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CASE REPORT

Hemophagocytic Lympho Histiocytosis (HLH)

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Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyper-inflammatory condition caused by a highly stimulated, but ineffective immune response, characterized by a dys-regulated activation and proliferation of macrophages leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes and their hematopoietic precursors throughout the reticulo-endothelial system. HLH is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly and hemophagocytosis in bone marrow, liver, or lymph nodes. HLH also occurs as a complication of rheumatic diseases and of malignancies. Awareness of the clinical symptoms and of diagnostic criteria for HLH (Histiocyte society; HLH study 2004) is crucial to starting life-saving therapy in time. We have reported a case of 7-year-old male child presenting with respiratory distress, distension of abdomen and deep jaundice. This case report may be an eye opener to the pediatricians and other physicians to recognize this rare entity of infection triggering fatal HLH and thus proper treatment may be instituted in those affected with this disease at the earliest.

Key Words: Fever; hepatosplenomegaly; lymphadenopathy; hemophagocytes in bone marrow; pancytopenia; thrombocytopenia; hyper ferritenemia; hypofibrinogenemia.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes that commonly appears in infancy, although it has been seen in all age groups. Fever, hepatosplenomegaly, pancytopenia, and lymphadenopathy often comprise the initial presentation. Incidence is estimated to be approximately 1.2 cases per million individuals per year[1]. It may present as Primary or Secondary. The Primary hemophagocytic lymphohistiocytosis is the Familial erythrophagocytic lymphohistiocytosis [FEL] which is inherited in the form of heterogeneous autosomal recessive manner. The Secondary hemophagocytic lymphohistiocytosis is an acquired hemophagocytic lymphohistiocytosis that occurs after strong immunologic activation, such as that which can occur with systemic infection, immunodeficiency, or any underlying malignancy. Both forms are characterized by the overwhelming activation of normal T lymphocytes and macrophages, invariably leading to clinical and hematologic alterations and death in the absence of treatment.

CASE REPORT

A 7-year-old male child weighing 18kg born after a full term normal vaginal delivery with a birth weight of 3 kg was referred to our institute with the history of fever, abdominal distention, deep jaundice and decreased appetite of 20 days duration. The child was apparently normal 20 days back, then he started having continuous fever of magnitude of 102°-04° C, without diurnal variation and not associated with chills and rigor. The child was treated with intravenous antibiotics for 10 days before he reported to our hospital. Also, the child had received injectable antimalarial drugs in adequate doses. Distention of abdomen started along with fever. The distention was gradually increasing. Urine frequency was normal. The child also had history of yellowish discoloration of both eyes since 15 days. Appetite gradually decreased. The urine was high colored. It was associated with non-bilious, non-projectile vomiting. On examination, he was conscious, febrile (102°F) and tachypneic (RR-34/min), with rt. axillary apical lymph nodes palpable >1cm diameter and bilateral inguinal lymph nodes palpable >1.5cm diameter. There was no cyanosis, odema and JVP was not raised. Pulse 120/min, regular, normovolumic, all peripheral pulses palpable with BP-100/60 mm Hg in Rt upper arm in supine position. Abdominal examinations revealed hepatomegaly (Liver span of 20 cm). Liver is firm, smooth margin and non-tender. Spleen is also enlarged (8 cm below LSCM) and firm. Shifting dullness and Fluid thrill were present. Normal Bowel sounds heard. All other systems revealed no clinical abnormality. Fundoscopy was normal.

CBC examination revealed Hb of 5.9 g/dl and TLC of 4.48 (10^3 U/L); RBC of 2.32 (10^6 U/L) with N: 47.6%; L: 50.6%; M: 0.7%; E: 0.4%; B: 0.7%. With ESR

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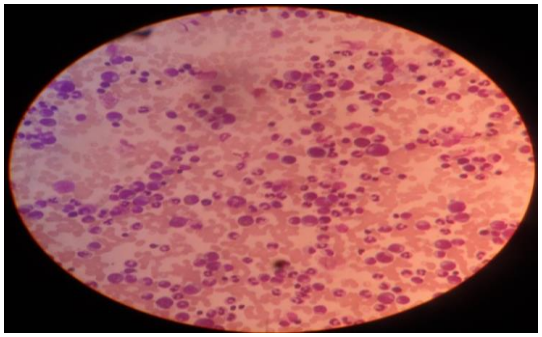
18 mm/1st hour. He had thrombocytopenia, with platelet count of 79 (10^ 3 U/L). Peripheral smear report showed atypical lymphocytes seen in 2 to 3%, Thromboctopenia of moderate degree and hypochromic microcytic anemia of moderate degree. Urine routine examination revealed normal findings. Liver function tests revealed Serum bilirubin direct: 4.7 mg/dl, Serum bilirubin Total: 6.6 mg/dl, SGOT/AST: 1232 U/L, SGPT/ ALT: 622 U/L, Alkaline Phosphatase: 108 U/L, Serum total protein: 5.2 g/dl, Serum albumin: 2g/dl. APTT: 57.4 sec, PT: 44.5 sec, INR: 1.11. RFT was normal. RBS- 106 mg/dl; with normal calcium and electrolyte levels within normal limit except for low sodium level. Blood and urine culture were sterile. Chest X-ray revealed no abnormality. Sonogram of whole abdomen revealed Minimal ascitis with Hepatosplenomegaly. From clinical finding & preliminary investigation, hematological malignancy was suspected and bone marrow examination was done. Bone marrow examination revealed no abnormality and bone marrow for Kala Azar K (39) was negative. So, we proceeded for further evaluation. Antinuclear antibody, viral markers for human immunodeficiency virus (HIV), hepatitis A, B, C and E, serology for Weil's and dengue, Widal test, rapid malarial test, Mantoux test, gastric lavage for AFB were negative. Thyroid profile was normal. Suspecting HLH, we have done Serum Ferrritin level (elevated with value of 10,887.7ng/ml) and serum fibrinogen level (decreased value 137 mg/dl). Serum Triglycerides level were also elevated with 490mg/dl. Serum cholesterol value was 216mg/dl. Compiling the clinical pictures and investigations and following the Histiocyte society; HLH study 2004 criteria we have given a provisional diagnosis of HLH and treatment was given as per the guideline. In view of persistent fever, gross hepatosplenomegaly, anemia, thrombocytopenia, hyperferritinemia, hypofibronigenimia and bicytopenia, a diagnosis of hemophagocytic lymphohistiocytosis was made.

The case was managed with injectable antibiotics covering both gram positive and negative organism (Piperacillin and Tazobactum and Netilmicin). There was no clinical improvement within 3 days of antibiotics. High dose Methylprednisolone (30 mg/ kg) was given after 72 hours of Antibiotics for 3 days. The clinical wellbeing of the child improved after administration of Methylprednisolone. The Cytopenia resolved gradually within a period of 15 days. On day 15 of admission the child was discharged without any complications. Follow up done at 1month and 3months the child is gaining weight with normal hematological parameters.

DISCUSSION

HLH is a potentially fatal hyper-inflammatory condition caused by a highly stimulated, but ineffective immune response, characterized by a dys-regulated activation and proliferation of macrophages leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes and their hematopoietic precursors throughout the reticulo-endothelial system.[2]



Normal Bone Marrow Picture

It may occur as Primary (familial) or Secondary. The familial form of HLH, the onset usually in infancy or early childhood <4 years (but may present at any age). It is autosomal recessive (chromosome no.-9q 33-34.1). It is also characterized by severe immunodeficiency. The Secondary form of HLH, commonly present at a later age (but may also present at any age). It occurs in association with severe infections (virus, bacteria and protozoa), malignancies, rheumatologic disorders and some metabolic disorders.[3]

Triggers of Macrophage Activation Syndrome (Infections Associated with Hemophagocytic Syndrome) [3,4]

Triggers / Infection Associated	Specific Agents
Viral infections	Adenovirus, Cytomegalo virus, Dengue virus, Ebstein-barr virus, Herpes Simplex virus (HSV1, HSV2, HSV6, HSV 8), Human Immunodeficiency virus, Parvovirus B19, Varicella –Zoster virus, Hepatitis virus.
Bacterial infections	*Babesia microti, Brucella abortus, Enteric Gram-negative rod, Hemophilus influenza, Mycoplasma Pneumonia, Staphylococcus aureus, Streptococcus pneumoniae*
Fungal infections	*Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum*
Mycobacterial	*Mycobacterium tuberculosis*
Rickettsial	*Coxiella brunetii*
Parasitic	*Leishmania Donovani*
Drugs	Sulphasalazine, Aspirin, Mornifulmate, indomethacin, other NSAIDs, Penicillamine, Gold salts, Etanercept, Phenytoin, Intravenous soluble lipids.

There is overwhelming activation of normal T cells and macrophages which can cause clinical and hematological alterations. The pathological hallmark of this disease is the

aggressive proliferation of activated macrophages and histiocytes, which phagocytose other cells, namely RBCs, WBCs and platelets, leading to the clinical symptoms. The uncontrolled growth is nonmalignant and does not appear similar to the lineage of cells in Langerhans cells histiocytosis (histiocytosis X). The spleen, lymph nodes, bone marrow, liver, skin and membranes that surround the brain and spinal cord are preferential sites of involvement. In viral- associated HLH, infection of T lymphocytes results in clonal proliferation and production of high levels of activating cytokines. There is elaboration of TNF-ά and IFN-ɣ which contributes to macrophage activation causing fever and systemic illness. The pathophysiology of Infection-associated HLH following infection with non-viral pathogens may also be related to the production of high levels of activating cytokines by host lymphocytes and monocytes ([5]). Death is inevitable in the absence of treatment. The clinical entity has to be suspected when patients present with fever unresponsive to antibiotics, general fatigue, pancytopenia of unknown origin and liver dysfunction with elevated ferritin.

***Diagnostic criteria for HLH (Histiocyte society; HLH study 2004)*[3]**

Presence of any one of the following:

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

OR

2) Having 5 out of 8 of the following:
   a) Fever ≥38.5°C for ≥ 7 days
   b) Splenomegaly >3cm
   c) Cytopenia affecting ≥ 2 cell lineages, hemoglobin ≤ 10g/dl
   d) Hypertriglyceridemia (>285 mg/dl) and/or hypofibrinogenemia ≤ 150mg/dl
   e) Hemophagocytosis in bone marrow, spleen, lymph nodes without evidence of malignancy.
   f) Low or absent NK cell cytotoxicity
   g) Hyper ferritinemia (≥ 500 mg/dl)
   h) Elevated soluble CD25 (IL-2Rc chain; ≥2,400 U/l)

In our case, almost all criteria were present except for the demonstration of Hemophagocytes in bone marrow.

Following shows the study of percentage of patients affected in different lineages [6]

Clinical features	**Shawney *et al.*,**	**Stephan *et al.*,**	**Emmenegger *et al.*,**	**Ravelli *et al.*,**	**Our case**
Fever	100	100	89	94	Yes
Skin rash	44.4	4.2	45	65	No
Hepatomegaly	88.9	58	44	88	Yes
Spleenomegaly	88.9	100	61	59	Yes
Lymphadenopathy	66.7	33	64	41	Yes
Hemorrhages	11.1	16.6	-	23	No
Liver dysfunction	88.8	98	89	-	Yes
Pulmonary involvement	33.3	50	44	-	No
Renal involvement	33.3	16	62	-	No
Cardiac involvement	-	42	-	-	No
Neurological dysfunction	22.2	50	-	-	No
Laboratory findings					
Anemia	88.8	-	70	82	Yes
Leukopenia	-	-	28	56	No
Thrombocytopenia	88.8	95.8	47	88	Yes
Coagulopathy	66.6	83.3	62	-	Yes
Reduced erythro-sedimentation rate	33.3	12	-	60	No
Elevated transaminases	88.8	98	-	94	Yes
Elevated bilirubin	33.3	-	82	46	Yes
Elevated lactate dehydrogenase	-	-	-	87	Yes
Hypoalbuminemia	-	-	-	15	Yes
Hypofibrinogenemia	22.2	100	-	89	Yes
Hypertriglyceridemia	-	100	-	86	Yes
Low sodium levels	-	-	-	58.3	Yes
Hyperferritinemia	-	-	97	100	Yes
Histopathological marker					
Hemophagocytosis in bone marrow	44.4	58.3	80	83.3	No

In early initial phases of the disease, we may not find Hemophagocytes in the bone marrow. [7]

The immediate aim of therapy in MAS is to suppress the uncontrolled hyper inflammation with immune suppressive / immuno modulatory agents or cytotoxic drugs. The combined use of immunosuppression and chemotherapy must interrupt the inflammatory cascade resulting in life-saving.

Primary forms of MAS can be treated following a standardized protocol called HLH-94 which

was developed in 1994 by the Histiocyte Society and modified in 2004[8,9]. Genetic cases can otherwise be cured with stem cell transplantation. A general therapeutic protocol for MAS is not available: first line treatment is usually represented by parenteral administration of high dose corticosteroids (intravenous infusion of methylprednisolone at the dose of 30mg/kg/day or 1g/m² for 3 to 5 days). Mild forms are reported to respond steroids alone in association with supportive medicaments. Steroid –resistant cases or the most severe forms of MAS require the addition of cyclosporine A: treatment usually begins with the intravenous infusion of 3-7 mg/kg/day, shifted to the oral administration after few days, but the whole duration of therapy cannot be foreseen. Corticosteroids and cyclosporine are the most used drugs in MAS due to their clinical efficacy, but other therapeutic regimens have been studied such as high-dose intravenous immunoglobulins, antithymocyte globulins, etanercept, etoposide and plasmapherasis[10,11]. Determination of hemoglobin, white blood cells and platelets are recommended at least every 2 weeks in the follow-up because cytopenia might be a possible marker of MAS reactivation. A relapse of the disease can also be suggested by elevated serum transaminases, ferritin and triglycerides or fever recurrence.

Recent case reports show promising results with an anti-TNF-α approach and plasmapheresis. Supportive care is needed to ensure that the patient with HLH remains stable until a bone marrow donor can be found. This includes transfusions of RBCs, platelets, and fresh frozen plasma, as well as nutritional support in addition to the treatment protocol[12]. This case is presented to enlighten Pediatricians and other physicians regarding the clinical entity of hemophagocytic lymphohistiocytosis to be kept in mind, when patients present with fever unresponsive to antibiotics, organomegaly, pancytopenia of unknown origin and liver dysfunction with elevated ferritin.

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