Case Report

A Rare Case of Macrophage Activation Syndrome in a Neonate

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Abstract

Macrophage activation syndrome is excessive proliferation of macrophages associated with hemophagocytosis in bone marrow. It is characterized by fever >38.5°C for ≥7 days, splenomegaly, cytopenias (≥2 lineages), hypertriglyceridemia/ hypofibrinogenemia & hemophagocytosis. MAS occurying in neonatal period is very rare & only 2 sporadic case reports are available.We report a case of a neonate with MAS who presented with unremitting fever, hepatosplenomegaly, cytopenia, hyperferritinemia, with bone marrow suggestive of Hemophagocytosis.

Keywords: Macrophage Activation Syndrome, Hemophagocytic Lymphohistiocytosis, Cytopenia, Hemophagocytosis

Introduction

MAS is caused by excessive activation & proliferation of well differentiated macrophages, T-lymphocytes & overproduction of cytokines particularly TNF. It is characterized by fever >38.5°C for ≥7 days, splenomegaly, cytopenias (≥2 lineages), hypertriglyceridemia/ hypofibrinogenemia & hemophagocytosis [1,2,3,4,5,6,7,8,9]. It is a very rare disorder & only 2 sporadic case reports with neonatal presentation are available [10,11]. MAS in older children usually occurs secondary to infections, neoplasms or rheumatic disorders [2,12,13,14,15,16,17,18,19,20,21]. Macrophages showing active hemophagocytosis are observed in bone marrow aspirate [6,14,19,22,23,24,25,26,27]. Incidence of MAS is approximately 1.2 cases per 1,000,000 individuals per year among pediatric population [28].

Case

A 2200 g female baby (37 weeks of gestation) was second born to healthy & unrelated parents with an uneventful pregnancy through vaginal delivery. There was no history of autoimmune disorders in the parents. On day 12 of life, she developed fever associated with decreased feeding & excessive crying. She was treated symptomatically with intravenous antibiotics. Her investigations done at this time showed anemia (Hb 10.4 g/dl), associated with thrombocytopenia (platelets 1.1 lakh/cu.mm). CRP was high (35.8 mg/l). Her subsequent investigations showed dropping platelet count and persistent anemia. In view of hepatosplenomeagly on clinical examination, USG Abdomen was done which showed enlarged Liver (8.3cm) & spleen (6.4 cm). Workup for malaria & dengue were negative. Her LFT done showed raised alkaline phosphatase. Ferritin was high (563.6 ng/ml). Triglycerides was high (397 mg/dl) & Fibrinogen was low (167 mg/dl). Despite initial treatment, the patient's condition did not improve & fever persisted for more than 7 days. In view of cytopenia, hyperferritinemia, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia & unremitting fever, a differential diagnosis of was considered. Immune deficiency panel was done which showed decreased CD3, CD4 & CD8 levels. Metabolic investigation & TORCH profile were normal. Peripheral smear showed moderate anisopoikilocytosis & platelets markedly decreased. Bone marrow aspiration showed macrophages with phagocytosed platelets & red cells. Perls stain showed decreased iron stores. Marrow cytology favoured hemophagocytosis. Trephine biopsy was done which showed very few foci of cellularity showing sparse hemopoetic foci. Symptomatic therapy with combined platelet & erythrocytes transfusion was administered. The baby is planned for cyclosporine therapy in view of MAS. The baby is on treatment and is on regular follow up.

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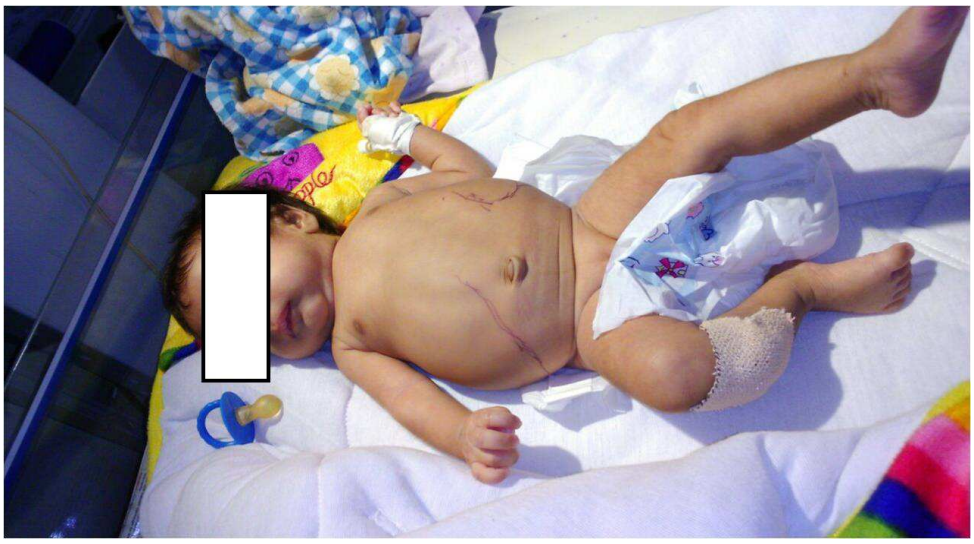
Table 1- Laboratory Profile

Column1	HB	WBC	PLT	CRP	RET	SGPT	SGOT	SAP	ALB	CD19	CD3	CD4	CD8	IGG	IGM	IGA	FIB	FER	TG
9-Oct	10.4	17900	110000	35.8															
10-Oct	10.2	22100	45000	42															
11-Oct	8.7	15,900	75000	22.5															
13-Oct	9.2	22,100	100000	16.2															
15-Oct	8	19,600	80000	5.6															
19-Oct	7.7	33,000	80000	38.4															
20-Oct	12.6	32,500	45000	17.4															
21-Oct	10.3	14,400	40000	5.9						59	33	25	7						
22-Oct					4	51	94	544	3.5										
23-Oct			39000																
24-Oct	8.2		44000	14.5										460	53	<40			
27-Oct				11.9															397
28-Oct	7.8			19.5													167	563.6	

Figure 1: Baby with Hepatosplenomegaly



Discussion

HLH was first described in 1952 by Scottish pediatricians James Farquhar & Albert Clarieaux, who encountered 2 infants with cytopenias, hepatosplenomegaly & unremitting fevers [9,29]. The term "macrophage activation syndrome" was introduced by Stephan et al., in 1993 [2]. Reactive hemophagocytic lymphohistiocytosis is a term which is interchangeably used with MAS [5,14,19,23,26,30,31,32,33].

Diagnosis

The diagnosis of HLH, as defined by Henter et al., includes five major criteria: 1) fever > 38.51^{o}C for ≥7days, 2) splenomegaly, 3) cytopenias (≥2 lineages), 4) hypertriglyceridemia/ hypofibrinogenemia & 5) hemophagocytosis [34]. All 5 criteria were positive in our case.

Parodi et al., gave a diagnostic criteria including1) Fever, 2) Splenomegaly, 3) Cytopenia ≥ 2 cell lines, Hemoglobin <120 g/L, Platelets <100 x 10^{9}/L, Neutrophils <1 x 10^{9}/L, 4) Hypertriglyceridemia &/or hypofibrinogenemia, Fasting triglycerides >3 mmol/L, Fibrinogen <1.5 g/L, 5) Ferritin > 500 mg/L, 6) Soluble interleukin-2 receptor (sCD25) >2400U/ml, 7) Decreased/ absent NK cell activity, 8) Hemophagocytosis (increased in bone marrow, liver, lymph nodes). 5 of the above 8 clinical & laboratory criteria are diagnostic of MAS [35]. 6 out of 8 criteria were positive in our case.

According to Histiocyte Society protocol, five of the following should be fulfilled [27,30,36] 1) Fever for ≥7 days, 2) Splenomegaly, 3) [Cytopenia (≥2 lineages), anemia (Hb <9.0g/dL], 4) [Hypertriglyceridaemia (≥265 mg/dL) &/or hypofibrinogenaemia (<1.5g/L)], 5) Hemophagocytosis , 6) Low/ absent NK cell activity, 7) Hyperferritinemia (≥500µg/L), 8) Increased soluble CD25 >2400units/mL. 6 out of 8 criteria were positive in our case. Hyperferritinemia is known to be remarkable heralding MAS [16,37]. The aetiology for depletion of haemoglobin, WBCs & platelets are haematophagocytosis, inhibitory lymphokines & depression of progenitor cell proliferation [3,38,39,40]. In

a series by Reiner AP et al.,[38] only platelet count had a dramatic fall.

Treatment

High dose corticosteroid treatment & Cyclosporin are the suggested initial treatment of choice for MAS[1,2,9,41,42,43,44,45,46,47,48,49].

Conclusion

Hemophagocytic syndrome should be taken into account in the differential diagnosis of fever with an obscure etiology. Mortality is high, even among patients who are treated. Thus, early recognition & treatment is essential to decrease the associated morbidity & mortality.

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