35-Year-Old Man With Thrombocytopenia and Generalized Lymphadenopathy

Jarrett J. Failing, MD; John V. Higgins, MD; and Jordan M. Kautz, MD, MPH

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.

Resident in Internal Medicine, Mayo School of Graduate Medical Education, Rochester, MN (J.J.F., J.V.H.); Advisor to residents and Consultant in General Internal Medicine, Mayo Clinic, Rochester, MN (J.M.K.).

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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c. Sepsis
d. Meningoencephalitis
e. Lymphoproliferative disorder

Immune reconstitution inflammatory syndrome is a common occurrence in patients with severe immunodeficiency at the start of antiretroviral therapy. However, in order to have immune reconstitution inflammatory syndrome, there must be an underlying infection to which the reconstituted immune system is responding. Although our patient did have a history of oral candidiasis and otitis media, neither of these was active at the time of admission. His localized genital herpes would be unlikely to cause a systemic reaction. In addition, testing for mycobacterial and fungal infections 1 month previously had yielded negative results. Adverse events due to IVIg occur during the infusion or 1 to 3 days afterward. Although low-grade fever is associated with IVIg infusion, a persistent cyclic fever occurring more than 3 days after infusion would not be attributable to IVIg.[4] Although direct infectious causes such as sepsis or meningoencephalitis are the most common cause of fever in patients with HIV,[5] extensive work-up had been unrevealing. The patient's lymphadenopathy could have been due to disseminated infection, but with no evidence of an infectious source and minimal improvement despite adequate antimicrobial therapy, infectious etiologies are unlikely. Lymphoproliferative disorders are relatively common in patients with AIDS. In this patient with diffuse lymphadenopathy, cytopenias, and no apparent infectious etiology, lymphoproliferative causes were deemed most likely to drive his symptoms.

The patient underwent ultrasound-guided biopsy of a cervical lymph node. Tissue was sent for pathologic examination and culture, and the results were consistent with Castleman disease. Because of the widespread lymphadenopathy in this patient, it was classified as multicentric Castleman disease (MCD).

4. Given the pathologic and culture results, which *one* of the following opportunistic infections is *most likely*?

a. Cytomegalovirus
b. Human herpesvirus 8 (HHV-8)
c. *Toxoplasma gondii*
d. *Cryptococcus neoformans*
e. *P jiroveci*

Cytomegalovirus can present with several complications in an HIV-infected patient, commonly gastrointestinal or pulmonary disease, retinitis, encephalitis, rhinitis, and/or polyradiculopathy. Although HHV-8 is typically associated with Kaposi sarcoma, other potential complications are primary effusion lymphoma and, as in this case, Castleman disease, a rare aggressive systemic lymphoproliferative disorder characterized by diffuse peripheral lymphadenopathy, fever, hepatosplenomegaly, weight loss, shortness of breath, and anemia.[6] Diagnosis is made by histologic examination. Toxoplasmosis presents with neurologic complications, encephalitis being the most common. Pneumonitis and chorioretinitis are the most common extracerebral manifestations of toxoplasmosis. *Cryptococcus* is most commonly associated with meningoencephalitis, often presenting with an indolent course over 1 to 2 weeks with fever, headache, malaise, and meningeal signs. Pulmonary infection can also occur with *Cryptococcus*. *Pneumocystis jiroveci* (previously called *Pneumocystis carinii*) is classically associated with pneumonia. For patients with CD4 counts below 200 cells/μL, trimethoprim-sulfamethoxazole or alternate prophylaxis is indicated.[7]

The patient was determined to be HHV-8 positive. His clinical status improved following diagnosis and institution of appropriate therapy.

5. Which *one* of the following is the *most appropriate* next step for treatment of the patient's MCD?

a. Surgical removal of affected lymph nodes
b. Cytotoxic chemotherapy
c. Rituximab
d. Valganciclovir
e. Palliative therapy alone

Although surgical removal of lymph nodes is effective and often curative in unicentric Castleman disease, it is not an effective treatment in multicentric disease. Previously, MCD was treated with cytotoxic chemotherapy, typically CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin [vincristine], and prednisone). Although some response was reported in small trials, adverse events were common, and now such therapy is typically reserved for aggressive forms of MCD.[6] Rituximab is the treatment of choice for this patient with MCD because it is better tolerated than systemic chemotherapy.[8]

Although the mechanism of action is not completely understood, HHV-8 is associated with increased expression of CD20, which may in part explain the monoclonal antibody's efficacy. In small published trials, it has been found to substantially reduce symptoms and produce hematologic and clinical stabilization. Anti-HHV therapy such as valganciclovir may be used for patients with localized consequences of HHV, but it is not an effective treatment against the systemic complications of HHV-8 such as Kaposi sarcoma or MCD. Although palliative care is an option for patients with multiple HIV-related complications, there are effective treatments available that both increase median survival and are relatively well tolerated.[6]

Our patient received 4 weekly infusions of rituximab and achieved clinical stability. Positron emission tomography 2 months later revealed resolution of the lymphadenopathy. His prognosis is promising, with recent studies reporting an 80% 2-year overall survival in HIV-infected patients with MCD receiving cART and rituximab.[8]

DISCUSSION

Human immunodeficiency virus infection, especially once progressed to AIDS, affects numerous organ systems. This case highlights some of the possible hematologic manifestations of HIV infection. Anemia, thrombocytopenia, and neutropenia, as well as AIDS-related lymphomas/lymphoproliferative disorders commonly occur in patients with HIV infection. The cytopenias can be a direct result of the HIV infection but also are caused by secondary factors such as opportunistic infections, medications for antiretroviral therapy and infection prophylaxis, hypersplenism, and neoplasms. Anemia will occur in more than 60% of patients at some point in their disease, with anemia of chronic disease being the most frequent cause.[1] Before the cART era, thrombocytopenia occurred in 10% to 30% of patients, with primary HIV-associated thrombocytopenia being the most common cause. Both anemia and thrombocytopenia are more common once HIV infection advances to AIDS.[1,2] The occurrence of these complications is most likely due to a combination of worsening HIV infection and the increase in opportunistic infections (eg, parvovirus B19, *M avium* complex, and histoplasmosis), medications needed to treat and prevent complications of AIDS (eg, trimethoprim-sulfamethoxazole, ganciclovir, amphotericin B), and AIDS-related neoplasms (eg, non-Hodgkin lymphoma).[1] However, with the advent of cART, the incidence of cytopenias has considerably decreased. Combination antiretroviral therapy decreases the incidence of most of the secondary causes, such as opportunistic infections. In addition, one study found that even when the secondary causes of cytopenias were excluded, cART was able to reverse cytopenias in 6 months in 84% of anemic, 100% of thrombocytopenic, and 91% of neutropenic patients.[9]

Human immunodeficiency virus infection is associated with numerous types of malignant neoplasms, including several that are considered AIDS-defining illnesses (Burkitt lymphoma, Kaposi sarcoma, primary cerebral lymphoma, immunoblastic lymphoma, invasive cervical cancer). Many of these disorders occur at a greater frequency in HIV-infected patients than in the general population. For example, patients with AIDS have up to a 70-fold increased risk of having non-Hodgkin lymphoma.[10] As with cytopenias, once HIV-infected patients' CD4 counts drop below 200 cells/μL, patients are at higher risk for development of lymphomas. Multiple processes drive this increased cancer risk. Human immunodeficiency virus infection suppresses the immune system, which decreases the immune system's natural antitumor activities. Immunosuppressed HIV-infected patients, although at no increased risk of carriage of latent virus, are more prone to manifest disease from other oncogenic viruses, such as Epstein-Barr virus and HHV-8. Although cART has decreased the incidence of AIDS-related lymphomas, the change has not been as drastic as the decrease seen in many of the other AIDS-defining conditions.[1] Cancer is currently responsible for 30% of deaths in HIV-infected patients, with over half being from AIDS-related malignant neoplasms.[11] Besides malignant disorders, there are other less common hematologic disorders associated with HIV, including Castleman disease and hemophagocytic lymphohistiocytosis. Interestingly, although most of the HIV-associated diseases have decreased in frequency with the use of cART, MCD has manifested the opposite trend. In one study, the incidence before the availability of cART was 2.3 per 10,000 patient-years vs 8.3 per 10,000 patient-years in

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the modern cART era.[12] Similarly, the incidence of Hodgkin disease has also increased. The reason for these observations is uncertain but may represent some immune-modulating effect of the cART medications. Although this effect is conjectural, perhaps in the future we will come to understand these conditions more in the spectrum of immune reconstitution inflammatory syndrome.

As illustrated in this case, it can be difficult to know when to ascribe the findings (such as thrombocytopenia and generalized lymphadenopathy) to the primary disease process of HIV infection vs secondary causes (such as Castleman disease). Even in the modern cART era, cases like this continue to occur, and understanding the pathophysiology and sequelae of HIV/AIDS is vital to ensuring that the correct diagnosis and treatment decisions are made.

Correspondence: Address to Jordan M. Kautz, MD, MPH, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (kautz.jordan@mayo.edu).

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