Fred Hutch Cancer Center

# Consultative Hematology

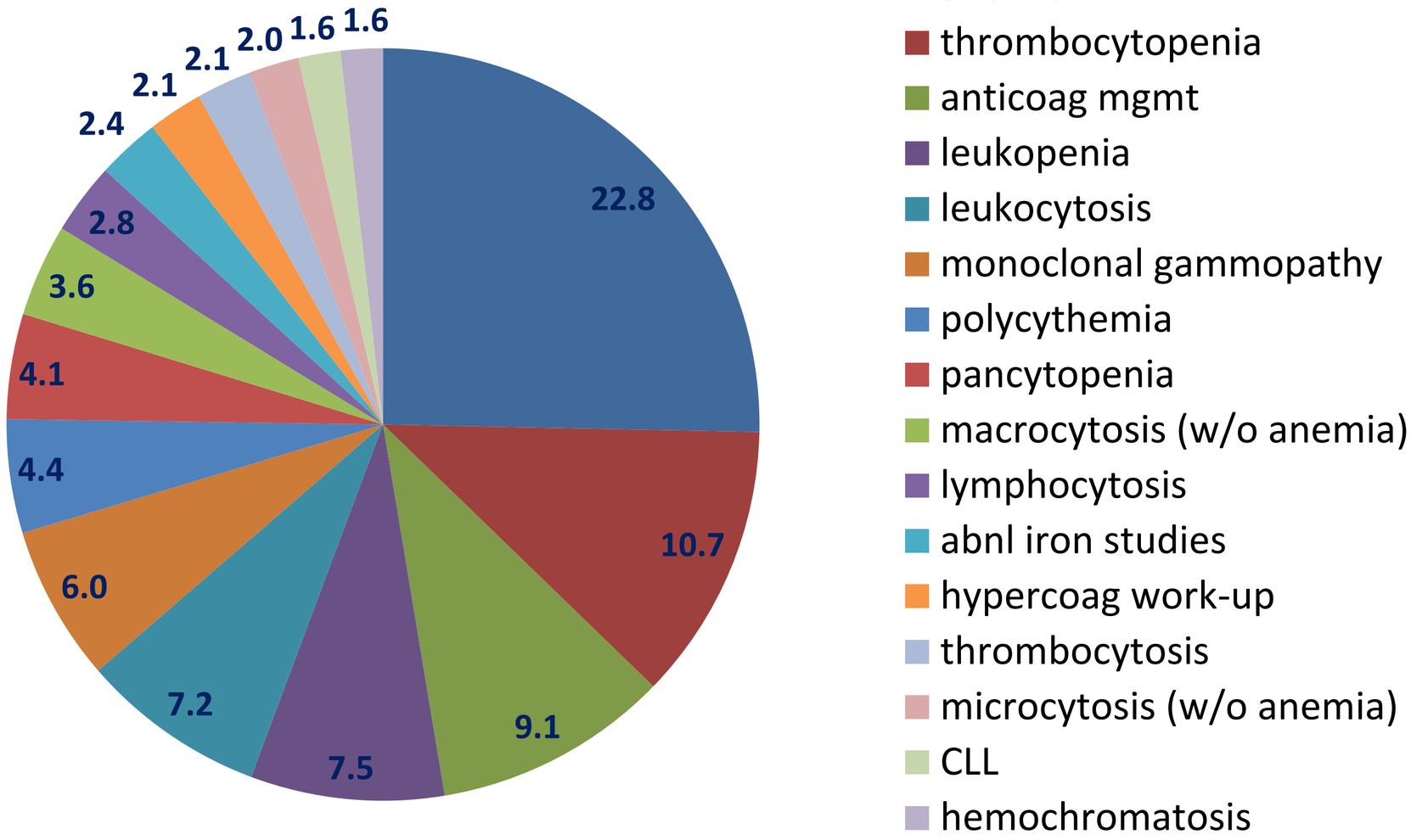
**Nicholas Burwick MD**
Associate Professor of Medicine
Division of Hematology
University of Washington
Puget Sound VA Health Care System

# Learning Objectives

- Identify common reasons for hematology consultation

- Review the differential diagnosis for common blood count abnormalities and describe examples of how a high-level consultative approach can help identify uncommon hematologic disorders

# Reasons for consult request to Hematology (N=598)






Burwick N, Unpublished data

# Hematologists are commonly asked to be diagnosticians

*Table 2.* Avoided Visit Rates and Primary Reason for e-Consult Across Specialties*

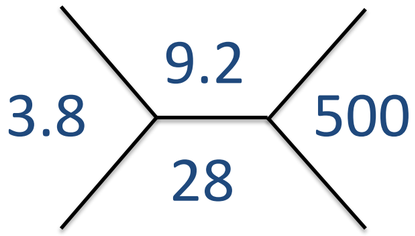
| Variable | Specialty | | | | |
|---|---|---|---|---|---|
| | Psychiatry (*n* = 891) | Infectious Disease (*n* = 1634) | Hematology (*n* = 2216) | Rheumatology (*n* = 287) | Dermatology (*n* = 1484) |
| Avoided visits 120 d after e-consult, *n (%)*† | 825 (92.6) | 1432 (87.6) | 1926 (86.9) | 187 (65.2) | 919 (61.9) |
| Primary reason for e-consult (based on subset manually reviewed), *n/N (%)*‡ | | | | | |
| Diagnosis | 2/145 (1.4) | 58/149 (38.9) | 102/150 (68) | 130/147 (88.4) | 50/150 (33.3) |
| Therapy | 135/145 (93.1) | 87/149 (58.4) | 46/150 (30.7) | 17/147 (11.6) | 85/150 (56.7) |
| PCP education | 4/145 (2.8) | 1/149 (0.7) | 2/150 (1.3) | 0/147 (0) | 9/150 (6.0) |
| Patient inquiry | 4/145 (2.8) | 3/149 (2.0) | 0/150 (0) | 0/147 (0) | 6/150 (4.0) |

e-consult = electronic consultation; PCP = primary care physician.
* Percentages may not sum to 100 due to rounding.
† Defined as lack of in-person visit referral within 120 d of placement of e-consult order.
‡ A subset of medical records (150 from each of the 5 specialties; 9 records were missing) was manually reviewed to assess the primary reason for e-consult.

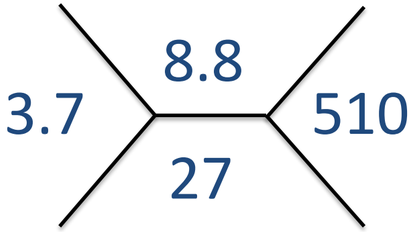


Ahmed S e al. Ann Int Med 2020

Case 1: 34-year-old female with anemia felt likely related to history of menstrual blood loss. You are consulted after her anemia fails to respond to 3 months of twice daily oral iron.



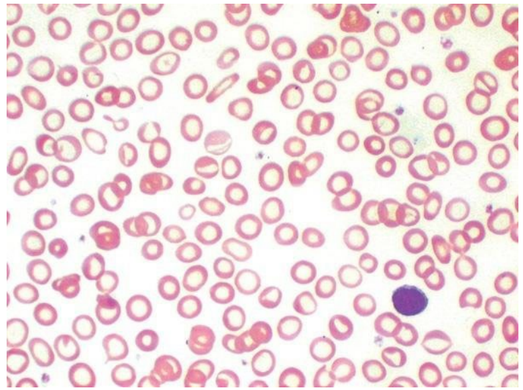

3 months
Oral Iron




MCV 72 fL
TSat 12%
Ferritin 15 ng/mL
TIBC 410 mcg/dL
Corrected retic 0.8%

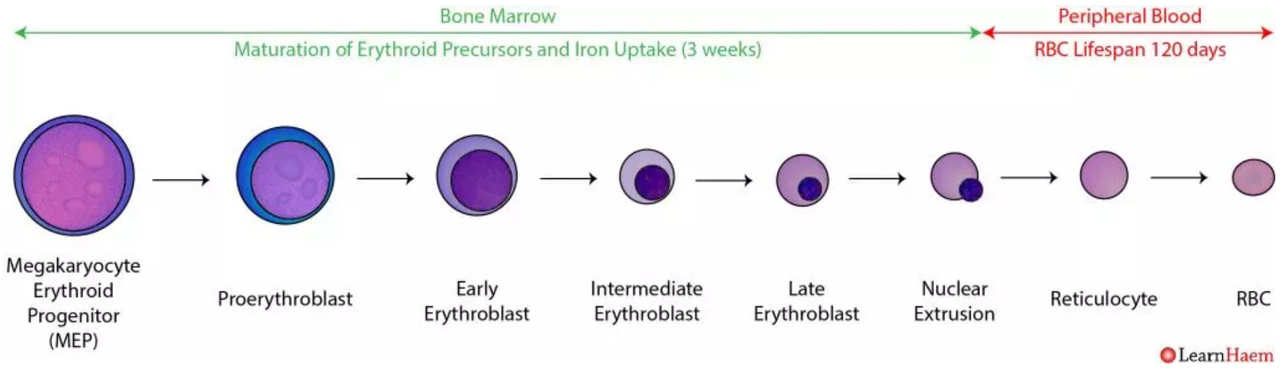
MCV 70 fL
Tsat 10%
Ferritin 10 ng/mL
TIBC 420 mcg/dL
Corrected retic 0.8%

Peripheral smear:



Microcytic hypochromic RBCs

# Differential diagnosis of ‘iron refractory’ anemia




While not strictly defined,  a hemoglobin rise <1g/dL after 4-6 weeks of oral iron repletion is suboptimal and warrants further clinical assessment.

**Differential Diagnosis**

- Excessive iron loss
- Iron intolerance/non-adherence
- Impaired absorption
- Impaired utilization [inflammatory block]
- Inherited disorder [IRIDA/mutations in TMPRSS6]

# Patients with IDA refractory to oral iron commonly have an identifiable underlying diagnosis

**Table 1. Main diagnostic categories and coexistent findings in 300 consecutive IDA patients**

| Diagnosis | Autoimmune gastritis | *H pylori** | Menorrhagia | Gastrointestinal lesions | Celiac | Negative |
|---|---|---|---|---|---|---|
| n (%) | 77 (26) | 57 (19) | 96 (32) | 31 (10) | 14 (5) | 21 (7) |
| Mean age ± 1 SD, y | 41 ± 16 | 37 ± 19 | 39 ± 10 | 60 ± 14 | 39 ± 14 | 33 ± 13 |
| Gender, M/F | 14/63 | 17/40 | 0/96 | 13/18 | 3/15 | 2/21 |
| Main diagnosis alone | 26 | 57 | 39 | 21 | 11 | 21 |
| *H pylori* | 39 | — | 57 | 10 | 2 | 0 |
| Menorrhagia | 11 | 0 | — | 0 | 1 | 0 |
| Gastrointestinal lesions | 1 | 0 | 0 | — | 0 | 0 |
| Aspirin or NSAID | 9 | 3 | 1 | 7 | 0 | 1 |
| Refractory to oral iron, % | 69 | 68 | 38 | 47 | 100 | 10 |



Hershko C et al. Blood 2014

You see the patient back in clinic and she reports that she has had abdominal discomfort for the past 6 months, which has worsened since starting the iron pills. Because of these symptoms, she also began taking a daily over-the-counter proton pump inhibitor  (PPI).

Fecal occult blood testing is performed and returns positive.  An EGD is scheduled

EGD demonstrates *H. pylori* gastritis

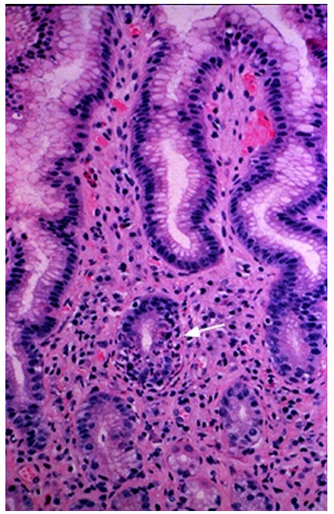
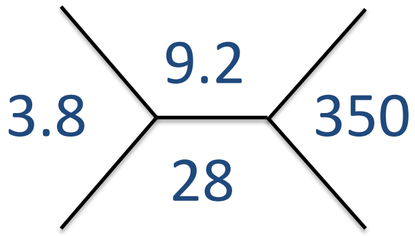


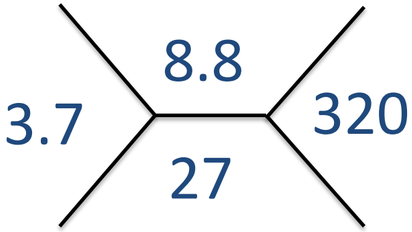


Figure: uptodate

Case 1: 34-year-old female with anemia felt likely related to history of menstrual blood loss.  Hematology is consulted after her anemia fails to respond to 6 months of twice daily oral iron.



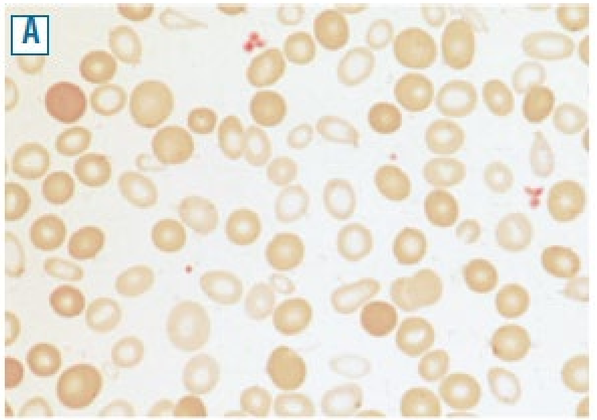

3 months
Oral Iron




MCV 72 fL
TSat 25%
Ferritin 125 ng/mL
TIBC 380 mcg/dL
Corrected retic 0.8%

MCV 70 fL
Tsat 35%
Ferritin 215 ng/mL
TIBC 370 mcg/dL
Corrected retic 0.8%

Peripheral smear



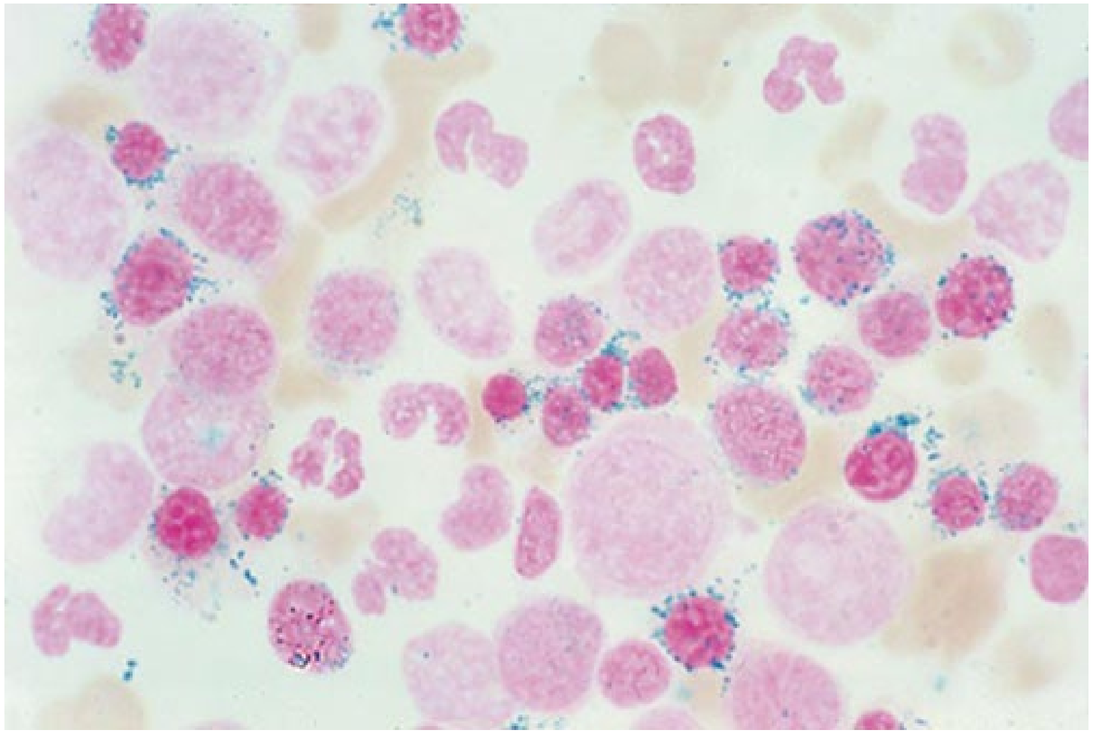

Dimorphic population of macrocytes and hypochromic microcytic RBCs

Additional lab results:
CRP and ESR normal
Hemoglobin Electrophoresis normal
Alpha globin DNA sequencing normal



Cazzola M Haematologica 2011

# Bone Marrow Aspirate with Iron Stain:



Prussian blue stain demonstrating ringed sideroblasts

# Differential Diagnosis for Sideroblastic Anemia

**Congenital:**

X-linked mutations in ALAS2, or other mutations which impact heme biosynthetic or metabolic pathways

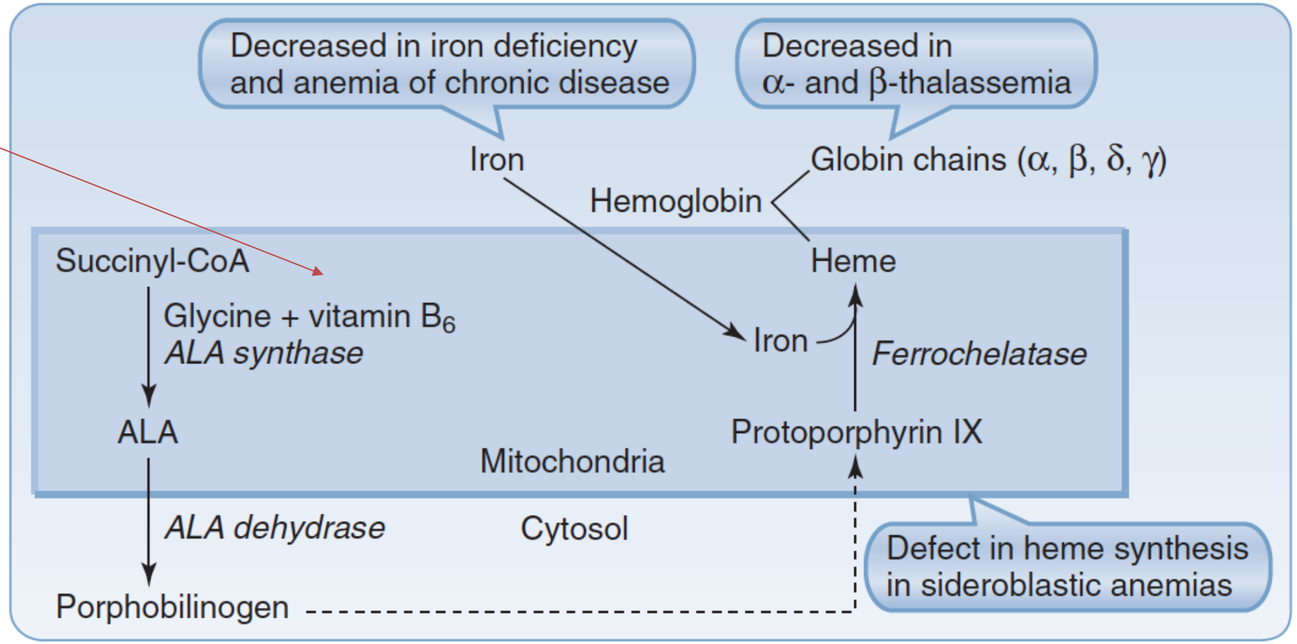
**Acquired:**

Clonal- Myelodysplasia with ringed sideroblasts, +/- thrombocytosis

Metabolic-
Copper Deficiency (Zinc excess)
Drugs (isoniazid, linezolid)
Excessive alcohol use
Hypothermia

Patient reports she was on isoniazid (INH) for tuberculosis prophylaxis

INH depletes Vitamin B6 (Pyridoxine)

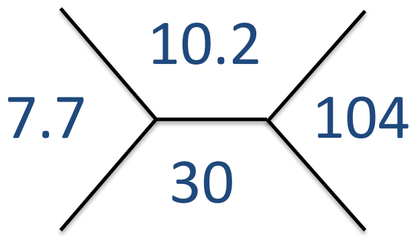



**12-8:** Pathophysiology of microcytic anemias. All microcytic anemias have a decrease in hemoglobin synthesis. A decrease in hemoglobin synthesis could be due to a decrease in the synthesis of heme or a decrease in the synthesis of globin chains. *ALA,* Aminolevulinic acid.



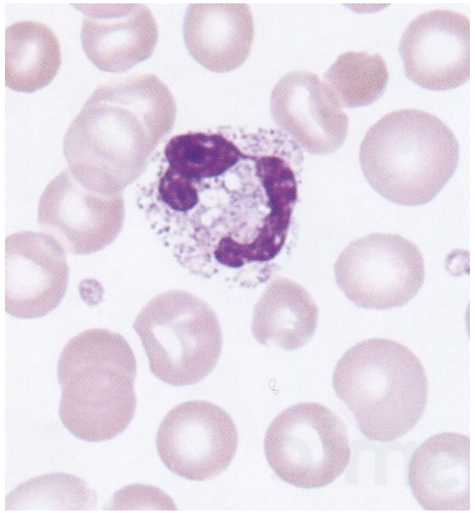
https://www.studyblue.com/notes/note/n/microcytic-anemia/deck/15362551

**Case 2**: 71-year-old male with history of relapsing polychondritis and fevers, poorly responsive to glucocorticoid therapy and oral methotrexate.  The patient has been off methotrexate for 6 months, but the rheumatologist notices that the patient has a persistent macrocytic anemia and asks if a bone marrow biopsy is needed?




MCV 119 fL
Corrected Retic 0.9%

## Peripheral blood smear

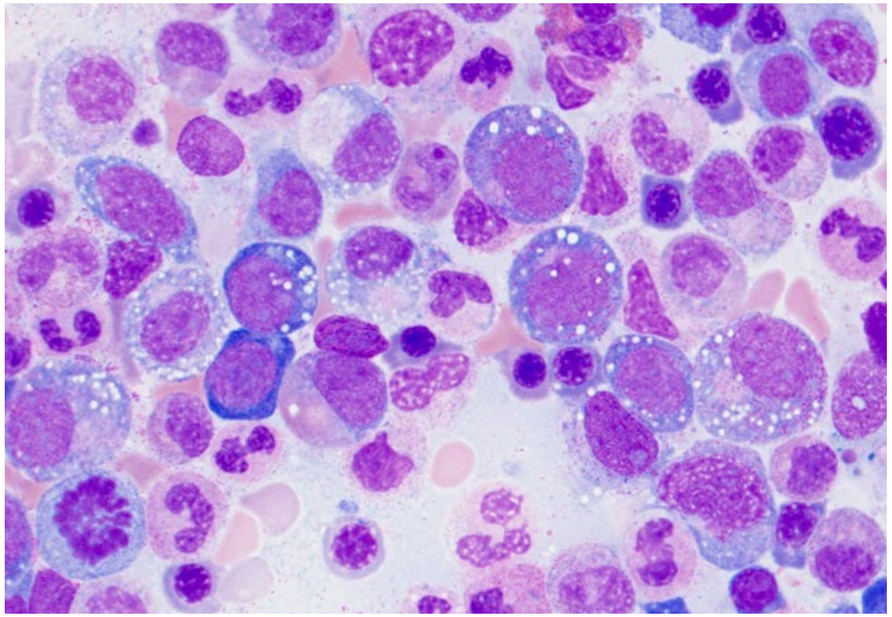


Macrocytes and neutrophils w/ toxic granulations and cytoplasmic vacuoles

**Additional lab results**

Vitamin B12: 807 pg/mL
Folic acid >20
Copper: 94ug/mL (nL)
CRP/ESR: **elevated**
Ferritin: **945 ng/mL**
Normal LFTs, TSH
Denies ETOH

# Bone Marrow Evaluation



Erythroid and megakaryocytic atypia with cytoplasmic vacuoles in erythroid precursors

Normal MDS FISH panel and cytogenetics
Myeloid NGS gene panel negative

? Drug/Toxin
? Infection/Inflammation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

Beck DB et al NEJM 2020

**V**acuoles
**E**1 enzyme (*UBA1*)
**X**-linked
**A**uto-inflammatory
**S**omatic

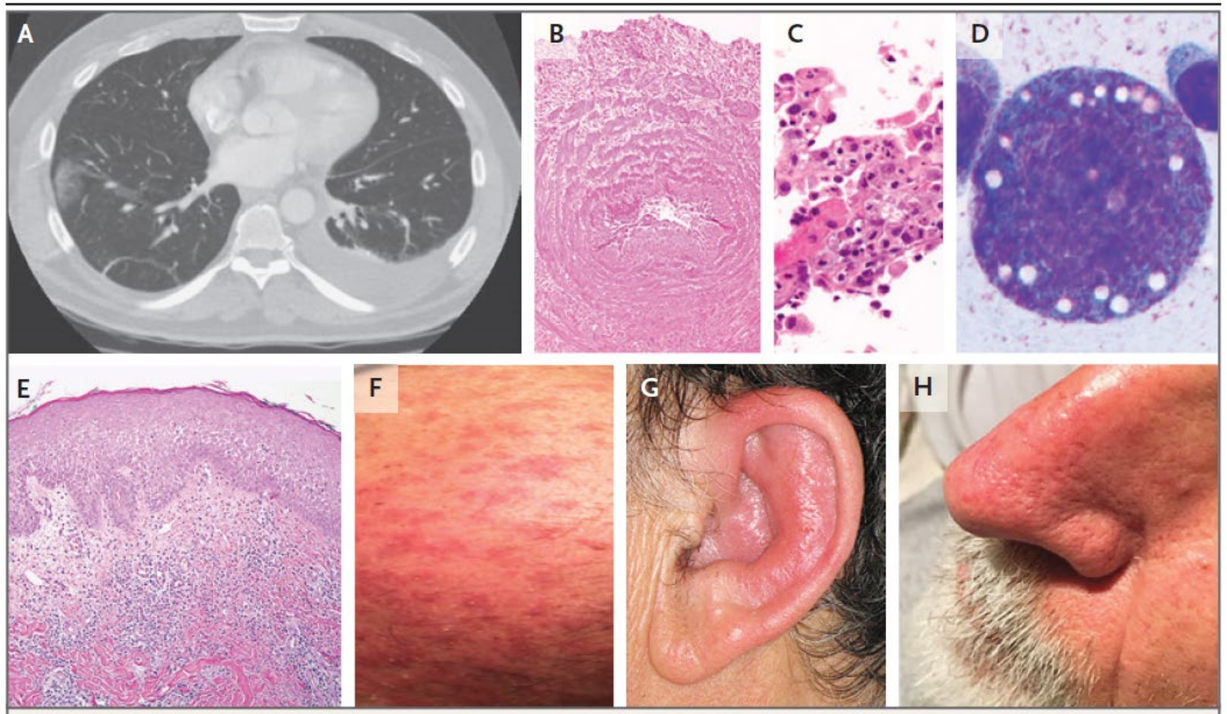



Figure 2. Clinical Manifestations of the VEXAS Syndrome.

| Key clinical features | |
|---|---|
| Fever — no. (%) | 23 (92) |
| Skin involvement — no. (%)† | 22 (88) |
| Pulmonary infiltrate — no. (%) | 18 (72) |
| Ear and nose chondritis — no. (%) | 16 (64) |
| Venous thromboembolism — no. (%) | 11 (44) |
| Macrocytic anemia — no. (%) | 24 (96) |
| Bone marrow vacuoles — no./total no. (%) | 18/18 (100) |

**UBA1 mutation detected**

**Case 3**: 45-year-old male is being evaluated by primary care for polycythemia. Hematocrit is 58% with an elevated serum erythropoietin and negative JAK2V617F DNA test. He smokes 1-2 cigarettes per day. He has no history of chronic obstructive lung disease or obstructive sleep apnea. You are asked if additional hematologic work-up is needed?

# Differential Diagnosis for Polycythemia

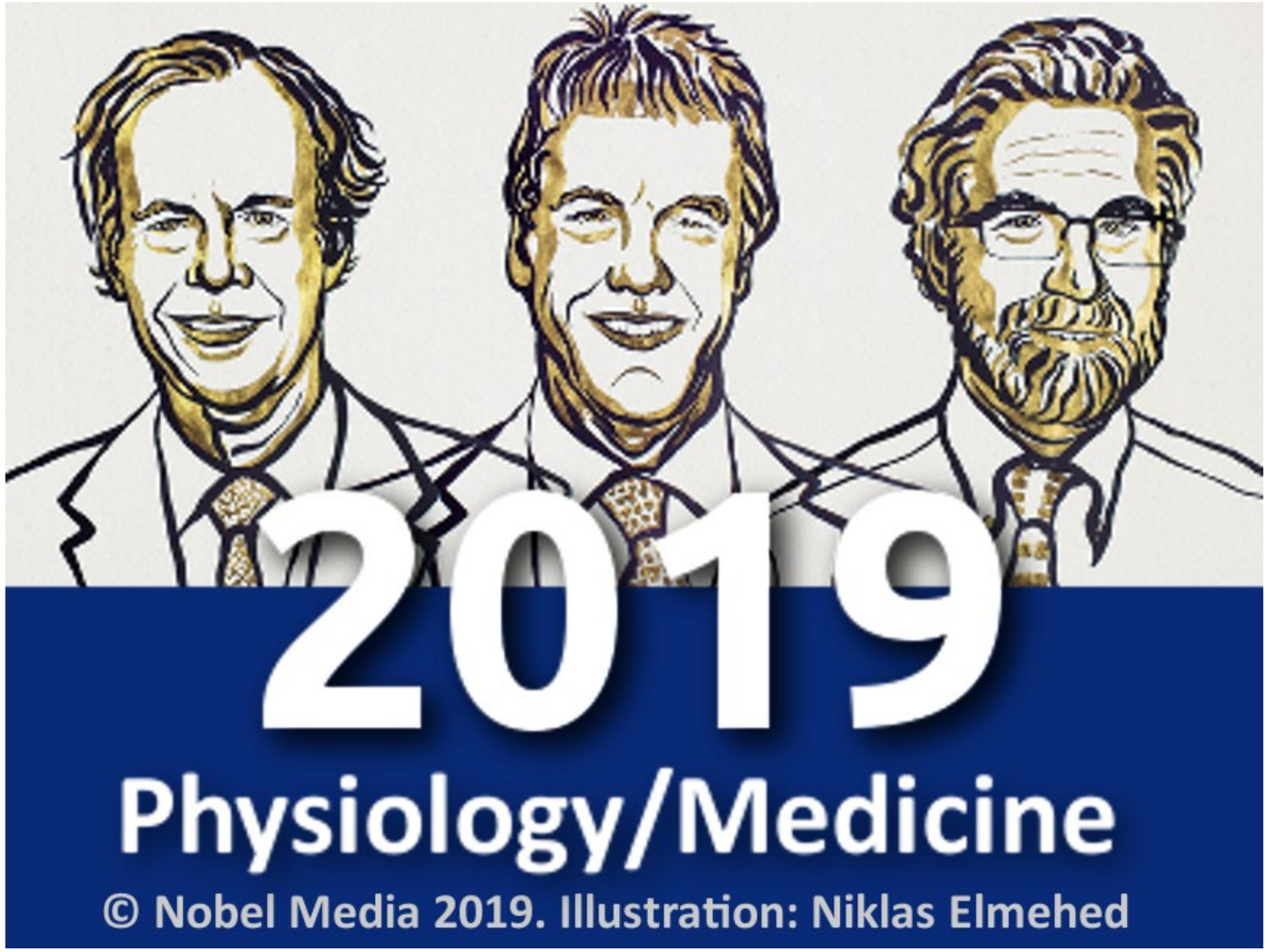
**Congenital:**
epoR mutations
Von Hippel Lindau mutations (Chuvash Polycythemia)
High oxygen affinity hemoglobin
Other mutations

**Relative Polycythemia:**
Volume Contraction– Smoking, Dehydration, Diuretics

**Secondary (Compensatory):**
Chronic Obstructive lung disease
Obstructive Sleep apnea
Chronic carbon monoxide
High Altitude living
Right to Left Cardiac Shunt
Obesity-Hypoventilation

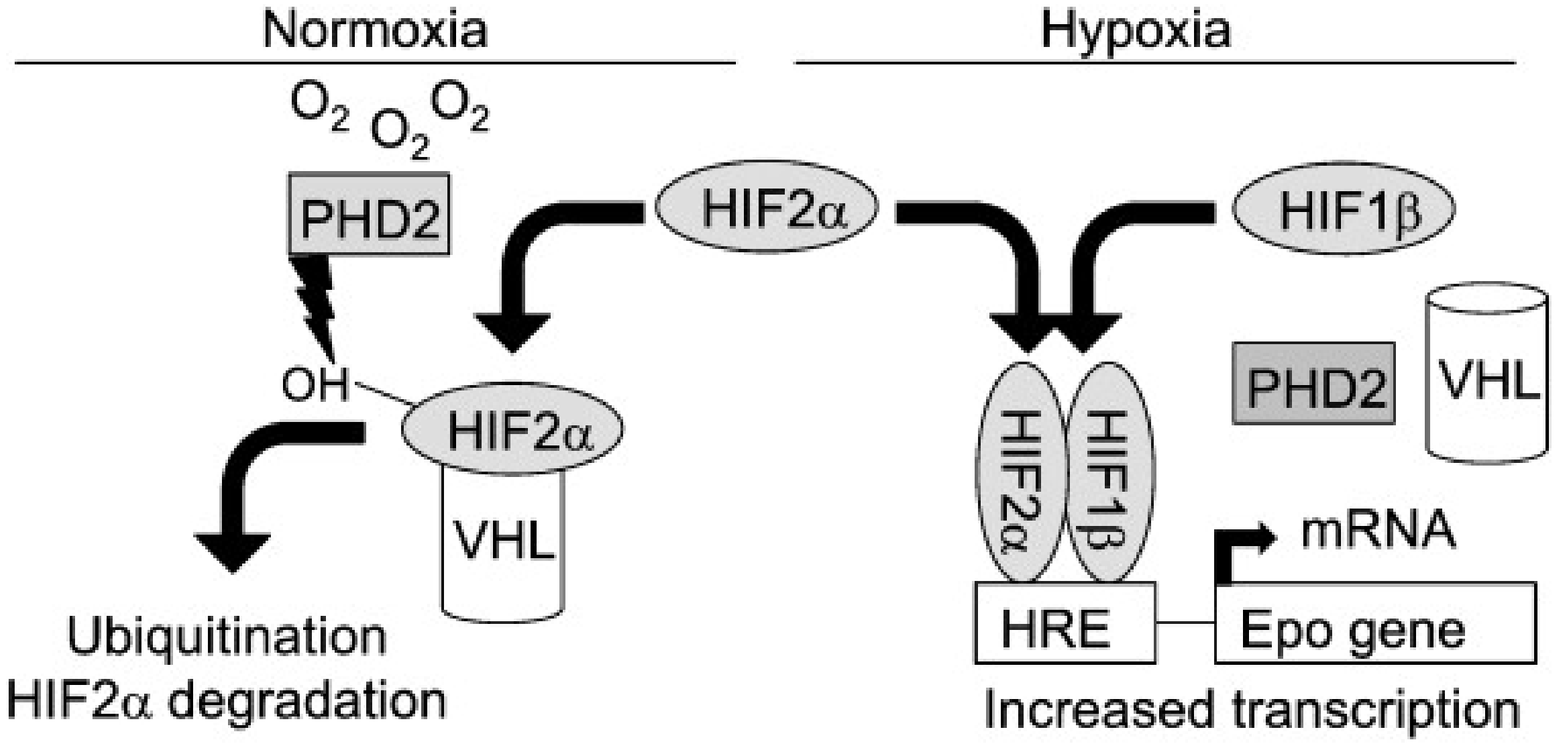
**Acquired:**
Polycythemia Vera (JAK mutations)
Other myeloproliferative neoplasms
Hepatocellular or Renal Cell Carcinoma
Syndromic: POEMS, TEMPI
Renal artery stenosis
Post-Kidney Transplant

**Medications/Drugs:**
Testosterone/Anabolic Steroids
ESAs
Luspatercept
SGLT2 inhibitors (empagliflozin)
Autologous blood doping




How cells sense and adapt to oxygen availability

# Low oxygen environments stimulate EPO transcription






*Lee G et al. European J Internal Med 2015*

## Test results for Case 3

- Hgb 18.4 g/dL, Hct 58%
- WBC and PLT normal
- JAK2V617F not detected
- Erythropoietin **54 IU/L** (nL 4-21)
- Chest X-Ray Normal
- Pulmonary Function Tests Normal
- Sleep Study Normal
- Carboxyhemoglobin **2.7%**

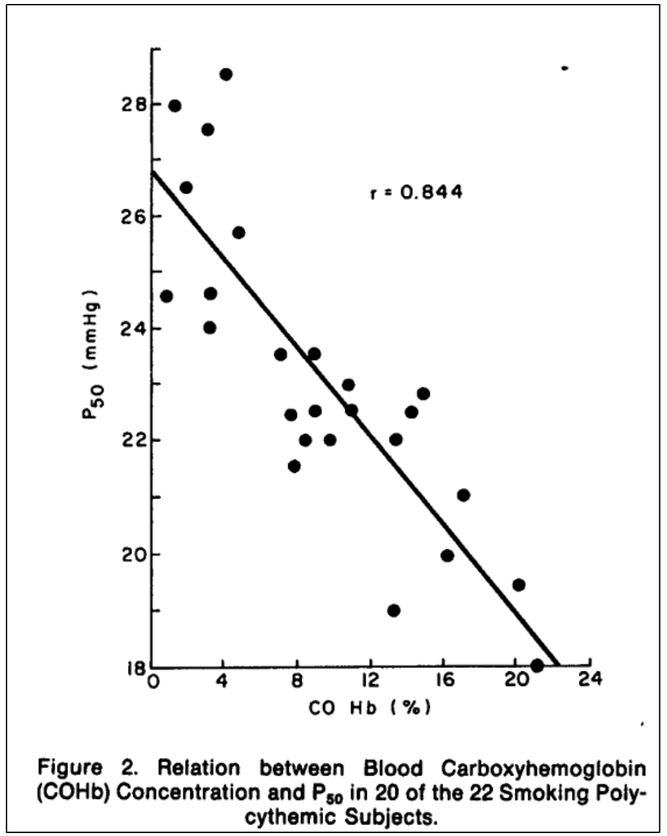


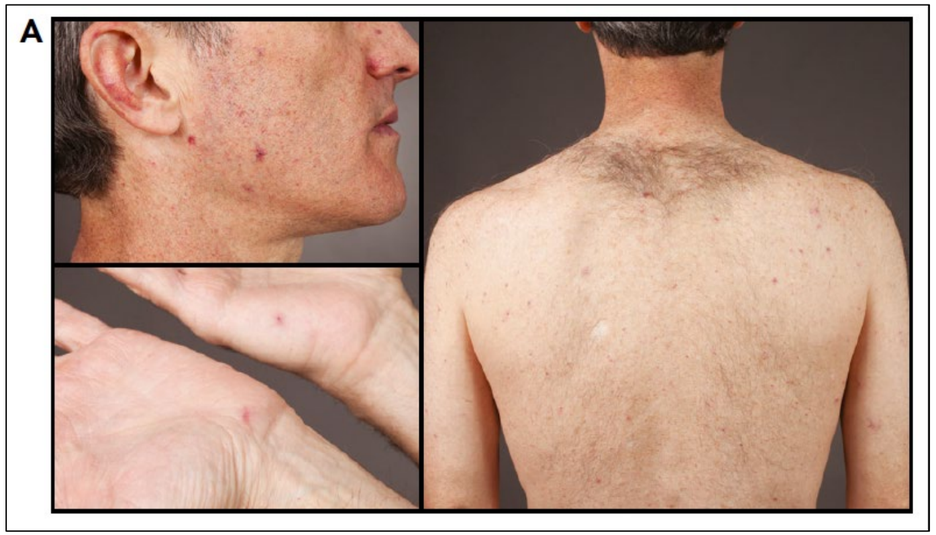

Figure 2. Relation between Blood Carboxyhemoglobin (COHb) Concentration and $P_{50}$ in 20 of the 22 Smoking Polycythemic Subjects.

Smith RJ NEJM 1978

Lower P50 = left shift of Hgb–Oxygen dissociation curve

Non-smokers: Average P50 26.7
(0.6% carboxy-hgb)

**Case 3**: The patient returns 1 year later, after pursuing an observational approach. He was able to quit smoking, but he reports increasing fatigue and headaches. He has noticed a 15-lb weight loss and new skin lesions




Sykes DB et al. Blood 2020

Hematocrit now 62%
and serum erythropoietin 2,400 IU/L

?? Epo secreting tumor

# Tumor associated polycythemia:

Infrequently observed, but includes 1-5% of renal cell carcinomas, and 3-12% of hepatocellular carcinomas

Also reported in hemangioblastoma, pheochromocytoma, uterine myomata

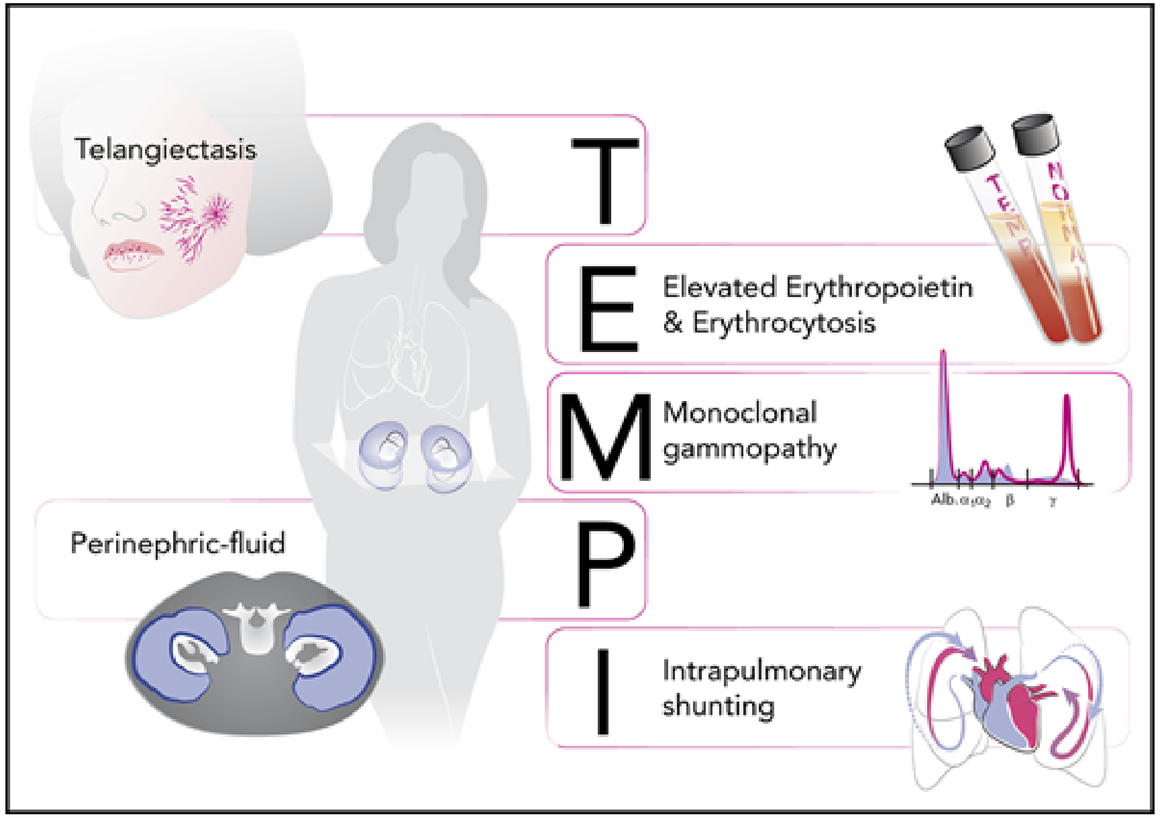


Da Silva et al. Blood 1990;
Sakisaka S et al. Hepatology 1992

## Chest/Abdomen/Pelvis CT

No evidence of malignancy is identified, but a **perinephric fluid collection** is detected, without renal cysts.

SPEP demonstrates 0.7 g/dL IgG-K Monoclonal protein

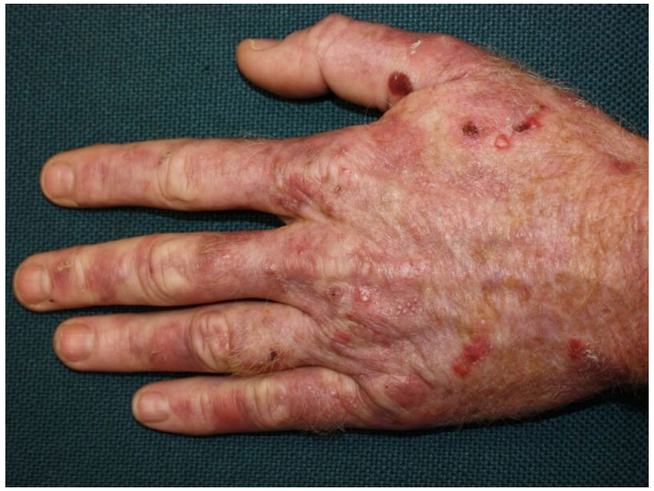





Sykes DB et al. Blood 2020

**Case 4**:  45-year-old male presents with painful blistering on the hands. He has a history of ETOH use and hepatitis C.

CBC with mild anemia (11.5g/dL) and thrombocytopenia (115k)
Ferritin is elevated at 345, Iron saturation 35%
HFE DNA screen is negative
ALT is mildly elevated at 45, with normal AST



blistering skin lesions, sun exposed skin

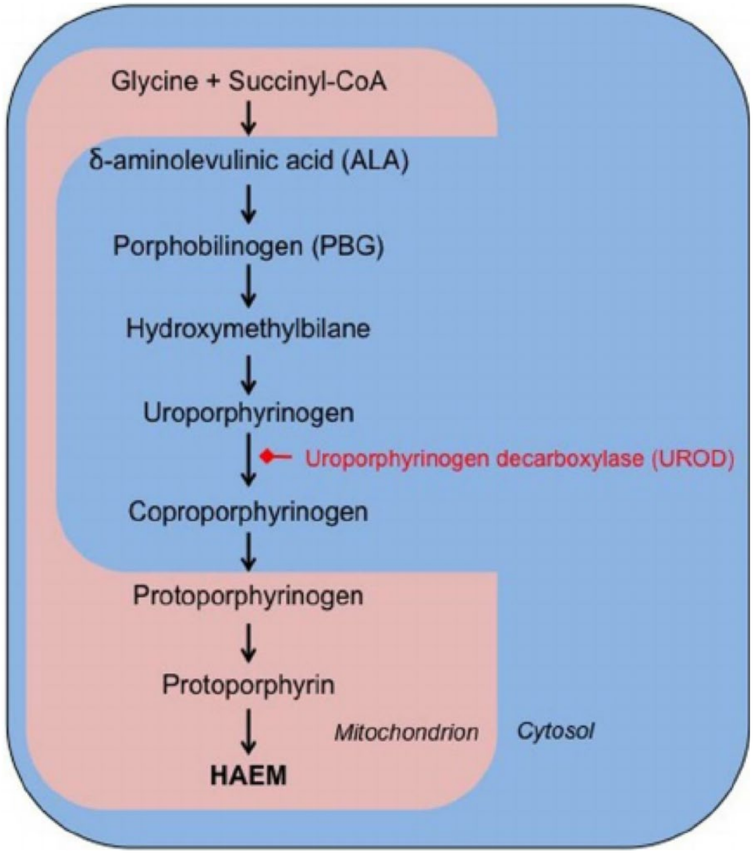
stat pearls: acute porphyria

## Case 4: Question

Acquired porphyria cutanea tarda (PCT) is suspected. Which is a feature of acquired PCT?

A. Responsiveness to vitamin B6
B. Defect in ferrochelatase activity
C. Build up of metal free protoporphyrin
D. Iron dependent UROD inhibition

# PCT: Inherited or Acquired deficiency of UROD

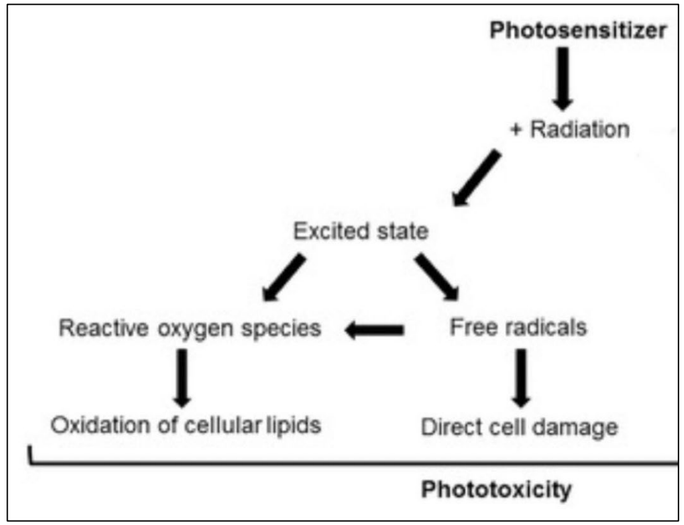



Plakke M et al. BMJ Case Reports 2013

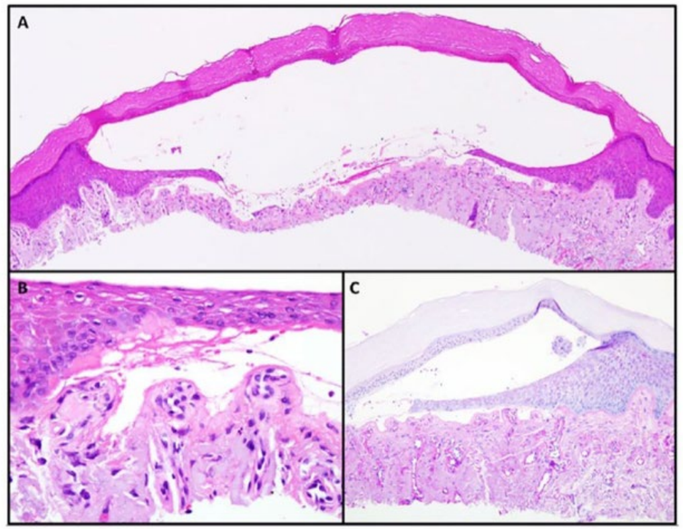
- Iron dependent UROD inhibition (hepatic specific)
- Low UROD activity <20%
- Build up of water-soluble uroporphyrins
- Porphyrins detectable in urine

- Risk factors: Hep C, ETOH, Hemochromatosis

- Treatment with Phlebotomy (ferritin <50) can be effective



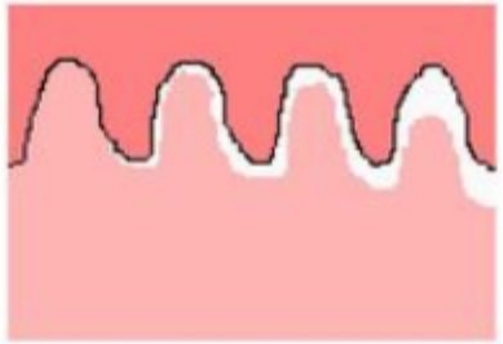

Hofmann GA et al. Dtsch Dermatol Ges 2021




Singh M et al. J Investigative Medicine 2019

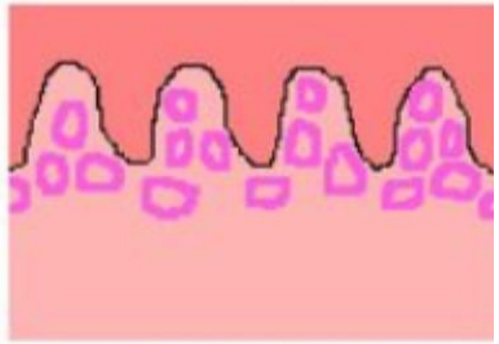
## Skin Histopathology in Porphyria

Slideplayer.com
porphyrias



Subepidermal blister formation with preservation of the shape of the dermal papillae

**Variegate / Cutanea Tarda**

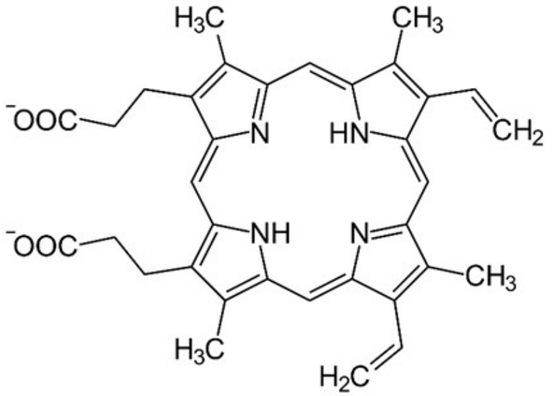


Intensely PAS-positive material deposited thickly around the blood vessels

**Erythropoietic Protoporphyria**

EPP: non-blistering photosensitivity

# EPP due to deficient activity of Ferrochelatase

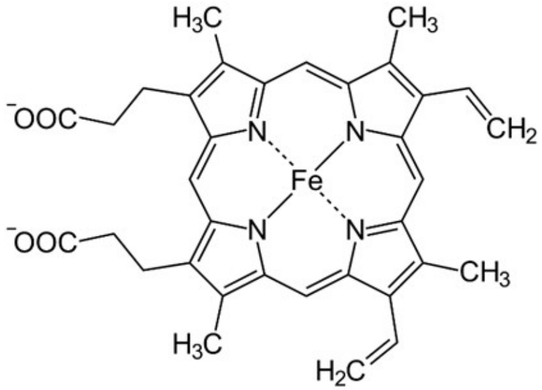



**Protoporphyrin IX (PPIX)**

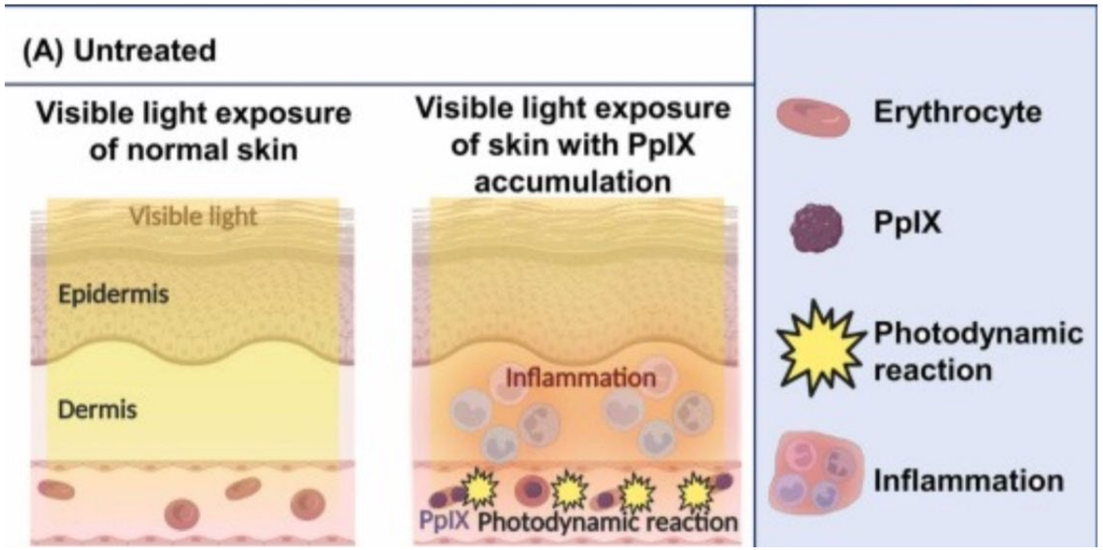
Ferrochelatase

$Fe^{++}$

Zinc incorporated when Fe++ unavailable



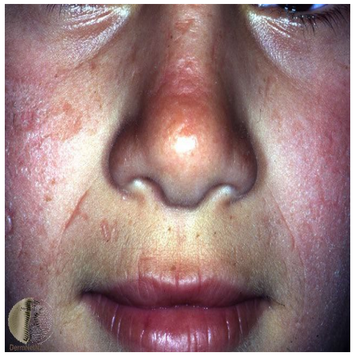

**Heme**




EPP: accumulation of lipid soluble Metal free protoporphyrin (PPIX)

Immediate photosensitivity on exposure to visible light

No porphyrins in urine



ASH Image Bank 2013; 17944.

Heerfordt IM et al. Biomedicine and pharmacotherapy 2023

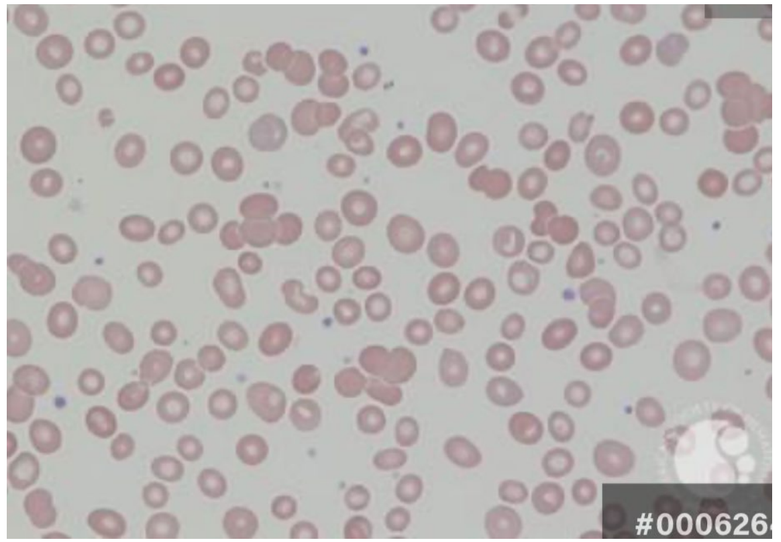
## Case 4: Question

Acquired porphyria cutanea tarda (PCT) is suspected. Which is a feature of acquired PCT?

A. Responsiveness to vitamin B6
B. Defect in ferrochelatase activity
C. Build up of metal-free protoporphyrin
**D. Iron dependent UROD inhibition**

**Case 5**: A previously healthy 34-year-old female presents to her family physician because of increasing fatigue and abdominal pain. She also states that her urine appears brown in color.  Ultrasound shows a portal vein thrombosis. Laboratory studies show:

RBC: 3 million/$mm^3$ (3.5-5.5 million)
Hemoglobin: 8 g/dL (12-16), Retic 3%
WBC: 3,500/$mm^3$ (4500 -11,000)
Platelets: 100,000/$mm^3$ (150,000-400,000)
Bilirubin 2.4  (0.3-1.0)




ASH image bank Goldberg R

## Case 5: Question

Which of the following best describes the pathophysiology behind this patient's most likely disorder?

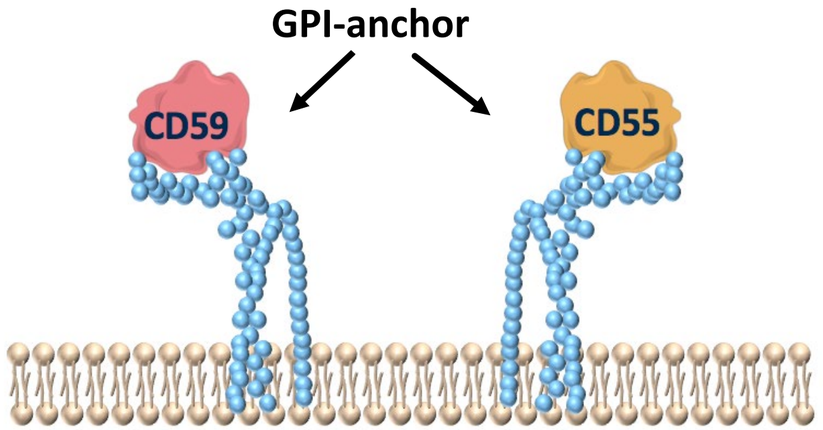
A. Complement-mediated hemolysis of RBC
B. Defect of RBC cytoskeleton-membrane protein
C. Increased oxidative injury
D. IgG bound to the RBC surface

# Paroxysmal nocturnal hemoglobinuria (PNH)

- Hematopoietic stem cell disorder (HSC)
- Nonmalignant clonal expansion of HSCs with a somatic mutation of X-linked *PIGA* (needed to synthesize GPI anchors)
- PNH cells lack surface proteins that require a GPI anchor, such as CD55 and CD59, which normally protect against complement-mediated hemolysis

**Clinical triad:**

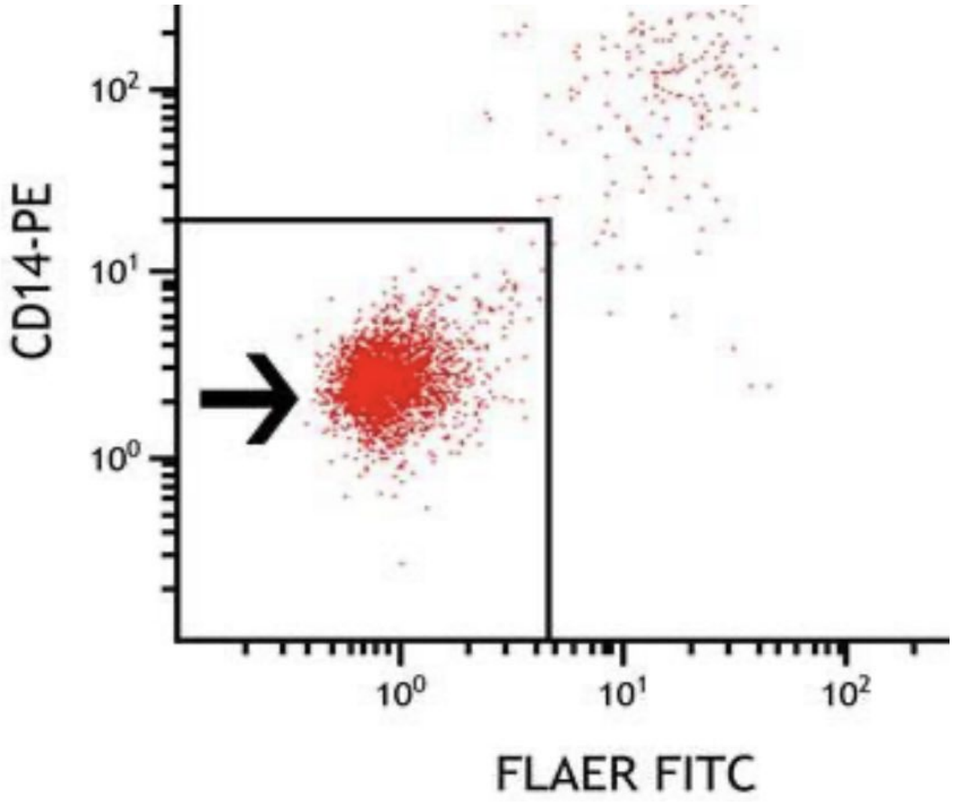
1. Intravascular hemolysis
2. Thrombosis
3. Cytopenia and risk of bone marrow failure



# PNH diagnosis

Flow cytometry:

- Loss of CD55, CD59 on RBC, WBC
- Loss of CD14 Monocytes
- Negative FLAER binding




Patients with hemolytic classic PNH generally have 40 to 99 percent PNH granulocytes, while patients with PNH with associated aplastic anemia have a much smaller percentage

Goldberg R et al. ASH Image Bank

# Case 5: Answer

An otherwise previously healthy 22-year-old female presents to her family physician because of increasing fatigue and abdominal pain. She appears pale despite spending many hours outdoors as a camp counselor. She also states that her urine appears brown in the morning.  Ultrasound shows a portal vein thrombosis. Laboratory studies show:

Which of the following best describes the pathophysiology behind this patient's most likely disorder?

**A. Complement-mediated hemolysis of RBC**
B. Defect of RBC cytoskeleton-membrane protein
C. Increased oxidative injury
D. IgG bound to the RBC surface

Thank you for listening!

Contact:
nburwick@uw.edu

# Thank You.