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Infection-associated hemophagocytic syndrome is a life-threatening condition characterized by prolonged fever, hepatosplenomegaly, and cytopenia—most commonly, thrombocytopenia and anemia. It is characterized by proliferation and activation of benign histiocytes, causing dysfunction of various organs.

Herein, we report on a 5-month-old boy whose clinical picture and laboratory findings were consistent with cytomegalovirus infection-associated hemophagocytic syndrome. The patient was successfully treated with intravenous administration of immune globulin and ganciclovir. He remained well 6 months later.

Keywords: Cytomegalovirus (CMV) • immune globulin • infection-associated hemophagocytic syndrome (IAHS)

Introduction

Hemophagocytic syndrome is a reactive disorder of the mononuclear phagocytic system, characterized by a benign, generalized histiocytic proliferation, with marked hemophagocytosis.1, 2 This syndrome was first described by Risdull et al in 1979 in a group of patients receiving immunosuppressive drugs for renal transplantation.3 The development of infection-associated hemophagocytic syndrome (IAHS) is possibly associated with an underlying immune disorder that results in the uncontrolled activation of the cellular immune system, giving rise to the term “cytokine disease” or “macrophage activation syndrome.”4,5 If left untreated, this disease has a high mortality rate.6

Two forms of hemophagocytic syndrome have been well characterized: familial erythrophagocytic lymphohistiocytosis (FEL) and IAHS. Hemophagocytic syndrome is not always induced by infection. In many cases, it is associated with a variety of malignant neoplasms, or use of some drugs such as phenytoin. Therefore, a more accurate description for this acquired form of the syndrome is “reactive hemophagocytic syndrome.”4, 5

In this report, an unusual case of cytomegalovirus (CMV) IAHS, whose clinical and hematologic findings at presentation were difficult to diagnose, is presented.

Case Report

A 5-month-old male infant was admitted to our hospital with a history of fever and lethargy for one month. He had an acute febrile illness without any specific diagnosis in an outpatient clinic. He was treated with oral prednisone and received blood transfusion on two occasions. Despite therapy, his symptoms persisted. He was admitted to our hospital 30 days after the onset of his illness.

On physical examination, his body temperature was 39ºC (axillary). He looked pale, and his sclera was subicteric. He had hepatosplenomegaly, but had no lymphadenopathy or focal neurologic signs.

At the time of admission, laboratory findings included a hemoglobin of 6.5 g/dL, white blood cell count of 10200/mm³ (with 25% neutrophils,
70% lymphocytes [mostly reactive], 5% monocytes), platelet count of 28000/mm³, and an erythrocyte sedimentation rate of 140 mm after the first hour. Other laboratory findings included a total bilirubin of 2.8 mg/dL (with 1.1 mg/dL conjugated), alkaline phosphatase of 525 U/L, AST of 98 U/L, ALT of 80 U/L, triglyceride of 850 mg/dL, LDH of 1300 IU/L, ferritin of 690 ng/mL (normal: 15 – 100 ng/mL), a PT of 18 sec, and a PTT of 62 sec.

No pathogens could be isolated from his throat, urine, feces, and blood. Anticytomegalovirus IgM antibody with >60 g/L was positive in this patient. In his cerebrospinal fluid, mild pleocytosis and a high level of proteins were detected. Abdominal ultrasonography and computerized tomography (CT) scan revealed hepatosplenomegaly. Brain CT scan showed the presence of a mild atrophy and existence of some hyperdense areas. Bone marrow aspiration showed erythroid hyperplasia without hemophagocytosis. Nonetheless, a repeat bone marrow aspiration after 15 days, showed an abnormal proliferation of histiocytes, with evidence of hemophagocytosis (Figure 1). The results of the immunologic studies are shown in Table 1.

Based on the clinical and laboratory findings, the diagnosis of IAHS was made. After bone marrow aspiration, the patient received intravenous immune globulin (1 g/kg/day) for three days and then ganciclovir (5 mg/kg/day) for 14 days. After one week of therapy, the platelet count rose to 120000/mm³ and hemoglobin level reached 10 g/dL. His platelet and hemoglobin levels gradually got better until six months later when he got full recovery.

**Discussion**

Our patient showed a fulminant clinical course with fever, bicytopenia, and hepatosplenomegaly. Since no other finding related to bacterial, protozoal, or other viral infections but CMV could be obtained, the patient was diagnosed as CMV IAHS.

**Table 1.** The results of immunologic studies.

<table>
<thead>
<tr>
<th>Serum immunoglobulins</th>
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<tbody>
<tr>
<td>IgG</td>
<td>19.7 g/L (N: 7 – 15 g/L)</td>
</tr>
<tr>
<td>IgM</td>
<td>60 g/L (N: 0.4 – 2.6 g/L)</td>
</tr>
<tr>
<td>IgA</td>
<td>0.9 g/L (N: 0.8 – 4 g/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphocyte subgroups</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>36% (N: 25 – 50%)</td>
</tr>
<tr>
<td>CD8</td>
<td>30% (N: 11 – 32%)</td>
</tr>
<tr>
<td>CD19</td>
<td>18% (N: 17 – 41%)</td>
</tr>
</tbody>
</table>

**Figure 1.** Typical hemophagocytosis observed within the bone marrow of the patient.

IAHS. This diagnosis was made on the basis of clinical and hematologic findings on bone marrow aspiration, revealing proliferation of mature histiocytes which have displayed notable erythrophagocytosis. In the literature, CMV infection has also been mentioned among the viral infections causing reactive hemophagocytic syndrome. The clinical presentation of our patient was similar to other reports.¹

IAHS is an unusual disease, with multiple etiologies and typical clinical features. IAHS has been reported in association with various infections including viral, bacterial, fungal, and parasitic infections.⁶

The major criteria required for the diagnosis of IAHS include fever, splenomegaly, cytopenia
(affecting ≥2 of the 3 lineages in the peripheral blood and not caused by a hypocellular or dysplastic bone marrow), and hypertriglyceridemia or hypofibrinogenemia. Histopathologic features are characteristic, though not pathognomonic. The most prominent feature is proliferation of benign histiocytes and hemophagocytosis in bone marrow, spleen, or lymph nodes, with no evidence of malignancy. In addition, the consistent findings with the diagnosis of IAHS are jaundice, edema, lymphadenopathy, circulating soluble interleukin-2 receptors, hyperferritinemia, hepatic enzyme abnormalities, and a high LDH level. Unfortunately, we were not able to check the cytokine levels in our patient.

When first described, IAHS was identified in immunocompromised patients receiving chemotherapy, and in those who had undergone organ transplantation. The clinical course is usually fulminant, with mortality rates of 30 – 40%. In a recent review, Imashuku et al reported 82 pediatric patients with hemophagocytic lymphohistiocytosis and predicted the four-year overall disease-free patient survival to be 57.2%. Although the pathogenesis of the syndrome is still poorly-understood, congenital, iatrogenic, or other acquired immunologic pathologies are established in many cases.

Histiocytic reactions secondary to known causes that do not result in a self-perpetuating hemophagocytic reaction, would be expected to resolve the underlying disease process. The macrophage is possibly reacting to a foreign entity absorbed onto the formed blood elements, including erythrocytes. This syndrome probably results from a defect in the regulation of the immune system such as an excess cytokine production, as well as an abnormal T-cell function. Jaffe et al isolated a lymphokine, produced by CD4 lymphocytes, which can stimulate a certain line of histiocytic cells to undergo differentiation and phagocytosis of IgG-coated red cells. Markedly elevated levels of serum-interleukin-2 (sIL-2) receptor have been noted in Epstein-Barr virus IAHS. Additionally, increased serum levels of interferon γ (IFN-γ), tumor necrosis factor alpha (TNFα), interleukin 6 (IL6), and macrophage colony-stimulating factor (MCSF) have been recently reported in patients with hemophagocytic syndrome. The major source of IL6 and TNFα is activated monocytes and macrophages. Therefore, an overproliferation of the activated T-cells appears to be a part of the syndrome, directed against cells infected by virus. Thereby, the virus may infect T-cells or monocytes/macrophages directly and result in their proliferation. Different mutations have recently been demonstrated in patients with HLH. Previously-reported therapeutic approaches to IAHS have had limited efficacy. Therapy has been varied and includes corticosteroids, cyclosporine, and clinical support. Withdrawal of the immunosuppressant treatment for the underlying infection should also be instituted. Immune globulins, immunomodulating agents (INF-α and γ), may also be given. The mechanism of action of intravenous immune globulin is complex and includes blockade of Fc receptor, antiidiotype effects, and possibly downregulation of immunoglobulin synthesis and stimulation of the immune system. In addition to the immuno-modulatory effects, it can influence the secretion of cytokines and receptors of cytokines. At present, bone marrow transplantation remains the only cure, but a better knowledge of the pathogenic mechanisms and underlying genetic defects could shed light over alternative therapeutic modalities, including possible gene therapy of HLH.

Our patient received intravenous immune globulin therapy plus ganciclovir.

In conclusion, hemophagocytic syndrome should be considered if a patient has fever of unknown origin, a variable degree of pancytopenia, and progressive development of multiorgan dysfunction, especially in the setting of immunosuppression. Under such a condition, histopathologic examination of bone marrow and/or lymph nodes is the most important initial diagnostic step. In the absence of an identifiable infectious process, and especially in an otherwise healthy individual, a neoplastic process is frequently responsible. The most important point is that the most appropriate treatment must be given to each HLH case, without delay. Rapid diagnosis of the disease, certainly, requires close cooperation between all specialists involved in treatment of such patients.

References

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