



# 56-Year-Old Man With Abdominal Pain and Dyspnea

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See end of article for correct answers to questions.

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A 56-year-old man presented with abdominal pain, dyspnea, and back pain. His medical history included eosinophilic fasciitis and chronic abdominal pain. Several months previously, he was diagnosed elsewhere as having deep morphea with features of eosinophilic fasciitis and idiopathic thrombocytopenic purpura (ITP), initially treated with prednisone, 70 mg/d for 2 weeks. However, his platelet count decreased from  $51$  to  $29 \times 10^9/L$  (reference range,  $150-450 \times 10^9/L$ ). Given the inadequate response, he subsequently received rituximab for 8 weeks. Because of continued thrombocytopenia, treatment with eltrombopag, 50 mg/d, was initiated. The patient had been taking eltrombopag for 1 week before the current admission. Other medications included omeprazole, sertraline, and prednisone. He reported no use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Before being transferred to our institution, the patient had presented to an outside hospital with a 2-day history of worsening dyspnea, abdominal pain, and lower back pain. Laboratory test results were notable for a platelet count of  $6 \times 10^9/L$ , prompting initiation of dexamethasone, 40 mg/d, and a platelet transfusion. Transthoracic echocardiography showed no abnormalities, and D-dimer and troponin levels were unremarkable. Computed tomography of the chest, abdomen, and pelvis revealed bilateral pleural effusions. The liver and spleen were normal. Pain was managed with intravenous (IV) hydromorphone and lorazepam.

On presentation at our institution, the patient was normotensive and afebrile, with an oxygen saturation of 92% while breathing room air. His back pain had resolved, but he continued to experience abdominal pain,

dyspnea, and decreased chest expansion. He reported no nausea, constipation, melena, or hematochezia. Physical examination revealed an uncomfortable-appearing and tachypneic man. No lymphadenopathy was noted. The cardiac examination findings were unremarkable. Lung sounds were decreased at the bases bilaterally. Abdominal examination revealed a diffusely tender and tense abdomen, without hepatosplenomegaly. No lower extremity edema was noted. Skin examination revealed diffuse thickening and erythema, most noticeable in the lower abdominal quadrants, which limited deep inhalation and chest expansion. Livedo reticularis was noted on his lower extremities bilaterally.

Initial laboratory studies at our institution (reference ranges provided parenthetically) revealed a new macrocytic anemia since 1 month previously (hemoglobin, 10.8 g/dL [13.2-16.6 g/dL] and mean corpuscular volume, 103 fL [78.2-97.9 fL]); thrombocytopenia (platelets,  $46 \times 10^9/L$  [ $135-317 \times 10^9/L$ ]); normal leukocyte count ( $4.8 \times 10^9/L$  [ $3.4-9.6 \times 10^9/L$ ]); neutrophils,  $4.13 \times 10^9/L$  ( $1.56-6.45 \times 10^9/L$ ); eosinophils,  $0.3 \times 10^9/L$  ( $0.03-0.48 \times 10^9/L$ ), elevated plasma lactate (2.6 mmol/L [0.6-2.3 mmol/L]); and respiratory alkalosis on venous blood gas measurement (pH, 7.46 [7.35-7.45];  $PCO_2$ , 38 mm Hg [35-45 mm Hg]; and bicarbonate, 26 mmol/L [22-29 mmol/L]). Creatinine, troponin T, and electrolyte values were within normal limits. Coagulation studies revealed an internationalized normalized ratio and activated partial thromboplastin time within normal limits and elevated plasma fibrinogen (1057 mg/dL [200-375 mg/dL]). There was no evidence of iron deficiency (ferritin, 3563  $\mu g/L$  [24-336  $\mu g/L$ ]), vitamin B<sub>12</sub> deficiency (550

ng/L [180-914 ng/L]), or folate deficiency (17.5 µg/L [ $\geq$ 4.0 µg/L]). Work-up was negative for hemolysis (haptoglobin, 622 mg/dL [30-200 mg/dL]; total bilirubin, 0.5 mg/dL [ $\leq$ 1.2 mg/dL]), negative results on polyspecific direct antiglobulin testing, and peripheral blood smear without features of hemolysis). Inadequate reticulocyte response (% reticulocytes, 1.89% [0.60%-2.71%]) and absolute reticulocyte count ( $52.0 \times 10^9/L$  [ $30.4-110.9 \times 10^9/L$ ]) were noted. Viral serologies yielded negative results, including those for human immunodeficiency virus and hepatitis B. The triglyceride level was normal at 129 mg/dL (<150 mg/dL). In addition, results of antinuclear antibody, rheumatoid factor, and connective tissue disease serologies were negative.

1. Which one of the following would be the best next step regarding work-up for this patient's bicytopenia?

- Peripheral blood flow cytometry
- Testing for antiplatelet antibodies directed against glycoproteins
- Measurement of ADAMTS13 activity
- Bone marrow biopsy
- Positron emission tomography/computed tomography

Although a primary hematologic malignancy cannot be completely ruled out, peripheral blood flow cytometry would not be the best next step. In addition, it is a very poor screening test for hematologic malignancies and should be reserved for patients with a lymphocytosis of undetermined etiology or to subclassify hematologic malignancies after the initial diagnosis. Testing for antiplatelet antibodies is not indicated in the routine work-up for autoimmune etiologies of thrombocytopenia such as ITP due to insufficient evidence.<sup>1</sup> ADAMTS13 testing is indicated when thrombotic thrombocytopenic purpura (TTP) is suspected. The earliest and most important finding to diagnose TTP is evidence of microangiopathic anemia. In our patient, the lack of microangiopathic hemolysis, renal dysfunction, altered mental status, and fever makes TTP unlikely. Bone

marrow biopsy is the best next step for this patient, especially given the bicytopenia accompanied by inappropriately normal reticulocyte count. Positron emission tomography/computed tomography is not appropriate at this time because there is no indication of a systemic process outside the bone marrow.

Although the patient's hemoglobin level remained relatively stable, his thrombocytopenia continued to worsen during hospitalization, without evidence of ongoing bleeding.

2. Which one of the following should be the initial step in managing the patient's persistent thrombocytopenia while awaiting bone marrow results?

- Plasmapheresis
- IV corticosteroids
- Urgent splenectomy
- IV immunoglobulin (IVIG)
- Rituximab

Plasmapheresis is of limited benefit for ITP and is not indicated.<sup>1</sup> Intravenous corticosteroids are the best initial treatment at this time and are the preferred first-line therapy for ITP, with response expected within 2 to 5 days.<sup>1</sup> Splenectomy is an effective treatment with curative potential for patients with ITP refractory to corticosteroids or IVIG. However, urgent splenectomy would not be indicated. Treatment with IVIG should be considered when a rapid increase in platelet count is required, such as before an urgent procedure. Furthermore, it has only a temporary effect,<sup>1</sup> Rituximab, an anti-CD20 agent, is an acceptable second-line treatment option for ITP.<sup>1</sup> However, it takes several weeks until a response is seen and would not be the best next step.

The patient received IV dexamethasone, 40 mg/d, for 5 days and then transitioned to prednisone, 100 mg/d. However, his platelets continued to decline despite treatment, reaching  $8 \times 10^9/L$ , and he received a unit of platelets. A 3-hour posttransfusion platelet count was  $51 \times 10^9/L$ , which would argue against an immune-mediated platelet destruction process. He was subsequently

noted to be somnolent, tachycardic, and hypoxic. His lactate level was elevated, and blood cultures were positive for *Streptococcus pneumoniae*. Intravenous vancomycin and ceftriaxone were initiated. Magnetic resonance imaging of the head did not reveal any central nervous system abnormalities, including hemorrhage. Results of follow-up blood cultures were negative. His anemia and thrombocytopenia continued to worsen. Results of bone marrow biopsy revealed hypocellular bone marrow (10%) with panhypoplasia, prominent erythrophagocytosis, and no morphologic features of myelodysplastic syndrome. In addition, no fatty or fibrous replacement of bone marrow was noted. Cytogenetic analysis revealed no clonal abnormalities. Interleukin 2 (CD25) soluble receptor level was 821 pg/mL ( $\leq 1033$  pg/mL) and decreased NK cell activity was noted.

**3. Based on the bone marrow findings, which one of the following is the most likely diagnosis?**

- a. Bone marrow suppression due to infection
- b. Hemophagocytic lymphohistiocytosis (HLH)
- c. Aplastic anemia
- d. Evans syndrome
- e. Unclear at this time, repeat bone marrow biopsy in 4 weeks

Bone marrow suppression from infection is typically either from aplasia secondary to viral infections (eg, human immunodeficiency virus, hepatitis, parvovirus B19) or infiltration by tuberculosis or fungal infections, which would be highly unlikely in this case. Further testing with repeated bone marrow biopsy would then be indicated to demonstrate resolution of the hypocellularity once the infection cleared. Although HLH is in the differential diagnosis, our patient does not meet diagnostic criteria (5 or more of the 8 criteria). Our patient has 4 of the findings: elevated ferritin level ( $>500$  mg/dL), cytopenia, hemophagocytosis in bone marrow, and decreased natural killer cell activity. However, he does not have any of

the remaining findings: hypertriglyceridemia and/or hypofibrinogenemia, splenomegaly, fever or increased soluble interleukin 2 receptor,<sup>2</sup> Aplastic anemia is in the differential diagnosis, although further testing is needed to confirm this diagnosis, especially since the bone marrow findings could be explained by an alternative diagnosis. Evans syndrome is a combination of ITP and autoimmune hemolytic anemia. Our patient did not have evidence of hemolysis.<sup>3</sup> Furthermore, both Evans syndrome and aplastic anemia are diagnoses of exclusion. The most likely diagnosis is unclear at this time because the cause of bicytopenia has not been determined. Repeated bone marrow biopsy is indicated in 4 weeks.

The patient's respiratory status improved with antibiotics and treatment of contributive anxiety with lorazepam. He was discharged home and completed a 2-week course of ceftriaxone and a prednisone taper. Eltrombopag was continued because it had been started just 1 week before admission and it was too soon to determine response. Trimethoprim-sulfamethoxazole was also continued for *Pneumocystis pneumoniae* prophylaxis. During the 2 weeks following discharge, his platelet count continued to decrease, and he required platelet transfusions on 2 separate occasions.

A repeated bone marrow biopsy was performed 4 weeks later to exclude bone marrow suppression due to infection and possible HLH. The biopsy confirmed an unchanged panhypoplasia with absent megakaryopoiesis, despite resolution of his bloodstream infection. In addition, no erythrophagocytosis, morphologic features of myelodysplasia, or lymphoproliferative disorders were noted, consistent with aplastic anemia.

**4. At this time, which one of the following would most negatively impact his prognosis in terms of aplastic anemia?**

- a. Age
- b. Presence of autoimmune diseases
- c. Previous infection
- d. Failure of eltrombopag
- e. NSAID use

Age is the correct answer. Although patients older than 50 years who are otherwise fit may be considered for donor-matched hematopoietic stem cell transplant for relapsed/refractory aplastic anemia, studies have shown an association between older age and higher incidence of graft failure and lower survival.<sup>4,5</sup> Thus, our patient's age is the most important factor for his prognosis. The presence of autoimmune diseases may actually present a treatable cause for his aplastic anemia if causal. The previous infection was treated without complication and no change in overall clinical status and would not be expected to impact prognosis at this time. Eltrombopag is approved for use in severe aplastic anemia refractory to immunosuppressive therapy and has demonstrated response in 40% of patients.<sup>6</sup> However, it was used in this case to treat ITP, and so its failure would not necessarily portend a poor prognosis without having a trial of immunosuppressive therapy. Nonsteroidal anti-inflammatory drugs have rarely been attributed to aplastic anemia, although our patient did not endorse NSAID use.

During the following 5 months, the patient had serial cell counts and continued to require blood and platelet transfusions. The leukocyte count eventually declined to leukopenia.

**5. Based on his latest bone marrow studies, which one of the following would be the best next treatment for our patient?**

- a. Supportive care only
- b. Immunosuppression with antithymocyte globulin (ATG) and cyclosporine
- c. Allogenic bone marrow transplant
- d. Alemtuzumab
- e. High-dose cyclophosphamide

Although supportive care is one of the components of the treatment of aplastic anemia, it is not reasonable to offer only supportive care to our patient because there are potential treatment options. Age is an important determinant of treatment options for aplastic anemia. In patients older than 50 years, such as our patient, the treatment of choice is immunosuppressive therapy

with ATG and cyclosporine.<sup>6</sup> Allogenic bone marrow transplant is the next step in younger patients once a donor is available and can be considered in patients aged 35 to 50 years, depending on the severity of anemia and the presence of comorbidities. In older fit patients, bone marrow transplant can be considered once immunosuppressive therapy has failed.<sup>6</sup> In disease refractory to standard immunosuppressive therapy, alemtuzumab, a humanized monoclonal antibody directed against CD52, can be used.<sup>7</sup> High-dose cyclophosphamide has been used for treatment of aplastic anemia but is associated with considerable hematologic toxicity resulting in a high incidence of infection and mortality and is therefore not recommended.<sup>6</sup>

The patient was subsequently hospitalized for inpatient treatment of aplastic anemia. Eltrombopag was discontinued, and he completed a 4-day course of ATG, cyclosporine, and corticosteroids. Since discharge, he has been taking cyclosporine and corticosteroids for management of both aplastic anemia and eosinophilic fasciitis but still requires monthly red blood cell transfusions and weekly platelet transfusions.

## DISCUSSION

Eosinophilic fasciitis is a rare connective tissue disease involving symmetric erythema and edema of the limbs and torso. This symptom is later replaced by skin induration secondary to collagenous thickening of the subcutaneous fascia in the setting of eosinophilia. Peripheral eosinophilia and hypergammaglobulinemia are often present. In rare cases, clinical features coexist with those of deep morphea due to associated dermal involvement, forming an overlap disorder.<sup>8</sup>

This case illustrates the rare hematologic progression of deep morphea and eosinophilic fasciitis overlap to aplastic anemia, for which there are few descriptions in the literature. Patients with eosinophilic fasciitis who experience progression to aplastic anemia tend to be men older than 50 years, as was our patient.<sup>8</sup> As demonstrated by our

case, the diagnosis may be delayed by the early phases of single-lineage hypoplasia resembling a refractory ITP. Aplastic anemia may also initially present in the setting of a systemic infection that may lead the clinician to believe that the bone marrow effects are secondary to infection instead of connective tissue disease. Unfortunately, prior cases have demonstrated a poor prognosis with very poor responses to standard aplastic anemia therapy. There is a high mortality rate with 8 deaths occurring in 19 cases reviewed in the literature, and essentially all cases were refractory to corticosteroid-containing regimens; 2 cases had long-term remission with cyclosporine immunosuppressive therapy, which our patient initiated.<sup>8</sup>

Recognition of the potential for progression to aplastic anemia in patients with predisposing conditions such as eosinophilic fasciitis is important so that the appropriate therapeutic approach can be initiated and complications of aplastic anemia anticipated.

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**CORRECT ANSWERS:** 1. d. 2. b. 3. e. 4. a. 5. b