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Case Report

A CASE REPORT OF PEDIATRIC HLH MIMICKING CHRONIC LIVER DISEASE

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ABSTRACT:
Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome characterized by reactive hyperactivity of cytotoxic T cells and histiocytes, leading to hypercytokinemic injury to cells and organ system, which leads to multiorgan dysfunction and ultimate failure. It is characterized by fever, pancytopenia, splenomegaly and hemophagocytosis in bone marrow, liver or lymph nodes. It has been associated with viral, bacterial, fungal and parasitic infection. Although an early diagnosis and treatment is the key to decrease the mortality but it is difficult to diagnose this case as it involves numerous laboratory tests which are non specific. We report a case of hemophagocytic lymphohistiocytosis in a 4 year old male child presenting with prolonged fever, pancytopenia, hepatosplenomegaly, progressive swelling of the abdomen, decreased urination and pedal edema. Based on our patient's presentation and initial laboratory findings, which revealed cytopenias, hypertriglyceridemia, hypofibrinogenemia, absent natural killer (NK) cell activity, high serum ferritin level; a diagnosis of HLH was made. He was started on broad-spectrum antibiotics, antifungals, and dexamethasone. In spite of all efforts, within short span the child developed MODS and succumbed. Thus early diagnosis and prompt treatment can bring hope in this type of life threatening condition.

Keywords: pancytopenia, hepatosplenomegaly, hemophagocytosis, hypofibrinogenemia

INTRODUCTION:

Hemophagocytic lymphohistiocytosis (HLH) is an infrequent but potentially life-threatening hematological disorder associated with an excessive systemic inflammatory response [1, 2]. It is caused by uncontrolled activation and proliferation of macrophages, lymphocytes, and dendritic cells, resulting in hemophagocytosis and cytokine storm[3,4].HLH can occur as a primary disorder, caused by a genetic mutation, or as secondary sporadic cases triggered by infection, autoimmune diseases, immunodeficiency, or malignant diseases. Signs and symptoms of HLH are nonspecific and usually compatible with other common diseases such as infections, tumors and rheumatological diseases.[5,6] HLH should be included in the differential diagnosis of other clinical conditions such as: (1) fever of unknown origin, (2) hepatitis with coagulopathy (3) sepsis with multiple organic failure, (4) lymphocytic encephalitis.[7]. This case is being presented to highlights the severity of the disease.

CASE REPORT:

A 4-year-old male child born out of 2° consanguineous marriage with normal perinatal and developmental history was admitted to the casualty with complaints of fever and progressive swelling of the abdomen for 4 months, decreased urination, and pedal edema for 7 days with a history of 1 unit of blood transfusion at the referral center. On examination, our patient was having HR-112/minute,regular,BP-98/70 mmHg,RR-24 breaths/minute and spo2-98% on room air.He had some pallor, icterus, bilateral pitting pedal edema and no lymphadenopathy. The anthropometric assessment was consistent with severe stunting Per-abdomen examination revealed ascites with massive firm non-tender splenomegaly(7cm below left costal margin) and firm non-tender hepatomegaly having span of 12cms. Other systemic examination was normal.

This patient was referred to us from another medical college as a case of chronic liver disease. Preliminary investigations had done by them which showed pancytopenia with deranged LFT but normal HPLC and

BM status. CECT abdomen was suggestive of chronic liver disease. After receiving the case, the child was offered with supportive medications, iv antibiotics and diuretics. Lab investigation showed pancytopenia. Beacause of HSM and history of blood transfusion, Gaucher's disease was suspected but glucocerebrosidase activity came as normal.In view of persistence of fever we have excluded the possibility of leukemia, Disseminated TB, scrub typhus and hemolytic anemia. Further investigations showed high ferritin, triglycerides, hypofibrinogenemia, and flow cytometry suggestive of low NK cell activity.(Table-1) So, we arrived at a final diagnosis of secondary HLH. Meanwhile patient developed pneumonia and two episodes of convulsions. Under the umbrella of antibiotics; Injection dexamethasone, etoposide regimen was started along with inj phenytoin to control seizure. Later patient developed severe respiratory distress, was intubated, and put on mechanical ventilation. He was continued on vasopressors to maintain his blood pressure, the rest of his regimen was revisited, Fluconazole and cefepime were added for prophylaxis secondary to his cytopenias. His condition continued to deteriorate; Finally, he developed hypoxia unresponsive to ventilator support and succumbed to hemophagocytosis syndrome on day 7 of admission.

Table: 1

LAB WORK UP	DAY-1	DAY-3	DAY 6
HB	6gm	6.8	6.6
TLC(N/L)	2.7	2.7(29/59)	4.1(52/41)
PLT	25	24	78
Sr Cr	0.5	0.37	
Sr Urea	25	12.7	
SGOT/SGPT	70/36	50/134	
TB	1.0	5.16	
DB	0.3	2.76	
ALP	712	1434	
TP/ALB	3.8/1.6	3.3/1.6	
Sr Na/k/ca	135/3.5/8.6	138/2.96/0.96	
CRP	2.0	6.3	
ESR	5mm/hr		
INR	1.76		
PT/APTT	20/15		
Sr FERRITIN		>2000ng/ml	
Sr TGs		385	
NK Cell act		absent	
Sr fibrinogen		73	

DISCUSSION:

Hemophagocytic lymphohistiocytosis (HLH) is an immunological disorder characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in bone marrow, liver, or lymph nodes along with hyperferritinaemia, hypercytokinaemia, hypofibrinogenaemia, hypertriglyceredimia, multi-organ failure. In order to improve the diagnosis of HLH, the Histiocyte Society published diagnostic guidelines in 1991, which were expanded in 2004 [7]. As per the revised criteria, five of the eight criteria are required to fulfil a clinical diagnosis of HLH, although patients with a molecular diagnosis, that is, one of the known FHL mutations, do not necessarily need to fulfil the diagnostic criteria (Table 2) [8].

Table: 2

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 ≥ 2 cell lineages; hemoglobin ≤ 9 g/dL [or ≤ 10 g/dL for infants < 4 wk of age], platelets < 100,000/μL, neutrophils < 1,000/μL) d) Hypertriglyceridemia (≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL) e) Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy f) Low or absent natural killer cell cytotoxicity g) Hyperferritinemia (≥ 500 ng/mL) h) Elevated soluble CD25 (interleukin-2Rα chain; ≥ 2,400 U/mL)

This case fulfilled 6 out of 8 criteria for the diagnosis of HLH. Fever, splenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia and absent NK cell activity were the six criteria which were positive in this child. This child had also features of sepsis and so he was started on antibacterial therapy. Since he was severly stunted and also having massive hepatosplenomegaly, storage disorder also suspected and ruled out. Later he did not respond to the best of antibiotics and supportive care, the suspicion of HLH was raised. Patients presenting in acute state to the general pediatrician or pediatric intensive visit with a clinical picture of likely sepsis (fever, laboratory evidence of inflammatory response, coagulopathy and thrombocytopenia)should be appropriately investigated and managed for sepsis, but the possible diagnosis of HLH should be borne in mind, particularly in the child who deteriorates despite maximal therapy. In addition upto 30% of cases can present with neurological symptoms and signs. This child developed encephalopathy later which is also a marked feature of HLH. Here the prolonged duration of fever for 4 months was due to HLH per se and there was also hepatic involvement at presentation, which progressed to involve CNS, later developed MODS and succumbed.

CONCLUSION:

HLH is an acute, rapidly progressive, potentially life-threatening syndrome. In a background of prolonged fever, organomegaly along with cytopenia simple investigations like high Ferritin(in thousands),high Tgs, low fibrinogen, low albumin will point towards HLH. Early detection and prompt treatment is necessary to prevent progression of disease and increasing disease free survival.

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