

Familial Hemophagocytic Lymphohistiocytosis Presenting With Neonatal Cholestasis

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Abstract

When a baby presents with cholestasis, we usually proceed to rule out surgical causes and investigate for causes of neonatal hepatitis, like TORCH infections, metabolic disorders, and so on. Here, we present a case of a neonate with conjugated jaundice and thrombocytopenia who had an unusual cause of cholestasis.

Keywords

Hematologic disorders, neonatal care, neonatology/perinatology, newborn

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Background

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of immune regulation characterized by accumulation of tissue macrophages or histiocytes. Neonatal HLH is rare and the incidence ranges somewhere between 1 in 50,000 and 1,50,000.¹ HLH can have varied presentations and mimic several disorders like sepsis, metabolic disorders, and so on. Here, we describe a 7 days old newborn who presented to us with fever, petechiae, and conjugated jaundice.

Case Presentation

A 7 days old female baby presented with fever and bleeding spots over her body for 1 day along with jaundice. She was born out of a nonconsanguineous marriage at 35 weeks by caesarian section with a birth weight of 1.9 kg. Antenatal history was uneventful. There was history of death of the previous sibling at 2½ months of age. The sibling's medical records revealed she had hepatosplenomegaly, ascites, conjugated jaundice, transaminitis, coagulopathy, anemia, thrombocytopenia, and her metabolic screening by tandem mass spectrometry (TMS) and gas chromatography mass spectrometry (GCMS) had been normal.

On admission, the baby was icteric and had multiple petechial spots. There was hepatosplenomegaly. No dysmorphism and no other congenital abnormalities were there. Suspecting sepsis, baby was started on empiric intravenous antibiotics. Initial investigations showed Hb 16.9 g/dL, total counts 18,630/cmm, and platelet counts 12,000/cm. C-reactive protein was negative and blood and urine culture showed no growth. Baby also had coagulopathy with prothrombin time 19.5 s and activated partial thromboplastin time 80.6 s. Liver function tests

showed total bilirubin was 7 mg/dL, direct fraction 3.5 mg/dL, AST 235 IU, and ALT 84 IU. Initially, we suspected a metabolic disorder, however, baby had no hypoglycemia, urine reducing sugar was negative, blood gas showed no metabolic acidosis, and extended metabolic screening by TMS and GCMS was within normal limits. Perinatal infections were also ruled out. Baby continued to deteriorate with increasing jaundice and liver enzymes and fall in Hb to 7.7 g/dL on day 14 and total count to 4,190/cmm on day 15. Platelets continued to be below 15,000/cmm despite daily platelet transfusions. In view of fall in all 3 cell lines and history of previous sibling death with similar symptoms, we considered the rare possibility of primary HLH. Ferritin was >13,000 ng/mL, fibrinogen 120 mg/dL, and triglyceride 418 mg/dL. On day 19, we started dexamethasone and cyclosporine. Bone marrow was not performed as baby had already met 5 out of 8 HLH 2004 criteria. Instead, in view of the strong family history, we sent exome sequencing and did not look further for secondary causes like Epstein-Barr virus infections. Baby continued to deteriorate rapidly with gastrointestinal bleeding and onset of respiratory distress. Parents refused further treatment and unfortunately baby died on day 20. The clinical exome sequencing sent earlier showed compound heterozygosity for PRF1 gene mutation confirming our diagnosis of familial HLH (FHL).

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Discussion and Conclusions

HLH is a potentially fatal immune disorder characterized by a cytokine storm and persistent activation of cytotoxic T cells, NK cells, and macrophages. According to the underlying etiology, it can be classified as primary (genetic) or secondary (acquired). FHL is the most common subtype of primary HLH. Five types of FHL are known of which FHL type 2 due to a defect in perforin from PRF1 mutation is the commonest and accounts for nearly 50% of primary HLH cases.¹⁻⁴

A diagnosis of HLH is made if there is a molecular diagnosis consistent with HLH or 5 out of 8 diagnostic criteria mentioned below for HLH are fulfilled:⁵

1. Fever
2. Splenomegaly
3. Cytopenias affecting ≥ 2 of 3 lineages in the peripheral blood (hemoglobin < 9 g/dL, in infants < 4 weeks: hemoglobin < 10 g/dL, platelets $< 1,00,000/\mu\text{L}$, neutrophils $< 1,000/\mu\text{L}$)
4. Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 265 mg/dL, Fibrinogen ≤ 150 mg/dL)
5. Hemophagocytosis in bone marrow or spleen or lymph nodes
6. Low or absent NK-cell activity
7. Ferritin ≥ 500 ng/mL
8. Soluble CD25 (ie, soluble IL-2 receptor) $\geq 2,400$ U/mL

Clinical manifestations of HLH include prolonged fever, jaundice, hepatosplenomegaly, bleeding, skin rash, and CNS abnormalities. Laboratory findings typical of HLH are bicytopenia or pancytopenia, coagulopathy, hyperlipidemia, hypofibrinogenemia, hyperferritinemia, transaminitis, hyperbilirubinemia, hypoalbuminemia, and hyponatremia.²

HLH has been reported in neonates presenting as early as first week of life with features similar to ours.⁶ In another report, a 60-day-old infant presented with fever, pancytopenia, coagulopathy, and liver dysfunction and cholestasis. He was initially suspected to have neonatal hemochromatosis, but bone marrow found hemophagocytes, and genetic mutation consistent with FLH was found. What is interesting to note was that there was history of prior stillborn sibling with hydrops and hepatosplenomegaly which makes us wonder that immune dysregulation can occur in the fetus as well.⁷

When faced with a case of infantile cholestasis, we usually proceed to rule out surgical cause amenable to correction like biliary atresia, followed by other common causes like paucity of intrahepatic bile ducts. With multisystem manifestations, TORCH infections or metabolic causes like galactosemia and tyrosinemia are usually suspected. We should remember that HLH can present similarly.

HLH can also mimic gestational alloimmune liver disease (GALD).⁷ GALD, commonly known as neonatal hemochromatosis is one the most common causes of neonatal acute liver failure. It presents with liver dysfunction, coagulopathy,

and high ferritin levels similar to HLH.⁸ However, cytopenias and hemophagocytosis are absent and extrahepatic siderosis is seen in GALD.⁹

HLH was found to be the second most common cause of acute liver failure after metabolic liver disease in infants and young children in an Indian study.¹⁰ However, in a study by a French Centre for Liver Transplantation, HLH was less common and seen in only 3 out of 80 infants. Metabolic liver diseases (42.5%), followed by neonatal hemochromatosis (16.2%), were far more common causes of acute liver failure in infancy.¹¹

It is time that HLH is considered in the differential diagnosis of acute liver failure, cholestasis, cytopenias, and hepatosplenomegaly in the neonatal period so as not to miss this fatal disorder.

Authors' Contributions

Priti Khemka: Case management, literature search, drafting, and revising the manuscript; Priyankar Pal: case management and revision of manuscript.

Declaration of Conflicting Interests

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