Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Title: Consultative Hematology

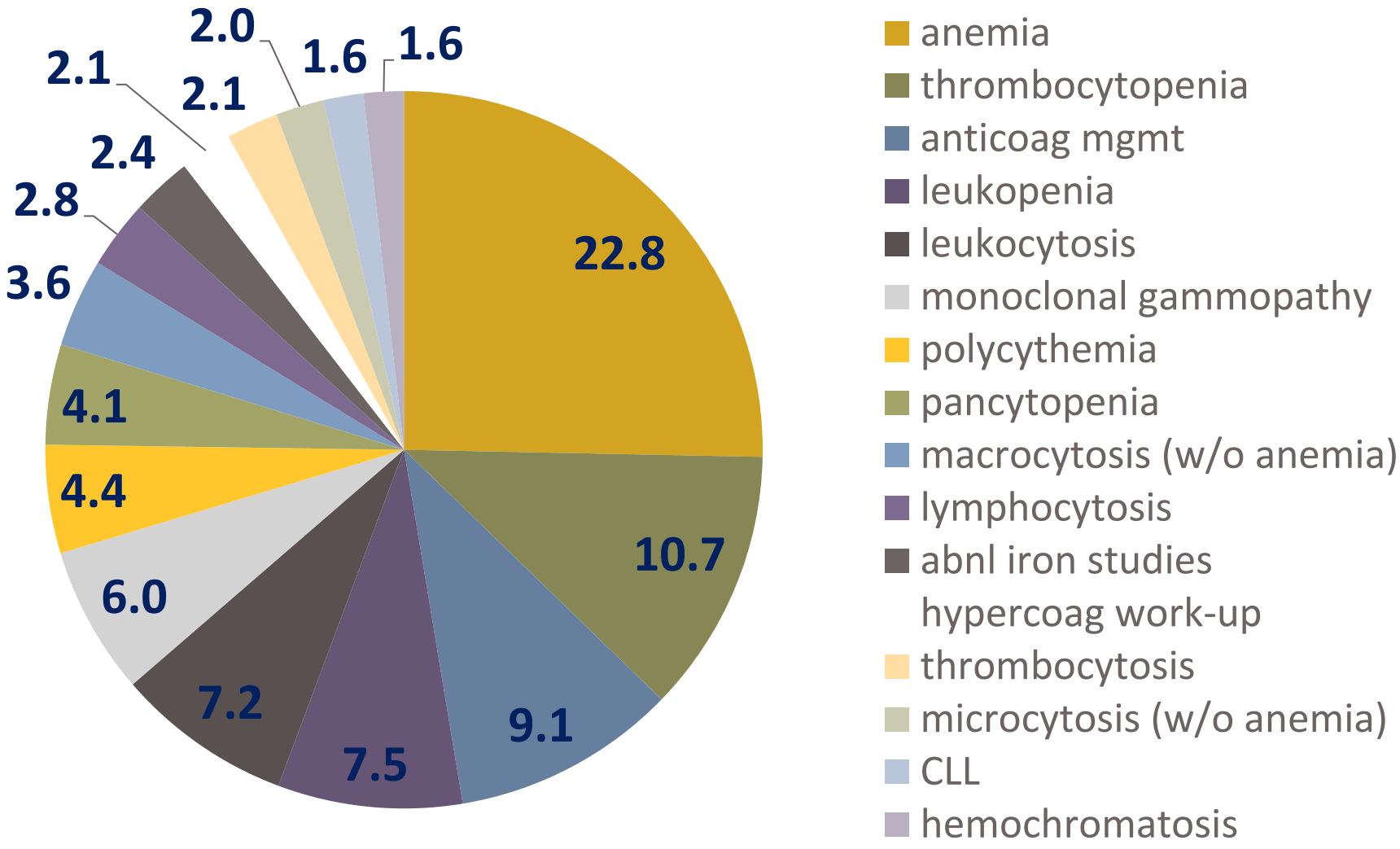
Learning Objectives

- 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Burwick N, Unpublished data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

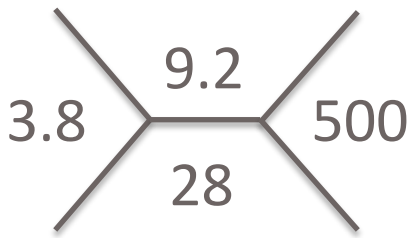
Table 2. Avoided Visit Rates and Primary Reason for e-Consult Across Specialties*

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.

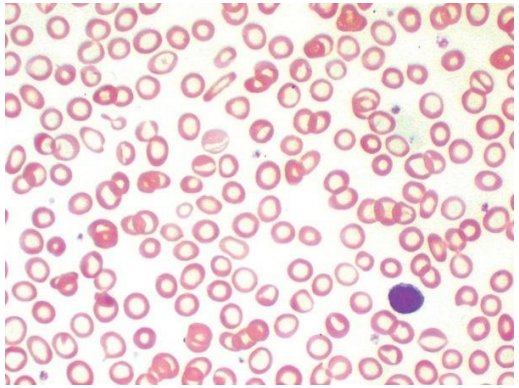


3 months
Oral Iron

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

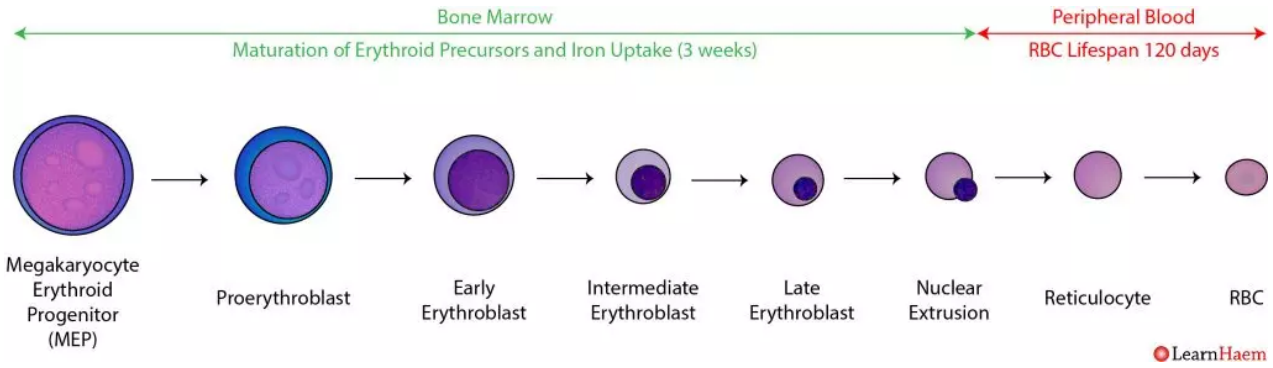
MCV 70 fL
Tsat 10%
Ferritin 10 ng/mL
TIBC 420 mcg/dL
Corrected retic 0.8%

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).

- You recommend holding the PPI and decreasing iron to every other day dosing
- Fecal occult blood testing is performed and returns positive. An EGD is scheduled…

EGD demonstrates *H. pylori* gastritis

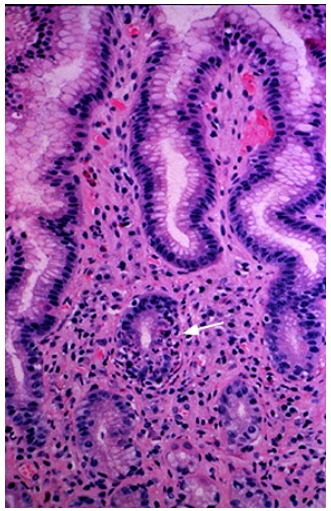
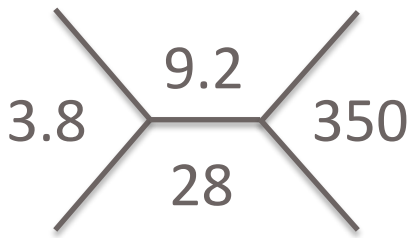


Figure: uptodate

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.



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Ferritin 215 ng/mL
TIBC 370 mcg/dL
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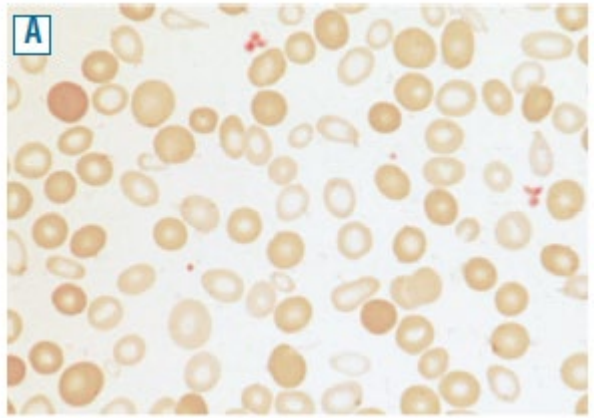
Peripheral smear

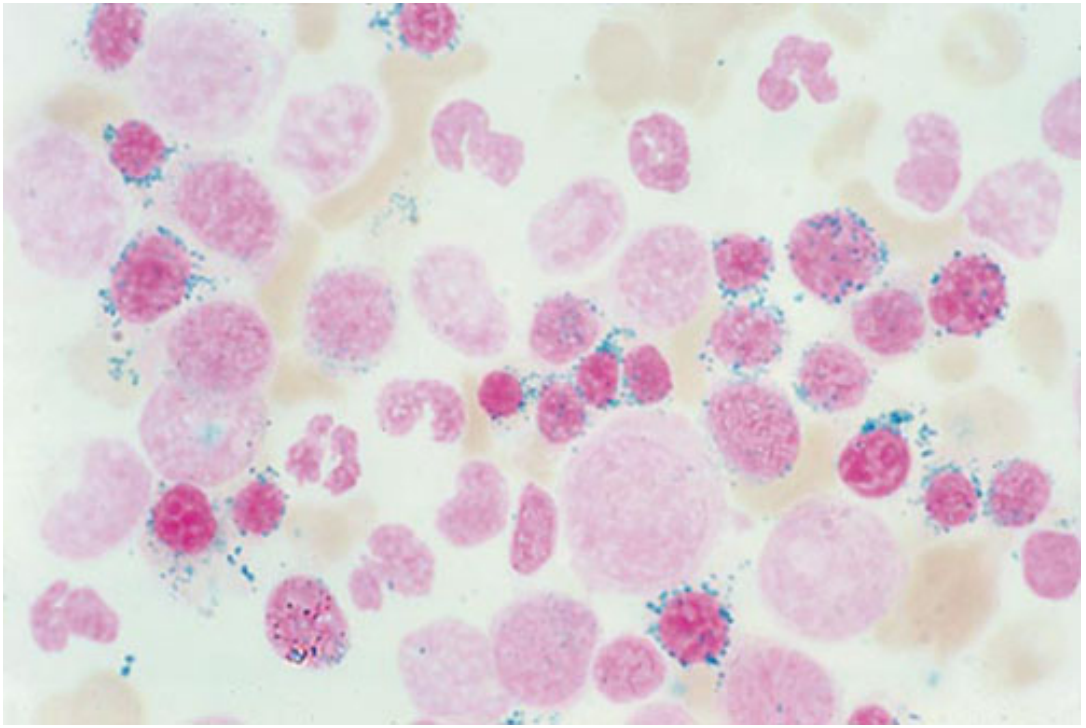


Dimorphic population of macrocytes and hypochromic microcytic RBCs

Cazzola M Haematologica et al. 2011

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

Bone Marrow Aspirate with Iron Stain:



Prussian blue stain demonstrating ringed sideroblasts [5+ iron granules encircling 1/3 or more of the nuclear circumference in erythroid precursors]

Differential Diagnosis for Sideroblastic Anemia

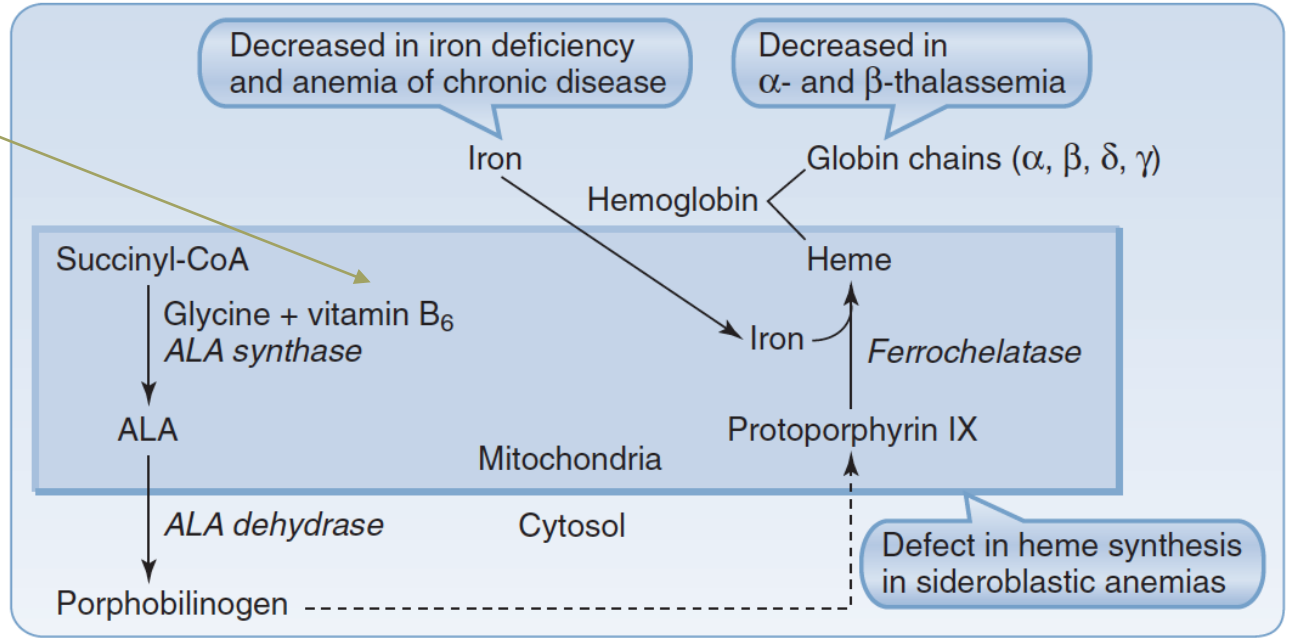
Congenital:
X-linked mutations in ALAS2, or other mutations which impact heme biosynthetic or metabolic pathways

Acquired:
Clonal- Myelodysplasia with ringed sideroblasts, +/- thrombocytosis

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

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

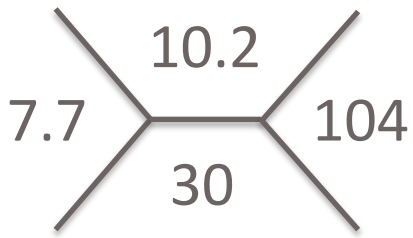
INH depletes Vitamin B6 (Pyridoxine)



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.

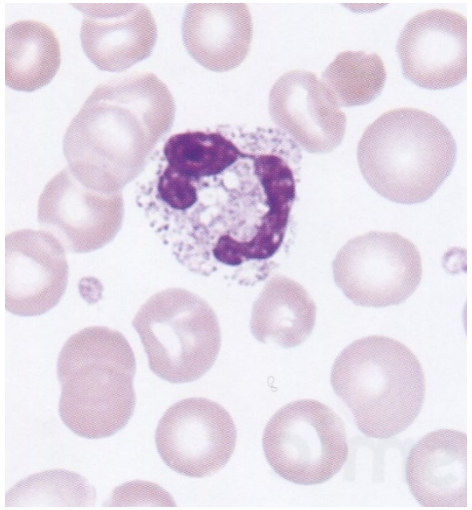
https://www.studyblue.com/notes/note/n/microcytic-anemia/deck/15362551

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%

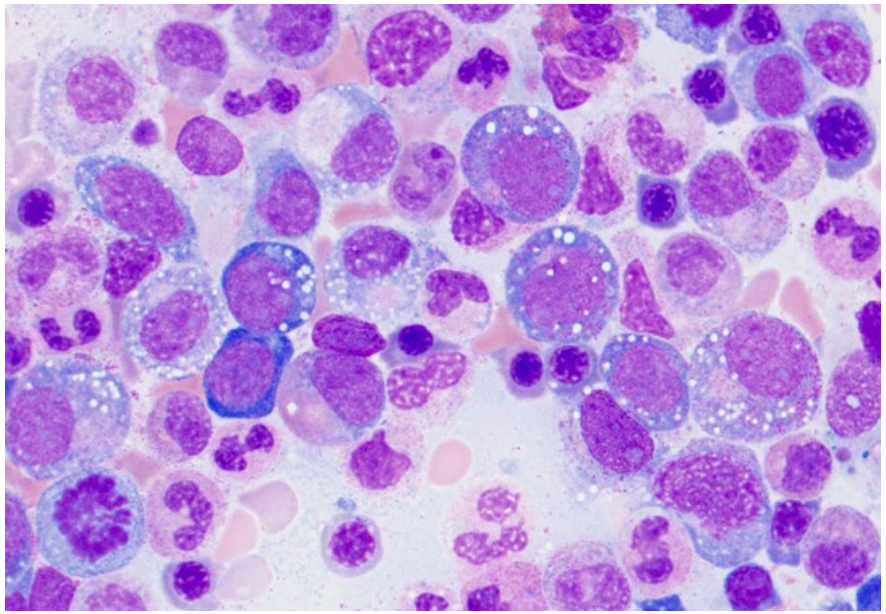
Peripheral blood smear



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

Vacuoles
E1 enzyme (*UBA1*)
X-linked
Auto-inflammatory
Somatic

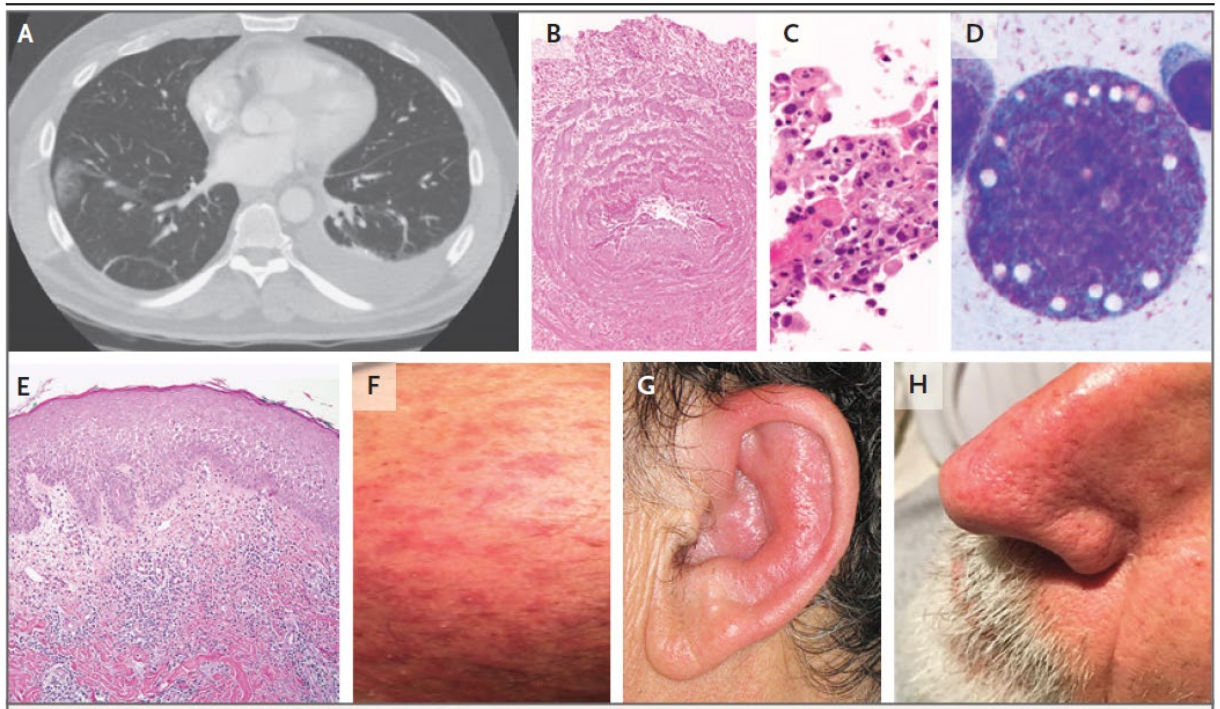


Figure 2. Clinical Manifestations of the VEXAS Syndrome.

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

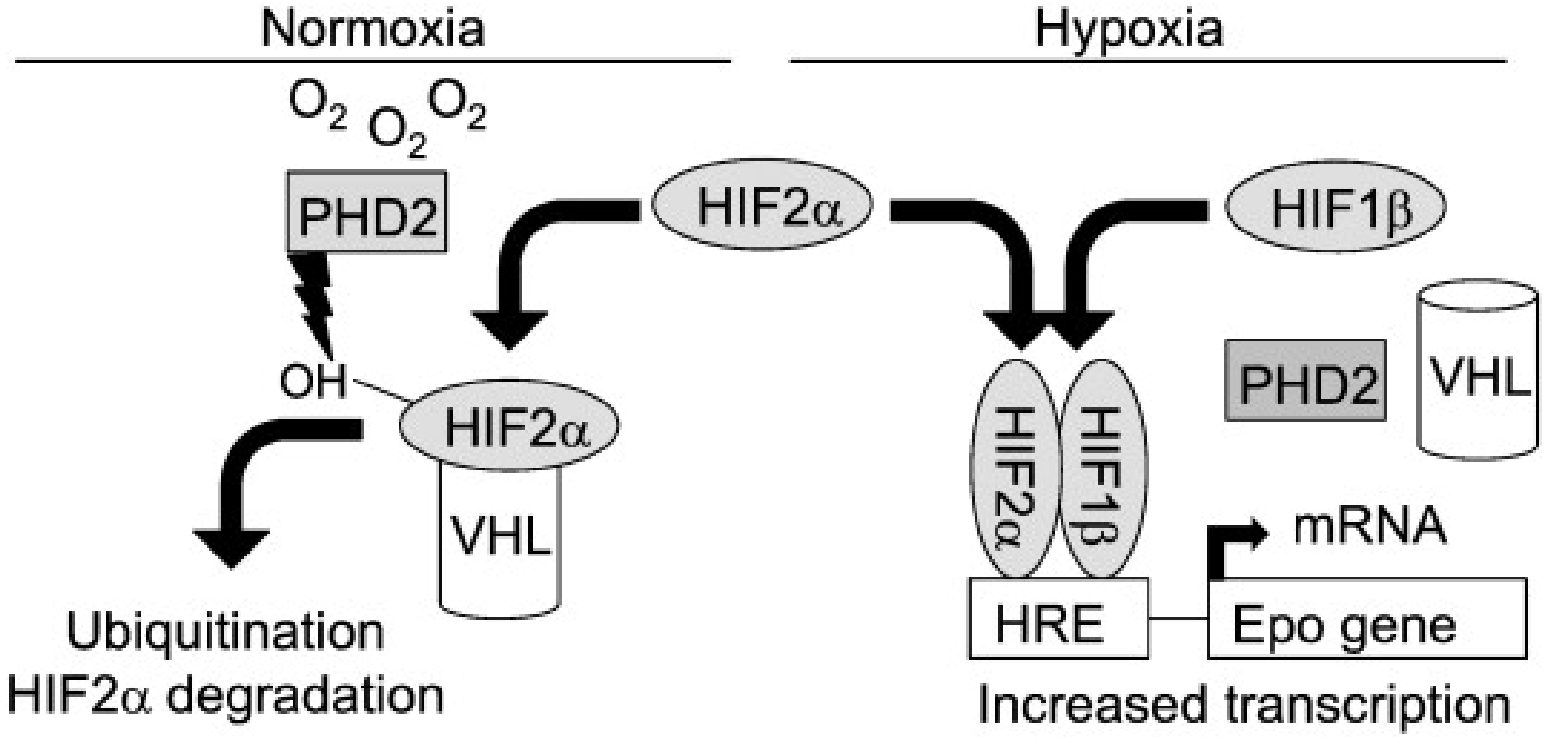
Secondary (Compensatory):
Chronic Obstructive lung disease
Obstructive Sleep apnea
Chronic carbon monoxide
High Altitude living
Right to Left Cardiac Shunt
Obesity-Hypoventilation

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
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%**

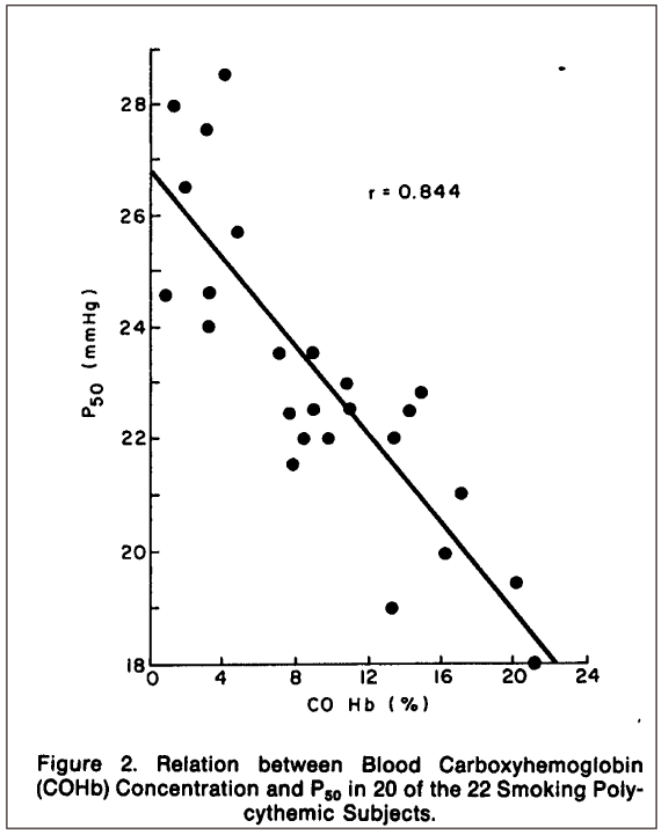


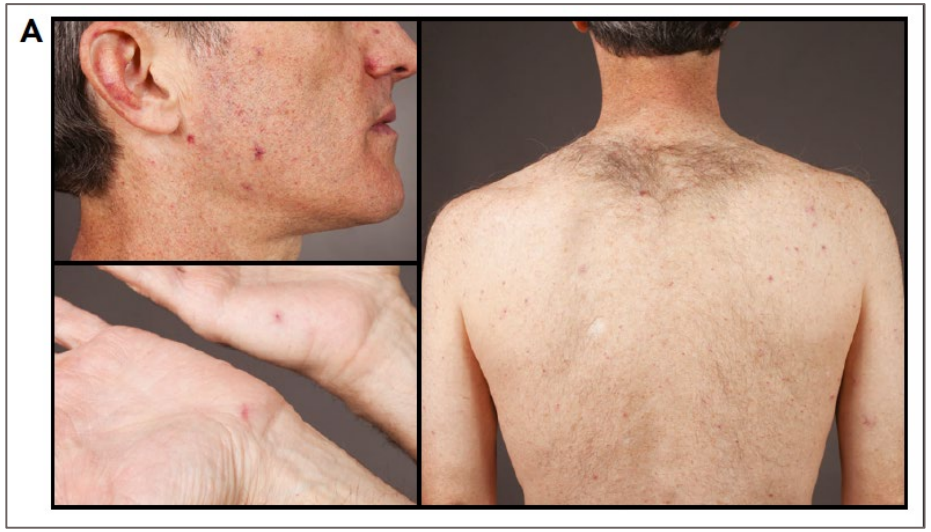
Figure 2. Relation between Blood Carboxyhemoglobin (COHb) Concentration and P_{50} in 20 of the 22 Smoking Polycythemic Subjects.

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 caricnomas, and 3-12% of hepatocellular carcinomas

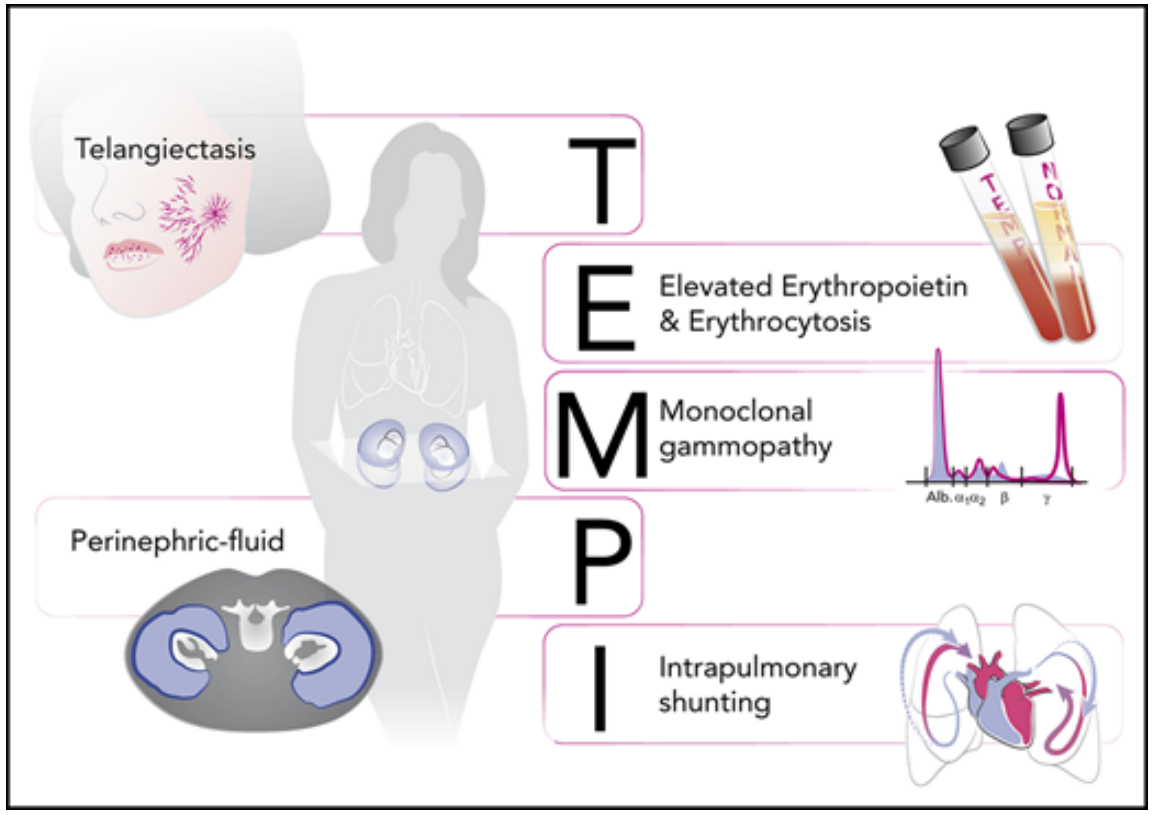
Also reported in hemangioblastoma, pheochromacytoma, uterine myomata

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

Thank you for listening!