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Hemophagocytic lymphohistiocytosis as an initial manifestation of acute lymphoblastic leukemia

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a severe and potentially fatal hyperinflammatory syndrome characterized by uncontrolled immune activation and massive cytokine release. In pediatrics, it can present as an unusual form of hematologic malignancy; it poses a diagnostic challenge due to its overlap with infectious conditions and manifestations typical of cancer. Early recognition is crucial because of rapid clinical deterioration and the need to initiate specific treatment promptly.

We present the case of an 8-year-old boy, previously healthy, who presented with prolonged febrile syndrome and pancytopenia and was diagnosed with T-cell acute lymphoblastic leukemia (T-ALL). During remission induction, we observed associated clinical and laboratory findings (elevated ferritin, decreased fibrinogen, and elevated triglycerides), leading to a diagnosis of HLH. We administered immunomodulatory treatment, which resulted in a favorable outcome.

This case demonstrates the importance of considering HLH as a possible presentation in pediatric patients with an oncohematologic onset.

Keywords: *hemophagocytic lymphohistiocytosis; acute lymphoblastic leukemia; hyperferritinemia; fibrinogen deficiency; pediatrics.*

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by dysregulated immune activation, excessive cytokine production, tissue damage, and multiple organ failure.[1]

It is classified into primary forms—of genetic origin—and secondary forms, associated with infections, autoimmune diseases, or neoplasms, particularly hematologic ones.[2] Within this latter group, leukemias and lymphomas may be associated with the development of secondary HLH, either as an underlying disease or as a trigger for the hyperinflammatory syndrome.

HLH poses a diagnostic challenge because of its nonspecific presentation, including persistent fever, cytopenias, elevated ferritin, decreased fibrinogen, and elevated triglycerides—symptoms that can be mistaken for infections or complications of cancer treatment.[3]

In pediatrics, the association between HLH and oncohematological diseases has been described; however, its presentation as the initial form of acute lymphoblastic leukemia (ALL) is rare, which can delay diagnosis and the initiation of specific treatment.[4] We present the case of a pediatric patient in whom HLH was the initial manifestation of T-cell ALL, highlighting the associated diagnostic and therapeutic challenges.

CLINICAL CASE

An 8-year-old boy with no significant past medical history presented at the Hospital General de Niños Ricardo Gutiérrez (HNRG) with a febrile illness that had lasted 8 days, accompanied by isolated episodes of vomiting. He had previously visited another medical facility, where he was prescribed symptomatic treatment, which was ineffective and led to a subsequent deterioration in his condition.

On physical examination, the patient was in good general condition, tachycardic, and breathing normally. The patient had petechiae on the neck and a 1-cm abdominal hematoma. On palpation, no lymphadenopathy or visceromegaly was evident. The patient had no fever.

Considering these findings, laboratory tests were performed, which showed pancytopenia (white blood cells 700/mm^3, hemoglobin 9.6 g/dl, and platelets 38 000/mm^3), elevated lactate dehydrogenase (1280 U/L), and a coagulation profile within normal limits. Given these abnormalities, the patient was admitted for evaluation and potential treatment.

A bone marrow aspiration (BMA) identified blast cells with an immunophenotype consistent with T-cell acute lymphoblastic leukemia (expressing CD45, CD34, CD7, CD3, CD99, CD44, and TdT), with no evidence of hemophagocytic events. Based on these results, we initiated chemotherapy per the GATLA ALLIC BFM 2022 protocol and implemented measures to prevent tumor lysis syndrome.

Forty-eight hours after admission, he developed febrile syndrome and distributive shock that responded to fluid therapy; blood cultures and urine cultures were negative, and enterovirus/rhinovirus was detected in the nasopharyngeal secretion aspirate. He received empirical antibiotic therapy with piperacillin-tazobactam and vancomycin, which was discontinued 4 days later after negative blood cultures and identification of the viral infection.

For 20 days, he remained febrile with multiple negative blood cultures and a progressive increase in inflammatory markers: ferritin of 8976 ng/ml, severe hypofibrinogenemia (<40 mg/dl), hypertriglyceridemia (755 mg/dl), and pancytopenia (white blood cells 980/mm^3, hemoglobin 7.9 g/dl, platelets 109 000/mm^3). We retrospectively interpreted the clinical picture as HLH in the context of an oncohematological debut.

We administered gamma globulin at 1 g/kg, resulting in a partial response; however, the patient continued to require fibrinogen replacement on multiple occasions and had elevated ferritin, hypertriglyceridemia, and pancytopenia. The patient received treatment with dexamethasone at a dose of 0.6 mg/kg/day for 15 days, with a gradual reduction in dosage until the 28th day, showing a slow but sustained improvement in immunohematological parameters: fibrinogen 260 mg/dl, prothrombin time 13.8 seconds, activated partial thromboplastin time 33 seconds, and ferritin 2033 ng/ml.

Initially, as part of the evaluation of persistent febrile syndrome, we performed multiple blood cultures, all of which were negative. Polymerase chain reaction (PCR) testing for Epstein-Barr virus, cytomegalovirus, parvovirus B19, adenovirus, herpes simplex viruses 6 and 7, and JC and BK polyomaviruses were also negative, ruling out an infectious cause.

Because the patient presented with HLH in the context of a rapidly progressing first-time hematologic malignancy, immunoglobulin levels were measured: IgG 833 mg/dl, IgA 105 mg/dl,

IgM 62 mg/dl. With IgG and IgM below the lower limit, amoxicillin prophylaxis was prescribed. A complement test and lymphocyte counts were normal, as were cytoplasmic antinuclear antibodies, anti-smooth muscle antibodies, type 1 anti-hepatorenal microsomal antibodies, a normal celiac profile (IgA anti-transglutaminase antibodies), and normal levels of perforins and CD25.

During the illness, the patient developed fluid overload with edema, bilateral pleural effusion, ascites, and pericardial effusion with left-sided cardiac chamber dilation, which resolved with diuretics. The patient also presented with asymptomatic hyponatremia, interpreted as syndrome of inappropriate antidiuretic hormone secretion secondary to systemic inflammation.

Although he initially showed sustained improvement in his immunohematological parameters following the initiation of treatment, at 6 months, following a new course of chemotherapy, he presented with abnormal laboratory values (thrombocytopenia, hypofibrinogenemia, hypertriglyceridemia, hyperbilirubinemia, hypertransaminasemia, and elevated ferritin) despite being asymptomatic. Given his history of HLH, we interpreted this as a new reactivation, and he received gamma globulin, after which his parameters returned to normal.

One year after diagnosis, the patient is on maintenance therapy and in remission from leukemia. As complications of the underlying disease, he has tubulopathy secondary to chemotherapy, which requires potassium and calcium supplementation, and secondary hypertension, which is being treated with enalapril.

DISCUSSION

Hemophagocytic lymphohistiocytosis is a clinical syndrome caused by a dysregulated immune response to infectious, neoplastic, autoimmune, or metabolic triggers.[5] It is characterized by the overproduction of proinflammatory cytokines capable of causing irreversible multiorgan tissue damage. Two forms are recognized: the primary (or genetic) form and the secondary form, which is associated with infections, neoplasms, rheumatologic diseases, or autoimmune diseases.[6] In the latter context, it is often referred to as macrophage activation syndrome (MAS).

LHH associated with oncohematological diseases is one of the most severe forms of the disease, with a high mortality rate, especially when diagnosis is delayed.[3] Although it has been described, its presentation as the initial form of ALL is rare and can delay diagnosis and specific treatment.[4] A recent series by Lehmberg *et al*. estimated that approximately 8% of pediatric cases of HLH were associated with malignancy, predominantly T-cell lymphomas.[7] Furthermore, both chemotherapy and certain immunotherapies have been linked to the development of HLH.[8]

In this case, persistent fever, cytopenias, and elevated inflammatory markers posed the main clinical challenge: distinguishing infection, tumor activity, and macrophage activation. The literature widely describes this clinical overlap, which explains the frequent diagnostic delay.[3]

In this context, markedly elevated ferritin levels, hypofibrinogenemia, and hypertriglyceridemia are findings suggestive of HLH. Ferritin levels above 5000-10 000 ng/ml are strongly associated with this diagnosis.[1]

The pathophysiology of HLH in patients with ALL involves aberrant activation of T cells and macrophages, accompanied by massive release of proinflammatory cytokines, such as IFN-γ, IL-1, IL-6, and TNF-α, that perpetuate the hyperinflammatory state.[1,5,6] This phenomenon may be particularly relevant in T-cell ALLs, given the central role of these lymphocytes in regulating the immune response.

Another important aspect is the role of infectious triggers. In this patient, the detection of enterovirus/rhinovirus may have acted as an inflammatory trigger in a host with underlying oncohematological disease, a mechanism previously described in secondary forms of HLH.[1,2,6]

Treatment involves treating both the inflammation and the underlying cause simultaneously.[5,6,8] In the case presented, corticosteroids and immunoglobulin were used, resulting in a partial response, in line with therapeutic strategies used for secondary forms. The course of the disease, with biochemical relapse following further cycles of chemotherapy, reinforces the concept that HLH can be reactivated by additional inflammatory stimuli, even in clinically stable patients.[1]

In recent years, targeted therapies such as emapalumab (anti-IFN-γ), approved for refractory or recurrent primary HLH,[9] and ruxolitinib (JAK1/JAK2 inhibitor), have been introduced, with promising results in the pediatric population.[10]

Anakinra (an IL-1 antagonist) is a particularly

useful alternative in cases of secondary HLH and MAS.[11] These strategies reflect an increasingly individualized approach to exacerbated inflammation.

Finally, this case highlights several important points: HLH can be the initial presentation of a hematologic neoplasm, early suspicion is essential to avoid diagnostic delays, and management requires a multidisciplinary approach. Early identification and timely treatment can improve prognosis. It should be noted that the initial presentation of HLH in T-cell ALL, as in the case described, is a particularly rare scenario, since most reported cases involve HLH that developed during chemotherapy rather than as the initial manifestation of the disease. ■

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