Fatal hemophagocytic syndrome as a manifestation of immune reconstitution syndrome in a patient with acquired immunodeficiency syndrome

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and potentially life-threatening condition characterized by uncontrolled hyper inflammation caused by various inherited or acquired immune deficiencies. We report a case of a 42-year-old man, newly diagnosed with HIV on the basis of a low CD4 T lymphocyte count (17 cells/mm³ [normal range: 500–1000 cells/mm³]) and HIV viral load >100,000 copies/mL by polymerase chain reaction tests who was undergoing an antiretroviral regimen (emtricitabine, tenofovir disoproxil fumarate, ritonavir, and darunavir) and opportunistic infection prophylaxis (clarithromycin and atovaquone). Six weeks after HAART initiation, he was admitted to the hospital due to a 3-week history of high fever (maximum temperature, 39.4°C), chills, and malaise. He was taking no other medications, had no recent travel or animal exposure, and had no history of shortness of breath, chest pain, odynophagia, oral thrush, abdominal pain, diarrhea, dysuria or any skin rash. His physical characteristics upon admission were as follows: oral temperature 39.8°C; pulse 110 beats/min; blood pressure 110/70 mm Hg; respiratory rate 24 breaths/min; heart rate 110 bpm; and blood pressure 110/70 mm Hg. Upon examination, he was febrile and had jaundice. His liver was palpable 4 cm below the right costal margin. Laboratory findings included a white blood cell count of 5600/mm³, hemoglobin 10.2 g/dL, platelet count 16,000/mm³, and a normal prothrombin time. Serological tests for HIV, hepatitis B, and hepatitis C were negative. He was found to have an elevated ferritin level (4800 ng/mL) and triglycerides (270 mg/dL). A bone marrow biopsy showed hemophagocytosis, and a diagnosis of HLH was made. He was treated with dexamethasone, cyclosporine, and intravenous immunoglobulin. Despite treatment, he developed progressive pancytopenia and died 2 weeks later.

Case Report. A 42-year-old man, newly diagnosed with HIV on the basis of a low CD4 T lymphocyte count (17 cells/mm³ [normal range: 500-1000 cells/mm³]) and HIV viral load >100,000 copies/mL by polymerase chain reaction (PCR) tests who was undergoing an antiretroviral regimen (emtricitabine, tenofovir disoproxil fumarate, ritonavir, and darunavir) and opportunistic infection prophylaxis (clarithromycin and atovaquone). Six weeks after HAART initiation, he was admitted to the hospital due to a 3-week history of high fever (maximum temperature, 39.4°C), chills, and malaise. He was taking no other medications, had no recent travel or animal exposure, and had no history of shortness of breath, chest pain, odynophagia, oral thrush, abdominal pain, diarrhea, dysuria or any skin rash. His physical characteristics upon admission were as follows: oral temperature 39.8°C; pulse 110 beats/min; blood pressure 110/70 mm Hg; respiratory rate 24 breaths/min; heart rate 110 bpm; and blood pressure 110/70 mm Hg. Upon examination, he was febrile and had jaundice. His liver was palpable 4 cm below the right costal margin. Laboratory findings included a white blood cell count of 5600/mm³, hemoglobin 10.2 g/dL, platelet count 16,000/mm³, and a normal prothrombin time. Serological tests for HIV, hepatitis B, and hepatitis C were negative. He was found to have an elevated ferritin level (4800 ng/mL) and triglycerides (270 mg/dL). A bone marrow biopsy showed hemophagocytosis, and a diagnosis of HLH was made. He was treated with dexamethasone, cyclosporine, and intravenous immunoglobulin. Despite treatment, he developed progressive pancytopenia and died 2 weeks later.
20/min; and SpO₂ 98% on room air. His physical examination revealed a significant hepatosplenomegaly. His initial laboratory test results were as follows: white blood cell count of 3.81 x 10⁹/L, with 67.9% segmented neutrophils, 18% lymphocytes, 8.8% monocytes, and 1% basophils. Hemoglobin was 7.8 g/dL and the platelet count was 47 x 10⁹/L. There was no evidence of bleeding or hemolysis. Initial renal, hepatic, and autoimmune profiles as well as vitamin B12 and folate levels were normal. Over the next 2 days, the patient exhibited hemodynamic deterioration and became confused. Blood, urine, and sputum cultures were negative for bacteria, mycobacteria, and fungi. Computed tomography scans of the brain was also unremarkable. Moreover, all serological tests were negative, including the presence of Mycoplasma pneumonia, parvovirus, Coxsackie B virus, hepatitis A-C, Brucella, malaria, varicella, cytomegalovirus, Epstein-Barr virus, and toxoplasmosis, thus failure to identify the underlying cause of pancytopenia. The CD4 count was 410 x 10⁶/L and HIV PCR detected only 67 copies/mL. A peripheral smear showed worsening pancytopenia with few lymphoplasmacytoid cells. Abdominal and pelvic CT scans showed hepatosplenomegaly with enlarged mesenteric, retroperitoneal, external iliac, and para-aortic lymph nodes. He had persistent fever, confusion, and progressive pancytopenia. Immune reconstitution syndrome was suspected; hence, dexamethasone along with broad-spectrum antibiotics including meropenum, vancomycin, acyclovir, and caspofungin were administered. After ruling out all possibilities, bone marrow was examined for malignancy and other causes of pancytopenia. Surprisingly, the bone marrow exhibited significant hemophagocytosis with very active hematopoietic cells and engulfment of normal hematopoietic cells (Figures 1 and 2).

The patient remained febrile with temperatures up to 40°C. Within a few days, he became more hypotensive and developed acute respiratory distress due to rapid bilateral pleural effusion and his mental condition started deteriorating along with a rapid increase in creatinine level from 87-243 mc mol/L, (50-100 mc mol/L) necessitating continuous renal replacement therapy (CRRT). Meanwhile, his white blood cell count decreased to 1.7 x 10⁹/L, (normal range: 4.8-10.8 x 10⁹/L) hemoglobin dropped to 6.5 g/dL (normal range for male: 13.6-17.5 g/dL) and he developed severe thrombocytopenia with a platelet count of 4 x 10⁹/L (normal range 150-450 x 10⁹/L). Moreover, international normalized ratio (INR) increased to 4.6 (normal: 0.8-1.2) with rapidly increasing values for liver transaminases, and direct bilirubin. Other parameters suggestive of hemophagocytosis were increasing lactate dehydrogenase and ferritin levels of 2099 U/L (normal: 88-230 U/L) and 31,435 mcg/L (16-300 mcg/L), respectively, as well as a high triglyceride level of 3 mmol/L. However, rapid clinical and biochemical deterioration continued despite antibiotics and antiretrovirals, indicating disseminated intravascular coagulation.

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Discussion. Hemophagocytic lymphohistiocytosis is a rare fulminant disease with multi-organ involvement. It is primarily due to the invasion of all organs and tissues by abnormal proliferated histiocytes and lymphocytes, which secrete large amount of cytokines, leading to severe hyper-inflammation. All genetic and acquired forms of HLH share almost the same pathophysiology. According to the HLH-2004 protocol, at least 5 out of 8 diagnostic criteria are required to establish the diagnosis of HLH unless there is an established molecular diagnosis or underlying family history. These include 5 initial diagnostic criteria as proposed in the HLH-94 protocol-fever, splenomegaly, hypertriglyceridemia ≥265mg/dL, hypofibrinogenemia ≤150 mg/dL, and bicytopenia, with at least 2 of the following: hemoglobin ≤9 g/dL, platelets <100 × 10³/µL, neutrophils <1.0 × 10³/µL, and neutrophils <1.0 × 10³/µL in the peripheral blood; evidence of hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy; and 3 new criteria introduced in the HLH-2004 protocol: low or absent NK cell activity, hyperferritinemia ≥500 µg/L, and increased soluble interleukin 2 receptor levels HLH may be the first HIV manifestation.

In summary, the present patient had fever, pancytopenia, hypertriglyceridemia, hyperferritinemia, splenomegaly, high transaminases, high bilirubin, and hemophagocytosis, which were subsequently confirmed from a bone marrow specimen without evidence of malignancy. Moreover, imaging studies and a variety of cultures and serological tests for a number of pathogens failed to reveal any association with other opportunistic infections, suggesting that HLH be considered in cases of IRIS that manifests 3 weeks after the initiation of HAART therapy. As the pathophysiology of HLH and IRIS share many features, they may have been responsible for the fatal presentation of this patient.

In conclusion, HLH can manifest as IRIS within weeks or months after the initiation of HAART and is associated with significant morbidity and mortality.

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References


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