CASE DISCUSSION

More is Not Always Better

Madhuchanda Kar[1], Somnath D Gupta[2]

Bengal Physician Journal (2021): 10.5005/jp-journals-10070-7015

A 60-year-old male evaluated for 1-month history of headache, blurred vision, early satiety, and itching that occur after showering

1. What is the specific symptom in this patient?
   Postshower itching (aquagenic itching) is very much suggestive of polycythemia vera (PV).
2. What is polycythemia?
   Polycythemia/erythrocytosis may be relative or absolute.
   Relative polycythemia may be due to dehydration due to a reduction in plasma volume.
3. What are the causes of absolute polycythemia?
   Primary polycythemia is associated with normal or decreased erythropoietin (EPO) while secondary polycythemia is associated with increased EPO.
   - Etiology—Absolute polycythemia
     - Secondary
       Reactive: increased EPO EPO-producing tumors
       RCC, HCC, cerebellar hemangioblastoma, uterine myoma
       Hypoxemia: cardiopulmonary diseases, obstructive sleep apnea, high altitude, smoking, obesity, chronic obstructive pulmonary disorder, Cushing's syndrome, anabolic steroids
     - Primary (with mutation) PV (JAK 2)
       Chuvash polycythemia (VHL)
       Other genetic mutations
4. What is the definition of PV?
   PV: increase in red blood cell (RBC) mass with/without an increase in granulocytes and platelets in the absence of physiologic stimulus
   Hemoglobin >16.5 (female) or >18.5 (male)
   Hematocrit >48 (female) or >52 (male)
5. How to measure RBC mass?
   RBC mass is measured by chromium-51 release assay

   RBC Mass: Chromium-51 Assay

	RBC	*Plasma*	*Total blood volume*
Female	25 mL/kg >32 mL/kg	35 mL/kg	60 mL/kg
Male	28 mL/kg >36 mL/kg	33 mL/kg	61 mL/kg

6. What are the signs and symptoms of PV?
   Symptoms:
   Hyperviscosity: headache, dizziness, tinnitus, blurry vision
   Thrombosis: transient vision disturbances, erythromelalgia, Budd–Chiari syndrome, deep vein thrombosis, acute myocardial infarction, stroke
   Bleeding: easy bruising, epistaxis
   Pruritis:
   Signs: hypertension, plethora, splenomegaly, gout

[1]Department of Oncology, Peerless Hospitex Hospital, Kolkata, West Bengal, India

[2]PGT Medicine, IPGMER and SSKMH, Kolkata, West Bengal, India

Corresponding Author: Madhuchanda Kar, Department of Oncology, Peerless Hospitex Hospital, Kolkata, West Bengal, India, Phone: +91 9830155915, e-mail: madhuchandakar@yahoo.com

How to cite this article: Kar M, Gupta SD. More is Not Always Better. Bengal Physician Journal 2020;7(1):17–19.

Source of support: Nil

Conflict of interest: None

This patient is suspected to be suffering from PV.
The patient's EPO level <normal range.
JAK2 mutation analysis ordered—exon 14 JAK2 mutation detected.
Diagnosis of PV is confirmed.

7. What are the WHO criteria for PV?
   Revised WHO Criteria 2016
   Major criteria
   - Hb >18.5 g/dL-16.5 in men and 16.5 g/dL-16 in women or
     Hematocrit >49% in men and >48% in women or
     Red cell mass >25% above mean normal predicted value
   - Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.
   - Presence of JAK2V617V mutation or JAK2 exon 12 mutation

   Minor criteria
   Serum EPO level <normal
   [3 major OR 1st and 2nd major + 1 minor]
8. What is the survival in PV?[1]
   Risk of CV death/major thrombosis increased four-fold if HCT >55% and risk of CV events increased by three-fold if HCT >45%
   Although PV patients live for many years, their life expectancy is shorter than the average population of the same age
   - *Median survival:* 14.1 years
   - *High-risk patients, median survival:* 8.3 years

   Prognostic factors—higher risk of death
   - Advanced age
   - Leukocytosis
   - Venous thrombosis
   - Hematocrit >45%
   - Resistance/intolerance to hydroxyurea therapy

   Prognosis:
   - *Untreated median survival:* 6–18 months
   - *Treated median survival:* 13 years[2]

- *Most common cause of death:*
  - thrombosis (29%)
  - hematologic malignancies (23%)
  - nonhematologic malignancies (16%)
  - hemorrhage (7%)
  - myelofibrosis (3%)

9. What are the sites of thrombosis in PV?[3]

Types of Thrombosis (PVSG 01 Study)

Event	*%*
Cerebrovascular accident	35
Venous thrombosis	26
Myocardial infarction	12
Pulmonary arterial	9
Pulmonary infarct	6

10. How does leukocytosis affect prognosis in PV?
    Leukocytosis increases the risk of death, transformation to secondary myelofibrosis, or AML. The risk of thrombosis is 1.7 times greater if leukocyte count is >15 × 10^9/L2†.
11. What is the therapeutic goal in PV?
    - To prevent the occurrence and recurrence of thrombosis
    - To control disease-related symptoms
    - To delay/prevent progression into myelofibrosis or AML

Treatment

- *Phlebotomy:* Goals Hct < 42% (female)/45% (male)[4]
- Low-dose aspirin in all cases.
- Hydroxyurea if high risk of thrombosis (age >60, history of thrombosis)
- Symptomatic (allopurinol, antihistaminics)
- Targeted therapy/ruxolitinib

Symptom-directed therapies: aquagenic pruritus

- Antihistaminics can be used but are largely ineffective.
- Topical agents such as cooling cream, lidocaine cream, capsaicin, or corticosteroids may be helpful.
- Patients can try to reduce discomfort by lubricating the skin and minimizing bathing.
- Pruritus is due to more mast cells.

12. Role of phlebotomy in PV
    Removes excess red cell mass to a safe level and thereby improves blood circulation by lowering the viscosity.
    And 250–500 mL of blood removed alternate day or twice a week till target HCT reaches—45% (male) and 42% (female).
    Patients with impaired cardiovascular function are better if offered with smaller, more frequent phlebotomies.
    Phlebotomy has its limitations
    - No improvement in pruritus.
    - Iron deficiency—reactive thrombocytosis, restless leg syndrome, fatigue.
    - Tonic-clonic seizures—serious but infrequent adverse event.
    - Occasional vasovagal attacks; fainting in 5.3% first time, more often in female blood donors.
    - Raised platelet count >800,000.

Hydroxyurea is quick and effective in lowering blood counts, reduces spleen size, risk of thrombosis is low, leukemia risk is low, and has very few side effects.

A disadvantage of hydroxyurea is that it needs dose monitoring, compliance monitoring, risk in childbearing age, and increased risk of leukemogenecity. With the use of hydroxyurea, the risk of thrombosis is 22% whereas with phlebotomy the risk is 37%.

The patient was treated with hydroxyurea but developed leg ulcers and severe mucositis after four months. It was decided to switch over to ruxolitinib that blocks the abnormal stimulation of JAK/STAT pathways that occur in PV.

Ruxolitinib improves cytokine-related symptoms like tiredness, muscle aches, and night sweats. It also causes improvement in hyperviscosity-related symptoms like headache, cognitive disturbances, and erythema as well as splenomegaly-related symptoms like abdominal fullness and discomfort.

These responses are durable and sustained till nearly 80 weeks. Although well tolerated, ruxolitinib may be associated with a fever, grade 3/4 cytopenias, and higher rates of herpes zoster infections.

13. In addition to aspirin and hydroxyurea, the patient underwent phlebotomy of 250 cc of blood being removed every other day until his hematocrit fell below 45%. During a follow-up appointment, he stated, he was doing well with some mild pruritus. Follow-up labs show:
    Ferritin: 10 (L) (nL: 15–200 µg/L)
    Iron: 5 (L) (nL: 11–29 µmol/L)
    Transferrin sat: 20% (L)

    Which is the most appropriate management of this patient's new iron-deficiency state?
    a. Start oral iron therapy 2.
    b. Start parenteral iron therapy
    c. Give 1 unit PRBC
    d. No intervention
    Ans: d

    Since phlebotomy is effective in controlling polycythemia by producing a state of relative or absolute iron deficiency, iron supplementation should not be given. (In other words, you want the patient to be iron-deficient. Iron deficiency indicates effective phlebotomy therapy.)
14. Five years later, the patient urgently presents to your clinic with severe right upper quadrant pain and jaundice. On examination, you note scleral icterus, new moderate hepatomegaly with RUQ tenderness on palpation, and an abdominal fluid wave sign. AST: 250, ALT: 300, ALK PHOS: 300, TBili: 2.5

    §You send the patient to the ER and order some imaging. What are you most concerned about?
    a. Autoimmune hepatitis
    b. Drug-induced hepatitis
    c. Budd–Chiari syndrome
    d. Acute cholecystitis
    Ans: c

As many as 50% of all cases of Budd-Chiari syndrome may be due to an underlying chronic myeloproliferative disorder (including PV) and an accompanying hypercoagulable state. In a study with 163 Budd–Chiari cases, the most common risk factor was myeloproliferative disorders.[3]

According to UpToDate: "*We suggest that patients diagnosed with Budd-Chiari syndrome in whom no underlying disorder can be identified be tested for a JAK2 mutation.*"

13. The patient was treated appropriately for his Budd–Chiari syndrome and went back home. The patient was doing well

until 5 years later, he complained of slow progressive fatigue.
His Hb: 12.5, WBC: 14,400, Plt: 1.48l.
Bone marrow could not be aspirated.
The patient developed myelofibrosis and eventually succumbed to his disease.
Lifetime transformation rate in patients with PV

- PV to Myelofibrosis: 20%
- PV to AML/MDS: 7%
- PV to CML: rare

Treatment Summary for PV[5]

Management of atherosclerotic risk factors
Aspirin 75 mg/day, unless contraindicated
Phlebotomy to maintain Hematocrit <0.45 (male), <0.42 (female)
Hydroxyurea
Ruxolitinib

References

1. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood 2014;124(16):2507–2513. DOI: 10.1182/blood-2014-05-579136.
2. Polycythemia Vera (PV): types, symptoms, treatment, and complications. Available from: www.my.cleavelandclinic.org
3. Murad SD, Plessier A, Hernandez-Guerra M, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med 2009;151(3):167. DOI: 10.7326/0003-4819-151-3-200908040-00004.
4. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera treatment algorithm. Blood Cancer J 2018;8(1):3. DOI: 10.1038/s41408-017-0042-7.
5. Spivak JL. How I treat polycythemia vera. Blood 2019;134(4):341–352. DOI: 10.1182/blood.2018834044.