CASE REPORT

Cytomegalovirus infection associated hemophagocytic syndrome

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ABSTRACT

Virus-associated hemophagocytic syndrome (VAHS) is a rare complication in early cytomegalovirus (CMV) infection. It is a life-threatening condition characterized by prolonged fever, hepatosplenomegaly, and cytopenia. There is no standard therapy for VAHS and the clinical course is variable. Herein, we report a 3-month-old boy whose clinical and laboratory findings were consistent with CMV infection-associated hemophagocytic syndrome. In spite of prompt diagnosis and treatment, the infant expired due to progressive respiratory failure.

Key words: Cytomegalovirus, infection-associated hemophagocytic syndrome, respiratory failure

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH), also called hemophagocytic syndrome (HPS), is a disorder of the mononuclear phagocytic system, which is characterized by uncontrolled activation and proliferation of macrophages and T cells. Activated macrophages engulf the red blood cells, leukocytes, platelets, and their precursor cells.[1]

HLH can follow infections, connective tissue disorders, malignancies, and genetic disorders.[2-4] Two forms of HPS have been well established: familial erythrophagocytic lymphohistiocytosis (FEL) and infection-associated hemophagocytic syndrome (IAHS).

Virus-associated hemophagocytic syndrome (VAHS) was described primarily in association with Epstein–Barr virus (EBV). HPS has been linked to other viruses including cytomegalovirus (CMV), adenovirus, and herpes simplex virus (HSV), as well as with a variety of non-viral infections. There is no standard therapy for VAHS and the clinical course is variable. If left untreated, this disease has a high mortality rate.

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CASE REPORT

A 3-month-old male infant was referred from a local hospital to our Institute of Maternal and Child Health (IMCH) with history of fever, cough of 11 days duration, and an episode of seizure the previous night. Fever was of low grade, associated with nasal discharge and cough. Cough was productive with no diurnal variation and associated with post-tussive vomiting. There was no history of sore throat, joint pain, bleeding, jaundice, or skin infections. The child was delivered by cesarean section, with a birth weight of 2.6 kg. Postnatal period was uneventful. Baby was on exclusive breast feeding, had no developmental delay, and was fully immunized for age.

On examination, he looked pale with no facial dysmorphism. He had hepatosplenomegaly, no lymphadenopathy, or focal neurological signs. His heart sounds were heard normally with no murmurs. Chest was clear on auscultation. After admission in our hospital, baby developed maculopapular rash all over the body and had recurrent seizures.

Investigations

Routine examination of blood showed hemoglobin 8.6 gram/100ml, total leukocyte count 15,900/mm^3 (polymorphs 27, lymphocytes 59), platelet count 119,000/mm^3, and an erythrocyte sedimentation rate (ESR) of 31 after the first hour. The levels of serum electrolytes were as follows: sodium 137

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mg%, potassium 4.2 mg%, blood urea 37 mg%, and creatinine 1 mg%. Alanine aminotransferase was 222 U/L, triglyceride 343 mg/dl, and ferritin 1446 ng/ml (normal 30-400 ng/ml).

Peripheral smear showed microcytic hypochromic anemia with neutrophils showing shift to left. Cerebrospinal fluid study was normal. Abdominal ultrasonography revealed hepatosplenomegaly. Blood and bone marrow cultures were sterile. Bone marrow aspiration showed no hemophagocytosis.

As the child had fever, hepatosplenomegaly, bicytopenia (hemoglobin and platelet count decreased), elevated transaminases, hypertriglyceridemia, and hyperferritinemia, the diagnosis of HPS was considered.

Patient's blood was sent for detection of viral markers by polymerase chain reaction (PCR) and was negative for enterovirus, respiratory syncytial virus, adenovirus, parvovirus, human herpes virus 6 and 7, and EBV. Gastric aspirate was negative for tuberculosis.

Blood sample of patient was sent for quantitative CMV PCR. Serum was separated and subjected to DNA extraction using DNA extraction kit (Qiagen, Netherlands). Fifteen microliters of mastermix, which included primer specific for Early Antigen (IEgene) of human CMV, was added to 10 μL of the extracted nucleic acid. Thermal cycling was performed in mini opticon sequence detection system (Bio-Rad, California US). CMV DNA was amplified with 1.84×10^6 copies/ml. We concluded that this was a case of HPS with primary CMV infection.

Empiric treatment for HPS was initiated on the 5th day of admission with methyl prednisolone. The baby was administered 30 mg/kg/day for 3 days. Despite prompt diagnosis and treatment, condition of the baby deteriorated. He developed fever spikes and dyspnea on 13th day after admission and was put on ventilator. In spite of supportive measures, the baby expired next day morning due to respiratory failure.

DISCUSSION

HPS is an unusual disorder that is characterized by uncontrolled proliferation of mature histiocytes, hemophagocytosis, and upregulation of inflammatory cytokines.[5] Primary CMV infection in the immunocompetent host rarely causes serious illness. However, CMV infection is the first cause of VHAS, representing 10.5% of the infectious causes of the HPS in immunocompromised host.[6] The clinical features of HLH include fever, hepatosplenomegaly, nonspecific neurological abnormalities, pancytopenia, coagulopathy, hyperferritinemia, hypofibrinogenemia, and lipid abnormalities. Fever and splenomegaly are the most common clinical signs, but hepatomegaly, lymphadenopathy, jaundice, and rash can occur.[3] The low fibrinogen level is associated with low ESR, which may be an early clue to the diagnosis of HLH.

The diagnosis is established by fulfilling one or two of the following: (1) a molecular diagnosis consistent with HLH (e.g. PRF [Perforin] mutations, SAP [Serum amyloid P component] mutations) or (2) having five out of eight of the following: fever, splenomegaly, cytopenia (affecting $\geq$2 of the three lineages in the peripheral blood and not caused by a hypocellular or dysplastic bone marrow), hypertriglyceridemia ($\geq$265 mg/dl), hyperferritinemia ($\geq$500 ng/ml), low or absent Natural Killer (NK) cell cytotoxicity, elevated soluble CD25, and hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy.[7] Histopathologic features of hemophagocytosis are characteristic, though not pathognomonic.

When first described, IAHS was identified in immunocompromised patients receiving chemotherapy and in those who had undergone organ transplantation. Early diagnosis and treatment is crucial because the disease is associated with high mortality and morbidity. The prognosis is still poor, with reported mortality rates of 20-70%.[8] The treatment remains controversial. Our case illustrates the possibility of HPS during the course of CMV early infection. Cyclosporin or steroid is considered to be the first-line therapy in HPS. Ganciclovir has no indication in the treatment of CMV primary infection in the non-immunocompromised hosts, except in the case of CMV pneumonia. In this case, steroids were given in the appropriate dosage, but the condition of the patient deteriorated later. It is necessary to perform prospective study of VHAS to determine the place of each treatment. The role of intravenous immunoglobulin (IVIG) in the treatment of VHAS remains unclear. Remission after such therapy has been reported in adults and children with underlying immune dysfunction.[9-12] It was shown that IVIG improved the prognosis of VHAS in adults and children. The anti-inflammatory potential is the most likely mechanism of action of IVIG in VHAS. In a case series of renal transplant recipients with HPS, Asci *et al*. report a patient with CMV-associated hemophagocytic syndrome in whom there was no response to antiviral drugs and only IVIG was efficient.

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