Successful Treatment of Infection-Associated Hemophagocytic Syndrome with Intravenous Immunoglobulin

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ABSTRACT

Hemophagocytic syndrome is a rare disorder characterized by a group of clinical, laboratory and histopathological findings such as fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, and hemophagocytosis in the bone marrow, spleen, and lymph nodes. Hemophagocytic syndrome may occur as a primary or secondary disease. Primary type of hemophagocytic syndrome is also known as familial erythrophagocytic lymphohistiocytosis and secondary type is mostly associated with an viral infection and known as infection-associated hemophagocytic syndrome (IAHS). Rapid diagnosis is very important in these patients since suggested treatment strategies for the two types have been different and mortality rate is very high. In this report we present the clinical and laboratory findings and the outcome of two children with IAHS to emphasize the importance of early diagnosis and the effectiveness of intravenous immunoglobulin therapy in these patients.

Key Words: Infection-associated hemophagocytic syndrome, Immunoglobulin therapy.

ÖZET

Infeksiyona Bağlı Hemofagositik Sendromun İntrakapsülöz Immünglobulin ile Başarılı Tedavisi


Anahtar Kelimeler: Infeksiyona bağlı hemofagositik sendrom, Immünglobulin.


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INTRODUCTION

Hemophagocytic syndrome is a rare disorder characterized by a group of clinical, laboratory and histopathological findings such as fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, lymphohistiocytosis and hemophagocytosis in the bone marrow, spleen, and lymph nodes[1]. These characteristic findings result from the overproduction of cytokines, including IFN-γ, IL-2, IL-4, IL-10, IL-12, IL-18 and TNF-α by activated T-lymphocytes and macrophages[2,3]. Especially, IFN-γ and α have been reported to play an essential role in the activation of macrophages, leading to hemophagocytic syndrome[3].

Hemophagocytic syndrome may occur as a primary or secondary disease. Primary type of hemophagocytic syndrome is also known as familial erythrophagocytic lymphohistiocytosis (FEL) and secondary type is mostly associated with an viral infection and known as infection associated hemophagocytic syndrome (IAHS)[4]. The distinction between these two types is subtle and controversial: Presence of a family history, consanguinity, autosomal recessive inheritance and frequent central nervous system involvement in the former, and association with infection in the latter. Rapid diagnosis is very important in those patients since suggested treatment strategies for the two types have been different and mortality rate is very high[4,5].

In this report we present the clinical and laboratory findings and the outcome of two children with IAHS to emphasize the importance of early diagnosis and the effectiveness of intravenous immunoglobulin (IVIG) treatment in those patients.

CASE 1

A 12.5-year-old male patient, diagnosed and followed as ß-thalassemia trait and chronic idiopathic neutropenia for four years, was admitted to our hematology department with the chief complaints of 39.5°C axillary fever, oral ulcerations and fatigue. He was recently treated with an orally administered antibiotic treatment by his physician for acute maxillary sinusitis. On physical examination pallor, oral mucositis, pharyngeal hyperemia and bilateral cervical microlymphadenopathies were present. His initial blood count showed a hemoglobin level of 8.2 g/dL, a white blood cell count of 2.2 x 10^9/L, with an absolute neutrophil count of 0.4 x 10^9/L and platelet count 200 x 10^9/L. Intravenous meflofenem and amikacin treatment was started because of severe neutropenia. On follow-up, high fever persisted and moderate hepatosplenomegaly and pancytopenia developed on the fourth day (Table 1). His blood cultures and results of serologic tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV) and parvovirus were negative. His immunological tests including antinuclear antibody, antidouble-stranded DNA antibody, and compleman levels were unremarkable. Immunoglobulin levels were in normal ranges. A bone marrow aspirate revealed abnormal histiocytic proliferation with phagocytosis of progenitor cells (Figure 1).

After bone marrow aspiration, IVIG therapy 400 mg/kg for five days was added to therapy because of persistant fever and rapid disease progression. After the second dose of IVIG therapy, his fever disappeared, and his hemoglobin level and platelet count rised to normal levels on the fifth day of IVIG therapy. A week later, repeated bone marrow aspiration revealed normal features. Two years later, his clinical course is uneventful except the persistence of chronic idiopathic neutropenia.

CASE 2

A 16.5-year-old female patient was admitted to our hospital with fever, fatigue, somnolence and headache for four days. Her past and family history were unremarkable. On physical examination axillary fever of 38.6°C, tachycardia, tachypnea, evident pallor, hepatosplenomegaly and confusion were present. There was no meningeal irritation sign and no other pathologic neurologic feature. The laboratory data on admission are shown in Table 1. Her bone marrow aspirate revealed abnormal histiocytic proliferation with phagocytosis of progenitor cells, and additionally diserythropoiesis and dismlyelopoiesis. Her blood cultures and results of serologic tests for viral infections including hepatitis A-D, HIV, CMV, EBV and parvovirus were negative. Serum levels of folic acid, vitamin B12, ammonia, lactic acid, and pyruvic acid were in normal range. Direct Coomb’s test was negative. Her immunological tests including antinuclear antibody, antidouble-stranded DNA antibody, and compleman levels were unremarkable. Immunoglobulin levels were in normal ranges.

Supportive treatment was started and intravenous vitamin K, transfusions of packed erythrocytes and
thrombocyte suspension were administered on the first day. Disseminated intravascular coagulation (DIC) findings developed later on the same day. IVIG therapy 400 mg/kg for five days was added to therapy; after the second dose of IVIG therapy, fever, hepatosplenomegaly, and DIC features disappeared and hematologic parameters was in normal limits. Hepatic tissue enzyme levels decreased to normal range rapidly. She required no further therapy. After complete clinical improvement, her blood cell counts and bone marrow aspirate findings were in normal limits. Twelve months later, she in well condition without any pathologic features.

**DISCUSSION**

Infection-associated hemophagocytic syndrome was first described in immunocompromised patients and afterwards in previously healthy people[4]. The known causative microorganisms are viruses, especially Herpes virus family, bacteria and also parasites[6-11]. Further, IAHS can be seen rarely in clinical progress of some autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease and inherited metabolic disease[12-16]. The following criteria are required for diagnosis of hemophagocytic syndrome: ≥ 38.5°C fever lasting seven days or over; splenomegaly; cytopenia (at least affected two cell line in peripheral blood, Hb ≤ 9 g/dL, thrombocytes < 100 x 10^9/L or neutrophil count < 1.0 x 10^9/L); hypertriglyceridemia (serum levels > 2 mmol/L); and histopathologic criteria (hemophagocytosis without any finding of ma-

<table>
<thead>
<tr>
<th>Laboratory data of the patients on the day of admission</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte (x 10^9/L)</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>ANC (x 10^9/L)</td>
<td>0.12</td>
<td>0.48</td>
</tr>
<tr>
<td>RBC (x 10^{12}/L)</td>
<td>3.35</td>
<td>3.15</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>6.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>19.2</td>
<td>22</td>
</tr>
<tr>
<td>Reticulocyte (%)</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Thrombocyte (x 10^9/L)</td>
<td>46</td>
<td>22</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
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<td>18.6</td>
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<tr>
<td>Partial thromboplastin time (seconds)</td>
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<td>96</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
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<td>1.1</td>
</tr>
<tr>
<td>D-dimer (µg/mL)</td>
<td>-</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>34</td>
<td>4871</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
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<td>3335</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
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<tr>
<td>Direct Coomb’s test</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>9.89</td>
<td>7.29</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
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<td>5.3</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>1604</td>
<td>830</td>
</tr>
</tbody>
</table>

Figure 1. Bone marrow aspirate of the patient demonstrating hemophagocytosis.
lignancy in the bone marrow and/or lymph nodes)\textsuperscript{[11]}. However all of these features are not necessary for diagnosis. Although we could not be able to document the virus or bacteria infection in our cases, depending on their clinical and laboratory findings and hemophagocytic syndrome criterias, both of them were diagnosed as IAHS. In addition, there were no history of familial hemophagocytic syndrome and consanguinity. DIC and hyperferritinemia are also reported in some cases with IAHS as in our cases\textsuperscript{[6,17]}.

IAHS was defined as a nearly fatal disorder initially. The prognosis is still poor and mortality rate is reported about 20 to 70% in different patient series\textsuperscript{[5,6,18]}. In treatment, corticosteroids, cyclosporin-A, supportive treatment and cessation of immunosuppressive treatment were recommended previously; later, it was shown that IVIG improved the prognosis\textsuperscript{[5,17,19-21]}. Etoposide and corticosteroids are recommended in familial cases, but in IAHS immunosuppressive treatment modalities should be avoided\textsuperscript{[17]}. Because of some adverse events of etoposide such as myelosuppression, mucositis, infection, secondary leukemia and MDS, it is not recommended as the first line therapy in IAHS\textsuperscript{[22-24]}. However, in progressive and fatal conditions, etoposide and corticosteroids can also be used in IAHS and good results with these drugs are reported\textsuperscript{[5,25,26]}. In our patients, whose clinical conditions were progressively worsening, we were able to control IAHS features with IVIG administration in a short time and we wanted to emphasize this good clinical and hematologic response in our cases.

REFERENCES


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