Case Report: Hemophagocytic Lymphohistiocytosis Caused by Disseminated Histoplasmosis in a Venezuelan Patient with HIV and Epstein–Barr Virus Reactivation Who Traveled to Japan

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Abstract. We describe a Venezuelan visitor to Japan who was diagnosed with hemophagocytic lymphohistiocytosis (HLH). The patient was also diagnosed with human immunodeficiency virus (HIV) and Epstein–Barr virus infection by the Western blot and polymerase chain reaction (PCR) tests, respectively. The cause of HLH was considered to be these two infections at first; however, the patient did not recover with antiretroviral/anti-herpes virus therapy. Thereafter, diagnosis of disseminated histoplasmosis was confirmed with an antigen detection test, culture, and PCR test of blood, urine, and bone marrow, and the patient improved gradually after the initiation of liposomal amphotericin B. This case highlights the importance of ruling out endemic mycosis as a cause of HLH even if other probable causes exist in patients from endemic areas.

Hemophagocytic lymphohistiocytosis (HLH) is an immune-mediated life-threatening disease caused by impaired natural killer and cytotoxic T-cell function. This condition is classified into primary (genetic) and secondary (reactive) HLH. Hemophagocytic lymphohistiocytosis can occur at any age, but in adults, the main causes of HLH are infections, neoplasms, and autoimmune diseases,¹ whereas primary HLH most often affects children less than 2 years of age.² Among the infectious diseases, herpesvirus (including Epstein–Barr virus [EBV], cytomegalovirus [CMV]), and HIV have been reported as the main causative organisms of HLH, whereas fungal infections, including endemic mycoses, are rarely reported as a cause of HLH.¹ The wide range of causes and possible coinfection with multiple organisms make it difficult to determine the precise cause of HLH.

Here, we report a patient with HLH who also presented with advanced HIV infection and EBV reactivation, in whom establishment of the diagnosis of disseminated histoplasmosis as the cause of HLH was challenging.

CASE REPORT

A 56-year-old female presented to our hospital with high fever, altered mental status over several days, and diffuse muscle pain and weakness since 11 months earlier. She had arrived in Tokyo, Japan, from Venezuela 6 days earlier and was referred to our hospital suspected of myositis based on muscle pain and weakness.

Clinical examination showed body temperature of 38.4°C, tachycardia (110 beats per minute), and blood pressure of 114/82 mmHg, with SpO₂ of 97% on room air. Physical examination showed vesicles on the lips and trunk, abdominal tenderness over the stomach, and shallow perianal ulcers. Apart from the altered mental status, no abnormal neurological findings were observed.

Laboratory tests showed anemia (Hb 7.0 g/dL) and mildly elevated aspartate aminotransferase (AST, 196 U/L), alanine aminotransferase (ALT, 60 U/L), γ-guanosine triphosphate (GTP, 116 U/L), creatinine kinase (CK, 610 U/L), and C-reactive protein (CRP, 4.71 mg/dL). Lactic acid dehydrogenase (LDH, 1,471 U/L) and ferritin (41,391 ng/mL) were substantially elevated. In addition, she was confirmed to be HIV positive

(CD4 13/μL, HIV-RNA 1.9×10^6 copies/mL) by Western blot and polymerase chain reaction (PCR) tests. Cerebrospinal fluid (CSF) analyses, including PCR test for EBV, CMV, herpes simplex virus (HSV), varicella zoster virus (VZV), JC virus, and tuberculosis, were negative. Except for plasma tests for EBV [DNA-PCR 10,000 copies/mL, EB viral capsid antigen (EBVCA) IgM 1: < 10, EBVCA IgG 1:320, EBV nuclear antigen 1:40] and HSV (PCR 600 copies/mL), those for CMV, VZV, and human herpesvirus-8 were unremarkable.

The chest X-ray was unremarkable. Enhanced computed tomography scan and positron emission tomography of the body showed hepatosplenomegaly and lymphadenopathy without any lung lesion (Figure 1A), and magnetic resonance imaging of the head showed diffuse cerebral atrophy.

After admission, hepatobiliary enzymes continued to rise for 6 days (AST 346 U/L, ALT 53 U/L, LDH 3,892 U/L, alkaline phosphatase [ALP] 2,016 U/L, and γ-GTP 370 U/L) and serum soluble IL-2 receptor was high (3,207 U/mL), although CK improved to within normal range shortly after admission. Treatment with intravenous acyclovir (10 mg/kg three times daily) for suspected disseminated HSV or VZV infection was initiated on day 3 after admission. At first, HLH due to AIDS-related lymphoma was strongly suspected. Therefore, combination antiretroviral therapy of tenofovir, emtricitabine, and dolutegravir was also initiated on day 5 after admission. On day 14 after admission, although the levels of hepatic enzymes and ferritin started to decrease, other laboratory tests were still high without improvement (ALP 2,004 U/L, γ-GTP 546 U/L, and CRP 24.4 mg/dL) and persistent high-grade fever (> 39°C) continued.

Bone marrow smear and biopsy, collected on day 4 after admission, demonstrated small particles in addition to hemophagocytosis, but no evidence of lymphoma (Figure 1B–D). Based on the shape of these particles, history of residence in an endemic area, and possible opportunistic infection in an HIV-infected patient, endemic mycoses, such as histoplasmosis, paracoccidioidomycosis, and coccidioidomycosis, were suspected. Finally, she was diagnosed with disseminated histoplasmosis following the detection of *Histoplasma capsulatum* in the bone marrow specimen re-collected on day 11 after admission by antigen detection test of serum, urine, and bone marrow (that of CSF was negative); culture of blood and bone marrow; and PCR of bone marrow. On the other hand, PCR for the genus *Coccidioides* and *Paracoccidioides* were negative. After the initiation of intravenous liposomal amphotericin

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FIGURE 1. (A) Positron emission tomography on day 6 after admission demonstrated left supraclavicular, axillary, and para-aorta lymphadenopathy and hepatosplenomegaly. (B) May-Giemsa stains illustrated phagocytosed encapsulated yeast forms and red blood cells in macrophages on a bone marrow smear. (C, D) Grocott and PAS stains also illustrated yeast forms in the specimen of bone marrow biopsy. This figure appears in color at www.ajtmh.org.

B (L-AMB, 3 mg/kg/day) on day 14 after admission for 2 weeks, followed by oral itraconazole (200 mg three times daily for 3 days, and then 200 mg twice daily), symptoms and laboratory abnormalities improved gradually. The serum and urine antigen detection tests became negative 1 month after the initiation of L-AMB treatment and were negative thereafter (at 3 and 5 months later) until she moved to another country. The patient was discharged 2 months after admission.

DISCUSSION

This case highlights the importance of ruling out histoplasmosis in a patient with HLH who has a travel history to an endemic area, even when the patient had other probable causes of HLH, because of the poor prognosis of disseminated histoplasmosis without proper treatment.³⁻⁵ One case report from Spain, describing an AIDS patient with disseminated tuberculosis and HLH, who was later found to have disseminated histoplasmosis on autopsy, supports the importance of ruling out disseminated histoplasmosis, which can coexist with other infections.⁶

Although epidemiological data of endemic mycoses from Venezuela are limited, several studies are available for such information. In studies conducted in the Bolívar state in 2005, the percentage of people reactive to metabolic antigen from *H. capsulatum* in the urban city was 34%,⁷ whereas that detected in 2004 in a rural area was 42.7%, and in both areas, the percentage of such people was higher than that of people reactive to antigen from *Paracoccidioides brasiliensis* (urban city: 19.7%, rural area: 13.2%).⁸ In another study in Caracas metropolitan area, 53 of 158 (33.5%) cases with histoplasmosis

were HIV positive and 79 of 158 (50%) cases were reported as disseminated histoplasmosis, which is the most commonly diagnosed endemic mycosis in patients with HIV infection.⁹

The diagnosis of disseminated histoplasmosis is usually challenging, particularly outside endemic areas, for several reasons. First, the clinical features of disseminated histoplasmosis are quite similar to those of other diseases, such as tuberculosis, disseminated non-tuberculosis mycobacterial infection, other endemic mycosis, and AIDS-related lymphoma.⁶ Second, chest radiography findings can be normal even in disseminated histoplasmosis. One study reported that such cases reached 54% of all disseminated histoplasmosis.¹⁰ Third, it is difficult to identify *Histoplasma capsulatum* outside the endemic area because it requires skilled and experienced medical personnel. For example, in the previous case report,⁶ although Giemsa staining of the bone marrow showed extracellular rounded forms, only HLH was diagnosed and disseminated histoplasmosis was overlooked.

In conclusion, in an increasingly globalized world, clinicians outside endemic areas should remember to rule out endemic mycosis as a cause of HLH even when other probable causes exist in a patient from or with travel history to an endemic area because the diagnosis of endemic mycosis is challenging and overlooking such infections might result in poor prognosis of patients.

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