The Internists Approach to Polycythemia and Implications of Uncontrolled Disease

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Disclosures

NONE

Overview

1. Objectives
2. Case Study
3. Diagnosis of polycythemia
4. Risk factors of polycythemia
5. Treatment strategies
6. Summary

Objectives

- Identification of S & S
- Definition
- Identification of risk factors in hospitalized patient
- Identification of treatment plans in hospitalized patient
- Identification of factors to consider for post op follow up care

Case Study

- 48 yo cau male presented for outpatient cholecystectomy.
- CBC pre op revealed WBC 13,000 Hb 17.1 HCT 51
- Pre Surg clearance requested
- EMR revealed ultrasound of abd hepatocellular dysfunction with partial obstruction of biliary duct and splenomegaly (mild)

History

- ETOH and cocaine abuse-rehabilitated
- Hypertension
- Smoker 2 packs/d
- No hx of DVT
- Works as lawn maintenance
- Degenerative disc disease of lumbar spine
- Pruritus-thinks may be allergies

Diagnosis of Polycythemia

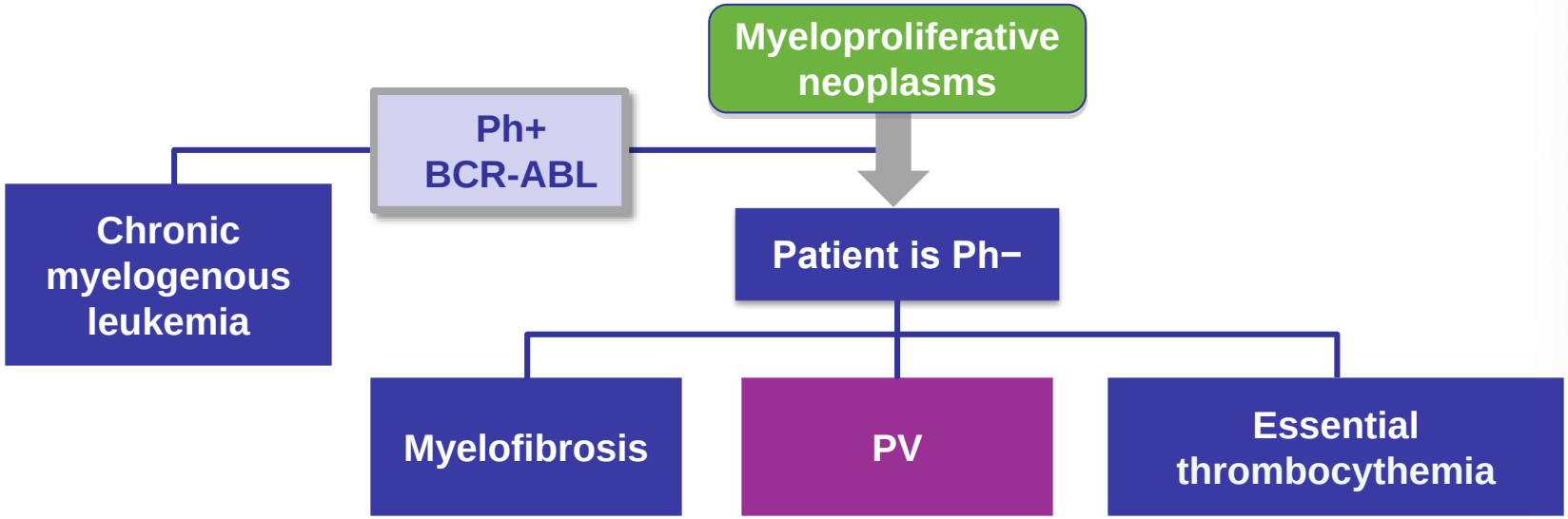
- Definition: Hct > 50
- Primary versus Secondary
- Primary: PRV and implications
- Secondary: chronic hypoxic conditions excess erythropoietin production such as paraneoplastic

Signs & Symptoms

- Fatigue
- Itching
- Headache and blurred vision
- Sweating, numbness of hands and feet
- Excess bleeding from minor cuts
- Bone pain

Polycythemia Rubra Vera

PV is one of the interrelated Ph– myeloproliferative neoplasms



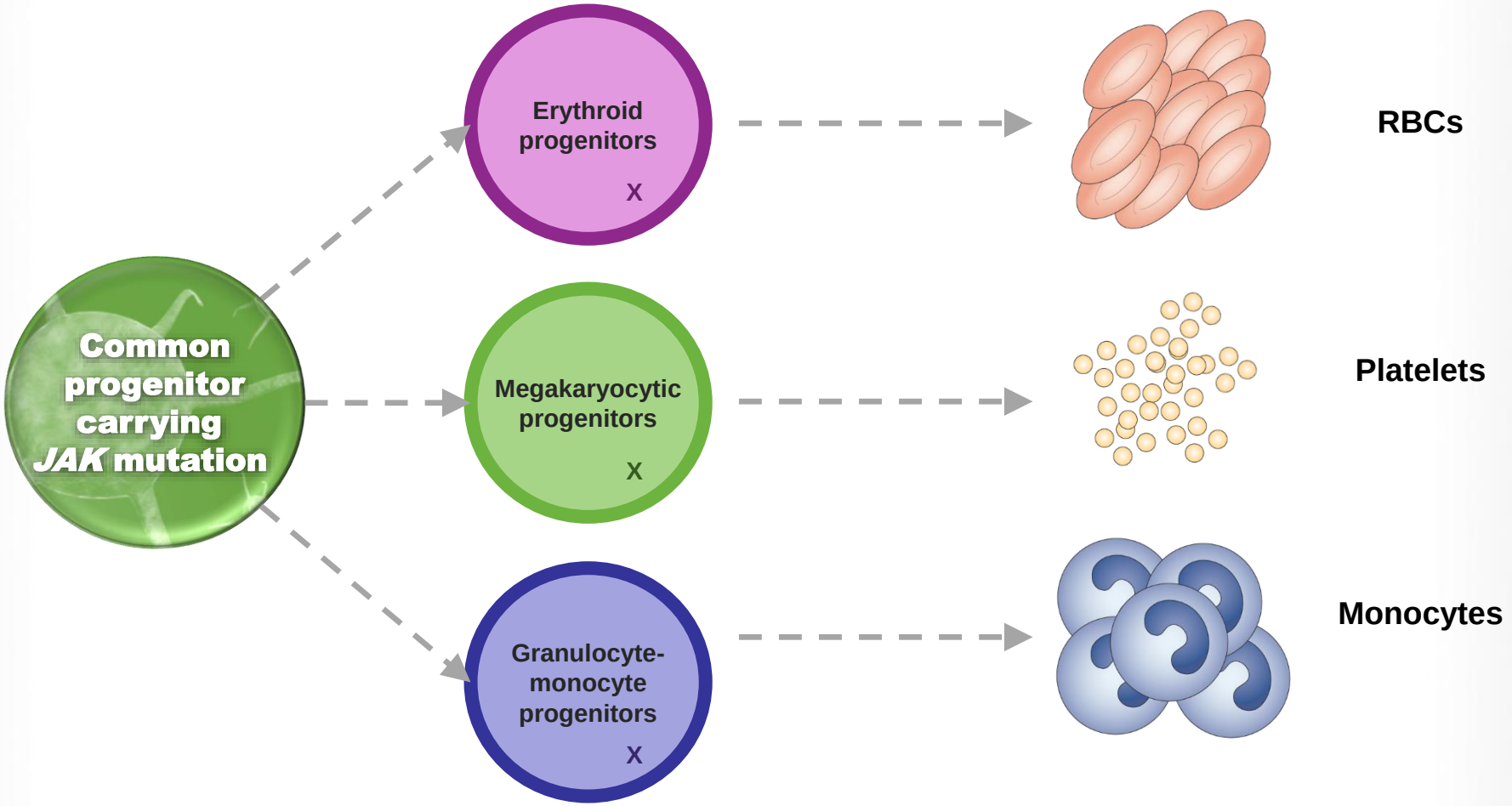
- PV is a trilineage myeloproliferative neoplasm[1-4]
  - Characterized by clonal expansion of abnormal hematopoietic stem cells or progenitor cells driven by JAK pathway overstimulation
- In PV, chronic unregulated proliferation may occur in ≥1 myeloid cell line, including erythrocytes, platelets, and sometimes granulocytes[4,5]

BCR-ABL, breakpoint cluster region−Abelson leukemia virus; JAK, Janus-associated kinase; Ph–, Philadelphia chromosome–negative; Ph+, Philadelphia chromosome–positive; PV, polycythemia vera.

References: 1. Vannucchi AM et al. *Haematologica*. 2008;93(7):972-976. **2.** Vannucchi AM et al. *CA Cancer J Clin*. 2009;59(3):171-191. **3.** Skoda RC et al. *Cancer Cell.* 2011;19(2):161-163. **4.** Delhommeau F et al. *Int J Hematol*. 2010;91(2):165-173. **5.** Spivak JL. *Ann Intern Med.* 2010;152(5):300-306.

Polycythemia Rubra Vera

Overactive JAK pathway signaling is a key driver of pathogenesis leading to overproduction of RBCs, WBCs, and platelets



JAK, Janus-associated kinase; RBC, red blood cell; WBC, white blood cell.

Reference: Levine RL et al. *Nat Rev Cancer*. 2007;7(9):673-683.

Polycythemia Rubra Vera

PV diagnosis[1] and risk assessment[2]

- PV diagnosis requires meeting all 3 major criteria or the first 2 major criteria and the minor criterion

WHO Major Diagnostic Criteria

1. Hb >16.5 g/dL in men, >16.0 g/dL in women **or** Hct >49% in men, >48% in women, **or** increased red cell mass >25% above mean normal predicted value
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation

WHO Minor Diagnostic Criterion

Subnormal serum erythropoietin level

High-risk stratification criteria that may call for cytoreductive therapy in PV[2]

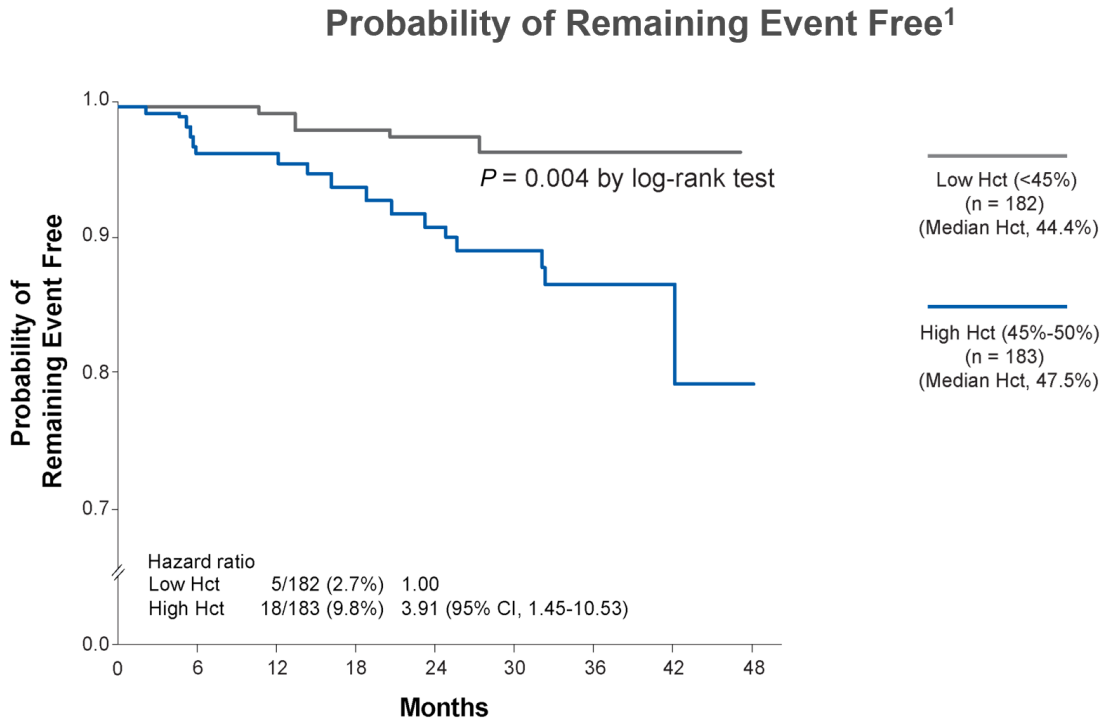
- History of thrombosis (arterial or venous thrombosis; microcirculatory disturbances)
- Age >60 years

Hb, hemoglobin; Hct, hematocrit; JAK, Janus-associated kinases; PV, polycythemia vera; WHO, World Health Organization.

References: 1. Arber DA et al. *Blood*. 2016;127(20):2391-2405. **2.** Tefferi A et al. *Am J Hematol.* 2013;88(6):507-516.

Risk Factors of Uncontrolled Disease

Elevated Hct levels increased risk of cardiovascular death or major thrombosis



Patients with an Hct target of 45% to 50% had a 4-fold higher incidence of cardiovascular death or major thrombosis than patients with an Hct target <45%[1]

From *N Engl J Med*, Marchioli R, Finazzi G, Specchia G, et al, Cardiovascular events and intensity of treatment in polycythemia vera, Volume No. 368, Page No. 29. Copyright © 2013 Massachusetts Medical Society. Reproduced with permission from Massachusetts Medical Society.
Kaplan-Meier curves for primary composite end point.
CI, confidence interval; Hct, hematocrit.

Reference: 1. Marchioli R et al. *N Engl J Med.* 2013;368(1):22-33.

Elevated WBC counts were associated with increased risk of thrombosis

Time-Dependent Multivariate Analysis on the Risk of Major Thrombosis in CYTO-PV study (N=365)[a]

WBC Count (x 10^9/L)	Events/Pts (%)	Hazard Ratio (95% CI), *P*
<7.0	4/100 (4.0)	1.00
7.0–8.4	4/84 (4.8)	1.58 (0.39-6.43), 0.52
8.5–11.0	8/88 (9.1)	2.69 (0.80-9.05), 0.11
≥11.0	12/93 (12.9)	3.90 (1.24-12.3), 0.02

[a]Adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and Hct levels.

In this study, the results indicate the risk of thrombosis was increased in patients with a WBC count >7 x 10^9/L (ie, HR >1), becoming statistically significant at WBC >11 x 10^9/L

CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; pts, patients; WBC, white blood cell.

Reference: Barbui T et al. *Blood*. 2015;126(4):560-561.

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Scoring for thrombotic risks in hospitalized patient

Original $CHADS_2$ Score		
C	Congestive Heart Failure	1
H	Hypertension (>140/90mmHg)	1
A	Age $\geq$ 75	1
D	Diabetes Mellitus	1
S_2	Prior TIA or stroke	2

ACCF/AHA/ESC 2006 Guidelines and 2011 Focused Update

Risk Category	Recommended Therapy
No risk factors	• Aspirin (81-325 mg daily) or no therapy
1 moderate risk factor	• Aspirin (81-325 mg daily) or warfarin • Alternative dabigatran (nonvalvular AF)*[2]
Any high risk factor or >1 moderate risk factor	• Warfarin • Alternative dabigatran (nonvalvular AF)*[2]

The European guidelines recommend anticoagulation over aspirin for most patients with a CHA_2DS_2-VASc score of ≥1 for nonvalvular AFib[13]

Less validated/ weaker risk factors[1]

- Female sex
- Age 65 to 74 years
- Coronary artery disease
- Thyrotoxicosis

Moderate-risk factors[1]

- Age ≥75 years
- Hypertension
- Heart failure
- LVEF ≤35%
- Diabetes mellitus

High-risk factors[1]

- Previous stroke, TIA, or embolism
- Mitral stenosis
- Prosthetic heart valve*

Abbreviations: **ACCF** = American College of Cardiology Foundation; **AHA** = American Heart Association; **ESC** = European Society of Cardiology; **HRS** = Heart Rhythm Society; **LVEF** = left ventricular ejection fraction; **TIA** = transient ischemic attack.

*Dabigatran is an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function).

(For references, see text.)

Treatment Strategies

- Consider thrombotic risk factors & rec
- Consider effects of elevated WBC & rec
- Consider effects of elevated HCT & rec

Summary

- Consider each case evaluated
- Weigh benefit/risk odds
- Counsel on lifestyle
- Share concern of potential underlying etiology
  - Don’t be afraid to phlebotimize if needed after hydration

Questions?