Fever in a Man with HIV: An Unusual Case of an Immune System Gone Wrong

Emily Sutton, MD, Aishah Ali, MD

INTRODUCTION
Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of immune dysregulation that is often recognized as secondary to an underlying immune activating state, such as malignancy, rheumatologic disorders, and infections. This case highlights an association between HLH and human immunodeficiency virus (HIV) infection. Although HLH is a rare complication of HIV, it presents a difficult challenge for treatment. Without treatment, HLH is invariably fatal, but the consequence of the immunosuppressive treatment regimen in the setting of an underlying opportunistic infection can also have fatal outcomes.

CASE PRESENTATION
A 38 year-old man with a history of HIV infection with a CD4 lymphocyte count of 2 cells/mm³ presented with fevers two weeks after starting antiretroviral therapy (ART). His initial extensive infectious workup was negative, including cryptococcal antigen in the serum and cerebrospinal fluid. His liver enzymes then began to rise, prompting concern for drug toxicity. At this time, ART and trimethoprim/sulfamethoxazole were discontinued, but he continued to have high-grade fevers as well as hypotension, pancytopenia and hypofibrinogenemia and was transferred to the medical intensive care unit (MICU). On admission to the MICU, he was febrile with a temperature of 103.6°F, hypotensive with a blood pressure of 78/37 mmHg, tachycardic with a heart rate of 127 beats per minute, tachypneic with a respiratory rate of 26 breaths per minute, and had an oxygen saturation of 97% on room air. On exam, he was thin, in moderate distress, and lethargic. He had no thrush or nuchal rigidity. He had cervical lymphadenopathy and hyperpigmented maculopapular rashes on his lower extremities; otherwise his exam was unremarkable.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis included opportunistic infections given his CD4 count of 2 cells/mm³, immune reconstitution inflammatory syndrome (IRIS) given his

Figure 1: The patient’s bone marrow biopsy demonstrating hemophagocytosis of platelets (short arrow) and erythrocytes (long arrows).
recent initiation of ART, drug reaction or toxicity, and hemophagocytic lymphohistiocytosis (HLH). Further laboratory studies revealed an elevated ferritin level of 83,987 ng/mL (normal range = 30-400), which was highly suspicious for HLH. The diagnosis was confirmed with a bone marrow biopsy revealing hemophagocytosis (Figure 1) as well as an elevated interleukin 2 receptor (IL2R) level of 9020 pg/mL (normal range = 0-1033).

OUTCOME AND FOLLOW-UP
The patient was treated with intravenous immune globulin, high dose dexamethasone, and anakinra, an IL1R inhibitor, resulting in cessation of his fevers, resolution of his respiratory distress, and improvement in his cell lines. He was transferred back to the floors with plans to restart ART. As no underlying infection had been found, his HLH was thought to be secondary to his HIV infection. However, three days later, he became acutely short of breath and hypotensive and was found to have Cryptococcus neoformans fungemia, although his initial blood and cerebrospinal fluid fungal studies were negative. He was transferred back to the MICU, initiated on intravenous amphotericin B/flucytosine, and ART was discontinued. However, he continued to decompensate rapidly and expired from septic shock and acute pulmonary edema later that day.

DISCUSSION
Hemophagocytic lymphohistiocytosis (HLH) is a severe and rapidly progressive disorder of immune activation and dysregulation that can occur as a familial disorder or, as is becoming increasingly recognized, secondary to a variety of underlying conditions. Secondary HLH occurs after strong immunologic activation, such as with severe infection, immunodeficiency, or underlying malignancy. In the past, HLH was also sometimes referred to as hemophagocytic syndrome. Another disorder on the spectrum of this disease state includes macrophage activation syndrome, which is a form of HLH associated with rheumatologic diseases.1 Although the immune cells in HLH are functionally normal, it is thought to be the result of proliferation of activated T cells that go on to activate macrophages, as well as the lack of appropriate apoptosis of immunogenic cells. As these overly active macrophages and histiocytes proliferate and run rampant, they phagocytize other cells, including erythrocytes, leukocytes, and platelets, leading to the clinical symptoms. This highly stimulated immune system results in life-threatening cytokine storm and inflammatory reactions.1,2

As the clinical entity of HLH is a syndrome, it has features that can be seen in other clinical states, but it is the combination of findings that make the diagnosis likely. The diagnostic criteria for HLH include fever, splenomegaly, cytopenia of at least 2 of 3 cell lines, elevated ferritin, hypofibrinogenemia and/or hypertriglyceridemia, elevated CD 25 (IL-2 receptor), low or absent natural killer (NK) cells, and hemophagocytosis seen in the bone marrow, liver, spleen, or lymph nodes. Five of these eight criteria must be met in order to establish the diagnosis (Table 1).1 Notably, the criteria only require a ferritin level >500 ng/mL, but a level >10,000 ng/mL is thought to be highly suspicious for HLH, with a specificity of 96%.6 The ferritin level upon diagnosis has also been found to have prognostic value, and its decline correlates with response to treatment. The soluble IL-2 receptor was found to be a more sensitive marker than ferritin with a sensitivity of 93% and also carries prognostic implications.5
Patients presenting with a clinical picture of fever and highly elevated inflammatory markers should raise the suspicion for hemophagocytic lymphohistiocytosis (HLH). Five of the eight criteria must be met for the diagnosis, but a ferritin level >10,000 ng/mL is highly suspicious. HLH is fatal without treatment, but immunomodulatory therapy directed at HLH may be perilous in the setting of underlying infection. Currently, there are no guidelines on empiric antibiotic use for patients with HIV and HLH, but one must be vigilant in searching for underlying infections given the risk of the immunosuppressive regimen required to treat HLH in the setting of HIV.

REFERENCES