Case Report

Haemophagocytic Lymphohistiocytosis: A Case Report

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Abstract

A 60 years old lady, a diagnosed case of hypertension and hypothyroidism, admitted in CMH Dhaka with the complaints of high grade continuous fever, headache, vomiting and lower abdominal pain following total hysterectomy about two weeks back. On general and physical examination, she was found febrile, mildly anaemic, pitting oedema over both legs and erythematous skin rash over face, trunk and extremities. Relevant laboratory investigations were done including bone marrow aspiration which revealed haemophagocytic lymphohistiocytosis.

Key-words: Haemophagocytic lymphohistiocytosis, Bone marrow study, Serum ferritin.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory condition caused by a highly stimulated but ineffective immune response[1]. It may be genetic or acquired. Most of the genetic defects involve defect in granule mediated cytotoxicity and NK-cell function. Familial haemophagocytic lymphohistiocytosis usually presents within the first year of life with a symptom free interval after birth. Epstein-Barr virus is the triggering agent in about 75% cases of infection associated haemophagocytic lymphohistiocytosis. The terminal stages of any malignancy including malignant lymphoma may be associated with this syndrome[2]. It was first recognized as a familial immune dysregulatory disorder of childhood, called "familial haemophagocytic reticulosis"[3] in 1952. Acquired form was first described years after the genetic form in 1979 by Risdall and colleagues[4].

Case Report

Mrs Nazma Hossain, 60 years of age, was admitted in CMH Dhaka on 18 Feb 2014 with the complaints of high grade continuous fever for 02 days along with severe headache, vomiting, passage of loose stool and lower abdominal pain. She is a diagnosed case of hypertension and hypothyroidism for last 14 yrs for which she has been taking Tab Lisinopril and Tab Thyroxin. Her total hysterectomy was done on 06 Feb 2014 due to bulky uterus. On general examination she was found febrile, anaemic and erythematous skin rash over face, trunk and extremities. Pitting oedema was found over both legs. Other general and systemic examination revealed no abnormality. So the provisional diagnosis was Septicaemia with Hypertension and Hypothyroidism.

Laboratory investigations were done accordingly. Complete blood count revealed bicytopenia (leucopenia and thrombocytopenia) and there was progressive decrease in leucocyte and platelet count. Liver function test was normal except elevated serum SGPT (338 U/L). Serum lipid profile revealed elevated serum Triglyceride (TG) (350 mg/dl) [reference range: <150 mg/dl]. Serum ferritin level was raised (625 ng/L) [reference range: 10-291 ng/L]. Serum LDH was also increased (571 U/L) [reference range: 225-480 U/L]. Viral markers for Hepatitis virus were normal. Serum electrolytes, serum urea, serum creatinine, serum calcium, serum magnesium, inorganic phosphate all were within normal limit. Coagulation profile was also found normal. Her blood culture, urine culture, tracheal aspirate culture, stool culture yielded no growth. Ultrasonography of the whole abdomen and chest X-ray P/A view revealed no abnormality. As the patients leucocyte and platelet count was decreasing gradually her bone marrow aspiration was done and bone marrow study revealed haemophagocytic lymphohistiocytosis. The patient was treated with broad spectrum parenteral antibiotic, antiviral drugs, antifungal drugs, Inj Etoposide, Tab Prednisolone along with other supportive treatment. But the patient during the course of her above mentioned treatment, developed acute coronary syndrome with increased Troponin I and ultimately she expired .

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Discussion

Haemophagocytic lymphohistiocytosis are of two types, genetic and acquired. Genetic form is familial and immunodeficiency related syndrome. Familial form is an autosomal recessive disease in which defects in genes with important immune functions have been reported which includes mutations in the genes for perforin (PRF-I), Munc 13-4 (UNCI3D) and syntaxin II (stXII). It affects neonates and infants in 1 in 50,000 live births[5]. Males and females are equally affected and two-thirds of cases occur in siblings. HLH may also occur as a secondary disorder in association with severe infections, malignancies, rheumatologic disorders and some metabolic diseases[6].

Acquired forms of haemophagocytic lymphohistiocytosis are commonly precipitated by viral (particularly EBV and other herpes virus), bacterial, fungal and protozoal infection, occurring frequently in an immunocompromized host[7]. Other factors that have been associated with acquired haemophagocytic lymphohistiocytosis include malignancies (particularly lymphoproliferative disorders), drugs (such as phenytion) and rarely with inborn errors of metabolism (lysinuric protein intolerance and multiple sulphatase deficiency)[5]. Acquired form may also be associated with Chediak-Higashi syndrome, Griscelli syndrome and X-linked lymphoproliferative syndrome[2].

Despite recent gains in knowledge, the pathogenesis of HLH is as yet unclear, but primary HLH is thought to involve defective termination of the immune response that results in persistent activation of macrophages and cytotoxic T cells. An alternative hypothesis involves failure to remove antigen (Ag), which results in ongoing stimulation of the immune effector cells. It is possible that both failure to clear the pathogen, resulting in continued antigen stimulation and failure to terminate the immune response play important roles.

Pathogenesis of secondary (acquired) HLH is even less clear, although patients with secondary forms of HLH are increasingly being found to have heterozygous changes or polymorphisms in the familial HLH genes. More detailed discussion of the genetic basis of HLH and the concepts underlying pathogenesis can be found in several recent reviews[8-10].

The patients of haemophagocytic lymphohistiocytosis usually presents with high fever, anorexia, malaise, irritability and vomiting. Common signs are hepatosplenomegaly, lymphadenopathy and neurological signs which include cranial nerve palsy, seizure etc. Cutaneous involvement occurs in as many as 65% of patients[11]. Skin manifestation includes generalized maculopapular erythematous rash, generalized erythroderma, panniculitis, morbiliform erythroderma, oedema, petechiae and purpura[3]. Detection of cutaneous involvement can assist in the initial diagnosis and potentially signify recurrences[7]. Laboratory features include pancytopenia, hypertriglyceridaemia, hypofibrino-genaemia, cerebrospinal fluid pleocytosis, coagulopathy, transaminitis and hyperbilirubinaemia.

Bone marrow study reveals hyperplastic marrow with increased number of haemophagocytic histiocytes. Lymph node biopsy shows infiltration by lymphocytes and histiocytes and characteristic prominent erythrophagocytosis and haemophagocytosis[5]. Revised criteria from the Histiocyte Society for the diagnosis of acquired haemophagocytic lymphohistiocytosis include eight criteria and for diagnosis of haemophagocytic lymphohistiocytosis at least five criteria is required. The eight criteria are a) Fever, b) Splenomegaly, c) Cytopenia in two or more cell lines (Hb <9 gm/dl, platelet <100x10^9/L, Neutrophil <1x10^9/L), d) Hypertriglyceridaemia and/or hypofibrinogenaemia (Fasting TG >3mmol/L, Fibrinogen <1.5 g/L), e) Ferritin >500 ng/L, f) sCD25 >2400 U/ml, g) Decreased or absent NK cell activity, h) Haemophagocytosis in bone marrow, CSF or lymph nodes[5].

Whether the patient has genetic or acquired haemophagocytic lymphohistiocytosis, should be evaluated for identifying treatable infectious agent, if found, appropriate antimicrobial therapy should always be employed[2]. Other treatment options include the use of corticosteroids (dexamethasone), immunoglobulin infusion, cyclosporin and etoposide. In patients with CNS disease, intrathecal therapy using methotrexate with or without corticosteroids is given. Although by giving treatment early responses are observed, disease recurrence within months is common. Haemopoietic stem cell transplantation from a matched sibling or unrelated donor remains the definitive treatment modality in patients with genetic forms of HLH[5].