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Hematopoietic stem cell transplantation in an adult patient with primary hemophagocytic lymphohistiocytosis

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory condition characterized by uncontrolled immune activation and excessive production of pro-inflammatory cytokines, which may rapidly progress to multiorgan failure. Despite efforts to simplify the diagnosis and treatment of this entity, it remains a major challenge in clinical practice, especially in adults. We report a case of suspected primary HLH in an adult patient with a prolonged history of recurrent inflammatory episodes and a fulminant presentation requiring intensive care support. Despite the absence of identifiable genetic mutations, the clinical course was highly suggestive of an underlying primary immune dysregulation. The patient achieved remission with HLH-2004–based therapy and subsequently underwent haploidentical hematopoietic stem cell transplantation (HSCT) due to high risk of recurrence. Seven months after transplantation, she remains in complete remission with full donor chimerism and only mild chronic graft-*versus*-host disease. This case highlights the diagnostic complexity of adult HLH, the limitations of genetic testing, and supports early consideration of HSCT in selected high-risk patients.

Keywords: Cytokine Release Syndrome; Hematopoietic Stem Cell Transplantation; Lymphohistiocytosis; Hemophagocytic.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by hyperactivation of the immune system, resulting in overproduction of pro-inflammatory cytokines and potentially rapidly evolving to multiple organ failure[1,2]. Despite advances in diagnostic criteria and treatment strategies, this condition remains a major challenge in clinical practice[3–5].

This article aimed to present a case of primary HLH in an adult patient with difficult diagnosis and management, even within a specialized hematology center, with refractory evolution and, ultimately, hematopoietic stem cell transplantation (HSCT).

METHODS

This is a case report with a narrative review of the literature. Clinical, laboratory, histopathological and follow-up data were retrospectively collected through medical record review. The narrative literature review was carried out in the PubMed/MEDLINE, Scientific Electronic Library Online (SciELO) and ScienceDirect databases, using the descriptors "hemophagocytic lymphohistiocytosis," "HLH," "adult HLH,"

"HLH-2004," "HScore" and "hematopoietic stem cell transplantation." Review articles, case series, clinical case reports, and relevant guidelines were included, with no year restriction. The selected information was synthesized descriptively.

This study was approved by the Research Ethics Committee of the Instituto Nacional do Câncer (INCA), Rio de Janeiro (RJ), Brazil (Approval number 8.147.101; CAAE: 95207526.2.0000.5274; approved on February 2, 2026). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments[6]. All patient identifying information was removed to ensure confidentiality.

CASE REPORT

A 26-year-old woman was admitted to Instituto Estadual Arthur de Siqueira Cavalcanti (HEMORIO) in April 2018 with severe thrombocytopenia and anemia suggestive of thrombotic thrombocytopenic purpura (TTP). She was managed as TTP, with corticosteroid therapy, rituximab, and plasmapheresis, with clinical response. At that time, it was not possible to confirm TTP because ADAMTS13 measurement was unavailable.

During outpatient follow-up, she never experienced recurrence of probable TTP, but on two occasions she presented signs and symptoms of systemic inflammatory disease, with periods of fever of unknown origin (FUO), sometimes accompanied by arthralgia and painful cervical lymphadenopathy. Extensive investigation during these episodes never established infectious or rheumatologic diseases[2,7].

In March 2021, during a new episode of prolonged FUO and cervical lymphadenopathy, serologies for Epstein-Barr virus, cytomegalovirus, toxoplasmosis, rubella, human immunodeficiency virus, and Bartonella were negative, and rheumatologic screening was also negative. Lymph node histopathology revealed areas of necrosis and histiocytosis with reactive lymphocytes on immunohistochemistry, without granulomas[4]. Once again, the condition resolved spontaneously, while the patient consistently maintained a tendency toward mild leukopenia and mild thrombocytopenia in routine laboratory tests.

In January 2024, she again presented with asthenia, fever, worsening cytopenias, and new cervical lymphadenopathy. A new lymph node biopsy showed mild effacement of the usual architecture, and immunohistochemistry demonstrated reactive lymphoid hyperplasia. Rheumatologic screening was repeated, and all markers were negative. Empirical corticosteroid therapy with prednisone was initiated, but the patient suddenly progressed with clinical and laboratory deterioration, marked adynamia, apathy, anorexia, decreased level of consciousness, acute hepatocellular injury, lactate dehydrogenase (LDH) > 2,300 U/L, pancytopenia, reticulocytopenia, ferritin > 15,000 ng/mL, acute kidney injury requiring dialysis, and the need for sedation and mechanical ventilation[1,7]. A new ADAMTS13 measurement was performed and was normal (57%). In this context, the HScore for HLH was applied, resulting in 169 points (40–54%)[8]. Bone marrow aspirate was hypocellular, making visualization of hemophagocytosis impossible, and bone marrow immunophenotyping showed no relevant abnormalities.

Treatment according to the HLH-2004 protocol with dexamethasone and etoposide was initiated, with evident clinical and laboratory response[3]. There was complete recovery of renal and hepatic function, recovery of the neurological condition, improvement of pancytopenia and a decrease in ferritin to < 500. After hospital discharge, during outpatient follow-up, the patient again developed leukopenia and moderate thrombocytopenia, still without systemic signs of inflammation or organ dysfunction. Dexamethasone was resumed, with improvement of the cytopenias.

A next-generation sequencing panel for familial HLH was performed at Hospital Israelita Albert Einstein in September 2024 and was negative, which did not exclude the diagnosis, since in up to 30% of primary HLH cases no molecular alteration is identified[4,9]. Due to the high risk of disease recurrence, the patient was referred for HSCT at INCA[5].

In June 2025, the patient underwent haploidentical HSCT from her mother. The conditioning regimen used was FluMelTBI, and graft-*versus*-host disease (GvHD) prophylaxis consisted of post-transplant cyclophosphamide, tacrolimus, and mycophenolate, according to the haploidentical transplant protocol. The source of hematopoietic stem cells was mobilized peripheral blood[10].

The patient achieved neutrophil engraftment on day +13 and platelet engraftment on day +15. During HSCT, complications included grade III mucositis and engraftment syndrome, both rapidly resolved. After transplantation, in July 2025, she developed *Clostridioides difficile* infection with suspected gastrointestinal GvHD, which was ruled out by endoscopy; she was treated for cytomegalovirus reactivation in August 2025 and had one episode of tacrolimus-related renal toxicity, rapidly resolved after temporary drug suspension.

Currently, seven months after HSCT, the patient is undergoing treatment for mild chronic GvHD in the mouth, using only topical medication, with blood count showing hemoglobin 12.2 g/dL, leukocytes 6,290/µL, neutrophils 3,648/µL, and platelets 157,000/µL, aspartate aminotransferase 19 U/L, alanine aminotransferase 19 U/L, total bilirubin 0.51 mg/dL, alkaline phosphatase 80 U/L, gamma-glutamyl transferase 32 U/L, ferritin 139 ng/mL, LDH 182 U/L, triglycerides 139 mg/dL, and graft with complete chimerism by polymerase chain reaction technique, and she is asymptomatic[11].

DISCUSSION

HLH in adults remains an underrecognized and frequently delayed diagnosis[2,4], particularly in patients presenting with atypical or relapsing inflammatory manifestations[7,12]. In the present case, the patient experienced multiple self-limited inflammatory episodes over several years before developing a fulminant presentation.

This clinical trajectory suggests that adult HLH may, in some cases, follow a smoldering course prior to overt hyperinflammation, a pattern that is likely underappreciated in routine practice. The initial presentation mimicking TTP underscores the substantial overlap between hyperinflammatory syndromes and thrombotic microangiopathies. In resource-limited settings, in which ADAMTS13 testing may not be readily available, this overlap can lead to diagnostic anchoring and delay the recognition of HLH[3,9].

This case reinforces the need for heightened clinical suspicion in patients with unexplained cytopenias, systemic inflammation, and multiorgan dysfunction, even when alternative diagnoses appear plausible. An additional layer of complexity arises from the absence of pathogenic variants in the genetic panel for familial HLH. While next-generation sequencing has significantly advanced the understanding of HLH pathophysiology, a considerable proportion of patients with a clinical phenotype suggestive of primary HLH remain genetically undefined. In such scenarios, clinical behavior, including recurrence, severity, and corticosteroid dependence, should play a central role in guiding therapeutic decisions, rather than reliance on molecular confirmation alone.

The decision to proceed with haploidentical HSCT was driven by the high risk of recurrence and the inability to achieve sustained disease control with conventional therapy. Importantly, transplantation was considered not merely as salvage therapy, but as an early intervention aimed at modifying the natural history of the disease.

The favorable outcome observed in this case supports this strategy and aligns with emerging evidence advocating for earlier transplant consideration in selected adult patients with high-risk features. Finally, this case highlights systemic challenges in access to transplantation for HLH patients, particularly in countries where the disease is not formally incorporated into national transplant registries[13]. Expanding access to alternative donors, including haploidentical transplantation, may represent a critical step toward improving outcomes in this population.

CONCLUSION

Adult HLH remains a complex and potentially fatal condition, frequently associated with diagnostic delays and therapeutic uncertainty. This case illustrates the importance of recognizing atypical and relapsing presentations, as well as the limitations of genetic testing in defining disease etiology. Early consideration of HSCT should be pursued in selected high-risk patients, even in the absence of molecular confirmation, as a strategy to prevent recurrence and improve long-term outcomes.

CONFLICTS OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Zielak SL, Maradei SC and Boechat TO. **Conception and design:** Zielak SL. **Acquisition of data:** Zielak SL. **Analysis and interpretation of data:** Zielak SL, Maradei SC and Boechat TO. **Technical procedures:** Zielak SL. **Histopathological examinations:** Zielak SL, Maradei SC and Boechat TO. **Statistics analysis:** Zielak SL. **Manuscript preparation:** Zielak SL. **Manuscript writing:** Zielak SL. **Critical revision:** Zielak SL, Maradei SC and Boechat TO. **Final approval:** Maradei SC.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors used an artificial intelligence (AI)-assisted language tool solely for grammatical revision and improvement of textual clarity. The tool was not used to generate clinical data, interpret medical findings, establish diagnoses, conduct the literature review, or formulate the conclusions of the case report. All AI-assisted modifications were critically reviewed and edited by the authors, who take full responsibility for the accuracy, originality, integrity, and final content of the manuscript. No identifiable or confidential patient information was entered into the AI tool.

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