Case Report

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Hemophagocytic Lympohistiocytosis: Malaria The Cause

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Abstract

Hemophagocytic lymphohistiocytosis (HLH), is a rare, fatal condition characterised by excessive activation of lymphocytes and macrophages due to a highly stimulated but ineffective immune process. We report a case of secondary Hemophagocytic Lymphohistiocytosis in a 13 year old boy presenting with fever, splenomagaly and bicytopenia due to infection caused by P.falciparum.

Keywords: Hempphagocytic Lymphohistiocytosis; Malaria; Fever; Splenomegaly.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a condition characterized by fever, splenomegaly, pancytopenia and haemophagocytosis in bone marrow and other tissues[1]. It can be primary (familial) HLH, or secondary (reactive) to an underlying autoimmune, Neoplastic or infectious disease. Infectious agents triggering reactive HLH primarily involve the herpes virus group, predominantly Epstein—Barr virus (EBV). Here we Report a patient presenting with reactive HLH precipitated by *Plasmodium falciparum* infection.

Case report

A 13 year male adolescent from Raichur district in Karnataka state presented to us with on and off fever with one month presently febrile since 4days. He also complained of mylgia, headache nausea, vomiting and passing of high coloured urine.

Clinical examination revealed icterus, pallor, splenomeagaly(8cm below coastal margin in right spino umbilical line), and inguinal lymphadenopathy was noted. Investigations revealed leucopenia(5500cells/cumm), neutropenia (1558cells/cumm) platelet count of(2.4lakh cells/cumm), raised serum bilirubin ,raised liver enzymes. Thick and thin smear for malarial parasites was prepared (clinical suspicion and hails from malaria endemic area) which revealed presence of P. Falciparum. With a definitive diagnosis of severe malaria he was started on quinine (10mg/kg/dose TID) and other supportive medications. On starting the treatment the fever spikes reduced for the initial 2 days. From day 4 child was found febrile and not responding to the treatment. Meningismus was noted on day4. A repeat blood counts was done which showed worsening in all the parameters was noted with deepening of leucopenia, neutropenia and thrombocytopenia. The blood culture report obtained was found negative. A repeat smear showed persistence of P. Flaciparum malariae. On day 5 clinical suspicion of HLH was made and evaluated for the same. Child was found to have hyperferritenimia (1200ng/ml. Bone marrow biopsy was done which showed hypercellular marrow with mild myeloid hyperplasia and benign-appearing histiocytes and haemophagocytes. Nuclear atypia was absent. Diagnosis of HLH was established with the diagnostic criteria for HLH laid down by The Histiocyte Society. Child continued to be febrile even after treatment targeted for p. Falciparum malaria. Hence HLH directed treatment (corticosteroid – methyl prednisolone) was started. Day 8 child was found to be afebrile and the general condition of the child improved. After the course of antimalarial repeat investigation showed

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improvement in haematological parameters and smear negative for malarial parasites. Child was discharged with good health.

Table 1: laboratory parameters of the patient on respective days of admission

Parameters	Day 1	Day4	Day8
Total leucocyte count (cells/cumm)	5500	3500	7640
Absolute neutrophils Cells/cumm	1558	253	4125
Haemoglobin level	9.2g/dL	7.4g/dL	8g/dL
Platelet count	2.6lakhs/cumm	1.6lakhs/cumm	3.85lakhs/cumm
Serum ferritin		1200ng.ml	
LDH		555.34U/L	
Triglyceride level		345mg/dl	
Fibrinogen level		90mg/dl	
Bone marrow biopsy on day 4	Hypercellular with mild myeloid series hyperplasia and presence of histiocytes		

Discussion

The term haemophagocytosis, describes the pathologic finding of activated monocytes, macrophages and histiocytes engulfing erythrocytes, leukocytes and platelets in bone marrow and other tissues[1,2].

Hemophagocytic lymphohistiocytosis (HLH) is called as haemophagocytic syndrome as well as referred as histiocytic medullary reticulosis.[4]. The syndrome first reported in 1939 by Scott and Robb-Smith. They described the pathologic finding of HLH. The pathological findings found were, macrophages histiocytes engulfing blood cells in bone marrow and other tissues [1,2]. The syndrome is also characterised by variable cytopenias, hyperferritinaemia**,** hypofibrinogenaemia, hypercytokinaemia, multi-organ dysfunction and very often death.[4] It has the widest geographic distribution throughout the world, and is usually found in Central and South America, India, and Southeast Asia.[3]

Pathophysiology

Many studies have demonstrated that p.flaciparum contain many soluble exoantigens which induces macrophage activation and Th1 stimulated hypercytokinemia leading to overproduction TNFá and INF-ã(8).which are some of the major cytokines responsible for HLH[5].

Classification

HLH has been classified majorly as[6]

1. familial HLH originally called as familial erythrophagocytic lymphohistiocytosis – as autosomal recessive disorder, mutations affect the ability of the T cells and NK cells to produce and release perforin as well as granzymes. Thus leading to reduction in formation of cytotoxic granule.
2. secondary HLH. –
   i. infection associated - Numerous viral, bacterial, fungi, are found to be the etiology.
   ii. associated with albinism syndrome
   iii. associated with immunocompromised states
   iv. associated with autoimmune/ autoinflammatory states.

Criteria for the diagnosis of HLH[6,7]

HLH diagnosis is established by fulfilling one of the following 2 criteria

1. A molecular diagnosis consistent with HLH (e.g. PRF mutations, SAP mutations)

   or

2. Having 5 of the following 8 signs or symptoms
   a. Fever
   b. Splenomegaly
   c. Cytopenia(affecting e”2 cell lineages, hemoglobinn d”9g/dl, platelets d”1lakh/µl, neutrophils <1000/µl)
   d. Hypertriglyceridemia (e”265mg/dL) and/ or hypofibrigenemia (d”150mg/dL)
   e. Hemophagocytosis in bone marrow, spleen or lymphnodes without evidence of malignancy
   f. Low or absent NK cell cytotoxicity

g. Hyperferritinemia (e"500ng / mL)

h. Elevated soluble CD25(IL-2Rá - e"2400u / mL)

Secondary HLH has been found to closely resemble sepsis, having fever, shock, multi organ dysfunction in common. NK cell activity and soluble CD25 (sIL2Rá) counts have found to be helpful to diagnose as these 2 parameters have 100% sensitivity to HLH.[8]

Upon reviewing the English literature regarding HLH and malaria in children and adolescent age group, 8 cases were found in which malarial infection was associated with HLH among those cases, details of 5were available, which has been tabulated below. (Table 2).

Age / Gender	5yr/M	19/M	15/M	19/M	21/F	Our Case 13/M
Symptoms	Fever	Fever	Fever	Fever	Fever	Fever
Jaundice	+	+	-	+	-	+
Splenomaegaly	+	-	-	+	+	+
Hepatomegaly	-	-	+	+	-	+
Lymphadenoapthy	-	+	+	-	-	+
The Lowest						
Hemoglobin	↓	8	2.9	7.8	8.2	7.4
Tlc	↓	1500	2530	3100	900	3500
Pc	↓	1.94	0.20	0.62	↓	1.6
Total / Direct Bilirubin	↑/↑	4.9/3	2.68/2	8.3/-	Deranged	
Ast/Alt	↑/↑	792/592	663/250	1283/57	Deranged	
Serum Ferritin	5890	4102	1163	4000	2000	1200
Serum Fibrinogen	Nk	375	Nk	225	400	90
Serum Ldh	Nk	3791	1482	535	Nk	555.3
Serum Triglycerides	Nk	727	40	292	446	345
Bone Marrow Examination	Nk	Normocellular Histiocyte +	Myeloid Hyperplasia	-	-	Hypercellular + Mild Myeloid Hyperplasia
Peripheral Smear	P.Falciparum Parasitemia <1%	P.Falciparum	P.Falciparum	P.Vivax	P.Vivax	P.Falciparum
Others	Cd 25 Level - 4352		Nk Cell Activity – 11%			-
Co-Morbidity	-	-	Concurrent Klebsiella Infection	Dengue Serology +	-	-
Treatment	Iv Quinine + Clindamycin	Atovoquine + Proguanil	Nk	Nk	Nk	Iv Quinine + Methyl Prednisolone
Outcome	Improved	Good	Good	Good	Good	Good
Nation	Portugal	Belgium	India	Pakistan	India	India
Reference	5	9	10	11	12	Present Case

In our case 6 out of 8 criteria for diagnosis of HLH were met along with the evidence of P.flaciparum

malarial infection on peripheral smear. Thus he was diagnosed to be suffering secondary HLH cause being P.falciparum malaria infection treated accordingls and discharged with good health.

Conclusion

This case illustrates that HLH should be considered as the differential diagnosis in any patient presenting with persisting fever and bi or pancytopenia. Early recognition enables timely initiation of immunosuppressive treatment. It has been noted that in many cases the successful treatment of the underlying condition with or without steroids has found to resolve the secondary HLH. At times HLH directed treatment is required if no response / deterioration in clinical status. The timely management prevents morbidity and mortality from a fatal condition .

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