A Man With an Elevated Hemoglobin

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A 50-year-old male with history of severe gout and degenerative joint disease presented to his PCP for a physical. On routine blood work he was found to have an elevated hemoglobin/hematocrit. This was confirmed on repeat analysis and work-up was pursued.

His past medical and surgical history includes hypertension, severe gout, degenerative joint disease of the knees and shoulders, hypokalemia, and right ulnar nerve manipulation at the elbow. He denied IV drug or tobacco use, although he occasionally smokes cannabis, and has a history of moderate alcohol use for which he was in rehabilitation in 1998. His parents are both alive with diabetes and hypertension, and he has three healthy siblings. There is no family history of blood disorders. He denied any recent travel and has always lived in Delaware or Maryland except when stationed in Germany when he was in the military. He lives alone and previously worked as an item processor.

On review of systems, he denied fevers, sweats, or chills. He had noted an approximate 15lb weight gain over the past year, which he attributed to dietary indiscretions. He denied any change in vision, or hearing and had not experienced any lightheadedness or dizziness. He denied chest pain, shortness of breath, but occasionally notes palpitations with increased activity. He also denied skin changes, flushing, or pruritus.

His medications include:
Allopurinol 300mg po qd
Folic acid 1mg po qd
Magnesium oxide 420mg po qd
Multivitamin 1 tab po qd
Naprosyn 500mg po bid prn
Potassium chloride 8meq po qd
Thiamine 100mg po qd
ASA 325mg po qd

Physical examination revealed a ruddy-faced male, in no acute distress, with stable vital signs. Significant findings included hepatomegaly at 16cm and a spleen tip palpable 3-4 fingerbreadths below the costal margin. His left third digit PIP had mild erythema and swelling, per his typical gouty attacks, and he had a few excoriations on his chest. The remainder of the exam was unremarkable.

Multiple Laboratory Studies

Lab study	Patient value	Reference range
WBC	15.0	4.0-11.0 B/L
Neutrophils %	69.4	40-73%
Monocytes %	5.7	3-13%
Lymphocytes %	22.2	20-44%
Eosinophils %	1.4	0-6%
Basophils %	1.3	0-3%
HgB 20.0	12.5-15.0 g/dL	
Hct	60.0	36.0-46.0 g/dL
Platelets	253	140-400 B/L
Iron 243	40-155 mcg/dL	
TIBC 379	250-400 mcg/dL	
% Iron Saturation	64	20-55%
Ferritin	436.9	12-300ng/mL
Erythropoietin	4.4	4.0-15.4 mU/mL
B12	559	100-250 pg/mL
B12 binding capacity	1986	1000-2000 pg/mL
Folate	3.4	>2ng/mL
LAP 132	11-95	
Uric acid	9.2	3.4-7.0 mg/dL
AST 45	2-50 u/L	
ALT 40	2-60 u/L	
ABG on room air	7.44/ 30/ 109/ 96	

Ultrasound studies showed normal kidneys, splenomegaly, and fatty change of the liver. No space-occupying lesions or ductal dilatation was noted. The blood flow and waveforms of the hepatic vein, portal vein, and IVC were unremarkable. Chest x-ray was negative. Based on the patient's hemotolgical abnormalities on labs, a bone marrow biopsy of the left iliac crest was performed. Mild hypercellularity was seen, with increased megakaryocytes, normoblastic erythropoiesis, and myeloid precursors in all stages, without a block in maturation. Reticulin stain demonstrated foci of early fibrosis, while Prussian blue staining identified increased iron stores with rare ringed sideroblasts (See Figures B and C, Color Plates page 19). After careful review, findings appeared consistent with polycythemia vera. It was felt that the patient was likely early in the course of disease, given the larger than expected iron stores consistent with the amount of erythropoiesis.

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The patient was phlebotomized 3.5 units initially, and then again another 3 units to keep his hematocrit less than 45%. He tolerated these procedures without difficulty and was scheduled for repeat blood work and future phlebotomies.

Discussion

The myeloproliferative disorders include polycythemia vera, essential thrombocytosis, and myelofibrosis with myeloid metaplasia. Chronic myelogenous leukemia is often considered separately because of its known chromosomal association: the Philadelphia chromosome. Polycythemia vera (PV) demonstrates a clonal proliferation of hematopoietic stem cells and is characterized by an increased red blood cell mass. The erythroid cells proliferate independently of erythropoietin (EPO). Overproduction of all three cell lines can be seen.

PV is more common in males than females with a ratio of 1.2:1. Epidemiological studies completed in Rochester, Minnesota show an incidence of 2.3/100,000. Median age at diagnosis is approximately 60 years. [1]

Presenting signs and symptoms of PV are often nonspecific and include headache, tinnitus, fatigue, epigastric discomfort, hepatomegaly, splenomegaly (75%), and facial plethora. Pruritus, especially after a hot bath or shower, is typical. The exact etiology of this is uncertain but is likely linked to histamine release or prostaglandins. Erythromelalgia, burning sensations in one's hands or feet with concomitant pallor, cyanosis, or erythema, in presence of palpable pulses, is also seen. This is felt to be a microvascular complication of the disease.[2] Episodes of thrombosis, like Budd Chiari syndrome, as well as bleeding and peptic ulcer disease can be evident. A prothrombotic latent phase of approximately two years involving arteries and veins has been described.[5] Increased uric acid levels are often noted as well. [1]

Typically, an increased hemoglobin/hematocrit is noted. The hemoglobin is usually greater than 16.5 g/dL and 18.5 g/dL in women and men, respectively. A spurious polycythemia can be noted when a patient is volume depleted. This is often seen in patients on diuretic therapy and reverts to normal with volume repletion. Once an elevated hemoglobin is noted, decisions must be made to determine whether it is a primary or secondary polycythemia. Secondary polycythemia can be due to hypoxia from cardiac or pulmonary disease, as well as from high altitude. Smoking is another etiology of erythrocytosis. Renal disease should be excluded as an EPO secreting tumor may be present. [2] If there is a decreased MCV and iron studies, indicative of iron deficiency anemia in the presence of a high normal hemoglobin, some have advocated iron supplementation to see if an erythrocytosis is unmasked. This would place the patient at an increased risk of thrombosis and it is more prudent to assume that the patient has a true erythrocytosis. [4]

In the 1960s-1970s, the Polycythemia Vera Study Group set forth diagnostic criteria. These criteria were made to select patients for clinical trials. It included three major and four minor criteria. The main criteria included increased red cell mass (males >36mL/kg, females > 32mL/kg), normal hemoglobin oxygen saturation (> 92%), and splenomegaly. A leukocytosis > 12,000cell/uL, thrombocytosis >400,000cell/uL, elevated leukocyte alkaline phosphatase > 100, and an increased vitamin B12 or B12 binding capacity were minor criteria.[3] As leukocytosis may be secondary to other etiologies, an ANC >10,000 has been used of late. Recently, there has been a trend away from using these criteria due to the number of false positive and negative results. Rather than diagnostic criteria many clinicians are using an algorithmic approach.

Once an elevated hemoglobin has been noted and the diagnosis of PV is suspected, a full work-up should ensue. In the past, an increased red blood cell mass was needed for diagnosis. This test is not widely available and is expensive. If the patient is early in the disease process or has concomitant microcytic anemia, it may be falsely negative, and if using hemoglobin measurements greater than 2 standard deviations greater than the mean, the test is typically positive. Therefore, in most cases, this test is not ordered and a serum EPO level is measured.[2] If it is high, etiologies of secondary polycythemia should be further investigated. If it is normal or low, PV is possible. In PV, it is typically low but may be low normal. Many then proceed to a bone marrow biopsy. Bone marrow biopsy in PV demonstrates hypercellularity, increased megakaryocytes, decreased iron stores, and

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mild reticulin fibrosis. If the diagnosis is still uncertain, futher cytogenetic tests may be completed. For example, a decreased expression of the TPO receptor by megakaryoctes supports the diagnosis. 1 An endogenous erythroid colony assay, not widely available, could be done. This study determines if erythroid colonies proliferate in the absence of EPO.[2]

The main treatment for PV continues to be phlebotomy. The goal is to keep the hematocrit below 45% in males and 42% in females. This is to avoid thrombotic complications. Patients should be instructed to avoid iron supplementation. In patients who are felt to be at especially high risk for thrombosis, based on platelet count, past medical and family history, chemotherapy may be an option. Hydroxyurea, busulfan, alpha-interferon, 32P, and anagrelide have been used. The concern is adverse effects of the drugs including leukemia.[1] Alkylating agents especially are associated with an increased risk of neoplasm. Phlebotomy alone is associated with an increased risk of thrombosis and fibrosis.[5] A survey in 2002 by the American Society of Hematology demonstrated that 69% of physicians used phlebotomy as first line of treatment. Nearly 28% used the combination of phlebotomy and hydroxyurea, and only 10% employed the use of hydroxyurea alone.[3] Erythromelagia seems to respond to low dose aspirin. The pruritus often responds to aspirin, antihistamines, and in some instances selective serotonin reuptake inhibitors.1 Low dose aspirin (30-75 mg/day) may also be beneficial in preventing thrombosis and is not associated with the increased risk of bleeding seen at higher dosages.[5] Allopurinol is used in those with symptomatic hyperuricemia.[1]

Previously, untreated PV had a life expectancy of 6 to 18 months after diagnosis but with current treatment approaches it is felt to be greater than 15 years. The main complications are those of thrombosis and progression of the disease to myeloid metaplasia with myelofibrosis (MMM) or acute myeloid leukemia. The most frequent causes of death linked to thrombosis include myocardial infarction, ischemic cerebrovascular events, and thromboembolism. The risk of thrombosis increases with age. There is debate over the percentage of patients who progress to MMM.[4] It is currently felt that about 10 years after diagnosis, approximately 10% of patients will have MMM. [1] This number increases with length of survival.4 In the same time frame, there is approximately a 5% transformation rate to acute leukemia.[1] Research to explore other therapeutic options for PV is ongoing.

References

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