

Haemophagocytic Lymphohistiocytosis – A Report of Two Cases and Review of Literature



Medical Science

KEYWORDS : Pancytopenia, Haemophagocytic lymphohistiocytosis, Macrophage activation syndrome, Malignancy associated haemophagocytic syndrome, Splenomegaly, Bone marrow, Cytotoxic T cells, NK Cells

Dr Sangeeta Sharma

Associate Professor, Department of Pathology, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India

Dr Ujwala Maheshwari

Dr Ujwala Maheshwari, Professor, Department of Pathology, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India

Dr Kuldeep Singh

Resident, Department of Pathology, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India

ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a rare and unusual syndrome, more common in the paediatric age group, characterized by fever, splenomegaly, bicytopenia or pancytopenia, and proliferation of macrophages and histiocytes in the bone marrow, liver, spleen. These histiocytes are morphologically benign but hyperactive and demonstrate phagocytosis of other blood cells including erythrocytes, leukocytes, platelets and their precursor haemopoietic cells. Primary or Familial HLH is an autosomal recessive inherited disorder, while Secondary or Acquired HLH is caused by abnormal immunological activation such as in immunodeficiency or after systemic infections. We present two cases of Secondary HLH, which presented with pyrexia and cytopenias, raised triglycerides, raised LDH levels, and bone marrow findings typically suggestive of Haemophagocytic lymphohistiocytosis. The two cases had different trigger factors – one patient had infection induced HLH, while the other patient had autoimmune disease induced HLH.

Introduction:

The term haemophagocytosis describes the pathological finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets and their precursor cells (Favara, 1992). HLH is an aggressive and life-threatening haematological disorder with hyper-activation of the immune system and proliferation of lymphocytes and histiocytes demonstrating haemophagocytosis. The syndrome most frequently affects infants from birth to 18 months of age, but the disease has been observed in children and adults of all ages. A hallmark of Haemophagocytic lymphohistiocytosis (HLH) is impaired or absent function of natural killer (NK) cells and cytotoxic T-cells (CTL) (Janka & Schneider, 2004, and Janka, Imashuku, Elinder, Schneider, & Henter, 1998). HLH can occur as a primary familial disorder or as a secondary sporadic disorder, which may be triggered by a variety of events that disrupt the immune homeostasis. Infection is a common trigger, both in those with a genetic predisposition and in sporadic cases. Prompt initiation of treatment is essential for the survival of affected patients, but often the greatest barrier to a successful outcome is the delay in diagnosis. Diagnosis is difficult because of the rarity of the syndrome, the variable clinical presentation, and the lack of specificity of clinical and laboratory findings. Bone marrow aspiration and smear can play an important part in the diagnosis of the syndrome.

Case Reports:

Case 1

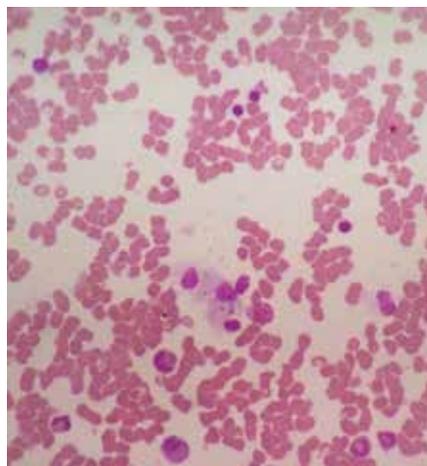
A 2 year old girl presented with high grade fever for 15 days with 2 episodes of generalised tonic-clonic convulsions. The illness progressed rapidly with onset of sepsis and shock for which she was put on intravenous antibiotics and IPPV ventilator. Patient was thoroughly investigated for fever and no obvious cause found as tests for malaria, dengue, leptospirosis, and Widal were negative. Routine examination of the cerebrospinal fluid (CSF) was normal. Urine examination showed trace proteins and a few pus cells. Blood examination revealed pancytopenia with haemoglobin (Hb) of 9.3 g/dl, total leukocyte count (TLC) of 3,100 cells/cu mm, and a platelet count of 1.23 lakhs/cu mm. Ultrasonography (USG) of the abdomen revealed mild hepatosplenomegaly, and a chest X-ray exhibited consolidation of the right lung. Serum lactate dehydrogenase (LDH) level was 779 U/L, (against a normal control of less than 247 U/L). Blood culture was sterile, but culture of bone marrow aspirate showed a growth of *Staphylococcus aureus*. A bone marrow aspirate smear demonstrated moderate increase in macrophages with

signs of active haemophagocytosis (Figure 1). The patient was treated as a case of infection induced haemophagocytosis and Toxic Shock Syndrome. Intravenous hydrocortisone was started following which the child started to recover clinically, and subsequently the pancytopenia also improved.

Case 2

A 15-year-old boy, a known case of Systemic Juvenile Rheumatoid Arthritis, presented with high grade fever for 15 days not associated with fever and chills. Mild hepato-splenomegaly was present. No obvious cause of fever was found on routine investigation. Complete blood count (CBC) revealed haemoglobin of 10.2 g/dl, total leukocyte count (TLC) of 3,600 cells/cu mm, and a platelets count of 2.20 lacs/cu mm. Serum lactate dehydrogenase level was 572 U/l (against a normal control of less than 247 U/L). Other investigations were within normal limits. Bone marrow aspiration study demonstrated an increased number of eosinophils and their precursor forms with a mild increase in granularity of the myeloid series. Macrophages were increased in number and some showed haemophagocytosis (Figure 2 and Figure 3). Therefore, a diagnosis of HLH secondary to systemic juvenile rheumatoid arthritis was made and the patient was treated with steroids following which he improved clinically.

Figure 1: Bone marrow smear showing macrophages engulfing polymorphs



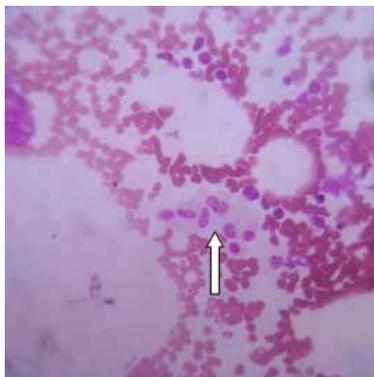


Figure 2: Bone marrow smear showing increased number of macrophages phagocytising haemopoietic cells

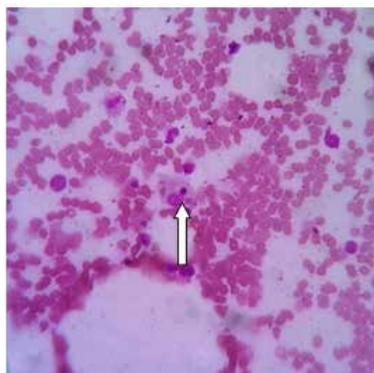


Figure 3: Bone marrow smear showing macrophages which contain lymphoid cells

Discussion:

The terms used to describe HLH and related syndromes have evolved since the first patient was described as having 'familial hemophagocytic reticulosis' in 1952. Haemophagocytic lymphohistiocytosis (HLH) is an unusual and rare syndrome characterised by fever, splenomegaly, pancytopenia and the pathological finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leucocytes, platelets and their precursors) in the bone marrow and other tissues. HLH has two different forms and presentations, a primary form and a secondary form.

Approximately 25% of HLH cases are primary or familial. Primary HLH is an autosomal recessive disorder and typically presents during infancy or early childhood. Infants are most commonly affected, with the highest incidence in those less than 3 months (Henter, Elinder, Söder & Ost, 1991). It is usually fatal, if untreated, with a median survival of less than two months after diagnosis.

Secondary HLH can develop due to strong immunological activation, for example after severe infection. Secondary HLH has also been described in immuno-compromised hosts, usually in association with viral or bacterial infection, and may also develop during malignancy (malignancy associated haemophagocytic syndrome or MAHS).

Macrophage activation syndrome (MAS), also known as reactive haemophagocytic syndrome, is a secondary variant of HLH that occurs in patients with autoimmune or auto-inflammatory diseases. Most MAS cases have been described in association with systemic juvenile idiopathic arthritis (sJIA) and its adult-onset form, but also in association with systemic lupus erythematosus and other rheumatic diseases.

The pathogenesis of HLH is characterised by uncontrolled activation and proliferation of macrophages and T cells leading to multi-organ infiltration and dysfunction. The excessive infiltration is thought to be caused by a deficiency of normal down regulation of activated macrophages and lymphocytes by natural killer cells (NK cells) and cytotoxic T lymphocytes (CTL) (Filipovich, McClain & Grom, 1991). The normal elimination of activated macrophages by NK cells and CTL occurs through the process of perforin dependent cytotoxicity. In this process, NK cells and CTL lyse target cells in a series of steps – formation of an immunologic synapse, creation of pore in macrophages, and delivery of cytolytic granules in macrophages. Most of the genetic defects in patients with familial HLH encode proteins involved in this process.

The diagnostic criteria for HLH proposed by the HLH study group of the Histiocytes Society have been revised recently (Henter, Horne & Arico, 2007), and the following diagnostic criteria are recommended by them:

- Molecular identification of an HLH-associated gene mutation (ie, PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, or BIRC4)

Or

- Fulfilment of any five out of the following eight clinical and laboratory criteria:

- Fever $\geq 38.5^{\circ}\text{C}$
- Splenomegaly
- Peripheral blood cytopenia, with at least two of the following:
 - Haemoglobin $< 9 \text{ g/dl}$ (in infants < 4 weeks haemoglobin $< 10 \text{ g/dl}$)
 - Leucopenia with absolute neutrophil count $< 1000 / \text{mm}^3$
 - Platelets $< 100,000 / \text{mm}^3$
- Hypertriglyceridaemia (fasting triglycerides $> 265 \text{ mg/dl}$) and / or hypofibrinogenaemia (fibrinogen $< 150 \text{ mg/dl}$)
- Ferritin $> 500\text{ng/ml}$
- Haemophagocytosis in bone marrow, spleen, lymph node or liver
- Low or absent NK cell activity
- Elevated soluble CD25 (soluble IL-2 receptor alpha) > 2 standard deviations above age-adjusted laboratory-specific norms

Additionally, in cases of familial HLH, there should be no apparent evidence of malignancy

Supportive evidence includes cerebral symptoms with moderate pleocytosis and / or elevated proteins, elevated transaminase, bilirubin, or lactate dehydrogenase.

It is common for a patient to exhibit only three or four of the above eight diagnostic criteria, but also demonstrate CNS symptoms, hypotension and renal or respiratory failure. To address this issue, a modification of the diagnostic criteria has been proposed, which requires three of four clinical findings (fever, splenomegaly, cytopenias, hepatitis) along with one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or significantly reduced NK cell function) (Jordan, Allen & Weitzman, 2011 and Filipovich, 2009).

In both our cases, patients presented with high grade fever, hepato-splenomegaly, peripheral blood cytopenias, hypertriglyceridaemia, elevated lactate dehydrogenase, along with haemophagocytosis of haemopoietic cells as demonstrated in bone marrow aspirate smears. Thus the diagnostic criteria of HLH

were fulfilled. Both the patients were treated as secondary HLH after identifying the trigger factors and were treated as per HLH 2004 treatment guidelines. Both the patients responded well to the treatment and recovered.

Conclusion:

HLH should be considered in the differential diagnosis of unexplained cases of fever, splenomegaly and pancytopenia. A bone marrow aspiration and smear in cases of unexplained fever may aid in establishing the diagnosis of HLH and many times may be life saving. HLH may be associated with malignancy, autoimmune diseases or any infectious illnesses including sepsis, tuberculosis and viral infections. Many times, the causative agents may not be identified, which knowledge is important, as HLH may mask malignant or infectious diseases, and may be their first presenting sign. HLH is rapidly fatal in untreated cases, and despite treatment, the prognosis of both familial and acquired forms of HLH can be poor. Treatment of the triggers, along with vigorous supportive management, aids patient recovery and improves the clinical outcome.

REFERENCE

1. Favara BE; Hemophagocytic lymphohistiocytosis: A hemophagocytic syndrome; *Semin Diagn Pathol* 1992; 9(1):63-74. | 2. Filipovich AH; Hemophagocytic lymphohistiocytosis (HLH) and related disorders; *Hematology Am Soc Hematol Educ Program* 2009; 127. | 3. Filipovich A, McClain K, Grom A; Histiocytic disorder: recent insight into pathophysiology and practical guidelines; *Biol Blood Marrow Transplant* 2010; 16:825. | 4. Henter JL, Elinder G, Söder O, Ost A; Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis; *Acta Paediatr Scand* 1991; 80:428. | 5. Henter JL, Horne A, Arico M, et al; HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis; *Pediatr Blood Cancer* 2007; 48(2):124-131. | 6. Janka G, Imashuku S, Elinder G, Schneider M, Henter JL; Infection and malignancy-associated hemophagocytic syndromes – Secondary hemophagocytic lymphohistiocytosis; *Hematol Oncol Clin North Am* 1998; 12(2):435-44. | 7. Janka GE, Schneider EM; Modern management of children with hemophagocytic lymphohistiocytosis; *Br J Haematol* 2004; 124(1):4-14. | 8. Jordan MB, Allen CE, Weitzman S, et al; How I treat hemophagocytic lymphohistiocytosis; *Blood* 2011; 118:4041. |