Successful Treatment of Infection-Associated Hemophagocytic Syndrome with Intravenous Immunoglobulin

Hale ÖREN, Hüseyin GÜLEN, Canan UÇAR, Murat DUMAN, Gülersu İRKEN

Department of Pediatric Hematology, Dokuz Eylül University Faculty of Medicine, İzmir, TURKEY

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

İnfeksiyona Bağlı Hemofagositik Sendromun İntravenöz İmmünglobulin ile Başarılı Tedavisi

Hemofagositik sendrom, ateş, hepatosplenomegali, sitopeni, hipertrigliseridemi, kemik iliği, dalak ve lenf bezlerinde hemofagositoz gibi bir grup klinik, laboratuvar ve histopatolojik bulgu ile karakterize nadir bir hastalıktır. Primer veya sekonder olabilir. Primer tipine familyal eritrofagositik lenfohistiyositoz adı verilir. Sekonder tip ise sıklıkla bir viral infeksiyona eşlik eder ve infeksiyona bağlı hemofagositik sendrom (IAHS) adı da verilir. Bu hastalarda hızlı tanı önemlidir, çünkü bu iki tip arasında tedavi stratejileri farklıdır ve mortalite hızı yüksektir. Bu yazıda IAHS'li iki çocuğun klinik ve laboratuvar bulguları ve sonuçlarını sunarak, intravenöz immünglobulin tedavinin ve ekren tanının önemini vurgulamaya çalıştık.

Anahtar Kelimeler: İnfeksiyona bağlı hemofagositik sendrom, İmmünglobulin.

Turk J Haematol 2003;20(2): 95-99

Received: *13.07.2001* ***Accepted:*** *23.11.2001*

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 contraversial: Presence of a family history, consanquinity, 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 fatique. 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 meropenem 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 persistance of chronic idiopathic neutropenia.

CASE 2

A 16.5-year-old female patient was admitted to our hospital with fever, fatique, 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 dismyelopoiesis. 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

Table 1. Laboratory data of the patients on the day of admission

	Case 1	Case 2
Leukocyte (x 10^9/L)	2.3	2.1
ANC (x 10^9/L)	0.12	0.48
RBC (x 10^{12}/L)	3.35	3.15
Hemoglobin (g/L)	6.2	7.3
Hematocrit (%)	19.2	22
Reticulocyte (%)	1.0	0.3
Thrombocyte (x 10^9/L)	46	22
Prothrombin time (seconds)	-	18.6
Partial thromboplastin time (seconds)	-	96
Fibrinogen (g/L)	-	1.1
D-dimer (µg/mL)	-	< 0.5
AST (IU/L)	34	4871
ALT (IU/L)	54	3335
LDH (IU/L)	600	11.280
Direct Coomb's test	Negative	Negative
Triglyceride (mmol/L)	9.89	7.29
Cholesterol (mmol/L)	4.55	5.3
Ferritin (ng/mL)	1604	830

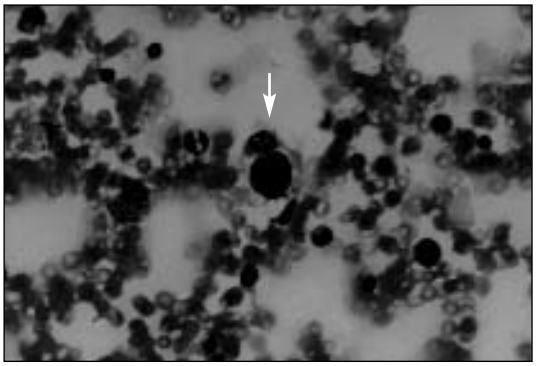

Figure 1. Bone marrow aspirate of the patient demonstrating hemophagocytosis.

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 criterias 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-

lignancy in the bone marrow and/or lymph nodes)[1]. 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 consanquinity. DIC and hyperferritinemia are also reported in some cases with IAHS as in our cases[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[5,6,18]. In treatment, corticosteroids, cyclosporin-A, supportive treatment and cessation of immunosupressive treatment were recommended previously; later, it was shown that IVIG improved the prognosis[5,17,19-21]. Etoposide and corticosteroids are recommended in familial cases, but in IAHS immunosupressive treatment modalities should be avoided[17]. Because of some adverse events of etoposide such as myelosupression, mucositis, infection, secondary leukemia and MDS, it is not recommended as the first line therapy in IAHS[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[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

1. Henter JI, Elinder G, Ost A, and FHL Study Group of the Histiocytic Society. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Semin Oncol 1991;18:29-33.
2. Ohga S, Matsuzaki A, Nishizaki M, Nagashima T, Kai T, Suda M, Ueda K. Inflammatory cytokines in virus-associated hemophagocytic syndrome. Am J Pediatr Hematol Oncol 1993;15:291-4.
3. Imashuku S, Ikushima S, Esumi N, Todo S, Saito M. Serum levels of interferon-g, cytotoxic factor and soluble interleukin-2 receptor in childhood hemophagocytic syndromes. Leuk Lymphoma 1991;3:287-92.
4. Risdall RJ, McKenna RW, Nesbit ME, Kriwit W, Balfow HH, Simmons RL, Brunnig RD. Virus-associated hemophagocytic syndrome: A benign histiocyte proliferation distinct from malignant histiocytosis. Cancer 1979;44:993-1002.
5. Imashuku S. Advances in the management of hemophagocytic lymphohistiocytosis. Int J Hematol 2000;72:1-11.
6. Ningsanond V. Infection associated hemophagocytic syndrome: A report of 50 children. J Med Assoc Thai 2000;83:1141-9.
7. Olson NY, Olson LC. Virus associated hemophagocytic syndrome: Relationship to herpes group viruses. Pediatr Infect Dis J 1986;5:369-73.
8. Potter MN, Foot ABM, Oakhill A. Influenza A and the virus-associated hemophagocytic syndrome: Cluster of three cases in children with acute leukemia. J Clin Pathol 1991;44:297-9.
9. Mills MD. Postviral hemophagocytic syndrome. JR Soc Med 1982;75:555-7.
10. Rissdall RJ, Brunning RD, Hernandez JI, Gordon DH. Bacteria associated hemophagocytic syndrome. Cancer 1984;54:2968-72.
11. Auerbach M, Haubenstock A, Soloman G. Systemic babesiosis: Another cause of the hemophagocytic syndrome. Am J Med 1986;80:301-3.
12. Morales Polanco M, Jimenez Balderas FJ, Yanez P. Storage histiocytes and hemophagocytosis: A common finding in the bone marrow of patients with systemic lupus erythematosus. Arch Med Res 1996; 27:57-62.
13. Wong KF, Hui PK, Chan JK, Chan YW, Ha SY. The acute lupus hemophagocytic syndrome. Ann Intern Med 1991;114:387-90.
14. Kanaji S, Okuma K, Tokumitsu Y, Yoshizawa S, Nakamura M, Niho Y. Hemophagocytic syndrome associated with fulminant ulcerative colitis and presumed acute pancreatitis. Am J Gastroenterol 1998; 93:1956-9.
15. Gürsel T, Koçak U, Tüner L, Hasanoğlu A. Bone marrow hemophagocytosis and immunological abnormalities in a patient with lysinuric protein intolerance. Acta Haematol 1997;98:160-2.
16. Duval M, Fenneteau O, Doireau V, Faye A, Emilie D, Yotnda P, Drapier JC, Schlegel N, Sterkers G, de Baulny HO, Vilmer E. Intermittent hemophagocytic lymphohistiocytosis is a regular feature of lysinuric protein intolerance. J Pediatr 1999;134:236-9.
17. Chu T, D' Angio GJ, Fauara BE, Ladisch S, Nesbit M, Pritchard J. The Writing Group of the Histiocytic Society. Histiocytic syndromes in children. Lancet 1987;2:41-2.
18. Close P, Friedman D, Uri A. Virus-associated hemophagocytic syndrome. Med Pediatr Oncol 1990; 18:119-22.
19. Goulder P, Seward D, Hatton C. Intravenous immunoglobulin in virus-associated hemophagocytic syndrome. Arch Dis Child 1990;65:1275-7.

20. Freeman B, Rathore MH, Salman E, Joyce MJ, Pitel P. Intravenously administered immunoglobulin for the treatment of infection associated hemophagocytic syndrome. J Pediatr 1993;123:479-81.
21. Chen RL, Lin KH, Lin DT, Su IJ, Huang LM, Lee PI, Hseih KH, Lin KS, Lee CY. Immunomodulation treatment for childhood virus-associated hemophagocytic lymphohistiocytosis. Br J Haematol 1995;89: 282-90.
22. Pui CH, Behm FG, Raimondi SC, Dodge RK, George SL, Rivera GK, Mirro J Jr, Kalwinsky DK, Dahl GV, Murphy SB. Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. N Engl J Med 1989;321:136-42.
23. Henter JI, Elinder G, Lubeck PO, Ost A. Myelodysplastic syndrome following epipodophyllotoxin therapy in familial hemophagocytic lymphohistiocytosis. Pediatr Hematol Oncol 1993;10:163-8.
24. Whitlock JA, Greer JP, Luken JN. Epipodophyllotoxin related leukemia. Cancer 1991;68:600-4.
25. Blanche S, Caniglia M, Fischer A, Griscelli C. Epstein-Barr virus associated hemophagocytic syndrome: Clinical presentation and treatment. Pediatr Hematol Oncol 1989;6:233-5.
26. McClain K, Gehrz R, Grierson H, Purtilo D, Filipovich A. Virus associated histiocytic proliferations in children: Frequent association with Epstein-Barr virus and congenital or acquired immunodeficiencies. Am J Pediatr Hematol Oncol 1988;10:196-205.

Address for Correspondence:

Hale ÖREN, MD

Department of Pediatric Hematology
Dokuz Eylül University Faculty of Medicine
35340, Balçova, İzmir, TURKEY

e-mail: *hale.oren@deu.edu.tr*