Hemophagocytic lymphohistiocytosis secondary to disseminated histoplasmosis in a patient with HIV/AIDS

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Abstract

Introduction: hemophagocytic lymphohistiocytosis (HLH) is a serious, rare disorder characterized by uncontrolled activation of macrophages and T lymphocytes, resulting in blood cell phagocytosis and overproduction of cytokines, leading to multiple organ dysfunction and death, if not treated early.

Case presentation: this was a 22-year-old male with stage C3 human immunodeficiency virus (HIV) infection, diagnosed with disseminated histoplasmosis confirmed by a skin biopsy and bone marrow tests. He completed the induction phase with liposomal amphotericin B and was discharged on itraconazole as maintenance therapy, as well as antiretroviral treatment, to which he was not adherent. He was readmitted due to septic shock, and an undertreated opportunistic infection was suspected, for which he was restarted on antifungal treatment. However, the laboratory tests showed pancytopenia, hyperferritinemia, splenomegaly, hypertriglyceridemia and hypofibrinogenemia, which led to a suspicion of HLH, meeting the HLH-2004 consensus diagnostic criteria. He was prescribed steroid treatment according to the HLH-94 protocol and was restarted on antiretroviral treatment and maintained on antifungal treatment, with a rapid and progressive rise in the cell lines and normalized organ function. **(Acta Med Colomb 2025; 50. DOI: https://doi.org/10.36104/amc.2025.4693).**

Conclusion: secondary HLH should be suspected in patients with advanced HIV who develop pancytopenia, multiple organ dysfunction and elevated inflammatory markers, especially with coexisting opportunistic infections.

Keywords: *hemophagocytic lymphohistiocytosis, HIV, AIDS, disseminated histoplasmosis*.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a serious, rare, rapidly progressive disorder characterized by unregulated macrophage and T-lymphocyte activation. This causes hematopoietic cell phagocytosis and overproduction of inflammatory cytokines, leading to uncontrolled systemic hyperinflammation that induces profound cytopenias, multiple organ dysfunction, and death (1-3). Hemophagocytic lymphohistiocytosis may be primary, related to genetic defects, or secondary, when acquired as a result of infections, neoplasms, or autoimmune diseases.

The incidence and prevalence of secondary HLH are hard to estimate. There is significant underdiagnosis, explained by a lack of clinical suspicion, the complexity of the diagnosis, and its coexistence of multiple severe diseases. Diagnosis requires the presence of at least five clinical and laboratory criteria defined by the Histiocyte Society. These include fever, splenomegaly, cytopenias, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, low or absent natural killer (NK) cell activity, elevated CD25 (soluble IL-2 alpha chain receptor) levels, and histological evidence of hemophagocytes. The last criterion is no longer considered a conditioning or independent marker for diagnosis (1, 2).

Hemophagocytic lymphohistiocytosis generally has a poor prognosis, even with early identification and proper treatment. In patients with acquired human immunodeficiency syndrome (AIDS), secondary HLH may be associated with both the human immunodeficiency virus (HIV) infection itself, as well as immune reconstitution inflammatory syndrome due to opportunistic infections, which gives it a more aggressive and fulminant course.

Disseminated histoplasmosis is endemic in Colombia, one of the main opportunistic infections in patients with AIDS, and a known trigger for secondary HLH (4). Diagnosing HLH in this scenario is even more challenging, as several of the diagnostic criteria, like fever, cytopenia, and organomegalies, are common in patients with HIV.

Treatment consists mainly of a corticosteroid regimen and chemotherapeutic agents like etoposide, along with antibiotics aimed at the underlying opportunistic infection and early

initiation of anti-retroviral therapy (ART) (1,5). There are no known clinical trials in patients with HLH and HIV. Furthermore, both analytical and descriptive observational studies in this population are scarce, and therefore the efficacy of these treatments is unknown.

Below, we present the case of a young patient with HIV infection in whom HLH secondary to disseminated histoplasmosis was diagnosed, with a favorable clinical outcome after prompt, multimodal, interdisciplinary treatment.

Clinical case

This was a male patient in his 20s with a history of subclinical hypothyroidism, unspecified asthma with no treatment, and inhalant drug use. He was diagnosed with stage C3 HIV infection, with a naive immunovirological profile characterized by a CD4 count of 4 cells/mm^3 and a viral load of 1,850,861 copies/mL. At diagnosis, he debuted with *Pneumocystis jirovecii* pneumonia and oral candidiasis, which were treated, and he was subsequently started on antiretroviral therapy with tenofovir/emtricitabine and efavirenz, once contraindications were ruled out.

He was readmitted to the hospital for fever, secondary to disseminated histoplasmosis confirmed through a skin biopsy and bone marrow tests. Induction treatment was started with liposomal amphotericin B, followed by itraconazole in the ambulatory maintenance phase. However, he was not adherent to either this treatment or the antiretroviral therapy. This led to reactivation of the histoplasmosis on two occasions, and he had to restart the induction phase with each episode, once again without ambulatory adherence to the instated treatments.

Three months after the last hospitalization, he was readmitted in septic shock. At this time, his laboratory tests showed severe pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and liver and kidney failure. In light of these findings, he was diagnosed with HLH, meeting the diagnostic criteria of the HLH-2004 consensus (Table 1, Figure 1), including the presence of hemophagocytes in the bone marrow.

Hospital treatment included giving transfusions, restarting treatment with amphotericin B, and beginning

Table 1. *Admission laboratory tests.*

Laboratory tests		Values on admission	Reference values
Complete blood count	Hemoglobin	3.5 g/dL	13 – 18 g/dL
	Hematocrit	11.3%	42 – 52%
	MCV	68.3 fL	86 – 98 fL
	MCH	26.7 pg	27 – 32 pg
	MCHC	31.5 g/dL	33 – 37 g/dL
	Leukocytes	0.25 x 10^3/ul	5 – 10 x 10^3/ul
	Platelets	46 x 10^3/ul	150 – 450 x 10^3/ul
Serum iron		52.7 ug/dL	33 – 193 ug/dL
Transferrin		59.50 mg/dL	200 – 360 mg/dL
Ferritin		28.524 ng/mL	30 – 40 ng/mL
Vitamin B12		1.579 pg/mi	160-950 pg/mi
Creatinine		0.51 mg/dL	0,67 – 1,17 mg/dL
BUN		8.9 mg/dL	6 – 20 mg/dL
ASAT		228 U/L	6 – 40 U/L
ALAT		28.2U/L	6 – 41 U/L
LDH		642 U/L	135 – 250 U/L
Alkaline phosphatase		884 U/L	40 – 129 U/L
Serum chloride		91.80 mmol/L	98 – 107 mmol/L
Serum sodium		120 mmol/L	135 – 148 mmol/L
Serum potassium		4.23 mmol/L	3.5 – 4.5 mmol/L
Magnesium		1.79 mg/dL	1.6-2.2 mg/dL
Fibrinogen		162 mg/dL	200-400 mg/dL
Triglycerides		267 mg/dL	0-200 mg/dL
Thyroid stimulating hormone		1.60	0.27-4.2 uIU/mL
Blood cultures 1-2		Negative	Negative
Urine culture		Negative	Negative
Hepatitis B-C		Negative	Negative
Syphillis (VDRL)		Negative	Negative
Mycobacterium tuberculosis AFB bacilloscopy-PCR		Negative	Negative

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; PCR: polymerase chain reaction; BUN: blood urea nitrogen; ASAT: oxaloacetic transaminase; ALAT: pyruvic transaminase; LDH: lactate dehydrogenase.

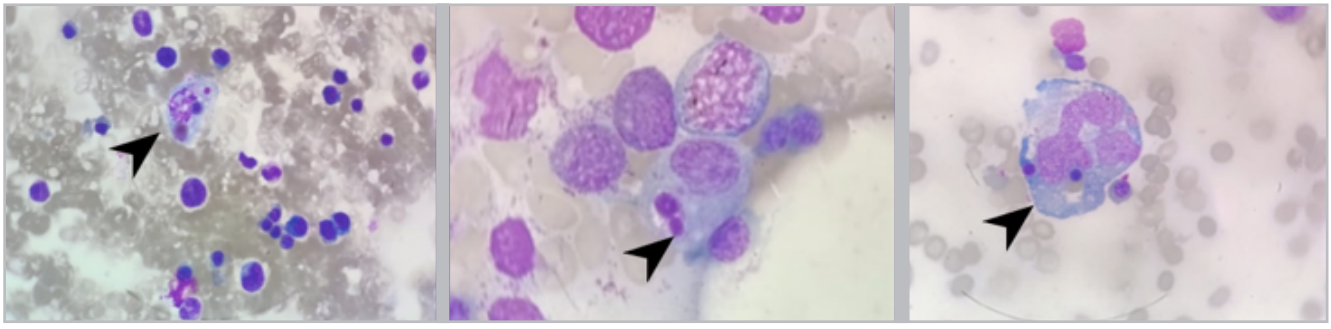

Figure 1. *Microscopy showing hemophagocytosis in the contxt of HLH. The black arrows indicate activated histiocytic cells phagocytizing hematopoietic cells. Stain used: Wright-Giemsa.*

the HLH-94 regimen, based on steroid monotherapy. In addition, his ART was switched to tenofovir/emtricitabine plus dolutegravir, achieving a rapid, progressive rise in his cell lines (Figure 2). *E. coli bacteremia was found during his hospitalization, which was treated with meropenem, and he was finally discharged with clearly improved cell lines*.

Discussion

Secondary HLH in immunocompromised patients, such as those with advanced HIV, has a more aggressive course and constitutes a diagnostic and treatment challenge due to its overlap with other more common conditions, like untreated opportunistic infections or sepsis (6). This report describes the case of a young man with stage C3 HIV in whom HLH secondary to disseminated histoplasmosis was diagnosed, with a positive clinical outcome after multimodal treatment.

The behavior of HLH in HIV patients varies, and the available information comes mainly from case reports. A higher prevalence has been reported in patients with advanced chronic immunosuppression, with a median duration of the infection of approximately four years and a CD4 T-cell count of 73 cells/mm^3. In this case, the patient had a significantly lower count (4 cells/mm^3), which suggests that this condition develops more often in patients with uncontrolled chronic infection (7).

Secondary HLH is diagnosed based on the criteria established by the HLH-2004 consensus, which included the presence of severe cytopenia, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia and histological evidence of hemophagocytes in the bone marrow. Repetitive reactivation of fungal infections due to lack of adherence to antimicrobial and antiretroviral treatment probably contributed to this patient´s hyperinflammatory state.

The literature highlights three laboratory criteria almost universally present in HLH: fever, ferritin levels ≥500 μg/L, and low NK cell activity (8). The median ferritin reported in literature reviews is 14,716 μg/L (IQR 6,347–31,540) (9), suggesting that significantly elevated levels increase diagnostic specificity for the disease. The case we presented had documented hyperferritinemia above the reported median,

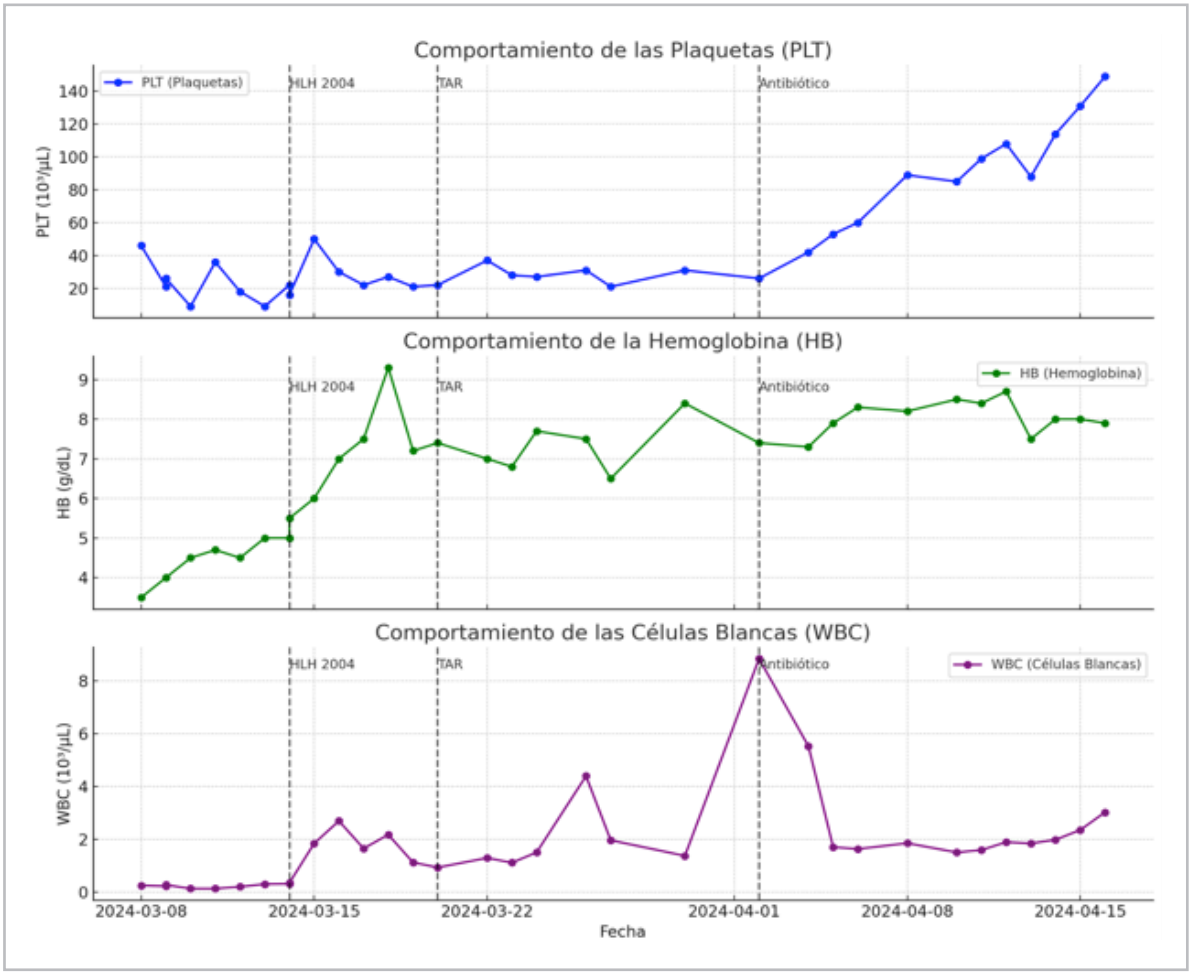

Figure 2. *Behavior of platelets (PLT), hemoglobin (Hgb) and white blood cells (WBCs) over time, with therapeutic interventions highlighted (HLH 2004, ART, Antibiotic). The data are expressed in PLT (10^3/ul), Hgb (g/dL), and WBC (10^3/ul). It is important to note that HLH therapy began after transfusion.*

along with multiple organ dysfunction, which led to early suspicion of the disease and rapid treatment that may have contributed to the patient´s positive response.

Although NK cell activity and soluble CD25 assays are useful, they are expensive and not available in most non-specialized centers, such as our own; therefore, they could not be measured. Up to 88% of patients with HLH have hemophagocytic activity in the bone marrow (9). In this patient, it was visible on the myelogram but not the bone block. However, the HLH-2004 consensus establishes an HLH diagnosis with five of the eight clinical and laboratory criteria, in which evidence of hemophagycytosis on histopathology does not determine the diagnosis (10, 11).

It is important to point out that the disease course varies. In some cases, the initial tests do not meet the diagnostic criteria levels, but they are reached in the course of the disease. This underscores the importance of ongoing assessment and careful clinical judgement, especially in HIV positive individuals.

With regard to treatment, the information is even less conclusive. While treatment of primary HLH is better documented, with induction protocols including steroids, etoposide and, in some cases, cyclosporine for eight weeks (1, 12-14), there is extensive debate regarding secondary HLH, especially in patients with HIV, as a considerable number of cases appear to resolve simply with treatment of the opportunistic infection.

In the scenario of HLH secondary to disseminated histoplasmosis, treatment is still less clear. Studies based on case reports describe that most patients treated with amphotericin B survived and were able to resolve both conditions (8, 13). In this patient, given the evidence of severe hyperinflammatory involvement, treatment included an antifungal agent and steroid monotherapy under the HLH-94 regimen. Given his rapid, sustained response, etoposide was not considered necessary. This approach helped control immunological activation while the underlying infection was being treated.

The rapid clinical and hematological improvement after starting multimodal therapy reinforces the importance of prompt diagnosis and treatment, including beginning or reinstating ART (15). In these cases, adherence to ART and maintenance antifungal prophylaxis is essential to prevent opportunistic infection relapses and recurrent episodes of HLH.

Conclusion

This case underscores the importance of suspecting HLH in patients with advanced HIV who present with pancytopenia, multiple organ dysfunction, and elevated inflammatory markers, especially with coexistent opportunistic infections. Disseminated histoplasmosis is an endemic disease in Colombia and should be considered a potential and frequent trigger of HLH in our setting. Prompt, appropriate treatment is essential for modifying the natural course of the disease and reducing morbidity, mortality, and neurological complications.

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