MASSACHUSETTS GENERAL HOSPITAL
PATHOLOGY

SH2017-0332

TP53 mutation in a patient with paroxysmal nocturnal hemoglobinuria

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Clinical History

74M in overall good health, found to have anemia and thrombocytopenia

Past Medical History

- Hypertension

Family History

- CAD (multiple family members)
- No malignancies or hematologic disorders

Social History

- Prior smoker (quit 40 years ago)
- 1x glass red wine per night

Clinical History

Medications

- Irbesartan (BP)
- Aspirin
- Folate
- Glucosamine
- Fish oil
- Vitamin C

Allergies: NKDA

Clinical History

November 2016 (OSH)

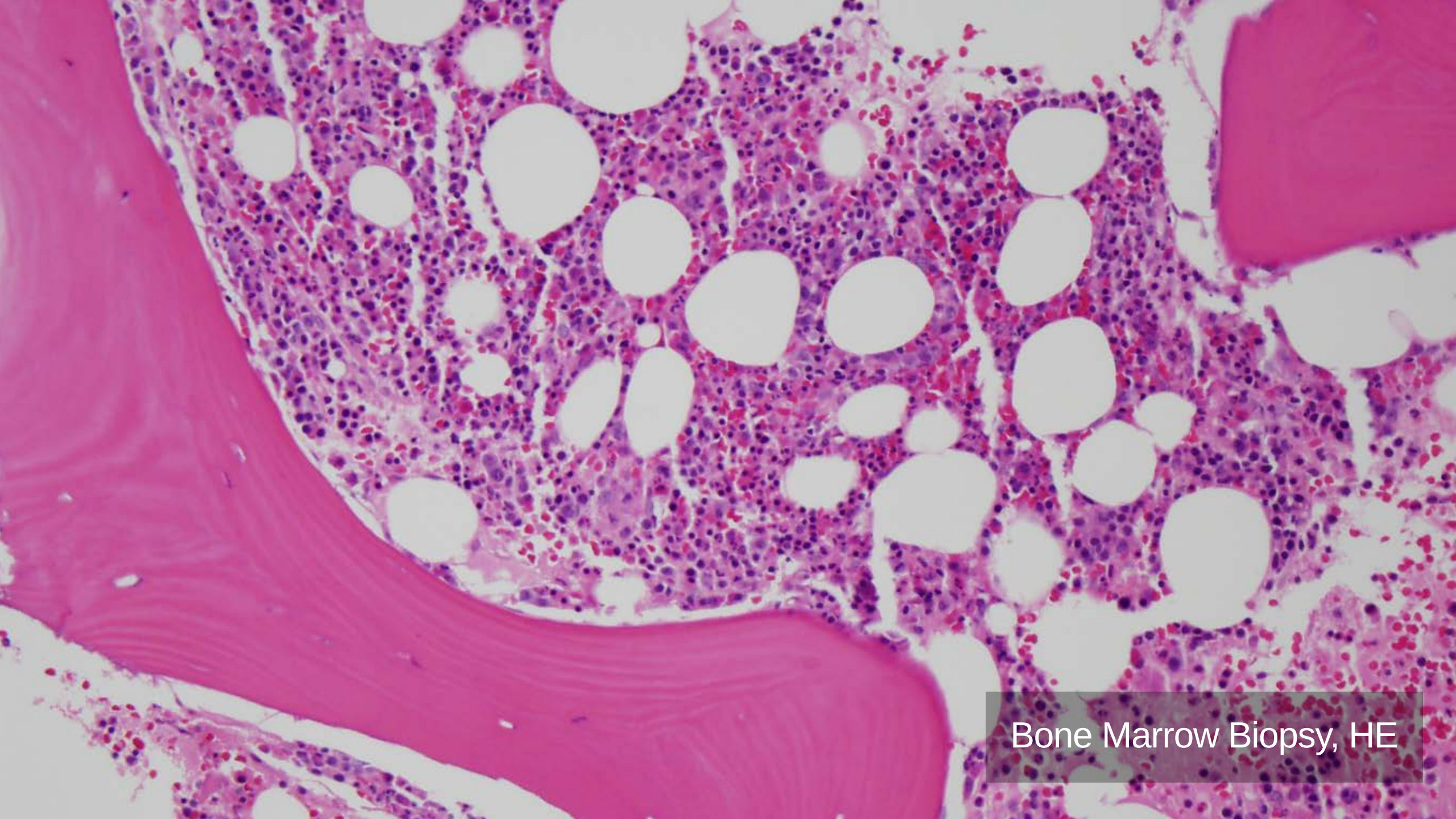
- Routine blood work revealed new onset anemia and thrombocytopenia
- Coombs negative
- Normal iron, B12, folate
- No evidence of kidney disease
- No hypothyroidism
- Flow cytometry: paroxysmal nocturnal hemoglobinuria (per report)
  - 58% granulocytes (loss of GPI)
  - 52% monocytes (loss of GPI)
  - 0.3% red blood cells (type II)
  - 15% red blood cells (type III)

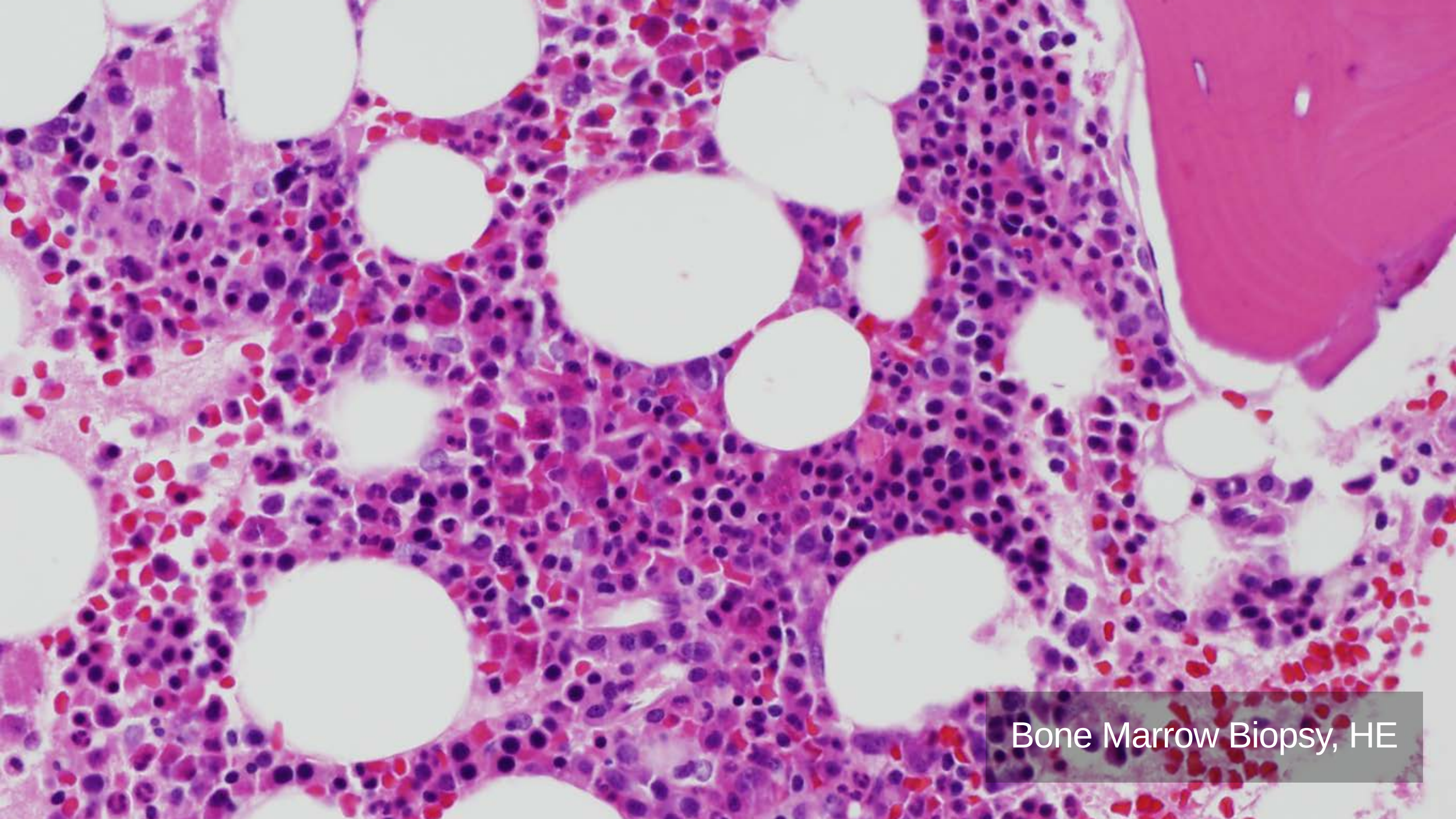
Clinical History

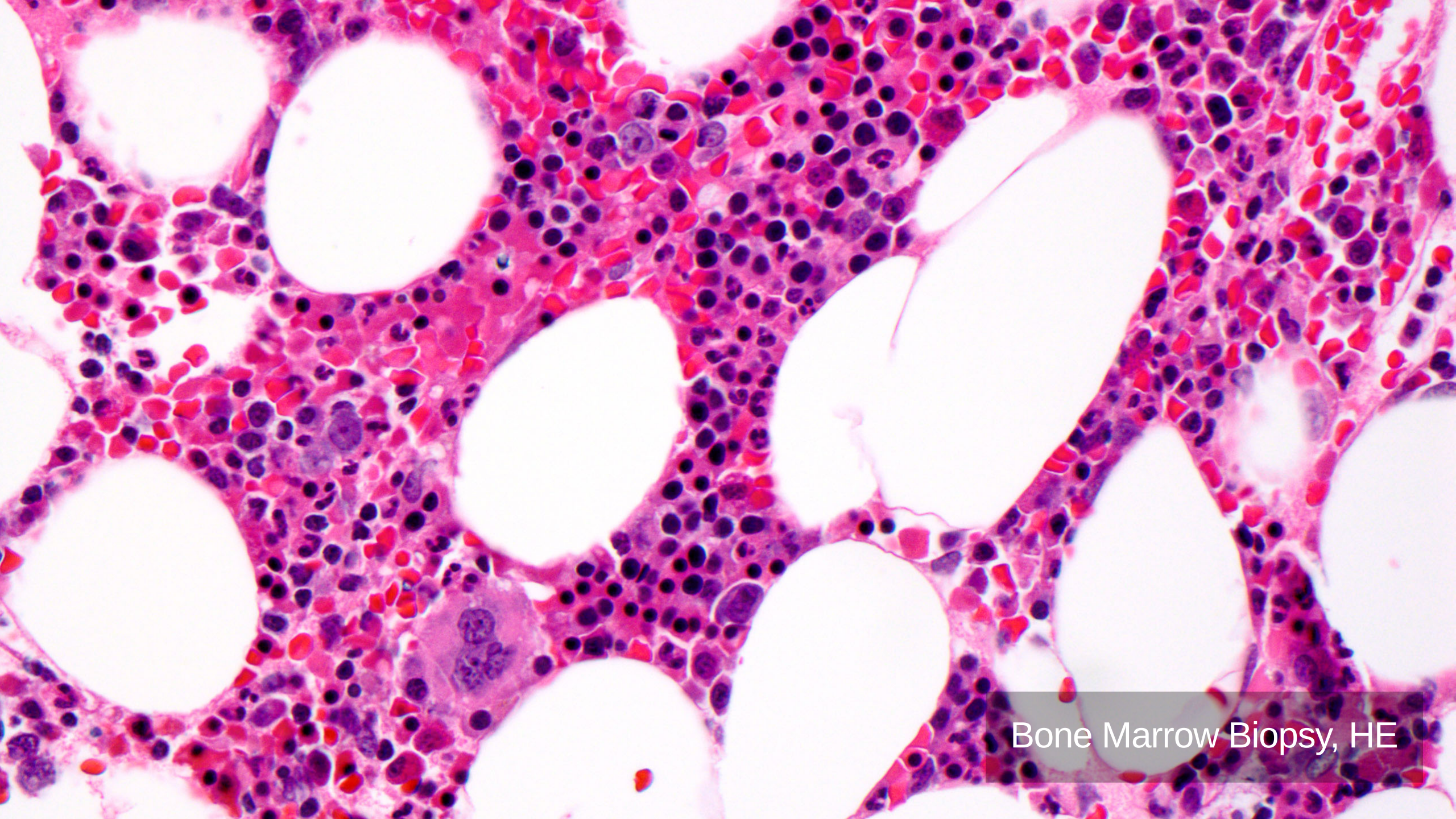
	1/6/17
WBC (K/uL)	5.10
Hgb (g/dL)	9.6
HCT (%)	27.4
MCV (fL)	111.4
PLT (K/uL)	96
Retics (%)	6.2
LDH (U/L)	1229
T-Bili (mg/dL)	1.1

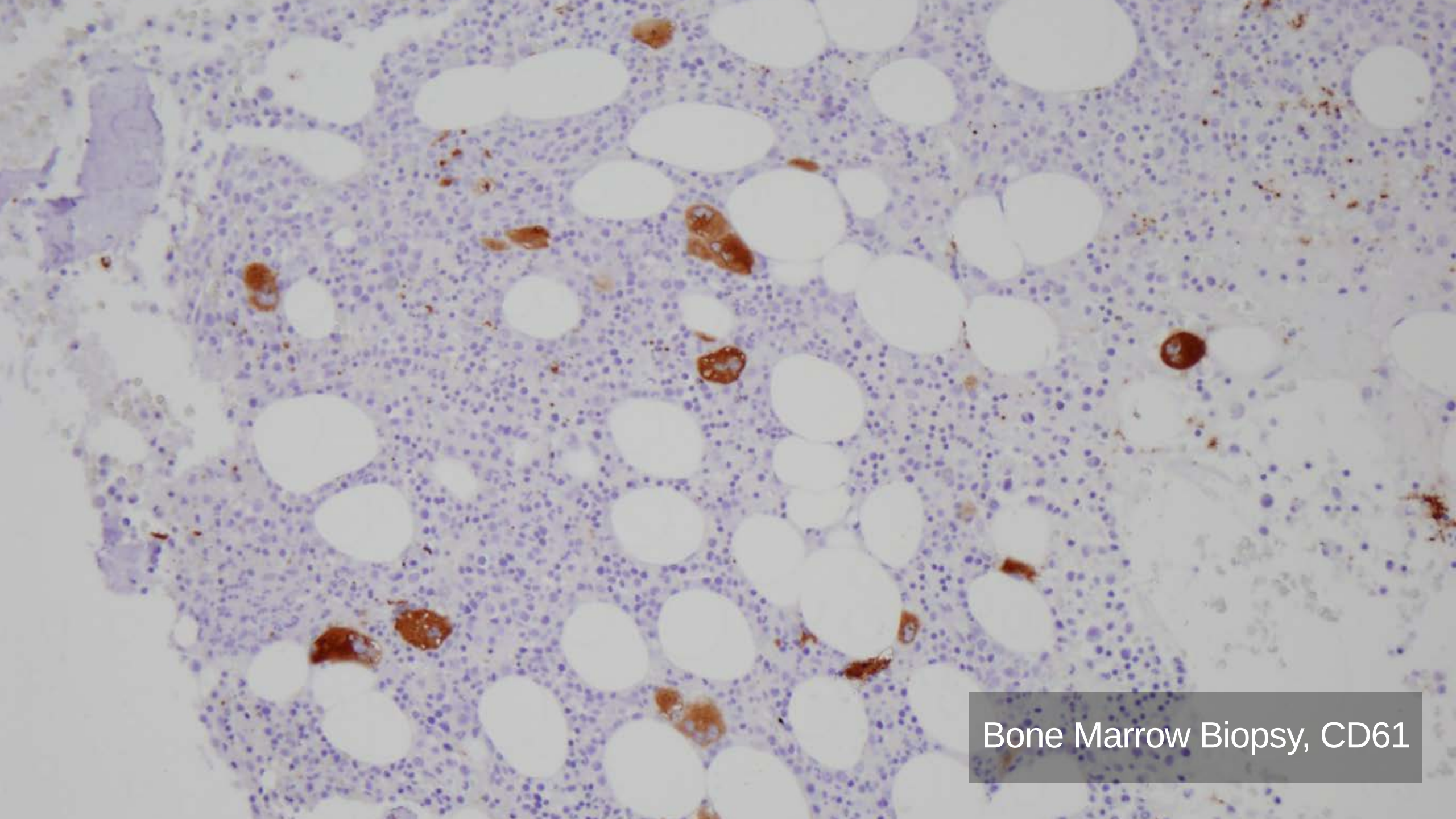
January 2017

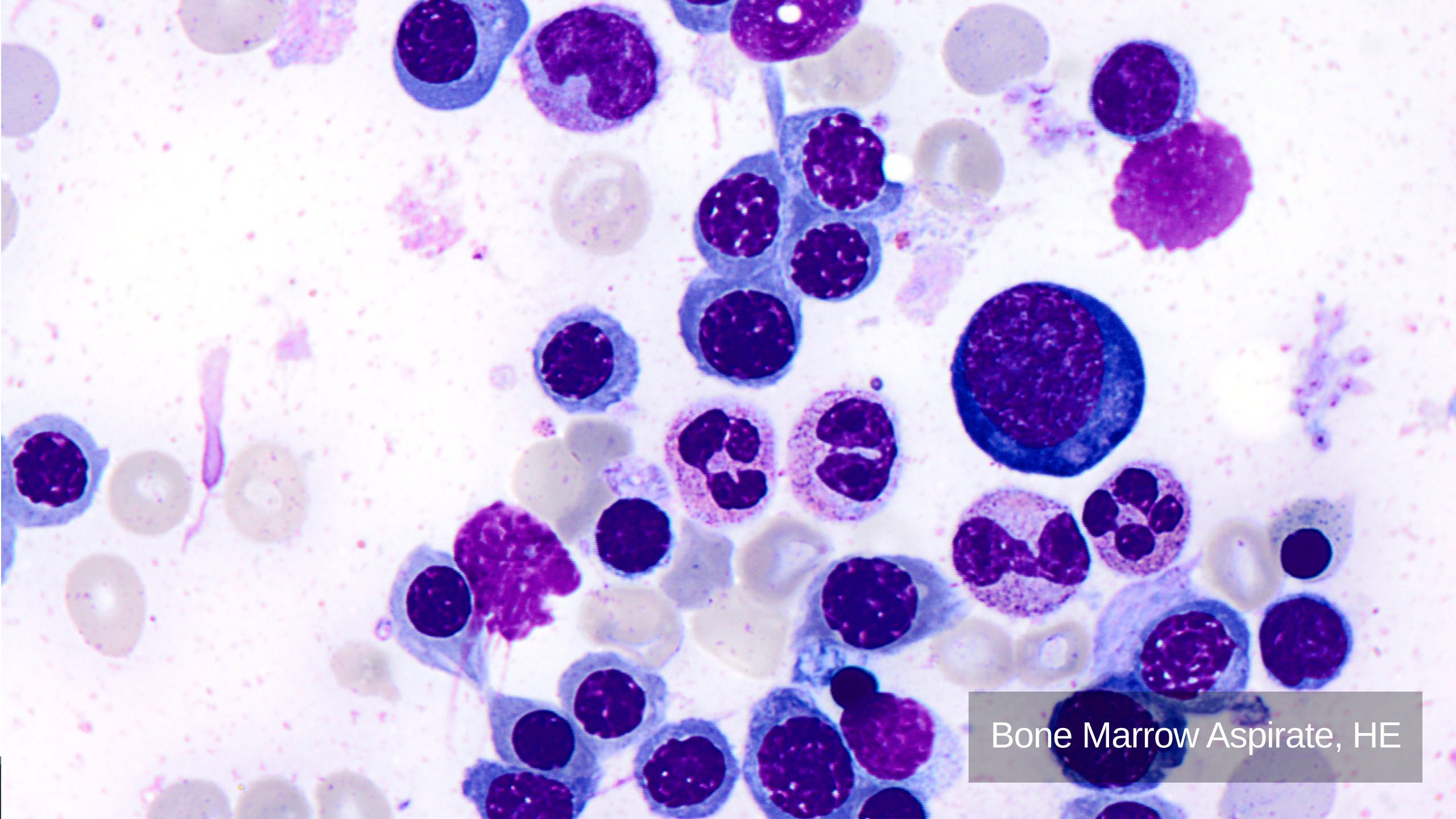
- Asymptomatic
- Labs drawn
- Bone marrow biopsy
- Molecular studies (NGS)


Bone Marrow Biopsy, HE


Bone Marrow Biopsy, HE


Bone Marrow Biopsy, HE


Bone Marrow Biopsy, CD61


Bone Marrow Aspirate, HE

Bone Marrow Biopsy

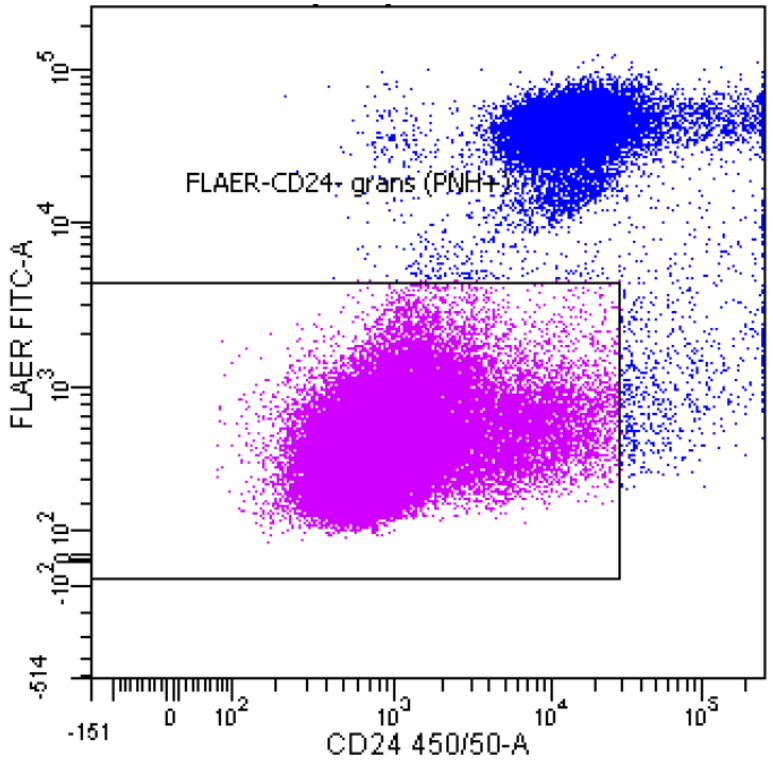
FINAL DIAGNOSIS:

Moderately hypercellular marrow with maturing trilineage hematopoiesis and slight erythroid hyperplasia.

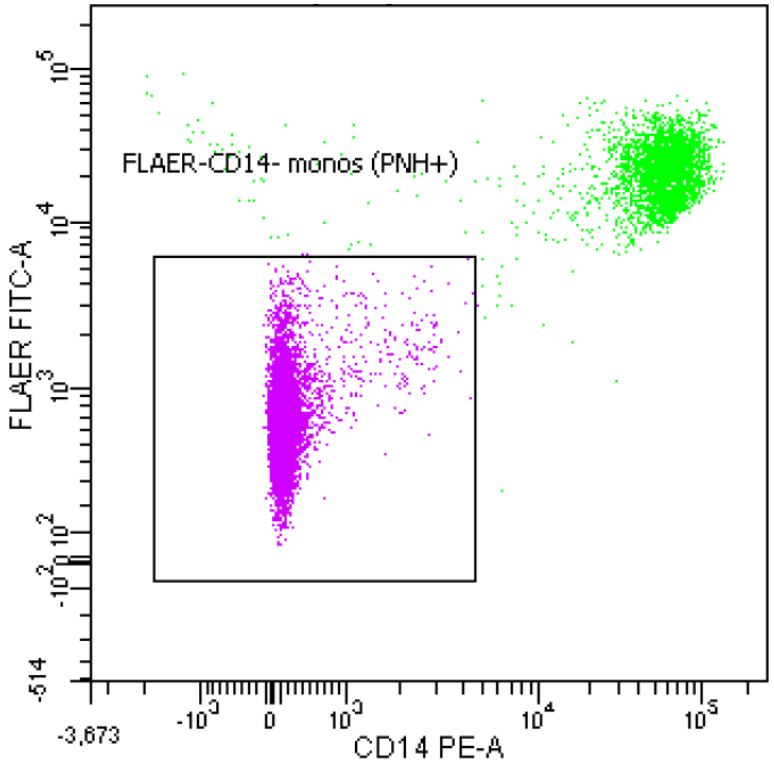
Note: Diagnostic features of MDS are not recognized and there is no evidence of an aplastic process.

Flow (March 2017)

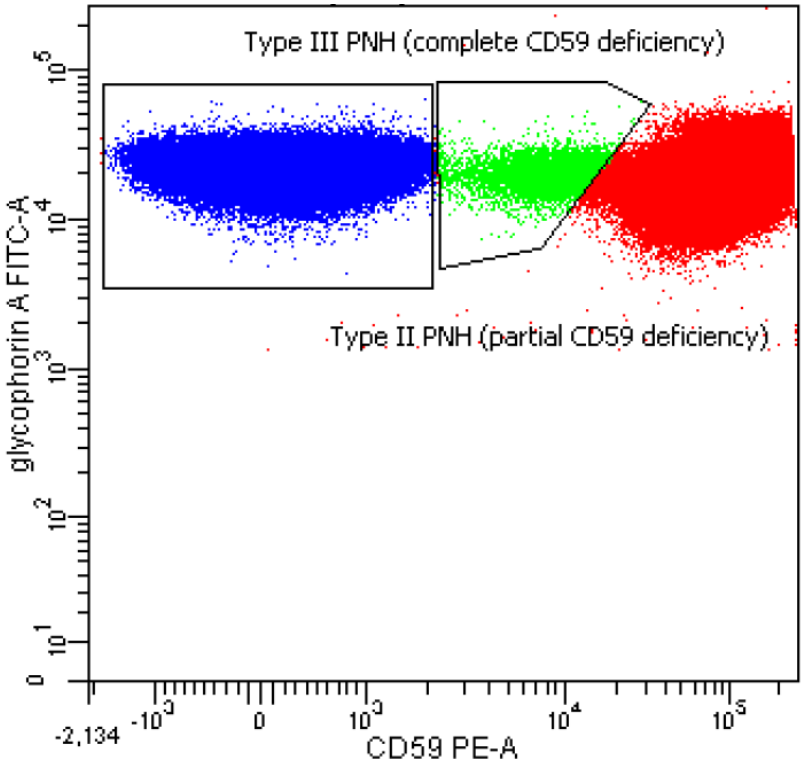
Granulocytes 82.8%



Monocytes 79.6%



RBC II: 0.6%, III: 16.8%



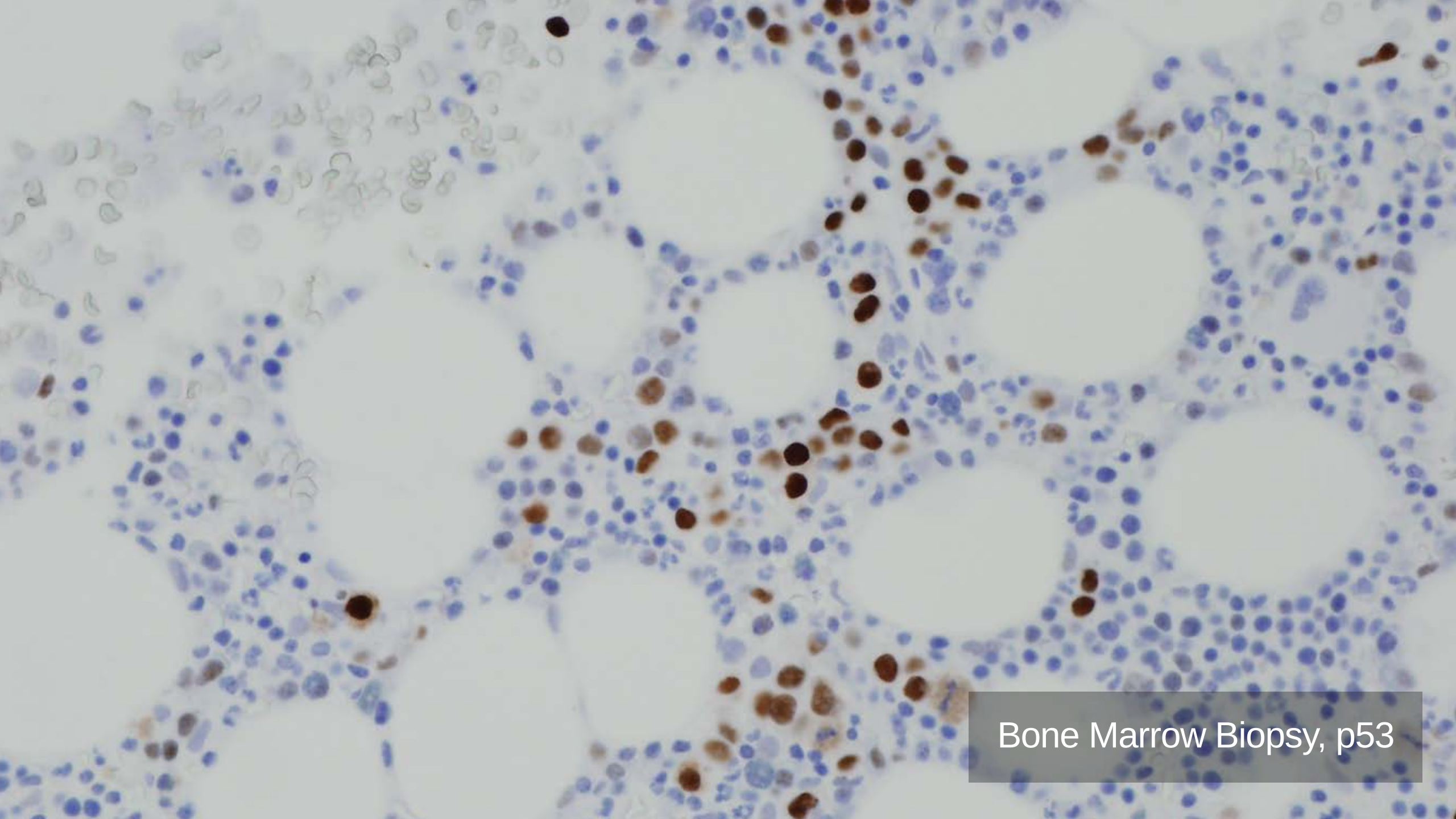
Additional Testing

Cytogenetics:

- 45,X,-Y[15]/46,XY[5]
- Loss of the Y chromosome is commonly seen in older men and although it may reflect a clonal process, and is not considered sufficient to diagnose MDS in a cytopenic patient

SNaPshot @ MGH (1/12/17)

- **TP53** ENSP00000269305.4:p.Tyr163Cys (ENST00000269305.4:c.488A>G)
- 73% variant allelic frequency
- Subsequent NGS
  - Rapid Heme Panel @ BWH (6/2/2017) – 51% VAF
  - SNaPshot @ MGH (8/8/2017) – 63% VAF


Bone Marrow Biopsy, p53

Patient Follow-Up

Progressive anemia resulting in 4U RBC transfusions in 2017

Started on eculizumab in March

- Marked decrease in LDH, but no response in Hgb/Hct
- Lab evidence of an autoimmune hemolytic anemia (DAT+)

Started on steroids

- Side effects not tolerated

Multiple heme-onc consults

- Increased dose of eculizumab
- Consider EPO
- No clear clinical trajectory for controlling hemolysis/symptoms

Discussion

PNH

- Non-malignant clonal disease of hematopoietic stem cells associated with hemolysis, marrow failure and thrombophilia
- Monogenic disease due to somatic mutation in PIGA (required for synthesis of GPI-anchored proteins)
  - Confers growth advantage
  - Leaves cells susceptible to complement destruction (loss of CD55 and CD59)
  - Hemolytic anemia

Discussion

No PIGA mutation!

- Whole exome sequencing of PNH identified multiple other genes with mutations arising as either subclones of PIGA or prior to PIGA (Shen et al, 2014)
  - Similarities to MDS: clonal hematopoiesis, persistent aberrant stem cell clone

Unexpected TP53 mutation

- Positive strong IHC staining suggestive that mutation is pathogenic
- Associated with aggressive myeloid neoplasms; concerning for evolution to MDS
- No prior reports of *TP53* mutation in PNH
- Primarily reported as a somatic mutation (lung, breast, ovary, GI)
- One report of germline mutation in pediatric patient with osteosarcoma and family history of malignancies (McIntyre 1994)

Discussion

Further workup

- Given high variant allelic frequency, is the mutation germline?
  - No personal or family history of malignancies
- Is the mutation confined to the PNH clone?
  - Attempt at NGS on PNH+ vs. PNH- populations failed (not enough cells sorted)

Panel Diagnosis

?

Proposed: Paroxysmal nocturnal hemoglobinuria with a pathogenic *TP53* mutation (clonal hematopoiesis of indeterminate potential, CHIP)

Acknowledgements

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