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# Fatal Hemophagocytic Lymphohistiocytosis Complicating Dengue Virus Infection In An Young Adult.

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## Abstract

Secondary infection associated with hemophagocytic lymphohistiocytosis (HLH)is a potentially fatal condition due to infection complicated by cytokines storm. Dengue infection is a rare cause of HLH. Here we report the presentation on dengue virus infection complication as hemophagocytic lymphohistiocytosis in which inappropriate stimulation of macrophages occur in lymphoid tissues and bone marrow.

**Keywords:** Hemophagocytic lymphohistiocytosis,cytokine storm,Dengue infection

## Background

Dengue is a mosquito-borne viral disease in the world caused by any four of the mosquito transmitted dengue viruses(DEN1-4) and is characterized by fever, headache, myalgia,thrombocytopenia,leukopenia and sometimes bleeding.[1]The severity of dengue can be classified as severe plasma leakage,severe hemorrhage and severe organ impairment with or without warning signs.[2].A benign histiocytic proliferation with marked hemophagocytosis in the background of a systemic viral infection occurs in Virus-associated hemophagocytic syndrome.[3]Hemophagocytic syndrome results from a inappropriate stimulation of macrophages in bone marrow and lymphoid organs, which leads to phagocytosis of blood cells and production of high amounts of pro-inflammatory cytokines.[4]HLH may be diagnosed in association with malignant, genetic, or autoimmune diseases but is also prominently linked with bacterial, virus, parasitic infection.[5]Differential diagnosis of HLH and sepsis is important as immunosuppressive treatment in HLH is absent in sepsis,moreover hyperinflammation and fever,which is present in both conditions,makes difficult to diagnose.We report the case of a 20-year-old man who had dengue hemorrhagic fever complicated by the development of hemophagocytic lymphohistiocytosis.

## Case Report

A 20 year old male patient presented to us at SSG hospital with 6 days history of high grade fever ,headache, and abdominal pain and history of altered sensorium since 2 days. On admission pulse was 120/min, respiratory rate 24/min, blood pressure 100/70 mm Hg, Temperature was 104 F, oxygen saturation was 86% on room air. On general examination the patient's submental, submandibular and inguinal lymph nodes were enlarged 1.5-2cm in diameter, soft and mobile. Petechiae of 1-2 mm, round, purple in color, were present in cluster over back,trunk and flexor surfaces of both upper limbs. Icterus was present in the upper bulbar conjunctiva and signs of pallor were seen. On admission he was drowsy, with Glasgow Coma Scale 9/15,so on admission we did intubation and put on mechanical ventilation.

On admission Ultrasonography examination showed splenomegaly(15 mm),Hepatomegaly(20 mm)and mild to moderate pleural effusion.ABG (Arterial Blood Gas) analysis showed respiratory alkalosis. ECG was normal. Other investigations are shown in Table 1.

**Appendix**

| Date | 16-10-2019 | 17-10-2019 | 18-10-2019 | 19-10-2019 | 20-10-2019 |
|---|---|---|---|---|---|
| Hemoglobin (gm/dl) | 7.0 | 8.7 | 8.8 | 8.6 | 7.7 |
| WBC (cells/cu.mm) | 16,900 | 16,000 | 15,800 | 13,800 | 13,990 |
| Platelet count(cells/cu. mm) | 58,000 | 84,000 | 1,64,000 | 1,41,000 | 1,30,000 |
| Malarial parasite | Not detected | | | | |
| Creatinine (mg/dl) | 0.83 | 0.43 | 0.40 | 1.44 | 0.9 |
| Bilirubin (Total) (mg/dl) | 0.77 | 2.467 | 3.19 | 3.26 | 7.8 |
| (Direct) (mg/dl) | 0.47 | 1.506 | 2.04 | 2.06 | 2.5 |
| (Indirect) (mg/dl) | 0.30 | 0.96 | 1.15 | 1.20 | 5.3 |
| SGPT (U/L) | 3460 | 1780.20 | 899 | 900 | 236 |
| SGOT (U/L) | 3890 | 3305.60 | 1396 | 1236 | 210 |
| Total protein (gm/dl) | 5.9 | | | 5.050 | 5.05 |
| Albumin/ Globulin ratio | 2.58 | | | 1.14 | |
| PT time | 21.9 sec | 15 sec | | | 28.8 |
| INR | 2.11 sec | 1.21 sec | | | 2.17 |
| aPTT | 38.3 | 28.8 | | | 38.3 |
| S.Na+ (mEq/L) | 154.12 | 140 | | | |
| S.K+ (mEq/L) | 4.9 | 4.6 | | | |

| Peripheral smear | | Target cells, schistocytes sickle like cells present | | Target cells, schistocytes sickle like cells present | |
|---|---|---|---|---|---|
| ESR | 14 | | | | |

DAY 1.On admission, Patient came with reports of anemia(7.7 gm/dl) and thrombocytopenia(84,000 Lakhs/ccmm),differential diagnosis of DHF complicated by dengue fulminant hepatic failure, cerebral malaria, sepsis, encephalitis and multiorgan dysfunction was made. Patient was initially started on pain medications and continuous intravenous fluids(50 cc per hour).

DAY 2.Clinically the condition was the same. Investigations showed negative dengue markers (IgM antibodies and IgG antibodies by ELISA Kit),Dengue viral load came positive with 8000 virus /ml(cartridge based fully automated rtPCR NAAT).Peripheral smear examination for malarial parasite was negative.

Hepatitis A,hepatitis B,hepatitis C,hepatitis E ,Leptospira IgM antibodies turned out negative. Ferritin(97850 ng/ml, normal value 12-300 ng/ml) was elevated. serum CRP level ( 105 mg/dl, normal value ) and LDH (4423.00 U/L , normal value 180-360 U/L ) were elevated. Serum fibrinogen level was on lower side(137 mg/dl,normal value 200-400 mg/dl).Bone marrow examination was not possible so we did CD25 activity/sIL-2 receptor, which turned out elevated(4000 U/ml) from normal (<2400 U/ml).So diagnosis of secondary HLH in settings of DHF (Dengue Hemorrhagic Fever) was considered, patient was started on injection dexamethasone for 3 days and Intravenous immunoglobulin 2 gm/kg total dose over 4 days period.

DAY 3: Patient's conscious level improved to 10/10 T, and shifted to CPAP (Continuous Positive Airway Pressure) mode of ventilation. One episode of Generalized Tonic Clonic convulsion occurred and the patient was given intravenous sodium valproate.

DAY 4: Patient became fully conscious and oriented responding to verbal command, laboratory investigations were improving.(Table 1)

## Outcome

DAY 5: Patient developed sudden onset breathlessness, tachycardia, tachypnea. Chest examination was clear. Oxygen saturation dropped to 70% , on ABGs PO2 was 46 mmHg. Hypotension developed, ECG showed sinus tachycardia, T wave inversion on V1-V4 (right precordial leads),right axis deviation and echocardiography showed mcconnell sign(Right ventricular strain) with paradoxical septal motion and dilated inferior vena cava.Chest x-ray showed prominent dilated central pulmonary artery and clear lung field. Patient was started on inotropic support and injection heparin(80 units/kg IV bolus then continuous infusion 18 units/kg/hour).Patient's condition did not improve, and the patient went into asystole and resuscitated but could not be revived. Probable cause of death can be pulmonary embolism due to thrombo-embolic tendency of HLH.

## Discussion

HLH is characterized by non-specific activation of macrophages leading to hemophagocytosis of blood cells and accumulation in bone marrow, spleen, lymph nodes, liver, etc.[4] Hemophagocytic lymphohistiocytosis (HLH) covers a wide array of related disease including HLH ,autosomal recessive familial HLH(FHL),familial erythrophagocytic lymphohistiocytosis, viral associated hemophagocytic syndrome and autoimmune associated macrophage activation syndrome(MAS).Severe cytopenias are observed due to excessive hemophagocytosis.[7]Regardless of cause, physiologically, HLH is characterized by defective cytotoxic cell function coupled with unbridled macrophage activity, leading to excessive cytokines production, subsequent immune dysregulation, and tissue damage. The primary HLH refers to an underlying genetic abnormality causing the disorder

due to defects in transport, processing and function of cytotoxic granules in natural killer cells and cytotoxic T lymphocytes, and are not restricted to manifestation in childhood.Whereas the secondary HLH, acquired forms of HLH are encountered in infections, autoinflammatory and autoimmune, metabolic conditions, malignancies, acquired immune deficiency.[6,7]

Secondary HLH can be diagnosed based on a number of clinical signs and laboratory findings. Due to the relatively different nature of the clinical picture,and significant mixing with other illnesses, diagnosis is often delayed.[6] The official diagnosis of HLH, established by the Histiocyte Society, is based on fulfilling one or both of the following criteria:

1. A molecular diagnosis consistent with HLH

2 .Five out of the following nine diagnostic criteria for HLH: fever, splenomegaly, cytopenias (affecting two or more of three lineages in the peripheral blood), hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, hemophagocytosis in bone marrow/spleen/lymph nodes, low or absent natural killer (NK)-cell activity, or elevated soluble CD25 (interleukin [IL]-2 receptor).[7]

Low fibrinogen is found in the many of the patients,suggesting coagulopathy is important feature in HLH. It is believed that plasminogen activators secreted from macrophages, accelerates the conversion of plasminogen to plasmin, subsequently degrading fibrinogen. Coagulation studies have demonstrated normal factor V and factor VIII levels and absence of fibrin split products. These factors give evidence against disseminated intravascular coagulation, a diagnosis that may mix with HLH due to the similar findings of hypofibrinogenemia and thrombocytopenia.[7]

Treatment of HLH secondary to infection, treatment of the inciting infectious agent but treatment of infectious agent alone is not enough.Like EBV associated HLH treatment with chemotherapy and immune modifying agents. In a independent analysis of patients on regimens consisting of corticosteroids alone, intravenous immunoglobulins alone, CSA alone, or combination of treatments without etoposide versus another group of patients receiving etoposide ,early etoposide introduction was the only significant variable for improved survival.[7]

In the present case, patient had fever, splenomegaly, positive for dengue virus, cytopenia, hypofibrinogenemia, hyperferritinemia and elevated is CD25 activity/sIL-2 receptor.So six out of nine criteria fulfilled and so confirmed the diagnosis of HLH secondary to dengue infection.This is an unusual fatal case of dengue associated Hemophagocytosis. The occurrence of reactive infection associated with hemophagocytic is rare and that too in case of classic dengue fever.

## Learning Points

•HLH should be considered in the differential diagnosis of a patient present with prolonged fever,hepatosplenomegaly and cytopenia ,because early diagnosis and appropriate medication on time may result in good outcome particularly in infection associated with HLH.

•Clinicians should be aware of the fact that the occurrence of hemophagocytosis could be due to dengue virus infection in areas where the disease prevalence is more.

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