

Brucellosis presenting with pancytopenia due to hemophagocytic syndrome

Hemofagositik sendroma baęlı pansitopeni ile başvuran bruselloz olgusu

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Abstract

Reactive hemophagocytic syndrome is clinically characterized by fever, hepatosplenomegaly, pancytopenia, and coagulopathy, and is histologically characterized by excessive proliferation and activation of histiocytes or macrophages. It can occur with systemic infections, immunodeficiency, or underlying malignancy. Brucellosis is one of the rare causes of hemophagocytosis. Herein we report an 11-year-old male with pancytopenia due to hemophagocytosis during the course of brucellosis that responded favorably to therapy. Although rare, hemophagocytosis should be considered as a possible cause of pancytopenia in patients with brucellosis, especially in regions where brucellosis is frequently encountered. (*Turk J Hematol 2011; 28: 68-71*)

Key words: Brucellosis, pancytopenia, hemophagocytosis

Received: June 05, 2009

Accepted: September 18, 2009

Özet

Reaktif hemofagositik sendrom klinik olarak ateş, karaciğer ve dalak boyutlarında artış, pansitopeni ve pıhtılaşma bozuklukları; histolojik olarak da histiyosit ya da makrofajların artmış proliferasyon ve aktivasyonları ile karakterizedir. Sistemik hastalıklar, immün yetmezlikler ve altta yatan malignitelerle birlikte olabilir. Brusella, hemofagositozun nadir nedenlerinden biridir. Brusellanın sık görüldüğü ülkelerde pansitopenisi olan hastalarda hemofagositozu hatırlatmak amacı ile, brusella seyri sırasında hemofagositoza baęlı pansitopenisi olan, uygun tedavi sonrası iyileşen 11 yaşında bir erkek hasta sunulmaktadır. (*Turk J Hematol 2011; 28: 68-71*)

Anahtar kelimeler: Brusella, pansitopeni, hemofagositoz

Geliş tarihi: 5 Haziran 2009

Kabul tarihi: 18 Eylül 2009

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an unusual syndrome characterized by acute onset of fever, hepatosplenomegaly, lymphadenopathy, and jaundice, along with the pathological findings of hemophagocytosis (phagocytosis of erythrocytes, leukocytes, platelets, and their precursors by macrophages) in bone marrow and other tissues. Although de novo HLH can also be seen, it often occurs in the setting of another disorder - usually in association with malignant, infections, or autoimmune diseases that are prominently linked with Epstein-Barr virus (EBV) infection [1]. Non-viral infections and bacterial infections, including tuberculosis, are other major causes [2]. Fungal and parasitic causes of HLH have also been reported [3,4]. Brucellosis is one of the rare causes of hemophagocytosis. Herein we present a case of pancytopenia due to hemophagocytosis during the course of brucellosis.

Case Report

An 11-year-old male presented to our hospital with symptoms of fever, loss of appetite, and headache, which began 5 days earlier. The patient's parents were not consanguineous. His height was 138 cm (10th-25th percentile) and weight was 26 kg (3rd-10th percentile). His general health status was moderately good and neurological findings were normal. In physical examination the liver and spleen were 8 cm and 10 cm, respectively, and palpable below the costal margin of the midclavicular line, with multiple bilateral inguinal lymphadenopathies. He was diagnosed with pancytopenia based on the following laboratory findings: hemoglobin: 7.3 g dL; mean corpuscular volume: 77 fL; white blood cell count: 2600 mm³ (granulocyte: 900 mm³); platelet count: 85,000 mm³; SGOT: 65 U L⁻¹; SGPT: 16 U L; LDH: 1733 U L⁻¹; cholesterol: 155 mg/dL; triglycerides: 345 mg/dL; HDL: 13 mg/dL; VLDL: 73 mg/dL; LDL: 69 mg/dL; total bilirubin: 0.5 mg/dL; total protein: 5.3 g dL; albumin: 2.5 g dL; ferritin: 3167 ng/mL; prothrombin time: 14.1 sec; prothrombin activity: 60%; partial thromboplastin time: 29.3 sec; fibrinogen: 155 mg/dL. Burr cells and cells resembling sickle cells were observed in peripheral smear.

In order to exclude malignancy as a cause of pancytopenia, bone marrow aspiration was performed, which showed the presence of hemophagocytes (Figure 1). Based on the clinical, laboratory (pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevated ferritin level), and bone marrow aspiration findings, the patient was diagnosed with secondary hemophagocytic syndrome. Serological markers were examined for EBV, cytomegalovirus, hepatitis B, parvovirus, Salmonella, and Brucella. Wright agglutination test results were positive, with a titer of 1/2560. Immediately following the bone marrow biopsy and culture to confirm the diagnosis, a course of antibiotic treatment was initiated (oral doxycycline 200 mg/day for 6 weeks and intravenous gentamycin 5 mg/kg/day for 2 weeks). Blood and bone marrow cultures remained sterile.

Examination of the biopsy specimens showed that the bone marrow was normocellular and contained macrophages that phagocytized the lymphoid and erythroid elements. After 1 week of antibiotic treatment the patient was afebrile. At the end of the third week of doxycycline treatment the patient's white blood cell count was 2480 mm³ (granulocyte: 1680 mm³), hemoglobin was 9.7 g dL, and platelet count was 175,000 mm³. Six months after treatment began the patient's white blood cell count was 6640 mm³, neutrophils was 3600 mm³, hemoglobin was 13.8 g dL, and platelet count was 187,000 mm³. The patient remained symptom-free with progressive decrease in the titers of Wright agglutination test.

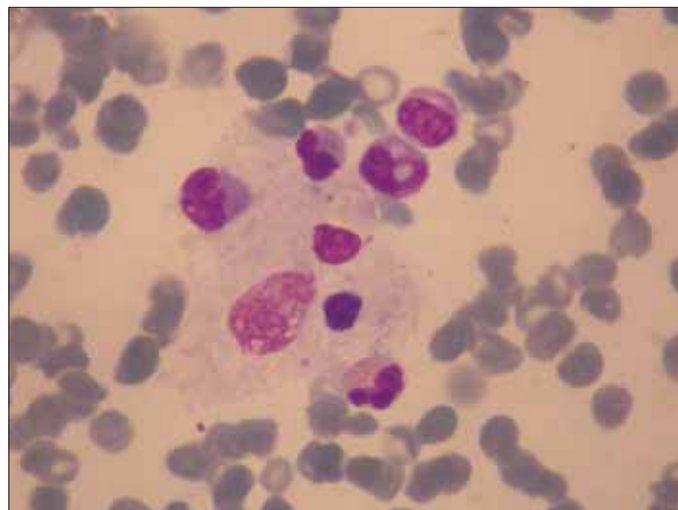


Figure 1. Bone marrow smear demonstrating hemophagocytosis by a large histiocyte (Giemsa stain, 1000×)

Written informed consent was obtained from the patient's family.

Discussion

HLH was first described by Scott in 1939 [5] and has since been associated with a variety of viral, bacterial, fungal, and parasitic infections, as well as collagen-vascular diseases and malignancies - particularly T-cell lymphomas. This diversity has led to the suggestion that HLH secondary to an underlying medical illness should be regarded as reactive hemophagocytic syndrome. Both sporadic and familial cases of HLH are often precipitated by acute infections, and HLH may mimic infectious illnesses such as overwhelming bacterial sepsis, which emphasizes the importance of the association between HLH and infection. As such, a better understanding of the pathophysiology of HLH may clarify the interaction between the immune system and infectious agents. Brucellosis is among the rare causes of secondary HLH, in which hematological alterations are common and pancytopenia is observed in 6% of patients [6].

Examination of bone marrow aspiration specimens shows normo-, hyper-, or hypocellularity [7]. In addition to pancytopenia, severe disorders - including hemophagocytic syndrome - have also been described in association with brucellosis. Although the mechanism of hemophagocytosis induction in cases of brucellosis is not well understood, immune system derangement, with defective T-cell functioning, T-cell and monocyte hyperactivation, hypercytokinemia, and selective deficiency in cellular cytotoxicity has been reported. [8]

Macrophages can be activated when they come into contact with foreign substances such as bacteria. This activation, in turn, can cause hemophagocytosis when macrophages come into contact with red blood cells, white blood cells, and platelets, leading to the clinical symptoms in the same non-specific way as when they come into contact with foreign organisms. Although the precise mechanism remains unclear, 1 currently accepted theory suggests the role of perforin and natural killer cells in HLH subtypes [9]. Patients with perforin deficiency may have impaired defenses against intracellular pathogens, which is also critically important to the mechanism of primary HLH. Decreased natu-

ral killer cell activity results in increased T-cell activation, immediately followed by cytokine production, which leads to an inflammatory reaction, and extensive damage and associated symptoms [10].

Hemophagocytic syndrome is less common in children than in adults. A search of the literature showed that there are only 3 published reports of hemophagocytosis secondary to brucellosis in children [11-13]. Hemophagocytic syndrome in children should be differentiated from familial HLH, which is characterized by early onset, a higher prevalence of parental consanguinity, and an association with immune deficiencies, such as Chediak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome. Both conditions can be triggered by infections or other stimuli; however, most patients with secondary HLH have no underlying immune deficiency. Brucellosis associated with pancytopenia and evidence of reactive hemophagocytosis were first reported by Zuazu et al. in 1979 [14]. The presented case had fever, hepatosplenomegaly, and pancytopenia. Pancytopenia associated with brucellosis is attributed to hypersplenism, hemophagocytosis, and granulomatous lesions of the bone marrow, which is usually hypercellular [13,15,16]. In the present case we think that hemophagocytosis was responsible for pancytopenia.

As isolation of the organism is difficult, serological tests are used for the routine diagnosis of brucellosis in most cases and the agglutination test is used as the principal test. When brucellosis is suspected in patients with negative cultures, rising agglutinin titers over 1:160 are considered diagnostic. [17] With the availability of effective therapy the mortality rate associated with brucellosis has declined. In some cases, intravenous immunoglobulin is used for treatment, which results in remission in adults and older children, particularly those with an underlying immune dysfunction; however, the role of this treatment in cases of hemophagocytosis is unclear [18]. The presented case recovered after antimicrobial treatment, without the need for intravenous immunoglobulin.

Brucellosis must be considered in the differential diagnosis of malignant or benign diseases associated with hemophagocytosis, especially in geographic areas where brucella infection is common. The pathogenesis of pancytopenia in brucellosis is not clear, but appears to be multi-factorial. Although

rare, hemophagocytosis should be considered a possible cause of pancytopenia in patients with brucellosis.

Conflict of interest statement

The authors declare that there are no conflicts of interest. None of the authors have a financial or proprietary interest in the case report preparation. All of the authors have been duly credited.

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