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Severe Neutropenia in Dengue- look out for Hemophagocytic Lymphohistiocytosis

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Abstract

A 22 year old female who had fever and other constitutional symptoms, and was diagnosed as having dengue had unusual persistence of fever beyond the usual course of illness with severe myeloid suppression with neutrophil counts going below 500/cu.mm. Hemophagocytic lymphohistiocytosis (HLH syndrome) was suspected. Bone marrow was advised but the patient refused and was treated on the basis of other circumstantial evidences with steroids and made a complete recovery. Our case is an interesting one, as it highlights that diagnosis of hlh can be made without a tissue diagnosis, although it is very necessary, if other evidences are present to point out to the illness.

Keywords

Hemophagocytic lymphohistiocytois; dengue infection; pancytopenia

Abbreviations

HLH-hemophagocytic lymphohistiocytosis; EBV-Epstein Barr Virus

Introduction

Hemophagocytic lymphohistiocytosis (HLH syndrome) was described in medical literature for the first time in 1939 as an unusual activation of the immune system [1]. The current diagnostic criteria for HLH syndrome stem from the 2008 review by the histiocyte society [2]. HLH syndrome occurs in the primary form as familial histophagocytic lymphohistiocytosis or secondary to strong immunologic activation due to any cause both of which occur typically in the pediatric age group.

Viral infections as a cause of HLH syndrome was first described in 1979 with the *Epstein Barr virus* (EBV) being the most commonly associated virus [4,5].

Dengue fever is endemic in the tropical climate with a predilection for the immediate post monsoon months in India, especially in urban locales where the vector *Aedes aegyptii* finds ample breeding grounds. Dengue fever typically affects the bone marrow with a depression in multiple cell lineages in the peripheral blood, typically thrombocytes and white blood cells. Hemophagocytosis is uncommon in dengue fever which though requires treatment has a favorable prognosis if recognized early [6].

We describe a case of a 22 year old female with thalassemia trait with a primary diagnosis of dengue fever that had atypical protracted course of dengue fever and was on evaluation found to have

laboratory parameters leading to a diagnosis of the secondary HLH syndrome

Case Presentation

A 22 year old female patient presented to the medicine out-patient department with a history of acute febrile illness of 1 week duration along with a sore throat and prodromal symptoms of headache and malaise. She had empirically self medicated with macrolide antibiotics with no relief obtained after a full course and at the time of presentation had high grade fever and a macular rash all over the body. She was a known case of beta thalasemia trait.

On examination she was found to be having tachycardia with a temperature of 103 degree Fahrenheit with remaining vitals being stable. She had pallor demonstrable on mucosa and a blanching evanescent rash all over the skin, with an otherwise unremarkable general examination. There were no systemic findings to suggest a focus of infection as a source of the febrile illness.

On initial investigation, she was found to have an total leucocyte count of 7140/cu.mm and a platelet count of 253,000/cu.mm. Due to a high index of suspicion considering the epidemiological features of an Indian setting in a densely populated urban locale with ongoing monsoons, initial investigations were carried out for malarial antigen, dengue antigen and antibodies and antibodies to leptospira. They revealed a positive serology for ns1 antigen of the dengue virus, though IgM and IgG was normal.

The patient was treated according to standard protocols with supportive therapy of adequate hydration with daily monitoring of blood counts and hematocrit. Her liver functions were done which were normal. There was an unusual persistence of fever spikes beyond 1 week with a drastic decline in white blood cells unusual for dengue fever. The WBC counts declined from 7140 on day 1 to 2900 on day 3 and 680 on day 5 with just 13% neutrophils. Thus there was severe neutropenia. The hemoglobin dropped from 9.2g/dL on day 1 to 8.2 g/dL on day 5; platelets dropped from 253.000 on day 1 to 89,000 on day 5. A peripheral smear study was done and revealed pancytopenia with microcytic hypochromic picture with severe leucopenia with relative monocytosis and multiple plasmacytoid lymphocytes with a reticulocyte count of 0.40%. Given the seriousness of the myeloid lineage suppression, that too in such a short period of time, HLH was suspected. Serum ferritin was studied and found to be significantly raised to 25,058 mg/dL. She was further investigated and found to have plasma fibrinogen levels 97.60 mg/dL [150-400mg/dL], D-Dimer levels >200 and deranged liver functions (ALT- 274, AST- 808, LDH- 1822 mg/dL, total bilirubin 0.3mg/dL). Prothrombin time and activated partial thromboplastin time was consistently normal, so were her blood and urine cultures. Fasting lipid profile was done which revealed total cholesterol- 154mg/dL, Triglycerides 355mg/dL, HDL- 44mg/dL and LDL-89mg/dL. Her erythrocyte sedimentation rate was 15mm at end of one hour by Westergren's method. Ultrasonography of the abdomen revealed hepatosplenomegaly.

Given the clinical picture and the laboratory features she was started injection dexamethasone 10mg/m^2 .This is as per the HLH 2004 protocol. In view of her severe neutropenia, injection filgastrim was administered.

Her serum ferritin levels peaked on day 6 of admission at 63065 ng/ml and serum fibrinogen on day 6 was at 147.9mg/dL. Her soluble CD25 receptors levels were normal and IgM antibobies to detect

viral capsid antigen for EBV was negative. The patient refused bone marrow examination even after repeated counseling.

Her complete blood count, platelets, creatinine, liver functions and blood sugar levels were monitored daily, prothrombin time, activated partial thromboplastin time, fibrinogen on alternate days and ferritin and lipid profile twice a week during the course of her treatment. This resulted in increase in neutrophil counts.

With pulse dexamethasone therapy, biochemical parameters steadied and finally showed decreasing trend. Symptomatically, the patient showed remission on day 8 of admission with resolution of fever spikes, bringing the duration of dengue fever from pre-admission to remission to a total of an unusually long 15 days. The patient being hemodynamically stable was discharged on a regimen of twice weekly pulses of intravenous dexamethasone along with a tapering regimen of oral dexamethasone. On follow up of 4 months the patient is symptomatically and hemodynamically stable with no evidence of relapse.

Discussion

Hemophocytic lymphohistiocytosis or HLH was first identified in familial groups and later on as a sporadic disease. It results in hyperacute activation of the immune system with overactive histiocytes and lymphocytes resulting in multiorgan damage. When associated with juvenile idiopathic arthritis, it is known as macrophage activating syndrome. Viral infections are the commonest causes of HLH with Epstein Barr virus being the most common associated virus [7]. Non-specific symptoms and signs like fever, lymphadenopathy, hepatomegaly herald the disease onset. Cytopenias, hepatic impairment with coagulopathy, hypofibrinemia, elevation of serum LDH and triglyceride levels, and ferritinemia may all be evident and provide a circumstantial evidence of the disease but the standard of diagnosis remains demonstration of hemophagocytosis in marrow or tissue biopsies [8].

Dengue virus is the world's most common and important arboviral disease with more than 50% of the world's population living in dengue endemic regions [9-13]. Dengue occurs in three phases- FEBRILE- where there is high grade fever with retro-orbital pain and myalgias. This phase lasts for 2-6 days. Only a few susceptible patients land into the next phase that is the CRITICAL PHASE. In this phase the patients who had previous dengue infection from a different serotype have recrudescence of fever and hypotension and plasma leakage in third spaces and go into dengue shock syndrome. This phase lasts for 24-48 hours. The last phase, the RECOVERY PHASE, results in resorption of leaked out fluid and overall recovery of the patient, although some myalgia may be present. High levels of TNF-α, IFN-γ and other pro-inflammatory cytokines are seen in patients with severe dengue infections, in particular in patients with dengue shock syndrome [14]. This overproduction of cytokines, especially interferon gamma and tumor necrosis alpha may play a role for generation of HLH [15].

Pancytopenia can occur in the setting of dengue. But the causes for the same have not been elicitated, given the paucity of literature on this topic. HLH and aplastic anemia, though rare, have been described in literature because of dengue.

Though viral infections are the most common cause of HLH, around 20 odd cases have been reported worldwide of dengue causing HLH [16], though one study from India has shown that dengue is

the commonest cause of HLH in children [16-18]. Leucopenia, thrombocytopenia do occurs in dengue, but such a severe degree of leucopenia with severe neutropenia is very uncommon in dengue. According to one study from Singapore, the prevalence of severe neutropenia, defined as absolute neutrophil count as less than 0.5×10^9/L was seen in only 11.8% of cases of dengue [19].

HLH should be suspected in patients suspected with viral illnesses like dengue when there is prolonged fever, sudden suppression of multiple cell lineages and presence of hepatosplenomegaly. Early initiation of treatment, even before prompt histological diagnosis improves the outcome.

Our case was unique for few reasons. First, this case contributes to the scarce existing literature of this topic. The presence of reactive HLH is rare and that too in the presence of classical dengue fever is rare. Second, as our patient had refused bone marrow examination for the tissue diagnosis of her disease, we still could make a likely diagnosis of HLH as per the protocol of HLH-2004 trial [20]. This trial laid down the important diagnostic and management protocols which are used worldwide for management of HLH. This criteria requires either molecular diagnosis of the involved genes in (i.e. PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A OR BIRC4) OR any five of the following- fever, cytopenias, hypertriglycerdiemia, hemophagocytosis in bone marrow or lymphnode, low or absent NK cell activity, ferritin >500mg/dL, elevated soluble CD25 receptors, splenomegaly.

Thus we could make a likely diagnosis of HLH without histopathological demonstration of hemophagocytosis. One study showed that there is only 83% sensitivity for detection of hemophagocytosis in the marrow in a patient suspected of HLH and the specificity is only 60% [21]. Thus there is evidence of rare hemophagocytosis in the bone marrow even in patients without clinical evidence of HLH. Also even if the initial marrow is negative then this should not defer the clinician from not considering the diagnosis of HLH and should go ahead with the treatment [22]. Our diagnosis was also seconded by the fact that our patient made a complete recovery after institution of steroids. Disseminated intravascular coagulation and sepsis would have been close differentials but because of consistently normal prothrombin time and activated partial thromboplastin time and normal erythrocyte sedimentation rate respectively ruled them out. We suspected HLH in our patient over aplastic anemia given the other circumstantial evidences pointing towards it.

Conclusion

Hemophagocytic syndrome is a devastating entity and requires a very high index of suspicion for its diagnosis. Clinicians should be aware of this disorder because prompt recognition can completely change the course of the illness and have a favorable outcome. This case highlights this particular fact and also that HLH can be readily diagnosed even if tissue diagnosis isn't available or not done, as in this case due to refusal from the patient, if other criteria are fulfilled.

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