



Dyspnea, pancytopenia, and splenomegaly

An extensive initial laboratory assessment, including testing for viral disorders, left the diagnosis unsolved.

CASE ► A 47-year-old man with a history of alcoholism came to our emergency department (ED) with a 3-week history of sore throat and dry cough. He said that for the past 2 months he had experienced worsening shortness of breath, increasing weakness, and episodes of light-headedness. He also said that his gums occasionally bled when he brushed his teeth.

Our patient owned a farm where he was exposed to pesticides and fertilizers, but he reported no contact with sick individuals, new medications, or recent travel. The patient had a 40 pack-year smoking history, but he had quit within the past year. His family history was negative for malignancies or rheumatologic diseases.

On physical exam, we noted splenomegaly (spleen was approximately 3 cm below costal margin); all other exam findings were within normal limits.

Lab results revealed pancytopenia: the patient's serum white blood cell (WBC) was 900/mcL, the absolute neutrophil count (ANC) was 447/mcL, and the absolute lymphocyte

count was 346/mcL. Hemoglobin was 5.4 g/dL and platelet count was 47,000/mcL. (Pancytopenia is defined as hemoglobin <13.5 g/dL [males] or 11.6 g/dL [females], platelet count <150,000/mcL, and WBC count <4000/mcL. Criteria for severe pancytopenia include an ANC <500/mcL, platelet count <20,000 mcL, and corrected reticulocyte count <1%.^{1,2})

A repeat complete blood count (CBC) showed similar results. Basic metabolic panel, chest x-ray film, and electrocardiogram results were all normal.

Based on the initial lab work, we ordered further testing for human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus, hepatitis, parvovirus B19, and anti-nuclear antibodies. All results were negative. B12 and folate levels were low normal, and the reticulocyte count was 2.31%. We admitted the patient for evaluation of his pancytopenia.

◉ WHAT ADDITIONAL TESTING WOULD YOU PURSUE AT THIS POINT?

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The authors reported no potential conflict of interest relevant to this article.

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We ordered a bone marrow biopsy and peripheral smear, which is protocol in a case such as this. Results showed leukemic and “hairy” cells.

Hairy cell leukemia

Hairy cell leukemia is an uncommon chronic B-cell lymphoproliferative disorder.³ It represents 2% of all adult leukemias; the median age of onset is 52 years, with a male predominance of 4:1. It is 3 times more common in Caucasians than in African Americans. There is still some controversy regarding its cell line, and its pathogenesis is still unknown. Exposures to ionizing radiation, EBV, organic chemicals, woodworking, and farming have been cited as possible causes.⁴

■ **Symptoms of hairy cell leukemia** include fatigue, weakness, and weight loss. Abdominal fullness or discomfort due to splenomegaly is seen in 25% of cases.^{5,6} Easy

bruising and bleeding secondary to severe pancytopenia are also seen in about 25% of cases.^{5,6} However, 25% of patients are initially asymptomatic and are found to have abnormal lab values during a routine well visit.⁶

Narrowing in on a diagnosis

The etiology of pancytopenia is broad, but the diagnostic possibilities (TABLE) narrow depending on the pathogenesis of a patient’s condition: decreased bone marrow production, increased destruction or sequestration of cells, inherited/congenital, or idiopathic.

■ **Testing.** After an initial CBC, a second CBC should be obtained to confirm the pancytopenia before ordering further tests.^{1,7} Such testing includes a peripheral blood smear, a reticulocyte count, serum iron studies, and viral studies such as HIV, EBV, or par-

TABLE

Is it pancytopenia? The differential³

Decreased bone marrow production	Increased destruction/sequestration of cells	Inherited/congenital
Chemotherapy, radiotherapy	Liver disease	Gaucher disease
Megaloblastic anemia	Portal hypertension	Fanconi’s anemia
Myelodysplastic syndromes	Hypersplenism due to myelo- or lymphoproliferative disorders	
Myelofibrosis	Evan’s syndrome	
Aplastic anemia	Infection (eg, brucellosis, leishmaniasis)	
Paroxysmal nocturnal hemoglobinuria	Heavy metal poisoning	
Lymphoma with bone marrow infiltration		
Leukemia		
Plasma cell myeloma		
Infection (eg, parvovirus B19, CMV)		
Anorexia nervosa		
Overlap		
Connective tissue disorders (eg, SLE, RA)		
AIDS		
Mycobacterial infection; sepsis; acute viral infection (eg, CMV, HIV, EBV)		

AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

vovirus, along with an autoimmune profile and liver function tests.⁸ A hematology consult with probable bone marrow aspirate is also indicated.⁸

Diagnosis is made based on clinical findings and lab work revealing pancytopenia. A peripheral smear exhibiting leukemic cells and “hairy” cells suffices to make the diagnosis, although bone marrow biopsy—which reveals tartrate-resistant acid phosphatase-positive cells on cytochemical staining in 95% of cases³—is often used to corroborate the diagnosis. More recently, immunotyping using flow cytometry has become the standard for confirming the diagnosis of hairy cell leukemia.³

Adjust treatment to symptoms and severity of pancytopenia

Indications for treatment include the development of one or more the following: ANC <1000/mcL with repeat infections; symptomatic anemia with hemoglobin <11 g/dL; platelet count <100,000/mcL associated with bleeding, symptomatic splenomegaly, or adenopathy; or constitutional symptoms.⁹

First-line therapy is with one of the cytotoxic agents, either cladribine or pentostatin. Splenectomy is another effective option, with results that last up to 10 years in 50% of cases.⁹ Another option is interferon-alpha.¹⁰

Before the advent of cytotoxic agents, the 4-year survival rate for hairy cell leukemia was reported as 68%. Today, durable remission is attained for many patients. Even after relapse, retreatment yields good responses. The 5-year survival rate now is higher than 85%.¹¹

Close follow-up of these patients is key

Potential complications of hairy cell leukemia include infections, bleeding, anemia, splenic rupture, and a second primary malignancy. There is a 2- to 3-fold increased risk of developing a second malignancy at a median

interval of 40 months after initial diagnosis.¹⁰

This increased risk may be related to immunosuppression due to hairy cell leukemia or its treatment. The incidence of a second malignancy occurring before the diagnosis of hairy cell leukemia is 10.2%, and concurrently with the diagnosis is 2.6%.¹⁰ This finding suggests some pretreatment predisposition to cancer; further studies are being carried out to evaluate this matter. The most common solid tumors include prostate cancer, skin cancer, lung cancer, and gastrointestinal adenocarcinomas.¹⁰

Our patient's outcome

During our patient's hospital admission, he received 6 units of packed red blood cells, 3 daily injections of 480 mcg subcutaneous filgrastim for 5 days, and ongoing vitamin B₁₂ supplementation to assist myeloid recovery. Upon discharge, his ANC level had increased to 1634/mcL. He began outpatient treatment with cladribine under the care of a hematologist. After almost a year of treatment, our patient is in complete remission. **JFP**

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PRACTICE POINTERS

- ▶ Obtain a thorough history to aid in narrowing the list of potential causes in pancytopenia's broad differential.
- ▶ Arrange for a peripheral smear and bone marrow biopsy to confirm the cause of pancytopenia.
- ▶ Screen any patient with hairy cell leukemia for a second primary malignancy.
- ▶ Base a treatment decision on the presence of symptoms and the severity of the pancytopenia.

▶ Hairy cell leukemia's pathogenesis is still unknown, but exposures to ionizing radiation, Epstein-Barr virus, organic chemicals, woodworking, and farming have been cited as possible causes.

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