Hemophagocytic Syndrome Associated with Bacterial Infections

Bakteriyel Enfeksiyonlarda Hemofagositik Sendrom

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is characterized by systemic proliferation and activation of benign histiocytes showing hemophagocytosis. It can be classified as primary and secondary or acquired HLH. Secondary HLH is associated with several infections, autoimmune diseases and malignancies. Here we report three cases of hemophagocytic syndrome (HS) associated with diverse bacterial infections that resolved with appropriate antibacterial therapy. *(J Pediatr Inf 2010; 4: 162-4)*

Key words: Hemophagocytic lymphohistiocytosis, salmonella, *Streptococcus pneumonia*, beta hemolytic streptococcus.

Özet

Hemofagositik lenfohistiyositoz (HLH) benign histiyositlerin proliferasyonu ve aktivasyonu sonucu ortaya çıkan klinik bir tablodur. Familial HLH'nin yanısıra özellikle viral enfeksiyonlar, otoimmün hastalıklar ve malignitelerle ilişkili görülebilir. Burada farklı bakteriyel enfeksiyonlar sırasında HLH tanısı almış ve uygun antibiyotik tedavisi ile düzelen üç olgu sunulmaktadır. *(J Pediatr Inf 2010; 4: 162-4)*

Anahtar kelimeler: Hemofagoistik lenfohistiyositoz, salmonella, *Streptococcus pneumonia*, beta hemolitik streptokok

Hemophagocytic lymphohistiocytosis (HLH) is characterized by systemic proliferation and activation of benign histiocytes showing hemophagocytosis (1-3). It can be classified as familial or acquired HLH. Acquired HLH is associated with several viral, bacterial, fungal and parasitic infections, also autoimmune diseases and malignancies (2-6). Although HLH associated with viral agents represents IAHS, various types of bacterial infection can also cause HLH (5,6).

We report three cases of hemophagocytic syndrome (HS) associated with diverse bacterial infections.

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Case 1

A 4-year-old previously healthy girl was first admitted to a local hospital with high fever. Her initial hemoglobin (Hb) level was 12.1 g/dl, white blood cell count (WBC) 18.8x10^9/L and platelet count 180x10^9/L. Three days later her Hb decreased to 8.1 g/dl, with atypical leukocytes on peripheral blood smear. She was referred to our hospital with the diagnosis of leukemia.

On physical examination, she was pale and looked ill. Her temperature was 38.6°C. Hepatosplenomegaly was noted, with the liver palpated at 3 cm and spleen palpated at 6 cm below the costal margins. She had multiple purpuric lesions.

Laboratory results included: Hb, 7.5 g/dl; WBC, 29.4x10^9 /L with a differential count of 60% lymphocytes, 36% neutrophils, 4% monocytes; platelet count, 90x10^9/L; C-reactive protein (CRP), 84.8 mg/dl; aspartate aminotransferase (AST), 510 U/L; alanine aminotransferase (ALT), 160 U/L; alkaline phosphatase (ALP), 891 U/L; total protein 8.23 g/dl; albumin 1.99 g/dl;

sodium 125 mEq/l; lactate dehydrogenase (LDH), 1064 U/L; triglyceride 267 mg/dl (normal 35-110 mg/dl); ferritin 675 ng/ml (normal 15-250 ng/ml); prothrombin time (PT) 16.9 seconds (N12-16), partial thromboplastin time (aPTT) 52.7 (N:33-42)seconds and fibrinogen 126 mg/dl (normal 200-400 mg/dl). Serological tests for Epstein Barr virus(EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), adenovirus, rubella, HIV and hepatitis A, B, and C viruses were all negative. Blood and urine cultures were obtained and empirical cefotaxime 200 mg/kg/day were initiated. Bone marrow aspiration revealed normal cellularity with marked hemophagocytic histocytes (Figure 1).

With a suspected diagnosis of infection associated hemophagocytic syndrome, single dose intravenous IgG (IVIG) (0.5 g/kg/d) was added to her empiric antibiotic therapy. Fever subsided and her clinical status improved. On the fourteenth day of admission, WBC was $8.4x10^9$/L; Hb 10.2 g/dl and platelet count was $301x10^9$/L. *Salmonella enterica* serotype enteritidis which was sensitive to ampicillin, cefotaxime and ceftriaxone grew on her admission blood culture.

Case 2

A 45 day old girl was referred to our hospital for the evaluation of hepatomegaly, prolonged jaundice and ascites.

On physical examination her temperature was 38.5°C. She had jaundice and bilateral corneal opacities. Abdominal distention, 2 cm palpable hepatomegaly and ascites were noted. Other physical findings were normal. Hematological examination revealed Hb 9.5 g/dl, WBC $40.3x10^9$/L, platelet count $134x10^9$/L. Total bilirubin level

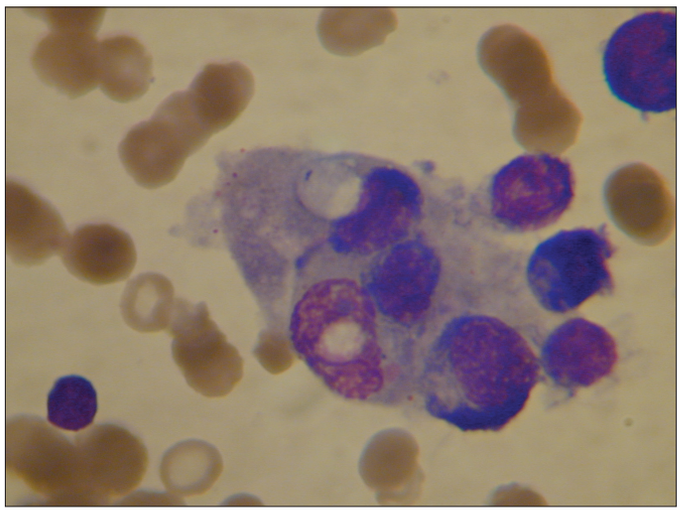

Figure 1. Bone marrow aspiration of case 1 reveals phagocytosis by a macrophage of several cells (Wright, x100)

11.6 mg/dl with 6.1 mg/dl direct reacting, AST 441 u/L, ALT 86 u/L, ALP 1590 u/L, GGT 36 u/L, total protein 4.72 g/dl, LDH 1195 U/L. Her triglyceride level was 235 mg/dl, ferritin 1869 ng/ml, fibrinogen 130 mg/dl, PT and aPTT were 26.6 seconds and 84.8 seconds respectively. Although bone marrow aspiration was performed to rule out storage disease, pronounced hemophagocytosis was noted. Serological investigations for EBV, CMV, HSV, adenovirus, rubella, HIV and hepatitis A, B, and C viruses were all negative. *Streptococcus pneumonia* sensitive to penicillin G, cefotaxime, ceftriaxone and vancomycin was grown on her admission blood culture. She was diagnosed with *Streptococcus pneumonia* associated hemophagocytic syndrome and cefotaxime treatment was started. With further search for cataracts and ascites, she was also diagnosed with galactosemia. Although liver functions did not improve, her status became stable shortly after antibiotic treatment and the ferritin and triglyceride levels normalized. The patient was referred to another hospital for follow-up of her metabolic disorder.

Case 3

A 4.5 year old girl referred to our hospital with tooth pain, malar swelling and high fever. Her temperature was 38,8°C. She had swelling, local warmth, hyperemia and tenderness on the right side of her face which extended from eye to neck. She also had gingival hyperemia, hypertrophy and gingival bleeding and minimal splenomegaly. Laboratory results included: WBC $22x10^9$/L, Hb 9.7 g/dl, platelet count $44x10^9$/L, AST 113 U/L; ALT 91 U/L; ALP 363 U/L; total protein 5.46 g/dl; albumin 2.2 g/dl; triglyceride 290 mg/dl; ferritin 476 ng/dl; CRP 193 mg/dl; PT 10.9 seconds and aPTT 27.8 seconds. Ceftriaxone and clindamycine was admnistered for deep neck infection. Multiple histiocytes with hemophagocytosis and myeloid hyperplasia were observed on bone marrow aspiration. She was diagnosed with infection associated hemophagocytic syndrome and single dose IVIG (0.5 g/kg) was given. Non-group A, non-group B beta hemolytic streptococcus species sensitive to clindamycine grew on blood culture. On the sixteenth day of treatment her clinical and hematological parameters returned to normal.

Discussion

Hemophagocytic lymphohistiocytosis is related to uncontrolled activation of T-lymphocytes and monocytes that leads to hypercytokinemia with tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), interleukin (IL) -6, IL-8, IL-10, IL-12 and IL-18. Although in immune

competent patients with the acquired form of HLH, the exact mechanisms are not clear, overproduction of cytokines which is attributable to inappropriate T-helper1 response to pathogens is suggested as the trigger for IAHS (1-3). In addition, TNF-α promoter polymorphism was associated with increased susceptibility to secondary HLH (7).

The diagnostic criteria for HLH include fever; splenomegaly; bi-cytopenia; hypertriglyceridemia and/or hypofibrinogenemia; and hemophagocytosis (2). However, these criteria are specified for primary HLH but not standardized for secondary HLH. Anemia and thrombocytopenia were found in our cases. Interestingly, they all had leukocytosis. Also, coagulation tests were normal in the third patient. While many of the symptoms of HLH may be observed in a patient with infectious disease, they are more pronounced in patients with HLH. The occurrence or progression of hepatosplenomegaly, cytopenia and marked biochemical parameters such as elevated ferritin, triglycerides, liver enzymes, and biluribin or low fibrinogen should alert the physician to an unusual response for infectious agent (1,2,5,8). Although triglyceride and ferritin may increase in severe bacterial infections, they usually remain below 265 mg/dl and 200 ng/ml, respectively (1).

Hemophagocytosis and symptoms of HLH have also been reported in association with inborn errors of metabolism. It is not clear which metabolic products may initiate the abnormal response (1). Our second case was diagnosed with galactosemia coexisting with IAHS due to *Streptococcus pneumonia.* We suggested that both her infectious and metabolic diseases might contribute to hemophagocytosis.

It is recommended that all patients with IAHS should have genetic testing for familial HLH. It is impossible to distinguish primary from secondary HLH on clinical grounds (9). Unfortunately, we could not perform a genetic analysis of the patients. Nevertheless, we accepted considered will be deleted them as IAHS, and follow-up them closely for a new attack.

The prognosis of HLH depends on the degree of cytokine disturbance and organ failure at the onset and the underlying infection. Supportive treatments, IVIG and sometimes immunochemotherapy are the treatment options in IAHS (1,2). Management with appropriate antibiotics and aggressive supportive treatment including IVIG seems to increase survival, as observed in our patients. In conclusion, although the criteria of familial HLH were not appropriate for IAHS, in patients with infection and progression of hepatosplenomegaly and cytopenia, the diagnosis of IAHS should be kept in mind.

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