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The Double Jeopardy in Dengue Associated with Hemophagocytic Lymphohistiocytosis in an 8-year Child: A Case Report

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Abstract

Dengue is an acute viral infection with potential fatal complications. Hemophagocytic lymphohistiocytosis (HLH) is an autoimmune-mediated phenomenon that can be triggered by various etiological agents including viral infections. Dengue-induced HLH is a serious condition and may prove fatal if not detected early and treated appropriately. Here we report a case of rapidly progressive and serious dengue infection that was complicated by HLH and multi-organ failure in a previously healthy 8-year-old male who initially presented with fever and abdominal pain. This case represents the importance of prompt diagnosis and treatment of such a potentially fatal clinical syndrome. [*Bangladesh Journal of Infectious Diseases, June 2024;11(1):71-75*]

Keywords: Dengue; hemophagocytic lymphohistiocytosis; diagnosis

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Introduction

Dengue fever is an acute febrile illness caused by the mosquito-borne virus of the flaviviridae family. Dengue fever is characterized by fever, headache, myalgia and leukopenia. The disease presentation can range from a self-limiting febrile illness to life-threatening shock[1]. Since the last decades, there have been increasing cases of dengue fever associated with HLH reported in literature. HLH is a hyperinflammatory syndrome that can occur in the setting of an autoimmune disease, chronic immunosuppression, malignancy and infections.

The viral infectious agents that have been previously linked with HLH are the EBV (Epstein Barr virus), influenza virus, cytomegalovirus (CMV) and HIV (human immunodeficiency virus). HLH is characterized by persistent fever, pancytopenia, hepatosplenomegaly, increased triglycerides and increased serum ferritin[2]. Many infections are known to cause HLH and this is often mistaken for sepsis and multiorgan dysfunction and carries high mortality. A high index of suspicion essential for the diagnosis of HLH and prompt initiation of treatment is of utmost importance for tackling such a rapidly progressive life-threatening condition.

Case Presentation

A 8-year old boy was brought by his parents to the ER with a history of four days of high grade fever associated with a headache, myalgia and abdominal pain. There was an episode of vomiting for one day.

On examination the child looked sick and had fever 101^0 F, tachycardia 118 beats /min, hypotension (80/50mm of hg) and increased respiratory rate (30/min). The patient also had scleral icterus. Rest of the physical examination was unremarkable. Systemic examination revealed right hypochondriac and epigastric abdominal tenderness. The child's vital parameters were managed symptomatically and routine laboratory tests were performed.

The hematological laboratory data showed moderate leucopenia and severe thrombocytopenia. Peripheral smear examination revealed 6.0% reactive lymphocytes with lymphocyte predominant. The biochemical parameters showed derangement of electrolytes with increased bilirubin and transaminase levels. The patients hematological and biochemical investigations during the hospital stay are listed in Table1.

Table 1: Laboratory Data Log

LAB Parameters	**Test results**						**Biological reference Interval**
Haemogram	**Day 1**	**Day 3**	**Day 5**	**Day 7**	**Day 12**	**Day 16**	
Hemoglobin	12	10.9	9.3	9.0	8.9	9.3	12-15 gm%
WBC	2600	2500	2400	1600	4100	4400	4000-11000 /cumm
Platelets	0.26	0.50	0.52	0.55	1.95	2.0	1.5 - 4.5 lakhs/cumm
Total Bilirubin	3.5		3.8	3.9	1.7	1.4	0.2 - 1.3 mg/dl
Direct	1.4		1.1	1.0	0.2	0.3	0-0.3 mg/dl
Indirect	2.1		2.7	2.9	1.5	1.1	0-1 mg/dl
SGOT	1139		1175	955	268	174	14-60 U/L
SGPT	404		440	394	116	230	0-35 U/L
Alkaline Phosphatase	396		574	478	502	401	38-126 U/L
Total Protein	5.6		6.6	6.7	7.0	7.3	6.3 - 8.5 gms/dl
Albumin	3.1		2.5	2.8	3.0	3.3	3.5 -5.0 gms/dl
Globulin	2.5		4.1	3.9	4.0	4.0	2.3 - 3.5 gms/dl
SLDH			1360			325	120 -246 U/L
S. Creatinine	0.7			0.8	0.5	0.3	0.7 - 1.2 mg/dl
S. Ferritin			3703	5064		410	13 - 150 ng/ml
Electrolytes							
a) Sodium	126	126	128	130		135	137-145mmol/L
b)Potassium	5.4	4.27	4.7	4.8		4.7	3.7-5.1mmol/L
c) Chloride	97	99	98	98		99	98-107mmol/L
PT	19.3	16.3			14.6	13.4	12.2-14.7 Sec
INR	1.59	1.25			1.12	0.98	
APTT	43.8	48			36	28	27-34 Sec
C reactive protein	38			27		5.0	
Procalcitonin				67		3.1	<0.1ng/ml

The serology for HIV-1, HIV-2, anti-hepatitis C antibody, hepatitis B surface antigen were negative. The workup for pyrexia profile were done including blood and urine culture, Viral capsid antigen, Dengue NS1, Dengue IgM, Malarial parasite antigen test, Typhi IgM, Weil-felix test and Scrub typhus IgM. The Dengue NS1 and Dengue IgM test was positive while all other tests were negative including culture. An abdominal ultrasound showed mild splenomegaly (140mm), gallbladder wall edema, mild ascites and bilateral mild pleural effusion. Considering clinical, laboratory preliminary reports, he was diagnosed to have dengue shock syndrome and treated with supportive care, intravenous fluids, antibiotics and antipyretic.

Despite treatment he remained unwell with spikes of fever, worsening abdominal pain, progressive pancytopenia, elevated liver enzymes, hepatomegaly and splenomegaly. Additional laboratory investigation showed increased ferritin, increased lactate dehydrogenase, serum procalcitonin and C reactive protein possibility of HLH suspected and bone marrow aspiration performed on day 11 of illness. The bone marrow study showed normocellular reactive marrow with macrophage activation and evidence of hemophagocytosis (Figure I).

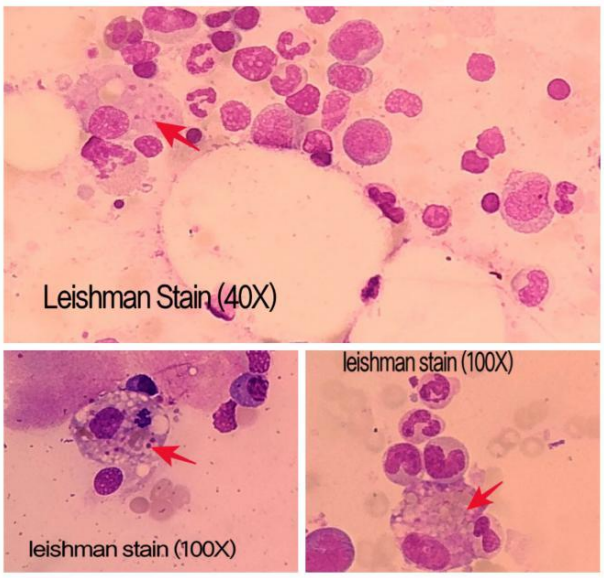

Figure 1: Bone Marrow Aspirate showing Phagocytosis of Blood Elements by Histiocytes (red arrow)

The patient thus fulfilled clinical, laboratory and cytopathological diagnostic criteria for reactive HLH (HLH-2004 trial) with dengue infection being the trigger. He was started on intravenous corticosteroids dexamethasone (10mg/m^2) along with higher antibiotics colistin. A good response to the treatment noted with the resolution of fever spikes and improvements in cell count with decreased bilirubin and transaminase levels. The ascites and pleural effusion gradually improved.

Discussion

Dengue is a major public health concern throughout tropical and subtropical regions of the world. Dengue infection occurs in all age groups of the human population and the pediatric age group was found to be most affected. Dengue fever is a flu-like illness from asymptomatic illness to severe fatal dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS), both conditions are associated with considerable mortality and morbidity. It has been established that DHF/DSS is caused by "Cytokine Tsunami" resulting in movement of body fluids in extravascular space[3].

Dengue associated with HLH was first reported in 1966 and prevalence has been increased in recent past decades but until this writing less than 50 cases have been reported in literature[4]. The dengue induced HLH have been reported more often in first episode of infections and only a few cases of second episode dengue triggered HLH have been documented in review of literature[5].

HLH also known as hemophagocytic syndrome (HPS), is an aggressive and life threatening syndrome to excess immune activation. It affects children and adults of all age groups. HLH can occur in two forms genetic and acquired. Genetic HLH associated with immune deficiencies and secondary HLH develop due to over activation of the immune system and has been associated with viral, bacterial, fungal, collagen vascular diseases and hemato-lymphoid malignancies. Infection is a common trigger in both forms of HLH[6].

Table 2: Diagnostic Guidelines for HLH-2004

The diagnosis of HLH can be established if one of either1 or 2 in below fulfilled	
1.A molecular diagnosis consistent with HLH	
2.Diagnostic criteria of HLH fulfilled (5out of the 8 criteria below)	
A) **Initial diagnostic criteria** (to be evaluated in all patient with HLH)	
Clinical criteria	
Fever (>101.3°F)	
Splenomegaly	
Laboratory criteria	
Hematological	
Cytopenia: 2 of 3 lineages in the peripheral blood	
Hemoglobin	<90g/L
Platelets	<100X10^9/L
Neutrophils	<1.0X10^9/L
Biochemical	
Fasting Triglycerides	>265mg/dl
Fibrinogen	<1.5g/L
Cyto-Histopathological	
Hemophagocytosis in bone marrow, spleen or lymph nodes	
No evidence of malignancy	
B) **New diagnostic criteria**	
1. Low or absent NK cell activity	
2. Ferritin more than 500 microgram/L	
3. Soluble CD25 (soluble interlukin-2 receptor)>2400 U/ml	

The pathogenesis related to sustained activation of the mononuclear phagocytic system due to defect in cytotoxic T cells resulting in stimulation by high levels of activating cytokines like interferon-gamma (IFN-γ), Tumor necrosis factor alpha(TNF-α), interleukin-2 and interleukin-6 by T helper cells. Elevated cytokines lead to an increase in body temperature and precipitate fever. Splenomegaly occur due to direct infiltration of excess macrophages. An elevation of TNF-α and IFN-γ lead to cytopenia and TNF-α can decrease lipoprotein lipase levels which can lead to hypertriglyceridemia. The phagocytosis of blood

elements and their precursors by monocytes or macrophages is a hallmark of HLH/HS[7].

The diagnosis of dengue is based on detection of virus nonstructural protein 1 (NS1) or detection by real time PCR. Serological IgM or IgG antibodies help in differentiation between primary and secondary infections[1]. However, the diagnosis of HLH is made based on the HLH-2004 protocol proposed by the Histiocyte Society[8].

Other common parameters consistent with diagnosis include hyponatremia, edema, rash, hypoalbuminemia and elevated LDH. The NK cell activity and soluble IL-2 receptor test are not done, as in routine clinical practice because of lack of specialized center and patient financial status. According to HLH-2004, our patient fulfilled five out of eight-point diagnostic criteria for HLH including fever, pancytopenia, splenomegaly, hyperferritinemia and histiocytic activity on a bone marrow aspirate. Other parameters like hyponatremia, increased transaminases and LDH supported the diagnosis of HLH (Table 2).

HLH is often difficult to differentiate from sepsis and multi organ dysfunction. In our case progressive pancytopenia, serum ferritin with presence of hemophagocytosis in bone marrow aspirate helped in establishing the diagnosis of HLH. There is no specific treatment or guidelines for dengue fever associated with HLH. The major tool is to identify the underlying etiology and initiate specific treatment.

Since there is no specific treatment for dengue fever other than fluid therapy and supportive care. The milder form of disease recovered spontaneously and with supportive treatment. However, for moderate to severe cases dexamethasone or pulse dosage of methylprednisolone with or without intravenous immunoglobulin G has been used[9].

Conclusion

The dengue fever is a major cause of morbidity and mortality. Clinicians in areas with endemic dengue should be aware of HLH as a potential complication of dengue. The possibility of HLH should be kept in mind in a patient with dengue with persistent low count, organomegaly and serial increase in serum ferritin. Bone marrow hemophagocytosis is a hallmark of HLH and helps to differentiate it from sepsis and multiorgan failure. Early prompt recognition and appropriate management can improve survival of patients.

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Conflict of Interest
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Literature search, Diagrams, writing-review done by first author and language correction and editing and review done by the coauthors. All authors reviewed and approved the final manuscript

Data Availability
Any questions regarding the availability of the study's supporti ng data should be addressed to the corresponding author, who can provide it upon justifiable request.

Ethics Approval and Consent to Participate
Not applicable.

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