



Mass General Brigham



HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL

# 82-year-old woman with fever of unknown origin

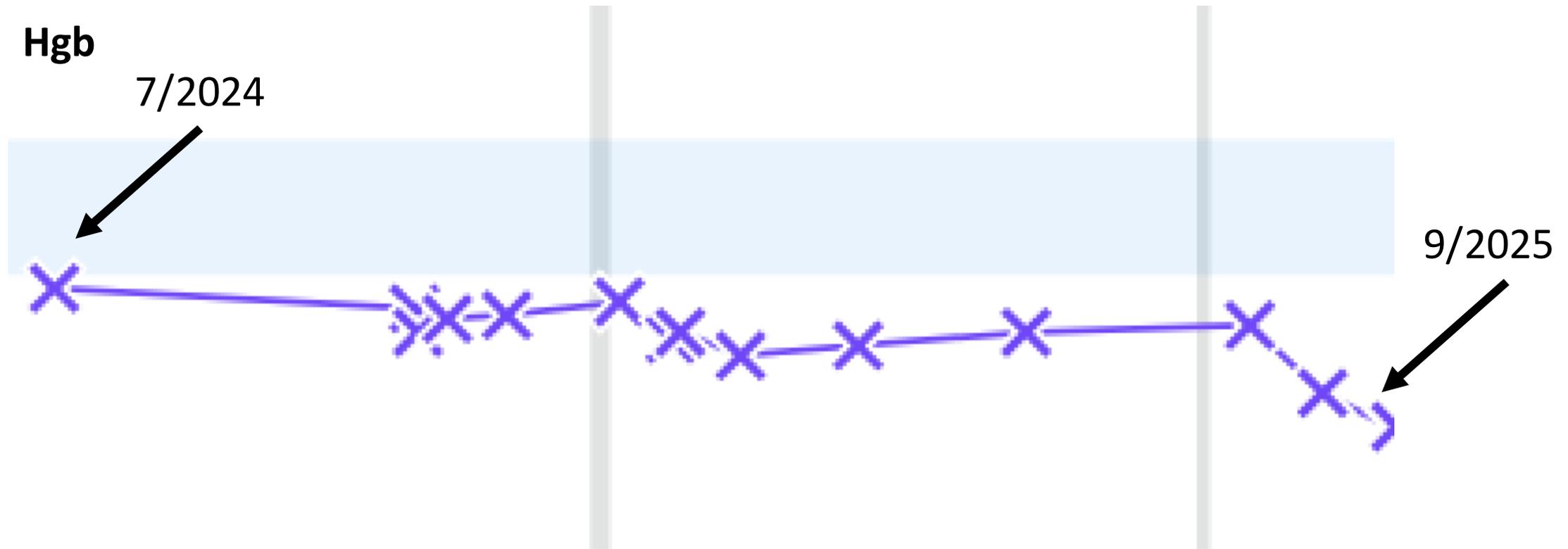
Derek Loneman, MD

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# Clinical presentation

82-year-old woman, non-contributory PMH:

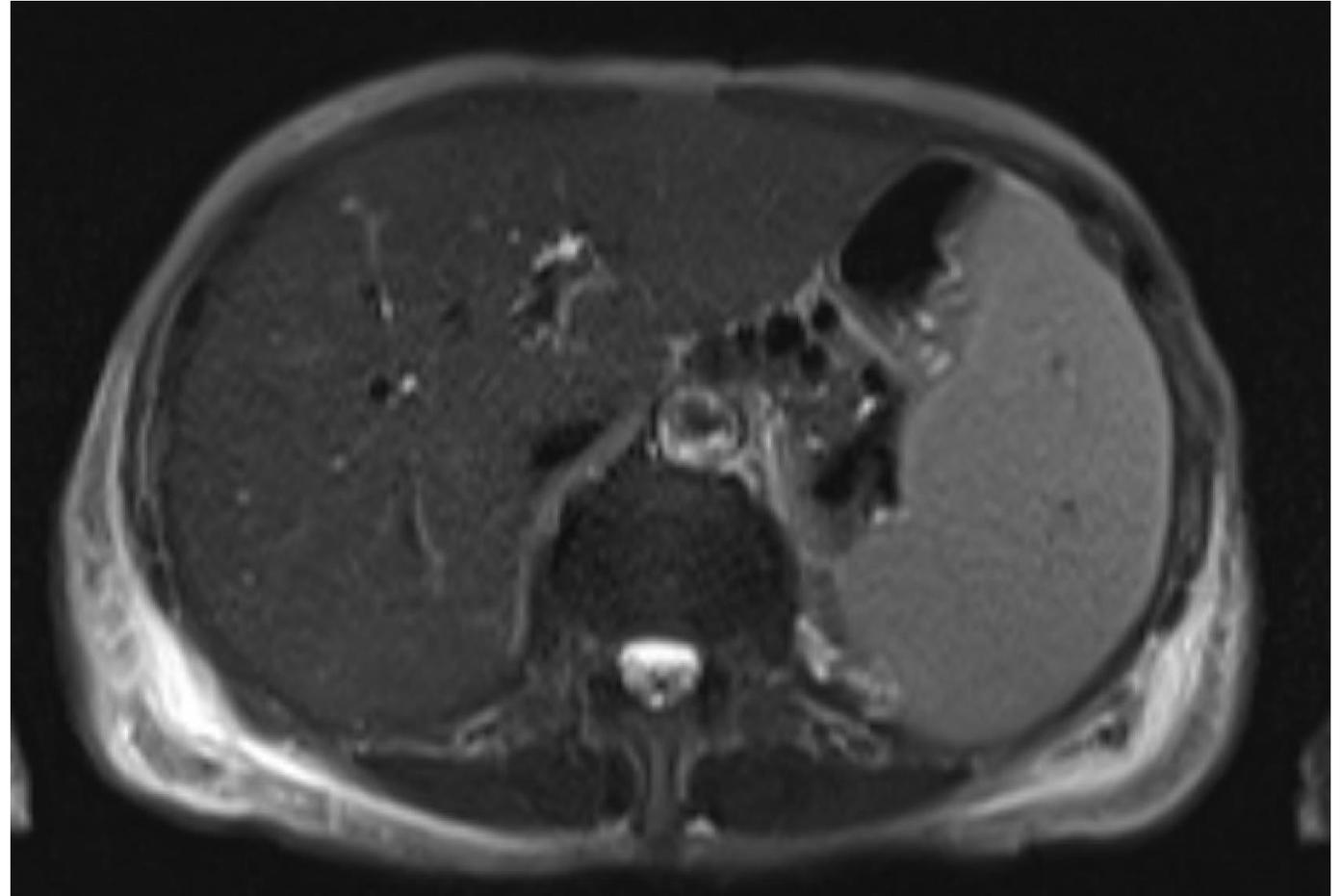
- Months of symptomatic anemia (normochromic/cytic) + fever + weight loss (~20 lbs), now presenting with hypotension (88/49)



# Clinical presentation

82-year-old woman, non-contributory PMH:

- Prior anemia workup within normal limits: Kidney function, EGD/colonoscopy, SPEP, hematinic factors, bone marrow biopsy, rheumatologic testing, etc.
- MRI on admission: mild splenomegaly (14 cm)



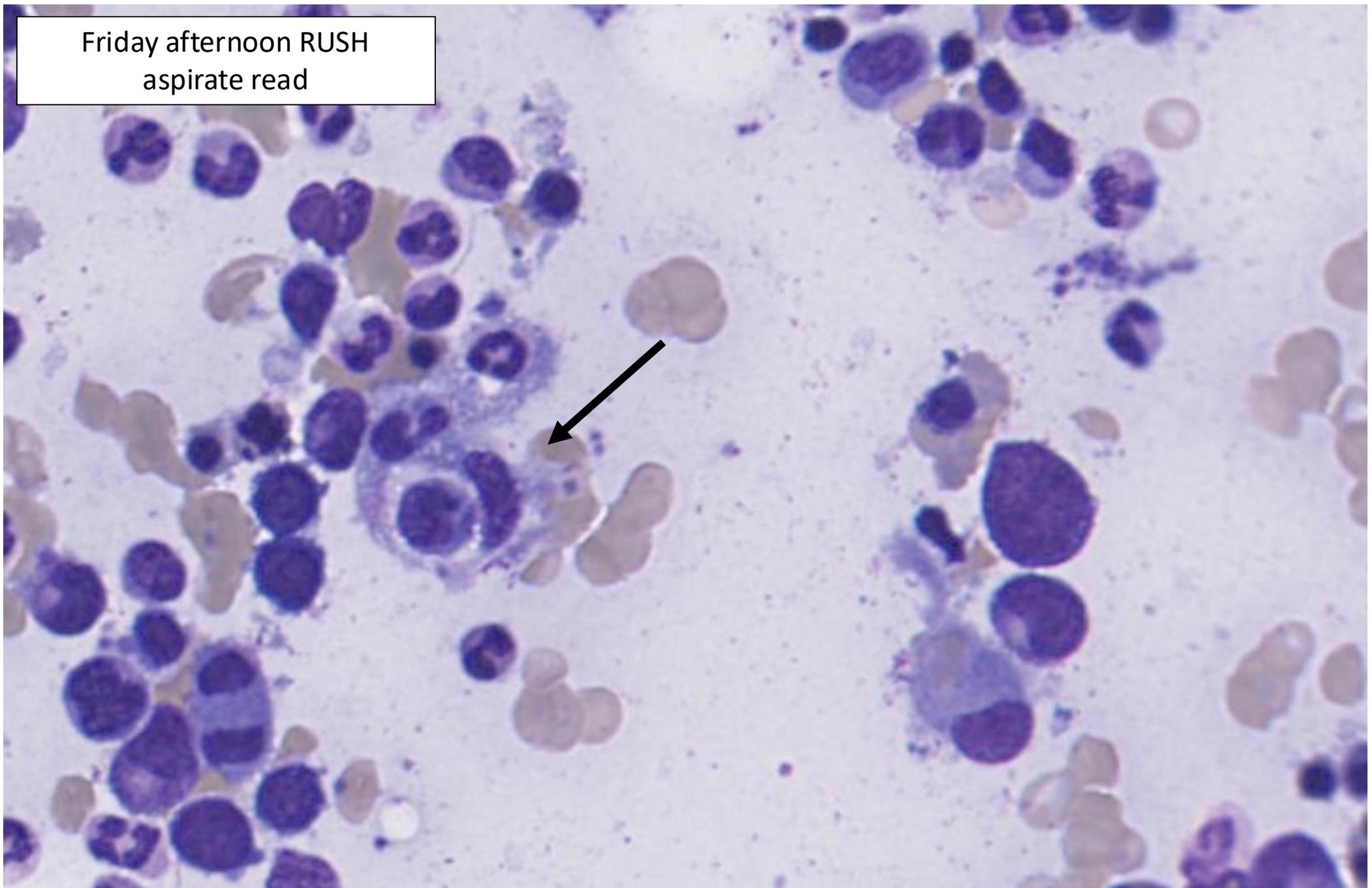
# Clinical presentation

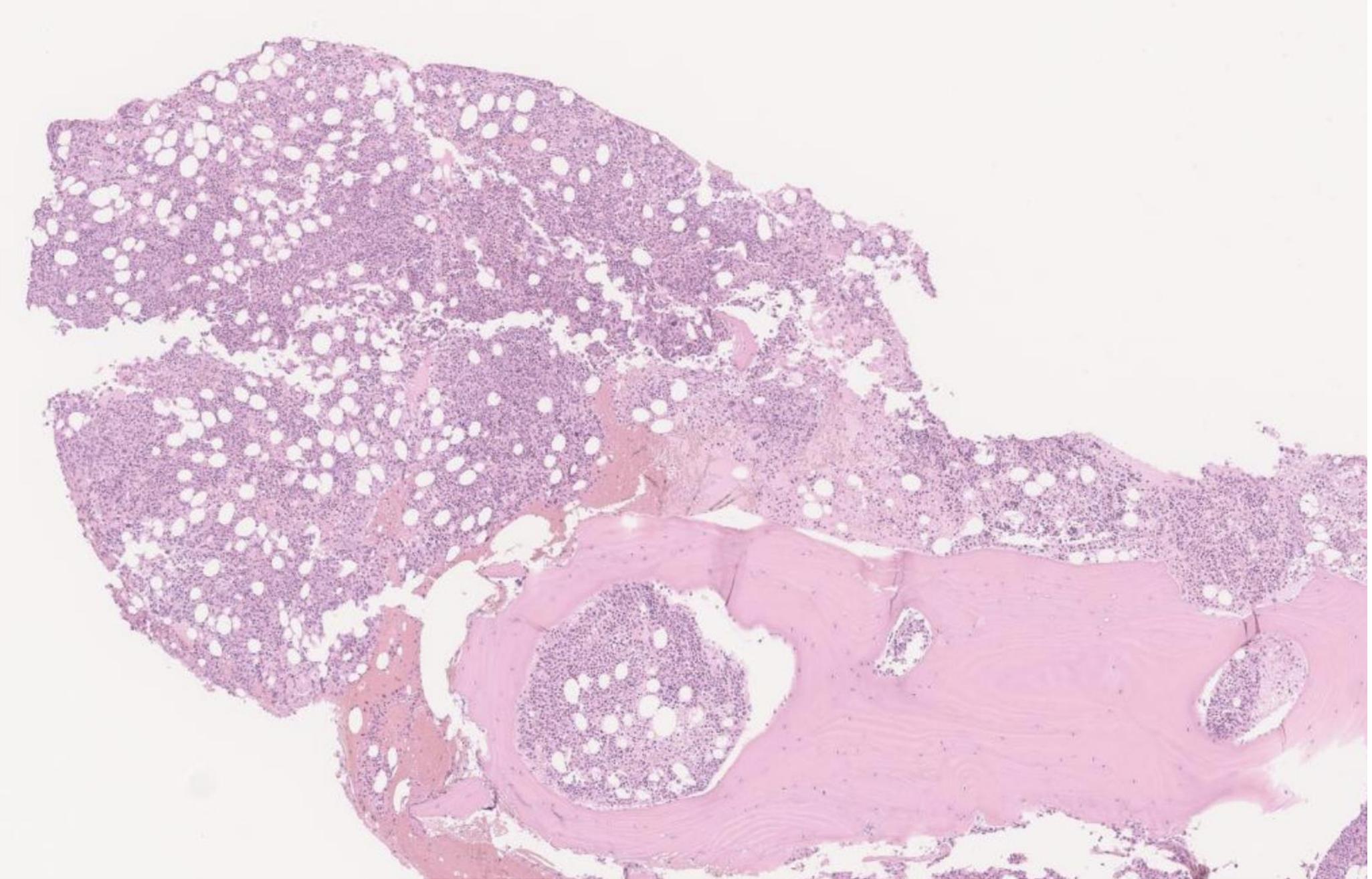
82-year-old woman, non-contributory PMH:

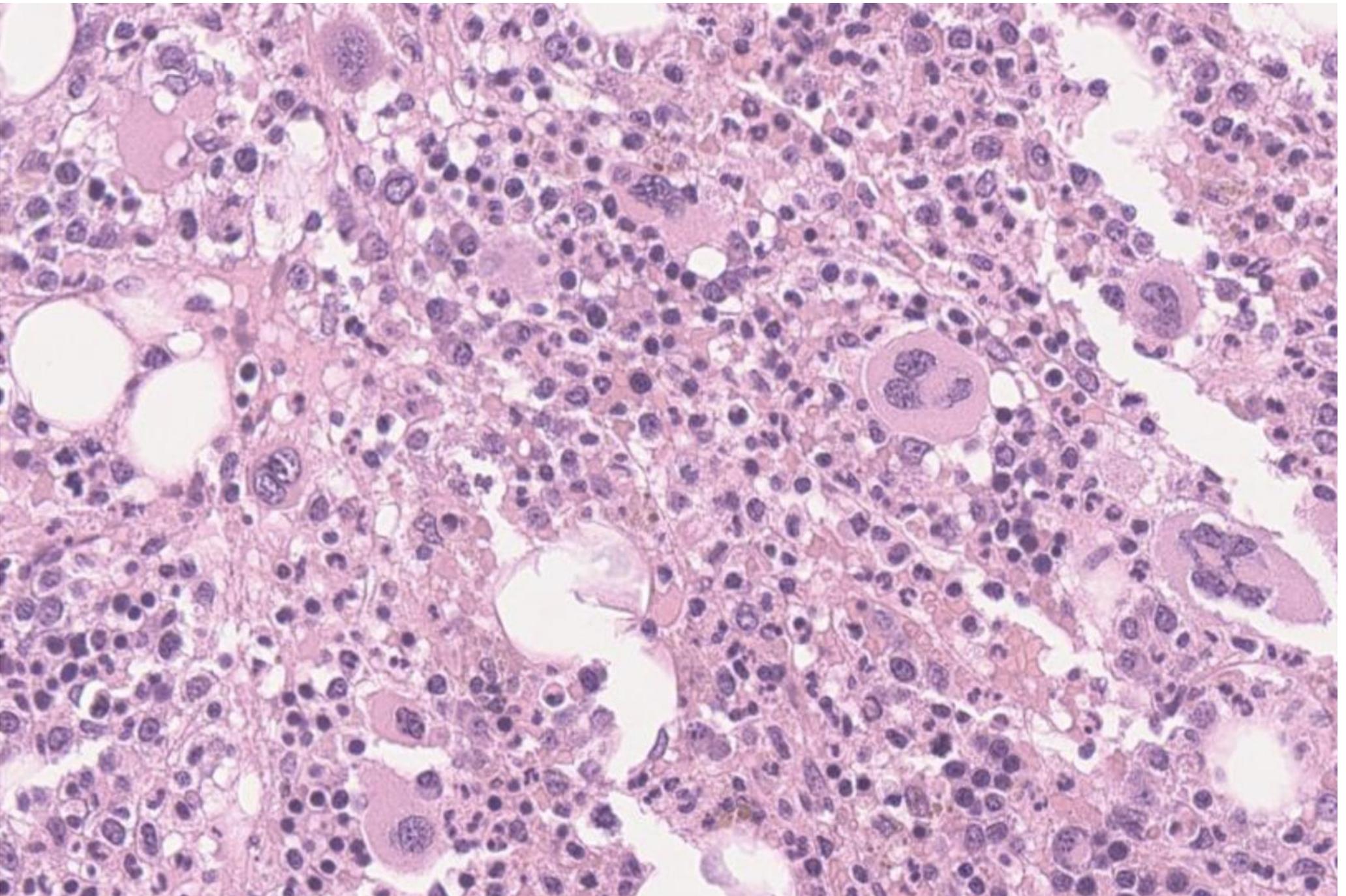
- Fever of unknown origin workup:
  - No significant travel, occupational, or other exposure history
  - No localizing signs/symptoms by history, exam, or imaging
  - Extensive testing negative:
    - Cultures (blood, urine)
    - TB (Interferon gamma release assay)
    - Tickborne illness panel
    - Viral panel (EBV, CMV, hepatitis viruses)
    - Fungal antigens
    - Metagenomic cfDNA testing (>1000 organisms covered)
    - Peripheral smear review



Friday afternoon RUSH  
aspirate read







# Compatible laboratory findings for hemophagocytic lymphohistiocytosis (HLH)

Revised 2004 HLH criteria (5 of 7 req)	Our patient
<b>Fever</b> ( at least 38.5 C)	<b>Yes</b>
<b>Splenomegaly</b> ( $\geq 2$ cm below the costal margin)	<b>Yes</b>
<b>Cytopenias</b> (at least 2: hemoglobin $< 90$ g/L; platelets $< 100 \times 10^9/L$ ; neutrophils $< 1.0 \times 10^9/L$ )	No (Hgb $< 90$ g/L only)
<b>Hypertriglyceridemia or hypofibrinogenemia</b> (fasting triglycerides $\geq 3.0$ mmol/L and fibrinogen $\leq 1.5$ g/L)	No (TGs wnl, fibrinogen elevated)
<b>Hyperferritinemia</b> ( $\geq 500$ $\mu\text{g/L}$ )	<b>Yes</b> (1,180 $\mu\text{g/L}$ )
<b>Hemophagocytosis</b>	<b>Yes</b>
<b>Elevated sCD25</b> (IL-2R, $\geq 2400$ U/mL)	<b>Yes</b> (23,082 U/mL)



Adapted from Henter, J, et al. *Blood* (2024)<sup>8</sup>

# What's the differential diagnosis for secondary HLH?

## BROAD!

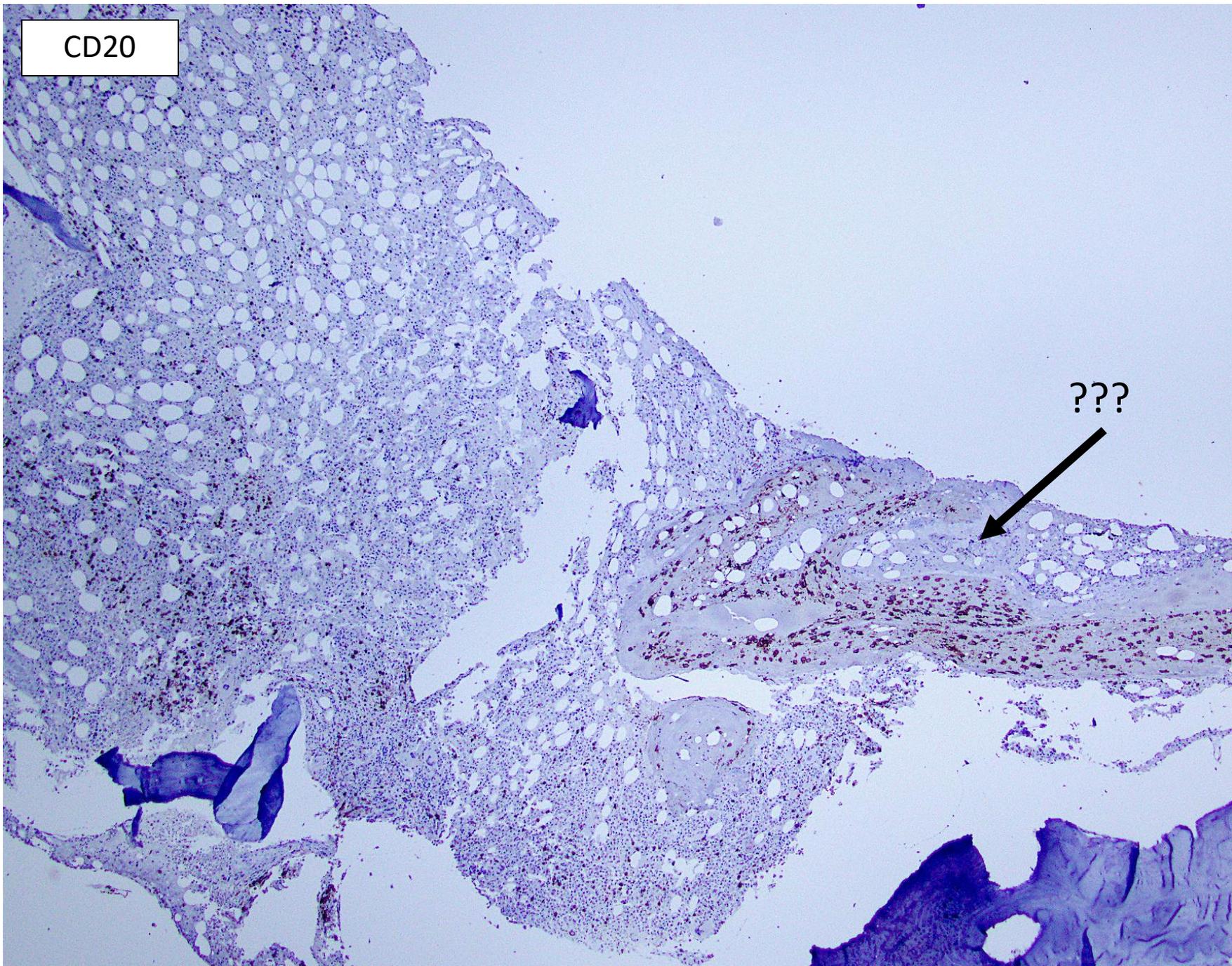
- Infection-associated (essentially any class of infectious agent)
  - Virus-associated commonly herpes viruses
- Malignancy-associated
  - Most commonly **lymphoma**; (sCD25:Ferritin > 2.0) + (sCD25 >4,999) => **96% PPD**
    - Frequently T-cell lymphomas, intravascular large B-cell lymphoma
- Autoimmune-associated (e.g., Still's disease, SLE)
- Others: transplant-associated, chemotherapy-associated, immunosuppression-associated, idiopathic



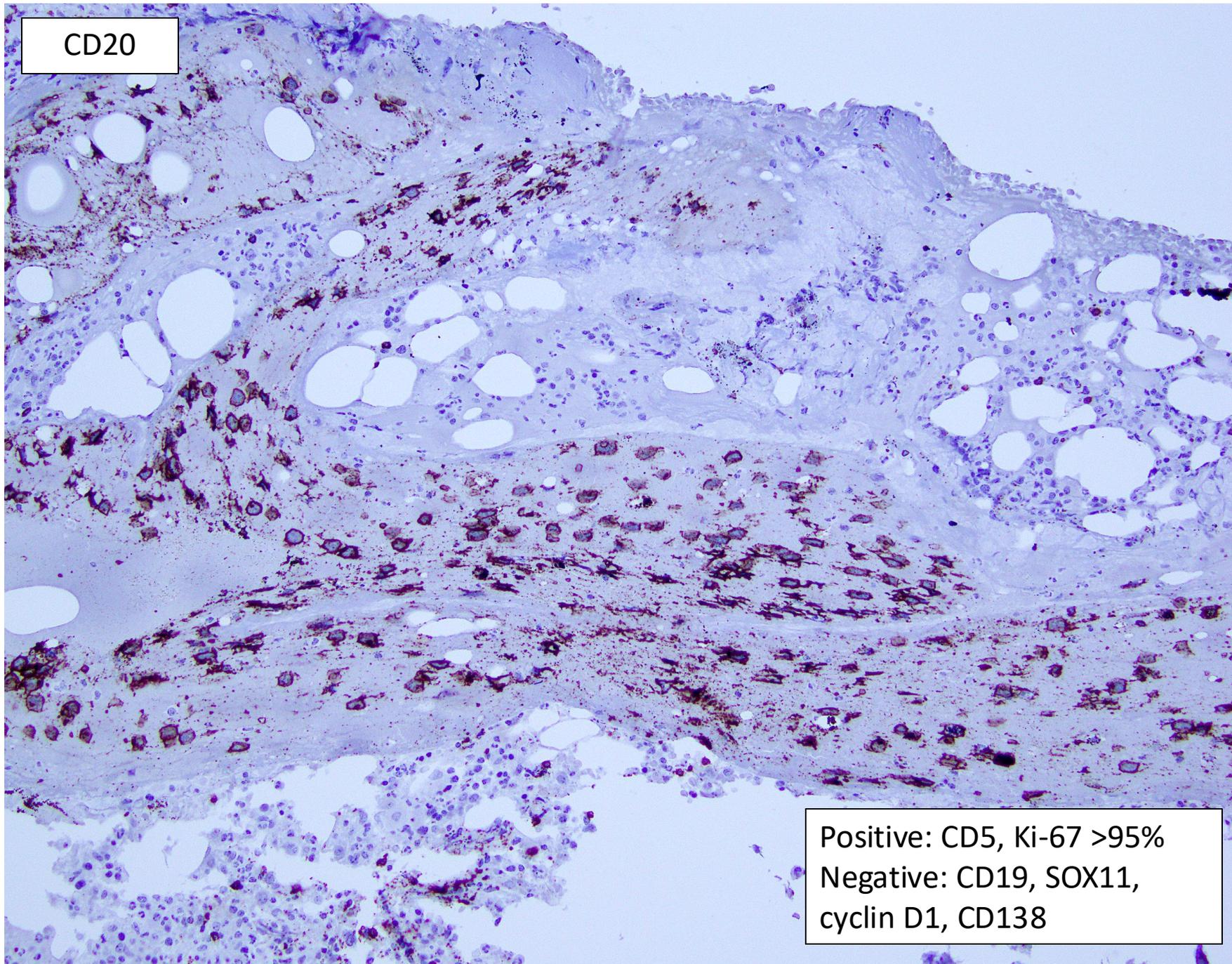
Preliminary diagnosis  
(immunostains pending):  
Hypercellular marrow with  
maturing trilineage hematopoiesis  
and hemophagocytosis?



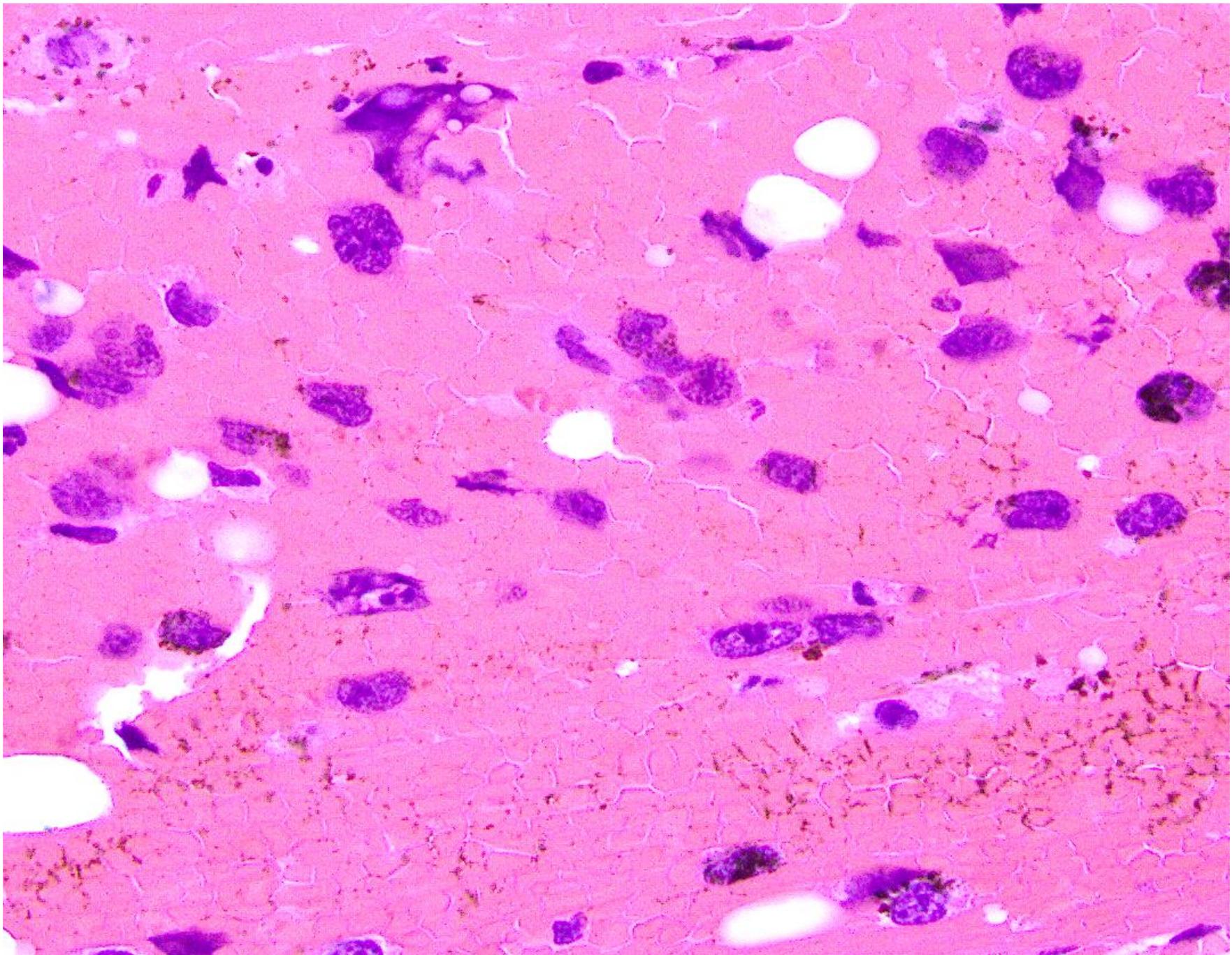
CD20



CD20



Positive: CD5, Ki-67 >95%  
Negative: CD19, SOX11,  
cyclin D1, CD138



Final diagnosis:

~~Hypercellular marrow with  
maturing trilineage hematopoiesis  
and rare hemophagocytosis?~~

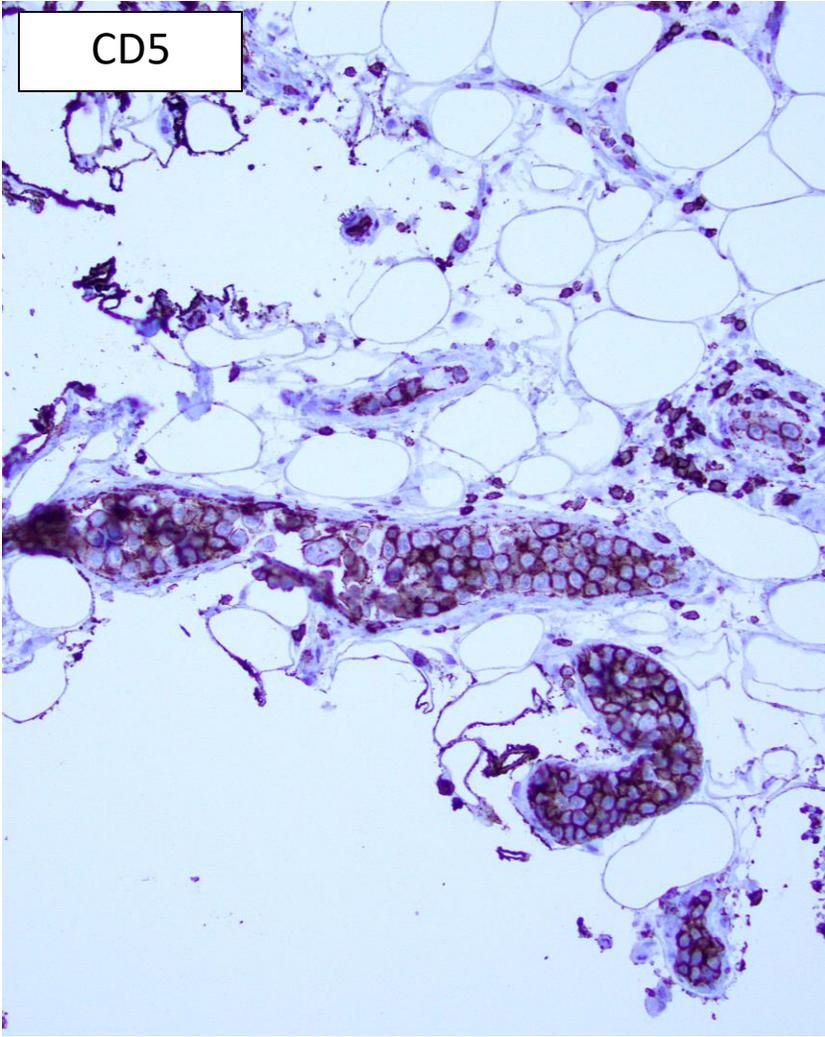
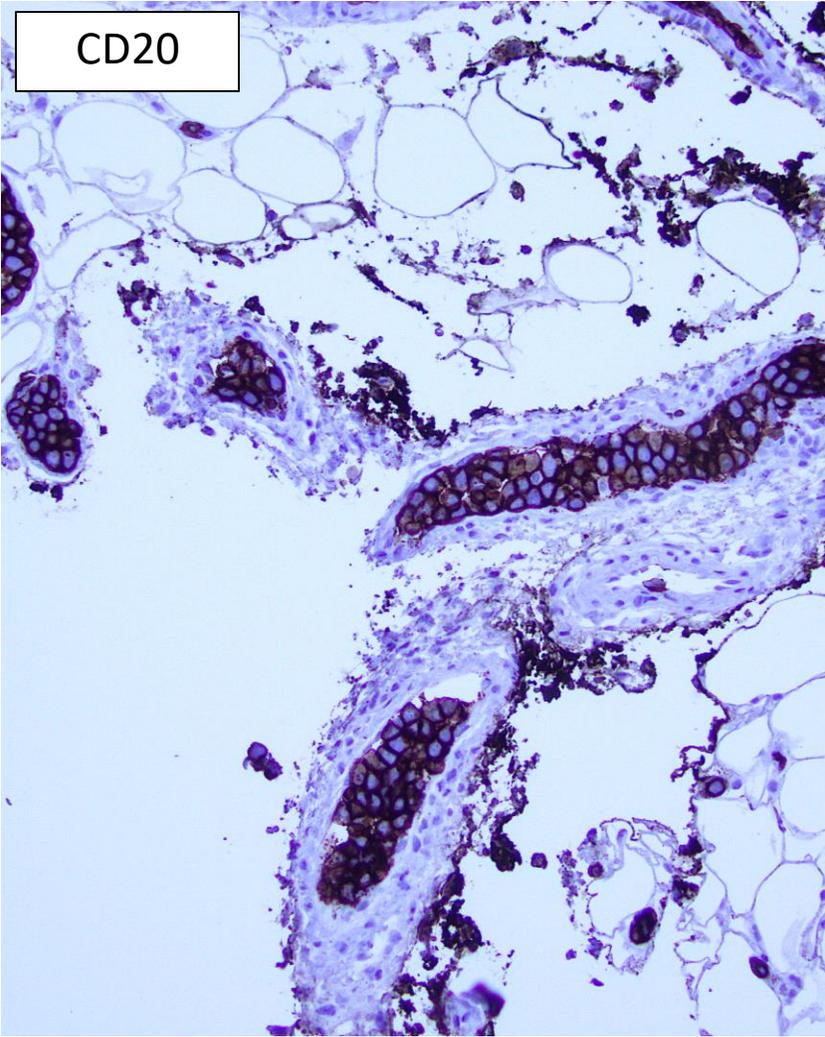
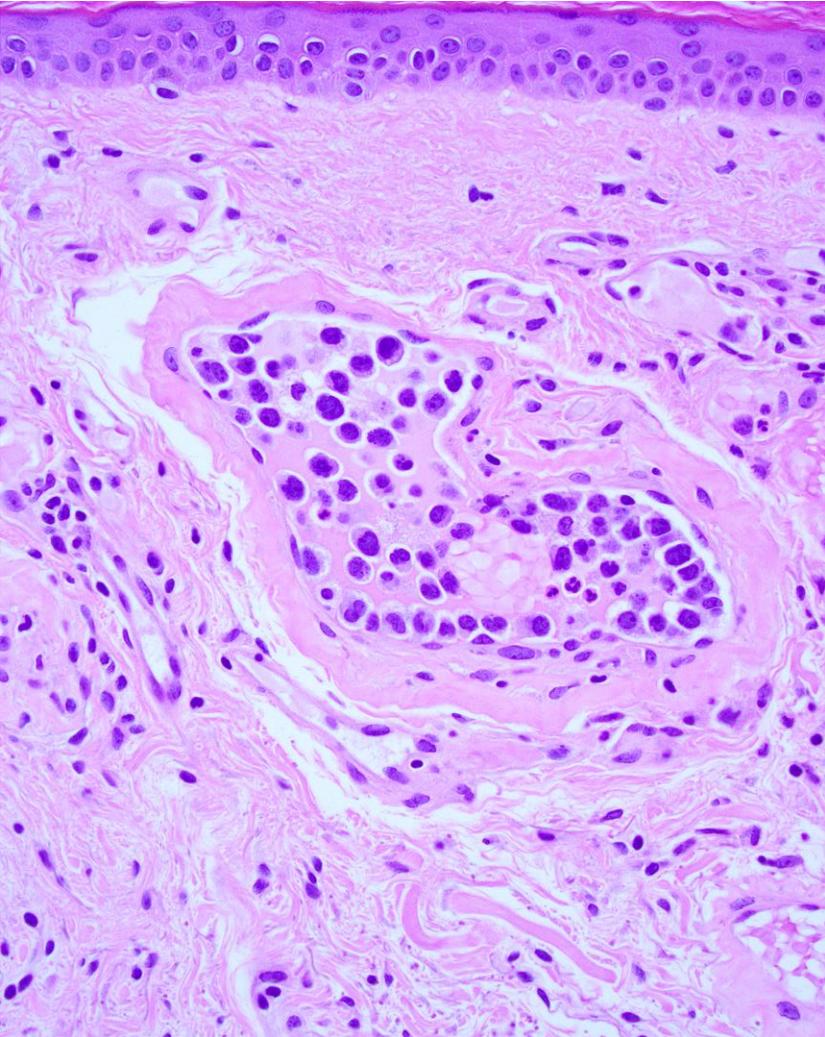


Final diagnosis:

1. Large B-cell lymphoma present only in blood, highly suggestive of **intravascular large B-cell lymphoma**
2. Hemophagocytosis







## Follow-up

Patient is now status post 2 cycles of Polatuzumab-R-CHP with minimal side effects and reportedly doing much better



# Key takeaways

- **Intravascular large B-cell lymphoma (IV-LBCL)** often presents in elderly patients & non-specifically (B symptoms + cytopenias)
- Organ and CNS involvement is common, but lymph node involvement & mass-forming lesions uncommon
- Commonly associated with HLH
- Random skin biopsy often diagnostic; targeted biopsy of cherry angiomas provides additional yield

