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An elderly man with intermittent right arm numbness and polycythemia

A 78-YEAR-OLD MAN presents to the emergency department because of frontal headaches and intermittent episodes of right arm numbness, which began 2 weeks previously. The numbness lasts for approximately 30 minutes before resolving spontaneously. These episodes occur once or twice daily and are not accompanied by changes in vision or speech. He also reports generalized pruritus after showering during the past 1 year, lethargy for the past month, and night sweats for 3 weeks.

His medical history includes coronary artery disease, coronary artery bypass graft surgery, hypercholesterolemia, and hypertension. He is married and a retired commercial fisherman. He has a 50 pack-year smoking history and consumes alcohol only rarely. He has no known drug allergies, and his only medication is aspirin 81 mg daily. His son, age 42, was diagnosed with polycythemia vera 1 year ago.

TABLE 1

The patient's laboratory values on admission

TEST	VALUE	NORMAL RANGE
White blood cell count, $\times 10^9$/L	15.5	4.0–11.0
Neutrophils, %	80	40–70
Lymphocytes, %	13	15–45
Monocytes, %	4.5	2–10
Eosinophils, %	1.7	1–6
Basophils, %	0.4	0–1
Hemoglobin, g/dL	20.1	13.5–17.5
Hematocrit, %	63.3	40–52
Platelet count, $\times 10^9$/L	636	150–400
Red blood cell count, $\times 10^{12}$/L	7.44	4.5–6.0
Mean corpuscular volume, fL	85.1	80–100
Mean corpuscular hemoglobin count, g/dL	31.8	32–36
Red cell distribution width, %	17.4	11.7–15.0

Physical examination

The patient has a ruddy complexion and is not in distress. His temperature is 36.1°C (97.0°F), heart rate 74, respiratory rate 18, and blood pressure 170/123 mm Hg. His oxygen saturation while breathing room air is 94%.

Fundoscopic examination reveals no papilledema. The pupils are equally reactive to light and accommodation. The extraocular muscles are intact. No cervical adenopathy is noted. The carotid arteries are normal bilaterally, with no bruits. Examination of the heart and chest is normal. Palpation of the spleen reveals no splenomegaly.

Neurologically, the patient appears alert and oriented to person, time, and place. His speech is normal. Motor tone is normal. Pronator drift of the right upper extremity is noted, ie, with his eyes closed and his arms straight forward and supinated, his right arm tends to pronate, suggesting a mild hemiparesis. Gross ataxia is not present. Motor strength is 5 on a scale of 5 for elbow flexion, extension, wrist extension, and finger abduction bilaterally. The biceps, triceps, brachioradialis, and patellar reflexes are rated 2 on a scale of 4 bilaterally. Stroking the soles of the feet elicits downward movement of the toes. Sensation to light touch and pinprick and the ability to perform rapid alternating movements are intact.

Laboratory values on admission

The patient's laboratory values on admission (TABLE 1) indicate a generalized polycythemia,

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with elevations in the white blood cell count, hemoglobin concentration, hematocrit, platelet count, and red blood cell distribution width.

WHAT IS THE CAUSE OF THE APPARENT POLYCYTHEMIA?

1 What is the most likely cause of polycythemia in this patient?

- ❑ Volume depletion
- ❑ Gaisböck syndrome
- ❑ Polycythemia vera

It is important to distinguish a true increase in blood cells (absolute polycythemia) from conditions in which they only appear to be elevated (relative or spurious polycythemia).

Volume depletion can cause hemoconcentration and spurious polycythemia. This patient, however, has no clinical signs of volume depletion.

Gaisböck syndrome is another cause of spurious polycythemia. It usually affects white, middle-aged, mildly obese men who are active, anxiety-prone, and hypertensive. Although the red blood cell count, hematocrit, and hemoglobin concentration are elevated in Gaisböck syndrome, the white blood cell and platelet counts are typically normal. This patient, however, has elevated white blood cell and platelet counts.

An elevated red cell mass may reflect low plasma volume

Polycythemia vera is a chronic, progressive disease caused by clonal proliferation of bone marrow stem cells, leading to excessive proliferation of erythroid, myeloid, and megakaryocytic elements within the bone marrow.[1]

The onset is usually insidious and occurs most commonly in the sixth decade of life. Presenting symptoms include headache, plethora, pruritus, erythromelalgia, thrombosis, gastrointestinal bleeding, and polycythemia. Patients with polycythemia vera generally have an elevated red blood cell mass and a hematocrit greater than 60% without evidence of volume depletion.

Polycythemia vera is the most likely cause of polycythemia in this patient, who presented with an increased hematocrit, thrombocytosis, and leukocytosis.

FURTHER LABORATORY WORKUP

2 What further laboratory studies are indicated for a patient who presents with an elevated hemoglobin level in whom polycythemia vera is suspected?

- ❑ Red blood cell mass
- ❑ Erythropoietin level
- ❑ Leukocyte alkaline phosphatase score
- ❑ Serum vitamin B_{12} level
- ❑ All of the above

If polycythemia vera is suspected, the initial laboratory evaluation should include all of the above. In polycythemia vera:

The red blood cell mass is elevated (≥ 36 mL/kg in men; ≥ 32 mL/kg in women). This patient's value was 43 mL/kg (normal range 25–30).

The erythropoietin level is low, in response to the high erythrocyte count. This patient's erythropoietin level was < 2.5 mU/mL (normal range 3.3–16.6).

The leukocyte alkaline phosphatase score typically is increased in the absence of fever or infection. This patient's value was 129 (normal range 8–100).

The serum vitamin B_{12} concentration typically is increased—although not in this patient. His value was 403 pg/mL (normal range 221–700).

PRIMARY VS SECONDARY ERYTHROCYTOSIS

3 Which is the best initial test to differentiate polycythemia vera from secondary erythrocytosis?

- ❑ Serum erythropoietin level
- ❑ Red blood cell mass
- ❑ Burst-forming units-erythroid count
- ❑ Tests for a karyotype abnormality, especially a deletion on chromosome 20q

Polycythemia vera must be distinguished from secondary erythrocytosis, ie, conditions in which the increase in red blood cells is an adaptive physiologic response to chronic tissue hypoxia.

The serum erythropoietin level is the best initial test. Erythropoietin is a glycoprotein hormone that regulates red blood cell

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production. In states of severe hypoxia and anemia, erythropoietin levels increase markedly. Erythropoietin binds to receptors on erythroid progenitor cells, stimulating them to produce more red blood cells. With more red blood cells in circulation the blood can carry more oxygen, and the resulting increase in tissue oxygen tension causes the erythropoietin level to return to normal.[2] Therefore, in secondary erythrocytosis the serum erythropoietin level is normal or high, while in polycythemia it is typically low.

The red blood cell mass would be elevated in both polycythemia vera and secondary erythrocytosis.

Burst forming units-erythroid, also called endogenous erythroid colonies, can be grown from the peripheral blood or bone marrow of patients with polycythemia vera, but not from patients with secondary erythrocytosis. Therefore, this test helps distinguish the two disorders. However, it is expensive and time-consuming, and few laboratories outside the research setting do it.

Chromosomal abnormalities may be increased in patients with polycythemia vera previously treated with cytotoxic agents. In general, 30% of patients with polycythemia vera may have an abnormal karyotype, with an interstitial deletion on chromosome 20q the most common.[4] However, because this abnormality is present in other premalignant and malignant myeloid diseases, this test is not specific for polycythemia vera. The test is also not useful in predicting survival or transformation to acute leukemia, although a change in the karyotype during the disease course may worsen the prognosis.[1]

COMPLICATIONS OF POLYCYTHEMIA VERA

4 Which is the most common complication of polycythemia vera?

- ❑ Gastrointestinal bleeding
- ❑ Uncontrolled hypertension
- ❑ Thrombosis

All of the above are common in patients with polycythemia vera, but thrombosis is the most common, occurring in one third of patients.

Thrombosis. Major arterial thrombotic disease involving the peripheral, cerebral, or coronary circulation occurs in 15% to 37% of patients with polycythemia vera.[5] Patients can also present with venous thrombotic events. Intra-abdominal venous thrombosis is particularly common, and polycythemia vera should be suspected in any patient who develops the Budd-Chiari syndrome (hepatic vein thrombosis). The peripheral microvascular symptoms of polycythemia vera include erythromelalgia (red, swollen extremities with burning pain), acroparesthesias described as tingling, burning sensations, or numbness without redness or swelling, and peripheral gangrene with normal pulses.

Erythromelalgia is a characteristic thrombotic complication in patients with myeloproliferative disorders, including polycythemia vera, and is usually confined to the ball of the foot or to one or more toes or fingers. Untreated, erythromelalgia can progress to ischemic acrocyanosis or gangrene. Erythromelalgia can be controlled by reducing the platelet count to normal values and by inhibiting platelet cyclooxygenase activity with aspirin. Phlebotomy alone is ineffective in treating erythromelalgia.

Hemorrhagic events occur in 30% to 40% of patients with polycythemia vera, and the gastrointestinal tract is the most common site of bleeding. Patients may have an increased incidence of esophageal bleeding due to portal hypertension.

Suspect polycythemia vera in patients with Budd-Chiari syndrome

Neurologic symptoms

Most patients with poorly controlled or untreated polycythemia vera experience neurologic symptoms including transient ischemic attack, cerebral infarction, fluctuating dementia, and chorea. The increased blood viscosity may result in dizziness, paresthesias, visual disturbances, tinnitus, or headaches.

DIAGNOSIS AND DISEASE COURSE

TABLE 2 lists the diagnostic criteria of the Polycythemia Vera Study Group as revised by Pearson and Messinezy.[6] An elevated red blood cell mass establishes the presence of

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TABLE 2

Diagnostic criteria for polycythemia vera

All three of the following:

Increased red cell mass
(≥ 36 mL/kg in men, ≥ 32 mL/kg in women)

Normal arterial oxygen saturation (≥ 92%)

Splenomegaly

Or increased red cell mass, normal arterial oxygen saturation, and two of the following:

Thrombocytosis (platelet count > 400×10^9/L)

Leukocytosis (white blood cell count > 12×10^9/L)

Elevated leukocyte alkaline phosphatase score
(> 100; no fever or infection)

Elevated serum vitamin B_{12} (> 900 pg/mL)

Elevated vitamin B_{12} binding capacity (> 2,200 pg/mL)

ADAPTED FROM PEARSON TC, MESSINEZY M. THE DIAGNOSTIC CRITERIA OF POLYCYTHEMIA RUBRA VERA. LEUK LYMPHOMA 1996; 22 SUPPL 1:87–93.

absolute erythrocytosis. The leukocyte alkaline phosphatase score and serum vitamin B_{12} concentration are no longer considered useful, since they are expensive and have low sensitivity.[4]

Disease course

The initial phase of polycythemia vera is proliferative, characterized by effective hematopoiesis. The bone marrow may reveal hyperplasia of erythroid, myeloid, and megakaryocytic elements ("trilineage hyperplasia"), and the bone marrow cellularity is usually higher than normal for age. The complete blood count shows elevated hemoglobin, platelets, and white blood cell count.

The "spent" phase occurs after about 10 years in 5% to 15% of patients. During this phase, the need for cytoreductive treatment decreases, the red cell mass decreases, and splenomegaly increases. A leukoerythroblastic blood smear, pancytopenia, extensive bone marrow fibrosis, and ineffective hematopoiesis with extramedullary hematopoiesis are common diagnostic features. Acute leukemia eventually develops in 20% of patients with polycythemia vera irrespective of previous treatment.

TREATMENT OF POLYCYTHEMIA VERA

5 Which is the best treatment option for this patient?

- ❑ Hydroxyurea
- ❑ Phlebotomy
- ❑ Hydroxyurea plus phlebotomy
- ❑ None of the above

Patients with polycythemia vera do poorly if untreated: Chievitz et al[7] reported that 50% of untreated patients died within 18 months of the onset of the first symptom, mainly of thrombosis.

Phlebotomy used alone reduces blood volume and iron stores and improves overall survival compared with no treatment.

Hydroxyurea (a myelosuppressive agent) alone suppresses the excess production of cells and also improves survival compared with no treatment.

Hydroxyurea plus phlebotomy. Kaplan et al[8] reported that the risk of thrombosis was lower in patients who received hydroxyurea and supplemental phlebotomy to maintain the hematocrit at ≤ 45% than in a retrospective control group who received phlebotomy alone. Because this patient's platelet count is above normal, placing him at especial risk of thrombosis, management calls for both phlebotomy and myelosuppressive therapy with hydroxyurea or a newer agent, anagrelide (Agrylin).

New therapeutic agents

New agents for the treatment of polycythemia include anagrelide and recombinant interferon alfa.

Anagrelide, a quinazoline derivative initially developed to inhibit platelet function, lowers the platelet count in patients with myeloproliferative disorders by slowing megakaryocyte maturation. It is an attractive treatment option, especially in younger patients, since it is not known at this time to cause leukemia.

Recombinant interferon alfa is myelosuppressive and can inhibit platelet-derived growth factor, which plays a major role in the pathogenesis of myelofibrosis.[4] In addition, research indicates that interferon decreases the incidence of splenomegaly,

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may relieve refractory pruritus, controls thrombocytosis and leukocytosis, and reduces the need for phlebotomy. Because it has no mutagenic or teratogenic effects, interferon is ideal to consider for young patients. However, its toxicity and cost currently limit its widespread use.

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