Hemophagocytic Syndrome in a Patient with HIV and Histoplasmosis: A not so Rare Correlation

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ABSTRACT: Hemophagocytic lymphohistiocytosis (HLH) is a disorder that occurs due to unsuitable monocyte activation in a variety of infections. In human immunodeficiency virus (HIV) infections, patients with advanced immunosuppression associated with opportunistic infections are at increased risk of developing HLH. We describe a clinical case of a 33-year-old male student diagnosed with HIV who was hospitalized for investigation of asthenia and dyspnea, accompanied by adynamia, decreased motor force in the left leg, dysphagia, and dysfluency. His general condition was regular, he was pale, feverish, and had normal cardiac and pulmonary auscultation. Physical examination revealed ulcerated lesions in the perianal region and hepatosplenomegaly without palpable lymph node enlargement. Laboratory parameters showed pancytopenia, a slight increase in liver function accompanied by high lactate dehydrogenase, and hiperferritinemia. The initial diagnosis was disseminated histoplasmosis, thus amphotericin B deoxycholate was empirically prescribed while waiting on myeloculture and blood cultures for fungi and mycobacteria. Other clinical procedures were blood transfusion, resumption of antiretroviral therapy (ART) and secondary prophylaxis. Myeloculture blood cultures of fungi and mycobacteria were negative. Patient evolved well in relation to the initial complaints and showed partial clinical and laboratory improvement. However, 23 days after hospitalization, he developed a febrile episode accompanied by chills and a convulsive crisis. The patient was transferred to the intensive unit care and developed septic shock and respiratory failure. He died 25 days after the onset of the condition. After the postmortem examination, histopathology revealed countless rounded fungal structures compatible with Histoplasma sp., which were observed in the peripancreatic lymph node, liver, and spleen, in addition to hemophagocytosis in the splenic parenchyma. We thus conclude that when the patient met criteria for HLH, such as fever, hepatosplenomegaly, hiperferritinemia, and pancytopenia, the evolution was fast due to the aggressive and rapidly fatal nature of HLH, despite anti-fungal and corticoid treatment. Therefore, this case report reinforces the need to consider hemophagocytic syndrome in patients with HIV and disseminated histoplasmosis, especially where histoplasmosis is highly endemic, in order for the treatment be started early when there is high clinical suspicion.

KEYWORDS: HIV, histoplasmosis, hemophagocytic lymphohistiocytosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of aggressive and life-threatening immune dysregulation, and is characterized by persistent activation of the mononuclear phagocytic system and is associated with a systemic and uncontrolled hyperinflammatory response.1 The diagnosis of HLH remains a challenge due to the wide spectrum of clinical presentations. The criteria for the diagnosis of HLH are as follows: fever (>38.5°C); splenomegaly; pancytopenia (affecting 2 of 3 peripheral bloodlines); hypertriglyceridemia (when fasting >265 mg/dL) or hypofibrinogenemia (<150 mg/dL); hyperferritinemia (>500 µg/L); and hemophagocytosis in bone marrow, spleen, or lymph nodes without evidence of malignancy.1-4 Hemophagocytosis is the key marker of HLH, but it is not the only criterion for diagnosis and should always be interpreted in the clinical context. Hyperferritinemia can be associated with several other more frequent pathologies such as renal failure, hepatocellular injury, some viral, fungal, bacterial and parasitological infections, hematopoietical diseases, rheumatological diseases, hemolytic anemias, and excessive iron.5

HLH can be primary (associated with genetic mutations that result in defects in the cytotoxic activity of NK cells and CD8+ T lymphocytes) or secondary HLH (triggered by infections of some viruses, fungi, and bacteria, as well as by malignancies and autoimmune diseases).1,5-10 HLH associated with HIV infection has several different scenarios, such as the HIV infection itself (acute or chronic phase), and in conjunction with immune reconstitution inflammatory syndromes in the context of opportunistic infections and other diseases, such as autoimmune syndromes and malignancies.5,11

Histoplasmosis is one of the most common mycoses in HIV patients and is endemic in various parts of the world. Immunocompetent people usually develop a self-limiting infection that is different from immunocompromised patients...
Disseminated histoplasmosis has been considered to be a defining disease of acquired immunodeficiency syndrome (AIDS). The etiology of the disseminated form can be misdiagnosed as tuberculosis due to the overlap of clinical-radiological and histopathological characteristics, for example, as granulomas in biopsies from the affected tissue, such as the spleen, liver, lung, and peripancreatic lymph nodes. In AIDS patients, disseminated histoplasmosis may trigger secondary HLH and lead to higher mortality rates.

The objective of this study was to present a case report involving a patient with advanced HIV disease that died from secondary HLH that had been triggered by disseminated histoplasmosis, which was diagnosed after postmortem biopsies of the spleen, liver, lung, and peripancreatic lymph nodes. Despite the patient having received treatment with an anti-fungal and corticoid, the evolution was fast and fatal.

**Clinical Case**

A 33-year-old male student diagnosed with HIV in 2013, with irregular use of ART and prophylaxis, had a CD4 T lymphocyte count of 9 cells/mm³ and viral load of 137,000 copies of HIV RNA in a milliliter of blood. The patient was hospitalized for investigation of asthenia and dyspnea after low levels of exertion, with 5 days of evolution. These symptoms were accompanied by adynamia, decreased motor force in the left leg, dysphagia, and dysfluency. He also reported weight loss of approximately 8 kg in the 3 months prior to the hospitalization and continuous episodes of forgetfulness.

On physical examination, the patient’s general condition was regular, though he was pale, febrile (38.9°C), and had normal cardiac and pulmonary auscultation. Liver and spleen were palpable at 2 cm from the right and left costal margins; however, lymph nodes were not palpable. In the perianal region, the patient presented ulcerated lesions with regular edges, regular and well demarcated edges and no phlogistic signs. The neurological examination revealed normal muscle strength in the limbs and preserved tactile sensitivity. The initial blood count showed pancytopenia (hemoglobin: 4.7, leukocytes: 1,670/mm³, lymphocytes: 290/mm³, platelets: 32,000 × 10⁹/mm³) with a slight increase in liver function (aspartate aminotransferase: 102 µg/L, alanine aminotransferase: 86 µg/L), normal renal function, triglycerides of 161 mg/dL, lactate dehydrogenase (LDH) of 588 U/L, and ferritin of 585 µg/mL.

In view of the clinical and laboratory findings, the initial diagnostic hypothesis was disseminated histoplasmosis. Blood cultures of fungi, mycobacteria, aerobes, and investigation of fungi in leukocyte cream were performed. Meanwhile, amphotericin B deoxycholate was empirically prescribed due to his advanced HIV disease. All results were negative. Other additional procedures were red blood cell transfusions, resumption of ART, and secondary prophylaxis. After a blood transfusion, the patient evolved well in relation to the initial complaints. The etiological investigation of pancytopenia continued, and the myeloculture of fungi and mycobacteria was negative.

Abdominal tomography showed moderate hepatosplenomegaly without nodules. Throughout his stay in the hospital, the patient showed partial clinical and laboratory improvement, but 23 days after hospitalization, he developed a febrile episode accompanied by chills and a convulsive crisis. A cranial CT showed no acute findings, and a chest CT showed a budding tree pattern and lesions with bilateral reverse halo signs. Antimicrobial therapy was initiated with piperazoline/tazobactam, which is therapeutic management for suspected pneumocystosis and pulmonary tuberculosis. Corticosteroids were also used, thus completing the vigorous therapy.

The patient was transferred to the intensive unit care and evolved to septic shock and respiratory failure, dying approximately 25 days after the onset of the condition. The patient underwent necropsy. Under gross pathology, the lungs weighed 540 g and presented a diffusely hemorrhagic appearance with consolidation spots, which corresponded to extensive areas of intra-alveolar hemorrhage observed under microscopy, foci of bronchopneumonia, bronchiolitis, and acute edema. Microscopically, the lungs presented diffuse alveolar damage in a proliferative phase, with foci of broncho-pneumonia, edema, and intra-alveolar hemorrhage.

Hepatosplenomegaly was observed, with the spleen measuring 15 cm and weighing 350 g, the liver was 25 cm in the largest axis and weighed 1900 g. No macroscopic alterations were observed in the liver. When cutting the spleen, numerous white nodules were noted, and these measured approximately 0.5 cm throughout the splenic surface (Figure 1A). The liver presented extensive areas of pallor that had perivascular permeation distribution in peripheral congestion areas and, under microscopy, areas of necrosis of hepatocytes in zones II and III, associated with macravacuolar steatosis, were observed. In the peripancreatic region, numerous coalescent lymph nodes could be seen, which were concentrated by cavitation containing purulent material (Figure 1B), and microscopy portrayed extensive areas of necrosis, surrounded by a lymphohistiocytic inflammatory infiltrate with a morphological pattern that was consistent with *H. capsulatum* (Figure 1C). Using Grocott’s method, the staining showed the presence of small, uniformly oval, narrow-based budding yeasts with eccentric acorn-like nuclei compatible with *Histoplasma* sp., which were also found in the liver and spleen (Figure 1D). In the latter, extensive areas of necrosis were observed, from permeation to congestion and, in the subcapsular area, the presence of red blood cells phagocytized by macrophages (Figure 1E). Others findings were hypercellularity with megakaryocytic hyperplasia in bone marrow, and edema in the brain. Data Use was approved by the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado Ethics Review Board; CAAE 50819121.2.0000.0005.
Discussion

Disseminated histoplasmosis is a major cause of death in patients with advanced HIV disease. It is often mistaken for pulmonary tuberculosis in patients with AIDS or with sarcoidosis in non-HIV patients, which is due to their similar clinical and radiological presentations. Furthermore, histoplasmosis is commonly empirically diagnosed in HIV patients with smear-negative pulmonary tuberculosis because microscopy and culture laboratory assays are not optimal for the diagnosis of either disease or because of a lack of trained clinical and laboratory personnel to make the definitive diagnosis. To worsen the situation, histoplasma antigen detection assays are no longer performed in low- and middle-income countries due high costs, despite their rapid and accurate diagnosis for the care of people with advanced HIV. Thus, this context reveals a sad reality; histoplasmosis cases are mostly discovered accidently and documented through case reports and case series. Here, disseminated histoplasmosis was diagnosed after postmortem biopsies from the spleen, liver, lung, and peripancreatic lymph nodes, thus corroborating that diagnosis of histoplasmosis is still a major issue in the management of patients with advanced HIV disease. Despite this, amphotericin B deoxycholate was empirically prescribed due to advanced immunosuppression of this patient. This procedure resembles the case report presented by Asanad et al, in which an immunosuppressant drug recommended by the Histiocyte Society for management of HLH was deferred while the treatment focused on disseminated histoplasmosis. Though their patient was discharged, our patient died despite vigorous treatment, which reveals the aggressive nature and rapid fatality of HLH in patients with advanced HIV disease.

Several reports have emphasized that HLH in advanced immunosuppressed HIV patients may progress rapidly and become a fatal disorder when an opportunistic infection is left untreated. Our patient had advanced HIV, but presented non-specific symptoms at the beginning of hospitalization, such as fever, fatigue, palpable liver and spleen, hyperferritinaemia, and pancytopenia. Despite the partial clinical and laboratory improvement throughout his stay in the hospital, he presented a clinical worsening accompanied by hepatosplenomegaly and suspected pneumonia, and he was promptly submitted to vigorous treatment with antibiotics and corticosteroids. HLH in AIDS patients with severe disseminated histoplasmosis has been described previously. Our patient succumbed to HLH secondary to disseminated histoplasmosis despite the prompt treatment as is recommended. This context might have had a different outcome if a more sensitive diagnostic assay had been used for the detection of histoplasmosis and if he had started vigorous therapy earlier.

HLH secondary to acute disseminated histoplasmosis in a patient with HIV/AIDS is none too rare, and the pathophysiological bases have not yet been fully elucidated. Multiple mechanisms may have contributed to the dysregulation of the immune system of this patient. The basic immunosuppression caused by the HIV virus, and the histoplasmosis that occurred at the same time, kept the immune system activated, acted as a trigger for an uncontrolled inflammatory response and continuous macrophage activation, and cytokine production, thus leading to the appearance of HLH. Our patient presented countless rounded fungal structures compatible with Histoplasma sp. in the liver and spleen. In secondary HLH, macrophages are activated as a result of an inciting immunogenic condition or agent, such as the reactivity of fungal structures, in this case, the disseminated histoplasmosis in the lymph nodes, liver, and spleen. The engorgement of red blood cells by the splenic subcapsular macrophages confirmed the presence of HLH syndrome in our patient, as has been observed by several other
studies.\textsuperscript{4,5,15,16} In addition, the reintroduction of antiretroviral therapy may have led to immune reconstitution inflammatory syndrome since the clinical worsening of the patient appeared 3 weeks after the onset of ART.\textsuperscript{4} Moreover, death usually occurs due to multiple organ failure from both the complication of HLH itself and from bleeding due to thrombocytopenia and complications of the underlying diseases.\textsuperscript{16} Herein, our patient presented severe thrombocytopenia, pulmonary impairment with extensive areas of intra-alveolar hemorrhages, and evolved to septic shock and respiratory failure due to bleeding, complications of AIDS, disseminated histoplasmosis, and HLH.

Conclusion
We relate the case presentation of a patient with advanced HIV that died from secondary HLH triggered by disseminated histoplasmosis, which was confirmed by postmortem biopsies. This fact corroborates that the conventional culture method for histoplasmosis diagnosis is still a limitation in health care for HIV/AIDS patients. Although the patient received the antifungal treatment empirically, as well as corticoids, he died due to the aggressive and rapidly fatal nature of HLH in advanced HIV disease. This case report reinforces the need to consider hemophagocytic syndrome among the differential diagnoses in patients with HIV and opportunistic diseases in order for the treatment be started early when there is high clinical suspicion.

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Author Contributions
Viviane Carvalho, Renata Spener, Christiane Rodrigues da Silva, and João Ricardo da Silva Neto: The acquisition of data for the work. Monique Freire; Luiz Carlos Ferreira and Paulo Afonso Nogueira: Writing the manuscript, reviewing drafts and final approval of the version to be published. Paulo Afonso Nogueira: Drafting the work.

Ethical Statements and Informed Consent Information
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