

Case Report:

Haemophagocytic lymphohistiocytosis

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ABSTRACT

We describe a 15-month-old child who presented with a history of fever for the preceding two days and multiple episodes of seizures of one day duration. Physical examination revealed generalized lymphadenopathy and hepatosplenomegaly. The child developed erythematous maculopapular rash, hypotension and required tracheal intubation and mechanical ventilation. Bone marrow aspiration confirmed the diagnosis of hemophagocytic lymphohistiocytosis (HLH). He was treated with dexamethasone, etoposide and cyclosporine, recovered and is doing well on follow-up. HLH is a rare haematological disorder involving the mononuclear phagocyte system. Since it mimics other disorders, its timely diagnosis remains a challenge. It is an aggressive and potential fatal disease of infancy and childhood, if left untreated. HLH may mimic a number of systemic infections thereby causing difficulty in early diagnosis.

Key words: *Haemophagocytic lymphohistiocytosis, Familial, Childhood*

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INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a rare potential fatal disease of infancy and early childhood. It is secondary to immune hyperactivation.¹ HLH can develop due to various aetiologies like genetic causes, infections, collagen vascular diseases, malignancy and or metabolic disorders.^{2,3} This entity is diagnosed as per criteria listed in Table 1.^{1,3}

CASE REPORT

A 15-month-old boy presented with a history of fever of two days duration and one day history of multiple episodes of seizures. He had a history of simple febrile seizures since the age of eight months. His birth and developmental history did not reveal any abnormality. He was born to a consanguineously married couple. There was no past history of dog bite, ear discharge, head injury

or any contact history of tuberculosis. He had obtained routine immunization, including measles vaccination at the age of nine months.

The fever was high-grade and intermittent in nature. It was not associated with rash, vomiting or loose stools. Generalized tonic-clonic seizures developed on the day of the fever following this, the child was admitted in a local hospital and he continued to have multiple episodes of seizures and high-grade fever. The child was then shifted to another hospital and there he developed erythematous maculopapular rash, hypotension and shock (Figure 1). Physical examination revealed generalized lymphadenopathy and hepatosplenomegaly. In view of respiratory distress the child was admitted to the intensive care unit (ICU), required tracheal intubation and mechanical ventilation, intravenous fluids and inotropic support. Laboratory investigations showed haemoglobin 8.9 g/dL, total leucocyte count

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Table 1: Criteria for the diagnosis of haemophagocytic lymphohistiocytosis*

1. A molecular diagnosis [Biallelic disease-causing mutations in any one of perforin 1 gene (PRF1), hMunc13-4 gene (UNC13D)] consistent with hemophagocytic lymphohistiocytosis; or
2. At least 5 out of the 8 criteria listed below are fulfilled
 - (i) Fever
 - (ii) Splenomegaly
 - (iii) Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood with haemoglobin < 10 g/dL, platelets $< 100 \times 10^9/L$ and neutrophils $< 1 \times 10^9/L$)
 - (iv) Hypertriglyceridemia and/or hypofibrinogenemia (fasting serum triglycerides > 265 mg/dL, serum fibrinogen ≤ 1.5 g/dL)
 - (v) Haemophagocytosis in bone marrow or spleen or lymph nodes
 - (vi) Low or absent natural killer-cell activity in peripheral blood detected by flow cytometry
 - (vii) Serum ferritin ≥ 500 $\mu\text{g/dL}$
 - (viii) High plasma concentrations of soluble interleukin-2 receptor ≥ 2400 U/mL

11000/mm³, platelet 330,000/mm³, serum aspartate aminotransferase 165 IU/L and serum alanine aminotransferase 88 IU/L.

Intravenous azithromycin was started as scrub typhus was suspected. But due to sterile culture and negative scrub typhus serology, antibiotics were stopped. Computed tomography of brain showed mild meningeal enhancement. Cerebrospinal fluid examination was normal. Polymerase chain reaction for herpes simplex B virus, serological testing for Epstein-Barr virus (EBV) and malaria parasite in the peripheral smear examination were negative. He continued to have persistent high grade-fever. Later he developed leucopenia, neutropenia and thrombocytopenia. Subsequent investigations revealed high serum ferritin

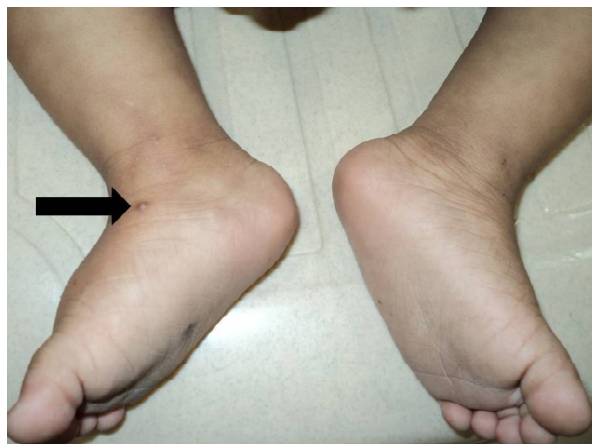


Figure 1: Clinical photograph showing erythematous maculopapular rash (arrow)

(1430 ng/mL corresponding to 143 $\mu\text{g/dL}$), high fasting levels serum triglyceride (298 mg/dL) and low serum fibrinogen (48 mg/dL) levels. His bone marrow aspiration showed features of hemophagocytosis (Figures 2 and 3). Since he fulfilled the required criteria (Table 1)^{1,3} he was diagnosed to have HLH. Perforin assay or genetic analysis could not be done due to non-availability.

He was started on treatment according to the HLH-2004 protocol.¹ He received oral dexamethasone (2 mg daily), intravenous etoposide (55 mg in 1000 mL normal saline over 4 hours) and oral cyclosporine-A (25 mg daily). His investigations at 14-months follow-up showed haemoglobin 7.5 g/dL, total leucocyte count 5000/mm³, and platelet 1.7 lakhs/mm³. Serum ferritin had reduced to 22.3 ng/mL. Currently the child is doing well on follow-up.

DISCUSSION

Haemophagocytic syndrome (HPS), is a rare syndrome that was first described in 1939.⁴ It is a disorder of the mononuclear phagocyte system, and is characterized by proliferation and activation of non-malignant histiocytes.⁵ The pathological hallmark of the syndrome is aggressive proliferation of macrophages and histiocytes.⁶ The histiocytes exhibit

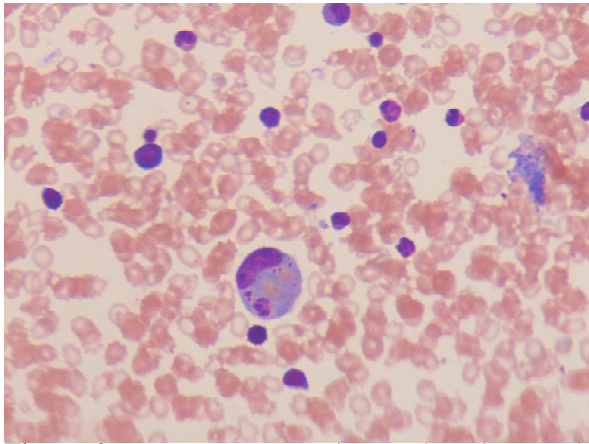


Figure 2: Bone marrow aspirate. Photomicrograph showing macrophage with phagocytosis (May-Grünwald Giemsa, $\times 40$)

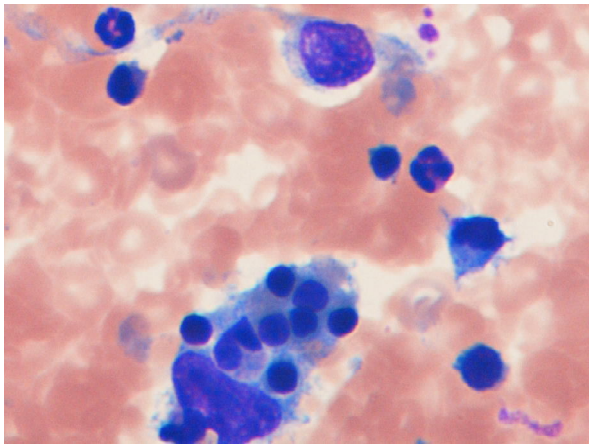


Figure 3: Bone marrow aspirate. Photomicrograph showing a macrophage with engulfed leucocyte (May Grünwald Giemsa, $\times 100$)

phagocytosis of erythrocytes, leucocytes, platelets and their precursors. The uncontrolled activation of T-lymphocytes and macrophages, together with an impaired cytotoxic function of natural killer (NK) cells, results in the overproduction of cytokines like interferon gamma ($\text{IFN-}\gamma$), tumour necrosis factor alpha ($\text{TNF-}\alpha$) and granulocyte macrophage colony stimulating factor (GM-CSF). This causes a sustained macrophage activation and tissue infiltration as well as production of interleukin-1 (IL-1) and interleukin-6 (IL-6).⁶ Ultimately it results in an inflammatory reaction which causes dysfunction of various organs.^{6,7}

There are two forms of HLH, namely, primary and secondary HLH.³ While primary HLH is familial or hereditary, secondary HLH can be

caused by causes like infections, malignancy and collagen vascular disease.²

EBV is an important cause of HLH. Salmonella, tuberculosis, malaria and leishmaniasis are other tropical infections which can trigger infection-associated haemophagocytosis. In the tropics, infections remain the most common triggers of HLH.²

Familial HLH is usually associated with mutations in the perforin gene.^{1,8} Perforin staining in cytotoxic cells by flow cytometry has been used as a screening test to identify children with familial HLH, who can then be subjected to genetic analysis.^{9,10} The present case fulfilled six out of the eight criteria mentioned in HLH-2004.¹

The clinical features of HLH are fever, hepatosplenomegaly, bleeding manifestations, lymphadenopathy, skin rash, shock, jaundice, central nervous system (CNS) manifestations, renal failure and arthritis.⁵ Apart from CNS, the other organs, which can be involved, include lungs, thymus, heart, kidneys, intestine and pancreas.⁵ The present case had fever, lymphadenopathy, skin rash and seizures. Soon after, the patient went to shock.

In an earlier study,⁸ the most common presenting features of HLH were fever and hepatomegaly, hyperferritinaemia, hypofibrinogenaemia and high lactate dehydrogenase (LDH) levels. Haemophagocytosis in bone marrow may not be present during the early phase of disease, and therefore its absence does not exclude a diagnosis of HLH.^{8,11}

Two highly sensitive diagnostic markers are an increased plasma concentration of the alpha chain of soluble interleukin-2 (IL-2) receptor (CD25) and impaired NK-cell activity.⁶

HLH may mimic a number of systemic infections thereby causing difficulty in early diagnosis. To establish the diagnosis, standardized clinical and laboratory criteria should be followed.

Usually, treatment of HLH is associated with high morbidity and mortality.⁷ So, whenever feasible, HLH patients should be referred to centers with experience in the treatment and care of HLH.⁷

The Histiocyte Society in 1994 developed a common treatment protocol (HLH-94).⁶ In the year 2004 a revised HLH treatment protocol, based on HLH-94 with minor modifications was developed. Both the protocols report high remission rate.^{1,6}

The HLH-2004 protocol uses cyclosporine with etoposide, dexamethasone and intrathecal methotrexate for patients with neurological signs, persistent active CNS disease and CNS reactivation of HLH. All children with familial disease, known mutations, severe and persistent non-familial disease and relapsed HLH are treated with continuation phase etoposide, dexamethasone, and cyclosporine. Stem-cell transplantation is performed as early as possible, when an acceptable donor is available. Therapy is discontinued otherwise at remission (8 weeks) as the completed regimen for patients with possible sporadic HLH and viral-triggered HLH. Patients with refractory disease are treated with antithymocyte globulin, rituximab or alemtuzumab for remission induction.²

In India HLH is under-reported and associated with a high mortality.^{2, 5, 6, 8, 12} In a large series of HLH patients from south India,⁸ the authors have noted less mortality and have attributed this to a high incidence of secondary HLH, early diagnosis and early institution of immunomodulatory treatment.⁸

We present this case to highlight the importance of clinical and diagnostic workup to treat this rather uncommon condition.

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