

Hemophagocytic Lymphohistiocytosis in a Pediatric Patient

Saad Waheed and Saima Gillani

Department of Pediatrics, Ayub Teaching Hospital, Abbottabad, Pakistan

ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is an uncommon but a potentially fatal disease characterised by high grade fever, hepato-splenomegaly, deranged liver functions, cytopenias and multi-organ involvement. HLH has its own diagnostic criteria, which comprise of various clinical and laboratory features, which were revised in 2004 by HLH Society for prompt identification and recognition. Here, we present a case of 9-year developmentally normal female with all the complaints as mentioned above, who received treatment for almost eight months as a case of pyrexia of unknown origin (PUO) without a definitive diagnosis. The differential diagnosis of HLH was considered in the patient and later, it was corroborated by hemophagocytic activity on bone marrow aspiration examination. The diagnosis of HLH was made after fulfillment of its criteria which was addressed completely and found veracious. After addressing the active complaints of the patient, she was referred to a pediatric oncologist for chemotherapy and further management; and counselled for hematopoietic stem cell transplantation (HSCT).

Key Words: *Hemophagocytic lymphohistiocytosis, Pyrexia of unknown origin (PUO), Pediatric hematopoietic stem cell transplantation.*

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INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) was described for the first time in 1952 by James Farquhar and Albert Clariaux with features of pancytopenia, hepato-splenomegaly, and non-resolving high grade fever.¹ A life-threatening rare syndrome of immune system disarrays that leads to multi-organ failure due to the hyperactivity of cytokines and macrophages.² HLH is a hyperactive inflammatory state resulting in release of activated lymphocytes and histiocytes, which cause tissues destruction and shares some similarities with the macrophage activation syndrome.^{3,4}

The activated macrophages engulf one's own hematopoietic stem cells and various blood cells as evident upon biopsies of bone marrow, liver, spleen etc.; hence, the name haemophagocytosis.⁵ It basically presents in two forms: a genetic (familial HLH) form and an acquired form secondary to infections, mostly, viral, acquired immune deficiency syndromes, auto-inflammatory diseases, auto-immune diseases and malignancies. HLH in children has a strong association with family history. Familial HLH is more frequently found in infants, but cases of infection-associated HLH are also encountered.

Overall incidence of HLH is approximately 1.2 cases per 1,000,000 individuals annually.⁶ Familial HLH (patients less than one year of age) comprises 70-80% of these.⁷ Hematologic and malignancies-associated HLH occur more commonly in adult group. The variable features and rarity of this disease make timely diagnosis and intervention difficult, thus resulting in a deadly outcome.

CASE REPORT

A 9-year unvaccinated child, born from consanguineous marriage, with growth parameters all falling below 5th centile, presented to us with high grade fever up to 102°F, mild abdominal distention and bilateral pedal edema for the last eight months. Fever was high grade, continuous but not associated with rigors and chills. Patient was prescribed previously paracetamol, penicillin (amoxicillin), aminoglycosides (amikacin), various 2nd and 3rd generation cephalosporins (cefuroxime, cefotaxime, ceftriaxone) and oral anti-malarials, but was never cured completely with these medications. According to parents, they had multiple consultations and patient was admitted thrice for same complaints during the last eight months. She also had history of respiratory tract infections. On general physical examination, there was pallor, mildly icteric sclerae and jaundiced skin, a high fever but no lymphadenopathy was noted. There was no clubbing of nails or koilonychia. A high pulse volume was present. Edema was bilateral; it was non-pitting and was restricted up to ankles. Cardiovascular and respiratory systems were normal except for tachycardia with normal vesicular breathing. Furthermore, the patient was completely oriented, active and alert with

*Correspondence to: Dr. Saad Waheed, Department of Pediatrics, Ayub Teaching Hospital, Abbottabad, Pakistan
E-mail: khana726@gmail.com*

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Glasgow coma scale (GCS) of 15/15 with normal power, tone, and reflexes in all limbs. On inspection of abdomen, there was no scar or striae, but mild distention was noted. Bowel sounds were normal on auscultation. On palpation, there was hepato-splenomegaly, liver span being 8 cms and spleen 11cms below costal margin, but no shifting dullness was noted. Abdominal examination helped us to make various differential diagnoses like leukemia, chronic liver disease, visceral leishmaniasis and HLH. Basic investigations were sent, along with tuberculosis (T-B) and visceral leishmaniasis work-up. At first, the complete blood count revealed bicytopenia, hemoglobin was 7.2 g/dl (normal = 11-12g/dl), platelets were 67,000/ μ L (Normal = 150- 400 $\times 10^9$ /L) and total leukocyte count (TLC) was 7.1×10^9 /L (normal = 4.5 to 11.0×10^9 /L).

In addition, differential leucocyte count (DLC) showed lymphocytosis, i.e., 68% (normal = 20 - 40%). Moreover, blood cultures returned indecisively. Inflammatory markers of ESR (70mm/1sthr) and CRP (>3.0g/L) were raised but there were no visceral leishmania antibodies. Gene expert of gastric aspirate for TB was negative with normal chest x-ray and negative Montoux test. Liver functions tests were impaired: serum total bilirubin was 5.9mg/dl (indirect, 2.8mg/-dl), alkaline phosphate was 950u/-L with normal ALT and renal function tests. In addition, hepatitis B, C and HIV testing was negative. Ultrasound abdomen showed hepato-splenomegaly with normal echo texture. The patient was given broad spectrum antibiotics, IV ceftriaxone 1gm (BD) and IV quinine (5 days) with oral paracetamol for fever. On third day of admission, she started improving, but there was low-grade intermittent fever and hepato-splenomegaly was increasing each day and there was appearance of small petechial spots on her right leg. Complete blood count (CBC) was repeated, bicytopenia was converted to pancytopenia (Hb = 6.9 g/dL, platelets = 37,000/ μ L and TLC = 3.8×10^9 /L). On 6th day, bone marrow aspiration was done. After consideration of HLH, serum ferritin and fasting triglyceride levels were also sent, which were significantly high [serum ferritin = 1500ng/ml (normal = up to 140 ng/ml and triglycerides = 424 mg/dl (normal = less than 150 mg/dl)], thus supporting the diagnosis of HLH. Whole blood transfusion was done thrice as supportive management. Jaundice improved somewhat. On the 11th day of admission, bone marrow biopsy report was received showing hemophagocytosis with moderate megaloblastic anemia (-started on vitamin B12 and folic acid). The diagnosis of HLH was confirmed after analysis of all clinical signs, symptoms and laboratory tests. Our patient scored 6 points out of total 8 points in the diagnostic protocol of HLH.⁷ The patient was started on oral dexamethasone immediately and referred to a pediatric oncologist for chemotherapy as a case of HLH. We also gave alternative therapy recommendations to parents about the hematopoietic stem cell transplantation (HSCT), which has better prognosis if the resources allow it.

DISCUSSION

A deadly illness, HLH is a hematological disorder manifested by clinical signs and symptoms of severe inflammation and uncon-

trolled activation of the immune system. It is most often characterised by pyrexia of unknown origin (PUO), hepato-splenomegaly and bi- or tri-lineage cytopenias. Moreover, elevated levels of liver enzymes, serum ferritin, serum triglycerides and low levels of fibrinogen are commonly seen in HLH patients. In 35-40 % of patients, skin manifestations such as a generalised transient maculopapular rash, erythroderma, petechiae and edema appear.⁸ In our patient, the diagnostic criteria for HLH were met as 6 out of the 8 criteria were present. Our patient had no family history of malignancy. Although HLH has basically two forms, the first being a congenital primary or familial form and the second being an acquired or secondary form, clinical presentation and diagnostic criteria for both are identical. The underlying risk for primary HLH is genetic abnormalities leading to fixed defects in the normal functioning of the cytotoxic T cells. Primary HLH is due to genetic defects in genes (PRF1, MUNC 13-4, STXBP2 and STX11) that are essential to the cytolytic secretion pathway, which enable perforin and granzymes to induce apoptosis in target cells.⁹ Etiology of acquired HLH is multi-factorial and potential causes include infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus (HSV). Moreover, autoimmune diseases such as systemic lupus erythematosus (SLE), Kawasaki syndrome and malignancies such as natural killer [NK] cell leukemia, B and T cell lymphomas may be the underlying causes in some cases.^{5,7} The pathogenesis of acquired HLH remains elusive, but heterozygous variations and polymorphisms in familial proteins are commonly seen in patient populations with this type of HLH.

In 1994, the Histiocyte Society devised its first standard definition which was revised in 2004 and proper diagnostic criteria were formulated.^{10,11}

Some protocol investigations could not be carried out due to non-availability in our area i.e. natural killer cells activity, CD25 (Interleukin-2 receptor) levels and molecular testing of HLH. Treatment modalities directly target the hyperactivity of the immune system (T cells and histiocytes) by using immunosuppressant drugs and chemotherapy (dexamethasone and etoposide in conjunction with cyclosporine). The HLH-94 trial, comprised of same above mentioned drugs and the HLH mortality plummeted from 95% to <30% (8 weeks of etoposide and dexamethasone therapy, followed by maintenance therapy with cyclosporine and pulse therapies of etoposide and dexamethasone). HSCT is also an option for this ailment, but it is mainly for familial HLH or relapsing HLH or EBV-associated HLH.¹² Because of rarity, timely diagnosis of HLH is often missed in initial workup, especially in primary and secondary healthcare set-ups. It should be considered in the differential diagnosis of PUO. A child with non-resolving and recurring fever should be referred to a tertiary care centre for proper workup. We emphasise early recognition and immediate commencement of treatment for HLH to reduce the high mortality, associated with this condition, especially in cases of delayed diagnoses.

PATIENT'S CONSENT:

Informed consent was obtained from the patient's parents.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SW: Conceptualisation, patient management and workup, write-up, literature search, proofreading.

SG: Literature search, proofreading.

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