



Case Report

A Rare Hematological Manifestation of Brucellosis: Reactive Hemophagocytic Syndrome

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Hemophagocytic syndrome (HS) may be primary, or secondary, to malignancy, or to metabolic, collagen vascular, and infectious diseases such as brucellosis, miliary tuberculosis and some viral and fungal infections. The diagnostic findings of HS are high fever, hepatosplenomegaly, cytopenia, high serum ferritin and triglycerides, and low serum fibrinogen levels. Brucellosis is a zoonotic disease, with fever, fatigue, sweating, arthritis, hepatosplenomegaly, lymphadenopathy, and cytopenia being the most common symptoms and findings. Hematological manifestations of the disease may include anemia, leucopenia, leukocytosis, thrombocytopenia, and thrombocytosis. Brucellosis may occur in association with HS. Here, we describe brucellosis associated HS in an 8 year-old male patient. The patient was admitted to our clinic with weight loss, arthralgia, prolonged fever, sweating, and fatigue. Physical and laboratory findings revealed hepatosplenomegaly, pancytopenia, elevated serum transaminases, triglycerides, lactate dehydrogenase, and ferritin, and with erythrocytes, leukocytes, and thrombocytes phagocytosed by macrophages indicating hemophagocytosis. The Brucella agglutination test was positive. The patient improved after treatment with Rifampin (15 mg/kg/day) and trimethoprim-sulfamethoxazole (10 mg/kg/day).

KEYWORDS: brucellosis, hemophagocytic syndrome

Introduction

Hemophagocytic syndrome (HS) is a hyperinflammatory condition with primary or secondary causes. Primary HS develops as a result of syntaxin 11, perforin 1, and

hMunc13-4 gene mutations, and usually occurs in infancy.¹⁻³ Secondary HS may occur in any age group and can develop as a result of malignancy, or metabolic, collagen vascular and infectious diseases such as brucellosis, miliary tuberculosis, Epstein-Barr virus, Cytomegalovirus, Parvovirus B19, human immunodeficiency virus, and some fungal infections.^{1,4,5} Both sporadic and familial cases of HS are often induced by acute infection. The diagnostic criteria for HS are high fever, hepatosplenomegaly, cytopenia (= 2 cell types), high serum ferritin (> 500 µg/L), and elevated triglycerides (fasting triglyceride = 3 mmol/L), soluble CD25 and soluble interleukin-2-receptor levels, low serum fibrinogen (< 1.5g/L), decreased and absent Natural Killer-cell activity, and hemophagocytosis evident in the bone marrow or spleen.^{1,6}

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Brucellosis is an infectious disease of animals caused by coccobacilli of the genus *Brucella*, and is transmitted to humans by direct contact with infected animals, and by consumption of infected animal products. In childhood the disease may present with many different symptoms and findings such as fever, fatigue, sweating, arthritis, hepatosplenomegaly, lymphadenopathy, and cytopenia.⁷ Fever is the most common feature of brucellosis, followed by osteoarticular involvement and sweating.⁸ Genitourinary complications such as glomerulonephritis, renal abscess and orchiepididymitis are seen in a few patients. Neurological findings like peripheral neuropathy, chorea, meningoencephalitis, transient ischemic attacks, and psychiatric manifestations are not uncommon.⁸ Anemia, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis, elevated C-reactive protein and erythrocyte sedimentation rate, and rheumatoid factor positivity can also be present. Agglutination tests and blood cultures are valuable for the diagnosis of brucellosis. A rare clinical presentation of human brucellosis is reactive HS.⁹ Reactive HS should be suspected if the patient presents with pancytopenia, hepatosplenomegaly, prolonged fever, high serum triglyceride and ferritin levels, and low serum fibrinogen. Bone marrow aspiration should be performed to obtain a definitive diagnosis.

Here, we report the case of an 8 year-old child presenting with fever, abdominal pain, fatigue, sweating, and pancytopenia, resulting in a diagnosis of reactive HS associated with brucellosis.

Case Report

An 8 year-old boy was admitted to our pediatric hematology clinic with prolonged fever, fatigue, sweating, and abdominal pain. The fever and fatigue had started 1 month previously. He described abdominal pain, especially in the morning. There was no weight loss or arthralgia in the patient's history, but he had ingested fresh milk products which were not cooked well. Physical examination revealed splenomegaly (a 3 cm increase in size) below the left costal edge and hepatomegaly (a 2 cm increase in size) below the right costal edge, pallor, and mild abdominal tenderness. Laboratory findings showed pancytopenia with hemoglobin levels of 8.9 g/dL, white blood cell count of 2×10^9 cells/L and a platelet count of 97×10^9 cells/L. The differential leukocyte count on the peripheral smear was 60%

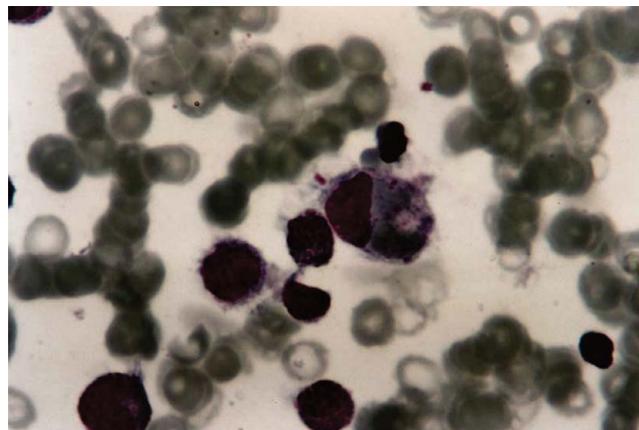


Figure. Bone marrow aspiration smear showing erythrocytes and thrombocytes phagocytosed by macrophages (Wright stain; original magnification, 100 \times).

neutrophils, 35% lymphocytes, 5% monocytes. The reticulocyte count was 2%. The erythrocyte sedimentation rate was 18 mm/h. Biochemical analysis revealed alanine transaminase=71 U/L, aspartate transaminase=105 U/L, serum triglyceride=227 mg/dL, lactate hydrogenase (LDH)=581 IU/L, ferritin=1243 ng/mL and fibrinogen=238 mg/dL. Other biochemical findings were within normal limits. Serological tests performed for Epstein-Barr virus, Cytomegalovirus, and *Salmonella* were all negative. Bone marrow aspiration showed that lymphocytes, thrombocytes, and neutrophils had been phagocytosed by macrophages, indicating hemophagocytosis (Figure). The *Brucella* agglutination test was positive with a ratio of 1:640. Blood and bone marrow cultures were also positive for *Brucella*. Reactive HS associated with brucellosis was diagnosed according to the above laboratory and clinical findings. Rifampin (15 mg/kg/day) and trimethoprim-sulfamethoxazole (10 mg/kg/day) treatment was initiated. The fever disappeared on the third day of therapy. The platelet count increased progressively during treatment and, on Day 7, the blood count showed hemoglobin level=9.2 g/dL, white blood cell count= 5.2×10^9 cells/L, and a platelet count of 281×10^9 cells/L. Biochemical abnormalities improved: serum triglyceride=174 mg/dL, ferritin=142 ng/mL, alanine transaminase=51 U/L, aspartate transaminase=45 U/L and LDH=328 IU/L. By Day 9 splenomegaly was reduced to 1 cm in size, palpable below the left costal edge, and hepatomegaly was not detected. The patient was followed-up in the out-patient clinic for 6 weeks and fully recovered after treatment.

Discussion

Hemophagocytic syndrome is a hyperinflammatory disease and may develop primary to syntaxin 11, perforin 1, and hMunc13-4 gene mutations, or secondary to malignancy, and metabolic, collagen vascular and infectious diseases.¹ The cardinal symptoms and findings are fever unresponsive to antibiotics, fatigue, cytopenia, hepatosplenomegaly, and hemophagocytosis by activated macrophages.^{1,4} Icterus, rash, lymphadenopathy, and neurological symptoms may also be present. All the symptoms of HS can be explained by high concentrations of inflammatory cytokines such as interleukin-1, interleukin-6, tumor necrosis factor- α and interferon- γ .¹ Laboratory findings include cytopenia, elevated serum triglycerides, ferritin and transaminase, and low serum fibrinogen levels.^{1,4} Tumor necrosis factor- α inhibits lipoprotein lipase leading to the elevation of triglycerides.¹ The bone marrow smear usually shows evidence of hemophagocytosis in the majority of cases.

Hyperinflammation caused by excessive cytokine levels should be treated with either corticosteroids or immunosuppressive agents. Corticosteroids are cytotoxic for lymphocytes and inhibit the expression of cytokines. Intravenous immunoglobulins, etoposide, cyclosporin A, and antithymocyte globulin are the other treatment choices, either in combination with corticosteroids, or alone.^{1,6,10} The genetic form of HS usually occurs in children below 1 year of age, and combination therapy with dexamethasone, cyclosporin A, etoposide, and intrathecal methotrexate is appropriate for this form of the disease. Infections associated with brucellosis and miliary tuberculosis should be treated with the appropriate antibiotics.^{5,11}

Various hematologic findings are seen in brucellosis. Especially, thrombocytopenia may be severe and steroid therapy is required in some cases.¹² Pancytopenia is usually due to hypersplenism.¹³ In addition, granulomatous bone marrow lesions and hemophagocytosis in the bone marrow are thought to be the other causes for pancytopenia.¹⁴ In an extensive investigation in Turkey, the hematological manifestations of 233 brucellosis cases were discussed, and anemia was the most common, followed by thrombocytopenia and leukopenia.¹⁵ Also, pancytopenia and mild to moderate hemophagocytosis on the bone marrow smear were detected in 8% of the cases.¹⁵ In another study, 54 children with brucellosis were evaluated, and pancytopenia

was determined in 14.8% of them.¹¹ Hemophagocytosis was detected in three of these cases. The pancytopenia was transient in all patients and resolved after appropriate antibiotic treatment. Our patient was treated with the combinations of rifampin and trimethoprim-sulfamethoxazole. Tetracycline treatment was not appropriate for the patient because of his age. The patient recovered after antibiotic treatment.

Our patient presented with prolonged fever, fatigue, hepatosplenomegaly, and pancytopenia. Bone marrow aspiration was done because the patient had pancytopenia, and high serum triglycerides, ferritin, and LDH. The bone marrow smear showed thrombocytes, neutrophils, and lymphocytes phagocytosed by macrophages. Reactive HS due to brucellosis was diagnosed as both blood and bone marrow aspiration cultures were positive for brucellosis, and the Brucella agglutination test was positive. Rifampin and trimethoprim-sulfamethoxazole treatment was initiated because the patient's age was not appropriate for tetracycline treatment. The patient recovered after antibiotic treatment.

In patients with brucellosis coupled with hepatosplenomegaly and cytopenia, an association with HS should be considered. Characteristic laboratory findings such as high serum ferritin and triglycerides, low serum fibrinogen levels, and pancytopenia support the diagnosis, and bone marrow aspiration should be performed. Evidence of hemophagocytosis by activated macrophages on bone marrow smears is supportive of the diagnosis, but may not be present.¹ Reactive hemophagocytosis should be considered in a patient having pancytopenia with brucellosis and early treatment with appropriate antibiotics will be life-saving.

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