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Case Report

Hemophagocytic Lymphohistiocytosis Presenting as Neonatal Cholestasis: A Case Report

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ABSTRACT

Background:. Hemophagocytic lymphohistosis (HLH) is a life-threatening clinical syndrome that involves liver dysfunction and can range from mild dysfunction to severe fulminant insufficiency. Cholestasis, which is a frequent finding in many severe newborn illnesses, may also be a symptom of HLH. Therefore, HLH should be considered in the differential diagnosis of all cholestatic patients with cytopenia. In this report, we identified a case of HLH with cholestasis. The patient met at least seven out of the eight requirements of the HLH-2004 criteria. The infant had a stable fever, jaundice (conjugated hyperbilirubinemia), cytopenia, elevated liver enzymes, high ferritin, low fibrinogen, and triglyceride. Although urine, blood, and cerebrospinal fluid (CSF) culture tests were negative, CSF analysis revealed 80 WBCs, including 68% polymorphonuclear neutrophils (PMNs), more than 100000 RBCs, 71 mg/dL sugar, 82 mg/dL protein and 102 U/L lactate dehydrogenase. Coagulation tests and TORCH screen were normal. We confirmed the diagnosis of HLH with a bone marrow aspiration test and started treatment with dexamethasone. An intravenous dose of dexamethasone (4 mg) was administered, followed by 1.5 mg daily with pressure control, which stopped the fever after 24 hours.

Case report: The patient was a 21-day-old infant with a birth weight of 3450 g. He developed fever and jaundice 10 days after a normal delivery, and he was referred to Sarakhs Hospital when he was 14 days old and hospitalized for 3 days. Later, he was sent to Ghaem Hospital and admitted to the Neonatal Intensive Care Unit. The infant had a stable fever, jaundice (conjugated hyperbilirubinemia), cytopenia, elevated liver enzymes, high ferritin, low fibrinogen, and triglyceride. According to his mother, there was no history of any problems from birth, and the baby's jaundice started after the first week. Examinations showed abdominal distention and hepatosplenomegaly. Due to neonatal cholestasis and fever, he underwent a complete sepsis workup with vancomycin and cefotaxime. Although urine, blood, and cerebrospinal fluid (CSF) culture tests were negative, CSF analysis revealed 80 WBCs, including 68% polymorphonuclear neutrophils, more than 100000 RBCs, 71 mg/dL sugar, 82 mg/dL protein, and 102 U/L lactate dehydrogenase. Coagulation tests and TORCH screen were normal. We confirmed the diagnosis of hemophagocytic lymphohistiocytosis (HLH) with a bone marrow aspiration test and started treatment with dexamethasone. An intravenous dose of dexamethasone (4 mg) was administered, followed by 1.5 mg daily with pressure control, which stopped the fever after 24 hours.

Conclusion:HLH is uncommon in the neonatal stage, and aberrant clinical and laboratory findings suggestive of HLH can be found in a variety of conditions. The severity of this condition makes it crucial to get a diagnosis as soon as possible. In the presence of additional variables, such as cytopenia and hyperferritinemia, HLH should be considered in the differential diagnosis of cholestasis in a neonate.

Keywords: Cholestasis, Fever, Hepatosplenomegaly, Jaundice, Lymphohistiocytosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease characterized by defects in the

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perforin or other related pathways in immune cells, resulting in excessive and persistent macrophage activation and hypercytokinemia. Primary HLH is a genetic disorder that affects infants less than one year of age, whereas secondary HLH is caused by environmental factors (1). Neonatal HLH is uncommon within the first four weeks of life, and diagnosis is frequently delayed (2). Without treatment, familial forms of HLH have a poor long-term prognosis (3).

Cholestasis, a common finding in many serious neonatal diseases, can be a sign of HLH. Therefore, HLH should be considered in the differential diagnosis of all cholestatic patients with cytopenia. For a definitive diagnosis of HLH, the patient's clinical and laboratory findings, including hyperferritinemia, hypertriglyceridemia, and bone marrow aspiration (BMA) should be carefully evaluated (3). A positive family history indicates a genetic etiology of HLH.

In this report, we diagnosed a case of HLH according to the HLH-2004 criteria (3). The patient was positive for at least seven out of eight criteria. There was fever, splenomegaly, increased ferritin levels, low fibrinogen levels, high triglyceride levels, positive BMA, and cytopenia. Serum ferritin level was higher than 1500 ng/ml, supporting a diagnosis of HLH..

Case report

The patient was a 21-day-old infant with a birth weight of 3450 g. The patient developed fever and jaundice 10 days after a normal delivery, he was referred to Sarakhs Hospital when he was 14 days old, and hospitalized for 3 days. Later, he was sent to Ghaem Hospital and admitted to the Neonatal Intensive Care Unit. The parents were cousins, and the neonate did not have significant weight loss. There was no positive family history. According to his mother, there was no history of any problems from birth, and the baby's jaundice started after the first week. Examinations showed abdominal distention and hepatosplenomegaly of about 4-5 cm below the costal margin. Due to the constant fever, the patient was tested for COVID-19, which yielded a negative polymerase chain reaction (PCR) result. The initial test results are summarized in Table 1.

To evaluate the distention, hepatosplenomegaly, and cholestasis, the patient underwent a complete abdominal and pelvic ultrasound to evaluate the triangular sign. The gall bladder was normal on ultrasound study. During the ultrasound, the liver was larger than expected, 5-6 cm below the costal margin, with slightly increased parenchymal echogenicity, and the spleen was 4 cm below the costal margin, with a diameter of 65 mm. Fluid ascites was observed to a lesser extent in the perihepatic area and Morison's pouch, favoring a liver parenchymal disease.

Due to neonatal cholestasis and fever, he underwent a complete sepsis workup with vancomycin and cefotaxime. Thyroid and metabolic examination showed normal results; in addition, the urine, blood, and cerebrospinal fluid (CSF) culture tests were negative; however, the CSF analysis showed 80 WBCs, including 68% polymorphonuclear neutrophils (PMNs), >100000 RBCs, 71 mg/dL sugar, 82 mg/dL protein, and 102 U/L lactate dehydrogenase. C-reactive protein was 1.1 mg/L. Coagulation tests and TORCH screen were normal.

Table 1. The patients' initial test results

Value	Result
Bilirubin total	21 mg/dL
Bilirubin direct	13 mg/dL
Hemoglobin	8 g/dL
Platelet	52000/µL
AST	248 IU/L
ALT	260 IU/L
Coagulation	Normal
Urine culture	Normal
Brain sonography	Normal

AST=Aspartate aminotransferase; ALT=Alanine aminotransferase

Because of the patient's persistent fever, cytopenia, hepatosplenomegaly, and the fact that other tests were normal, serum ferritin was checked. Amikacin and Imipenem were also added to the treatment, and because ferritin levels were above 1500 g/mL, HLH was suspected. Therefore, fibrinogen and triglycerides were measured. The fibrinogen level was less than 81 mg/dL, and the triglyceride level was 257 mg/dL. A BMA test for HLH and an acid-fast bacillus test were requested to confirm the diagnosis, which showed active bone marrow with increased hemophagocytic histiocytes. Epstein-Barr virus and Adenovirus were not checked. After the primary diagnosis of

meningitis, Vancomycin was given for 14 days, and after confirmation of the HLH via bone marrow aspiration culture, Dexamethasone was administered intravenously at a dose of 4 mg, followed by 1.5 mg daily with pressure control, which stopped the fever after 24h. A genetic workup was not done to rule out familial HLH.

Discussion

HLH is rare in infants and has a poor prognosis. If the risk of getting HLH through the herpes simplex virus is suspected, prompt diagnosis and treatment are essential. The onset of neonatal HLH is uncommon within the first four weeks of life, and diagnosis is often delayed, identified only at postmortem, or forgotten entirely (2). A Japanese study of neonatal HLH was performed to elucidate its cause and prognosis, assuming that neonatal HLH may be different from HLH in older children in terms of cause, manifestation, or laboratory findings. Herpes simplex virus, familial hemophagocytic lymphohistiocytosis, Coxsackievirus, severe combined immunodeficiency, methicillin-resistant Staphylococcus aureus and cause unkown were identified as the causes (2).

HLH is not a disease but a syndrome with specific clinical and laboratory findings of an inherited or acquired immune response, which when triggered, usually by an infectious agent, may cause it (4). Natural killer cells and cytotoxic T lymphocytes play a key role in the clearance of viral and intracellular bacterial infections through a granule-dependent cytotoxic pathway, which begins with the identification of the target cell and ends with the release of cytotoxic granules (5, 6). This granule-dependent cytotoxic pathway is defective in HLH and fails to eliminate antigens that cause uncontrolled hyperactivation and proliferation of cytotoxic T cells and macrophages, as well as the subsequent cytokine storm. Lymphohistiocytic infiltration accumulates in almost all organs including the liver, spleen, lymph nodes, bone marrow, and central nervous system, and leads to organ damage with systemic symptoms of hypercytokinemia (7, 8).

HLH is either primarily caused by an underlying genetic etiology or is secondary to infection, malignancy, and autoimmune or metabolic diseases. Genetic etiologies are mostly divided into familial HLH syndrome (FHLH) and immunodeficiency. FHLH is a type of primary HLH and an autosomal recessive disorder that most often manifests in infancy and is caused by mutations in genes that encode the major proteins of the granule-dependent cytotoxic pathway (9, 10). These genes include PRF1 (11), UNC13D (12), STX11 (13), and STXBP2 (9, 14-17). HLH-related immunodeficiency syndromes include Griscelli syndrome type 2, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome type II, and X-dependent lymphoproliferative syndrome types 1 and 2. They are characterized by mutations in the RAB27A, LYST, AP3B1, SH2D1A, and BIRC4 genes (18). Other primary immunodeficiencies, such as DiGeorge syndrome (19), severe combined immunodeficiency, and chronic granulomatous disease (20), may sometimes exhibit HLH characteristics.

Diagnosis of HLH requires molecular detection (i.e., mutations associated with the initial HLH or the fulfillment of five of the eight criteria of HLH-2004) (3). HLH criteria include fever, splenomegaly, cytopenia in more than two categories of peripheral blood (hemoglobin <90 g/L, platelets <100 × 1009 per liter, neutrophils <1 109×1 per liter), hypertriglyceridemia (fasting triglyceride 265 mg/dL) and/or hypofibrinogenemia (fibrinogen <1.5 g/L); ferritin level ⩾ 500 µg/L, hemophagocytosis in the bone marrow, spleen or lymph nodes. Lack or absence of NK cell activity and increased serum levels of soluble CD25 (2400 U/ml). In this report, a 10-day-old infant with cholestatic fever who met seven criteria and tested positive for cytopenia, hypofibrinogenemia, hypertriglyceridemia, high ferritin, splenomegaly, and BMA was presented. Dexamethasone treatment was started and discontinued 24 hours after the onset of fever.

Liver involvement is common in HLH due to direct liver damage caused by lymphohistiocytic infiltration or secondary indirect causes, such as severe infection or malignancy. The liver is a hematopoietic organ in the fetus and maintains some of its hematopoietic capacity throughout life. Thus, macrophage activation disorders and hemophagocytosis can functionally and pathologically impair liver cells. Pathologically, the liver develops a hepatitis-like pattern with lymphohistiocytic portal infiltration with or without hemophagocytosis in addition to macrophages predominantly seen in the portal and central veins. Bile duct damage can also be seen on liver biopsy or as a result of lymphocyte infiltration or secondary cytokine-mediated epithelial damage. Hepatomegaly, cholestasis, and elevated liver enzymes are seen in HLH patients (21). However, acute liver failure (ALF) is rarely a feature of HLH. Therefore, HLH should be considered in the

differential diagnosis of ALF patients, especially if associated with fever and cytopenia.

Neonatal cholestasis is a common finding in many serious neonatal diseases. Because HLH can be fatal quickly, effective and rapid diagnosis is essential. HLH is a disease that should be kept in mind in the differential diagnosis of all cholestatic patients with cytopenia. In a case report in Japan, an infant with cholestasis and HLH was reported. The patient had aspartate aminotransferase of 391 U/L (35-140), alanine aminotransferase of 295 U/L (6-50), lactate dehydrogenase of 180 U/L (170-580), gamma-glutamyl transferase (GGT) of 43 U/L (13-147 U/L), alkaline phosphatase (ALP) of 98 U/L (28-300), total bilirubin of 20.95 mg/dL (<8), direct bilirubin of 10.86 mg/dL (less than 0.2), and triglyceride of 89 mg/dL (36-86). According to HLH criteria, the patient was induced with chemotherapy as indicated in the HLH-2004 protocol. Despite laboratory improvements, the patient died one week after starting chemotherapy possibly due to sepsis (21). In our patient, hepatocellular enzymes were also elevated and we did not check GGT and ALP.

Conclusion

In a Japanese study of HLH neonates, CSF was evaluated in 10 patients, and abnormal results were found in 2 cases: one with a predominant polymorphonuclear cell pleocytosis and another with increased protein levels associated with normal white blood cell counts. One case also had a loss of consciousness (2).

To summarize, HLH is uncommon in the neonatal stage, and aberrant clinical and laboratory findings suggestive of HLH can be found in a variety of conditions. The severity of this condition makes it crucial to get a diagnosis as soon as possible. In the presence of additional variables, such as cytopenia and hyperferritinemia, HLH should be considered in the differential diagnosis of cholestasis in a neonate.

Acknowledgments

None.

Conflicts of interest

The authors declared no conflict of interest.

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