HEMATOLOGY CLINICAL PEARLS

Rakhi Naik, MD, MHS

Assistant Professor of
Medicine & Oncology,
Division of Hematology

JOHNS HOPKINS
SCHOOL of MEDICINE

Disclosures

None

Case #1

A 21-year-old Greek female presents to her PCP for establishment of care. She reports 3 months of progressive fatigue but has no other complaints. Family history is notable for anemia in her mother and older sister. Past medical history is positive for mild persistent asthma.

Her CBC reveals:

WBC 6.8 (normal 4.5-11.0 k/cu mm)

Hemoglobin 8.9 (normal 12-15 g/dL)

RDW 20.5 (11.5-15.4%)

Platelets 483 (normal 150-350 k/cu mm)

Case #1

- Which of the following tests is the most appropriate to diagnose the etiology of her anemia?

- A) Iron studies (iron, TIBC, ferritin)
- B) Erythrocyte sedimentation rate (ESR)
- C) Hemoglobin electrophoresis
- D) JAK2 mutational analysis
- E) Bone marrow biopsy

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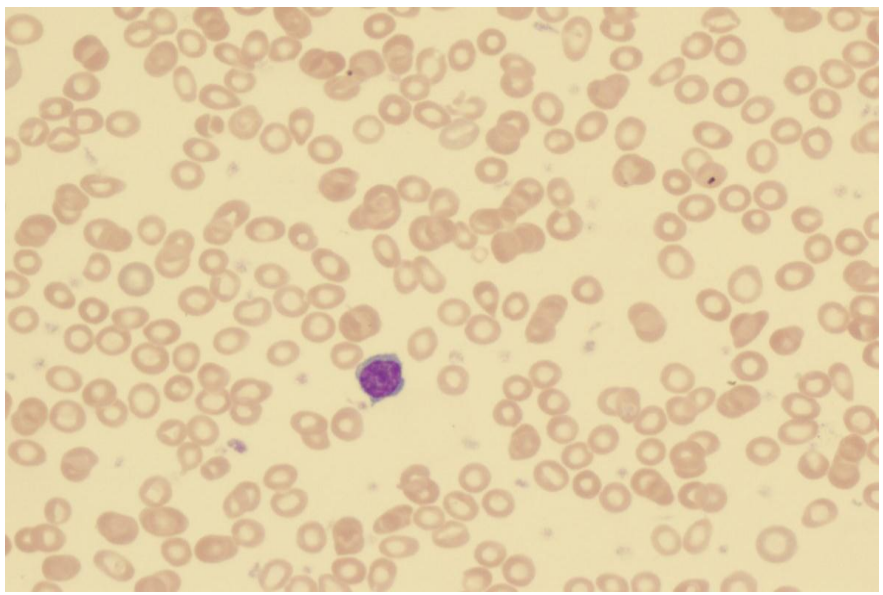
Microcytic Anemias

1. Iron deficiency
2. Anemia of chronic Disease (ACD), especially with severe inflammation/functional iron deficiency
3. Thalassemia – impaired production of either beta or alpha globin chains resulting in low hemoglobin production
4. Sideroblastic anemia (rare)



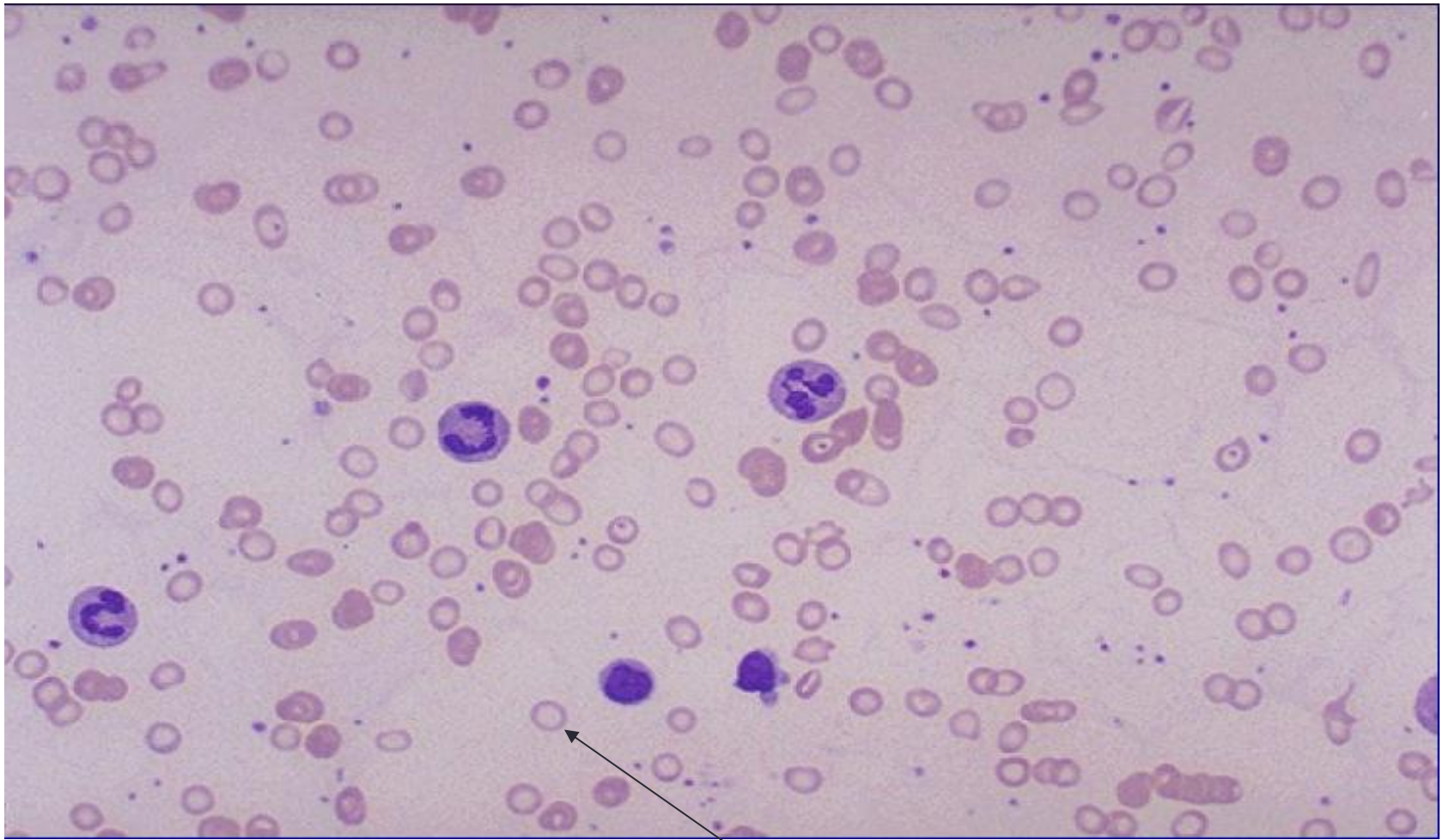
Important Indices in Microcytic Anemias

- MCV – Mean corpuscular volume (normal 80-100 fL)
  - Volume of PRBC/RBC count
  - Defines anemia as either microcytic (<80 fL), normocytic (80-100 fL), or macrocytic (>100 fL)
  - Contrary to popular belief, it is not a reliable marker to distinguish iron deficiency from thalassemia
- RDW – RBC distribution width (12 -15.5%)
  - Coefficient of variation of RBC volume
  - Indicates the variability in RBC size so is high in low iron states
- Platelet count (150-350 k/cu mm)
  - Can be elevated in iron deficiency (unclear mechanism) and ACD (inflammation)

Iron Studies in Microcytic Anemias

- **Percent transferrin saturation**
  - Ratio of serum iron to TIBC plasma
  - Measure of bound transferrin, which is the iron transporter protein
  - Carries less than 1% of total body iron
- **TIBC (total iron binding capacity)**
  - Indirect measure of transferrin
- **Ferritin**
  - Intracellular storage of iron
  - Only cause of low ferritin is IRON DEFICIENCY

Iron indices	Iron deficiency	ACD	Thalassemia
Iron	Low	Low	Normal/high
TIBC	High/normal	Low/normal	Normal
% saturation	Low	Low	Normal/high
Ferritin	Low	High	Normal/high



Marked hypochromasia, microcytosis

Case #2

An 83 year old male patient is followed in your clinic for iron deficiency anemia. Last year, he underwent an extensive GI evaluation with EGD, colonoscopy, and capsule study which revealed multiple small bowel AVMs. Over the past year, he has been taking TID oral iron supplementation and has required 3 hospitalizations for symptomatic anemia requiring transfusion. His last transfusion of PRBCs was 1 week ago.

His labs reveal:

Hemoglobin 10 (normal 13-17 g/dL)

MCV 83.2 (normal 80-100 fL)

Serum Iron 53 (normal 50-170 mcg/dL)

% Saturation 20 (normal 20-38 %)

Ferritin 3 (normal 10-300 ng/mL)

Case #2

- Which of the following is the most appropriate next step in management?

- A) Increase oral iron supplementation to QID dosing
- B) Initiate iv iron therapy
- C) Order scheduled q4 month transfusions
- D) Send anti-tissue transglutaminase Abs
- E) Obtain a repeat colonoscopy
- F) Perform a bone marrow biopsy

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TABLE 1. CAUSES OF IRON DEFICIENCY.

Inadequate absorption

Poor bioavailability
Antacid therapy or high gastric pH
Excess dietary bran, tannin, phytates, or starch
Competition from other metals (e.g., copper or lead)
Loss or dysfunction of absorptive enterocytes
Bowel resection
Celiac disease
Inflammatory bowel disease
Intrinsic enterocyte defects

Increased loss

Gastrointestinal blood loss
- Epistaxis
- Varices
- Gastritis
- Ulcer
- Tumor
- Meckel's diverticulum
- Parasitosis
- Milk-induced enteropathy of early childhood
- Vascular malformations
- Inflammatory bowel disease
- Diverticulosis
- Hemorrhoids

Genitourinary blood loss
- Menorrhagia
- Cancer
- Chronic infection

Pulmonary blood loss
- Pulmonary hemosiderosis
- Infection

Other blood loss
- Trauma
- Excessive phlebotomy
- Large vascular malformations

TABLE

Representative average wholesale prices* for various iron supplement formulations

Iron supplement group	Generic or brand name	Dosage	Cost of 1-month course
Ferrous salts	Ferrous sulfate (generic)	Tablet: 325 mg po tid	$0.63 to $5.11 (90 tabs)
	Ferrous fumarate (generic)	Tablet: 300 mg (99 mg iron) po bid	$1.80 (60 tabs)
	Ferrous gluconate (generic)	Tablet: 325 mg (36 mg iron) po tid	$2.70 to $5.00 (90 tabs)
Controlled-release	Slow FE (Novartis)	Tablet: 160 mg (50 mg iron) po tid	$18.92 (90 tabs)
	Ferro-Grad-500 (Abbott)	Tablet: 105 mg iron po bid	$31.84 (60 tabs)
Polysaccharide–iron complex	Niferex-150 (Schwarz Pharma)	Capsule: 150 mg iron po qd	$10.50 (30 caps)
Carbonyl iron	Feosol (SmithKline Beecham)	Tablet: 50 mg iron po tid	$18.38 (90 tabs)

*2001 Drug Topics, Red Book. Daily dosages given here deliver 150 to 210 mg of elemental iron and are for comparison of average costs. Actual dosage should be adjusted according to the calculated need for iron replacement and the results of laboratory monitoring.

Indications for iv Iron

- Failure of oral iron from GI intolerance
- Failure of oral iron due to absorption issues
  - H pylori infection, autoimmune gastritis, celiac disease, gastric bypass surgery, inflammatory bowel disease
- Anemia with chronic renal disease (with or without[?] dialysis dependance)
- Heavy ongoing GI or menstrual blood losses

Bastit et al JCO 26: 1511-1618 2008

Henry et al The Oncologist 2007;12:231–242

	Lmw Iron Dextran	Iron Sucrose	Ferric Gluconate	Ferumoxytol	Ferric Carboxy maltose
Administered Dosage	100mg	200 mg	125 mg	510mg	750mg
Total Dose Infusion	1000 mg	no	no	1020 mg 3d apart	1500mg 7d apart
Cost	Inexpensive	Inexpensive	Inexpensive	Expensive	Expensive
Indication	IDA	IDA in CKD	IDA in CKD/HD +epo	IDA in CKD	IDA + IDA in CKD
Test dose	Yes	none	none	None	None
Administration	Iv (preferred) or im	Iv push or 15m infusion	i.v push or 1hr infusion	17s i.v push or 15 m infusion	7.5 m iv push or 15 m infusion

Case #3

A 65 year-old male patient of yours presents to clinic for follow-up after a recent hospitalization for acute gastroenteritis. He has no past medical history and reports that he has been feeling much better after discharge. In the hospital, an conscientious resident sent an SPEP which revealed a 0.24 g/dL IgG-kappa M-spike.

You send additional labs which reveal a normal CBC and CMP. Kappa/lambda light chain (LC) studies show a kappa LC level of 18.3 (normal 3.3-19.4 mg/L), lambda LC level of 13.0 (normal 5.7-26.3 mg/L), and a normal ratio of 1.4 (normal 0.26-1.65).

Case #3

- What is the appropriate next step in management of this patient?

- A) Bone marrow biopsy
- B) Skeletal survey
- C) Small bowel biopsy for amyloidosis
- D) Yearly monitoring for symptoms and labs
- E) No further work-up

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Tests for Workup for MGUS

- Immunoglobulin quantification
  - Will see reciprocal depression in more advanced cases
- Serum protein electrophoresis (SPEP)
  - Used to quantify an M-spike
  - Can be negative in light chain only disease
- Serum IFE (immunofixation electrophoresis)
  - Will tell you the type of immunoglobulin (IgG, IgA, IgM)
  - Can also detect the corresponding light chain but may also miss light chain only disease
- Kappa/lambda light chains
  - Should be sent with any MGUS to quantify free light chains
  - UPEP/IFE usually sent if ratio is abnormal to look for Bence Jones proteinuria (free light chains in the urine)
- Skeletal survey
  - Can be deferred in low risk MGUS unless symptomatic

Who will transform to Myeloma?

Risk higher if:

1. Larger M-spike (>1.5g/dL)
2. Non IgG (IgM or IgA)
3. Abnormal free light chain ratio

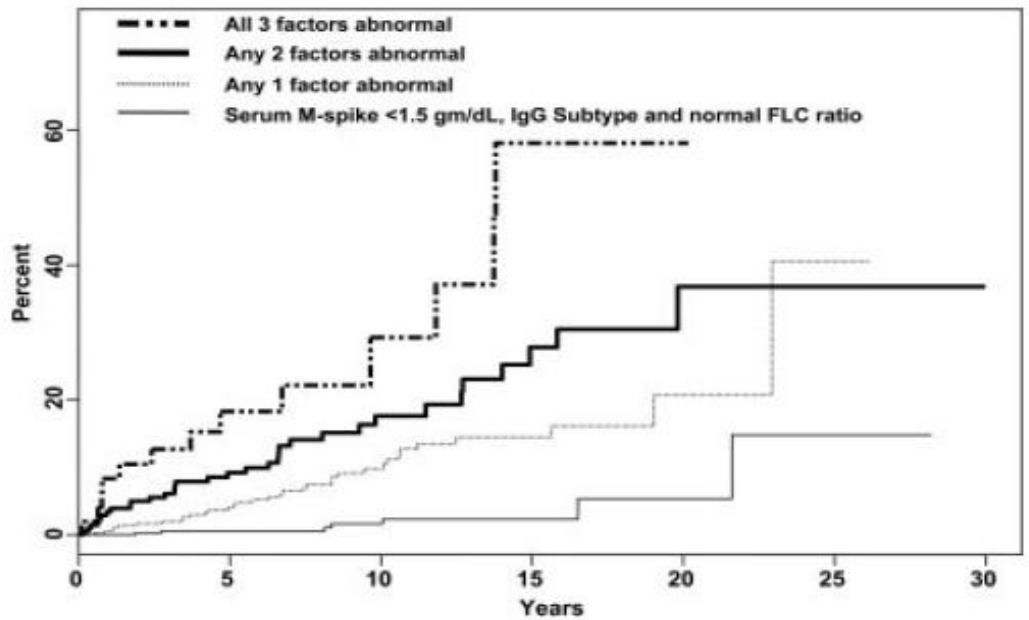
Who will transform to Myeloma?

3 risk factors (high-risk MGUS) — 58 percent

2 risk factors (high-int risk MGUS) — 37 percent

1 risk factor (low-int risk MGUS) — 21 percent

no risk factors (low-risk MGUS) — 5 percent



Monitoring MGUS

- Yearly counts, CBC, CMP, SPEP/SIFE, kappa/lambda LC
- New symptoms such as bony pain, weight loss, fever, night sweats
- CRAB criteria – hyperCalcemia, Renal disease, Anemia, Bony lesions
- Amyloidosis symptoms – Neuropathy, nephrotic range proteinuria, restrictive cardiomyopathy
- Lymphadenopathy, hepatomegaly, or splenomegaly

Case #4

A 43 year-old female presents to your clinic for her annual physical. She has no complaints and no chronic medical problems other than moderate obesity. She has never smoked cigarettes and drinks social alcohol only. Exam is normal.

Her CBC reveals:

WBC 11.6 (normal 4.5-11.0 k/cu mm)

Hemoglobin 17.5 (normal 12-15 g/dL)

Hematocrit 52.5 (normal 36-46%)

Platelets 453 (normal 150-350 k/cu mm)

You send an epo level which is slightly low at 2.0 (normal 2.6-18.5 mIU/mL). You also notice she has had borderline high platelet counts around 400k for the last 5 years.

Case #4

- What is the appropriate next step in management of this patient?

- A) Obtain a sleep study
- B) Order a renal ultrasound
- C) Send for JAK2 mutational analysis
- D) Observation with yearly follow-up
- E) Bone marrow biopsy

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- A) Obtain a sleep study
- B) Order a renal ultrasound
- **C) Send for JAK2 mutational analysis**
- D) Observation with yearly follow-up
- E) Bone marrow biopsy

Causes of Erythrocytosis

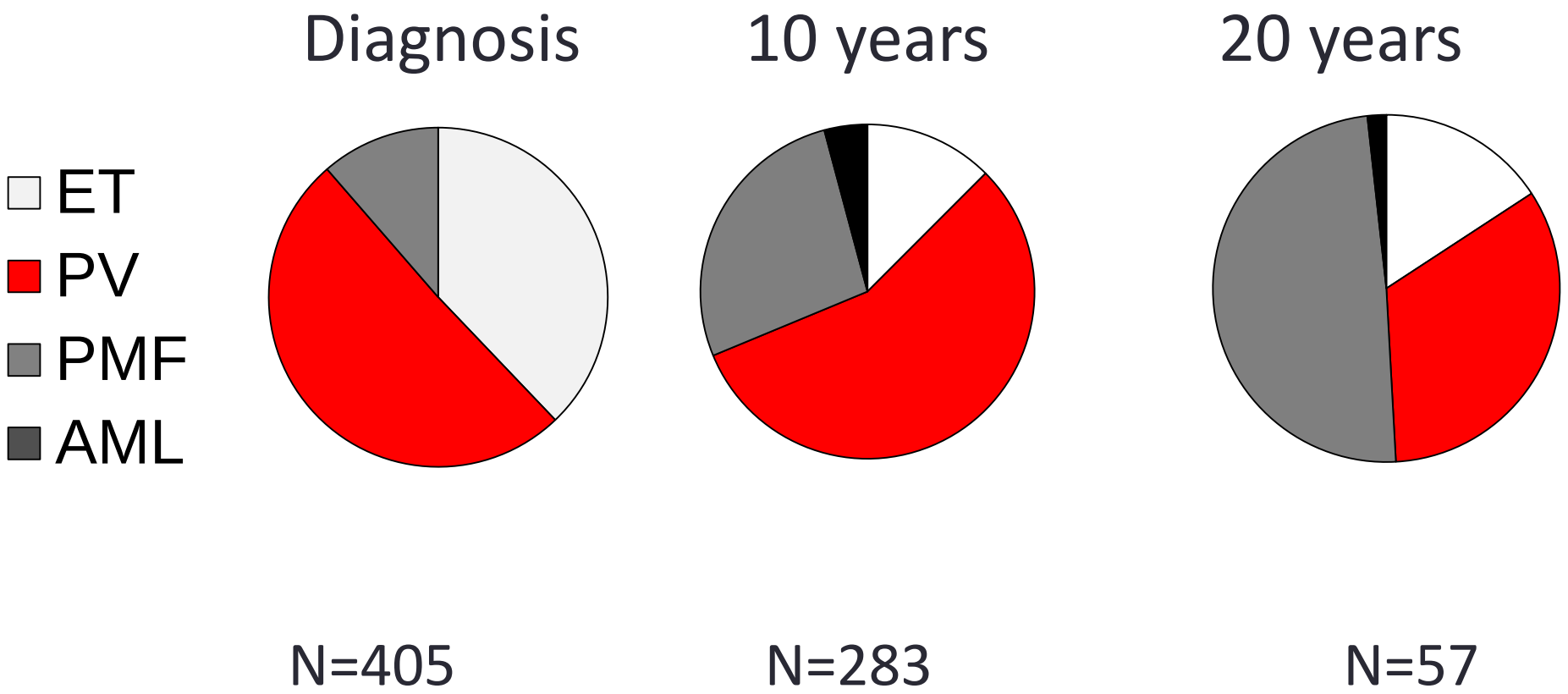
- Chronic hypoxia
  - Lung disease
  - Obstructive sleep apnea
  - Cyanotic heart disease
- Smoking
- Renal cell carcinoma (epo-producing tumors)
- Congenital hemoglobin disorders (rare)
- Polycythemia Vera (Primary erythrocytosis)
  - Erythropoetin level will be low or low normal
  - Features more suggestive of a primary bone marrow disorder include: elevated WBC, elevated platelet count, specific symptoms such as recurrent thrombosis, aquagenic pruritus, or splenomegaly

Diagnostic Criteria for PV (Revised WHO)

Major criteria	Minor criteria
1. Increased hemoglobin	1. Bone marrow biopsy with hypercellularity and panmyelosis
Males: ≥18 g/dL	2. Serum erythropoetin below the reference range for normal
Females: ≥16.5 g/dL	3. Endogenous erythroid colony formation in vitro
2. Presence of JAK2 mutation	

Diagnosis requires both major and 1 minor OR
First major and 2 minor

Hopkins500: Natural History



Courtesy of Dr. Moliterno

Treatment of Erythrocytosis

- Secondary causes
  - Treat underlying cause
  - Phlebotomy performed only if severe erythrocytosis (>19.0 g/dL)
- Polycythemia vera
  - Goal of treatment is to 1) treat symptoms if present, 2) prevent complications of thrombosis
  - Generally treatment aims are hematocrit <45% in men, <42% in women
  - Treatment options include phlebotomy, ASA, hydroxyrurea, interferon, ruxolitinib (now approved)

Questions

rakhi@jhmi.edu

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