Hemophagocytic Lymphohistiocytosis Associated With *Bartonella henselae* Infection in an HIV-Infected Patient

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Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome that often occurs in immunocompromised patients. We report the first case of HLH due to *Bartonella henselae* infection in a patient with human immunodeficiency virus infection. Early recognition of HLH and *B. henselae* through liver biopsy and serological tests led to the patient’s recovery.

**Keywords.** lymphohistiocytosis; hemophagocytic syndrome; *Bartonella henselae*; acquired immune deficiency syndrome; human immunodeficiency virus.

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening syndrome caused by a hyperinflammatory immune response. Currently, the classification of HLH by the Histiocyte Society distinguishes the primary (genetic) and secondary (reactive) forms related to infectious, autoimmune, or neoplastic conditions [1]. In adults, HLH is often caused by lymphomas or infectious agents such as mycobacteria and herpesviruses, mainly in a context of immunodeficiency. We report the first case of HLH associated with disseminated *Bartonella henselae* infection in an immunocompromised patient with human immunodeficiency virus (HIV) infection.

**CASE REPORT**

A 69-year-old man, born in Mali and living in France for 15 years, had recently acquired a kitten and had a 1-month history of weight loss, fatigue, and anorexia. On examination, he had a fever (temperature, 39.3°C), hepatomegaly, splenomegaly, asymmetric axillary lymphadenopathy, and no skin lesions. Other examination results were normal.

Laboratory evaluation revealed the patient had a total leukocyte count of 3430 × 10^6/L and thrombocytopenia (platelet count, 72 000 × 10^6/L) without anemia (hemoglobin, 137 g/L). His serum lactate dehydrogenase (LDH) level was 1415 UI/L, his aspartate aminotransferase level was 78 UI/L, and his alanine aminotransferase level was in the normal range. Serological testing for HIV-1 yielded positive results; the patient’s CD4+ T-cell count was 20 × 10^6/L, and his HIV load 6.37 log copies/mL. Multiple cultures of blood, urine, feces, cerebrospinal fluid, and sputum tested negative for bacteria, mycobacteria, and fungi. Serological results for hepatitis B and C were negative, and those for Epstein-Barr virus (EBV) were consistent with past infection. Serum human herpesvirus type 8 (HHV-8) immunoglobulin (Ig) G antibodies were detected as present in the absence of IgM antibodies, and high EBV and HHV-8 loads were detected using quantitative polymerase chain reaction (5.45 and 4 log copies/mL, respectively).

The patient’s clinical course rapidly worsened. He became confused and had a very high fever. His platelet count dropped to 6000 × 10^6/L and his hemoglobin level to 77 g/L. Liver transaminase levels rose to 202 UI/L for aspartate aminotransferase and 98 UI/L for alanine aminotransferase associated with cholestasis. Other serum levels were 10 000 µg/L for ferritin, 3.66 g/L for fibrinogen, 3.54 mmol/L for triglycerides, and 2045 UI/L (peak level) for LDH. A bone marrow aspirate sample demonstrated hemophagocytosis. Bone marrow cultures for mycobacteria and leishmania were negative. Positron emission tomography demonstrated no fluorodeoxyglucose uptake in the axillary lymph node.

A transjugular liver biopsy was performed, and the sample showed several foci of peliosis, consisting of blood-filled spaces replacing hepatocytes, with disruption of the sinusoidal lining. No epithelioid cell granuloma or lymphoid infiltration was observed. Ziehl–Neelsen staining did not show bacilli, and Whartin–Starry staining displayed bacilli in the peliotic foci. Throughout the liver biopsy sample, hyperplastic Kupffer cells with hemophagocytosis were observed in the sinusoids (Figure 1). It was not possible to perform liver culture or polymerase chain reaction owing to a lack of available liver tissue, but serological testing for *B. henselae* proved strongly positive for IgG antibodies (titer, 1:8192) but negative for IgM antibodies.

The patient received a single infusion of etoposide (150 mg), and treatment with doxycycline (200 mg/d) was started and continued for 6 months together with antiretroviral therapy. At week 2, a dramatic improvement was noted. After 2 months of antibiotic and antiretroviral therapy, the patient was asymptomatic, and he remained in good condition after 6 months of follow-up.

**DISCUSSION**

We here report for the first time the occurrence of bartonellosis-related HLH in an HIV-positive patient. HLH is an immune-
mediated life-threatening disorder caused by overproduction of inflammatory cytokines, especially interferon gamma. An interferon gamma amplification loop may in turn be related to impaired T-cell and natural killer cell cytotoxicity, leading to persistent stimulation by antigen-presenting cells. Chronic stimulation of some Toll-like receptors may also contribute to HLH [2].

Diagnosis of HLH is based on a set of clinical and biological criteria that include high-grade fever, organomegaly, marked cytopenias, elevated LDH levels, hyperferritinemia, and hypertriglyceridemia. Cytological features of hemophagocytosis are usually seen in tissue samples from, for example, bone marrow, the liver and/or the spleen. Our patient met >5 of the 8 criteria established in the pediatric HLH 2004 diagnostic guidelines and had a >99% risk of HLH according to the HSscore, a score developed for reactive HLH (HScore, 287) [3].

Secondary (or reactive) HLH is caused by various infectious, autoimmune or malignant conditions. A preexisting immune deficiency is found in 30%–60% of cases [4]. In a series of 58 HIV-infected patients with a diagnosis of secondary HLH, underlying hemopathy/malignancy (including Hodgkin lymphoma and HHV-8–related multicentric Castleman disease) or infection (including tuberculosis and cytomegalovirus) were highlighted, for 55% and 41% of patients, respectively [5].

In our patient, multicentric Castleman disease was initially suspected owing to a high HHV-8 load, but this diagnosis was subsequently ruled out because there was no fluorodeoxyglucose uptake in the lymph nodes at positron emission tomography and no plasmacytosis present on bone marrow smears. Furthermore, HHV-8 replication has been reported during disseminated bacterial, parasitic or fungal infections in

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Figure 1. A, Liver biopsy sample showed several foci of peliosis (arrows) corresponding to spaces filled with blood associated with disruption of the sinusoidal wall (hematoxylin-eosin; original magnification, ×100). B, Kupffer cell hyperplasia with hemophagocytosis (arrow) was observed throughout the biopsy specimen (hematoxylin-eosin; original magnification, ×400). C, Ziehl–Neelsen staining did not show any bacilli (original magnification, ×400). D, Whartin–Starry staining showed a small aggregate of bacilli (arrows) compatible with Bartonella (original magnification, ×1000).
HIV-infected patients [6]. EBV was not considered the cause of HLH in our patient, however, because a high EBV load is often observed in HIV-positive patients with HLH irrespective of the cause [7].

One previous case of HLH induced by Bartonella spp. was reported in 2014 by Poudel et al [8]. A 14-year-old girl who had undergone kidney transplantation presented with clinical and biological features of HLH. Bartonella infection was confirmed by serological testing for B. henselae, and the bone marrow aspirate sample showed marked features of HLH. The patient’s clinical course improved with corticosteroid, doxycycline, and azithromycin treatment.

Treatment of HLH requires a triple approach. First, supportive care is essential because of frequent life-threatening complications. Second, the use of immunosuppressive or cytotoxic drugs (eg, etoposide) is mandatory in severe cases to quickly suppress inflammatory response. Third, elimination of the trigger is crucial to achieving durable recovery.

Therefore, identifying the cause of HLH is key, and our case emphasizes the importance of tissue biopsy in obtaining a definitive diagnosis; liver biopsy has a 50% performance level [9]. The second important point is that screening for B. henselae should be considered in immunocompromised patients with HLH, especially those with a cat at home.

Notes

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