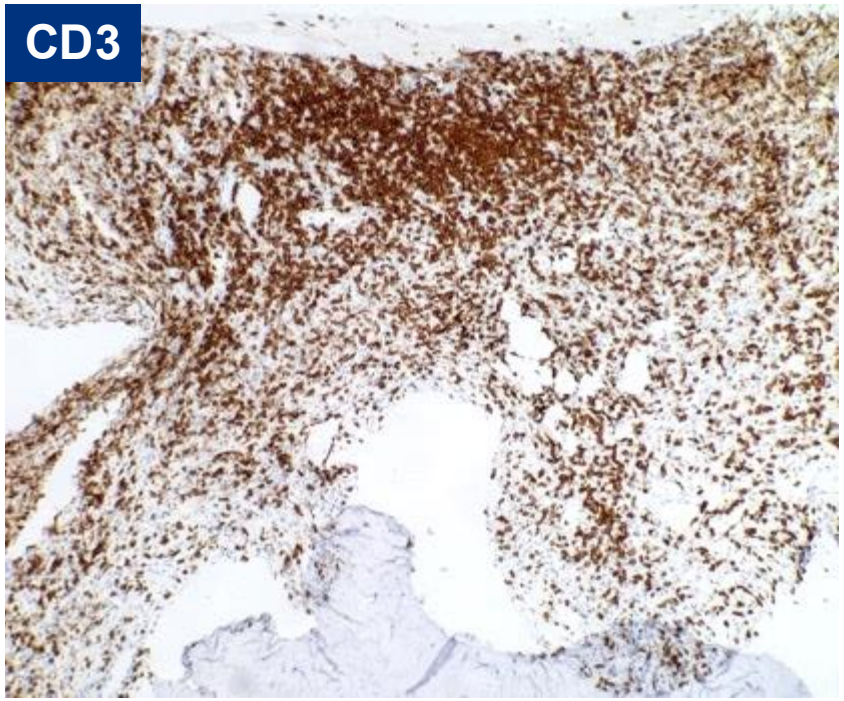


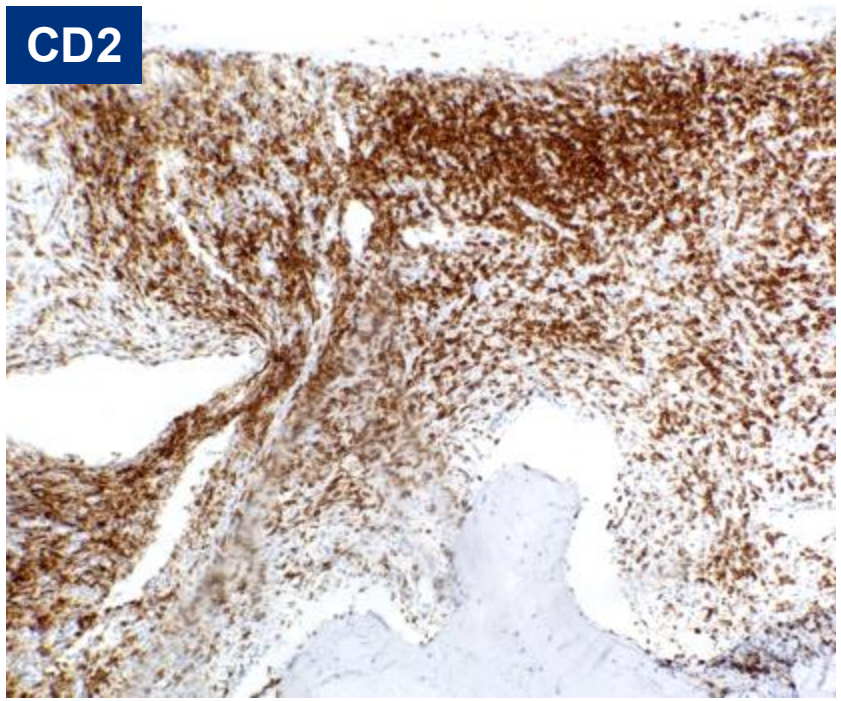
Bone Marrow #1, Core Biopsy

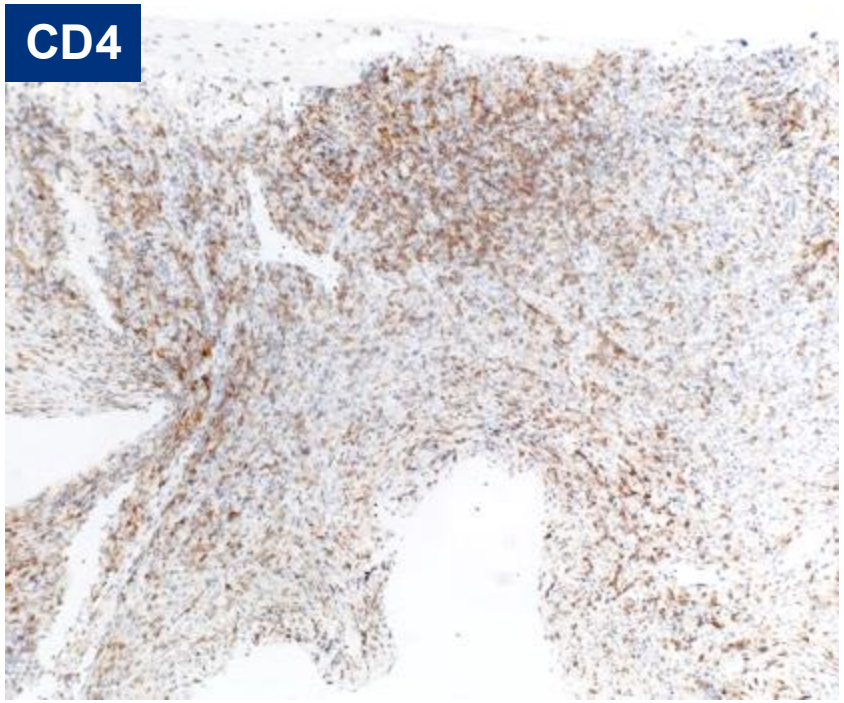


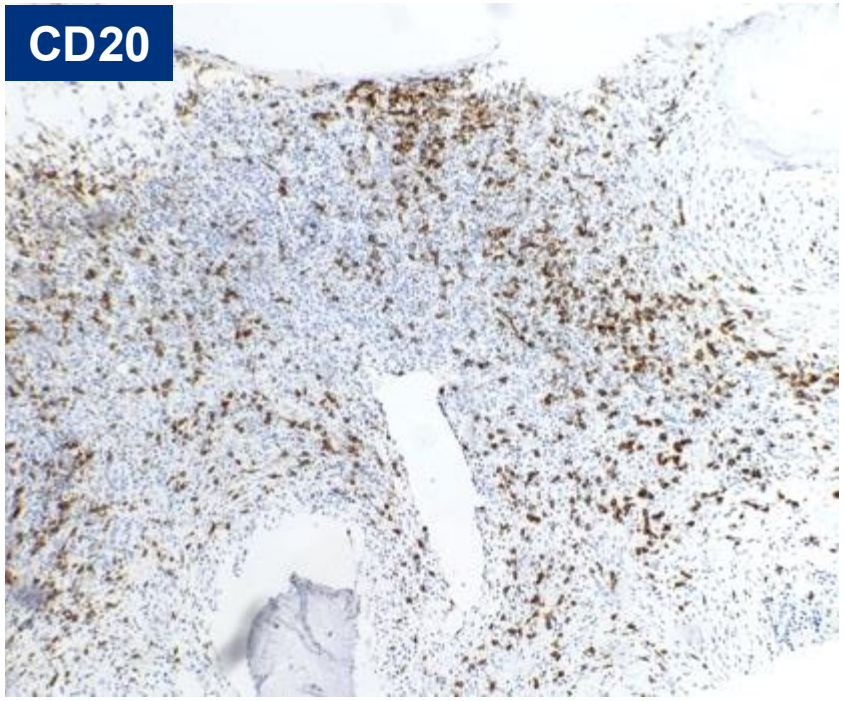
Extensive infiltrate with underlying fibrosis

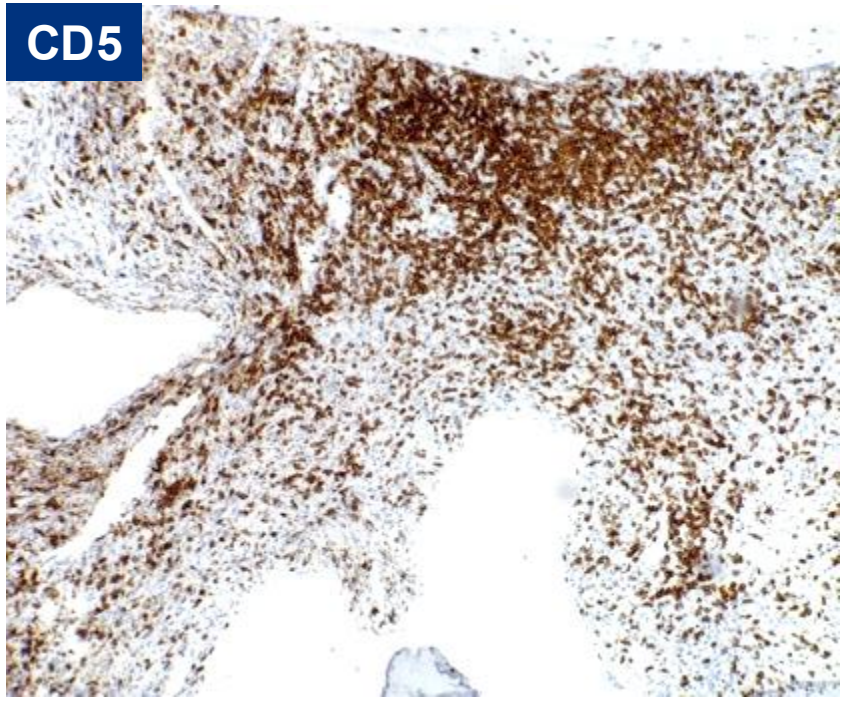


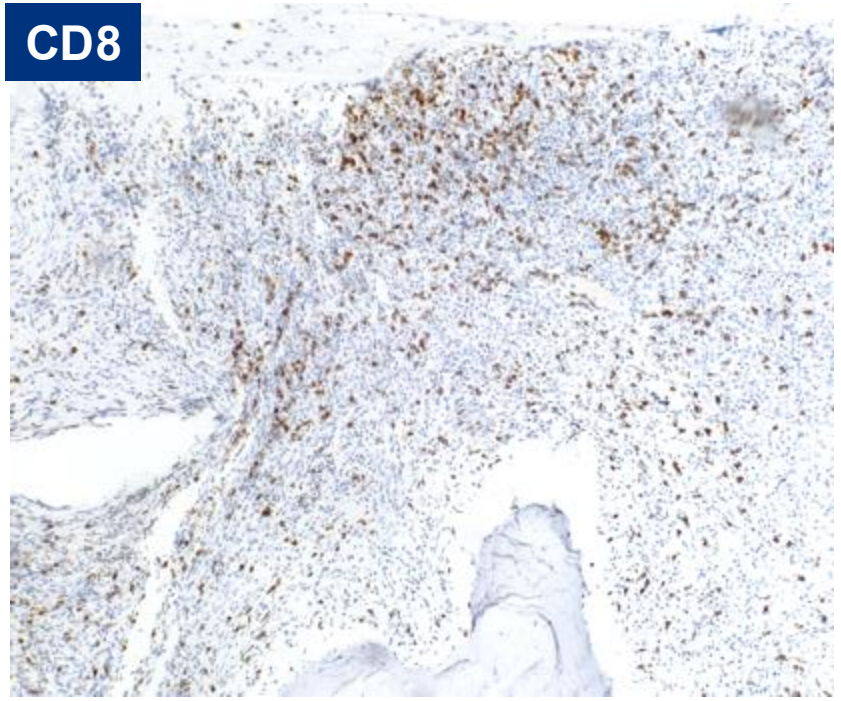

CD3


CD2


CD4


CD20


CD5


CD8

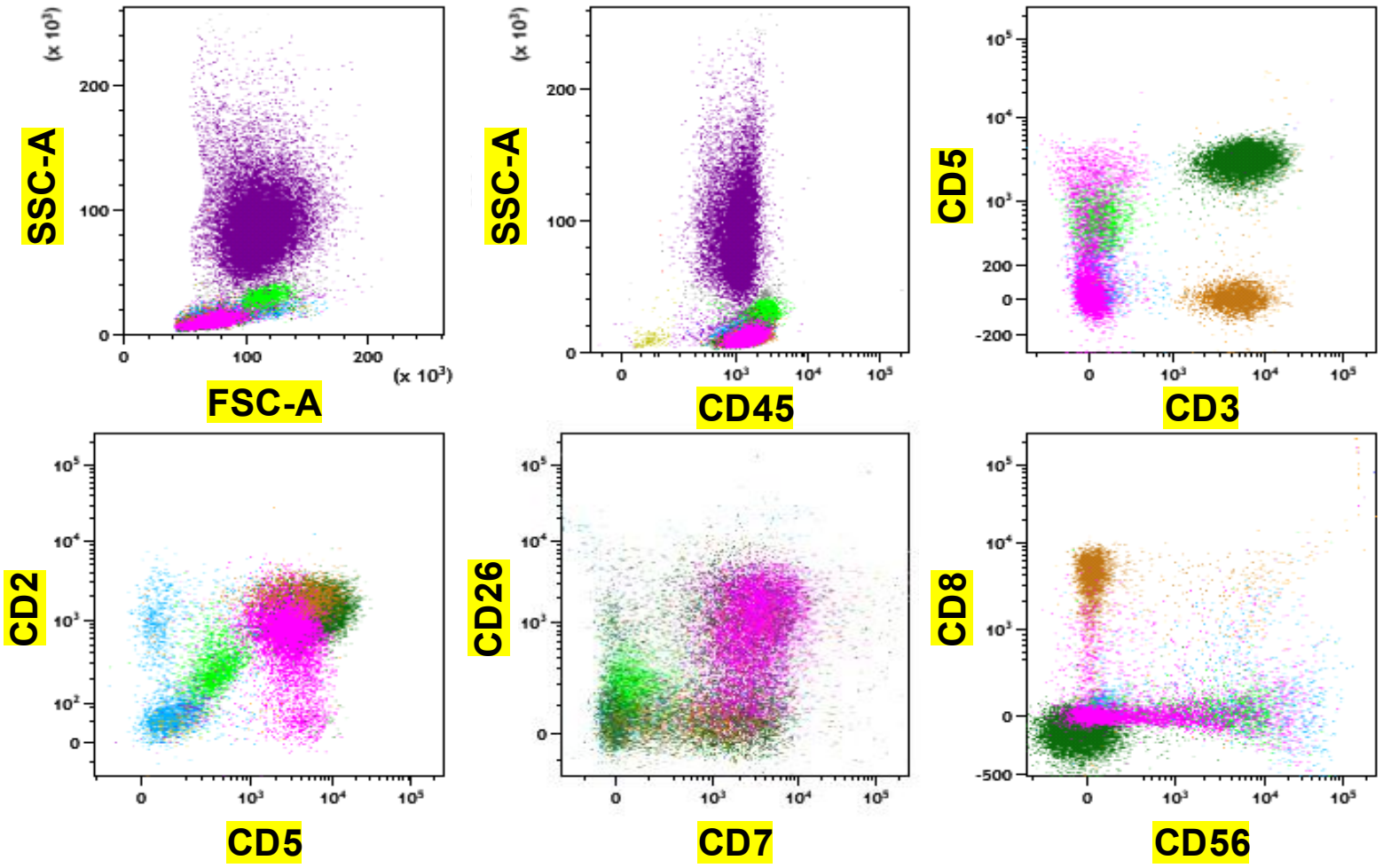
Summary of IHC & ISH on Bone Marrow

POSITIVE markers
CD2
CD3
CD5
CD4>CD8
CD25 (subset, 20%)
TCR BetaF1
PD1 (subset, 30-40%)
Ki67 <5%

NEGATIVE markers
TCR Gamma
CD20, PAX5
CD10
BCL6
MUM1
CD30
ALK1
ICOS, CXCL13
TdT
EBV ISH

Flow Cytometry on Bone Marrow

Atypical T-cell population (~12%) lacking surface CD3; similar findings on peripheral blood flow cytometry



Diagnostic Challenge

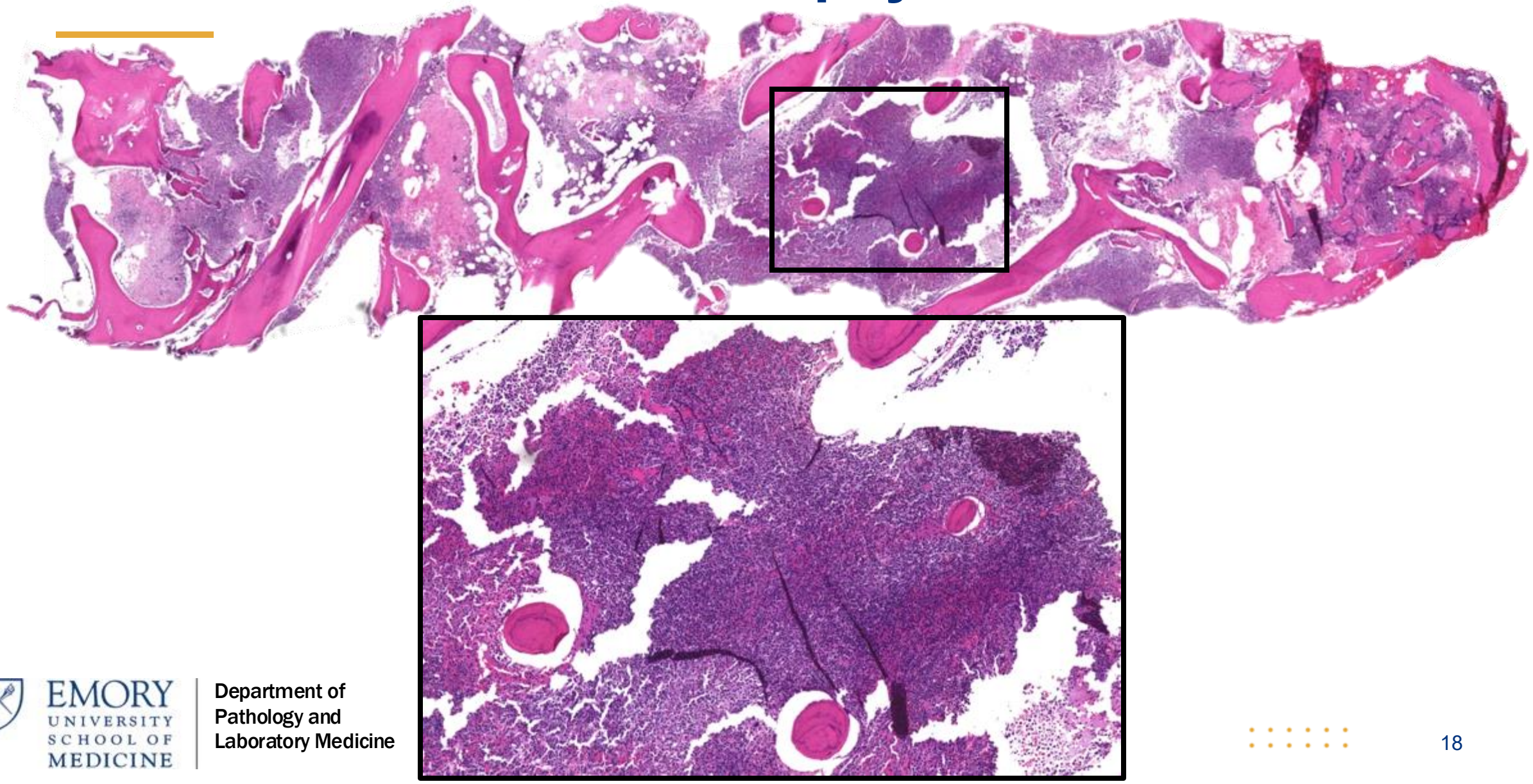
Mature T-cell lymphoproliferative disorder with systemic involvement and indolent course

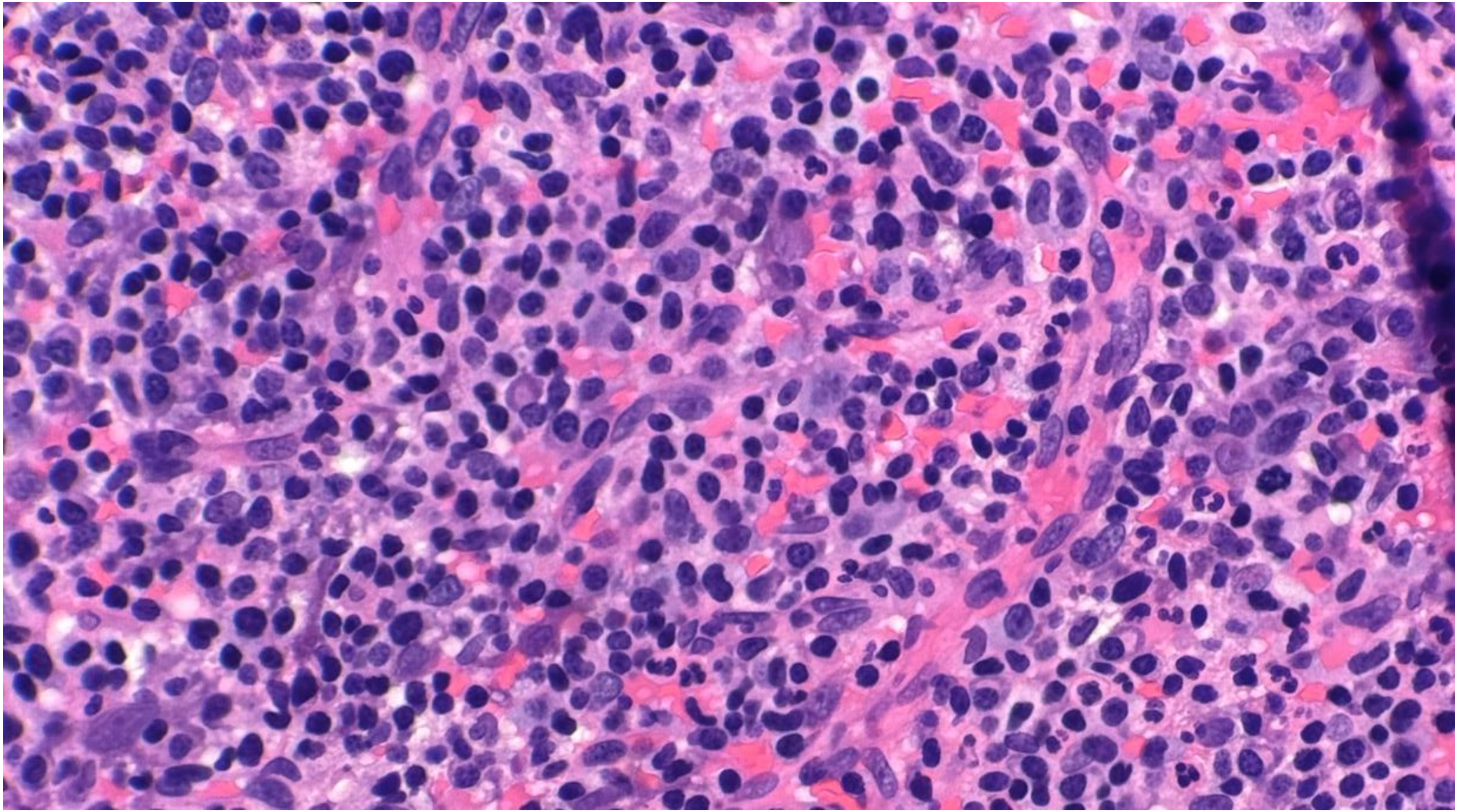
- Immunophenotype not specific and difficult to further classify
  - **NEGATIVE** for CD1a, TdT, CD25, CD30, ALK1, TIA1, CXCL13, ICOS, and EBER
  - **POSITIVE** for T-cell markers and partial PD1 (30-40%)
- Differential included:
  - Peripheral T-cell lymphoma, NOS → favored
  - Cutaneous T-cell lymphoma (mycosis fungoides, Sézary) → unusual clinical presentation
  - Adult T-cell leukemia/lymphoma → negative HTLV-1 serology
  - NK/T-cell lymphomas → non-aggressive course, negative EBV & cytotoxic markers

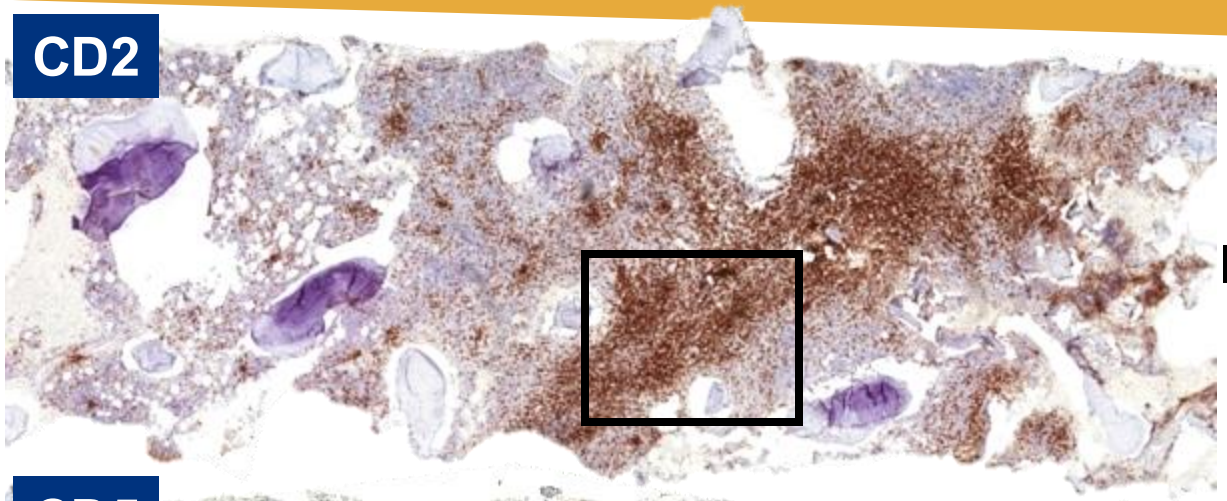
Next Steps

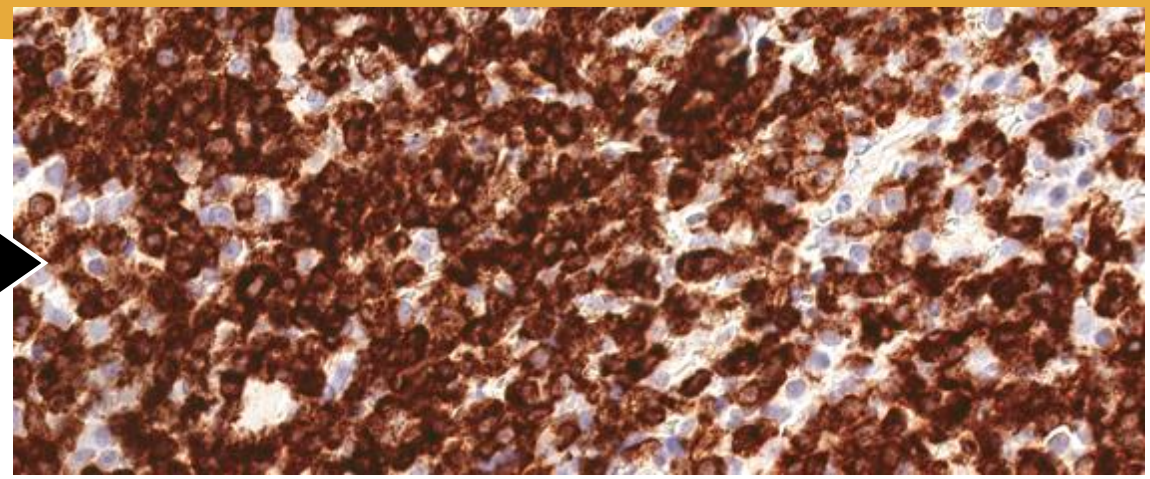
- Treated with 4 cycles of DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin)
- Restaging bone marrow biopsy performed

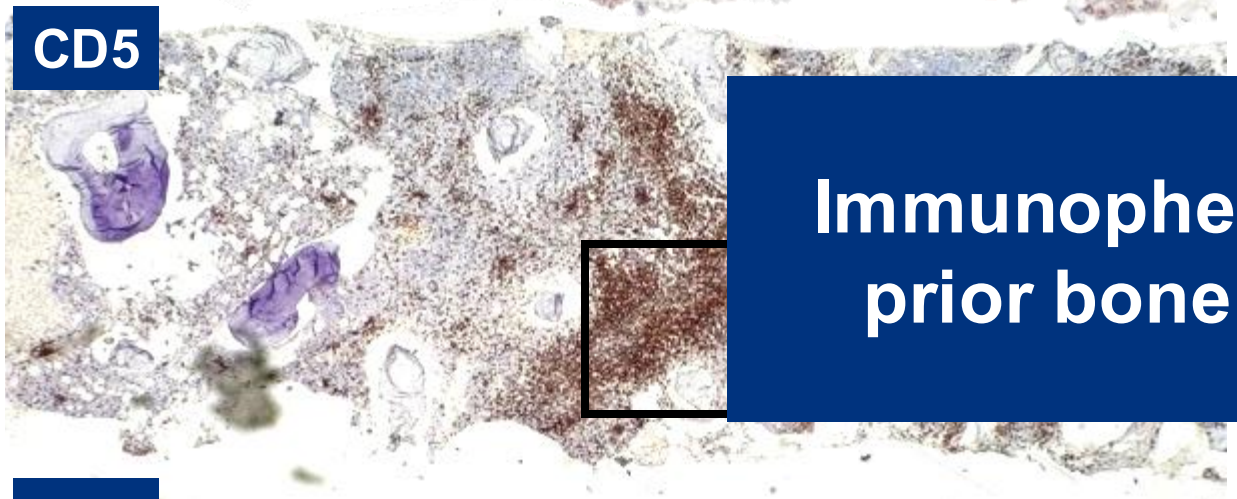
Bone Marrow #2, Core Biopsy



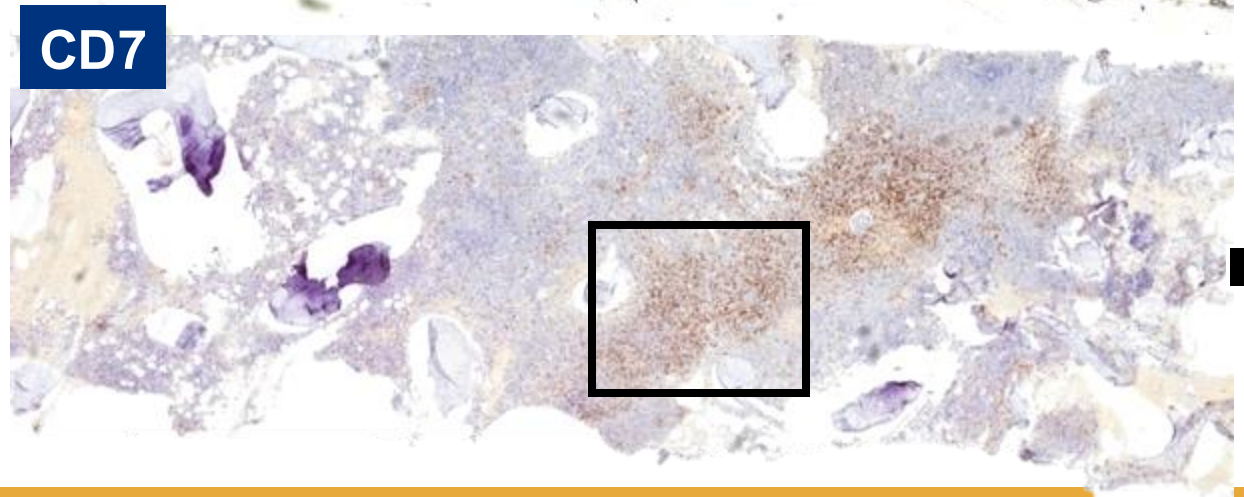


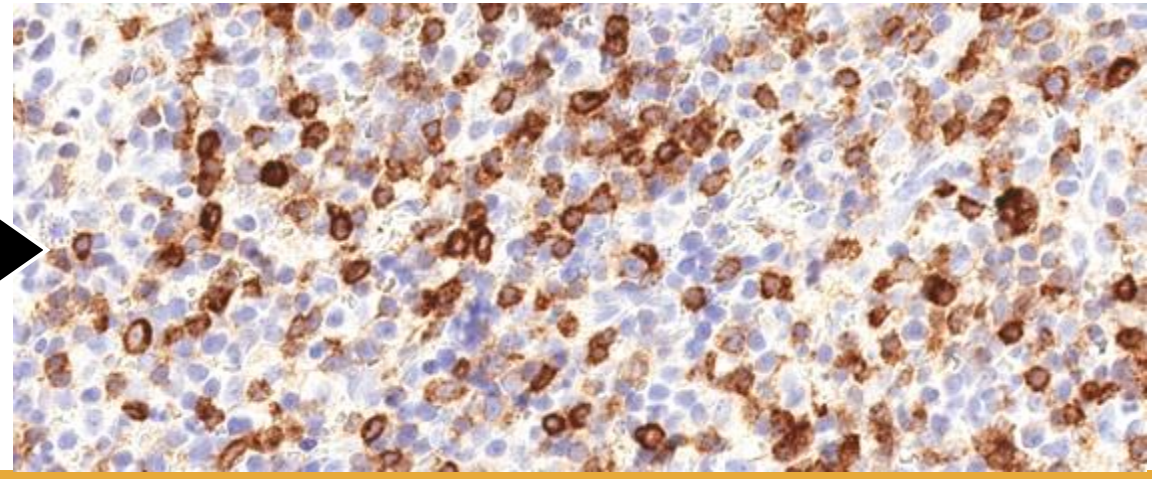






Immunophenotype similar to prior bone marrow biopsy





Additional Testing

- TCR showed a small clonal peak
- NGS on blood
  - No tier 1 mutations
  - No T-cell or myeloid neoplasm-associated mutations

Myeloid Mutation Panel (MMP75) on peripheral blood				
Gene	Transcript Variant	Protein Variant	VAF	Significance
FBXW7	c.2095G>A	V699M	15.01%	Tier 3

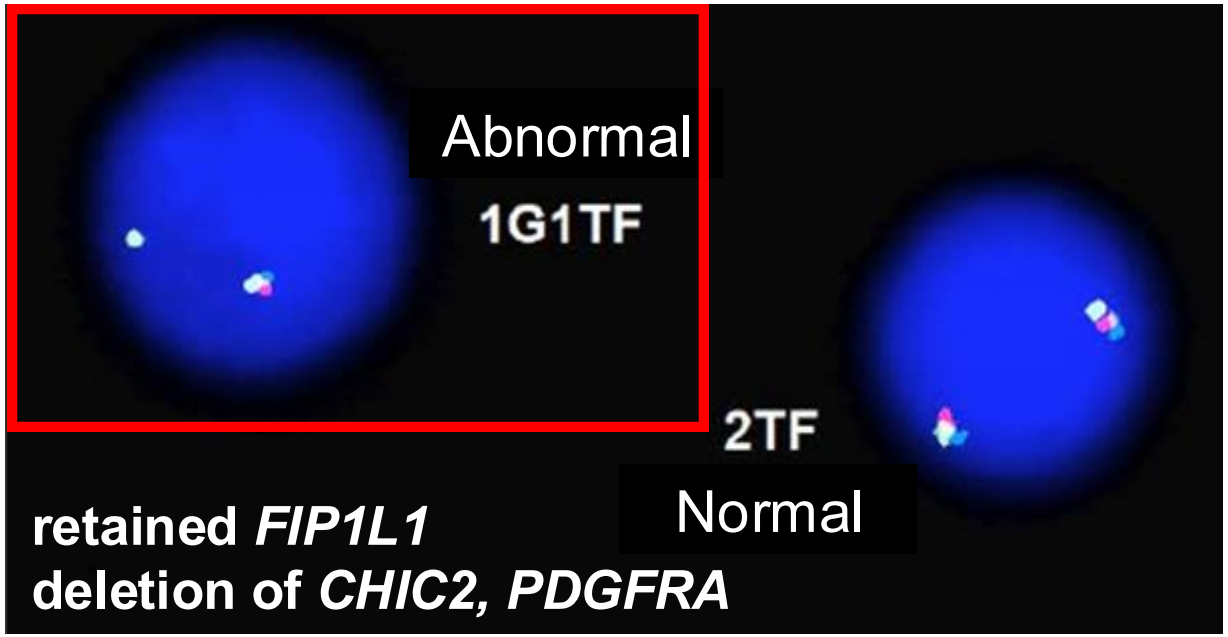
- Normal male karyotype: 46,XY[15]

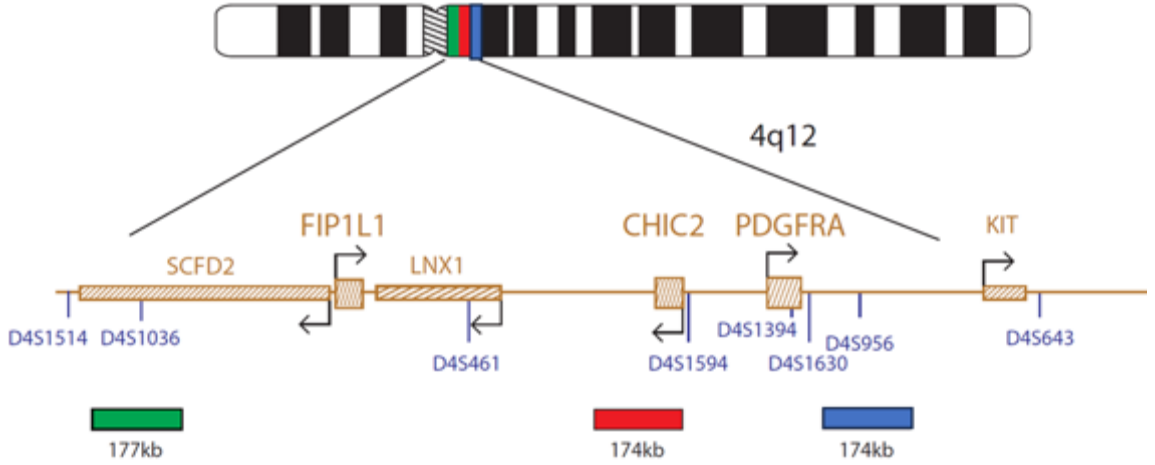
Given minimal response to chemotherapy and focal eosinophilia seen on initial bone marrow biopsy, additional work-up to exclude other etiology…

Eosinophilia FISH Panel on Bone Marrow

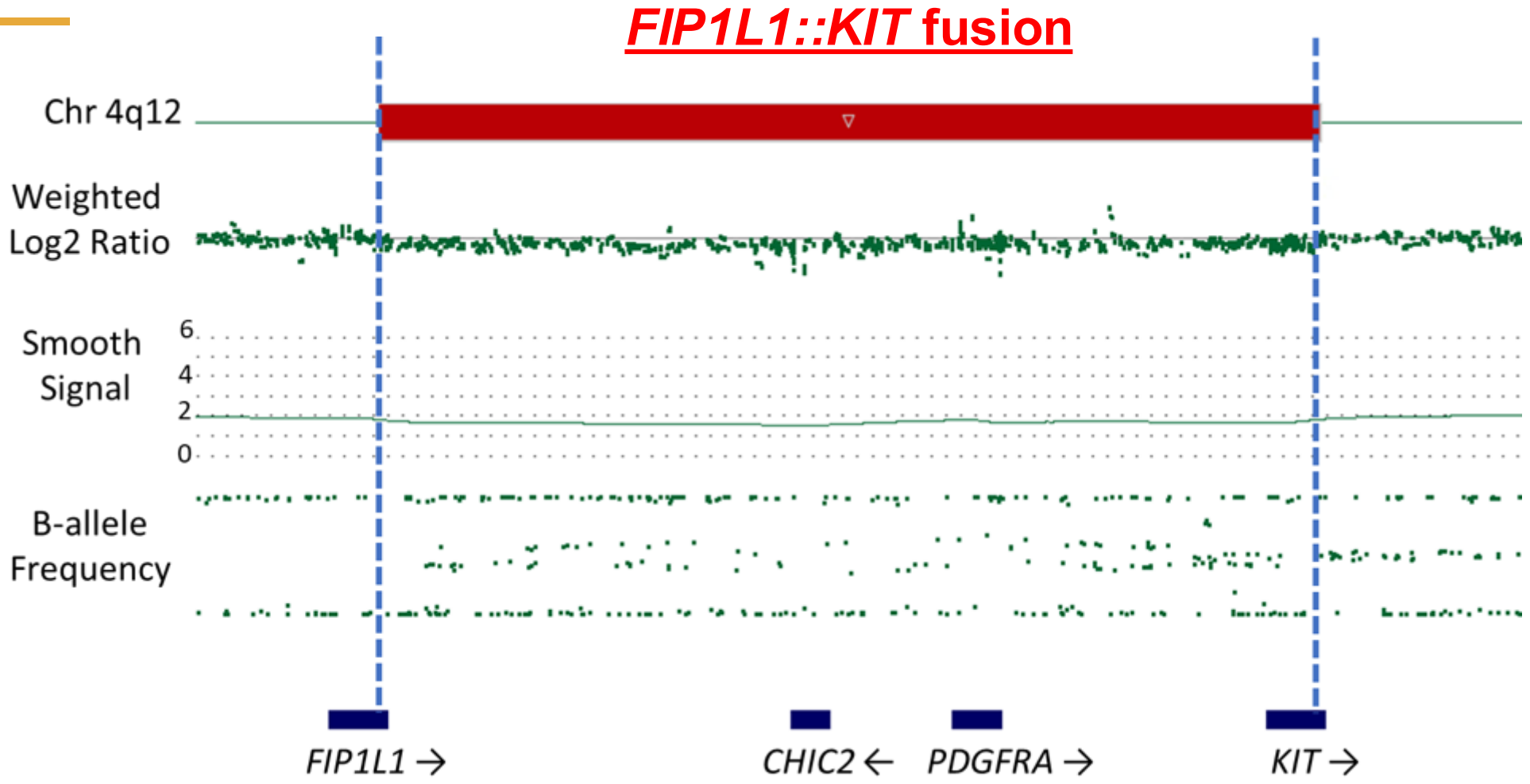
Probe(s)	Results
FIP1L1, CHIC2, PDGFRA for 4q12	**POSITIVE** for loss of both *CHIC2* and *PDGFRA* and retention of *FIP1L1* **(36%)**
PDGFRB	**NEGATIVE**
FGFR1	**NEGATIVE**
JAK2	**NEGATIVE**

- Identical findings on peripheral blood
- FISH is not enough to determine if retained *FIP1L1* gene rearranged with another gene





SNP-Microarray



Confirmatory **RNA sequencing** detected in-frame *FIP1L1::KIT* fusion with retained *KIT* tyrosine kinase domain

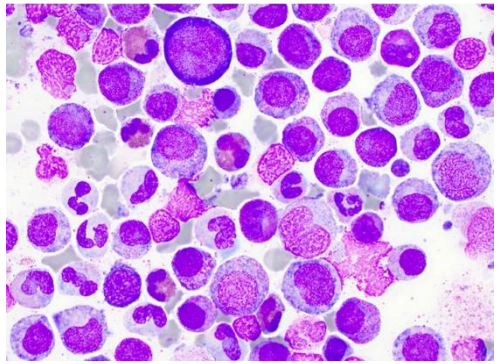
CASE REPORTS

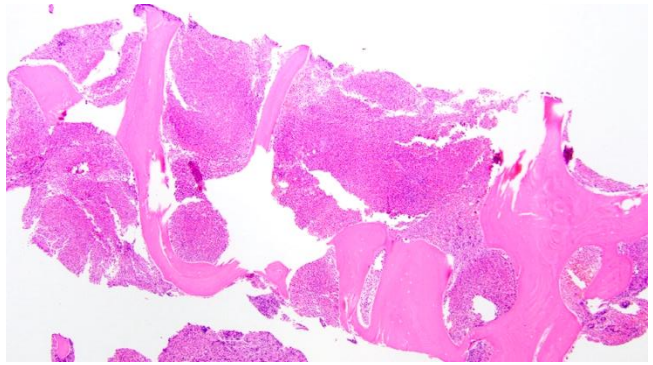
Novel *FIP1L1::KIT* fusion in a myeloid neoplasm with eosinophilia, T-lymphoblastic transformation, and dasatinib response

Aseel Alsouqi, Jeffrey Kleinberger, Taylor S Werner, Rashid Awan, Saurav Chopra, Bryan Rea, Nidhi Aggarwal, Svetlana A. Yatsenko, Rafic Farah, Nathanael G. Bailey

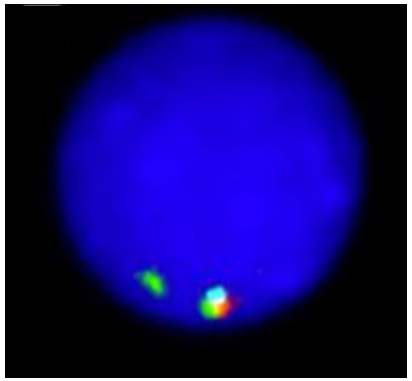
Vol. 108 No. 11 (2023): November, 2023 https://doi.org/10.3324/haematol.2022.282636

79F with myeloid neoplasm with monocytosis and eosinophilia



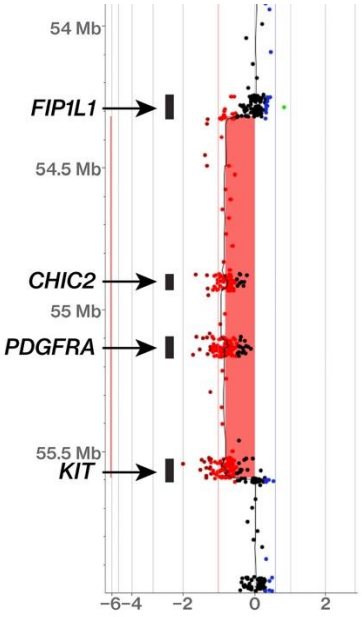


FISH: Abnormal

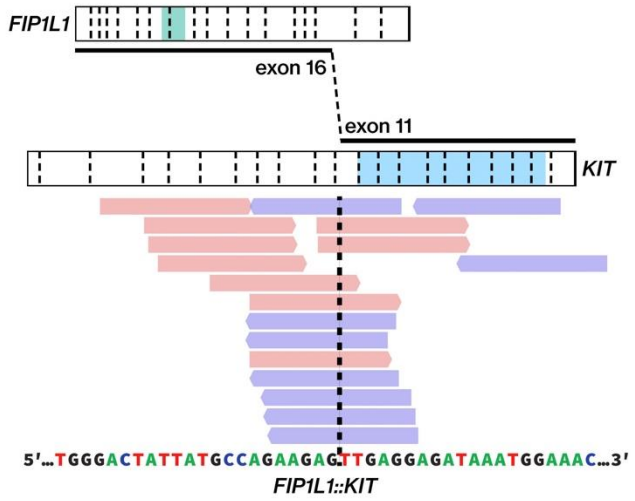


Loss of both *CHIC2* & *PDGFRA* signals; retention of 5' of *FIP1L1* signal

Whole-genome microarray analysis

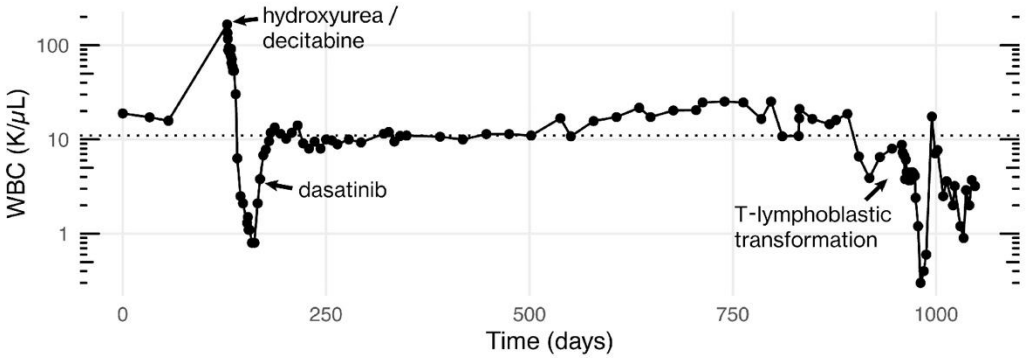


RNA sequencing



confirmed *FIP1L1::KIT* fusion

Therapy response and subsequent relapse



- Interruptions in dasatinib tx → relapse, transf. to T-ALL
- No response to chemotherapy
- Dasatinib restarted → significant improvement in LAD

- Established that *FIP1L1::KIT* fusion can be considered within spectrum of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)
- Expanded scope of TK gene fusions beyond the more common *FIP1L1::PDGFRA* fusion

Alsouqi A et al. *Haematologica.* 2023

Patient Treatment Course

- Confirmation of *FIP1L1::KIT* fusion → tyrosine kinase inhibitor (dasatinib) initiated with significant improvement in skin (itching and dryness also subsided)
- Decreased disease burden on subsequent testing:
  - Bone marrow showed decreased T-cell aggregates
  - FISH for 4q12 deletion decreased from 36% to 4% to eventually 0%
  - SNP-microarray negative for copy # or copy-neutral LOH abnormalities

Summary and Conclusions

- Long-standing refractory skin rash → mature T-cell lymphoproliferative neoplasm with skin, bone marrow and splenic involvement → *FIP1L1::KIT* fusion confirmed by molecular → dasatinib tx with significant improvement despite poor response to chemo
- Long-term response of both patients to TKI therapy supports that *KIT* fusions are targetable, similar to other tyrosine kinase fusions in MLN-TK
- Utility of SNP-microarray in investigating potential genomic deletions with an abnormal *PDGFRA*-directed FISH signal pattern
- Should we test for TK fusions in all unclassifiable T-cell lymphoproliferative disorders?

References

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Thank you