Case Report

A case of herpes simplex induced hemophagocytic syndrome

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Abstract

Hemophagocytic lymphohistiocytosis / hemophagocytic syndrome is a condition that mimics sepsis and hence can be easily missed. It is characterized by a highly stimulated but ineffective immune system. The presence of macrophages engulfing red blood cells i.e) hemophagocytosis on a bone marrow smear is pathognomonic. However, demonstrating the same on a bone marrow smear may require multiple bone marrow biopsies. Another hallmark of this condition is hyperferritinemia. If left untreated, HLH is potentially life threatening. A high degree of suspicion is and prompt treatment improve survival rates. Here, we describe a case of Herpes Simplex induced Hemophagocytic Syndrome.

Key words: hemophagocytosis, herpes simplex, thrombocytopenia, hyperferritinemia.

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INTRODUCTION

Hemphagocytic lymphohistiocytosis/ Hemophagocytic syndrome is characterized by a highly stimulated but ineffective immune system. The presence of hemophagocytosis or macrophages engulfing red blood cells on a bone marrow smear is pathognomonic of this condition. Other clinical features may resemble that of severe sepsis and can be fatal. Here, we describe a case of Viral Associated Hemophagocytic Syndrome.

CASE REPORT

An 18 year old student had been referred to our hospital ER as a case of dengue induced thrombocytopenia with suspected dengue encephalitis. A whole blood count done outside revealed Hemoglobin of 8.1 gm% , total counts of 3450 cells/cu.mm and platelets of 22, 000 per cu.mm. Viral serologies done at the outside hospital were pending. Repeat counts done in our hospital revealed Hemoglobin of 8 gm%, total counts of 800 cells per cu.mm and a platelet count of 45,000 per cu.mm. Initial routine evaluation also revealed elevated liver enzymes. All features were initially consistent with a diagnosis of dengue. Dengue serology was negative. Blood and urine cultures were sterile. Peripheral smear was negative for malarial parasite and malarial antigen was negative. Serologies for scrub typhus and Leptospira were also negative. ANA was negative. HIV ELISA was negative. HBsAg and Anti-HCV were negative. Initial chest X-ray was normal. Ultrasound abdomen done revealed hepatosplenomegaly. On day two of admission, patient developed one episode of GTCS in the ward following which he was shifted to the intensive care unit. Repeat counts done revealed Hemoglobin of 7.6 gm%, total white blood cell count of 1360 cells/cu.mm and platelet count of 75,000 cells/cu.mm. In the setting of thrombocytopenia, an intracranial hemorrhage had to be excluded and hence a CT brain was done and found to be normal. The possibility of viral encephalitis was considered and patient was empirically started on IV Acyclovir along with anti- epileptics. A lumbar puncture was done which showed decreased sugar and elevated protein along with lymphocyte predominance in the CSF. In view of one episode of ? GTCS at the hospital he was previously admitted in, CSF IgM HSV I was sent there and found to be positive. Patient started developing mucosal bleeding. Repeat platelets were found to be 30,000/cu.mm. Patient received platelet transfusions in

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view of active bleeding. Chest X-ray revealed a pulmonary contusion of day 4 of admission.

Figure: Gum bleeding that patient developed on day 3 of admission

The possibility of VAHS was considered. Serum ferritin, fibrinogen and triglycerides were sent. Serum ferritin was greater than 16,500 ng/ml. Serum triglyceride value was 220 mg/dl. A guarded bone marrow aspiration and biopsy was performed which however did not show evidence of hemophagocytosis. A repeat bone marrow biopsy was not done as patient's platelets were continuing to drop. In view of the elevated serum ferritin level, pancytopenia, fever and hepatosplenomegaly, a diagnosis of VAHS was made and the patient was started on IV corticosteroids and later switched to oral steroids. Patient recovered as he became afebrile and his counts normalized. In view of shortage of patient funds, patient was referred to the government cancer institute for chemotherapy with dexamethasone, etoposide and cyclosporine A.

DISCUSSION

Hemophagocytic lymphohistiocytosis is an aggressive and sometimes fatal disease which mimics sepsis and autoimmune disorders. Incidence of HLH is more among children than adults. Childhood HLH is strongly associated with underlying genetic disorders in contrast to HLH in adults. HLH occurs due to lack of perforin-dependent cytotoxicity secondary to impaired function of cytotoxic T- cells and NK- cells. When immune response is normal, viral antigens are presented by antigen presenting cells (APC's) to CD4+ and CD8+ cells which causes T cell activation, proliferation and differentiation during which cytokines such as IFN- gamma, IL-6 and IL-10 are released. These cytokines activate more APC's and continue to promote antigen presentation. This process is inhibited by cytotoxic T cells and NK cells via perforin dependent mechanisms. In HLH, the impaired function of the cytotoxic T cells and NK-cells, causes uninhibited production of cytokines causing a "cytokine storm". The hypercytokinemia has been attributed to the clinical presentation of HLH. For example, IL-1 causes fever, TNF- alpha causes hepatitis and coagulopathy, IFN-gamma causes cytopenias.

Table 1:

CAUSES OF HLH:
I.PRIMARY HLH:
a. Familial HS
b. X-linked lymphoproliferative syndrome
c. Chediak-Higashi syndrome
d. Griscelli Syndrome
II.SECONDARY HLH
a. Infections: EBV, CMV, HIV, HSV, Varicella zoster, malaria, kala-azar, tuberculosis, typhoid
b. Malignancy
c. Autoimmune disorders: SLE, Inflammatory bowel disease
d. Rheumatic diseases: Rheumatoid arthritis, Still disease, Systemic sclerosis
e. Post organ transplantation

The clinical features of HLH/ HS can mimic sepsis. Patients commonly develop fever, hepatitis, coagulopathy, hepatosplenomegaly, rash, swollen or bleeding gums. Neurological symptoms like seizures and meningismus have also been noted. Cytopenias, of two or all cell lines occur, associated with hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia and hyponatremia. Bone marrow aspirates characteristically show hemophagocytosis. However it is difficult to demonstrate hemophagocytosis in the initial bone marrow aspirates and hence bone marrow proof should not delay initiation of treatment. Diagnosis of HLH is made on the basis of the following diagnostic criteria.

Table 2:

2009 HLH diagnostic criteria
1. Molecular diagnosis of hemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP).
2. OR ATLEAST 3 OUT OF 4
a. Fever
b. Splenomegaly

c. Cytopenias (minimum 2 cell lines reduced)
d. Hepatitis
3. AND ATLEAST 1 OUT OF 4
a. Hemophagocytosis
b↑Ferritin
c. ↑sIL2Rα (age based)
d.Absent or very decreased NK function
4. Other results supportive of HLH diagnosis:
a. Hypertriglyceridemia
b. Hypofibrinogenemia
c.Hyponatremia

Ferritin levels > 10,000 micrograms/L is both highly sensitive and specific for a diagnosis of HLH. Okamoto *et al* found mean triglyceride levels at diagnosis of HLH to be 242 mg/dl. A molecular diagnosis of HLH is sufficient to confirm the diagnosis. The other criteria are of greater significance in cases of secondary HLH. The treatment of HLH targets the hyperinflammatory state. In secondary HLH, treatment of the triggering condition alone is not sufficient and has to be treated just as primary HLH is. Treatment of HLH was defined by the HLH-94 protocol. This protocol was revised in 2004. As per the HLH-2004 protocol, dexamethasone, etoposide and cyclosporine A form the mainstay of treatment. These drugs act together to overcome the cytokine storm and the hyperinflammatory state. The protocol also recommends using intrathecal corticosteroid with methotrexate in case of CNS involvement. Less severe cases, especially in adults is known to respond well to IVIg and corticosteroids. HLH-2004 protocol recommends the usage of dexamethasone, etoposide and cyclosporine A for a period of 8 weeks following which patients with familial HLH are put on maintenance cyclosporine A with alternating pulses of etoposide and dexamethasone. The use of this protocol has drastically reduced the mortality associated with HLH. Bone marrow transplantation is the ultimate aim in familial HLH and persistent or recurring HLH. With the use of immunochemotherapy and bone marrow transplantation, the outcome of patients with HLH has improved remarkably.

CONCLUSION

Hemophagocytic lymphohistiocytosis is a potentially life threatening but treatable condition if recognized early. It mimics sepsis and is triggered by a number of infections, autoimmune conditions and malignancies. . The key to improving survival rates is maintaining a high index of suspicion and early recognition.

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