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Case Report

Haemophagocytic Lymphohistiocytosis: an Uncommon Cause for Childhood Organomegaly

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Abstract

Haemophagocytic lymphohistiocytosis is a rare condition with over-reactive histiocytes and haemophagocytosis. It is characterized by peripheral pancytopenia, hepatosplenomegaly and repeated infections. It usually affects children but can be seen at all ages. We present a case of a five months old male child who presented with fever, pancytopenia and hepatosplenomegaly. He was referred for bone marrow examination with suspicion of leishmaniasis or any malignancy. Bone marrow aspiration did not show any atypical cells/blasts or any evidence of leishmaniasis. However there was a marked increase in histiocytes with hemophagocytosis. A diagnosis of haemophagocytic syndrome was made.

Key Words: Haemophagocytosis, lymphohistiocytosis, histiocytosis, pancytopenia, splenomegaly

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes usually affecting children but can be seen in all age groups. Though immune response is highly stimulated, but is generally ineffective. Estimated incidence is approximately 1.2 cases per million individual per year.[1] Initial presentation often comprises of fever, hepatosplenomegaly, pancytopenia, lymphadenopathy and rash. About 65% of these patients manifest with cutaneous involvement, its detection helps in initial diagnosis and signify recurrences. Aggressive proliferation of activated macrophages and histiocytes, which phagocytose other cells, namely red blood cells, white blood cells, and platelets, leading to the clinical symptoms is the pathological hallmark of this disease.[2] Hemophagocytic lymphohistiocytosis comprises of primary or genetic HLH and secondary or acquired hemophagocytic syndrome. These two categories are difficult to distinguish from one another.[3] Familial hemophagocytic lymphohistiocytosis is a subgroup of genetic HLH, its incidence is 1:50,000 live-births. Most children develop disease very early in life. Median survival is less than 2 months after diagnosis without treatment.[2]

Here we present a 5months old male infant with very early presentation

Case Report

A 5moths old male child born of consanguineous marriage resident of Azad Jammu Kashmir was admitted to Children Hospital, Pakistan Institute of Medical Sciences, Islamabad with two weeks history of fever. General physical examination of the child showed pallor, his liver was palpable 7 cm below the costal margin while spleen was enlarged 4 cm below the costal margin. His lymph nodes were not palpable. The laboratory findings were as follows: Red cell count $2.71x10^9$/l, Hemoglobin 75g/l, WBC $1.6x10^9$/l, platelets $40x10^9$/l, ALT was 82I u/l, LDH was 2809 u/l, bilirubin was 1.4 mg/dl. His typhidot test was negative. His serum ferritin was increased and serum fibrinogen was markedly decreased. Ultrasound abdomen revealed hepatosplenomegaly. The child was transfused with 2 units RCC and FFPs but didn't make significant change in counts. Antibiotic treatment was given for presumed systemic infection but condition continuously deteriorated. Bone marrow biopsy was planned to find out the etiology of pancytopenia and suspicion of leishmaniasis and malignancy and child was referred to haematologist for further evaluation. Bone marrow biopsy was performed and aspirate showed hypercellular marrow. Myeloid series was hypercellular while erythroid was found moderately cellular with megaloblastic change and dyserythropiesis. Lymphocytes were increased. There was marked increase in histiocytes with haemophagocytosis. Diagnosis of haemophagocytic syndrome was made. Child kept on deteriorating in spite of high potency antibiotics and died on 25^{th} day of his illness.

Discussion

Haemophagocytic syndrome is an uncommon non-neoplastic disorder of the mononuclear phagocytic system. HLH encompasses a rare but potentially fatal disorder due to prolonged and intense activation of antigen-presenting cells (macrophages, histiocytes) and CD8+ T cells and excessive

proliferation and ectopic migration of T-cells. HLH is further categorized into primary and secondary types.

Table 1: Revised Diagnostic Guidelines for Haemophagocytic Lymphohistiocytosis[11]

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (five out of the eight criteria below):
A. Initial diagnostic criteria (to be evaluated in all patients with HLH*)*
Fever
Splenomegaly
Cytopenias (affecting 2 of 3 lineages in the peripheral blood):
Hemoglobin <90 g/l (in infants <4 weeks: hemoglobin <100 g/L)
Platelets <100X10^9/L
Neutrophils <1.0 X10^9/l
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides >3.0 mmol/l (i.e. >265 mg/dl)
Fibrinogen <1.5 g/l
Haemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
B. New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin<500 mg/l
Soluble CD25 (i.e. soluble IL-2 receptor) 2.400 U/mL

forms.[4,5,6] Primary or genetic HLH is inherited in an autosomal recessive or X linked fashion and can be further divided into familial hemophagocytic lymphohistiocytosis and X linked lymphoproleferative syndrome. In familial form the clinical syndrome of HLH is the primary and only manifestation.[7] Onset of the disease is seen during the first year in 70% children. Acquired forms may develop because of strong immunological activation of the immune system caused by severe infection and malignancy. In infection associated hemophagocytic syndrome triggering agents belong to Herpes group, especially EBV and CMV. Some malignant diseases like lymphomas which can develop before or during treatment are associated with acquired form.[5] Much data is not available about the incidence in children and adults but from available literature it appears to be more common than previously believed. A study done in Sweden reported 32 children with FHL. The incidence was 1.2/1,000,000 children per year.[1]

Although HLH can occur in all age groups but early presentation is rare. There are very few reported studies and most patients have been published as case presentations.[8,9] Our patient presented with ten days history of fever and anemia. His diagnosis was delayed because initially it was thought to be a systemic infection and patient was treated on those grounds. As mentioned in literature it is difficult to establish the diagnosis as HLH may mimic a number of other diseases like congenital infection, sepsis or inherited metabolic disorders. HLH is an intriguing condition not only to diagnose but to treat as well. Due to the rarity of the disease and lack of a specific laboratory test, the diagnosis of HLH is often difficult, resulting in under diagnosis. To overcome diagnostic difficulties, the FHL study group of the Histiocytic Society has proposed diagnostic guidelines for HLH. However, it is important to know that some patients may present with an incomplete picture and develop the remaining abnormalities later. Other less well-known presentations are early cerebro-meningeal involvement, chronic persistent hepatitis or neonatal or prenatal presentation. In the absence of any specific marker, a strong clinical suspicion is often warranted for early diagnosis of HLH.[10]

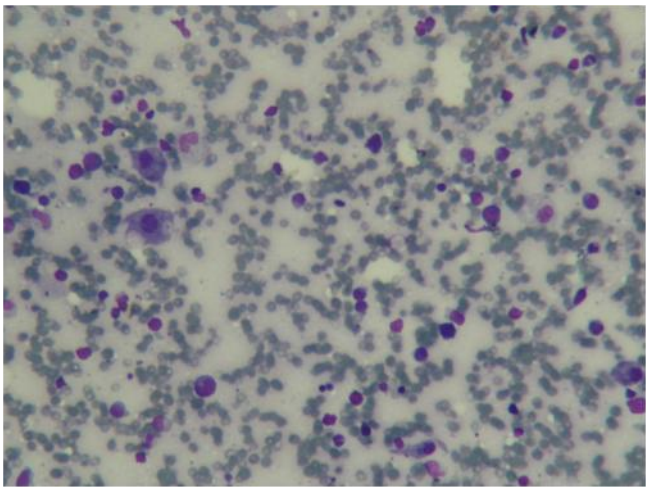

Figure 1. Bone marrow smear showing many histiocytes (Wright stain 10x10)

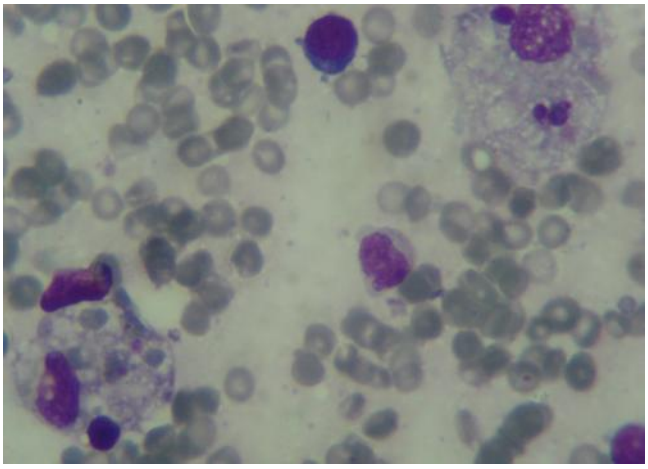

Figure 2. Bone Marrow smear showing haemophagocytosis (Wright stain 10x100)

According to revised diagnostic criteria for HLH (table 1) either 1 or 2 (at-least five of the eight diagnostic criteria) are needed for diagnosis and initiation of therapy.[11] In this particular case we met the diagnostic criteria. Our patient presented with fever and hepatosplenomegaly. Peripheral blood film showed bicytopenia. Aspiration of bone marrow revealed histiocytic hyperplasia with activated macrophages showing engulfment of erythrocytes, leucocytes, platelets and their precursors.

Molecular analysis could not be done in this case but very early presentation, serious clinical course without infectious or triggering factor, and a family history with suspicion of sibling that died in first month of life, suggest that the current case more likely suffered familial HLH. It is evident from previous reports that patients with FHL were usually born healthy but became ill in first six months of life.[11] When a patient presents with prolonged fever, hepatosplenomegaly and cytopenias the diagnosis of HLH should be considered. Minimal diagnostic requirements are a complete blood count, liver enzymes, bilirubin, triglycerides, ferritin and coagulation profile including fibrinogen. In the presence of cytopenias and hyperferritinemia referral to experienced haematologist is highly recommended. In majority of cases hemophagocytosis is not observed in initial bone marrow aspirates but that should not be a reason to rule out the diagnosis of HLH. In such cases serial marrow aspirates or material from other tissues may be required to document hemophagocytosis. Early establishment of diagnosis and timely start of treatment is life saving in this condition.

HLH is a potentially fatal condition is often missed in children and adults. It is a life threatening condition characterized by uncontrolled hyper-inflammation due to inherited or acquired immune deficiencies. Initially HLH may masquerade as a normal infection since all symptoms, even though less pronounced, may also be found in immune competent patients. Patients with HLH, however, cannot control the hyper-inflammatory response which, if untreated, is fatal in genetic cases and in a high percentage of acquired cases. Awareness of its clinical features and diagnostic criteria is very important for early diagnosis and early effective therapy to further reduce mortality.[12]

Early diagnosis of HLH is significant for timely commencement of the treatment before the disease makes irreversible damage and becomes less responsive to treatment.

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