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Case Report

Double trouble: hemophagocytic lymphohistiocytosis in a child with Dengue fever

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ABSTRACT

The epidemic of Dengue is steadily increasing in more than 100 endemic countries. During critical phase, of this disease, shock with organ dysfunction and severe bleeding, can occur. Rarely, it can be further complicated by Hemophagocytic lymphohistiocytosis (HLH), which results from aberrant activation of immune mechanism. HLH is a rare, frequently fatal if untreated condition. It challenging to diagnose because initial symptoms mimic other conditions which are more common. Dengue induced Secondary Hemophagocytic lymphohistiocytosis (HLH), may be responsible for severe form of Dengue with adverse outcomes. We describe a case of an infant, with Dengue fever whose clinical situation deteriorated after being stable during initial phases of illness due to development of Secondary Hemophagocytic lymphohistiocytosis (HLH). The child had persistent fever, anemia, hepatomegaly with deranged coagulation which directed towards diagnosis of Secondary Hemophagocytic lymphohistiocytosis (HLH). We discuss the features of our case and its management to sensitize the clinicians to consider this condition in patients with severe Dengue fever.

Keywords: Bicytopenia, Dengue fever, Ferritin, Infection, Immunoglobulin, Secondary hemophagocytic lymphohistiocytosis

INTRODUCTION

Dengue fever in its severe form, has significant morbidity and mortality. Worldwide, an estimated 500 000 people with severe dengue infection patients needed hospitalization each year and a large proportion of whom are children. About 2.5% of them die.[1] Apart from the common complications of Dengue fever, Infection induced Hemophagocytic Syndrome (IAHS), is a dreaded complication associated with this viral infection. It is a severe hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T-cells.[2] Infection-associated hemophagocytic syndrome is a disorder characterized by a benign histiocytic proliferation with marked hemophagocytosis in the background of a with a variety of viral, bacterial, fungal, and parasitic infections. It may be diagnosed in association with autoimmune diseases and malignancies.[3] Although an early diagnosis is crucial to decrease mortality, the definitive diagnosis is often challenging because of the lack of specificity of currently accepted diagnostic criteria.[4] We describe a case of an infant diagnosed with Dengue fever going on to develop Infection Associated Hemophagocytic Syndrome.

CASE REPORT

A 10 months old male child was hospitalised with fever, coryza and vomiting since 3 days. Child also had loose motions two days prior to hospitalization. Fever was high grade continuous and oral intake was poor. Child was born of non consangiuous marriage at term, 3.8 kg birth

weight and was immunised for the age. He had no significant illness in the past. He had normal development and no major illness in family. At the time of hospitalisation, child was febrile with heart rate of 110/ minute and respiratory rate of 26 per minute, peripheral pulses well felt with normal blood pressure and normal capillary refill time. He had mild pallor, no rash, oedema, icterus and lymphadenopathy. Anthropometrically, his weight for age and height was normal for age. Liver was 1cm and spleen was not palpable. On admission, hemogram showed Hb-7.6gm/dl, WBC- 5400/cu mm and platelets -4.82 lac per cu mm. The liver functions, Alanine transaminase and aspartate transaminase levels were 94 U/L and 54 U/L respectively, serum albumin was 3.1 gm/dl. The clinical diagnosis of dengue fever was made, and NS1 antigen (NS1 Ag) detection for dengue virus was performed. NS1Ag was detected. The patient started to improve with a conservative management but fever returned after 3 days. Child developed abdominal distension and respiratory distress with chest radiograph and ultrasonography suggestive of right sided moderate pleural effusion, liver was 3 cms palpable.

Table 1: Trend of laboratory results.

Invgt.	D1	D3	D5	D7	D9	D12	D14	D16	D19
HB(gm/dl)	9.4	11.2	8.3	7.8	6.7	7.9	7.2	8.3	10.8
WBC(mm^3)	11600	9300	7900	11700	4300	5000	4800	9600	13200
Platelets(Lac/$mm^{3)}$	4.8	1.21	1.02	2.08	0.83	0.73	0.84	1.44	1.96
ALT (IU/L)	54		287		622	458	624	400	290
PT/INR (sec)					20/1.5	120/3	180	15/1.1	
Ferritin(ng/ml)						29000			1462

DISCUSSION

HLH constitutes a medical emergency at any age. Due to overlap in clinical signs and laboratory investigations the timely diagnosis of HLH is difficult. Maintaining a high index of suspicion in appropriate patients is of paramount importance.

Clinical and laboratory criteria for the diagnosis of HLH based on HLH 2004 Trail.[5]

A. Molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18- 2, Rab27a, STX11, SH2D1A, or BIRC4

B. Five of the 8 criteria listed below are fulfilled:

(i) fever, (ii) splenomegaly, (iii) cytopenia in 2 of 3 lineages (iv) hypertriglyceridemia or (fasting, >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL) (v) Hemophagocytosis in the bone marrow, spleen, or lymph nodes, liver. (vi). Low or absent NK-cell activity (vii) Ferritin >500 ng/mL (viii). Elevated sCD25 (chain of sIL-2 receptor).

Patients are often categorized as having either “primary” or “secondary” HLH. Patients in the “primary HLH” category are those with clear familial inheritance or genetic causes, are usually infants or younger children, and are thought to have fixed defects of cytotoxic function. Such persons have a clear risk of HLH recurrence and are not likely to survive long-term without hematopoietic cell transplantation (HCT). Although the gene defects underlying the syndromes are distinct, they all lead to the common phenotype of impaired cytotoxic function by NK and T cells, and a predisposition to develop HLH. The term “secondary HLH” generally refers to older children (or adults) who present without a family history or known genetic cause for their HLH. These patients typically have concurrent infections/medical conditions that appear to trigger their HLH. such as EBV infection, malignancy, or rheumatologic disorders.[6]

About one third of secondary HLH are triggered by viral infections.[3] EBV is said to cause about one third of secondary HLH. Dengue is endemic in more than 100 countries in Southeast Asia, Latin America, Western Pacific, Africa and Eastern Mediterranean regions.[7]

Severe forms of Dengue shock Syndrome (DSS) and Dengue Haemorrhagic fever is seen in about 3.5% of patients. HLH is a Dengue-associated HLH cases, infants were most frequently affected and cases were associated with higher morbidity (100% ICU admission and longer length of stay) and mortality (4.5%) than hospitalized dengue patients.[8] A literature review of existing cases of dengue associated HLH showed that dengue induced HLH have been reported more often in first episode infections and only a few cases of second episode.[9]

As compared to dengue patients, the relationship between dengue-associated HLH patients and hepatomegaly, splenomegaly, anemia, and elevated aminotransferases was expected, since these aspects are clinically consistent with HLH but not necessarily dengue.[8] Various clinical features not featuring in the diagnostic criteria of HLH trial 2004,like hepatic derangement like in current case,

Disseminated intravascular coagulopathy (DIC), central nervous system involvement are found in many studies. Among the investigation serum ferritin above 10,000 ng/ml is very sensitive and specific marker for detecting HLH.[10] Another marker sCD25 is one of the most useful inflammatory markers, as it correlates with current disease activity more consistently than ferritin or other disease indices.[6]

The features of HLH may evolve over the course of illness, so it is required to review diagnosis at frequent interval in sick children. Whenever the cause is known, the specific therapy, like antimicrobial in bacterial infections would give good results. For certain infections like Epstein Barr virus (EBV) giving Rituximab, may be effective in controlling it. Intravenous immunoglobulin is an appropriate adjunct for most viral infections. Along with specific therapy, corticosteroids may or may be given but would need careful monitoring for worsening. With the exception of autoimmune disease and malignancy, we do not differentiate initial therapy for patients with suspected familial or reactive HLH.

Therapy should to be instituted even before definitive diagnosis of gene defect or specific causative trigger is identified, in sick children. The treatment is given according to HLH 94 protocol, as results of 2004 trial are not yet finalized and enrollment is still on.[6] The Induction therapy with, consists of a decrescendo course of etoposide and dexamethasone, with or without intrathecal therapy methotrexate and hydrocortisone, and later is recommended specially with CNS involvement. In cases, with familial HLH, once remission is achieved Hemopoietic Stem Cell Transplant (HSC) is recommended as also in the case of recurrent or progressive disease despite intensive therapy, and CNS involvement.

CONCLUSION

This case report, attempts to draw the attention of clinicians to rather rare and life threatening spectrum of common infectious disease, whereby high level of suspicion and timely evaluation for HLH may open an avenue to treating critical patients.

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