SUCCESSFULLY TREATED EPSTEIN-BARR VIRUS (EBV) ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) WITH PULSE STEROID

Murat Doğan MD, A. Faik Öner Prof. MD, Hayrettin Temel MD, Ertan Sal MD
Yuzuncu Yil University, Faculty of Medicine, Department of Pediatric, Van, Turkey

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease with fatal progression. This disease has two types familial and secondary HLH. Both of them have the same clinical spectrum. Fever, hepatosplenomegaly, pancytopenia, lymphadenopathy are the most observed signs and symptoms. In this article, 18 months old girl who was diagnosed with Epstein-Barr virus associated HLH and successfully treated with only pulse steroid is presented to emphasize that pulse steroid can be effective in EBV associated HLH. Therefore this agent may be used at the beginning of this diagnosis instead of commonly practiced HLH 2004 chemotherapy protocol.

• ***Key Words:*** *EBV, HLH, pulse steroid treatment* ***Nobel Med 2010; 6(3): 101-103***

PULSE STEROİD İLE BAŞARILI ŞEKİLDE TEDAVİ EDİLEN EPSTEIN-BARR VİRÜS (EBV) İLİŞKİLİ HEMOFAGOSİTİK LENFOHİSTİOSİTOZİS (HLH)

ÖZET

Hemofagositik lenfohistiyositozis (HLH) nadir görülen fatal seyirli bir hastalıktır. Hastalığın ailevi ve sekonder HLH olarak isimlendirilen iki tipi mevcuttur. Klinik spektrumu her iki hastalıkta aynıdır. Ateş, hepatosplenomegali, pansitopeni, lenfadenopati en sık gözlenen belirti ve bulgulardır. Bu makalede Epstein-Barr virüsü ile ilişkili HLH tanısı alan ve sadece pulse steroid ile başarılı bir şekilde tedavi edilen 18 aylık kız vaka pulse steroid tedavisinin Epstein-Barr visüs ile ilişkili HLH de etkili olabileceğini ve bu nedenle bu tedavi seçeneğinin hastalığın başlangıcında HLH 2004 kemoterapi protokolü yerine kullanılabileceği vurgulamak için sunuldu.

• **Anahtar Kelimeler:** EBV, HLH, pulse steroid tedavisi **Nobel Med 2010; 6(3): 101-103**

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is rare and fatal immunoregulatuar disease characterized by hemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors) in bone marrow and other tissues. There are two main types of HLH: Familial HLH and Secondary HLH. Both of them have similar clinical screen. Fever, hepatosplenomegaly, pancytopenia, lymphadenopathy are the most observed signs.[1,2] Familial HLH, which is inherited by autosomal recessive trait, is mostly seen at infant ages. In addition, secondary HLH occurs mostly after the viral infections and occasionally after the bacterial, fungal or protozoal infections (IAHS).[1,2] In this article, 18 months old girl who was diagnosed with Epstein-Barr virus (EBV) associated HLH and successfully treated with only pulse steroid is presented to emphasize that pulse steroid can be effective in EBV associated HLH, therefore this agent may be used at the beginning of this disorder instead of HLH 2004 chemotherapy protocol.

CASE REPORT

An 18 months girl was admitted to our hospital with fever lasting for 15 days, abdominal distention, mass on the neck and edema on eyelid and foots. She had no history of previous hospitalizations or serious illnesses. There was second-degree consanguinity between the parents. On physical examination; temperature was 38.5°C and multiple lymphadenopathies on cervical and axillary areas, edema on pretibial region, tachypnea and 1/6 degree short systolic murmur on mesocardiac focus were determined. In addition, liver and spleen were 6 cm and 4 cm palpable from the arcus costa on midclavicular line respectively. Her hemoglobin level was 7.7 g/dL and hematocrit was 22%. Platelet count was measured as $68x10^9L^{-1}$ and the white blood cell count was $3.4x10^9L^{-1}$ with differential of 20% segmented neutrophils, 70% lymphocytes, 10% monocyte. Total protein, albumin, triglyceride, lactic dehydrogenase, total bilirubin, direct bilirubin, aspartate amino transferase, alanine amino transferase, ferritin were 5 g/dL, 2.4 g/dL, 293 mg/dL, 1528 U/L, 4.3 mg/dL, 2.4 mg/dL, 195 U/L, 100 U/L, 683 µg/mL respectively. Renal function tests were normal. Prothrombin time was measured as 24.6 second, activated partial thromboplastin time as 28 second and fibrinogen as 25 mg/dL. D-Dimer level was 0.4 µg/mL. Although, there were no cells on cerebro-spinal fluid (CSF) examination, CSF protein level was 135 mg/dL. Toxoplasma, rubella, cytomegalovirus, herpes virus serologies, hepatitis antigens, Salmonella and Brucella serologies were negative. EBV VCA immunoglobulin M (Ig M) and Ig G were positive. On flow cytometric examination, CD 16+56 level (2.6%) was low, but CD4, CD8, CD3, CD19, CD20 levels were normal. On bone marrow examination, an increment of histiocytes counts and hemophagocytosis, which is characteristic feature of HLH, were seen (Figure). Blood, urine and CSF cultures were negative. The patient was diagnosed as EBV associated HLH and treated with methyl prednisolone (MTP). MTP was given as 30 mg/kg/day for 5 days, after that 20 mg/kg/days for 5 days, 10 mg/kg/days for 5 days and 2 mg/kg/day for 5 days and 1 mg/kg/day for 10 days. On the third day of MTP treatment, the fever recovered and bicytopenia were resolved on the 20th day. MTP treatment was ceased on the 30th day of treatment. She is still doing well and the remission has continued on the first year of follow up.

DISCUSSION

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.[3-5] Histiocyte Society has been published some criteria that have been used forh syndrome diagnosis (2004 HLH diagnostic guidelines).[2,6] These criteria are like; fever, splenomegaly, cytopenia affecting at least two of three lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis in bone marrow, spleen, or lymph nodes, low or absent Naturel Killer (NK) cell activity, hyperferritinemia, and high levels of sIL-2r.[2,6] Altogether, five of the eight criteria must be fulfilled, but patients with a molecular diagnosis consistent with HLH do not necessarily need to fulfill the diagnostic criteria.[2,6] Our patient had fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, hemophagocytosis in bone marrow and low NK cell counts on our examination. The levels of sIL-2r could not be performed because of technical insufficiency. Therefore, our patient fulfilled the seven of HLH 2004 diagnostic criteria.

HLH is a fatal disease if is not treated and the mean survival is 2 months. EBV associated HLH has poor prognosis too. The fatality ratio of IAHS is 50%.[7] Histiocyte Society published HLH 2004 treatment guidelines. This protocol, which continues 52 weeks, involves dexamethasone, etoposide, cyclosporine, intrathecal methotrexate and prednisolone treatment and it suggests stem cell transplantation when appropriated donor is found. But if IAHS is thought by laboratory analyses, familial history and genetic analyses, it is suggested that the first eight weeks treatment of HLH 2004 protocol is given and the infectious disease→

which triggered the HLH, is treated, after that the patient is followed and when the reactivation is found, stem cell transplantation must be applied.[2,6] In Turkey, HLH 94 treatment protocol is modified by addition of high dose MTP and intravenous immunoglobulin.[4] On the other hand, the treatment regimens, which include etoposide, were abstained due to its carcinogenic and immunosuppressant features. It is well known that the incidence of acute myeloblastic leukemia and myelodysplastic syndrome has been increased after the etoposide using and these chemotherapeutic protocols lead to infectious disease and death because of its immunosuppressant features.[8,9] Because of this reason, although the treatment regimens, which include etoposide, are the most suggested protocol at EBV associated HLH, the treatment protocols which include corticosteroids, IVIG or the combination of these drugs have been used worldwide. In addition to this, although some published articles have emphasized that IVIG and steroid were failed to treat HLH, some were defined opposite data.[10-14] Moreover, these second group published articles emphasized that the treatment time were associated with treatment success and these treatment agents should be given at the beginning of cytokines storm for success.[14] Therefore, pulse MTP treatment was applied initially to our patient and after that clinical and laboratory recoveries were observed in the first week and on the 20th day of treatment, respectively. We also observed that laboratory recovery had taken a long time in comparison with clinical recovery. Intrathecal treatment is suggested in HLH 2004 treatment guidelines when there are progressive neurological symptoms and continuation of abnormal CSF analyses.[6] In our patient, CSF analyses were normal after second week analyses, therefore the intrathecal treatment was not performed. This observation suggest that high dose MTP treatment as a monotherapy agent might be effective in cases with HLH which have CNS involvement.

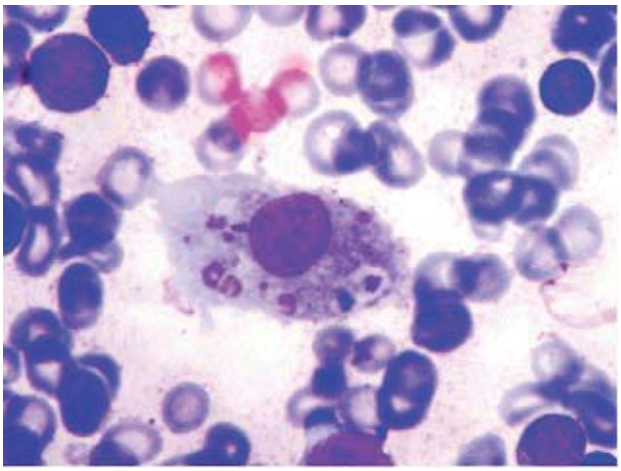

Figure. Hemophagocytosis in bone marrow

CONCLUSION

We suggest that high dose MTP can be effective in IAHS and EBV associated HLH, therefore this treating agent may be used at the beginning of these disorders instead of HLH 2004 chemotherapy protocol, which is an intensive, and immunosuppressing treatment protocols and leads to infectious disease and death. In addition to this suggestion, it is emphasized that when MTP treatment is fails, HLH 2004 chemotherapy protocols must be applied at the earliest.

C **CORRESPONDING AUTHOR:** Murat Doğan MD Hafiziye Mah. K. Karabekir Cad., Araştırma Hastanesi Arkası, Uğur Sitesi D blok, Van doganmurat.md@gmail.com

✓ **DELIVERING DATE:** 20 / 08 / 2008 • **ACCEPTED DATE:** 28 / 05 / 2009

REFERENCES

1 Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr 1983; 140: 221-230.

2 Henter JI, Elinder G, Öst A, and the FHL Study Group of the Histiocyte Society. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Semin Oncol 1991; 18: 29-33.

3 Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. Arch Dis Child 1952; 27: 519-525.

4 Bör Ö. Hemofagositik lenfohistiyositozis. Güncel Pediatri 2004; 2: 113-116.

5 Erduran E. Hemofagositik lenfohistiyositozis. Pediatrik Bilimler Özel Hematoloji Sayısı 2005; 3: 74-81.

6 Henter JI and Hemophagocytic Lymphohistiocytosis Study Group. E-Treatment Protocol of The Second International HLH Study Sweden 2004. (groups.yahoo.com/group/turkhistiosit /files/HLH 2004).

7 Arico M, Janka G, Ficher A, et al. Hemopaghocytic lymphohistiocytozsis. Report of 122 children from the Internationel Registry. Leukomia 1996; 10: 197-203.

8 Henter JI, Samuelsson-Horne A, Arico M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002; 100: 2367-2373.

9 Imashuku S, Hibi S, Kuriyama K, et al. Management of severe neutropenia with cyclosporin during initial treatment of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis. Leuk Lymphoma 2000; 36: 339-346.

10 Imashuku S, Kuriyama K, Teramura T, et al. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Clin Oncol 2001; 19: 2665-2673.

11 Su IJ, Wang CH, Cheng AL, Chen RL. Hemophagocytic syndrome in Epstein-Barr virus-associated T-lymphoproliferative disorders: Disease spectrum, pathogenesis, and management. Leuk Lymphoma 1995; 19: 401- 406.

12 Chen RL, Lin KH, Lin D-T, et al. Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 1995; 89: 282-290.

13 Alacacıoğlu İ, Çeneli S, Turgut N, et al. Hemofagositik Sendromun yüksek doz steroid ve intravenöz immünoglobulin ile tedavisi: XXXII. Ulusal Hematoloji Kongresi, 8-12 Kasım 2006, Antalya. Kongre kitabı, s:120.

14 Emmenegger U, Spaet PJ, Neftel KA. Intravenous Immunoglobulin for Hemophagocytic Lymphohistiocytosis. J Clin Oncol 2002; 20: 599-606.