Hemophagocytic Lymphohistiocytosis in a 19 Year Old Critically Ill Patient

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Abstract Haemophagocytic lymphohistiocytosis (HLH) describes a clinical syndrome of hyperinflammation resulting in an uncontrolled and ineffective immune response. It presents with a clinical picture of likely sepsis, i.e., fever, laboratory evidence of inflammatory response, coagulopathy and thrombocytopaenia should be appropriately investigated and managed for sepsis, but the possible diagnosis of HLH should be borne in mind. Awareness of the clinical symptoms and of diagnostic criteria for HLH is crucial to starting immunosuppressive/immunomodulatory and cytotoxic drugs in time. We present a case of HLH in a 19 year old male who presented with fever, neurological symptoms, cytopaenias, laboratory markers of inflammation and bone marrow aspirate showed hemophagocytosis.

Keywords Histiocytosis · Hemophagocytosis · Macrophage activation syndrome

A 19 year old student was admitted to this hospital with fever since 3 days. He was in his usual state of health until 2 weeks before admission when he noticed intermittent fever which subsided after treatment with antipyretics. It was not accompanied by rigors, rash, upper respiratory or urinary complaints. On presentation he was conscious, orientated to time and

person. Temperature of 38.6°C, pulse of 130 min⁻¹, blood pressure of 128/76 mm of Hg with respiratory rate of 20 cycles per minute. Meningitic signs were absent. Systemic examination was within normal limits. Apart from fever which was in range of 38.2–38.6 C and platelet count of 80,000 cells/mm³ patient was doing well until 36 h later of admission patient relatives noticed a sudden drop in sensorium, he was not responding to verbal commands. An hour later there was evidence of epistaxis and clothes soiled with dark black stools.

He was shifted to Medical intensive care unit (ICU) in view of sudden neurodeterioration. On examination he was unconscious with a Glasgow coma scale of 6; E1 V1 M4. Pupils were 4 mm round and reacting to light. His temperature was 38.4°C, heart rate of 142 min⁻¹, blood pressure of 108/68 mm of Hg, respiratory rate of 26 cycles per minute with saturation of 95% while breathing ambient room air. Plantar response was flexor, deep tendon jerk hyporeflexic. Bowel sounds were present, no abdominal guarding. Lungs were clear on auscultation.

Leptospiral Dridot test, malarial antigen test and Dengue IgM antibody by ELISA were negative. Review of investigation is shown in Table 1 urine examination was normal with stool examination showed presence of blood. Cerebrospinal fluid examination was normal. Chest radiograph was normal. Electrocardiograph showed sinus tachycardia heart rate of 140 min⁻¹ with normal axis. Computerized tomography of brain was normal. Abdominal ultrasound showed mild splenomegaly. Scopies of upper and lower gastrointestinal tract failed to show site of bleeding. Serial blood cultures were drawn. Transthoracic echocardiography did not reveal any vegetation.

The trachea was intubated for airway protection on arrival to ICU. Central venous pressure was maintained at 10 cm of water with infusion of normal saline. Platelets, fresh frozen plasma and packed cells were transfused resulting in slight

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Table 1 Review of investigations

Variable	Day of Indoor stay			
	Day 1	Day 2	Day 4	Day 6
Hemoglobin (g/dl)	10	9.9	9.5	8.6
White cell count (per mm ³)	3,500	3,100	1,000	2,000
Differential count (%)				
Polymorphs	81	80	92	86
Lymphocytes	15	11	5	8
Eosinophils	3	2	1	2
Basophils	0	0	0	0
Monocytes	1	7	2	4
Platelet count (per mm ³)	100,000	60,000	42,000	50,000
Smear	Schistocytes few		Macrocytes 1+ Tear drop cells 1+	
Reticulocyte (%)			0.9	
Activated partial thromboplastin time (sec)				
Test			42.8	
Control			30	
Prothrombin time (sec)				
Test			19	
Control			11	
Fibrinogen (mg/dl)			80	
Alanine transaminase(U/l)	45	56	287	
Aspartate transaminase (U/l)	71	240	443	
Alkaline phosphatase (U/l)	96	128	110	
Bilirubin (mg/dl)				
Total		4.3	8.4	
Direct		2.5	5.3	
Lactate dehydrogenase (u/l)			1,888	
Ferritin (ng/ml)			38,000	
Total cholesterol (mg/dl)			150	
Triglyceride level (mg/dl)			800	
Creatinine (mg/dl)	1.4	1.8	2.2	5.4

improvement of coagulation parameters. Artesunate, ceftriaxone, Vitamin K and metronidazole were administered.

Day 2 of MICU stay (fourth day of indoor stay) Patient continued to have fever with maximum recorded temperature of 39.5°C with no improvement in sensorium. Blood cultures were negative clot culture for salmonella typhi came back negative. Immunological investigations like antinuclear antibody, rheumatoid factor, anti neutrophil cytoplasmic antibody were negative. Viral screen which included Hepatitis B surface antigen, Human immunodeficiency virus and hepatitis C antibody were negative.

In background of pancytopenia, elevation of ferritin and triglyceride level a bone marrow aspirate was done. Findings on Wright Giemsa aspirate examination showed hypercellular marrow with decrease in erythroid precursor, Dysplasia of myeloid series, pseudopelger heut cells and decrease megakaryocytes. There was increase in

Fig. 1 Macrophage with marked hemophagocytic activity

Fig. 2 Nuclei of RBC and WBC precursor cells, within cytoplasm of macrophage

macrophage activity with marked hemophagocytosis with nucleated cells within its cytoplasm (Figs. 1 and 2).

A diagnosis of hemophagocytic lymphohistiocytosis was made as he satisfied 6 out of 8 criteria (Table 3) in light of laboratory and bone marrow findings. Patient was started on dexamethasone and etoposide, however, his blood pressure continued to drop while on inotropes, there was severe lactic acidosis, oliguria with creatinine of 5.4 mg/dl. Patient succumbed on day 4 of ICU stay.

Discussion

Hemophagocytic lymphohistiocytosis is a syndrome characterized by unbalanced expansion and activation of histiocytes and lymphocytes resulting in hypercytokinaemia, haemophagocytosis which can be either inherited or acquired.

HLH occurs in all age groups. It is classified into genetic (primary) or acquired (secondary) Table 2 [1].

Primary/Genetic HLH [2]

It is further subclassified as familial or due to distinct immune deficiency syndrome which can be inherited either as autosomal recessive or X linked manner.

- A) FHLH is characterized by male preponderance, 80% presenting below 1 year of age; and less than 10% symptomatic within the neonatal period. As an autosomal recessive disease, it is found especially in ethnic groups where consanguineous marriages are common. Five mutations leading to FHLH have now been identified and the underlying genetic defect described for four of these in genes namely PFR1, UNC13D, STX11 and STXBP13 for FHLH 2-5, respectively [3].
- B) Immune deficiency HLH present sporadically, these disorders have a defect in cell mediated cytotoxicity which prevents efficient removal of antigens, resulting in ongoing stimulation of immune response and hypercytokinemia.

Secondary/Acquired HLH

HLH has been associated with viral, bacterial, protozoal and fungal infection. Infectious HLH been associated even with primary infection; Epstein Barr Virus associated with fulminant course in children with XLH. When associated with rheumatic diseases systemic onset juvenile idiopathic arthritis, SLE and Kawasaki Disease it is classed as macrophage activation syndrome (MAS). Other causes include malignancy like lymphoma, leukemia and Human immunodeficiency (HIV) [2, 3].

Clinical Features

Fever, hepatosplenomegaly and cytopenias are cardinal features of HLH. Jaundice, transaminitis and cerbromeningeal HLH are seen in 30% at presentation. As seen in our patient clinical picture resembles that of sepsis hence HLH should be suspected when symptoms donot respond to treatment. Diagnostic criteria for HLH Table 3 [4].

Treatment options include a pro-apoptotic chemotherapy based regimen as per the HLH protocols of the Histiocyte Society. The HLH-94 and HLH-2004 trial protocols of the Histiocyte society are both based on use of corticosteroids, etoposide and cyclosporine A. In HLH 2004 protocol initial

Table 2 Classification of HLH

Genetic/primary		Acquired/secondary
Familial	Sporadic	Infectious
Known	Chiedak Higashi syndrome	Autoinflammatory/macrophage activation syndrome
Defects	Griscelli syndrome type 2	Malignancy
FHLH ^a 1–5	X linked lymphoproliferative disorder 1	Immunosuppression
Defects	X linked lymphoproliferative unknown disorder 2	Metabolic

^a FHLH Familial hemolymphohagocytosis

Table 3 Diagnostic criteria for hemophagocytic lymphohistiocytosis

1. Fever^a
2. Splenomegaly^a
3. Cytopenia affecting two or more blood-cell lineages^a
4. Hypertriglyceridemia, hypofibrinogenemia, or both^a
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes^a
6. Natural killer cell activity low or absent
7. Ferritin $\geq 500 \mu\text{g/l}^a$
8. Soluble interleukin-2 receptor (CD25) $\geq 2400 \text{ U/ml}$

^a Criteria satisfied by this patient

8 week induction protocol using dexamethasone, etoposide and earlier addition of cyclosporine unlike HLH 1994. Patients with evidence of continued or progressive central nervous system involvement after 2 weeks of systemic therapy require intrathecal therapy with methotrexate combined with corticosteroid induction followed by hematopoietic stem cell transplantation. Targeted immunotherapy which includes antithymocyte globulin, Anti IFN α

monoclonal antibody, immunoglobulins and rituximab is being explored [1, 5].

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