Editorial Comment: Hemophagocytic Syndrome—An HIV-Associated Quagmire

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By AIDS Reader [1]

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Sanchez and colleagues1 report a case of histoplasmosis-associated reactive hemophagocytic syndrome in a 61-year-old HIV-infected man. The association of hemophagocytic syndrome with HIV infection is important for several reasons: (1) Many of the features of the hemophagocytic syndrome are not specific in this setting, and, hence, may be easily overlooked or misdiagnosed. (2) The hemophagocytic syndrome can mimic an infection or lymphoma. (3) The hemophagocytic syndrome may obscure the diagnosis of a precipitating, treatable illness.

The hemophagocytic syndrome is a clinicopathological entity characterized by increased proliferation and activation of benign macrophages (histiocytes) with phagocytosis of hematopoietic cells throughout the reticuloendothelial system.2 The underlying pathological mechanism involves T/natural killer cell dysfunction with excess cytokine release that activates macrophages and promotes hemophagocytosis.3 Diagnosis of this macrophage activation syndrome requires documentation of a fluctuating fever, hepatosplenomegaly, pancytopenia (involving two or more cell lines), hepatic dysfunction, disseminated intravascular coagulation, and hypertriglyceridemia, as well as morphological evidence of hemophagocytosis principally in the bone marrow but also in the spleen, liver, lymph nodes, skin, or cerebrospinal fluid. Diagnosis thus requires tissue examination, typically of the bone marrow, which shows pronounced hyperplasia of benign histiocytes actively phagocytizing hematopoietic cells (the hallmark of this disease). Phagocytized blood elements include both mature and immature blood cells. The clinical course is often fulminant and can be fatal. An abrupt fall in blood cell counts may occur within a matter of days, requiring prompt transfusion support.4 Levels of numerous cytokines are increased (eg, interleukin [IL]-1, IL-2, IL-6, IL-10, IL-12, IL-18, interferon-α, tumor necrosis factor α), which may explain why patients with the hemophagocytic syndrome characteristically have high fevers and severe constitutional symptoms. Additional clinical features may include lymphadenopathy, rash, and neurological involvement. Hyperferritinemia is another important clue to the diagnosis of reactive hemophagocytic syndrome.5 Rarely, a more dramatic presentation, such as bowel perforation, may manifest.6 One of the important take-home messages illustrated by the case report of Sanchez and colleagues is that only if the clinician is astute will the aforementioned constellation of clinical and histopathological clues lead to the correct diagnosis and, hence, the appropriate management of the patient with reactive hemophagocytic syndrome.
The hemophagocytic lymphohistiocytic syndromes include primary (familial) disorders and secondary (reactive) hemophagocytic syndrome. Familial hemophagocytic lymphohistiocytic disorders present in infancy. Secondary hemophagocytic syndrome affects a wider range of persons and typically occurs in the setting of underlying immunodeficiency. The list of pathogens, conditions, and other factors associated with a reactive secondary hemophagocytic syndrome is lengthy and increasing (Table).

While viruses are most commonly involved, virtually any infectious agent can precipitate this syndrome. The mechanism(s) that causes macrophage activation with ensuing hemophagocytosis and, in turn, the collection of abnormal clinical and laboratory findings is quite similar across all types of the hemophagocytic syndrome. Often, the underlying condition is clinically occult. Therefore, a rigorous search for an underlying malignancy or infection is warranted once hemophagocytic syndrome is diagnosed.

Reactive hemophagocytic syndrome is uncommon. In a 1988 study conducted at Johns Hopkins Hospital, only 22 (0.8%) of 2634 marrow aspirates indicated a diagnosis of the hemophagocytic syndrome. In a more recent prospective study in which 31 HIV-infected patients with coexisting pancytopenia underwent bone marrow examination, only 1 patient received a diagnosis of the hemophagocytic syndrome. Given that the hemophagocytic syndrome occurs more commonly in the setting of immune deficiency, it is somewhat surprising that only a limited number of cases of the hemophagocytic syndrome associated with HIV infection have been reported (about 40). Because HIV-infected patients have a propensity for opportunistic infections and malignancies, such as lymphoma, they are presumably at increased risk for reactive hemophagocytic syndrome.

While the paucity of such cases could represent an underestimated cause of pancytopenia, perhaps other factors (eg, genetic susceptibility) are important in determining whether the hemophagocytic syndrome will result.

In a review of 39 HIV-infected patients with hemophagocytic syndrome, the majority (82%) were found to be men with a mean age of 38 years (range, 26 to 59). Many presented with fever (90%), cytopenia (anemia in 100%, thrombocytopenia in 80%, and leukopenia in 78%), hepatomegaly (67%), splenomegaly (55%), and hyperferritinemia (mean ferritin level, 280 times the normal range). In this review, most patients had a CD4+ cell count of less than 200/µL (mean, 132).

A few cases of HIV-associated hemophagocytic syndrome in children have been reported. While some authors have noted that the hemophagocytic syndrome tends to develop during an advanced stage of HIV disease, cases have been observed earlier in the course of HIV infection (eg, during acute seroconversion). Recurrent hemophagocytic syndrome has also been documented in 1 HIV-positive person.

Conditions previously observed in association with the hemophagocytic syndrome in the setting of HIV infection have included infection with Epstein-Barr virus, Cytomegalovirus, or human herpesvirus 8; disseminated histoplasmosis; toxoplasmosis; mycobacterial infection (tuberculous and atypical); candidiasis; penicilliosis; Kaposi sarcoma; and lymphoma. In several cases, no underlying trigger was identified, leading to the assumption that HIV infection itself may directly result in a reactive hemophagocytic syndrome. The exact role of HIV infection in the hemophagocytic syndrome still needs to be defined.

As mentioned above, many of the clinical and hemological signs of the hemophagocytic syndrome are nonspecific in the setting of HIV infection and, as a result, may go unnoticed or be mistaken for other conditions, such as lymphoma. In one study of 5 HIV-positive patients, hemophagocytic syndrome was diagnosed up to 12 weeks after the onset of symptoms, and in most patients, repeated examinations of the bone marrow were required. In one case, histiocytic infiltration was not even seen in the bone marrow—only in the patient’s liver and spleen.

The hemophagocytic syndrome carries a dismal prognosis. In general, the prognosis of infection-associated hemophagocytic syndrome appears to be better than that of the hemophagocytic syndrome secondary to malignancy. At least half of the deaths previously reported in HIV-infected persons occurred within 1 month after the diagnosis of hemophagocytic syndrome. We are aware of one unusual case in which the hemophagocytic syndrome appeared during primary HIV infection and reversed spontaneously.

The patient presented by Sanchez and coworkers was successfully treated. Their case report bears testimony to the fact that early identification and treatment of the underlying cause clearly helps in recovery. Unfortunately, there are no pathognomonic clinical and laboratory features of reactive hemophagocytic syndrome. Any dramatic, unexplained drop in a patient’s blood cell counts over a few days should raise the possibility of hemophagocytic syndrome. A high index of suspicion in the HIV-infected patient is critical for the management of this otherwise fatal disorder.
Once the diagnosis of hemophagocytic syndrome is established, thorough evaluation for any underlying treatable disease(s), including careful scrutiny for lymphoma, is required. Therapy is usually directed at supportive care and treatment of the underlying disease. While the initiation of highly active antiretroviral therapy has been suggested to improve the eventual outcome in some cases,\textsuperscript{14,27} there have been cases in which the hemophagocytic syndrome did not respond to such therapy.\textsuperscript{28} Moreover, a case of reactive hemophagocytosis associated with the initiation of antiretroviral therapy has been documented, probably representing a manifestation of the immune reconstitution inflammatory syndrome.\textsuperscript{29} The role of antiretroviral therapy in HIV-associated reactive hemophagocytic syndrome needs to be explored further.

Liron Pantanowitz, MD  
Assistant Professor of Pathology  
Baystate Medical Center  
Tufts University School of Medicine  
Springfield, Mass  
Bruce J. Dezube, MD  
Associate Professor of Medicine  
Beth Israel Deaconess Medical Center  
Harvard Medical School  
Boston

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