35-Year-Old Man With Thrombocytopenia and Generalized Lymphadenopathy

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A 35-year-old man presented to the emergency department with blood-streaked oral secretions. AIDS had been diagnosed 1 month previously, and combination antiretroviral therapy (cART) with efavirenz-emtricitabine-tenofovir had been initiated promptly. At that time, he was hospitalized for malaise, adenopathy, fever, and headache. His absolute CD4 count was 8 cells/μL (reference range, 365-1437 cells/μL); viral load was 148,000 copies/mL (reference range, <20 copies/mL). In addition to beginning cART, he was treated with fluconazole for 2 weeks for oral candidiasis, amoxicillin-clavulanate for 1 week for otitis media, and valacyclovir for 1 week for genital herpes simplex virus type 2. Results of tuberculosis testing by both QuantiFERON and fungal/mycobacterial blood cultures were negative before appropriate prophylaxis was initiated for *Pneumocystis jiroveci* pneumonia and *Mycobacterium avium* complex with trimethoprim-sulfamethoxazole and azithromycin, respectively.

On awaking the day of admission, he noticed bloody oral secretions. Apart from fatigue, he felt well, having no epistaxis, hematemesis, hemoptysis, hematochezia, melena, fever, or chills. His current medications included efavirenz-emtricitabine-tenofovir, trimethoprim-sulfamethoxazole, and azithromycin. He was born and raised in Sub-Saharan Africa and emigrated to the United States at age 22 years. He had no recent travel history, smoked 6 cigarettes daily for 15 years, and did not drink alcohol. He worked at a manufacturing plant but had no notable occupational exposures.

On examination, the patient was afebrile (temperature, 36.7°C), his blood pressure was 119/73 mm Hg, pulse rate was 95 beats/min, respiratory rate was 14 breaths/min, and oxygen saturation was 99% when breathing room air. Oozing blood was noted around a left upper molar (tooth 14). He stated that a cavity had been filled at the site a year and a half previously. There was no petechia, purpura (wet or dry), ecchymoses, hepatosplenomegaly, or palpable adenopathy. Three small herpetic genital ulcers were noted. On laboratory studies (reference ranges provided parenthetically), a complete blood cell count (CBC) revealed normocytic anemia (hemoglobin, 12.0 g/dL [13.5-17.5 g/dL]), a mean corpuscular volume of 84.0 fL (81.2-95.1 fL), mild leukocytopenia (white blood cell count, 2.7×10^9/L [$3.5\text{-}10.5 \times 10^9$/L]), and profound thrombocytopenia (platelet count, 3.0×10^9/L [$150\text{-}450 \times 10^9$/L]). A CBC performed 4 days previously had yielded similar results (hemoglobin, 12.1 g/dL; white blood cell count, 2.9×10^9/L) except for platelet count (172.0×10^9/L). The patient was admitted to the inpatient medicine teaching service. Repeated CBC in EDTA and citrated tubes confirmed thrombocytopenia. A peripheral blood smear was negative for schistocytes. The fibrinogen level was 427 mg/dL (200-375 mg/dL), prothrombin time was 13 seconds (9.5-13.8 seconds), activated partial thromboplastin time was 28 seconds (28-38 seconds), haptoglobin level was 217 mg/dL (30-200 mg/dL), and lactate dehydrogenase level was 213 U/L (122-222 U/L).

1. Which *one* of the following is the *most likely* cause of the patient's thrombocytopenia?

a. Pseudothrombocytopenia
b. Sepsis
c. Primary human immunodeficiency virus (HIV)—associated thrombocytopenia
d. Medication adverse effect
e. Thrombotic thrombocytopenic purpura

By confirming the platelet count in both EDTA and citrated tubes, laboratory error via clumping of platelets, or pseudothrombocytopenia, has effectively been ruled out. Sepsis resulting in disseminated intravascular coagulation would be of concern. However, the patient did not have any signs of systemic inflammation apart from stable mild leukopenia, was

See end of article for correct answers to questions.

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hemodynamically stable, and was afebrile. Furthermore, results of coagulation studies were normal. Thrombocytopenia is common in patients with HIV infection. The incidence and severity vary with the degree of immunosuppression and can occur at any point in the course of clinical illness, even as part of the initial or as the sole initial manifestation.[1,2] Primary HIV-associated thrombocytopenia is the most common cause of thrombocytopenia in a patient with HIV infection.[1] The primary pathophysiologic mechanism is immune-mediated peripheral platelet destruction, similar to immune thrombocytopenic purpura, and can occur suddenly. It can be difficult to distinguish from secondary HIV-associated immune thrombocytopenic purpura. Of the medications the patient was currently taking, none are associated with hematologic abnormalities except trimethoprim-sulfamethoxazole, which can be myelosuppressive. The patient's normal platelet count 4 days before presentation, the reduction in platelets out of proportion to the other 2 cell lines, and the fact that cell counts recovered despite continuing the medication argue against a medication adverse effect. Thrombotic thrombocytopenic purpura must remain a consideration in view of the patient's profound thrombocytopenia. However, other than thrombocytopenia, no other features of the classic pentad were present (microangiopathic hemolytic anemia, neurologic symptoms, renal failure, or fever). Although it is a diagnosis of exclusion, primary HIV-associated thrombocytopenia was believed to be the most likely diagnosis.

The patient did not experience any interval decompensation while initial laboratory studies were performed and results obtained.

2. Which *one* of the following is the *most appropriate* next step in management?

a. Continue aggressive cART therapy alone
b. Plasma exchange
c. Platelet transfusion
d. Oral corticosteroids and intravenous immunoglobulin (IVIg)
e. Urgent splenectomy

With the advent of antiretroviral therapy, the incidence of HIV-associated thrombocytopenia has decreased.[2] However, in a patient with risk of spontaneous bleeding, more urgent therapy is indicated beyond antiretroviral therapy alone. Plasma exchange is the mainstay of treatment for patients with thrombotic thrombocytopenic purpura, but there is no indication for plasmapheresis in the treatment of primary HIV-associated thrombocytopenia. Although platelet transfusion may be appropriate if the patient is actively bleeding, it is not definitive, but rather temporizing, therapy because these platelets are similarly consumed by circulating immunoglobulins. Oral corticosteroids combined with IVIg is the most appropriate initial therapy. Although patients can improve with oral corticosteroids alone, the response is more consistent when IVIg is administered concomitantly.[2] Unfortunately, the response is often not maintained once these therapies have been withdrawn. Although splenectomy is curative in approximately 50% of patients with primary HIV-associated thrombocytopenia, it is not an appropriate initial therapy and is extremely risky, especially in the setting of profound thrombocytopenia.[3] Also, in patients with AIDS, the risk of fulminant sepsis following splenectomy is high.

Treatment with 80 mg/d of prednisone and 1 g/kg of IVIg was initiated. His platelet count continued to remain at less than 10.0×10^9/L, and he received a unit of platelets and an additional dose of IVIg. Over the course of 3 days, his platelet count stabilized to 50.0×10^9/L, and he remained asymptomatic with regard to active bleeding. However, at this point in his hospital course, the patient experienced worsening normocytic anemia, cyclic fever with temperatures as high as 39.7°C, elevated liver enzymes, and headache. Lumbar puncture was negative for meningitis. Blood cultures and fungal serologies yielded negative results. Development of acute shortness of breath prompted contrast computed tomography of the chest, which revealed no pulmonary embolism but did document diffuse lymphadenopathy. Broad-spectrum antibiotics were administered, with no change in his clinical status over 1 week. Positron emission tomography revealed diffuse [^{18}F]-fluorodeoxyglucose–avid lymphadenopathy above and below the diaphragm.

3. Which *one* of the following is the *most likely* cause of this patient's recurrent fever?

a. Immune reconstitution inflammatory syndrome
b. Adverse reaction to IVIg

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