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Case report

COEXISTENCE OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TYPE 3 AND X-LINKED HYPER IGM SYNDROME IN A CHILD

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ABSTRACT

Background: *Hemophagocytic lymphohistiocytosis (HLH) is a severe, life-threatening hyperinflammatory syndrome characterized by excessive activation of the immune system, leading to symptoms such as fever, multilineage cytopenia, coagulopathy, and multi-organ failure, with a high risk of mortality. Its non-specific clinical presentation often poses a diagnostic challenge, especially when the line between primary and secondary HLH is blurred, as secondary triggers, such as infections, can unmask an underlying genetic condition. The incidence of HLH is elevated in patients with inborn errors of immunity (IEI).*

Case report: *We report the case of a 9-month-old male infant with classic HLH, including prolonged fever, hepatosplenomegaly, thrombocytopenia, elevated ferritin, and hemophagocytosis in the bone marrow aspirate. Notably, the patient also had an opportunistic Aspergillus infection, which is a hallmark of severe immunodeficiency. Genetic analysis revealed a rare co-occurrence of two pathogenic variants: a compound heterozygous c.859 - 3C>T mutation in UNC13D (causing familial HLH type 3) and a recessive c.158_161del mutation in CD40LG (causing hyper-IgM syndrome). To date, no patient carrying both defects concurrently has been reported in the medical literature. This case therefore represents the first documented instance of combined UNC13D and CD40LG deficiency, expanding the spectrum of HLH-associated immunogenetics in Southeast Asia. The patient fulfilled HLH-2004 criteria and responded to combined immunochemotherapy and immunoglobulin replacement.*

Conclusions: *This case highlights the importance of comprehensive genomic evaluation in HLH, particularly when clinical features suggest underlying immunodeficiency. Identifying rare combined genetic defects can clarify disease mechanisms and guide timely management, including consideration of hematopoietic stem cell transplantation.*

Keywords: *Hemophagocytic lymphohistiocytosis, primary immunodeficiency, inborn errors of immunity, hyper-IgM syndrome*

I. INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe hyperinflammatory syndrome with high mortality rate. This condition is characterized by overwhelming activation of the immune system, leading to multiorgan damage [1]. HLH is classified into two main types based on its etiology. Primary HLH (also known as familial HLH-FHL) is caused by genetic defects that impair the cytotoxic function of lymphocytes, whereas secondary HLH is triggered by factors such as infections, malignancies, or autoimmune diseases. FHL is further divided into five subtypes based on causative gene mutations, with the most common genes being PRF1, STX11, UNC13D, HPLH1, and STXBP2. Specifically, familial hemophagocytic lymphohistiocytosis type 3 (FHL3), caused by mutations in the UNC13D gene, is one of the most frequent causes of FHL, accounting for 15-25% of cases [2].

The diagnosis of HLH typically relies on clinical and laboratory criteria, including

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prolonged fever, hepatosplenomegaly, cytopenia, hyperferritinemia, and hypertriglyceridemia, as defined by HLH-2004 diagnostic guidelines [3]. The distinction between primary and secondary HLH can be challenging, as primary forms are often triggered by infections and secondary forms may be rooted in an unrecognized genetic predisposition. Recent studies have demonstrated that various inborn errors of immunity (IEI) other than FHL can predispose patients to HLH, particularly in cases with a history of persistent or opportunistic infections [4].

Hyper-IgM syndrome (HIGM) is a rare primary immunodeficiency disorder with six major subtypes classified based on different genetic defects [5]. The most common form, X-linked hyper-IgM syndrome (XHIGM or HIGM1), is caused by mutations in CD40LG, with an estimated incidence of 1 in 1,000,000 live male births. Patients with HIGM have low serum levels of IgG, IgA, and IgE, while IgM levels are normal or elevated, predisposing them to recurrent infections, especially in the respiratory and gastrointestinal tract [6].

The co-occurrence of a hyper-inflammatory disorder such as HLH and a humoral immunodeficiency like HIGM is an extremely rare clinical scenario that has not been widely described in the medical literature. Although these two conditions have distinct pathomechanisms, their interactions are potent. Chronic infections characteristic of HIGM can serve as a strong trigger, unmasking, and exacerbating the hyper-inflammatory phenotype of an underlying primary HLH.

In this report, we present a unique case of a male infant diagnosed with co-occurring pathogenic mutations in both UNC13D (FHL3) and CD40LG (XHIGM). This case underscores the importance of comprehensive IEI screening in patients with HLH, especially those with a history of recurrent infections, opportunistic infections, or an inadequate response to standard treatment protocols. Far from being an anecdotal rarity, this case underscores why rare disorders deserve careful documentation-they may redefine our understanding of immune pathophysiology and directly impact the care of future patients.

II. CASE REPORT

2.1. Initial presentation, diagnostics, and preliminary diagnosis

A 9-month-old male infant presented with a 3-day history of non-specific respiratory symptoms including mild cough with minimal sputum and no wheezing. He was initially admitted to a provincial hospital with pneumonia. Initial blood tests revealed a markedly elevated C-reactive protein (CRP) level of 102 mg/L. A complete blood count showed mild anemia (HGB 9.3 g/dL), leukopenia (WBC 2.46 x109/L), neutropenia (27% NEU), relative lymphocytosis (58% LYM), and normal platelet count (PLT 164 x109/L). The patient was treated with intravenous Ceftiam and Amikacin for four days. However, his high fever persisted, prompting a switch to Meropenem and Vancomycin for another three days. Due to the continued high fever (38.5 - 39.5°C) on the 10th day of broad-spectrum antibiotic treatment, the patient was transferred to Hue Central Hospital for further diagnosis and management.

On admission to Hue Central Hospital, physical examination revealed a febrile state with temperature spikes every 4-6 hours, peaking at 39.5°C. The patient appeared pale with slightly pale mucous membranes. The liver was palpable at 2-3 cm and the spleen was 2 cm below the costal margin. Respiratory, cardiovascular, and abdominal examinations were otherwise unremarkable. A detailed history revealed that the patient was the second child in the family with a healthy 6-year-old sister. The patient's birth history was unremarkable. The patient's medical history was notable for frequent upper respiratory tract infections and otitis media, starting at 7 months of age. He was fully vaccinated and had no history of daily medication use. The family denied any consanguineous marriage, history of immunodeficiency, early childhood deaths, or autoimmune diseases.

A complete blood count upon admission to Hue Central Hospital showed leukocytosis (19.2 x109/L) with lymphocytosis (69.2%), a mild decrease in hemoglobin (10.0 g/dL), and a reduced platelet count (119 x109/L). The CRP level remained elevated at 111.05 mg/L. Despite the change to broad-spectrum antibiotics, Meropenem and Vancomycin, the fever persisted. During the first week of hospitalization, the red blood cell and platelet counts showed a progressive decline (Table 1 and Table 2). Given the prolonged

fever and bicytopenia, a peripheral blood smear was performed; however, no atypical cells were found.

Biochemical analysis revealed a significantly elevated serum ferritin level (1762 ng/mL) and increased triglycerides (3.66 mmol/L). The levels of liver enzymes (AST/ALT) were initially within normal limits. Coagulation studies, including prothrombin time (PT), fibrinogen, APTT, and INR, were all normal. Chest and abdominal computed tomography (CT) showed bilateral pneumonia with pleural effusion, reactive lymphadenopathy in the left axilla and abdomen, and a significant amount of free fluid in the peritoneal cavity (Figure 1).

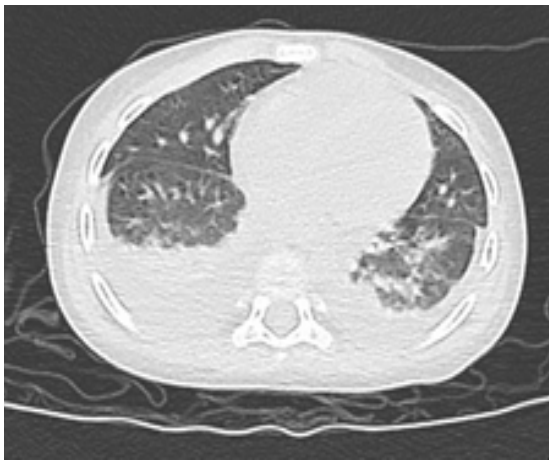

Figure 1: Chest CT scan showing scattered ground-glass opacities and consolidations in both lungs, with moderate bilateral pleural effusions.

Urine and stool test results were normal. Viral serology for the Epstein-Barr virus and TORCH panel was negative. Blood and sputum cultures were negative. However, galactomannan testing of bronchoalveolar lavage fluid was positive 6.43 (OD index ≥ 1.0, the threshold for positivity), suggesting invasive Aspergillus infection. A bone marrow aspirate showed hemophagocytosis but no evidence of malignancy, and no EBV or CMV was detected. Specialized immunological tests for soluble CD25, NK cell activity, and CD163 were not performed.

After 5 days of hospitalization, HLH was suspected because the patient met five of the eight diagnostic criteria of the HLH-2004 guidelines (Table 1). Furthermore, based on the history of recurrent respiratory infections and opportunistic Aspergillus infection, underlying immunodeficiency was suspected. HIV and tuberculosis tests were negative. Lymphocyte subset analysis showed normal T, B, and NK cell counts for the patient's age. However, serum immunoglobulin levels revealed significantly low IgG (< 0.448 g/L; reference range: 1.1 - 6.5 g/L) and IgA (< 0.0392 g/L; reference range: 0.0 - 0.3 g/L), while IgM was within the normal range (0.427 g/L; reference range: 0.3 - 0.9 g/L), prior to intravenous immunoglobulin (IVIG) therapy.

Table 1: Patient's clinical and laboratory findings in relation to HLH-2004 diagnostic criteria.

HLH-2004 Criteria	**Patient's clinical and laboratory findings**
Diagnosis is established if a patient fulfills either criterion A or B:	
A. Molecular genetic diagnosis consistent with HLH: Pathogenic variants in PRF1, UNC13D, STXBP2, Rab27a, STX11, SH2D1A, XIAP	N/A
B. Initial diagnosis:	
1. Fever ≥ 38.5°C *	Prolonged fever for 15 days
2. Splenomegaly *	Hepatosplenomegaly
3. Cytopenias affecting at least 2 of 3 lineages (Hb 90g/L; platelets < 100 x109/L; neutrophils < 1.0 x109/L)	NEU 4.4x109/L

HLH-2004 Criteria	Patient's clinical and laboratory findings
HGB 10 g/L	
PLT 119x109/L	
4. Hypertriglyceridemia and/or hypofibrinogenemia (triglyceride ≥ 3 mmol/l, Fibrinogen ≤ 1.5 g/l) *	Triglyceride 3.66 mmol/L (reference range: 0.51 - 2.38 mmol/L)
Fibrinogen 2.86 g/l (reference range: 0.82 - 3.83 g/L)	
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes. No evidence of malignancy *	Bone marrow aspirate showed hemophagocytosis
6. Low or absent NK cell activity	N/A
7. Ferritin ≥ 500 ng/ml *	Ferritin 1762 ng/mL (reference range: 7 - 140 ng/mL)
8. Increased soluble CD25 ≥ 2400 U/ml	N/A

** Patient meets this criterion, N/A: Not available*

2.2. Definitive diagnosis and treatment course

Following diagnosis, the patient was initiated on an HLH-specific treatment protocol, including Dexamethasone (0.3 mg/kg/day) and Etoposide (150 mg/m²/day) for 2 weeks. This was combined with broad-spectrum antibiotics (Meropenem, Linezolid, Colistin), the antifungal agent Voriconazole, and IVIG at a dose of 0.5 g/kg. The patient's clinical condition and laboratory parameters showed marked improvement: the fever subsided, the neutrophil count gradually increased, ferritin levels significantly decreased (Table 2) and (Figure 2). The serum galactomannan index decreased to 2.14 (OD index < 0.5, threshold for positivity) after the first month and subsequently became negative after two months of antifungal therapy.

Table 2: Hematological parameters during the patient's treatment course.

Parameter (Normal range)	Admission	Day 3	Day 7	Day 15	Day 30	Day 60	Day 90
WBC (7.7-13.1 x109/L)	19.2	11.9	17.1	9.7	7.0	3.3	6.9
NEU (2.5-6.4 x109/L)	4.4	3.6	3.3	2.4	4.4	0.4	2.8
LYM (2.3-5.5 x109/L)	13.3	7.2	12.7	7.0	1.6	2.3	4.1
HGB (10.4-12.5 g/L)	10.0	9.2	8.0	8.7	9.1	10.0	8.5
PLT (140-440 x109/L)	119	86	83	10	131	41	70

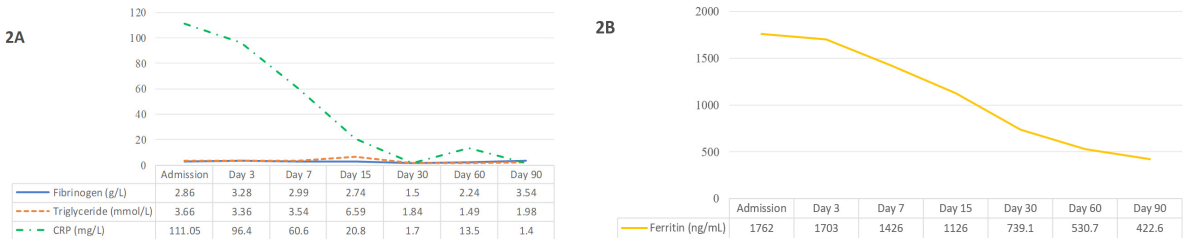

Figure 2: Changes in selected biochemical parameters during the first 3 months of hospitalization. (A) Fibrinogen, triglyceride, and CRP; (B) Ferritin.

The family was counseled, and consent was obtained for genetic testing via whole exome sequencing (WES). The analysis identified two pathogenic mutations: a compound heterozygous c.859 - 3C > T mutation in the UNC13D gene, which causes familial hemophagocytic lymphohistiocytosis type 3 (FHL3), and a recessive c.158_161del mutation on the X chromosome (XLR) in the CD40LG gene, which causes XHIGM, both variants were classified as pathogenic. Sanger sequencing confirmed that the mother was a heterozygous carrier of the CD40LG mutation, whereas the father was not a carrier. This suggests that the UNC13D variant is likely to be a de novo mutation. Based on these results, a definitive diagnosis was established as FHL3 on the background of XHIGM.

Currently, the patient continues treatment with the HLH protocol for 6 months, along with prophylactic antibiotics and antifungals (Trimethoprim/ sulfamethoxazole and Voriconazole), and periodic IVIG every 4 weeks. Although hematopoietic stem cell transplantation (HSCT) is the only curative option, it has not yet been performed at the family's discretion.

III. DISCUSSION

Inborn errors of immunity (IEI), formerly known as primary immunodeficiencies, comprise a complex group of over 450 rare genetic disorders. These conditions impair the number and/or function of one or more components of the immune system, increasing the risk of infections, autoimmune diseases, allergies, and cancer. According to the latest International Union of Immunological Societies (IUIS) classification, HLH is placed in the fourth category, "Diseases of immune dysregulation," among the ten groups of IEI [7].

This case report describes a 9-month-old male infant whose clinical presentation suggested the co-occurrence of two distinct immune disorders. The initial symptoms of prolonged fever, hepatosplenomegaly, and cytopenia are hallmark clinical features of HLH. These findings were supported by the biochemical findings of severe hyperinflammation, including markedly elevated ferritin (1762 ng/mL) and hypertriglyceridemia (3.66 mmol/L). The patient's fulfillment of five of eight HLH-2004 criteria provided a strong basis for the initial diagnosis [2]. However, the clinical picture was complicated by the patient's history. Recurrent respiratory tract infections and otitis media from 7 months of age, coupled with opportunistic Aspergillus infection, are strong indicators of severe underlying IEI. This was confirmed by immunoglobulin testing, which showed severely low levels of IgG and IgA with normal IgM, a classic finding in hyper-IgM syndrome.

The pivotal finding in this case was genetic analysis, which confirmed the rare co-occurrence of two pathogenic mutations in two different genes. A compound heterozygous c.859 - 3C > T mutation in the UNC13D gene causes FHL3, an autosomal recessive disorder. This gene encodes the Munc13-4 protein, which is essential for degranulation of cytotoxic granules from T and NK cells [2]. This functional impairment leads to an uncontrolled hyper-inflammatory response and the "cytokine storm" characteristic of HLH. Concurrently, the patient carried a recessive c.158_161del mutation on the X chromosome in the CD40LG gene, causing XHIGM. CD40LG encodes the CD40 ligand (CD40L) protein, which is vital for T-cell and B-cell interactions necessary for antibody class switching [8]. When this interaction is defective, B cells cannot switch from producing IgM to other immunoglobulin classes, leading to severe humoral immunodeficiency marked by susceptibility to recurrent pyogenic and opportunistic infections [5]. Genetic counseling was provided to the family, highlighting the X-linked inheritance of CD40LG and the associated risk of affected male offspring. Recommendations included preimplantation or prenatal genetic testing and screening of at-risk relatives to inform clinical management and family planning decisions.

A systematic review of pediatric HLH highlighted that HLH can be a clinical manifestation of various IEIs and that patients with IEI are at an increased risk of developing HLH [4]. Recurrent and persistent infections, which are hallmarks of hyper-IgM syndrome due to CD40L deficiency, can serve as a powerful trigger for an underlying FHL3. Secondary HLH can also manifest in other IEIs, particularly those with T-lymphocyte dysfunction such as severe combined immunodeficiency (SCID), DiGeorge

syndrome, Wiskott-Aldrich syndrome, chronic granulomatous disease... [4, 9]. This highlights how symptomatic overlap between HLH and infections complicates the diagnostic process, increasing the risk of severe complications and mortality. HLH and severe infections are closely interrelated, making diagnosis and management particularly challenging. Initial treatment requires the prompt initiation of empirical broad-spectrum antibiotics once infection is suspected, followed by de-escalation based on identified pathogens. Antimicrobial dosing should be optimized according to drug metabolism and pharmacokinetic characteristics [10].

The clinical phenotype of patients under both conditions is extremely complex. The classic symptoms of HLH can be triggered by infections associated with the hyperIgM syndrome, masking the underlying immunodeficiency. This can lead to misdiagnosis, missed diagnosis, or delayed diagnosis of either condition. Therefore, a comprehensive diagnostic approach is needed. HLH should be considered in any severely ill child and the HLH-2004 criteria must be evaluated. If these criteria are not fully met, close monitoring should be considered to detect disease progression. For children who meet ≥5 of the 8 criteria, an immunological workup to assess cellular cytotoxic function and HLH-related protein expression is required. If these tests are abnormal, targeted gene sequencing should be performed, particularly if the patient is under one year of age. If no cause is identified, WES should be performed to detect other potential underlying IEIs (Figure 3) [11].

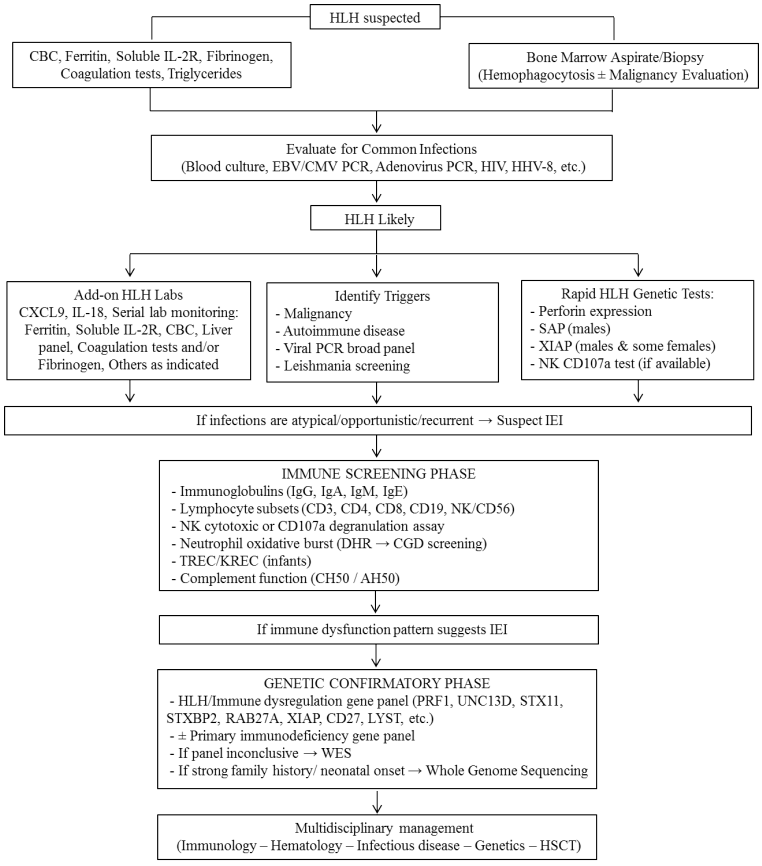

Figure 3: Tests that may be considered during the evaluation of pediatric patients with suspected HLH, particularly in the context of suspected IEI.

The patient was treated using a combined protocol that addressed both the pathologies. The HLH protocol (Dexamethasone and Etoposide) was used to control life-threatening hyperinflammation. Concurrently, prophylactic antibiotics/antifungals and IVIG were administered to compensate for the antibody deficiency of HIGM, reducing the risk of infections and preventing future HLH flares. Our

patient responded well to the combined approach. Some patients may experience HLH reactivation, defined as the recurrence of ≥ 3 of the 8 HLH-2004 criteria after achieving remission. Notably, the appearance of new central nervous system symptoms alone is sufficient to define reactivation, even in the absence of other criteria [3]. On day 15, the patient developed severe thrombocytopenia (10×10^9/L) and received platelet transfusion for supportive management. Many critically ill patients with HLH require multiple transfusions during the acute phase, particularly platelet transfusions and plasma products such as fresh frozen plasma or cryoprecipitate. Etoposide remains a cornerstone of HLH treatment; however, hematologic toxicity-including neutropenia, thrombocytopenia, and anemia-is a common adverse effect. According to the HLH-2004 protocol, temporary withholding or dose reduction of etoposide should be considered in cases of prolonged hematologic toxicity, such as persistent severe neutropenia, sustained severe thrombocytopenia, or progressive hepatic dysfunction [3, 12]. Importantly, these abnormalities must be carefully assessed to distinguish chemotherapy-related toxicity from disease reactivation. In such situations, decisions regarding dose modification should be made under the guidance of a hematology specialist.

However, these therapies are merely supportive and do not address underlying genetic defects. HSCT is considered the only curative treatment option for both conditions [1, 8, 13]. According to the literature, the overall survival rate after transplantation is 45% [11]. HSCT replaces defective hematopoietic cells, thereby restoring both cytotoxic degranulation in FHL3 and antibody class switching in HIGM. The family's decision not to proceed with HSCT is a critical factor that can severely impact the child's long-term prognosis. Transplantation can be hindered by various factors, including severe pre-transplant infections, organ damage (often to the liver or lungs), the lack of a suitable donor, or economic barriers, with the patient's age at the time of transplantation being a crucial determinant [13]. In the context of FHL, HSCT should be performed as early as possible once a suitable donor is available [3]. The optimal timing is when hyperinflammation has been effectively controlled, as indicated by decreasing ferritin levels and stabilization of organ function. In this patient, invasive Aspergillus infection was brought under control with appropriate antifungal therapy until both clinical and laboratory findings stabilized, allowing for safe transplantation preparation. Transplantation during active HLH or uncontrolled fungal infection is associated with increased mortality, a higher risk of HLH reactivation, and severe infectious complications [3, 10]. Current guidelines emphasize that a history of invasive fungal infection is not an absolute contraindication to HSCT [12].

To date, no patient carrying both defects concurrently has been reported in the medical literature. Our case therefore represents not only the first description of combined UNC13D and CD40LG deficiency worldwide, but also an epidemiologically novel finding that expands the spectrum of HLH-associated immunogenetics to an under-represented region of Southeast Asia. Although such "double-hit" cases are exceptionally rare, they should not be overlooked. On the contrary, they highlight two important lessons: first, that WES is essential when standard panels fail to fully explain the phenotype; and second, that even extremely uncommon combinations can reveal new insights into disease mechanisms and influence clinical decision-making, such as the early consideration of HSCT.

IV. CONCLUSION

HLH is a rare, but life-threatening clinical condition. IEI can be an underlying etiology of secondary HLH. Therefore, we recommend that comprehensive IEI screening is essential in the diagnostic workup of HLH, particularly in pediatric patients with a history of recurrent infections, opportunistic infections, or inadequate response to standard treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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