Hemophagocytic Syndrome in Severe Dengue Fever: A Rare Presentation

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Abstracts We describe a 2-year old boy developing virus-associated hemophagocytic syndrome in severe dengue fever. The condition was diagnosed according to the established criteria of the International Histiocyte Society. There was uneventful recovery with corticosteroid therapy. Secondary hemophagocytosis in children can mimic severe sepsis, systemic inflammatory response syndrome, or multi organ dysfunction syndrome and lead to diagnostic difficulties. This report adds to the limited pediatric cases of dengue related hemophagocytic syndrome reported in literature; and underlines the importance of prompt diagnosis and appropriate treatment of this rare but serious complication.

Keywords Hemophagocytic syndrome · Dengue · Hemophagocytic lymphohistiocytosis

Introduction

Dengue fever, caused by a mosquito-borne flavivirus, is increasingly prevalent in the Indian subcontinent. It is a single disease entity with different clinical presentations, and is classified into dengue and severe dengue, based on the extent of plasma leakage, bleeding and organ involvement [1].

Secondary hemophagocytic syndromes/hemophagocytic lymphohistiocytosis can arise in the setting of malignancies, autoimmune disorders, or viral and bacterial infections like Epstein–Barr virus, cytomegalovirus, parvovirus, herpes simplex, HIV or tuberculosis [2]. Dengue virus is being newly recognized as an etiologic agent in India [3]. Infection associated hemophagocytic syndrome carries a high mortality. The clinical manifestations can overlap with those seen in severe sepsis, systemic inflammatory response syndrome (SIRS), or multiorgan dysfunction syndrome (MODS) [4]. The prolonged and excessive activation of T-lymphocytes and antigen-presenting cells, with subsequent hypercytokinemia leads to systemic manifestations and progressive organ dysfunction. The International Histiocyte Society has laid down a newer set of diagnostic criteria to aid in quicker diagnosis and institution of appropriate therapy. Treatment is based on the guidelines of the HLH-2004 protocol, which includes immunosuppressive agents [5].

In this case, a 2-year old boy developed hemophagocytic syndrome associated with severe dengue fever. Few cases have been reported in the English literature, and are mostly associated with severe dengue [6–8].

Materials and Methods

Analytical instruments used were KX-21 hematology analyzers, CA-50 and CA-500 coagulation analyzers (Sysmex, Kobe, Japan); Cobas E411 Immunology Analyzer (Roche Diagnostics, Germany); VITROS 250 Chemistry System (Ortho-Clinical Diagnostics, New Jersey, USA); ELISA reader model 680 (Bio-Rad, California, USA); and BACTEC 9050 Blood Culture System (Becton–Dickinson Microbiology Systems, New Jersey, USA).

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Results

A 2-year old boy presented with a 10-day history of fever along with vomiting, diarrhea and abdominal swelling since 3 days. Physical examination revealed hepatosplenomegaly and mild ascites, but no edema, rash or lymphadenopathy was detected. A rapid immunochromatographic test for dengue NS1 antigen was positive, and a provisional diagnosis of dengue with secondary complications, was made. Dengue was confirmed by ELISA test for dengue antigen, and IgM capture ELISA test for anti-dengue antibodies. Anti-dengue IgM antibody was detected in patient's serum, while IgG was absent; indicating a primary dengue infection.

There was clinical deterioration in the next 2 days, with occasional spikes of temperature, decreasing alertness, and reduced feeding. Ascites worsened, with development of peripheral edema. Preliminary blood tests revealed decrease in hemoglobin (90 g/L) and platelet count ($103 \times 10^9/L$), with elevated leucocyte counts ($18 \times 10^9/L$). PT and APTT were prolonged indefinitely, but repeating the tests after mixing sample with normal plasma (1:1 ratio) yielded normal results, indicating a deficiency in clotting factors. Liver enzymes were elevated (AST = 1,675 U/L, ALT = 629 U/L, Alkaline phosphatase = 889 U/L, Gamma glutamyl transferase = 800 U/L), serum C-reactive protein level was raised (41 mg/L) and there was hyponatremia (serum Na^+ = 132 mEq/L). Serum albumin was low (16 g/L) and urinary protein/creatinine ratio was 2.28, far in excess of normal values (0–0.2). The clinical spectrum of fever, hepatosplenomegaly, cytopenias, hyponatremia, coagulopathy and elevated liver enzymes indicated an underlying cytokine storm, possibly due to macrophage activation secondary to dengue.

Further tests were done to confirm the possibility of hemophagocytic syndrome, and to rule out a super-added bacterial infection. Lactate dehydrogenase level was found to be elevated (11,250 U/L), and there was hypertriglyceridemia (426 mg/dL), marked hyperferritinemia (11,220 $\mu g/mL$), hypofibrinogenemia (60 mg/dL), as well as a high titre of fibrin degradation products (FDP). Bone marrow aspiration was done from the right posterior superior iliac spine, and smears showed evidence of hemophagocytosis along with relatively increased erythropoiesis (Myeloid:Erythroid ratio = 1:1) [Fig. 1].

No malignant cells or infiltration was found. Blood culture was negative after 4 days of incubation. As the findings fulfilled the diagnostic criteria for hemophagocytic lymphohistiocytosis, the patient was started on intravenous dexamethasone at a dose of 10 mg/m² day with appropriate supportive treatment. There was prompt response to therapy and within a week, liver enzymes dropped to 25 % of initial levels, ferritin was reduced by 50 %, while serum electrolytes, serum C-reactive protein levels, and platelet

counts reached normal levels. There was rapid improvement in urine protein/creatinine ratio (0:8), with serum albumin increasing to 28 g/L. The patient was afebrile, with improved oral intake and significant reduction in ascites and peripheral edema. The initial steroid therapy was continued for 6 weeks with a tapering schedule; and the patient showed complete recovery, with no signs of reactivation at the time of his 4-month followup.

Discussion

Hemophagocytic lymphohistiocytosis (HLH)/hemophagocytic syndrome (HPS) is a hyperinflammatory disorder characterized by proliferation of reactive non-dendritic histiocytes with evidence of hemophagocytic activities. There are four major subtypes: (1) Familial HLH, related to genetic defects in the pathway of granule-mediated cytotoxicity; (2) HLH associated with autoimmune disorders like SLE, rheumatoid arthritis, Sjogren's syndrome, polyarteritis nodosa or sarcoidosis; (3) Cancer associated HLH, usually reported in T cell lymphoid and NK cell malignancies; and (4) Infection-associated HLH, seen in viral or bacterial infections [2]. The prototypical and commonest association in this context is Epstein Barr virus (EBV)-induced HLH. Other viruses to be implicated are cytomegalovirus, parvovirus, HIV, herpes simplex, varicella and dengue virus. Dengue fever is a fast emerging pandemic-prone viral disease in many parts of the world. It is a mosquito-borne flavivirus, which can cause increased vascular permeability and thrombocytopenia leading to a bleeding diathesis. Severe dengue can clinically manifest as shock, severe bleeding, and hepatic, cardiac or neurologic dysfunction [1]. It has been recognized as a cause of secondary HLH/HPS in Southeast Asia, but overall worldwide incidence of dengue associated hemophagocytosis remains low [3, 6–8].

The pathophysiology of HPS is postulated to be due to disruption in the critical regulatory pathways which are responsible for the termination of immune or inflammatory responses. NK (natural killer) cells are responsible for modulating the initial response of antigen-presenting cells to pathogens, and in culling activated T cells and histiocytes to limit the immune response. Functional abnormalities in NK cells are often found in HLH/HPS. Recent research also indicates that patients developing secondary HLH/HPS may have underlying genetic mutations that decrease activation-induced apoptosis in lymphocytes. Subsequently, there is prolonged and excessive activation of T-cells and antigen-presenting cells like histiocytes. This causes persistently elevated circulating levels of proinflammatory cytokines like IL-1 (Interleukin-1), IL-6, IL-8, TNF α (Tumor necrosis factor- α), IFN- γ (Interferon- γ), and

Fig. 1 Macrophages in bone marrow, with engulfed blood cells (Oil Immersion; Leishman stain)

GM-CSF (Granulocyte–macrophage colony-stimulating factor); which underlies progressive organ dysfunction [9].

The clinical signs commonly include fever, anorexia and hepatosplenomegaly. Rash, diarrhea, vomiting, pulmonary infiltration, lymphadenopathy, cerebrospinal fluid pleocytosis, or neurologic symptoms are less commonly present [2, 9]. Nephrotic syndrome has been shown to arise in some cases of HPS, likely due to glomerular podocyte injuries caused by cytokines (TNF α) produced by activated T cells. The evolution of proteinuria and HPS are closely coordinated, with remission of HPS resulting in normalization of renal function and complete resolution of proteinuria [10]. Standard blood testing can reveal cytopenias, hepatic dysfunction, hypertriglyceridemia, hyponatremia, hypofibrinogenemia, and hypoalbuminemia. Bone marrow is the best tissue resource for establishing diagnosis, but repeated samples maybe required to document hemophagocytosis.

HLH clinically can mimic cardiovascular, hepatic, respiratory, renal or marrow failure. Both primary and secondary HLH share clinical and laboratory inflammatory phenotypes with severe sepsis, systemic inflammatory response syndrome (SIRS), or multi organ dysfunction syndrome (MODS); but the therapeutic options for these conditions are radically different. To aid in earlier diagnosis of HLH/HPS, the International Histiocyte Society has

broadened their diagnostic criteria to encompass both primary and secondary forms.

According to the revised diagnostic guidelines, HLH can be established if there is either (1) A molecular diagnosis consistent with HLH, or (2) At least five out of eight diagnostic criteria for HLH are fulfilled. These criteria are—fever, splenomegaly, bi- or pan-cytopenia, hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<1.5 g/L), hemophagocytosis in bone marrow/spleen/lymph nodes, absent or markedly reduced NK cell function, hyperferritinemia (>500 μ g/L), and increase in soluble CD25/IL-2 receptor (>2,400 U/mL) [5, 9].

After diagnosis, treatment needs to be started promptly, and effective initial therapy consists of a combination of pro-apoptotic chemotherapy and immunosuppressants which target activated macrophages/histiocytes (etoposide, steroids, high-dose IV IgG) and activated T-cells (Cyclosporine-A, steroids, antithymocyte globulin, Campath 1H). The underlying infection needs to be treated, and appropriate supportive treatment is necessary. The commonest regime of steroids, etoposide and cyclosporine used according to the HLH- 2004 protocol, needs to be adjusted according to clinical response [5, 9].

In conclusion, this case illustrates the importance of prompt diagnosis of secondary HPS, even in the setting of

infections not typically associated with it. Bleeding diatheses, renal symptoms and features of sepsis/MODS can arise independently in the course of systemic infections; and it is important for the clinician to be aware of the possibility of secondary HPS in such a setting. Therapeutic approaches are substantially different for sepsis and HPS, and prompt diagnosis and treatment of the latter condition carries a significantly better prognosis for the patient.

Sources of Support Nil.

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