A Case Report

Hemophagocytic Syndrome – A Rare Complication of Dengue Fever

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Introduction

Dengue fever is an acute febrile viral disease caused by the bite of Aedes Aegypti mosquito. It is a major health problem especially in tropical and subtropical areas including South East Asia and its incidence is increasing rapidly in Pakistan.

Virus associated Hemophagocytic syndrome is rare disease characterized by fever, splenomegaly, cytopenia and non-neoplastic histiocytic proliferation with hemophagocytosis in reticulo endothelial system. The pathogenesis of which is not clear.

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Case Report

An 18 years old female, student, resident of Shahdara admitted to us through emergency on 10.06.2011 with complaints of generalized weakness, numbness and pain in left hand for 1 month. She was in her usual state of health one and a half months back when she developed fever which was high grade upto 103°F – 104 °F intermittent associated with severe chills and rigors, body aches, retero orbital pain and severe headache. Few days later she developed petechial rash over her body and one day later she had an episode of gum bleed and epistaxis. She was admitted in Mayo Hospital Lahore, where a diagnosis of Dengue Hemothergic fever was made on the basis of positive Anti Dengue IgM antibodies, platelet count of 53×10^3/ul HB = 10.6 gm/dl, WBC = 1.9×10^3/ul LFT'S showed serum Bilirubin 1.3 mg/dl, ALT = 53 I U/l.

AST: 52 IU/L, Alkaline phosphatase 214 IU/L, Ultrasound showed thickened gall bladder wall with pericholecystic collection of fluid. Patient remain admitted in Dengue Isolation Ward for 7 days, recovered and was discharged.

Three weeks later she again developed fever which was low to high grade, intermittent, associated with generalized weakness and severe pain and numbness of her left hand.

On examination she was pale looking mildly jaundiced spleen was enlarged 3 cms below the costal margin, liver was enlarged 1 cm below the costal margin, no lymphadenopathy. On examination of her left hand

she had pain and difficulty during movement of her left ring finger and little finger. Sensory examination of the left hand revealed decreased sensations over medial one and a half fingers.

Laboratory Investigations showed pancytopenia with hemoglobin = 8.6 gm/dl, WBC = 0.6 × 10^3/uL, Platelets 64 × 10^3/ul, Hematocrit was 25% peripheral blood smears showed anisopoikilocytosis. S/Bilirubin = 3.2 mg/dl, AST 749 IU/L, ALT 524I U/L, Alkaline phosphatase 1250 IU/L. Anti Dengue IgM negative, anti Dengue IgG positive. Ultrasound showed spleen 17 cm liver 16 cm and of normal texture. Viral markers of hepatitis were negative. Renal profile and urine complete examination was normal, as well as chest x-ray. Bone marrow examination revealed hypo cellular marrow with marked increased in macrophages / histiocytes activity showing hemophagocytosis. Trephine biopsy was done which showed normal bony trabeculae and preserved fat spaces, trilineage hematopoesis was seen to be depressed. There was increase in macrophage / histiocyte activity showing hemophagocytosis. No malignant cells were seen. A diagnosis of hemophagocytic syndrome secondary to dengue fever was made. Later further tests were done in its favour which included raised LDH level = 12 l4 IU/L (N = 88 – 230 IU/L) Serum Ferritin increased to 728 ng/ml (N = 4 – 161 ng/ml in females). Fasting triglyceride increased to 880 mg/dl (N = 50 – 150 mg/dl). Serum fibrinogen decreased to 100 mg/dl (N = 175 – 433 mg/dl). Soluble CD_{25} cell count was not done due to non affordability of patient. Motor nerve conduction study of left ulnar nerve showed markedly reduced compound muscle action potential and decreased motor nerve conduction velocity with absent F – Wave response. Sensory nerve conduction study reveal absent response of left ulnar nerve. EMG showed acute motor axonal poly – neuropathy.

The patient condition met the diagnostic criteria of hemophagocytic syndrome which include fever, hepatomegaly, splenomegaly, jaundice, pancytopenia, hypertriglycerdenia, hypofibrinogenemia, hyperbilirubinemia, raised LDH and confirmed by bone marrow biopsy. Since patient was not responding to empirical treatment we kept the patient on intravenous Dexamethasone 16 mg/day. Fever subsided after 3 days, normalization of peripheral blood counts noted on 10^{th} day i.e. Hemoglabin increased to 10.8 gm/dl, TLC increased to 6.6 × 10^3/ul, platelets increased to 146 × 10^3/ul, serum Ferritin decreased to 514 ng/nl after 10 days. No other chemotherapy started as patient responded to Dexamethasone. The initial therapy continued for 8 weeks with tapering dose and patient was put on continuation therapy, at dose of 4 mg/day intravenously, to keep the disease non active over 9 – 40 weeks. Six months follow up showed no sign of reactivation.

Discussion

Dengue fever is an acute viral infection caused by a bite of aedes Aegyptie mosquito. It is characterized by high grade fever, bone breaking pain and skin rash.[1] Dengue hemorrhagic fever in manifested by hemorrhagic diathesis, thrombocytopenia and plasma leakage.[2] These patients can evolve to Dengue shock syndrome which includes cold clammy skin, rapid weak pulse, narrowing of pulse pressure and hypotension which may lead to death.

Hemophagocytosis is a rare complication of dengue fever.[3] Virus associated hemophagocytosis syndrome is a rare disease characterized by fever, splenomegaly, cytopenia and histiocytic proliferation with hemophagocytosis in reticuloendothelial system.[4]

There are two types of hemophagocytic syndrome. The primary or familial type is an autosomal recessive disorder that affects children[5] and is usually fatal, where as secondary or reactive type is associated with viral, bacterial, fungal or parasitic infection. It may be associated with connective tissue disorders and malignancy.[6]

The pathogenesis is not clear. Many believe that viral infection provokes an abnormal immune response in predisposed individuals leading to hyper activation of the helper cells, macrophage proliferation and secretion of large amount of cytokines. The resultant hypercytokinemia may be responsible for clinical and bio chemical manifestation of hemophagocytic syndrome.[7]

Proposed diagnostic criteria for hemophago cytic syndrome include fever, splenomegaly, hepatomegaly, lymphadenopathy, rash and neurological syndrome, while laboratory abnormality include anemia, thrombocytopenia, neutropenia, hypertriglyceridemia, hypofibrinogenenia and increased ferritin.[8] In our case patient had dengue fever with splenomegaly, hepatomegaly, left ulnar nerve involvement, pancytopenia, raised triglycerides decreased fibrinogen level and increased ferritin level.

The aim of treatment is suppression of increased inflammatory response and control of cell proliferation using immunosuppressive or immunomodulatory agents and cytotoxic drugs.[9] Chemotherapy using Dexa-

methasone, Cyclosporine and Etoposide is used. Since our patient responded to Dexamethasone therapy alone other chemotherapy drugs were not added. Role of immunoglobulin in treatment of hemophagocytic syndrome is not clear.[10] For patients with genetic hemophagocytic syndrome and severe or refractory hemophagocytic syndrome bone marrow transplantation should be considered.[11] The use of growth factors such as granulocyte – colony stimulating factor or GM – CSF can exacerbate hemophagocytic syndrome[12] and hence not used.

Hemophagocytic syndrome associated with infectious illness may resolve with treatment of underlying infection.

Conclusion

Hemophagocytic syndrome is a very rare complication of Dengue Fever. Since dengue fever is very much prevalent in our country and is increasing day by day more awareness should be created for prompt recognition and early institution of appropriate therapy which is the most important factor for recovery. Steps should be taken for prevention and control of dengue fever, like vector control by use aerosols and liquid sprays and by applying mosquito repellents on exposed parts of body in dengue epidemic areas.

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