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CLINICAL CASE

Hemophagocytic lymphohistiocytosis as a presentation of inflammatory bowel disease

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Abstract

Background: *Hemophagocytic lymphohistiocytosis (HLH) is considered a medical emergency that should be recognized in patients with fever, splenomegaly, and progressive deterioration of the general condition. Laboratory findings include cytopenia, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia. For HLH diagnosis, it is essential, although not mandatory, to perform a bone marrow biopsy. Given its nature, secondary causes of HLH should be sought, mainly infections, hemato-oncological disorders, autoimmune diseases, and auto-inflammatory conditions.* **Case report:** *We present the case of a female adolescent who presented with fever and lower gastrointestinal bleeding. Upon admission, acute liver failure and pancytopenia were documented. A bone marrow aspirate was performed, which revealed hemophagocytosis; other tests confirmed HLH diagnosis. During the diagnostic approach, inflammatory bowel disease was diagnosed. The patient received first-line treatment with an adequate response.* **Conclusions:** *Inflammatory bowel disease can be considered a cause of secondary HLH, particularly in patients with suggestive symptoms, such as digestive bleeding in the absence of other secondary causes of HLH.*

Key words: *Hemophagocytic lymphohistiocytosis. Inflammatory bowel disease. Ulcerative colitis.*

Linfohistiocitosis hemofagocítica como presentación de la enfermedad inflamatoria intestinal

Resumen

Introducción: *La linfohistiocitosis hemofagocítica (LHH) es considerada una urgencia médica que debe reconocerse en pacientes con deterioro progresivo del estado general, fiebre, pancitopenia y esplenomegalia. Los hallazgos de laboratorio incluyen citopenia, hipertrigliceridemia, hipofibrinogenemia e hiperferritinemia. Para su diagnóstico es importante, aunque no obligatoria, la realización de aspirado de médula ósea. Dada su naturaleza, se deben buscar causas secundarias de LHH, principalmente enfermedades infecciosas, hematooncológicas, autoinmunitarias y autoinflamatorias.* **Caso clínico:** *Se presenta el caso de una adolescente que inició con fiebre y sangrado digestivo bajo. A su ingreso, se documentó falla hepática aguda y pancitopenia. Se realizó aspirado de médula ósea y se encontró hemofagocitocis; el resto de los exámenes concluyeron LHH. Durante su abordaje se diagnosticó enfermedad inflamatoria intestinal. La paciente recibió tratamiento de primera línea con adecuada respuesta.* **Conclusiones:** *La enfermedad inflamatoria intestinal puede considerarse como una*

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causa secundaria de LHH, en particular en pacientes con clínica sugestiva, como es el sangrado digestivo, en ausencia de otras causas secundarias de LHH.

Palabras clave: *Linfohistiocitosis hemofagocítica. Enfermedad inflamatoria intestinal. Colitis ulcerativa.*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening condition with complications that include multiple organ failure. In children, it is characterized by a persistent fever, splenomegaly with cytopenia, hypertriglyceridemia, and hypofibrinogenemia[1]. HLH is caused by dysregulation in natural killer T-cell function, resulting in the activation and proliferation of lymphocytes or histiocytes with uncontrolled hemophagocytosis and cytokine overproduction[2].

There are two main types of HLH: primary and secondary. Primary HLH is inherited in an autosomal recessive or X-linked manner and can be divided into two subgroups: familial HLH and X-linked proliferative syndrome. Secondary HLH may arise from infectious, rheumatologic, malignant, metabolic conditions, and in immunocompromised patients, including those with inflammatory bowel disease (IBD)[3]. Both types of HLH can be diagnosed at any age and are often triggered by infections.

The objective of this report was to present the clinical evolution of a pediatric patient with HLH, probably triggered by ulcerative colitis (UC).

Clinical case

A 16-year-old female was referred to a tertiary care center. The patient had a history of frontal headache, intermittent fever, lower gastrointestinal bleeding, and 5 kg weight loss; the symptoms occurred 2 weeks before admission. She received empirical antibiotic treatment, transfusion of blood components, and hydroelectrolytic support.

The patient showed fever (38.9°C) and tachycardia (heart rate: 138) upon admission; the rest of the vital signs were normal. The initial physical examination revealed jaundice, dehydration, hepatomegaly with ascites, splenomegaly, edema, and obnubilation. No history of medical importance during the prenatal, natal, or postnatal stages was reported, nor was there any family medical history of illness.

At admission, pancytopenia, acute liver failure (ALF) (international normalized ratio [INR]: 1.53, with encephalopathy, alanine aminotransferase: 1058 U/l), and acute renal failure were documented. Bone marrow aspirate was performed, which revealed hemophagocytosis (Fig. 1). Laboratory tests were requested, and the patient was diagnosed with HLH (Table 1). Polymerase chain reaction tests of Epstein–Barr virus (EBV) and cytomegalovirus (CMV) in peripheral blood were negative; however, we did not perform immunohistochemical studies for CMV or EBV. Immunoglobulin levels and a non-contrast cranial computed tomography scan were normal.

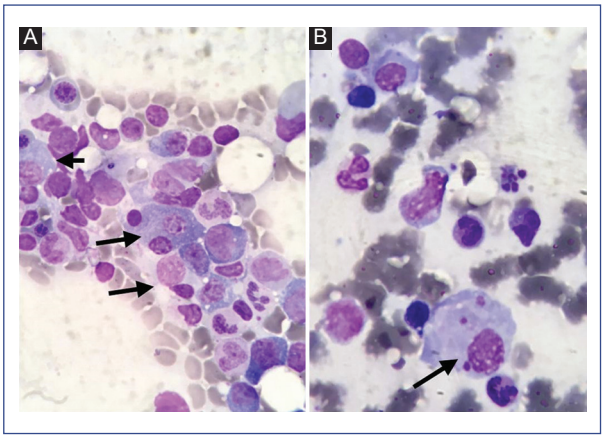

Figure 1. A: Bone marrow biopsy. **B:** Hemophagocytosis in the patient (arrows), compatible with hemophagocytic lymphohistiocytosis.

Treatment was initiated according to the recommendations of the Histiocyte Society 94 (HLH-94)[4]: corticosteroid bolus, intravenous immunoglobulin, transfusion support, and subsequently cyclosporine (CSA); the patient presented an adequate response to the treatment and partial improvement. Intentional search for immunological, infectious, and neoplastic diseases was performed with imaging studies and biochemical laboratory tests, but no conclusive diagnosis was obtained.

Due to the persistence of lower gastrointestinal bleeding, a colonoscopy was performed, which was highly suggestive of UC (Fig. 2). Ileocecal valve biopsy was compatible with chronic UC in the active phase (diffuse inflammatory cell infiltrate of the lamina propria, with plasma cells, lymphocytes, and neutrophils, as well as the presence of cryptitis, crypt abscess formation, and goblet cell mucin depletion). UC treatment initiated with azathioprine, prednisone, and mesalazine.

Table 1. HLH criteria presented by the patient, according to the diagnostic guidelines

Diagnosis criteria for HLH	Criteria in the patient
Fever	Present
Splenomegaly	Present
Cytopenia (minimum 2 of 3 lineages in peripheral blood): — Hemoglobin < 9 mg/dl — Platelets < 100 × 10^9/l — Neutrophils < 1.0 × 10^9/l	 — Hemoglobin: 8.3 mg/dl — Platelets: 35 × 10^9/l — Neutrophils: 1.3 × 10^9/l
Hypertriglyceridemia or hypofibrinogenemia: — Fasting triglycerides ≥ 265 mg/dl — Fibrinogen ≤ 1.5 g/l	 — Fasting triglycerides: 474 mg/dl — Fibrinogen: 1.4 g/l
Hemophagocytosis in bone marrow, spleen, or lymph nodes	Present
No evidence of malignancy	No malignancy was demonstrated in the bone marrow aspirate, tumor markers, and radiology studies
Low or absent NK-cell activity	CD16+CD56: 164 cells/µl
Ferritin > 500 µg/l	Ferritin: 4061 µg/l
Soluble CD25 ≥ 2400 U/ml	Soluble CD25: 4400 U/ml

HLH: hemophagocytic lymphohistiocytosis; NK: natural killer.

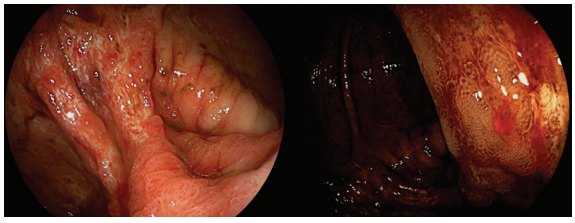

Figure 2. Colonoscopy compatible with ulcerative colitis: colon shows mucosal edema, friable, epithelial hemorrhage, multiple ulcers with non-delimited edges, excavated, with fibrin and without active bleeding.

After 30 days of hospitalization, the patient was discharged to continue outpatient medical treatment.

Molecular genetic analysis of targeted exome sequencing (Illumina Exome Panel), which included 32,765 genetic variants, was carried out with bioinformatic analysis focused on 382 genes associated with immunodeficiencies, hepatic, and renal failure. No large deletions/duplications in regions with less depth at 20 × (including the genes associated with immunodeficiency and HLH: PRF1, UNC13D, STX11, STXBP2, RAB27A, LYST, AP3B1, SH2D1A, ITK, CD27, X-linked inhibitor of apoptosis [XIAP], and MAGT1) were found in this analysis.

At present, the patient has an adequate clinical evolution, asymptomatic with IBD in remission, also presents routine liver function tests, no infectious diseases, and normal hematological studies (Table 2).

Discussion

There are multiple case reports of IBD patients under immunosuppressive therapy who developed EBV-associated HLH[5]. However, the patient reported in the present case did not present any infectious disease. Genetic, environmental, and microbial influences in IBD patients converge and result in a dysregulated mucosal immune response, producing an inflammatory state of the gastrointestinal tract[6,7]. Many pro-inflammatory cytokines and chemokines are associated with IBD development. Furthermore, the proposed principal HLH pathogenic mechanism involves the same proteins, in particular tumor necrosis factor (TNF)-α and interleukin (IL)-6 (secreted by activated monocytes/macrophages), interferon-γ, and soluble CD8 antigens (secreted by T lymphocytes[1,6]). These mechanisms present in both diseases could explain the aggressive presentation of IBD in the patient.

IBD is a disease highly associated with altered gut microbiota. The microbiota is efficiently separated from the gut mucosal immune system by the intestinal barrier, a single layer of highly specialized epithelial cells, some of which are equipped with innate immune functions to prevent or control access of bacterial antigens to the

Table 2. General laboratory tests performed on the patient during the evolution and follow-up

	Admission	Hospitalized evolution	Discharge	Outpatient follow-up (6 months)
Hemoglobin (g/dl)	8.3	12.1	13.9	13.7
Leukocytes (10^9/l)	2.6	9.2	8.8	9.1
Platelets (10^9/l)	35	241	382	223
INR	1.53	1	0.8	1.1
PT (s)	17.9	18	10.2	12.6
Fibrinogen (g/l)	1.4	4.2	5.8	3.74
Triglycerides (mg/dl)	474	248	153	192
CRP (mg/l)	123	4.8	1.9	—
IL-2R (U/ml)	4400	1600	201	170
Ferritin (µg/l)	4061	968	343	—
ALT (U/l)	1058	89	81	20
TB (mg/dl)	7.86	1.30	0.57	0.6
DB (mg/dl)	6.90	0.70	0.16	0.1
Albumin (g/dl)	2.1	4.5	4.7	4.8
Creatinine (mg/dl)	2.70	1.14	0.55	0.53

INR: international normalized ratio; PT: prothrombin time; CRP: C-reactive protein; IL-2R: interleukin-2 receptor; ALT: alanine aminotransferase; TB: total bilirubin; DB: direct bilirubin.

mucosal immune cells. IBD can be developed due to an excessive bacterial translocation into the bowel wall or dysregulated bacterial control in genetically susceptible hosts[8]. According to the literature, no studies have characterized intestinal microbiota in HLH patients; however, the development of HLH after a fecal microbiota transplant has been reported[9]. Multiple studies have observed the interaction between immunological diseases and disorders in the intestinal microbiota[10]. Therefore, these alterations could be additional factors in the inflammatory response present in HLH.

The patient presented ALF at admission. Liver injury has been found in most cases of HLH, but HLH as a cause of ALF has rarely been reported[11]. The mechanisms of liver injury caused by HLH remain unknown. It is generally considered that liver injury results from either infiltration of activated hemophagocytic histiocytes or overproduction of cytokines in patients with HLH.

HLH secondary to autoimmune hepatitis has also been reported; however, this patient did not meet the diagnostic criteria; hence, autoimmune hepatitis was ruled out as a cause of ALF[12,13].

The main HLH symptoms are prolonged fever, hepatosplenomegaly, and pancytopenia, which were symptoms observed in this patient. However, their absence should not change the diagnostic path. Characteristic laboratory findings include increased ferritin, triglycerides, transaminases, bilirubin, lactate dehydrogenase, soluble IL -2 receptor α-chain, decreased fibrinogen hyponatremia, hypoalbuminemia, and elevated D-dimers[2,14]. HLH symptoms reflect immune activation and hypercytokinemia. ILs and TNF cause fever. Cytokines suppress lipoprotein lipase and hematopoiesis. Activated macrophages produce increased levels of plasminogen activator, leading to hyperfibrinolysis, and high levels of ferritin, which also inhibit hematopoiesis. Therefore, the biochemical evaluation by laboratory studies should be extensive and well-founded. As discussed in table 1, the patient presented with most of the HLH diagnostic laboratory criteria.

Moreover, the patient responded adequately to conventional HLH-94 treatment, with CSA administration; however, CSA was discontinued on day 2, when the diagnosis of IBD was made. Derived from studies where the HLH-94 and HLH-2004 protocols were compared, early initiation of CSA is currently not recommended since it shows no further benefit and may increase comorbidities[4]. This drug was administered due to the aggressive presentation of HLH. Furthermore, the patient responded well to the IBD treatment with corticosteroids

and azathioprine, for which second-line therapies administration was unnecessary. However, as the patient presents a risk of reactivation or relapse, the patient follow-up is essential and includes monitoring with blood cytometry and general laboratory tests. IBD will be monitored clinically with the Pediatric UC Activity Index scale, C-reactive protein, and endoscopic controls with a histological assessment to evaluate disease activity.

Many conditions can lead to the clinical presentation of HLH and should be considered as part of the differential diagnosis, such as malignancies (leukemia, lymphoma, and other solid tumors), infections (viral, bacterial, or parasitic), and rheumatoid disorders[3,4]. As UC was identified in the patient, it was considered a secondary HLH.

Another important consideration is the age of presentation. In acquired HLH, the age of onset tends to be higher compared to primary HLH, the trigger cause is identified, and recurrence is unlikely[15].

It is important to consider other pathologies associated with immunodeficiency, such as the XIAP deficiency, also known as the X-linked lymphoproliferative syndrome type 2. XIAP deficiency is characterized by high susceptibility to develop HLH frequently triggered by EBV infection, recurrent splenomegaly, and IBD with the features of a Crohn's disease and hypogammaglobulinemia[16]. EBV infection was not documented in the patient. Moreover, she presented normal levels of serum immunoglobulins and characteristics of UC. The definitive diagnosis by exome did not conclude any immunodeficiencies.

It was necessary to report this case because IBD should be part of the spectrum of diseases to be ruled out in children with HLH, particularly in those with low digestive bleeding and weight loss, even if there is no EBV infection detected or immunosuppressive treatment. In the case of HLH suspicion, health professionals should refer the patients to specialized medical centers, to corroborate the diagnosis and grant adequate treatment, as well as to identify possible complications.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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