Human Immunodeficiency Virus–Associated Hemophagocytosis with Iron-Deficiency Anemia and Massive Splenomegaly

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We present a case of hemophagocytic syndrome in a human immunodeficiency virus–positive man with iron-deficiency anemia that did not respond to highly active antiretroviral therapy. Clinical resolution occurred only after a splenectomy was performed.

Hemophagocytic syndrome (HPS) is characterized by fever, severe constitutional symptoms, hepatosplenomegaly, variable lymphadenopathy, abnormal liver function test results, neurologic symptoms, and pancytopenia [1–3]. These symptoms are accompanied by a reactive infiltration of the bone marrow, lymph nodes, liver, and/or spleen with macrophages that are actively involved in the phagocytosis of RBCs, platelets, and/or leukocytes [2]. HPS may be primary or secondary to infection, malignancy, and/or drug therapy. HIV infection, alone [4–11] or in concert with other infections, is a known cause of HPS. The treatment for potentially-fatal HPS in HIV-associated cases has not been established. Single case reports have demonstrated the resolution of HIV-associated HPS with highly active antiretroviral therapy (HAART) [10] or splenectomy [4].

We report what is, to the best of our knowledge, the first case of HIV-associated HPS in which severe iron-deficiency anemia, resulting from marked splenic sequestration of iron, was successfully treated with splenectomy.

Case report. A 32-year-old white man with HIV-1 infection (CD4+ T lymphocyte count, 100 lymphocytes/mm3; HIV virus load, >100,000 copies/mL by ultrasensitive PCR) presented in June 2002 with intermittent fever, dyspnea, night sweats, dry cough, and anorexia. Symptoms had been present for 8–10 weeks. The patient’s only medication was iron supplementation, a treatment that had been started following the diagnosis of iron-deficiency anemia 10 months prior to presentation. He was receiving no other medications and had never received antiretroviral therapy. There was no history of gastrointestinal or genitourinary blood loss or splenomegaly. On physical examination, the patient appeared ill and had a temperature of 39.5°C, a pulse rate of 116 beats/min, a respiratory rate of 20 breaths/min, and an oxygen saturation level of 84% while breathing room air. He had oral hairy leukoplakia, splenomegaly that was palpable 6 cm below the left costal margin, and generalized lymphadenopathy. There was no skin rash or hepatomegaly, and the results of screening the patient’s stool samples for blood were negative.

Laboratory values were as follows: WBC count, 2800 cells/µL; hemoglobin, 6.9 g/dL; hematocrit, 20.1%; platelet count, 46 × 10³ platelets/µL; mean corpuscular volume, 77 fl; RBC distribution width, 17.6%; reticulocyte count, 0.6%; alanine aminotransferase, 33 IU/L; aspartate aminotransferase, 39 IU/L; lactate dehydrogenase, 399 IU/L; alkaline phosphatase, 45 IU/L; total bilirubin, 0.4 mg/dL; iron, 38 µg/dL; total iron binding capacity, 325 µg/dL; ferritin, 230 ng/mL; CD4+ T lymphocyte count, 100 lymphocytes/mm³; and HIV load, >100,000 copies/mL by PCR. The results of blood tests for cytomegalovirus (CMV) IgG, Epstein-Barr virus (EBV) VCA-IgG, EBV Epstein-Barr nuclear antigen IgG, and parvovirus B-19 IgG were all positive. However, results of tests for CMV IgM, CMV antigen, and parvovirus B-19 IgM, as well as results of the monospot test, were all negative. Blood cultures for bacteria, mycobacteria, and fungi were negative.

Findings of an abdominal CT scan demonstrated, in addition to marked splenomegaly, significant retroperitoneal, mesenteric, and inguinal lymphadenopathy. Lymphoma was suspected, and a bone marrow biopsy was performed. The bone marrow was hyperplastic, with a cellularity of 90% and a normal myeloid-to-erythroid ratio. There was no morphological or immunophenotypic evidence of a lymphoproliferative disorder. There were occasional macrophages with ingested RBCs. Iron stores in the marrow were markedly decreased. A cervical lymph node biopsy showed benign pathology with no evidence of hemophagocytosis. Cultures of marrow and lymph node tissue were negative for bacteria, mycobacteria, and fungi. The findings of a chest radiograph showed bilateral interstitial markings. However, the results of immunofluorescence tests performed on broncho-alveolar lavage (BAL) fluid samples were
Figure 1. Photomicrograph showing extensive hemophagocytosis involving the spleen and splenic hilar lymph nodes of an HIV-positive patient. A, Expansion of the splenic red pulp with prominent hemophagocytic macrophages (arrows) in the cords and sinuses (original magnification, ×600). B, Hilar lymph node showing an accumulation of hemophagocytic macrophages (arrow) in a dilated sinus (original magnification, ×600). C, Iron stain showing marked iron deposition in splenic macrophages (original magnification, ×400).
negative for Pneumocystis carinii pneumonia. No evidence of viruses (including evidence of CMV early antigen by shell vial assay), bacteria, fungi, Legionella, or mycobacteria was found by culture of BAL fluid samples.

The patient was empirically treated with trimethoprim-sulfamethoxazole, azithromycin, and ceftazadime. Because there was no clinical improvement in response to therapy with antibiotics, it was stopped, and treatment with HAART, consisting of efavirenz, lamivudine, and tenofovir, was started. Despite 3 weeks of receiving treatment with HAART, the patient remained febrile, dyspneic, and profoundly anemic. He became transfusion dependent. Because of the patient’s inappropriate response to blood transfusion (the hematocrit only increased from 21% to 24% following the transfusion of 9 units of packed RBCs over a 3-week period) and the lack of evidence of immune-mediated hemolysis, a semiurgent splenectomy was performed.

The spleen was markedly enlarged and weighed 2.2 kg. The splenic parenchyma was homogeneous without nodular lesions. Microscopically, the red pulp was expanded, with numerous macrophages in the splenic cords and sinuses. Many of the macrophages showed prominent erythrophagocytosis (figure 1A) and leukophagocytosis. Sections of the splenic hilar lymph nodes also showed hemophagocytic macrophages in the dilated sinuses (figure 1B). Iron staining showed abundant iron deposition in the splenic macrophages (figure 1C). The findings indicated extensive hemophagocytosis involving the spleen and the lymph nodes, as well as sequestration of iron in the spleen. No other cause of splenomegaly was found.

One day after the splenectomy was performed, the patient defervesced, and his hematocrit level stabilized. Clinically, the patient’s HPS resolved. He has continued to do well, with no recurrence of HPS during 1 year of follow-up. Clinical diagnosis and resolution occurred only after the splenectomy was performed.

Discussion. HPS caused by HIV infection alone has not been widely reported, and, to our knowledge, no case of an iron-deficiency anemia associated with HPS has been described. In our patient, HPS was attributed to HIV infection alone because no underlying malignancy, drug reaction, or other infectious process could be demonstrated. Iron-deficiency anemia in HIV-positive patients has been reported to be the result of decreased nutritional intake or blood loss (mainly from the gastrointestinal tract, due to Kaposi sarcoma or lymphoma), as well as the result of malabsorption due to infection or gastric hypoacidity [13, 14]. Our case is unique in that the patient’s iron-deficiency anemia appears to be caused by the marked sequestration of iron in his spleen, which was enlarged as part of his HIV-associated HPS. The striking lack of iron stores in the patient’s bone marrow was in stark contrast to the iron deposition in his spleen. His iron deficiency could not be explained by blood loss, inadequate intake (because he was compliant with his iron supplement regimen), or malabsorption (because the results of iron studies normalized following iron therapy).

Only 1 recent review of HIV-related anemia lists HPS as a cause of anemia in patients with HIV infection [12]. As illustrated in this case report, we suggest that HPS be strongly considered as a potential diagnosis among HIV-infected individuals with unexplained iron-deficiency anemia. Although a bone marrow biopsy often provides evidence of HPS [2, 3], in this case a splenectomy proved to be both diagnostic and therapeutie. Therefore, this case further demonstrates that the results of a bone marrow biopsy cannot always be relied on in making a diagnosis of HPS.

HIV-associated HPS has been treated successfully with HAART [10]. Our patient received 3 weeks of HAART without an improvement in his clinical condition or his anemia. Instead, our patient recovered within 24 h after the splenectomy and has remained healthy since that time. There is only 1 other case report of a splenectomy being performed on a patient with HIV-associated HPS [4]. In that case, the patient had fevers, drenching sweats, inappropriate response to blood transfusions, and massive splenomegaly, and a bone marrow biopsy did not show evidence of hemophagocytosis. The findings of a pathologic examination of the spleen did show hemophagocytosis, and the patient’s symptoms resolved after the splenectomy.

In conclusion, we describe a patient with HIV-associated HPS that resulted in severe iron-deficiency anemia who recovered following a splenectomy. We propose keeping HPS high in the differential diagnosis of HIV-infected patients presenting with B-type symptoms, iron-deficiency anemia, and splenomegaly. If the findings of a bone marrow or lymph node biopsy are not diagnostic in such cases, splenectomy should be considered for both diagnosis and treatment.

References