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Case Report

Congenital Hemophagocytic Lymphohistiocytosis: Diagnostic and Therapeutic Challenges

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome characterized by dysregulated immune activation, uncontrolled proliferation of lymphocytes and macrophages, and a life-threatening cytokine storm. Owing to its heterogeneous and often nonspecific presentation, HLH can be particularly difficult to recognize in the neonatal period. We report a case of neonatal familial HLH diagnosed by genetic testing despite incomplete fulfillment of clinical diagnostic criteria and apparent clinical improvement in the absence of HLH-directed therapy.

Keywords: Hemophagocytic Lymphohistiocytosis; HLH; Familial HLH; Neonatal HLH; CD107a; PRF1

Abbreviations and Acronyms

HLH: Hemophagocytic Lymphohistiocytosis; FHL: Familial Hemophagocytic Lymphohistiocytosis; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; PCR: Polymerase Chain Reaction; cfDNA: Cell-Free DNA; sIL-2R: soluble Interleukin-2- Receptor; WBC: White Blood Cell; RBC: Red Blood Cell; MRI: Magnetic Resonance Imaging; LDH: Lactate Dehydrogenase; CNS: Central Nervous System; LP: Lumbar Puncture; NK: Natural Killer

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe immune dysregulation disorder marked by uncontrolled activation of cytotoxic T lymphocytes and macrophages, resulting in overwhelming systemic inflammation and multiorgan injury. The clinical picture is often dominated by nonspecific yet serious features such as prolonged fever, hepatosplenomegaly, cytopenias, coagulopathy, and, in some cases, neurological involvement. This variable and overlapping presentation frequently mimics more common conditions, including severe infection or metabolic disease, making early diagnosis challenging, particularly in neonates [1,2].

HLH is broadly classified into two categories: primary (familial) and secondary (acquired). Primary HLH refers to cases associated with inherited defects in cytotoxic lymphocyte function, typically inherited in an autosomal recessive manner and collectively termed familial hemophagocytic lymphohistiocytosis (FHL). Secondary HLH occurs in association with infections, autoimmune disease, malignancy, or other inflammatory triggers. Distinguishing between these entities at initial presentation is often challenging, yet critically important for management and prognosis [1,3].

Although HLH can occur at any age, neonatal onset is exceedingly rare, accounting for approximately 4% of reported cases. Most children with FHL are born healthy and develop symptoms within the first two to six months of life; presentation in the immediate neonatal period is uncommon and associated with particularly high morbidity and mortality. The rarity of neonatal HLH, combined with its overlap with more common neonatal conditions, such as sepsis, frequently leads to delayed diagnosis and treatment [3,4].

The true incidence of neonatal HLH is uncertain but has been estimated at 1 in 50,000 to 150,000 live births, with higher prevalence in populations with increased consanguinity. Despite advances in diagnostic tools and supportive care, HLH remains associated with a high fatality rate, underscoring the importance of early recognition and prompt initiation of therapy [4,5].

We describe a case of FLH presenting in the early neonatal period and highlight the diagnostic challenges and management considerations unique to this population.

Case Presentation

A male infant was born at 39 weeks 6 days' gestation via vacuum-assisted vaginal delivery following an uncomplicated pregnancy. He required brief continuous positive airway pressure at birth but remained in room air thereafter and was discharged home without complications.

On day of life 13, he presented to his pediatrician with firm abdominal distension and bilateral scrotal swelling. Vital signs were within normal limits. He was transferred to the emergency department, where he appeared alert and active but fussy. He had been feeding well with an appropriate number of wet diapers and stools. Physical examination revealed irritability, tachycardia, abdominal distension with tenderness, and non-tender bilateral scrotal swelling.

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Capillary refill was <2 seconds.

A sepsis evaluation was initiated, and empiric broad-spectrum antibiotics with anaerobic coverage were started given concern for an intra-abdominal source. There was no history of fever, bloody stools, emesis, diarrhea, cough, or upper respiratory symptoms.

Initial evaluation

Two-view abdominal radiography demonstrated findings concerning for pneumatosis intestinalis versus fecal burden. Laboratory studies revealed hyponatremia (130 mmol/L), thrombocytopenia (47×10^3/μL), leukopenia (7×10^3/μL) with neutropenia (absolute neutrophil count 910/μL), and elevated C-reactive protein (2.1 mg/dL). Given these findings, Bell stage IIA necrotizing enterocolitis was suspected, and standard management was initiated, including bowel rest, nasogastric decompression, intravenous fluids, and antibiotics. The infant was admitted to the intensive care unit, and pediatric surgery was consulted.

Blood and urine cultures remained negative. Respiratory viral testing was negative. Liver function testing demonstrated elevated transaminases (ALT 49 U/L, AST 125 U/L). Coagulation studies showed prolonged prothrombin time (19 seconds), elevated international normalized ratio (2.0), hypofibrinogenemia (73 mg/dL), and normal activated partial thromboplastin time (28.7 seconds).

Hematologic evaluation

Persistent thrombocytopenia prompted hematology consultation. The thrombocytopenia was considered acute in onset and of unclear etiology. Infection remained the leading diagnostic consideration despite negative cultures. Disseminated intravascular coagulation, thrombosis (including occult renal vein thrombosis), and splenic sequestration were also considered; however, there was no clinical evidence of thrombosis, splenomegaly, or central venous catheter–related complications. There were no congenital anomalies or dysmorphic features suggestive of a syndromic condition. Maternal history was negative for thrombocytopenia or relevant medication exposures. Neonatal alloimmune thrombocytopenia was considered unlikely given the delayed presentation, prior tolerance of invasive procedures (frenectomy and circumcision), and typically earlier onset of disease.

Management included evaluation for coagulopathy and supportive platelet transfusions to maintain counts >30,000/μL (>50,000/μL if bleeding occurred). Testing for alloimmune thrombocytopenia was discussed but deferred due to low clinical suspicion.

Clinical deterioration

Over the subsequent days, the infant developed worsening cytopenias (platelet nadir 19×10^3/μL), progressive neutropenia, coagulopathy, hypoalbuminemia, and rising lactate (peak 5.4 mmol/L). He required multiple transfusions of platelets, fresh frozen plasma, and cryoprecipitate.

Abdominal ultrasound demonstrated mild to moderate ascites and gallbladder wall edema without evidence of volvulus or renal vein thrombosis. Cranial ultrasound showed no intracranial hemorrhage. Scrotal ultrasound revealed large bilateral hydroceles with normal perfusion.

The infant subsequently developed a single febrile episode (maximum temperature 38.3°C). Peripheral smear demonstrated atypical lymphocytosis, raising concern for disseminated viral infection; however, viral testing, including urine cytomegalovirus PCR, blood Epstein–Barr virus PCR, herpes simplex virus PCR, serum Enterovirus PCR and respiratory viral panel, gastrointestinal pathogen panel, and broad infectious workup remained negative. Infectious diseases consultation was obtained. Karius test [non-invasive, next-generation sequencing blood test that detects over 1,000 pathogens, bacteria, DNA viruses, fungi, and parasites, by identifying microbial cell-free DNA (cfDNA) in plasma] resulted negative.

Hypoalbuminemia worsened, necessitating albumin infusions. Ascites increased, contributing to respiratory compromise.

Evaluation for hemophagocytic lymphohistiocytosis

Hematology was reconsulted for persistent thrombocytopenia and soluble interleukin-2- receptor (sIL-2R), ferritin level and triglycerides were sent based clinical suspicion of HLH

Given the constellation of cytopenias, liver dysfunction, coagulopathy, hyperferritinemia (3,864 ng/mL), and elevated sIL-2R (7,417 pg/mL), HLH was suspected, prompting genetic evaluation. However, the infant did not meet full diagnostic criteria for HLH, and the absence of persistent high fever was considered atypical. Intravenous immunoglobulin therapy was administered without clinical improvement. Whole-genome sequencing was subsequently performed, and a CXCL9 assay later returned markedly elevated at 27,399 pg/mL. Triglyceride levels remained normal at 63 mg/dL.

Ascites evaluation and hepatic workup

Because of worsening ascites and respiratory compromise, diagnostic paracentesis was performed, yielding approximately 100 mL of cloudy fluid. Analysis revealed WBC 205/μL (95% lymphocytes), RBC <2,000/μL, and no evidence of acute inflammatory predominance. Fluid studies were not consistent with cirrhosis or portal hypertension–related ascites.

Further evaluation showed rising direct hyperbilirubinemia, though matrix metalloproteinase-7 testing was normal. Liver Doppler ultrasonography demonstrated elevated hepatic arterial resistive indices without reversal of flow or portosystemic shunting. Coagulation factor assays (factors II, V, and VIII) were normal.

Magnetic resonance imaging (MRI) with MR cholangiopancreatography demonstrated moderate-to-large ascites without septations, splenomegaly (8.1 cm), trace right pleural effusion, periportal edema, pericholecystic fluid, and a large fluid-containing left inguinal hernia.

Ascitic fluid studies showed glucose 71.5 mg/dL, LDH 311 U/L, total protein 2.54 g/dL, triglycerides 47.7 mg/dL, bilirubin 1.74 mg/dL, albumin 1.82 g/dL, amylase 7.48 U/L, and creatinine 0.317 mg/dL.

Hepatology consultation concluded that the ascites was of unclear etiology with low serum-ascites albumin gradient, suggesting a non–portal hypertensive process. Differential diagnoses included lymphatic abnormalities, intra-abdominal malignancy, pancreatitis, biliary leak, or nephrotic processes. Liver function tests gradually improved, arguing against end-stage liver disease.

Genetic diagnosis

Whole-genome sequencing ultimately identified biallelic pathogenic variants in the PRF1 gene (c.445G>A [p.G149S] and c.217T>C [p.C73R]), consistent with autosomal recessive familial hemophagocytic lymphohistiocytosis type 2 (FHL2).

At the time of diagnosis, the infant had cytopenias, coagulopathy, transaminitis, conjugated hyperbilirubinemia, splenomegaly, and elevated inflammatory markers but had shown partial spontaneous clinical improvement, leading to continued multidisciplinary deliberation regarding initiation of HLH-directed therapy. Additional studies, including CXCL9 and interleukin-18 levels, were sent, and bone marrow evaluation was planned once clinically stable.

After confirmation of diagnosis, lumbar puncture (LP) was obtained which showed central nervous system (CNS) HLH (elevated WBC, hemophagocytosis and elevated neopterin). MRI brain was overall unremarkable. Dexamethasone and Etoposide treatment was started per HLH-2004 guidelines. Intrathecal chemotherapy was initiated with Methotrexate. Throughout the treatment, infant remained on bacterial prophylaxis with Trimethoprim-Sulfamethoxazole and fungal prophylaxis with Fluconazole. The response to treatment was measured with decreasing/normalizing sIL-2R and CXCL9 levels. CNS disease resolved on subsequent LPs.

Currently, the infant is doing well and is awaiting matched unrelated donor bone marrow transplant.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome caused by impaired cytotoxic function of natural killer (NK) cells and cytotoxic T lymphocytes, resulting in uncontrolled immune activation. The term hemophagocytic refers to the engulfment of hematopoietic cells by activated macrophages, while lymphohistiocytosis reflects the proliferation of lymphocytes and histiocytes. The syndrome was first described in 1952 in two siblings presenting with fever and hepatosplenomegaly, and subsequent observations identified both familial and sporadic forms associated with infection, malignancy, and rheumatologic disease. Familial forms of HLH are caused by inherited defects in cytotoxic granule–mediated cell killing, with mutations in the PRF1 gene encoding perforin identified as one of the earliest described genetic etiologies [6,7].

In normal immune regulation, NK cells and cytotoxic T lymphocytes eliminate infected or activated antigen-presenting cells through granule-mediated cytotoxic pathways. Defects in this pathway impair immune termination, resulting in persistent antigen stimulation, uncontrolled T-cell activation, and excessive cytokine production. This process culminates in the characteristic hyperinflammatory state of HLH with markedly elevated levels of interferon-γ, tumor necrosis factor-α, interleukin-6, interleukin-8, interleukin-10, and interleukin-18, which together contribute to macrophage activation, hemophagocytosis, and progressive multiorgan dysfunction [2,6,8].

Neonatal HLH is particularly difficult to recognize because early manifestations are nonspecific and often indistinguishable from sepsis or other inflammatory conditions. Common findings include cytopenias, hepatosplenomegaly, liver dysfunction, and coagulopathy, although atypical presentations such as hydrops fetalis, fetal distress, or isolated thrombocytopenia have been reported. Fever, a hallmark feature in older children, may be absent; neonates may instead present with normothermia or hypothermia due to their limited thermoregulatory capacity [1]. Reliance on fever as a prerequisite for diagnosis may therefore delay recognition and treatment in this population.

FLH is inherited in an autosomal recessive pattern and typically presents in infancy or early childhood. Mutations affecting cytotoxic granule exocytosis, including PRF1, UNC13D, STX11, and STXBP2, impair immune regulation and predispose to disease. Without treatment, FHL is rapidly fatal, with historically poor survival rates. Because infections may trigger disease in genetically predisposed individuals, distinguishing familial from secondary HLH based solely on clinical features can be difficult, making genetic confirmation essential for diagnosis, prognosis, and family counseling [1,2,8].

When molecular testing is unavailable or pending, diagnosis relies on the HLH-2004 criteria established by the Histiocyte Society, which require either identification of a pathogenic mutation or fulfillment of at least five of eight clinical and laboratory features: fever, splenomegaly, cytopenias affecting at least two cell lines, hypertriglyceridemia and/or hypofibrinogenemia, low or absent NK cell activity, hyperferritinemia (≥500 μg/L), elevated sIL-2R, and hemophagocytosis in bone marrow or other tissues [2,7-9].

It is important to recognize that the HLH-2004 diagnostic criteria were originally developed for clinical trial enrollment and should not be interpreted as absolute requirements for diagnosis. In clinical practice, many patients—particularly neonates-may not fulfill five of the eight criteria at initial presentation. Therefore, HLH should remain in the differential diagnosis in any patient with evidence of hyperinflammation and evolving end-organ dysfunction, including cytopenias, liver injury, or coagulopathy. Increasingly, adjunctive diagnostic modalities are being utilized to support early diagnosis. Flow cytometry–based assays, including evaluation of CD107a expression and intracellular perforin, can assess the integrity of cytotoxic pathways in natural killer and $CD8^+$ T cells and help identify underlying defects in immune regulation. These tools are particularly valuable when clinical criteria are incomplete but suspicion for HLH remains high [10,11].

Our case further illustrates these diagnostic challenges. Despite significant clinical deterioration, the infant lacked one of the hallmark features of HLH-persistent fever-and never fulfilled five of the eight HLH-2004 diagnostic criteria during the initial evaluation. The diagnosis was ultimately established through identification of biallelic pathogenic variants in the PRF1 gene, underscoring the critical role of early genetic testing when HLH is suspected but classical criteria are not met.

HLH is rapidly progressive and often fatal, and early initiation of therapy is the most important prognostic factor. Control of hyperinflammation prior to hematopoietic stem cell transplantation has been associated with improved transplant outcomes in patients with familial HLH [12]. Current recommendations support starting treatment in critically ill patients with strong clinical suspicion, even when full diagnostic criteria are not yet met, while additional investigations are pursued [12]. In our case, HLH-directed therapy was not initiated because the infant demonstrated clinical improvement following diagnostic paracentesis, which likely provided symptomatic relief through reduction of intra-abdominal pressure and improvement in respiratory compromise and liver enzymes. This atypical course further complicated diagnostic decision-making.

Overall, this case highlights the need for a high index of suspicion for HLH in neonates presenting with unexplained cytopenias, liver dysfunction, coagulopathy, or hyperinflammation, even when classical diagnostic features are incomplete.

Conclusion

HLH in neonates remains challenging to diagnose due to its rarity, heterogeneous presentation, and overlap with more common neonatal conditions. Untreated HLH is rapidly fatal but potentially curable with timely therapy. Clinicians must therefore maintain a high index of suspicion even when classical diagnostic criteria are not fully met. Early consideration of HLH and prompt pursuit of definitive testing, including genetic evaluation, may be lifesaving.

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