Brigham and Women's Hospital
Founding Member, Mass General Brigham

(Six) Hematology Cases: Common, Complex and Rare

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- Residency at Massachusetts General Hospital
- Heme/Onc Fellowship at MGH/DFCI
- Assistant Professor of Medicine at HMS
- Clinical: Neutrophils & Rare hematologic disorders
- Niche: Discovered the TEMPI syndrome

DISCLOSURES

- I am an advisor to **Clear Creek Bio** (they make the drug brequinar which is a DHODH inhibitor) and **X4 Pharma** (they make the drug mavorixafor which is used for a rare disorder called the WHIM syndrome).

KEY LEARNING OBJECTIVES

1. Interpret white blood cell abnormalities with a focus on chronic leukemias and indolent lymphoma.

2. Interpret anemias with a focus on red blood cell membrane and enzyme defects.

3. Interpret abnormalities in the platelet count with a focus on benign conditions and myeloproliferative neoplasms.

CASE

40F with abdominal pain and hemolysis

40-year-old female

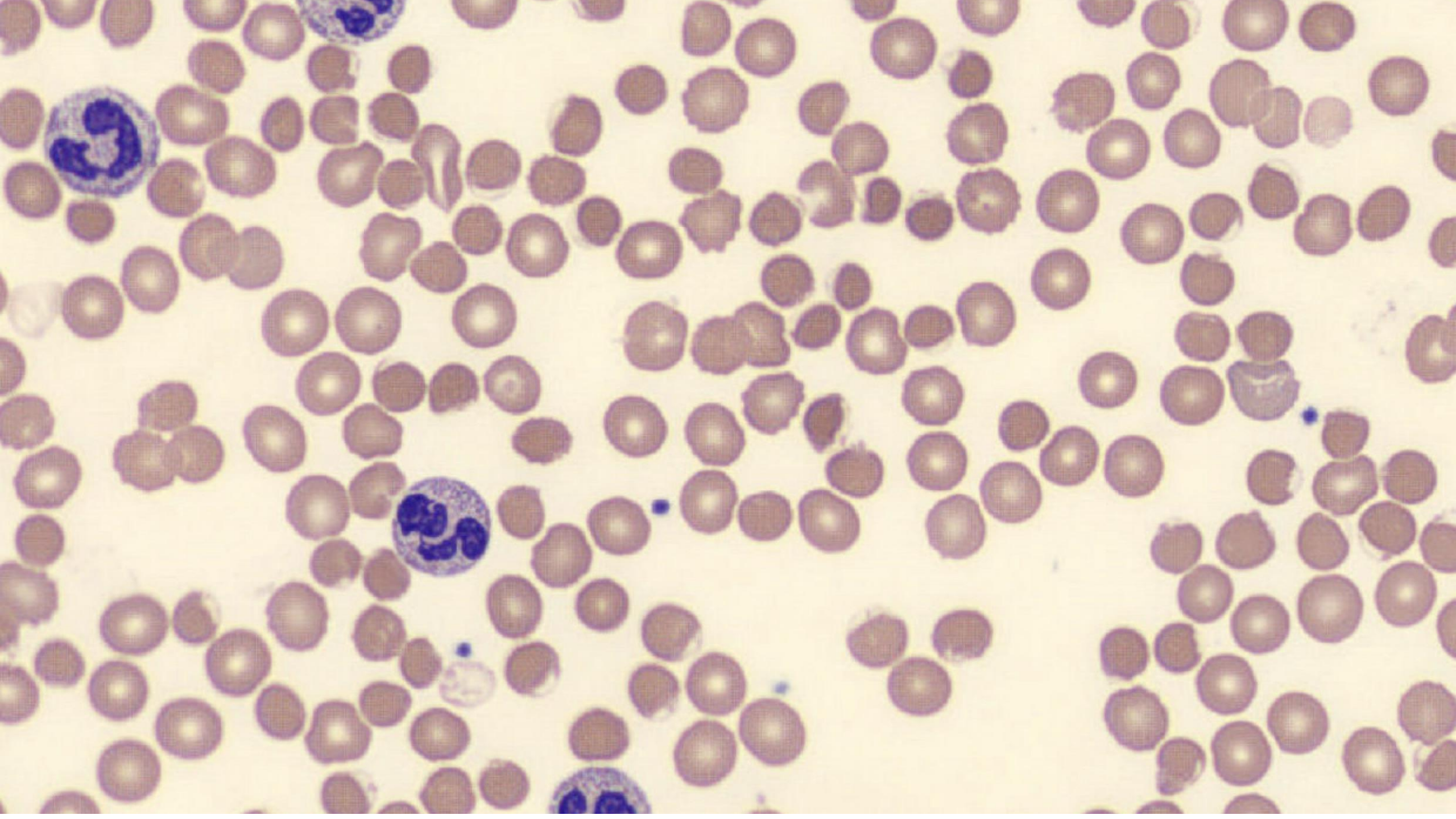
- No significant past medical history
- No medications, no supplements, no alcohol.
- G1P1, 1 healthy daughter

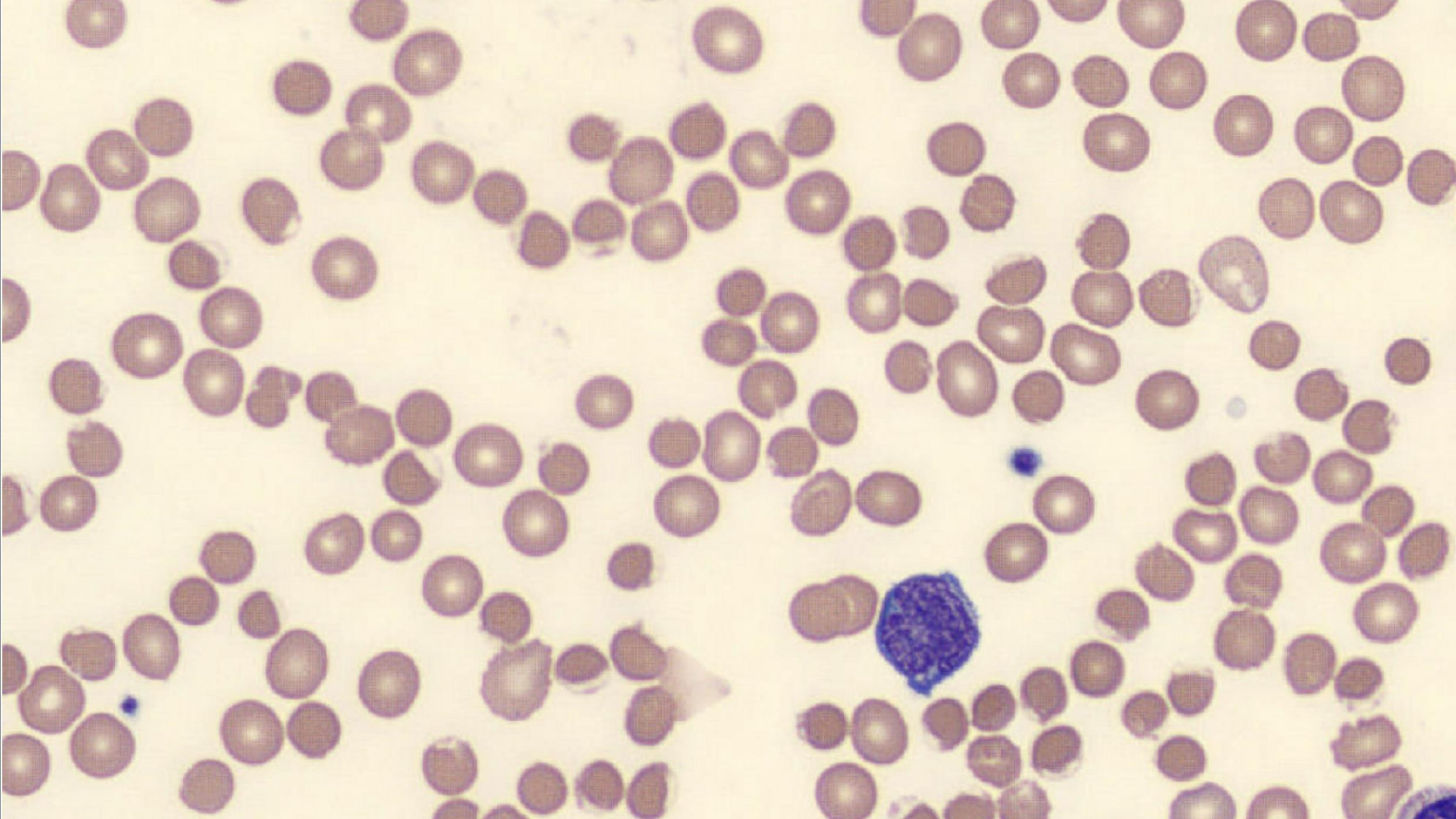
- “Caught a bad cold”

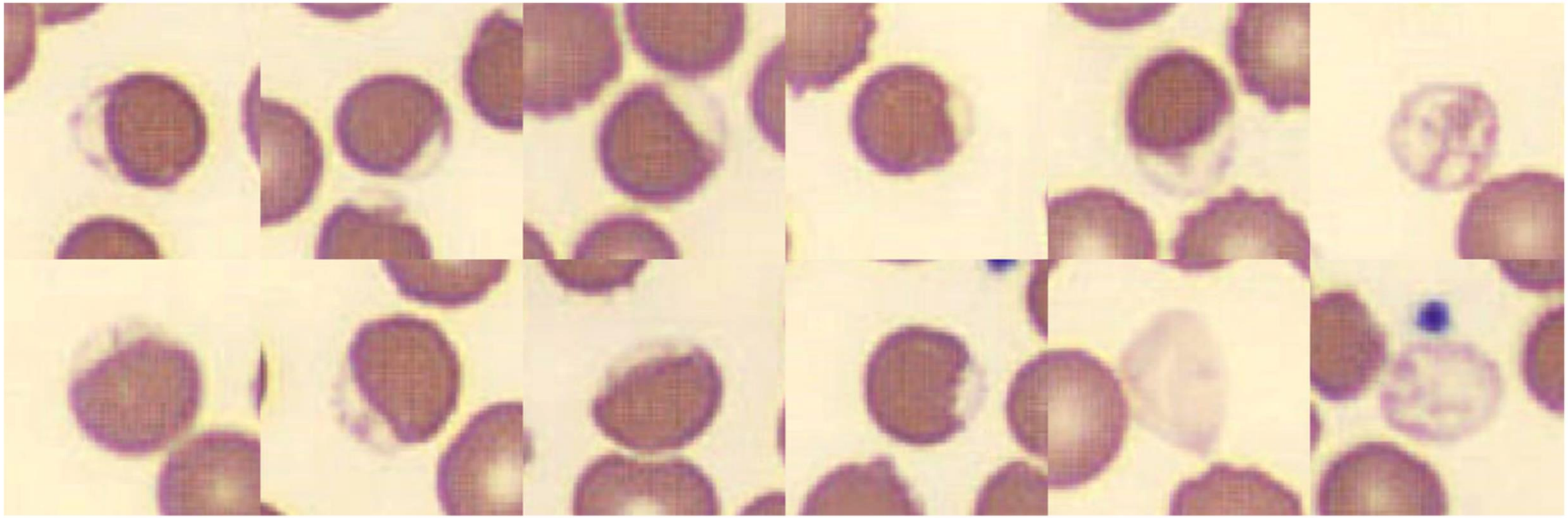
- Took Tylenol for 2 days
  - 1000 mg every 6 hours x 2-days = 8000 mg
- Developed abdominal pain and “yellow eyes”
- Presented to the emergency room

40F with abdominal pain and hemolysis

- BILIS = 12.6 / 3.0
- LDH = 22,270
- AST = 25,317
- ALT = 14,002
- FERRITIN = 179,082
- HAPTOGLOBIN = <10
- HGB = 8.6 (baseline 13.2)
- HCT = 29.1 (baseline 41.3)
- RETIC = 15.3%
- INR = 2.6
- FIBRINOGEN = 160







Hemolysis, liver failure, blister cells… what is going on?

A. Autoimmune hemolytic anemia
B. Cold agglutinin disease
C. Oxidative damage to the cells in the setting of G6PD deficiency
D. Hereditary spherocytosis acute exacerbation
E. Spur cell anemia secondary to liver dysfunction

Hemolysis, liver failure, blister cells… what is going on?

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** G6PD deficiency is X-linked and one of the most common human enzyme deficiencies **

G6PD testing

- Normal G6PD enzyme activity.
  - The patient's G6PD enzyme level was elevated above normal.

- (Reminder: G6PD enzyme activity can sometimes be falsely normal in the setting of an acute exacerbation due to the higher G6PD enzyme activity level in reticulocytes).

Panel of genetic testing reveals a **VUS**

Reason for testing

Diagnostic test for a personal history of disease

Test performed

Sequence analysis and deletion/duplication testing of the 40 genes listed in the Genes Analyzed section.

- Invitae Hereditary Hemolytic Anemia Panel

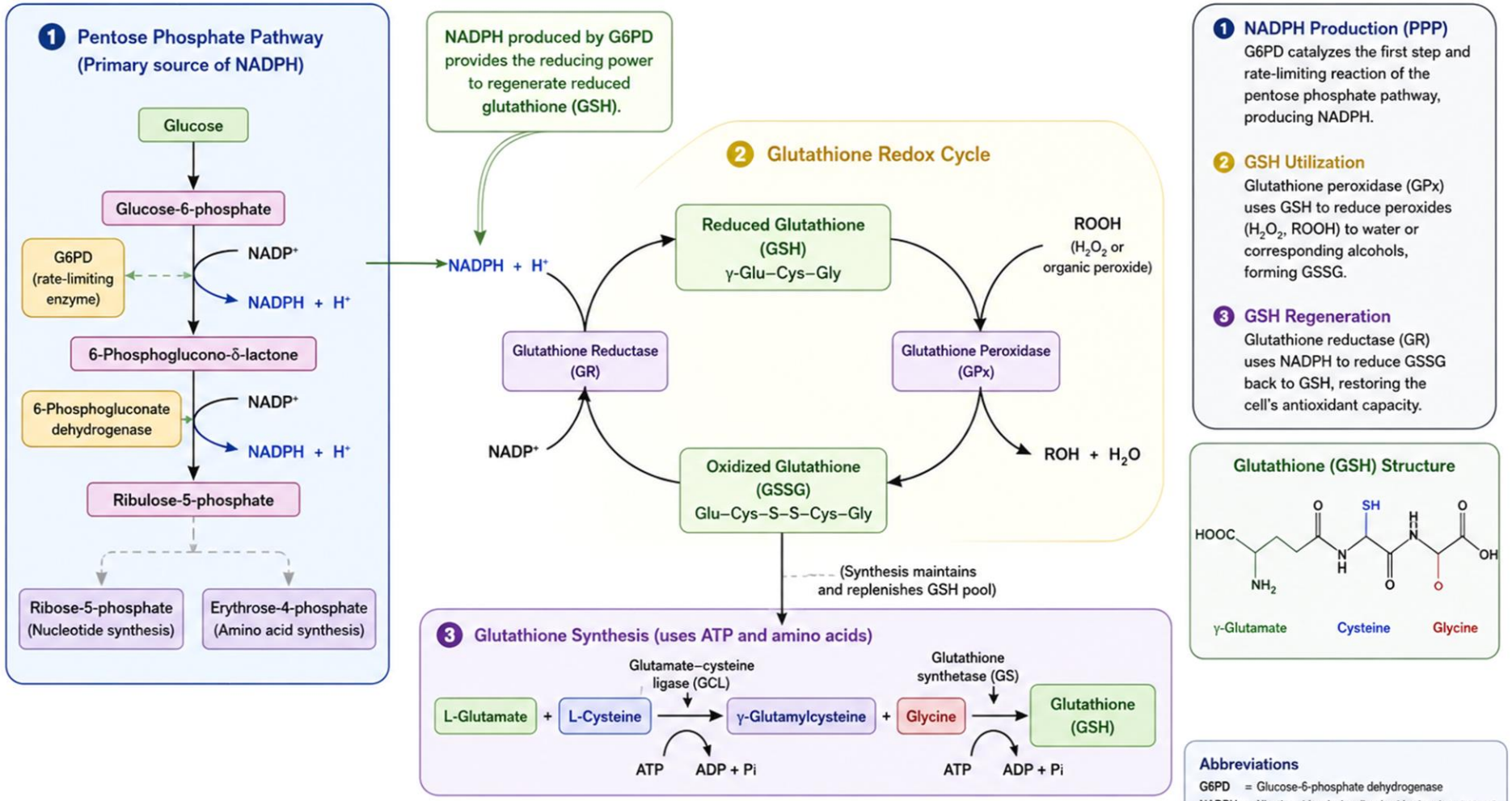
RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
GSR	c.306C>G (p.Cys102Trp)	homozygous	Uncertain Significance

Glutathione Regeneration by G6PD and Other Enzymes

Maintenance of cellular redox balance



1 NADPH Production (PPP)
G6PD catalyzes the first step and rate-limiting reaction of the pentose phosphate pathway, producing NADPH.

2 GSH Utilization
Glutathione peroxidase (GPx) uses GSH to reduce peroxides (H_2O_2, ROOH) to water or corresponding alcohols, forming GSSG.

3 GSH Regeneration
Glutathione reductase (GR) uses NADPH to reduce GSSG back to GSH, restoring the cell's antioxidant capacity.

Glutathione (GSH) Structure

Key Point: G6PD generates NADPH, which glutathione reductase uses to recycle GSSG back to GSH. This NADPH-dependent system is essential for detoxifying peroxides, maintaining redox balance, and protecting cells from oxidative stress.

Abbreviations

G6PD	= Glucose-6-phosphate dehydrogenase
NADPH	= Nicotinamide adenine dinucleotide phosphate (reduced)
GSH	= Reduced glutathione
GSSG	= Oxidized glutathione
GPx	= Glutathione peroxidase
GR	= Glutathione reductase

GSR c.306C>G (p.Cys102Trp) VUS

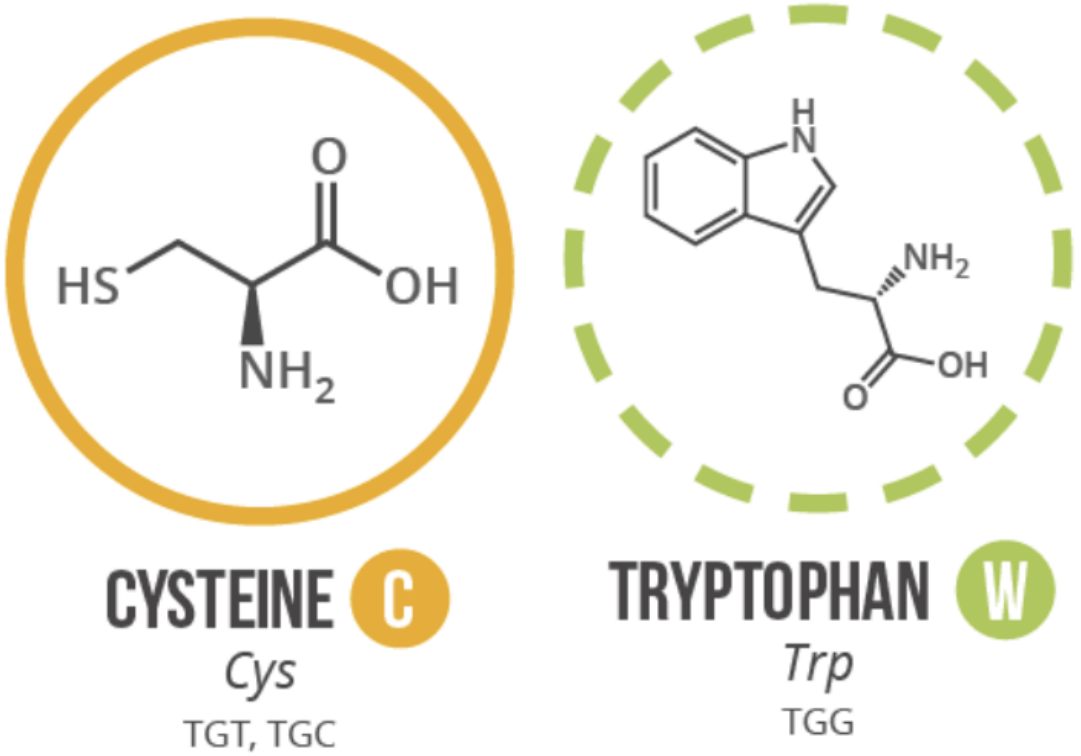
- GSR = glutathione reductase
  - Glutathione-disulfide reductase (GSR)
  - Associated with autosomal recessive hemolytic anemia

- Exon 1
  - c.306C>G (p.Cys102Trp)
  - Homozygous

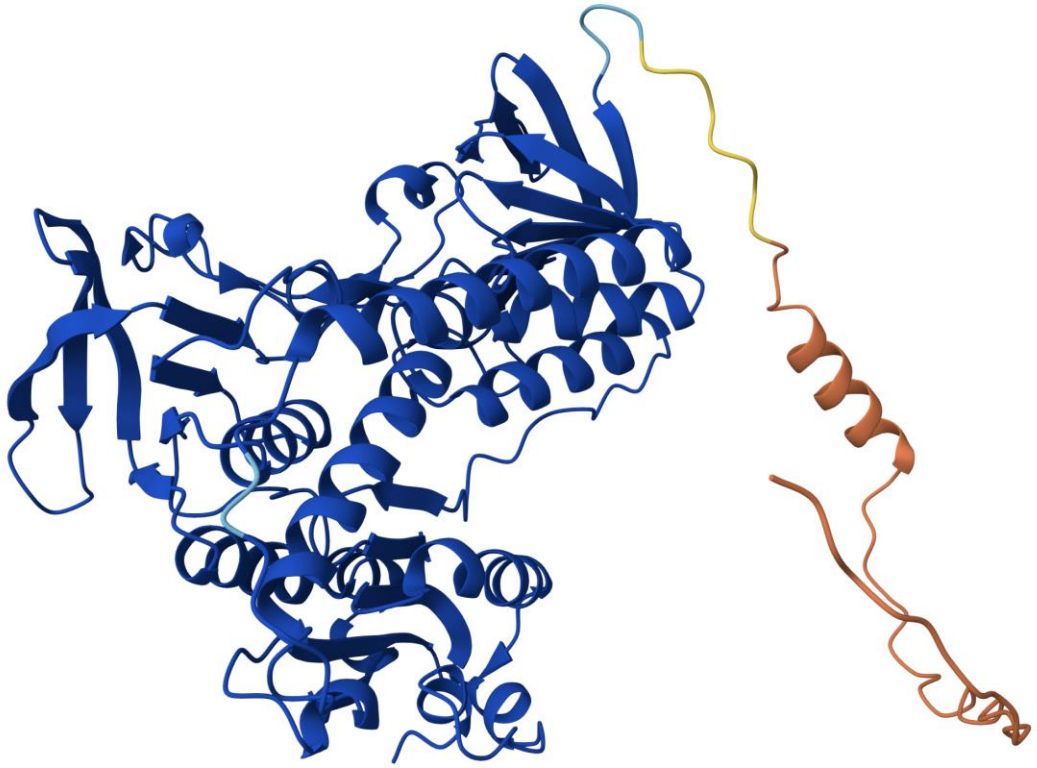
- Variant of Unknown Significance
  - What do we make of this “unknown significance”?

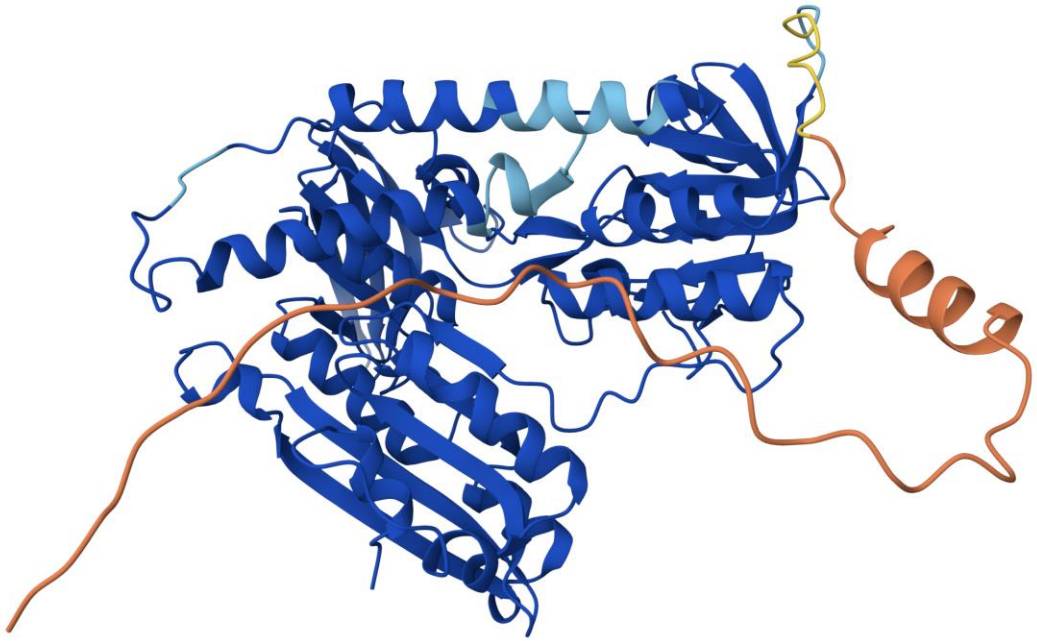
VUS : how do we know if it is pathogenic?

- GSR c.306C>G (p.Cys102Trp)
- Cysteine → Tryptophan
- The variant is found in whole exome population databases
  - gnomAD = 0.009%
  - About 1/10,000



Alpha-Fold WT vs. C102W structures





How does this happen?

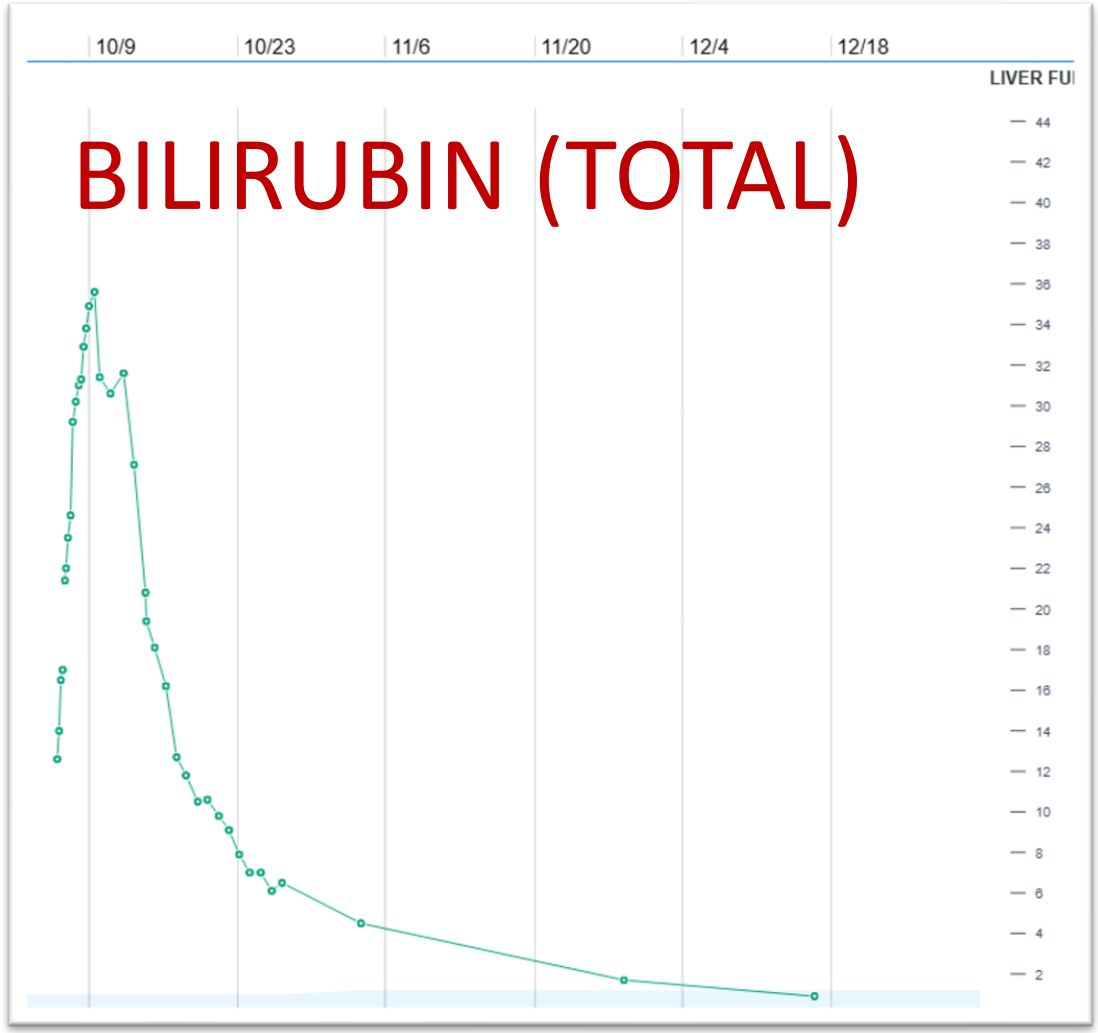
- https://gnomad.broadinstitute.org/gene/ENSG00000104687?dataset=gnomad_r4

- Cys102Trp has been reported.
- 8 heterozygotes out of 1,537,010 sequences.
- 1 in 200,000
- No homozygotes reported.

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Germline classification	Flags	Allele Count	Allele Number	Allele Frequency	Number of Homozygotes
8-30727530-G-C	E G	p.Cys102Trp	missense				8	1537010	5.20e-6	0
8-30727530-G-GC	E G	p.Cys102TrpfsTer20	frameshift			pLoF flag	7	1537010	4.55e-6	0
8-30727530-G-T	E G	p.Cys102Ter	stop gained			pLoF flag	2	1537008	1.30e-6	0
8-30727530-G-A	E G	p.Cys102Cys	splice region				159	1537126	1.03e-4	0
8-30727532-A-G	E	p.Cys102Arg	missense				19	1537278	1.24e-5	0

Spontaneous and complete recovery

- The patient made a steady recovery with supportive care and was discharged on HD#22
- Decreased GSR enzyme activity level was confirmed in the lab.
- *(Don’t forget about G6PD deficiency!)*



CASE

40M with thrombocytopenia

40M presents to the ED with an ankle laceration

- Working in construction.
- Feeling otherwise well.
- No bruising.
- Ankle laceration bleeding easily controlled with a bandage.

	8/18/2021 2009	8/18/2021 1843	8/18/2021 1735
COMPLETE BLOOD COUNT			
WBC	4.87	4.36 ↓	5.24
RBC	4.64	4.56	4.75
Hgb	12.4 ↓	12.2 ↓	12.7 ↓
HCT	38.4 ↓	37.9 ↓	39.7 ↓
MCV	82.8	83.1	83.6
MCH	26.7	26.8	26.7
MCHC	32.3	32.2	32.0
PLT	7 ↓↓	4 ↓↓	7 * ↓↓
MPV	Not measured	Not measured	8.2 ↓
RDW	14.1	14.0	14.0

What is the next step?

A. Platelet transfusion.
B. Hematology consult.
C. Bone marrow biopsy.
D. Check PT/INR, aPTT.
E. Check peripheral blood smear.

	8/18/2021 2009	
COMPLETE BLOOD COUNT		
WBC	**4.87**	
RBC	**4.64**	
Hgb	**12.4**	▼
HCT	**38.4**	▼
MCV	**82.8**	
MCH	**26.7**	
MCHC	**32.3**	
PLT	**7**	▼▼
MPV	**Not measured**	
RDW	**14.1**	

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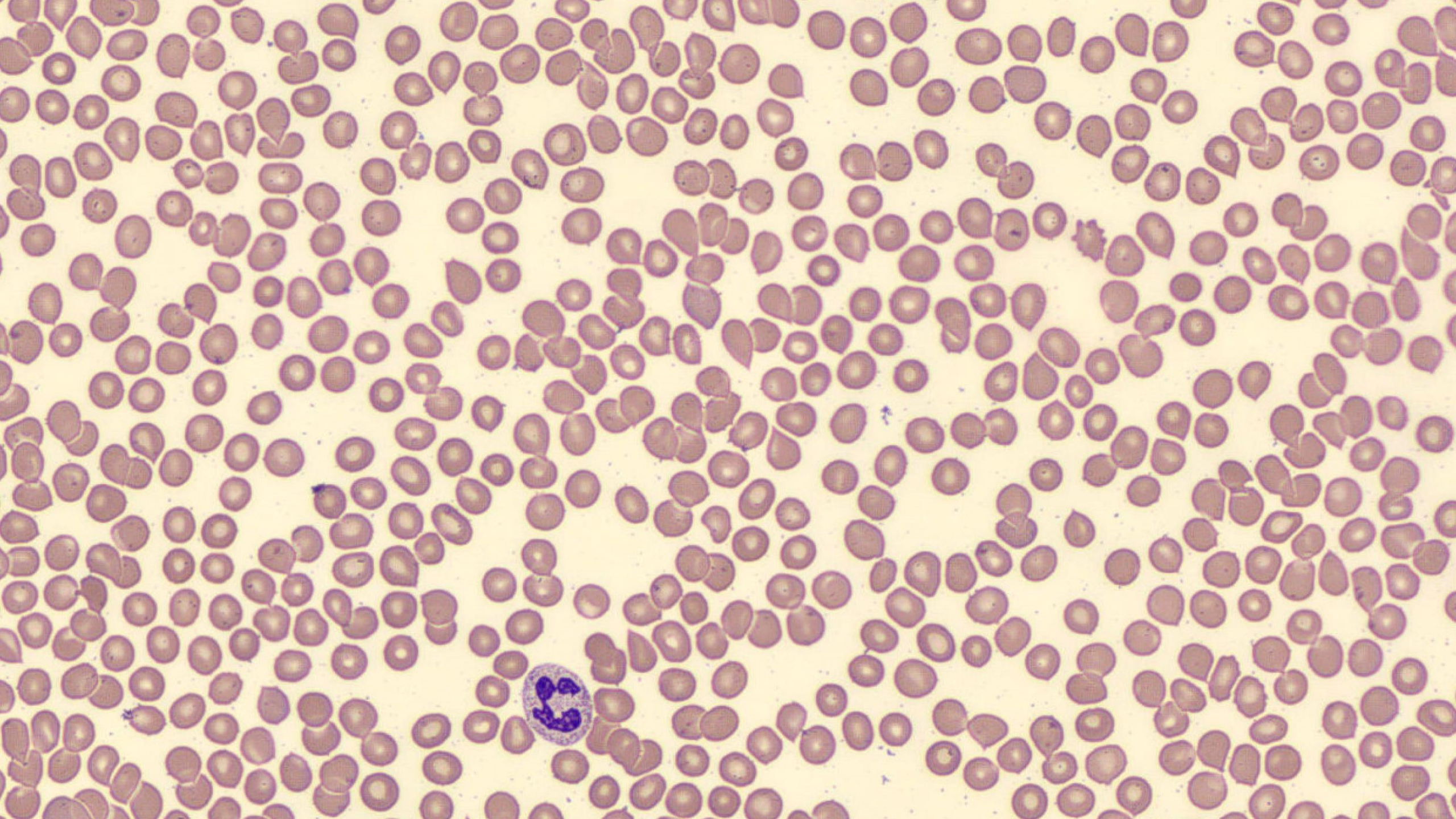
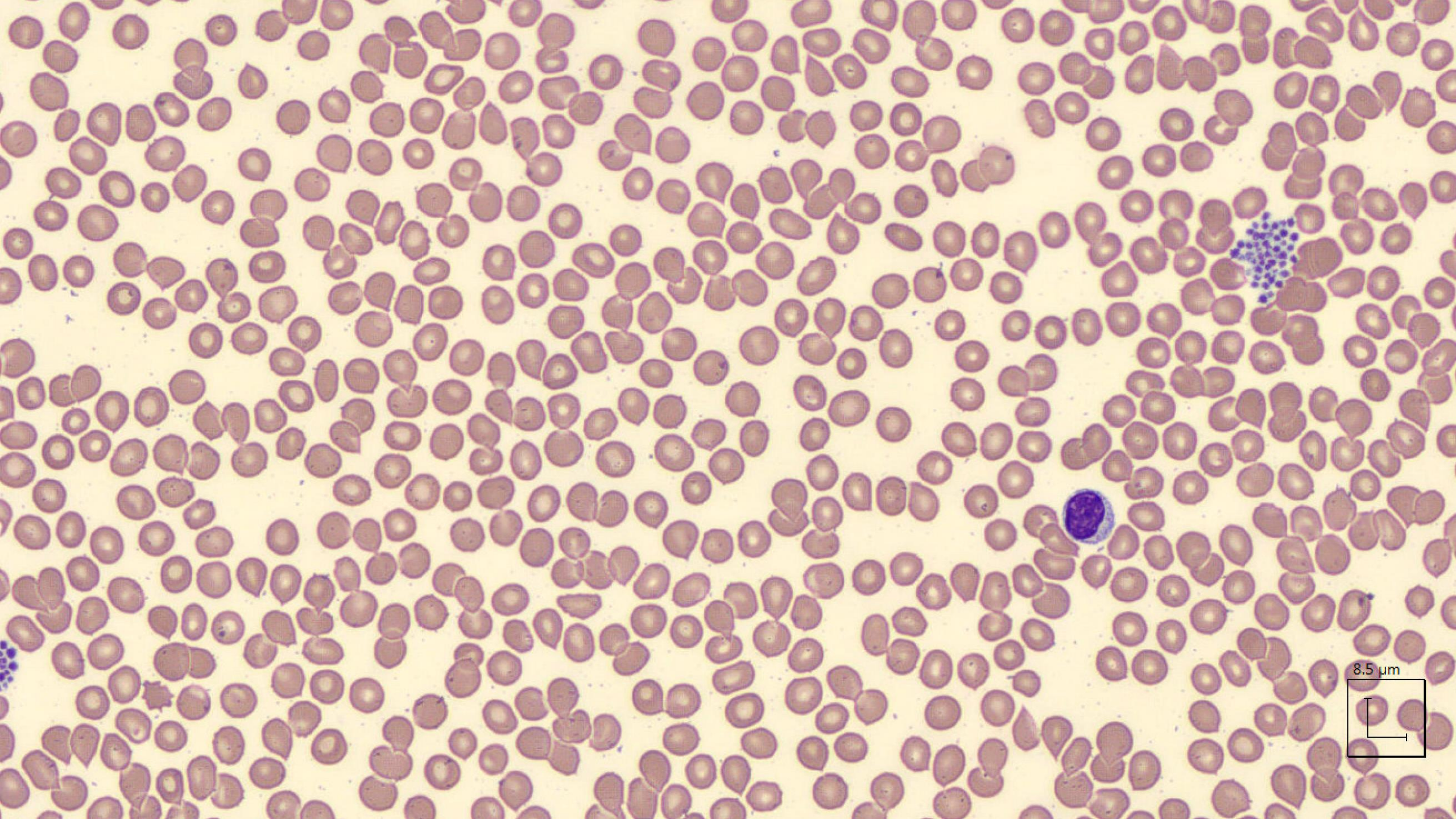
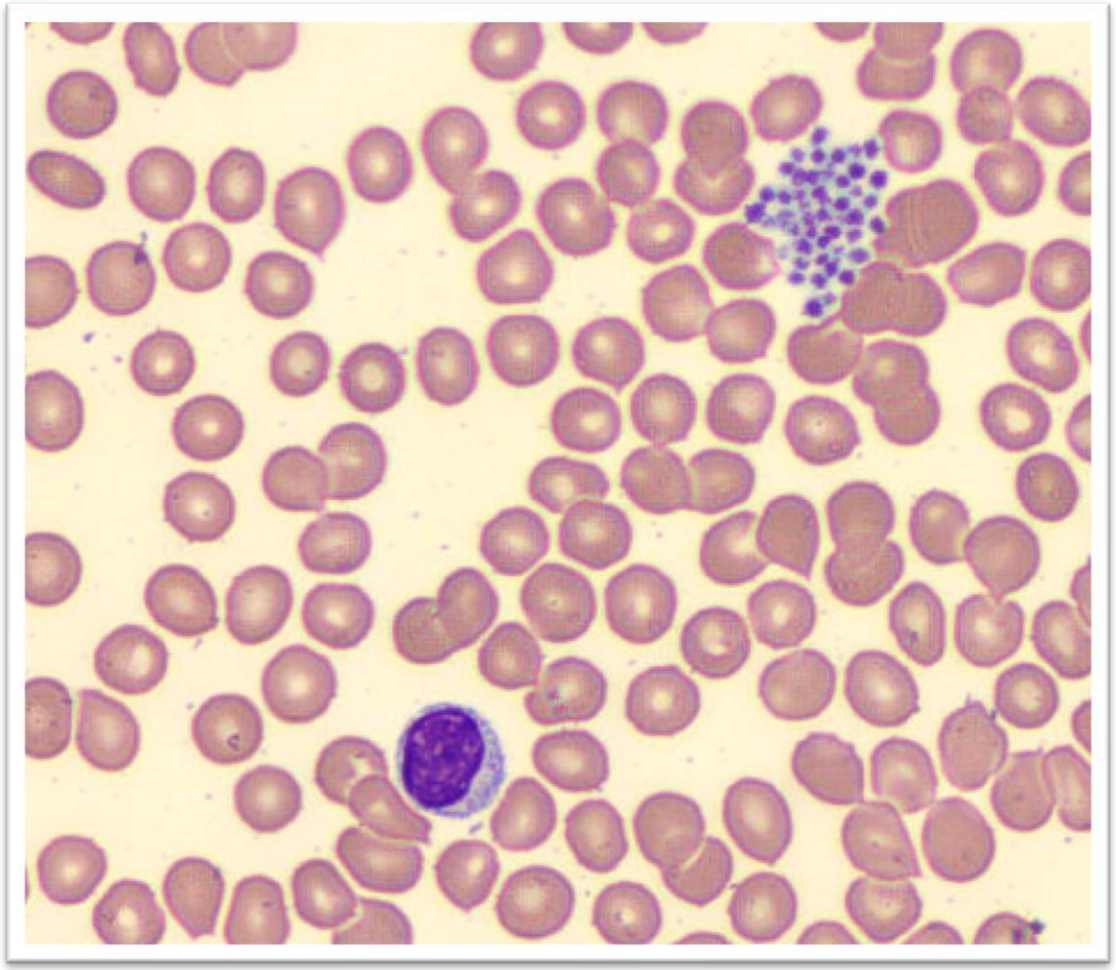



8.5 µm

Now what is the next step?

A. Platelet transfusion.
B. Steroids and IVIG.
C. Bone marrow biopsy.
D. Citrated platelet count.
E. Nothing



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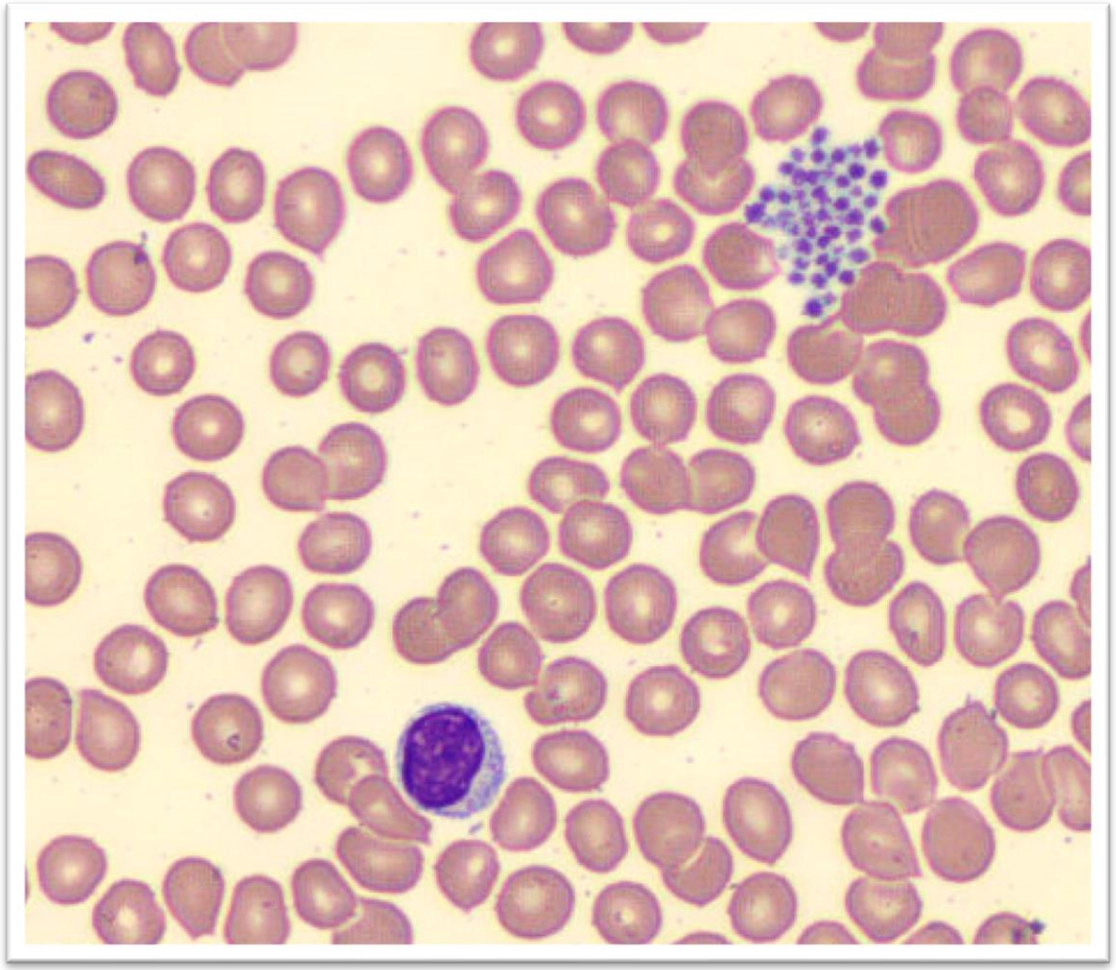
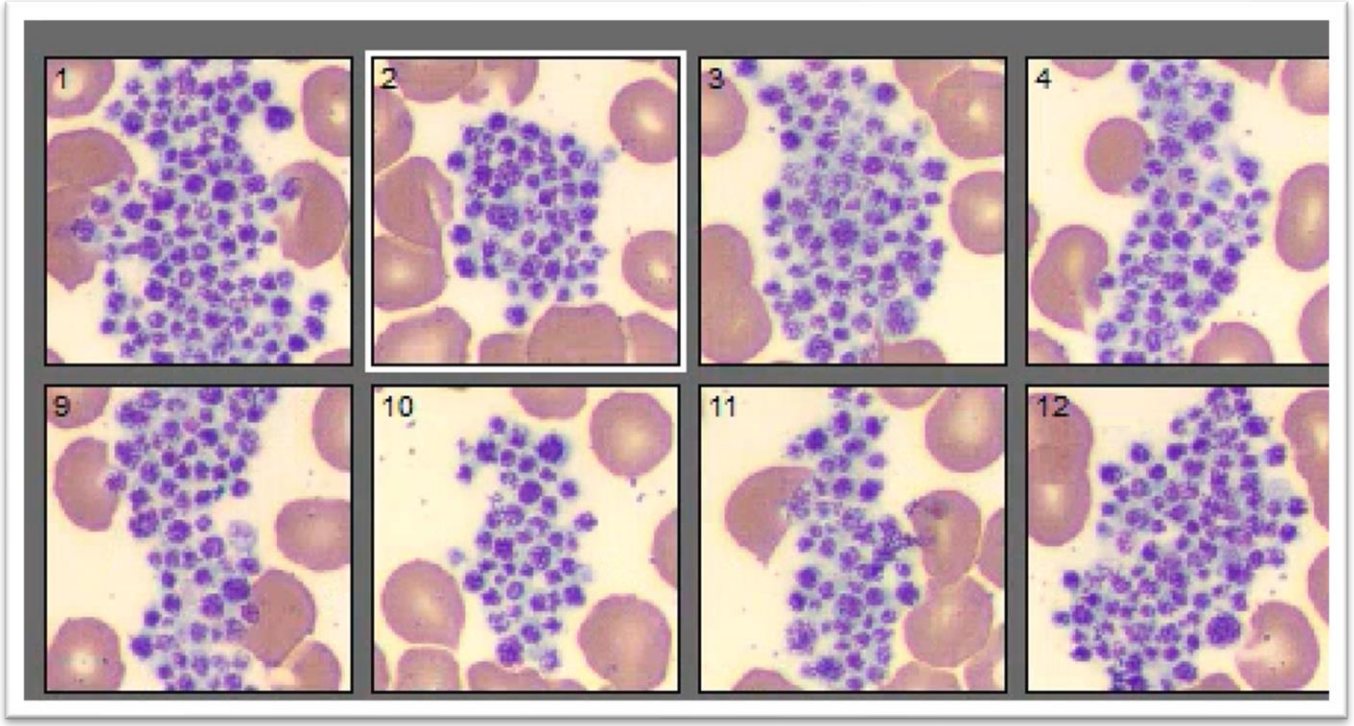


Pseudothrombocytopenia



COMPLETE BLOOD ...		
WBC		4.87
RBC		4.64
Hgb		12.4 ↓
HCT		38.4 ↓
MCV		82.8
MCH		26.7
MCHC		32.3
PLT		7 ↓↓
PLT (citrated bld)	187	

Citrated platelet count

** Clumping occurs in the TUBE and not in the PATIENT **

CASE

21M with fatigue and anemia

21M with fatigue and anemia

- Healthy student.
- Presents to his primary care physician.
- Unusually fatigued.
- Abdominal fullness.

	5/25/2020 0632	
COMPLETE BLOOD COUNT		
WBC	276.55 *	⏫
RBC	3.16	⏬
Hgb	9.5	⏬
HCT	28.7	⏬
MCV	90.8	
MCH	30.1	
MCHC	33.1	
PLT	259	
MPV	12.6	⏫
RDW	18.3	⏫

21M with fatigue and anemia

	5/25/2020 0632	
COMPLETE BLOOD COUNT		
WBC	276.55 *	⏫
RBC	3.16	🔻
Hgb	9.5	🔻
HCT	28.7	🔻
MCV	90.8	
MCH	30.1	
MCHC	33.1	
PLT	259	
MPV	12.6	🔺
RDW	18.3	🔺

BLOOD DIFF - ABSOLUTE		
Neutrophil #	149.32 * c	🔺
Lymph#	8.30	🔺
Mono#	8.30	🔺
Eos#	8.30	🔺
Baso#	16.59	🔺
Myelocyte#	49.78	🔺
Metamyelocyte#	8.30	🔺
Promyelocyte#	19.36	🔺
NRBC#	3	🔺
NRBC#, auto	2.52	🔺
Metamyelocytes	3.0	🔺
Promyelocytes	7.0	🔺
SMEAR MORPHOLOGY		
Anisocytosis	2+	!
Poikilocytosis	1+	!
Polychromasia	1+	!
Microcytes	1+	!
Ovalocytes	1+	!
PLT Estimate	NORMAL	
OTHER HEMATOLOGY		
Retics (%)		
HEMATOLOGY MISCELL...		
Other cells (Diff)	8.30	🔺

What does this look like?

A. Acute myeloid leukemia (AML).
B. Acute lymphoid leukemia (ALL).
C. Chronic myeloid leukemia (CML).
D. Chronic lymphoid leukemia (CLL).
E. Polycythemia vera

	5/25/2020 0632	
COMPLETE BLOOD COUNT		
WBC	276.55 *	⇈
RBC	3.16	↓
Hgb	9.5	↓
HCT	28.7	↓
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PLT	259	
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MCH	30.1	
MCHC	33.1	
PLT	259	
MPV	12.6	↑
RDW	18.3	↑

	5/25/2020 0632
LYTES/RENAL/GLUCOSE	
Sodium	143
Potassium	3.3 ▼
Chloride	103
Carbon Dioxide	23
BUN	11
Creatinine	0.98
GFR (estimated)	110 *
Glucose	109 ▲
Anion Gap	17

US Abdomen Complete

Performed: 5/26/2020 at 4:42 PM

Reason For Exam

PAC

new leukemia ? splenomegaly; *Splenomegaly

Impression

Marked splenomegaly, measuring 22.5 cm craniocaudally.

	5/26/2020 0820
LIVER FUNCTION TESTS	
ALT (SGPT) (U/L)	14
AST (SGOT)	16
Alk Phos	67
Bilirubin (Total)	0.8
Bilirubin (Direct)	0.2
Albumin	4.3
Globulin	2.4

	5/25/2020 0632
ROUTINE COAGULATION	
PT	14.7 ▲
PT-INR	1.2 ▲
PTT	34.6 *
Fibrinogen	439

	5/26/2020 0820	5/26/2020 0213
GENERAL CHEMISTRIES		
Albumin	4.3	
Bilirubin (Direct)	0.2	
Bilirubin (Total)	0.8	
Calcium		9.0
Calcium, ionized		
LDH	805 ▲	
Magnesium	2.2	
Phosphorus		
Total Protein	6.7	
Uric acid		8.1 ▲

Is it time to panic?

- Creatinine is normal.
- LFTs are normal.
- PT/INR, PTT, Fibrinogen normal.
- HGB 9.5.
- PLT 259.

	5/25/2020 0632	
COMPLETE BLOOD COUNT		
WBC	276.55 *	⇈
RBC	3.16	↓
Hgb	9.5	↓
HCT	28.7	↓
MCV	90.8	
MCH	30.1	
MCHC	33.1	
PLT	259	
MPV	12.6	↑
RDW	18.3	↑

CML: What is the most likely mutation?

A. JAK2 V617F mutation.
B. BCR/ABL translocation.
C. P53 mutation.
D. EGFR exon 20 mutation.
E. DNMT3A mutation.

CML: What is the most likely mutation?

A. JAK2 V617F mutation.
B. BCR/ABL translocation.
C. P53 mutation.
D. EGFR exon 20 mutation.
E. DNMT3A mutation.

- BCR/ABL is the classic t(9;22) chromosomal translocation that leads to constitutive ABL kinase signaling.

21M with chronic myeloid leukemia

- BCR/ABL (+), translocation between chromosomes 9 & 22
- Started on Dasatinib (PO)

	5/28/2020 0730	6/1/2020 1205	6/8/2020 1430	6/15/2020 1223	6/29/2020 1246	7/10/2020 1543	8/17/2020 1000
COMPLETE							
WBC	200.24 ⇈	158.35 * ⇈	69.7 ↑	7.00	3.95	5.3	5.97
RBC	3.17 ↓	3.20 ↓	3.21 ↓	3.45 ↓	3.85 ↓	4.18 ↓	4.92
Hgb	9.3 ↓	8.8 ↓	9.1 ↓	10.1 ↓	11.5 ↓	12.2 ↓	13.9
HCT	28.4 ↓	27.9 ↓	29.8 ↓	30.8 ↓	34.9 ↓	39.6	42.6
MCV	89.6	87.1	92.8	89.3	90.7	94.7	86.6
MCH	29.3	27.6	28.3	29.2	29.8	29.2	28.4
MCHC	32.7	31.7 ↓	30.5 ↓	32.6 ↓	32.8 ↓	30.8 ↓	32.8 ↓
PLT	237	227	209	125 ↓	86 ↓	175	101 ↓
MPV	12.6 ↑	10.1	11.9	9.9	8.8	10.8	8.5
RDW	17.9 ↑	18.3 ↑	19.7 ↑	21.6 ↑	20.4 ↑	16.7	15.4

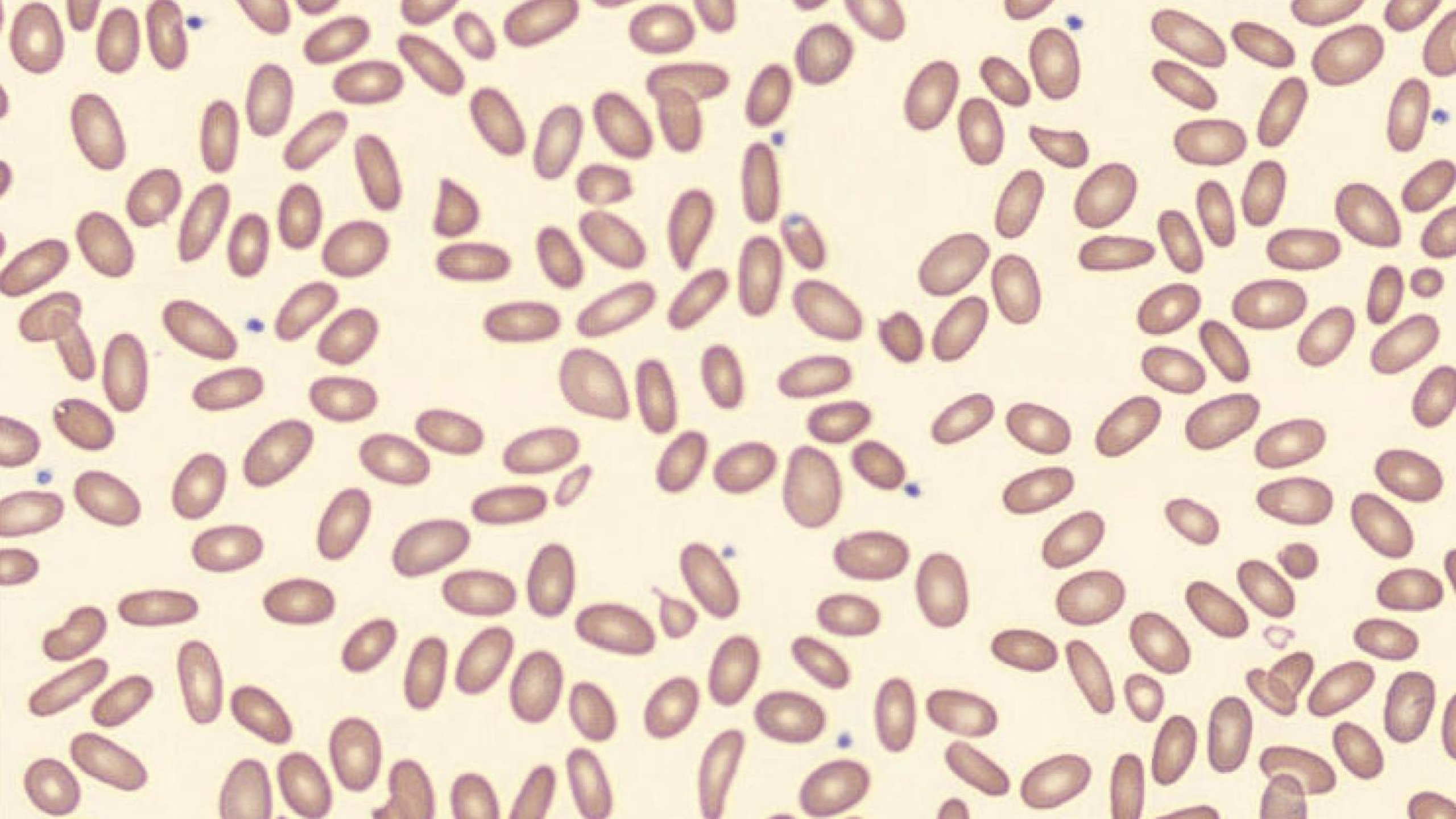
CASE

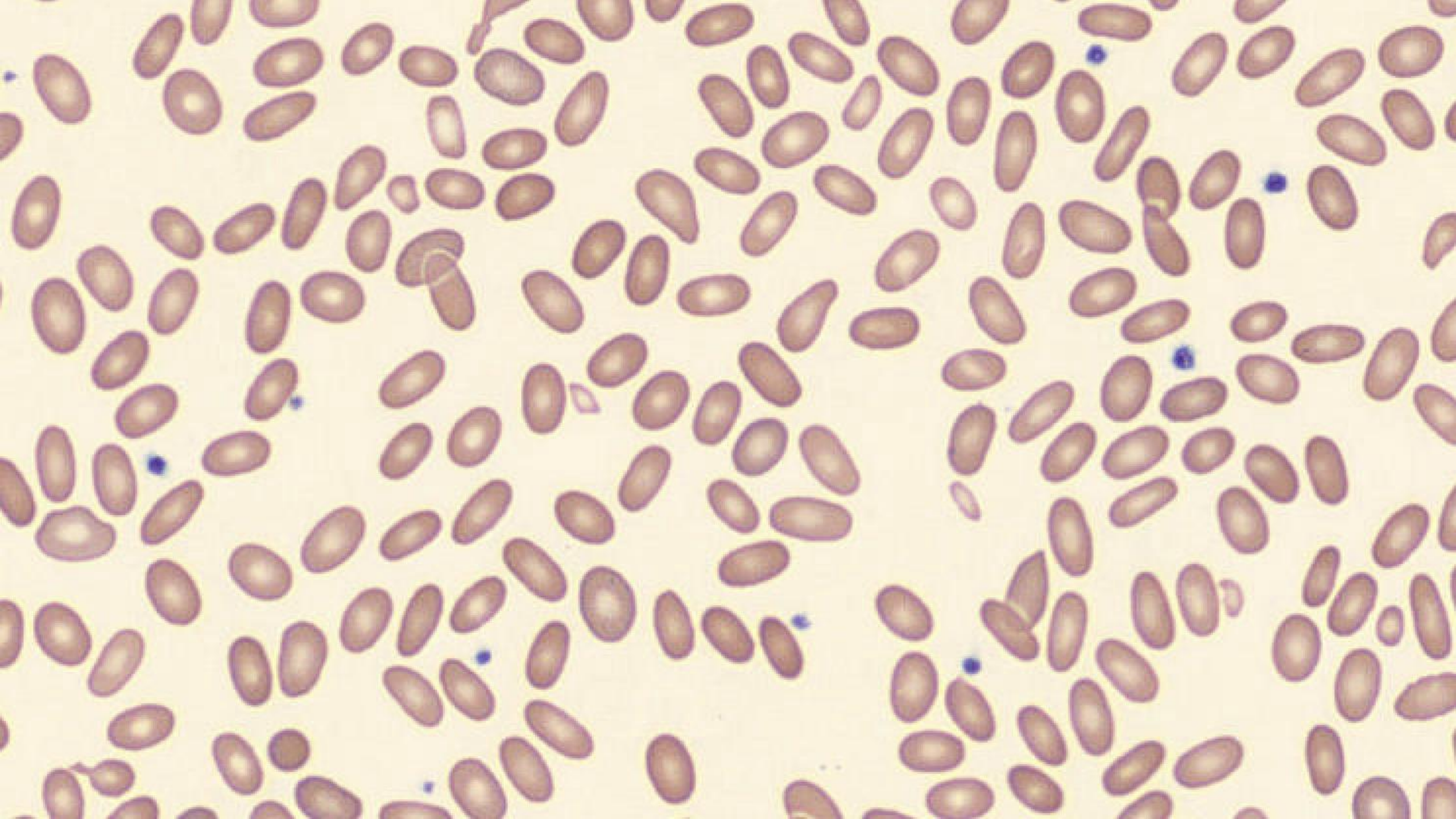
41F referred for an evaluation of her beta-thalassemia

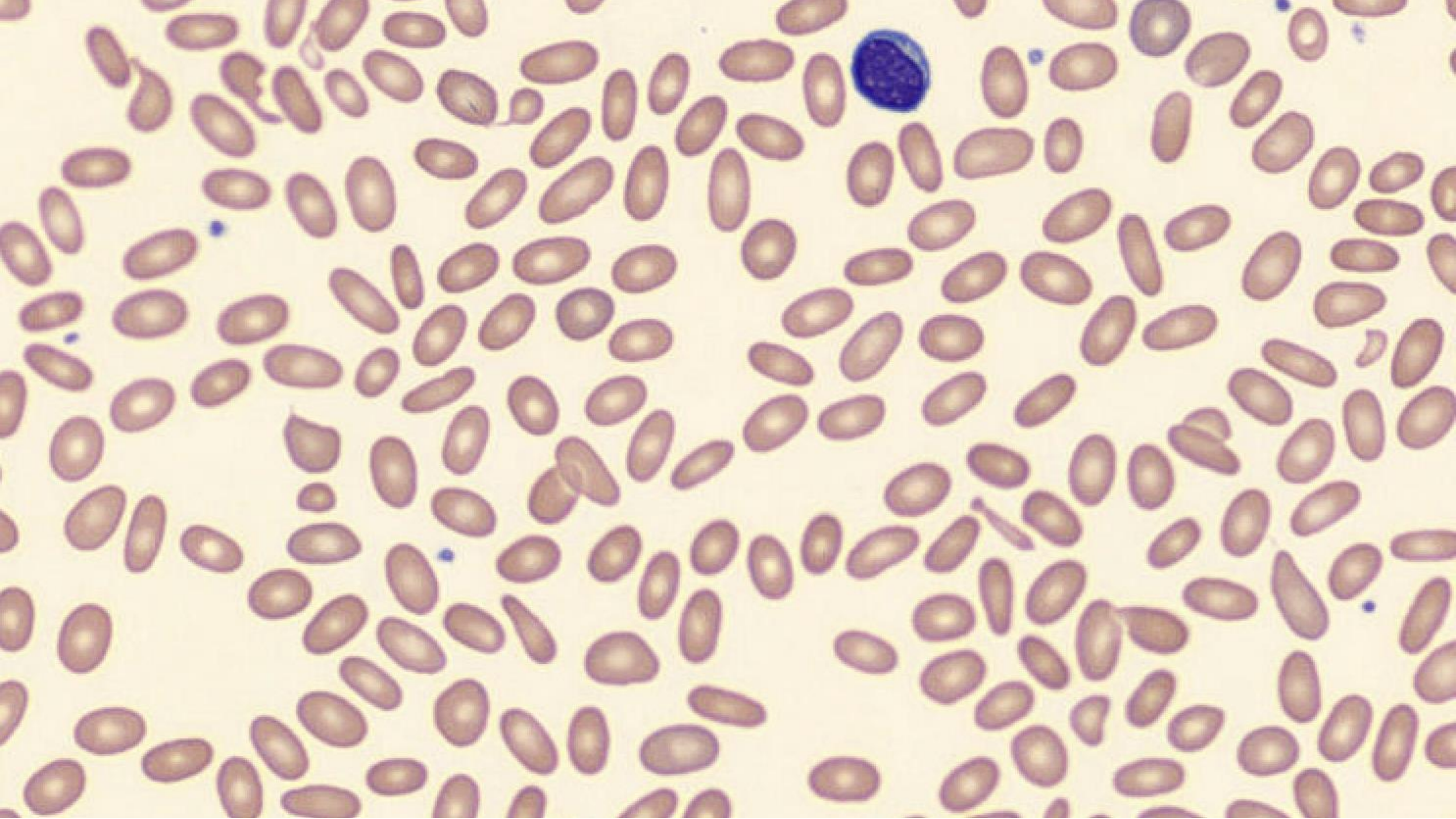
41F with beta-thalassemia

- Long history of mild anemia.
- Marathon runner.
- Intermittent treatment with oral iron.
- Adopted from Korea.
- Korean government did genetic testing.
- Told her that she had beta thalassemia.
- Referred to hematology.
- Very healthy lady.
- S/P cholecystectomy.

	2026 3/5/26 15:58	2025 12/20/25 10:33	 12/9/25 07:32
COMPLETE BLOOD C...			
WBC	6.23	4.39	3.24 ↓
RBC	3.66 ↓	3.81 ↓	3.56 ↓
Hgb	11.6 ↓	12.5	11.5 ↓
HCT	34.5 ↓	35.3 ↓	33.6 ↓
MCV	94.3	92.7	94.4
MCH	31.7 ↑	32.8 ↑	32.3 ↑
MCHC	33.6	35.4	34.2
PLT	200	279	172
MPV	11.2	12.7 ↑	12.0
RDW	14.9 ↑	14.9 ↑	14.6 ↑
Abs Neut Count (ONC)			
OTHER HEMATOLOGY			
Retics (%)	5.3 ↑		6.5 ↑







What is going on?

A. Appears consistent with beta-thalassemia.
B. The preparation of the peripheral smear looks “off”.
C. Consistent with hereditary spherocytosis.
D. Consistent with hereditary elliptocytosis.
E. Consistent with iron deficiency anemia.

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B. The preparation of the peripheral smear looks “off”.
C. Consistent with hereditary spherocytosis.
D. Consistent with hereditary elliptocytosis.
E. Consistent with iron deficiency anemia.

This does not look like beta-thalassemia!

- Hemoglobin electrophoresis = normal
- Hemolysis markers:
  - BILI = 1.5
  - LDH = 259
  - HAPTO = 15
- Smear: Elliptocytes
- Genetic testing: SPTA1 mutation.
  - Alpha-Spectrin protein
  - Red blood cell membrane key component
  - SPTA1 (autosomal dominant elliptocytosis)
  - P.SER591PRO (het)

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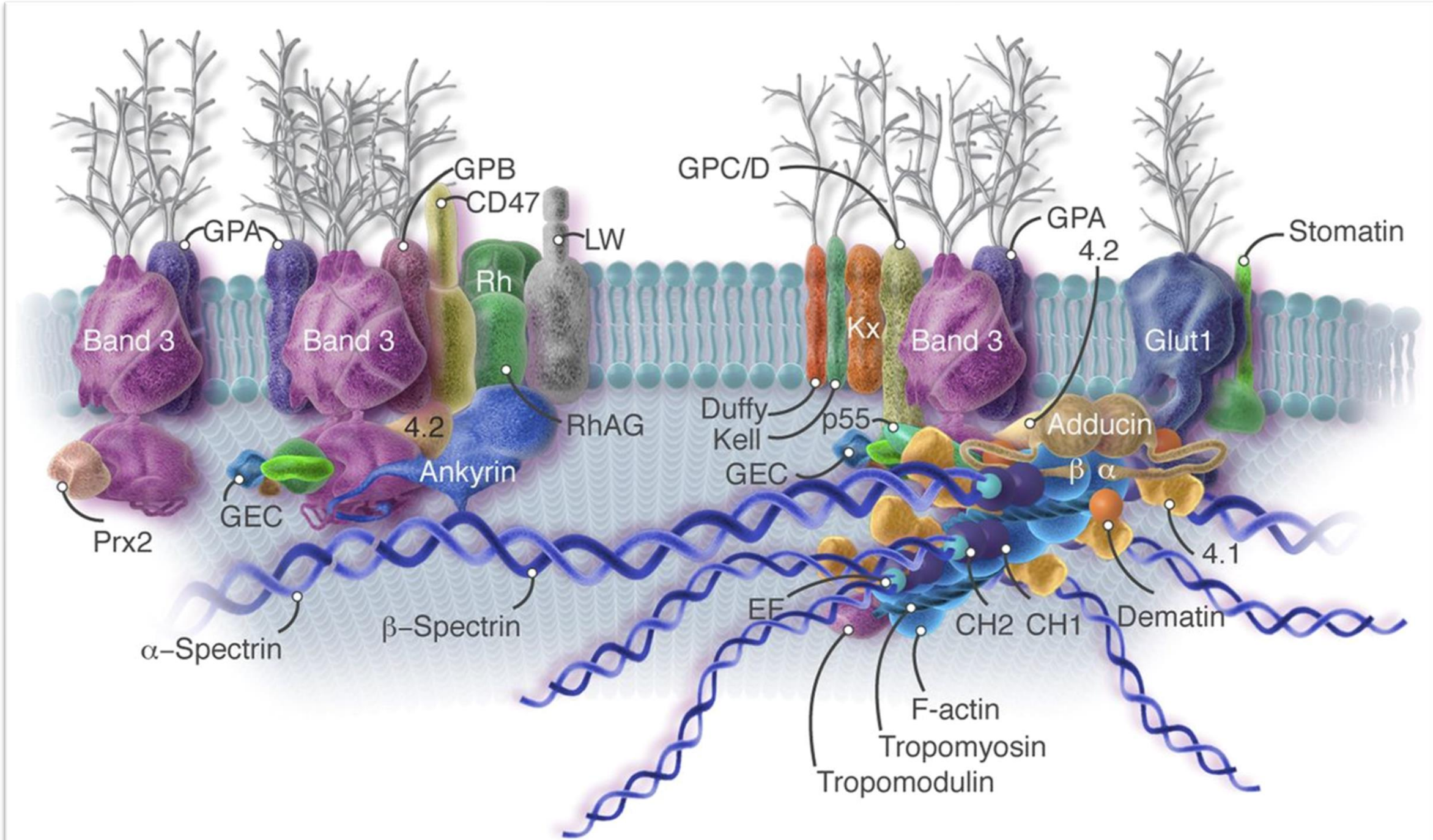
Abs Neut Count (ONC)			
OTHER HEMATOLOGY			
Retics (%)	5.3 ↑		6.5 ↑

RBC membrane defects

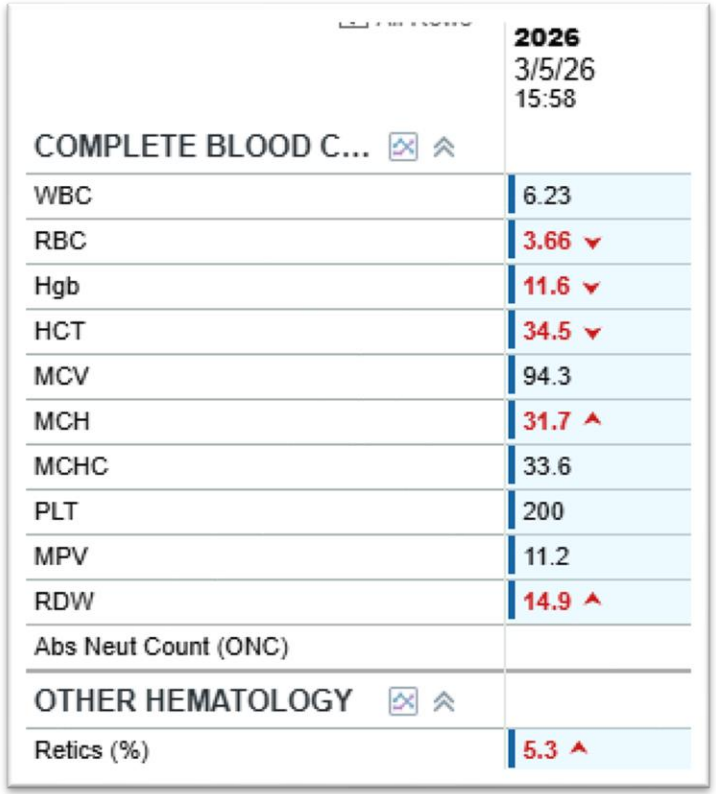
- Generally benign
- Shortened RBC lifespan
  - Increased reticulocyte count
  - Pro tip: Hemoglobin A1c is a good marker of RBC lifespan
  - Further shortened in the settings of stress or infection
- Splenomegaly? (she did not have splenomegaly)
- Gallstones? (she was s/p cholecystectomy → pigment stones)
- Iron overload
  - Try to avoid unnecessary iron supplementation


GPB
CD47
LW
GPA
Rh
Band 3
Band 3
4.2
RhAG
Ankyrin
GEC
Prx2
α–Spectrin
β–Spectrin
GPC/D
GPA
4.2
Stomatin
Kx
Band 3
Glut1
Duffy
Kell
p55
GEC
Adducin
β α
4.1
EF
CH2 CH1
Dematin
F-actin
Tropomyosin
Tropomodulin

Interpreting the reticulocyte count

- Average person:
  - RBC lifespan 120 days (~100 days)
  - Reticulocyte count 1% (1/100)
  - 1% of RBC are recycled and replaced each day

- Hereditary elliptocytosis
  - Reticulocyte count 5.3%
  - 5% of RBC are recycled and replaced each day
  - RBC lifespan ~20 days?



COMPLETE BLOOD C...	2026 3/5/26 15:58
WBC	6.23
RBC	3.66 ↓
Hgb	11.6 ↓
HCT	34.5 ↓
MCV	94.3
MCH	31.7 ↑
MCHC	33.6
PLT	200
MPV	11.2
RDW	14.9 ↑
Abs Neut Count (ONC)	
OTHER HEMATOLOGY	
Retics (%)	5.3 ↑

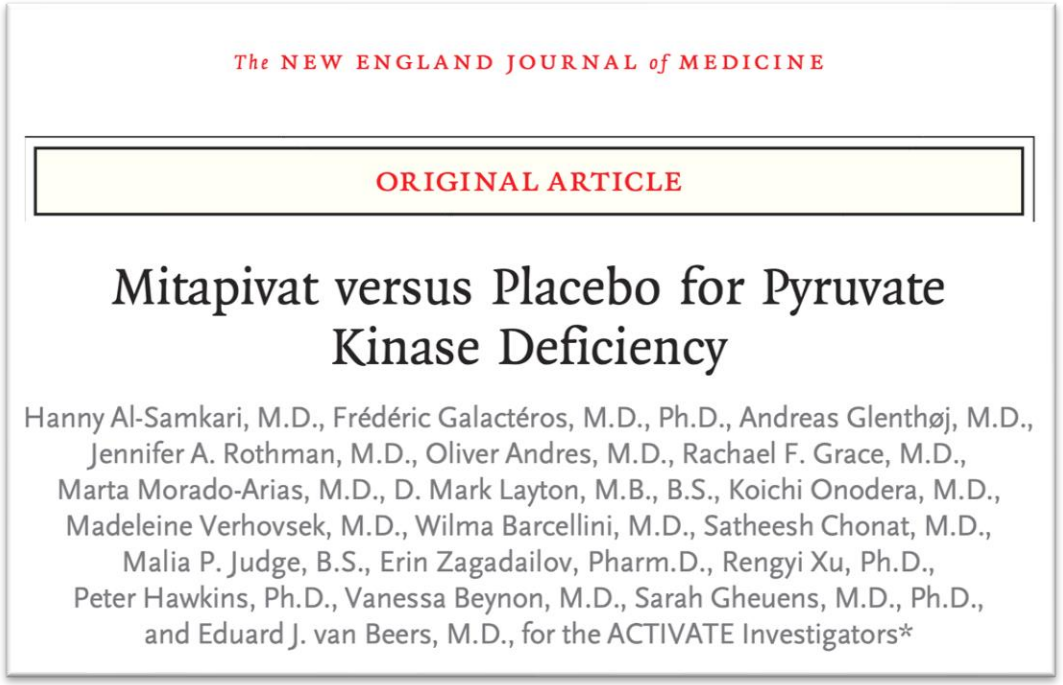
  - ** This is why folks get into trouble with a Parvovirus B19 infection **

New therapies for RBC problems?

- Mitapivat is a PK activator (boosts the enzyme activity of mutant pyruvate kinase).

- Hemoglobinopathies:
  - Thalassemia
  - Sickle cell disease

- Membranopathies/enzymopathies
  - Hereditary spherocytosis
  - Hereditary xerocytosis



NEJM, 2022

CASE

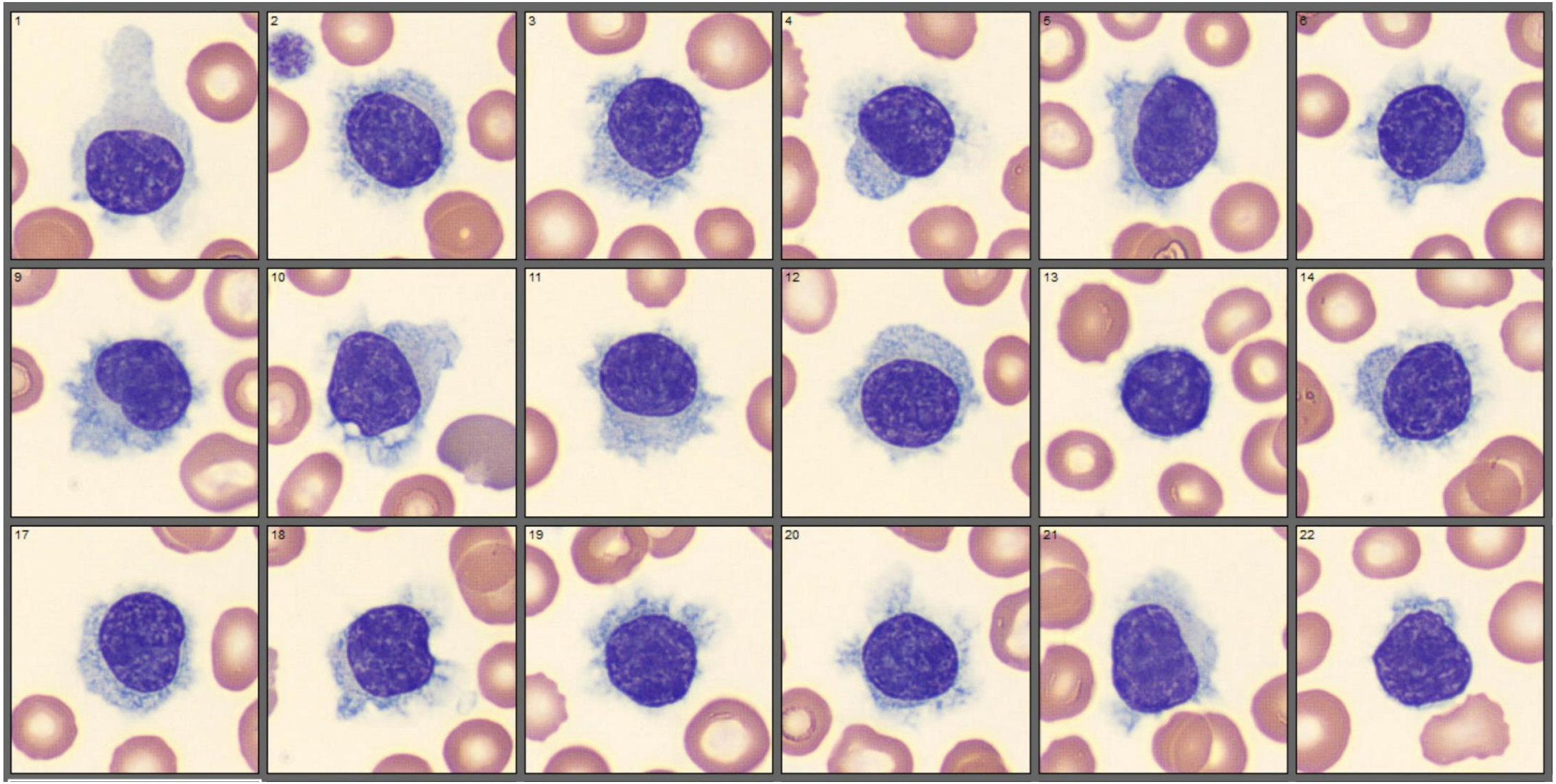
68F with anemia, thrombocytopenia, leukocytosis

68F with anemia (incidental discovery)

Time Mark	2/2/25 05:25	2/1/25 17:45	2/1/25 02:30
COMPLETE BLOOD C...			
WBC	31.72 ▲	31.09 ▲	30.91 ▲
RBC	2.01 ▼	2.39 ▼	1.96 ▼
Hgb	6.8 ▼	7.8 ▼	6.7 ▼
HCT	21.3 ▼	25.2 ▼	21.5 ▼
MCV	106.0 ▲	105.4 ▲	109.7 ▲
MCH	33.8 ▲	32.6 ▲	34.2 ▲
MCHC	31.9 ▼	31.0 ▼	31.2 ▼
PLT	25 ▼▼	35 ▼▼	30 ▼▼
MPV	Not measured	12.0	12.7 ▲
RDW	24.4 ▲	24.7 ▲	23.6 ▲
BLOOD DIFFERENTIA...			
Diff Method	Manual	Manual	Manual
Total Cells Counted	112	115	231
Neutrophils	5.4 ▼	2.6 ▼	3.5 ▼
Lymphs	15.2 ▼	45.2 ▲	70.5 ▲
Other WBC's(%)	79.4 ▲	52.2 ▲	26.0 ▲
Differential Comment			Differential r...
NRBC% (auto)	2.00 ▲	3.20 ▲	2.90 ▲
Interpretation:			PENDING
OTHER HEMATOLOGY			
Retics (%)	2.4		

Time Mark	2/2/25 05:25	2/1/25 17:45
ROUTINE COAGULATI...		
PT	12.5	
PT-INR	1.1	
PTT	31.2	
D-Dimer (ng/mL)	1,281 ▲	1,696 ▲
Fibrinogen	363	426 ▲

Peripheral smear



68F with anemia, leukocytosis, unusual WBC.

A. Acute lymphoblastic leukemia.
B. Acute myeloid leukemia.
C. Chronic lymphoid leukemia.
D. Chronic myeloid leukemia.
E. Indolent B-cell lymphoma.

68F with anemia, leukocytosis, unusual WBC.

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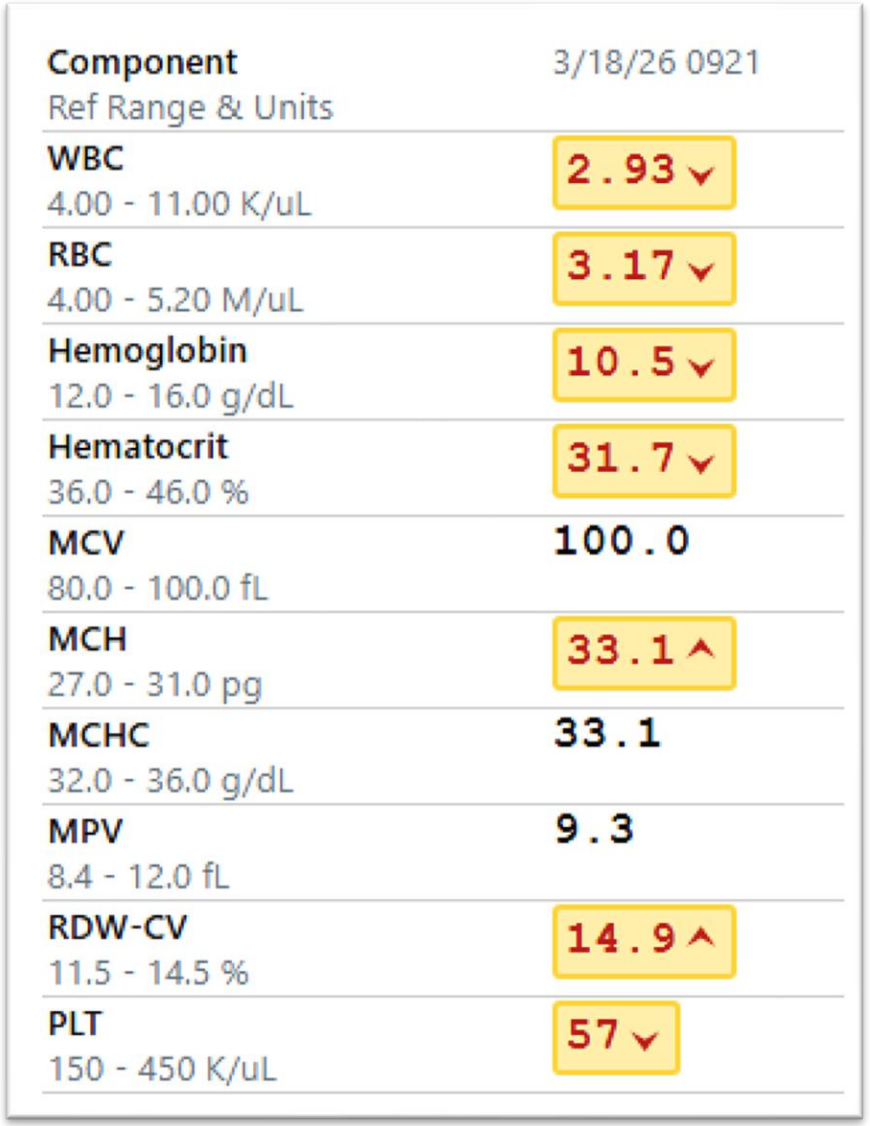
Peripheral blood flow cytometry & CT scans

- Flow cytometry
- 84% B cells
- CD19+ CD20+ CD5- CD10- CD23-/+ CD38- CD11c+ CD103+ CD25+
- Monoclonal B-cell count: 22,848/uL
- Circulating B cell lymphoma.
- Peripheral smear shows abundant small to medium size mature-appearing lymphoid cells that frequently have filamentous cytoplasmic projections.
- The morphologic and immunophenotypic findings are diagnostic of **hairy cell leukemia**.

- CT Chest / Abdomen / Pelvis
- Markedly **splenomegaly** (24.3 cm) with multiple hypodense focal lesions, likely secondary to leukemic involvement.

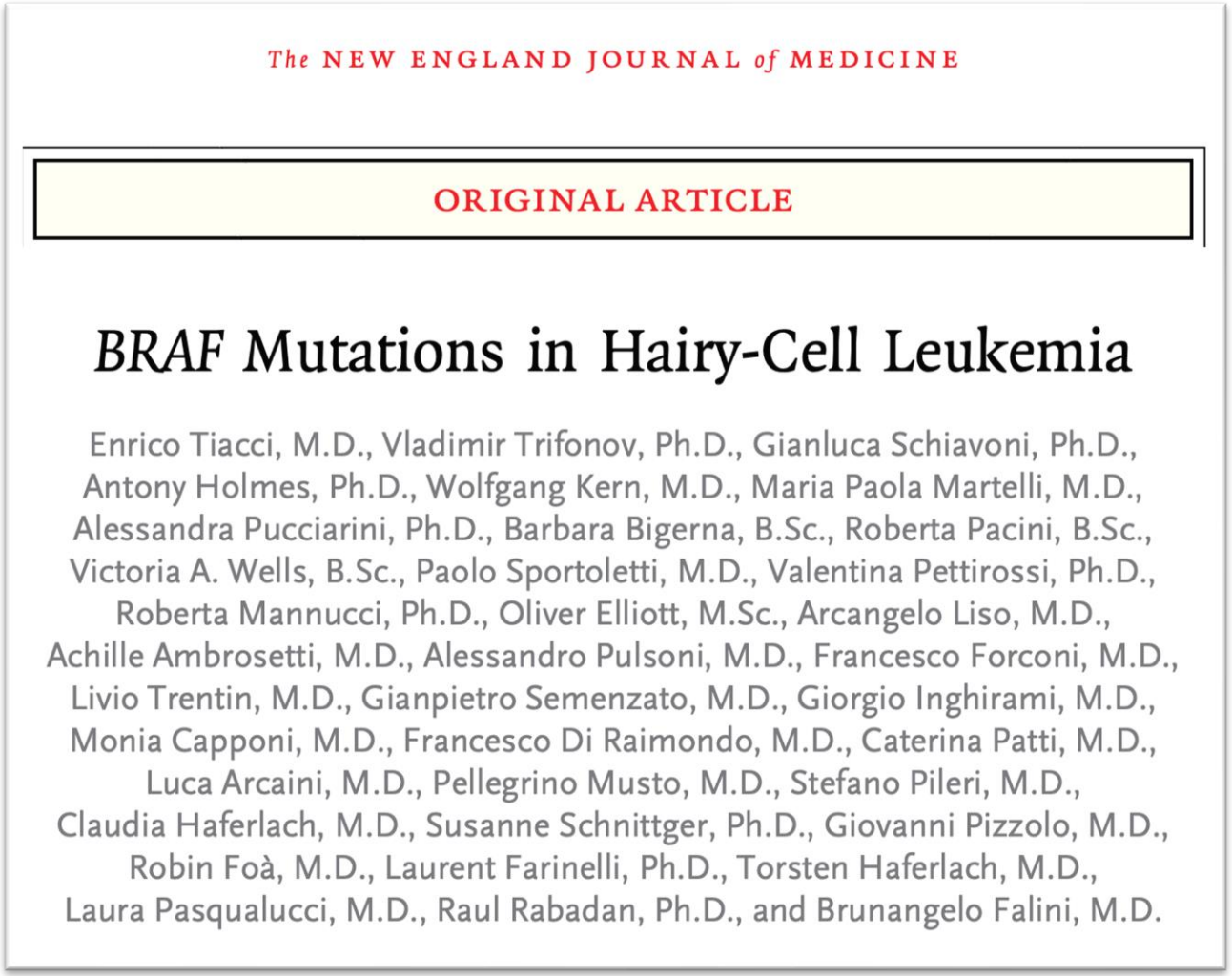
Molecular testing in Hairy Cell Leukemia

- 43F referred for anemia.
- I sent a panel of mutational testing from the peripheral blood.
- BRAF
  - c.1799T>A (p.**V600E**) 1.6% VAF



Component Ref Range & Units	3/18/26 0921
WBC 4.00 - 11.00 K/uL	2.93 ⌄
RBC 4.00 - 5.20 M/uL	3.17 ⌄
Hemoglobin 12.0 - 16.0 g/dL	10.5 ⌄
Hematocrit 36.0 - 46.0 %	31.7 ⌄
MCV 80.0 - 100.0 fL	100.0
MCH 27.0 - 31.0 pg	33.1 ⌃
MCHC 32.0 - 36.0 g/dL	33.1
MPV 8.4 - 12.0 fL	9.3
RDW-CV 11.5 - 14.5 %	14.9 ⌃
PLT 150 - 450 K/uL	57 ⌄

BRAF V600E mutations in almost 100% of HCL



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BRAF Mutations in Hairy-Cell Leukemia

Enrico Tiacci, M.D., Vladimir Trifonov, Ph.D., Gianluca Schiavoni, Ph.D., Antony Holmes, Ph.D., Wolfgang Kern, M.D., Maria Paola Martelli, M.D., Alessandra Pucciarini, Ph.D., Barbara Bigerna, B.Sc., Roberta Pacini, B.Sc., Victoria A. Wells, B.Sc., Paolo Sportoletti, M.D., Valentina Pettirossi, Ph.D., Roberta Mannucci, Ph.D., Oliver Elliott, M.Sc., Arcangelo Liso, M.D., Achille Ambrosetti, M.D., Alessandro Pulsoni, M.D., Francesco Forconi, M.D., Livio Trentin, M.D., Gianpietro Semenzato, M.D., Giorgio Inghirami, M.D., Monia Capponi, M.D., Francesco Di Raimondo, M.D., Caterina Patti, M.D., Luca Arcaini, M.D., Pellegrino Musto, M.D., Stefano Pileri, M.D., Claudia Haferlach, M.D., Susanne Schnittger, Ph.D., Giovanni Pizzolo, M.D., Robin Foà, M.D., Laurent Farinelli, Ph.D., Torsten Haferlach, M.D., Laura Pasqualucci, M.D., Raul Rabadan, Ph.D., and Brunangelo Falini, M.D.

NEJM, 2011

CASE

46M with thrombocytosis

Asymptomatic, Incidentally discovered

Component Ref Range & Units	2/17/12 1510
WBC 4.5 - 11.0 th/cmm	7.9
HCT 41.0 - 53.0 %	45.9
HGB 13.5 - 17.5 gm/dl	15.0
RBC 4.50 - 5.90 mil/cmm	5.20
PLT 150 - 400 th/cumm	999 ! (Abnormally H)
MCV 80 - 100 fl	88
MCH 26.0 - 34.0 pg/rbc	28.9
MCHC 31.0 - 37.0 g/dl	32.7
RDW 11.5 - 14.5 %	13.7

What is the most likely explanation for his thrombocytosis?

A. Iron deficiency anemia.
B. Chronic myeloid leukemia.
C. Polycythemia vera.
D. Essential thrombocytosis.
E. Acute inflammation.

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WBC 4.5 - 11.0 th/cmm	7.9
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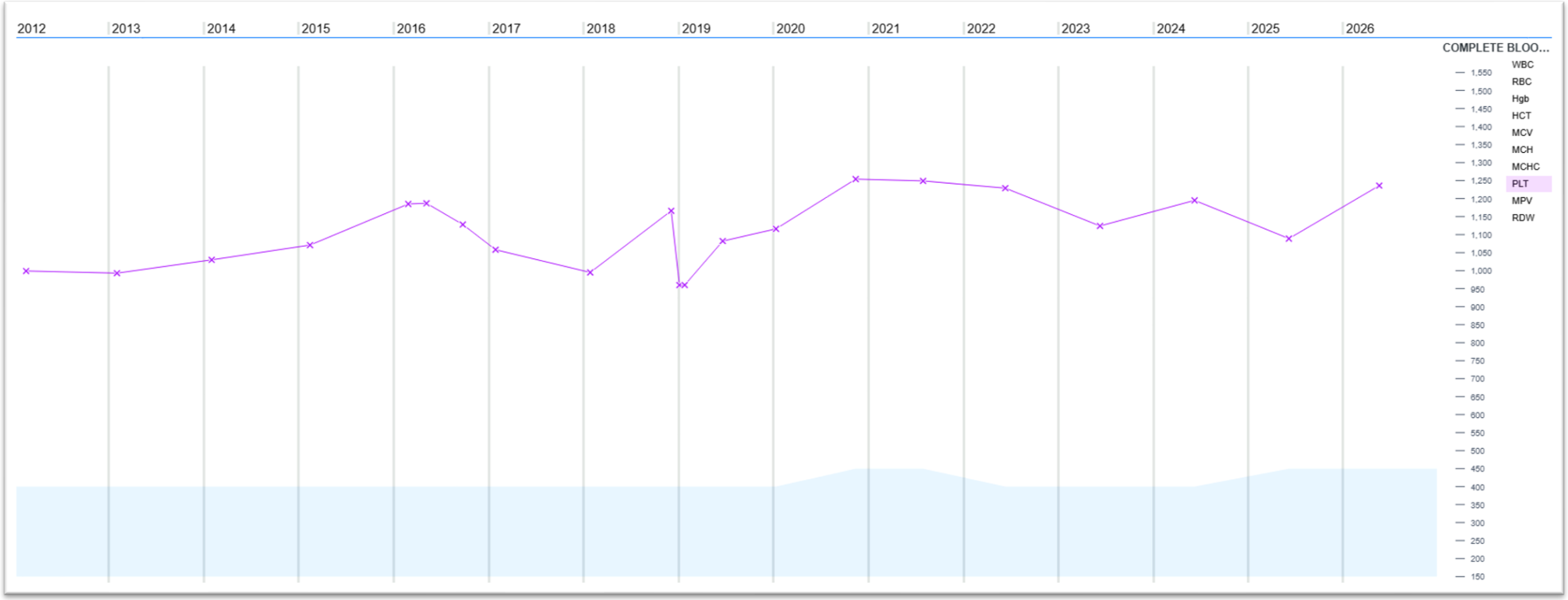
Platelet count 2012 - 2026



What is the most likely mutated gene in this patient?

A. JAK2
B. CALR
C. MPL
D. BCR/ABL
E. TET2

What is the most likely mutated gene in this patient?

A. JAK2
B. CALR
C. MPL
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E. TET2

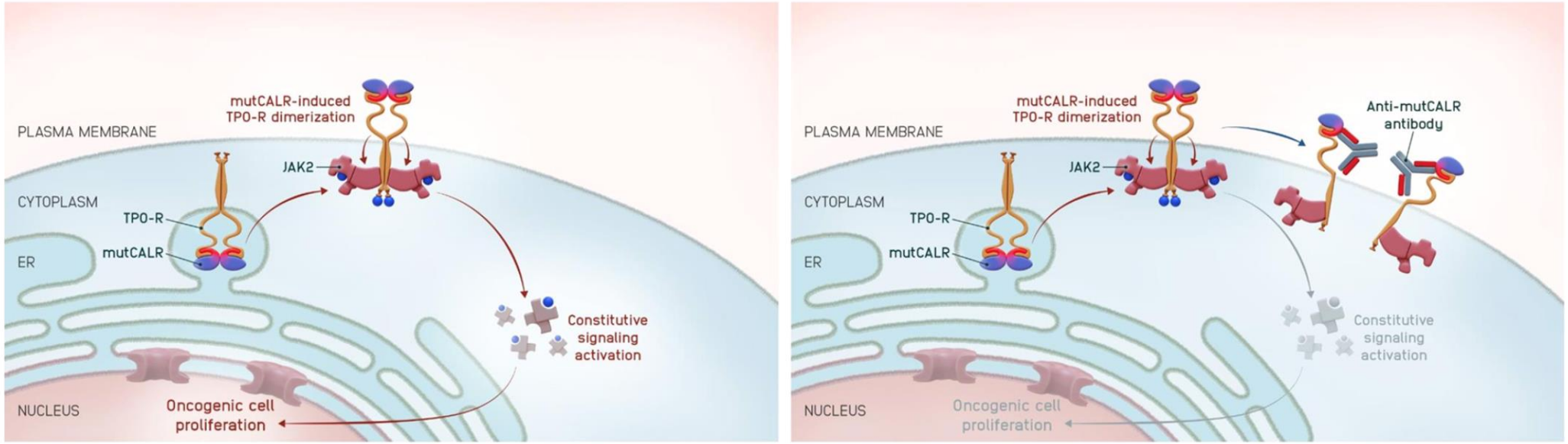
Targeting mutant calreticulin

- MPL
  - Thrombopoietin (TPO) receptor → activates platelet production
- Normal (wild-type) CALR
  - Chaperone in the endoplasmic reticulum.
  - Does not activate MPL
- Mutant CALR
  - Does activate MPL
  - 52 bp insertion or 5 bp deletion or frameshift = new C-terminal tail
  - Neo-antigen

INCA033989

INCA33989 Is a Mutant-Specific Targeted Therapy for Patients With *CALR* Mutations

- INCA33989 has a unique mechanism of action compared with other available therapies
  - INCA33989 is a high-affinity, fully human IgG1 monoclonal antibody that selectively targets mutCALR in complex with TPO-R (MPL) to inhibit cell signaling and proliferation[1]



MOC SUMMARY and KEY TAKE-AWAYS

1. Findings of leukocytosis, anemia, thrombocytopenia and splenomegaly should prompt an evaluation for indolent B-cell lymphomas including hairy cell leukemia, characterized by BRAF mutations.
2. Findings of leukocytosis, anemia, thrombocytopenia and splenomegaly should prompt an evaluation for myeloproliferative neoplasms including chronic myeloid leukemia, characterized by BCR/ABL.
3. Incidentally discovered thrombocytopenia in an asymptomatic individual should raise suspicion for a benign condition of platelet clumping called pseudothrombocytopenia.
4. Incidentally discovered thrombocytosis in an asymptomatic individual should raise suspicion for essential thrombocytosis, most commonly caused by mutations in JAK2, CALR, or MPL.
5. An acute anemia secondary to hemolysis with “bite cells” or “blister cells” on the blood smear should raise suspicion for oxidate damage due to a defect in glutathione metabolism (e.g., G6PD deficiency).
6. A longstanding anemia characterized by non-immune hemolysis and a shortened red blood cell lifespan should prompt evaluation for a red blood cell membrane or enzyme defect (e.g., hereditary spherocytosis).

References

1. Glucose-6-phosphatedehydrogenasedeficiency. Luzzatto, L. et al. *Blood*, 2020.

2. BRAF Mutations in Hairy-Cell Leukemia. Tiacci, E et al. *NEJM*, 2011.

3. Safety and efficacy of the mutant calreticulin-specific monoclonal antibody INCA033989 as monotherapy or in combination with ruxolitinib in patients (pts) with myelofibrosis (MF): Preliminary results from dose escalation of two global Phase 1 studies. Mascarenhas, J et al. *ASH 2026 annual meeting,* (https://submit.hematology.org/program/presentation/680685)

4. Mitapivat versus Placebo for Pyruvate Kinase Deficiency. Al-Samkari, H et al. *NEJM*, 2022.