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Hemophagocytic Lymphohistiocytosis - Case History and Review of Literature

Sasidharan PK[1*] and Priyadarshini B[2]

[1]Department of Medicine, Govt. Medical College, Kozhikode, Kerala, India Presently Consultant Physician, PVS Hospital, Kozhikode, Kerala, India

[2]Department of Medicine, Govt. Medical College, Kozhikode, Kerala, India

***Corresponding author**: Puthenpurakkal Kunhumon Sasidharan*

Former Professor & Head, Department of Medicine, Govt. Medical College, Kozhikode, Kerala, India, Presently Consultant Physician, PVS Hospital, Kozhikode, Kerala, India, Tel: 9847005177; E-mail: sasidharanpk@gmail.com

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Abstract

Hemophagocytic lymphohistiocytosis or HLH is a very rare underdiagnosed potentially fatal entity which frequently leads to multiorgan failure and death due to immune dysregulation. It can be either primary which is supposed to be an inherited disorder seen in infancy and childhood or secondary to infections, connective tissue disorders or malignancies which is seen in all ages. The disease manifestation is due to massive release of inflammatory cytokines (cytokine storm) into the circulation which is out of control of the immune system. The cytokines activate the macrophages which lead to phagocytosis of the hemopoietic cells including precursors leading to cytopenias. Clinically it is mistaken for bone marrow infiltrating diseases like leukemia, lymphoma, and several other entities. It is important to have a high index of suspicion for diagnosis since an early diagnosis is crucial to decrease the significant mortality associated the disease. The definitive diagnosis still remains a challenge due to the varied clinical presentations with which this disease can present. This article gives two case histories and reviews the varied clinical presentations, pathophysiology, prognosis and treatment of the entity.

Keywords: Hemophagocytic lymphohistiocytosis; Macrophage activation; Cytokine storm; Immune dysregulation; Phagocytosis

Case 1

A 35-year-old male from Saudi Arabia, presented with high-grade fever of three months, palpitation and exertional breathlessness of two months duration. He had 4-5 episodes of watery stools five days prior to admission which subsided after three days. He had no significant weight loss and review of symptoms pertaining to organ systems was normal. Past history and family history were unremarkable. On examination, vitals were stable. Pallor was present, there was clubbing, bilateral posterior cervical and inguinal lymph nodes were enlarged. Liver was palpable 4 cm below the right costal margin and spleen was palpable 3 cm below the left costal margin.

On investigation: Hb-7.4 g%, TC-2000/ mm3, DLC P-62 L-32 M6, Plt-47000/ mm3, ESR-75 mm/1st hr, Urine routine was normal, Blood Urea 35 mg/dl, Serum Creatinine-0.8 mg/dl, LFT showed normal bilirubin levels, Total protein of 6.7(Alb 4.3 g/dl & Globulin 2.5 g/dl) SGPT-was 64 U/l (normal<40) and Alkaline phosphatase was normal (53 U/l), PT-INR-1.12, Retroviral screening was negative, Peripheral Smear for Malarial Parasite was Negative, Chest X-ray was normal. Mantoux test was negative.

The initial possibilities considered were, Lymphoma with bone marrow infiltration, or Chronic infections like Brucellosis, Leishmaniasis, and Tuberculosis. On further investigation, Peripheral smear showed leucopenia with thrombocytopenia and few atypical lymphocytes. Widal and IgM Brucella was negative and blood cultures were negative, echocardiography did not show any vegetation. Bone marrow aspirate examination showed histiocytic proliferation with hemophagocytosis. Bone marrow Trephine confirmed sheets of histiocytes with evidence of hemophagocytosis. S. Ferritin was 10900 micrograms/L, Triglycerides 334 mg/dl, Serum C Reactive Protein was 178.4 mg/L. ANA and Rheumtoid Factor was negative. Splenic Aspirate was done to look for Leishmania Donovan (LD bodies), which showed Macrophages showing hemophagocytosis. It was consistent with macrophage activation syndrome, but no LD Bodies were seen.

The patient was treated with cefotaxime, doxycycline and artesunate for 5 days initially. Methyl prednisolone was given for 3 days. Subsequently he was started on oral prednisolone, cyclosporine and etoposide as per HLH protocol. Supportive treatment and broad spectrum antibiotics were also given. Patient showed improvement, but after one week he developed left shoulder pain followed by left sided chest pain and hypotension. Chest X ray revealed a non homogenous opacity in the left midzone. He was managed as pneumonia with septic shock and coexisting pulmonary thromboembolism. Patient's condition worsened in spite of treatment and he succumbed to his illness.

Case 2

A 32 year old female from Kuwait was admitted in a hospital there 2 months back with a history of incomplete abortion and fever of one month duration. She had 2 children, last child birth was 10 years back, had a history of tubal pregnancy 3 years back. She conceived 4 weeks before her hospitalization at Kuwait and had a history of attempted medical termination of pregnancy at four weeks of gestation by self-medication with some oral medicine. She underwent D&C in the hospital following incomplete passage of products of conception. Two days after hospitalization she developed high grade fever and was managed as septic abortion. Subsequently she developed gum bleeding and epistaxis. During her hospital stay, she was treated with antibiotics and dexamethasone with which she became better. She was referred to

our center for further evaluation and management. When we received the patient, she was afebrile and had no bleeding manifestations. She was asymptomatic except for tiredness and constipation. Past history was unremarkable except for vascular headache. There was no history of joint pains, photosensitive rashes or recurrent oral ulcers. On examination she was pale; there was no clubbing, icterus lymphadenopathy, edema. All systems were with in normal limits. There was no hepatosplenomegaly when we had seen the patient.

Investigation from Kuwait, Hb 8.7 g%, TC 1100/ mm^3, DC N50 L40, Platelet 81000/ mm^3, ESR 10 mm/1^{st} hr. Total Bilirubin was 19.9 mg/dl, Direct bilirubin was 6 mg/dl, ALT 71 U/I, AST 339 U/I. Peripheral smear showed leucopenia, anisopoikilocytosis, microcytic hypochromic anaemia. Bone marrow cellularity was 45-50 %, all haemopoetic lineages were seen. Megakaryocytic lineage showed dysplastic changes. Myeloid lineage was of normal morphology. There was an increase in interstitial lymphocyte which were positive for CD3 and CD5 but negative for CD20. There was an increase in macrophages and most of them were reactive and some of them showed hemophagocytosis. Serum ferritin was 640 micrograms/L and serum triglyceride was 288 mg/dl. She received dexamethasone injections and became asymptomatic and was refereed to our center.

The clinical picture of pancytopenia, low ESR with cellular marrow without any infiltrative diseases was consistent with macrophage activation syndrome. At our center, being a young female, we thought of SLE as a possible underlying cause. Hemogram here also showed pancytopenia, we did not repeat the bone marrow but asked for ANA which was positive at 4.08 IU (Normal less than 1 IU) and Anti ds DNA was 398 IU/ml (normal less than 60 IU). Therefore a final diagnosis of HLH secondary to SLE, and septic abortion was made. We used the Kozhikode Criteria, which we have developed for diagnosing SLE in this patient [1,2]. Patient was managed with steroids and cyclosporine and other symptomatic measures. She improved dramatically. Later she was put on Azathioprine and steroid and is still doing well on follow up.

Review Article

Introduction

The index case of hemophagocytic lymphohistiocytosis was reported several years ago by Scottish pediatricians James Farquhar and Albert Claireaux. They called it *familial hemophagocytic reticulosis* as they noticed the familial occurrence of the disease characterized by proliferation of tissue macrophages in various organs and the phagocytosis of blood cells by macrophages in the bone marrow. However, the nearly simultaneous occurrence of fatal HLH in a father and son in 1965 indicated that infections might have a role [3]. As of our understanding today, though initially described in infants, the disease is seen in all ages. In adults this occurs as a result of strong and dysregulated immune activation secondary to common systemic infections or malignancies. Primary Hemophagocytic syndrome is an inherited autosomal recessive disorder and usually seen in infancy and childhood [4]. Secondary Hemophagocytic syndrome occurs secondary to infections, connective tissue disorders or malignancies. Hemophagocytic syndrome whether primary or secondary is characterized by the uncontrolled activation of T lymphocytes and macrophages, with massive release of cytokines (cytokine storm) leading to distinct clinical and hematologic manifestations and virtually leading to multiorgan dysfunction or failure which can be fatal in the absence of prompt treatment [5].

Our knowledge about the disease is still incomplete. Over the past two decades there has been an increasing awareness about the entity among physicians. Though it is associated with high mortality rate, early diagnosis can significantly alter the course and prognosis if the secondary cause is appropriately addressed. But the process of macrophage activation and its consequences will mask the clinical picture of the underlying secondary cause, making the diagnosis extremely difficult. Very often the clinician is alerted to the possibility of HLH only after receiving the bone marrow report showing hemophagocytosis. In order to save the patient, it has to be suspected clinically on receiving the hemogram report showing pancytopenia and we need to look for the supporting evidence of HLH (like low or normal ESR, elevated ferritin and triglyceride, etc.) and further a search for all possible secondary causes in that given clinical setting is to be done. Timely initiation of treatment for the possible secondary causes and the suppression of cytokine storm with steroid and immunosuppressant are essential to save the patient. Therefore good clinical approach and a high index of suspicion are absolutely essential to save the patient. Spontaneous partial regression has also been reported in the literature [6].

HLH is a puzzling clinical entity characterized by fever, cytopenias, splenomegaly, lymphadenopathy and evidence of hemophagocytosis in organs rich in lymphoid tissues such as bone marrow, lymph nodes, liver, spleen or the skin. HLH has been associated with a variety of infections, as well as connective tissue disorders and malignancies, like anaplastic and T-cell lymphomas [7-9]. Infection associated HLH forms the bulk of secondary HLH particularly in developing countries like India. The term *macrophage activation syndrome* (MAS) is often applied to HLH in the context of rheumatologic diseases, like systemic-onset juvenile idiopathic arthritis (soJIA), adult-onset Still disease, and systemic lupus erythematosus [10]. But it may be more appropriate to use MAS for all the secondary causes of HLH and reserve HLH for the unrecognized causes or the so called idiopathic or the primary forms.

Pathophysiology

The pathological hallmark of this entity is the dysregulated non-clonal proliferation of activated macrophages and histiocytes, which phagocytose RBCs, WBCs, and platelets, leading to the clinical symptoms of cytopenias and multiorgan failure and eventually death. This entity differs from Langerhan Cell Histiocytosis in that the proliferation of cells is not clonal and hence not malignant. The most common sites of involvement are the organs that are rich in lymphoid tissue namely the spleen, lymph nodes, bone marrow, liver and the skin.

Initially the pathogenesis was thought to be due to inability to clear antigen from the body due to inefficient immune system as in immunocompromised patients [11]. However the subsequent descriptions of the disease in immunocompetent hosts led to better understanding of the pathogenesis. As of what we know today HLH is a highly activated, but ineffective and dysregulated, immune response to antigens, which results in life-threatening surge of inflammatory cytokines into the circulation leading to inflammation in various tissues and organs [12].

A currently accepted theory proposes the role of perforin and natural killer (NK) cells in the pathogenesis of HLH although the pathogenesis is still not completely elucidated. Following an antigenic stimulus in a given clinical setting, in certain predisposed patients, NK cells release granules that contain perforin and granzymes. These form

pores in the host cell membranes and cause osmotic lysis and protein degradation. Patients with perforin mutations have poor defenses against intracellular pathogens and tumor cells. Decreased NK cell activity results in increased T-cell activation and expansion, which in turn results in cytokine storm through uncertain mechanisms. Large quantities of Tumour Necrosis Factor alpha, Interferon gamma and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) are released into the circulation which causes activation and recruitment of macrophages into tissues leading to irreparable damage to the organs resulting in death.

Primary hemophagocytic syndromes are autosomal recessive disorders. Various types have been described based on genetic linkage analysis and chromosomal localization accounting for 90 % of all patients [13].

Clinical Features

HLH is considered to be a medical emergency. Due to the nonspecific nature of the clinical presentation and lack of awareness among treating doctors about this entity, this disease is often overlooked [14]. HLH should be suspected in any individual who presents with fever, hepatosplenomegaly, rash, jaundice, generalized lymphadenopathy, and cytopenias of unexplained etiology. Most often the striking features are the hepatospelneomegaly and pancytopenia with a cellular marrow. Hemophagocytosis may not be evident always on histopathological evaluation. One has to go by other supporting evidences like falling erythrocyte sedimentation rate (ESR) and elevated ferritin and triglyceride and absence of a recognized cause for cytopenia. Central nervous system involvement in the form of encephalopathy and seizures have been reported in the literature [15]. HLH may also present with multiorgan dysfunction at initial presentation itself. The initial diagnostic criteria were put forth by the Histiocyte society, which included clinical, laboratory and histopathological features. All 5 criteria are to be met to make a diagnosis of Hemophagocytic syndrome (Table 1).

Histiocyte Society Diagnostic Criteria

Fever	>38.5
Splenomegaly	>3 CM from Left costal margin
Cytopenia	In at least 2 lineages: Absolute neutrophils less than 1000/μL Platelets less than 100,000/μL **Hemoglobin** less than 9.0 g/dL
Hypertriglyceridemia/ Hypofibrinogenemia	 Fasting greater than 2 mmol/L or levels greater than 3 standard deviations above the age-adjusted reference range value Fibrinogen less than 1.5 g/L or levels greater than 3 standard deviations below the age adjusted reference range value.
Hemophagocytosis	Tissue demonstration from lymph node, spleen, or bone marrow

Table 1: All 5 criteria to be met.

Criteria for Diagnosis Hlh 2004

HLH can be diagnosed if either of the following two are met:

A gene mutation consistent with familial HLH is present OR

At least five out of the eight diagnostic criteria for HLH are fulfilled:

Fever

Splenomegaly

Cytopenia affecting ≥ 2 of 3 lineages: Hemoglobin < 90 g/L , Platelets < 100 x109 /L; Neutrophils < 1.0 x109 /L

Hypertriglyceridemia and/ or hypofibrinogenemia: fasting triglycerides ≥ 3.0 mmol/L (≥ 265 mg/ dl), OR fibrinogen ≤ 1.5 g/L

Hemophagocytosis in bone marrow, spleen or lymph nodes

Low or absent NK-cell activity (using local laboratory reference ranges)

Ferritin ≥ 500 ug/L

Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/m

Laboratory Findings

No laboratory finding is specific for the diagnosis of HLH and there is no confirmatory gold standard investigation. Hence clinical suspicion and judgement plays the most important role in the early diagnosis of this entity. Some of the laboratory abnormalities which can support the diagnosis are mentioned below. These abnormalities provide corroborative evidence of existence of HLH in any given patient when other common conditions are reasonably ruled out or when HLH is suspected to be associated with another common condition (where HLH is thought to be secondary to that common condition). The most striking laboratory abnormality in Hemophagocytic lymphohistiocytic syndrome is cytopenia affecting at least 2 lineages in the peripheral blood, which may be profound in some cases. Affected patients frequently have hyperbilirubinemia, elevated transaminases and lactate dehydrogenase levels and points towards liver dysfunction [16]. Affected patients commonly have hypertriglyceridemia and marked elevation of ferritin. Serum fibrinogen levels are usually low, and patients may have disseminated intravascular coagulation [17]. Perforin gene (*PRF1)* mutation in Primary Hemophagocytic syndrome can be determined on flow cytometry in lymphocytes by staining perforin.

Histopathological Findings

The histopathological hallmark for the diagnosis of HLH is Hemophagocytosis. Hemophagocytosis is seen in bone marrow, spleen, lymph nodes, skin and occasionally the central nervous system. Activated macrophages in the tissues are seen to engulf erythrocytes, leukocytes, and platelets and their precursors (Figures 1a and 1b). These cells appear "stuffed" with blood cell precursors. Hemophagocytosis may also be present in the liver, but more commonly lymphocytic infiltration of the hepatic portal tracts is seen [18].

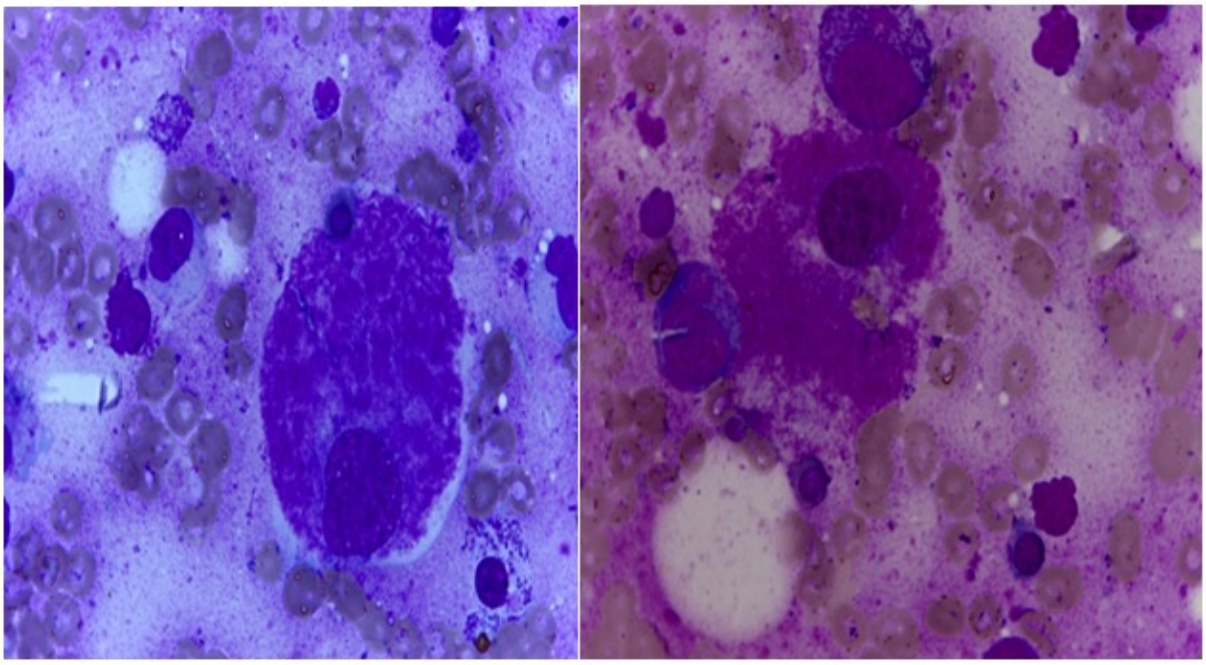

Figure 1a and 1b: Activated macrophages showing phagocytosis

The hemophagocytosis may be often cyclical so the initial bone marrow aspirates may be negative in a substantial proportion of the patients with Hemophagocytic syndrome hence a negative result histopathologically is not sufficient to rule out the problem. Repeated examinations may be necessary or the treatment may be based on corroborative evidence. An additional bone marrow finding includes dyserythropoiesis, that could be observed in the absence of hemophagocytic histiocytes.

Infection Associated Hlh

This subgroup constitutes the bulk of HLH cases in a tropical country like India. Several reports in the literature suggest the strong association of Epstein Bar Virus (EBV) infection with HLH but other viruses including hepatitis viruses, Cytomegalovirus (CMV), Mumps, Herpes Simplex Virus (HSV), Dengue, Parvovirus B19 and enterovirus have been associated. Influenza-associated HLH has also been reported [19]. HLH is known to occur as the initial presentation of a human immunodeficiency virus (HIV) infection [20].

Bacteria are also a common culprit of HLH associated with infections. Tuberculosis which is endemic in India is one of the most common causes. There are as many as 36 reported cases of Tuberculosis associated HLH in the literature as of today. *Campylobacter, Mycoplasma, Chlamydia, Legionella, Salmonella Typhi Rickettsia, Brucella, Ehrlichia* and *Borrelia burgdorferi* are the other common bacteria associated with HLH. Parasitic infections like malaria, leishmaniasis, toxoplasmosis, babesiosis and strongyloidiasis have been described as trigger in HLH. Fungal infections as triggers have been described in immunocompromised patients, retroviral

infection, transplant recipients and those on chronic steroid and immunosuppressant use. We had come across HLH in association with all infections including Typhoid fever, Malaria, Viral Hepatitis and Visceral Leishmaniasis.

Therefore virtually any infection can act as a trigger in susceptible individuals and lead to Hemophagocytic syndrome. But what exactly are the individual susceptibility factors is not very clear at the moment.

Malignancy Associated Hlh

Both hematological and solid organ malignancies have been described in association with HLH in adults as well as children. Among Hematological malignancies, peripheral NK cell lymphomas, acute lymphocytic leukemias, T-cell lymphomas and anaplastic large-cell lymphoma are frequently described as initial triggers [21] Hodgkin lymphoma and multiple myeloma have also been implicated as triggers for secondary HLH. Non Hodgkin B cell Lymphoma is typically not known to be a trigger for HLH.

Collagen Vascular Disease and HLH

HLH can occur secondary to connective tissue disorders like SLE, Adult Onset Stills disease and systemic-onset juvenile idiopathic arthritis. It has also been described in association with Sjogren syndrome, polyartertis nodosa, Kawasaki disease and mixed connective tissue disorders [22]. The most important concern in these patients is the recognition of HLH in the context of the underlying connective tissue disorders which can be difficult in many cases. Though Juvenile Idiopathic arthritis is the most common association with HLH in the literature, we had one case of HLH associated with SLE and the other in a patient with Adult Onset Stills disease. HLH in the context of collagen vascular disease is frequently missed and can have an unfavorable effect on the prognosis of the patients.

Treatment and prognosis

The mainstay of management in HLH is immunosuppression. Immunosuppressants suppress the exaggerated immune response when started early in the course of the disease. The initial treatment regime was proposed by the Histiocyte Society in 1994 but later on modified in 2004. HLH 2004 protocol recommends a therapy with corticosteroids, etoposide, and cyclosporine A for 8 weeks during induction [23]. The protocol aims at attaining clinical stability by using various modalities along with treatment for the underlying disorder. But in familial cases further cure is attained by bone marrow transplantation. In acquired HLH, no further treatment is indicated if clinical stability is attained through immunosuppression and treatment of the underlying disorder alone. Intrathecal methotrexate is indicated in patients with abnormal cerebrospinal fluid (CSF) findings or worsening neurologic signs and symptoms. Trimethoprim sulfamethoxazole prophylaxis is recommended throughout the treatment to prevent opportunistic pneumocystis pneumonia (PCP) due to immunosuppression. Antifungal agents to treat possible underlying fungal infection or to prevent fungal infection accompany initial doses of dexamethasone. Intravenous immunoglobulin (IVIg) is also thought to be of significant benefit in the treatment of this disease though more randomized controlled trials are required to prove the true efficacy of this modality of treatment.

The overall mortality of the disease seems to be high and depends on the time of optimal intervention and the underlying disorder. Hence there have been varying outcomes in various studies. However the prognosis of HLH associated with malignancy seems to be poor. People with hemophagocytic lymphohistiocytosis are thought to have an increased risk for posterior reversible encephalopathy syndrome (PRES) [**24].** So far we have not come across any such association but the instances of PRES itself are probably unrecognized cerebral vein thrombosis in the posterior circulation [25]. Central nervous system (CNS) involvement of hemophagocytic lymphohistiocytosis may trigger this syndrome.

Conclusion

HLH is a rare but uniformly fatal disease if underdiagnosed and undertreated. A strong suspicion and good clinical judgment is required for early diagnosis of the disease as timely intervention can significantly alter the course and prognosis of this entity. It is hoped that the continued efforts at clinical research on the entity will lead to a better understanding of the disease and thereby provide more insights into the therapy of HLH. It is also essential that doctors in all specialities be aware of this entity so that they can promptly recognize the condition without delay and institute appropriate timely treatment to decrease the mortality of the disease. The clinical settings in which they develop the problem of HLH and the individual predispositions are to be studied in future to identify the etiological factors in this curious clinicopathologic entity.

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