

# Hemophagocytic Lymphohistiocytosis in a Neonate: Case Report

Pari Zarrini<sup>1</sup>, Ziba Mosayebi<sup>1</sup>, Asghar Ramyar<sup>1</sup>, and Hosein Dalili<sup>2</sup>

<sup>1</sup> Department of Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Department of Pediatrics, Breast Feeding Research Center, Tehran University of Medical Sciences, Tehran, Iran

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**Abstract-** Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic immune activation, occurring as either a familial disorder or a sporadic condition, in association with a variety of triggers. This article will introduce a neonate with HLH in Iran. We report a case of HLH presenting with respiratory distress and fever, hepatosplenomegaly, jaundice and pancytopenia on the second day of life. Typical clinical and laboratory findings were detected in the neonate. HLH was diagnosed according to HLH-2004 guidelines. In spite of initiating the treatment, the disease did not cure. Post-mortem, extensive hemophagocytosis was found in multiple organs. No specific genetic defect was identified. Since HLH is a potentially lethal childhood illness, early diagnosis of this disorder and commences the therapy is important for pediatricians.

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## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic immune activation, occurring as either a familial disorder or a sporadic condition, in association with a variety of triggers (1). HLH comprises two different conditions: primary or genetic HLH, and secondary or acquired hemophagocytic syndrome (secondary HLH, sHLH). These two forms may be difficult to distinguish from one another (2).

This immune dysregulation disorder is prominently associated with cytopenias and a unique combination of clinical signs and symptoms of extreme inflammation (1). This disorder is characterized by the widespread accumulation of lymphocytes and mature macrophages, sometimes with hemophagocytosis, primarily involving the spleen, lymph nodes, bone marrow, liver and cerebrospinal fluid (2). The symptoms and signs may vary widely, but the most typical findings are prolonged fever, hepatosplenomegaly, and cytopenias (3).

This article will introduce a neonate with HLH in Iran. The patient was suspicious with sepsis and accompanying pancytopenia prior to diagnosis of HLH.

## Case Report

A 9-day-old male neonate was referred to Children's

medical center in Iran because of fever, hepatosplenomegaly, jaundice, and pancytopenia. During the first hours of life, the child developed respiratory distress in the hospital of birth. On the second day of life, the patient referred to our center with mentioned clinical presentation. He was born by elective caesarean section (G2 P1AB0) with a birth weight of 3.300 g, from a 22 and 28-year-old mother and father respectively. His parents were not close consanguineous. In physical examination, the temperature of 38.5°C, liver, and spleen palpable at 3 cm below rib edge, icter, pallor and poor feeding were detected.

Various consultations were made for diagnosing. toxoplasmosis, syphilis, rubella, hepatitis B, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV) (TORCH) Tests were negative in baby and his mother. The laboratory findings were as follows: RBC 2,7/mm<sup>3</sup>, hemoglobin 5,3 g/L, WBC 3280/mm<sup>3</sup>, platelets 15000/mm<sup>3</sup>.B/c (neg) Anti-Ro/SS-A, anti-La/SS-B antibodies, ANA (nl) -VDRL(nl) -CSF (nl), HIV Ab were normal.

Considering continued problems, specific lab tests were carried out to rule out Hemophagocytic Lymphohistiocytosis (HLH). Bone marrow biopsy and flow cytometry were normal. Lab test results were: ferritin: 12.514 ng/ml (high), fibrinogen: 128 (low), urine beta2 microglobulin: 10.5 mcg/ml (urine<2.4,

**Corresponding Author:** H. Dalili

Department of Pediatrics, Breast Feeding Research Center, Tehran University of Medical Sciences, Tehran, Iran  
Tel: +98 21 66591315, Fax: +98 21 66591315, E-mail address: hdalili@tums.ac.ir

serum <2.5), triglyceride: 615 mg/dl, SGOT: 126 u/l, SGPT: 137 u/l, Alkaline phosphatase: 1887 u/l, LDH: 997, total bilirubin: 10.9 mg/dl, direct bilirubin: 5.4 mg/dl, antitrypsin: normal. At first sepsis work up and empirical therapy with ceftazidime and vancomycin was started. Considering evidences and HLH diagnostic criteria, HLH treatment protocol 2004 (dexamethasone 10 mg/m<sup>2</sup>, etoposide 150/m<sup>2</sup>) was administered subsequently (4). The patient was followed up and hospitalized 3 times during three months. In this period, he received a blood transfusion and IVIG frequently. Treatments for cholestasis and pancytopenia were ineffective. Unfortunately, the patient died with severe pancytopenia and DIC features in PICU center.

## Discussion

Our case was the first child of healthy parents. Maternal serum screening tests for TORCH, and human immunodeficiency virus (HIV) were negative. Prenatal ultrasound examinations and family history were normal. On admission to our center, the patient was febrile and icteric with hepatosplenomegaly and pancytopenia. After antibiotic therapy and HLH treatment, the baby didn't respond to the treatment.

HLH consists of a heterogeneous class of rare potentially fatal disorders characterized by multisystem inflammation, which results from prolonged and vigorous activation of antigen-presenting cells and CD8+T-cells, and proliferation and ectopic migration of T-cells (5). It is containing two different kinds: primary or genetic, and secondary or acquired form. Genetic HLH is inherited in an autosomal recessive or X-linked pattern (6,7).

Secondary forms may induce due to an intensive immunological activation, which may be a result of a severe infection and malignancy. Leading triggering agents in infection-related forms are viruses of the herpes group, especially EBV and CMV, (4) which was negative in our case. Despite attempts to differentiate primary from secondary HLH, the clinical presentation is highly overlapping (5).

Prolonged fever (>7 days) and hepatosplenomegaly are two main findings which were present in our case.

Neurological symptoms may present in the initial clinical course, in the form of irritability, seizures, hypo- and hypertonia, cranial nerve palsies, and altered consciousness. In our case neurological manifestations were Lymphadenopathy, skin rash; jaundice, edema, and diarrhea are less frequent (2) which the only icter was seen in this case.

In laboratory tests, characteristic findings are cytopenias (especially anemia and thrombocytopenia), coagulopathy with hypofibrinogenemia and hypertriglyceridemia. Abnormal liver function tests such as elevated lactate dehydrogenase, hypoalbuminemia, and hyponatremia are often seen (5). We found in our patient's lab tests, pancytopenia, hypertriglyceridemia, hyperbilirubinemia, elevated LDH, hypofibrinogenemia that guided us towards the diagnosis. Two highly diagnostic parameters are an increased plasma concentration of the alpha chain of the soluble interleukin-2 receptor (sCD25) and impaired NK cell activity.

Since the lumbar puncture (LP) is recommended as part of a diagnostic workup, because of increasing protein content and pleocytosis in the majority of patients even in the absence of neurological symptoms (5). We performed LP and found normal bone marrow aspiration is a helpful procedure for diagnosing HLH. Although severe hemophagocytosis may not be discovered early in the course of the disease, like our patient, but serial bone marrow aspiration may be beneficial for diagnosis (4).

The revised diagnostic criteria for HLH (2), in the absence of a family history or specific molecular diagnosis, an assemblage of at least five of the eight diagnostic criteria are needed for a diagnosis of HLH and initiation of therapy that existed in our patient.

HLH is a difficult condition not only to diagnose but also to treat. The first target of the treatment is to reduce life-threatening hyperinflammation (4).

Current international HLH 2004 protocol which was used for the present case has been designed for treatment of all patients with different forms of HLH.

The protocol represents systemic chemo-immunotherapy including dexamethasone, cyclosporine A, etoposide upfront, and, in selected patients, intrathecal therapy with methotrexate (4).

In pediatric protocols, dexamethasone is preferred than prednisolone since it crosses the blood brain barrier (4).

In spite of initiating the treatment, the disease did not cure. At autopsy, extensive lymphohistiocytic hemophagocytosis was identified in the bone marrow, lungs, liver, and spleen. Post-mortem genetic tests for FHL including PRF1 (FHL2), UNC13D (FHL3), and STX11 (FHL4) were negative. No mutations were found in both parents. Since HLH is a potentially lethal childhood illness, early diagnosis of this disorder and commences the therapy is important for pediatricians.

**References**

1. How we treat hemophagocytic lymphohistiocytosis. *Blood*. (Accessed in May 2015, 1, at <http://www.bloodjournal.org/content/early/2011/08/09/blood-2011-03-278127.full-text.pdf+html>).
2. Henter JJ, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124-31.
3. Janka G, zur Stadt U. Familial and acquired hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program* 2005:82-8.
4. Roganovic J, Kvenic B, Jonjic N, Seili-Bekafigo I, Kardum-Skelin I. Neonatal Hemophagocytic Lymphohistiocytosis, case report. *Coll Antropol* 2010;34:285-90.
5. Filipovich AH. Hemophagocytic lymphohistiocytosis and other emophagocytic disorders. *Immunol Allergy Clin North Am* 2008;28:293-313.
6. Janka GE. Hemophagocytic syndromes. *Blood Rev* 2007;21:245-53.
7. Trottestam H, Beutel K, Meeths M, Carlsen N, Heilmann C, Pasić S, et al. Treatment of the X-linked lymphoproliferative, Griscelli and Chédiak-Higashi syndromes by HLH directed therapy. *Pediatr Blood Cancer* 2009;52:268-72.