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Hemophagocytic lymphohistiocytosis in a child with human immunodeficiency virus in the setting of opportunistic viral co-infections

Romina Potanski[a], *Lucia Barsante*[a], *María C. Garreta*[a], *Camila Lisanti*[a], *Sonia Rojas*[a], *Arturo de Mena*[a]

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare condition characterized by a hyperinflammatory state secondary to dysregulated immune activity with multisystem involvement. HLH may be primary or hereditary, or triggered by various diseases. Mortality without a timely treatment reaches 50% of the cases.

Here we describe the case of a 1-year and 8-month-old female patient with a recent diagnosis of human immunodeficiency virus infection in the AIDS stage. She was hospitalized for assessment and initiation of antiretroviral therapy during which she developed multiple intercurrent infectious and immune conditions. Two episodes of hemophagocytic lymphohistiocytosis in the setting of uncontrolled acquired immunodeficiency and opportunistic co-infections stand out.

The objective of this case report is to highlight the importance of suspecting HLH for a relevant diagnosis and treatment.

Keywords: *hemophagocytic lymphohistiocytosis; HIV; pediatrics.*

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[a] *Clinical Pediatrics, Hospital General de Niños Ricardo Gutiérrez, City of Buenos Aires, Argentina.*

Correspondence to *Romina Potanski: romipotanski@gmail.com*

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive, life-threatening immune dysregulation syndrome that was first described in 1939.[1] Since then, knowledge about this disease has increased considerably. There are 2 subtypes of HLH: primary, related to genetic mutations of the immune system, and secondary, associated with various triggering factors (infections, tumors, autoimmune disorders, etc.).[2] In most cases, HLH is triggered by an infectious agent; the association with viral (Epstein Barr virus [EBV], cytomegalovirus [CMV], herpes simplex virus [HSV], human immunodeficiency virus [HIV]), bacterial (mycobacteria), fungal (*Candida*), and parasitic infections (*Leishmania*) is more common.

The diagnosis of HLH is problematic because of its variable presentation and the non-specific clinical features it shares with other pathological processes.[2] The typical clinical presentation consists of febrile syndrome, hepatosplenomegaly associated with laboratory alterations such as pancytopenia, elevated transaminases, hyperbilirubinemia, hypofibrinogenemia, coagulopathy, hypoalbuminemia, hyponatremia, hypertriglyceridemia, and hyperferritinemia.[2] To facilitate its recognition, the International Histiocyte Society established diagnostic criteria based on clinical features and laboratory findings (*Table 1*).[2,3]

Mortality from untreated secondary HLH is estimated to be 50%; however, in patients with underlying diseases, such as immunodeficiency, uncontrolled HIV infection, or cancer, it may be higher, even with treatment.[4] Notwithstanding this, with current therapies, survival rates have been reported to range from 50% to 70%.[2]

The objective of this study is to alert about this low-frequency, but potentially fatal, condition, which may be confused with other diseases, such as sepsis or severe infections, due to a lack of clinical suspicion or ignorance of HLH.

CASE REPORT

This was an otherwise healthy 1-year and 8-month-old female patient who attended a children's hospital located in the City of Buenos Aires due to prolonged febrile syndrome and extensive oral candidiasis. On physical examination, she was in regular general condition, clinically and hemodynamically compensated, with normal body weight and skin and mucosal pallor. She had acute bilateral otitis media, but no lymphadenopathy, visceromegaly, or other positive findings. In this context, laboratory tests showed increased transaminase level (aspartate aminotransferase [AST] 2737 IU/L, alanine aminotransferase [ALT] 752 IU/L) with normal blood count, kidney function tests, and coagulation profile. Due to suspected hepatitis of unknown etiology, she was hospitalized for assessment.

She was diagnosed with vertically-transmitted HIV infection, with positive polymerase chain reaction (PCR), viral load greater than 1 000 000 copies/mL, and a total CD4+ T cell count of 456/mm^3 (14%). Multiple supplementary tests were ordered to rule out the main opportunistic infections (tuberculosis, *Pneumocystis jiroveci*, toxoplasmosis, cryptococcosis, encephalitis, CMV, EBV) and other sexually transmitted infections (hepatitis B, syphilis) and antiretroviral therapy (ART) was initiated with raltegravir,

Table 1. Diagnostic criteria for hemophagocytic lymphohistiocytosis[2,3]

At least 5 of 8 criteria should be fulfilled
1. Fever > 38 ºC
2. Splenomegaly
3. Cytopenias (affecting at least 2 lineages in the peripheral blood): a. Hemoglobin < 9 mg/dL b. Platelets < 100 000/mm^3 c. Neutrophils < 1000/mm^3
4. Hypertriglyceridemia and/or hypofibrinogenemia a. Triglycerides ≥ 265 mg/dL b. Fibrinogen ≤ 1.5 g/L
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or cerebrospinal fluid (CSF)
6. Low or absent natural killer-cell activity
7. Ferritin > 500 µg/L
8. Soluble CD25 (soluble IL-2 receptor) above normal limits for age

lamivudine, and zidovudine.

After 10 days in the hospital, and 24 hours after starting ART, she presented with worsening of her general condition, tachycardia, and tachypnea, without evidence of visceromegaly, associated with recurrence of febrile syndrome and laboratory alterations (tricytopenia, persistent increase in transaminase levels, hypertriglyceridemia, and increased ferritin and D-dimer levels with normal C-reactive protein) (*Table 2*). The microbiological cultures (2 blood cultures and a urine culture) were negative, and empirical antibiotic therapy with cefotaxime and amikacin was started, without response. In this setting, the probability of a case of HLH secondary to uncontrolled HIV infection was considered. Tests for concomitant viral infections were performed, which showed a positive PCR for EBV (2454 copies, previous PCR had been negative) and a negative PCR for CMV. Given that the patient met 4 diagnostic criteria, that soluble CD25 and NK-cell activity could not be determined due to the unavailability of these tests, and that this disease had an ominous prognosis, treatment was initiated with methylprednisolone pulses at 30 mg/kg/dose for 3 consecutive days and human hyperimmune gamma globulin at 1 g/kg/dose. Subsequently, her febrile syndrome resolved, her general condition and laboratory parameters improved (decreased transaminase, ferritin, and triglyceride levels), and this was interpreted as a good response to therapy. She remained on maintenance corticosteroid therapy (dexamethasone 10 mg/m^2/day).

After 22 days of treatment with dexamethasone, in the setting of dose down-titration, the patient showed clinical deterioration together with recurrence of the inflammatory syndrome (*Table 2*). Tests were repeated, which showed persistent CD4+ lymphopenia 506/mm^3 (13%) and PCR for CMV 6 645 000 copies; HLH was again suspected. A bone marrow

Table 2. Patient course

Parameters		Upon admission	First HLH event, day 12	Second HLH event, day 40
1. Fever > 38 °C		Prolonged febrile syndrome syndrome	Recurrence of febrile syndrome	Recurrence of febrile syndrome
2. Splenomegaly		Not present	Not present	Not present
3. Cytopenias	Hemoglobin NV: 10.5–12 g/dL	9.9	9.2	9.6
	Neutrophils < 1000/mm^3	5110	2410	190
	Platelets < 100 000/mm^3	182 000	151 000	51 000
4. Hypertriglyceridemia and/or hypofibrinogenemia	Triglycerides NV < 75 mg/dL	217	377	177
	Fibrinogen NV: 150–450 mg/dL	359	199	222
5. Hemophagocytosis in BM, spleen, lymph nodes, or CSF		Not performed	Not performed	BMAP with hemophages
6. Low or absent NK-cell activity		Not performed	Not performed	Not performed
7. Ferritin	NV: 4.6–204 ng/dL	3706	9423	23 045
8. Increased soluble CD25 (soluble IL-2 receptor)		Not performed	Not performed	Not performed
Other	Alanine-aminotransferase NV: < 33 IU/L	961	1512	2700
	Aspartate-aminotransferase NV: < 32 IU/L	3309	8104	1879
	EBV	Undetectable	2454 copies	Undetectable
	CMV	Undetectable	Undetectable	6 6450 00 copies
	HIV	1 000 000 copies/mL (> 7 log)	Not repeated	338 copies/mL (2.53 log)
	CD4+ cells	456/mm^3 (14%)	Not repeated	506/mm^3 (13%)

HLH: hemophagocytic lymphohistiocytosis, NV: normal value, BM: bone marrow, CSF: cerebrospinal fluid, BMAP: bone marrow aspiration puncture, EBV: Epstein-Barr virus, CMV: cytomegalovirus, HIV: human immunodeficiency virus.

aspiration puncture (BMAP) found megakaryocytic hyperplasia and hemophagocytosis (*Figure 1*), confirming the diagnostic presumption. The patient received the same treatment associated with antiviral therapy with intravenous ganciclovir for 33 days until her viral load was negative and target organ involvement was ruled out.

After 94 days of hospitalization, with appropriate treatment of the opportunistic infection, HIV, and HLH, the patient reached a stable clinical and immune status and was able to continue with her outpatient follow-up.

DISCUSSION

HLH is a potentially fatal clinicopathological syndrome characterized by an uncontrolled and ineffective immune response leading to a state of prolonged and intense inflammation with multisystem involvement.[5] It is classified into primary and secondary HLH; the latter includes macrophage activation syndrome.[2]

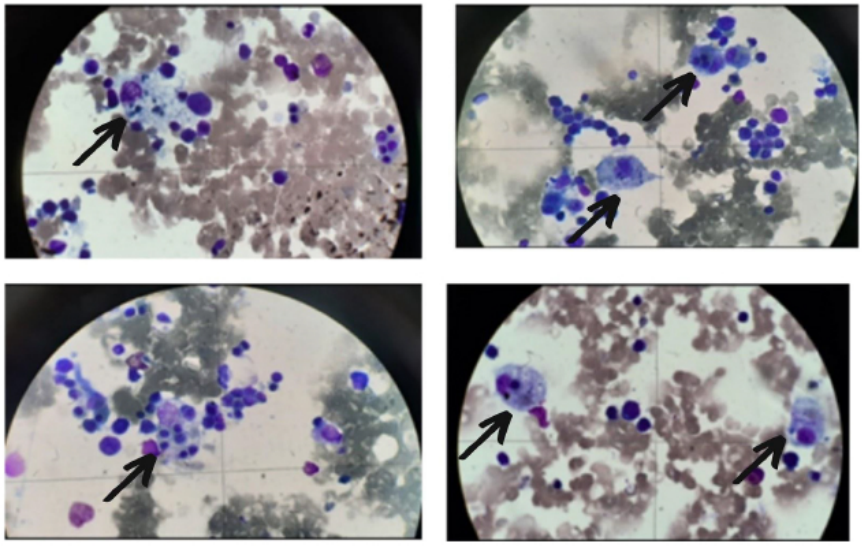
Primary HLH is caused by alterations in the function of T cells and natural killer cells due to mutations in various genes or in association with primary immunodeficiency.[2,5] In our patient, primary HLH was ruled out because there was no family or personal history and, since she had a concomitant acute infection, it was assumed to be secondary HLH.

In contrast, secondary HLH is associated with various immune homeostasis interruptions in the absence of genetic mutations and family history. The most frequent form of secondary HLH is associated with viral infections (EBV, CMV, HSV, HIV), bacteria (mycobacteria), fungi (*Candida*), and parasites (*Leishmania*).[2] Among these, EBV has been described as the main infectious agent capable of developing secondary HLH,[2] as it has tropism for B cells, helps with the proliferation of cytotoxic T cells and macrophage activation.[2] Therefore, when secondary HLH is suspected, it is critical to do a PCR for EBV.[6] In our case, EBV was negative upon admission of the patient; then, her viral load was too low to assume an association; and the subsequent screening was negative. For this reason, the first HLH event was assumed to be secondary to uncontrolled HIV infection, a situation previously described in the bibliography.[4,7]

In patients with HIV infection, the course of the disease is more fulminant; this could be due to their immune dysregulation and underlying immunodeficiency, which makes them more vulnerable to opportunistic infections. In turn, recurrent HLH has been described, as observed in our patient.[8]

In addition, HLH may develop in the setting of malignant neoplasms (leukemias or lymphomas), metabolic disorders, or prolonged treatment with immunosuppressants.[2,9] A variant of

Figure 1. Hemophagocytosis in the bone marrow



Morphologically and phenotypically normal macrophages in active phagocytosis.

secondary HLH is the macrophage activation syndrome, which occurs as a complication of some autoimmune diseases, such as juvenile idiopathic arthritis, systemic lupus erythematosus or Kawasaki syndrome, all of these were ruled out or not observed in our case.[10,11]

The second event in our patient clearly seemed related to CMV infection, with a high viral load. As a differential diagnosis in a patient with uncontrolled HIV infection with a very high viral load and a low CD4 count after ART initiation, immune reconstitution inflammatory syndrome (IRIS) should be considered.[12] IRIS was ruled out in our patient given the persistence of CD4+ lymphopenia and the fact that the BMAP was compatible with HLH.

Due to the nature of this syndrome and the existence of disease modifying therapies, an early diagnosis is crucial.[13] The treatment of HLH includes eliminating triggering factors and clinical support, as well as anti-inflammatory drugs and immunosuppressants. These treatments aim to suppress the hyperinflammatory state and immune dysregulation that leads to organ damage and increased susceptibility to infections.[11] Corticosteroid therapy (dexamethasone 10 mg/m^2 according to the HLH-94 and HLH-2004 protocols, in primary forms, methylprednisolone in secondary forms), immunosuppressants, cytostatics, immunomodulators, monoclonal antibodies, and anticytokine agents, such as immunoglobulins, cyclosporin A, etoposide, anakinra, thymoglobulin, alemtuzumab, rituximab are usually used.[3] In the case described here, it was not necessary to use the latter drugs because her hyperinflammatory state was controlled with corticosteroids and her etiological treatment included antivirals.

Due to a dynamic course, a risk for relapse, and the adverse effects of the drugs used, it is difficult to establish a strict treatment protocol based on the experience of each facility.[9,14]

To conclude, secondary HLH is a rare, but serious, syndrome that should be taken into account as a differential diagnosis in the presence of hyperinflammatory state. Due to the high mortality of this syndrome, it is worth emphasizing the importance of raising awareness about it, since an early identification and a timely treatment help to modify the prognosis and mortality of patients. ■

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REFERENCES

1. Scott RB, Robb-Smith AHT. Histiocytic medullary reticulosis. *Lancet.* 1939;234:194-8.
2. Standage SW, Filipovich AH. Hemophagocytic Lymphohistiocytosis Syndromes. *Pediatric Critical Care Medicine.* 2014:385-93.
3. Henter JI, Horne A, Aricó M, Egeler RM, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48(2):124-31.
4. Tabaja H, Kanj A, El Zein S, Comba IY, et al. A Review of Hemophagocytic Lymphohistiocytosis in Patients with HIV. *Open Forum Infect Dis*. 2022;9(4):ofac071.
5. Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program*. 2015;2015:177-82.
6. Chellapandian D, Das R, Zelley K, Wiener SJ, et al. Treatment of Epstein Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo-immunotherapeutic regimens. *Br J Haematol*. 2013;162(3):376-82.
7. Fane M EL, Sellam I, Lakhal I, Lemkhanet Z. Hemophagocytic Syndrome in Patients Living with HIV. *J HIV AIDS Infect Dis.* 2019;5:1-5.
8. Ramon I, Libert M, Guillaume MP, Corazza F, Karmali R. Recurrent haemophagocytic syndrome in an HIV-infected patient. *Acta Clin Belg.* 2010;65(4):276-8.
9. Kaçar AG, Celkan TT. Hemophagocytic Lymphohistiocytosis. *Balkan Med J.* 2022;39(5):309-17.
10. Henderson LA, Cron RQ. Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Childhood Inflammatory Disorders: Diagnosis and Management. *Paediatr Drugs.* 2020;22(1):29-44.
11. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med.* 2014;5:69-86.
12. Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV AIDS (Auckl).* 2015;7:49-64.
13. Hines MR, von Bahr Greenwood T, Beutel G, Beutel K, et al. Consensus-Based Guidelines for the Recognition, Diagnosis, and Management of Hemophagocytic Lymphohistiocytosis in Critically Ill Children and Adults. *Crit Care Med.* 2022;50(5):860-72.
14. Yanagaisawa R, Matsuda K, Ohga S, Kanegane H, et al. Factors predicting the recurrence of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children after treatment using the HLH-2004 protocol. *Int J Hematol.* 2019;109(5):612-7.